



# TRAUMATIC BRAIN INJURY

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## Summary of Recommendations

The Evidence-based Practice Panel’s recommendations are based on critically appraised higher quality research evidence and on expert consensus observing First Principles when higher quality evidence was unavailable or inconsistent (see Methodology). The reader is cautioned to utilize the more detailed indications, specific appropriate diagnoses, temporal sequencing, preceding testing or conservative treatment, and contraindications that are elaborated in more detail for each test or treatment in the body of this Guideline in using these recommendations in clinical practice or medical management. These recommendations are not simple “yes/no” criteria.

All ACOEM guidelines include analyses of numerous interventions, whether or not FDA-approved. For non-FDA-approved interventions, recommendations are based on the available evidence; however, this is not an endorsement of their use.

Recommendations are made under the following categories:

- Strongly Recommended, “A” Level
- Moderately Recommended, “B” Level
- Recommended, “C” Level
- Insufficient-Recommended (Consensus-based), “I” Level
- Insufficient-No Recommendation (Consensus-based), “I” Level
- Insufficient-Not Recommended (Consensus-based), “I” Level
- Not Recommended, “C” Level
- Moderately Not Recommended, “B” Level
- Strongly Not Recommended, “A” Level

<b>Acupuncture</b>	Acupuncture for Acute or Subacute Cervicothoracic Pain	Not Recommended, Insufficient Evidence (I)
	Acupuncture for Chronic Cervicothoracic Pain	Recommended, Evidence (C)
<b>Allied Health</b>	Meniett Device	Recommended, Insufficient Evidence (I)
	Transcranial Direct Current Stimulation	No Recommendation, Insufficient Evidence (I)
	Transcranial Magnetic Stimulation	No Recommendation, Insufficient Evidence (I)
<b>Attention Tests / Training</b>	“Captain’s Log”- Computer Training Program for Attention Skills with Tasks for Vigilance, Inattention, Prudence, Impulsivity, Focus, Variability, and Speed	No Recommendation, Insufficient Evidence (I)
	Attention Process Training	Recommended, Insufficient Evidence (I)
	Attention Regulation Training	Recommended, Evidence (C)
	Attention Tests	Recommended, Insufficient Evidence (I)
	Computerized Attention Training with Visual, Auditory, and Divided Training	Recommended, Insufficient Evidence (I)
	Reaction Time Training	No Recommendation, Insufficient Evidence (I)
	Recreational Computing	Recommended, Insufficient Evidence (I)
	Restorative Computer and Non-Computer Attention Remediation	No Recommendation, Insufficient Evidence (I)
<b>Audiological Tests</b>	Audiometry	Recommended, Insufficient Evidence (I)
	Brainstem Auditory Evoked Response	Recommended, Insufficient Evidence (I)

	Tympanometry	No Recommendation, Insufficient Evidence (I)
<b>Balance Tests / Training</b>	Computerized Dynamic Platform Posturography	No Recommendation, Insufficient Evidence (I)
	Computer & Video Games for Balance	Recommended, Insufficient Evidence (I)
	Electro- or Video Nystagmography	No Recommendation, Insufficient Evidence (I)
	Electronystagmogram Studies	Recommended, Insufficient Evidence (I)
	Rotary Chair Testing	Recommended, Insufficient Evidence (I)
	Vestibular Rehabilitation	Recommended, Evidence (C)
	Virtual Reality for Balance	Recommended, Evidence (C)
<b>Behavioral / Psych</b>	Anger Management Therapy	Recommended, Insufficient Evidence (I)
	Behavioral Programs	Recommended, Insufficient Evidence (I)
	Cognitive Behavioral Therapies	Recommended, Evidence (C)
	Community-Based Life Goals	No Recommendation, Insufficient Evidence (I)
	Emotional Training	Recommended, Insufficient Evidence (I)
	Goal Setting	Recommended, Insufficient Evidence (I)
	Motivational Interviewing	Recommended, Insufficient Evidence (I)
	Peer-Mentoring Program	No Recommendation, Insufficient Evidence (I)
	Psychosocial Functioning and ADLs	Recommended, Insufficient Evidence (I)
	Substance Abuse Counseling	Recommended, Insufficient Evidence (I)
	Suicide Prevention	Recommended, Evidence (C)
	Video Feedback on Task Performance	Recommended, Insufficient Evidence (I)
<b>Biofeedback</b>	Biofeedback for TBI Patients	No Recommendation, Insufficient Evidence (I)
<b>Biomarkers</b>	Biomarkers	No Recommendation, Insufficient Evidence (I)
<b>Botox</b>	Botulinum Toxin	Recommended, Evidence (C)
<b>Debridement</b>	Debridement	See Guideline
<b>Decompression</b>	Decompression and Facial Nerve Decompression	See Guideline
<b>Education</b>	Education Program	Recommended, Insufficient Evidence (I)
<b>EEG</b>	Electroencephalography	Recommended, Insufficient Evidence (I)
	Quantitative Electroencephalograph	No Recommendation, Insufficient Evidence (I)
<b>Electrical Stimulation</b>	Functional Electrical Stimulation	No Recommendation, Insufficient Evidence (I)
	Neuromuscular Electrical Stimulation	No Recommendation, Insufficient Evidence (I)
<b>Electrodiagnostics</b>	Electromyography and Nerve Conduction Studies	Recommended, Insufficient Evidence (I)
	Electroneuronography	Recommended, Insufficient Evidence (I)
<b>Evoked Potentials</b>	Somatosensory Evoked Potentials	Recommended, Insufficient Evidence (I)
	Vestibular Evoked Myogenic Potentials	No Recommendation, Insufficient Evidence (I)
<b>Executive Function</b>	Executive Function Tests	Recommended, Insufficient Evidence (I)
<b>Exercise</b>	Aerobic Exercise	Recommended, Insufficient Evidence (I)
	Aquatic Therapy	Recommended, Evidence (C)
	Strengthening Exercises	Recommended, Insufficient Evidence (I)
	Stretching and Flexibility Exercises	Recommended, Insufficient Evidence (I)
<b>Family Visits</b>	Family Visits	Recommended, Evidence (C)

<b>Functional Capacity Evaluations</b>	FCEs for Acute Cervicothoracic Pain, Acute or Subacute Radicular Syndromes, or Post-Surgical Cervical or Thoracic Pain	Not Recommended, Insufficient Evidence (I)
	FCEs for Chronic Disabling Cervical or Thoracic Pain	Recommended, Insufficient Evidence (I)
	FCEs for Chronic Stable Cervicothoracic Pain or Post-operative Recovery	No Recommendation, Insufficient Evidence (I)
	FCEs for TBI Patients	Recommended, Insufficient Evidence (I)
<b>Group Discussions</b>	Group Discussions	No Recommendation, Insufficient Evidence (I)
<b>Hyperbaric Oxygen</b>	Hyperbaric Oxygen Therapy	Mild: Moderately Not Recommended; Moderate: No Recommendation; Severe: Moderately Recommended
<b>Hyperventilation</b>	Hyperventilation	Recommended, Insufficient Evidence (I)
<b>Hypothermia</b>	Induced Hypothermia	Not Recommended, Evidence (C)
<b>Imaging</b>	Brain Acoustic Monitor	No Recommendation, Insufficient Evidence (I)
	Computed Tomography	Recommended, Evidence (C)
	Diffusion Tensor Imaging	Recommended, Evidence (C)
	Functional Magnetic Resonance Imaging	No Recommendation, Insufficient Evidence (I)
	Magnetic Resonance Imaging	Moderately Recommended, Evidence (B)
	Magnetic Resonance Spectroscopy	No Recommendation, Insufficient Evidence (I)
	Positron Emission Test	No Recommendation, Insufficient Evidence (I)
	Single-Photon Emission Computerized Tomography	No Recommendation, Insufficient Evidence (I)
	Skull X-Rays	Recommended, Insufficient Evidence (I)
	Ultrasonography	Recommended, Insufficient Evidence (I)
	Vascular Imaging Tests	Recommended, Insufficient Evidence (I)
<b>Intelligence Tests</b>	Automated Neuropsychological Assessment Metrics [1]	Moderately Recommended, Evidence (B)
	Wechsler Adult Intelligence Scale (WAIS, WAIS-III))	Moderately Recommended, Evidence (B)
<b>Intracranial Pressure</b>	Intracranial Pressure Monitoring and Thresholds	Recommended, Evidence (C)
<b>Lab Tests</b>	Laboratory Testing	See Guideline
<b>Laser Therapy</b>	Laser Therapy/Low-Level Laser Therapy	No Recommendation, Insufficient Evidence (I)
<b>Lumbar Puncture</b>	Lumbar Puncture	See Guideline
<b>Manipulation / Mobilization</b>	Cervical Manipulation for Tension Headaches	Not Recommended, Evidence (C)
	Deep Thalamic Stimulation	No Recommendation, Insufficient Evidence (I)
	Manipulation for Cervical Spine Conditions	Not Recommended, Insufficient Evidence (I)
	Manipulation for Chronic Cervicogenic Headache Pain	Recommended, Evidence (C)
	Manipulation for Radicular Pain Syndromes with Acute Neurological Deficits	Not Recommended, Insufficient Evidence (I)
	Manipulation for Radicular Pain Syndromes without Neurologic Deficits	No Recommendation, Insufficient Evidence (I)
	Manipulation/Mobilization for Acute, Subacute, or Chronic Cervicothoracic Pain	Recommended, Insufficient Evidence (I)
Regular or Routine Manipulation or Mobilization	Not Recommended, Insufficient Evidence (I)	
<b>Medications</b>	Amantadine for Mild TBI Patients, Pre/Peri/Post-Operative	No Recommendation, Insufficient Evidence (I)

Amantadine for Subacute, Moderate TBI Patients	Recommended, Insufficient Evidence (I)
Amantadine for Subacute, Severe TBI Patients	Moderately Recommended, Evidence (B)
Aminosteroids for TBI Patients	Not Recommended, Insufficient Evidence (I)
Antidepressants for TBI Patients	Recommended, Insufficient Evidence (I)
Antiseizure Prophylaxis (Anticonvulsants) for TBI Patients	No Recommendation, Insufficient Evidence (I)
Anti-spasticity Medications for TBI Patients	Recommended, Evidence (C)
Atypical Antipsychotics for TBI Patients	Recommended, Insufficient Evidence (I)
Barbiturates for TBI Patients	Not Recommended, Evidence (C)
Benzodiazepines for TBI, Most Patients	Not Recommended, Insufficient Evidence (I)
Benzodiazepines for TBI, Select Patients	Recommended, Insufficient Evidence (I)
Beta Blockers for TBI Patients	Recommended, Evidence (C)
<i>Boswellia Serrata</i> for TBI Patients	No Recommendation, Insufficient Evidence (I)
Bromocriptine for TBI Patients	No Recommendation, Insufficient Evidence (I)
Cabergoline for TBI Patients	No Recommendation, Insufficient Evidence (I)
Cannabinoids for TBI Patients	No Recommendation, Insufficient Evidence (I)
Cerebrolysin for TBI Patients (not currently approved for use in U.S.)	No Recommendation, Insufficient Evidence (I)
Citicoline for TBI Patients	No Recommendation, Insufficient Evidence (I)
Corticosteroids for TBI Patients	Moderately Not Recommended, Evidence (B)
Cyclosporine for TBI Patients	No Recommendation, Insufficient Evidence (I)
Deamino Arginine Vasopressin (DDAVP) for TBI Patients	No Recommendation, Insufficient Evidence (I)
Dextromethorphan for TBI Patients	No Recommendation, Insufficient Evidence (I)
Donepezil for TBI Patients	Recommended, Insufficient Evidence (I)
Excitatory Amino Acid Inhibitors for TBI Patients	No Recommendation, Insufficient Evidence (I)
H2 Blockers	Recommended, Evidence (C)
Magnesium for TBI Patients	Not Recommended, Insufficient Evidence (I)
Memantine for TBI Patients	No Recommendation, Insufficient Evidence (I)
Methylphenidate for TBI Patients	Recommended, Insufficient Evidence (I)
Modafinil for TBI Patients	No Recommendation, Insufficient Evidence (I)
Mood Stabilizers for TBI Patients	No Recommendation, Insufficient Evidence (I)
NSAIDs for Febrile Control	Recommended, Insufficient Evidence (I)
NSAIDs for TBI Patients	No Recommendation, Insufficient Evidence (I)
Other Alternative, Complementary, Homeopathic Treatments for TBI Patients	No Recommendation, Insufficient Evidence (I)
Physostigmine (Eserine) for TBI Patients	No Recommendation, Insufficient Evidence (I)
Piracetam for TBI Patients	No Recommendation, Insufficient Evidence (I)
Progesterone for TBI Patients	Not Recommended, Insufficient Evidence (I)
Proton Pump Inhibitors (PPIs)	Strongly Recommended, Evidence (A)
Rivastigmine for TBI Patients	Recommended, Insufficient Evidence (I)
Sedatives, Sedative Hypnotics, and Opioids for TBI Patients	No Recommendation, Insufficient Evidence (I)
Substance P Antagonists for TBI Patients	No Recommendation, Insufficient Evidence (I)

	Sucralfate	Moderately Recommended, Evidence (B)
	Tranexamic Acid for TBI Patients	Recommended, Evidence (C)
	Triptans and Ergot Alkaloids for Post-TBI Migraine Headaches	Recommended, Insufficient Evidence (I)
<b>Memory / Malingering Tests</b>	California Verbal Learning Test (CVLT-I and CVLT-II)	Recommended, Insufficient Evidence (I)
	Cognitive Event Related Potential	Recommended, Evidence (C)
	Memory and Malingering Tests	Recommended, Insufficient Evidence (I)
	Repeatable Battery of the Assessment of Neuropsychological Status (RBANS)	Recommended, Insufficient Evidence (I)
	Test of Memory Malingering	Moderately Recommended, Evidence (B)
	Wechsler Memory Scale III (WMS-III)	Moderately Recommended, Evidence (B)
<b>Memory / Motor Imagery</b>	Computer Memory Retraining Group	Recommended, Evidence (C)
	Handheld Computers as Memory Aids	Moderately Recommended, Evidence (B)
	Memory Rehabilitation	Recommended, Insufficient Evidence (I)
	Memory/Reasoning Tasks, Games, Computer Games	Recommended, Insufficient Evidence (I)
	Restorative Functional Skills Training	No Recommendation, Insufficient Evidence (I)
	Restorative Imagery Training	Moderately Recommended, Evidence (B)
<b>Nerve Blocks</b>	Occipital Nerve Blocks for Cervicogenic Headache	Recommended, Evidence (C)
	Occipital Nerve Blocks for Migraine Headache	No Recommendation, Insufficient Evidence (I)
	Radiofrequency Neurotomy for Cervicogenic Headache	Moderately Not Recommended, Evidence (B)
	Radiofrequency Neurotomy, Neurotomy, or Facet Rhizotomy for Chronic Cervicothoracic Pain	No Recommendation, Insufficient Evidence (I)
<b>Nerve Stimulation</b>	Implantable Occipital Nerve Stimulation Devices	Not Recommended, Insufficient Evidence (I)
	Non-Invasive Occipital and Supraorbital Nerve Stimulation	Recommended, Evidence (C)
<b>Neuropsych Tests</b>	Neurocognitive Testing	Recommended, Insufficient Evidence (I)
	Neuropsychological Assessment	Recommended, Insufficient Evidence (I)
<b>Nutritional Support</b>	Nutritional Support in TBI Patients	Recommended, Evidence (C)
<b>Orthotics</b>	Adaptive Devices, Casting and Orthotics	Recommended, Insufficient Evidence (I)
	Ankle-foot Orthotics for Treatment of Foot Drop	Recommended, Insufficient Evidence (I)
<b>Osmotherapy</b>	Hypertonic Saline for Intracranial Pressure	Recommended, Insufficient Evidence (I)
	Mannitol for Intracranial Pressure	Recommended, Insufficient Evidence (I)
	Ringers Lactate for Intracranial Pressure	No Recommendation, Insufficient Evidence (I)
<b>OT / PT</b>	Action Sequences	Recommended, Insufficient Evidence (I)
	Body Weight Support Treadmill Training for TBI Patients	Recommended, Insufficient Evidence (I)
	Cognitive-Motor Dual-Tasking	Recommended, Insufficient Evidence (I)
	Constraint-Induced Movement Therapy (CI) for TBI Patients	Recommended, Evidence (C)
	Neuroplasticity	No Recommendation, Insufficient Evidence (I)
	Occupational Rehabilitation	Recommended, Evidence (C)
	Occupational Therapy	Recommended, Insufficient Evidence (I)
	Physical Therapy	Recommended, Insufficient Evidence (I)

	Specific Motor Stimulation	Recommended, Insufficient Evidence (I)
	Systematic Instruction	Recommended, Evidence (C)
	Television Assisted Rehabilitation	Recommended, Evidence (C)
	Whole Body Vibration (WBV) for TBI Patients	No Recommendation, Insufficient Evidence (I)
<b>Oxygen Monitoring</b>	Oxygen Monitoring and Thresholds	Recommended, Evidence (C)
<b>Pain Pumps</b>	Intrathecal Baclofen (ITB) Pump for TBI Patients	Recommended, Insufficient Evidence (I)
<b>Perception</b>	Perceptual Skills Training	No Recommendation, Insufficient Evidence (I)
	Verbal Labeling Training and Compensatory Interpersonal Process Recall	Recommended, Insufficient Evidence (I)
<b>Personality Tests</b>	Minnesota Multiphasic Personality Inventory (MMPI)	Recommended, Evidence (C)
<b>Post-concussion</b>	Immediate Post-Concussion Assessment and Cognitive Testing	Recommended, Insufficient Evidence (I)
	King-Devick	Recommended, Evidence (C)
	Military Acute Concussion Evaluation	No Recommendation, Insufficient Evidence (I)
	Sport Concussion Assessment Tool (SCAT)	Recommended, Insufficient Evidence (I)
<b>Problem-Solving</b>	Compensatory Skills Training	Recommended, Insufficient Evidence (I)
	Group Sessions for Problem Solving, Discussion of Social Isolations and Frustrations	Recommended, Evidence (C)
	Restorative and Compensatory Computer Assisted Cognitive Remediation (CACR) and External Aids	No Recommendation, Insufficient Evidence (I)
<b>Rehab, General</b>	Distance-based Healthcare (Telehealth; Telemedicine)	See Initial Approaches to Treatment Guideline
	Inpatient: Comprehensive Integrated Interdisciplinary Rehabilitation	Recommended, Insufficient Evidence (I)
	Outpatient: Home and Community-Based Rehabilitation	Recommended, Insufficient Evidence (I)
	Residential Rehabilitation	Recommended, Insufficient Evidence (I)
	Skilled Nursing Facilities	Recommended, Insufficient Evidence (I)
	Supported Living Programs	Recommended, Insufficient Evidence (I)
<b>Rehab, Other</b>	Computer-Assisted Cognitive Rehabilitation	Recommended, Evidence (C)
	Games, Art, and Self-Expression	Recommended, Insufficient Evidence (I)
	High-Order Reasoning Training	Recommended, Evidence (C)
	Muscle Tone and Joint Restriction Management	No Recommendation, Insufficient Evidence (I)
	Music Therapy	No Recommendation, Insufficient Evidence (I)
	Neuromuscular Re-Education	No Recommendation, Insufficient Evidence (I)
	Opioid/Chemical Treatment Programs	Recommended, Insufficient Evidence (I)
	Reading Comprehension Exercises	No Recommendation, Insufficient Evidence (I)
<b>Relaxation</b>	Relaxation Exercises	No Recommendation, Insufficient Evidence (I)
<b>Rest</b>	Rest	Not Recommended, Evidence (C)
<b>Return to Work</b>	Job Site Evaluations	See Guideline
	Return to Work	Recommended, Insufficient Evidence (I)
	Vocational Rehabilitation Programs	Recommended, Insufficient Evidence (I)
<b>Robotics</b>	Robotics	Recommended, Evidence (C)
<b>Stimulation</b>	Multimodal and Unimodal Coma Stimulation	Recommended, Evidence (C)

<b>Surgery</b>	Surgical Recommendations	See Guideline
<b>Swallow Tests</b>	Swallow Studies	See Guideline
<b>Vestibular Function Tests</b>	Vestibular Function Test	Recommended, Insufficient Evidence (I)
<b>Vision Tests / Training</b>	Electroretinogram (ERG)	No Recommendation, Insufficient Evidence (I)
	Fluorescein Angiography	Recommended, Insufficient Evidence (I)
	Oculomotor Training	Recommended, Insufficient Evidence (I)
	Optical Coherence Tomography	No Recommendation, Insufficient Evidence (I)
	Vision Training	Recommended, Insufficient Evidence (I)
	Visual Acuity Testing	Recommended, Insufficient Evidence (I)
	Visual Evoked Potentials (VEP)	Recommended, Insufficient Evidence (I)
	Visual Field Testing	Recommended, Insufficient Evidence (I)
	Visual Perceptual Testing	Recommended, Insufficient Evidence (I)

## Overview

This clinical practice guideline presents recommendations for assessing and treating adults with traumatic brain injury (TBI). Topics include the initial assessment and diagnosis of patients with TBI, identification of red flags that may suggest the presence of a serious underlying medical condition, initial clinical evaluation, management, diagnostic considerations and special studies to identify clinical pathology, work-relatedness, modified duty and activity, rehabilitative strategies, and return to work, as well as further management considerations including delayed recovery.

This TBI treatment guideline provides evidence-based guidance on the treatment of working-age adults who have sustained TBI, as well as the evaluation and management of symptoms ranging from acute/subacute to chronic. The primary target users of this guideline are health care providers. Although the primary patient population is working adults, the principles may apply more comprehensively. This guideline does not address several broad categories, including the impact of cerebrovascular accidents, concomitant congenital disorders, or malignancies. It also does not address specific intraoperative procedures.

The objectives of this TBI guideline include baseline evaluations, diagnostic tests and imaging, physical activity, return to work, medications, physical and occupational therapy, injections, and rehabilitation. Comparative effectiveness is addressed where available. This guideline does not address comprehensive psychological and behavioral aspects of pain management; these are addressed separately in the ACOEM Chronic Pain guideline.

The literature is routinely monitored and searched at least annually for evidence that would overturn the guidance. The guideline is planned to be comprehensively updated at least every five years, or more frequently should evidence require it. The health questions for acute, subacute, chronic, and post-operative TBI disorders addressed by this guideline include the following:

- What evidence supports the initial assessment and diagnostic approach?
- What red flags signify serious underlying condition(s)?
- What diagnostic approaches and special studies identify clinical pathology?
- What initial treatment approaches have evidence of efficacy?

- What is the evidence of work-relatedness for various diagnoses?
- What modified duty and activity prescriptions and limitations are effective and recommended?
- When is return to work status recommended?
- When initial treatment options fail, what evidence supports other interventions?
- When and for what conditions are injections and other invasive procedures recommended?
- When and for what conditions is surgery recommended?
- What management options are recommended for delayed recovery?

A detailed list of search questions in a PICO-type format (Patient/Population, Intervention, Comparison, Outcome) is in Appendix 2. A detailed methodology document used for guideline development is available online as a full-length document [2] and has also been summarized elsewhere [3, 4]; the methodology document includes evidence selection, scoring, incorporation of cost considerations,[5, 6] and formulation of recommendations. All evidence garnered from 7 databases (Medline, EBM Online, Cochrane, TRIP, CINAHL, EMBASE, PEDro) was included in this guideline. Comprehensive searches for evidence were performed with both PubMed and Google Scholar up through 2016 to help assure complete capture. There was no limit on year of publication. Search terms are listed with each table of evidence. Guidance was developed with sufficient detail to facilitate the assessment of compliance[5] and auditing/monitoring.[6] Alternative options to manage conditions are provided. It is recognized that there are differences in workers' compensation systems.[7] There also are regional differences in treatment approaches.[8-10]

This guideline has undergone extensive external peer review. All AGREE II [6, 11], IOM [5] [12], AMSTAR , and GRADE criteria are adhered to. In accordance with the IOM's Trustworthy Guidelines, detailed records are kept, including responses to external peer reviewers.[5]

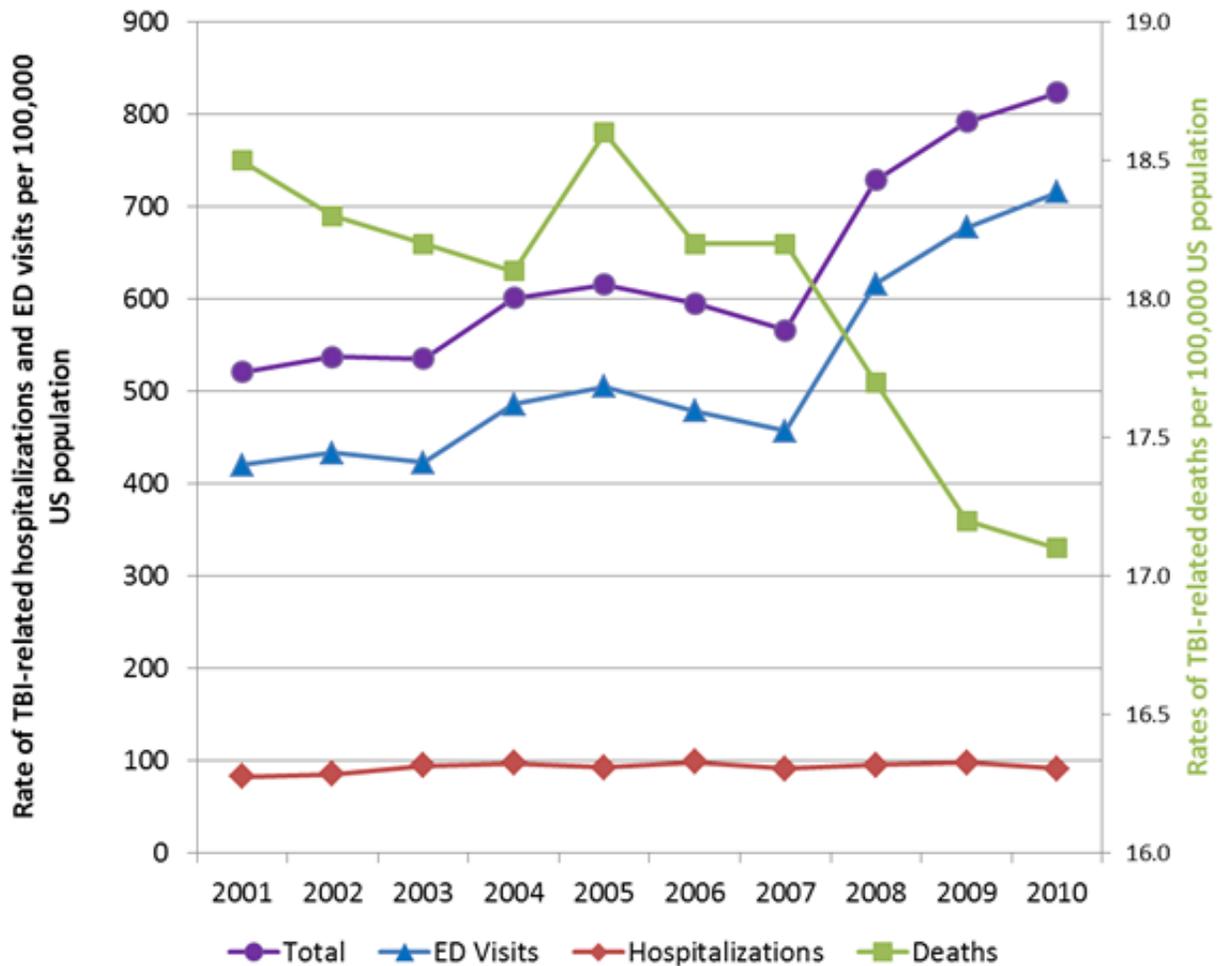
The Evidence-based Practice Traumatic Brain Injury Panel and the Research Team have complete editorial independence from the American College of Occupational and Environmental Medicine and Reed Group, which have not influenced the guidelines.

## Impact

Traumatic brain injury (TBI) has been estimated to affect 1.7 to 10 million people annually in the general United States population [13-16]. The incidence of TBI has steadily risen from 2001 to 2010, as measured by combined emergency department (ED) visits, hospitalizations, and deaths. However, the rates of death from TBI have trended down modestly (see Figure 1). From 2001 to 2005, the TBI rate increased from 521 to 616 per 100,000; in 2010, it increased to 824 per 100,000 population [17]. TBI-related ED visits increased by 70% from 2001 to 2010, while hospitalization rates increased by only 11%. Additionally, deaths related to TBI decreased by 7% over the same 10-year span [17]. It is believed that factors such as automobile safety, seat belt use, helmet use, and better overall treatment for severe TBI in prehospital and hospital settings, while unable to prevent TBIs entirely, have somewhat mitigated the severity of TBI and thus mortality. Jager et al. reported a rate of 18/100,000 TBIs occurring in the workplace from 1992-1994 [18]. TBI may occur less frequently in the workplace compared to other injuries, but it carries enormous per capita costs, in large part due to vocational issues of impairments, employability, and productivity. It is estimated that the average lifetime cost of a TBI patient ranges from \$600,000 to \$1,875,000. [19]. Between 3.2 and 5.3 million persons (1.1%-1.7% of the U.S. population) live with long-term disabilities that result from TBI [20], with another estimate of more than 10 million affected individuals and approximately 50% on long-term disability [21]. These are likely underestimates of the prevalence of TBI because they do not include persons with TBI sequelae who

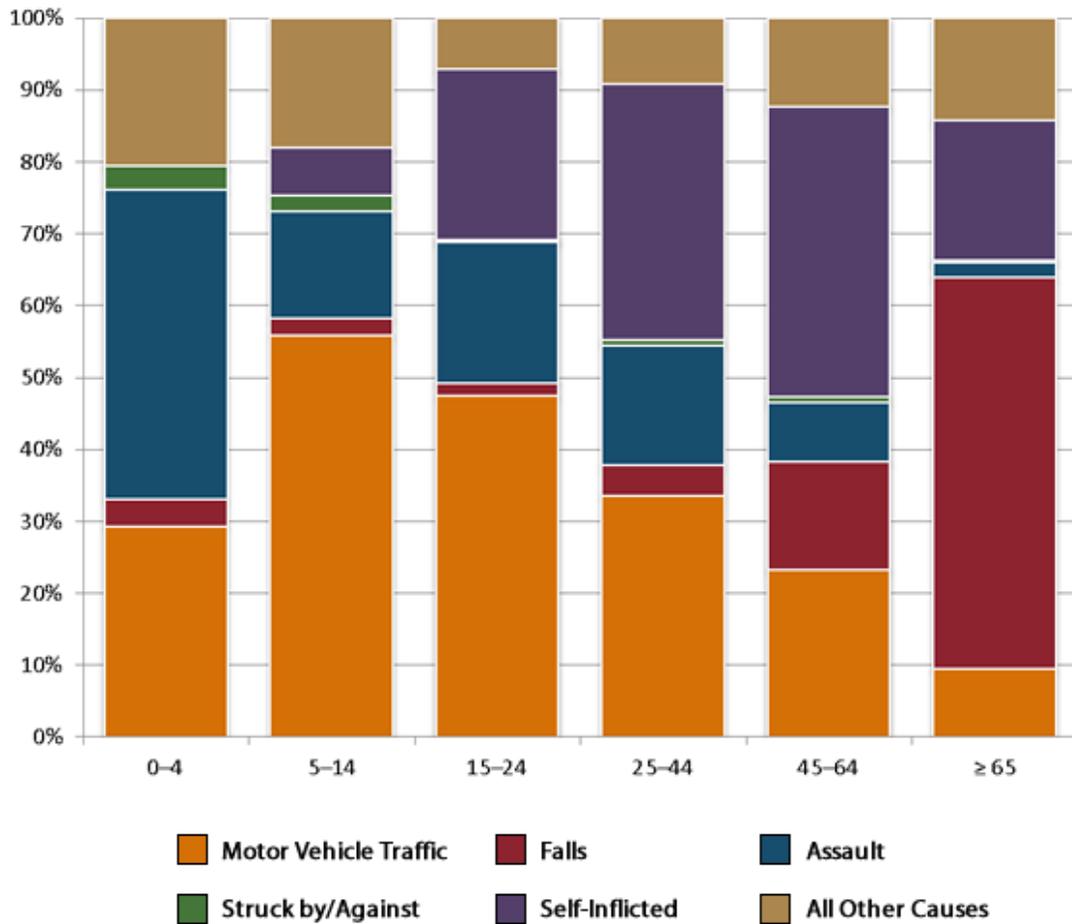
were treated and released from EDs, those who sought care in other health-care settings, and those who did not seek treatment [22-24].

**Figure 1.** Rates of TBI-related Emergency Department Visits, Hospitalizations, and Deaths in the United States, 2001–2010



Adapted from the Centers for Disease Control and Prevention, *Rates of TBI-related Emergency Department Visits, Hospitalizations, and Deaths — United States, 2001–2010* (<https://www.cdc.gov/traumaticbraininjury/data/rates.html>).

**Figure 2.** Percent Distributions of TBI-related Deaths by Age Group and Injury Mechanism — United States, 2006–2010



Adapted from the Centers for Disease Control and Prevention, *Percent Distributions of TBI-related Deaths by Age Group and Injury Mechanism — United States, 2006–2010*

([https://www.cdc.gov/traumaticbraininjury/data/dist\\_death.html](https://www.cdc.gov/traumaticbraininjury/data/dist_death.html)).

## Definitions and Related Terms

**Active Therapy:** The term “active therapy” is generally thought of as the patient taking an active role in the treatment of their disorder via various modalities. Although there is not one specific treatment defined by this term, it may include psychological, social, and educational components in conjunction with therapeutic exercises.[25] Therapeutic exercises could include light aerobic activity, directional exercises, muscle reconditioning (light-weight lifting or resistance training), physiotherapy, and active physical or occupational therapy.[26]

**Acute, Subacute and Chronic:** *Acute, subacute and chronic pain* are categorized as less than 1 month, 1 to 3 months, and greater than 3 months duration respectively. *Acute, subacute and chronic TBI* are categorized as less than 1 month, 1 to 3 months, and greater than 3 months duration respectively.

**Chronic Traumatic Encephalopathy:** Chronic Traumatic Encephalopathy (CTE) is hypothesized to be a neurodegenerative disorder with deposition of hyperphosphorylated tau (p-tau) as neurofibrillary tangles. [27]. This disease is hypothesized to result from exposure to multiple TBI injuries over time and has been diagnosed in many different populations, particularly including elite athletes and military personnel [28, 29]. CTE is thought to develop years after being exposed to repeated head trauma with symptoms of irritability, impulsivity, aggression, depression, short-term memory loss and purportedly heightened suicidality [30]. With a more advancing disease, more severe neurological changes purportedly develop to include dementia, gait and speech abnormality, and Parkinsonism. The late stages of the disease may be similar to Alzheimer’s regarding frontotemporal dementia [31]. Some reports suggest CTE may be distinguished by generalized atrophy of the cerebral cortex, medial temporal lobe, diencephalon and mammillary bodies with enlarged ventricles; cavum septum pellucidum, often with fenestrations and extensive p-tau immunoreactive neurofibrillary tangles and astrocytic tangles in frontal and temporal cortices [32]. The overall quality of epidemiological studies supporting a relationship between TBIs and CTE is relatively poor. At present, there is insufficient quality evidence to support CTE as something beyond a pathological diagnosis.

**Concussion:** Concussion has been variously defined [33, 34]; in general medicine mTBI (mild traumatic brain injury) may be used as equivalent terms [35, 36]. For purposes of this guideline, concussion is defined as a prolonged transient alteration in neuronal function and in cerebral blood flow caused by a blow to the head, neck and/or body with transmission of force to the head, brain, and brainstem resulting in rotational and/or translational (i.e. angular and lateral) movement of the head resulting in immediate or delayed neurological symptoms that resolve sequentially over time. The implications of the biomechanical mechanisms, complex pathophysiology, and clinical phenotype have important implications on occupational medicine questions of fitness for duty, return to work, and pre-placement.

**Delayed Recovery:** Delayed recovery is an increase in the period of time prior to returning to work or usual activities compared with the length of time expected based on average expectations, severity of the disorder, and treatments provided.

**Dementia:** Dementia has been theorized to occur as a more severe outcome of chronic traumatic encephalopathy (see above). Regardless of the mechanism, many studies have reported increased risk of dementia in those sustaining TBI [37-42]. Often the diagnosis of mild cognitive impairment (MCI) is a predecessor of dementia [43, 44]. The risk of dementia after moderate brain injury has been estimated at 2.3-fold increased risk, and 4.5-fold after a severe head injury [38]. TBI in older veterans has been associated with a 60% increased risk [39]. Evidence after mild TBI is less strong [45, 46].

**Functional Capacity Evaluation:** A functional capacity evaluation (FCE) is a comprehensive battery of performance-based tests to determine an individual’s ability to do work-like tasks and conduct activities of daily living.[47] An FCE may be done to identify an individual’s willingness/ability to perform specific tasks associated with a job (job-specific FCE), or his or her willingness/ability to perform physical activities associated with any job (general FCE). The term “capacity” used in FCE may be misleading, as an FCE generally measures performance tolerance (current demonstrated ability) and effort, rather than capacity. FCEs may be utilized for “Medical-Legal” purposes to attempt to address residual physical tolerances and potential for rehabilitation in preparation for judicial determination of loss of earning capacity.

**Functional Improvement (especially Objective Evidence):** Evaluation of the patient prior to the initiation of treatment should include documentation regarding objective physical findings (e.g., range of motion,

reflexes, strength), pain level (if any), and current functional abilities both at home and at work. This should include a clear statement regarding what objective or functional goals are to be achieved through use of the treatment. These measures should be tracked during treatment and evidence of progress towards meeting these functional goals should be sought. Examples of documentation supporting improved function would be increased physical capabilities (with focus on job specific activities), reduction in workplace or avocational limitations, and through tools such as ANAM, SCAT [48] [49], and MACE [50] [51]. If there are spine pain issues, usable tool(s) may include the Neck Disability Index,[52-59] Bournemouth Neck Disability Questionnaire,[60] Modified Oswestry Questionnaire,[61, 62] Patient Specific Functional Scale, and Roland-Morris Disability Questionnaire.[63, 64] Resolution of physical findings (such as cognitive function, increased muscle tone, radicular symptoms, or weakness), increased range of motion, strength, or aerobic capacity may be physical examination correlates of improved function.

**Functional Restoration:** Functional restoration, like active therapy, is not one specific set of exercises, processes or therapies, but a blend of various techniques and programs (both physical and psychosocial). The basic principle for all of these individually tailored programs is to help patients cope with pain and return to the functioning level required for their daily needs and work activities.[65] Functional restoration refers to a full-day multidisciplinary program lasting from 3 to 6 weeks.[66] There also are work conditioning and work hardening programs that are utilized[67, 68] (see Chronic Pain guideline for further discussion).

**Glasgow Coma Scale (GCS):** The Glasgow Coma Scale is a neurological scale that provides an objective measure of the conscious state of a person for initial as well as subsequent assessment ([69]). Since 1974, the Glasgow Coma Scale has provided a practical method for bedside assessment of impairment of conscious level, the clinical hallmark of acute brain injury. The scale was designed to be easy to use in clinical practice in general and specialist units and to replace previous ill-defined and inconsistent methods. Forty years later, the Glasgow Coma Scale has become an integral part of clinical practice and research worldwide. Findings using the scale have shown strong associations with those obtained by use of other early indices of severity and outcome. However, predictive statements should only be made in combination with other variables in a multivariate model. Individual patients are best described by the three components of the coma scale; whereas the derived total coma score should be used to characterize groups. Adherence to this principle and enhancement of the reliable practical use of the scale through continuing education of health professionals, standardization across different settings, and consensus on methods to address confounders will maintain its role in clinical practice and research in the future. [69]

The GCS is scored between 3 and 15, 3 being the worst, and 15 the best. It is composed of three parameters: Best Eye Response, Best Verbal Response and Best Motor Response.

**Table 1. Glasgow Coma Scale**

Response	Scale	Score
<b>Eye Opening Response</b>	Eyes open spontaneously	4 Points
	Eyes open to verbal command, speech or shout	3 Points
	Eyes open to pain (not applied to face)	2 Points
	No eye opening	1 Point
<b>Verbal Response</b>	Oriented	5 Points
	Confused conversation but able to answer questions	4 Points
	Inappropriate responses but words discernable	3 Points
	Incomprehensible sounds or speech	2 Points
	No verbal response	1 Point
<b>Motor Response</b>	Obeys commands for movement	6 Points
	Purposeful movement to painful stimulus	5 Points
	Withdraws from pain	4 Points
	Abnormal (spastic) flexion, decorticate posture	3 Points
	Extensor (rigid) response, decerebrate posture	2 Points
	No motor responses	1 Point

\*Adapted from Teasdale G, Jennett B. Assessment of coma and impaired consciousness. Lancet 1974; 81-84.

**Myofascial Pain:** Proponents believe that pain arising from muscles and fascia can be recognized as distinct from pain arising from ligaments, joints, and discs. However, there is no valid way to determine whether the source of neck or thoracic pain is or is not from muscles or fascial structures. Even though some authors have published on “myofascial neck pain”, in this review myofascial pain is considered as non-specific cervical or thoracic pain (see Shoulder Disorders guideline for myofascial pain and trigger points).

**Neck Disability Index:** The Neck Disability Index is a revised form of the Oswestry Low Back Pain Index for the assessment of activities of daily living of cervical pain patients, particularly from whiplash type injuries.[52-57, 59] It contains 10 sections addressing the impact of the cervical pain including – pain intensity, personal care, lifting, reading, headaches, concentration, work, driving, sleeping, and recreation.[52] However, the tool is not standardized and is frequently modified, making interpretations difficult.[70]

**Neck Pathology and Occipital Neuralgia:** Occipital Neuralgia, also known as C2 neuralgia (or neuralgia of the second cervical nerve), is pain in the greater, and/or lesser occipital nerves. Posterior head and neck pain may also occur with involvement of other nerve roots, e.g., C3 and C4. There are many potential causes of the condition which is due to mechanisms including nerve entrapment, irritation, and/or nerve trauma [71]. Compression or irritation of the nerve structures may cause pain in the posterior head and neck. Traumatic mechanisms often involve pain thought to originate in the atlantoaxial or upper zygapophyseal joints or in the muscles and insertion areas [72]. TBIs frequently involve injuries to these structures. [73].

**Occupational Therapy:** Occupational therapy typically involves a collaborative, client-centered approach that emphasizes engaging an individual in “occupations” and/or everyday activities to maximize functional independence. Contexts and environments may include activities of daily living (ADL’s), work, play, education, social participation, rest/sleep, and leisure.

**Outcome Predictors (Cognitive OP, Psychological OP, Vocational OP):** Outcome predictors are measured variables used to estimate the impacts of a specific injury. They usually include tests and

batteries of tests. They may include clinical signs, although for TBIs, various cognitive function tests are prominent examples of outcomes predictors used. They may be used both for baseline assessments, prognostic assessments, as well as to track clinical progress. TBIs are a heterogeneous group of injuries that have a wide range of possible effects from learning handicaps, speech and communication problems to walking and balance impairments, all of which may have acute, subacute and/or chronic effects [14]. Therefore, there is a similarly wide array of potentially useful outcome predictors for these types of TBIs. Current predictors for TBI include the Glasgow Outcome Scale, imaging tests (e.g., CT scans), gender and cognitive tests [74] [75].

Among the higher cortical function prognostic tests, these predictors may be broken down further into three separate groups: *cognitive, psychological, and vocational*. Cognitive outcome predictors are used to estimate abilities to learn about information and understand it. Examples that may be used include measuring S100B, a biomarker of TBI, 12-36 hours post-injury, length of coma (LOC), and posttraumatic amnesia (PTA) and headache [76] [77] [78]. Psychological outcome predictors are used to foresee possible behavioral changes and mental and emotional instability within a patient post-injury. Examples of these predictors are injury severity and the Hospital Anxiety and Depression Scale (HADS) [79], [80]. Many psychological predictor outcomes have less supportive evidence of their utility. Regardless, these include emotional expression recognition, understanding of others' mental state, and cognitive fluency or flexibility [81] [82]. Vocational outcome predictors are used to estimate a patient's ability to return to work and working performance. A few of these predictors include age, pre-morbid educational status, motivation, accurate self-awareness, and full acceptance of returning to work [79, 83, 84].

**Passive Modality:** Passive modalities refer to various types of treatment given by a provider that usually involve administration of some form of stimulus being applied to the body as opposed to the individual actively doing some sort of therapy (see Active Therapy). Forms of passive modality include massage, hydrotherapy (whirlpools, hot tubs, spas, etc.), ultrasound, and hot/cold compresses.

**Parkinson, and Parkinson Pugilistica:** Parkinson's disease (PD) is the second most common neurodegenerative disorder next to Alzheimer's disease that has an incidence rate of approximately 13.4 per 100,000 per year. The cause is most commonly idiopathic, but may include genetic and environmental factors. Parkinson's disease is theorized to occur with increased incidence in cases of chronic traumatic encephalopathy, sometimes termed Parkinson Pugilistica (see above). [85-88]

**Physical Therapy:** The term "physical therapy" is used in ACOEM's *Guidelines* generically to mean physical medicine, therapeutic and rehabilitative evaluations and procedures (e.g., massage). Much of the available research uses this term generically. This rehabilitative therapy may be performed by or under the direction of trained and licensed individuals such as physical therapists, occupational therapists, exercise physiologists, chiropractors, athletic trainers, and physicians. Jurisdictions may differ on the qualifications for licensure to perform these interventions. The *Guidelines* are not meant to restrict physical therapy to being performed only by physical therapists.

**TBI** –Traumatic brain injury (TBI) is a nondegenerative, noncongenital insult to the brain from an external mechanical force, possibly leading to temporary or permanent impairment of cognitive, physical, and psychosocial functions, with an associated diminished or altered state of consciousness [89-91]. Menon [90] reported a consensus definition that, "TBI is an alteration in brain function, or other evidence of brain pathology, caused by an external force."

The most common, historic classification of TBI severity is based on length of loss of consciousness and the Glasgow Coma Score. However, this has a tenuous relationship with duration of symptoms and need of

treatment (e.g., some individuals with mild impairment have ongoing symptoms while some sustaining moderate have rapid, full recovery). As this guideline is based on quality evidence and most studies have used the traditional severity classification system, it is advised that caution be used to emphasize treatment of the patient's symptoms and not rigidly apply the traditional severity system.

Mild/moderate may thus be clinically defined as: persistent symptoms i.e. headache, dizziness, neurocognitive, sleep, behavioral for more than six months without evidence on standard or advanced neuroimaging studies e.g., CT, MRI, DTI MRI of structural or micro structural damage (i.e., SAH, ICH, DAI, SDH, EDH), however with evidence on neuropsychological testing of abnormalities (e.g., decreased processing speed, executive function, attention and concentration, learning and memory) and may include a significant drop in premorbid intelligence. There should be no evidence of malingering and other possible causes of the patients symptoms, e.g., medications, metabolic, substance abuse. Symptoms may worsen with cognitive and at times physical exertion. Severe TBI may then be clinically defined as having the same attributes as mild/moderate with additional evidence of neuroimaging damage.

**Categories of TBI.** There are multiple definitions for TBI and there is no clear consensus definition. There are 3 broad acuity categories of TBI commonly used (mild, moderate, severe) and often these definitions are dissimilar. Although there are multiple definitions for all categories, MTBI (mild TBI) seems to have the greatest degree of variation in its definition. Some experts equate mild TBI to concussion and others do not. Regardless, for purposes of definitions, to provide a basis for discussion of patient treatment based on severity, and recognizing there is potential overlap for some cases, nevertheless, the following definitions are used:

**Mild TBI (MTBI)** is defined as including at least one of [92]:

- The person was not unconscious or was unconscious for less than 30 minutes.
- Memory loss lasted less than 24 hours.
- The GCS was 13 to 15

**Moderate TBI** is defined as [92]:

- The person was unconscious for more than 30 minutes and up to 24 hours.
- Memory loss lasted anywhere from 24 hours to 7 days.
- The GCS was 9 to 12.

**Severe TBI** if [92]:

- The person was unconscious for more than 24 hours.
- Memory loss lasted more than 7 days.
- The GCS was 8 or lower.

Other terms used to describe mild TBI include concussion, minor head trauma, minor TBI, minor brain injury and minor head injury.

NICHD-supported research has found that the diagnosis of mild TBI (concussion) in practice, uses inconsistent criteria and relies heavily on patients' self-reported symptoms. A patient with TBI is a person who has had a traumatically induced physiological disruption of brain function.

The above categories are not absolute. For example, some suggest that those with an intracranial bleed but otherwise categorized as "mild" should be categorized as "moderate." [93, 94] Others have

suggested relying more heavily on neuropsychological impairment to classify severity [94] as well as for the determination of longer term impairments [95].

**Trigeminal Nerve:** Damage to this nerve causes pain. TBI has a broad range of mechanisms and consequences of injury that may cause multiple types of pain that may include the trigeminal nerve. These mechanisms may or may not involve skull fractures and/or contusions. [96]. The trigeminal nerve is the primary sensory nerve to the face. Patients with trigeminal neuralgia or pain in the area of the trigeminal nerves due to inflammation frequently have pain in one or more of the three branches of the medium nerve (ophthalmic (V<sub>1</sub>), maxillary (V<sub>2</sub>), mandibular (V<sub>3</sub>)). This pain may be dull, sharp and/or shooting. reduced reflexes and some experience burning pain [97].

**Visual Analog Scale:** Visual Analog Scales (VAS) are figures of lines that are used to measure a patient's level of subjective pain. There are different types of VAS pain scales, but nearly all range in value from "0" or "no pain" to "10" or "worst pain" (or 0 to 100). Some have no numeric designation on them; instead a line is drawn between the extreme ends of the line noted as "no pain" and "severe pain" and the patient's "x" on the line is used to measure the fraction or distance between the ends. Some are 0 to 100mm in length. Some have additional verbal anchors such as "mild" and "moderate." Despite these nuances, the performance of these various VAS scales is believed to be valid and reliable.

## Risk and Causation

Traumatic brain injury affects nearly 10 million people every year and an estimated 10% of these cases are work-related [16]. Additionally, the mechanisms of TBI injury differ in the workplace compared with the general population. Workplace TBI is more commonly a result of falling, being struck by an object, or machinery accidents than for non-work-related TBI. A direct blow to the head is not required for a TBI to occur because rapid acceleration or deceleration is a TBI mechanism. Military populations incur both blast- and non-blast-related TBI [98-101]. The majority of work-related TBI cases are not fatal and are considered mild. [102]. Estimates of the proportions from various causes in the general population are provided in Figure 2.

A determination of the work-relatedness of TBI is generally simple. The employment context for the event determines the work-relatedness of the TBI (see Work-relatedness Guideline). Work-relatedness may become considerably more complex if there are long-term sequelae and a history of multiple events and some occurred at work while some occurred avocationally. In such cases, factors such as determination of which event(s) led to the disability and apportionment may arise in some jurisdictions. Nevertheless, caution is warranted in interpreting pre- compared with post-injury symptoms [103-108] [109-115], as there is a propensity toward under-reporting pre-injury symptoms especially in mild TBI cases as well as high rates of similar symptoms in non-concussed individuals [105] [108, 109, 111, 113, 115]. Persistence of symptoms after TBI has been shown to be increased in those who are older [107, 116, 117], female [118], and had a more severe injury [107, 116, 117] [107, 119]. Yet, from an objective perspective, it is concerning that persistence of symptoms has been associated with alcohol [109, 116], drug use [109, 116], psychological/psychiatric history [109, 115, 116, 118], seeking compensation [115] and lower socioeconomic status [120]. Similar findings of worse outcomes with lower parental education, school achievement, and a history of learning problems, have been reported in pediatric TBI patients [107, 117] [121].

The ability to distinguish mild TBI from controls is reportedly only moderately successful [122]. One case series found insufficient effort in 45% of workers compensation TBI cases [123]. Effort has been reported to be more important than TBI injury severity ("diagnosis threat") [124-126] [127] [128, 129].

Similarly, a patient's perception of adverse consequences after mild TBI and/or stress are also important in the ongoing perception of symptoms persistence [127, 130, 131] [104] [110]. Stress, psychiatric history, low social support, low intelligence, anxiety and depression have all been found to predict persistence of symptoms after TBI [130, 132-135]. Worse return to work status has been reported among those who are older, had a lower Glasgow Coma Score, had extremity injuries, had prior job instability, and have lower education [136].

## Individual Factors

Male gender is a strong risk factor for TBI [137, 138]. Severity measures also indicate that men incur worse TBIs than women, as men accrue more lost work time, and incurred higher average health care costs [139]. Age is another risk factor for TBI, with varying insults over the lifespan. A strong bimodal distribution is present with those in their teens and again those in the elderly years incurring far higher rates of automobile accidents [140]. Assaults are common in among youth, while falls are increasingly common with advancing age [138, 141]. Increasing age has been associated with a poorer outcome for TBI [142]. Social support, education, social economic status, and age play a role in returning to work after TBI and the severity of injury is a strong determinant of (re)employability [143]. Other risks, especially for delayed recovery include prior mental disorder(s), attention deficit disorder, ADHD, drug use and pre-existing intellectual and physical disabilities. There is no significant evidence yet shown for risks from lack of exercise, genetics [144], cardiovascular disease [145], and illness [146].

## Psychosocial and Work Organizational Factors

Work-related TBI may be accompanied by physical, emotional and psychosocial costs. Depression, anxiety, sleep disturbance, fatigue inability to function socially, and other physical problems are negative consequences following TBI [115, 143, 147, 148]. Psychosocial characteristics, such as anxiety, depression, locus of control, and somatization have been used to assess impacts affecting those sustaining TBI injuries [118, 149]. Sleep problems and fatigue commonly affect all categories of TBI patients [150, 151] Additional factors lacking quality evidence, yet thought to influence impacts of TBI and return to work include history of sexual abuse, job strain, occupational support, nonoccupational support, and job satisfaction.

Particularly after severe TBI injuries, obtaining another job or returning to work may be difficult due to the various emotional and/or physical problems [152]. Comparatively minimal emotional issues are reported after mild TBI [153]. After TBI, inadequately addressing safety, poor social support, and financial burdens of injury may all influence returning to work [154].

Research conducted on Iraqi war veterans (N=277) suffering from mild TBIs showed that most had attendant psychosocial difficulties such as underemployment, low income, marital problems, low community integration, and life satisfaction. These difficulties were often still present three years after the initial TBI. [155]. Yet, it has also been reported that mild TBI is not adversely impacted by PTSD and other psychiatric disorders in veterans [156].

Clinical research suggests that most patients with pre-morbid employment with a perceived higher quality of life had a subsequently higher return to work probability, improved psychosocial characteristics, and better adjustments to physical ailments. In contrast, those with pre-morbid employment with a perceived lower quality of life, had a subsequently lower return to work probability, limited psychosocial changes, and limited changes to physical ailments.

## Job Physical Factors

Many severe TBI patients experience long-term difficulties with behavior, physical mobility, and/or cognitive tasks when returning or attempting to work. Regarding physical mobility factors, patients may be limited in performing work-related tasks, as well as daily routine tasks. Yet, quality research into these factors is relatively sparse and likely hampered somewhat by the great diversity in clinical TBI presentations and persistent debilities.

In one report, approximately half of a group of 175 TBI patients that had prior employment were not able to return to work due to physical limitations [157]. One factor making return to work more difficult for some is the gradual enlargement, and thus complexities of many jobs to include far more tasks than in prior decades.

Correlations between questionnaire(s), clinical assessment, physical examination, and self-assessment is needed to validate a TBI patient’s current physical limitations prior to determining a return to work status [158].

## Red Flags

Features of the patient’s history or examination that indicate the possibility of potentially serious disorders are referred to as “red flags.” These include features that suggest the possibility of intracerebral hemorrhages, increased intracranial pressure, central nervous system impairments, visual impairments, hearing impairments, skull fractures, spine fractures, acute dislocations, spinal infection, or serious or progressive neurologic deficit. While recognizing these “red flag” disorders is clearly important, there are no high quality prospective cohort studies to provide the evidence base for this section of the guidelines.

**Table 2. Red Flags for Potentially Serious TBI (including Neck/Thoracic Spine Conditions)**

Disorder	Medical History	Physical Examination/Diagnostic Testing
<b>SPINAL DISORDERS</b>		
Increased Intracranial Pressure	Altered consciousness, coma Headache History of hypertension Organ-system relevant history features if history of focal intracranial damage or bleeding	Altered mental status Altered consciousness Concurrent elevated blood pressure Organ-system relevant physical examination features if history of focal intracranial damage or bleeding
Intracerebral hemorrhages	Headache Nausea & vomiting Organ-system relevant history features if history of focal intracranial damage or bleeding	Altered consciousness Organ-system relevant physical examination features if history of focal intracranial damage or bleeding
Central nervous system Impairments	Abnormal balance Loss of consciousness Nausea Visual difficulties Organ-system relevant history features if history of focal intracranial damage or bleeding	Vertigo lasting for more than seconds Vestibular dysfunction Hearing loss (unilateral) Visual dysfunction Organ-system relevant physical examination features if history of focal intracranial damage or bleeding

Fracture	Major trauma, such as vehicular accident or fall from height[159] [159] Minor trauma or strenuous lifting in older or potentially osteoporotic patients Metabolic risks for osteopenia (including renal failure, hyperthyroidism, rheumatic disorders, debility and inheritance)	Percussion tenderness over specific spinous processes Careful neurological examination for signs of neurological compromise
Substance Abuse with Risk of Withdrawal	Substance(s) abuse Prior substance(s) withdrawal	Dilated Pupils Tachycardia Sweating
Progressive Neurologic Deficit	Progressive limb numbness or weakness, bowel or bladder control impairment, gait ataxia Progressive loss in any sensory function (e.g., vision, hearing, balance, sensation) Severe spine pain	Progressive loss in any sensory function (e.g., visual acuity/Snellen, visual fields, audiometry, Romberg, balance, sensation) Significant and progressive myotomal motor weakness Significant and increased sensory loss – in anatomical distribution Radicular signs Corticospinal tract involvement (gait ataxia, Babinski sign, hyperreflexia, and limb spasticity, etc.) Other neurological impairment(s)
Myelopathy	Ataxic gait, impaired upper limb coordination, poor or reduced finger movements, bladder and/or bowel control impairment (incontinence)	Hyperreflexia, ataxia, clonus, pathologic reflexes (Babinski, Hoffman) Other neurological impairment(s)

Adapted from van den Hoogen 95; Jarvik 02; Bigos 94.[160-162] , Silbert 95 (1517-22), Hurwitz 96 (1746-61), Grad 1989 (281-4), Szmirnai 2001 (68-71), Bruce 2001(688-93), Berger 99 (175-81), Snyder 93 (253-8), Zaki 93 (110-12), Forsyth 93 (1678-83), Hiroki 2003 (34-100), Hong 2003 (210-14)

## Absence of Red Flags

Absent red flags, TBI can be classified into one of three working categories:

**Mild TBI**, which includes at least one of [92]:

- The person was not unconscious or was unconscious for less than 30 minutes.
- Memory loss lasted less than 24 hours.
- The GCS was 13 to 15

**Moderate TBI**, which includes [92]:

- The person was unconscious for more than 30 minutes and up to 24 hours.
- Memory loss lasted anywhere from 24 hours to 7 days.
- The GCS was 9 to 12.

**Severe TBI**, which includes [92]:

- The person was unconscious for more than 24 hours.
- Memory loss lasted more than 7 days.
- The GCS was 8 or lower.

Mild TBI is generally relatively benign and self-limited; however, in a small percentage of cases the symptoms persist. Most patients have resolution of symptoms over a period of a few days to a month. Symptoms have shown to persist up to a year [163]. Some patients can display symptoms beyond one year post-injury [164] [165, 166]. Moderate TBI is generally longer lasting, with symptoms lasting weeks to a few months. Severe TBI includes those with persistent symptoms. Many patients with severe TBI incur at least some permanent impairment.

## Diagnosis

### Initial Assessment

Thorough medical and work histories and a focused physical examination (see General Approach to Initial Assessment and Documentation guideline) are sufficient for the initial assessment of a patient complaining of potentially work-related TBI. Findings of the medical history and physical examination may alert the physician to other pathology (e.g., not of TBI origin) that can present concomitantly. Such findings include fractures, intracranial hemorrhages, vision impairments, hearing impairments, central nervous system impairments and peripheral nervous system impairments. In this assessment, certain findings, referred to as red flags, raise suspicion of serious underlying medical conditions (see Table 2). The absence of red flags and conditions rules out the need for special studies, referral, or inpatient care. During this time, spontaneous recovery is expected, provided any associated workplace factors are mitigated [167].

There also are potential psychological conditions that may be confounding and/or interacting and should be evaluated, such as substances use, psychological/psychiatric disorders, PTSD, suicidality, childhood sexual abuse, hallucinations or intoxication.

### Medical History

As TBI clinical presentations are so varied, comprehensive medical histories and physical examinations are necessary to assess the patient's TBI [168]. This section will review the medical history, including the questions that should generally be asked. The diagnostic approach also needs tailoring to the specific patient, particularly as factors such as the patient's exact mechanism of injury(ies), age, past medical history, underlying medical conditions, prior injury history and genetic predilections all probabilistically adjust the diagnostic approach and prognoses [169].

As the history especially in subacute and chronic TBI patients may sometimes be unreliable [103, 105, 107-109], a suggested approach to consider is to: [170] take into account the patient's current physical and emotional state, (2) establish historical anchor points and/or memorable milestones, (3) decompose generic memories by finding distinctions from each other and (4) obtaining a retrograde clinical history, from recent to remote. [108]

Questions may include the following:

- When were you injured? How? What happened?
- Did you lose consciousness? For how long?
- Do you have any memory of what happened? For how much time are you missing your memory or have amnesia?
- Inquire specifically about each symptom or area of symptoms below, since individuals with TBI may have difficulty organizing and communicating their symptoms without prompting.

Document results, whether subtle or pronounced, so that there is a baseline status recorded, as well as the potential for subsequent comparisons. For each of the following symptoms that is present, answer specific questions asked.

- What is the frequency, severity, and duration of headaches? Are they throbbing or ice-pick or squeezing/tension-like?
- Is there dizziness or vertigo? How often? How severe?
- Is there weakness or paralysis? Where? When did that start?
- Are there vision problems? Can you see out of both eyes? What can't you see?
- Are there hearing problems? Ringing in the ears (one or both)?
- Are there balance problems?
- If ambulatory, are there any problems walking?
- Are there memory problems? What have you noticed?
- Are there problems thinking?
- Do you have difficulty concentrating?
- Do you have difficulty with executive functions (speed of information processing, goal setting, planning, organizing, prioritizing, self-monitoring, problem solving, judgment, decision making, spontaneity, and flexibility in changing actions when they are not productive)?
- Do you have speech or swallowing difficulties? Expressive aphasia? Difficulty with articulation?
- Do you have pain? What is the severity, duration, location? Does pain radiate?
- Do you have bowel or bladder problems?
- Do you have a history of any psychological or psychiatric issues? Mood swings, anxiety, depression, other (describe)?
- Do you have a history of substance use? What type? Last use(s)?
- Do you have any sensory changes, such as numbness or paresthesias? Location and type?
- Any decreased sense of taste or smell?
- Any history of recent or past seizures? What type, how often? When last experienced?
- Do you have any symptoms of (autonomic dysfunction, such as) heat intolerance, excess or decreased sweating, etc.
- other symptoms, including symptoms of endocrine dysfunction or cranial nerve dysfunction – describe.

Caution is warranted in interpreting the history as there are reported problems with reliability for decision-making that may impact diagnosis, treatment and return to work [103, 105, 107-109] [171]. Under-reporting of pre-injury symptoms is reportedly problematic [105, 109]. Additionally, pre-injury conditions such as alcohol and drug use and the preexistence of psychological conditions and pre-existing pain have been shown to be recalled at significantly lower rates in comparison with preinjury medical records [109].

As cervical spine trauma is often present with TBI, the following questions regarding the cervical spine are included.

#### 1. What are your symptoms?

- Do you have pain or stiffness?
- Do you have numbness or tingling?
- For traumatic injuries: Was the area deformed? Did you lose any blood or have an open wound?
- Is the discomfort located primarily in your neck? In your arm?

- Do you have pain or other symptoms elsewhere? (Patients who present with a primarily with upper extremity pain may well have radiculopathy from a cervical disc herniation or other spine pathology.)
- When did your symptoms begin? Have you ever had symptoms like this before?
- Are your symptoms constant or intermittent? What makes the problem worse or better?
- What is the day pattern to your pain? Are you better first getting out of bed in the morning, during the morning, mid-day, evening, or while asleep? Worse as the day progresses? Do you have a problem sleeping? What position is most comfortable? Is there any pain with cough, sneezing, deep breathing, or laughing?
- How long can you sit, stand, walk, and bend?
- Can you lift? How much weight (use items such as gallons of milk, groceries, etc., as examples)?

2. How did your condition develop?

*Past:*

Have you had similar episodes previously?

Have you had previous testing or treatment? With whom?

*Cause:*

What do you think caused the problem?

How do you think it is related to work?

Did your symptoms begin gradually or suddenly? Did you notice the pain the day after the event?

Did you slip, trip, or fall?

Were you doing anything at the time your symptoms began? (It is important to obtain all information necessary to document the biomechanical forces of injury.)

*Job:*

What are your specific job duties?

How long do you spend performing each duty on a daily basis?

Do you have assistance of other people or lifting devices?

*Off-work Activities:*

What other activities (hobbies, workouts, sports) do you engage in? At home or elsewhere?

Any heavy lifting? How? How often?

Any physically demanding activities requiring awkward postures, prolonged sitting or standing?

How do these symptoms limit you?

What activities of daily living are limited? Are there specific challenges in your home environment (e.g., steep steps)?

How long have your activities been limited? More than 4 weeks?

Have your symptoms changed? How?

3. Do you have other medical problems?

4. What are your expectations regarding your return to work and disability from this health problem?

5. What are your concerns about the potential for further injury to your low back as you recover?
6. What is your job? What do you do on the job? How do you like your job? Your supervisor and coworkers? What is your relationship with your co-workers and supervisor and how do they treat you?
7. What do you hope to accomplish during this visit?

## Physical Exam

The objective of the initial physical examination of the TBI patient is to assess those physical and cognitive abnormalities that evaluate the magnitudes and possible causes of loss of function that were elicited during the medical history [172]. Pertinent negatives are also sought. The overall initial impression is an important metric of functional status, as well as helping guide the speed of assessment(s) required. Vital signs, such as elevated blood pressure may suggest elevated intracranial pressure. Elevated temperature, may suggest the presence of an infection. Tachycardia may be a sympathetic nervous system response to the patient's pain, a sign of increased intracranial pressure, or it may be anxiety related. For those being assessed after the initial trauma assessment, a comprehensive physical examination, neurological evaluation, psychological evaluation and cognitive assessment should generally be performed [168]. For those undergoing more advanced testing for chronic TBI impacts, tachycardia may be relevant as indicating potential psychological disturbance, and illicit medication use.

1. **Vital Signs.** Assess vital signs. Assess postural changes in blood pressure and tachycardia as autonomic dysfunction may occur.
2. **Initial screen for cognitive impairment, examine scalp.** For those with impaired mentation, assess with the Glasgow Coma Scale. Next, assess orientation to person, place, time. Consider additional cognitive testing (e.g., recall of presidents, immediate/5-minute recall of 3 items). Palpate for bony step-offs and other signs of potential fractures. Predictors for estimating durations of loss of consciousness and post-traumatic amnesia are available [173].
3. **Vision and hearing screening examinations.** Assess eye opening. Screen for visual acuity and perception. Consider confrontational testing. Assess peripheral vision. Examine pupils, extraocular movements, funduscopic exam. Assess smooth pursuits and near point convergence. Assess qualitative hearing. Perform otoscopic exam.
4. **Balance and vestibular examination.** Assess balance and vestibular functions. Consider Single leg stance, Balance Error Scoring System (BESS), Berg Balance Scale, Timed Up and Go, and the Functional Gait Assessment. Assess sway on Romberg.
5. **Oral, facial examination.** Examine oral cavity. Examine facial structures.
6. **Cranial nerves.** Assess the remaining cranial nerves and exam, paying particular attention to those with evidence of potential damage (e.g., facial trauma).
7. **Neck exam.** Evaluate the cervical spine for trauma and/or fracture. Include gentle range of motion, pain with range of motion, muscle tenderness, and tender spinous processes.

- 8. Examine heart, lungs.** Perform exams on the heart, lungs, abdomen and then any area with evidence of trauma. Evaluation for orthostatic hypotension in those with longer-term TBI [174] [175].
- 9. Motor function.** Assess cooperation with motor testing. Assess motor strength in all major muscle groups. More specificity in assessing affected muscles in all areas of weakness or paralysis is generally next performed using the standard muscle grading scale. To the extent possible, identify the peripheral nerves or innervations for the weakened or paralyzed muscles, even when the weakness or paralysis is of central origin. Standard muscle grading scale: 0 = Absent No muscle movement felt. 1 = Trace Muscle can be felt to tighten, but no movement produced. 2 = Poor Muscle movement produced only with gravity eliminated. 3 = Fair Muscle movement produced against gravity, but cannot overcome any resistance. 4 = Good Muscle movement produced against some resistance, but not against "normal" resistance. 5 = Normal Muscle movement can overcome "normal" resistance. It is particularly important in TBI patients to make an assessment of strength that incorporates expected strength based on muscle bulk. For example, strength is not the same across the lifespan (including differences based on differential aging impacts on proximal vs. distal and upper vs. lower extremities), between sexes, and include different body frames. Comparisons with an unaffected side, when possible, are particularly helpful. Yet, especially in chronic cases, poor effort has been reported [176] Green 01 [125, 128].
- 10. Muscle tone, reflexes.** Describe any muscle atrophy or loss of muscle tone. Examine and report deep tendon reflexes (usually 0-4 scale) and any pathological reflexes.
- 11. Sensory function.** Describe exact location of any area of abnormal sensory function, noting methods of sensory testing used. Identify the peripheral nerve(s) that innervate the areas with abnormal sensation.
- 12. Gait, spasticity, cerebellar signs.** Describe any gait abnormality (if possible), imbalance, tremor or fasciculations, incoordination, or spasticity. If there is spasticity or rigidity (e.g., Ashworth Scale), assess any limitation of motion of joint (including joint contracture) by following the Joints examination protocol. (A tandem gait assessment (walking in a straight line with one foot directly in front of the other) is recommended.) Consider dual switching tests, such as tandem gait plus counting backwards from 100.
- 13. Autonomic nervous system.** Describe any other impairment of the autonomic nervous system, such as orthostatic (postural) hypotension (if present, state if associated with dizziness or syncope on standing), hyperhidrosis, delayed gastric emptying, heat intolerance, etc.
- 14. Cognitive impairment/Psychological Impairment.** Consider a Mini-Mental State Examination (MMSE)) to perform a screen for cognitive impairment. Does the screening show problems with memory, concentration, attention, executive functions, mood, depression etc.? For subacute to chronic cases especially, a comprehensive neuropsychological evaluation is necessary [95] [168].
- 15. Psychiatric manifestations.** Conduct a screening examination for psychiatric manifestations, including neurobehavioral effects particularly if there is a history of same.
- 16. Skin.** Describe any areas of trauma or skin breakdown.

**17. Endocrine dysfunction.** If evidence of endocrine function is identified or suspected, select and follow the additional appropriate examination protocol for the type of endocrine disorder identified.

**18. Other abnormal physical findings.**

As cervical spine trauma is a common accompaniment of TBI, the examination for the cervical spine is guided by the medical history and includes:

- General observation, including changes in positions, stance
- Gait while walking an extended distance, typically in the hallway, and changes in gait with distance walked
- Regional examination of the spine
- Examination of organ systems related to appropriate differential diagnosis
- Neurologic screening
- Testing for nerve root tension
- Monitoring pain behavior during range of motion and while seated as a clue to the problem's origin

The completely objective parts of the spine examination are circumferential measurements for atrophy or findings of fasciculations. All other findings require the patient's cooperation, although reflexes are generally more objective than subjective.

## Neurologic Screening

The most important neurologic deficit to recognize is myelopathy from spinal cord compression. Patients may have symptoms of cervical pain, and arm numbness and/or weakness like other patients with neck disorders. However, many also have additional symptoms of gait abnormality, leg numbness and/or weakness, and some have bowel or bladder control impairment [177].

Physical examination findings that correlate with significant myelopathy are:

- Hyperreflexia (Grade 3 or greater);
- Hoffman reflex (observing reflex flexion of the thumb distal phalanx when the distal phalanx of the middle finger is "flicked" or suddenly passively pushed into flexion at the DIP joint);
- Inverted brachioradialis reflex (during testing the brachioradialis reflex there is a decreased response from the brachioradialis and an abnormal flexion response of the fingers);
- Ankle clonus (forcefully dorsiflexing the ankle and maintaining pressure on the sole of the foot to maintain ankle dorsiflexion and observing for rhythmic beats of ankle flexion and extension, at least 4 "beats" required for sustained clonus to be abnormal);
- Babinski sign or reflex – firmly sweeping the pointed end of a reflex hammer from the lateral sole to the base of the toes and observing for an extensor response of the hallux (great toe);
- Cervical stenosis – while not a physical examination finding per se, it should be recognized that myelopathy is strongly linked to cervical stenosis, particularly congenital.

The neurologic examination most commonly focuses on a few tests that reveal evidence of nerve root impairment, peripheral neuropathy, or spinal cord dysfunction. The most common herniated disc in the cervical spine is the C5-C6 disc with impingement of the C6 nerve root. The clinical features of cervical nerve root compression are summarized in Table 3.

## 1. Testing for Muscle Strength

There are no specific muscle tests for the C1 to C2 nerve roots.

**Table 3. Physical Examination Correlates of Cervical Nerve Root Dysfunction**

Root Level	Sensory Deficit	Motor Weakness	Reflex
C3	Ear, anterior neck, occiput, posterior temporal area	Not usually detectable	None
C4	Shoulder, posterior upper arm, upper chest	Not usually detectable	None
C5	Lateral shoulder, upper arm	Shoulder abduction, elbow flexion	Biceps
C6	Lateral forearm, <b>thumb*</b> and perhaps index finger	wrist extension (ECRL/ECRB) and elbow flexion (biceps)	Brachioradialis, and possibly biceps
C7	<b>Middle</b> finger*	Elbow extension (triceps), wrist flexion, finger extension	Triceps
C8	Distal forearm, ulnar ring, and <b>little*</b> finger	Finger flexion	Triceps
T1	Medial upper forearm and arm	middle finger flexion, finger abduction and adduction	None
T2-T12	Unilateral, dermatomal based on nerve root(s) affected	Generally none unless multiple roots affected	None

\*These are the most common sensory nerve deficits related to cervical nerve root dysfunction.

## 2. Circumferential Measurements

Muscle atrophy is one of the few purely objective findings and can be measured with bilateral circumferential measurements of the upper arms and forearms at a fixed distance from an anatomic point (e.g., olecranon process). However, the dominant upper extremity usually may have an increase of up to 1cm. in circumference at the forearm and, possibly, also of the upper arm. Additional disparities in circumference are possible based on asymmetrical job physical requirements.

## 3. Reflexes

The biceps reflex primarily tests the C5 root, and to a lesser extent, the C6 root. The brachioradialis reflex tests the C6 root. The C7 root is assessed with the triceps reflex. The Hoffmann pathologic reflex in combination with clonus may indicate an upper motor neuron lesion.

## 4. Sensory Examination

Testing to light touch and pinprick (sharp dull perception) in the forearm and hand is usually sufficient to detect common nerve root compromise, but it may be necessary to perform sensory examination of the area from the neck to the forearm to test for higher nerve root compromise. Decreased sensation over the lateral deltoid muscle is a sign of C5 nerve root or axillary nerve compromise. Loss of sensation in the area of the radial forearm and thumb (and perhaps the index finger) suggests C6 nerve root involvement. Decreased sensation in the middle finger (3<sup>rd</sup> digit) may be a sign of C7 involvement, although it also is supplied occasionally by the C6 or C8 nerve root. The C8 root may show ring and little finger sensory findings. The ulnar side of the little finger (5<sup>th</sup> digit) is the purest area of C8 innervation. The T1 nerve root can be tested by evaluating sensation in the upper medial forearm and medial arm. The examiner should determine whether light touch can be felt, and whether the patient can distinguish between sharp and dull stimuli. These findings are more reliable than the report that sensory stimuli feel odd or “different” to the examinee, and yet each sensory stimulus is perceived [178].

## 5. Physical Examination Tests

Ideally, the treatment of cervical or thoracic pain should be based upon a correct diagnosis. However, for most patients a specific diagnosis that indicates the pain generating structure and the pathophysiology is not possible, and their diagnosis is non-specific cervical pain. Physical examination

rules out major neurologic involvement and provides a baseline from which to judge improvement over time. For a variety of reasons, a patient's response to a single test may not be reflective of the presence of identifiable underlying pathology.

## Diagnostic Recommendations

### Basic Imaging

Skull radiography has been used to diagnose fractures, and thus assessing in the evaluation of TBI patients. [188] [189] [190].

#### Skull X-Rays

##### Recommended.

Skull radiography is recommended for the evaluation of TBI patients.

##### Strength of Evidence – Recommended, Insufficient Evidence (I)

Level of Confidence – Moderate

<i>Indications:</i>	Head trauma thought to be sufficiently forceful to potentially fracture the skull. Indicated as well for further evaluation of bony step-offs and other clinical signs of fracture.
<i>Benefits:</i>	Identification of fracture, which helps to suggest severity of the injury and potential severity of TBI.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Generally only obtained at presentation. Occasionally re-x-rayed at followup.
<i>Rationale:</i>	There is one study suggesting no significant differences between a 2-view and 3-view skull series [191]. Skull X-Rays are not invasive, have no adverse effects, are low cost, are helpful in diagnosing skull fractures and thus are recommended for evaluating TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: skull radiography, skull x-ray, head x-ray; brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed head or penetrating head or craniocerebral; sensitivity, specificity, predictive value of tests, gold-standard, accurate, accuracy, precision, precise, or test. We found and reviewed 1247 articles in PubMed, 81 in Scopus, 42 in CINAHL, 42 in Cochrane Library, 13800 in Google Scholar, and 4 from other sources. We considered for inclusion 7 from PubMed, 2 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 4 from other sources. Of the 15 articles considered for inclusion, 1 diagnostic study and 2 systematic studies met the inclusion criteria.
<i>Comments:</i>	

### Evidence for the Use of Skull X-Rays

Author Year Score:	Category:	Study type:	Conflict of Interest:	Number:	Age/Sex	Area of Head:	Diagnoses:	Type of X-rays:	CT Used:	MR Used:	More than one rater:	Blinding of rater:	Myelography:	Surgery Performed:	Clinical Outcomes Assessed:	Long-term Follow-up (mean when noted):	Results:	Conclusion:	Comments:
McGlinchey, 1998 (5.0)	Skull X-Ray	Diagnostic	No mention of COI.	N=50	No mention of age or gender.	Skull	Traumatic Brain Injury	Radiography	-	-	+	-	-	-	-	-	Two film and three film series were utilized and a 94.4% confidence level for 2 films and 94.6% for 3 series. Of the 150 skull fracture series viewed	“A two-view skull series has no statistically deleterious effect on either diagnostic accuracy or confidence of interpretation when compared with a three-view series given an accurate clinical history. A two-view skull series can safely be adopted in the routine assessment of head injury given	Data suggest comparable results with no benefit of using a three-view skull series over two-view series.

																		<p>d as 2 films, 87 were correctly diagnosed with a confidence level of 92.7%. When viewed as 3 films, 92 were correctly diagnosed with a confidence level of 93%. No statistical difference was observed with 2 or 3 film series.</p>	<p>dependency on site of trauma. It should be stressed that such a policy does not preclude a more extensive skull series given an unreliable history, severe trauma or suspicious findings on the initial films."</p>	
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Computerized tomography (CT) has been used to evaluate TBI patients, especially in the acute presentation phase. [192-198].

## Computed Tomography (CT)

### Recommended.

Computed tomography is recommended for the evaluation of TBI patients.

*Strength of Evidence* – **Recommended, Evidence (C)**

*Level of Confidence* – High

<i>Indications:</i>	<p>Head trauma thought to be sufficiently forceful to potentially cause cranial fracture, intracranial hemorrhage, epidural hemorrhage, subdural hemorrhage and/or other traumatic brain injury(ies). Generally not indicated after the initial evaluation, as MRI is generally preferred for subacute to chronic brain parenchymal evaluation. [199] [200-205].</p> <p>The New Orleans decision rule for indications for CT scans among those with Glasgow Coma Score of 15 are: headache, seizure, intoxication, short-term memory deficit, vomiting, aged &gt;60yrs, or injury above the clavicles. The reported sensitivity is 100% and specificity of 24.5% [198].</p> <p>The Canadian Head CT rule for indications for CT scans among those with Glasgow coma Score of 13-15 are: high-risk are GCS&lt;15 at 2hrs post-injury, suspected skull fracture, any sign of basal skull fracture, vomiting at least twice, aged at least 65 yrs; medium risk are retrograde amnesia &gt;30min, and dangerous mechanism (pedestrian vs. motorized vehicle, ejected from vehicle, fall from height &gt;1m or 5 stairs). The reported sensitivity is 98.4% and specificity of 49.6% [198]. There are limited mild TBI cases where the severity or loss of consciousness or combinations of risks (e.g., in the elderly) may result in a clinical determination of the need for a CT scan.</p>
<i>Benefits:</i>	<p>Identification of surgical emergencies, fractures, and assisting in identifying or suggesting the severity of the TBI. Generally considered superior to MRI for unstable patients. Scoring with the Helsinki score is reportedly superior to the Rotterdam and Marshall scores [206].</p>
<i>Harms:</i>	<p>Radiological exposure. May miss non-hemorrhagic abnormalities for which MRI is superior to CT for evaluation [199-205].</p>
<i>Frequency/Dose/Duration:</i>	<p>Generally only obtained at presentation or at the initial, comprehensive evaluation.</p>
<i>Rationale:</i>	<p>There are quality studies assessing CT for diagnosis of TBI. CT is particularly useful for unstable patients with potential need of surgical intervention. CT is not invasive, has no adverse effects (other than radiation exposure), is high cost, has evidence of diagnostic efficacy, and thus is recommended for diagnosis and treatment planning of TBI.</p>
<i>Evidence:</i>	<p>A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: x-ray computed tomography, computed tomography, computerized tomography, CT scan, CAT scan, computerized axial tomography, traumatic brain injury, intracranial</p>

injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 2,462 articles in PubMed, 773 in Scopus, 468 in CINAHL, 3,290 in Cochrane Library, 53,400 in Google Scholar, and 16 from other sources. We considered for inclusion 4 from PubMed, 1 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 16 from other sources. Of the 23 articles considered for inclusion, 11 diagnostic studies, 2 prognostic studies and 7 systematic studies met the inclusion criteria.

## Evidence for the Use of Computed Tomography (CT)

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Area of Body:</i>	<i>Diagnoses:</i>	<i>Type of CT used:</i>	<i>Surgery Performed:</i>	<i>Clinical Outcomes Assessed:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Orrison 1994 (6.5)	CT	Diagnostic	No mention of COI.	N= 107	No gender or age distribution mentioned	Brain	emergency room-referred head trauma patients, between May 15, 1988 and June 30, 1989	high-resolution CT system (9800 Quick, General Electric, Milwaukee, Wis)  Vs 0.064-T permanent magnet (MTP Access, Toshiba America MRI, South San Francisco, Calif)  All participants underwent both imaging	None	CT - conventional gantry angulation, section thickness (3 to 10 mm), radiographic techniques, and contrast enhancement (when clinically indicated)  MR - T1-weighted spin-echo sequence (400-600/20-40/2-4 [repetition time/echo time/excitations] ) or a gradient-echo sequence (68/24/3) with a flip angle of 60°, and more T2-weighted spin-echo images ( 1500-2500/30-105 /2)	MR sensitivity was significantly higher than CT for detecting contusions (p < 0.001), subdural and epidural hematoma (p < 0.001), shearing white matter injury (p < 0.001), and sinus involvement (p < 0.001). CT sensitivity was significantly higher than MR in detecting fracture (p < 0.001). Both scans did not differ significantly for detecting superficial	“CT and MR are complementary studies in the evaluation of acute head trauma. MR is necessary to define or exclude contusions, deep shearing injury, and extraaxial fluid collections in acute head trauma.”	Data suggest CT and MRI are good imaging tools for assessing acute head injuries. MRI is able to exclude contusions, shearing injuries and detect extra-axial fluid collection.

								processes			soft tissue injury. MR sensitivity overall for detecting abnormalities was 96.4%. CT sensitivity was 63.4%.		
Raj 2014 (5.0)	CT	Diagnostic	No COI. Supported by Finska Läkaresällskapet, the Maire Taponen Foundation, and a Helsinki University Hospital	N= 869	No gender distribution was described  Mean age overall 57 years (ranges from 43 – 68)	Brain	Moderate to severe TBI (GCS score 3-13) and complicated mild TBI (GCS score 13-15)	Marshall CT classification, Rotterdam CT score, Helsinki CT score	None	mass lesion type, size, presence, location, thickness of traumatic subarachnoid hemorrhage (tSAH), presence of intraventricular hemorrhage (IVH), status of suprasellar cisterns, status of ambiens cisterns, status of fourth ventricle, midline shift, and cortical sulcus effacement	The Helsinki CT score was better than the Marshall and Rotterdam CT scores (AUC, 0.74-0.75 vs 0.63-0.70; P<.001). Using the Helsinki score increased the prognostic result of the clinical model (AUC neurological outcome + 0.02, p=0.002, AUC mortality +0.01, p=0.21). The Marshall and Rotterdam scores did	“The use of the Helsinki CT score significantly improved outcome prediction accuracy, and the Helsinki CT score is a feasible alternative to previous CT scoring systems. The Rotterdam and Marshall CT systems were of modest value in predicting long-term outcome in this large sample of patients with mild complicated, moderate, and severe TBI. External validation of the Helsinki CT score in independent data sets is advocated to	Data suggest Helsinki CT score helped improve the accuracy of the outcome of the outcome predictions at 6 months post TBI.

											not provide an improved predictive value to the model (p > 0.05).	show generalizability.”	
Williams MW 2013 (5.0)	CT	Observational Study	Supported by Wayne State University Graduate School, National Institute of General Medicine - Initiative for Maximizing Student Development, and the National Institute on Disability & Rehabilitation Research – Traumatic Brain Injury Model Systems Project (H133A080044).	N= 288	60 females, 228 males  Mean age 38.1 years (ranging from 16 – 86)	Brain	mild complicated, moderate or severe traumatic brain injury	CT scan including the Marshall classification	None	Glasgow Coma Scale, midline shift > 5 mm, presence or absence of additional indices (intracranial hemorrhage, subarachnoid hemorrhage, intraventricular hemorrhage, punctate/petechial hemorrhage, and intraparenchymal fragments), Neuropsychological Battery scale, Disability Rating Scale, Satisfaction with Life Scale	The use of CT characteristics and neuropsychological tests did not improve prediction of life satisfaction. These variables did help improve prediction of return to work at 2 years post injury. Neuropsychological tests added to outcome predictions of functional disability. CT characteristics did not improve prediction of long-term functional disability.	“This study adds to the body of literature supporting the unique value of inpatient neuropsychological evaluations in making long-term functional outcome predictions for individuals with traumatic brain injury.”	Data suggest the addition of neuropsychological tests to CT results provides additional information for long term outcome prediction.
Bosco	CT	Diagnostic	No COI.	N= 81	22 female	Brain	Those admitted	CT scans of six	None	Glasgow Coma Scale,	The final model	“A spatial mapping of all	Data suggest that

2014 (4.5)					s, 59 males  Mean age 26 ± 14 years		d to intensiv e care unit after severe head injury, with GCS score ≤ 8	regions of interest: frontobas al (f), central (c), parietal (p), temporal (t), occipital (o), subcortic al (sc), and mesence phalic (mc)		encephalograph y within first six days after injury, intracranial mass lesions, neurophysiologic al investigation using electric stimulation of median nerve (at the wrist for 0.2 ms)	created for predicting the outcome of a TBI patient included the somatosens ory-evoked potentials (SEPs) primary complex (pN20/fP20/ cP22), SEPs middle latency (N30/P45/N 60), and CT scan hypodensity values. These variables combined showed a significantly improved predictive power of the Glasgow Outcome Scale ratings when compared to just using pN20 alone (p<0.0001).	early SEPs components on frontocentral- parietal areas of both major- lesion and minor-lesion hemispheres allows a detailed analysis of outcome prediction and a better prognostic evaluation than using the N20- P25 cortical component alone.	the addition of early cortical somatosens ory- evoked potentials (SEPs) components provide statistically enhanced outcome prediction in acute TBI.
Ward law JM 2002 (4.0)	CT	Prospect ive Observat ional Study	Supported by the UK Medical Research Council	N= 1,13 1	No gender distribu tion describ	Bra in	Those with THI, all grades of THI,	Evaluate which features on the admissio	None	Size of lesions (extradural haematoma, subdural	Age, Glasgow coma score (GCS), pupil reaction,	“Age, GCS, and pupil reaction were all previously shown to be significant	Data suggest multiple variables may be

			and the Clinical Research Initiative in Clinical Neurosciences		ed other than a 3:1 ratio  Mean age for all 37 years		admitted to neurosurgical center from January 1, 1989 to July 16, 1996	n CT scan might add significantly to other baseline clinical information for predicting survival in patients with head injury.		haematoma, subarachnoid haemorrhage, parenchymal contusions, white matter lesions, basal ganglia; presence of depressed fracture or intracranial air, of amount of any midline shift, of compressed, dilated, or normal ventricles and basal cisterns	presence of subarachnoid blood, and the simple grading of the overall appearance of the scan (all $p < 0.001$ ).	predictors of patient survival after head injury. A further two, easy to identify, CT scan variables are independent prognostic variables, and might help to identify patients at high risk of death at the time of admission."	significant for predicting post head injury survival.
Mars hall LF 1991 (4.0)	CT	Prospective Observational Study	Supported by National Institute of Neurological Disorders and Stroke Contracts (Pilot Traumatic Coma Data Bank)	N= 746	No gender or age distribution described	Brain	Severe traumatic brain injury	Not specified	None	the status of the mesencephalic cisterns, the degree of midline shift in millimeters, and the presence or absence of one or more surgical masses	CT diagnosis was a highly significant independent predictor of mortality ( $p = 0.0001$ ) when age and motor score were included in the model; when CT diagnosis was not included, the fit was poor ( $p = 0.041$ ).	This more accurate categorization of diffuse head injury, based primarily on the result of the initial CT scan, permits specific subsets of patients to be targeted for specific types of therapy. Patients who would appear to be at low risk based on a clinical examination, but who are known from the CT scan	Data suggest this is a more accurate classification system for categorizing head injury and helps guide therapy.

												diagnosis to be at high risk, can now be identified.	
Petro ni G 2010 (NA)	CT	Prognostic Study	No COI. Supported by U.S. Department of Education, National Institute on Disability and Rehabilitation Research, Fogarty International Center of the National Institutes of Health, and National Institute of Neurological Disorders and Stroke and Fogarty International Center of the NIH	N= 148	28 females, 120 males  Mean age 34 years (ranging from 14 – 77 years)	Brain	create an accurate and reliable instrument for predicting outcome from TBI that physicians in Argentina, and perhaps other middle- and low-income countries, can use to make treatment decisions, guide prognostic discussions with patients and families, and conduct	Within 24 hours, type not specified	None	Globally: presence or absence of abnormalities, specifically: presence or absence of compression of basal cisterns, midline shift (> 5 mm), extradural hematoma, subdural hematoma, contusion, and traumatic subarachnoid hemorrhage (TSAH)	More than 58% of the patients died, 33.8% within the first 24 hours and 19.6% during acute care.	This study provides rigorous, prospective data that [170] validates the generalizability of the five World Health Organization/Organization Mondiale de la Sante' TBI prognostic predictors outside of the developed world, and (2) provides outcome benchmarks for mortality and morbidity from severe TBI in developing countries.	Prognostic Study validating benchmarks for morbidity and mortality outcome predictors in developing countries.

							research						
Thomas BW 2009 (NA)	CT	Prognostic Study	No COI.	N=887	266 females, 621 males  Mean age 42 ± 20.8 years	Brain	mild (GCS 13-15), moderate (GCS 9-12), or severe (GCS 3-8) TBI	Scheduled repeat brain CT (SRBCT)	None	Injury Severity Score (ISS), history of vascular disease and anticoagulant/antiplatelet use, prothrombin and international normalized ratio at admission, hours from IBCT to SRBCT, admitting Glasgow Coma Scale (GCS), total number of CT scans during hospitalization, type of brain injury (subdural hematoma, epidural hematoma, intraparenchymal hemorrhage, or mixed bleed)	692 (78%) patients had no worse SRBCT and neurological changes later developed in 11 (1.6%) patients	"A worse SRBCT is more likely to result in neurologic intervention. SRBCT remains useful in assessing patients with TBI."	Prognostic Study suggesting that a worse SRBCT is associated with longer hospitalization, higher mortality and probably will result in extended medical and surgical interventions.

Magnetic resonance imaging (MRI) has been commonly used to assess both acute and chronic TBI patients [207, 208].

## **Magnetic Resonance Imaging (MRI)**

### **Moderately Recommended.**

Magnetic resonance imaging is moderately recommended for the evaluation of TBI patients.

*Strength of Evidence* – **Moderately Recommended, Evidence (B)**

*Level of Confidence* – High

<i>Indications:</i>	Head trauma thought to be sufficiently forceful to potentially cause intracranial hemorrhage, epidural hemorrhage, subdural hemorrhage and/or other traumatic brain injury(ies). May be indicated for a followup MRI study for evaluation of ongoing symptoms, to assess a missed diagnosis, and/or resolution of prior defects.
<i>Benefits:</i>	Identification of surgical emergencies, fractures, and assisting in identifying or suggesting the severity of the TBI.
<i>Harms:</i>	May have the potential to mislead regarding prognosis, as minor abnormalities are common and there is some evidence that clinical findings are superior to only MRI findings [209] [210].
<i>Frequency/Dose/Duration:</i>	Generally only obtained at presentation. Sometimes obtained to evaluate ongoing symptoms to assess a missed or secondary diagnosis.
<i>Rationale:</i>	There are multiple moderate quality studies suggesting utility of MRI for evaluation of TBI patients. MRI is reportedly superior to CT for assessing intracranial injuries, especially those without hemorrhage [199-204]. MRIs are not invasive (or minimally invasive with IV contrast), have no adverse effects, are high cost, but are helpful in diagnosing surgical emergencies and evaluation of the extent of TBI injury(ies) and are thus recommended for evaluating TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Magnetic Resonance Imaging OR MRI AND Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 1612 articles in PubMed, 891 in Scopus, 450 in CINAHL, 102 in Cochrane Library, 15700 in Google Scholar, and 0 from other sources. We considered for inclusion 6 from PubMed, 2 from Scopus, 3 from CINAHL, 1 from Cochrane Library, 1 from Google Scholar, and 25 from other sources. Of the 38 articles considered for inclusion, 31 diagnostic studies and 2 systematic studies met the inclusion criteria.

## Evidence for the Use of Magnetic Resonance Imaging (MRI)

Author Year (Score):	Category:	Study type:	Sample size:	Age/Sex:	Sponsorship/COI:	Area of Body:	Diagnoses:	Type of MRI used:	Type of CT used:	T1 Weighted	T2 weighted	X-ray:	Myelography:	More than	Surgery	Clinical	Long term follow-up:	Results:	Conclusion:	Comments:
Yuh 2013 (7.0)	MRI	Prospective Study	N=135	97 males, 38 females; Mean age 40 ± 17.	Supported by the National Institutes of Health grants. No COI.	No specific planes/regions mentioned.	Patients with mild traumatic brain injury.	Yes	No specification	No	No	No	No	No	No	Yes	12 ± 3.9 days	MRI identified many more acute traumatic intracranial lesions than CT. 64/135 vs 37/135 abnormalities.	"We show for the first time that traumatic intracranial findings on conventional CT and MRI account for a significant portion of the variability in outcome in MTBI. Routine performance of brain MRI on MTBI patients may not currently be cost-effective."	Data suggest MRI identified more traumatic intracranial findings than did CT to predict 3 month outcomes post mild TBI.
Lagaras 2009 (6.5)	MRI	Prospective	N = 100	83 males, 17 females;	Study was supported by a grant	Frontal unilateral, bifrontal, temporal, bitemporal	Traumatic brain injury		No	Yes	Yes	No	No	No	No	Yes	6 months	MRI findings located frontal unilateral	"The anatomical substrate of TBI	Data suggest MRI added benefit

				Mean age of 33 (15-71)	from the Fundacion Mutua Madrilen a.													in 23%, bifrontal 41%, temporal 14%, bitemporal 8%.	depicted by MR could be a useful prognostic tool in patients suffering moderate and severe head injury."	to aid in prognosis of moderate to severe TBI patients with a GCS of 4 or less.
Gentry 1988 (6.5)	MR	Prospective	N = 40	32 males, 8 females; Mean age of 26.6 years.	No mention of spinal or COI.	Axial Coronal	Acute closed-head trauma	0.5 Tesla cryogenic system	Pickering 600/1200 scanner	Yes	Yes	No	No	No	No	Yes	No	For diffuse axonal injury, CT only detected 19% of lesions. T1-weighted MR was also more sensitive (72.3%), but less sensitive than T2-weighted MR (92.4%). For cortical contusion CT detected 15.4%, T1-weighted MR 58.3%, and T2-weighted MR 95%.	"In summary, MR has significant advantages over CT in evaluating patients with closed head trauma."	Data suggest MRI and CT are comparable for the detection of hemorrhagic lesions but MRI better for detecting non-hemorrhagic lesions but CT is best for assessment of unstable TBI patients possibly requiring surgery.

																		For hemorrhagic sensitivity was similar across all imaging methods.		
Kara 2008 (6.0)	MRI	Prospective	N = 124	76 males, 48 females; male mean age 61 (15-40), female age 63 (41-70).	No mention of sponsorship or COI.	Coronal, axial, sagittal planes	Severe head trauma with neurological deficits despite normal CT scans.	1.5 Tesla	Yes	No	No	No	Yes	No	No	Yes	6 months	Detection of contusional lesions on both T1 (92.6%) and T2 (96.3%) weighted slices. Most corpus callosum were in the temporal region (50.3%), frontal (29%), and parietooccipital (14.5%).	"This study supports the importance of MRI in detecting acute and subacute hemorrhagic and nonhemorrhagic lesions, infarcts and brainstem injuries in severe CCI."	Data suggest MRI can detect subtle lesions which go undetected in CT but correlate with neuropsychological condition which may have prognostic benefit.
Moen 2012 (5.5)	MRI	Longitudinal	N = 58	43 males, 15 females; Mean age 33.4 (11.4-63.4)	KGM and TS have, during the study period, received a research grant from the liaison	Hemispheres, corpus callosum, brainstem, thalamus/BG/cerebellum	Moderate to severe traumatic brain injury	1.5 Tesla	No	Yes	Yes	No	No	No	No	Yes	1 year	Only 60% of patients with traumatic axonal injury (TAI) stage 3 in early MRI had brainstem	"The most important finding was that non-hemorrhagic TAI lesions depicted in FLAIR sequence	Data suggest early MRI predict clinical outcome as later MRI shows less lesions such that

					committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU). No COI.													m lesions at 3-months post injury. Diffusion sequences had fewer lesions than the T2*GRE and T2 fluid attenuated inversion recovery (FLAIR) sequences.	s, including brainstem lesions, often disappeared during the first 3 months.”	prognosis is likely related to early MRI results.
Lui 2014 (5.5)	MRI	Prospective Study	N=23	17 males, 6 females; Mean age of 33.65 ± 11.21.	Supported in part by grants from the National Institute of Health. No COI.	Thalamus, Frontal lobe.	Mild Traumatic Brain Injury	3.0 Trio MRI	None	No	No	No	No	No	No	Yes	23 days	Best classifiers for MTBI diagnosis included the mean kurtosis of the Thalamus which had a 74% accuracy. All features which had an 80% accuracy. And minimal-redundancy maximal-relevance	“This work serves as a pilot study showing that a combination of features including MRI metrics can classify patients with mTBI and controls with 86% accuracy, up from 74% for the best single feature	Pilot study. Data suggest a combination of tools including MRI and classification metrics can accurately classify mild TBI patients. 86% accuracy which is better than any single tool.

																		(mRMR) of 86%.	alone. Furthermore, mRMR feature selection optimizes this process by selecting relevant and no redundant features."	
Huisman 2003 (5.5)	MR	Retrospective	N = 25	19 males, 6 females; Mean age 31 ± 10.	No mention of spinal cord injury or COI.	Corticomedullary junction, central white matter, corpus callosum, brainstem, anterior/posterior capsula.	Acute closed head injury	1.5 Tesla	Yes	Yes	Yes	No	Yes	No	No	Yes	No follow up reported.	MRI within 48 hours with 427 shear injury lesions were seen in 25 patients. Diffusion-weighted imaging (DWI) missed 117 or 427 lesions that were seen on T2/fluid-attenuated inversion recovery (FLAIR) or gradient echo (GRE).	"DWI yields additional information in closed head injury and could represent a valuable tool in the depiction of DAI."	Data suggest DWI is beneficial in visualizing shearing injuries not seen with T2/FLAIR or T2* sequences but DWI is less sensitive than T2* for imaging hemorrhagic lesions.

Geurts 2012 (5.5)	MRI	Retrospective	N=56	33 males, 23 females; Median age & range 31 (12-78).	No sponsors hip or COI.	Frontal, temporal, parietal or occipital lobar grey and/or white matter, corpus callosum, subcortical, cerebellum, brain stem.	Traumatic Brain Injury	3 T MRI	None	No	Yes	No	No	No	No	Yes	7 weeks	Post-hoc Wilcoxon signed rank tests with Bonferroni correction (p<0.008) revealed that with SWI (Susceptibility Weighted images) more lesions were detected compared to T2*-GRE (T2-gradient recalled echo) (p<0.001), FLAIR (Fluid Attenuated Inversion Recovery) (p<0.001) and T2WI (T2-Weighted Imaging) (p<0.001). In turn, T2*-GRE showed more	“Susceptibility Weighted Imaging is the most sensitive sequence in the detection of small haemorrhagic lesions.”	Data suggest significant inter-rater reliability disagreement in the interpretation of TBI lesions. T2-GRE and SWI show better sensitivity than T2WI and FLAIR in the detection of hemorrhagic lesions from trauma.
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																		lesions than T2WI (p<0.001) and FLAIR (p<0.001)		
Snow 1986 (5.0)	MR	Prospective, case studies	N = 35	No mention of mean age or all genders.	No mention of sponsors hip or COI.	None specified.	Head trauma	0.5 Tesla	8800	Yes	Yes	No	No	No	No	Yes	No	21 cases had intracerebral lesions. 7 patients with head trauma had normal findings on CT and MRI scans. After 72 hours MRI was found to be superior to CT in the detection of intra- and extracerebral traumatic lesions.	"[I]f CT is negative or the abnormalities identified on CT are insufficient to explain the clinical condition of the patient, MRI should be performed."	Data suggest MRI superior to CT for visualization of non-hemorrhages continuous CT superior in diagnosing SAH or acute parenchymal bleeds.
Wilson 1988 (4.5)	MR	Retrospective/Prospective	N = 25	Distributions of age: 16-30 (N=10) 31-45 (N=4)	Research was supported by the Medical Research Council.	Head	Close head injury	0.15 Tesla, 6.38 MHz	EMI 1010	Yes	Yes	No	No	No	No	Yes	11 months	Neuropsychological tests were associated with neuroimaging abnormal	"[C]ontrasts should be sought between primary shearing injuries	Data suggest classifications of early and late MRI were strongly correlate

				46-60 (N=5) 61-73 (N=6)/ 18 Males 7 Females														ities than others. The depth of lesion detected by MRI was correlated with psychological impairment. Late MRI was significantly associated with outcomes on neuropsychological tests (p<0.001).	and secondary ischemic damage, and we consider that serial MRI investigations of Head injured patients are a priority for future research."	d. Neurological outcomes were strongly correlated with late MRI and had minor correlation or no correlation with early MRI or early CT suggesting outcomes relate to lesions seen on late MRI.
Hughes 2004 (4.5)	MRI	Longitudinal study	N = 80	59 males, 21 females; Mean age of 31.	No mention of sponsorship or COI.	Head	Mild traumatic brain injury	1.0 Tesla		Yes	Yes	No	No	No	No	Yes	2 years	Initial MRI showed abnormalities in 26/80 patients. 2/26 had findings definitely related to traumatic injury. MRI showed non-specific abnormalities in patients with mild	"We have demonstrated using routine MRI techniques that non-specific abnormalities are common in a group of patients with MTBI."	Data suggest non-specific abnormalities are common in mild TBI patients as seen on MRI. Abnormal MRI did not predict a poor outcome.

																		traumatic brain injury. However, abnormal MRI did not predict poor long-term outcome.		
Wilberger 1987 (4.5)	MRI	Diagnostic/case study	N=24	No mention of Gender; Mean age of 28.	No mention of sponsors hip or COI.	All different planes without patient movement.	Severely head injured patients	0.35 & 0.5 T super conducting magnet	Siemens DR3 scanner	Yes	Yes	No	No	No	No	Yes	3 days	MRI demonstrated lesions that were not seen on CT. There were a total of 10 contusions, 5 brain stem injuries, 5 diffused white matter injuries, and 4 subdural hematomas. White matter injuries were seen on either T2 or T1 images. Brain stem injuries were	"MRI is anatomically sensitive and pathologically specific in patients with severe head injuries. Suspected white matter shear injuries or contusions, brain stem injuries, diffuse white matter injuries, and subdural hematomas can all be demonstrated	Data suggest MRI is more sensitive in imaging severe head injury in lieu of a normal CT and normal ICP.

																		best seen using T2 weighted images.	rated by MRI."	
Ingebrigtsen 1999 (4.5)	MRI	Prospective	N = 50	29 males, 21 females; Mean age of 33 (10-72).	The study was supported by The Lærdal Foundation for Acute Medicine, the Norwegian Research Council, and the Skane County Council's Research and Development Foundation.	Transverse plane of whole brain.	Traumatic Brain Injury	0.5 Tesla	Yes	Yes	Yes	No	Yes	No	No	Yes	3 months	CT scans within 12 hours, MRI within 48 hours. 14 (28%) had detectable serum levels S-100 protein. Detectable limits were associated with MRI finding of brain contusion and related to cranial fracture. 8/14 had normal MRI despite detectable serum levels.	"Detectable serum levels are related to a brain contusion revealed by MRI and impaired neuropsychological functioning on measures of attention, memory, and information processing speed."	Data suggests that the presence of serum S-100 protein correlated to diminished attention memory and the speed of information processing.
Giugni 2005 (4.5)	MRI	Prospective	N = 21	19 males, 2 females; Mean age 26.8 (18-40).	No mention of sponsorship or COI.	Whole brain, frontal lobe, temporal lobe, parietal lobe, occipital lobe, basal ganglia,	Severe traumatic injury and suspected diffuse	1.5 Tesla	No	Yes	Yes	No	Yes	No	No	Yes	No	Turbo proton echo-planar spectroscopic imaging (t-PEPSI) and gradient-	"Substantial benefits may be gained from rapid T2*-weighted MR	Relatively small sample. Data suggest comparable efficacy for detection

						corpus callosum, periventricular, infratentorial	axonal injury (DAI).											recalled echo (GRE) were used to increase sensitivity. GRE was superior to t-PEPSI in depicting DAI lesions in the temporal lobe (74 vs. 37; p<0.004). In the other regions the sequences had similar sensitivities.	imaging in patients with severe TBI.”	of diffuse axonal damage in severe TBI patients between GRE and t-PEPSI.
Huang 2015 (4.5)	MR	Prospective Controlled Trial	N=222 (111 w/ TBI)	TBI Group : 43 males, 68 females; Mean age 37.14 ± 12.76. Control Group :46 males, 65	No sponsors hip or COI.	Transverse plane of whole brain.	Mild Traumatic Brain injury	3 T MR Scanner	Yes, unknown.	Yes	Yes	No	No	No	No	Yes	24.76 days	36/11 in TBI group showed micro bleeds using Susceptibility Weighted Angiography (SWAN) and 12/111 in control group. K value of interobserver	“We recommend addition of SWMRI technique as a complementary sequence to the MRI protocol for	Data suggest the presence of TBI-related microbleeds are correlated to short term memory function which could possibly be a

				females; Mean age 39.67 ± 9.38														Inter agreement for detection of micro bleeds by SWAN was 0.908. Digit spans scores were lower in the micro bleed group (p=0.017). No difference in continuous performance test results between micro bleed group and control.	patients with mTBI.”	biomarker for TBI severity.
Jenkins A 1986 (4.0)	MRI	Prospective	N = 50	No mention of gender or age.	No mention of sponsorship or COI.	Transverse plane. Looking at cortical/subcortical lesions.	Mild and severe head injury	1.5 Tesla	EMI 1010	Yes	Yes	No	No	No	No	Yes	No	25/50 had abnormal CT scans, significantly less than detected by MRI (p<0.001). 46/50 had abnormalities with the T2	“MRI can provide a striking picture of the immediate effects on the brain of a head injury.”	Data suggest detects post TBI brain damage better than CT. Also, lesions in the cerebral hemisphere of 15 comatose

																		weighted studies were more sensitive. MRI detected cortex lesions in 44/50 and Ct scan showed 23/50.		Patients may be a key factor for unconsciousness.
Wedekind 1999 (4.0)	MRI	Prospective	N = 57	44 males, 13 females; Mean age for female 28 (14-49) and males 36 (13-68).	This study was supported by the Bundesministerium für Bildung und Forschung.	Transverse, sagittal, coronal planes	Mild, moderate, and severe head injury based on the Glasgow Coma Scale (GCS).	1.0 or 1.5 Tesla	None	Yes	Yes	No	No	No	No	Yes	No	MRI was superior to electrophysiologic (EP) due to its higher density prognostic information obtained.	"MRI in head injury provides several features relevant to prognosis."	Data suggest MRI visualized lesions in the corticobulbar region and midbrain were linked to poorer outcomes.
Laalo 2014 (4.0)	MRI	Diagnostic	N= 89	No mention of Gender of age.	No sponsorship or COI.	The locations used were frontal lobe, temporal lobe, parietal lobe, occipital lobe, corpus callosum, basal ganglia, brain stem and Cerebellum.	Traumatic Brain Injury	1.5 T MRI	No	Yes	Yes	No	No	No	No	Yes	66 months	First neurologist with more experience [170] found 370 findings vs less experienced neurologist (R2) who found	"The interpretation of TBI findings in late-stage MRI is difficult, yielding significant variability even between	Data suggest late stage chronic TBI as imaged by MRI shows significant interpretative variability which affects

																		264, and original findings totaled 173. Most common findings were white matter hypersensitivities (172/370). No statistically relevant correlations were found between the misinterpretation of findings and clinical parameters.	specialists in neuroradiology.”	diagnosis.
Himannen 2005 (4.0)	MRI	Prospective	N = 61	41 males, 20 females; Mean age 29.4 ± 10.8.	This work was supported by grants from Turku University Central Hospital and the Turku University Foundation.	Left /right hippocampus, lateral ventricle.	Traumatic brain injury	1.5 Tesla	Yes	Yes	Yes	No	Yes	No	No	Yes	1 month to 20.1 years.	The volume of the left hippocampus from MR scans was significantly associated with lower Wechsler Memory	“In conclusion, the long-term memory impairments after TBI are associated with MRI volumetric	Data suggest TBI severity is not as prognostically important as the degree of diffuse injury developing into atrophic changes



## Advanced Imaging

Magnetic resonance spectroscopy (MRS) is a noninvasive diagnostic tool similar to MRI with the additional capability of measuring the metabolite concentrations [211-220].

### Magnetic Resonance Spectroscopy (MRS)

#### No Recommendation.

There is no recommendation for or against the use of magnetic resonance spectroscopy for the evaluation of TBI patients.

#### *Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

##### *Level of Confidence – Low*

###### *Rationale:*

There are quality studies assessing MRS for diagnosis of TBI. There is consistent, quality evidence that MRS findings are correlated with TBI [221-226]. There also is evidence that MRS findings are predictive of subsequent clinical outcomes [221] [222]. Some evidence suggests intelligence factors may confound or interact with the MRS findings [224]. One comparative study reported higher sensitivity with SPECT than MRS [227]. Still, there is no quality evidence that MRS alters the clinical course beyond that already obtained from MRI or other imaging. MRS is not invasive has no adverse effects, is high cost, and has evidence of diagnostic efficacy. Yet, without quality evidence it alters the clinical course, there is no recommendation for or against MRS for the diagnosis of TBI.

###### *Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Magnetic Resonance (MR) Spectroscopy, Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, and Craniocerebral Trauma; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 72 articles in PubMed, 8 in Scopus, 28 in CINAHL, 6 in Cochrane Library, 50 in Google Scholar, and 8 from other sources. We considered for inclusion 7 from PubMed, 2 from Scopus, 2 from CINAHL, 1 from Cochrane Library, 1 from Google Scholar, and 8 from other sources. Of the 21 articles considered for inclusion, 16 diagnostic studies and zero systematic studies met the inclusion criteria.

## Evidence for the Use of Magnetic Resonance (MR) Spectroscopy (MRS)

Author/Year Study Type	Category	Study type	Conflict of Interest	Sample Size	Age /Sex	Area of Head	Diagnoses	Type of MRS used	Type of imaging used	CT	T1 weighted images	T2 weighted images	X-ray	Myelography	Mor eth an on e rate r	Surgery Performed	Clinical outcomes assessed	Long term follow-up (mean when not ed)	Results	Conclusion	Comments
Tollard 2009 (5.0)	MR Spectroscopy	Diagnostic	Sponsored by Assistance Publique-Hopitaux de Paris and French Health Ministry (AOM 05 101 to LP). No COI.	N = 58 TBI group 1 (n= 19) TBI group 2 (n= 24) Healthy controls (n= 15)	Mean age was 35 40 males and 3 females.	Whole brain	Closed-TBI	H-MRS	MRI	+	+	+	-	-	+	+	+	1 year	At the 1 year follow-up 19 patients had unfavorable outcomes (44%) and 24 had favorable outcomes (56%). MRS had 75% sensitivity and 75% specificity . Combined MRS and FA data predicted unfavorable outcomes with up to 86% sensitivity and 97%	“FA and NAA/Cr may potentially be quantitative outcome prediction tools at the subacute phase of TBI. H-MRS and DTI show higher levels of accuracy when compared to MRI alone.”	Data suggest FA and Naa/Cr may be of use for predicting TBI outcomes in the subacute phase.

																			specificity		
Friedman 1999 (4.5)	MR Spectroscopy	Diagnostic	Sponsored by the European Community project TMR/Networks ERBFMRX CT970160. No mention of COI.	N = 28	Mean age was 33.9 26 males and 2 females	Whole brain	mTBI and/or sTBI TBI group (n=14) Healthy control (n=14)	H-MRS - STEAM	MRI-1.5 Tesla	-	+	+	-	-	+	-	+	6 months	H-MRS diagnostic testing shows early NAA concentrations in gray matter predict overall neuropsychological performance (r = 0.74, p = 0.01). Neuropsychological function improved in patients with TBI (t=-4.36, p=0.002). Proton MRS shows neurochemical changes in normal WM and GM after TBI.	"H-MRS provides a rapid, noninvasive imaging tool to assess the extent of neuronal damage after sustaining a TBI. Proton MRS can be paired with conventional MR examinations with minimal additional time."	Data suggest H-MRS, while non-invasive may assist in determining injury severity post TBI when combined with MR and help predict outcomes.

Signoretto 2008 (4.5)	MR Spectroscopy	Diagnostic	Sponsored by National Institutes of Health Grant NS12587 to Drs. Bullock and Marmaro, and by National Institutes of Health Grant NS19235 to Dr. Marmaro. No mention of COI.	N = 30	Mean age was 33.2 sTBI group: 18 males and 7 females Control group: No gender data available	L/R hemisphere	Severe TBI sTBI group (n=25) Healthy control (n=5)	H-MRS	CT	+	+	+	-	-	-	-	+	-	The NAA/Choline and NAA/Creatines were significantly correlated with GOS scores at 6 months (p<0.01). High metabolite ratios were associated with good outcomes.	"When conventional neuroimaging techniques reveal no abnormalities, it is possible H-MRS can detect posttraumatic neurochemical damage."	Data suggest the use of HMR can detect neurochemical damage in the post TBI injured brain when conventional imaging cannot and mitochondrial integrity appear correlated to NAA levels.
Yeo 2011 (4.5)	MR Spectroscopy	Diagnostic	Sponsored by the National Institutes of Health (grants R24-HD050836, R21-NS064464-01A1, and 3 R21 NS064464-01S1 to	N = 60	Age range: 18-50 26 males and 34 females	L/R temporal, occipital, parietal, and frontal lobes.	mTBI mTBI group (n=30) Healthy controls (n=30)	H-MRS	CT	+	+	+	-	-	-	-	+	3-5 months	No differences between the healthy controls and mTBI patients in attention, working memory, memory, processing speed,	"Results indicate that neurometabolite concentrations are systematically altered by mTBI. H-MRS can detect changes	Data suggests that an estimate of pre-morbid intelligence was positively associated with

			A.M.). No COI.														and executive functioning during neuropsy- chological performa- nce (p>0.10). There as a positive relationsh- ip between mTBI and white matter creatine (WM Cr) and glutamat- e- glutamine signal (Glx) (p=0.002) . Metabolit- e levels were elevated for white matter Cr (p=0.026) and Glx (p=0.028) compared to healthy controls. T1 and T2 images found no trauma- related pathology .	in neurome- tabolites with fewer errors than conventi- onal neuroim- aging.”	the magnit- ude of the metab- olite normal- ization seen during follow- up suggest- ing those factors which underly intellig- ence may be related to faster recover- y..
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Dhandapani 2013 (4.5)	MR Spectroscopy	Diagnostic	No sponsorship or COI.	N = 53	Mean age was 33.44 males and 9 females	Whole brain	Closed-TBI TBI group (n=41) Healthy controls (n=unknown)	Single voxel (SV) MRS	1.5 Tesla	+	-	-	-	-	-	-	+	3 months	41 patients underwent MRS (36/41 show abnormalities) and 56 patients underwent SPECT (41/56 show hypoperfusion). CT scans revealed 50% had MRS abnormalities and 64% had SPECT hypoperfusion.	"ECD-SPECT examinations proved to have a greater sensitivity, incremental validity, and prognostic value than proton MRS."	Data suggest SPECT has better sensitivity than MRS in some types of patients with moderate head injuries which may help guide treatment and predict prognoses.
Maudsley 2015 (4.0)	MR Spectroscopy	Diagnostic	Sponsored by the National Institute of health research grants R01NS055107 and R01EB000822. No COI.	N = 69	Mean age was 28.239 males and 30 females	Whole brain	Closed-TBI TBI group 1 (n=20) TBI group 2 (n=20) Healthy controls (n=29)	Volumeetric MSRI & DTI	MRI	-	+	+	-	-	-	-	+	-	The MRS-observed patients showed increases in Cho and Cho/NAA were broadly distributed. DTI group detected localized changes in major white matter tracts and	"The study demonstrates that MRSI and DTI have a complementary nature."	Data suggest MRSI and DTS are useful in the detection of altered metabolism and injury post TBI but areas located by the 2 metho

																		adjacent tissues.		ds are different.	
Govind (4.0) 2010	MR Spectroscopy	Diagnostic	Sponsored by National Institutes of Health grants R01NS055107 and R01EB000822. No COI.	N = 81	Mean age was 26.25 males and 4 females.	Whole brain	Closed-head TBI with brief loss of consciousness (<20min) TBI group (n=29) Healthy control (n=52)	MRSI EPSI	MRSI FLAIR Diffusion-weighted MRI	-	+	+	-	-	-	-	+	Mean: 20.5 days	MRS imaging shows a widespread decrease of NAA and NAA/Cr, and increases of Cho and Cho/NAA in all lobes. No significant correlation found between MRSI or NPT measures.	"The results indicate that significant and widespread alterations of proton MRS - observed metabolites occur throughout the brain as a result of mild-to-moderate TBI."	Data suggest that in mild to moderate TBI patients there are significant and widespread metabolite alterations which correlate to cognitive performance.

Functional magnetic resonance imaging attempts to assess neural function using blood oxygen level-dependent (BOLD) contrast. BOLD utilizes hemodynamic factors, which include cerebral blood volume, metabolic rate of oxygen, and cerebral blood flow (CBF). When the increase in CBF exceeds cerebral metabolic rate the result is a higher ratio of oxygenated to deoxygenated hemoglobin [228]. The use of fMRI via BOLD contrast is thought to be sensitive to changes in neural activity after a traumatic brain injury. [229-234]

## Functional MRI

### No Recommendation.

There is no recommendation for or against the use of functional MRI for the evaluation of TBI patients.

### Strength of Evidence – No Recommendation, Insufficient Evidence (I)

#### Level of Confidence – Low

##### Rationale:

There are a few quality studies assessing Functional MRI for diagnosis of TBI. However, there are no quality studies showing fMRI alters the clinical course compared with other diagnostic testing such as traditional MRI. Most studies utilizing fMRI have focused on working memory tasks and not for diagnostic purposes [228]). Functional MRI diagnostic test is minimally invasive, has no adverse effects, is high cost, but has no quality evidence of altering the clinical course and thus there is no recommendation for or against use of fMRI.

##### Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: fMRI, Functional MRI, Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 1529 articles in PubMed, 146 in Scopus, 50 in CINAHL, 32 in Cochrane Library, 9430 in Google Scholar, and 0 from other sources. We considered for inclusion 5 from PubMed, 2 from Scopus, 3 from CINAHL, 1 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 11 articles considered for inclusion, 5 diagnostic studies and 1 systematic studies met the inclusion criteria.

## Evidence for the Use of Functional MRI

Author Year (Score):	Category:	Study type:	Sample size:	Age/Sex:	Sponsorship/COI:	Area of Body:	Diagnoses:	Type of MRI used:	Type of CT used:	T1 Weighted Images:	T2 Weighted Images:	X-ray:	Myelography:	Morphology:	Surgery Performed:	Clinical Outcomes Assessed:	Long Term Follow-up (mean when noted):	Results:	Conclusion:	Comments:
Zuniga 2014 (5.0)	fMRI	Prospective	N=19	9 males, 10 females; mean Age 22.29 ±7.57	No sponsorship or COI.	frontal, middle line, and occipital regions.	Mild Head injury	1.5 T MRI System	Yes	No	Yes	No	No	No	No	Yes	6 & 12 months	No significant results using spectroscopy.	"The majorly affected groups were pediatric and young individuals. We consider them the most vulnerable. Through our study of PCS, we identified physical and neuropsychological	Data suggest that fMRI can detect PCS in mild head injured patients via frontal lobe changes evidenced in neuro metabolic alterations

																			anomalies affecting the areas of memory and learning.”	which affect memory and learning.
Dettwiler 2014 (4.5)	fMRI	Longitudinal	N=15 (w/Concussion) vs 15 (w/o concussion)	12 males, 3 females; Mean age of 19.8	No sponsorship or COI.	Axial plane	Concussion	3T Siemens	No	Yes	No	No	No	No	No	Yes	Follow-up at 2 days, 2 weeks, & 2 months	Participants with concussion showed a significantly larger amount of activation at 2 days vs 2 months, and between control groups. Blood oxygen level dependent increased in	“The longitudinal nature of this study advances our understanding of the neural correlates of SRC by demonstrating alteration of brain activation subsequent to a return to normal	Data suggest brain activation functions persist 2 months post-TBI but the working memory is comparable to

																		concussed participant during working memory load tasks.	scores on NP tests."	controls.
Palacios 2012 (4.0)	fMRI	Cross-Sectional	N=38 (19 w/ TBI)	22 males, 16 females; control group mean age 27.47 ±6.04 . TBI group mean age 26.78 ±5.55 .	Authors supported by a fellowship from the Institute of Biomedical Research August Pi I Sunyer. No COI.	All planes and regions of brain.	Traumatic Brain Injury.	3T Siemens	No	Yes	No	No	No	No	No	Yes	No	Activation pattern IC1, showed TBI decreased activation in cerebral regions in comparison to control group within the default network (p<0.009). No difference in visual system activation.	"The present study provides strong evidence of the role of structural damage in dysfunctional patterns of working memory and default mode networks in TBI	Data suggest reduced memory performance is likely related to structurally changed white matter alterations in chroni

																	Lower white matter integrity showed a decreased Functional acuity scores (p=0.006). Significant correlation found in TBI patients in the default mode and working memory networks with the accuracy measure p=0.009).	patients. Both structural and functional alterations contribute to working memory deficits.”	c TBI patients seen with fMRI images.
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Diffusion tensor imaging (DTI) is an advanced magnetic resonance imaging technique that is commonly used to evaluate TBI patients [235-247]. DTI can be utilized to study the brain structure on a regional or whole-brain level, including to define white matter tracts [248]. Regional and whole-brain approaches use average diffusion values such as fractional anisotropy (FA) or apparent diffuse coefficient (ADC) is taken from voxels within the regions or tracts [248]. FA and ADC is the degree of water diffusion in the brain, which when resistance in the brain is absent, will yield higher ADC and lower FA values [249].

## Diffusion Tensor Imaging (DTI)

### Recommended.

Diffusion tensor imaging is recommendation for the evaluation of TBI patients.

### Strength of Evidence – Recommended, Evidence (C)

#### Level of Confidence – Low

<i>Indications:</i>	Symptoms of mild TBI, especially with somewhat unclear severity and need to perform imaging to assess ongoing symptoms to identify that there are no abnormalities consistent with TBI on DTI.
<i>Benefits:</i>	Able to help identify existence of abnormalities consistent with TBI on imaging, as well as extent of abnormalities.
<i>Harms:</i>	Potential for misinterpretation when all other tests are normal and then conclusion drawn that permanent injury based on DTI and/or SPECT alone. Potential for confounding based on other brain abnormalities.
<i>Frequency/Dose/Duration:</i>	Single evaluation. Infrequently, second evaluation may be helpful to assess progress and/or residual changes.
<i>Rationale:</i>	There are quality studies assessing DTI for diagnosis of TBI. Most [250] [251, 252] but not all [253] studies suggest it may help identify abnormalities consistent with TBI injuries. One study found a need to adjust results by age, sex and GCS [254]. One study suggests DTI findings are clinically predictive [255] and another suggests long lasting changes are identifiable with DTI [256]. DTI is minimally invasive, has no adverse effects, is high cost, and has some evidence of diagnostic efficacy, thus it is selectively recommended for evaluation of TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: DTI, Diffusion Tensor Imaging, Diffusion Functional Imaging, Diffusion Spectrum Imaging, DSI, Diffusion Weighted Imaging, DWI, Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 324 articles in PubMed, 257 in Scopus, 80 in CINAHL, 18 in Cochrane Library, 13,900 in Google Scholar, and 0 from other sources. We considered for inclusion 5 from PubMed, 2 from Scopus, 1 from CINAHL, 1 from Cochrane Library, 1 from Google Scholar, and 16 from other sources. Of the 26 articles considered for inclusion, 23 diagnostic studies and 3 systematic studies met the inclusion criteria.

### Evidence for the Use of Diffusion Tensor Imaging (DTI)

Author or Year (Score):	Category:	Study type:	Sample size:	Age/Sex:	Sponsorship/COI:	Area of body:	Diagnoses:	SP EC T or SP ET:	MRI or CT:	T1 weighted images:	T2 weighted images:	More than one rater:	Clinical outcomes assessed:	Long term follow-up:	Results:	Conclusion:	Comments:
Lang et al 2015 (4.5)	DTI	Diagnostic	N=108	78 males, 30 females; Mean age Group 1: 34.1±11.3. Group 2: 34.1±10.4 Group 3: 31.6±10.2	This work was primarily supported by the Canadian Institutes of Health Research. No COI.	genus, body, and splenium of corpus callosum; (b) pontine crossing tract, fornix, and middle cerebellar peduncle, corticospinal tract, medial lemniscus, inferior cerebellar peduncle, superior cerebellar peduncle, cerebral peduncle, anterior limb of	Group 1: N=52 patients with TBI with post-concussion syndrome (PCS). Group 2: N=20 patients with TBI, no PCS. Group 3: N=36 Control.	1.5	3T Philips Achieva scanner	No	Yes	No	5 hour neuropsychological assessment which included neurocognitive functioning, self reported mental health, and post concussion symptoms.	No follow up, DTI taken 6-8 weeks past injury.	Significant Differences Tract-based spatial statistics (TBSS) between groups 1 vs 3 in DTI measures of Mean Diffusivity (MD), radial diffusivity (RD) increased in TBI group (p<0.05). TBSS revealed significant white-matter differences between the Group 1 vs group 3.	“In this study, symptoms of depression and anxiety differentiated patients with MTBIs who met criteria for the postconcussion symptom versus those who did not. In contrast, these groups did not differ on diverse metrics of DTI.”	Data suggests change in white matter did not serve as a significant predictor in mild TBI patients.

						<p>internal capsule, posterior limb of internal capsule, retrolenticular part of internal capsule, anterior corona radiata, superior corona radiata, posterior corona radiata, posterior thalamic radiation, sagittal stratum, external capsule, cingulum (cingulate gyrus), cingulum (hippocampus), fornix/stria terminalis, superior longitudinal fasciculus, superior fronto-occipital fasciculus</p>											
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						, uncinate fasciculus , and tapetum.												
Sidaros 2008 (4.5)	DTI	Prospective	N = 60	23 males, 7 females; Mean age of 23.	Study supported by a grant from the Elsass Foundation. No COI.	Posterior limb of internal capsule (PLIC), posterior corpus callosum (PCC), cerebral peduncle (CP), centrum semiovale [188], Putamen (PUT), and cerebrospinal fluid (CSF).	Traumatic brain injury (n=30), healthy controls (n=30).	DTI	MRI	Yes	Yes	No	Glasgow Coma Scale (GCS), fractional anisotropy (FA), apparent diffusion coefficient (ADC), mean diffusivity (MD), axial diffusivity, and radial diffusivity	12 months	At initial scan fractional anisotropy (FA) significantly decreased in regions of interest versus controls (p=0.0000 1).	“Our findings indicate microstructural alterations during the chronic stage of severe TBI, which may represent structural reorganization relevant to clinical recovery. DTI non- invasively provides quantitative pathophysiological information in vivo, and the prospect of tracking white matter microstructure	Data suggest DTI is a TBI biomarker.	

																ctural changes over time holds the promise of measuring neuroplasticity and repair following TBI, which eventually may offer a way of monitoring therapeutic response.	
Betz 2012 (4.5)	DTI	Retrospective	N = 59	43 males, 16 females; Mean Age 37.2±16.8	No sponsors hip or COI.	Internal capsule, genu, splenium, and body of corpus callosum	Severe closed-head trauma. Compared scores to mild traumatic injury controls (n=18)	1.5 Tesla	MRI 1.5 T	Yes	Yes	No	Apparent diffusion coefficient (ADC), fractional anisotropy (FA), axial and radial diffusivity, and Glasgow Coma Scale (GCS).	No	Favorable outcomes associated with higher mean ADC in whole brain white matter (p=0.011). higher axial diffusivity had a strong relationship with favorable	“Our study demonstrated that DTI parameters at the whole-brain level and regional level can provide prognostic information about the discharge	Data suggests that prognostic ability is improved when DTI is adjusted for age, gender and GCS.

																	<p>outcomes (p&lt;0.0001). Poor patient outcome (death or severe injury) was associated with greater heterogeneity in DTI values measured by the coefficient of variation of ADC (p&lt;0.0001) and axial diffusivity (p&lt;0.0001). The genu of the corpus callosum had lower average of ADC (p=0.0068) and axial diffusivity (p&lt;0.0001) which was significantly correlated</p>	<p>status of a patient, while circumventing many problems associated with currently used clinical measures, including the GCS.”</p>	
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															with poor outcomes . DTI at whole brain and regional level correlated with GCS ratings and patient discharge status.		
Murugavel 2014 (4.0)	DTI	Longitudinal	N=37	37 males, 0 females; Mean ages, Group 1: 20.19 ±1.03 Group 2: 19.9± 1.67.	This work was funded by the New Jersey Commission for Brain Injury Research , the American Medical Society for Sports Medicine AMSSM Foundation, the Goldstein Family Fund, and the	The regions implicated are all in the right hemisphere, posterior limb of the internal capsule (IC), retroventricular part of the IC, sagittal stratum (inferior longitudinal fasciculus and inferior fronto-occipital	(N=21) male collegiate athletes that play contact sports (Concussion) (N=16) noncontact sport male athletes.	3.0 T MRI	3.0 T MRI	Yes	No	No	athletic history, physical exam, and baseline NP testing, including SCAT2 and Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT).	2 days, 2 weeks , 2 months.	Radial Diffusivity (RD) 2 days vs 2 wks showed decrease in concussed group (p=0.025). RD higher in concussed group @ 2 days (p=0.002). fractional anisotropy (FA) values lower in concussed group at 2 days (p=0.0008 ), and at 2	“This study provides support for the hypothesis of increased RD and reduced FA within 72 h post injury followed by patterns of recovery. ...RD was found to be a sensitive marker of SRC with potential for	Data suggest RD is a sensitive measure of sports-related concussion injuries and shows reduced RD as well as FA within 72 hours post-TBI.

					Peter & Cynthia Kellogg Foundation. No COI.	fasciculus), and anterior thalamic radiation									months (p=0.044).	personalized imaging-based diagnosis.	
Perlbarg 2009 (4.0)	DTI	Prospective	N = 30	28 males, 2 females; mean Age of 37±12	No mention of sponsorship or COI.	Inferior longitudinal fasciculus (ILF), posterior limb of internal capsule (PLIC), posterior corpus callosum (PCC), cerebral peduncle (CP)	Severe traumatic brain injury (n=30), split by unfavorable outcome at 1-year (n=15) and favorable 1-year outcome (n=15)	DTI 1.5 T	MRI	Yes	Yes	No	Glasgow Coma Scale (GCS), fractional anisotropy (FA), apparent diffusion coefficient (ADC)	No	FA was significantly lower (p<0.05) for the unfavorable outcome group compared to favorable in the ILF, CP, PLIC, and PCC. No ADC differences were seen between both outcome groups (p>0.05). Authors concluded that FA was a relevant biomarker for predicting TBI outcomes.	"This article confirms that FA measured in several specific brain areas is a relevant biomarker for early outcome prediction in TBI."	Data suggest ADC is not a good marker for the 1 year prognostic outcome reduced FA is associated with a poorer outcome and FA measurements show good sensitivity and specificity.

Kumar 2009 (4.0)	DTI	Diagnostic	N = 83	62 males, 21 females; Mean Age 34.25 ±10.28	Sponsored by Indian Council of Medical Research. No COI.	Corpus Callosum; Frontal, temporal, parietal, and occipital	Mild (n=26) and moderate (n=57) traumatic brain injury	1.5 T	1.5 T MRI	Yes	Yes	No	Neuropsychological tests: figure connection, picture completion, digit symbol test, block design test, picture arrangement, object assembly	6 months	Across all neuropsychological tests healthy controls compared to mild and moderate brain injury performed significantly better (p=0.00). Diffusion tensor imaging abnormalities in the corpus callosum for those with moderate brain injury were positively correlated with worse outcome after 6 months.	"It is concluded that DTI abnormalities in the regions of CC (Corpus Callosum) were more in patients with moderate TBI compared to mild TBI and predicted a trend towards worse outcome at 6 months, as suggested by neuropsychological scores."	Data suggest DTI abnormalities more prevalent in CC regions of moderate TBI patients vs mild TBI patients and these findings were associated with a poor outcome 6 months post injury.
Farbota 2012 (4.0)	DTI	Prospective	N = 21	14 males, 7 females; TBI	This study was supported by a	Superior longitudinal fasciculus (SLF),	Traumatic brain injury (n=12) and	DTI 3.0 T	MRI 3.0 T	Yes	Yes	No	Fractional anisotropy (FA), axial diffusivity	Visit 1 (mean =63 days), visit 2	TBI patients had a significant decrease	"In this study, we show that TBI patients	Relatively small sample. Data suggest

				mean age 35.0±12.8 vs 29.2± for control.	Merit Review Grant from the Department of Veterans Affairs, NIH, and by William S Middleton Memorial Veterans Hospital. No COI.	interior longitudinal fasciculus (ILF), internal/external capsule, fornix, corpus callosum, uncinate fasciculus (UF), cerebral peduncle.	healthy controls (n=9).						(AD), radial diffusivity (RD), visuomotor speed (SS), neuropsychological tests, Glasgow Coma Scale (GCS)	(mean =318 days), and visit 3 (mean =1187 days).	in FA in the corpus callosum from visit 1 to 2. There was no significant correlation between GCS scores and regional white matter FA during any of the time points. The TBI group did not have greater FA during any of the time points of regions.	exhibit longitudinal WM changes that continue for at least four years post-injury.”	TBI patients exhibit WM changes for at least 4 years post-injury. Suggesting TBI is a prolonged disease state.
Rutgers 2008b (4.0)	DTI	Prospective	N=50	27 males, 12 females; Mean 34±12	This work was supported by the Institut pour la Recherche sur la Moelle	Corpus callosum : genu, body, and splenium .	Mild traumatic brain injury (n=24), moderate TBI (n=9), severe TBI (n=6)	DTI	MRI	Yes	Yes	No	Glasgow Coma Scale (GCS), fractional anisotropy (FA), apparent diffusion coefficient (ADC)	No	Compared to healthy controls patients with mild traumatic injury showed no significant difference	“Our study shows that there are local differences in DTI characteristics within the corpus	Data suggest that mild TBI is associated with DTI abnormalities in the





## Dynamic Imaging

Single-photon emission computerized tomography (SPECT) or single-photon emission tomography (SPET) is a neuroimaging technique that detects cerebral blood flow (CBF) and brain metabolism. SPECT has been used for diagnostic testing in TBI patients [257-262].

### Single-Photon Emission Computerized Tomography (SPECT)

#### No Recommendation.

There is no recommendation for or against the use of SPECT in the evaluation of TBI patients.

#### Strength of Evidence – No Recommendation, Insufficient Evidence (I)

##### Level of Confidence – Low

###### Rationale:

There are quality studies assessing SPECT for diagnosis of TBI. SPECT has been previously used to detect brain death [263], although that is no longer a typical use. Data are somewhat conflicting regarding the usefulness of SPECT. While quality data suggest SPECT is superior to CT for detecting parenchymal lesions, data conflict regarding whether SPECT is superior to MRI for detection of parenchymal TBI findings [264] [265] [266] or not superior [267]. SPECT has been used to attempt to objectify subjective complaints [268] [269] [270]. A few studies suggest SPECT findings are predictive of clinical outcomes [271] [272] [268] [273] [274]. SPECT is not invasive has no adverse effects, is high cost, has no clear evidence of diagnostic efficacy for TBI and thus there is no recommendation.

###### Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Single-photon emission computerized tomography, SPECT, SPECT scan, SPET, Single-Photon Emission Computer-Assisted Tomography, Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma; Sensitivity and Specificity, Predictive Value of Tests, Gold-standard, accurate, accuracy, precision, precise, test; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 60 articles in PubMed, 40 in Scopus, 20 in CINAHL, 21 in Cochrane Library, 40 in Google Scholar, and 22 from other sources. We considered for inclusion 7 from PubMed, 2 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 22 from other sources. Of the 32 articles considered for inclusion, 30 diagnostic studies and 2 systematic studies met the inclusion criteria.

**Evidence for the Use of Single-Photon Emission Computerized Tomography (SPECT) or Single-Photon Emission Tomographic (SPET)**

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Sponsorship/COI</i>	<i>Area of head:</i>	<i>Diagnoses:</i>	<i>SPECT or SPET:</i>	<i>MRI or CT:</i>	<i>More than one rater:</i>	<i>Surgery Performed:</i>	<i>Clinical outcomes assessed:</i>	<i>Long term follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Newton 1992 (7.5)	SPECT	Prospective	N = 19 with severe head injury	Mean age of 29 years old. 4 Females, 15 Males	No mention of sponsorship or COI	Coronal, transverse, and sagittal plane imaging	Closed head injury	SPECT TC-99m Tc-HMPAO	CT - GE 9000 and MRI-0.8 Tesla	No	No	Yes	No	In the nineteen patients 43 perfusions were detected using SPECT, 21 focal lesions were shown by MRI, and 13 by CT scan. Both CT and MRI did not show a left hemisphere lesion, but SPECT showed a perfusion defect	“We conclude that SPECT reveals areas of cerebral damage, which may be either contusional or ischaemic, frequently not shown by CT or MRI. Defects on SPECT may correlate with focal neurolo	Pilot study. Data suggests SPECT detects cerebral damage undetected by either MRI or CT. The most neurologically disabled patient show the greatest number of lesions.

														in the left parietal region.	gical deficit. The most disabled patients tend to show the most number of lesions on SPECT.”	
Joglekar 2014 (7.0)	SPECT	Retrospective	N = 63 patients who had undergone SPECT	Mean age of 59 years old. 40 Females, 23 Males	No mention of sponsorship or COI.	Brain	Head trauma, tinnitus, vertigo, or a combination	SPECT	Both	Yes	No	No	Not mentioned	Abnormalities were found in 15 of 63 SPECT scans, 16 of 62 MRIs, and 14 of 60 CTs. Out of the three test, MRI was the most sensitive for all three diagnoses. 13 of 60 exhibited areas of cerebral	“We conclude that SPECT may be a valuable complementary diagnostic modality for making a comprehensive neurologic evaluation and that it may detect abnormalities in some	Data suggest SPECT may be useful as an adjunct test combined with MRI or CT.

														hypofusion on SPECT, but their MRI and CT scans were normal.	patients whose other imaging is read as normal. However, we did not find that SPECT was the most sensitive of the three modalities in neurologic evaluation, as we had previously found in a preliminary study that the senior author (R.T.S.) published in 1996."	
Munari 2005 (6.5)	SPECT	Prospective Study	N = 20 clinically brain	Mean age of 43.3 years	No sponsorship or COI.	Brain	Brain Dead	SPECT – Triple -	CT	No	No	No	Not mentioned	Both angiography and SPECT	"Our results confirm the	Data suggest SPECT is a

			dead patients	old. 10 Females, 10 Males				headed gamma-camera (IRIX)						confirmed all 19 patients with BD. Contrast angiography showed slight and late filling of the cerebral arteries. SPECT showed weak perfusion of the brain stem and posterior part of the brain.	reliability of SPECT in the diagnosis of BD; because SPECT is noninvasive, it is a good candidate for the "gold standard" of diagnosis.	useful non-invasive imaging tool for diagnosing brain death.
Bavetta 1994 (6.5)	SPECT	Prospective	N = 10 with significant head injury	Mean age of 29.4 years old. 2 Females, 8 Males	Sponsored by the Saint Bartholomew's Joint Research Board. No mention of COI.	Temporal, frontal, basal ganglia, parieto-occipital, parietal, extracerebral	Severe closed-head injury	SPET 99m-Tc HMP AO	Non-enhanced CT and MRI 0.08 Tesla	No	No	Yes	No	In SPET 32 lesions were detected 10 patients, 10 lesions in CT, and 14 lesions in MRI. Of the 32 detected	"The results suggest that lesions in the temporal lobes, frontal lobes and basal ganglia are related to poor	Small sample. Data suggest SPET yields more useful prognostic data than either MRI or CT followi

														by SPET, 22/32 were only found on SPET, 6/32 were found on CT or MRI.	prognosis and that SPET yields more useful prognostic data than the other methods.”	ng severe close head injury.
Roper 1991 (6.0)	SPECT	Prospective	N = 15 patients with acute closed-head injury	Mean age of 32 years old. 1 Female, 14 Male	No mention of sponsorship or COI	Frontotemporal, parietal, frontal, occipital	Acute closed-head injury	SPECT <sup>99m</sup> Tc HMPAO	X-ray CT scan	Yes	No	Yes	No	There were a total of 44 focal lesions found in 15 patients. 15/44 were found on both CT and SPECT. 12/44 were seen on CT only and 17/44 on SPECT.	“This study shows that SPECT can detect focal disturbances of cerebral blood flow that are not seen on x-ray tomography. It also suggests that there are two types of contusions: those with a	Small sample. Data suggest SPECT can detect focal disturbances with cerebral blood flow not seen with CT.

																decreased cerebral blood flow (i.e., detectable on SPECT) and those with a cerebral blood flow equal to that of the surrounding brain."	
Jacobs 1994 (5.5)	SPECT	Prospective	N = 67 closed cranial trauma	Mean age of 35 years old. 26 Females, 41 Males	No mention of sponsorship or COI.	Transaxial, coronal and sagittal plane imaging.	Closed cranial head trauma	SPECT 99mTc HMPAO	CT	No	No	Yes	3 months	For those with moderate head trauma the initial SPECT revealed abnormalities in 25/42, CT found 10/42, and 17/42 had normal SPECT evaluation	"Our results show that:[170]SPECT alterations correlate well with the severity of the trauma; (2) a negative initial SPECT study is a reliable predictor	Data suggest SPECT alterations correlate with the severity of head trauma and negative SPECT results suggest a favorable	

																	ons. For those with middle head trauma SPECT revealed 9/25 had abnormalities and 16/25 were normal.	r of a favorable clinical outcome; (3) in cases with a positive initial SPECT, a follow-up consisting of a combination of SPECT and clinical data is necessary; (4) in patients suffering from post-concussive symptoms, SPECT offers an instrument to objective sequela e"	patient outcome.
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Lorberboym 2002 (5.5)	SPECT	Prospective	N = 16 with head injury	Mean age of 31.6 years old. 4 Females, 12 Males	No mention of sponsorship or COI.	Transaxial, coronal, and sagittal plane imaging.	Mild to moderate head trauma	SPECT 20mCi of 99mTc HMPAO	No	No	No	Yes	No	All patients had no abnormal CT scan. SPECT revealed that 12/16 had regional perfusion abnormalities and 8/12 had more than one abnormality. SPECT results significantly predicted amnesia severity (p<0.001) and accounted for 84% of the amnesia variation.	"Amnesia after mild head injury is associated with a high incidence of early regional cerebral perfusion abnormalities. Amnesia lasting more than half an hour is associated with bilateral cerebral hypoperfusion. SPECT evaluation in the ED may be a useful additional tool in the objective	Small sample. Data suggest SPECT may be useful in the assessment of post-traumatic amnesia.
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															assessment of PTA.”	
Romeo 2015 (5.5)	SPECT	Case Control	N = 84 patients with mTBI	Mean age of 32.1 years old. 29 Females, 55 Males	Sponsored by the Canadian Institute for Health Research. No mention of COI.	Brain	TBI	SPECT – Prism 3000 XP	Neither	Yes	No	No	Follow up 1 year after baseline.	There was a negative association (P = 0.03) between SPECT perfusion and Stroop scores at baseline and follow up. SPECT scans categorized as normal or abnormal had no difference on any cognitive measure or symptom scale.	“SPECT scans categorized as normal or abnormal by radiologists did not differentiate cognitively impaired from intact subjects. These results demonstrate the clinical utility of SPECT in mild TBI, but only when data are subjected to blood flow quantification	Data suggest SPECT may be useful in predicting cognitive traction.

															analysis.	
Stamatakis 2002 (5.5)	SPECT	Prospective	N = 61 head injured	Mean age of 27.6 years old. No mention of sex distribution	Sponsored by the Chief Scientist Office. No mention of COI.	L/R frontal gyrus, L/R cingulate, L/R parietal lobule, corpus callosum	Acute head trauma	SPECT <sup>99m</sup> Tc - HMP AO	MRI 1.5T T1 and T2-weighted	No	No	Yes	6 months	SPECT detected more abnormalities than MRI. The average lesion volumes of focal (56.31 vs. 53.93) and diffuse (12.61 vs 5.68) on SPECT and MRI. The volume was not significant at acute (p<0.32), but was significant at follow-up (30.39 vs 18.82; p<0.001).	“ SPM has a role in SPECT image interpretation because it allows better visualization than other methods of quantitative analysis of the spatial distribution of abnormalities in focal and diffuse head injury. Frontal lobe blood flow abnormality (particularly	Data suggest statistical parametric mapping (SPM) has some role in the interpretation of SPECT imaging as it enhances the visualization of abnormalities.

																anterofrontal regions and mesiofrontal areas) is common after head injury."	
Jacobs 1996 (5.5)	SPECT	Prospective	N = 136 patients with closed-cranial trauma	Mean age of 36 years old. 51 Females, 85 Males	No mention of sponsorship or COI.	Left temporal/frontotemporal Left temporoparietal L/R frontal L/R parieto-occipital	Closed-cranial trauma	SPECT <sup>99m</sup> Tc HMPAO	No	No	No	Yes	12 months	At the 3-month follow-up 37/136 (27%) had positive clinical evaluations and 45/139 (33%) had positive SPECT. At 6-months 18/136 (13%) had positive clinical evaluation and 29/136 (21%) had positive SPECT.	"A normal <sup>99m</sup> Tc-HMPAO SPECT scan is a reliable tool in the exclusion of clinical sequelae of mild head injury. At 12 mo. post injury, a positive SPECT study is also a reliable predictor for clinical	Data suggest that at 12 months post mild head injury a positive SPECT result is a reliable predictor for outcome.	

														At the final 12-month follow-up 9/136 (7%) had positive clinical evaluation and 12/136 (9%) had positive SPECT results.	outcome.”	
Ichise 1994 (5.5)	SPECT	Prospective	N = 46 with TBI or control	Mean age of 30.9 years old. 21 Females, 25 Males	Sponsored by Sterling-Winthrop Imaging Research Institute Grant. No mention of COI.	Frontal, temporal, parietal, and occipital lobes, cerebellum and subcortical grey matter	Minor traumatic brain injury (n=15) and major traumatic brain injury (n=14). Normal control (NC) group had (n=17).	SPECT <sup>99m</sup> Tc HMPAO	CT non-enhanced and MRI 1.5 Tesla T1 and T2-weighted	No	No	Yes	No	3/17 in the NC had abnormalities. In the TBI patients 19/29 (66%) had abnormal SPECT, 13/29 (45%) abnormal MRI, and 10/29 (34%) had abnormal CT scan. SPECT detected 42	“ In evaluating chronic TBI patients , HMPAO SPECT, as a complement to CT or MRI, may play a useful role by demonstrating brain dysfunction in morphologically intact	Data suggest SPECT complements either CT or MRI to assist in determination of the morphology of brain dysfunction.

														abnormalities in 19/29 TBI patients, 33/42 (79%) were focal cortical perfusion deficits with no CT or MRI shard findings. CT and MRI detected diffuse cortical atrophy in 7/29 TBI patients that SPECT did not detect. All CT lesions were detected by MRI.	brain regions and providing Objective evidence for some of the impaired NP performance”	
Gray 1992 (5.0)	SPECT	Prospective	N = 53 with TBI	For Controls (N = 14): Mean age of	No mention of sponsorship or COI.	L/R frontal, temporal lobes, corpus callosum, L/R parietal and	Traumatic brain injury (in the last 6 months).	SPECT <sup>99m</sup> Tc HMPAO	X-ray CT scan	No	No	Yes	No	The healthy controls did not reveal any	“In the evaluation of TBI patients ,	Data suggest SPECT more sensitive than

				32 years old. 7 Females, 7 Males. Gender and age not given for TBI Group.		occipital regions.	Minor TBI (n=20) Major TBI (n=33) Excluded those with more than one TBI, drug/alcohol abuse, and neuropsychiatric problems. Health control group (n=14)							abnormalities. In the TBI patients regional cerebral blood flow (rCBF) was not abnormal, but focal and/or diffuse deficits were found in 42/53 (80%). CT scan revealed 29/53 patients had morphological abnormalities. The CT and SPECT concordance was 11/20 (55%) in the minor TBI and 27/30 (82%)	HMPAO SPECT is a useful technique to demonstrate regional brain dysfunction in the presence of morphological integrity as assessed by CT."	CT for detection of abnormal finding in patient with a history of mild TBI.
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														for major TBI.7/33 major TBI patients had abnormalities on SPECT, but normal CT scan.		
Amen 2015 (5.0)	SPECT	Retrospective Study	N = 20746 neuropsychiatric patients	Mean age of 39.5 years old. 10100 Females, 10646 Males	No sponsorship. COI: Author TH is President and owner of Dr. Theodore Henderson, Inc. and the Synaptic Space and co-owner of NeuroLuminance Corp. DA is the owner of Amen Clinics Inc and	Brain	TBI	High resolution Picker (Philips) Prism XP 3000 triple-headed camera.	None	Yes	No	No	Not mentioned	All PTSD regions were more active than the TBI regions. The two TBI/PTSD model produced similar sensitivity, specificity, and accuracy that ranges from 1% to 11%. PTSD shows an increase in perfusion,	“This study demonstrates the ability to separate PTSD and TBI from healthy controls, from each other, and detect their co-occurrence, even in highly comorbid samples, using SPECT. This	Data suggest SPECT may be beneficial in distinguishing PTSD from TBI.

					KW and DT are employed by Amen Clinics Inc									particularly in the frontal lobe. TBI showed a decrease in perfusion compared to PTSD.	modality may offer a clinical option for aiding diagnosis and treatment of these conditions”	
Mitchener 1997 (5.0)	SPECT	Prospective	N = 32 patients with a closed head injury	Mean age of 31 years. 5 Females, 27 Males	No mention of sponsorship or COI	Frontal, anterior/posterior temporal, occipital, parietal	Closed-head injury.	SPECT <sup>99m</sup> Tc HMP AO	CT and MRI 1.5 Tesla T1 and T2 weighted	No	No	Yes	6 months	CT identified 45 lesions in 27/32 patients. SPECT showed 49 perfusion deficits in 30/32 patients. 22/49 perfusions appeared normal on CT scans. 48 lesions were detected by late MRI (4-6 months	“ Our study has shown that, although on some occasions the presence of lesions on SPECT, MRI, or both can help to explain a poor clinical outcome, it is not necessarily an indicatio	Data suggest that at 6 months post head injury SPECT abnormalities correlate with clinical outcome.



															impact. This is the subject of further investigation."	
Gowda 2006 (5.0)	SPECT	Prospective	N = 92 with mTBI	Mean age of 27.6 years old. 17 Females, 75 Males	No mention of sponsorship or COI	Temporal lobe, temporal lobe, basal ganglia and thalamus, parietal lobes, cerebellum, occipital lobe.	Mild traumatic brain injury (mTBI).	SPECT <sup>99m</sup> Tc -ECD	CT	No	No	Yes	No	All underwent SPECT and CT. 58/92 had perfusion abnormalities. 29/58 had positive and 29/28 had negative CT scan. 34/92 had negative findings and of those 2/34 had positive and 32/34 had negative CT scan.	"Tc99m-ECD SPECT can be used as a complementary technique to CT in initial evaluation of patients with MTBI. It is particularly useful in patients having PCS, LOC, or PTA with normal CT scan."	Data suggest SPECT may be used in addition to CT in the evaluation of patient with mild TBI.

Kant 1997 (5.0)	SPECT	Prospective	N = 43 with TBI	Mean age of 34.9 years old. 12 Females, 31 Males	No mention of sponsorship or COI	Frontal, parietal, and temporal lobes.	Mild closed head injury (loss of consciousness less than 20 minutes)	SPECT <sup>99m</sup> Tc - HMPAO	CT, MRI and EEG.	No	No	Yes	No	23/23 had abnormal SPECT findings with 37 lesions detected. 39/43 underwent MRI scans that found abnormalities on 3/39. 21/43 underwent CT scan with 2/21 having abnormalities. 33/43 had EEG and 3/33 had abnormal findings. 2/3 abnormal EEG findings had normal MRI, CT, and	“We conclude that SPECT scan is more sensitive than MRI or CT scan in revealing the number of cerebral lesions after mild head injury in patients who are suffering PPCS. It could be a useful investigational tool in patients with PPCS who have normal MRI and/CT scan of the brain.”	Data suggest SPECT is more sensitive in imagining the number of brain lesions in mild head injured patient compared to both MRI and CT.
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														SPECT scans.		
Abu-Judeh 1999 (4.5)	SPECT	Prospective	N = 32 patients with mTBI	Mean age of 42 years old. 17 Females, 15 males	No mention of sponsorship or COI	Frontal lobe, thalami and basal ganglia, temporal lobes, parietal lobes.	Mild traumatic brain injury (mTBI).	SPET <sup>99</sup> Tc-HMPAO	Neither	No	No	Yes	3 months	19/32 had abnormal SPET with 17/19 having a total of 48 focal lesions. Frontal lobes. 26/32 had headaches. Patient complaints: 15/32 memory deficits, 13/32 dizziness, sleep disorders 8/32, generalized weaknesses 7/32, visual complaints 5/32, depression 2/32, and hearing	“Our findings suggest that there are significant brain perfusion abnormalities in symptomatic patients who sustain an mTBI injury without loss of consciousness in the absence of X-ray CT abnormalities. We also stress the importance of early SPET brain perfusion	Data suggest SPET imaging is more sensitive than CT for evaluating cerebral perfusion post mild TBI.

														difficulties 1/32.	n imagining in these patients because the incidence of brain perfusion abnormalities was higher in patients imaged less than 3 months post-injury compared to those imaged more than 3 months from the date of the accident."	
Nedd 1993 (4.5)	SPECT	Prospective	N = 16 with TBI.	Mean age of 37.44 years old. 4 Femal	No mention of sponsorship or COI	Frontal hemisphere	Mild to moderate traumatic brain injury	SPECT <sup>99m</sup> Tc - HMP AO	CT 9800	No	No	Yes	No	SPECT detected regional cerebral blood flow	The results in this indicated that in patients	Small sample size. Data suggest SPECT



														SPECT detected decreases in rCBF for 5/8 with fractures.		
Hofman 2001 (4.5)	SPECT	Prospective	N = 21 with mTBI	Mean age of 22.8 years old. 9 Females, 12 Males	No mention of sponsorship or COI.	Temporal lobe and frontal lobe.	Mild traumatic brain injury (mTBI)-closed head injury	SPECT Tc99m-HMPAO	MRI 1.5 Tesla T2 FLAIR	No	No	Yes	6 months	21 underwent MRI and 18 SPECT. 11/28 (61%) had abnormal SPECT findings and 12/21 (57%) had abnormal MRI findings. 77% of patients had either an abnormal MRI or SPECT imaging.	“Brain lesions are common after mTBI; up to 77% of patients may have abnormal findings either on MR images or SPECT scans, and these lesions may lead to brain atrophy. The association between hypoperfusion	Data suggest approximately ¼ of TBI patient may have MRI or SPECT imagery showing abnormal finding which “may” lead to brain atrophy. Also, there is an association between hypoperfusion visualized on

															seen on acute SPECT and brain atrophy after 6 months suggests the possibility of (secondary) ischemic brain damage. There is only a weak correlation between neuroimaging findings and neurocognitive outcome.”	acute SPECT and brain atrophy after 6 months suggesting there may be secondary ischemic brain damage.
Raji 2015 (4.5)	SPECT	Retrospective	N = 196 patients	Mean age of 42.1 years old. 28 Females,	No mention of sponsorship. No COI.	Brain	TBI and/or PTSD	SPECT – High resolution Picker (Philips) Prism	Neither	No	No	No	Not mentioned	Quantitative SPECT distinguished veterans with PTSD from	“ This study demonstrates the ability to separate PTSD	Data suggest SPECT imaging can be used to differentiate

				168 Males				XP 3000 triple headed gamma camera						those with TBI with an accuracy of 87-94%. Distinguishing PTSD from those with PTSD and TBI has an accuracy of 85-92%. PTSD had increased perfusion in the brain while TBI had a decreased perfusion.	and TBI from each other in a veteran population using functional neuroimaging.”	PTSD from TBI by examining DMN acuity.
Atighechi 2013 (4.5)	SPECT	Prospective Study	N = 63 with head injuries	Mean age of 32.5 years old. 18 Females, 44 Males	No mention of sponsorship or COI	Brain	Head trauma	SPECT – Double detector device	MRI – 1.5-T Siemens	Not mentioned	No	No	Not mentioned	MRI and SPECT had similar specificity and sensitivity for both anosmia	“According to our study, both brain MRI and SPECT have high	Data suggest both MRI and SPECT have good sensitivity and

				1 missing gender										and hyposmia (87.7, 82.1 vs 87.7, 85.7, 85.7, 66.7 vs 85.7, 81.25, respectively). Both have similar PPVs but SPECT has a higher NPV. When both are used together, it increases the accuracy.	sensitivity and specificity in the diagnosis of traumatic anosmia, although brain SPECT is slightly superior to MRI. If the two techniques are applied together, the accuracy will be increased.”	specificity for detection of olfactory dysfunction post TBI but SPECT trended toward a slightly better result.
Dhandapani 2014 (4.5)	SPECT	Case Control	N = 53 patients with a closed head injury	Mean age of 33 years old. 9 Females, 44 Males	No sponsorship or COI.	Brain	Head injury	SPECT – Dual-headed rotating scintillation gamma camera	CT	No	No	No	Not mentioned	There was a non-significant association between SPECT and MRS findings (P = 0.81).	“To conclude, ECD-SPECT seems to have greater sensitivity, incremental validity and	Data suggest SPECT has better sensitivity than MRS in some types of patients with

														The more severe the injury, the greater number of patients with MRS and SPECT abnormalities. SPECT had more abnormalities than MRS.	prognostic value than single voxel proton MRS in select patients with head injury, with only severe hypoperfusion in SPECT significantly associated with unfavorable outcome independent of other confounding factors"	moderate head injuries which may help guide treatment and predict prognoses.
Masdeu 1994 (4.5)	SPECT	Prospective	N = 41 subjects with head trauma, HIV encephalopathy or are healthy.	Mean age of 39.3 years old. 15 Females, 26 Males	No mention of sponsorship or COI.	Inferior basal ganglia, upper thalamic, frontal lobe and posterior temporooccipital region.	Mild head trauma (n=14) HIV encephalopathy (n=12) Normal	SPECT <sup>99m</sup> -Tc HMPAO	All 14 head trauma had negative CT	2	No	Yes	No	In head trauma patients 4/14 were read by both raters as having HIV	"SPECT is more sensitive than CT in detecting brain injury after mild	Data suggest SPECT is a more sensitive imaging tool compar

							control (n=15)		scans					encephalopathy. 10/14 head trauma patients had abnormal scans. None of the normal controls were classified as having trauma, but 3/15 for rater 1 and 5/15 for rater 2 were classified as having HIV encephalopathy.	head trauma."	ed to CT in the detection of brain injury post mild head trauma.
Abdel-Dayem 1987 (4.0)	SPECT	Prospective	N = 19	No mention of mean age or sex distribution	No mention of sponsorship or COI.	Left and right cerebral hemispheres	Acute traumatic head injury	SPECT <sup>99m</sup> Tc - HMPAO	CT	Yes	No	No	No	14 trauma patients and 5 healthy volunteer (controls). SPECT detected 54 lesions	"Tc-99m-HM-PAO SPECT was shown to have the following advantages: It	Small sample. Data suggest cerebral perfusion changes correlated to

														on 14 of the trauma patients and 54 lesions with CT scan. All 54 lesions were correlated with clinical examinations and considered true-positive by both raters. 16/22 lesions found on CT were also found with SPECT.	reflected perfusion changes, was more sensitive than CT in demonstrating more lesions, and demonstrated lesions at an earlier stage than those demonstrated with CT.”	lesions which then determined progress.
Prayer 1993 (4.0)	SPECT	Prospective	N = 18 with severe closed head injury	Mean age of 31 years old. 7 Females, 11 Males	Sponsored by Ludwig Boltzmann Institute for Radiological Tumor Diagnosis	Frontal lobe, temporal lobe, parietal lobe, occipital lobe, cerebellar hemisphere	Severe closed head trauma	SPECT <sup>99m</sup> Tc HMPAO	CT and MRI 1.5 Tesla T1 and T2-weighted	No	No	Yes	36 months	17/18 had cortical contusions and 9/18 diffuse axonal injury on MRI. 105 lesions	“Our results strongly suggest that in patients with subacute or chronic severe	Small sample size. Data suggest MR in combination with SPECT. Increases

					s. No mention of COI.									were found in 18 patients using MRI. With SPECT reduced cortical cerebral blood flow was seen in 16/18. Hypofusion of white matter was found in 13/18 patients.	closed head injury and normal cranial CT; MR imaging and SPECT will provide important information regarding posttraumatic brain damage.	es the ability to assess post-traumatic brain damage.
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Positron emission testing (PET) is a test that attempts to demonstrate physiological or functional defects in the brain and has been used in TBI patients [275-280].

## **Positron Emission Test (PET)**

### **No Recommendation.**

There is no recommendation for or against the use of PET in the evaluation of TBI patients.

### **Strength of Evidence – No Recommendation, Insufficient Evidence (I)**

#### *Level of Confidence – Low*

*Rationale:*

There are few quality studies assessing PET for diagnosis of TBI. PET is not invasive, has no adverse effects, is low cost, has limited evidence of diagnostic efficacy in TBI [280] without quality evidence the test alters the clinical course and thus there is no recommendation for or against PET for diagnosis of TBI.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Positron-Emission Tomography, Traumatic brain injury, Intracranial injury, Closed Head injury Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 20 articles in PubMed, 10 in Scopus, 10 in CINAHL, 10 in Cochrane Library, 30 in Google Scholar, and 5 from other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 5 from other sources. Of the 7 articles considered for inclusion, 6 diagnostic studies and 1 systematic studies met the inclusion criteria.

## Evidence for the Use of Positron Emission Test (PET)

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnosis:	Comparison:	Results:	Conclusion:	Comments
Coles 2004 (4.0)	PET	Case-Control	Sponsored by Medical Research Council, UK Government, Royal College of Anesthetists of Anesthesia, Research Training Fellowship, Wellcome Foundation and Veverley and Raymond Sackler Studentship award. No mention of COI.	22 Patients	Mean age of 30 years old 4 Females, 18 Males	Head Injury	Head Injury (N = 12) – Head injury within last 24 hrs.  Vs  Control (N = 10) – Healthy volunteers	The voxel-based technique suggests that a large portion of the cortex ipsilateral to the lesions is at risk for ischemic damage and neuronal loss. Statistically significant increases in IBV were produced in the control sets when comparing a mean CBF of 37 with reduced CBF of 20, 10 and 5 (All three were P < 0.05)	“This study shows that voxel-based analysis of PET OEF maps is sensitive at defining tissue at risk of ischemic injury after early head injury”	Data suggest PET maps are useful tools in defining and quantifying brain ischemia post TBI.
Steiner LA, 2003 (4.0)	PET	Cohort	Sponsored by Myron B. Laver Grant, Margarete and Walter Lichtenstein-Stiftung grant, Overseas Research Student Award,	N=20	Mean age was 33 years old. Mean age of 33 years old. No mention of sex distribution.	TBI	All patients admitted to the Neurosciences Critical Care Unit with severe (admission Glasgow Coma Score [GCS] 8) or moderate (admission	TCD FV <sub>m</sub> correlated significantly with PET CBF in both hemispheres (CPP 70 mm Hg: left, r <sub>2</sub> =0.24, P< 0.03; right, r <sub>2</sub> =0.33, P<0.01; pooled, r <sub>2</sub> =0.23, P<0.002; CPP 90 mm Hg: left, r <sub>2</sub> =0.33, P 0.01; right, r <sub>2</sub> =0.36, P< 0.01;	“[T]he static rate of autoregulation calculated from TCD data and PR <sub>x</sub> provide useful information on autoregulation in head-injured patients. Studies grading	Data suggest some variability in autoregulation methods but SROR <sub>PET</sub> and PR <sub>x</sub> may be of some benefit in approximating auto autoregulation

			Wellcome Research Training Fellowship, Beverley and Raymond Sackler Studentship, Codman grant, and the UK government. No mention of COI.				GCS 12) traumatic brain injury, with secondary neurological deterioration requiring intubation and mechanical ventilation, were eligible for included in the study.	pooled, $r^2=0.34$ ; $P<0.0001$ ). There was a significant correlation between SRORPET and SRORTCD (left, $r^2=0.53$ , $P<0.001$ ; right, $r^2=0.32$ ; $P<0.01$ ), suggesting that SRORTCD is a useful approximation of autoregulation within the MCA territory.	autoregulation on that basis of changes in AJDO2 need to be interpreted with caution. PRx seems to be a more robust estimator of autoregulation than Mx. More data are needed to validate Mx. At least when our methods are used, all measurements may be influenced by flow-metabolism coupling."	in head injured patients.
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## Vascular Imaging

Vascular imaging tests are diagnostic tests that use high frequency waves to view blood flow of vessels. These tests encompass a few different types including: arteriography, ultrasound, noninvasive vascular assessment, and brain acoustic monitor [281]. Digital subtraction angiography has been used to detect vessel injury after penetrating brain injuries [282].

### Vascular Imaging Tests

#### Recommended.

Vascular imaging tests are recommended for the evaluation of TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

<i>Indications:</i>	Symptoms and/or signs consistent with vascular injury
<i>Benefits:</i>	Identify treatable condition(s)
<i>Harms:</i>	Adverse effects of the procedure, including bleeding, vascular injury for the invasive procedures.
<i>Frequency/Dose/Duration:</i>	Usually only one assessment is needed. Tests include diagnostic ultrasound, arteriography, magnetic resonance angiography (MRA) and CT.
<i>Rationale:</i>	There are few quality studies assessing Vascular Imaging Tests for diagnosis of and effects of TBI. Vascular Imaging tests are invasive have adverse effects, are high cost, have some evidence of diagnostic efficacy, and are selectively recommended for diagnosis of vascular problems associated with TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Vascular Imaging Tests, Arteriography, Venography, Noninvasive Vascular Assessment, NIVA, Brain Acoustic Monitor, Traumatic Brain Injury, Closed Head Injury, Penetrating Head Injury, Concussion, Craniocerebral Injury, diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 414 articles in PubMed, 0 in Scopus, 7 in CINAHL, 141 in Cochrane Library, 8980 in Google Scholar, and 1 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 1 from other sources. Of the 4 articles considered for inclusion, 2 diagnostic studies and 0 systematic study met the inclusion criteria.

## Evidence for the Use of Vascular Imaging Tests

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Biffi, 2006 (6.0)	Vascular Imaging Tests	Diagnostic	No mention of industry sponsorship or COI.	N=313 patients	Mean age: 37.7±1.8 years. 225 males, 88 females.	Blunt cerebrovascular Injury	CTA: Computed Tomographic Angiography Vs. DSA: Digital Subtraction angiography	The GCS score averaged 12.9. Seventeen patients had C-spine injuries and 9 had BCVI. Eighteen patients had 20 blunt cerebrovascular injuries. Two patients had sign related to BCVI before diagnosis. Concordance between CTA and DSA was excellent. Four patients had false-positive CTA studies.	“CTA detected all clinically significant injuries during this study period. Liberal screening with 16-slice CTA is appropriate and is likely to miss very few significant injuries. A multicenter trial will help to clarify risk factors and the accuracy of noninvasive diagnostic modalities.”	Data suggests 16 slice CTA is reliable fore detecting BCVI and is non-invasive.
Bodanapally, 2014 (6.0)	Vascular Imaging Tests	Diagnostic	No mention of sponsorship. No COI.	N=45 patients all had CTA and DSA.	Mean age: 31 years. 35 males, 10 females.	Penetrating Brain Injury	CTA: helical CT angiography Vs. DSA: digital subtraction angiography	Sensitivity of CTA for detecting arterial injuries was 72.7% (95% CI 49.8%–89.3%); specificity, 93.5% (95% CI 78.6%–99.2%); PPV, 88.9% (95% CI 65.3%–98.6%); and NPV, 82.9% (95% CI 66.4%–93.4%). CTA correctly identified all 7 TICAs. Sensitivity, specificity, PPV, and	“Computed tomography angiography had limited overall sensitivity in detecting arterial injuries in patients with PTBI. However, it was accurate in identifying TICAs, a subgroup of injuries usually managed by either	Data suggest CTA good for detection of TICAs but limited for detection of PTBI arterial injuries.

								NPV of CTA in detecting TICAs were 100%. To compare agreement with DSA, the standard of reference, confidence scores categorized as low, intermediate, and high probability yielded an overall effectiveness of 77.8% (95% CI 71.8%–82.9%).	surgical or endovascular approaches, and non-TICA injuries involving the first-order branches of intracranial arteries.”	
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BAM has been used to aid in the evaluation of TBI. [281] BAM is designed to detect, amplify and display sound waves from the skull. The system consists of 2-cm circular sensor placed on the forehead, connected by wire to a signal conditioning box. Signals are collected and displayed in real time. [281, 283-286]

## **Brain Acoustic Monitor (BAM)**

### **No Recommendation.**

There is no recommendation for or against the use of a brain acoustic monitor in the evaluation of TBI patients.

### *Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

#### *Level of Confidence – Low*

##### *Rationale:*

There are quality studies assessing BAM for diagnosis of TBI. The reported correlation between BAM signal measured early after admission and subsequent anatomic and functional evidence of TBI indicates a high sensitivity (93-100%), but quite low specificity (14-30%) [283, 287]. Thus, the false positive rate is considerable and limits the utility of the technology. The BAM diagnostic test is not invasive, has no adverse effects, is low cost, has limited evidence of diagnostic efficacy, and thus there is no recommendation.

##### *Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed dead or penetrating head or craniocerebral; Sensitivity and Specificity, Predictive Value of Tests, Gold-standard, accurate, accuracy, precision, precise, test; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 6 articles in PubMed, 1 in Scopus, 1 in CINAHL, 6 in Cochrane Library, 11400 in Google Scholar, and 5 in other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 in Google Scholar, and 5 from other sources. Of the 7 articles considered for inclusion, 1 diagnostic study, 2 prognostic studies and 1 systematic study met the inclusion criteria.

## Evidence for the Use of Brain Acoustic Monitor (BAM)

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Dutton 2011 (4.5)	Brain Acoustic Monitor (BAM)	Diagnostic	No Mention of Sponsorship or COI.	N=369 suspected with mTBI Glasgow Coma Score (GCS) 13-15. N=79 healthy volunteers and Non-TBI patients;	Mean Age 41 (18-89)	Traumatic Brain Injury	Clinical Assessment as well as Computed Tomographic (CT).	25 patients had abnormal CT scan, 14 of the 25 patients had abnormal BAM (Sensitivity 100%, Specificity 30.06%). BAM vs Clinical Assessment: Final Diagnosis results, Sensitivity 0.71, Specificity 0.30. Among those initially categorized incorrectly, predictive power of abnormal BAM was 0.89.	“There is no gold standard for the diagnosis of mTBI. BAM screening is a useful diagnostic adjunct in patients with mTBI and may facilitate decision making. An abnormal BAM reading adds significance to LOC as a predictor of a new abnormality on head CT. In our study, opting not to CT scan patients with a normal BAM signal would have missed no new CT findings and no patients who required medical intervention for TBI, at a cost savings of \$202,950.”	Data suggest no single method for detecting mild TBI is adequate and using BAM as an adjunct method may be useful.
Dutton 2005 (4.5)	Brain Acoustic Monitor (BAM)	Diagnostic	John Sewell is the inventor and patent holder for the brain acoustic	N=206 patients who had blunt trauma, TBI symptoms, or visible	Mean Age 40.9	Traumatic Brain Injury	Computed Tomographic Scan (CT) and Glasgow Outcome Score (GOS)	Abnormal BAM with abnormal CT scan; Sensitivity 93%. Positive predictive value of 54% large	“BAM screening was highly sensitive to the presence of anatomic findings on CT scan, but not highly specific.	Data suggest BAM sensitive to CT imaging but not specific.

			monitor technology. Dutton et al hold no financial interest in BAM.	injury to the head;				number of false positive (14.3% Specificity). BAM screening compared to GOS, 100% Sensitivity as well as a 13% Specificity.	This may reflect oversensitivity of interpretation or transient perturbations in cerebral perfusion that were not associated with CT-detectable brain abnormalities. Early BAM screening of patients with TBI has the potential to guide diagnostic and therapeutic decisions prehospital and in the ED, but further refinement of specificity is required."	
Dutton 2002 (4.0)	Brain Acoustic Monitor (BAM)	Diagnostic	No Sponsorship or COI.	N=28 patients who had severe Traumatic Brain Injury;	Mean Age 35.7 years. 24 males, 6 females.	Traumatic Brain Injury	Brain acoustic monitor and Glasgow outcome score	BAM vs Clinical Status: Positive Predictive value (PPV) 83%, Negative Predictive Value 100%. Initial BAM recording predicted clinical status at discharge 25/28 cases (p<0.01). Initial BAM results and Continual BAM screenings did not differ in 25/28 patients.	"It is possible that the BAM can be used to screen patients with TBI and indicate the need for more invasive care in much the same fashion that the pulse oximeter does for patients with thoracic injury or respiratory distress. Whether the BAM can be refined to the point of guiding clinical decision	Data suggest the BAM signal correlated with low GCS scores or death.

									making in the absence of direct determination of ICP is an open question and the subject of our continued research."	
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## Electroencephalography

Electroencephalography (EEG) has been used to detect brain activity, propensity towards seizures, and has been used in the evaluation of TBI patients [288-295].

### Electroencephalography (EEG)

#### Recommended.

Electroencephalography (EEG) is recommendation for use in the evaluation of TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – High

<i>Indications:</i>	Known or suspected TBI injury. Evaluation of seizure-like activity or evaluation of risk of seizures. May include sleep-deprived EEG especially if awake EEG is normal but clinical suspicion of seizures is present.
<i>Benefits:</i>	Identification of seizures. Previously used for identification of brain death, but that use has been largely replaced by other imaging tests.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Generally only one assessment.
<i>Rationale:</i>	There are no quality studies assessing EEG in comparison with other commonly used tests for diagnosing the extent of TBI. EEG is not invasive, has no adverse effects, is moderate cost, and has utility in the diagnosis and management of seizures related to TBI and is thus recommended for diagnosis of TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms; Quantitative Electroencephalograph (QEEG), Electroencephalography (EEG). Brain Injuries, Head Injuries, Penetrating, Brain Concussion, Concussion, Craniocerebral Trauma, Traumatic brain, Intracranial, Closed Head, Penetrating, Head, Craniocerebral Trauma, Injury, and Injuries. (Diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 2 articles in PubMed, 0 in Scopus, 1 in CINAHL, 0 in Cochrane Library, 0 in Google Scholar, and 8 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 7 from other sources. Of the 10 articles considered for inclusion, 8 diagnostic studies and 1 systematic study met the inclusion criteria.

### Evidence for the Use of Quantitative Electroencephalograph (QEEG) and Electroencephalography (EEG)

Author Year (Score)	Category:	Study type:	Sponsorship and COI	Sample size:	Age/Sex:	Diagnoses :	Comparison:	Results:	Conclusion:	Comments:
Ayaz 2015 (6.5)	EEG/QEEG	Diagnostic	Supported in part by funding from BrainScope Company, Inc, which covered expenses related to data acquisition. The device used for electroencephalogram data acquisition is under development by BrainScope Company, Inc. COI, Leslie S Prichet is a scientific consultant to BrainScope Company, Inc, who provided the funds for this research. Brian J O'Neil discloses that BrainScope sponsored the study at Wayne State University covering technical costs; however, BrainScope did not participate in the data analysis or writing of the	N = 152	(104 males, 48 females). Mean age is 36.6 years.	TBI	QEEG Vs. NOC Vs. CCHR VS. Nexus II	QEEG had a sensitivity of 92.3% and specificity of 57.1%. ; NOC sensitivity 96.1. Specificity: 15.8; CCHR sensitivity: 46. Specificity: 86.5; Nexus II sensitivity: 96.1. Specificity: 31.7.	“At a sensitivity of greater than 90%, QEEG discriminant score had better specificity than NOC and NEXUS II. Only CCHR had better specificity than QEEG discriminant score but at the cost of low(b50%) sensitivity.”	Data suggest that when sensitivity was >90% of EEG had better specificity than NEC and NEXUS II for predicting intra-cranial lesions via head CT from mild TBI patients CCHR had better specificity than EEG but sacrificed a reduced sensitivity (50%)

			manuscript. No other financial relationships were present.							
Slobounov 2012 (4.0)	EEG/QEEG	Diagnostic	This work was supported by National Institutes of Health Grant RO1 NS056227-01A2 "Identification of Athletes at Risk for Traumatic Brain Injury". No mention of COI.	N = 380	(270 males, 110 females). Mean age is 21.0 years.	TBI	Alpha power suppression standing Vs. Sitting.	The magnitude of alpha power suppression predicted the rate of recovery of this measure in sub-acute and chronic phases of injury ( $r^2 = 0.609$ , $p < 0.01$ ). Finally, 85% of MTBI subjects who showed more than 20% of alpha power suppression in the acute phase of injury did not return to pre-injury status up to 12 months post-injury.	"Neurophysiological measures are excellent tools to assess the status and prognosis of patients with MTBI."	Study demonstrates that use of a balance study with EEG over time in mild TBI patients helps identify residual cerebral dysfunction.

## Electroencephalography

Quantitative electroencephalogram has been used to assess brain activity among TBI patients [288-295].

### Quantitative Electroencephalograph (QEEG)

#### No Recommendation.

There is no recommendation for or against the use of quantitative electroencephalograph (QEEG) in the evaluation of TBI patients.

#### *Strength of Evidence* – No Recommendation, Insufficient Evidence (I)

##### *Level of Confidence* – Low

###### *Rationale:*

There are no quality studies assessing QEEG in comparison with other commonly used tests for diagnosing the extent of TBI, and no quality evidence QEEG is meaningfully superior to EEG. QEEG is not invasive, has no adverse effects, is moderate cost, but has no clear superiority for evaluation of TBI patients and thus there is no recommendation.

###### *Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms; Quantitative Electroencephalograph (QEEG), Electroencephalography (EEG). Brain Injuries, Head Injuries, Penetrating, Brain Concussion, Concussion, Craniocerebral Trauma, Traumatic brain, Intracranial, Closed Head, Penetrating, Head, Craniocerebral Trauma, Injury, and Injuries. (Diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 2 articles in PubMed, 0 in Scopus, 1 in CINAHL, 0 in Cochrane Library, 0 in Google Scholar, and 8 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 7 from other sources. Of the 10 articles considered for inclusion, 8 diagnostic studies and 1 systematic study met the inclusion criteria.

## Evoked Potentials

Somatosensory evoked potentials have been used to determine if neurological damage has occurred from a traumatic brain injury [296-299].

### Somatosensory Evoked Potential (SSEP)

#### Recommended.

Somatosensory evoked potentials (SSEP) are recommended for use in the evaluation of TBI patients.

#### Strength of Evidence – Recommended, Insufficient Evidence (I)

##### Level of Confidence – Low

<i>Indications:</i>	Severe TBI with inability to test sensory system with more common methods, such as bedside testing.
<i>Benefits:</i>	Ability to assess the sensory system
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	May be used at baseline. If there are abnormalities and the injury continues to preclude other testing, then followup testing with somatosensory evoked potentials is reasonable.
<i>Indications for Discontinuation:</i>	Resolution of TBI, improvement sufficient to undergo standard testing.
<i>Rationale:</i>	There are quality studies assessing Somatosensory Evoked Potential (SSEP) for diagnosis and followup of TBI. Somatosensory Evoked Potential (SSEP) testing is not invasive has no adverse effects, is low cost, has evidence of diagnostic efficacy, and is recommended for selective diagnosis and assessment of TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Somatosensory Evoked Potential, Traumatic Brain Injury; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 19 articles in PubMed, 16 in Scopus, 1 in CINAHL, 1 in Cochrane Library, 2240 in Google Scholar, and 0 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

### Vestibular Evoked Myogenic Potentials

#### No Recommendation.

There is no recommendation for or against the use of vestibular evoked myogenic potentials to diagnose traumatic brain injury.

#### Strength of Evidence – No Recommendation, Insufficient Evidence (I)

##### Level of Confidence – Low

<i>Rationale:</i>	There are no quality studies assessing Vestibular Evoked Myogenic Potentials for evaluation of TBI. Vestibular Evoked Myogenic Potentials is not invasive, has no adverse effects, is low cost, but
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*Evidence:* absent quality evidence of diagnostic efficacy, there is no recommendation for evaluation of TBI. A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Vestibular evoked myogenic potentials, VEMP, Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 5 articles in PubMed, 5 in Scopus, 2 in CINAHL, 1 in Cochrane Library, 582 in Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

*Comments:*

Electromyography (EMG) measures the health of the muscles and the nerves that control your muscles. This is done by evaluating the electrical activity levels in the muscles while resting and contracting. A nerve conduction study is often part of the EMG evaluation and examines how well nerves are functioning. The speed and velocity of the electrical signals produced by stimulated nerves is recorded [300].

## **EMG and Nerve Conduction Studies**

### **Recommended.**

Electromyography and nerve conduction studies are recommended for the evaluation of TBI.

### **Strength of Evidence – Recommended, Insufficient Evidence (I)**

*Level of Confidence – Moderate*

<i>Indications:</i>	Known or suspected peripheral nerve injuries or CNS injuries with peripheral nerve sequelae (e.g., identification of extent of partial paralysis).
<i>Benefits:</i>	Identification and quantification of peripheral nerve injury(ies). Occasionally may result in need for surgery to improve the clinical outcome.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Generally only one assessment.
<i>Rationale:</i>	There are no quality studies assessing EMG/NCS for diagnosis of peripheral nerve injury(ies) or consequences of central nervous system injury(ies) associated with TBI, although there are a few quality studies for evaluation of the distal upper extremity (see Hand, Wrist Forearm Guideline). facial nerve injury from TBI. EMG/NCS is minimally invasive, has no adverse effects, is moderate to high cost depending on extent of the examination required, and is thought to aid in the identification of either peripheral nerve injury(ies) and/or peripheral consequences of central nervous system insults from TBIs and thus is selectively recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Electromyogram, EMG, Nerve conduction studies, Traumatic brain injury Closed Head injury,

Penetrating Head Injury, Concussion, Craniocerebral Injury; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 14 articles in PubMed, 62 in Scopus, 3 in CINAHL, in Cochrane Library, 16 in Google Scholar, and zero from other sources. Zero articles met the inclusion criteria.

## Electrodiagnostic Studies

Electroneuronography (ENoG) is a neurological test that assess the integrity and ability of the facial nerves. The purpose of ENoG is to quantify the percentage of nerve fibers that can be stimulated [301]. The assessment of the facial is thought to be useful in managing facial nerve disorders and identifying disorders that affect facial nerves.

### Electroneuronography (EnoG)

#### Recommended.

Electroneuronography is recommended for use in the evaluation of TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – Low

<i>Indications:</i>	Known or suspected facial nerve injuries.
<i>Benefits:</i>	Identification and quantification of facial nerve injury(ies). Occasionally may result in need for surgery to improve the clinical outcome.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Generally only one assessment.
<i>Rationale:</i>	There are no quality studies assessing EnoG for diagnosis of facial nerve injury from TBI. EnoG is minimally invasive, has no adverse effects, is moderate cost, and is thought to aid in the identification of facial nerve injury and thus is selectively recommended to identify facial nerve injuries associated with TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: electroneurography Electroneuronography, Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 11 articles in PubMed, 16 in Scopus, 0 in CINAHL, 1 in Cochrane Library, 10 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

## Ultrasound

### Ultrasonography

#### Recommended.

Ultrasonography is recommended for use in the evaluation of TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – Low

<i>Indications:</i>	Head trauma thought to be sufficiently forceful to potentially fracture the skull.
<i>Benefits:</i>	Identification of fracture, which helps to suggest severity of the injury and potential severity of TBI.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Generally only obtained at presentation.
<i>Rationale:</i>	There are no quality studies assessing Ultrasonography for diagnosis of TBI. Ultrasonography is not invasive has no adverse effects, is low cost, has evidence of diagnostic efficacy, and is recommended for diagnosis of skull fractures associated with TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Ultrasonography, Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 424 articles in PubMed, 151 in Scopus, 65 in CINAHL, 1 in Cochrane Library, 27900 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

## Post-Concussion and Sideline Testing

Multiple concussion screening tests are typically used on the sidelines of contact sports to manage concussion injuries [302-309]. These include but are not limited to ImPACT, MACE, King-Devick and SCAT. [310-312]. Post-concussion and/or sideline testing often consists of a computerized test battery. Tests of brain function are typically included, such as symptoms, attention, memory, processing speed, and reaction time.

### Immediate Post-Concussion Assessment (ImPACT)

#### No Recommendation.

There is no recommendation for or against the use of Immediate Post-Concussion Assessment (ImPACT) in the evaluation of TBI patients.

*Strength of Evidence* – **No Recommendation, Insufficient Evidence (I)**

*Level of Confidence* – Low

*Rationale:*

There are a few quality studies assessing ImPACT for diagnosis of TBI [302, 305-307], although it is cumbersome to use and nearly all data are from adolescent or young adult athletes raising questions about the applicability to occupational settings and its overall utility is disputed [313]. While the body of evidence suggests some utility for this tool, the studies somewhat conflict regarding the overall sensitivity of the test. Sensitivity tends to be higher with batteries of tests used and overall sensitivity estimates range from approximately 40-85%. However, there are some data suggesting prognostic value of IMPACT in severe TBI [314-317]. The ImPACT diagnostic test is not invasive, has no adverse effects, is low cost, has somewhat conflicting evidence of efficacy, and thus there is no recommendation.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms Traumatic brain injury, Intracranial injury, Closed Head injury Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma; Sensitivity and Specificity, Predictive Value of Tests, Gold-standard, accurate, accuracy, precision, precise, test; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 934 articles in PubMed, 26 in Scopus, 18 in CINAHL, 10 in Cochrane Library, 0 in Google Scholar, and 0 from other sources. We considered for inclusion 4 from PubMed, 2 from Scopus, 2 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 8 articles considered for inclusion, 2 diagnostic studies, 4 prognostic studies and 1 systematic study met the inclusion criteria.

### Evidence for the Use of Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT)

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Schatz 2006 (5.5)	ImPACT	Diagnostic	No mention of sponsorship or COI.	N = 138	(86 males, 52 females). Mean age is 16.9 years.	Concussion	ImPACT Vs. Post-Concussion Symptom Score (PCSS)	The combined sensitivity of ImPACT and PCSS is 81.9%. The specificity is 89.4%. Hotelling Trace (F=16.6; p=.001). Verbal Memory (F=32.4, p=.001). Visual Memory (F=34.9; p=.001). reaction time (F=43.6; p=.001). Processing speed (F=61.1; p=.001). Symptom Scale score (F=.3; p=.87). Age didn't emerge as covariate (F=1.58; p=.16).	"ImPACT is a useful tool for the assessment of the neurocognitive and neurobehavioral sequelae of concussion, and can also provide post-injury cognitive and symptom data that can assist a practitioner in making safer return to play decisions."	ImPACT provides post-injury cognitive and symptom data which could assist clinicians in clinical guidance post concussion.

Echemendia 2016 (4.0)	ImPACT	Diagnostic	No mention of sponsorship. No COI.	N = 187 athletes	Mean age is 20.95 years. No mention of gender.	Concussion	ImPACT's indices are composed of subscores from six cognitive modules: Word Discrimination Modules, Design Memory Modules, Symbol Matching, Color Match, and Three Letters module.	Speed index across multiple language two factor model is promising. Time composites from .52-.74. Speed composite of .73 for English. Visual motor=.65. Reaction time = .81. Speed composite (for Czech) =.82. Improvement in Memory composite is evident.	"The increased stability in test scores improves the test's ability to detect cognitive changes following injury, which increases the diagnostic utility of the test and allows for better return to play decision-making by reducing the risk of exposing an athlete to additional trauma while the brain may be at a heightened vulnerability to such trauma."	Data suggest that the 2-factor approach increases the one year reliability of ImPACT.
Nelson 2015 (4.0)	ImPACT	Diagnostic	One or more of the authors has declared the following potential conflict of interest or source of funding: This work was supported by the US Army Medical Research and Materiel Command under award number W81XWH-12-1-0004. This	N = 2063	(1584 males, 479 females) . Mean age is 17.8 years.	Concussion	ANAM Vs. Axon Vs. ImPACT	ImPACT had the lowest invalid profile score of 2.7%. ANAM had 10.7%. Axon had 11.3%. ANAM vs Axon (OR=.95; P=.686). Axon and ANAM vs. ImPACT (OR=4.20; P<.001).	"The validity criteria for these CNTs may not identify the same causes of invalidity or be equally sensitive to effort. The validity indicators may not be equally appropriate for some athletes (eg, those with neurodevelopmental disorders)."	Data suggest ANAM, Axon Sports and ImPACT may be variable in terms of sensitivity to effort.

			publication was also supported by the Clinical and Translational Science Institute grant 1UL1-RR031973 (-01) and by the National Center for Advancing Translational Sciences (National Institutes of Health) grant 8UL1TR000055.					Axon vs ImPACT (OR=4.41; P<.001).		
Blake 2015 (3.0)	ImPACT computerized test.	Diagnostic	No mention of sponsorship. COI, a. Summer Ott has received honoraria from ImPACT Applications to conduct educational workshops. However, ImPACT Applications, Inc., had no role in the conceptualization of the study, the collection or analysis of the data, the writing of the article, or the decision to submit it for publication. b. Philip Schatz has served as a	N = 58	Mean age is 22 years. (13 males, 45 females)	Concussion	ImPACT Vs. Symptom Scale	English vs Spanish (F=.75, p=.59). English first vs. English second; English Composite (F=.56, p=.69), Spanish Composite (F=1.73, p=.16). Hotelling's Trace (F=3.05, p=.01). Verbal Memory (F=6.64, p=.013). Visual Memory (F=.46,	"Suggest a need for separate normative data for Spanish-speaking individuals completing the ImPACT battery if baseline data are not present."	Data suggest a need for separate normative data for Spanish speaking persons taking ImPACT of baseline data are unavailable

			<p>consultant to ImPACT Applications, Inc., however, ImPACT Applications, Inc., had no role in the conceptualization of the study, the collection or analysis of the data, the writing of the article, or the decision to submit it for publication. c. Margaret Blake, Elizabeth Villanyi and Katia Kazhuro have no relevant conflicts of interest to disclose.</p>					<p>p=.50). Reaction Time (F=.47, p=.50). Total Symptoms scores (F=3.78, p=.057).</p>		
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Military Acute Concussion Evaluation [318] is a two-part cognitive assessment typically used in military settings to evaluate the extent of neurological damage from a TBI. The first section of the screening requires the patient's medical history and a general physical exam. The second section of the screening applies a Standardized Assessment of Concussion (SAC), which includes a neuropsychological battery to test patient orientation, immediate memory, concentration, and memory recall. MACE is based upon a 30-point scale, where a perfect score is 30 and an abnormal score is anything below 25 [318].

## **Military Acute Concussion Evaluation**

### **No Recommendation.**

There is no recommendation for or against the use of Military Acute Concussion Evaluation in the evaluation of TBI patients.

*Strength of Evidence* – **No Recommendation, Insufficient Evidence (I)**

*Level of Confidence* – Low

*Rationale:*

There are no quality studies assessing MACE for diagnosis of TBI in occupational populations. There is one study that attempted to determine utility of the MACE in a military population and suggests some discriminatory ability [310]. The MACE diagnostic test is not invasive, has no adverse effects, is low cost, but has no documented evidence of diagnostic efficacy in typical employed populations, and thus there is no recommendation regarding its use in occupational populations for the evaluation of TBI. As some occupational TBI cases have similar ballistics as many military TBI cases, the applicability of the test to select patients may still be reasonable, although that needs to be determined in quality studies.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Military acute concussion evaluation, MACE, Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 13 articles in PubMed, 2 in Scopus, 6 in CINAHL, 0 in Cochrane Library, 7830 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 prognostic study and 0 systematic studies met the inclusion criteria.

### Evidence for the Use of Military Acute Concussion Evaluation [318]

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:		Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
McCrea 2014 (4.5)	Other Military Acute Concussion Evaluation [318]	Diagnostic	The study was funded by a cooperative agreement with the United States Medical Research and Military Command (USAMRMC) (PT 073286) through USAMRMC Funding Opportunity Number W81XWH-07-TBI-CA (M. McCrea, Principal Investigator). No mention of COI.	N = 723 military personnel	Mean age: 23.62. 553 males, 54 females		Concussion/TBI	(N = 179) documented MACE data from day of mTBI vs. (N = 544) MACE normative control group	On the day of mTBI event, the mTBI group had significantly lower MACE scores than the control group (23.48 vs. 26.92, p <0.00001).	“Findings from the current study support the use of the MACE as a valid screening tool to assess for cognitive dysfunction in military service members during the acute phase after mTBI.”	Data suggest MACE may be used to evaluate mild TBI in U.S. military personnel.

The King-Devick screen has been used in the assessment of TBI, especially at sports [311, 319-338].

### King-Devick (K-D)

The King-Devick screen is recommended for use in the evaluation of TBI patients.

#### Recommended.

*Strength of Evidence* – **Recommended, Evidence (C)**

*Level of Confidence* – Low

<i>Indications:</i>	Mild, moderate or severe TBI patients or athletes. Generally used among those with a known baseline measurement. King-Devick is a visual performance test to and has been used most often in contact sport athletes to enhance the detection of concussion. Concussion is frequently associated with saccade abnormalities, pursuit eye movement, convergence, accommodation and vestibular-ocular reflex. The King-Devick Test involves having the individual rapidly reads the numbers on 3 test cards with the score being the total time required in seconds [339].
<i>Benefits:</i>	Simple test that can be implemented with minimal training including among non-medically trained and can be performed rapidly at the sideline. Helps assess degree of TBI.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Baseline evaluation. Then measured after subsequent potential TBI event(s).
<i>Indications for Discontinuation:</i>	N/A
<i>Rationale:</i>	There are several moderate quality studies assessing King-Devick for diagnosis of sports related concussion [323, 326-331, 333] [334] [335] [340] [337, 338] although most data are from adolescent or young adult athletes raising questions about the applicability to occupational settings. While the body of evidence suggests some utility for this tool, the studies somewhat conflict regarding the overall sensitivity of the test. The King-Devick diagnostic test is not invasive, has no adverse effects, is low cost, has somewhat conflicting evidence of efficacy, but has moderate evidence suggesting prognostic utility and thus is recommended for evaluation of mild-moderate to severe TBI. King-Devick testing may be performed at the rapidly by non-professional individuals.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms Traumatic brain injury, Intracranial injury, Closed Head injury Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma; Sensitivity and Specificity, Predictive Value of Tests, Gold-standard, accurate, accuracy, precision, precise, test; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 934 articles in PubMed, 26 in Scopus, 18 in CINAHL, 10 in Cochrane Library, 0 in Google Scholar, and 0 from other sources. We considered for inclusion 4 from PubMed, 2 from Scopus, 2 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 8 articles considered for inclusion, 2 diagnostic

studies, 4 prognostic studies and 1 systematic study met the inclusion criteria.

## Evidence for the Use of King Devick

Author Year (Score)	Category:	Study type:	Conflict of Interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Galetta, 2015 (6.5)	TBI	Prospective-Diagnostic	No mention of sponsorship. COI, S.L. Galetta has received honoraria for speaking from Biogen-Idec, Vaccinex, and Genzyme.	N = 332 athletes (243 youth, 89 collegiate)	Mean age: Youth group 11±3, Collegiate group 20±1.  Sex(M:F) 270:62	Concussion	Baseline scores of a 2min visual performance measure of rapid number naming (King Devick test) and post-injury or control scores.	Concussed athletes had significant mean change of -5.2 seconds from baseline in King-Devick (KD) scores in comparison to the control group who scores were improved by a mean of 6.2seconds (p=0.002).  In comparison to timed tandem gait (TG), Standardized assessment of concussion (SAC), KD had the greatest capacity of distinguishing concussed vs control groups based on logistic regression models. (KD = 0.92, TG = 0.87, SAC = 0.68 (p<0.001)).	"Adding a vision-based performance measure to cognitive and balance testing enhances the detection capabilities of current sideline concussion assessment."	Data Suggest the addition of a vision-based performance measure to cognitive and balance testing increases concussion identification.
Fischer 2015 (5.0)	King Devick	Diagnostic	Sponsored by grants from Mission Connect, a program of TIRR Foundation. No COI.	(N=30)	21 males, 9 females; mean age for group M 33±16.5, group O 31±11.6, and group N 33±15.0.	Patients had a variety of injuries and were grouped accordingly, 10 mTBI patients (M), 7 orthopedic injury group (O), and 12	Comparison between groups of a King-Devick tablet based test in controls, orthopedic injuries, and possible concussion (M) group.	KD task showed no significant difference between all three groups. Anti-Point response time with AUROC of 0.98 (0.96-1.00 (95%CI)). Pro-Point response time (RT) showed AUROC of 0.93 (0.84-1.00 (95%CI)).	"[I]n conclusion, these findings demonstrate that these quick tablet-based measures are able to reliably detect sensorimotor and cognitive impairments within hours after a mild traumatic brain injury and in the	Data suggest tablet based tasks may provide a more sensitive metric for functional deficits leading to early detection and prognosis.

						normal control (N)			future may prove useful in evaluating interventions or predicting persistent post-concussion Symptoms at the time of injury onset."	
King 2015 (4.5)	King Devick	Observational Diagnostic	No sponsorship or COI.	(N=104)	104 males, 0 females; Mean age 23.7±5.0	Some patients had been diagnosed previously with concussions because of athletics	Comparison between individuals with witnessed concussive events during their season and those who did not receive a concussion during their season.	Baseline KD score vs Post match KD score, witnessed concussion group: 43.6 (31.1 – 54.3) vs 48.0 (38.8 – 58.6) (p<0.05), difference of 6.2 s. Baseline KD score vs Post match KD score, unwitnessed concussion group: 40.6 (34.2 – 48.6) vs 45.9 (38.1 – 53.3), difference of 4.6 s.	"The K–D and SCAT3 tests helped identify cognitive impairment in players without clinically observable symptoms post-match. The rate of undetected concussion was higher than detected concussions by using the K–D test routinely following matches."	Data Suggest K-D test detects a high number of undetected concussions following rugby matches.
Munce 2014 (4.0)	King Devick	Observational Study	Authors' received financial support from Sanford Research, South Dakota. No COI.	(N=10)	10 males, 0 females; Mean age of 13.04±0.7.	Patients were not diagnosed with any neurological impairment.	Compared adolescent football players before and after a 12-week season to investigate affection on cognitive function.	King-Devick test 1, pre vs post season (sec): 14.63±1.80 vs 13.18±1.31 (p<0.05). Balance with eyes closed, pre vs post season: 3.33±2.31 vs 1.72±1.38 (p<0.05). ImpACT composite score Reaction time pre vs post season: 0.58±0.04 vs 0.54±0.04 (p<0.05).	"In conclusion, selected clinical measures of neurologic function were not adversely affected in 10 youth football players tested before and after a 12-week season. There were, however, significant improvements in some measures of postural stability, oculomotor performance, and reaction time."	Data suggest all measures of neurological function remained unchanged.
King 2013 (4.0)	King Devick	Observational Diagnostic	No mention of sponsorship. No COI.	(N=37)	37 males, 0 females; Mean age 22.0±4.0.	(N=30) patients were previously diagnosed	Comparison between pre and post-match KD and SCAT	precompetition	"[T]he KD was able to identify players with a suspected concussion and players with a	Data suggest K-D test good for rapid assessment of concussion and

						with concussion with clinical criteria.	tests as well as comparing athletes with previous concussion and no previous concussion pre match.		concussion that was not reported or witnessed. The ease-of-use of the KD made it more acceptable to team management and players, as it provided immediate feedback to the player and coaching staff.	identified some players who had not previously reported any sign or symptoms of concussion.
Galetta, 2013 (4.0)	TBI	Prospective Diagnostic	No mention of sponsorship. COI, Dr. Galetta received honoraria from Biogen-Idec, Questcor, and Teva.	N = 27 hockey players	Mean age: 28±5 Sex(M:F) 27:0	Concussion	King-Devick Test and SCAT2 SAC test.	A 1 point reduction in SAC immediate memory score was associated with an average increase of 7.3 seconds in the K-D test ( $R^2=0.62$ , $p<0.001$ ).  A reduction of 1 point in total SAC score was associated with an average increase of 2.2seconds in the K-D test ( $R^2=0.25$ , $p=0.01$ ).	"A composite of brief rapid sideline tests, including SAC and K-D (and balance testing for non-ice hockey sports), is likely to provide an effective clinical tool to assess the athlete with suspected concussion."	Data suggest a combination of rapid assessment tests such as K-D and SAC as well as balance testing may be effective for identification of concussion.
Galetta, 2011 (4.0)	TBI	Longitudinal Diagnostic Study	No mention of Sponsorship. COI, Dr.Devick is an employee of King-Devick Test, LLC. Dr. Galetta has received honoraria from Biogen-Idec, Teva, and Novartis.	N = 219 collegiate athletes	Mean age: 20.3±1.4  Sex(M:F) 182:37	Concussion	Baseline K-D test scores, post-season scores, and post-concussion scores when applicable.	K-D testing immediately after a concussion showed significantly worse median scores in comparison to median baseline scores (46.9 seconds vs 37.0 seconds ( $p = 0.009$ )).	"This study of collegiate athletes provides initial evidence in support of the K-D test as a strong candidate rapid sideline visual screening tool for concussion."	Data suggest K-D test may be a good rapid screening tool for concussion.
Alsalaheen, 2015 (4.0)	TBI	Diagnostic	Sponsored by Dr. Ben F. Bryer Foundation Research Fund. No COI.	N = 157 high school athletes	Mean age: 15.4 Sex(M:F) 157:0	Concussion	K-D test, Balance Error Scoring System (BESS), and Limits of	Faster Velocity of LOS was associated with better K-D score ( $r= -0.22$ , $p=0.024$ ).  No significant differences were	"The K-D test was reliable over a short time interval, yet further research is needed to support the long-term reliability of the K-D	Data suggest K-D test detects specific aspects of ocular motor brain function not detected in balance tests.

							Stability (LOS)	observed in median K-D scores from participants with a concussion history, and those without (41.1sec vs 43.2sec; $p=0.438$ ).	test over clinically relevant periods.”	
Leong D, 2015 (4.0)	King-Devick test	Diagnostic	Dr. Leong is an employee of King-Devick Test, LLC as a Director of Research. Dr. Balcer has served as a consultant for Biogen Idec, Questcor, and Novartis; and has received research support from the NIH/NEI and the National MS Society. Dr. Galetta has served as a consultant for BiogenIdec and Vaccinex. The work performed in this study was not funded by any of the above sources and the remaining authors have no disclosures.	N= 127 athletes	Mean age: 19.6 years	TBI	<p>The King-Devick test Vs.</p> <p>Modified sport concussion assessment Tool 2(SCAT2)</p> <p>K---D testing was administered immediately on the sidelines for football players with suspected head injury during regular games and changes compared to baseline were determined. Post-season testing was also performed to compare non-concussed athletes’ test performance.</p>	<p>Concussed athletes (<math>n = 11</math>) displayed sideline K---D scores that were significantly higher (worse) than baseline (<math>36.5 \pm 5.6</math> s vs. <math>31.3 \pm 4.5</math> s, <math>p &lt; 0.005</math>, Wilcoxon signed-rank test). Post- season testing demonstrated improvement of scores and was consistent with known learning effects (<math>35.1 \pm 5.2</math> s vs. <math>34.4 \pm 5.0</math> s, <math>p &lt; 0.05</math>, Wilcoxon signed-rank test). Test-retest reliability was analyzed between baseline and post-season administrations of the K-D test resulting in high levels of test-retest reliability (intraclass correlation coefficient (ICC) = 0.95 [95% Confidence Interval 0.85---1.05])</p>	<p>“The data show worsening of K---D test scores following concussion further supporting utility of the K---D test as an objective, reliable and effective sideline visual screening tool to help identify athletes with concussion.”</p>	Data suggest athletes with higher K-D scores, compared to baseline most likely have suffered a concussion.

Ventura R 2015 (4.0)	King-Devick test	Diagnostic	No COI or sponsorship mentioned	N= not mentioned	not mentioned	TBI	The King-Devick (K-D) test and Sports Concussion Assessment Tool	The King-Devick (K-D) test is a visual performance measure that may increase the sensitivity of detecting concussions on the sideline when used in combination with tests of cognition and balance that are part of the Sports Concussion Assessment Tool (3rd ed.; SCAT3). Portable eye movement trackers and pupillometry may in the future improve our neuro-ophthalmic assessment after concussions. Combining visual tasks with neuroimaging and neurophysiology has allowed subtle changes to be detected, may refine our ability to make appropriate return-to-play decisions, and could potentially determine susceptibility to long-term sequelae of concussion	"[A] combination of visual processing tasks, neuroimaging, serum biomarkers, and electrophysiologic recordings may allow subclinical brain injury to be further studied, and may provide insights into those vulnerable to long-term sequelae."	Data suggest a combination of assessment tools such as neuroimaging and visual tasks allows for better concussion related decision making
Tjarks BJ 2013 (4.0)	King-Devick test	Diagnostic	No COI. No mention of sponsorship	N=35 concussed individuals	Age range: 12–19 y; 18 females, 17 males)	TBI	King-Devick test and impact	KD times improved with each visit ( $\Delta V1-V2: 7.86 \pm 11.82$ ; $\Delta V2-V3: 9.17 \pm 11.07$ ; $\Delta V3-V4: 5.30 \pm 7.87$ s) and paralleled improvements in PCSS ( $\Delta V1-V2: 8.97 \pm 20.27$ ; $\Delta V2-V3: 8.69 \pm 14.70$ ; $\Delta V3-V4:$	"Cognitive visual performance testing using KD has utility in concussion evaluation. Validation would further establish KD as an effective ancillary tool in longitudinal concussion	Data suggest both the King-Devick and impact have similar scores during concussion recovery. Data suggest use of King-Devick in acute health

								6.31 ± 7.71), RT ( $\Delta V1-V2$ : 0.05 ± 0.21; $\Delta V2-V3$ : 0.09 ± 0.19; $\Delta V3-V4$ 0.03 ± 0.07) and VMS ( $\Delta V1-V2$ : -5.27 ± 6.98; $\Delta V2-V3$ : -2.61 ± 6.48; $\Delta V3-V4$ : -2.35 ± 5.22). Longer KD times were associated with slower RT ( $r = 0.67$ ; $P < 0.0001$ ) and lower VMS ( $r = -0.70$ ; $P < 0.0001$ ), respectively	management and research.	care settings as a tool in concussion assessment.
Silverberg N 2014 (4.0)	King-Devick test	Diagnostic	No COI. This study has been supported by the Medical Research Fund of Tampere University Hospital, the Maire Taponen Foundation and the Emil Aaltonen Foundation.	Participants with MTBI (n=26) and controls with non-head injuries (n=33)	Mean age: 38.6 years; 23 females, 36 males	TBI	Sport Concussion Assessment Tool 2 (SCAT2) vs. King Devick test (K-D)	The patients with MTBI differed from those without MTBI on components of the SCAT2, including the Symptom Scale (Cohen's $d=1.02-1.15$ , $p<0.001$ ) and Standardized Assessment of Concussion ( $d=0.81$ , $p=0.004$ ), but not the K-D test ( $d=0.40$ , $p=0.148$ ). In a logistic regression analysis, the K-D Test did not contribute over and above these two measures in predicting group membership (MTBI vs. control), $p=0.191$ . Low K-D Test scores in the MTBI group ( $<1$ SD below controls) were not associated with poor SCAT2 performance, loss of consciousness or traumatic abnormalities on MRI,	"The present findings do not support the K-D Test for the assessment of civilian MTBI in an ED setting.	Data do not suggest use of K-D test for mTBI in an emergency department

								suggesting these cases may have been false positives.		
Seidman D 2015 (4.0)	King-Devick test	Diagnostic	No COI. No mention of sponsorship	N= 343 athletes from local high school football teams	Mean age: 15.5 years; gender not specified	TBI	The King-Devick (KD) test	Of the 343 athletes, nine were diagnosed with concussions. In all concussed players, cumulative read times for the KD test were significantly increased (p b 0.001). Post-season testing of non-concussed athletes revealed minimal change in read times relative to baseline. Univariate analysis revealed that history of concussion was the only demographic factor predictive of concussion in this cohort.	"The KD test is an accurate and easily administered sideline screening tool for concussion in adolescent football players."	Data suggest K-D test is easy to administer as well as accurate.
Benedict P 2015 (4.0)	King-Devick test	Prognostic	Dr. S. Galetta has received speaking and consulting honoraria from Biogen, Genzyme, and Teva. Dr. Balcer has received consulting honoraria from Biogen and Genzyme, and has served on a clinical trial advisory board for Biogen. The authors have no financial	N= 206 with sport related injuries (concussions) and non-sports injuries	Mean age: 35 years, gender: no of females, males not reported	TBI	Standardized Assessment of Concussion (SAC), modified Balance Error Scoring System (BESS), and K-D	Symptom Evaluation scores showed a higher severity and a greater number of symptoms to be associated with older age (r=0.31, P=0.002), female gender (P=0.002, t-test), and longer time between the concussion event and first appointment at the concussion center (r= 0.34, P = 0.008). Performance measures of K-D and BESS also showed associations of worse scores with	"This study demonstrates a novel use of sideline concussion assessment tools for evaluation in the outpatient setting, and implicates age and gender as predictors of outcomes for these tests."	Data suggest age and gender are predictors of outcome for SCAT, SAC and KD and BESS

			interest in the SCAT3 or King-Devick tests; the work performed in this study was not funded by any of the above sources.					increasing patient age ( $r = 0.32-0.54$ , $P \leq 0.001$ ), but were similar among males and females and across the spectrum of duration since the concussion event. Patients with greater Symptom Severity Scores also had the greatest numbers of referrals to specialty services in the concussion center ( $r=0.33$ , $P=0.0008$ ). Worse Immediate Memory scores on SAC testing correlated with slower K-D times, potentially implicating the dorsolateral prefrontal cortex as a commonly involved brain structure.		
Leong DF 2014 (3.5)	King-Devick test	Diagnostic	No mention of COI or sponsorship	N=34 amateur boxers	Mean age: not reported	TBI	Military acute concussion evaluation [318] vs K-D test	Post-fight KD scores were lower (better) than the best baseline score (41 vs. 39.3 s, $P=0.34$ , Wilcoxon signed-rank test), in the absence of concussion. One boxer sustained a concussion as determined by the ringside physician. High levels of test-retest reliability were observed (intraclass correlation coefficient 0.9 [95% CI 0.84-0.97]. additionally 6 boxers who participated showed no worsening of their K-D times	"Results demonstrate that the K-D test is a rapid ringside screening tool for concussion that can be accurately and easily administered by non-medically trained sports parents to help identify athletes with concussions."	The K-D test is a concussion screening test, which doesn't require professionally trained personnel to administer.

								further supporting that scores are not affected by the fatigue associated with sparring.		
Van Wyk A 2014 (3.5)	King-Devick test	Diagnostic	No COI. Research funding to conduct the study was obtained from the Medical Research Council of South Africa.	N= 24 patients with Unilateral spatial neglect	Mean age: not reported.	TBI	The effect of saccadic eye movement training with Visual scanning exercises (VSEs) integrated with task-specific activities on USN post stroke. King-Devick Test vs Star Cancellation Test	Statistical significant difference was noted on the King-Devick Test ( $P = .021$ ), Star Cancellation Test ( $P = .016$ ), and Barthel Index ( $P = .004$ ).	“ Intensive saccadic eye movement training with VSE integrated with task-specific activities has a significant effect on USN in patients post stroke. Results of this study are supported by findings from previously reviewed literature in the sense that the effect of saccadic eye movement training with VSE as an intervention approach has a significant effect on the visual perceptual processing of participants with USN post stroke. The significant improved visual perceptual processing translate to significantly better visual function and ability to perform activities of daily living following the stroke.	Data suggest improved visual processing read to increased visual function and performance.
Walsh D 2016 (3.5)	King-Devick test	Diagnostic	This research was funded by the Military Operational Medicine	N= 200 active duty military personnel with diagnosed	Mean age: 26.31 years; all males	TBI	K-D test	The mTBI group had approximately 36%mean slower performance time with significant differences between	“ Significant differences in KD test performance were seen between the acute mTBI and control	Data suggest K-D test may be utilized for acute mTBI .

			Research Program of the U.S. Army Medical Research and Materiel Command (USAMRMC), and FY13 Department of Defense Army Rapid Innovation Fund Research Program of the Office of the Congressionally Directed Medical Research Programs (CDMRP). No mention of COI.	acute mTBI ( $\leq 72$ h) and age-matched controls				the groups ( $p < 0.001$ ) in both tests. There were significant differences between the two KD test administrations in each group, however, a strong correlation was observed between each test administration	groups. The results suggest the KD test can be utilized for screening acute mTBI. A validated and rapidly administered mTBI, screening test with results that are easily interpreted by providers is essential in making return-to-duty decisions in the injured warfighter.”	
Vernau B 2015 (3.5)	King-Devick test	Diagnostic	No mention of COI or sponsorship.	N=108 youth ice hockey players	Mean age:12.5 years, gender: not specified	TBI	King-Devick (K-D) Test, Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT), Sport Concussion Assessment Tool 3 (SCAT3), and convergence	Pearson correlation analysis did not identify any relationship between baseline convergence, ImPACT or K-D times. Worse (higher) K-D times were associated with worse [341] scores on the ImPACT visual motor speed and reaction time subtests. There was no association between K-D score and SCAT3 memory score. Of the 10 patients who took the K-D test post-injury, eight scored faster and two scored one second slower than their baseline	“ Further research is needed to determine which combination of concussion assessments provides the most clinically useful, non-overlapping information in managing pediatric concussion. In addition, our exploratory study may indicate that annual baseline assessments in children may not be frequent enough in light of their ongoing neurodevelopment.”	Data suggest no correlation between ImPACT and K-D scores where higher K-D scores were associated with lower ImPACT scores

								(range 2–19 days, M = 8, SD = 5.4). Six patients took ImpACT after their injury (range 2–19 days, M = 10, SD = 1.4).		
Vartiainen M 2015 (3.0)	King-Devick test	Diagnostic	No mention of COI or sponsorship	N= 185 male ice hockey players	Mean age: 23.8 years, all males	TBI	Sport Concussion Assessment Tool – 3rd Edition and King-Devick test	The average K-D score was 40.0 s (SD = 6.1 s, range = 24.0–65.7 s). K-D test performance showed no association with age, education, or the number of self-reported previous concussions in this sample. The association between trials 1 and 2 of the K-D test was good (ICC = 0.92, Pearson = 0.93).	“Research is needed on the intra rater reliability, test-retest reliability over clinically relevant intervals (e.g., 1 day, 1 week, 1 month, and 3 months), validity, and clinical usefulness of the test in athletes with concussions before health care professionals can have more confidence in using it. In our sample, each athlete performed the test without errors. Compared with the SCAT3, the test measures different aspects of functioning, so it may prove to have value as an additional method for assessing the acute effects of Concussion.”	Data suggest King-Devick test results do not vary by age, education or concussion history
King, 2015 (3.0)	TBI	Prospective observational study	No mention of sponsorship or COI.	N = 19 junior league rugby team	Mean age: 10.4 ± 0.9 Sex(M:F) 14:5	Concussion	Pre-season baseline K-D test scores and Post-season or post-	Concussed athletes experience a mean change of 7.4seconds from baseline in post-match K-D times (p=0.018).	“The K-D test was quickly and easily administered making it a practical sideline tool as part of the continuum of	Data suggest K-D test is a quick concussion detection test.

							concussion scores.		concussion assessment tools for junior rugby league players.”	
Rizzo 2016 (3.0)	King Devick	Diagnostic	Sponsored by 5K12HDOO1097 NICHD and NCMRR, National Institutes of Health Rehabilitation Medicine Scientist Training Program (JRR) and Empire Clinical Research Investigator Program (ECRIP). No COI.	N=67	24 males, 43 females; Mean age of 32.	N=25 individuals who were diagnosed with a concussion by the BYU concussion center.	Comparison between patients with a history of concussion and healthy controls with no history of concussion.	Total KD time (s), concussion patient vs nonconcussion patients: 53.4±14.04 vs 43.8±8.55 (p<0.004). Intersaccadic interval analysis (ISI) (msecs), concussion vs non concussion patients: 324.4±85.6 vs 286.1±49.7 (p=0.027). Saccade spatial analysis, incorrect direction percentage of concussed vs non concussed participant: 14.43±8.26 vs 10.13±5.33 (p=0.028).	“Despite a wealth of literature noting prolonged KD test times following concussion, mechanisms explaining these findings have not been formally examined. We report on a number of eye movement findings in subjects with chronic concussion during performance of the KD test. Prolonged KD test times were associated with prolonged ISI values, an increased number of saccades (particularly at smaller amplitudes), and increased saccadic dysmetria.	Data suggest that in chronic concussion there may be disruption of the network which mediates visual function.

The Sport Concussion Assessment Tool-3 (SCAT-3), with SCAT-5 release planned for 2017, is an assessment tool particularly used to evaluate athletes [342, 343]. The SCAT-5's components include symptoms, the Glasgow coma scale, the standardized assessment of concussion (SAC) cognitive assessment, Maddock's score, and an evaluation of balance and coordination. SCAT-5 scores can be summed, but there is no normal score of cutoff point. It has been recommended that the SCAT-5 be compared with a baseline screen and subsequent tests following a TBI [344].

## Sport Concussion Assessment Tool (SCAT)

### Recommended.

The Sport Concussion Assessment Tool (SCAT) is recommended for use in the evaluation of TBI patients.

### Strength of Evidence – Recommended, Insufficient Evidence (I)

#### Level of Confidence – Low

<i>Indications:</i>	The SCAT is a screening evaluative tool and not a diagnostic tool. Use of possible post-TBI testing. Repeat testing to follow progress may also be helpful.
<i>Benefits:</i>	Identification of severity of concussion, follow-up of symptoms and at resolution of symptoms.
<i>Harms:</i>	Negligible. Potential for occasional misinterpretations especially where baseline data are missing.
<i>Frequency/Dose/Duration:</i>	Administered after TBI and monitored periodically during recovery. For high risk situations, baseline or pre-concussion testing may help measure the baseline [344]. Baseline, pre-TBI testing would rarely be indicated in occupational settings.
<i>Rationale:</i>	There are quality studies assessing SCAT for diagnosis of TBI [345] [312, 346]. One comparative study suggested the SCAT 2 is superior to the MACE [312]. One study suggested utility of SCAT, although it also found differences by age and gender, potentially rendering interpretations more challenging [345]. The SCAT diagnostic test is not invasive has no adverse effects, is low cost, has some evidence of diagnostic efficacy, and is recommended for diagnosis and follow-up testing of TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: SCAT, sport concussion assessment tool, brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed dead or penetrating head or craniocerebral; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 50 articles in PubMed, 40 in Scopus, 20 in CINAHL, 3 in Cochrane Library, 20 in Google Scholar, and 1 from other sources. We considered for inclusion 6 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 1 from other sources. Of the 8 articles considered for inclusion, 1 diagnostic study, 3 prognostic studies and 4 systematic studies met the inclusion criteria.

### Evidence for the Use of SCAT

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Putukian 2013 (5.5)	SCAT	Diagnostic	Sponsored by American Medical Society for Sports Medicine Foundation and the New Jersey Commission on Brain Injury Research. COI: Putukian has nonfinancial support from National Football League Head Neck and Spine Committee, US Lacrosse Sports Science Safety Commission and National Collegiate Athletics Association. Echemendia has personal fees from Princeton	N = 263 Athletes	Mean age of 20.3 years old. 87 Females, 176 Males	Concussion	Concussed Athletes (N = 32)  Vs.  Non-concussed Athletes (N = 231)	Concussed athletes have increased post concussive symptoms from baseline to post-injury testing for SCAT-2 (P < 0.001), symptom severity score (P < 0.001), total symptoms (P<0.001) and m-BESS (P<0.05). No significant change was seen in concussed athletes on the SAC.	“The SCAT-2 total composite score and each subcomponent are useful in the assessment of concussion.”	Data suggest assessment of concussion is aided by SCAT-2 and subcomponents.

			University and nonfinancial support and personal fees from National Hockey League and Major League Soccer. Bruce reports personal fees from Princeton University, National Hockey League and Archives of Clinical Neuropsychology.							
Luoto 2014 (5.0)	Neuropsychological Assessment	Cohort Study	No mention of sponsorship. No COI.	82 Patients meeting inclusion criteria (TBI or Control).	Mean age of 37.5 years old. 32 Females, 50 Males	mTBI	TBI Group (N = 49)  Vs  Control Group (N=33)  Follow up one month after enrollment.	Patients with TBI had more symptoms and worse symptoms severity than the controls. SAC alone has a sensitivity of 34% and 94% specificity. Adding SCAT2 Symptom Score with the SAC increased the sensitivity to 64% while the specificity stayed at 94%.	"Emergency and military clinicians evaluating a patient with an mTBI within the first few days postinjury should consider including the SCAT2/SCAT3 or its key components as part of their assessment."	Data suggest SCAT 2 better than MACE in the detection of acute mTBI symptoms and cognitive impairment.

Snyder 2014 (5.0)	SCAT	Diagnostic	No sponsorship or COI.	N = 761 patients	Mean age of 14.8 years old. 105 Females, 656 Males	Concussion	No comparison group mentioned	There is a significant effect of age on SCAT2 total score ( $P < 0.001$ ). Younger ages are associated with lower SCAT2 total score. Games-Howell analyses showed that the youngest age group (9 and 10) scored significantly lower on the SCAT2 compared to the older age group (17 and 18).	"[F]indings suggests that the SCAT2 may have less clinical utility in children under the age of 11 since variance in component scores for these children may be too limited to detect changes after a concussion has been sustained."	Data suggest SCAT-2 is useful for assessment of baseline function of adolescents but clinical utility may be best for children <11 years old.
Benedict 2015 (4.0)	SCAT	Diagnostic	Sponsored by the NYU School of Medicine. No mention of COI.	N = 206 with concussion	Mean age of 35 years old. No mention of sex distribution	Concussion	K-D Test  Vs.  SCAT3	Symptom severity scores were associated with a high K-D score ( $P = 0.002$ ) and a low SAC (SCAT) score ( $P = 0.03$ ). Low SAC scores were associated with high K-D scores ( $P = 0.005$ )	"This study demonstrates a novel use of sideline concussion assessment tools for evaluation in the outpatient setting, and implicates age and gender as predictors of outcomes for these tests."	Data suggest age and gender are predictors of outcome for SCAT, SAC, K-D and BESS.

## Neuropsychological Assessment

Neuropsychology is a specialized branch of psychology involving the assessment, management and rehabilitation of people suffering illness or disease (particularly to the brain). Neuropsychologists evaluate symptoms and neurocognitive (dys)function. Patient injuries and disorders evaluated include, but are not limited to TBI. Other disorders evaluated and treated by neuropsychologists include neurodegenerative disorders, multiple sclerosis, strokes, neurodevelopmental conditions, etc.

Neurocognitive dysfunction may be reflected in personality, intelligence, attention, executive function, reasoning, problem solving, information processing, and memory. Cognitive testing generally consists of a comprehensive evaluation of the patient's cognitive status by specific neurologic domains. Various testing batteries have been used, including for the evaluation of TBI patients [303, 304, 347, 348]. Neuropsychological assessments frequently include analyses of effort and signs of exaggeration.

Neuropsychology occupies a prominent role in the evaluation and treatment of TBI patients, especially moderate and severe patients. In most cases, mild TBI resolves within a few days and thus there is little role for professional evaluation(s) and treatment(s) other than natural recovery. However, neuropsychology is also highly helpful in the evaluation of mild TBI patients with persistent symptoms beyond one month. Neuropsychology employs assessments that frequently consist of a thorough clinical and neuropsychological assessment of TBI and various types of tests and test batteries to identify abnormalities related to TBI [93, 95, 349-352]. These tests typically undergo frequent revisions and the most up-to-date version of the tests should be administered. Normally, patients are given a battery of tests in numerous different domains (e.g., intelligence, memory, executive function, speech, language, visual spatial) to assess impacts of, and plan treatment of, TBI patients. Some of these tests are referred to below according to specific cognitive domains (e.g., intelligence, attention and concentration, memory). It should also be noted that this review is not intended to be all inclusive. Many tests and test batteries are not included in this review, as there are hundreds of various tests of neuropsychological and cognitive functioning. Additional tests may be included for review in subsequent revisions. Neuropsychological rehabilitation for TBI may consist of psychotherapy, cognitive exercises and retraining. Neuropsychological tests and treatments are reviewed individually by topic in later sections.

### Neuropsychological and Neurocognitive Assessment Recommended.

Neuropsychological assessment is recommended for the evaluation and treatment of TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – High

*Indications:*

Moderate or Severe TBI patients experiencing cognitive difficulties. Mild TBI patients with ongoing symptoms are also candidates for neuropsychological assessments, although most mild cases are expected to rapidly resolve and not require evaluation. May be performed to help guide treatment, oversee psychological and cognitive-related treatments and may later be performed as part of an evaluation for end-of-healing and clinical plateau. Well performed

	neuropsychological evaluations are widely considered indispensable for evaluation of TBI impairments [95].
<i>Benefits:</i>	Identify and measure psychological, neuropsychological, social, behavioral and cognitive capabilities, potentially allowing better tailoring of therapy(ies) to address the specific deficit(s).
<i>Harms:</i>	Negligible.
<i>Frequency/Dose/Duration:</i>	Generally, a comprehensive assessment with a battery of tests is performed once or twice assessing numerous different domains (e.g., intelligence, memory, executive function, speech, language, visual spatial). Ongoing focused assessments and treatments are then provided targeting deficits or functional issues identified in the assessment. May be used to target specific rehabilitation strategies. May later help determine end of healing and extent of residual deficits, if any.
<i>Rationale:</i>	Neuropsychological Assessments are not invasive, have no adverse effects, are moderately costly, are thought to be effective for evaluation of TBI patients and are thus recommended for the evaluation of TBI patients. Tests that are used should utilize the most recent versions.
<i>Evidence:</i>	<p>A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Neuropsychological Assessment, Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 20 articles in PubMed, 10 in Scopus, 10 in CINAHL, 10 in Cochrane Library, 10 in Google Scholar, and 0 from other sources. We considered for inclusion 8 from PubMed, 4 from Scopus, 5 from CINAHL, 4 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 22 articles considered for inclusion, 9 diagnostic studies and 8 systematic studies met the inclusion criteria.</p> <p>A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Neurocognitive testing, Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury, diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 181 articles in PubMed, 580 in Scopus, 37 in CINAHL, 28 in Cochrane Library, 60 in Google Scholar, and 2 from other sources. We considered for inclusion zero from PubMed, one from Scopus, one from CINAHL, zero from Cochrane Library, zero from Google Scholar, and 2 from other sources. Of the 4 articles considered for inclusion, 4 diagnostic studies and zero systematic studies met the inclusion criteria.</p>

The MMPI-2 (also MMPI-2-RF) has been widely used to assist in comprehensive psychological evaluations, including those of persons with traumatic brain injury [353-358]. Its use has been reported among TBI patients, including for the identification of malingering and/or exaggeration.

## Personality/Psychological Assessment

### Minnesota Multiphasic Personality Inventory (MMPI)

#### Recommended.

The Minnesota Multiphasic Personality Inventory is recommended for use in the evaluation of TBI patients.

*Strength of Evidence* – **Recommended, Evidence (C)**

*Level of Confidence* – **Moderate**

<i>Indications:</i>	Post-TBI testing. Repeat testing to follow progress may sometimes be helpful. There may be limited indications in mild TBI patients.
<i>Benefits:</i>	Measure of psychological and emotional factors, including developing support for a psychiatric disorder (e.g., somatic symptom disorder, Major Depressive Disorder) or identify maladaptive personality characteristics that may better account for an individual's symptom complaints. May assist with identification of over-reporting of symptoms as well as malingering [253, 359-364] [365]. Often used in conjunction with clinical picture to attempt to substantiate subjective complaints.
<i>Harms:</i>	Negligible. Potential for occasional misinterpretations especially where baseline data are missing.
<i>Frequency/Dose/Duration:</i>	May be administered to assist with identification of psychological and emotional factors.
<i>Rationale:</i>	There are quality studies assessing MMPI for evaluation of patients who sustained TBI. The MMPI is not invasive, has no adverse effects, is moderate cost, has evidence of accuracy especially for detecting malingering, and is thus recommended for evaluation of TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Minnesota Multiphasic Personality Inventory (MMPI) and Hs (Hypochondriasis) and Hy (Hysteria); Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 122 articles in PubMed, 92 in Scopus, 14 in CINAHL, 14 in Cochrane Library, 430 in Google Scholar, and zero from other sources. We considered for inclusion 13 from PubMed, zero from Scopus, 2 from CINAHL, one from Cochrane Library, zero from Google Scholar, and zero from other sources. Of the 15 articles considered for inclusion, 2 prognostic studies, 11 diagnostic and 2 systematic studies met the inclusion criteria.

## Evidence for the Use of MMPI

Author Year (Score)	Category:	Study type:	Conflict of interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
LaChapelle 2005 (7.0)	MMPI	Diagnostic	No mention of COI or sponsorship	N= 49 individuals with TBI and spinal cord injury (SCI)	39 males, 10 females  Mean age: 30.3 for TBI group, 43.4 years for SCI	TBI (n= 32)  Vs. SCI (n=17)	MMPI VS. Center for epidemiological studies depression scale (CESD) VS. Revised neurobehavioral scales of the MMPI	The group with TBI scored significantly higher on the Cognitive scale and significantly lower on the Inactivity scale than the group with SCI (with or without depression as a covariate). The Glasgow Coma Scale correlated significantly and negatively with the Cognitive scale in the group with TBI. Discriminant function analysis revealed that together the scales correctly classified individuals with sensitivity and a positive predictive value (with respect to TBI) of 87% and 81%, respectively. Specificity and a negative predictive value (with respect to SCI) were 68% and 76%, respectively. The overall rate of correct classification of individual cases was 80% (with or without depression in the analysis). The	“Concurrent validation of specific TBI-related MMPI items against objective indexes of neurocognitive function, for example, might lead to the derivation of a more valid neurocorrective index than simple deletion of the items from the profile. Although an earlier effort to correlate MMPI neurocorrective factors with performance on neuropsychological tests in TBI met with little success (see Brulot et al., 1997), the results of this study suggest that such an approach be further examined in light of the high sensitivity and specificity for TBI of the Cognitive scale identified in this study.”	Data suggest the revised neurobehavioral scales of the MMPI correctly classified TBI patients with a sensitivity of 87% and a PPV of 81% giving support for use of MMPI-2.

								Cognitive scale alone correctly classified individuals in the group with TBI with a positive predictive value of 84%.		
Greve K 2006 (6.5)	MMPI	Diagnostic	No mention of COI or sponsorship	N= 259 participants with traumatic brain injury and N=133 general clinical patients.	137 females, 255 males  42.9 mean age.	Mild TBI Mod/severe TBI  Vs. Clinical diagnoses CVA, Memory disorder Psync, Tumor, Encephalopathy Infection Seizure Multiple sclerosis Substance abuse Academic problems Lupus	Scales and indicators examined in this study included: Infrequency (F), Infrequency-back (Fb), Infrequency, psychopathology (Fp), Fake Bad Scale, Dissimulation revised (DS-r), F minus K (F-K raw), Obvious minus Subtle (O-S raw), Lie (L), Correction (K), Ego Strength (ES), and the Meyers Composite Index (MI raw)  The relevant indices of classification accuracy (and therefore error rate, the reciprocal of accuracy) are Sensitivity, Specificity, and Predictive Power	Significant group effects were observed for all scales except L. Generally, the No Incentive and Incentive Only groups did not differ (except for O-S) and the MND (Statistically Likely, Probable, Definite) groups generally did not differ. Thus, these results show a clear relationship between the amount of evidence suggestive of cognitive malingering and exaggeration on the MMPI-2	“A diagnostic system that does not take into account multiple modalities of disability presentation (i.e., focuses only on cognitive manifestations) likely misses important information. Thus, in the future, the system may benefit from modification and expansion to allow the diagnosis of malingering in its various behavioral and functional manifestations.”	Data suggest diagnosing malingering is challenging and must consider disability presentation as well as cognitive manifestations or key information is missed.
Alkemade 2015 (6.5)	MMPI	Diagnostic	No COI. No mention of sponsorship	N= 259 TBI patients	162 males, 97 females Mean age: 35.7 years	TBI	Exploratory factor analysis (EFA) vs. confirmatory factor analysis (CFA) vs.	Results showed that the MMPI-2 RF was able to differentiate across the groups with the MMPI-2 RF specific problem scale	“In summary, the four-factor model of MMPI-2 Hs defined in this study was found to satisfy the criteria for partial measurement	Data suggest continued use of MMPI-HS items to determine

							<p>invariance testing, vs. MMPI-2 Scale Hs</p>	<p>Anxiety adding incrementally to MMPI-2 Restructured Clinical scales in predicting PTSD. Both MMPI-2 RC1 (Somatic Complaints) and MMPI-2 RF head pain complaints predicted mTBI screen but did not add incrementally to each other. Of note, all of the MMPI-2 RF validity scales associated with overreporting, including Symptom Validity—Revised (FBS-r), were not significantly elevated in the mTBI group.</p>	<p>invariance across a TBI sample and a gender-matched subset of the MMPI-2 normative sample. None of the items from the Gass correction model that are included in the Hs scale were found to fail the test of invariance. In addition, practical impact analysis of the four-factor model supports retaining all items of the Hs scale when assessing patients with a TBI. Furthermore, while this study assessed the factormodel with a TBI sample, additional groups from the spectrum of neurological impairments require evaluation because patients experiencing diverse illnesses and injuries may also endorse physical and neurological symptoms potentially complicating interpretation of the MMPI-2.”</p>	<p>the health of TBI patients.</p>
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Jones A 2016 (6.0)	MMPI	Diagnostic	No COI. No mention of sponsorship.	N=300 participants from a military sample with traumatic brain injury	248 males, 52 females mean age: 31.6 years	non-malingering group (NM ) (n=145)  Vs. Three malingering groups (NM) (n=155)	Response Bias Scale (RBS) Vs. the Symptom Validity Scales (FBS, FBS-r) vs Infrequent Somatic Responses scale (Fs), vs. the Henry–Heilbronner Indexes (HHI, HHI-r).	Cutoffs were developed by comparing a psychometrically defined non-malingering group (NM) with three psychometrically defined malingering groups (probable PM, probable to definite PDM, and definite malingering DM) and a group that combined all malingering groups. RBS had the largest mean effect size (d) when the malingering groups were compared to the non-malingering group (d range = 1.23–1.58).	“This research examined the performance of MMPI-2 and MMPI-2-RF C-S SVTs in a military sample of mostly closed head-injured patients with mTBI. The results indicate that RBS had the largest “mean” effect size (d = 1.58) in distinguishing the NM and the three malingering groups used for this research. This was followed by HHI and HHI-r; d was 1.50 for both scales. The lowest mean effect size was for Fs (1.23). These results suggest that there is not much difference in the C-S SVTs based on this metric, and that they all have utility. For the CM group, the results indicated that RBS, HHI, and HHI-r performed in a very similar fashion (d range = 1.39–1.42) with RBS having the largest effect size.”	Data suggest Response Bias Scale (RBS) was lost at discriminating malingering from non-malingering.
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Whitney 2013 (6.0)	MMPI	Diagnostic	No mention of COI or sponsorship	N= 194 participants	Age 21 to 77  181 males, 13 females  50.67 years mean age.	Patients with TBI referred to the author for neuropsychological testing within a VA Medical Center.	Pass TOMM (N=149) RBS VS F VS Fb VS Fp VS FBS VS HHI  Against Fail TOMM (N=45) RBS VS F VS Fb VS Fp VS FBS VS HHI  TOMM=Test of Memory Malingering;	There was a statistically significant difference between passed TOMM (N=149) and failed TOMM (N=45) at for Pass TOMM (N=149) M: (11.4, 67.8, 66.2, 53.2, 20.6, 8.1) and SD: (4.1, 18.9, 22.2, 13.1, 5.6, 3.7) VS failed TOMM (N=45) M: (14.6, 82.1, 82.4, 61.5, 23.8, 10.7) and SD: (4.0, 20.8, 25.1, 17.0, 5.8, 3.2)	“Although the TOMM and the MSVT were used to classify individuals as demonstrating performance invalidity in the present study, it should be emphasized that the diagnosis of invalid presentation, especially if malingering is in question, is a clinical judgment that cannot be made on the results of symptom validity tests alone, but must be made in consideration of other psychometric, behavioral, and collateral data (Slick et al., 1999).”	Data suggest RBS and HHI show poor performance in predicting malingering.
Arbisi 2011 (5.5)	MMPI	Diagnostic	No mention of COI. This research was supported by grants from the University of Minnesota Press and U.S. Department of Defense Congressionally Directed Medical Research Program.	N= 229 National Guard soldiers, who were also administered questionnaires to identify posttraumatic stress disorder (PTSD) and mild traumatic brain	Mean age: 32.1 years  Gender: not specified	Controls (n=166)  PTSD (post-traumatic stress disorder ) only (n=21)  TBI only (n=33)  PTSD and TBI (n=9)	Minnesota Multiphasic Personality Inventory–2 Restructured Form for PTSD Vs Minnesota Multiphasic Personality Inventory–2 Restructured Form for TBI	On the basis of responses to the screening instruments, the National Guard soldiers who produced a valid MMPI-2 RF were classified into four groups: 21 soldiers who screened positive for PTSD only, 33 soldiers who screened positive for mTBI only, 9 soldiers who screened positive for both conditions, and 166 soldiers who did not screen positive for either	“In sum, this study is the first of its kind to examine the utility of the MMPI-2 RF in discriminating between recently returned soldiers who screened positive for PTSD and mTBI from those who did not report symptoms consistent with those conditions. Generally, conceptually related scales such as RC7 and ANX from the	Data suggest MMPI-2RF is useful in assessment of PTSD in non-treatment seeking veterans and was able to differentiate between mTBI, PTSD and normal.

				injury (mTBI)				condition. Results showed that the MMPI-2 RF was able to differentiate across the groups with the MMPI-2 RF specific problem scale Anxiety adding incrementally to MMPI-2 Restructured Clinical scales in predicting PTSD. Both MMPI-2 RC1 (Somatic Complaints) and MMPI-2 RF head pain complaints predicted mTBI screen but did not add incrementally to each other. Of note, all of the MMPI-2 RF validity scales associated with overreporting, including Symptom Validity—Revised (FBS-r), were not significantly elevated in the mTBI group.	MMPI-2 RF were found to be effective in identifying the PTSD group. However, the MMPI-2 RF scales associated with somatic concerns were also significantly elevated in the PTSD group, suggesting that beyond symptoms commonly associated with PTSD, veterans returning from the war in Iraq who screen positive for PTSD report poor health and a range of somatic concerns.”	
Peck CP 2013 (5.5)	MMPI	Diagnostic	No mention of COI. No mention of sponsorship	N= 100 patients with TBI with invalid TBI, valid TBI and patients with psychogenic non-epileptic seizures (PNES)	Mean age: 40.9 years 39 males 61 females	Valid TBI (n=27)  Vs. TBI invalid (n=18)  Vs. PNES (n=55)	the Symptom Validity Scale vs. Response Bias Scale (RBS) from the Minnesota Multiphasic Personality Inventory-2	Results indicate that a >30 raw score cutoff for the Symptom Validity Scale accurately identified 50% of the invalid traumatic brain injured group, while misclassifying none of the valid traumatic brain injured group and 6% of the psychogenic non-epileptic seizure disorder group. Using a >15 RBS raw cutoff score accurately classified 50% of the invalid traumatic	“Findings from this preliminary study suggest that the conjunctive use of the Symptom Validity Scale and the RBS from the Minnesota Multiphasic Personality Inventory-2 may be useful in differentiating probable malingering from individuals with brain injuries and conversion disorders.”	A litigating sample. Data suggest RBS and FBS (both from the MMPI-2) help to distinguish those individuals who are malingerers from those with brain injuries and

								brain injured group and misclassified fewer than 10% of the valid traumatic brain injured and psychogenic non-epileptic seizure disorder groups. These cutoff scores used conjunctively did not misclassify any members of the psychogenic non-epileptic seizure disorder or valid traumatic brain injured groups, while accurately classifying 44% of the invalid traumatic brain injured individuals.		conversion disorders.
McCusker 2003 (5.5)	MMPI	Diagnostic	No mention of COI or sponsorship	N= 63 participants	59 males, 4 females mean age was 30.8 years	Diagnoses included (not mutually exclusive): psychotic disorders (40%), affective disorders (52%), anxiety disorders (14%), substance abuse disorders (54%), personality disorders (40%), dissociative disorders (5%), sexual disorders (5%), organic mental disorders (6%), impulse control	Structured Interview of Reported Symptoms (SIRS) scores Vs. Minnesota Multiphasic Personality Inventory—2 (MMPI-2)	Despite differences between facilities in terms of seriousness of subjects' offenses, mean scores on the malingering tests were similar. Cutting scores for F(p) and F resulting in substantial correspondence between these scales and the SIRS were derived. Use of the cut score for F(p) proposed by Arbisi and Ben-Porath (1995) resulted in less agreement with the SIRS than did a lower cut score. No substantial difference between F(p) and F in each scale's overall agreement	"It is an experience that malingering and genuine psychopathology are by no means always mutually exclusive. Clinicians who perform assessments to rule out malingering are encouraged to establish local norms for F(p), F, and the SIRS in their assessment settings, using clinical ratings as the criterion for malingering and choosing cut scores that would reflect the relative importance of positive	Data suggest test scores in addition to interviews and clinical information.

						disorders (3%), and no or unclear diagnoses (9%)		with the SIRS was observed. A principal components analysis of the SIRS primary scales produced two factors, interpreted as Overreporting of Symptoms and Implausible Symptoms. F(p) was observed to correlate significantly with Implausible Symptoms but not with Overreporting of Symptoms; F was significantly correlated with both factors.	or negative predictive power in those settings.”	
Ross 2004 (5.5)	MMPI	Diagnostic	No mention of sponsorship or COI.	N = 59 participants with head injury.	25 males, 34 females. Meang age is 40 years.	Traumatic Brain Injury with clinical scales of Hypochondriasis , Depression, Hyysteria, Psychopatic-Deviate, Masculinity-Femininity, Paranoia, Psychasthenia, Schizophrenia, Hypomania, Social Introversion.	Minnesota Multiphasic Personality Inventory -2 (MMPI-2) vs. Recognition Memory Test (RMT)	A cutoff score of 65 on the F scale provided a sensitivity of 66% and specificity of 64% for and overall correct classification rate of 65%, p<.001. A cutoff score of -6 on F-K index resulted in a sensitivity of 58% and specificity of 56% for an overall classification rate of 57%, p<.05. A cutoff greater than or equal to 21 for FBS resulted in 90% correct classification, p<.001. A cutoff score of 20 had a specificity of 85% and sensitivity of 95% A cutoff score of 25 had a sensitivity of 81% and specificity of 95%.	“The FBS appears to provide rather unique – and powerful – predictive power in identifying likely malingering in MHI, over and above traditional MMPI-2 validity indices and relevant clinical scales.”	Data suggest the MMPI-2 FBS has the excellent sensitivity and specificity for accurate identification of effort in mild head injured persons.

Larrabee 2003 (5.0)	MMPI	Diagnostic	No mention of sponsorship or COI	N = 26 litigants performing worse significantly ( $p < .05$ ).	14 males, 12 females. Mean age is 34.72 years.	Traumatic Brain Injury	Minnesota Multiphasic Personality Inventory -2 (MMPI-2) vs Portland Digit Recognition Test (PDRT)	MMPI-2 validity scales for malingering and closed head injuries in the order of scale, malingers, closed head injury, p value and effect size. F, 64.81, 57.10, $p = .052$ , 0.54. Fb, 66.19, 55.28, $p = .051$ , 0.54. F(p), 54.00, 58.73, $p = .151$ , -0.39. FBS, 26.15, 15.67, $p = .001$ , 1.81, FBS, 26.15, 15.67, $p = .001$ , 1.81. Meyers' Index, 3.31, 0.79, $p = .001$ , 1.01. F-K, -7.15, -8.48, $p = .519$ , 0.18. Ds-r, 57.52, 53.96, $p = .320$ , 0.27. Subtle-obvious, 81.50, 35.47, .018, 0.66. Es, 28.05, 41.77, $p = .001$ , -1.05.	"The sensitivity of the FBS to malingering in neuropsychological settings is superior to any other MMPI-2 validity or standard clinical scale and F, Fb, and F(p) are generally insensitive to malingering of neuropsychological symptoms."	
Nelson 2011 (4.5)	MMPI	Diagnostic	Supported by Grants funded by the Congressionally Directed Medical Research Programs (number PT074550, contract W81XWH-08-2-0038) to Scott R. Sponheim Ph.D. and the Minnesota Veterans Research Institute (MVRI) to Nathaniel W. Nelson, Ph.D.	N = 128. Divided into three groups of forensic (N=42), clinical (N=43), and research (N=43) with combat related traumatic brain injury.	123 males, 5 females. Mean age is 31.8 years.	Psychological Function with respect to Traumatic Brain Injury	Minnesota Multiphasic Personality Inventory -2 (MMPI-2) vs Minnesota Multiphasic Personality Inventory -2 – Restructured Form (MMPI-2-RF)	Analyses of MMPI-2/RF scales resulted in significant overall models. Fp, $p = .323$ , Fp-r $p = .021$ were the only scales that did not show significant differences. RCd $p < .001$ , RC1 $p < .001$ , MLS $p < .001$ , GIC $p < .001$ , HPC $p < .001$ , COG $p < .001$ , STW $p < .001$ , AXY $p < .001$ and ANP $p < .001$ . Participants with active disability claims were four times more likely to elevate on FBS $p = .001$ ; OR=3.86, 95% CI=1.73-8.63. Also 3 more times likely to elevate on FBS-r $p = .018$ ; OR=2.64, 95%	"The current findings suggest that rates of possible symptom exaggeration, particularly over-endorsement of somatic and cognitive symptoms, increases dramatically in forensic and clinical contexts relative to settings in which primary and secondary gain issues are less salient to OEF/OIF concussion groups."	Data suggest litigation significantly influences injury severity reporting as reflected in the MMPI-2.

			No mention of COI.					CI=1.16-6.04 and RBS, p=0.15; OR=3.07, 95% CI=1.19-7.92.		
Youngjohn 1997 (4.5)	MMPI	Diagnostic	No mention of sponsorship or COI.	N = 60 patients with vary levels of head injury.	42 males, 18 females. Mean age is 33.15 years.	Traumatic Brain Injury	Two groups of head injury compared using Minnesota Multiphasic Personality Inventory-2 (MMPI - 2). Moderate/Severe head injuries (N=30) vs. Minor/mild head injury (N=30).	Significant differences were found on the basic scales Hs, D, Hy, Pt, and Sc. On scales Hs, all three groups were significantly different from one another. LOC for group 1 was 653, group 2 was 470, group 3 was .01. GCS group 1:6.9, group2: 7.27, group 3: 15.00. PTA for group1: 1,238, group 2: 774, and group 3:2. Large subset of patients completed the MMPI-2 content with 13 supplementary scales including F Back (fb) Variable Response Inconsistencies (VRIN), and True Response Inconsistencies (TRIN).	“The virtually 100% prevalence of litigation in symptomatic minor/mild head injury gives rise to the obvious hypothesis that persisting symptoms and disability in this population are entirely determined by involvement in litigation.”	Data suggest litigation significantly influences injury severity reporting as reflected in the MMPI-2.
Greiffenstein 2002 (4.5)	MMPI	Diagnostic	No mention of sponsorship or COI.	N = 68 patients with moderate-severe closed-head injury.	Mean age is 33.14 years.	Moderate/severe traumatic brain injury.	Claimants and all participants were administered the MMPI-2. FBS raw scores were tabulated.	AMHI and MSCHI groups had a significant difference in FBS group means p<.0001. No significant difference between groups on MMPI-F scale (t=-.833) or F-K index (t=-.907). Improbability ranking with FBS scores within the AMHI group	“FBS appears to be superior to the standard MMPI infrequency scales in differentiation of atypical versus better-documented neurological injury when litigation status is held constant. Correlational analyses	Data suggest FBS is superior to MMPI-2 F and F-K scales for distinguishing atypical vs real brain injury outcomes.

								obtained a significant r of .305 ( $p < .001$ ). FBS had significant correlations with other MMPI scales with; Hs, Hy, D, Pt, Si, Sc, Pa, Pd, and Gough in descending magnitude. No significant correlations with L, K, Mf or Ma.	showed the FBS is not a pure validity construct measuring one type of spurious symptom over reporting.”	
Van Dyke S, 2013 (4.5)	MMPI	Diagnostic	No mention of COI or sponsorship	N= 120 participants	Age 17 to 85 94% male, 6% female 32.6 years mean age.	Patients with TBI from the urban Department of Veterans Affairs Medical Center	2-factor I SA VS VA 2-factor II C VS SR 3-factor I CP VS PV VS SR 3-factor II C VS SS VSS SV 4-factor PV VS SS VS SV	There was a statistically significant difference on individuals performing better on the MSVT ( $M = 96.48$ , $SD = 6.55$ ) when compared to other referrals ( $M = 92.36$ , $SD = 12.94$ ), $t(118) = 2.30$ , $p = .023$ .	“Overall, the current study contributes to the clarification of relationships between the constructs underlying cognitive performance measures, performance validity measures, symptom self-report measures, and symptom validity measures. The findings extend the consensus that forensic and clinical neuropsychological assessments should include a multifactorial assessment of effort (Bush et al., 2005; Heilbronner et al., 2009) to also encourage separate assessment of performance validity and symptom validity.”	Data suggest performance validity should be evaluate separately from symptom validity.

Bolinger 2015 (4.5)	MMPI	Diagnostic	No COI No mention of sponsorship.	N= 79 Young adults with a history of mild head injury	Mean age: mean 18.97 years.	Those randomly assigned to simulate head injury and who showed evidence of following simulator directions by failing at least one PVT, as described above (n = 32) vs. Those randomly assigned to perform with their best effort and who showed no evidence of poor performance on any PVTs (n = 46).	Neurological Complaints (NUC) vs Cognitive Complaints [366] scales of the Minnesota Multiphasic Personality Inventory-2 Restructured Form (MMPI-2-RF)	Results showed that both scales, but especially NUC, are elevated in individuals simulating head injury, with medium to large effect sizes. Although both scales were highly correlated with all MMPI-2-RF over-reporting validity scales, the relationship of Response Bias Scale to both NUC and COG was much stronger in the simulators than controls. Even accounting for over-reporting on the MMPI-2-RF, NUC was related to general somatic complaints regardless of group membership, whereas COG was related to both psychological distress and somatic complaints in the control group only. Neither scale was related to actual neuropsychological performance, regardless of group membership.	“The present results support the need for further examination of self-reported cognitive and neuropsychological complaints using objective cognitive tests (including PVTs). Clinicians need to remember that self-reported cognitive symptoms can be due to many causes, not necessarily cognitive impairment, or can be exaggerated in a non-credible manner. It remains imperative that clinicians interpret high scores on cognitive symptom scales in light of measures of non-credible symptom report, PVT performance, actual cognitive test performance, evidence of everyday functioning, and overall psychological distress.”	Data suggest self-reported cognitive symptoms result from many causes not simply or necessarily cognitive impairment and may be exaggerated.
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Kim JS 2013 (4.0)	MMPI	Diagnostic	No mention of COI. The study was supported by the 2009 Yeungnam University Research Grant	N= 219	Mean age: 37.87 years 161 males, 58 females	Participants with mild brain injury	Korean Wechsler Adult Intelligence Scale (K-WAIS) Vs. Korean Memory Assessment Scale (K-MAS) Vs. Korean Boston naming test (K-BNT) Vs. Symptom Checklist-90-revised (SCL-90-R) Vs. Minnesota Multiphasic Personality Inventory (MMPI)	Over a quarter (26.9%) experienced severe psychopathological symptoms and 43.4% experienced mild or moderate psychopathological symptoms, and all of the mild TBI patients showed a significant relationship between neurocognitive functions and subjective and/or objective psychopathic symptoms, but the degree of this relationship was moderate. Variances of neurocognitive function were explained by neurotic and psychotic symptoms, but the role of these factors were different to each other and participants did not show intelligence and other cognitive domain decrement except for global memory abilities compared to the non-psychopathology group	“In this study, we demonstrated a relationship between the neuropsychological performance of patients with mild TBI and their psychopathological characteristics assessed in the DE process. We examined the variables that influenced psychopathological characteristics in neuropsychological performance among patients with mild TBI via statistical clustering of the same characteristics in mild TBI. Certain patients with mild TBI displayed psychopathological symptoms, but these were not directly related to cognitive decrement, and psychopathology and cognitive decrement were discrete aspects in patients with mild TBI.”	Data suggest some mild TBI patients showed psychopathological symptoms but they did not appear to be directly related to cognitive decrement.
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Youngjohn 2011 (4.0)	MMPI	Diagnostic	No mention of sponsorship or COI.	N = 82 participants with claimed TBI.	54 males, 28 females. Mean age is 45 years.	Diagnoses were categorized into Mild traumatic brain injury, complicated mild traumatic brain injury, and moderate/severe traumatic brain injury.	Minnesota Multiphasic Personality Inventory—2 Restructured Form (MMPI-2RF) vs. Portland Digit Recognition Test (PDRT) vs. Word Memory Test (WMT) vs. Dot Counting Test (DCT) vs.	Two way MANOVA comparing validity scales profiles of MMPI-2-RF showed no significant differences $p=0.07$ . Somatic/cognitive scales using MANOVA did not indicate significant differences $p=.32$ . The resulting function of somatic/cognitive scales classified 70.7%	“MMPI-2-RF scales FBS-r, RC1, and the Somatic/Cognitive scales (MLS, GIC, HPC, and NUC) can be useful tools in assessing symptoms, disability, and over-reporting in TBI litigants.”	Data suggest the use of MMPI-2 RF is effective in neuropsychological assessment of TBI litigants in an attempt to identify poor effort, somatization or over reporting of symptoms.
Thomas 2009 (4.0)	MMPI	Diagnostic	No mention of sponsorship or COI.	N = 83 patients with claimed TBI.	55 males, 28 females. Mean age is 45 years.	Diagnoses were categorized into Mild traumatic brain injury, complicated mild traumatic brain injury, and moderate/severe traumatic brain injury.	Minnesota Multiphasic Personality Inventory—2 Restructured Form (MMPI-2RF) vs. Portland Digit Recognition Test (PDRT) vs. Word Memory Test (WMT) vs. Dot Counting Test (DCT) vs.	Two way MANOVA comparison of TBI severity groups indicated no significant differences; $p=.31$ . Profiles of SVT status differed significantly $p=.01$ . TBI severity and SVT status were not significantly different $p=.08$ . MANOVA comparing RC scales were not significantly different $p=.29$ . RC scales of SVT status differed significantly $p=.02$ .	“RC scales of the MMPI-2-RF will perform functionally comparable to the traditional clinical scales of the MMPI-2 in litigating TBI populations. The MMPI-2 validity, clinical, and RC scales all appear to be accurate and effective means by which to identify somatization and malingering.”	Unequal sample size for TBI severity categories. Data suggest MMPI-RC scales help diagnose malingering in TBI patients.

Intelligence testing has been widely used to assist in comprehensive neuropsychological evaluations, including those of persons with traumatic brain injury. [367] One of the more commonly used intelligence tests is the Wechsler Adult Intelligence Scale (WAIS), [368-370] having been commonly used [371] for estimating full scale IQ score (FSIQ) among TBI patients also for the identification of malingering and/or exaggeration. [369, 372-384].

## Intelligence Testing

### Wechsler Adult Intelligence Scale

#### Recommended.

The Wechsler Adult Intelligence Scale is moderate recommended for use in the evaluation of TBI patients.

*Strength of Evidence* – **Moderately Recommended, Evidence (B)**

*Level of Confidence* – **High**

<i>Indications:</i>	Post-TBI testing. Repeat testing to follow progress may be sometimes helpful.
<i>Benefits:</i>	Identification of severity of TBI, follow-up of symptoms and at resolution of symptoms. May assist with identification of malingering. [372-376] [377-380]. The WAIS is often used in conjunction with clinical picture as well as Wechsler Memory Scale IV to attempt to substantiate subjective complaints.
<i>Harms:</i>	Negligible. Potential for occasional misinterpretations especially where baseline data are missing.
<i>Frequency/Dose/Duration:</i>	Administered after TBI to assist with patient management.
<i>Rationale:</i>	There are several moderate quality studies suggesting utility of WAIS and/or WAIS-IV for evaluation of patients who sustained TBI [372-375] [376-378] [379, 380]. WAIS is not invasive, has no adverse effects, is of moderate cost, has evidence of accuracy for assessing IQ and for detecting malingering, and is thus recommended for evaluation of TBI patients. The test is periodically updated and the most recent version is recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Minnesota Multiphasic Personality Inventory (MMPI) and Hs (Hypochondriasis) and Hy (Hysteria); Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 122 articles in PubMed, 92 in Scopus, 14 in CINAHL, 14 in Cochrane Library, 430 in Google Scholar, and zero from other sources. We considered for inclusion 13 from PubMed, zero from Scopus, 2 from CINAHL, one from Cochrane Library, zero from Google Scholar,

and zero from other sources. Of the 15 articles considered for inclusion, 2 prognostic studies, 11 diagnostic and 2 systematic studies met the inclusion criteria.

Traumatic Brain Injury– A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Wechsler Adult Intelligence Scale-III, WAIS-III, WAIS-IV, Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 42 articles in PubMed, 21 in Scopus, 18 in CINAHL, 17 in Cochrane Library, 2480 in Google Scholar, and 2 from other sources. We considered for inclusion 12 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 2 from other sources. Of the 14 articles considered for inclusion, 14 diagnostic and 0 systematic studies met the inclusion criteria.

### Evidence for the Use of Wechsler Adult Intelligence Scale (WAIS)

Author Year (Score)	Category:	Study type:	Conflict of Interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Reid-Arndt, 2011 (score=5.0)	WAIS III	Diagnostic	No mention of COI or sponsorship.	N=176 individuals with a history of TBI.	Mean age: 34.3±12.2 years; 102 males, 74 females.	Traumatic brain injury	All patients completed 7 subtests of WAIS-III. (Short-form 1-7: SF1-7)	Estimated FSIQ from all WAIS-III short forms correlated with actual WAIS-III FSIQ (allrs>.91, ps<.001). ANOVA results showed highest validity for both short forms. Short-form 1 showed highest percentage of estimated FSIQ ±5 points of actual FSIQ (75.6%). Short-form 4 resulted in next highest percentage within ±5 pts of actual FSIQ (71.6%). SF-1 provided 71% correct classification of individuals while, SF-4 resulted in 73.9% correct classification.	“Thus, two tetrad versions were consistently superior to others in accuracy of estimating FSIQ; these may be helpful when time constraints or other issues necessitate use of an abbreviated battery for estimating FSIQ among individuals with TBI.”	Data suggest two tetrad versions consistently accurately estimated FSIQ which may be beneficial when there are time constraints in TBI individuals as the estimated FSIQ correlated well to the actual FSIQ.
Greve, 2003 (score=5.0)	WAIS-III	Diagnostic	No mention of COI or sponsorship.	N=65 traumatic brain injury patients.	Mean age: 36.6 years; 43 males, 22 females.	Traumatic brain injury	All or most patients completed WAIS, WMS, and one SVT.	Group effect was observed for DFS (F[1, 57]=10.93 p<.01), Significant group	“This study has added to the literature by reporting sensitivity and	Data suggest the DFS and V-DS in combination does not result in improved

							Probable: (n=28) vs Control: (n=37)	(F[1, 57]=6.601, p<.05), and FSIQ level (F[1, 57]=5.360, p<.05) for VDS. Cutoffs were used to determine sensitivities and specificities.	specificity of Mittenberg's WAIS formula in the diagnosis of malingering as applied to both the revised and third edition of the WAIS, to different levels of brain injury severity, and to different IQ levels. These results indicate that a positive finding in the presence of substantial external incentive is associated with malingering."	diagnostic accuracy. Additionally, a positive finding in the presence of substantial external incentive was associated with malingering.
Miller, 2004 (score=5.0)	WAIS-III	Diagnostic	No mention of COI or sponsorship.	N=100 persons with either a history of alcohol abuse, polysubstance abuse, or TBI.	Mean age: 42.5 years; 86 males, 14 females.	Malingering Alcohol abuse, polysubstance abuse, head trauma	Alcohol abuse group: (n=30) vs polysubstance abuse: (n=43) vs TBI group: (n=27)	Vocabulary (WAIS)-Digit Span (DS or WMS) called V-DS score misclassified 0% of alcohol group, 2% of polysubstance group and 0% of TBI group. Overall V-DS score correctly classified 99% of cases. RMI misclassified 3% of alcohol group, 5% of polysubstance	"The specificities of the screening indexes in the present investigation, 99% (V-DS) and 95% (RMI), support the conclusions of previous investigators. In addition, the index cutoff scores do not represent prevalent test patterns produced by	Mixed population of alcohol abuse, polysubstance abuse, and TBI patients. Data suggest both the V-DS and the RMI detected symptom exaggeration with high accuracy 99% for V-DS and 95% for RMI.

								group, and 7% of TBI group. Overall RMI correctly classified 95% of cases.	individuals diagnosed with AA or PA, indicating that among individuals with these clinical diagnoses, the test patterns under investigation are not characteristic of these disorders, despite frequent patient complaints of attention and memory problems.”	
Mathias, 2002 (score=5.0)	WAIS-III	Diagnostic	No mention of COI or sponsorship.	N=54 traumatic brain injury patients.	Mean age: 35.96 years; 38 males, 16 females.	Traumatic brain injury	All patients completed WAIS, WMS, and SVT tests. Probable group: (n=24) vs Control group: (n=30)	Group effect was observed for RDS score $F(1, 52) = 44.77, p < .01$ . Sensitivity and specificity were measured at specific cutoffs of 5, 6, 7, 8. Only cutoff 8 showed greatest sensitivity of 88 with specificity of 80. Cutoff 5 showed sensitivity of 21, but specificity of 100. Issues of false positives/negatives	“This study has replicated previous work in demonstrating that the RDS test is sensitive to MND in TBI while maintaining excellent specificity and extends previous work by classifying patients in terms of Slick et al.’s (1999) proposed criteria for MND.”	Data suggest RDS is sensitive to MND in TBI patients and has very good specificity.

								es were observed.		
Wilbur 2008 (score=4.5)	WAIS-III	Diagnostic	No mention of sponsorship. No COI.	N=214 patients. 42 with diagnosed traumatic brain injuries, 42 with diagnosed learning disabilities and 40 with emotional diagnoses.	Age and gender not reported.	Traumatic brain injury (TBI)	Participants' self-predicted and observed standardized sub-test scores (R) on 17 WAIS-III subtests and participants' predicted and observed sub-tests scores (B).	Significant relationship among the WAIS-III and self-monitoring measures, $p < 0.0001$ . No differences among the groups on the FSIQ, VIQ, POI and WMI measures, $p > 0.05$ .	"The R and B measures are two valid and reliable indices of self-monitoring that can be conveniently estimated from the WAIS-III."	Mixed population of TBI, emotionally disabled and learning disability patients. Data suggest that 2 measures are useful in measuring self-monitoring and discriminating between the 3 different groups.
Walker 2009 (score=4.5)	WAIS-III & WMS	Diagnostic	No sponsorship or COI.	N=200 patients. 100 patients with moderate to severe traumatic brain injury (TBI). 100 controls.	Mean age: TBI 30.68 years. Controls 40.07 years. TBI: 81 males/19 females. Controls: 70 males/30 females.	Moderate to severe traumatic brain injury (TBI).	Wechsler Adult Intelligence Scale-III (WAIS-III) and Wechsler Memory Scale-III (WMS-III) indices vs. age corrected indices.	Age corrected indices correctly classified 77% [154385] of all participants, with 82% sensitivity and 72% specificity. Demographically corrected indices correctly classified 74% [148385] of participants, with 76% sensitivity and 72% specificity.	"[F]or mostly younger white individuals with lower levels of education, the demographic corrections for the WAIS-III and WMS-III do not provide an advantage in the classification of moderate to severe TBI over and above age corrected indices."	Data suggest demographically corrected WAIS-III and/or WMS-III indices did not provide better diagnostic accuracy than age corrected indices in TBI patients.
Strong 2005 (score=4.5)	WAIS-III	Diagnostic	Supported by a grant from the Campbell Foundation and was based in part on	N=200 patients. Mild TBI (n = 53), Moderate-Severe TBI (n = 47) and standardization	Mean age: Mild TBI 35.94 years, 33 males/ 20 females. Moderat	Traumatic brain injury (TBI).	Demographically corrected norms vs. traditional age-corrected norms	Demographically corrected norms were not clearly advantageous or disadvantageous for use in	"[D]emographically corrected WAIS-III norms do not offer a clear advantage or disadvantage	Data suggest there is no advantage for using demographically corrected WAIS III norm

			standardization data derived from the Wechsler Adult Intelligence Scale. No mention of COI.	controls (n = 100)	e-severe: 31.64 years, 33 males/ 14 females. Controls 34.29 years, 33 males/ 20 females.		Evaluation with the WAIS-III.  Mild TBI (n=53), Moderate-Severe TBI (n=47), controls (n=100)	the diagnostic classification of moderate-severe TBI in a primarily Caucasian sample.	compared to traditional age-corrected norms in the assessment of patients with TBI who are Caucasian and who have at least a middle school level of education."	compared to traditional age corrected norms in the assessment of Caucasian TBI patients with a minimum of a middle school level of education.
Langeluddecke, 2003 (score=4.0)	WAIS-III	Diagnostic	No mention of sponsorship or COI.	N=150 subjects with mild TBI.	Mean age: 35.2 years; 130 males, 75 females.	Moderate to severe traumatic brain injury	All patients interviewed and tested via GCS score, then tested with WAIS-III. Extremely severe TBI: (n=41) vs Severe: (n=74) vs Moderate: (n=35) vs Controls: (n=50)	Greatest effect size between controls and TBI groups was observed for PSI (F=21.0). Moderate TBI group mean differences in most of IQ and Index scores were small, averaging <5 IQ points. PSI was the only measure that moderate TBI group differed with $p < .03$ from control group. Differences between severe TBI and control group were observed for all measures with an effect size of -.57 for WMI to -.96 for PSI. For extreme TBI	"Findings for the entire moderate to extremely severe TBI sample in the present study indicate a significant "dose response" relationship between WAIS-III IQ/Index scores and TBI severity."	Data found a significant dose-response relationship between TBI severity and all WAIS-III index/IQ scores.

								group similar results to moderate group with difference in all measure and effect size of -.78 for WMI to -1.5 for PSI. Effect size for controls vs combined TBI group were highest ( $d \geq 0.9$ ) for similarities, digit symbol, picture arrangement, and symbol search.		
Greve 2008 (score=4.0)	WAIS-III	Diagnostic	No mention of sponsorship or COI.	N=211 TBI patients. Not-Malingered Neurocognitive Dysfunction (MND) (n=87), Indeterminate (n=68), and MND (n=56).	Mean age 38.3 (SD=13.6) .60 females, 151 males.	Traumatic Brain Injury (TBI)	WAIS-III, VIQ, PIQ, and FSIQ.	No difference in latency as a function of injury severity ( $\eta^2=0.02$ ) or malingering status ( $\eta^2=0.00$ ) PIQ differential was accurate in mild TBI but did not differentiate MND from Not-MND in moderate-severe TBI.	“This study indicates that VIQ declines of greater than 24 points are rare except in very severe TBI. Particularly in mild TBI, such differentials likely indicate intentional suppression of WAIS-III performance consistent with MND.”	Data suggest verbal IQ declines of more than 24 points are uncommon except in rare cases of severe TBI. If such decline is found in M-TBI it is possibly due to intentional suppression of WAIS-III performance and is likely malingered neurocognitive dysfunction.
Curtis 2009 (score=4.0)	WAIS-III	Diagnostic	No mention of sponsorship or COI.	N=83 total TBI patients. Mild TBI not-malingered neurocognitive	Mean age 37.4 (SD=12.8) .23	Traumatic Brain Injury (TBI)	WAIS-III, Verbal IQ, Verbal Comprehension Index, and	VIQ, VCI, and WMI scores differentiated malingers	“Overall, a dose-response relationship between injury severity and all	Data suggest V-DS and the Mittenberg formula failed in

				dysfunction (MND) ( <i>n</i> = 26), mild TBI MND ( <i>n</i> = 31), moderate/severe (M/S) TBI not-MND ( <i>n</i> = 26).	female/60 males.		Working Memory Index.	from nonmalingerers with a high degree of accuracy, detecting ≥26% of malingerers with an FP rate of ~5%.	WAIS-III scores was observed, with PSI showing the largest effect size.”	the differentiation of malingerers from non-malingerers.
Fischer, 2000 (score=3.5)	WAIS-III	Diagnostic								Data suggest WAIS-III results showed IQ and index scores of MTBI patients were similar to controls but moderate-severe TBI patients had significantly lower mean scores across all measures.
Donders, 2001 (score=3.5)	WAIS-III	Diagnostic								Data suggest letter-number-sequencing and symbol search have moderate criterion validity but should be used with other metrics in neuropsychological evaluations. Additionally, Matrix Reasoning show little of any

										sensitivity to TBI sequelae.
Ryan, 2005 (score=3.5)	WAIS-III	Diagnostic								Mixed population of TBI, stroke, Parkinson's disease, dementia, or Alzheimer's disease. Data suggest the MR subtest is not sensitive to TBI, but sensitive to stroke and dementia.
Kennedy, 2003 (score=3.0)	WAIS-III	Diagnostic								Data suggest TBI patients reflect WAIS-III PSI scores involving perceptual processing speed and working memory. However, motor speed had had a very small effect on WAIS-III PSI scores.

Automated Neuropsychological Assessment Metrics [1] is a computerized neuropsychological battery that has been primarily used in military settings [386-395]. This assessment includes six tests, including: Simple Reaction Time (SRT), Continuous Performance Test (CPT), Sternberg Memory [396], Mathematical Processing (MTH), Matching to Sample (MSP), Code Substitution-Delayed (CDD), and Spatial Processing (SPD) [390].

## Automated Neuropsychological Assessment Metrics

### Moderately Recommended.

Automated Neuropsychological Assessment Metrics is moderately recommended for use in the evaluation of TBI patients.

#### Strength of Evidence – Moderately Recommended, Evidence (B)

##### Level of Confidence – Moderate

<i>Indications:</i>	Post-TBI testing. Not used for diagnostic purposes, but is used as a test of neurocognitive functioning to help provide support to confirm or disconfirm the presence of mild TBI symptoms. Repeat testing to follow progress may also be helpful [397].
<i>Benefits:</i>	Follow-up of symptoms and at resolution of symptoms, although test re-test reliability may be concerning.
<i>Harms:</i>	Negligible. Potential for occasional misinterpretations especially where baseline data are missing.
<i>Frequency/Dose/Duration:</i>	Administered after concussion and monitored periodically during recovery. For high risk situations, baseline or pre-concussion testing may help measure the baseline. Baseline, pre-concussion testing would rarely be indicated in occupational settings.
<i>Rationale:</i>	There are several quality studies assessing ANAM for diagnosis of TBI [393, 397-403]. All studies suggest utility of ANAM for diagnosis and/or prognosis, although the populations assessed in the quality studies are largely military. Some studies were primarily of athletes. The ANAM diagnostic test is not invasive has no adverse effects, is low cost, has evidence of diagnostic efficacy, and is recommended for diagnosis of TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Google Scholar, and Cochrane Library without date limits using the following terms: automated, neuropsychological, assessment, metrics, ANAM, neck, neck pain, cervical, radicular pain or radiculopathies, neck pain diagnosis, diagnostic, diagnosis, sensitivity, specificity, positive and negative predictive value, predictive value of tests, vertebrae or vertebral or spine; brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed head or penetrating head or craniocerebral; Sensitivity and Specificity, Predictive Value of Tests, Gold-standard, accurate, accuracy, precision, precise, test; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 18 articles in PubMed, 13 in Scopus, 13 in CINAHL, 3 in Cochrane Library, 3460 in Google Scholar, and 0 in other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar and 15 from other sources. Of the 17 articles considered for inclusion, 15 diagnostic studies and 0 systematic studies met the inclusion criteria.

### Evidence for the Use of Automated Neuropsychological Assessment Metrics [1]

Author Year (Score)	Category:	Study type:	Conflict of Interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Nelson 2016 (Score=5.5)	ANAM	Diagnostic	No COI. Sponsorship provided by the U.S. Army Medical Research, Materiel Command, the Clinical and Translational Science Institute, and the National Center for Advancing Translational Sciences, National Institutes of Health.	N = 165 concussed high school and collegiate athletes and N = 166 matched non-injured controls	Mean age: Concussed group – 17.46, Non-injured group – 17.64; 276 males and 55 females	Concussion qualifying as a mTBI	Three computerized neurocognitive tests (CNTs): ANAM, Axon Sports/Cogstate Sport, and ImPACT. Testing occurred 24 hours post-injury, as well as 8, 15, and 45 days post-injury. Each subject only participated in two CNTs.	Sensitivity to concussion at 24 hr: 6.0–23.8% for ANAM, 6.8–48.6% for Axon, and 24.4–39.5% for ImPACT. Sensitivity diminished at day 8 (median difference between hit and false positive rate at day 8 for ANAM, Axon, ImPACT: 0.4%, 4.9%, and 2.4%, respectively).	“Analyses of group effect sizes, discrimination, and sensitivity and specificity suggested that the CNTs may add incrementally (beyond symptom scores) to the identification of clinical impairment within 24 hr of injury or within a short time period after symptom resolution but do not add significant value over symptom assessment later.”	Data suggest ANAM, AXON and ImPACT are time limited in detecting concussion and of little use, if any, performed after 8 days post injury. They are best performed within the first 24 hours.
Luethcke C 2010 (4.5)	ANAM	Retrospective Study	No sponsorship or COI.	N = 82 military personnel and civilians	Mean age of military personnel 26.62 years with all male population. Age range no provided. Follow-up duration not provided.	Acute and mild stages of Traumatic brain injury	(N = 38) Non-blast Group vs. (N= 39) Blast Group. No follow-up analysis were conducted.	No significant results difference was found in return to duty (RTD) after treatment for TBI clinic in both groups. Blast injuries were less frequently associated with loss of consciousness (LOC) when compared to non-blast injuries (54.8%) P=0.604	"Despite this limitation, these results have important clinical implications and provide a solid foundation for future research, since this is the first study that we could identify to capture symptom expression among deployed military personnel within 72 hr of mTBI."	Data suggest few differences exist between concussive symptoms of acute blast versus nonblast mild TBI individuals.

								for RTD and p=0.035 for LOC. No significant differences were found from blast and non-blast injury type p=0.650.		
Cernich 2007 (4.5)	ANAM	Case Control Study	Funded by Cooperative Agreement #DAMD17-00-1-0056 from the US Army Medical Research Materiel Command to the National Rehabilitation Hospital. No COI.	N = 122, high school and college aged; this study looked at the use of the ANAM-sports-medicine battery (ASMB) for use in concussion surveillance and management.	High school and college aged 15-27 with mean of 17.2 years	Concussions	(N = 68), cadets were concussed vs. (N= 18) cadets were not concussed.	MTH scores showed the greatest specificity for concussive injury; SRT and CPT showed a decline between the baseline assessment and the first post-injury assessment.	"Future development of the ASMB is discussed as it relates to interpretation of ASMB, development of appropriate norms, and defining adequate baseline assessment."	Data suggest ANAM may be valuable as a clinical tool for tracking cognitive recovery.
Bryan 2012 (4.0)	ANAM	Retrospective Study	No mention of sponsorship or COI.	N=116 service members referred to a TBI clinic in central Iraq for a TBI evaluation	92.2% males with an average age 27.74 years	Mild traumatic brain injury with any period of loss of or decreased level of consciousness, any loss of memory for events immediately before or after the injury, any alteration in	(N = 96) with TBI vs. (N= 20) without TBI.	Results indicate that service members with TBI demonstrate greater declines in speed and throughput as compared both those service members without TBI regardless of timing of the assessment.	"Assessment of cognitive impairment following TBI in a combat zone may assist providers in making treatment recommendations for service members with mild TBI."	Data suggest TBI cognitive impairment from a combat zone may aid clinicians in making treatment recommendations for military personal with mild TBI.

						mental state at the time of the injury, neurological deficits that may or may not be transient, and intracranial lesion.				
Kelly MP, 2012 (4.0)	ANAM	Case Control Study	Sponsored by U.S. Army Medical Research Acquisition Activity Project W81XWIH-09-2-0057. No COI	N= 212 Male participants only	Aged 18-55 years old with a mean of 25	Traumatic brain injury	(N = 66) Cases vs. (N= 146) Controls. Two control groups were used: healthy group of U.S. Army soldiers from deployed units volunteering for participation, acutely injured U.S. Army soldiers presenting for outpatient care who were neither head-injured nor exposed to a blast.	Cases reported more headaches, blackouts, confusion, and flashbacks. Cases also endorsed more frequent alcohol problems. ANAM, particularly SRT, can detect changes in cognition following a concussion incurred in the combat environment that are both "statistically and clinically significant"; cases performed more poorly than controls on multiple ANAM subtests.	"Results clearly demonstrate that ANAM, and particularly SRT, is more effective than the traditional brief sports medicine neuropsychological battery in differentiating concussed from non-concussed participants in the combat environment when administered within 72 h of injury."	Data suggest ANAM SRT if administered within 72 hours post-TBI has good sensitivity and specificity and can distinguish between concussed and non-concussed individuals.
Vincent 2012 (4.0)	ANAM	Retrospective Study	No sponsorship or COI.	N = 107,500 active duty service member 17-65 years of age with	17-65 years of age with mean age of 27.4 years	Previous brain injury with ongoing TBI related symptoms	The following tests were compared to each other; CDD (N=107523)	Analyses examining the influence of age and gender indicate statistically	"Future research should examine the effects of other potential intervening factors on performance, such as	Data suggest ANAM-4 established a comprehensive age and gender

				97067 males and 10604 females.			vs CDS (N=107546)vs M2S (N=10767) vs MTH (N=107651)vs PRO (107353) vs SR2 (N=107413)vs SRT (N=107662)	significant effect of both "below average" and "clearly below average" on ANAM scores.	military service, ethnicity/race, education, and rank."	stratified set of norms useful for chemical practice.
Norris J 2014 (4.0)	ANAM	Retrospective Study	Sponsored by the Navy Bureau of Medicine and Surgery, under Work Unit No. N24LB. No COI.	N=210 patients with blast-related Mild Traumatic brain injury	Aged 18-50 years with Mean age of cadets 24.80 years with all male population. Follow-up 48-72 hours following visit.	Concussion or Mild Traumatic brain injury	(N = 142) No LOC (LOC is Loss of Consciousness no more than 30 mins) Group vs. (N= 39) LOC Group. Follow-up 48-72 hours after initial visit	A difference in ASRs between no LOC and LOC patients (9.2% vs. 23.5% p<=0.01). At follow-up, LOC reported sleep difficulty 30.3% to 48.5% no LOC p<=0.01. A significant main effect ASR at intake p<=0.001 but not for LOC at p=0.09.	"Computerized neuropsychological tests such as ANAM, when combined with the computer classrooms available at many schools, make it possible to do baseline testing of large numbers of athletes rapidly and inexpensively."	Data suggest ASR from ANAM may partially mediate cognitive dysfunction and symptoms presentation in the acute phase of mTBI post blast.
Vincent 2008 (4.0)	ANAM	Retrospective Study	Sponsored by the DVBC and Cooperative Agreement DAMD17-00-1-0056 with the US Army Medical Research and Materiel Command and the National Rehabilitation Hospital. No COI.	N= 5,247 aged 18-51 years old with 4773 males and 474 females.	aged 18-51 years old with mean age of 26.0	Traumatic brain injury	The following tests were compared to each other using the following logarithmically transformed processes MCRT, PC, TP, & LTP. Test are CDD vs CDS vs MSP vs MTH vs CPT vs SRT. N= 5247	Overall, the data suggest that a general decline in performance with age should be expected on most tests in the ANAM TBI battery.	"This article presents reference data for a military population tested with the ANAM TBI battery."	Data suggest ANAM may have utility in analyzing TBI patients in the general population.

Norris J 2013 (4.0)	ANAM	Retrospective Study	Sponsored by the Navy Bureau of Medicine and Surgery, under Work Unit No. N24LB. No COI.	N=165 concussed active duty personnel (active 188oncussio n)	Aged 19-41 years with Mean age of patients 22.00 years with all male population. Follow-up not conducted	Concussion or Acute concussions	Session 1 N=165 vs Session 2 N=165 Test were against each other SRT vs CDS vs PRO vs MTH vs M2S vs CDD vs SR2.	The reaction time- based substests SRT, and PRO at 0- 25% and RTD time of 19 days for SRT, SR@, and PRO. The upper 0-25% had a median RTD time of approximately 7 days for SR2 AND PRO. No statistically significant results, Session 1 SRT p=0.37, and PRO p=0.35, and Session 2 SRT p=0.50, and PRO p=0.50.	“This study of 165 cases shows that computer-based testing is able to capture useable data that otherwise would have required over 80 hours of clinician time for test administration.” “This report supports the CRCC clinician use of the SRT tests in their initial and follow-up assessments of concussion.”	Data suggest the ANAM4 TBI battery has prognostic value.
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## Memory, Malingering, Exaggeration & Poor Effort Testing

Memory tests have been used to assess TBI patients [404-418]. There are many different types of memory tests used, including: Everyday Memory Questionnaire (EMQ), Spatial Recall Test [409] Short Orientation Memory and Concentration Test (SOMC) [406], Recognition Memory Tests (RMT) [410], the Wechsler Memory Scale (WMS), standardized assessment of concussion (SAC) (O’Neil 14; McCrea 97,98,01; Barr 01; Yan 17), Montreal Cognitive Assessment (MOCA) (deGuise 13,14; Zhang 16a,b; Lim 16), as well as many others.

Malingering tests have been used to assess TBI patients [361, 364, 368, 369, 371, 372]. In addition to tests specifically designed to assess effort and malingering, there are standardized tests of neuropsychological functioning that have been shown to demonstrate the ability to detect suboptimal effort, although they are not malingering tests per se. These are commonly referred to as “embedded measures” of malingering. There various different types of malingering tests used, including: the Test of Memory Malingering (TOMM) [371] [414], Word Memory Test (WMT) [361], the Portland Digit Recognition Test [168], Reliable Digit Span test (Hall 2014), the Wisconsin Card Sorting test [372], as well as others.

### Memory and Malingering Tests

#### Recommended.

Memory and malingering tests are recommended for use in the evaluation of TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – Moderate

<i>Indications:</i>	Moderate or Severe TBI patients experiencing cognitive difficulties. May be performed to help guide treatment. May later be performed as part of an evaluation for end-of-healing and clinical plateau. Generally not used for mild TBI patients, however highly selective use among those with either high and critical occupational cognitive demands and/or memory complaints may also be indicated.
<i>Benefits:</i>	Memory tests used to identify and measure memory difficulties, potentially allowing better tailoring of therapy(ies) to address any memory deficits. Malingering tests used to identify and measure intentional production of exaggerated or false symptoms.
<i>Harms:</i>	Negligible in most patients. Memory testing is strongly subject to malingering and many comparative studies exclude all patients involved in any litigation. Thus, careful interpretation and potential pairing with tests for malingering are indicated especially where there is strong potential for secondary gain(s).
<i>Frequency/Dose/Duration:</i>	Generally not performed more than once or twice. May be used to target specific cognitive rehabilitation strategies. Memory tests may later help determine end of healing and extent of residual deficits, if any.
<i>Rationale:</i>	There are quality studies assessing Memory Tests for diagnosis of TBI. There are also quality studies assessing Malingering Tests fo diagnosis of TBI. However, there are few comparative trials of sufficient size and rigor to allow a recommendation of one type of testing over another.

*Evidence:*

Memory and malingering tests are not invasive, have no adverse effects, are low cost, have evidence of diagnostic efficacy, and are thus recommended for diagnosis and evaluation of TBI patients.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: memory test, letter memory or test of memory malingering or word memory test, traumatic brain injury, intracranial injury, closed head injury penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; sensitivity and specificity, predictive value of tests, gold-standard, accurate, accuracy, precision, precise, test; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 941 articles in PubMed, 546 in Scopus, 793 in CINAHL, 4 in Cochrane Library, 10200 in Google Scholar, and 1 from other sources. We considered for inclusion 11 from PubMed, 3 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 6 from Google Scholar, and 1 from other sources. Of the 21 articles considered for inclusion, 15 diagnostic studies and 0 systematic studies met the inclusion criteria.

### Evidence for the Use of Memory and Malingering Tests

Author Year (Score)	Category :	Study type:	Sponsorship / COI:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Hall 2014 (6.5)**	Memory and Malingering	Diagnostic	No mention of COI or sponsorship	48	27 female, 21 male  Mean age 39 years	Minimal to mild head injury, in acute stages post-injury	Trail Making Test vs. Verbal Fluency (FAS) test vs. Colour Word Interference Test vs. Word Memory Test vs. Test of Malingering Memory (TOMM) vs. Reliable Digit Span vs. PDI vs. MSPQ  Processing Speed Index [419] from WAIS-III vs. Word List Recognition	At the 82.5% cutoff for WMT, the false positive rate (FPR) was 18%. Those who failed the IR or DR also failed the WMT, resulting in a joint failure rate of 18%. In the IR the FPR was 8% and 3% for the DR. The difference between those who passed and failed the WMT was also significant in regards to the verbal fluency test ( $p < 0.05$ , effect size $d \leq 0.7$ ).  Sensitivity for various subtests: RDS = 0.41, TOMM = 0.61; WLR = 0.81; PSI = 0.55; PDI = 0.59; MSPQ = 0.9.	"[T]he results of this study suggest that the WMT consistency index cut-off may be too aggressive with minimal to MHI individuals within the early stages post-injury."	All participants were not involved in litigation and this did not fit malingering criteria. Data suggest WMF may be the result of a specific verbal processing deficit in the acute phase of mild head injury.
Armistead-Jehle 2013 (6.0)	Memory and Malingering	Diagnostic	No COI. No mention of sponsorship.	280	12 female, 268 male  Mean age 32 years	U. S. military service members on active duty with history of mild TBI	Word Memory Test (computer administered verbal memory test with multiple subtests designed to assess verbal memory, effort, and response consistency)	106 participants (37.9%) failed WMT. 18 (6.4%) failed ACS subtests at 10% base rate level and 23 (8.2%) failed at 15%. 173 (62%) passed both tests at 10% and 17 (6%) failed both. 89 (32%) passed ACS subtests but failed WMT. 1 participant (0.4%) failed ACS tests but passed WMT.	"Despite these limitations, the current data replicate previous studies demonstrating the limited sensitivity of embedded effort measures relative to standalone	Primarily Caucasian male population. Data suggest ACS has adequate specificity but poor sensitivity

							vs  Embedded indices testing/subtests: Advanced Clinical Solutions package – WAIS-IV, WMS-IV, RDS, LM-rec, VPA-rec, and VR-rec subtests  All participants underwent both testing	170 (61%) passed both at 15% base rate level, along with 19 (7%) failing both, 87 (31%) failing WMT, and 4 (1%) failing ACS subtests.  At 10% and 15% base rate levels ACS subtest specificity high (0.99, 0.98, respectively) but sensitivity low (0.16, 0.18). Positive predictive power (0.91, 0.85) and likelihood ratios (16.0, 7.80) high, but negative predictive power (0.66, 0.66) and likelihood ratios low (1.18, 1.19). At 25% base rate level specificity = 0.94, but sensitivity = 0.27.	instruments designed to gauge respondent effort on neuropsychological testing.”	compared to WMT.
Das Nair 2012 (6.0)	Memory and Malingering	RCT	Sponsored by grants from The Stroke Association, Remedi (2006/05), Universities UK (Overseas Research Students Award Scheme), and the University of Nottingham. No COI.	N = 72 with memory problems following traumatic brain injury, stroke or multiple sclerosis.	Mean age 47.7, (10.2) years; 32 males and 40 females.	Compensation, 10 sessions (N = 24) vs Restitution treatment programmes, 10 sessions (N = 24) vs A self-help group control 10 sessions (N = 24).	7-months	No significant effect of treatment on the Everyday Memory Questionnaire, (p = 0.97). At 7-months, mean score for compensation vs restitution vs self-help; 41.0 vs 36.6 vs 44.1. Internal memory Aids questionnaire, (p = 0.002). Treatment groups used more internal memory aids vs to self-help, (p < 0.01). Measure of mood / adjustment / and activity of daily living, (p > 0.05).	“These results show few statistically significant effects of either compensation or restitution memory group treatment as compared with a self-help group control.”	Dissimilar time since diagnosis between groups. Mixed population of TBI, MS and Stroke patients. At 7 months data suggest similar efficacy between all groups for mood, memory functions and dialing living activities although the compensation

										and restitution groups used significantly more internal memory aids than did the self help group.
Barhon 2015 (6.0)	Memory and Malingering	Diagnostic	No mention of sponsorship or COI	N = 92	Mean age: 19.7 years; 25 males, 67 females.	TBI	Word Choice Test (WCT) vs. Test of Memory Malingering (TOMM) Full-Effort Group (N=46) vs. Distraction Group (N=46) vs. Uncoached Group (N=22) vs. Coached Group (N=24)	Statistical significance found between full effort group and uncoached group ( $p < .0005$ ) and between full effort group and coached group ( $p < .0005$ ), and no statistical significance between full effort group and distraction group ( $p < .0005$ ). At a cut score of 48, TOMM had a sensitivity of 91.3, specificity of 89.13. At a cut score of 48, WCT had a sensitivity of 86.96, and a specificity of 78.26.	"The WCT was found to be as effective as the TOMM in differentiating simulators from participants applying full effort. The WCT is primarily a measure of effort rather than cognitive ability."	Data suggest similar efficacy between TOMM and WCT in the detection of cognitive impairment. Both TOMM and WCT are primarily tests of validating poor effort.
Iverson GI 2002 (5.5)	Memory and Malingering	Diagnostic	No mention of COI or sponsorship.	N= 571 participants presenting to the trauma service with a known or suspected head injury	405 males, 166 females Mean age: 35.8 years	Traumatic brain injury	Trail making test And tests of effort were Computerized Assessment of Response Bias Word Memory Test	The hospital patients with more severe traumatic brain injuries performed more poorly than the patients with less severe brain injuries on Trails A and Trails B. The performances of the head injury litigants who exaggerated on at least one well-validated symptom validity test were compared to these cutoffs. Very high positive predictive values for individuals with very mild head injuries on Trails A and B	"In conclusion, the results of this study do not support the use of the TMT as a reliable predictor of deficits during neuropsychological testing. Based on individual patient comparisons in this study, the TMT's clinical utility as means of identifying poor effort was	571 patients non-litigated and 228 patients involved in head trauma litigation. Data do not support the use of TMT as a reliable predictor of either poor effort or exaggerated effort. Brain injury severity was not

								were identified (i.e., both 100%); lower positive predictive values were obtained for individuals with more severe head injuries (55.6–60%). The negative predictive values were only moderate (range=66.4–78.2%), and the sensitivity was very low (range=7.1–18.5%) for all groups.	extremely limited. Thus, they may be indicative of deliberate exaggeration. Typically, this process relies on multiple test results and sources of information. The TMT has a very limited value in this process due to its low sensitivity.”	necessarily correlated with effort.
Lange 2010 (5.5)	Memory and Malingering	Diagnostic	No mention of COI or sponsorship.	63 individual with mild TBI who were receiving financial compensation from the Workers’ Compensation Board	Mean age: not specified; 40 males, 23 females.	Mild TBI	TOMM pass (n = 48) vs. TOMM fail (n = 15). All participants underwent the following tests: Post-Concussion Scale (PCS), British Columbia Cognitive Complaints Inventory (BC-CCI), selected test from Neuropsychological Assessment Battery Screening (S-NAB)	Between TOMM pass and fail groups: significant main effects and large effect sizes for PCS (d=0.79, p=0.002), BC-CCI (d=0.98, p=0.011). Those in TOMM fail group scored higher for both measured compared to TOMM pass group. TOMM fail group scored lower on attention (d=1.26, p=0.004), memory (d=1.16, p=0.006), and executive functioning (d=0.70, p>0.05) indexes	“These results highlight the importance of considering the influence of poor effort, in conjunction with a growing list of factors that can influence, maintain, and/or mimic the persistent postconcussion syndrome.”	All participants receiving financial compensation . Data suggest poor effort must be considered in addition to multiple other factors which can mimic post-concussion syndrome.
Flaherty 2015 (5.5)	Memory and Malingering	Diagnostic	No COI. No mention of sponsorship.	257 veterans with possible mild TBI	Mean age: 29.5 years; 248 males, 9 females.	Possible mild TBI	Rey Fifteen-Item Memory Test (FIT) (n = 257). Out of the 257 participants that underwent the FIT, some completed the Digit Span (n = 148) and some completed	Four (1.6%) participants failed the FIT (according to standard cut-off of <9 items), three (1.2%) failed the FIT (cut-off of <8 items), and 198 (77%) obtained perfect scores.	“Despite its popularity, the FIT is not supported as an appropriate measure of performance validity in veterans	Data suggest FIT is not a good tool for performance validity in veterans being evaluated for mTBI.

							the Digit Span and the TOMM (n = 109)		undergoing evaluation for possible mTBI. Therefore, inferences regarding neuropsychological data reliability with adequate statistical certainty require use of other measures of performance validity with greater sensitivity."	
Schroeder 2013 (5.5)	Memory and Malingering	Retrospective	No sponsorship or COI.	62 consecutive forensic cases, with complaints related to TBI	Mean age 40.83 years for pass MND, 44.08 years for fail MND; 38 males, 24 females.	Mild TBI, complicated mild TBI, moderate-to-severe TBI, or a number of other conditions including major depressive disorder, frontotemporal dementia, and mental retardation to name a few.	Malingered Neuropsychological Dysfunction Criteria (MND) Pass group (n = 26) vs. MND Fail group (n = 36). All participants underwent TOMM trial 1, TOMM trial 2, TOMM retention, and the Albany Consistency Index tests.	Group performances between pass and fail MND groups, respectively (mean score, mean rank, Mann-Whitney U, p-value) - TOMM trial 1: 47.17 vs. 35.92, 41.89 vs. 17.12, 94.00, (p < 0.01), TOMM trial 2: 49.86 vs. 41.96, 41.08 vs. 18.23, 123.00, (p < 0.01), TOMM Retention: 49.69 vs. 39.88, 41.35 vs. 17.87, 113.50, (p < 0.01), ACI: 46.89 vs. 30.15, 42.57 vs. 16.17, 69.50, (p < 0.01)	"Evidence was provided for convergent and divergent validity for all TOMM indices, which increases confidence for the clinical utility of both the new and traditional indices. Although each index well differentiated patients passing and failing MND criteria, the ACI was found to be the superior index."	Data suggest both the new and the traditional TOMM indices are valid and have good clinical value. However, the ACI was found to be the superior index.
Guisse 2010 (score= 5.0)	Memory and Malingering	Diagnostic	No mention of COI or sponsorship	N=176 TBI patients (archival data).	Mean age mild TBI/good effort: 38.1 (SD=9.7). 26	Mild to severe TBI	Mild TBI/Good Effort (n = 40) vs. Mild TBI/Poor Effort (n = 42) vs. Moderate-severe	Effort was found to have a greater effect on test performance (0.79) than injury severity (0.47).	"Moderate-severe TBI produced overall worse	Data suggest effort has a greater effect on text performance

					males, 13 females mild TBI/good effort group.		TBI/Good Effort (n = 40) vs. Moderate-severe TBI/Poor Effort (n = 14) vs. Control (n=40).  Portland Digit Recognition Test vs. Test of Memory Malingering (TOMM).		performance than mild TBI patients and control subjects. Mild TBI showed some effect on test performance, but deficits were likely due to secondary factors including financial incentive, psychological overlay, and poor effort."	than does injury severity.
Teichner 2004 (score= 5.0)	Memory and Malingering	Diagnostic	No mention of COI or sponsorship	N=78 elderly cognitively intact, cognitively impaired (non-dementia), and with dementia	Mean age was 70.5 (SD=8.5). 33 males and 45 females.	Cognitively intact, cognitively impaired (non-dementia), and with dementia.	Test of Memory Malingering (TOMM) vs. Wechsler Adult Intelligence Scale—Third Edition (WAIS-III) vs. Wechsler Memory Scale—Third Edition (WMS-III) vs. Mini-Mental State Examination (MMSE).	100% of normals and 92.7% of the cognitively impaired group made fewer than five errors (the suggested cut-off) on Trial 2 or the Retention trial of the TOMM.	"Results suggest that the TOMM is an useful index for detecting the malingering of memory deficits, even in patients with cognitive impairment, but only when dementia can be ruled out."	Data suggest TOMM is a useful test for the detection of malingering and memory defects even in those with cognitive impairment if and only if dementia can be ruled out.
King 1999 (5.0)	Memory and Malingering	Cross-validation sample	No mention of sponsorship or COI.	N = 57 with mild to moderate head injuries.	Mean age 32 (13) years; 43 males and 23 females.	TBI	Short Orientation Memory and Concentration Test (SOMC), Rivermead Post-Concussion Symptoms Questionnaire (RPQ)	At 3 months, SOMC scores accounted for 74%of the variance in RPQ Scores, combination of IES and SOMC scores accounted for 55% of the variance in RPQ scores at 7±10 days.	"[T]he results from this study largely support the previous findings and confirm that it is a combination of measures – emotional, organic and neuropsychologic	Data suggest combining HADS and IES are useful for prognostic screening and predicting PCS.

									al – which best predict early on post –injury those most likely to suffer persisting PCS.”	
Sherer M 2015 (5.0)	Memory and Malingering	Diagnostic (prospective cohort, observational study)	No COI. Supported by the National Institute on Disability and Rehabilitation Research, U.S. Department of Education [grant number H133B090023], [grant number H133A120020]	491 medically documented participants with TBI	369 males, 122 females. Mean age: 38 years.	TBI	Word memory test (WMT) vs. performance validity test (PVT)	117 participants showed poor performance validity using the standard cutoff. Variable cluster analysis was conducted as a data reduction strategy. Findings revealed that the 10 cognitive tests and questionnaires could be summarized as 4 indices of emotional distress, speed of cognitive processing, verbal memory, and verbal fluency. Regression models revealed that verbal memory, emotional distress, age, and injury severity (time to follow commands) made unique contribution to prediction of poor performance validity	“Poor performance validity was common in a research sample of persons with medically documented TBI who were not evaluated in conjunction with litigation, compensation claims, or current report of symptoms. Poor performance validity was associated with poor performance on cognitive tests, greater emotional distress, lower injury severity, and greater age. Many participants expected to have residual deficits based on initial injury severity showed poor performance validity.”	Secondary analyses using a subset from (Sherer et al 2015). Data suggest that persons with medically documented TBI commonly exhibited poor performance validity and thus increasing age, lower injury severity and increasing emotional distress.

Hegedish Hall 2015 (5.0)	Memory and Malingering	Diagnostic	No mention of COI and sponsorship	N=81 participants: 21 healthy control, 20 coached simulators, 40 patients with acquired brain injury	Mean age was 27.4 years	TBI	TMST=Temporal Memory Sequence Test Vs. TOMM=Test of Memory Malingering Vs. WMT=Word Memory Test	One-way ANOVA revealed significant differences between healthy controls (TMST IR, M=97.12% correct, SD=2.81; TMST DR, M=98.81% correct, SD=2.57) and coached simulators (TMST IR, M=62.88% correct, SD=17.45; TMST DR, M=61.25% correct, SD=16.06), on TMST IR, $F(1, 39)=78.74, p < .001$ , and TMST DR, $F(1, 39)=111.84, p < .001$ . The TMST correctly classified 100% of the healthy controls and 95% of the coached simulators. Thus, the TMST yielded 100% specificity, 95% sensitivity, and a 98% overall hit rate.	"To further establish the TMST as a valid test of NRB detection, the suggested cutoff should be cross-validated, and larger samples of patients with ABI should be examined. To broaden its external validity, the TMST should be administered to "extreme" populations, such as young children, schizophrenics, and patients with dementia. The paradigm of temporal order can also be applied in a recognition method by presenting alternative threesomes for the response choice."	Data suggest the TMST showed high negative correlations with GCS supporting an association between mild TBI and probable malingering.
Boone KB 2002 (5.0)	Memory and Malingering	Diagnostic	No COI. No mention of sponsorship.	N=178	80 males, 98 females mean age: 44.6 years	Presenting diagnoses included: head trauma, "stress" or depression,	Rey 15 item Memorization test was followed by Rey 15 item recognition trial	A free recall score <9 was found to have excellent specificity (97-100%), although sensitivity was modest (47%). However, use of a combined recall and recognition score (i.e., free	"[T]he data from the current study suggest that the addition of a recognition trial to the standard administration	All controls were paid to participate and all study participants with "suspect effort" were in litigation,

						<p>learning disability, toxic exposure, psychosis or bipolar disorder, stroke, somatoform or factitious disorder, dementia, chronic fatigue syndrome, anoxia, narcolepsy, and decreased memory from ECT</p> <p>clinic referrals included Patients were excluded from the study if they were in personal injury litigation</p> <p>learning disabled college students (who due to their</p>		<p>recall.[recognition -false positives] &lt;20) substantially increased sensitivity (71%) while maintaining high specificity (≥92%).</p>	<p>format may enable the test to meet standards for "probable" certainty in identifying suspect effort (defined as 75% correct classification of individual subjects). It may be possible to modify the test through brief additions to existing test administration format, thereby enabling it to approach this standard</p>	<p>seeking to maintain obtain disability. Data suggest combining recall and recognition scores substantially increases sensitivity and specificity is maintained.</p>
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						disability might be expected to have difficulty in processing and recall of the Rey 15-item stimuli), and normal controls.				
Greve KW 2002 (5.0)	Memory and Malingering	Diagnostic	No mention of COI or sponsorship.	N= 89 TBI referrals for comprehensive neuropsychological evaluation	58 males, 32 females  Mean age: 35.8 years	Traumatic brain injury	4 potential Wisconsin card sorting test malingering indicators  (Unique Responses Perfect Matches-Missed; Bernard; Suhr)	Individual Sensitivities were greater than .33 with acceptable Specificity. Combined Sensitivity for two of the indicators was greater than .60.	"In summary, this study indicated three relatively independent approaches or strategies used by malingerers on the WCST. Two reflect attempts to appear impaired while one appeared to reflect valid, unimpaired performance. It should be noted that one False Negative was impaired on the WCST.	Participants were derived from workers compensation population. Data suggest detection of malingerers with WCST were derived from 3 different approaches and attempts to maximize sensitivity should be carefully evaluated so as to not decrease specificity.
Bashem 2014 (5.0)	Memory and Malingering	Diagnostic	Supported by grants from Wayne State University, the Del Harder	109	No gender distribution described	Those with TBI, ranging from mild complicated to severe	Premorbid intelligence, measured via Wechsler Test of Adult Reading	TOMM highest hit rate (68%). TOMM highest sensitivity (50%) and MSVT highest specificity (94%). RDS smallest	"The findings should be generalized with caution, but if	Participants were each compensate \$30. Data suggest use of

			Foundation, and the National Institute on Disability and Rehabilitation Research. No mention of COI.		Mean age 44.0 years	(n=51) vs Neurologically healthy controls (n=58)  All participants underwent all testing	(WTAR) vs Performance Validity Test (PVT) - Test of Memory Malingering (TOMM)  vs PVT – Word Choice Test (WCT)  vs PVT – Medical Symptom Validity Test (MSVT)  vs Embedded indices – Forced Choice Recall (CVLT-II)  vs Embedded indices – Reliable Digit Span (RDS)	hit rate (54%), specificity (77%), and sensitivity (35%).  TOMM and CVLT highest agreement within TBI participants (86% passed both, 2% failed both, 88% overall agreement rate). RDS and WCT had lowest overall agreement rate (68%) in those with TBI.  Overall agreement highest between TOMM and MSVT (84%) in controls. 40% failed both tests and 45% passed both.	only one index will be employed, this study provides support for administering the TOMM alone and reserving the MSVT as an equivalent, alternate measure for future assessment.”	TOMM with CVLT or use of MSVT with CVLT for the best diagnostic accuracy to assess TBI associated memory function. Any more than 2 tests does not significantly increase diagnostic accuracy.
Krishnan M 2011 (5.0)	Memory and Malingering	Diagnostic	The authors' clinical practice, as employees of a non-profit hospital, includes about 15% of medicolegal referrals, which are	155 participants were referred for neuropsychological examinations for traumatic	76 males, 39 females  Mean age: 40.7 years	TBI	Performance on the Test of Memory Malingering (TOMM) Vs. Word Memory Test (WMT)	Individuals who failed the TOMM or WMT were almost six times more likely to fail the CVMT validity criteria than those who passed the TOMM or WMT. The addition of compensation seeking increased this odds ratio to 9.80. The area under the curve for the latter	“[T]his supports the conclusion that the CVMT SVT is useful clinically as an embedded measure of negative response bias in	Data suggest CVMT may be useful if used in conjunction with other established tests.

			<p>predominantly of defense origin. They do not receive any extra benefits from such referrals as compared to clinical referrals.</p> <p>This work was supported by a grant from the Campbell Foundation.</p>	brain injury				<p>classification was 0.74. Maximum likelihood ratio optimization of the CVMT validity test cutoff score indicated sensitivity of 0.25 and specificity of 0.99 at a revised cutoff of ,12 items. Classification accuracy was 91%. The original cutoff score of ,14 items also performed acceptably, with a classification accuracy of 88%.</p>	<p>neuropsychological assessments. It is best used as an adjunct to other measures of symptom validity, such as in combination with a stand-alone measure and one or more other embedded measures of response bias, as well as other clinical information about the patient, in order to obtain a reasonable overall sensitivity.”</p>	
Hampson 2013 (4.5)	Memory and Malingering	Diagnostic	No mention of COI or sponsorship	47	<p>15 female, 32 male</p> <p>Mean age for those with acute brain injury 54.6 years, for community brain injury 47.0, and for epilepsy 36.6</p>	<p>Acute brain injury (n=11)</p> <p>vs</p> <p>Community brain injury (n=20)</p> <p>vs</p> <p>Intractable epilepsy (n=16)</p>	<p>Word Memory Test (WMT)</p> <p>Coin-in-Hand Test</p> <p>Autobiographical Memory Index</p> <p>Digit-Symbol Coding</p> <p>Mental Control</p> <p>Short Recognition Memory Test for Faces</p>	<p>Community injuries scored lower memory results than epilepsy in WMT paired associated (t(32)=2.43, p=0.021) and the Free Recall tests (t(32)=3.14, p=0.004).</p> <p>Overall failing rates on WMT Immediate or Delayed Recognition portions: 27.3% in acute, 35.0% in community, and 18.8% in epilepsy group.</p>	<p>“The WMT was able to identify failures associated with significant cognitive impairment through the application of profile analysis and/or lowered cutoff levels. Implications for clinical assessment, effort test interpretation,</p>	<p>A significant proportion of study participants were either currently receiving benefits risking malingering or had prior litigation benefits which could bias responses. Data suggest</p>

									and future research are discussed.”	WMT able to identify significant cognitive impairment particularly in severe TBI patients via lowered cutoff pounds or profile analyses.
Constantinou 2004 (score= 4.5)	Memory and Malinger ing	Diagnostic	No mention of COI or sponsorship	N=69 litigants with mild TBI.	Mean age 42.41 (SD=12.45). 36 females and 33 males.	Mild TBI.	Test of Memory Malinger ing (TOMM) vs. general performance patterns on the WAIS-R vs. Halstead–Reitan Neuropsychological Battery for Adults (HRNB-A).	TOMM was associated (P <0.05/15 = 0.003 (Bonferroni method for control of Type I error) with decreased VIQ (Correlations r=0.47), PIQ (Correlations r=0.52), FSIQ (Correlations r=0.52) scores and decreased performance on WAIS-R subtests	“[I]t appears that a poor performance on the TOMM is predictive of a generalized poorer performance on standardized measures such as the WAIS-R and the HRNB-A.”	Data suggest a poor performance on TOMM trial 2 was generally positively correlated to a poor performance on WAIS-R and HRNB-A.
Heyanka 2015 (4.0)	Memory and Malinger ing	Diagnostic	No COI. No mention of sponsorship.	160	9 female, 151 male  Mean age 31.7 years	Mild TBI	Word Memory Test (WMT) – IR, DR, CNS trials  vs  TOMM  vs  California Verbal Learning Test-Second Ed. (CVLT-II)	Significant correlation (p<0.001) between CVLT-II and TOMM (0.40-0.68), CVLT-II and WMT (0.43-0.61), and WMT and TOMM (0.51-0.75) observed.	“Our findings support assertions that PVTs measure effort independent of memory in veterans with mild TBI.”	Data suggest PVTs are measuring effort which is independent of memory in mild TBI veterans.
Lippa 2014 (4.0)	Neuropsychological Assessment	Cohort Study	No mention of sponsorship or COI.	44 Participants with TBI	Mean age of 38.4 years old. 12 Females, 32 Males	Moderate or severe TBI	No mention of comparison groups. All participants were examined with same tests.	The final model, which included years of education, PTA length, and RBANS effort index, showed that the variance accounted for by the	“Findings suggest that more in-depth analysis of validity test performance is	Data suggest that intense analyses of validity test performance

								predictors were statistically significant.	beneficial to gauge a patient's level of effort and is important to consider when interpreting results and in treatment planning."	is important when determining level of effort in acute TBI patients.
Zacks 2015 (4.0)	Neuropsychological Assessment	Longitudinal Study	Sponsored by training grant T32AG000030 and R01MH070674. No mention of COI.	157 Participants in the Vietnam Head Injury Study.	Mean age of 63.32 years old. 0 Females, 57 Males	Male veterans suffering from pTBI.	Veterans with pTBI (N = 123)  Vs  Non-injured control (N=23)	pTBI had a poorer segmentation agreement than NC (P<0.001). For recognition, pTBI group recognized fewer pictures than NC. However, most pTBI had large lesions (P<0.001). When large lesions were excluded, effect became non-significant. Likewise for order memory. Many individuals in pTBI group had large lesions which made the comparison significant. When large lesions were excluded, the comparison became non-significant.	"[P]atients with pTBI showed substantial impairments in comprehension and memory for movies of everyday activity."	Data suggest pTBI patients showed comprehension and memory defects and event segmentation interventions could improve memory.

## California Verbal Learning Test (CVLT-I and CVLT-II)

### Recommended.

*Strength of Evidence* – Recommended, Insufficient Evidence (I)

*Level of Confidence* – Moderate

<i>Indications:</i>	Generally used in mild TBI patients, particularly for evaluating learning, memory and malingering.
<i>Benefits:</i>	Assess memory and learning. Identification of malingering.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Generally used on one occasion if use is for detecting malingering. May be used on subsequent occasions to track learning and memory progress.
<i>Rationale:</i>	The two highest quality studies suggest CVLT-II is useful for evaluating memory and malingering [420, 421]. One moderate quality study suggests CVLT-II is more sensitive for memory measures than the Word Memory Test [422]. CVLT is not invasive, has negligible adverse effects, is low cost and is recommended for evaluation of TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: California Verbal Learning Test Second Edition, CVLT-II; Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 36 articles in PubMed, 11 in Scopus, 5 in CINAHL, 18 in Cochrane Library, 20,400 in Google Scholar, and 0 from other sources. We considered for inclusion 7 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 8 articles considered for inclusion, 8 diagnostic studies and 0 systematic studies met the inclusion criteria.

### Evidence for the Use of CVLT

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Curits 2006 (score=6.0)	CVLT-II	Diagnostic	No mention of sponsorship or COI	N=275 with TBI	Mean age: 40.82 years; 77 females, 198 males	TBI	Malingered Neurocognitive Dysfunction (MND) of four individual California Verbal Learning Test (CVLT) variables and eight composite CVLT malingering indicators	Within TBI, persons with the strongest evidence for malingering (Probable and Definite) had the extreme scores. Good sensitivity (approximately 50%) in the context of excellent specificity (> 95%) was found in the TBI samples	"[R]egardless of the severity of the injury, proper application of these findings requires that a given patient's data be interpreted based on the appropriate comparison groups. When appropriately used, the formulaic composites derived from the CVLT are powerful indicators of poor effort and malingering."	Data suggest CVLT is useful in the detection of malingering in mild TBI patients and is influenced by both cognitive capacity and effort.
Greve 2009 (score=5.5)	CVLT-II	Diagnostic	No mention of COI or sponsorship.	N=442 TBI patients, and =378 chronic pain patients	Mean age (TBI)= 38.7 years (Chronic pain)= 42.4 years;	TBI and chronic pain	2 versions of California Verbal Learning Test (CVLT 1 & 2)	Performance on the CVLT-2 was poorer than on the CVLT-1. The difference between CVLT-1 and CVLT-2 was larger in the pain patients than in the TBI patients. These findings mean that at the same cutoffs, malingering indicators on the CVLT-2 will be	"In summary, this study determined that the two versions of the CVLT are equally accurate in detecting malingering in TBI and chronic pain. However, they are not interchangeable. The use of CVLT-1 cutoffs with the CVLT-2 may result in an increased risk of FP error. The results of this study provide preliminary	Data suggest CVLT-II and CVLT-I are good for detecting malingering but are not interchangeable as current cutoff points may cause increased false positive rates.

								<p>associated with a higher rate of FP errors than the CVLT-1. The difference between the two versions was most pronounced when cutoffs associated with lower FP rates were examined. CVLT-1 cutoffs associated with FP error rates of approximately 10% (a conservative upper bound) always resulted in CVLT-2 FP error rates of 15% or more, even in TBI. In the TBI patients, cutoffs associated with a 5% FP error rate in the CVLT-1 resulted in similar FP rates in the CVLT-2. In the pain sample, Recognition Hit accuracy was comparable but the cutoffs for the Linear Shrinkage score needed to be adjusted upward to maintain a comparable FP rate.</p>	<p>data for the use of some CVLT-2 indicators for the detection of invalid performance and malingering in TBI and chronic pain.”</p>	
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Davis 2016 (score=4.5)	CVLT-II	Diagnostic	No COI. No mention of sponsorship.	N= 104 participants with different TBI severity	Mean age: 40.26 years; 28 females, 76 males.	TBI	Word Memory Test (WMT) vs. California Verbal Learning Test-Second Edition (CVLT-II).	Participants grouped by TBI severity significantly differed on the CVLT-II but not WMT. Post-traumatic amnesia (PTA) significantly correlated with the CVLT-II but not WMT. In a non-medicolegal sample subset (N = 61), TBI severity groups significantly differed on CVLT-II and WMT free recall (FR); PTA significantly correlated with the CVLT-II and WMT FR. CVLT-II impairment groups differed on all WMT variables. Participants grouped by neuroimaging findings differed on CVLT-II but not WMT. WMT FR predicted two-level TBI severity using logistic regression but did not contribute in a model including the CVLT-II.	“Overall, WMT memory subtests appeared less sensitive to TBI severity than the CVLT-II. The current findings provide preliminary support that, at least, FR on the WMT may have some utility as a memory measure. Cross-validation of the preliminary regression results presented here would be helpful for refining the model and comparing WMT memory indices with other measures.”	Data suggest that overall the CVLT-II is more sensitive than the WMT for memory measures in TBI patients.
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Donders 2007 (score=4.5)	CVLT-II	Diagnostic	Study was supported in part by a grant from the Campbell Foundation. No mention of COI.	N= 46 healthy controls and patients with moderate-severe TBI	Mean age: 34.9 years; 16 females, 30 males	TBI	California Verbal Learning Test, Second Edition (CVLT II)	Patients with traumatic brain injury recalled fewer correct words, and also made more intrusive errors, on CVLT-II short and long delay, free and cued recall trials ( p < .02 for all variables after Stepdown Bonferroni correction). However, recall discriminability indices yielded a classification of clinical versus control participants (72%) that was not significantly different from one based on traditional variables (74%).	“CVLT-II recall discriminability indices do not routinely provide an advantage over traditional variables in patients with traumatic brain injury.”	Data suggest CVLT-II provides no advantage over established recall discriminability tests.
Moore 2004 (score=4.0)	CVLT-II	Diagnostic	No mention of COI or sponsorship	N= 132 individuals (referrals) from a 3 year series	Mean age: 35.77 years; 50 females, 82 males	TBI	Test of Memory Malingering (TOMM) and the California Verbal Learning Test-Second Edition (CVLT-II)	Twenty patients (15%) performed in the invalid range when held to a priori specified criteria for invalid test performance (i.e. TOMM <45/50 on Trial 2 or CVLT-II <15/16 on Forced-Choice	“The TOMM and CVLT-II are sensitive to the potential impact of current financial compensation seeking and prior psychiatric history on neuropsychological test performance after TBI”	Data suggest both TOMM and CVLT-II are sensitive to financial incentive and previous psychiatric history post TBI.

								recognition trial). Both psychiatric history and financial compensation seeking were associated with an almost 4-fold increase in likelihood of invalid responding.		
Bauer 2005 (score=4.0)	CVLT-II	Diagnostic	No mention of COI or sponsorship	N= 120 head injured patients	Mean age: 28.43 years; gender: not specified.	TBI	five California Verbal Learning Test-Second Edition (CVLT-II) variables	The discriminant function seemed to best predict those who put forth adequate effort while testing (95.6% correct) but not those who failed to put forth adequate effort during testing (only 13.8% correct). Hence, although the overall classification rate was moderately impressive (75.8%), the model's sensitivity in classification of the incomplete effort group was low.	"In sum, this study provides some evidence that recognition variables in the CVLT-II show promise in their ability to supply information about effort during neuropsychological testing. Therefore, using CVLT-II performance to measure effort in larger and more diverse populations needs to be examined."	Data suggest some information regarding recognition variables in CVLT-II at the test did not show great sensitivity in discriminating those with incomplete effort.
Jacobs 2008 (score=4.0)	CVLT-II	Diagnostic	The study was supported by a grant from the Campbell	N= 114 Patients with TBI, selected from a 5-year series of consecutive	Mean age: 38.24 years; 51 females, 63 males	TBI	Seven California Verbal Learning Test-Second Edition CVLT-II	Various performance contrasts (i.e., proactive interference, retroactive	"It is concluded that performance discrepancies on the CVLT-II should never be used in isolation to	Data suggest CVLT-II should not be used as a standalone test to determine the

			Foundation. No mention of COI.	rehabilitation referrals			variables of interest	interference, rapid forgetting, and retrieval problems) were evaluated. Initial analyses revealed higher rates of rapid forgetting in the TBI group as compared to the standardization sample. There were 10 patients (8.77%) who had PI effects $\leq -1.5$ ; 14 patients (12.28%) who had RI effects $\leq -1$ ; 24 patients (21.05%) who had RF1 effects $\leq -1$ ; 15 patients (13.16%) who had RF2 effects $\leq -1$ ; 5 patients (4.38%) who had RP1 effects $\geq 1.5$ ; and 3 patients (2.63%) who had RP2 effects $\geq 1.5$ . Only for the RF1 Contrast was the difference with the respective prevalence in the CVLT-II standardization sample statistically significant ( $z = 2.22, p < 0.013; p > 0.10$ for	determine the presence or absence of acquired cerebral or memory impairment. However, regardless of the cause, such discrepancies may still be relevant for clinical treatment recommendations.”	presence or absence of acquired cerebral or memory dysfunction.
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								all other comparisons).		
Donders 2011 (score=3.5)	CVLT-II	Diagnostic	No mention of COI or sponsorship	N=100 patients with TBI	Mean age: 37.5 years; 55 females, 45 males	TBI	California Verbal Learning Test – Second Edition (CVLT–II) and World memory test(WMT	Although the CVLT–II logistic regression formula demonstrated a statistically significant level of agreement with results from the Word Memory Test, it was associated with an unacceptably high proportion of false positives. The component variables of the logistic regression were sensitive to length of coma but did not covary with psychosocial complicating factors (e.g., unresolved prior psychiatric history) that were associated with a higher relative risk of failure of WMT validity criteria.	“we conclude that the Wolfe et al. CVLT–II response bias formula is not yet ready for routine application in general clinical settings where assessment of effort is used first and foremost to determine the validity of test results, as opposed to the detection of malingering in a medicolegal context. The current results do not suggest that the Wolfe et al. formula is useless. It is possible that it might have fared better if we had used a sample with a different balance of cases with sufficient vs invalid effort and who were seen several years post injury.”	Data suggest multiple measures should be used in assessing effort testing to limit numbers of false positives.

## Repeatable Battery of the Assessment of Neuropsychological Status (RBANS) Recommended.

The Repeatable Battery of the Assessment of Neuropsychological Status is recommended for use in the evaluation of TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – Low

<i>Indications:</i>	Patients with ongoing cognitive symptoms from TBI. May also be used to assess effort and malingering [423, 424].
<i>Benefits:</i>	Assess cognitive function in 5 domains. Malingering is potentially able to be evaluated with 2 subscales [423].
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Generally used on one occasion if use is for detecting malingering. May be used on subsequent occasions to track learning and memory progress.
<i>Rationale:</i>	The highest quality studies suggest RBANS is useful for evaluating cognitive function [425, 426] and malingering [423, 424]. RBANS is not invasive, has negligible adverse effects, is low cost and is recommended for evaluation of TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Repeatable Battery for the Assessment of Neuropsychological Status, RBANS; Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 17 articles in PubMed, 12 in Scopus, 12 in CINAHL, 21 in Cochrane Library, 3,760 in Google Scholar, and 0 from other sources. We considered for inclusion 4 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 4 articles considered for inclusion, 4 diagnostic studies and 0 systematic studies met the inclusion criteria.

## Evidence for the Use of RBANS

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Lippa 2017 (score=7.0)	RBANS	Diagnostic	No mention of COI or sponsorship.	N= 250 military service members	Mean age:28.4 years; 235 males, 15 females	TBI	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Test of Memory Malingering (TOMM)	Participants were divided into two groups based on their performance on the Test of Memory Malingering: PVT-Pass, <i>n</i> =193; PVT-Fail, <i>n</i> =57. For the EI, recommended cut-offs for extremely probable, highly probable, and probable poor effort were established. A cut-off score of >3 resulted in low sensitivity (.14), high specificity (.99) and positive predictive power (.94), and moderate negative predictive power (.68)	“the findings support the use of the EI over the ES to identify poor effort in mild TBI patients, but also suggest that additional PVTs are generally required to accurately rule poor effort in or out. The EI and ES should continue to be validated in various patient samples, as it appears their usefulness and ideal cut-offs vary by sample.	Data suggest the RBANS E1 and ES are useful for detecting possible poor effort in mild TBI but additional PVTs are recommended.

								and is recommended for identifying highly probable poor effort. For both the EI and ES, cut-offs for probable poor effort were identified.		
McKay 2008 (score=6.0)	RBANS	Diagnostic	No mention of COI or sponsorship.	N= 51 TBI cases and 34 non-head-injured controls	Mean age: 41.7 years; 44 females, 41 males.	TBI	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)	Across RBANS' Index Scores, the TBI group performed at a significantly lower level than the controls; sensitivity to TBI and likelihood ratios ranged from modest to strong; and specificity was high. Particularly efficacious was the clinical efficiency exhibited by the Total Scale Index (summary score) of the RBANS.	"In conclusion, the results of this study demonstrate the clinical utility of the RBANS within the TBI population, specifically in terms of its sound sensitivity and specificity. The RBANS has been found to be a clinically useful cognitive screening measure in dementia, Parkinson's disease, multiple sclerosis,	Data suggest RBANS is a sensitive and specific test for detecting TBI especially with the Total Scale Index Summary subtest.

									stroke, and with this current evidence, the TBI population.”	
Novitski 2012 (score=5.5)	RBANS	Diagnostic	No mention of COI or sponsorship.	N= 25 mild TBI patients, 69 clinical subjects with amnesic MCI (n= 15) or probable Alzheimer’s disease (n=54),	Mean age: 49 (mildTBI patients), 89 ( clinical subjects); Gender: not specified	TBI	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)	Receiver-operating characteristic analyses demonstrated much better sensitivity and specificity of the ES (effort scale), with a marked reduction in false positive errors.	“Additional validation work is necessary to more firmly establish the clinical utility of the newly derived RBANS ES, and, as with any measure of effort, the ES should be considered in the context of clinical history, presentation, and pattern of performance across other measures. Specifically, it would be helpful to validate the ES in conjunction with stand-alone measures of effort. Once the calculation of	Data suggest ES is better than E1 demonstrating better sensitivity and specificity and reduced numbers of false positives but should only be used in cases where there is previous concern for impairment and/or lack of effort demonstrated on Digit Span or List Recognition subtests.

									an ES score is triggered by unusually low performance on one or more of these two subtests, ES scores ,12 should be considered suspicious for suggesting poor effort. Additional measures of effort should be examined under most circumstances in order to clarify the finding.”	
Lippa 2013 (score=4.5)	RBANS	Diagnostic	No COI. No mention of sponsorship.	N=51 with acute TBI patients.	Mean age: 39.6 years; 13 females, 38 males.	TBI	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)	In this sample of acute TBI patients (n=51), the mean index scores on the RBANS ranged from 1.59–2.36 SD below the mean of the standardization sample. Each WRAT-4 Reading sub-test score was above the corresponding RBANS Total Scale Index score (t (31) =10.32,	“The RBANS appears to be a useful tool in assessing the presence and severity of acute TBI.”	Data suggest RBANS is a sensitive tool for detecting cognitive domains in TBI patients and could be useful in acute care settings.

								p<0.001). Regression analyses revealed that Delayed Memory ( $\beta=-0.365$ , $p<0.007$ ) and Total Score ( $\beta=-0.297$ , $p<0.023$ ) indices were significantly predicted by post traumatic amnesia (PTA) length after controlling for age and education.		
Couillet 2010 Score = 4.0)	RBANS	Diagnostic	Sponsored by grants from the Programme Hospitalier de Recherche Clinique and by Assistance Publique-Hopitaux de Paris. No mention of COI.	N = 12 patients in the stages of subacute or chronic after a severe TBI.	Mean age of AB group: 23.8 (N=5)  BA group: 26.7 (N=7)  No mention of Sexes	An AB vs. BA crossover design was used. Each phase was six weeks and consisted of four one-hour training sessions a week for a total of 24 hours of training.  A phase was the control phase,	Follow up at 6 weeks, 12 weeks, and one month after the end of the trial.	Effect of time and the group x time interaction in Divided attention subtest of the TAP: Mean Reaction Time: AB group: $F(3, 21) = 21.5$ , ( $p < .0001$ ); BA group: $F(3, 21) = 20.7$ , ( $p < .0001$ )  Number of Omissions: AB Group: $F(3, 18) = 22.3$ , ( $p < .0001$ )	“In summary, these results suggest that the specific rehabilitation programme for divided attention had specific effects on divided attention and was useful and helped patients to deal more rapidly and more accurately with dual-task situations.”	Small sample randomized crossover study. At 6 weeks, the data suggest specific divided attention training was better than control for most tasks. but executive function and working memory tasks improved to a lesser degree.

						<p>consisting of cognitive tasks that did not use the patient's divided attention or working memory.</p> <p>B phase consisted of specific dual attention training.</p>		<p>BA group: <math>F(3, 18) = 13.2, (p &lt; .0001)</math></p> <p>Effect of time and the group x time interaction were both significant for the go-no go dual-task reaction times:  AB group: <math>F(3, 18) = 12.3, (p &lt; .0001)</math>.  BA group: <math>F(3, 18) = 17.5, (p &lt; .0001,)</math></p> <p>Digit Span Dual Task:  AB group: <math>F(3, 18) = 84.6, (p &lt; .0001)</math>;  BA group: <math>F(3, 18) = 28.4, (p &lt; .0001)</math></p>	
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Wechsler Memory Scale has been used to assess memory impairments which may occur with moderate and especially severe TBI, although mild traumatic brain injury (MTBI) typically does not result in significant and persistent memory impairment [135, 427-429]. When substantial memory dysfunction is present, as indicated on the WMS-III, [368] other factors not related to trauma-induced neuropathology such as pre-existing problems, psychological issues or lack of motivation (effort) during testing should be considered. [430].

## **Wechsler Memory Scale** **Moderately Recommended.**

The Wechsler Memory Scale is moderately recommended for use in the evaluation of TBI patients.

*Strength of Evidence* – **Moderately Recommended, Evidence (B)**

*Level of Confidence* – **Moderate**

<i>Indications:</i>	Assess memory after TBI. May be used in select cases of mild TBI with ongoing symptoms. Repeat testing to follow progress may sometimes be helpful. May help evaluate potential symptoms exaggeration and malingering.
<i>Benefits:</i>	Identification of severity of TBI, follow-up of symptoms and at resolution of symptoms. May assist with identification of malingering. Often used in conjunction with WAIS-III as well as the clinical picture to attempt to substantiate subjective complaints. [430], [431]Langeluddecke, 2003 #2479}[124, 432-434].
<i>Harms:</i>	Negligible. Potential for occasional misinterpretations especially where baseline data are missing.
<i>Frequency/Dose/Duration:</i>	Administered after TBI, often at the point of maximum recovery.
<i>Rationale:</i>	Multiple moderate quality studies suggest utility of WMS-III for evaluation of patients who sustained TBI [135, 427-429]. The WMS-III is not invasive, has no adverse effects, is moderate cost, has evidence of utility for memory assessment, and is thus recommended for evaluation of TBI patients. The test is periodically updated and the most recent version is recommended.  <i>Evidence:</i> A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Minnesota Multiphasic Personality Inventory (MMPI) and Hs (Hypochondriasis) and Hy (Hysteria); Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 122 articles in PubMed, 92 in Scopus, 14 in CINAHL, 14 in Cochrane Library, 430 in Google Scholar, and zero from other sources. We considered for inclusion 13 from PubMed, zero from Scopus, 2 from CINAHL, one from Cochrane Library, zero from Google Scholar, and zero from other sources. Of the 15 articles considered for

inclusion, 2 prognostic studies, 11 diagnostic and 2 systematic studies met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Wechsler Adult Intelligence Scale-III, WAIS-III, Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 42 articles in PubMed, 21 in Scopus, 18 in CINAHL, 17 in Cochrane Library, 2480 in Google Scholar, and 2 from other sources. We considered for inclusion 12 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 2 from other sources. Of the 14 articles considered for inclusion, 14 diagnostic studies and 0 systematic studies met the inclusion criteria.

### Evidence for the Use of WMS-III

Author Year (Score)	Category:	Study type:	Conflict of Interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Ord 2008 (Score = 5.5)	Wechsler Memory Scale-III	Diagnostic	No mention of sponsorship or COI.	N = 208 patients with TBI	Mean age: 48.92 years; 118 males, 90 females.	TBI	All patients received WMS-III examination. Mild TBI non-malingering (N = 34) vs Mild TBI malingering (N = 31) vs Moderate/severe TBI non-malingering (N = 28) vs General clinical group (N = 93)	MTBI MND group performed worse than MTBI groups on all eight indices (P < .01)	"This study indicates that the WMS-III primary indices can accurately identify malingered neurocognitive dysfunction in mild TBI when used as part of a comprehensive classification system."	The majority of study patients were financially incentivized. Data suggest the primary WMS-III indices can be used as an accurate measure to identify malingered neurocognitive dysfunction in mild TBI if used as a component of a comprehensive classification system
Glassmire 2003 (Score = 5.5)	Wechsler Memory Scale-III	Diagnostic	Sponsorship from The Defense and Veterans Head Injury Program and the Medical research Service of the Department of Veterans Affairs. David	N = 60 patients with TBI	Mean age: 33.3; 55 males, 5 females.	TBI	Both groups received the WMS-III Faces I subtest for assessment of Malingering. Nonlitigating traumatic brain injury (N = 30) vs Control (N = 30)	(TBI vs. Control) by Testing Condition (SA vs. IM) interaction was significant, $F(1, 58) = 8.70$ , ( $p = .005$ ) Average raw Faces score in SA condition (M = 36.3, SD = 4.9) IM condition (M = 23.3, SD = 6.9), Difference	"The findings of the current study indicated that the Faces I subtest (Faces) provides important information when screening for the presence of malingered memory impairment on the WMS-III."	"Data suggest the WMS-III faces subset holds promise for validity in the measurement of malingering for memory impairment in TBI."

			Glassmire is currently affiliated with Patton State Hospital					, $F(1, 58) = 150.95$ , ( $p < .001$ .)		
Langeluddecke 2003 (Score = 5.0)	Wechsler Memory Scale-III	Diagnostic	No mention of sponsorship or COI.	N = 75 Patients with TBI	Mean age: 35.4 years; 54 males, 21 females.	TBI	Both groups received the WMS-III Malingers (N = 25) vs Nonmalingers (N = 50)	Malingers vs Nonmalingers Auditory immediate 70.2 vs 92.1 (t = 6.11) Visual immediate 62.4 vs 88.6 (t = 8.10) Immediate memory 60.2 vs 88.8 (t = 8.40) Auditory delayed 70.8 vs 94.2 (t = 7.12) Visual delayed 62.1 vs 90.2 (t = 8.71) Auditory recognition-delayed 67.4 vs 97.5 (t = 9.31) General memory 60.3 vs 92.1 (t = 9.03) Working memory 82.2 vs 100.0 (t = 4.44)	“The results of the present study suggest that the inclusion of auditory recognition memory subtests and indexes on the WMS-III is a major improvement on the WMS-R in facilitating the detection of malingering.”	Data suggest <10% of severe TBI patients, only about 10% returned scores below the cut-off score for malingering in mild TBI patients.
Hacker 2009 (Score = 5.0)	Wechsler Memory Scale-III	Diagnostic	No mention of sponsorship. No COI.	N = 27 patients with TBI mild to severe. N = 60	Mean age: 33.6; 27 males, 50 females, 10 not stated.	TBI	All groups received the WMS-III test, Wechsler test of Adult Reading, and Wechsler	Sensitivity to malingering: Difference between the word list	“Overall the findings provide preliminary evidence to support the use of the WLR as an embedded	Data suggest the WLR of the WMS-III discriminated between a simulator and TBI group which

				control group N = 87 total patient.			abbreviated Scale of Intelligence. TBI and control optimal group took test to best of their abilities. Analogue malingerer was instructed to take as if they had a brain injury. TBI (N = 27) Vs Control (N = 300 vs Analogue malingerer (N = 30).	recognition (WLR) performance of the AM group and the TBI group (t = -6.216; p<0.01) WASI FSIQ CO 116.13 vs TBI 85.13 vs AM 82.13. Difference TBI vs AM (p = .52)	symptom validity indicator. These findings, however, require further cross-validation with larger clinical samples in order to assess its ecological validity."	suggest it may have validity as an "embedded symptom validity indicator."
Walker 2009 (score=4.5)	WAIS-III & WMS-III	Diagnostic	No sponsorship or COI.	N=200 patients. 100 patients with moderate to severe traumatic brain injury (TBI). 100 controls.	Mean age: TBI 30.68 years. Controls 40.07 years. TBI: 81 males/19 females. Controls: 70 males/30 females.	Moderate to severe traumatic brain injury (TBI).	Wechsler Adult Intelligence Scale-III (WAIS-III) and Wechsler Memory Scale-III (WMS-III) indices vs. age corrected indices.	Age corrected indices correctly classified 77% [154385] of all participants, with 82% sensitivity and 72% specificity. Demographically corrected indices correctly classified 74% [148385] of participants, with 76% sensitivity and 72% specificity.	"[F]or mostly younger white individuals with lower levels of education, the demographic corrections for the WAIS-III and WMS-III do not provide an advantage in the classification of moderate to severe TBI over and above age corrected indices."	Data suggest demographically corrected WAIS-III and/or WMS-III indices did not provide better diagnostic accuracy than age corrected indices in TBI patients.
West 2011 (Score = 4.5)	Wechsler Memory Scale-III	Diagnostic	No mention of sponsorship or COI.	N=132 patients with TBI.	Mean age Mod/Sev TBI group: 29.9 (SD=10.1).	TBI	N=44 mild TBI patients with good effort vs. N=48 mild TBI patients with poor	Moderate-severe TBI group scored the lowest on WMS-III Visual indices. Effort	"[F]indings of this study are consistent with the TBI outcome literature and emphasize the	96% of patients had some sort of financial incentive. Data suggest effort

					91 males, 41 females.		effort vs. N= 40 moderate–severe TBI patients with good effort. WMS_III index scores were main outcome: Auditory Immediate, Visual Immediate, Immediate Memory, Auditory Delayed, Visual Delayed, Auditory Recognition Delayed, General Memory, and Working Memory.	had a larger effect than injury severity on WMS-III scores average Cohen’s d =-1.27).	importance of controlling for effort in neuropsychological assessments.”	had more impact on WMS-III scores than did injury severity. Additionally, a dose-response relationship was found between injury severity and WMS-III scores.
Langeluddecke 2005 (Score = 4.5)	Wechsler Memory Scale-III	Diagnostic	No mention of sponsorship or COI.	N= 180 litigants with post-acute moderate to extremely severe TBI, classified.	Mean age of 35.5 Years. 117 males, 63 females.	TBI	Moderate TBI (N=44) vs severe-severe TBI (N=86) vs. Extremely severe (N=50) vs. Normal Control Group (N=50). Main outcome was WMS-III indexes and core subtests.	Mean scores related to severity on all index measures, with lower scores in the more severely brain injured. Mean±SD Visual immediate comparing controls vs. moderate vs. severe vs. extremely severe: 101.3±15.3 vs. 88.8±14.0 vs. 85.3± 15.1 vs. 74.9±13.1, p=0.006.	“Differences between WMS-III memory indexes are unlikely to be of diagnostic utility although memory-intelligence discrepancies may be.”	Data suggest a significant dose-response relationship exists between TBI injury severity and most WMS_III indices and subtests. Also, TBI effected results indices more than auditory indices. Also, revised Tulskey indices did not result in increased severity compared to the original ones.

Hawkins 1998 (Score 4.0)	Wechsler Memory Scale-III	Diagnostic	No mention of sponsorship or COI.	N= 214 principal subjects are the clinical samples for whom complete WAIS-III and WMS-III data are presented in the Technical Manual. Only 22 patients had TBI.	Mean age of TBI patients: 26.9 (SD=5.9).14 males, 8 females among those with TBI.	TBI	Immediate Memory Index (WMS-III) vs. WMS-III General Memory Index. Details sparse.	WMS-III Visual Index may also prove highly sensitive to brain compromise. Verbal comprehension was the high point for five of the seven conditions (mean VCI-PSI difference = 14.23, SD = 7.6), with the exceptions being the TBI [66] and Korsakoff's samples (WMI). The VCI was 2.5 points lower than POI for the TBI group.	"[C]ompared with the Immediate Memory Index, the WMS-III General Memory Index (measuring delayed recall and recognition) does not exhibit greater sensitivity to the memory deficiencies of most of the patient samples for whom data are available"	Population included Alzheimer's Huntington's disease, Parkinson's disease as well as TBI patients, chronic alcohol abusers and Korsakoff's syndrome, and schizophrenia patients. Data suggest the WMS-III general memory index does not have superior sensitivity to memory deficits in most patients compared to the immediate memory index.
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Multiple tests have been used to correctly identify TBI injury severity resulting in cognitive dysfunction versus insufficient effort or malingering and or symptom exaggeration [128]. Poor effort has been proven to significantly impact post-concussion symptoms as well as test performance. [122, 435-438]. The TOMM evaluates validity of the test performance that is being used to establish the presence or absence of neurocognitive dysfunction associated with TBI.

## **Test of Memory Malingering (TOMM)**

### **Recommended.**

The Test of Memory Malingering is moderately recommended for use in the evaluation of TBI patients.

#### ***Strength of Evidence – Moderately Recommended, Evidence (B)***

#### ***Level of Confidence – High***

<i>Indications:</i>	Post-TBI testing. Repeat testing to follow progress may sometimes be helpful [435] [122, 168, 405, 436-445] [365, 411, 414] There may be select patients with ongoing symptoms from mild TBI who are candidates.
<i>Benefits:</i>	Identification of severity of TBI, follow-up of symptoms and at resolution of symptoms. May assist with identification of malingering and to attempt to substantiate subjective complaints.
<i>Harms:</i>	Negligible.
<i>Frequency/Dose/Duration:</i>	Administered after TBI, generally early in the clinical course. May be administered in evaluations at the point of maximum recovery.
<i>Rationale:</i>	There are several moderate quality studies assessing TOMM evaluation of patients who sustained TBI. This test is not invasive, has no adverse effects, is of moderate cost, has evidence of accuracy especially for detecting malingering in MTBI, and is thus recommended for evaluation of TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Minnesota Multiphasic Personality Inventory (MMPI) and Hs (Hypochondriasis) and Hy (Hysteria); Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 122 articles in PubMed, 92 in Scopus, 14 in CINAHL, 14 in Cochrane Library, 430 in Google Scholar, and zero from other sources. We considered for inclusion 13 from PubMed, zero from Scopus, 2 from CINAHL, one from Cochrane Library, zero from Google Scholar, and zero from other sources. Of the 15 articles considered for inclusion, 2 prognostic studies, 11 diagnostic and 2 systematic studies met the inclusion criteria.

### Evidence for the Use of TOMM

Author Year (Score)	Category :	Study type:	Conflict of Interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Hall 2014 (6.5)	TOMM	Diagnostic	No mention of COI or sponsorship	48	27 female, 21 male  Mean age 39 years	Minimal to mild head injury, in acute stages post-injury	Trail Making Test vs. Verbal Fluency (FAS) test vs. Colour Word Interference Test vs. Word Memory Test vs. Test of Malingering Memory (TOMM) vs. Reliable Digit Span vs. PDI vs. MSPQ  Processing Speed Index [419] from WAIS-III vs. Word List Recognition	At the 82.5% cutoff for WMT, the false positive rate (FPR) was 18%. Those who failed the IR or DR also failed the WMT, resulting in a joint failure rate of 18%. In the IR the FPR was 8% and 3% for the DR. The difference between those who passed and failed the WMT was also significant in regards to the verbal fluency test ( $p < 0.05$ , effect size $d \leq 0.7$ ).  Sensitivity for various	"In conclusion, the results of this study suggest that the WMT consistency index cut-off may be too aggressive with minimal to MHI individuals within the early stages post-injury."	All participants were not involved in litigation and this did not fit malingering criteria. Data suggest WMF may be the result of a specific verbal processing deficit in the acute phase of mild head injury.

								subtests: RDS = 0.41, TOMM = 0.61; WLR = 0.81; PSI = 0.55; PDI = 0.59; MSPQ = 0.9.		
Whitney 2013 (6.0)	TOMM	Diagnostic	No mention of COI or sponsorship	N= 194 participants	Age 21 to 77  181 males, 13 females  50.67 years mean age.	Patients with TBI referred to the author for neuropsychologic al testing within a VA Medical Center.	Pass TOMM (N=149) RBS VS F VS Fb VS Fp VS FBS VS HHI  Against Fail TOMM (N=45) RBS VS F VS Fb VS Fp VS FBS VS HHI  TOMM=Test of Memory Malingering;	There was a statistically significant difference between passed TOMM (N=149) and failed TOMM (N=45) at for Pass TOMM (N=149) M: (11.4, 67.8, 66.2, 53.2, 20.6, 8.1) and SD: (4.1, 18.9, 22.2, 13.1, 5.6, 3.7) VS failed TOMM (N=45) M: (14.6, 82.1, 82.4, 61.5, 23.8, 10.7) and SD: (4.0, 20.8, 25.1, 17.0, 5.8, 3.2)	“Although the TOMM and the MSVT were used to classify individuals as demonstrating performance invalidity in the present study, it should be emphasized that the diagnosis of invalid presentation, especially if malingering is in question, is a clinical judgment that cannot be made on the results of symptom validity tests alone, but must be made in consideration of other psychometric, behavioral, and collateral data (Slick et al., 1999).”	Data suggest RBS and HHI show poor performance in predicting malingering.

Barhon 2015 (6.0)	TOMM	Diagnostic	No mention of sponsorship or COI	N = 92	Mean age: 19.7 years; 25 males, 67 females.	TBI	Word Choice Test (WCT) vs. Test of Memory Malingering (TOMM) Full-Effort Group (N=46) vs. Distraction Group (N=46) vs. Uncoached Group (N=22) vs. Coached Group (N=24)	Statistical significance found between full effort group and uncoached group (p<.0005) and between full effort group and coached group (p<.0005), and no statistical significance between full effort group and distraction group (p<.0005). At a cut score of 48, TOMM had a sensitivity of 91.3, specificity of 89.13. At a cut score of 48, WCT had a sensitivity of 86.96, and a specificity of 78.26.	“The WCT was found to be as effective as the TOMM in differentiating simulators from participants applying full effort. The WCT is primarily a measure of effort rather than cognitive ability.”	Data suggest similar efficacy between TOMM and WCT in the detection of cognitive impairment. Both TOMM and WCT are primarily tests of validating poor effort.
Lange 2010 (5.5)	TOMM	Diagnostic	No mention of COI or sponsorship.	63 individual with mild TBI who were receiving	Mean age: not specified; 40 males,	Mild TBI	TOMM pass (n = 48) vs. TOMM fail (n = 15). All participants	Between TOMM pass and fail groups:	“These results highlight the importance of considering the	All participants receiving financial compensation.

				financial compensation from the Workers' Compensation Board	23 females.		underwent the following tests: Post-Concussion Scale (PCS), British Columbia Cognitive Complaints Inventory (BC-CCI), selected test from Neuropsychological Assessment Battery Screening (S-NAB)	significant main effects and large effect sizes for PCS (d=0.79, p=0.002), BC-CCI (d=0.98, p=0.011). Those in TOMM fail group scored higher for both measured compared to TOMM pass group. TOMM fail group scored lower on attention (d=1.26, p=0.004), memory (d=1.16, p=0.006), and executive functioning (d=0.70, p>0.05) indexes	influence of poor effort, in conjunction with a growing list of factors that can influence, maintain, and/or mimic the persistent postconcussion syndrome."	Data suggest poor effort must be considered in addition to multiple other factors which can mimic postconcussion syndrome.
Flaherty 2015 (5.5)	TOMM	Diagnostic	No COI. No mention of sponsorship.	257 veterans with possible mild TBI	Mean age: 29.5 years; 248 males, 9 females.	Possible mild TBI	Rey Fifteen-Item Memory Test (FIT) (n = 257). Out of the 257 participants that underwent the FIT, some	Four (1.6%) participants failed the FIT (according to standard cut-off of <9 items), three	"Despite its popularity, the FIT is not supported as an appropriate measure of performance	Data suggest FIT is not a good tool for performance validity in veterans being

							completed the Digit Span (n = 148) and some completed the Digit Span and the TOMM (n = 109)	(1.2%) failed the FIT (cut-off of <8 items), and 198 (77%) obtained perfect scores.	validity in veterans undergoing evaluation for possible mTBI. Therefore, inferences regarding neuropsychological data reliability with adequate statistical certainty require use of other measures of performance validity with greater sensitivity.”	evaluated for mTBI.
Schroeder 2013 (5.5)	TOMM	Retrospective	No sponsorship or COI.	62 consecutive forensic cases, with complaints related to TBI	Mean age 40.83 years for pass MND, 44.08 years for fail MND; 38 males, 24 females.	Mild TBI, complicated mild TBI, moderate-to-severe TBI, or a number of other conditions including major depressive disorder, frontotemporal dementia, and mental retardation to name a few.	Malingered Neuropsychological Dysfunction Criteria (MND) Pass group (n = 26) vs. MND Fail group (n = 36). All participants underwent TOMM trial 1, TOMM trial 2, TOMM retention, and the Albany Consistency Index tests.	Group performance between pass and fail MND groups, respectively (mean score, mean rank, Mann-Whitney U, p-value) - TOMM trial 1: 47.17 vs. 35.92, 41.89 vs. 17.12, 94.00, (p < 0.01), TOMM trial 2: 49.86 vs. 41.96, 41.08 vs. 18.23, 123.00, (p <	“Evidence was provided for convergent and divergent validity for all TOMM indices, which increases confidence for the clinical utility of both the new and traditional indices. Although each index well differentiated patients passing and failing MND criteria, the ACI was found to be the superior index.”	Data suggest both the new and the traditional TOMM indices are valid and have good clinical value. However, the ACI was found to be the superior index.

								0.01), TOMM Retention: 49.69 vs. 39.88, 41.35 vs. 17.87, 113.50, (p < 0.01), ACI: 46.89 vs. 30.15, 42.57 vs. 16.17, 69.50, (p < 0.01)		
Guise 2010 (score= 5.0)	Memory Test	Diagnostic	No mention of COI or sponsorship	N=176 TBI patients (archival data).	Mean age mild TBI/good effort: 38.1 (SD=9.7). 26 males, 13 females mild TBI/good effort group.	Mild to severe TBI	Mild TBI/Good Effort (n = 40) vs. Mild TBI/Poor Effort (n = 42) vs. Moderate-severe TBI/Good Effort (n = 40) vs. Moderate-severe TBI/Poor Effort (n = 14) vs. Control (n=40).  Portland Digit Recognition Test vs. Test of Memory Malingering (TOMM).	Effort was found to have a greater effect on test performance (0.79) than injury severity (0.47).	“Moderate-severe TBI produced overall worse performance than mild TBI patients and control subjects. Mild TBI showed some effect on test performance, but deficits were likely due to secondary factors including financial incentive, psychological overlay, and poor effort.”	Data suggest effort has a greater effect on text performance than does injury severity.
Teichner 2004 (score=5.0)	Memory Test	Diagnostic	No mention of COI or sponsorship	N=78 elderly cognitively intact, cognitively impaired (non-dementia), and with dementia	Mean age was 70.5 (SD=8.5). 33 males and 45 females.	Cognitively intact, cognitively impaired (non-dementia), and with dementia.	Test of Memory Malingering (TOMM) vs. Wechsler Adult Intelligence Scale—Third Edition (WAIS-III) vs. Wechsler Memory Scale—	100% of normals and 92.7% of the cognitively impaired group made fewer than five errors	“Results suggest that the TOMM is an useful index for detecting the malingering of memory deficits, even in patients with cognitive impairment, but	Data suggest TOMM is a useful test for the detection of malingering and memory defects even in those with cognitive

							Third Edition (WMS-III) vs. Mini-Mental State Examination (MMSE).	(the suggested cut-off) on Trial 2 or the Retention trial of the TOMM.	only when dementia can be ruled out.”	impairment if and only if dementia can be ruled out.
Haber 2006 (5.0)	TOMM	Retrospective Study	No mention of sponsorship or COI	50 Cases with head-injury.	Mean age of 39.1 years old. 27 Females, 22 Males	TBI	TBI Group (N = 22)  Vs  IME Group (N=28)	The TBI group was moderately to severely impaired for memory performance . Nobody in the TBI group scored below 45 on Trial 2 despite being impaired visually.	“[T]he TOMM appears to have adequate sensitivity and excellent specificity vis-a-vis traumatic brain injury, allowing the clinician to have high confidence that positive scores reflect incomplete effort.”	Data suggest that TOMM is useful in the detection of suboptimal effort especially for those individuals with mild head trauma.
Bashem 2014 (5.0)	TOMM	Diagnostic	Supported by grants from Wayne State University, the Del Harder Foundation, and the National Institute on Disability and Rehabilitation Research. No mention of COI.	109	No gender distribution described  Mean age 44.0 years	Those with TBI, ranging from mild complicated to severe (n=51)  vs  Neurologically healthy controls (n=58)  All participants underwent all testing	Premorbid intelligence, measured via Wechsler Test of Adult Reading (WTAR)  vs  Performance Validity Test (PVT) - Test of Memory Malingering (TOMM)  vs  PVT – Word	TOMM highest hit rate (68%). TOMM highest sensitivity (50%) and MSVT highest specificity (94%). RDS smallest hit rate (54%), specificity (77%), and sensitivity (35%).	“The findings should be generalized with caution, but if only one index will be employed, this study provides support for administering the TOMM alone and reserving the MSVT as an equivalent, alternate measure for future assessment.”	Participants were each compensated \$30. Data suggest use of TOMM with CVLT or use of MSVT with CVLT for the best diagnostic accuracy to assess TBI associated memory function. Any more than 2 tests does not significantly

							Choice Test (WCT) vs PVT – Medical Symptom Validity Test (MSVT) vs Embedded indices – Forced Choice Recall (CVLT-II) vs Embedded indices – Reliable Digit Span (RDS)	TOMM and CVLT highest agreement within TBI participants (86% passed both, 2% failed both, 88% overall agreement rate). RDS and WCT had lowest overall agreement rate (68%) in those with TBI.  Overall agreement highest between TOMM and MSVT (84%) in controls. 40% failed both tests and 45% passed both.		increase diagnostic accuracy.
Ashendorf 2004 (score=4.5)	Memory Test	Diagnostic	No mention of COI or sponsorship	N=197 community-based older adults with mild-to-moderate depression and anxiety as measured by Beck Depression Inventory	Mean age 64.57 (SD=5.52). 101 females and 96 males.	Mild-to-moderate depression and anxiety.	Test of Memory Malingering (TOMM).	All TOMM Trial 2 scores were 48 or higher, suggesting an absence of malingering.	“These findings demonstrate that depression and anxiety levels in an older community-dwelling sample do not negatively affect performance on the TOMM.”	Data suggest that although TOMM appears resistant to many conditions including TBI, depression and anxiety do not negatively affect TOMM performance.

				(BDI) and. State-Trait Anxiety Inventory (STAI).						
Constantino u 2004 (score=4.5)	Memory Test	Diagnostic	No mention of COI or sponsorship	N=69 litigants with mild TBI.	Mean age 42.41 (SD=12.45). 36 females and 33 males.	Mild TBI.	Test of Memory Malingering (TOMM) vs. general performance patterns on the WAIS-R vs. Halstead-Reitan Neuropsychological Battery for Adults (HRNB-A).	TOMM was associated (P <0.05/15 = 0.003 (Bonferroni method for control of Type I error) with decreased VIQ (Correlations r=0.47), PIQ (Correlations r=0.52), FSIQ (Correlations r=0.52) scores and decreased performance on WAIS-R subtests	"[I]t appears that a poor performance on the TOMM is predictive of a generalized poorer performance on standardized measures such as the WAIS-R and the HNRB-A."	Data suggest a poor performance on TOMM trial 2 was generally positively correlated to a poor performance on WAIS-R and HRNB-A.
Heyanka 2015 (4.0)	TOMM	Diagnostic	No COI. No mention of sponsorship.	160	9 female, 151 male  Mean age 31.7 years	Mild TBI	Word Memory Test (WMT) – IR, DR, CNS trials  vs  TOMM  vs  California Verbal Learning Test-Second Ed. (CVLT-II)	Significant correlation (p<0.001) between CVLT-II and TOMM (0.40-0.68), CVLT-II and WMT (0.43-0.61), and WMT and TOMM (0.51-0.75) observed.	"Our findings support assertions that PVTs measure effort independent of memory in veterans with mild TBI."	Data suggest PVTs are measuring effort which is independent of memory in mild TBI veterans.

Stenlik 2013 (4.0)	TOMM	Diagnostic	No mention of COI or sponsorship.		Mean age: 45.52 years; 20 males, 24 females	44 with history of mTBI (defined by the American Congress of Rehabilitation Medicine (ACRM) Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group)	All participants underwent the TOMM Trial 1, Trial 2, and Retention Trials. Comparison of standard TOMM cutoff values (n = 44) vs nonstandard cutoff of <49 on Trial 2 (n = 44) vs nonstandard cutoff of ≤39 on Trial 1 or Retention Trial (n = 44). Criteria for performance invalidity equal to failing two or more SVTs (Rey 15-Item Test, Victoria Symptom Validity Test, Word Memory Test, and Reliable Digit Span)	Classification accuracy statistics for cutoffs (sensitivity, specificity, false negative rate, and false positive rate, respectively) - standard TOMM cutoffs: .4, 1.0, .6, .00. <49 on Trial 2/Retention Trial cutoff: .75, .92, .24, .08. ≤39 on Trial 1 cutoffs: .6, .96, .4, .04.	“These findings support the use of nonstandard cutoffs to increase the TOMM’s classification accuracy.”	Data suggest non-standard cutoffs likely to increase the classification accuracy of TOMM.
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Following a mild TBI, up to 15% of patients report having cognitive problems including memory deficits, reduced information processing speed, concentration problems, etc. [446] [349]. Some general measurements of cognitive function, including intelligence tests have been suggested to be insufficient. Therefore, cognitive event-related potential latency has been proposed as a more reliable diagnostic measure for cognitive impairment following TBI [447].

## **Cognitive Event-Related Potential Recommended.**

Cognitive event-related potential has been recommended for use in the evaluation of TBI patients.

### *Strength of Evidence* – **Recommended, Evidence (C)**

#### *Level of Confidence* – Low

<i>Indications:</i>	Post-TBI patients who either have symptoms of cognitive deficits and/or have sustained a TBI sufficient to cause same.
<i>Benefits:</i>	Identification of cognitive deficits that may potentially be addressed by further cognitive therapy.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Baseline evaluation. May be used to evaluate progress and/or residual cognitive deficits.
<i>Indications for Discontinuation:</i>	Sufficient recovery, plateau, end of healing.
<i>Rationale:</i>	There are a few quality studies assessing Cognitive Event Related Potential for diagnosis of cognitive impacts of TBI and suggesting efficacy. Cognitive Event Related Potential is not invasive, has no adverse effects, is low cost, has evidence of diagnostic efficacy, and is recommended for diagnosis of cognitive impacts of TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Cognitive Event Related Potential, Event Related Potential, Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury, diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 386 articles in PubMed, 88 in Scopus, 34 in CINAHL, 14 in Cochrane Library, 10100 in Google Scholar, and 12 from other sources. We considered for inclusion 4 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 3 from Google Scholar, and 0 from other sources. Of the 7 articles considered for inclusion, 2 randomized trials and 4 systematic studies met the inclusion criteria.

### Evidence for the Use of Cognitive Event Related Potential

Author Year (Score)	Category:	Study type:	Conflict of Interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Gosselin 2012 (4.0)	Cognitive Event Related Potential	Diagnostic	Study was supported by the Canadian Institutes of Health and Research and by the Defense Research & Development. No COI.	N=44 Patients w/ TBI. N=40 Controls.	44 females, 40 males; Mean age 30.3±11.1 (TBI group), 28.6±10.5 (Control group)	Individuals who had sustained an mTBI event within the last 36 months.	Comparison between healthy controls and TBI patients of frontal ERP (Event related potential) components (N200, N350). Working Memory (WM) processes and partial ERP would have (P200, P300)	N350 amplitude showed smaller amplitude for mTBI group during the decision phase of WM (F(1,80) = 6.11 (p=0.016)). P300 amplitude in WM decision phase was smaller in mTBI stuff (F(1, 80) = 9.33 (p<0.01)).	“This study showed that abnormal ERP results are observed in patients in their post-acute and long-term stages after MTBI... Clinicians should be aware that patients with MTBI or sports concussion probably have underlying mild but persistent cerebral dysfunctions that require further investigation.”	Data suggest patients with mild TBI exhibit abnormal ERP results including in the non-acute post injury stage which often goes undetected
Soldatovic 2014 (4.0)	Cognitive Event Related Potential	Diagnostic	No sponsorship or COI.	N=90 patients with varying severities of TBI.	No mention of sex; Mean age of 38.18±13.17.	Patients with mild, moderate and severe TBI within the past year.	(N=41) mild TBI, (N=27) moderate TBI, (N=22) Severe TBI groups we compared in P300 cognitive evoked potentials.	P300 ERPs latency was significantly different between mild and severe, 326.8 ±36.76 vs 350.55±31.71 (p=0.03). Mild and moderate, 326.83±36.76 vs 355.67±42.32 (p=004).	“As regards neuropsychological assessment of cognitive deficits, our data show that the WCST has a great significance for detecting cognitive impairment, as well as for assessing the severity of TBI.”	Date suggest p300 ERP correlates to increased response latency and NCST useful for discriminating TBI severity and thus both tests have benefit in the detection of cognitive impairment.

## Attention Testing

Recent studies have shown that various aspects of attention are affected following TBI, especially after severe TBI. These deficits include the ability to initially attend to and encode information [448], information processing speed [349, 449], maintain focus [450, 449], shift attention [451], attention span [449], supervisory attentional control [449], focused/selective attention [449], and sustain attention [449, 452]. Age was not found to be a significant factor by some [449] but not all studies [453].

However, Ginstfeldt [454] found that sustained attention was most vulnerable to TBI in children. There are many studies that have used attention testing in the evaluation of TBI patients [455, 456, 457, 458-474].

### Attention Tests

#### Recommended.

Attention tests are recommended for use in the evaluation of TBI patients.

#### Strength of Evidence – Recommended, Insufficient Evidence (I)

##### Level of Confidence – Moderate

<i>Indications:</i>	Moderate or Severe TBI patients experiencing cognitive difficulties that include attention. May be performed to help guide treatment. May later be performed as part of an evaluation for end-of-healing and clinical plateau.
<i>Benefits:</i>	Identify and measure attention difficulties, potentially allowing better tailoring of therapy(ies) to address any memory deficits.
<i>Harms:</i>	Negligible in most patients. Testing is strongly subject to malingering. Thus, careful interpretation and potential pairing with tests for malingering are indicated especially where there is strong potential for secondary gain(s).
<i>Frequency/Dose/Duration:</i>	Generally not performed more than once or twice. May be used to target specific cognitive rehabilitation strategies. May later help determine end of healing and extent of residual deficits, if any.
<i>Rationale:</i>	There are quality studies assessing Attention testing for diagnosis and evaluation of TBI. However, there are few comparative trials of sufficient size and rigor to allow a recommendation of one type of testing over another. Attention testing is not invasive, has no adverse effects, is low cost, has evidence of diagnostic efficacy, and thus is recommended for evaluation of TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: attention test, sustained attention to response task or monotone counting or variables of attention test, traumatic brain injury, intracranial injury, closed head injury penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; sensitivity and specificity, predictive value of tests, gold-standard, accurate, accuracy, precision, precise, test; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy,

and efficiency. We found and reviewed articles in 747 PubMed, 310 in Scopus, 496 in CINAHL, 4 in Cochrane Library, 25800 in Google Scholar, and 8 from other sources. We considered for inclusion 11 from PubMed, 8 from Scopus, 2 from CINAHL, 3 from Cochrane Library, 3 from Google Scholar, and 8 from other sources. Of the 35 articles considered for inclusion, 19 prognostic studies, 1 randomized trial and 5 systematic studies met the inclusion criteria.

### Evidence for the Use of Attention Tests

Author Year (Score)	Category:	Study type:	Sponsorship / COI	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Twamley 2014 (4.0)	Attention Test	Randomized controlled trial	Sponsored by the DOD award. Dr. Delis received royalties from the sale of the CVLT-II and D-KEFS. No mention of other COI.	N = 50 Veterans with TBI.	Age and sex information only available for post-treatment sample. Mean age: 29; 32 males and 2 females.	TBI	<p>Comparison data only available for post-treatment sample.</p> <p>Supported employment plus CogSMART (N = 16) vs Control group, received enhanced supported employment that controlled for therapist attention (N = 18).</p> <p>Attention and working memory measured with the Wechsler Adult Intelligence Scale-3rd Edition Digit Span scaled score, Verbal learning/memory measured with the CVLT-II. Follow-up for 12 weeks.</p>	<p>CogSMART-associated improvements in postconcussive symptoms / and prospective memory performance: NSI: <math>p = 0.01</math> / and MIST 24 h probe: <math>p = 0.05</math>.</p> <p>CogSMART showed small-medium effect size improvements in psychiatric symptom severity / and HAM-D: CAPS: <math>d = 0.43</math> / and HAM-D: <math>d = 0.37</math> compared to controls.</p>	“Results suggest that adding CogSMART to supported employment may improve postconcussive symptoms and prospective memory.”	Pilot RCT. Data suggest Cog SMART “may” improve post concussive symptoms in Veterans with TBI.
Rogers 2014 (NA)	Attention Test	Prognostic	Sponsored by a University of Western Australia International Postgraduate Research Scholarship awarded to the	N = 10 with history of mild traumatic brain injury (mTBI) and	Aged 17–34 (18) and 18–30 (18.5) for controls. 12 males and 8 females.	mTBI and healthy subjects	<p>Mild TBI, time since injury &gt; 2 months, completed Paced Auditory Serial Addition Task (PASAT) as a measure of attention process, at four separate sessions</p>	Performance differences from the first (Session 1A) to the second experimental block (Session 1B) at each of the 4 inter-stimulus interval	“These preliminary results suggest sustained mental effort is required to achieve ‘normal’ performance	Data suggest practice of mental effort post TBI is important for improving functional recovery.

			first author. No COI.	10 healthy subjects.			(N = 10) vs Healthy matched controls completed PASAT at 4 sessions (N = 10).	rates or ISIs: F (1, 18) = 12.90, p < 0.01, n <sup>2</sup> p = 0.42. The mean number of correct PASAT responses, the main effects of session: F (2.02, 36.43) = 91.16, p < 0.01, n <sup>2</sup> p = 0.84 and ISI: F (1.35, 24.24) = 51.85, p < 0.01, n <sup>2</sup> p = 0.74, were significant.	levels following mTBI and support the use of practice-related, ERP indices of recovery from mTBI as a sensitive correlate of persistent post-concussion symptoms.”	
Wäljas 2014 (NA)	Attention Test	Prognostic	Sponsored by Competitive Research Funding of the Pirkanmaa Hospital District, Tampere University Hospital. No COI.	N = 109 with mTBI.	Aged 37.4 (13.2) years, 52 male and 57 females.	mTBI	Outcome measures; Self-report questionnaires, post-concussion symptoms, depression, fatigue, and general health, measured with the Rivermead Post Concussion Questionnaire (RPSQ). Attention and executive functioning were assessed with the Stroop Color Word Test (Golden version), Trail Making Test A and B, and 2 verbal fluency tasks: animal naming and single letter-based word generation.	RTW rates: 1 / 2 / 3 / and 4 weeks; 46.8% / 59.6% / 67.0% / and 70.6%.  2 months / and 1 year; 91.7% / and 97.2%.  Significant predictors of the number of days to RTW: age, multiple bodily injuries, intracranial abnormality at the day of injury, and fatigue ratings (all, p < 0.001). Participants who returned to work fewer than 30 days after injury (n = 82,	“Return to work is one important marker of functional recovery following mTBI.”	Data suggest time until RTW post mild TBI is correlated with the number of bodily injuries, age, intracranial injury and fatigue.

							Follow-up or 3 to 4 weeks.	75.2%) vs 30+ days (n = 27, 24.8%).		
Oldenburg 2015 (NA)	Attention Test	Prognostic	No mention of sponsorship. No COI.	N = 102 with mild traumatic brain injury (mTBI) with N = 35 controls.	Aged 15-65 years.	mTBI	<p>Post-concussion symptoms (PCS) (N = 34)</p> <p>vs Recovered (N = 68)</p> <p>vs Control (N = 35).</p> <p>Self-report questionnaire and</p> <p>Neuropsychological test:</p> <p>The Paced Auditory Serial Addition Test (PASAT) processing speed, information processing and</p> <p>attention; Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span, WAIS-R Block Span,</p> <p>The Selective Reminding Test</p> <p>The Stroop Color and Word Test</p>	<p>Only 102 subjects had PCS data and only 88 had neuropsychological assessment data.</p> <p>Recovered patients: WAIS-R Digit Span / WAIS-R Block Span / PASAT (2.4 sec) / and PASAT (1.6 sec);</p> <p>(N = 55) 9.8 (2.8) / (N = 28) 16.8 (2.8) /</p> <p>(N = 53) 55.4 (7.0) / and (N = 51) 54.3 (8.4).</p> <p>Controls; WAIS-R Digit Span / WAIS-R Block Span / PASAT (2.4 sec) / and PASAT (1.6 sec);</p> <p>(N = 28) 10.1 (2.9) /</p> <p>(N = 55) 17.0 (3.1) /</p>	<p>"mTBI may be linked to subtle executive memory deficits. Lower cognitive reserve appears to be a risk factor for PCS and indicates individual vulnerabilities."</p>	<p>Data suggest mTBI "may" be linked to deficits in working memory.</p>

								(N = 28) 54.3 (7.0) / and (N = 26) 54.6 (5.8). Statistical significance between the 3 groups above, for each of the 4 attention test domains; (p = 0.673) (p = 0.236). (p = 0.102). (p = 0.526).		
Nash 2014 (NA)	Attention Test	Prognostic	No mention of sponsorship or COI.	N = 207 seriously injured persons.	Aged at least 16 years.	mTBI	Moderate / severe group A (N = 48) vs Mild group (N = 89) vs Severe injuries without brain trauma (N = 70). Outcome measures: Questionnaire, Post-traumatic Stress Disorder Checklist Scale, Neurobehavioral Rating Scale, and	The most frequently observed symptoms (> 15%): anxiety (52.2%) / irritability (38.6%) / memory disorders (38.6%) / depressive mood (30.4%) / attention disorders (28.0%) / mood lability (26.6%) / and guilt feelings (16.4%). Memory and attention disorders were significantly more frequently found in the two	"The presence and the initial severity of a traumatic brain injury condition the nature and frequency of residual effects after one year."	Data suggest irritability or a depressive mood are not specific to TBI.

							The Trail Making Test, measurement of mental flexibility or attention-switching capability.	TBI groups than in the non-TBI group.		
Dockree 2015 (NA)	Attention Test	Prognostic	Sponsored by grants from the Health Research Board (PA-06-17) of Ireland, the National Rehabilitation Hospital Trust, University College Dublin Seed funding, and the National Disability Authority awarded to Dr. Simone Carton. No COI.	N = 62 with impaired self-awareness after TBI.	Mean age 34.37 (11.85), 49 males and 13 females.	Impaired self-awareness after TBI	All participants underwent the following testing: National Adult Reading Test (NART), Modified Six Elements Test (M-SET), Hospital Anxiety and Depression Scale (HADS), Sustained Attention to Response Test (SART), the Dual-task Attention to Response Test (DART), the Error Awareness Task (EAT), Cognitive Failures Questionnaire (CFQ), and the Frontal Systems Behaviour Scale (FrSBe).	Relationship between patient self-reports and SART no-go errors, (all $p > 0.1$ ). Positive relationship between CFQ ratings and SART errors ( $r = 0.31$ , $p = 0.01$ ). Relationships between FrSBe other reports vs SART errors ( $r = 0.18$ ; $p = 0.1$ ) and PCRS other reports and SART errors ( $r = -0.19$ ; $p = 0.08$ ). Self-other discrepancy measures derived from the CFQ, FrSBe & PCRS were inter-correlated: CFQ-FrSBe: $r = 0.48$ ; CFQPCRS: $r = 0.51$ ; FrSBe-PCRS: $r = 0.61$ , (all $p < 0.0005$ ).	“This relationship supports the idea that the monitoring of errors in daily tasks will foster a growing self-awareness of daily functioning after brain injury, which, in turn, may necessitate a change in strategy or a commitment to rehabilitation to accomplish daily tasks more efficiently.”	Data derived from diaries written by significant others. Data suggest emergent awareness was determined to be the only good predictor of performance on a modified 6 element test.
Johansson 2015 (NA)	Attention Test	Prognostic	Sponsored by grants from AFA Insurance, The Local Research and Development Board for	N = 76 with mild traumatic brain injury (mTBI) and	Mean age for mTBI and controls: 43.3 (12.2) / and 41.1 (12.3). 45	mTBI	mTBI, using the Mental Fatigue Scale (MFS) questionnaire and WAIS-III measuring information processing speed, and Digit Span, and	The TBI group significantly slower vs control on the complex sub-test ( $F = 17.116$ , $p < 0.001$ ,	“The results indicate a less efficient performance over time in complex and demanding	Data suggest mental fatigue post TBI correlates with diminished

			Gothenburg and Sodra Bohuslan, The Health & Medical Care Committee of the Vastra Gotaland Region, The Swedish Stroke Association and the Swedish Association For Survivors of Accident and Injury (RTP). No COI.	45 healthy controls.	males and 76 females.		WAIS-III, measuring attention and working memory (N = 76) vs Control (N = 45).	$\eta p^2 = 0.099$ ), and there was a significant interaction effect over time ( $F = 2.797, p = 0.044, \eta p^2 = 0.023$ ), controls faster at the end of the test, vs TBI subjects remained on a similar level. TBI with a lower MFS rating (between 10.5 – 19.5, $N = 29$ ) and one with a higher MFS rating ( $>20, N = 46$ ) showed an interaction trend with those with a higher MFS rating becoming slower at the end of the complex computer test, ( $p = 0.091$ ).	cognitive tasks for individuals experiencing from mental fatigue after brain injury.”	performance for complex cognitive tasks.
Maki-Marttunen 2015 (NA)	Attention Test	Prognostic	Sponsored by the Academy of Finland and the Competitive Research Fund of Pirkanmaa Hospital District. No COI.	$N = 27$ mTBI and $N = 17$ ankle injury.	mTBI mean age 41 years, and ankle injury: 12 females and 15 males	mTBI	MTBI, biomechanical force applied to the head resulting in loss or alteration of consciousness, confusion, and/or post-traumatic amnesia or PTA ( $N = 27$ ) vs Controls with previous ankle injury ( $N = 17$ ).  Questionnaires, including BRIEF-A, Rivermead Post Concussion	mTBI patients were faster vs controls in the emotion relevant condition, mTBI vs controls: $T = 2.13, p = 0.039$ , effect size = 0.58). $N2$ peak amplitude was significantly enhanced by emotional Go signals in the mTBI group, ( $N2$ , interaction effect emotion by group: $F = 8.13, P = 0.007$ ;	“mTBI may be associated with enhanced allocation of attentional and executive resources to threat-related stimuli.”	Data suggest mild TBI patients had reported more emotional symptoms than controls when threat stimuli were evoked, the mTBI group responded quicker than controls suggesting

							Symptoms and Beck's Depression Inventory (BDI). Executive reaction time (RT) test computer-based Go-NoGo visual discrimination alterations in emotion-attention interaction.	post-hoc t test in mTBI, threat vs. neutral: T = 7.3, P < 0.001, effect size = 0.45).		TBI patients have enhanced threat related attention functions.
Zimmermann 2015 (NA)	Attention Test	Prognostic	Sponsored by Conselho Nacional de Desenvolvimento Cientifico e Tecnologico (CNPq) for the first author studentship. No COI.	N = 84 with mild and moderate/severe TBI.	Aged 18-72 years. 62 males and 22 females.	Mild and moderate/severe TBI	Cluster 1, focused attention (Time A Composite score), cognitive flexibility, inhibition, speed for focused attention (N = 35) vs Cluster 2, focused attention (Time A Composite score, cognitive flexibility, inhibition, speed for focused attention, and working memory (N = 15) vs Cluster 3, no significant deficits (N = 34). All participants underwent the following tests: Hayling test, Trail Making Test, Modified Wisconsin Card Sorting Test (48 cards), Verbal fluency tasks-Montreal Communication Assessment Battery, and Auditory oral word span in sentences-Brief Neuropsychological Assessment Battery NEUPSILIN	No difference in clinical or demographical variables for the 3 clusters.	"The first cluster replicated findings of previous studies on TBI EF profiles."	Data suggest EF profiles in TBI adults is more important for rehab outcomes than demographic or clinical variables.

Cicerone 2002 (NA)	Attention Test	Prognostic	No mention of sponsorship or COI.	N = 64 with cognitive impairments after mild traumatic brain injury (mTBI) and subgroup persistent post-concussion syndrome (PCS).	Mean age 39.4 (9.6) for PCS and 37.2 (9.7) for controls.	mTBI	Post-concussion syndrome or PCS (N = 32) vs Controls (N = 32). Attention tests; Digit Span, Trail Making Test, Part A and Part B, Stroop Color-Word Test, Continuous Performance Test of Attention (CPTA), paced Auditory Serial Addition Test (PASAT), and Ruff 2 & 7 Selective Attention Test.	The greatest overall efficiency was apparent for the CPTA at a criterion level of -1.5 z. The CPTA exhibited acceptable levels of sensitivity and specificity and exhibited a moderately positive association with PCS, (LR = 4.5). Positive associations were also apparent for the Stroop Color (LR = 7.4) and Stroop Color - Word trials (LR = 3.4).	“Examination of the Odds Ratios indicated that measures assessing processing speed had a reliable, positive association with PCS, while measures without a processing speed component did not.”	Data suggest those measures with high specificity such as stroop color and processing speed were shown to have strong positive predictive power. Those measures with high sensitivity such as CPTA reflect strong negative predictive power for diagnosing PCS.
Kurča 2006 (NA)	Attention Test	Prognostic	No mention of sponsorship. No COI.	N = 60 with mTBI.	Mean age for; MRI traumatic / MRI nontraumatic and MRI traumatic and non-traumatic controls: 33.71 ± 14.24 / 31.57 ± 11.30 / and 32 ± 13.47 / 29.39 ± 11.82, 42 males and 19 females.	mTBI	Mild traumatic brain injury MTBI, Concentration and Attention Test (CAT), Disjunctive Reaction Time test (DRT) (N = 30) vs Control group consisted of sex- and age-matched healthy volunteers (N = 30).	The MRI nontraumatic group significantly differed vs control in scores of recall after first reading (TS1R), working memory and quantity score in the CAT, Mann-Whitney U-test MRI traumatic vs non-traumatic, QS / SEr / and QualS: 0.71 / 0.02 / and 0.19. MRI nontraumatic vs controls and	“There is evidence that MTBI patients with true traumatic MRI lesions are neuropsychologically different from MTBI patients with nonspecific MRI lesions or normal brain MRI.”	Data suggest that these may be MRI visible traumatic lesions associated with mild TBI causing associated signs and symptoms and there lesions are distinctly different from non special

								traumatic vs control: 0.01 vs 0.14 / 0.59 vs 0.07 / 0.84 vs 0.03.		MRI lesions or normal MRI images.
Nolin 2006 (NA)	Attention Test	Prognostic Experimental	No mention of sponsorship or COI.	N = 85 with mTBI examined 12 to 36 months post-injury.	Aged 16 to 65 years.	mTBI	Those with mTBI who had returned to work (n = 67) vs. those with mTBI who had not returned to work (n = 18). All participants participated in these tests or questionnaires: MTBI Consultation Questionnaire / Paced Auditory Serial Addition Task / Stroop ColorWord Test / California Verbal Learning Test	PASAT, Stroop, and CVLT were related to return to work, beta coefficients were nonsignificant.	"Patient characteristics, injury severity indicators, and cognitive functions were not associated with vocational status."	Quasi-experimental design. Data suggest severity of injury and cognitive functions not associated with vocational status. Patients not returning to work had reported a higher number of symptoms.
Pastorek 2004 (NA)	Attention Test	Prognostic	Sponsored in part by National Institutes of Health Grants as well as National Institute of Disability and Rehabilitation Research Grant. No mention of COI.	N = 105 with head injury.	Mean age 31.5 (12.7), 92 males and 13 females.	Head injury	All participants underwent the following comparisons:  Best Day 1 GCS of 3–8, an abnormal neurological evaluation, and abnormal CT findings  Best Day 1 GCS of 9–12  Complicated mild traumatic brain injury associated with Best Day 1 GCS of 13–15 and abnormalities on CT	At 1 month, post injury increased the odds of a favorable GOS outcome at 6 months post injury by a factor of 28.2 for VNS, 26.7 for ANS, 17.1 for CIM, and 12.9 for MTT. At 1-month post injury accounted for substantially less variance in DRS scores (7.7–8.4%).	"Neuropsychological data, including the testability of patients, collected uniformly at 1 month following injury can contribute to the prediction of global outcome."	Data suggest that the neuropsychological data derived from closed head injury 1 month after the injury may predict ultimate global outcomes.

							Best Day 1 GCS was uniformly defined as the highest GCS score obtained during the first 24 hours post injury  Attention tests: Auditory Number Search Test (ANS) and Visual Number Search Test (VNS)			
Willmott 2009 (NA)	Attention Test	Prognostic	Sponsored by the Victorian Neurotrauma Initiative and the Wenkart Foundation. No mention of COI.	N = 40 with traumatic brain injury (TBI) and 40 healthy controls.	Aged 16 to 60 years, 55 males and 25 females.	TBI	Traumatic brain injury (N = 40) vs Healthy controls (N = 40).  Symbol Digit Modalities Test (SDMT), 2&7 Selective Attention Test (2&7), Selective Attention (SAT), Sustained Attention to Response Task (SART), Four Choice Reaction Time (4CRT) tasks, Letter Number Sequencing Task (LNS), and Wechsler Test of Adult Reading (WTAR)	The TBI participants were significantly slower vs control $F(1, 76) = 19.28, p < 0.001$ , and performance was slower on the complex vs simple condition $F(1, 76) = 448.92, p < 0.001$ .	"The present study provides evidence for a significant contribution of slowed processing speed to impaired performance on attentional tasks after TBI."	Data suggests significant attentional impairments post TBI and decreased informational processing results in poor task performance.
Withaar 2003 (NA)	Attention Test	Prognostic	No mention of sponsorship or COI.	N = 26 with subacute closed head injury (CHI) and 25 orthopedic controls.	Aged 15 to 55 years, 39 males and 12 females.	Closed head injury	subacute closed head injury or CHI (N = 26) vs Orthopedic controls (N = 25).  Reaction time (RT) task, Trail Making Test and Continuous Tracking and Arrow identification task	CHI needed longer than controls to finish the Trail Making B task; longer time needed to finish the Trail Making test for patients and Trail making B version; $F = 5.71, p = 0.021$ and $F = 60.46, p < 0.001$ .	"Additional impairments in complex divided attention tasks only emerged in the most complex tasks (that is the strategy driven flexibility task)."	Data suggest that divided attention impairments are related to a decreased rate of the processing of information.

								Single and dual task performance between two groups, $F = 6.89$ , $p = 0.011$ .		
King 1996 (NA)	Attention Test	Prognostic	No mention of sponsorship or COI.	N = 50 with mild or moderate head injury had a range of measures administered at 7-10 days after injury.	Aged 17 to 65, 23 males and 27 females.	Head injury	All participants underwent the same testing. Information processing subtest of the adult memory and information processing battery (AMIPB), Stroop test, and PASAT.	5 scores accounted for 68% of the variance in RPQ scores; including, HADS anxiety, post-traumatic amnesia, SOMC, PASAT 2.4, and PASAT 1.6. At 7-10 days not significantly correlated with any of the neuropsychological tests of divided attention (Stroop, PASAT, and AMIPB subtests).	"A combination of measures may significantly aid the prediction of persistent PCS."	Data suggest combination of measures, specifically HADS, post-traumatic amnesia, SOMC, PASAT and RPQ enhance the prediction of persistent PCS.
Chan 2005 (NA)	Attention Test	Prognostic	Sponsored by the 100-Scholar Plan of the Sun Yat-Sen University, and Erik Kvan Fellowship from the University of Hong Kong. No mention of COI.	N = 51 with TBI and 51 matched controls.	Mean age for TBI / and controls; 42.9 (6.35) / and 41.7 (5.74), 42 males and 9 females.	TBI	Mild to moderate TBI (N = 51) vs Matched controls (N = 51).  The Sustained Attention Response to Task (SART), Monotone Counting Test, The Glasgow Coma Scale	For Monotone Counting Test and SART performance, the corresponding effect sizes ranged from modest to very large (0.25 1). A cut-off of less than 1 SD gives optimal diagnostic information in terms of sensitivity in the present sample. The SART was also associated with loss of consciousness in patients with TBI ( $r = 0.247$ , $p = 0.05$ ).	"These findings suggest that the SART and Monotone Counting Test are sensitive to patients with mild TBI."	Data suggest SART and MCT are sensitive in mild TBI patients and SART detected attention impairment. Patients with mild TBI performed significantly worse than did controls on both SART and MCT.

French 2014 (NA)	Attention Test	Prognostic	No sponsorship and no COI.	N = 109 military with mild-severe TBI.	Aged 19-56 years, 109 males.	mTBI	Mild TBI (N = 50) vs Moderate to severe TBI (N = 59). All participants underwent these tests: WAIS-III Letter Number Sequencing; Trail Making Test Part A and B; Auditory Consonant Trigrams (ACT) 36" Interval Delay, Conner's Continuous Performance Test-Second Edition (CPT-II) Omissions, Commissions, and Hit Rate, California Verbal Learning Test-Second Edition (CVLT-II) Total 1-5 and Long Delayed Recall, Rey Complex Figure Test (RCFT) Immediate Recall and Delayed Recall, WAIS-III Digit Symbol Coding and Block Design, RCFT Copy; Tower of London (TOL) Total Correct, Moves, and Initiation Time	83.4% had a valid PAI profile, 71.9% had been administered WMT and 88.6% passed the WMT, 80.6% completed PCL-C, 58.5% completed Neurobehavioral Symptom Inventory (NSI) (of sample), and 74.3% completed a core set of neurocognitive measures. Self-reported cognitive complaints significantly correlated with psychological distress (PCL-C total: $r = 0.50-0.58$ ; half the PAI clinical scales: $r = 0.40-0.58$ ).	"In sum, self-reported cognitive complaints were not associated with neurocognitive test performance, but rather were associated with psychological distress."	Data suggest self-reported cognitive complaints seem not to be associated with test performance but likely associated with psychological distress.
Tramontana 2014 (3.5)	Attention Test	RCT	Sponsored by Shire Pharmaceuticals, Michael G. Tramontana, PhD, Principal Investigator. No mention of COI.	N = 22 with TBI, newly acquired attention deficits persisting for 6-34 months post-injury.	Aged 16-45, 9 males and 4 females.	TBI	Lisdexamfetamine dimesylate or LDX 30 mg po on study day 1 for 1 week, 50 mg at week 2 and 70 mg at week 3 (N = 13) vs Placebo repackaged to appear identical to treatment (N = 13). All participants underwent these attention tests: Wisconsin Cart Sorting Test, Trail	15% reported having a history of pre-injury attention problems. Better performance on vs. off LDX on WAIS-IV Digit Span-Backward, ( $p = 0.003$ ). Lower self-ratings of inattentive symptoms on the CAARS-Long Form, ( $p = 0.040$ ).	"Positive treatment effects were found involving selective measures of sustained attention, working memory, response speed stability and endurance and in aspects of executive functioning."	Small number of patients completed the trail. Data suggest LDX may have some benefit for improving selected measures of memory, attention, response

							<p>Making Test-Part A and B, Conners Continuous Performance Test, Digit Span – Forward and Backward, Stroop Colour/Word Test, Digit Symbol-Coding, Paced Auditory Serial Addition Test (PASAT), Verbal Paired-Associate Learning, Benton Visual Retention Test, Conners Adult ADHD Rating Scale (CAARS)-Long Form</p> <p>Follow-up for 12 weeks.</p>			speed and endurance.
Niemann 1990 (NA)	Attention Test	Prognostic	No mention of sponsorship or COI.	N = 29 outpatients suffering from moderate to severe traumatic brain injury.	Mean age for experiment and control groups; 28.9 and 34.3.	Severe TBI	<p>Experimental group or measures of attention + memory, 9 weeks for 2-hour sessions per week (N = 13) vs Control group or measures of attention, 9 weeks for 2-hour sessions per week (N = 13).</p> <p>Measures of attention: d2 test, Paced Auditory Serial-addition task revision (PASAT-R), Divided Attention Test and Trail Making Test Part B test.</p> <p>Memory tests: Rey Auditory Verbal Learning Test-modified (RAVLT-M), and Learning Block span learning test (BSLT).</p>	The attention group improved vs memory group on four measures of attention, Wilks's lambda = 64, approximated: F (4, 21) = 2.93, p < 0.02, one-tailed.	“The experimental design evaluated outcome by juxtaposing a multiple baselining procedure for a 1st set of measures of attention and memory with a pre and post group comparison that relied on 2nd set of neuropsychological tests.”	Data suggest significant improvement in experimental groups vs. controls when attention retraining occurred prior to memory retraining.

Executive functions are “higher-order supervisory processes that initiate, maintain or inhibit other cognitive processes to facilitate goal-directed behavior” [475, 476]. Many types of executive function testing have been used to assess executive function in patients with traumatic brain injury [477-486].

## Executive Function

### Executive Function Test

#### Recommended.

Executive function tests are recommended for use in the evaluation of TBI patients.

#### Strength of Evidence – Recommended, Insufficient Evidence (I)

##### Level of Confidence – Moderate

<i>Indications:</i>	Moderate or Severe TBI patients experiencing cognitive difficulties that include executive functions. Mild TBI patients are expected to have no durable executive dysfunction [126], but may be indicated in select circumstances where there is ongoing impairment. May be performed to help guide treatment. May later be performed as part of an evaluation for end-of-healing and clinical plateau. Selective use among those with mild TBI with ongoing difficulties, high and critical occupational cognitive-executive demands and/or executive function complaints may also be indicated.
<i>Benefits:</i>	Identify and measure executive function difficulties, potentially allowing better tailoring of therapy(ies) to address any deficits.
<i>Harms:</i>	Negligible in most patients. Testing may be subject to malingering. Thus, careful interpretation and potential pairing with tests for malingering are indicated especially where there is strong potential for secondary gain(s).
<i>Frequency/Dose/Duration:</i>	Generally not performed more than once or twice. May be used to target specific cognitive rehabilitation strategies. May later help determine end of healing and extent of residual deficits, if any.
<i>Rationale:</i>	There are quality studies assessing Executive function testing for diagnosis of TBI. However, there are few comparative trials of sufficient size and rigor to allow a recommendation of one type of testing over another. Executive function testing is not invasive, has no adverse effects, is low cost, has some evidence of diagnostic efficacy, and is thus recommended for evaluation of TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Executive Function Test, Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma; Sensitivity and Specificity, Predictive Value of Tests, Gold-standard, accurate, accuracy, precision, precise, test diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 333 articles in PubMed, 10 in Scopus, 25 in CINAHL, 0 in Cochrane Library, 0 in Google Scholar, and 0 from other sources. We considered for inclusion 2 from PubMed, 4 from Scopus, 3 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 9 articles considered for inclusion, 9 prognostic studies and 0 systematic studies met the inclusion criteria.

### Evidence for the Use of Executive Function Tests

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Adjorlolo, 2016 (NA)	Executive Function Test	Prognostic	No Industry sponsorship or COI	N=100- 50 patients with TBI, 50 controls	Mean age was 32.0 years. 63 males, 37 females	Moderate Traumatic Brain Injury	Stroop test - This test measures selective attention and interference control vs. Trail Making Test - The TMT is a test of speed processing, sequence alternation, cognitive flexibility, visual search, motor performance, and complex attention. vs. Controlled Oral Word Association - This test required the participants to produce as many words as they can, beginning with the letters F, A, and S. vs. Revised Quick Cognitive Screening Test (RQCST) - This test screen for deficits in several neurocognitive domains	The sensitivity and specificity were given for the following tests respectively; Stroop Word (80%, 78%), Stroop Color (76%, 90%), Stroop Color-Word (80%, 84%), Stroop Interference (74%, 63%), Controlled Oral Word Association Test (97%, 57%), Trail Making Test (94%, 84%), RQCST (90%, 92%).	“In general, this study has shown that commonly used EF tests in Western countries have diagnostic accuracy, sensitivity, and specificity when administered in Ghanaian samples.”	Data suggest EF tests which are typically used in Western countries may be administered in Ghana and maintain diagnostic accuracy sensitivity & specificity.
Cossette, 2014 (NA)	Executive Function Test	Prognostic	No mention of Sponsorship or COI	N= 14 – 7 patients with Traumatic Brain Injury, 7 controls	Mean age was 20±1.6 years in TBI group, 22.4±1.4 years in control	Mild Traumatic Brain Injury	Cognitive Conditions –Stroop, Verbal Fluency, Arithmetic. vs.	The Mild Traumatic Brain Injury Group indicated significantly lower	“These preliminary results suggest that both absolute gait	Small sample (N=14). Data suggest in mild TBI patients, dual

					group. 2 males, 12 females		Gait Condition - walking 6m unobstructed, walking 6m and stepping over a 15-cm obstacle placed 4m from the start position, and walking 6m and stepping down from a 15-cm step 4m in front of the start position.	gait speed for the obstacle avoidance task paired with the various cognitive conditions when compared to the control group. The P values for each cognitive condition goes as follows: verbal fluency, .021; Stroop, .037; arithmetic, .039.	speed and calculated dual-task costs during the combination of stepping over an obstacle with a simultaneous cognitive task are sensitive to revealing executive dysfunction in persons with MTBI. Gait speed can be easily measured in the clinic to provide important information to make diagnoses and decide about return to play or function.”	task costs (DTCs) in gait speed during obstacle avoidance may be sensitive to executive function differentiation.
Clarke, 2012 (NA)	Executive Function Test	Prognostic	No Industry Sponsorship or COI	N= 60 – 21 patients with Mild Traumatic Brain injury, 19 with spinal injury, 20 neurological-normal controls	Mean age was 35.6 years in the Mild Traumatic Brain Injury group, 34.1 years in the spinal injury group, 19 years in the control group. The gender in the MTBI, Spinal	Mild Traumatic Brain Injury	Attention Index – Working Memory Index of Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) Vs. Memory Index – Rey Auditory Verbal Learning Test and the Rey-Osterrieth Complex Figure Test Vs.	The mean values in terms of z-scores for the Attention index, Memory Index, Executive Function Index, and Speed of Processing Index in the Mild Traumatic Brain Injury group are 0.86, 0.37, -0.04, and 0.15	“It was concluded that long-term post-concussive symptoms are largely representative of psychological symptoms and not brain damage, but	Data suggest PCS related to psychological symptoms and cognitive deficits may persist post mild TBI for long periods of time.

					injury, and control were given respectively; 14 males and 7 females, 14 males and 5 females, and 12 males and 8 females.		Executive Function Index – Trail Making Test and Controlled Oral Word Association Test Vs. Speed of Processing Index - Symbol Digit Modalities Test and Trail Making Test	respectively. The Mild Traumatic Brain Injury group depicts R-values under the Affective Factors Index as Neuropsychological index - -0.48 with $p < 0.05$ , PACCQ total – 0.55 with $p < 0.01$ , RPQ total – 0.57 with $p < 0.01$ . Under Neurophysiological Index -0.66 PACCQ total with $p < 0.01$ and -0.57 RPQ total with $p < 0.01$ . Under cognitive complaint 0.79 RPQ total with $p < 0.001$ .	that genuine, albeit subtle, cognitive deficits also may be present for long-term periods following mild traumatic brain injury.”	
Morton, 2010 (NA)	Executive Function Test	Prognostic	No Industry Sponsorship or COI	N= 34 – 11 patients with Moderate Traumatic Brain Injury, 23 patients with Severe Traumatic Brain Injury	Mean age was 35 years. 31.6 years in the moderate traumatic brain injury group, 36.6 in the severe traumatic brain injury group. The sex within the moderate group is 10 males and 1 female. In the severe traumatic brain injury group the sex is 22	Moderate Traumatic Brain Injury Vs. Severe Traumatic Brain Injury	Self-ordered Pointing Test (SOPT) - measure of response monitoring Vs. The Sorting Test (ST) -measure of concept formation Vs. The Brixton - measure of strategy initiation and response inhibition Vs. Verbal Fluency task – FAS, modality specific distractor task	The total group mean scores for executive function measures for the moderate TBI group were 14.2 – SOPT, 9.2 – ST, 6.2 – Brixton, and 37.7 – FAS. For the severe group they were 24.1 with $p < .05$ SOPT, 6.6 with $p < .05$ ST, 5.4 Brixton, and 27.8 with $p < .05$ FAS. The severe group showed lower scores on Sorting test $U=62.5$ , $p=.02$ ;	“Severe injuries resulted in greater impairments across most awareness, executive and implicit measures compared with moderate injuries, although deficits were still seen in the moderate group.”	Data suggests increasing injury severity correlated with greater dysfunction in most awareness, executive and implicit measures when compared to moderate injuries but deficits were observed in both groups.

					males, 1 female.			FAS verbal fluency U=70, p=.04, and SOPT U=65.5, p=0.2 than the moderate group.		
Paxton, 2014 (NA)	Executive Function Test	Prognostic	Sponsored by the National Institute on Disability and Rehabilitation Research (N.D.C., H133A070037 & H133P090009). No COI.	N= 45 patients with moderate or severe traumatic brain injury.	Mean age was 39.29 years. 33 males, 12 females.	Moderate or severe traumatic brain injury	Prospective memory measures from Rivermead Behavioral Memory Test – test belonging, appointment, and message. Vs. Neuropsychological evaluation – with subcategories: Retrospective Memory – tested with California Verbal Learning Test, Open Trial Selective Reminding Test, and Prose Memory from the Memory Assessment Scales. Executive Functioning – tested with the Trail Making, Color-Word Interference, Tower, and Verbal Fluency subtests from the Delis-Kaplan Executive Function System. Working Memory – tested with Digit Span subtest from the Wechsler Adult Intelligence Scale – Third Edition and	The correlation values for the Total PM compared to Immediate memory is 0.49, p<0.01, delayed memory is 0.56, p<0.01, learning is 0.22, executive achievement 0.44, p<0.01, rule monitoring is 0.43 p<0.01, processing speed is 0.24, and working memory is 0.32, p<0.5. Immediate memory compared to the same factors listed above respectively are DM 0.70, p<.01; L 0.44, p<.01; EA 0.53, p<.01; RM 0.28; PS 0.42, p<.01; and WM 0.34, p<.05. Delayed memory compared to L 0.31, p=.05; EA 0.43, p<.01; RM 0.31, p=.05; PS 0.29; WM 0.25. Learning compared to EA 0.26, RM 0.18, PS -	“Results suggest that PM performance is dependent upon rule monitoring abilities only when RM is impaired following TBI.”	Data suggest TBI patients with impaired RM show a dependent relationship between PM performance and rule monitoring.

							Letter Number Sequencing subtest from the Wechsler Memory Scale – Third Edition.	0.12, WM 0.01. Executive Achievement with RM 0.44, p<.05; PS 0.54, p<.01; WM 0.29. Rule monitoring with PS 0.26 and WM 0.36, p<.05. Processing Speed with WM 0.32, p<.05.		
Ponsford, 2008 (NA)	Executive Function Test	Prognostic	Sponsored by Monash University and the Transport Accident Commission. No COI	N=103, 60 patients with TBI, 43 patients in control group.	Mean age for the TBI group was 31.37 years. 33 males, 27 females. Mean age for control group was 42.30 years. 24 males, 19 females.	Traumatic Brain Injury, Not specified	The Extended Glasgow Outcome Scale (GOSE) Vs. Current cognitive abilities - Digit Span Forwards Test and Digit Span Backwards Test, Trail Making Test Part A, Sustained Attention to Response Task, Symbol Digit Modalities Test, and Digit Symbol Coding (DSC) Test. Vs. Memory - Rey Auditory Verbal Learning Test and Doors and People Test Vs. Executive function were total error scores from the TMT Part B, SART, Hayling and Brixton Tests, Porteus Maze Test– Vineland Revision,	The patient GOSE groups (Upper/lower good outcome, disability/poor outcome) with TMT A mean value is (26.2, 40.1), p<.001; with SDMT (56.5, 44.0), p<0.001; DSC (77.6, 54.5), p<.001; Digit Span Forward (10.8, 9.4), p=.046; Digit Span Backward (7.8, 5.6), p<.001; RAVLT (51.8, 42.9), p=.002; Doors (18.7, 16.2), p=.02; People (27.5, 20.5), p<.001; Shapes (33.3, 26.5), p=.001; Names (20.4, 17.3), p<.001; Porteus Mazes errors (2, 4.8), p=.01; COWAT (42.1, 31.6), p<.001; and HADS	“Participants showing poorer outcome on the GOSE had significantly longer posttraumatic amnesia duration; less education; performed more poorly on cognitive measures of information processing speed, attention, memory, and executive function; and showed higher levels of anxiety on the HADS.”	At 10 years, patients performed more poorly on cognitive measures and showed higher levels of anxiety on HADS.

							Controlled Oral Word Association Tests. Vs. Hospital Anxiety and Depression Scale (HADS)	anxiety (3.6, 6.5), p=.01.		
Jelicic, 2013 (NA)	Executive Function Test	Prognostic	Sponsored by Department of Neuroscience: Sciences NPSRR. No COI.	N=5	Median Age was 37±12.9 years. 5 males, 0 females.	Traumatic Brain Injury	MRI scan Vs. Neurophysical Evaluation – compromised of: Global Cognitive performance – Mini-Mental State Examination (MMSE) Attention – Digit Cancellation Test and Trail Making Test (TMT) Working Memory – Immediate Brief Story Recall, Immediate Rey Auditory Verbal Learning Test, and Digit Span Forward and Backward tests, Verbal and Visual spatial memory – Delayed Brief Story Recall, Delayed RAVLT, Delayed Rey–Osterrieth Complex Figure (ROCF) Visual-Constructive Abilities - ROCF Copy and the Clock Drawing Test (CDT) Language- Phonemic and Semantic Fluency tests	The Pre-cranioplasty and Post-cranioplasty neuropsychological test respectively report mean scores for MMSE (26.2±3.7, 27.4±3.1, p=0.36), Digit Cancellation (41.9±8.5, 42.7±10, p= 0.6), TMT-A (55.6±22.5, 60±38.7, p=0.73), TMT-B (208.6±110, 140.8±55, p=0.04), CDT (8.1±3.8, 8.8±3, p=0.18), RAVLT Immediate (32.1±16.7, 39.1±15.4, p=0.04), Story Recall Immediate (11.6±8.1, 15.4±5.2, p=0.03), Digit Span Forward (4.6±1.1, 5.3±0.8, p=0.07), Digit Span Backward (3.1±0.7, 3.6±1, p=0.11), Letter Fluency (23.6±16.9, 29.6±17.6, p=0.02), RAVLT Recall Delayed (6.1±4.9, 7.3±4.6,	“The cognitive improvement induced by cranioplasty, even when performed after a long interval from craniectomy, may be due to the restoration of physiological cerebrospinal fluid circulation which, in turn, allows an efficient brain volume transmission signal circulation. The restoration of this essential way of signal communication seems to affect large-scale neuronal networks responsible for the executive functions.”	Sample size too small for conclusions.

								p=0.14), Story Recall Delayed (14±8.4, 18±4.2, p=0.09), ROCF Recall Delayed (14.8±9.8, 19.2±7.7, p=0.05), ROCF copy (30.4±5.2, 33±5.1, p=0.17), and Semantic Fluency (33.6±13.2, 37.4±16.6, p=0.25).		
Muller, 2010 (NA)	Executive Function Test	Prognostic	No mention of industry sponsorship or COI	N= 30, 15 Severe Traumatic Brain Injury Patients, 15 normal control group	Mean age of STBI group was 37.2 years. 13 males, 2 females. Mean age of Control Group was 37 years. 13 males, 2 females.	Severe Traumatic Brain Injury	Neurophysical Assessment: Wechsler Adult Intelligence Scale-Revised (WAIS-R), Stroop Color Word Test A and B, Verbal fluency, and California Verbal Learning Test (CVLT) Vs. Theory of Mind (ToM) Test: Faux Pas Test First Order False Belief Task (FOFBT) Second Order False Belief Task (SOFBT) Character Intention Task (CIT) Reading the Mind in the Eyes Test (RMET)	The correlation between the Theory of Mind tests with TMT-B, Stroop Test, semantic verbal fluency, and formal fluency respectively are: Faux Pas Test (r= -.40, p=.20), (r=-.25, p=.40), (r=.47, p=.10), (r=.22, p=.47); FOFBT (r=-.19, p=.55), (r=-.42, p=.15), (r=.47, p=.10), and (r=.19, p=.53); SOFBT (r=-.63, p=.02), (r=-.33, p=.27), (r=.50, p=.08), and (r=-.03, p=.91); CIT (r=-.34, p=.27), (r=.07, p=.83), (r=.33, p=.27), and (r=.15, p=.63); RMET (r=-.13, p=.68), (r=-.22, p=.46), (r=.23,	“In conclusion, the present findings have implications for the evaluation of ToM impairment after TBI. They confirm an impairment in the ability to make inferences about others’ mental states following TBI.”	Data suggest ToM deficit is most likely independent from other types of social cognition like empathy & communication.

								p=.45), and (r=.24, p=.42).		
Simmons, 2014 (NA)	Executive Function Test	Prognostic	No industry sponsorship or COI	N=12, 4 patients with Traumatic Brain Injury and 8 patients who underwent a Cerebrovascular accident	Mean age for patients was 53.9 years. 8 males, 4 females.	Traumatic Brain Injury and Acquired Brain Injury	Executive Function Performance Test (EFPT) – independent living tasks: simple cooking, telephone use, medication management, and bill payment. Vs. EFPT skills - Initiation of task, organization, sequencing, and safety and judgment. Vs. PreMotor Exercise Game [487]	Changes in EFPT in overall task completion report a mean difference of -0.3 from baseline 1 to baseline 2 and -1.1 from baseline 2 to post intervention. Changes in overall performance report a mean difference of +0.2 from baseline 1 to baseline 2 and -9.4, p<0.05 from baseline 2 to post intervention.	“Using PEGs as a modality for both motor and cognitive intervention is a potentially beneficial adjunct to rehabilitation and warrants further study.”	Small sample (N=12). Data suggest improvement in chronic TBI patients (both motor & cognitive) using PEGs.

## Vision Testing

Visual acuity testing is the primary test used to evaluate visual function. Visual acuity testing is typically used to assess and screen the vision system for its most basic function. **See Eye Guideline.**

### Visual Acuity Testing Recommended.

Visual acuity testing is recommended for use in the evaluation of TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – High

<i>Indications:</i>	Generally only an issue with severe TBI. Significant impacts on the vision system would be additional indications.
<i>Benefits:</i>	Identification of deficits in visual acuity.
<i>Frequency/Dose/Duration:</i>	Generally one assessment. May be used a second time to detect improvement or resolution.
<i>Rationale:</i>	There are no quality studies assessing Visual Acuity Testing for evaluation of TBI impairments. See also Eye Guideline. Visual Acuity Testing is not invasive, has no adverse effects, is low cost, but is the primary means to evaluate impairments in visual acuity and thus is recommended for the evaluation of TBI patients.
<i>Evidence:</i>	<p>A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Visual Field Testing, Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury, diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 51 articles in PubMed, 4 in Scopus, 1 in CINAHL, 3 in Cochrane Library, 40800 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.</p> <p>A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Low Vision Evaluation, Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 4 articles in PubMed, 12 in Scopus, 32 in CINAHL, 452 in Cochrane Library, 2290000 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 0 randomized trials and 1 systematic studies met the inclusion criteria.</p>

Visual evoked potentials (VEPs) have been used to attempt to predict outcome after brain injury [297].

## Visual Evoked Potentials (VEP)

### Recommended.

Visual evoked potentials are recommended for use in the evaluation of TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – Low

<i>Indications:</i>	Severe TBI with inability to test visual system with more common methods, such as bedside testing, or Snellen testing.
<i>Benefits:</i>	Ability to assess the visual system
<i>Harms:</i>	Negligible.
<i>Frequency/Dose/Duration:</i>	May be used at baseline. If there are abnormalities and the injury continues to preclude other testing, then followup testing with visual evoked potentials is reasonable.
<i>Indications for Discontinuation:</i>	Resolution of TBI, improvement sufficient to undergo standard vision testing.
<i>Rationale:</i>	There are no quality studies assessing Visual Evoked Response for diagnosis or evaluation of TBI. VEPs are not invasive have no adverse effects, are low cost, but appear to have utility to assess the visual system when other testing is not possible, and thus have limited evidence of diagnostic efficacy, and are selectively recommended to assess the visual system when other more common testing is not possible.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: evoked potential, evoked potential response, evoked potential responses, somatosensory evoked potential; traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, efficiency, Gold-standard, accurate, and accuracy. We found and reviewed 74 articles in PubMed, 223 in Scopus, 34 in CINAHL, 19 in Cochrane Library, 6,360 in Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

## Visual Field Testing

Visual field testing is commonly used to evaluate impairments of the vision system, particularly patchy, quadrant, or hemianopsias of the visual fields. Visual field testing is not typically used as a standalone diagnostic tool for Traumatic Brain Injury. It has been used to assess the visual field defects in individuals with strokes, as well as some TBIs [496].

### Visual Field Testing

#### Recommended.

Visual field testing is recommended for use in the evaluation of TBI patients. **See Eye guideline.**

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – High

<i>Indications:</i>	Generally only an issue with severe TBI. Significant impacts on the vision system would be additional indications.
<i>Benefits:</i>	Identification of deficits in fields.
<i>Frequency/Dose/Duration:</i>	Generally one assessment. May be used a second time to detect improvement or resolution.
<i>Rationale:</i>	There are no quality studies assessing Visual Field Testing for evaluation of TBI impairments. See also Eye Guideline. Visual Field Testing is not invasive, has no adverse effects, is low cost, but is the primary means to evaluate impairments in visual fields and thus is selectively used for the evaluation of TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Visual Field Testing, Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury, diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 51 articles in PubMed, 4 in Scopus, 1 in CINAHL, 3 in Cochrane Library, 40800 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

## Visual Perceptual Testing

Visual perception testing involves assessing the meaning of what is seen. This contrasts with visual acuity testing, which is merely an assessment that something is seen.

### Visual Perceptual Testing

#### Recommended.

Visual perceptual testing is selectively used for severe TBI.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

### *Level of Confidence – Low*

<i>Indications:</i>	Generally only an issue with severe TBI. Significant impacts on the vision system would be additional indications.
<i>Benefits:</i>	Identification of deficits in the interpretation of visual inputs.
<i>Frequency/Dose/Duration:</i>	Generally one assessment. May be used a second time to detect improvement or resolution.
<i>Rationale:</i>	There are no quality studies assessing Visual Perceptual Testing for evaluation of TBI impairments. Visual Perceptual Testing is not invasive, has no adverse effects, is low cost, but is the primary means to evaluate impairments in visual perception and thus are selectively used for the evaluation of TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Visual Perceptual Testing, Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury, diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 10 articles in PubMed, 3 in Scopus, 47 in CINAHL, 3 in Cochrane Library, 10300 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

## **Other Tests**

Electroretinogram or ERG is typically not used as a reliable diagnostic tool for TBI.

### **Electroretinogram (ERG)**

#### **No Recommendation.**

There is no recommendation for or against the use of ERG in the evaluation of TBI patients.

#### **Strength of Evidence – No Recommendation, Insufficient Evidence (I)**

##### *Level of Confidence – Low*

<i>Rationale:</i>	There are no quality studies assessing electroretinogram for diagnosis of TBI. Electroretinogram is minimally invasive, has minimal adverse effects, is moderate cost, but has no evidence of diagnostic efficacy in TBI patients, and thus there is no recommendation for evaluation of TBI patients.
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Fluorescein angiography is a procedure in which a dye is injected into the bloodstream in order to highlight vessels to be photographed. This is typically used for evaluation of visual impairments.

## Fluorescein Angiography

### Recommended.

Fluorescein angiography is recommended for use in the evaluation of TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – Low

<i>Indications:</i>	Impaired visual system function where visualization of the retinal blood vessels is important.
<i>Benefits:</i>	Assists in diagnosing select visual impairments associated with TBI.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Generally a one-time assessment.
<i>Rationale:</i>	There are quality studies assessing fluorescein angiography for evaluation of TBI patients. Fluorescein angiography is minimally invasive, has no adverse effects, is moderate cost, and while there is not quality evidence of diagnostic efficacy in TBI patients, it is the gold standard for evaluation of the retinal blood supply and so is recommended for select evaluation of visual impairments associated with TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Fluorescein Angiography, Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury, Eye blood vessel imaging, diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 19 articles in PubMed, 0 in Scopus, 0 in CINAHL, 0 in Cochrane Library, 6860 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

Optical coherence tomography is a technology that creates cross-sectional imaging of microstructures in the human body. Optical coherence tomography may be used as a diagnostic test to diagnose traumatic brain injuries [497].

## Optical Coherence Tomography

### No Recommendation.

There is no recommendation for or against the use of optical coherence tomography in the evaluation of TBI patients.

*Strength of Evidence* – **No Recommendation, Insufficient Evidence (I)**

*Level of Confidence* – Low

<i>Rationale:</i>	There are no quality studies assessing Optical Coherence Tomography for evaluation of TBI. Optical Coherence Tomography is not invasive, has no adverse effects, is low cost, but in the absence of diagnostic efficacy, there is no recommendation for diagnostic evaluation of TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Optical Coherence Tomography, Traumatic Brain Injury; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 26 articles in PubMed, 15 in Scopus, 1 in CINAHL, 1 in Cochrane Library, 6,390 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

## Audiometry/Otology

Damage to the hearing structures is a common effect of a TBI. Conducting Audiological tests to assess the level of damage may be useful in identifying hearing impairments and other disorders affiliated with TBI [498].

### Audiometry Recommended.

Audiometry is recommended for use in the evaluation of TBI patients.

#### *Strength of Evidence* – Recommended, Insufficient Evidence (I)

*Level of Confidence* – Low

<i>Indications:</i>	TBI with reduced hearing or tinnitus, especially but not solely if the mechanism of injury was a blast. There is a low threshold for screening all TBI patients with audiometry.
<i>Benefits:</i>	Identification and quantification of hearing deficits. Potential to identify candidate for hearing aids.
<i>Harms:</i>	Negligible. However, there is little quality evidence of effective treatments other than hearing aids.
<i>Frequency/Dose/Duration:</i>	Baseline measure. May need second assessment at end of healing.
<i>Rationale:</i>	There are few quality studies assessing Audiometry for diagnosis and evaluation of TBI, yet there is extensive evidence for evaluation of hearing for other conditions and audiometry is considered the gold standard for evaluation of hearing. Audiometry is not invasive, has no adverse effects, is low cost, has evidence of diagnostic efficacy, and is recommended for diagnosis of hearing impairments from TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Audiometry AND Traumatic Brain Injury, Closed head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 63 articles in PubMed, 11 in Scopus, 22 in CINAHL, 2 in Cochrane Library, 7250 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic studies met the inclusion criteria.

### Evidence for the Use of Audiometry

Author Year (Score)	Category:	Study type:	Conflict of Interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Munjal 2011 (4.0)	Audiometry	Diagnostic	No mention of Sponsorship or COI.	N=290 w/ TBI. N=50 Control	No mention of sex; No mean age, Age Range from 18-45.	Traumatic Brian injury using Glasgow Coma Score. TBI split into Mild, Moderate, and Severe.	Audiological tests including: pure tone audiometry (PTA), speech audiometry, tympanometry, auditory brain stem response (ABR) audiometry, and middle latency response (MLR) audiometry.	PTA 1 (500, 1000, 2000 Hz) mean scores of mild, moderate, and severe closed head injury (CHI), vs Control: 23.97 dB, 19.66 dB, 23.75 dB vs 10.70 dB (p<0.001). PTA 2 (4000, 8000, 12000 Hz) CHI groups vs control: 23.4 dB, 28.17 dB, 29.9 dB vs 9.23 dB (p<0.001). Speech Reception Threshold difference between Chi groups and control (p<0.01). ABR wave 1 significant difference for right ear (p<0.01), left ear (p<0.05). MLR Na wave CHI groups vs control: 19.62 msec, 19.47 msec, 19.75 msec vs 18.23 msec (p<0.05). No significant differences in Tympanometry.	“To conclude, there is a high incidence of audiological deficits in head injured subjects. Peripheral and central auditory areas are affected as revealed by the subjective as well as electrophysiologic auditory investigation.”	Data suggests hearing loss is prevalent post closed head injury with MLR abnormalities occurring more frequently than ABR.

Brainstem auditory evoked response is a test that produces information about specific brain function [499]. The test has been used for assessing traumatic brain injury when standard behavioral audiometry was not possible due to mechanism of injury [500]. BAER has also shown usefulness in monitoring auditory nerve and brainstem dysfunction [501].

## **Brainstem Auditory Evoked Response Recommended.**

Brainstem auditory evoked response is recommended for use in the evaluation of TBI patients.

### **Strength of Evidence – Recommended, Insufficient Evidence (I)**

#### *Level of Confidence – Low*

<i>Indications:</i>	Severe TBI with inability to test auditory system with more common methods, such as bedside testing, or audiometry.
<i>Benefits:</i>	Ability to assess the auditory system
<i>Harms:</i>	Negligible.
<i>Frequency/Dose/Duration:</i>	May be used at baseline. If there are abnormalities and the injury continues to preclude other testing, then followup testing with auditory evoked potentials is reasonable.
<i>Indications for Discontinuation:</i>	Resolution of TBI, improvement sufficient to undergo standard audiometric testing.
<i>Rationale:</i>	There are no quality studies assessing Brainstem Auditory Evoked Response for diagnosis or evaluation of TBI. Brainstem Auditory Evoked Response is not invasive has no adverse effects, is low cost, but appears to have utility to assess the hearing system and thus has evidence of diagnostic efficacy, and is recommended for selective use to assess the hearing system when other more common testing is not possible.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury, BAER, ABR, diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 75 articles in PubMed, 21 in Scopus, 2 in CINAHL, 5 in Cochrane Library, 11900 in Google Scholar, and 5 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 5 from other sources. Of the 6 articles considered for inclusion, 0 randomized trials and 6 systematic studies met the inclusion criteria.

Tympanometry is a method for assessing the current state of the tympanic membrane, the ossicles and attachments, and the air cushion of the tympanic cavity within the ear [502]. It is commonly used to diagnose hearing loss [502].

## **Tympanometry**

### **No Recommendation.**

There is no recommendation for or against the use of tympanometry in the evaluation of TBI patients.

*Strength of Evidence* – **No Recommendation, Insufficient Evidence (I)**

*Level of Confidence* – Low

<i>Rationale:</i>	There are no quality studies assessing Tympanometry for diagnosis of TBI. Tympanometry is not invasive, has no adverse effects, is low cost, but in the absence of quality evidence of diagnostic efficacy, there is no recommendation for evaluation of TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Vestibular function tests, test, Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, craniocerebral Injury, Craniocerebral Trauma; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 74 articles in PubMed, 7 in Scopus, 24 in CINAHL, 2 in Cochrane Library, 44 in Google Scholar, and 0 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 2 diagnostic studies and 0 systematic studies met the inclusion criteria.
<i>Comments:</i>	

## Vestibular Function Testing

Vestibular function testing is used to quantify and assess the status of an individual's vestibular system workings [503]. Vestibular function testing has been used to help define the severity and possible outcomes of an individual's dizziness and balancing issues [503]. Testing includes specific tests such as electro- or video-nystagmography (ENG/VNG), rotary chair testing, computerized dynamic platform posturography, electrocochleography (ECoG), and vestibular evoked myogenic potentials (VEMP) [504].

### Vestibular Function Testing Recommended.

Vestibular function testing is recommended for use in the evaluation of TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

<i>Indications:</i>	Equivocal results of a medical history and/or questionnaire(s) regarding vestibular symptoms
<i>Benefits:</i>	Ability to better define extent of vestibular problems
<i>Harms:</i>	Negligible.
<i>Frequency/Dose/Duration:</i>	May be used at baseline. One or two follow-up assessments are reasonable to define progress.
<i>Indications for Discontinuation:</i>	Resolution of vertiginous symptoms, improvement sufficient to not need further rehabilitation.
<i>Rationale:</i>	There are few quality studies assessing tests of Vestibular function for diagnosis of impacts of TBI. There are no studies showing testing is superior to a medical history or questionnaires. There are reports of vestibular dysfunction in TBI patients [168]. Vestibular function tests are not invasive, have few adverse effects, are low cost, have limited evidence of efficacy and are selectively recommended for use in patients with unclear results from a medical history and/or questionnaires.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Vestibular function tests, test, Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, craniocerebral Injury, Craniocerebral Trauma; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 74 articles in PubMed, 7 in Scopus, 24 in CINAHL, 2 in Cochrane Library, 44 in Google Scholar, and 0 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 2 diagnostic studies and 0 systematic studies met the inclusion criteria.

### Evidence for the Use of Specific Vestibular Function Test

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Gottshall 2010 (4.0)	Specific Vestibular Function Tests	Diagnostic	No mention of COI or sponsorship.	N = 82	3 female, 79 male  Mean age overall 24 years	Soldiers, blast injuries including secondary mTBI, diagnosed with 1 out of 4 vestibular disorders – benign paroxysmal positional vertigo, exertion-induced dizziness, blast-induced disequilibrium, and blast-induced disequilibrium with vertigo	Series of vestibular-visual-cognitive tests: Static visual acuity, perception time, target acquisition, target following (TF), dynamic visual acuity (DVA), gaze stabilization tests  All participants underwent all tests	Mean pre-VPT measures for perception time and target acquisition similar to normative values, no significant changes. TF and DVA scores below normative at time 0 but elevated to normative at week 8. Gaze stabilization also below normative but improved at week 8.	“A battery of vestibular-visual-cognitive tests is valuable for establishing initial functional levels and can be used to document improvement. These outcome measures may also be useful to determine return to duty/work status as well as return to physical activity status for military personnel.”	Data suggest use of vestibular-visual-cognitive tests useful for baseline determination of balance dysfunction through recovery.
Hoffer 2016 (3.5)	Specific Vestibular Function Tests	Diagnostic	Supported by Head Health Challenge II grant from the National Football League, Underarmor, and General Electric, and a grant from the Department of	N = 150	43 female, 107 male  Mean age for mTBI group 26.6 years, mena age for control	100 controls, 50 mTBI	Series of vestibular function tests including the following areas: Post-Traumatic Headache/Migraine, Nausea, Emotional/Affective, Fatigue/Malaise, and Dizziness/Mild Cognitive Impairment	mTBI group had higher prevalence of headache, dizziness, and cognitive dysfunction compared to controls. Sleep disorders and emotional	“A fairly simple set of questions inquiring about dizziness, headache, and cognitive issues may provide diagnostic accuracy but it remains unclear if other symptoms are	Data derived from questionnaire. Data suggest a simple question set may provide useful diagnostic and prognosis information in mild TBI patients

			Defense grant. No COI.		group 29.4 years			issues also were more prevalent	more important for prognostic information or treatment planning.”	
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## Balance Testing

Following a mild traumatic brain injury, up to 30% of patients report having balance disorders including, dizziness, impaired balance, and reduced coordination [505]. Typically, clinicians diagnose balance impairment following Traumatic Brain Injury using subjective measures. However, objective measures can be assessed using a computerized dynamic posturography platform [506].

### Computerized Dynamic Platform Posturography

#### No Recommendation.

There is no recommendation for or against the use of computerized dynamic platform posturography in the evaluation of TBI patients.

*Strength of Evidence* – **No Recommendation, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

*Rationale:*

There are no quality studies assessing Computerized Dynamic Platform Posturography for evaluation of TBI. Computerized Dynamic Platform Posturography is not invasive, has no adverse effects, is low cost, but without quality evidence of diagnostic efficacy, and there is no recommendation for evaluation of TBI.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Computerized Dynamic Platform Posturography, Posturography, Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury, diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 22 articles in PubMed, 9 in Scopus, 20 in CINAHL, 7 in Cochrane Library, 1 in Google Scholar, and 1 from other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 1 from CINAHL, 1 from Cochrane Library, 1 from Google Scholar, and 1 from other sources. Of the 5 articles considered for inclusion, 2 randomized trials and 1 systematic studies met the inclusion criteria.

### Evidence for the Use of Computerized Dynamic Platform Posturography

Author Year (Score)	Category:	Study type:	Conflict of Interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Kaufman 2006 (3.0)	Computerized Dynamic Platform Posturography	RCT	No mention of sponsorship or COI.	N=10 w/ TBI N=10 Control	12 males, 8 females; Mean age 41 (11)	Traumatic brain Injury based on medical history and clinician evaluation.	Sensory Organization Test [493] between TBI patients and controls.	Controls scored higher for all SOT conditions. Mean Composite SOT score, TBI vs Control, 70±12 vs 80±8 (0.04). Correlation between Dizziness and Posturography test 6, however not statistically significant.	“Moreover, this study has also demonstrated that gait analysis can be used to objectively quantify the subjective complaints of unsteadiness reported by patients with TBI.”	Small sample (n=10).  Data suggest objective measurement are useful for quantification of functional deficits post TBI.

Videonystagmography is a useful laboratory tool used for assessing balance function in individuals who have suffered from TBI. It tests the functional capabilities of the vestibular system, studying eye movement behavior of the patient [507].

### **Electronystagmography or Videonystagmography**

#### **No Recommendation.**

There is no recommendation for or against the use of electronystagmography or videonystagmography in the evaluation of TBI patients.

*Strength of Evidence* – **No Recommendation, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

<i>Rationale:</i>	There are no quality studies assessing electronystagmography or videonystagmography for evaluation of TBI patients. Electronystagmography and videonystagmography are not invasive, have no adverse effects, are low cost, but have no quality evidence of efficacy, and thus there is no recommendation for evaluation of TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Electronystagmography, Videonystagmography, Traumatic brain injury, Closed Head Injury, Penetrating Head Injury, Concussion, Craniocerebral Injury; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 207 articles in PubMed, 4 in Scopus, 2 in CINAHL, 4 in Cochrane Library, 28000 in Google Scholar, and 0 from other sources. We considered for inclusion 3 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 1 randomized trials and 2 systematic studies met the inclusion criteria.

Rotary chair testing is used to diagnose vestibular impacts of traumatic brain injuries. Rotary chair testing examines vestibular and oculomotor functioning [508].

### **Rotary Chair Testing**

#### **Recommended.**

Rotary chair testing is recommended for the evaluation of TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

<i>Indications:</i>	TBI patients with vestibular problems needing further diagnostic evaluation
<i>Benefits:</i>	Secure a diagnosis and potentially improve treatment efficacy.
<i>Harms:</i>	Negligible.

*Frequency/Dose/Duration:*

Generally only assessed once.

*Rationale:*

There are few quality studies assessing Rotary Chair Testing for evaluation of vestibular impacts of TBI. Vestibular dysfunction is reportedly problematic in TBI patients [168]. Rotary Chair Testing is not invasive, has no adverse effects, is low cost, has evidence of diagnostic efficacy, and is recommended for diagnosis of vestibular impacts of TBI.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Rotary Chair testing, traumatic brain injury; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 2 articles in PubMed, 0 in Scopus, 1 in CINAHL, 0 in Cochrane Library, 3,220 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 Diagnostic study met the inclusion criteria.

### Evidence for the Use of Rotary Chair Testing

Author Year (Score)	Category:	Study type:	Conflict of Interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Akin 2016 (4.0)	Rotary Chair Testing	Diagnostic	No mention of Sponsorship or COI	N = 31 Veterans with history of blast exposures and/or mTBI.	Mean Age: 37 years, No mention of sex	Dizziness and/or imbalance	Vestibular and Balance assessment tests including : rotary chair, videonystagmography, Cervical vestibular evoked myogenic potential (cVEMP), Subjective Visual Vertical (SVV), Dux-Hallpike and roll test, ocular motor fixation test, sensory organization test [493], and Dizziness Handicap Inventory (DHI)	Horizontal semicircular canal dysfunction (caloric weakness and/or abnormal rotational testing) was found in 29% of patients. In comparison, Otolith dysfunction (abnormal cVEMP and/or SVV) was found in 84% of patients.	“Preliminary results in the authors’ laboratory suggest that otolith testing may be an important component of the vestibular test battery in patients with mTBI and/or blast exposure.”	Data suggest otolith testing may be beneficial in the vestibular testing battery in m TBI patents and/or blast exposed patients

Electronystagmogram (ENG) is a diagnostic test that measures involuntary eye movements and is typically used as part of an assessment of balance problems and dizziness [509].

## **ENG Studies for Balance**

### **Recommended.**

ENG studies for balance are recommended for use in the evaluation of TBI patients.

#### **Strength of Evidence – Recommended, Insufficient Evidence (I)**

##### **Level of Confidence – Low**

<i>Indications:</i>	TBI patients with balance problems needing further diagnostic evaluation
<i>Benefits:</i>	Secure a diagnosis and potentially improve treatment efficacy.
<i>Harms:</i>	Negligible.
<i>Frequency/Dose/Duration:</i>	Generally only assessed once.
<i>Rationale:</i>	There are no quality studies assessing ENG Studies for evaluation of balance or dizziness in TBI patients. However, ENG has proven helpful in the evaluation of patients with other disorders. ENG is not invasive, has no significant adverse effects, is low cost, has evidence of diagnostic accuracy for other disorders, and thus is recommended for evaluation of TBI patients with balance and dizziness problems.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Electronystagmography, balance, Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, Gold-standard, accurate, accuracy, precision, precise, diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 4 articles in PubMed, 10 in Scopus, 0 in CINAHL, 3 in Cochrane Library, 150 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

## Laboratory Testing

Injury severity and medications dictate testing in the TBI patient. In moderate and severe TBI, electrolyte status usually needs close monitoring. Complete blood counts and coagulation studies are also required. The cerebrospinal fluid (CSF) contains biomarkers which may be present after acute injury signaling a pre- (chronic traumatic encephalopathy) CTE state and assisting in clinical treatment and guiding prognosis [510]. Also, since approximately 15-20% of MTBI cases involve hypopituitarism, endocrine tests are commonly required; in such cases, electrolytes should be closely monitored as concomitant syndrome of inappropriate antidiuretic hormone [511-515] and hypopituitarism are common [516].

## Biomarkers

Biomarkers are under investigation as potentially predictive tools, particularly to supplement clinical assessment and neuroimaging tests [179, 180]. Biomarkers with some evidence of associations with TBI include autoantibodies against proteins, lipids, peptides, proteins, and RNA. Proteins studied include S-100 [181] [182] [183] [184] [185]. Reduced copeptin has been associated with TBI [186]. Galectin 3 [186] and occludin [186] has been associated with TBI. Problems with biomarker measurements include technical and instrumentation methods that require further development [180].

There are some data suggesting biomarkers may be associated with longer-term outcomes from TBI. While there is considerable evidence that biomarkers are associated with TBI, how measurement of these substances alters the management of TBI patients is unclear and thus there is **No Recommendation, Insufficient Evidence (I)** for or against biomarkers. Quality studies showing biomarkers impacting the management of patients are needed. Another potential use is to identify resolution of TBI [187], yet that too requires more sensitive methods and further investigation.

## Lumbar Puncture

**Lumbar puncture (LP)** is performed to examine cerebrovascular fluid in cases of injury and disease for signs of hemorrhage [1, 517-521]. It is the most common test performed to evaluate signs of infection, thus in TBI patients is probably most commonly used after penetrating injury when fever occurs and there are concerns about meningitis. LP is also performed to identify blood in the cerebrospinal fluid from subarachnoid hemorrhage and a negative CT scan. However, this procedure has inherent risks and is not recommended for acute spinal cord trauma, elevated intracranial pressure, bleeding problems, and epidural abscess. If there is suspicion of elevated intracranial pressure, a fundoscopic examination should generally occur initially followed by MRI or CT.

## Surgical Recommendations

### Operative and Surgical Procedures

The TBI patient may require surgery particularly during the acute stage depending upon the individual injury mechanism and clinical presentation [588]. Many of these procedures occur in the setting of severe TBI. However, especially in older workers, surgical evacuations of subdural and epidural hemorrhages are more common and do not necessarily occur solely with severe TBI and/or loss of consciousness. Thus, those cases may technically be classified as mild TBI based on loss of consciousness criteria, but also classified as severe based on requiring neurosurgery. Attention to the clinical presentation, an understanding of the demographic group's risk factors, and careful attention to the clinical course are required to detect many of these cases.

There are numerous procedures used on TBI patients, and these are patient-specific and require physician discretion. It is not within the scope of this guideline to provide all potential surgeries. Common procedures include:

- Craniectomy for elevated intracranial pressure relief
- Cranioplasty [589]
- Debridement
- Decompression of nerves
- Evacuation of fluids
- Lumbar drains for cerebrovascular fluid (CSF) leaks or CSF fistula
- Maxillofacial fracture surgeries (including maxillofacial surgery, repairs, reconstruction and releases) [590, 591]
- Nerve repair/reconstruction/release
- Orthopedic surgeries for fractures
- Rhizotomy for spasticity as well as intrathecal Baclofen (see Medications)
- Soft tissue repairs
- Relief of vascular occlusions
- Ventricular shunting
- Ventriculostomy for ICP and obstructive hydrocephalus

**There are no specific surgical recommendations as the requirements of the individual patient are wide-ranging and beyond the scope of this guideline.**

### Burr Holes, External Ventricular Drains, and Ventriculostomy

External ventricular drains (ventriculostomy) have been used in severe traumatic brain injury patients to reduce intracranial pressure rapidly [592]. This may be followed by permanent shunting [593]. These procedures are performed to attempt to improve cerebral blood flow, thus hopefully enhancing perfusion of the brain tissue and thus improving TBI prognosis [593-596]. Another type of ventriculostomy, percutaneous

### Evidence for the Use of Burr Holes, External Ventricular Drains, and Ventriculostomy

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Liu 2015 (4.0)	Ventriculostomy	Prospective observational study  Randomized controlled	No mention of sponsorship and no COI.	N = 122 with TBI ≥ 13 years old.	Mean age 43.37 ± 14.40 years, 101 male and 21 female.	External ventricular drain or EVD (N = 62) vs Intraparenchymal fiberoptic monitor or IPM (N = 60).	6 mo	AT 1-month survival rate 90.3% in the EVD group vs 76.7% in the IPM group (log-rank test, p = 0.04), 6-month postinjury survival rate vs with those treated with IPMs (88.7% vs. 68.3%, log-rank test, P [ 0.006), and patients managed with EVDs had a significantly higher.	“Device selection for ICP monitoring provides prognostic discrimination, and use of EVDs may have a bigger advantage in controlling refractory intracranial hypertension.”	Not an RCT, an observational study. Data suggest ICP device selection may benefit prognostic outcome.

## Craniectomy

Decompressive craniectomy is most commonly used for TBI and ischemic stroke as a third-tier therapy [592, 597-610]. It is performed to decrease intracranial pressure (ICP) by lowering the volume constraints on the cranial contents [599, 603, 607]. Complications related to decompressive craniectomy include infection, homeostatic reaction, hygroma, seizures, and bone resorption [607]. The procedure has been advocated to be performed early purportedly to confer a better prognosis [600, 607]. In Jelcic 2013, there was evidence for improvement of executive functions after late craniectomy.

There is one high-quality RCT comparing decompressive craniectomy plus standard care to standard care alone [611, 612]. There also are 2 moderate-quality RCTs comparing different surgical techniques. The non-randomized studies have shown mixed results [592, 597-608].

The sole trial comparing craniectomy to non-surgical management has conflicting results, with clear short-term benefits including 28% lower ICU length of stay, 27% lower days of mechanical ventilation and 24% reduction in hospitalization days [611] [612]. However, the longer-term outcomes are not positive as shown by 70% vs. 51% unfavorable Extended Glasgow Outcome Scale Scores. Randomized controlled trials are investigating use of craniectomy for TBI patients and are tending to suggest only limited applicability to severe TBI patients refractory to medical management [613].

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: evacuation of hematoma, or subdural hematoma, or epidural hematoma, Traumatic, brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1113 articles in PubMed, 91 in Scopus, 28 in CINAHL, 82 in Cochrane Library, 3730 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 2 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 0 randomized trials and 2 systematic studies met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Lumbar drains for cerebrovascular fluid (CSF) leaks or CSF fistula, Traumatic brain injury, Closed, Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 102 articles in PubMed, 0 in Scopus, 5 in CINAHL, 0 in Cochrane Library, 2390 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: maxillofacial fracture surgery, bone, surgery, fracture, fractures, maxillofacial nerve repair, maxillofacial reconstruction, maxillofacial release; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 209 articles in PubMed, 0 in Scopus, 0 in CINAHL, 3 in Cochrane Library, 10020 in Google Scholar, and 0 from other sources. We considered for

inclusion 4 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Vascular Occlusions Relief , Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, Closed Head Trauma, Penetrating Head Trauma, Penetrating Craniocerebral Trauma, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 0 articles in PubMed, 2 in Scopus, 0 in CINAHL, 2 in Cochrane Library, 3670 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Ventriculostomy for ICP and obstructive hydrocephalus, traumatic brain injury, closed head injury, penetrating head Injury, concussion, craniocerebral injury, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2 articles in PubMed, 20 in Scopus, 7 in CINAHL, 1 in Cochrane Library, 391 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 0 randomized trials and 1 systematic studies met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Rhizotomy for spasticity, Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 4 articles in PubMed, 11 in Scopus, 0 in CINAHL, 0 in Cochrane Library, 2022 in Google Scholar, and 0 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 0 randomized trials and 1 systematic studies met the inclusion criteria.

## Evidence for the Use of Craniectomy

There is 1 high- and 2 moderate-quality RCTs incorporated into this analysis. There are 15 systematic reviews.

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Cooper J 2011 (8.5)	Decompressive craniectomy	RCT	(Funded by the National Health and Medical Research Council of Australia and others; DECRA Australian Clinical Trials Registry number, ACTRN012605000009617.) No mention of COI	N= 152 patients with a severe, nonpenetrating traumatic brain injury	120 males, 32 females Mean age: 24 years	Decompressive Craniectomy (n=73) Vs. Standard Care (n=82)	6 months	Mean intracranial pressure after randomization: craniectomy 14.4±6.8 mm Hg v. standard care 19.1±8.9 mm Hg, p<0.001. Median intracranial hypertension index after randomization: craniectomy 11.5 v. standard care 19.9, p<0.001. Median cerebral hypoperfusion index after randomization: craniectomy 5.7 v. standard 8.6, p=0.03. Median days of mechanical ventilation: craniectomy 11 v. 15, p<0.001. Median days in ICU stay: craniectomy 13 v. 18, p<0.001. Median days of hospitalization: NS. Extended Glasgow Outcome Scale median score 6 months after injury: craniectomy 3 v. standard 4, p=0.03; unfavorable score of 1	"[I]n patients with severe diffuse traumatic brain injury and increased intracranial pressure that was refractory to first-tier therapies, the use of craniectomy...decreased the mean intracranial pressure and the duration of both ventilatory support and the ICU stay but was associated with a significantly worse outcome at 6 months, as measured by the score on the Extended Glasgow Outcome Scale."	Data suggest short-term benefits of craniectomy including 28% shorter ICU stays. However, long term worse outcomes (70% vs. 51%, OR=2.2).

								to 4 (no.) craniectomy 51 v. standard 42, p=0.02.		
Jiang J 2005 (7.5)	Decompressiv e craniect omy	RCT	No mention of industry sponsorshi p or COI.	N= 486 with severe TBI	Mean age: 44.5 years, 347 males, 139 females	Standard trauma Craniectomy - a unilateral frontotempo roparietal bone flap (N=245)  Vs Learning Craniectomy with a routine temporopari etal bone flap (N=241)	6- month follow-up	Glasgow Outcome Scale (GOS) at 6 months: STC good recovery/moderate deficit 39.8%, severe deficit/persistent vegetative status 34%, death 26.2% v. LC good recovery/moderate deficit 28.6%, severe deficit/persistent vegetative status 36.3%, death 35.1%, p<0.05. Intracranial pressure before and after craniectomy: NS. Post-operative complications: delayed hematoma STC 26 v. LC 43, p<0.05; incision CSF fistula STC 6 v. LC 18, p<0.05; encephalomyelocele, NS; traumatic epilepsy, NS; intracranial infection, NS.	"Our multicenter prospective, randomized, controlled clinical study confirms that unilateral STC significantly improves the outcome in severe TBI with refractory intracranial hypertension and unilateral cerebral contusion."	Data indicate higher survival in the limited craniectomy group.

Qiu W 2009 (score 7.0)	Decompressive craniectomy	RCT	This study was supported by the Scientific Research Fund of Zhejiang Health Department, the Scientific Research Fund of Hangzhou Health Department and the Scientific Research Fund of Science and Technology Department of Zhejiang, China.  No COI.	N= 74 patients with acute post-traumatic brain swelling (BS) with midline shifting > 5 mm from TBI with Glasgow Coma Scale (GCS) of 8 or less.	Mean age: 40.1 years  51 males, 23 females	Unilateral Decompressive Craniectomy (DC) (n=37)  Vs. Control group (n=37)	Six months	Mean ICP at 24, 48, 72, and 96 hours: unilateral DC (15.19±2.18 mmHg, 16.53±1.53, 15.98±2.24, and 13.518±2.33) v. control (19.95±2.24 mmHg, 18.32±1.77, 21.05±2.23 and 17.68±1.40), no p-value presented but authors noted a significant difference. Mortality rates 1 mo. after craniotomy: unilateral DC 27% v. control 57% (p=0.010). Glasgow Outcome Score (GOS) 1 year after injury for good neurological recovery: unilateral DC 56.8% v. control 32.4%, no p-val but authors stated significance.	"Although the application of DC in severe TBI is controversial and the population in the present study is small, our study demonstrated that unilateral DC had superiority in lowering ICP, reducing the mortality rate and improving neurological outcomes over routine temporoparietal craniectomy."	Data suggest lower mortality and better neurological outcomes in the decompressive craniectomy group vs. unilateral routine temporoparietal craniectomy. However, higher delayed intracranial hematoma and subural effusion in DC group.
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Moein 2012 (4.5)	Decompressive Craniectomy	Pilot RCT	No mention of sponsorship. No COI.	N = 20 with head injury	Aged 18 - 60 years, gender not specified.	Group A, received surgical and conservative treatment (N = 10) vs Group B, underwent conservative treatment (N = 10).	Unknown	GCS improved after surgery in group A, difference between the 2 groups not statistically significant, (p = 0.087). Death rate higher in group B 30% vs 10% in group A, (p = 0.28).	“Decompressive craniectomy seems to be helpful and may lead to a better GOS achievement and improve the mortality rate among traumatic brain injury patients...”	Data suggest decompressive craniotomy may reduce mortality and improve Glasgow outcomes scale.
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Bhat 2013 (4.0)	Craniectomy	RCT	No mention of sponsorship or COI.	N = 225 with severe brain trauma.	Aged 21-40 years, 180 males and 45 females.	Glasgow coma scale or GCS (N = 119) vs Controls or open-dural flap (N = 106).	Unknown	Survival of multi-dural stab group vs open dural flap; 77.31% (92/119) /and with good recovery 42.02% (50/119) and / mortality 22.69% (27/119) vs 46.23% (49/106) / 15.09% (16/106) and good recovery and mortality of 53.77% (57/106).	“This new approach, known as SKIMS-Technique or Combined Technique i.e., “decompressive craniectomy with multi-dural stabs”, proved much effective in increasing survival of low GCS and severe traumatic brain edema patients with acute subdural hematoma.”	Data suggest the SKIMS(combined technique) is more than 2x as effective as conventional decompressive craniectomy re. survival for severe TBI (22.7 v. 46.2% mortality).
Xu 2014 (4.0)	Decompressive Craniectomy	RCT	No mention of sponsorship or COI.	N = 169 with severe traumatic brain injury (STBI).	80 years or older, 119 males and 50 females.	pressure dressing (N = 82) vs Control group (N = 87)	Hospital stay of 30 days or less	No significant difference in age, sex, GCS score, or GOS score between groups, (p > 0.05). Significant differences were found in the subdural effusion incidence rate $W^2 = 5.449$ , (p = 0.021) and hospitalization time $W^2 = 5.245$ , (p = 0.027).	“The results of this study suggest that early pressure dressing 7 to 10 days after DC, which is a noninvasive, simple procedure, reduces the incidence rate of subdural effusion and shortens hospitalization time in patients with STBI.”	Data suggest application of an early pressure dressing 7-10 days post discharge decreased subdural effusion rate and rate of rehospitalization post-DC.

Wang 2014 (4.0)	Decompressive craniectomy	RCT: Quasi-randomized (every other)	No mention of COI. Supported by the Nanjing Military Region.	N = 128 with severe head injury, GCS 3-8	20 female, 108 male. Mean age decompressive craniectomy 41.8±13.9 years, controlled decompression 44.2±14.2 years	Decompressive craniectomy (DC) (n = 64) vs controlled decompression (CD) (n = 64)	6 months	Clinical outcome measures: Intracranial pressure – DC 45.6±9.8 mmHg, CD 45.0±9.9 mmHg, (P=0.741). Glasgow Outcome Scale (Good Recovery, Moderate Disability, Severe Disability, Vegetative State, Dead): DC – 23, 8, 5, 5, 23, CD – 34, 7, 4, 4, 15, (P=0.417).	“Controlled decompression may reduce or delay intraoperative acute brain swelling by delaying hematoma formation in patients with severe head injury.”	Data suggest controlled decompressive craniectomy may be better than conventional decompressive craniectomy in controlling acute brain swelling in TBI patients.
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## Orthopedic Surgery for Fractures

Orthopedic surgery involves surgery with the musculoskeletal system. Not many studies are found dealing with orthopedic surgery and traumatic brain injury. Most studies found deal with surgery with the brain itself or with the spine which are not relevant.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Orthopedic Surgery, Brain Injuries, Head Injuries Closed, Head Injuries Penetrating, Brain Concussion, Concussion, Craniocerebral Trauma, Traumatic Brain Injury, Intracranial Injury, Craniocerebral Injury, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 55 articles in PubMed, 76 in Scopus, 0 in CINAHL, 0 in Cochrane Library, 0 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 0 randomized trials and 2 systematic studies met the inclusion criteria.

## Soft Tissue Repairs

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: **soft, tissue, repair, traumatic, brain, injury, intracranial, closed, head, penetrating, concussion, craniocerebral, trauma** controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 42 articles in PubMed, 0 in Scopus, 0 in CINAHL, 1 in Cochrane Library, 15700 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 15743 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria. Zero articles met the inclusion criteria.

## Ventricular Shunting

Ventricular shunting is the process of surgically inserting a shunt into the head in order to drain fluid and to relieve pressure. This is done usually on patients who have hydrocephalus, which is the build-up of fluid in the brain. It is, per se, not a treatment for TBI.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: **Ventricular shunting OR Ventriculoperitoneal (VP) shunt OR VP Shunting AND Brain injuries, head injuries, closed, penetrating, brain concussion, concussion, craniocerenal trauma, traumatic brain, intracranial, injury, injuries**, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 26 articles in PubMed, 19 in Scopus, 3 in CINAHL, 1 in Cochrane Library, 2570 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 1 randomized trials and 0 systematic studies met the inclusion criteria.

## Debridement

Debridement is the removal of damaged tissues or foreign objects. Surgical considerations for debridement surgery in traumatic brain injury patients is not a commonly used treatment, unless in cases of foreign object entrance to the brain.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Debridement, Brain Injuries, Head Injuries, Penetrating, Brain Concussion, Concussion, Craniocerebral Trauma, Traumatic Brain, Intracranial, Closed Head, Penetrating Head, Craniocerebral, Injury, Injuries, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 12 articles in PubMed, 56 in Scopus, 0 in CINAHL, 1 in Cochrane Library, 6900 in Google Scholar, and 0 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 0 randomized trials and 2 systematic studies met the inclusion criteria.

## Decompression and Facial Nerve Decompression

Facial nerve decompression surgery has been used to treat facial nerve paralysis after temporal bone fractures [614], but there is no evidence that facial nerve decompression is used to treat TBI.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Surgical Decompression OR Facial Nerve Decompression, Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion Craniocerebral Injury, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 168 articles in PubMed, 419 in Scopus, 46 in CINAHL, 3 in Cochrane Library, 4490 in Google Scholar, and zero from other sources. We considered for inclusion 1 from PubMed, 2 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 0 randomized trials and 2 systematic studies met the inclusion criteria.

Rapidly emerging innovative technologies for rehabilitation include robotics [615]. Robotic devices includes end-effector and exoskeleton devices that allow paraplegics and quadriplegics to walk, sometimes referred to as locomotor training with robotic assistance and robotic-assisted gait training [616-619].

## Robotics

### Recommended.

Robotics are recommended for use in the treatment of select TBI patients.

*Strength of Evidence* – **Recommended, Evidence (C)**

*Level of Confidence* – **Moderate**

<i>Indications:</i>	Reached a plateau such that not able to walk without robotic assistance, also having sufficient interest and motivation.
<i>Benefits:</i>	Ability to ambulate, although current technology allows for only a slow, somewhat ratcheting gait.
<i>Harms:</i>	Potential for falls
<i>Frequency/Dose/Duration:</i>	N/A
<i>Indications for Discontinuation:</i>	Falls, inability to tolerate, disinterest, disuse.
<i>Rationale:</i>	There are two moderate quality RCTs studies using robotics for treatment of TBI [620, 621]. One trial reported greater walking distance and no need for second therapists for training sessions with a robotic device compared with locomotor training [621]. Another trial reported mostly comparable efficacy with manually-assisted treadmill training [620]. There also are numerous successes of wheelchair-bound patients regaining the ability to walk [622-632] and there is one RCT in stroke patients [632]. Robotics is not invasive, has modest adverse effects, is very high cost, but has mostly empiric evidence of treatment efficacy, and is recommended for treatment of select severe TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Robotics, Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, Closed Head Trauma, Penetrating Head Trauma, Penetrating Craniocerebral Trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 25 articles in PubMed, 12 in Scopus, 7 in CINAHL, 1 in Cochrane Library, 70 in Google Scholar, and zero from other sources. Zero articles met the inclusion criteria.

## Evidence for the Use of Robotics

Author Year (Score):	Category :	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Esquenazi 2012 (4.5)	Body Weight Support Treadmill Training	RCT	No COI. Study was supported by grants from MossRehab Research Fund Disclosure and Department of Defense, CDC.	N = 16 with TBI and baseline over group walking self-selected velocity of $\geq 0.2$ m/s to 0.6 m/s	Mean age for RATT $37.1 \pm 10.6$ (5 female, 3 male). Mean age for MATT $41.9 \pm 16.8$ (4 female, 4 male)	Robotic-assisted treadmill training (RATT), 45 minutes 3 times a week Vs. Manually assisted treadmill training, 45 minutes 3 times a week	6 to 8 weeks	All parameters produced no significant between-group differences. The average SSV increased in RATT by 49.8% ( $p=0.01$ ) and by 31% ( $p=0.06$ ) for MATT. RATT group average maximal velocity increased by 14.9% ( $p=0.06$ ) and MATT group increased by 30.8% ( $p=0.01$ ). RATT group step-length asymmetry ratio improved by 33.1% ( $p=0.01$ ) and by 9.1% ( $p=0.73$ ) for MATT group. RATT group distance walked increased by 11.7% ( $p=0.21$ ) and MATT group increased by 19.3% ( $p=0.03$ ). Mobility improvement was present for both groups ( $p=0.03$ ).	“The results of this study demonstrate greater improvement in symmetry of gait (step length) for RATT and no significant differences between RATT and MATT with regard to improvement in gait velocity, endurance, and SIS. Our study provides evidence that participants with a chronic TBI can experience improvements in gait parameters with gait training with either MATT or RATT.”	Small Sample. Data suggest comparable results for both RATT and MATT on all outcome measures except greater improvement of step length, <b>gait velocity, endurance stroke impact scale [545]</b> .
Freivogel 2009 (4.0)	Robotics	RCT	No mention of sponsorship and no COI.	N = 16 with stroke, severe brain or spinal injury.	Mean age for Group AB / BA: 22.4 (6.0) / 25.8 (6.1); 11 males	Study intervention sequence AB: 20 treatments of locomotor training with an electromechanical gait	6-weeks	Between group significance after Intervention A: mean 0.9 (SD 1.4), median 0 (IQR	“Locomotor training with or without an electromechanical gait trainer leads to improved gait ability; however,	Crossover RCT. Mixed pop. Of spinal cord injury, TBI or stroke. Duration of illness dissimilar

					and 5 females.	device (N = 8) vs Study intervention sequence BA: 20 treatments of locomotor training with treadmill or task-oriented gait training (N = 8).		2.0); after intervention B: mean 0.5 (SD 1.0), median 0 (IQR 1.0); p = 0.155). The distance walked during training sessions was significantly higher during intervention A, mean 553 m (SD 116) vs intervention B, mean: 400 m (SD 245), p = 0.009.	using the electromechanical gait trainer requires less therapeutic assistance, and therapist discomfort is reduced."	between groups. Conclusions derived from patient reports and not objective measures.
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## Nonoperative Treatment Recommendations

### Intracranial Pressure Monitoring and Thresholds

Intracranial pressure monitoring and cerebral perfusion pressure monitoring are used to measure blood flow within the brain and adjust therapy to attempt to maintain sufficient cerebral perfusion in TBI patients [522-526].

#### Intracranial Pressure Monitoring and Thresholds Recommended.

Intracranial pressure monitoring is recommended for use in the evaluation of TBI patients.

*Strength of Evidence* – **Recommended, Evidence (C)**

*Level of Confidence* – **Moderate**

<i>Indications:</i>	Severe TBI injuries with concerns for inadequate cerebral perfusion due to intracerebral pressure
<i>Benefits:</i>	Potential to alter treatment to raise or maintain sufficient cerebral perfusion
<i>Harms:</i>	Infections, bleeding, further brain tissue damage
<i>Frequency/Dose/Duration:</i>	Early severe TBI patient monitoring until either there are no episodes of elevated intracerebral pressure, episodes of elevated intracerebral pressure have ceased and/or intracerebral pressure is thought to not be problematic.
<i>Rationale:</i>	There are some quality studies assessing Intracranial Pressure Monitoring & Thresholds for monitoring and treatment of TBI. Studies consistently demonstrate correlations between intracranial pressure and clinical outcomes [522, 524-527]. Intracranial Pressure Monitoring is invasive, has adverse effects, is high cost, has some evidence of efficacy, and thus is selectively recommended for treatment and monitoring of some severe TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury, Intracranial Pressure, Cerebral Perfusion Pressure, Monitoring thresholds ;diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 18 articles in PubMed, 13 in Scopus, 9 in CINAHL, 6 in Cochrane Library, 18500 in Google Scholar, and 0 from other sources. We considered for inclusion 4 from PubMed, 2 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 5 from Google Scholar, and 0 from other sources. Of the 11 articles considered for inclusion, 4 prognostic studies and 3 systematic studies met the inclusion criteria.

## Evidence for the Use of Intracranial Pressure Monitoring and Thresholds

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Kirkness, 2005 (NA)	Intracranial Pressure Monitoring	Prognostic	No mention of COI or sponsorship.	N=157 patients	Mean age 37.1±18.1 Years. 124 males, 33 females.	Traumatic Brain Injury	CPP Vs. TBI outcome	Post-resuscitation GCS scores showed moderate to severe TBI, with 73% having a score of 8 or less. The mean ISS score was 29.1. The percent time that CPP was below threshold levels over the first 4 days of monitoring ranging from 5% for 55 mmHg threshold to 29% for the 70 mmHg threshold. Patients with less percent time below fixed CPP thresholds ranging from 55-70 mmHg were more likely to have better outcomes by higher GOSE scores.	“Although differences in GOSE scores at six months were not significant, those with less time below CPP thresholds were more likely to survive. Accumulated episodes of low CPP had a stronger negative relationship with outcome in patients with more severe primary brain injury.”	Data suggest increased episodes of low CPP have a stronger negative outcome in severe TBI patients.
Kahraman, 2011 (NA)	Intracranial Pressure Monitoring	Prognostic	No mention of COI or sponsorship.	N=60	Mean age: 33.9±14 Years. 51 Males, 9 Females.	Traumatic Brain Injury	ICP: intracranial pressure monitoring Vs. CPP: cerebral perfusion pressure monitoring	Thirty-five of 60 patients had a good outcome. Injury severity was similar for both good and poor outcomes (p<0.1-0.7). Eight patients died and 14 patients had craniectomy. BTI<2 was better than CPP<60 mm Hg in	“Calculation of a BTI from continuous digital data predicts outcome in severe TBI and has potential for the design of real-time bedside early warning systems.”	Data suggest the BTI can predict outcome in severe TBI patients.

								predicting unfavorable Extended Glasgow Outcome Scale at 6 months ( $p < 0.05$ ). BTI, CPP, and ICP graphs were provided.		
Kuo, 2006 (NA)	Intracranial Pressure Monitoring	Prognostic	No mention of COI or sponsorship.	N=30 patients	Mean age: $36.8 \pm 14.9$ years. 20 males, 10 females.	Traumatic Brain Injury	ICP: Intracranial pressure monitoring Vs. CPP: Cerebral perfusion monitoring	Initial ICP for unfavorable outcomes was $47.4 \pm 21.4$ mmHg, resulting in a CPP of $22.8 \pm 12.83$ mmHg. The initial ICP for favorable outcomes were $26.4 \pm 10.1$ mmHg, resulting in a CPP of $48.8 \pm 13.4$ mmHg. The CPP thresholds of 37 mmHg, 51.8 mmHg (intraoperative) and 52 mmHg (after scalp closure). The ROC curve analysis showed that CPP was a better predictor of outcome than ICP.	"We conclude that the initial ICP may be higher than suspected and CPP very low in patients with severe head injury, particularly those with unfavorable outcomes. Based on ROC curve analyses, CPP is a better predictor of outcome than ICP."	Data suggests CPP predicts outcomes better than ICP.
Narayan, 1981 (NA)	Intracranial Pressure Monitoring	Prognostic	No mention of COI or sponsorship.	N=133 severely head-injured patients	Mean age: 27 years. No mention of gender.	Traumatic Brain Injury	ICP: Intracranial Pressure Vs CT: Computerized Tomography Vs MEP: Multimodality Evoked Potential	Glasgow Coma Scale score, pupillary response, presence of surgical mass lesions, extraocular motility, and motor posturing were used to predict outcome of severe head injury with 82% accuracy, 43% with over 90% confidence. The GCS score was accurate in 80% of predictions, but a	"The clinical examination remains the strongest basis for prognosticating outcome in severe head injury, but additional studies enhance the reliability of	Data suggest reliable outcome predictors utilize a combination of clinical data and CT and ICP can add to the predictive value but alone, CT and ICP are poor prognostic indicators.

								<p>lower CI level (25% at over 90% level). CT and ICP proved to be poor prognostic indicators; however, increased number of predictions made with over 90% to 52-55%. Data from MEP was the most accurate with 91% correct, 25% at over 90% confidence level. MEP data showed 89% accuracy rate, with 64% over 90% confidence level.</p>	<p>such predictions.”</p>	
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Brain oxygen monitoring has been performed to attempt to monitor and mitigate the effects of cerebral tissue hypoxia [528-540].

## Oxygen Monitoring and Thresholds

### Recommended.

Oxygen monitoring is recommended for use in the evaluation of TBI patients.

#### **Strength of Evidence – Recommended, Evidence (C)**

##### **Level of Confidence – Moderate**

<i>Indications:</i>	Severe TBI injuries with concerns for brain tissue hypoxia
<i>Benefits:</i>	Potential to alter treatment to reduce brain hypoxia
<i>Harms:</i>	Infections, bleeding, further brain tissue damage
<i>Frequency/Dose/Duration:</i>	Early severe TBI patient monitoring until either there are no episodes of tissue hypoxia, episodes of tissue hypoxia have ceased and/or tissue hypoxia is thought to not be problematic.
<i>Rationale:</i>	There are quality studies assessing Brain Oxygen Monitoring and Thresholds for treatment and monitoring of TBI [529-540]. The Brain Oxygen Monitoring and Thresholds diagnostic test is invasive, has adverse effects, is high cost, but has evidence of clinical efficacy, and thus is selectively recommended for treatment of severe TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: brain, brain tissue, oxygen, monitoring, thresholds, traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 168 articles in PubMed, 105 in Scopus, 25 in CINAHL, 118 in Cochrane Library, 31,800 in Google Scholar, and 13 from other sources. We considered for inclusion 6 from PubMed, 2 from Scopus, 2 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 6 from other sources. Of the 17 articles considered for inclusion, 12 prognostic studies and 5 systematic studies met the inclusion criteria.

### Evidence for the Use of Brain Oxygen Monitoring and Thresholds

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Eriksson 2012 (NA)	Brain Oxygen Monitoring	Prognostic	No COI. No mention of sponsorship.	N= 32	9 females, 22 males  Mean age 39 years ± 16.5 years	Severe TBI	pBtO <sub>2</sub> levels: monitor (Licox) 2-3 cm below dura  vs  Intracranial pressure (ICP) levels and cerebral perfusion pressure (CPP): ICP monitor/ventricular ostomy  All participants underwent both monitoring	The mean injury severity score was 27.78 ± 10.7 and the mean GCS score was 6.6 ± 3.4. 68% of participants survived. Those who died showed lower pBtO <sub>2</sub> levels, taking into account age (F = 12.898, p<0.001). pBtO <sub>2</sub> levels were higher at 8 hours, 12 hours, 20-44 hours, 52-60 hours, and 72 hours during monitoring (p<0.05). ICP and CPP levels were not significantly different (F=1.690, p=0.204 and F=0.764, p=0.389, respectively) between nonsurvivors and survivors. The threshold that pBtO <sub>2</sub> was more predictive for mortality was 29 mm Hg.	“The first 72 hours of pBtO <sub>2</sub> neurologic monitoring predicts mortality. When the pBtO <sub>2</sub> monitor remains below 29 mm Hg in the first 72 hours of monitoring, mortality is increased. This study challenges the brain oxygenation threshold of 20 mm Hg that has been used conventionally and delineates a time for monitoring pBtO <sub>2</sub> that is predictive of outcome.”	Data suggests that brain tissue oxygenation in the first 72 hours post TBI predicts mortality such that if levels remain below 29 mmHg mortality increases.
Leal-Noval 2010 (NA)	Brain Oxygen Monitoring	Prognostic	No mention of COI. Supported by Spanish Government funds (Fondo de Investigación Sanitaria–	N= 22	No gender distribution described  Mean age 33 ± 13 years	Severe TBI (GCS ≤ 9), intraparenchymal ICP/PbrO <sub>2</sub> catheter previously inserted, passing initial resuscitation phase,	ICP and PbrO <sub>2</sub> levels: Monitor LICOX IMC system  Vs  Regional transcranial oxygen saturation (rSO <sub>2</sub> ): monitored by	PbrO <sub>2</sub> and rSO <sub>2</sub> displayed direct and independent correlation in an adjusted regression (β = 0.36, 95% CI (0.35-0.37) as well as logistic regression analyses (adjusted odds ratio = 1.11, 95% CI (1.10-1.12)) with PbrO <sub>2</sub> C15 mmHg being the dependent variable. rSO <sub>2</sub> had lower accuracy for identifying moderate	“In patients with severe TBI, PbrO <sub>2</sub> and rSO <sub>2</sub> were directly and significantly related. Severe intracerebral hypoxia was better detected by rSO <sub>2</sub> than was moderate intracerebral hypoxia. However, the diagnostic accuracy of rSO <sub>2</sub> was limited, and this	Regional oxygen saturates measured by NIRS cannot precisely predict PbrO <sub>2</sub> .

			FIS– Proyecto de Investigación) and by Consejería de Salud de la Junta de Andalucía .			under controlled mechanical ventilation	near-infrared spectroscopy (INVOS 5100 Cerebral Oximeter)  All participants underwent both monitoring	intracerebral hypoxia (PbrO2 B15 mmHg) on a receiver-operating characteristic curve (area under curve = 0.62). This ROC displayed a likelihood ratio of a positive test being 1.2 and an optimal cutoff of rSO2 ≤ 70%. rSO2 was moderately accurate for detecting severe intracerebral hypoxia (area under curve = 0.82, likelihood ratio = 5.3) with an optimal cutoff of rSO2 ≤ 60%.	measure should not be considered a substitute for routine PbrO2 monitoring.”	
Santbrink 2003 (NA)	Brain Oxygen Monitoring	Prognostic	No mention of COI or sponsorship.	N= 41	6 females, 35 males  Mean age 33 ± 16	Severe TIB, GSC ≤ 8	Intracranial pressure (ICP): monitored by fiberoptic device (Camino lab)  vs  Local brain tissue partial pressure of oxygen  All participants underwent both monitoring	PbrO2 ranged from 4 to 50 mmHg at baseline. PaO2 values ranged from 73-237 mmHg. When FiO2 was at 1, PrbO2 ranged from 9.1-200 mmHg and PaO2 ranged from 196-499 mmHg. A stable plateau pattern of PbrO2 was more prevalent 48 hours post injury. This pattern was related to a positive outcome (p=0.06) if seen within the first 24 hours post injury. TOR mean level for all test was 0.73 ± 0.59. Those who had negative outcomes presented higher TOR (1.03 ± 0.60) compared to those with positive outcomes (0.61 ± 0.51) within the first 24 hours. Using tissue oxygen response as a predictive value for negative outcomes was verified and	“Evaluation of TOR affords insight in (disturbances in) oxygen regulation after traumatic brain injury, is of prognostic value and may aid in identifying patients at (increased) risk for ischemia.”	The evaluation of tissue oxygen response (TOR) leads information in oxygen disruptions post TBI.

								supported through a multiple logistic regression analysis (OR = 4.8). Mean TOR dropped significantly from $0.75 \pm 0.54$ to $0.65 \pm 0.45$ (Wilcoxon test, $p = 0.06$ ) during increased hyperventilation. A decrease in TOR after hyperventilation was significantly related to more negative outcomes ( $p=0.01$ ) within the first 24 hours post injury.		
Adamides 2009 (NA)	Brain Oxygen Monitoring	Prognostic	Supported by a Victorian Trauma Foundation best practice grant.	N= 30	8 females, 22 males  Mean age overall 36.57 years	Severe TBI, post-resuscitation GCS < 9	Brain tissue oxygen (PbrO <sub>2</sub> ): not treated, monitored through Licox probes within uninjured frontal white matter (n=10)  vs  Same measurements and probes, treated according to brain tissue oxygen-guided algorithms (to improve cerebral oxygen availability) (n=20)	Group 1 (control) presented mean duration times of brain hypoxic episodes (PbrO <sub>2</sub> <15 mmHg) of 106 minutes where group 2 presented a significantly different mean time of 34 minutes ( $p=0.01$ ). Group 1 has brain tissue oxygen levels <15 mmHg for 10% of the time while group 2 only presented the same levels 2.8% of the time ( $p=0.12$ ). Mean Injury Severity Score (ISS) was statistically higher for those undergoing cerebral hypoxia compared to those not suffering those events (33.7 vs 24.2, $p=0.04$ ). Neurological outcomes between the two groups were not statistically significant.	“The introduction of a brain oxygen-guided algorithm into the management of patients with severe TBI was associated with decreased duration of episodes of cerebral hypoxia and a trend towards better neurological outcome. Episodes of inadvertent hyperventilation and systemic hypoxia significantly decreased, and brain tissue oxygen monitoring enabled selective optimisation of CPP in individual patients. Cerebral hypoxia was more likely to occur in patients with multiple systemic injuries and higher ISS. The peak incidence of episodes of cerebral hypoxia occurred during post-injury day 5	No difference in outcome between patients treated with or without oxygen guided therapy.

									suggesting that brain oxygen monitoring and mechanical ventilation may optimally be	
Stiefel 2005 (NA)	Brain Oxygen Monitoring	Prognostic	No mention of COI or sponsorship.	N= 53	11 females, 42 males  Mean age of ICP/ CPP group 44 ± 14 years. Mean age of brain tissue PO2 group 38 ± 18 years	Severe TBI, between January 2000 and July 2002, GCS score < 8, ISS ≥ 16	Group A: ICP and CPP treatment, ICP monitor (Camino) inserted via frontal burr hole (n=25)  vs  Group B: brain tissue PO2-directed management, ICP and brain tissue PO2 and temperature probes inserted through triple-lumen bolt (Licox CMP Triple Lumen Monitoring System) (n=28)	Mean ICP monitoring time, mean daily ICP, and mean daily CPP were not statistically different as well as mean maximal daily ICP, mean minimal daily CPP, mean number of episodes of elevated ICP (> 20 mmHg), and reduced CPP (< 60 mmHg). Group B presented a mean daily brain tissue PO2 of 34.7 ± 12.3 mmHg. During monitoring periods this group presented 142 episodes of compromised brain tissue PO2 levels (PO2 < 25 mmHg) and 35 episodes of ischemic PO2 levels (< 15 mmHg). In group A 44% of participants died whereas a statistically smaller amount of 25% died in group B (p=0.05). 14 participants (17%) of the survivors in group A underwent additional hospitalization or nursing home placement, whereas zero from group B experienced either result. Of those in group B, those who died displayed more frequent cerebral hypoxia episodes (< 15 mmHg) than those who survived (1.23 ± 1,	“The concept of multimodality monitoring is not new. As brain tissue PO2 monitoring gains increasing acceptance at head-injury centers and in neurointensive care units, it is critical to compare its use to ICP monitoring alone. In addition, as new information about current CPP management compels questions, we must identify better resuscitation end points. Brain tissue PO2 monitoring may help in this process. Our results, although preliminary, are compelling and provide the first evidence that the use of multimodality monitoring with both an ICP and a brain tissue PO2 monitor as well as therapy directed at brain O2 can be associated with a reduced patient mortality rate after severe TBI.”	Data suggest decreased mortality associated with use of ICP and brain tissue PO2 monitors and therapy.

								0.34 ± 8, respectively, p=0.007). Survivors presented shorter cumulative periods of compromised cerebral oxygenation (< 25 mmHg) than those who died (164.9 ± 362.9, 364.1 ± 422.7 minutes, respectively, p=0.04).		
Valadka 1998 (NA)	Brain Oxygen Monitoring	Prognostic	Supported by grant from the National Institutes of Health. No mention of COI.	N= 43	9 females, 34 males  Mean age 32 ± 14 years	Severe head-injured, GCS ≤ 8	PbtO2 monitored using Licox or Paratrend probes containing miniaturized Clark electrodes  All participants underwent continuous PbtO2 monitoring	PO2 readings at room temperature = 141 ± 20 torr (18.8 ± 2.7 kPa, range 82-187 torr or 10.9-24.9 kPa) for Licox probes, 138 ± 1.3 torr (18.4 ± 1.3 kPa, range 131-145 torr or 17.4 ± 19.3 kPa) for Paratrend probes  In blood gas standard calibration solution (Level I arterial blood gas control) PO2 readings were 70 ± 8 torr (9.3 ± 1.0 kPa, range 49-80 torr or 6.5-10.6 kPa) for Licox probes and 68 ± 32 torr (9.0 ± 4.3 torr, range 45-90 torr or 6.0-12.0 kPa) for Paratrend probes.  Licox probes stabilized within 15 minutes at 0.3 ± 0.3 torr (0.04 ± 0.04 kPa) in zerooxygen solution. Paratrend probes showed higher PO2 values of 7.0 ± 1.4 torr (0.9 ± 0.2 kPa) after 30 minutes.	“Analysis of the PbtO2 monitoring data suggested that the likelihood of death increased with increasing duration of time at or below a PbtO2 (2) of 15 torr (2.0 kPa) or with the occurrence of any PbtO2 values of <or=to6 torr (<or=to0.8 kPa).”	Data suggest increased mortality associated with increased duration of time at or below 15 torr.

Bardt 1998 (NA)	Brain Oxygen Monitoring	Prognostic	No COI or sponsorship mentioned.	N= 35	7 females, 28 males  Mean age 33.2 ± 11.3 years	Severe head injury, GCS ≤ 8	Continuous brain tissue (PtiO2) via Licox microcatheter, placed into non-injured frontal white matter in 8-125h post-injury  All participants underwent the same monitoring	Mean PtiO2 was 22.7 ± 9.1 mmHg. Cerebral hypoxia incidence was 15.0 ± 23.2 hours when indicated by PtiO2 levels < 10 mmHg. 12 participants underwent <30 minutes of PtiO2 < 10 mmHg. PtiO2 was <15 mmHg for 7.8 ± 2.6 hours for this group. 11 participants died, 22 were in a severely disabled or vegetative state, and 2 had more positive outcomes. After six months after injury 13 participants had died, 6 were still disabled, and 16 had more positive outcomes.  More frequent periods of hypoxic PtiO2 < 10 mmHg was correlated with poor neurological outcomes. Of those who underwent <30 minutes of hypoxic PtiO2 80% were in a vegetative state at discharge, 20% had a positive outcome, and 0% died in the acute phase. After six month post injury over 72.8% of participants had a positive outcome, 18.2% had a negative outcome, and 9% died. Of those who underwent >30 minutes of hypoxic PtiO2 48% died in the acute phase and 52% had negative outcomes at discharge. 55.6% died, 22.2% were disabled, and	“These result underscore the associated of cerebral hypoxia with poor neurological outcome and stress the meaning of monitoring PtiO2 as an independent parameter in patients following TBI.”	Data support correlation between cerebral hypoxia post TBI and poor neurological outcomes.
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								<p>22.2% had a positive outcome at six month.</p> <p>Intracranial hypertension (ICP &gt; 20 mmHg) was associated with cerebral hypoxia in 11.5% of patients. In 16.8% of patients CPP was compromised &lt;60 mmHg. Hypocarbica was present in 48.0% of the time during hypoxic PtiO2 episodes.</p>		
Cormio 1999 (NA)	Brain Oxygen Monitoring	Prognostic	No mention of COI. Supported by a grant from the National Institutes of Health.	N= 450	63 females, 387 males  Median age of 30 years (range 23-41 years)	Severe head injury, between 1986 and 1997	<p>Intracranial pressure (ICP): ventriculostomy, a parenchymal microtransducer, or a fiberoptic monitor</p> <p>vs</p> <p>SjvO2: via oximeter (IL-284 CO-Oximeter), blood samples drawn through indwelling catheter in jugular bulb</p> <p>All participants underwent all monitoring</p>	<p>Group classification: Group 1 had high SjvO2 (75% of higher), Group 2 had normal SjvO2 (56-74%), and Group 3 had low SjvO2 (55% or lower).</p> <p>19.1% of participants underwent a high SjvO2 measurement. SjvO2 and simultaneous cerebral blood flow had no consistent relationship. There was also no relationship between SjvO2 and cerebral perfusion pressure.</p> <p>Those in group 1 had significantly greater CBF and lower cerebral metabolic rate of oxygen (CMRO2). Group 1 had 48.8% of participants either died or were in a vegetative state and 25.6% were severely disabled. These percentages were significantly higher</p>	<p>“Posttraumatic elevation of SjvO2 is common but cannot be automatically equated with hyperemia. Instead, elevated SjvO2 is a heterogeneous condition that is associated with poor outcome after head injury and may carry important implications for the management of comatose patients.”</p>	Data suggest post-traumatic elevation of jugular venous oxygen saturations correlates with poorer outcomes.

								compared to groups 2 and 3. Those who had poor outcomes in group 1 were older and more likely to suffer from a focal head injury. These individuals had lower CMRO2 levels and higher rates of cerebral lactate production.		
Cruz 1998 (NA)	Brain Oxygen Monitoring	Prognostic	No mention of COI. The Rotary Foundation of Rotary International supported a PostGraduate Fellowship for this study.	N= 353	No gender distribution described  Mean age of cerebral extraction of oxygen group 30 ± 9 years. Mean age of initial cerebral perfusion pressure group 29 ± 8 years.	Severe acute closed brain trauma, in a coma, GCS score from 3-8	(CEO2) Continuous fiberoptic monitoring and management of jugular bulb oxyhemoglobin saturation and cerebral extraction of oxygen with cerebral perfusion pressure (n=178)  vs  (CPP) Continuous monitoring and management of cerebral perfusion pressure only (control group) (n=175)	16 participants in the CEO2 group died (9%) while 53 participants in the CPP group died (30%) post-injury. Overall figures in outcome were significantly better in CEO2 group compared to the control group. Categories of the Glasgow Outcome Scale were compared between the two groups and resulted in the following: good recovery of moderate disability (G-M) – 132 participants in CEO2 group, 98 in CPP group, and severe disability (S) – 25 CEO2, 21 CPP, vegetative state or death (V-D) – 21 CEO2, 56 CPP. These differed significantly (p < 0.00005).  In the CEO2 group cerebral perfusion pressure monitoring occurred over 6.5 ± 1.5 days, while in the control group it occurred over 10.5 ± 2 days (p < 0.001).	“In patients with severe acute brain trauma and intracranial hypertension associated with compromised cerebrospinal fluid spaces, monitoring and managing cerebral extraction of oxygen in conjunction with cerebral perfusion pressure result in better outcome than when cerebral perfusion pressure is managed alone.”	Data suggest in severe brain trauma patients with intracranial hypertension the management of cerebral perfusion pressure in tandem with cerebral extraction of oxygen leads to better patient outcomes.

								Participants were matched for the following variables: age, postresuscitation Glasgow Coma Scale scores, and initial levels of intracranial pressure and cerebral perfusion pressure, between-group rates of early arterial hypotensive episodes (before intensive care monitoring), pupillary abnormalities, small lateral ventricles, compromised basilar cisterns, and acute surgical intracranial hematomas. There were no significant differences between the two groups in these variables.		
Robertson 1995 (NA)	Brain Oxygen Monitoring	Prognostic	Supported by a grant from the National Health Institute. No mention of COI.	N= 177	19 females, 158 males  Mean age 32.9 ± 14.7 years	Severe head injury, GCS ≤ 8	Jugular venous oxygen saturation (SJVO2), catheter placed on dominant side  All participants underwent this monitoring	In the participants monitored, jugular venous desaturation (SJVO2 < 50%) occurred within 39% at least during monitoring. Episodes of this desaturation were due to intracranial hypertension and systemic causes. Oxygen depletion was associated with a negative outcome.  6 out of 8 participants monitored during emergency evacuation of a traumatic intracranial hematoma displayed jugular venous desaturation. 28% was the lowest level of SJVO2. SJVO2 levels increased	“Despite these limitations, the present data suggest that SjvO2 monitoring is useful in detecting episodes of cerebral hypoperfusion in patients with severe head injury. The incidence of observing jugular venous desaturation is frequent enough to justify the small risk of the catheter. The occurrence of jugular venous desaturation is strongly associated with a poor neurological outcome. The causes of the hypoperfusion are often	Data suggest jugular venous oxygen monitoring is critical in detection of cerebral hypoperfusion in head injured patients.

								<p>from <math>47 \pm 10\%</math> to <math>63 \pm 5\%</math> after evacuation of hematoma.</p> <p>Lactate concentration increased from <math>0.9 \pm 0.3</math> to <math>2.4 \pm 0.5 \mu\text{mol/L}</math> and glutamate elevated from <math>11.5 \pm 8.5</math> to <math>55.0 \pm 10.4 \mu\text{mol/L}</math> within 8 episodes of jugular venous desaturation in 7 of 22 patients monitored with microdialysis.</p>	<p>treatable systemic insults."</p>	
Stocchetti 2004 (NA)	Brain Oxygen Monitoring	Prognostic	No mention of COI or sponsorship.	N= 229	39 females, 190 males  Mean age was 36 years.	Severe head injury, comatose, GCS $\leq 8$	<p>Intracranial pressure (ICP)</p> <p>vs</p> <p>Mean arterial blood pressure (MAP)</p> <p>vs</p> <p>Cerebral perfusion pressure (CPP)</p> <p>vs</p> <p>Samples from artery and internal jugular samples, via catheter inserted into internal jugular vein, tip positioned at superior bulb, analyzed with cooximeter and</p>	<p>Mean SJO<sub>2</sub> (jugular hemoglobin oxygen saturation) level was 68%. Mean AJDO<sub>2</sub> difference was 4.24 vol% (sd = 1.3 vol%).</p> <p>304 measurements (17.6%) had SJO<sub>2</sub> levels &gt;75% and 80 (4.6%) with levels &lt;55%.</p> <p>8 calculations (0.4%) of AJDO<sub>2</sub> resulted in higher than 8.7 vol% and 718 calculations (42%) resulted in lower than 3.9 vol%. AJDO<sub>2</sub> results were higher during the first measurements and over the course of a few days decreased steadily.</p> <p>Those who were severely disabled or in a vegetative state at six months post injury had mean AJDO<sub>2</sub> of 3.8 vol% (sd = 1.3 vol%) and those who died had</p>	<p>"We conclude that low levels of AJDO<sub>2</sub> are correlated with a poor prognosis, whereas normal or high levels of AJDO<sub>2</sub> are predictive of better results"</p>	<p>Data suggest low levels of arterio-jugular difference of oxygen content correlate to poor prognoses.</p>

						<p>gas analyzer (IL 481 Co-oxymeter)</p> <p>vs</p> <p>Arterio-jugular difference of oxygen content (AJDO2), calculated as the following: AJDO2 = (art Sat % - j Sat %) x 1.34 x Hb x [(art PO2 - j PO2) x 0.003]</p> <p>All participants underwent all monitoring</p>	<p>mean AJDO2 measures of 3.6% (sd = 1.0 vol%). Those with a more positive outcome had a significantly higher AJDO2 measure of 4.3 vol% (sd = 0.3 vol%) compared to those who were severely disabled, in a vegetative state, or those who had died combined (p &lt; 0.001).</p>			
van den Brink 2000 (NA)	Brain Oxygen Monitoring	Prognostic	No COI. No mention of sponsorship.	N= 101	18 females, 83 males  Mean age 34 ± 16 years	Comatose, severe head injury, GCS ≤ 8	<p>All participants were monitored for the following: heart rate, respiratory rate, mean arterial blood pressure via a pressure transducer calibrated at level of heart, peripheral oxygen saturation, ICP via Camino fiberoptic device, CPP, PbrO2 via Clark-type microcatheter and Licox partial pressure of oxygen</p>	<p>PbrO2 monitoring started 7.0 ± 3.5 hours post-injury. 83 participants were monitored for over 24 hours with average monitoring time being 86 hours (range 4-180 hours).</p> <p>When monitoring PbrO2, post-measurement calibration resulted in average zero display error of 0.42 ± 0.85 mm Hg. PO2 display error (calibrated at mean room air PO2 of 157.6 ± 1.5 mm Hg) was 0 ± 6%.</p> <p>In first 12-24 hours low initial values occurred in over 50% of participants. 57 cases had values lower</p>	<p>“Monitoring the partial oxygen pressure of local brain tissue is a safe and reliable method for regulating cerebral oxygenation. Because brain tissue hypoxia occurs frequently and is significantly related to poor outcome, future efforts should be aimed at the treatment of brain tissue hypoxia. The effects of such brain hypoxiatargeted treatment need to be established in a multicenter study.”</p>	Data suggest ability to monitor brain partial oxygen pressure to detect hypoxia which leads to poor outcomes in severe head injury.

						<p>measuring computer</p> <p>Local brain oxygen tension probes, inserted in undamaged part of frontal region</p> <p>vs</p> <p>CT scanning using the Marshall classification</p>	<p>than 15 mm Hg, 42 had values lower than 10 mm Hg, and 22 had values lower than 5 mm Hg.</p> <p>Of those with initial low values, 30 displayed an overshoot in mean high value of PbrO<sub>2</sub> (46 mm Hg in 36-48 hours post-injury). Occurrence of overshoot not related to outcome.</p> <p>After using the Spearman rank coefficient, no significant correlations were found for between low initial values and clinical variables. Compression of cisterns was the only significantly correlated variable in CT scans with initial low PbrO<sub>2</sub>.</p> <p>Survivors presented higher PbrO<sub>2</sub> values. 24 out of 43 participants with low initial values died. Only 14 out of 66 participants with higher values died. When outcomes were dichotomized into negative versus positive outcomes the odds ratio of death was 3.8 (p = 0.002). The odds ratio for unfavorable outcome was 2.8 (p = 0.015).</p> <p>Low values within 24 hours post-injury were broken</p>	
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								<p>into &lt;5, &lt;10, and &lt;15 mm Hg. Lower PbrO2 values related to higher risk of death.</p> <p>There was no increase in risk of death after several hours. The odds ratio for death was 3.8 (95% CI = 1.6-8.9) at 30 minutes.</p> <p>Low initial PbrO2 remained an independent prognostic factor when analyzed in a logistic regression model. Status of perimesencephalic cisterns were related to PbrO2 and reduced the prognostic value.</p>	
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## Osmotherapy, including: Mannitol, Hypertonic Saline, Lactate, Albumin

Increased intracranial pressure is associated with considerably worse mortality from TBI; thus, therapies to reduce intracranial pressure have been used for decades. Mannitol or mannite is a sugar alcohol that has the capability to cross the blood-brain barrier and used extensively in osmotherapy as a means of attempting to control elevated pressure following head trauma. Excessive use purportedly increases skull pressure and brain swelling and for this reason, mannitol has been recommended for patients with raised intracranial pressure or poor neurological status [541-549]. Hypertonic saline, sodium lactate solutions, lactated Ringer's solution, glycerol, crystalloids or albumin have also been used for reducing intracranial pressure from traumatic brain injury [550-554].

There also are many studies of resuscitation with hypertonic saline [80, 553, 555-558], dextran plus hypertonic saline [555, 557, 559, 560], and normal saline [556, 557, 559-562] for resuscitation including during transport and/or in ICUs. There are studies of lactated Ringer's solution for use in resuscitation [80, 553, 555, 558]. There are a few studies of albumin for use in resuscitation [561, 563].

### Mannitol for Intracranial Pressure

#### Recommended.

Mannitol is recommended for reducing intracranial pressure in TBI patients.

*Strength of Evidence* – Acute, Severe- **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – Moderate

<i>Indications:</i>	For decreasing brain swelling in acute, severe TBI patients, used as an osmotic diuretic
<i>Benefits:</i>	Reduced brain swelling post TBI
<i>Harms:</i>	Hypotension, acidosis, drug allergy
<i>Frequency/Dose/Duration:</i>	Administration adjusted to pressure measures from a direct pressure device. Common targets also include increasing serum osmolarity to an initial target of 300-320mOsm/L or increase the serum sodium to 145 -150mmol/L.
<i>Indications for Discontinuation:</i>	Hypotension, pulmonary congestion, fluid and electrolyte imbalance, acidosis, electrolyte loss, dryness of mouth, thirst, marked diuresis, urinary retention, edema, headache, blurred vision.
<i>Rationale:</i>	Nearly all quality evidence regarding mannitol used active controls. There is only one placebo controlled trial of normal saline that assessed early, in-field administration of mannitol [564]. One moderate-quality trial found much worse mortality for those treated with pentobarbital compared with mannitol [542]. Most of the remaining quality evidence compared mannitol with hypertonic saline and found no significant differences in outcomes [565, 566], thus showing comparable efficacy between mannitol and hypertonic saline. Mannitol is invasive, has significant adverse effects and is costly over time, but with strong evidence of mortality from increased intracranial pressure, it is one of the recommended options for treatment. There is no evidence to recommend hypertonic saline over mannitol, thus hypertonic saline is similarly recommended (see below).
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the

following terms: mannitol or mannite or manna sugar; brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed head or penetrating head or craniocerebral; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, retrospective studies, or prospective studies. We found and reviewed 194 articles in PubMed, 405 in Scopus, 40 in CINAHL, 4 in Cochrane Library and 0 in other sources. We considered for inclusion 17 from PubMed, 0 from Scopus, CINAHL, Cochrane Library and other sources. Of the 17 articles considered for inclusion, 8 randomized trials and 8 systematic studies met the inclusion criteria. There are 7 moderate-quality RCTs incorporated into this analysis. There are 6 low-quality RCTs. There are 8 systematic reviews.

## Evidence for the Use of Mannitol

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Cottenceau 2011 (score = 5.5)	Mannitol vs Hypertonic Saline	RCT	No mention of sponsorship. No COI.	N = 47 TBI patients with increased intracranial pressure (ICP) Ages 36.1±16.8 for Mannitol group and 42.7±19.9 for Hypertonic saline group		Mannitol (MTL) group. Received 20% (4 ml/kg) (N =25 ) vs. Hypertonic saline [567] group. Received 7.5% (2ml/kg) (N =22). Baseline assessment was followed by additional tests performed at 30 and 120 min.	Neurological outcome was assessed at 6 months during follow-up examinations.	As a correlate for Intracranial pressure decrease, there was a noticeable and significant increase in cerebral perfusion pressure (CPP) at 30 min in both groups (Main effect of measurement time p = 0.0001). Although cerebral blood flow (CBF) increased in both groups at 30 min, it was more pronounced in the HTS group, p=0.0087. There was a significant elevation of hematocrit at 30 min following MTL infusion.	“MTL was as effective as HTS in decreasing ICP in TBI patients although both solutions failed to improved cerebral metabolism. HTS showed an additional and stronger effect on cerebral perfusion of potential benefit in the presence of cerebral ischemia. Treatment selection should therefore be individually based on sodium level and cerebral hemodynamics”.	Data suggest similar efficacy but HTS showed a benefit on cerebral perfusion in the presence of cerebral ischemia.
Francony 2008 (score = 5.0)	Mannitol vs Hypertonic Saline	RCT	No mention of sponsorship or COI.	N = 20 with severe brain injury (n=17 TBI) and (n=3 stroke) with intracranial pressure (ICP) greater than 20 mmHg for more than 10 minutes. Mean age		Mannitol 20% 231 mL (N = 10) vs. Hypertonic saline solution 7.45% (HSS) 100mL (N = 10). Osmolar dose was 255	Follow-up for 120 minutes.	At every time point both mannitol and HSS significantly reduced ICP in the two groups. Mannitol reduced ICP by 45% +/- 19% from baseline to 60 minutes (-14	“[2]0% mannitol is as effective as 7.45% HSS in treating stable patients with sustained elevated ICP...Both osmotic agents exerted a clear and comparable effect on ICP, lasting >120	Data suggest comparable reductions in ICP including better cerebral blood flow with mannitol.

				mannitol 43±11 years, HSS 37±16 years.		mOsm for each treatment.		+/- 8 mmHg). HSS reduced ICP by 35% +/- 14% from baseline to 60 minutes (-10 +/- 5 mmHg). Mean arterial blood pressure remained unchanged and was significantly different between groups (p=0.32). HSS blood flow velocities after treatment was significantly reduced compared to mannitol at every time point (p<0.01).	mins, whereas CPP and cerebral blood flow velocities rose significantly in the mannitol group only."	
Schwartz 1984 (score = 4.5)	Mannitol vs Pentobarbital	RCT	Sponsored by the Sunnybrook Medical Center grant. No mention of COI.	N = 59 with elevated intracranial pressure from severe head injury. Glasgow Coma Scale scores <8. Mean age mannitol 30.1 years, pentobarbital 28.9 years.		Mannitol 20% 1g/kg with a serum osmolality of 320mOs/L (N = 31) vs. Pentobarbital IV bolus of 10mg/kg and continuous infusion at 0.5-3mg/kg/hr. (N = 28). All patients given CT scan.	Follow-up at 3 months and one year.	Scores on the GCS correlated with survival rates at 3 months 16/28 patients had dies in the pentobarbital group and at 1-year 6/12 remained hospitalized. For mannitol 13/31 had died and at 1-year 8/16 were hospitalized. Twice as many patients starting with pentobarbital had to use mannitol as	"There is no evidence that pentobarbital is 25 percent better than mannitol, either for the control of raised intracranial pressure or for improving survival in patients with intracranial hypertension due to head injury."	For patients experiencing elevated episodes of ICP they were given rescue medicine, making the study a cross-over, unblinded study. Severe TBI. Data suggest mannitol superior for mortality (77 % vs. 41%).

								rescue medicine, making pentobarbital not 25% better (p=0.04) than mannitol.		
Sayre 1996 (score = 4.5)	Mannitol vs Normal Saline	RCT	Supported by grants from the Aeromedical Research Foundation and The Department of Emergency Medicine, University of Cincinnati. No mention of COI.	N=44 with head injuries, a Glasgow Coma Scale<12, IV access, airway control with an endotracheal tube, and were being hyperventilated. Mean±SD age: Mannitol: 29±12 years. Placebo: 27±8 years.		Control group: 5mL/kg of 0.9% saline solution (308 mOsmoVL) (n=21) Vs. Treatment group: 5mL/kg of 20% mannitol (1,098 mOsmoVL) (n=20).	Follow-up 120 minutes.	Systolic BP 2 hours after treatment: Mannitol vs. placebo: 116±24mmHg vs. 142±25mmHg, p<0.003.	“Out-of-hospital administration of mannitol did not significantly change systolic BP in this group of head-injured multiple-trauma patients.”	Out of hospital administration of mannitol did not significantly change systolic BP.
Ichai 2009 (score = 4.0)	Mannitol vs Lactate	RCT	Sponsored by Innogene Kalbiotech Pte. Ltd. 24 Raffles Place 27-06 Clifford Center, Singapore. No mention of sponsorship. No mention of COI.	N = 34 with isolated severe traumatic brain injury with a Glasgow Coma Scale greater than 8. Mean age MAN 33.8±3.2 years, LAC 37.6±4.0 years.		Lactate solution contained Na 504 mmol/L, K 4 mmol/L, Ca 1.36 mmol/L, Cl 6.74 mmol/L and lactate 504.1 mmol/L (n=17) vs. Acute infusion of 1.5 ml/kg of either mannitol (20%, i.e., 0.3 g/ kg) vs. Lactate over 15 min (n=17).	Follow-up 240 minutes.	Intracranial pressure: LAC was lower than MAN (group effect p=0.016). Lactate infusion increased arterial pH (+0.5±0.1%, p<0.001).	“Acute infusion of a sodium lactate-based hyperosmolar solution is effective in treating intracranial hypertension following traumatic brain injury. This effect is significantly more pronounced than that of an equivalent osmotic load of mannitol. Additionally, in this specific group of patients, long-term outcome was better in terms of GOS in those receiving as compared to mannitol. Larger	Severe TBI. Data suggest greater reductions with lactate and more treatment failures with mannitol measured by ICP. Better outcomes with lactate at 1 year.

									trials are warranted to confirm our findings.”	
Biestro 1997 (score = 4.0)	Mannitol vs Glycerol & Saline	RCT	No mention of sponsorship or COI.	N=17 with severe head injury including two craniocerebral gunshot wounds (GSW), 31% with a Glasgow Coma Scale score (GCSs) of 6 or less, 50% with a GCSs of 7. Mean age: mannitol 34 years (range: 15-69) group. Glycerol was 39.5 years (range: 15-68).		15% mannitol, 100 ml given in ten minutes [860 mOsm170] Vs. 10% glycerol in 0.5 normal saline at rate of 250 ml per 1 hour [1.300 mOsm170].	2 hour follow up.	ICP decrease Mannitol: At two hours: 36.8±2.9 (SE) to 18.6±1.8 (SE) mmHg, p<0.0005. Glycerol group: 41.8±3.0 (SE) to 26.8±2.9 (SE) mmHg, p<0.0005.	“[M]annitol would be most indicated as a bolus to control sudden rises in ICP whereas glycerol would be most indicated.” as a basal treatment.	Small sample. Data suggest similar efficacy between mannitol and glycerol for decreasing ICP and increasing CPP.
Smith 1986 (score = 4.0)	Mannitol (ICP) vs. Mannitol (empirical)	RCT	No mention of sponsorship or COI.	N = 77 with head injury with a Glasgow Coma Scale rating of 8 or less. Average age of 27 years) range 8 months to 78 years).		Group I mannitol therapy based on intracranial pressure (ICP) levels (N = 37) vs. Group II mannitol empirical therapy (N = 40).	Follow-up at 1 year.	Death occurred in 13/37 (35%) of group I and 17/40 (42.5%) group II. All patients that died had abnormal CT scan. The outcomes from both group I and group II did not differ significantly for good recovery, moderate disability, severe disability, or vegetative state. There were no other statistically significant differences between groups in outcomes.	“The finding that empirically treated patients had lower mean ICP curve overall than patients given mannitol only when ICP rose above 25 mmHg suggests that the regular and frequent administration provides a smoother ICP curve overall and prevents ICP from rising above 25 mmHg...”	Data suggest no differences.

Vialet 2003 (score = 3.5)	Mannitol vs Hypertonic Saline	RCT	No mention of sponsorship or COI.	N = 20 with severe head trauma and persistent coma. Mean age mannitol 30.8±19 years, saline 35.0±18 years.		Mannitol 2mL/kg 20% (N = 10) vs hypertonic saline solution 2mL/kg 7.5% (N = 10).	Follow-up for mortality or 9- day neurologic status.	Episodes of intracranial pressure (ICP) were elevated in the mannitol group (p<0.02) and length of ICP was significantly longer (p<0.04) compared to HSS. Episodes of cerebral perfusion pressure were not significantly different between the groups. Treatment failure was significantly higher in the mannitol (7/10) group compared to HSS (1/10; p<0.01). Plasma osmolality was also significantly higher in the HSS group (p<0.01).	"[I]ncreasing the osmotic load during osmotic therapy (from 175 +/- 12 mOsm of 20% mannitol to 361 +/- 13 mOsm of HHS) was followed by a better efficacy on the number and the duration of established ICH episodes..."	Severe TBI. Lower initial Glasgow in hypertonic saline solution (4.7 vs. 6.0). Data suggest hypertonic saline solution lowered ICP better. No differences in outcomes.
Mir 2012 (score = 3.5)	Mannitol vs Hypertonic Saline	RCT	No sponsorship. COI, this paper is the outcome of the first author thesis study and was supported by TUMS. Since the third author is the Editor-in- Chief of the	N=33 patients, Ages not reported		Received mannitol 20% as a bolus of 1g/kg. Repeated dosing was given at 0.25 to 0.5 g/kg as needed (Group A n=10) Vs. Received 125 cc Hypertonic Saline [567] 5% as bolus in 1 hour every 6	Follow-up at baseline, 7 days and 60 days.	There was a correlation between mean APACHE II, SOFA and GCS scores in treatment groups, (p=0). There was a difference between expired and alive patients in mean APACHE II (p=0.005), SOFA (p=0.006) and GCS scores (p=0.000) after 60 days.	"Heart rate can be a prognostic factor for estimating mortality rate in brain injury patients along with APACHE II and SOFA scores in patients with brain injury".	Open label trial suggesting heart rate can be used as a prognostic measurement. Similar efficacy between groups. Small sample.

			journal; all review process and decisions on the submission were managed by one of the section Editors.			hours (Group B, n=11) Vs. Received 500 cc HTS 5% as infusion during 24 hours (Group C, n=12) In all groups, Acute Physiology and Chronic Health Evaluation (APACHE II), the sequential organ failure assessment (SOFA) and Glasgow coma scales (GCS) scores and heart rate were collected				
Scalfani 2012 (score = 3.5)	Mannitol vs Hypertonic Saline	RCT Pilot Study	Sponsored by NIH grant members. No COI.	N=8 patients with acute TBI. Ages, 37.4±17.4 years old.		Received 1.0 g/kg of 20% mannitol Vs. 0.686 mL/kg of 23.4% saline In both groups, treatments were infused for 15 min, and 1 hour after initiation of infusion.	Follow-up for 3 days	There were no differences in results from patients who received HS and mannitol were and combined for all analyses. Serum sodium concentration rose 4 hours after osmotic therapy (p=0.05) After intervention, CBF increased by 20% (p=0.001), and OEF decreased (both p<0.05) The number of regions with CBF less than	“Osmotic agents, in addition to lowering ICP, improve CBF to hypo perfused brain regions in patients with intracranial hypertension after TBI”.	Small sample (n=8). Data suggest similar efficacy between mannitol vs. hypertonic saline in TBI patients with intracranial hypertension.

								25 mL per 100 g/min decreased by 40% from a mean of 13 per patient 8 per patient (P<0.001)		
Sakellaridis 2011 (score = 2.5)	Mannitol vs Hypertonic Saline	RCT	No COI. No mention of sponsorship.	N=29 (199 hypertensive events) with severe head injury (GCS score ≤ 8) during the time period 2006–2008. Age range: 14 to 82 years (mean 36 years).		Mannitol 20% at a dosage of 2 ml/kg administered over 20 minutes (N=NA) vs. Hypertonic saline 15% at 0.42 ml/kg administered as a bolus via a central venous catheter (n=NA).	Follow-up for 3 months.	Mean duration of effect: Mannitol: 3 hours 33 minutes (SEM 31 minutes) vs. Saline: 4 hours 17 minutes (SEM 50 minutes), p=0.40.	“No difference between the 2 medications could be found with respect to the extent of reduction of ICP or duration of action.”	Crossover design. Data suggest comparable efficacy. Sparse methods.
Hendoui 2013 (score = 1.5)	Mannitol vs Hypertonic Saline	RCT	No mention of sponsorship or COI.	N = 39 with moderate to severe TBI. Aged between 18 to 65 years		Group A, 1 g/kg mannitol of 20% as a bolus, repeated with a dose of 0.25-0.5 g/kg every 6 hours based on patient’s response for 3 days ( N = 10) vs. Group B, 125 cc of hypertonic saline or HTS 5% every 6 hours as bolus (N = 11) vs. Group C, 500 cc of HTS 5% as infusion for 24 hours (N = 12).	Follow-up for 3 days of treatment and 60 days of survival.	No significant difference in 60 days survival of patients in different groups, (p = 0.1). Concentration of S100B was 0.01 ± 0.004 µg/l for control group vs the healthy control group, TBI patients had significantly higher initial serum levels of S100B at ICU admission, (p < 0.0001). Increased GCS levels, (p = 0.047) and	“S100B is closely related to the pathophysiological mechanism in TBI and may be useful as a therapeutic tool for treatment monitoring in TBI patients HTS is a safe and effective osmotic agent in TBI setting.”	Moderate and severe TBI. Small sample size. Open label. Baseline differences that appear to favor bolus HTS and concerning for randomization failure.

								reduced SOFA scores, (p = 0.002). MAP was significantly increased in bolus of HTS (p = 0.002) and infusion of HTS groups (p < 0.0001).		
Mojtahedzadeh 2014 (score = 1.5)	Mannitol vs Hypertonic Saline	RCT	Sponsored by Tehran University of Medical Sciences. No COI.	N = 39 with Glasgow coma scale (GCS) ≤12, closed head trauma and evidence of brain edema on head computed tomography (CT) scan. Aged between 18 and 65 years.		Group A, mannitol 20%, 1 g/kg administered over 20 min via central venous catheter and repeated with a dose of 0.25-0.5 g/kg every 6 h based on patient response (N = 10) vs. Group B, received 125 cc HTS 5%, over an hour via central venous catheter every 6 h for 3 days. And in the third group (C) 500 cc HTS 5% was continuously infused over 24 h for 3 days (N = 11) vs. Group C, as a continuous infusion of HTC (N = 12). Both groups of healthy	Follow-up at baseline and 3 days.	Serum concentration of ROS was 1.57 ± 0.5 picoM for the control group vs healthy group. TBI group had higher serum level of ROS at ICU admission, (p = 0.01), this reduction was significant for infusion part of HTS and mannitol, (p = 0.001 and 0.003). Serum TAP significantly decreased in mannitol group, (p = 0.004).	“HTS 5% has significant effects on the oxidant responses compared with mannitol following TBI that makes HTS as a perfect therapeutic intervention for reducing unfavorable outcomes in TBI patients.”	Second report of Hendoui 2013

						volunteers (N = 30) assessed for establishment of normal serum levels of ROS.				
Battison 2005 (score = 1.0)	Mannitol vs Hypertonic Saline plus Dextran	RCT Crossover Pilot Study	No mention of sponsorship or COI.	N = 9 with traumatic brain injury patients with intracranial pressure (ICP) >20mmHg.		Mannitol 20% 200mL 1245 mOsm/kg (N = 9) vs. Saline 7.5% and dextran-70 solution 6% (HSD) 100 mL (N = 9). Each patient received two treatments of mannitol and two HSD in a random order.	210 minutes	HSD reduced the minimum ICP more than mannitol (mean difference -5 mmHg; 95% CI -10.8 to -3.0; (p=0.014)). HSD reduced ICP to ≤16 mmHg in 2/18 treatments. Mannitol reduced ICP to ≤18 mmHg in 14/18 treatments. HSD significantly lowered mean arterial pressure (mean difference 7.0 mmHg; 95% CI 0.5 to 22.3; (p=0.044)). There was no significant difference between groups for cerebral perfusion pressure.	“It is the first trial to show that HSD reduced ICP more effectively than mannitol. This has implications for management of ICP. HSD may be a useful alternative in the treatment of increased ICP, but it remains to be seen if there is a clear fluid balance advantage of HSD over mannitol.	Pilot. Crossover trial. Sample size = 9. Deaths unclear.

## Hypertonic Saline for Intracranial Pressure

### Recommended.

Hypertonic saline is recommended for reducing intracranial pressure in TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Moderate**

<i>Indications:</i>	Severe TBI with intracranial pressure >20mmHg for more than 5 minutes.
<i>Frequency/Dose/Duration:</i>	100mL of 7.5% Saline over 5 min by central venous catheter [568]; [566]. Administration adjusted to pressure measures from a direct pressure device. Common targets also include increasing serum osmolarity to an initial target of 300-320mOsm/L or increase the serum sodium to 145-150mmol/L.
<i>Indications for Discontinuation:</i>	Fever and other adverse effects
<i>Benefits:</i>	Reduces ICP but maintains cerebral perfusion
<i>Harms:</i>	Fever
<i>Rationale:</i>	There are a few moderate quality trials comparing hypertonic saline with other solutions for managing increased intracranial pressure. Two trials found comparable results with mannitol [565, 566]. One trial suggested no difference between hypertonic saline and equimolar sodium bicarbonate [569]. Hypertonic saline is invasive, has significant adverse effects and is costly for administrations over time, but with strong evidence of mortality from increased intracranial pressure, it is one of the recommended options for treatment. There is no evidence to recommend hypertonic saline over mannitol, thus mannitol is similarly recommended (see above).
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: mannitol or mannite or manna sugar; brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed dead or penetrating head or craniocerebral; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, retrospective studies, or prospective studies. We found and reviewed 194 articles in PubMed, 405 in Scopus, 40 in CINAHL, 4 in Cochrane Library and 0 in other sources. We considered for inclusion 17 from PubMed, 0 from Scopus, CINAHL, Cochrane Library and other sources. Of the 17 articles considered for inclusion, 8 randomized trials and 8 systematic studies met the inclusion criteria.

## Ringers Lactate for Intracranial Pressure

### No Recommendation.

There is no recommendation for ringers or lactated solutions for treatment of intracranial pressure.

#### *Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

#### *Level of Confidence – Low*

*Benefits:*

Reduction in ICP

*Harms:*

Lactate acidosis

*Rationale:*

Relatively few studies have assessed lactated solutions for treatment of TBI. One trial reported lactate produced greater reductions in intracranial pressure compared with mannitol [551], while another found more treatment failures with mannitol [551].

One randomized controlled trial concluded that a 48 hour half-molar sodium lactate infusion aids in reducing the number of elevated intracranial pressure episodes for those experiencing severe traumatic brain injury, while decreasing chloride and fluid balances [550] [551]. One trial suggests hyperosmolar sodium lactate is superior to mannitol [551]. Another trial suggested One randomized prospective trial established that lactated Ringer's solution in combination with hypertonic saline assisted in controlling rising intracranial pressure following a traumatic brain injury [552]. Another study found that dextran 70 and sodium chloride solution serves to more effectively raise blood pressure and improve survival than lactated Ringer's solution when administered before hospitalization[553].

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: mannitol or mannite or manna sugar; brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed dead or penetrating head or craniocerebral; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, retrospective studies, or prospective studies. We found and reviewed 194 articles in PubMed, 405 in Scopus, 40 in CINAHL, 4 in Cochrane Library and 0 in other sources. We considered for inclusion 17 from PubMed, 0 from Scopus, CINAHL, Cochrane Library and other sources. Of the 17 articles considered for inclusion, 8 randomized trials and 8 systematic studies met the inclusion criteria. There are 17 moderate-quality RCTs incorporated into this analysis.

## Evidence for the Use of Hypertonic Saline

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Ichai 2013 (score = 5.5)	Treatment Evidence for Hypertonic Saline: vs Lactate	RCT	No mention of sponsorship. No COI.	N= 60 with severe non-penetrating TBI with an initial Glasgow Coma Scale (GCS) score of \9, and required measurement of ICP as part of their management within the first 12 h following injury.	Mean±SD age: Control group 33±15 years. SL group 40±18 years.	NaCl 0.9% (n=30) Vs. Half-molar sodium lactate (n=30).	Follow-up for 48 hours.	ICP episodes at 48 hours: SL vs. control group: 23 vs. 53 episodes, p<0.05).	“[S] L solution could be considered as an alternative treatment to prevent raised ICP following severe TBI.”	Data suggest SL decreased ICP episodes in severe TBI patients compared with NS.
Hui 2014 (score = 4.0)	Treatment Evidence for Hypertonic Saline vs Ulinastatin	RCT	No mention of sponsorship or COI.	N=92 with a diagnosis of sTBI by computed tomography or magnetic resonance imaging; Glasgow Coma Scale (GCS) score of <8; and admittance to ICU within 8 h after injury.	Age range: 28-63 years.	Control group (n=46): Conventional therapy plus a placebo (0.9% sodium chloride) vs. observation group (n=46): conventional therapy plus 200,000 units ulinastatin via intravenous	Days 1, 3, 5 and 7.	Mean±SD jugular venous blood lactate at day 7: Observation group 1.32±0.39 vs. Control group 2.85±0.36, p<0.05. Cerebral extraction of oxygen at day 7: Observation 40.18±5.47 vs. Control	“[U]linastatin effectively improved cerebral oxygen metabolism and reduced the CRP level in patients with sTBI.”	Sparse methods. Data suggest ulinastatin “may” be beneficial in TBI patients by improving cerebral oxygen metabolism and decreasing CRP levels (at one week).

						injection twice a day for seven days.		32.43±4.15, p<0.05.		
Shackford 1998 (score = 3.5)	Treatment Evidence for Hypertonic Saline vs Saline	RCT	Sponsorship, supported by Grant NINDS P20 NS 30324 from the National Institute of Health. No mention of COI.	N=34 With blunt mechanism of injury, GSC score ≤13 requiring monitoring of ICP or operative therapy and postoperative monitoring of ICP.		Hypertonic patients received 1.6% hypertonic saline [567] given at a rate of 15 mL/kg/day. Vs. Hypotonic patients received lactated Ringer's solution (LRS).	Follow-up for 5 days.	Mean maximum ICP with therapy was negative in the HTS group (-9.1±3.6 mm Hg) and positive in the LRS group (2.5±3.3, p<0.05).	“As a group, HTS patients had more severe head injuries. HTS and LRS used with other therapies effectively controlled the ICP. The widely held conviction that sodium administration will lead to a sustained increase in ICP is not supported by this work.”	Baseline comparability differences between groups (HTS group with more severe head injuries). Suggests randomization failure.
Schatzmann 1998 (score = 3.5)	Treatment Evidence for Hypertonic Saline vs Saline	Experimental	No mention of sponsorship or COI.	N=6 with trauma and severe head injury.	Mean (range) age: 40 (16-73) years.	Hypertonic saline (100ml 10% NaCl)	Follow-up at 6 hours.	The ICP decrease was 43% (28%-58%). The corresponding pressure drop was 18mmHg [570]. Relaxations lasted for 93 min [171] and a relative ICP min was reached 26min [234] after infusion.	“[T]he infusion of hypertonic saline reduces ICP in patients suffering from SHI. The pressure drop, duration and dynamic behavior are suspected to depend on the pressure level to reduce and concomitant medications.”	Small sample (n=6). Data suggest administration of hypertonic saline reduces ICP in severe head trauma patients.

## Evidence for the Use of Sodium Lactate

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Ichai 2013 (score = 5.5)	Treatment Evidence for Sodium Lactate vs Saline	RCT	No mention of sponsorship. No COI.	N= 60 with severe non-penetrating TBI with an initial Glasgow Coma Scale (GCS) score of \9, and required measurement of ICP as part of their management within the first 12 h following injury.	Mean±SD age: Control group 33±15 years. SL group 40±18 years.	NaCl 0.9% (n=30) Vs. Half-molar sodium lactate (n=30).	Follow-up for 48 hours.	ICP episodes at 48 hours: SL vs. control group: 23 vs. 53 episodes, p<0.05).	"[S] L solution could be considered as an alternative treatment to prevent raised ICP following severe TBI."	Data suggest SL decreased ICP episodes in severe TBI patients compared with NS.
Ichai 2009 (score = 4.0)	Treatment Evidence for Sodium Lactate vs Mannitol	RCT	Sponsored by Innogene Kalbiotech Pte. Ltd. 24 Raffles Place 27-06 Clifford Center, Singapore. No mention of sponsorship. No mention of COI.	N = 34 with isolated severe traumatic brain injury with a Glasgow Coma Scale greater than 8.	Mean age MAN 33.8±3.2 years, LAC 37.6±4.0 years.	Mannitol 20% (MAN) 1160 mOsm/L (N = 17) vs. Lactate solution (LAC) 1100 mOsm/L (N = 17).	Follow-up 1 year after treatment.	The LAC treatment group shad a significant decrease in ICP (p=0.016) compared to MAN. For the interaction between time and group effects there was a significant difference (p=0.0049), which indicates a longer and pronounced change. At the fourth hour the ICP was decreased by - 5.9 +/- 1 mmHg compared to MAN -3.2 +/- 0.9 mmHg (p=0.009). The LAC group had a significant increase in glucose (p=0.04), lactate (p<0.00001), and plasma osmolality (p=0.04) compared to MAN. Mean	"[H]yperosmolar sodium0lactate solution appears to be an interesting alternative in the treatment of episodes of cranial hypertension in TBI patients. This solution is more effective on ICP than the reference treatment mannitol."	Severe TBI. Data suggest greater reductions with lactate and more treatment failures with mannitol measured by ICP. Better outcomes with lactate at 1 year.

								arterial pressure (p=0.96) and cerebral perfusion pressure (p=0.51) were not statistically significant between the two treatments.	
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### Evidence for Resuscitation of Hypertonic Saline vs. Ringer's Lactate

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Cooper 2004 (score = 8.5)	Resuscitation Evidence for Hypertonic Saline vs Ringer's Lactate	RCT	No COI. Sponsorship, grant 124330 from the National Health and Medical Research Council, Australia, and grants from the Australian and New Zealand Intensive Care Research Foundation, the Victorian Trauma Foundation, the Neurosurgical Research Foundation, and the Alfred Hospital, Melbourne, Australia	N=229 with TBI who were comatose (Glasgow Coma Scale score, <9) and hypotensive (systolic blood pressure, <100 mm Hg).	Mean±SD age: Hypertonic saline 38±19 years. Control group: 37±19 years.	250-mL Infusion of Hypertonic Saline (n=114) Vs. 250-mL Infusion of Ringer's Lactate Solution (Control) (n=115).	Follow up for 6 months.	No differences between the groups with respect to ICP (p=0.08), CPP (p=0.40), duration of CPP of less than 70 mm Hg (p=0.06), gas exchange (PaO <sub>2</sub> /FIO <sub>2</sub> ratio), or duration of mechanical ventilation. Median (IQR) GOSE score at 6 months: Hypertonic vs control: 5 (3-6) vs. 5 (5-6), p=0.45.	"[P]atients with hypotension and severe TBI who received prehospital resuscitation with HTS had almost identical neurological function 6 months after injury as patients who received conventional fluid."	Data suggest administration of prehospital hypertonic saline [567] to patients with hypotension and severe TBI not superior to conventional (LR) solution at 6 months.

Vassar 1991 (score = 6.0)	Resuscitation Evidence for Hypertonic Saline with Dextran vs Ringer's Lactate	RCT	Supported in part by grant 1-ROM1- GM38508 from the National Institutes of Health and by Pharmacia Inc. COI, George C. Kramer, PhD, and Dr.Holcroft, hold rights to a patent that describes the use of hypertonic saline/hyperoncotic solutions for the resuscitation of patients in shock.	N= 166 trauma patients undergoing transport, systolic blood pressure of ≤100 mm Hg, palpable peripheral pulse or a sinus complex on electrocardiography, age≥18 years.	Median (IQR) age: HSD 29 (21-42) years. LR 33 (21-42) years.	Solution of 7.5% sodium chloride in 4.2% dextran 70 solution (HSD) (n=83) vs. 250 mL of lactated Ringer's (LR) solution (n=83).	Follow- up through day 8.	Rate of survival: 32% HSD vs. 16% LR group, p=0.044. Median (IQR) Serum osmolality (mOsm/kg): HSD 333 (319-354) vs. LR 308 (296-333), p=0.0001.	“Administration of small volumes of sodium chloride/dextran 70 before hospitalization increased the blood pressure of severely injured patients more effectively than did lactated Ringer's solution and showed tendencies toward improving survival in the patients with severe head injuries.	Data suggest 7.5% NaCl with Dextran before hospitalization trended towards increased blood pressure in severe TBI injured patients vs. LR.
Ponsford 2008 (score = 4.5)	Resuscitation Evidence for Hypertonic Saline vs Ringer's Lactate with Crystalloid or Colloid or Combination	RCT	No sponsorship or COI.	N=229 with severe blunt head trauma, initial GCS<9 and hypotension.	Mean±SD age: Male 33.8±16.3 years, Female 43.3±23.1 years.	Saline resuscitation: 250 ml intravenous infusion of 7.5% saline [567] vs. conventional fluid management: 250ml intravenous infusion of Ringer's lactate solution. Following infusion, a 10- ml/kg crystalloid, Ringer's	Follow up for 6 months.	Median (IQR) Glasgow outcome scale extended at 6 months male vs. female: 3 (1- 5) vs. 1 (1- 5), p=0.006). No gender differences in GCS score or injury severity scores.	“The study provides no evidence that females fare better than males following severe TBI, suggesting rather that females may fare worse.”	Data suggest females do not do better post TBI when compared to males.



Rhind 2010 (score = 5.5)	Resuscitation Evidence for Hypertonic Saline vs Saline	RCT	No COI. No mention of sponsorship.	N=65 who experience loss of consciousness due to isolated blunt head trauma and/or had a Glasgow Coma Scale (GCS) score <8.	Mean±SD age: HSD 41.8±17.4 years. NS 42.8±18.8 years.	A single prehospital bolus infusion of 250-mL of 7.5% hypertonic saline in combination with 6% dextran-70 (HSD) (n=30) vs. 250-mL of the standard 0.9% normal saline (NS) (n=35).	Follow-up for 48 hours.	Mean±SEM Leukocytes count at 48 hours: HSD: 11.4±0.6, p<0.05 vs. age-matched healthy controls. NS: 11.4±0.5, p<0.05 vs. age-matched healthy controls.	“These findings support an important modulatory role of HSD resuscitation in attenuating the upregulation of leukocyte/endothelial cell proinflammatory/prothrombotic mediators, which may help ameliorate secondary brain injury after TBI.”	Small sample of a larger RCT (Morrison 2011). Data suggest HSD resuscitation may help reduce secondary brain injury post TBI when compared to NS by causing functional changes to inflammatory cells.
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## Resuscitation Evidence for Albumin vs. Saline

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Myburgh 2007 (score = 8.5)	Resuscitation Evidence for Albumin vs Saline	Saline versus Albumin Fluid Evaluation (SAFE Study), Post-hoc RCT	Sponsored by the Victorian Trauma Foundation. Main SAFE study was supported by the Auckland District Health Board and the Australian Commonwealth Department of Health and Aged Care (CSL). COI, Dr. Davies and Dr. Stephens own shares in CSL.	N=515 with traumatic brain injury, score $\leq 13$ on the Glasgow Coma Scale.	Median (IQR) age: Albumin group: 37 (23-55) years, Saline 35 (23-50) years.	4% albumin group (N=255) Vs. Normal saline group (0.9%) (N=260).	Follow up for 24 months.	Death rate at 24 month albumin vs. saline group: 33.2% (RR, 95%CI: 1.63, 1.17-2.26) vs. 20.4%, p=0.003.	"[F]luid resuscitation with albumin was associated with higher mortality rates than was resuscitation with saline."	Posthoc study of critical TBI patients. Data suggest fluid resuscitation with albumin associated with higher mortality (41.8% vs. 22.2%).

Cooper 2013 (score = 5.0)	Resuscitation Evidence for Albumin vs Saline	Post hoc analyses of the SAFE study	Sponsored by CSL Limited. COI, authors received travel refund to present study findings from CSL Limited.	N=321 with TBI, score $\leq 13$ on the Glasgow Coma Scale.		Mean $\pm$ SD age: Albumin 37.8 $\pm$ 17.4 years, Saline 36.0 $\pm$ 15.8 years. 4% albumin group (N=164) Vs. Normal saline group (0.9%) (N=157).	Follow up: 14 days post-randomization.	Mean $\pm$ SD ICP values comparing albumin vs. saline: Day 7: 19.2 $\pm$ 1.07 vs. 15.4 $\pm$ 1.06mm, p=0.01. No differences at day 3 or 14.	"The use of albumin for resuscitation in patients with severe TBI is associated with increased ICP during the first week."	A post-hoc analysis subset of a previous RCT. Data suggest TBI patients treated with albumin have an increased ICP during the first week post injury compared with saline likely associated with the significant increased mortality rate in these patients.
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### Resuscitation Evidence for Dextran-Saline vs. Saline

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Baker 2009 (score = 7.5)	Resuscitation Evidence for Dextran-Saline vs Saline	RCT	No sponsorship or COI.	N= 64 blunt trauma patients with severe head injuries. Coma or loss of consciousness due to isolated blunt head trauma and/or a Glasgow Coma Scale (GCS) score of ≤8.	Mean (range) age: 41.4 (18.8) years.	Single 250-mL intravenous infusion of 7.5% hypertonic saline in 6% dextran 70 (HSD; RescueFlow Bio-Phausia AB, Stockholm, Sweden) (n=31) vs. 250mL of 0.9% isotonic normal saline (n=33) (NS).	Follow up 48 hours.	Overall mortality rate was 16%. No significant differences between both groups. GOS score HSD vs. NS: 3.3±1.4 vs. 3.3±1.4, p=0.87. DRS score: 3.0±4.3 3.9±4.6, p=0.26.	“Pre-hospital resuscitation with HSD is associated with a reduction in serum S100B, NSE, and MBP concentrations, which are correlated with better outcome after severe TBI.”	Data suggest the lowest biomarker levels were seen in survivors resuscitated with HSD and patients with high biomarker levels were seen in NS resuscitated patients with fatal outcomes.

Bulger 2010 (score = 7.5)	Resuscitation Evidence for Dextran-Saline vs Saline	RCT	Sponsored by the National Heart, Lung, and Blood institute. No COI.	N=1331 with blunt trauma, Glasgow Coma Scale scores ≤ 8.	Mean ± SD age Saline/dextran: 38.5 ± 18.6 years, hypertonic saline: 38.6 ± 17.3 years, Normal saline: 39.5 ± 19.2 years.	A single 250ml bolus of: 7.5% saline/6% dextran 70 (hypertonic saline/dextran) (N=373) vs. 7.5% saline (hypertonic saline) (N=355), vs. 0.9% normal saline (N=603).	Follow up: 6 months.	No differences between groups for initial ICP or decreased cerebral perfusion pressure over first 12 hours. Survival at 28 days: 74.3% saline/dextran vs. 75.7% hypertonic saline vs. 75.1% normal saline, p=0.88.	“Among patients with severe TBI not in hypovolemic shock, initial resuscitation with either hypertonic saline or hypertonic saline/dextran, compared with normal saline, did not result in superior 6-month neurological outcome or survival.”	Data suggest hypertonic resuscitation with either hypertonic saline or hypertonic saline/dextran not superior to normal saline for neurological outcomes or survival at 6 months.
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Morrison 2011 (score = 6.5)	Resuscitation Evidence for Dextran-Saline vs Saline	RCT	Sponsorship, in part from the DRDC grant no. w7711-027801/001/TOR (Government of Canada). No mention of COI.	N=107 with head injured, blunt trauma adult patients with a Glasgow Coma Scale of <9.	Mean±SD age: HSD 46±21years vs. 43±21 years.	A single dose of 250mL of hypertonic saline and dextran (HSD) (n=50) Vs. Control group receiving 250 mL normal saline (NS) intravenously (n=57).	Follow up for 12 months.	Median disability rating scale (IQR): HSD vs. NS: 0.5 (0, 2.9) vs. 1.5 (0, 7).	“It is feasible to conduct a prehospital randomized controlled trial with HSD for treatment of blunt trauma patients with head injuries; however, consent for neurofunctional outcomes in this cohort is problematic and threatens the feasibility of definitive trials using these potentially meaningful end points.”	High dropout rate (48% completed trial). Data suggest HSD not superior to NS in blunt head injury patients for survival or better neurological outcomes at 30 days.
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Vassar 1993 (score = 6.5)	Resuscitation Evidence for Dextran- Saline vs Hypertonic Saline- Dextran vs Lactated Ringers	RCT	Sponsorship, supported in part by a grant from Kabi- Pharmacia, Piscataway, Nf. COI, George C. Kramer, PhD, and Dr.Holcroft, through the University of California-Davis, Sacramento, hold rights to a patent that describes the use of combined 7.5% sodium chloride and dextran solutions for the resuscitation of patients in shock.	N=194 trauma patients undergoing transport, systolic blood pressure of ≤90 mm Hg.	Mean±SD age: LR 37±18, HS 31±13, HSD 6% 30±12, HSD 12% 34±15 years.	250 mL of: lactated Ringer's (LR) solution Vs. 7.5% sodium chloride (hypertonic saline solution [HS]) vs. 7.5% sodium chloride combined with 6% dextran 70 (HSD-6%) vs. 7.5% sodium chloride combined with 12% dextran 70 (HSD-12%).	Follow- up for 7 days.	Mean±SD change in systolic blood pressure: HSD vs. lactated Ringer's solution group (34±46 vs. 11±49 mmHg, p<0.03).	“Prehospital infusion of 250 mL of 7.5% sodium chloride is associated with an increase in blood pressure and an increase in survival to hospital discharge compared with survival predicted by the MTOS norms. Patients with low baseline Glasgow Coma Scale scores seem to benefit the most from 7.5% sodium chloride resuscitation. Hypertonic saline solution without added dextran 70 is as effective as the more expensive solutions that contain dextran 70.”	Data suggest addition of dextran to hypertonic saline solutions is not superior to hypertonic saline alone for resuscitation of trauma patients with SBP <90 resuscitated either in the field or during helicopter transport.
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Vassar 1993 (score = 6.0)	Resuscitation Evidence for Dextran- Saline vs Saline	RCT	Sponsorship, supported in part by a grant from Kabi- Pharmacia, Piscataway, Nf. No mention of COI.	N=258 trauma patients transported by ambulance to the hospital, systolic blood pressure of ≤90 mm Hg.	Mean±SD age: NS 31±12, HS 32±15, HSD 31±14 years.	250 mL of: normal saline (NS) (n=84) Vs. 7.5% NaCl (HS, for hypertonic saline) (n=85) vs. 7.5% NaCl in 6% dextran 70 (HSD) (n=89).	32 month trial.	Indicators of survival: ISS (p<0.0005), RTS (p<0.004) and age (p<0.01).	“The addition of a colloid, in the form of 6% dextran 70, did not offer any additional benefit, at least in this setting of rapid urban transport.”	Data suggest addition of dextran to hypertonic solution did not add benefit in prehospital resuscitation.
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## Resuscitation Evidence for Saline

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Roquilly 2008 (score = 7.5)	Resuscitation Evidence for Saline	RCT	COI, Karim Asehnoune and Yvonnick Blanloeil have received honoraria from Braun Medical for public speaking. No mention of sponsorship.	N=42 with severe traumatic brain injury (TBI) (Glasgow Coma Scale score ≤8) on mechanical ventilation within the first 12 hours after brain injury.	Mean (IQR) age: Saline 47 (28-57) years. Balanced 49 (27-77) years	Balanced group (allocated solutions, crystalloids: Isofundine/HES: Tetraspan; B Braun Medical, Melsungen, Germany) (n=21) vs. Saline group (allocated solutions, crystalloids: 0.9% saline solution/HES: HEAfusine, B Braun Medical) (n=21).	Follow-up for 48 hours.	Hyperchloraemic acidosis: 19 (95%) in the saline group vs. 13 (65%) in the balanced group presented with within the first 48 hours (hazard ratio = 0.28, 95% CI: 0.11-0.70; p=0.006.	"[B]alanced solutions reduce the incidence of hyperchloraemic acidosis in brain-injured patients compared to saline solutions. Even if the study was not powered sufficiently for this endpoint, intracranial pressure did not appear different between groups."	Pilot study (small sample). Data suggest balanced fluid resuscitation solutions reduce hyperchloraemic acidosis in brain injured patients compared to saline solution.

Ponsford 2008 (score = 4.5)	Resuscitation Evidence for Hypertonic Saline vs Ringers Lactate with Crystalloid or Colloid or Combination	RCT	No sponsorship or COI.	N=229 with severe blunt head trauma, initial GCS<9 and hypotension.	Mean±SD age: Male 33.8±16.3 years, Female 43.3±23.1 years.	Saline resuscitation: 250 ml intravenous infusion of 7.5% saline [567] vs. conventional fluid management: 250ml intravenous infusion of Ringer's lactate solution. Following infusion, a 10-ml/kg crystalloid, Ringer's lactate solution, or a colloid solution, or both was administered.	Follow up for 6 months.	Median (IQR) Glasgow outcome scale extended at 6 months male vs. female: 3 (1-5) vs. 1 (1-5), p=0.006. No gender differences in GCS score or injury severity scores.	"The study provides no evidence that females fare better than males following severe TBI, suggesting rather that females may fare worse."	Data suggest females do not do better post TBI when compared to males.
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## Hyperbaric Oxygen Therapy (HBO or HBOT)

Hyperbaric oxygen has been used as a treatment for TBI [385, 571-580].

### Hyperbaric Oxygen Therapy (HBO or HBOT)

#### Sometimes Recommended.

Hyperbaric oxygen therapy is sometimes recommended for the treatment of TBI patients.

*Strength of Evidence* – **Mild TBI: Moderately Not Recommended, Evidence (B)**  
**Moderate TBI: No Recommendation, Insufficient Evidence (I)**  
**Severe TBI: Moderately Recommended, Evidence (B)**

*Level of Confidence* – **Moderate**

<i>Indications:</i>	Acute severe head injury (Glasgow Coma Scale score of 9 or less) admitted to a Level I trauma center in the highest quality study showing efficacy [581]. Not recommended in mild TBI and no recommendation in moderate TBI.
<i>Benefits:</i>	Improved outcomes, earlier improvements in Glasgow Coma Score. Reduced mortality in one study with randomization within 24 hrs. of severe TBI [582]
<i>Harms:</i>	Negligible.
<i>Frequency/Dose/Duration:</i>	100% oxygen to 1.5 atm absolute (ATA) at a rate of 1 psi/min for 60 minutes every 8 hours for 2 weeks or until brain dead or could consistently respond to commands [581].
<i>Indications for Discontinuation:</i>	Brain dead, able to consistently respond to commands [581].
<i>Rationale:</i>	The top three quality studies all showed negative effects of HBO for treatment of mild TBI/post-concussive symptoms [583] [584] [585]. Three moderate quality trials among severe TBI patients found significant improvements in mortality in the HBO group [581], 10; [586, 587]. Hyperbaric Oxygen Therapy is not invasive, usually has minimal adverse effects, is high cost, has evidence of treatment efficacy for severe TBI, and is recommended. There is quality evidence of lack of efficacy for treatment of mild TBI and so it is not recommended for that indication. There is no quality evidence and thus no recommendation for treatment of moderate TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: hyperbaric oxygen therapy, HBO, HBOT, traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 100 articles in PubMed, 1062 in Scopus, 14 in CINAHL, 17 in Cochrane Library, 1790 in Google Scholar, and 0 from other sources. We considered for inclusion 13 from PubMed, 1 from Scopus, 0 from CINAHL, Cochrane Library, Google Scholar, and 0 from other sources. Of the 13 articles considered for inclusion, 10 randomized trials and 3 systematic studies met the inclusion criteria.

## Evidence for the Use of Hyperbaric Oxygen Therapy (HBO or HBOT)

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age / Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Miller 2015 (6.5)	Hyperbaric Oxygen Therapy	Case Control	Sponsored by US Army Medical Materiel Development Activity, Naval Health Research Center, Army Contracting Command and US Army Office of the Surgeon General. No mention of COI.	N = 72 with TBI, military personnel. Mild TBI, symptoms at least 4mo. after TBI.	Mean age of 31.4 years. 3 females, 69 males.	Standard Care group, no-chamber sessions (N = 23) vs HBO group plus TBI care, assigned intervention (N = 24) vs Sham group plus TBI care, assigned intervention (N = 25).	Follow up time not mentioned	The group randomized to no supplemental chamber intervention showed no improvement during the 3-month observation period. The HBO group improved symptomatically with a mean change score of 1.2 (p = 0.04) on the RPQ-3 scale and 0.5 (p = 0.008) on the total RPQ. The sham group also improved with a score of 1.5 (p = 0.04) on the RPQ-3 scale and 5.4 (p = 0.008) on the total RPQ.	"Among service members with PCS, HBO showed no benefits over an air sham compression procedure, but symptoms in both groups improved compared with mTBI care without supplemental chamber interventions."	Outcome measures derived from questionnaire. Data suggest lack of efficacy of hyperbaric oxygen on post-concussion symptoms when compared to sham suggesting any observed improvements were not oxygen mediated.
Walker 2014 (6.0)	Hyperbaric Oxygen Therapy	RCT	Sponsored by a Defense Advanced Research Projects Agency grant, US Navy Bureau of Medicine and Surgery for contract funding temporary duty requirements, and the US Army Medical Materiel Development Activity for	N=60 Marine patients with combat-related mild TBI and PCS persisting for 3 to 36 months	Mean age: 23.2±2.9 5 years; 60 males, 0 females	2.0 ATA Group: (n=21) breathed 10.5% oxygen (balance 89.5% nitrogen) at 2.0 ATA vs 1.5 ATA Group: (n=18) the 1.5-ATA oxygen group breathed 75% oxygen (balance 25% nitrogen) at	Follow up at baseline and 10 weeks	No differences between groups were observed in WAIS-III Working memory index, Stroop, BVMT-R Delayed Recall total, or BVMT-R Recognition discrimination index. Post hoc t-test showed that 1.5 ATA group recognition total hits compared to 2.0 ATA group was p=0.006 and p=.035 compared to Sham group.	"These results do not support the use of HBO2 to treat cognitive, balance, or fine motor deficits associated with mTBI and PCS."	Data suggest lack of efficacy. No benefit on either cognitive or psychomotor performance measures compared to sham.

			end-of-study contract funding. Drs Franke's and Walker's efforts were additionally supported, in part, through contracts from the Defense and Veterans Brain Injury Center. No COI.			2.0 ATA vs Sham Group: (n=21) the 2.0-ATA oxygen group breathed pure oxygen (0% nitrogen) at 2.0 ATA				
Rockswold 2013 (score=5.5)	Hyperbaric (HBO2) & Normobaric Hyperoxia (NBH)	RCT	Sponsored by the National Institute of Neurological Disorders and Stroke Hyperbaric and Normobaric Oxygen in Severe Brain Injury Grant.	N=42 patients with severe TBI with GCS at or less 8 after resuscitation. Randomized within 24 hrs of injury.	Mean age 65; 33 males, 9 females.	Group 1 (N=20) received HBO2/NBH treatment which consisted of 100% FiO2 for 60 min at 1.5 atmospheres absolute (ATA) followed by 3 hours of 1.0 ATA vs. Group 2 (N=22) received standard care (not detailed)	Follow up at baseline, and 6 months.	Mortality rate group 1 vs group 2 at 6 months: 16% vs 42% (p=0.0482). Number with Favorable outcome on Glasgow Outcome Scale (GOS), group 1 vs 2: 14-19 (74% vs 8/21 (38%) (p=0.0239).	"The combined HBO2/NBH treatment significantly improved markers of oxidative cerebral metabolism in relatively uninjured brain tissue but, importantly, also in pericontusional tissue. The combined HBO2/NBH treatment reduced intracranial hypertension and thereby decreased the therapeutic intensity of treatment of intracranial hypertension."	Data suggest that combination therapy of HBO2/NBH is superior to either HBO2 or NBH alone for improving markers of oxidative metabolism, reducing intracranial hypertension and cerebral toxicity.
Rockswold 1992 (5.5)	Hyperbaric Oxygen Therapy	RCT	Sponsored by the Minneapolis	N = 168 with acute severe head injury	Mean age of 31.5	Hyperbaric oxygen – compression	2 weeks	Mean ± SD peak ICP in each treatment group: hyperbaric oxygen and	"Hyperbaric oxygen treatment dramatically reduced	Data suggest HBO did not increase numbers of

			Medical Research Foundation. No mention of COI.	(Glasgow Coma Scale score of 9 or less) admitted to a Level I trauma center.	years; 125 males and 43 females.	, 100% oxygen to 1.5 atm absolute (ATA) at a rate of 1 psi/min for 60 minutes every 8 hours for 2 weeks or until brain dead or could consistently respond to commands intracranial pressure (ICP), collected every 15 minutes during the 60-minute treatment and after hourly for 7 hours (N = 84) vs Controls ICP collected every hour (N = 84).		myringotomy (22.1±11.7) v. only hyperbaric oxygen (33.0±20.6), p<0.05) v. control (30.3±24.3), p < 0.05. Patient mortality data at 12 months: hyperbaric oxygen 17% v. control 32%, (p = 0.04). Favorable outcome at 12 months: NS.	the mortality rate among the severely head-injured patients assigned to receive it."	patients with favorable outcome defined by these authors as good recovery and moderate disability and there was no significant difference between groups. However the HBO treated groups had increased survival (mortality was 17% in HBO group vs. 34% in control group).
Rockswold 2010 (4.5)	Hyperbaric Oxygen Therapy	RCT	Sponsored by Minneapolis Medical Research Foundation Bridging Fund,	N = 74 with severe traumatic brain injury (TBI), GCS score ≤ 8 after	Mean age of 35 years; 58 males and 11 females.	HBO <sub>2</sub> , 100% FiO <sub>2</sub> (fraction of inspired oxygen) delivered for 60 minutes at 1.5 ATA	24 -hours	Cerebral blood flow (CBF): for 6 hours after HBO <sub>2</sub> - elevated by 26% vs controls, (p = 0.0061) At 6 hours after treatment, cerebral metabolic rate of oxygen	"Hyperbaric O <sub>2</sub> has a more robust posttreatment effect than NBH on oxidative cerebral metabolism related to its ability to	Data suggest HBO had a significantly better posttreatment effect compared to normobaric hyperoxia (NBH).

			National Institute of Neurological Disorders and Stroke, and the Western Family Foundation. No mention of COI.	resuscitation at a Level I trauma center.		for 3 treatments (N = 26) vs Controls or normobaric hyperoxia or (NBH), 100% FiO2 given for 3 hours at 1.0 ATA for 3 treatments (N = 21) vs Standard care (N = 22).		(CMRO2): increased by 32% for HBO2 vs controls (p = 0.0103). After 6 hours ventricular CSF lactate levels, decreased in the NBH vs controls, (p < 0.05). At 5 hours; dialysate lactate levels: significantly decreased by 13% in HBO2 vs controls, (p = 0.0170). NBH levels decreased by 7% vs controls, NS. Microdialysate lactate/pyruvate (L/P) ratios: post treatment decreased by 10% for HBO2 (p < 0.0001) and by 3% for NBH, (p = 0.0037) vs controls. Intracranial pressure (ICP): HBO2 was lower than control after treatment until the next treatment (p = 0.0010). TIL score: decreased from pre to post treatment for HBO2 compared to control, (p = 0.0006).	procude a brain tissue PO2 ≥ 200 mm Hg."	ICP was not reduced in NBH group but was treated less rigorously in HBO group.
Ren 2001 (4.0)	Hyperbaric Oxygen Therapy	RCT	No mention of sponsorship or COI.	N = 55 with severe brain injury (SBI), Glasgow Coma Scale (GCS) ≤ 8.	Mean age of 35.3 years; 42 males and 13 females.	HBO for 40-60 minutes with 10 minute breaks each time, 10 times of the treatment equaled 1 therapy course; total 3-4 courses of treatment (N = 35)	6 - months	GCS score after 3 courses: treatment group was higher than control group, p<0.01. Glasgow Outcome Scale (GOS) prognosis evaluated 6 months after injury: good recovery or mild disability (29 treatment patients v. 6 controls), p<0.01; middle-severe disability (6 treatment patients v. 13 controls), p < 0.001.	"[H]BO treatment benefits recovery of brain function, improves prognosis, GCS, BEAM and GOS and reduces the mortality rates of SBI patients."	Data suggest HBO improved GCS, BEAM and GOS in severely brain injured patients.

						vs Control receiving dehydrating, cortical steroid and antibiotic therapy (N = 20).				
Rockswold 2001	Hyperbaric Oxygen Therapy	RCT	Sponsored by Grant to Dr. Rockswold from the National Institute for Neurological Disorders and Stroke. No mention of COI.	N = 37 with closed head brain injuries.	Mean age of 36 years. 10 females, 27 males	HBO group, 100% oxygen, 1 psi/minute for 15 minutes (N = 32) vs Class A group (N = 5).	24 hours up to 5 more days.	AVDO2 measurements were compared by both groups. There was significant difference between values for Session 1 and the rest of the sessions. Both before and after treatment values for session 1 were higher when compared to other sessions (p = 0.042). Intracranial pressure values higher than 15 mmHg were decreased 1 hour and 6 hours after HBO.	"The increased CMRO2 and decreased CSF lactate levels after treatment indicate that HBO may improve aerobic metabolism in severely brain injured patients."	Not an RCT. Data suggest improved aerobic metabolism in severely brain injured patients may be the result of shorter but more frequent HBO treatments which may successfully decrease CSF lactate and increase CMRO2.

## Nutritional Support

### Nutritional Support in TBI Patients

#### Recommended.

Patients with TBI commonly develop nutritional deficits such as hypercatabolism, hypermetabolism, and glucose intolerance [633]. Most severe TBI patients experience altered/delayed gastric emptying at least one week post injury and some experience this for considerably longer periods of time which may affect their ability to tolerate enteral feedings.

Nutritional support is usually not required in TBI patients other than select, severe TBI patients. Those who are unable to eat or adequately protect the airway need nutritional support. If the GI tract is functional, then the preferred treatment is a gastric or other enteric feeding tube. Using the functioning GI tract is far preferable to total parenteral nutrition as the GI tract helps to maintain better nutritional status as well as improving serum electrolyte control [634] showed patients who initially had rapid or normal gastric emptying tolerated full-strength full-rate feedings significantly earlier compared with those who experienced delayed gastric emptying.

Total parenteral nutrition is needed if there is an estimate beyond several days for use of the GI tract due to either: [170] an inability to use the GI tract (e.g., injured abdomen, abdominal surgery, prior disease) or (2) delayed gastric emptying sufficiently severe to preclude adequate nutrition using an enteric feeding tube.

**There are no specific nutritional support recommendations as the requirements of the individual patient are wide-ranging and beyond the scope of this guideline.**

## Evidence for TPN in TBI Patients

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Acosta-Escribano 2009 (score=4.0)	Gastrointestinal Complications	RCT	No mention of sponsorship or COI.	N=104 patients with Closed Head Injury.	Mean age: 38.4±19.5 years. 90 males, 14 females.	TPF: Transpyloric feeding (N=50) given diet of 25 kcal kg <sup>-1</sup> day <sup>-1</sup> for 30 days. GF: gastric feeding (N=54) given diet of 25 kcal kg <sup>-1</sup> day <sup>-1</sup> for 30 days.	30 days	Mean efficacious volume of diet for TPF vs GF, (92±7 vs. 84±15% p < 0.01)TF patients had a (14%) rate of Gastrointestinal complications. GF group had a (27%) rate. (OR: 0.2, 95% CI 0.06–0.4; p = 0.001). TPF patients had a (7%) rate of increased gastric residuals. GF group had a (28%) rate. (OR 0.2, 95% CI 0.04–0.6; p = 0.003).	“Enteral nutrition delivered through the transpyloric route reduces the incidence of overall and late pneumonia and improves nutritional efficacy in severe TBI patients.”	Data suggest that the TPF-TBI group experienced improved nutritional efficacy and less overall as well as late onset pneumonia compared to the GF-TBI group

## Evidence for Enteral Nutrition in TBI Patients

Taylor 1999 (score=4.0)	Enteral Nutrition	RCT	Sponsored, in part, by the South and West Research and Development Directorate, Bristol, UK. No	N=82 patients suffering with head injury and requiring mechanical ventilation.	Median age group 1, 34, group 2, 28; no mention of sex.	Group 1 (N=4) patients received standard enteral nutrition (EN) initially at estimated metabolic rate vs Group 2 (N=41) patients received	Follow-up at baseline, 1 week, 3 months, and 6 months.	Percentage of energy & nitrogen, at 1 week, group1 vs group 2: 59.2% vs 36.8% (p=0.008) & 68.7% vs 37.9% (p<0.001). Good neurological outcome at 3 months post injury, group 1 vs group 2: 61% vs 39% (p=0.08), risk ratio 1.6 (0.99-2.5).	“In conclusion, enhanced EN increased the percentage of estimated energy and nitrogen requirements delivered during the first week after head injury. This improvement in EN appears to speed up	Data suggest a trends toward early EN accelerating recovery in head injured patients.
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			mention of COI.			EN at 15 mL/hr initially and increase by 15 mL/hr until estimated energy and nitrogen needs met.			neurologic recovery but does not change the ultimate outcome. In addition, enhanced EN reduces the number of patients suffering infective and total complications.”	
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## Acute Therapeutic Procedures

Prophylactic hyperventilation therapy has been used to improve intracranial pressure (ICP) and neurologic functioning. Intracranial pressure is increased in 50% to 75% of patients with severe head trauma [635, 636] and the duration of increased intracranial pressure >20 mm Hg has been found to be strongly correlated with worse outcomes [637].

### Hyperventilation

#### Recommended.

Hyperventilation is selectively recommended for the treatment of patients with TBI.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Moderate**

<i>Indications:</i>	Selectively recommended for brief control of severe TBI with increased intracranial pressure (usually >20mmHg), or perfusion pressure <70mmHg until other more effective measures may take effect. Addition of tromethamine may reduce adverse effects [638, 639].
<i>Benefits:</i>	Improved control of intracranial pressure, which may improve survival and neurological outcomes.
<i>Harms:</i>	Respiratory alkalosis, seizures, muscle spasms
<i>Frequency/Dose/Duration:</i>	Use until more effective measures are in place.
<i>Indications for Discontinuation:</i>	Perfusion pressure and/or intracranial pressure normalized. May be discontinued after other measures effective.
<i>Rationale:</i>	Hyperventilation has been historically used for TBI and empirically reduces intracranial pressure on a short-term basis. As this treatment has long been in place, this somewhat impairs the size and quality of the evidence base. Nevertheless, there are no quality studies showing efficacy of Hyperventilation for treatment of TBI. Hyperventilation is not invasive, has multiple adverse effects, is high cost, has empirical evidence of short term efficacy for treatment of TBI and thus is selectively recommended for treatment of increased intracranial pressure pending efficacy of more effective measures.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: hyperventilation, traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 67 articles in PubMed, 268 in Scopus, 24 in CINAHL, 2 in Cochrane Library, 7800 in Google Scholar, and 0 from other sources. We considered for inclusion 12 from PubMed, 0 from Scopus, CINAHL, Cochrane Library, Google Scholar, and 0 from other sources. Of the 12 articles considered for inclusion, 5 randomized trials and 5 systematic studies met the inclusion criteria.

## Evidence for the Use of Hyperventilation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Muizelaar 1991 (7.0)	Hyperventilation	RCT	Sponsored by grant from the National Institutes of Health. Additional support provided by the Richard Roland Reynolds Neurosurgical Laboratories and the Lind Lawrence Fund. No mention of COI.	N = 113 with TBI.	Median age 27 / 26 / and 25 for Control / HV + THAM / and Controls; 78 males and 35 females.	Hyperventilation or HV group (N = 36) vs Hyperventilation or HV + Buffer Tromethamine or THAM group (N = 36) vs Control group or normoventilation (N = 42)	3, 6, and 12 months	At 12 months, fewer patients with favorable outcome in HV group vs control, ( $p < 0.05$ ). At 12-months, 34% of the controls died vs 25% in the HV groups.  HV group fared worse than the corresponding control group, ( $p < 0.03$ ). Hourly ICP average was below the treatment threshold of 25 mm Hg for all groups during the 5-day period of observation. Those treated with HV + THAM exhibited the most stable ICP course with minimal variability vs control and HV groups.	"When sustained hyperventilation becomes necessary for ICP control, its deleterious effect may be overcome by the addition of THAM."	Data suggest that in severely head injured patients, sustained, hyperventilation may become deleterious and be decreased by addition of THAM.
Bourgoin 2003 (7.0)	Hyperventilation	RCT	No mention of sponsorship or COI.	N = 25 with severe head injury.	Aged 16-75 years, 19 males and 6 females.	Sedation with a continuous infusion of ketamine-midazolam (N = 12) vs Continuous infusion of sufentanil-midazolam (N = 13).	4-days	The average infusion rates during 4-days of sedation: $82 \pm 25$ mg-kg <sup>-1</sup> min <sup>-1</sup> ketamine and $1.64 \pm 0.5$ mg-kg <sup>-1</sup> min <sup>-1</sup> midazolam in the ketamine group and $0.008 \pm 0.002$ mg-kg <sup>-1</sup> min <sup>-1</sup> sufentanil and $1.63 \pm 0.37$ mg-kg <sup>-1</sup> min <sup>-1</sup> midazolam	"The results of this study suggest that ketamine in combination with midazolam is comparable with a combination of midazolam-sufentanil in maintaining intracranial pressure and cerebral perfusion	Data suggest comparable efficacy.

								in the sufentanil group. The number of the intracranial pressure elevations similar in both groups. Heart rate values were significantly higher in the ketamine group on therapy days 3 and 4, (p < 0.05).	pressure of severe head injury patients placed under controlled mechanical ventilation.”	
Wolf 1993 (4.5)	Hyperventilation	RCT	Sponsored by grant from the National Institutes of Health. No mention of COI.	N = 149 with acute head injury.	Aged 16-75 years, 123 males and 26 females.	Tromethamine or THAM group, 0.3-M solution (N = 73) vs Control group received intravenous electrolyte solution (N = 76).	3, 6 and 12 months	Day 4, pCO <sub>2</sub> lower vs those in THM group, (p < 0.005). At 3 months, 47.4% and 35.6% THAM-treated patients had good outcomes, and only 40% of the posturing patients had good results vs 66% of those with a best motor response score of 4 or 5, (p < 0.05). First 48 hours – 18.2% were above 20 mm Hg in the THAM group vs 34.2% in control, (p < 0.05).	“[T]HAM ameliorates the deleterious effect of prolonged hyperventilation, may be beneficial in ICP control, and warrants further study as to the dose and timing of administration”.	Data suggest addition of THAM in severely head injured patients may be of benefit in the control of ICP thus reducing the deleterious effect of prolonged hyperventilation.

Induced hypothermia has been used to slow down some of the brain changes that cause continuing damage after a traumatic brain injury. However, induced hypothermia poses some risks as it increases the risk of pneumonia and heart complications and can present blood flow problems [396, 640-648] and [649-678].

## Induced Hypothermia

### Not Recommended.

Induced hypothermia is not recommended for the treatment of TBI patients.

*Strength of Evidence* – **Not Recommended, Evidence (C)**

*Level of Confidence* – **Moderate**

*Rationale:*

There are multiple moderate quality studies assessing the utility of Induced Hypothermia for treatment of TBI [651-653, 655-661, 664, 665, 667, 669, 670, 673-675, 677-679]. While there are some lower quality studies that suggested efficacy, all of the 3 highest quality studies show a lack of efficacy [651, 652, 655] and two were terminated early because of futility. There is no evidence of efficacy for prophylactic treatment. Induced Hypothermia is not invasive, has multiple adverse effects, is moderate cost, has quality evidence of a lack of utility in treatment of TBI and thus is not recommended for treatment of TBI. This may be a treatment option for management of intracranial pressure when other treatments with documented efficacy have failed.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: hypothermia, induced, induced hypothermia, therapeutic hypothermia, protective hypothermia, targeted temperature management, traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral, trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 543 articles in PubMed, 1,904 in Scopus, 60 in CINAHL, 166 in Cochrane Library, 3,220 in Google Scholar, and 37 from other sources. We considered for inclusion 8 from PubMed, 2 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 37 from other sources. Of the 47 articles considered for inclusion, 29 randomized trials and 16 systematic studies met the inclusion criteria.

## Evidence for the Use of Induced Hypothermia

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Harris 2009 (7.0)	Induced hypothermia	Prospective RCT	No COI. No mention of sponsorship.	N = 25 adults with severe traumatic brain injury.	3 female, 22 male  Mean age 35.4 ± 17.3 years	Treatment group patients received a cooling cap and were treated with selective cerebral hypothermia for 24 hrs. then rewarmed over 24 hrs (N = 12)  vs.  Control group patients who did not receive a cooling cap. (N = 13).	Data collected every 15 mins for the first 2 hrs of treatment and then every hour for 70 more hrs  28 days	After hour 3, the treatment group had a significantly lower temperature than the control group (P < 0.05) at all time points except for hours 4 (P = 0.08) and 6 (P = 0.08). Only 2/11 patients in the treatment group achieved the target temperature of 33°C. There was no significant intergroup difference in mortality rate or in time to death.	"[T]he Discrete Cerebral Hypothermia System cooling cap is not beneficial for the management of TBI."	Small sample. Data suggest groups equal (in) efficacy.
Andrews 2015 (7.0)	Induced Hypothermia	RCT	Supported by the National Institute for Health Research Health Technology Assessment Program, the European Society of Intensive Care	N = 387 with TBI, intracranial-pressure > 20 mm HG for at least 5 minutes within 10 days post-injury	No gender distribution described  Mean age for control group 36.7 ± 14.9 years, mean age for hypothermia	Control group – mannitol, hypertonic saline, inotropes (keep cerebral perfusion pressure ≥ 60 mm Hg) (n = 192)  Vs.  Hypothermia	28 days post-admission, 6 months	Adjusted OR for GOS-E score = 1.53, (95% CI 1.02-2.30, P=0.04), pointing towards a more negative outcome in hypothermia group compared to control.	"In patients with an intracranial pressure of more than 20 mm Hg after traumatic brain injury, therapeutic hypothermia plus standard care to reduce intracranial	Open label study. Enrollment stopped due to safety concerns in 2014. Some data suggest lack of efficacy.

			Medicine, the University of Edinburgh and NHS Lothian. Andrews and Rhodes received lecture fees from C. R. Bard and Integra LifeSciences.		a group 37.4 ± 15.4 years	group – same treatment options as control group along with induced hypothermia therapy (n = 195)		Favorable outcome (GOS-E score 5-8) in 26% of hypothermia group, 37% of control group (P=0.03).	pressure did not result in outcomes better than those with standard care alone."	
Clifton 2011 (6.5)	Induced hypothermia	RCT	Funded by grant from the National Institute of Neurological Disorders and Stroke. No COI.	N = 97 with severe brain injury	No gender distribution described  Mean age hypothermia group 26 ± 9 years, mean age normothermia group 31 ± 11	Normothermia group patients were maintained at 37°C (N = 45)  vs.  Hypothermia group patients were maintained at 35°C (N = 52)	2 weeks, 4 weeks, 3 month, and 6 months post-injury	Outcome was poor in 31 of 52 patients in the hypothermia group and 25 of 56 in the normothermia group (relative risk [RR] 1.08, 95% CI 0.75-1.53; P = 0.67). Twelve patients died in the hypothermia group and 8 died in the normothermia group (RR 1.30, 95% CI 0.58-2.52; P = 0.52). Patients in the normothermia group needed more interventions for raised intracranial pressure (P = 0.002) and had	"We found no significant difference in outcome in patients treated with hypothermia compared with those treated with normothermia; however, patients in the hypothermia group did have a significantly higher number of episodes of increased intracranial pressure than those in the normothermia group."	High dropout rate for final 6 month analyses. Track terminated early for futility.

								more interventions in total (P = 0.0006). Patients in the hypothermia group seemed to have negative cumulative fluid balances less often (P = 0.08) and had higher cumulative fluid balances (P = 0.01).		
Maekawa 2015 (6.0)	Induced Hypothermia	RCT	No COI. Supported by grants from the Japanese Ministry of Health, Labour and Welfare and the Japanese Human Science Association 2002-2004.	N = 148 with severe TBI, GCS 4-8	45 female, 103 male  Mean age for hypothermia group 39±19 years, fever control group 39±18 years	Therapeutic hypothermia (32-34°C) (n=98)  Vs.  Fever control (35.5-37°C) (n=50)	6 months	53% of those in therapeutic group and 48% of those in fever control group had poor neurological outcomes at six months. Likelihood of poor neurological outcome (relative risk RR = 1.24, 95% CI 0.62-2.48) and likelihood of mortality (RR 1.82, 95% CI 0.82-4.03) were not statistically significant between the groups.	"Prolonged TH (≥72 h) for patients with severe TBI together with tight hemodynamic management and slow rewarming (<1.0°C/day) did not improve neurological outcomes or mortality compared with strict fever control. However, the CIs for the primary outcome were wide, and do not exclude either benefit or harm for MTH.	Data suggest that tight hemodynamic control and gradual rewarming with prolonged hypothermia did not increase outcomes or decrease mortality vs strict temperature control.

Marion 1993 (5.5)	Induced hypothermia	Preliminary RCT	No mention of COI. Funded by grants from the Brain Trauma Foundation and the National Institute of Neurological Disorders and Stroke	N = 40 with a severe closed head injury.	6 female, 34 male  Mean age for normothermia group 32.1 years, hypothermia group 31.9 years	The hypothermia group was cooled to a brain temperature of 32 to 33°C using cooling blankets and cold saline gastric lavage maintained for 24 hrs and rewarmed to 37 to 38°C over 12 hrs. (N = 20) vs. the normothermia group was maintained at 37 to 38°C (N = 20).	The last follow-up was at 3 months.	During the cooling period, the hypothermia group had a significantly lower mean ICP (P < 0.004). In the first 36 hrs. after injury revealed that the incidence of hourly ICP measurements over 20 mm Hg was significantly lower in the hypothermia group (13% of time) vs. normothermia group (25% of time, P < 0.001). In both groups the cerebral metabolic rate for oxygen declined in the first 5 days after injury, but the decline was greater in the normothermia group (p < 0.001). During hypothermia, the global cerebral blood flow values in the hypothermia group were	"[H]ypothermia significantly reduces ICP and CBF during the period of cooling and that no rebound increase occurs in these parameters after rewarming."	Data suggest a trend towards better outcomes with hypothermia.
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								significantly lower vs normothermia (P < 0.001).		
Marion 1997 (5.5)	Induced hypothermia	RCT	No mention of COI. Funded by grant from the National Institute of Neurological Disorders and Stroke.	N = 82 with severe closed head injuries.	13 female, 69 male  Mean age for hypothermia group 31 ± 12 years, normothermia group 35 ± 15 years	Moderate hypothermia group was cooled using cooling blankets to a rectal temperature of 33°C and was kept between 32-33°C for 24 hrs. Then was rewarmed passively for the 12 hrs. to 37-38.5°C at a rate no greater than 1°C per hr. (N = 80) vs. Normothermia group was kept above 37°C (N = 42).  All patients were given continuous infusions of vecuronium bromide, 10 mg/hr and fentanyl citrate, 50-100 µg/hr.	Follow-ups were at 3, 6, and 12 months.	Three months after injury 15 (38%) in the hypothermia group had a score on the Glasgow Outcome Scale of 4 or 5 as compared with 7 (17%) in the normothermia group (P = 0.03). Patients with more severe coma scores benefited from hypothermia more than did patients with coma scores of 3 or 4 in the Glasgow coma, whereas those with scores of 5-7 did. Among the patients with the higher scores, 16 (73%) in the hypothermia group and 9 (35%) in the normothermia group had a good outcome at 6 months (P = 0.008).	"[T]reatment with moderate hypothermia (a temperature of 32 or 33°C) for 24 hours, initiated soon after severe traumatic brain injury, significantly improved the outcomes at three and six months in patients without flaccidity or decerebrate rigidity (those with Glasgow coma scores of 5 to 7) on initial evaluation."	Data suggest there may be improved GCS and neurological outcomes from the use of moderate hypothermia for 24 hours post injury.

Mayer 2004 (5.5)	Induced hypothermia	RCT	Funded by grant from Medivance Inc. (SAM). Mayer received speaking honoraria from Medivance, Inc.	N = 53 admitted to the Columbia-Presbyterian Medical Center Neurologic Intensive Care Unit.	30 female, 17 male  Mean age for Arctic Sun group 54 ± 15 years, SubZero group 51 ± 16 years	Group 1 treated with an arctic sun temperature management system keeping the core body temp at 37°C (N = 26). Vs. Group 2 treated with a conventional water-circulating cooling blanket placed over the patient with the blanket set at 4°C (N = 27).	The last follow-up was at discharge of the patient.	The arctic sun resulted in a 75% reduction in fever burden compared with the sub-zero blanket, from 16.1 to 4.1°C-hrs (P = 0.001). The arctic sun also reduced the time febrile by 81%, which resulted in a 20 times increase in normothermic, a 36% increase in the likelihood of attaining normothermia, and a 73% reduction in time to attain normothermia. Minute to minute measurement of body temperature averaged over 15-min intervals were lower in the arctic sun group (P = 0.008).	"The Arctic Sun Temperature Management System is superior to conventional cooling-blanket therapy for controlling fever in critically ill neurologic patients."	Data suggest Arctic sun temp Mgt system may be superior to conventional cooling blanket therapy.
Qiu 2007 (5.0)	Induced hypothermia	RCT	Funded by the Health Bureau of Hangzhou, Zhejiang Province. No	N = 80 with severe traumatic brain injury.	28 female, 52 male  Mean age hypothermia group	Mild hypothermia group (N = 40) vs.	The last follow-up was at 1 year after treatment.	The ICPs of the hypothermia group at 24, 48, and 72 hrs were significantly lower (about	"[T]herapeutic mild hypothermia not only could reduce the ICP and increase the	Data suggest mild therapeutic hypothermia in severe TBI post craniectomy

			mention of COI.		41.3 years, control group 40.2 years	Control group treated with normothermia (N = 40).		10%) than those of the normothermia control group at the same time point ( mild hypothermia: 23.49 ± 2.38, 24.68 ± 1.71, and 22.51 ± 2.44 mm Hg; control; 25.87 ± 2.18, 25.90 ± 1.86, and 24.57 ± 3.95 mm Hg, respectively (P = 0.000 and P = 0.006, respectively). No differences were found between the groups for overall neurologic outcomes at 1 yr. There was a difference found favoring the hypothermia group at in favorable neurologic outcome (70.0% vs. 47.5%, P = 0.041: odds ratio, 2.58; 95% confidence interval, 1.03-2.46). The mortality rate was 22.5% in	serum SOD levels, but also improve the neurologic outcome in patients with severe TBI after craniotomy."	may be beneficial.
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								the hypothermia group and 32.5% in the control group (odds ratio, 1.66; 95% confidence interval, 0.61-4.48).		
Liu 2006 (5.0)	Induced hypothermia	Preliminary RCT	No COI. No mention of sponsorship.	N = 66 with severe traumatic brain injury.	24 female, 42 male  Mean age for SBC group 40.2 years, MSH group 39.6 years, and Control group 42.3 years	Selective brain cooling (SBC) group was treated using a cooling cap around the head in which 4°C water was circulating keeping the brain temperature at 33-35°C (N = 22)  vs.  Mild systemic hypothermia (MSH) group was treated using a cooling blanket and refrigerated ice bags maintaining the rectal temperature at 33-35°C (N = 21)  vs.  Normothermia group was treated with the same conventional	The last follow-up was at 2 years.	The ICP values of the groups receiving hypothermia were significantly lower 24, 48, and 72 h after injury than those of the control group (P < 0.05), no differences were seen between the hypothermia groups. The serum SOD level increase of the two hypothermia groups on days 3 and 7 were 45% and 76% in the SBC group and 60% and 86% in the MSH group on the respective days (Day 3 r = 0.948 in the SBC group and 0.965 in the	"[S]BC, as applied in this preliminary study – an easy and noninvasive method of producing hypothermia – cannot only reduce elevated ICP and increase serum SOD levels, but can also improve the prognosis without severe complications in patients with severe TBI."	Data suggest SBC may reduce ICP and increase SOD levels and may improve prognostic outcomes in severe TBI patients.

						treatment as the other groups without hypothermia (N = 23)		MSH group and day 7 r = 0.968 in the SBC group and 0.906 in the MSH group, respectively). The frequency of mild or no disability was significantly higher in the normothermia group (P < 0.05).		
Clifton 2012 (4.5)	Induced hypothermia	Post hoc/RCT	Funded by grants from the National Institute of Neurological Disorders and Stroke. No mention of COI.	N1 = 392 with severe brain injury and N2 = 97 with severe brain injury	No gender distribution described for either trial  Age distribution for trials: N1 - Mean age of five centers of recruitment: 31 ± 12, 32 ± 13, 32 ± 14, 30 ± 12, 33 ± 11  N2 - Mean age hypothermia group 26 ± 9 years, mean age normothermia group 31 ± 11	Patients treated with standard management and normothermia (N = 264)  vs.  Patients treated with standard management and hypothermia (N = 128)	Physiological variables were recorded hourly for the first 96 hours  6 months	The first 24 hrs had significantly fewer poor outcomes than those treated with normothermia (hypothermia, 5/15 (33%) vs normothermia 9/13 (69%) relative risk 0.44, 95% CI 0.22-0.88; P = 0.02). Outcome was poor in 14/31 (45%) of patients reaching 35°C within 1.5 hrs of surgery, in 14/23 (61%) reaching 35°C more than 1.5 hrs of surgery, and in 35/58 (60%) of patients in the normothermia	"Induction of hypothermia to 35°C before or soon after craniotomy with maintenance at 33°C for 48 hours thereafter may improve outcome of patients with hematomas and severe traumatic brain injury."	Data suggest use of hypothermia (35 °C) before or immediately after craniotomy may improve outcomes.

								group (relative risk 0.74, 95% CI 0.49-1.13; P = 0.16		
Clifton 2001 (4.5)	Induced hypothermia	RCT	Funded by grant from the National Institutes of Health (For Clifton and Choi). No mention of COI.	N = 392 with severe brain injury	No gender distribution described.  Mean age of five centers of recruitment: 31 ± 12, 32 ± 13, 32 ± 14, 30 ± 12, 33 ± 11	Patients treated with standard management and normothermia (N = 264)  vs.  Patients treated with standard management and hypothermia (N = 128)	6 months	No relation was seen between the time to reach the target temperature and the outcome. No differences were seen in mean intracranial pressure for between the groups. In the first 96 hours, the percentage of patients with an intracranial pressure of more than 30 mmHg was lower in the hypothermia group (P = 0.02). More patients in the hypothermia group had serum creatinine concentrations greater than 2.5 mg per deciliter (P = 0.05). Ten percent of the hypothermia patients had critical	"Treatment with hypothermia, with the body temperature reaching 33°C within eight hours after injury, is not effective in improving outcomes in patients with severe brain injury."	Data suggest treatment of TBI patients with hypothermia (temps reaching 33° within 8 hours post injury) does not improve outcomes.

								hypotensionn, while only 3% had it in the normothermia group. (P = 0.01). Mortality was 28% in the hypothermia group and 27% in the normothermia group. Death in both groups was greater in patients over 45 years old (P = 0.001). There were more poor outcomes in those over 45 in the hypothermia group than the normothermia group (88% vs. 69%, P = 0.08).		
Shiozaki 2001 (4.5)	Induced hypothermia	Prospective RCT	No mention of COI. Funded by grant from the Ministry of Health and Welfare in Japan.	N = 91 with severe head injury.	25 female, 66 male  No mean age given. Majority of participants in HT group between ages 10-39 (27 total, 60%), in NT group between ages 40-69	Mild hypothermia group (HT group) kept at 34°C with cooling blankets above and below the patient and with nasogastric lavage with iced saline (N = 45)  Vs.  Normothermia group (NT group) kept at 36.5-	Follow-up was at 3 months after the injury.	Five patients died in the HT group and 2 died in the NT group due to uncontrollable intracranial hypertension. In 21/45 (47%) of the patients in the HT group and in 27/46 (59%) of the patients in the NT group a favorable	"Mild hypothermia should not be used for the treatment of severely head injured patients with low ICP because this therapy conveys no advantage over normothermia in such patients."	Poor replication. Data suggest mild hypothermia should not be used in severe TBI patients with low ICP.

					(25 total, 54%)	37.5°C by surface cooling for 5 days (N = 46).		outcome was achieved (P = 0.251). No overall effect was seen by the GOS scores at 3 months.		
Zhao 2011 (4.5)	Induced hypothermia	RCT	No mention of COI or sponsorship.	N = 81 with traumatic brain injury.	22 female, 59 male  Mean age for normothermia group 37.5 ± 15.2 years, for hypothermia group 36.9 ± 14.8 years	Normothermia group (N = 41)  Vs.  Mild hypothermia group kept at 32.7°C for 72 hrs. (N = 40).	Follow-up was at 3 months after the injury.	The intracranial pressure in the hypothermia group was lower than normothermia group at 72 hrs (P < 0.01). Glucose and lactate levels were lower in the hypothermia group (P < 0.05). More patients in the hypothermia group had a favorable recovery (GOS 4-5, 75.0% vs. 51.2%, P = 0.038). The hypothermia group also had a lower percentage of poor recovery (GOS 2-3, 25.0% vs 48.8%, P = 0.038). Glucose was inversely correlated with the GOS scores in hypothermia	"[H]yperglycemia after severe TBI was associated with a poor neurologic outcome, whereas the predictive value of blood lactate level requires further investigation. Mild hypothermia therapy for 72 hours improves functional recovery 3 months after the injury, and reduction in blood glucose may be partly responsible for the favorable outcomes of the hypothermia therapy."	Data suggest hypothermia may lower blood glucose thus improving TBI outcomes.

								group (r = -0.562, P < 0.01) and in normothermia group (r = -0.677, P < 0.01). The same was seen for lactate levels in the hypothermia group (r = -0.302, P < 0.05) and in normothermia group (r = -0.366, P < 0.05).		
Hifumi 2016 (4.5)	Induced Hypothermia	RCT [post-hoc of article upon]	See previous study.	N = 129 with severe TBI	42 female, 87 male  Mean age for AIS 3-4 hypothermia group 30, AIS 3-4 fever control 42, AIS 5 hypothermia 24, AIS 5 fever control 11	See previous study.  Also classified participants into AIS head score 3-4 (n=78) and AIS head score 5 (51)	See previous study.	TBI-related mortality was significantly reduced in the fever control group compared to the hypothermia group (9.7% vs. 34.0%, P=0.02). In patients with AIS 3-4, there was no significant difference in favorable neurological outcomes between the fever group and hypothermia group (64.5% vs. 51.1%, respectively, p=0.26). No difference in	"Fever control may be considered instead of MTH in patients with TBI (AIS 3-4)."	Post hoc study at 6 months (B-HYPO Study). Data suggest fever control management in MTH TBI patients with (AIS 3-4) may reduce mortality and increase good outcomes.

								mortality or favorable outcome among AIS 5 patients.		
Yan 2001 (4.5)	Induced Hypothermia	RCT	No mention of COI or sponsorship.	N = 44 with severe closed head injury (GCS 3-8)	14 female, 30 male  Overall mean age 41.8 years	Groups classified by GCS value: Group A = GCS 3-5 (n=20), Group B = GCS 6-8 (n=24)  Randomized into: Hypothermia treatment (32-34°C) (n=10 from A, 14 from B)  Vs.  Controls (n=10 from A, 10 from B)	4, 24, 48, 72, 96, 120 hours post-injury	Group B – N <sub>20</sub> amplitude in SLSEP and I/V amplitude in BAEP differed significantly between those treated with mild hypothermia treatment and controls (p<0.05). Group A – no statistically significant difference in parameters discovered.	“These results demonstrate that mild hypothermia treatment (32-34°C) in the Group B has a significant neuroelectrophysiological effect on severe brain injury. Nevertheless, the effect of mild hypothermia in Group A is not apparent and needs further studying.”	Data suggest group B was effected by mild hypothermia as compared to controls but group A did not show an effect.
Smrcka 2005 (4.0)	Induced Hypothermia	RCT	No mention of COI. Supported by grant from the Internal Grant Agency of the Czech Ministry of Health.	N = 72 with severe head injury	21 female, 51 male  Mean age overall 41 years	Hypothermia treatment of 34° C for 72 hours (n=37)  Vs.  Controls (n = 35)	72 hours post-injury, 6 months	Normothermia and primary lesions (n=17): median GCS at admission = 5, mean ICP = 18.9, mean CPP = 73, median GOS = 4  Normothermia and extracerebral hematomas (n=20): GCS = 4, ICP = 16, CPP = 71, GOS = 3	“Hypothermia decreased ICP and increased CPP regardless of the type of brain injury. Hypothermia was not able to improve outcome in patients with primary brain lesions but this pilot study suggests that it significantly improves	Pilot study. Data suggest hypothermia did not improve brain injury outcomes but increased CPP and decreased ICP.

								<p>Hypothermia and primary lesions (n=21): GCS = 4.62, ICP = 10.81, CPP = 78.1, GOS = 4</p> <p>Hypothermia and extracerebral hematomas (n=14): GCS = 5, ICP = 13.2, CPP = 78, GOS = 5</p>	outcome in patients with extracerebral hematomas."	
Sinz 1998 (4.0)	Induced hypothermia	RCT	No mention of COI. Partially funded by the Charles Schertz Fellowship Grant, Department of Anesthesiology and Critical Care medicine, and by the Laerdal Foundation, the National Institute of Neurological Disorders and Stroke, and the Center for Injury Research and Control, University of Pittsburgh.	N = 39 with a traumatic brain injury.	7 female, 32 male  Mean age for normothermia group 39 ± 17 years, for hypothermia group 32 ± 14 years	Hypothermia group kept at 32°C using cooling blankets and nasogastric lavage with iced saline (N = 16)  Vs.  Normothermia group kept at 37-38.5°C (N = 23).	The last follow-up was at 120 hrs.	Patients who died had higher levels of quinolinic acid versus survivors (P = 0.003) after controlling for the effect of time. An association between time after TBI and increased CSF quinolinic acid was found (P < 0.0001).	"[T]he excitatory neurotoxin, quinolinic acid, markedly increases in eSF after severe TBI in humans and is strongly associated with mortality."	Data suggest quinolinic acid is elevated in the CSF of TBI patients which may be associated with increased mortality.

Aibiki 2000 (4.0)	Induced Hypothermia	Prospective RCT	No mention of COI or sponsorship.	N = 26 with traumatic brain injury (TBI) who have been ventilated.	6 female, 20 male  Mean age normothermic group 38 ± 8 years, mean age hypothermic group 34 ± 6 years	Hypothermic group consisted of cooling the patients to 32 to 33°C after being giving vecuronium, midazolam, and buprenorphine. Hypothermia lasted for 3 to 4 days and afterwards the patients were rewarmed at 1°C per day (N = 15)  vs.  Normothermic group consisted of controlling the patients' body temperature at 36 to 37°C by cooling using the same treatment as the other group. Body temperature control was started 3 to 4 hrs after the injury (N = 11)	The last follow-up was at 6 months.	Arterial thromboxane (TXB2) increased in both groups on admission, but 6-keto prostaglandin F1α did not increase, however, the hypothermia group eliminated prostanoid differences and permitted an improvement in the imbalance of TXB2 and 6-keto PGF1α. Patients in the hypothermic group showed a significant increase in 6-keto PGF1α levels on day 5 after injury. The arterial internal jugular bulb differences in TXB2 were suppressed throughout the study only by hypothermia.	"The current results from a limited number of patients suggest that moderate hypothermia may reduce prostanoid production after TBI, thereby attenuating an imbalance of thromboxane A2 and prostaglandin I2."	Data suggest moderate hypothermia may decrease prostanoid production post TBI.
Clifton G 1993 (4.0)	Induced hypothermia	RCT	No mention of COI or sponsorship.	N = 46 with severe nonpenetrating brain injury and a post	No gender distribution described  No mean age listed.	Normothermia group patients were treated with standard management and were kept at 37°C	First 12 hours, 60 hours, 72 hours, 84 hours  Three months GOS measured	Heart rate was significantly lower in the hypothermia only in the second time	"Based on evidence of improved neurologic outcome with minimal toxicity,	Data suggest improved GCS in (GRIMD) groups as compared to (SDIVD) group.

				resuscitation GCS of 4 to 7.	A majority of participants were between ages 15-25 (50%)	with cooling blankets and were given acetaminophen for 80 h after injury (N = 22)  vs.  Hypthermia group patients treated with standard management and keeping the patients cooled by securely wrapping the patients in cooling blankets set at 5°C. Metocurine 10 mg/h and morphine-sulfate 10 mg/h were given continuously until the patient warmed to a temperature of 35°C (N = 24)		period (p < 0.001). Mean arterial pressure (MAP) was significantly different in the two groups only in the third time period with a 13 mmHg lower MAP in the hypothermia group. There was no differences seen in ICP. Cerebral perfusion pressure (CPP) was 16 mmHg lower in the hypothermia group in the third time period with a mean value in normothermia of 80.9 ± 3.42 and in hypothermia 64.96 ± 2.13 mmHg.	we believe that phase III testing of moderate systemic hypothermia in patients with severe head injury is warranted."	
Jiang 2000 (4.0)	Induced hypothermia	RCT	No mention of COI or sponsorship.	N = 87 with severe traumatic brain injury.	15 female, 72 male  Mean age hypothermia group 42.2, mean age for normothermia group 40.6 years	Long-term mild hypothermia group with temperatures at 33-35°C for 3-14 days (N = 43)  vs. Normothermia group with	The last follow-up was at 1 year.	At 1 year, the hypothermia had 25.58% (11/43) mortalities and 46.51% (20/43) had a favorable outcome, the normothermia group had 45.45% (20/44)	"The data produced by this study demonstrate that long-term mild hypothermia therapy significantly improves outcomes in	Data suggest that at 1 year TBI patients receiving long term mild hypothermia had significantly better outcomes.

						temperatures at 37-38°C (N = 44).		mortalities and 27.27% (12/44, p < 0.05). On the 7th day the mean ICP for the hypothermia group was 18.9 ± 1.5 mm Hg and 28.13 ± 2.25 mm HG in the normothermia group (P < 0.01).	patients with severe TBI."	
Lee 2010 (4.0)	Induced hypothermia	RCT	No COI. Funded by grant from the China Medical University Hospital (Taichung, Taiwan, Republic of China)	N = 45 with severe traumatic brain injury.	18 female, 27 male  Mean age for group A 43.5 ± 16.4 years, group B 44.0 ± 15.1 years, and group C 38.8 ± 18.0 years	Group A was treated with intracranial pressure/cerebral perfusion pressure (ICP/ CPP) guided management only (N = 16) vs.  Group B was treated with mild hypothermia and ICP/ CPP guided management (N = 15) vs.  Group C was treated with mild hypothermia and PtiO2 guided with ICP/ CPP management (N = 14).	6 months	The highest ICP was observed 72 hrs after injury in Group A and 24-48 hrs in Groups B and C with the values in B and C much less than in Group A (P = 0.0459). The mean ICU stay was significantly longer in Groups B and C with Group A averaging 9 days, Group B 11.33 days and Group C averaging 11.6 days (P < 0.05). The total hospital costs were \$5257 in Group A, \$5915.35 in Group B, and \$5815 in Group C.	"[T]he hypothermia groups reduce elevated ICP earlier than 24 hours after injury, and daily variations of ICP were significantly different among the three treatment groups after the third posttraumatic day."	Poor replication. Data suggest combining a strategy PO2 of hypothermia with guided CPP ICP is beneficial for treating TBI patients.

Idris 2014 (4.0)	Induced Hypothermia	RCT	No COI. Supported by the Short Term Grant of Universiti Sains Malaysia	N = 32 with severe TBI, GCS score 6-7	5 female, 27 male  Mean ages of mild cooling group 28.9 years, deep cooling 26.7 years, and control group 45.5 years	Mild cooling (n = 10)  Vs.  Deep cooling (n = 9)  Vs.  No cooling (n = 13)	6 months	Patients in the cooling groups had no significantly different outcomes compared to controls. Good GOS scores at 6 months obtained by 63.2% of those in cooling group and by 15.4% of those in noncooling group (P=0.007). 70% of those in mild cooling group had good GOS compared to 15.4% of control (P=0.013) Those within the deep cooling group did not do significantly better compared to controls (P=0.074) and compared to mild cooling (P=0.650).	"This preliminary or pilot study found that direct regional brain hypothermia may have potential benefits in treating the severely head injured patients with initial GCS of 6 or 7. Other than a safe and practicable approach, this direct regional brain cooling therapy may serve as an added therapy for patients who require urgent decompressive craniectomy, irrespective of the underlying etiologies in the future.	Pilot study. Data suggest use of hypothermia in severe TBI patients may be useful.
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## Swallow Studies

Swallowing impairment (dysphagia) is common in some severe TBI patients due to prolonged intubation or tracheostomy, the traumatic injury itself, medications or weakened swallowing muscles due to lack of use [680-682]. These patients may require testing to determine swallow function, extent of dysfunction, and adequacy of airway protection. There are several different types of swallow studies ranging from the bedside clinical assessment, the modified Evans Blue-Dye Test (MEBDT), to instrumental evaluations like barium swallow, modified barium swallow (MBS) fiberoptic endoscopy (FEES), fiberoptic endoscopic evaluation with sensory testing (FEEST) and a videofluoroscopic study which adds oropharyngeal pressure assessment (MSE). Although there are many different tests they all evaluate the ability of the patient to swallow. The threshold for evaluating swallow studies is low among those with prolonged intubation, tracheostomy, difficulty swallowing or signs of gagging or aspiration.

## Family Visits

Family visits have been used to attempt to induce increased and earlier arousal from coma [683, 684]. Many individuals with traumatic brain injury (TBI) experience a longer period of sensory deprivation [683]. This is in part due to the increased hospitalization, immobilization, and isolation. To help recovery structured family visits are used to increase sensory stimulation including; visual, tactile, gustatory, tactile, and equilibrium stimuli [684].

### Family Visits

#### Recommended.

Family visits are recommended for the treatment of comatose TBI patients.

#### Strength of Evidence – Recommended, Evidence (C)

##### Level of Confidence – Low

<i>Indications:</i>	Comatose patients.
<i>Benefits:</i>	Potential for increased and earlier arousal from coma.
<i>Harms:</i>	None
<i>Rationale:</i>	There are two moderate quality studies suggesting increased family visits may result in either increased arousal or earlier arousal [683, 684]. Family visits are not invasive, have negligible adverse effects, are low cost, have evidence of efficacy and are thus recommended for comatose patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Family Visit; Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 12 articles in PubMed, 56 in Scopus, 3 in CINAHL, 82 in Cochrane Library, 310 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 2 randomized trials and 0 systematic studies met the inclusion criteria.

## Evidence for the Use of Family Visits

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Abbasi 2009 (5.5)	Family Visits	RCT	No mention of sponsorship or COI.	N = 50 comatose patients with a head injury. GCS score 6-8, age 18-45 years.	Mean age: Intervention on 30.4 (6) VS control 30.4 (7). 172 males total 48 females, groups age gender not specified.	Control group received	6 days	GCS of control group/Intervention group day 1: 6.9 (0.9)/7.0 (.08) (p = 0.7500). GCS On the 6 <sup>th</sup> day control/Intervention: 6.8 (1.4)/ 8.8 (0.7) (p = 0.0001).	"The results of the present study provided evidence to support that a regular family visiting program could induce the stimulation of comatose patients."	Data suggest regular family visits may stimulate consciousness in comatose patients 6 days after admission.
Kalani 2016 (4.5)	TBI: Family Visits	RCT	No mention of sponsorship. No COI.	N 64 with GCS score 5-8 age 18-64.	Mean age 37.7. 51 males. 13 females.	Intervention family visits for 45 minutes to an hour, patients received touch and auditory stimulations. (N= 32) vs The control group received the usual meeting in accordance with hospital and ICU rules. Each group tested for level of consciousness 30 minutes before and after treatment (N =32).	2 weeks	GCS score on the 1st Day: intervention group 6.6 (0.9) vs control GCS 6.6 [170], (p = 1.0). GCS score on the 14th day: Intervention group 12.8 (1.6) vs control 7.6 (0.9), (p = 0.001). Difference of GCS scores: Intervention group 6.2 control group 1, (p = 0.001).	"Guided and targeted meetings by the patient's family is effective for improving the level of consciousness in comatose patients."	Cluster randomization. Inclusion criteria of GCS 6-8, but mean scores reported as 1.25-1.33. Data suggest sig. improved level of consciousness at 14 days.

## Multimodal and Unimodal Coma Stimulation

Multimodal coma stimulation has been used to treat comatose TBI patients [685-688].

### Multimodal and Unimodal Coma Stimulation

#### Recommended.

Multimodal and unimodal coma stimulation are recommended for the treatment of comatose TBI patients.

*Strength of Evidence* – Recommended, Evidence (C)

*Level of Confidence* – Low

<i>Indications:</i>	Comatose TBI patients. The highest quality study included those with Glasgow Coma Score <8 [685]
<i>Benefits:</i>	Improved arousal, lessening of coma severity
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	5 times/day, 20 min./session. 2 hrs between session. Stimulations consisted of visual, auditory, tactile, olfactory and gustatory. Two trials either utilized a family member talking to the patient [689] or a familiar voice telling stories in common with the patient [690].
<i>Rationale:</i>	There is one moderate quality trial suggesting multimodal coma stimulation results in improvement in Glasgow Coma Score [685]. Two trials of familiar voices suggest successful improvements [689, 690]. Uni-or multimodal coma stimulation is not invasive, has no adverse effects, may be low (familiar voice) to moderate to high cost in aggregate (multimodal), has evidence of efficacy and thus is recommended for comatose TBI patients.
<i>Evidence:</i>	Multimodal Coma stimulation– A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: traumatic brain injury, closed head injury, penetrating head Injury, concussion, craniocerebral injury controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 4 articles in PubMed, 15 in Scopus, 6 in CINAHL, 6 in Cochrane Library, 1410 in Google Scholar, and 0 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 3 from other sources. Of the 5 articles considered for inclusion, 1 randomized trials and 0 systematic studies met the inclusion criteria.

### Evidence for the Use of Multimodal Coma Stimulation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Pape 2015 (6.5)	TBI	RCT	Sponsored by the Department of Veterans Affairs, Office of Research and Development, Rehabilitation Research and Development Merit and career development transition award, and Northwestern University's Clinical and Translation Sciences Institute. No COI.	N = 15 in disordered consciousness (DOC).	Mean age 35.1 (11); 12 males and 3 females.	Familiar Auditory Sensory Training or FAST (N = 8) vs Placebo of silence (N = 7).	6-weeks	Mean DOCS; FAST = 13.5 (8.2) vs placebo = 18.9, (15.6). FAST had more CNC gains (p = 0.049, FAST = 1.01, (0.60) vs placebo = 0.25 (0.70). Mixed-effects models CNC findings, (p = 0.002). Treatment effect, based on CNC (d = 1.88, 95% CI = 0.77, 3.00).	"For persons with DOC 29 to 170 days after TBI, FAST resulted in CNC gains and increased neural responsivity to vocal stimuli in language regions."	Data suggest FAST participants had better neural responses to stimuli and CNC improvement compared with placebo.

Megha 2013 (6.0)	Multimodal Coma Stimulation	RCT	No sponsorship or COI.	N = 30 comatose patients with TBI.	Mean age:39.7 years. No mention of gender.	Group A, high frequency group, 5 sessions of multimodal coma stimulation a day, 20 minutes 2 weeks 5 days a week, 5 times a day with a 2 hours in between (N = 10) vs Group B, low frequency group, 2 sessions of multimodal coma stimulation a day for 50 minutes, 5 days a week, 5 cycles of stimulation 50 minutes, 2 times a day (N = 10) vs Group C, control or conventional physiotherapy, including positioning, stretching and passive movement, 2 times a day 5 days a week for 2 weeks, repeated passively 10 times a minute for 2 minutes (N = 10).	2 weeks	Pre Glasgow Coma Scale (GCS) scores between groups / post GCS: A vs B vs C, (p = 0.969) / (p = 0.009). Western Neuro Sensory Stimulation Profile (WNSSP) scores between groups / post WNSSP: A vs B vs C, (p = 0.801) / (p = 0.000). Post GCS comparison group A vs B (p = 0.579), A vs C (p = 0.005), B vs C (p = 0.019). Post WNSSP comparison: A vs B (p = 0.005), A vs C (p = 0.000), B vs C (p = 0.002).	"The data obtained replicates the effectiveness of multimodal coma stimulation in improving the consciousness levels of TBI comatose patients when compared to the control group."	Data suggest increased frequency short duration multimodal stimulation is better than longer duration stimulation or standard BID PT as measured by GCS and Western Neuro Sensory Stimulation Profile scores.
Parveen 2015 (4.5)	TBI	RCT	No mention of sponsorship or COI.	N = 80 comatose patients with TBI.	Age range 15-65; 67 males and 13 females.	Intervention group, auditory stimulation provided by a family member for 10 minutes, twice daily (N = 40) vs Control group monitored at admission (N = 40).	2-weeks	GCS Baseline scores / Day 7 / and Day 14: 5.10 ± 1.37 vs 5.12 ± 1.20 control, p-value not given / 7.26 ± 2.39 vs 5.54 ± 1.75, p = 0.001 / and 8.17 ± 2.06 vs 6.34 ± 2.36, p = 0.004.	"Auditory stimulation by family members appears to be effective in improving level of consciousness in comatose patients with TBI."	High dropout rate. Data suggest early auditory stimulation of comatose patients by family member improves LOC.

Lippert-Gruner (3.0)	Multimodal Coma Stimulation	Prospective Study	Supported by German Federal Government (BMBF-Projekt 01 KO 9517 Verbund Neuro-/Polytrauma Köln) No mention of COI.	N=24 patients	Mean age: 38 years. 19 males, 5 females.	All patients received multimodal coma stimulation and early onset rehabilitation.	12 months	Patients GCS score changed from 5.3 to 7.8 after rehabilitative treatment. Mean CRS score changed from 3.7 to 8.5. Spearman correlation analysis showed significance with GCS score with Barthel index ( $r=.54$ ; $p=.02$ ), with duration of early onset rehabilitation ( $r=.72$ ; $p=.001$ ), and with DRS score ( $r=.57$ ; $p=.01$ ). Duration of coma was significant with Barthel index ( $r=.47$ ; $p=.049$ ), FIM score ( $r=.50$ ; $p=.03$ ), with GOS score ( $r=.51$ ; $p=.03$ ), with duration of early-onset rehabilitation ( $r=.77$ , $p<.001$ ), and with DRS score ( $r=.52$ ; $p=.03$ ).	"Despite intensive rehabilitation treatment, severe traumatic brain injury is still burdened with significant mortality and morbidity."	2-year follow-up of Gates 2004. Suggest Meniett device associated with reduction in vertiginous symptoms.
Gorji 2014 (1.5)	TBI	RCT	No mention of sponsorship. No COI.	N = 30 coma patients.	Aged 35-44 years and controls 15 – 24; gender not specified.	Intervention group, 10-minutes MP3 voice of a loved one twice a day (N = 15) vs Control group, GCS recorded in the same manner as intervention (N = 15).	About 6-months	Amount of time to reach GCS = 15 $\chi^2 = 12.96$ , ( $p < 0.0001$ ). Averages of consciousness before the 1 <sup>st</sup> day 6.46 (1.53) vs 12.26 (5.53) in the controls.	"Results showed that a highest percentage of subjects in the intervention group were 35 to 44-year-old and in control group age range was 15 to 24."	Sparse methods. Data suggest interventional group (auditory stimulation) improved LOC.

## Occupational Therapy

Occupational therapy is broadly defined as patient- or client-centered interventions aiming to return individuals to his/her everyday activities and occupation. Most occupational therapists are trained to recognize cognitive, psychological, sensory-perceptual, and physical issues that may influence the treatment and recovery of patients with TBI. Occupational therapy surrounding cognitive rehabilitation is traditionally broken into two approaches [691]. The remedial approach focuses on the restoration of cognitive functions, while the adaptive approach focuses on overcoming the limitations caused by a traumatic brain injury [78]. Similar to physical therapy, there is little quality evidence to support occupational therapy as an aggregate intervention.

### Occupational Therapy

#### Recommended.

Occupational therapy is recommended for moderate to severe TBI patients with functional deficits, especially those that impair employability.

#### Allied Health Interventions

*Strength of Evidence* – Recommended, Insufficient Evidence (I)

*Level of Confidence* – Low

<i>Indications:</i>	For moderate to severe TBI patients with functional deficits, especially those that impair employability
<i>Frequency/Dose/Duration:</i>	Regimens varied widely. They included: 16 weeks of 15 hours per week of intensive OT [692]; 1.5-2.5hr/day for 60 days [166];
<i>Indications for Discontinuation:</i>	When desired improvement has been achieved, clinical plateau or failure to improve.
<i>Benefits:</i>	Self perceived quality of life, faster recovery and shortened hospitalization time which decreases costs associated with TBI.
<i>Harms:</i>	Negligible
<i>Rationale:</i>	There are 5 moderate quality studies involving the use of OT [166, 692-694] and [695]. Cicerone suggest a comprehensive approach is best but all studies show either modest benefits or no differences. Details of the studies are limited. Occupational therapy is not invasive, has low adverse effects, is high cost, but some modalities and treatments are likely effective, thus occupational therapy is recommended. Better evidence-based guidance is able to be found from structured trials of specific interventions.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Occupational therapy, Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 29 articles in PubMed, 1011 in Scopus, 17 in CINAHL, 1 in Cochrane Library, 5750 in Google Scholar, and 0 from other sources. We considered for inclusion 5 from PubMed, 1 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 8 articles considered for inclusion, 5 randomized trials and 2 systematic studies met the inclusion criteria.

## Evidence for the Use of Occupational Therapy

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Cicerone 2008 (7.0)	Occupational therapy	RCT	Supported by the National Institute on Disability and Rehabilitation Research NO COI.	N = 68 with traumatic brain injury (TBI) recruited from clinical referrals and the community.	Standard Neurorehabilitation group 34.5 ± 12.4  Intensive cognitive rehabilitation group 38.7 ± 11.1  Gender (M:F) 46:22	Standard neurorehabilitation , includes physical, occupational and speech therapies (N = 34) vs. Intensive Cognitive Rehabilitation, includes communication group, cognitive group and life skills group (N = 34). Both groups received 15 hours of treatment for week for 16 weeks. Primary/ Secondary outcomes; Community integration (CIQ), Life satisfaction (PQOL) / NP functioning, Perceive self-efficacy, community based-employment.	6 months	There were no significant main effects for treatment or condition on the CIQ / PQOL / NP scores / Self – efficacy scores. 74% participant after completion of the study required follow – up treatment. Participants showed improvement on CIQ scores from post treatment to follow – up (p = 0.04).	“Improvements seen after intensive cognitive rehabilitation may be related to interventions directed at the self-regulation of cognitive and emotional processes and the integrated treatment of cognitive, interpersonal, and functional skills.”	Data suggest a comprehensive NP rehab plan post TBI improves self perceived quality of life and community functions.as measured by CIQ and PQOL.
Andersson 2007 (5.5)	Occupational therapy	RCT	Supported by Swedish National Board of Health and Welfare, 95–170; The Vardal foundation,V2000-263, V2002-027, Sweden; The Health	N = 395 patients with Mild traumatic brain injuries	Intervention group: 32 years Control group: 34; Gender (M:F) 245:150	Intervention group: 264 patients were allocated to the intervention group, yet only 96 patients accepted intervention. Out of the 96, 78	1 year	No statistical differences were found between the intervention group and control group in primary	“In this particular MTBI sample, early Active rehabilitation did not change the outcome to a statistically-significant degree. Further studies should	Data suggest no significant differences between groups. patients who suffered few PCS 2-8 weeks

			and Medical Care Executive Board of the Västra Götaland Region, Sweden; The Trygg-Hansa Insurance Company, Sweden; The ForeningSparbanken Foundation for Scientific Research at Borås and Skene Hospital, Sweden; The Foundation Forenings Sparbanken Sjuhärads, Borås, Sweden; The Axel Linders Foundation, Alingsås, Sweden; The Alice Swenzons Foundation for Scientific Research, Borås, Sweden. No mention of COI.			patients received occupational therapy  Control group: (N=131) received standard care		effect variables defined by Post concussion symptoms and LiSat-II.	focus on patients with several complaints during the first 1–3 months and test various types of interventions.”	post injury and refused rehab recovered at pre-injury level where those with multiple PCS and accepted the rehab were not recovered at one year.
Slade 2002 (5.5)	Occupational therapy	RCT	This work was funded by the Nuffield Institute and the NHS executive (Northern & Yorkshire), and the United Leeds Hospital Trust. No mention of COI	N=141 patients with TBI, stroke or multiple sclerosis	53 years old; chronic TBI as well as stroke, MS and other neurological deficit patients.	Experimental group (N=75) received 67% more therapy than control group, 62.5% of total therapy time Control group (N=66) received 37.5% of total therapy time.  Therapy was a mix of physiotherapy and occupational therapy.	No long term follow-up mentioned	The experimental group received significantly more therapy hours than the control group ( 126.4 vs 81.7 (p=0.0001))  A second multiple regression showed that the experimental	“In summary, enhanced levels of physiotherapy and occupational therapy (to a planned intensity of 67% above the standard) show results which vary according to the specification of the model used in the analysis. Adjusting for confounders, a slight non-significant trend in favour of the experimental group was observed. Accounting for	Data suggest intensive therapy group benefit from additional OT and PT as was demonstrated by a statistically significant shortened length of stay which also decreased hospital costs. However, the duration of the study is not

								group had a significant reduction of 14 days in length of stay in a rehabilitation unit compared to the control group. (p<0.01)	impairment/disability mix, and the consequent response of therapy, a significant benefit to the experimental group was demonstrated.”	included in this article so conclusions are difficult to surmise.
Vanderploeg 2008 (4.5)	Occupational Therapy	RCT	No mention of sponsorship or COI	366, 18+yo with mod-severe nonpenetrating TBI <6mo ago with GCS score ≤12, in coma for 12+ hrs, PTA for 24+ hrs, RLAS cognitive level 5-7, active duty military member or veteran, and needing 30+ of acute interdisciplinary TBI rehabilitation.	Mean age cognitive 33.2±13.5 years, functional 31.7±12.9 years. 335 males, 25 females.	Cognitive rehab (n=184) targeted 4 cognitive domains: attention, memory, executive functions, and pragmatic communication; one on one sessions  vs  Functional-experiential rehab (n=182) with real-life performance situations and common tasks to compensate for functional deficits after brain injury; group sessions.  All received 1.5-2.5hr/d TBI protocol-specific therapy, 2-2.5hr/d OT, PT, ST. Care	1 year	NS between groups at 1 year for: %RTW or school (38.9 vs. 35.4%, p=0.50), and % living independently (56.3 v 61.6% (p=0.27)). Cognitive FIM post treatment: cognitive (27.3±6.2) v. functional group (25.6±6.0) (p=0.01). NS between groups for motor FIM and DRS. No memory problems: cognitive 22.2% v. functional 27.6% (p=0.05).	“[N]o difference between cognitive-didactic and functional-experimental approaches to brain injury rehabilitation on the primary 1-year global outcome measures of the study. However, patients in the cognitive treatment arm had better posttreatment cognitive performance than patients in the functional treatment arm.”	Data suggest both groups improved with similar long term global functional outcome. Data suggest more improvement in short term functional cognitive outcome for the cognitive treatment arm.

						continued until ready to discharge home or to community transitional rehabilitation program or completed 60 days specific protocol treatment.		Those with more education more often lived independently at 1 year in functional (69.1%) vs. cognitive group (47.4%) (p<0.02). Younger more often working at 1 year in cognitive (53.3%) vs. functional group (37.8%) (p<0.03)).		
Ghaffar 2006 (4.0)	Occupational Therapy	RCT	Supported by the Physician Services Incorporated. No mention of COI	N = 191 patients with mild traumatic brain injuries	Treated group 30.7 ±10.9 Nontreated group: 33.3±12.4 Gender (M:F) 124:67	Treated Group (N=97) received assessment, education, and therapy by an occupational therapist.  Control Group (N=94) did not receive any treatment.	6 months	The two groups didn't not differ in any outcome measure. In patients with preinjury psychiatric difficulties, subjects in the treated group did had significantly fewer symptoms in comparison to the control group. (F=6.8, (P=.01))	"These findings suggest that routine treatment of all MTBI patients offers little benefit; rather, targeting individuals with preinjury psychiatric problems may prove a more rational and cost-effective approach."	Data suggest traditional treatment for MTBI patients may be of little benefit in treatment but assessing preinjury psychiatric issues may be useful in determining which individuals are likely to benefit the most from a multidisciplinary treatment program.

## Physical Therapy

The term “physical therapy” is used here in the generic sense to include physical medicine and therapeutic and rehabilitative evaluations and procedures. Physical therapists are major health care providers who render many of these services through multiple, specific interventions (e.g., exercise, ultrasound, manipulation). The majority, if not all, of these interventions are also employed by other health care practitioners. However, there are a few RCTs of “physical therapy.” The studies in this section include numerous interventions and lack structuring of treatments within the arms of these trials. Thus, there are no strong conclusions that may be drawn from this body of evidence with respect to the value of individual modalities and comparisons between generic treatment programs are weak. These studies of “physical therapy” are reviewed here for completeness.

### Physical Therapy

#### Recommended.

Physical therapy is recommended for use in the treatment of chronic severe or moderately severe TBI patients with functional physical deficits.

#### *Strength of Evidence – Recommended, Insufficient Evidence (I)*

#### *Level of Confidence – Low*

<i>Indications:</i>	For subacute, chronic severe or moderately severe TBI patients with functional physical deficits, such as balance, strength or coordination.
<i>Frequency/Dose/Duration:</i>	Trials have used daily to weekly visits for 8 weeks [166, 696]. One trial used twice daily visits for 2 weeks [697].
<i>Indications for Discontinuation:</i>	When desired improvement has been achieved, clinical plateau or failure to improve.
<i>Benefits:</i>	Quicker recovery and return to work with accelerated independence.
<i>Harms:</i>	Negligible
<i>Rationale:</i>	There are 6 moderate quality studies involving PT [166, 696-699, 700] The trials are generally not well described, used multiple interventions and were not well structured. Most suggested improvements with higher intensity of therapy. In one [701] there was no evidence of efficacy. In [698] there was a quicker return to work with intensive therapy, but at one year the functional outcomes were similar between groups and also in [699] there was seen a faster resumed independence and accelerated time to discharge from hospitalization. Physical therapy is not invasive, has low adverse effects, is high cost, but some modalities and treatments are likely effective, thus physical therapy is recommended. Better evidence-based guidance is able to be found from structured trials of specific interventions.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, physical therapy, physical rehabilitation, physical rehab; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled

trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 428 articles in PubMed, 1500 in Scopus, 39 in CINAHL, 228 in Cochrane Library, 100 in Google Scholar, and 2 from other sources. We considered for inclusion 8 from PubMed, 3 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 2 from other sources. Of the 14 articles considered for inclusion, 7 randomized trials and 4 systematic studies met the inclusion criteria.

## Evidence for the Use of Physical Therapy

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Schneider 2014 (7.0)	Physical Therapy	RCT	Sponsored by the Alberta Centre for Child, Family and Community Research. KJS is sponsored by the Alberta Heritage Foundation for Medical Research Studentship Award and the Alberta Children's Hospital Research Institute. CAE is sponsored by the Alberta Innovates Health Solutions Population Health Investigator Award and the Children's Hospital Foundation. No COI.	N = 31 patients with persistent symptoms of dizziness, neck pain and/or headaches following a sport-related concussion.	No mention of mean age. Median age of 15 yrs (12-30)  18 Males, 13 Females	Control Group (N=16) – Seen by physiotherapist once a week for 8 weeks or until medical clearance.  Vs  Intervention Group (N=15) – Same treatment as the control group, but with an addition of cervical spine physiotherapy and vestibular rehabilitation.	No follow up mentioned.	73% of the intervention group (11/15) were medically cleared within 8 weeks while only 7% (1/14) were in the control group. The intervention group was 3.91 (95% CI 1.31-11.34) times more likely to be medically cleared by 8 weeks.	“A combination of cervical and vestibular physiotherapy decreased time to medical clearance to return to sport in youth and young adults with persistent symptoms of dizziness, neck pain and/or headaches following a sport-related concussion.”	Small sample. Data suggest the combination of cervical and vestibular PT significantly decreases the time to medical clearance in concussion patients
Zhu 2007 (7.0)	Physical Therapy	RCT	Sponsored by Hong Kong Health Service Researched Fund. No mention of COI.	N = 68 patients with moderate to severe TBI.	Control Group (N=36) Mean age of 36 ± 13. 28 Males, 8 Females  Intensive Group (N=32) Meant age of 13 ± 13. 27 Males, 5 Females	Control Group (N=36) – 2 hrs of therapeutic training each day for 5 days a week.  Vs  Intensive Group (N=32) – 4 hrs of therapeutic training each day for 4 days a week.	6 months	The Functional Independence Measure (FIM) was significantly higher in the intensive group than the control group at the third month (47% vs 19%, p=0.015). The intensive Glasgow Outcome Scale (GOS) had higher scores than the	“Early intensive rehabilitation may improve the functional outcome of patients with TBI in the early months post-injury and hence increase the	Data suggest intensive rehab resulted in quicker return to work but did not affect functional outcomes as both groups were similar at one year.

						Up to 6 months of treatment for both groups.		control group on the second (28% vs 8%, p=0.34) and third (34% vs 14%, p=0.044) months. Overall, no significant differences in the FIM and Neurobehavioral Cognitive Status Examination (NSCE).	chance of their returning to work early”	
Krewer 2014 (6.5)	Physical Therapy	RCT	No mention of sponsorship or COI.	N = 66 patients with severe hemiparesis and mild to moderate spasticity resulting from a stroke or TBI.	rpMS Group (N=31) – Mean age of 55±13 19 Males, 12 Females  Sham Group (N=32) – Mean age of 54±13 19 Males, 13 Females	rpMS Group (N=31) received rpMS stimulation  Vs  Sham Group (N=32) received sham stimulation  20 minute sessions of stimulation plus 20 minutes of OT, 2 times a day, 5 days a week, for 2 weeks.	2 Weeks	rpMS group showed significant effects on spasticity for wrist flexors (P=.048) and elbow extensors (P<.045) when compared to the sham group. Are motor function was not significantly different between the two groups. But rpMS had a positive effect on sensory stimulation.	“Therapy with rpMS increases sensory function in patients with severe limb paresis. The magnetic stimulation, however, has limited effect on spasticity and no effect on motor function.”	Baseline comparability was unequal as time since injury differed between groups.(26 weeks vs 37 weeks).Data suggest use of rpMS therapy in severe limb paresis patient increasing sensory function but has no benefit for motor function and only a slight effect on spasticity.
Shiel 2001 (6.0)	Physical Therapy	Prospective Controlled	Sponsored by the NHS National Research and Development Programme for People with Physical and Complex Disabilities.	N = 56 with moderate to severe head injuries.	Mean age of 36.7 ± 15.2 years. No mention of sex.	Intervention group (N=24) – Received routine treatment with additional treatment  Vs  Routine Group (N=27) – Received routine treatment.	No follow up mentioned.	The results mostly compared the two centres were the study took place instead of the two groups. However, the study stated that subjects receiving more intensive therapy made more rapid	“Increasing the hours per week of therapy given adults recovering from brain injury in hospital can accelerate the	Data suggest brain injured patient with increasing hours of therapy make faster recoveries and acquire personal independence quicker and are discharged from

			No mention of COI.					progress and were discharged sooner.	rate of recovery of personal independence and result in their being discharged from hospital sooner."	hospitalization much sooner.
Vanderploeg 2008 (4.5)	Physical Therapy	RCT	No mention of sponsorship or COI	366, 18+yo with moderate-severe nonpenetrating TBI <6mo ago with GCS score ≤12, in coma for 12+ hrs, PTA for 24+ hrs, RLAS cognitive level 5-7, active duty military member or veteran, and needing 30+ of acute interdisciplinary TBI rehabilitation.	Mean age cognitive 33.2 ±13.5 years, functional 31.7±12.9 years. 335 males, 25 females.	Cognitive rehab (n=184) targeted 4 cognitive domains: attention, memory, executive functions, and pragmatic communication; one on one sessions  vs  Functional-experiential rehab (n=182) with real-life performance situations and common tasks to compensate for functional deficits after brain injury; group sessions.  All received 1.5-2.5hr/d TBI protocol-specific therapy, 2-2.5hr/d OT, PT, ST. Care continued until ready to discharge home or to	1 year	NS between groups at 1 year for: %RTW or school (38.9 vs. 35.4%, p=0.50), and % living independently (56.3 v 61.6% (p=0.27)). Cognitive FIM post treatment: cognitive (27.3±6.2) v. functional group (25.6±6.0) (p=0.01). NS between groups for motor FIM and DRS. No memory problems: cognitive 22.2% v. functional 27.6% (p=0.05). Those with more education more often lived independently at 1 year in functional (69.1%) vs. cognitive group (47.4%) (p<0.02). Younger more often working at 1 year in cognitive (53.3%) vs. functional group (37.8% (p<0.03)).	"[N]o difference between cognitive-didactic and functional-experiential approaches to brain injury rehabilitation on the primary 1-year global outcome measures of the study. However, patients in the cognitive treatment arm had better posttreatment cognitive performance than patients in the functional treatment arm."	Data suggest both groups improved with similar long term global functional outcomes. Data suggest more improvement in short term functional cognitive outcomes for the cognitive treatment arm.

						community transitional rehabilitation program or completed 60 days specific protocol treatment.				
Wilson 2006 (4.0)	Physical Therapy	RCT Open label trial	Sponsored by the National Institute on Disability and Rehabilitation Research, United States Department of Education, under the Office of Special Education and Rehabilitation Services.  No mention of COI.	N = 38 adults with a TBI diagnosis	Mean age of 29.6 ± 12.4 yrs.  35 Males, 3 Females	Experimental group receiving PWB gait training (N=19)  Vs  Control group receiving traditional physical therapy. (N=19)	No follow up mentioned.	Both groups showed significant improvements (P<0 .05) in both groups on the Functional Ambulation Category, Standing Balance Scale, Rivermead Mobility Index and FIM. However, there was no significant difference between the two groups.	“Results did not support the hypothesis that 8 wks of partial weight-bearing gait retraining improves functional ambulation to a greater extent than traditional physical therapy in individuals after traumatic brain injury based on common clinical measures.”	Baseline comparability differences in months post injury (4.0 vs 2.8) and ages differences between groups. Data suggest similar efficacy between groups and that 8 weeks of partial weight bearing PT post TBI was not better than control group.

## Exercise

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: **Exercise Therapy, Exercise, Circuit-Based Exercise, Resistance Training; Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma,** controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 86 articles in PubMed, 619 in Google Scholar, and 0 from other sources. We considered for inclusion 7 from PubMed, 2 from Google Scholar, and 0 from other sources. Of the 9 articles considered for inclusion, 6 randomized trials and 0 systematic studies met the inclusion criteria.

## Evidence for the Use of Exercise

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Hassett, 2009 (6.0)	Traumatic Brain Injury	RCT	Sponsored by a grant from the Motor Accidents Authority of New South Wales, Australia; and by a scholarship from the Menzies Foundation. No mention of COI.	N= 62 participants with severe traumatic brain injury	Mean age: Fitness centre group 35.4 Home group 33  Sex (M:F) 53:9	Fitness centre group (N=32) received personal training in a strength and fitness training programme 3 times a week for 12 weeks  The home group completed the strength and fitness training at home, unsupervised	Follow up at 3months after end of interventions.	Initial comparisons of pre-intervention and post intervention tests for the experimental group showed significant improvement in the digit symbol task (T12 = 5.21 (p<.01)), verbal learning (T12=3.03, (p<.05)), and immediate retention to visual memory task (T12=2.99 (p<.01)).  Two-way AVOVA tests also showed that in comparison to the control population that the fitness group showed significant improvement in all attention and information processing tasks (F2,18 = 5.93, (p<.05)).	"Exercising in a virtual environment offers the potential for significant gains in cognitive function."	Data suggest comparable efficacy.

Hassett, 2012 (6.0)	Traumatic Brain Injury	RCT	Sponsored by The Menzies Foundation. No COI.	N = 40 patients with severe traumatic brain injury.	Mean age: Experimental group: 39 Control group: 29  Sex(M:F) 27:13	Experimental group (N=20) received circuit class therapy and received heart rate feedback.  Control group (N=20) received circuit therapy without any heart rate feedback.	1 week	No significant difference between the experimental group and the control group for the time spent in the heart rate training zone during the intervention period or during the re-assessment period.	“The low intensity, long duration structure of circuit class therapy can provide sufficient exercise dosage for a fitness training effect for 62% of people with traumatic brain injury. Feedback from heart rate monitors does not necessarily influence exercise intensity.”	Followup only 1 week post fitness training. Data suggest circuit training (low intensity high duration) provided sufficient exercise in 62% of TBI. Heart rate monitor feedback does not appear to influence intensity.
Hoffman 2010 (5.0)	Exercise	RCT	No mention of sponsorship or COI.	N = 84 with a history of prior TBI of at least 6 months to 5 years post injury with a ≥ on the patient health questionnaire.	Mean age for control and treatment; 37.1 vs 39.7. 40 males and 40 females.	Exercise group weekly supervised sessions with education, warm up, 30 minutes or aerobic exercise (that reached a heart rate goal of 60% estimated maximal heart rate), and cool down plus encourage home exercise (4 times a week	10-weeks	Both control and exercise groups had increases in their total minutes per week exercised. There was no difference between groups in total increased minutes, (p = 0.064). There was a difference in days per week of exercise (3.68 vs. control: 2.05 p = 0.004). Control vs. exercise outcomes: Depression (Beck	“Because of its potential positive effect on cognition as well as mood, as well as its attractiveness to people with TBI as a means of treating depression, further efforts should be made to investigate the efficacy of exercise and means of fostering	Data suggest comparable (in)efficacy. Subgroup analyses showed highest levels of exercise/wk had less depression, improved sleep and better quality of life.

						for 30 min) for 10 weeks (N = 37) Vs Control group not exercise intervention until after the 10-week assessment (N = 39) .		depression) 21.2 vs. 16.4, ( $p = 0.250$ ).	adherence with exercise prescriptions in those with TBI.”	
Bellon, 2014 (3.5)	Traumatic Brain Injury	RCT	Sponsored by grants from the National Institute on Disability and Rehabilitation Research. No mention of COI.	N = 69 patients with TBI.	Mean age 43.7 Sex (M:F) 41:18	Walking-nutrition group (N =28 ) used pedometers daily during a 12 week program. Participants were assigned a walking coach and were given weekly walking goals. After 12 weeks, the group was evaluated then assigned to the nutritional intervention.  vs Nutrition-walking group (N =39 ) was asked to identify areas of their diet that needed improvement, and were assigned a nutritional coach. After 12	12 weeks and 24 weeks from baseline	A significant effect was found for Assessment Time ( $F(2,130)=5.185$ , ( $p = .007$ )) and depression with depression scores decreasing by 24 weeks.  A significant interaction was found between Stress levels and Time of Assessment and Intervention Order ( $F(2,134) = 5.274$ , ( $p= .006$ )) with larger declines during the walking interventions of each group.  A significant effect for Assessment Time ( $F(2,134) = 5.304$ ), ( $p = .006$ )	“While limitations existed with the study, it is evident that walking can be used as an efficient and cost-effective tool to manage perceived stress and depressive symptoms in persons who have sustained a TBI.”	

						weeks, the group was evaluated and assigned to the walking intervention.		with stress scores decreasing at 24 weeks.		
Grealy, 1999 (3.5)	Traumatic Brain Injury	RCT	No sponsorship. No COI.	N = 13 patients with traumatic brain injury	Mean age of experimental group 32.4  Sex (M:F) 8:5	The experimental group (N=13) received one exercise session on a non-immersive virtual reality bicycle.  Control populations were collected from a database of 320 TBI patients. Controls had similar age $\pm 2$ years, similar injury GCS $\pm 1$ , and similar time post injury $\pm 2$ weeks.		After the 4-week intervention patients performed significantly better than controls on the digit symbol ( $t = 5.21$ ( $p < .01$ )), verbal ( $t = 3.03$ ( $p < .01$ )), and visual learning tasks ( $p < .05$ ).  Significant improvements in reaction times ( $p < .01$ ) and movement times ( $p < .05$ ) were gained following a single bout of VR exercise.	"Exercising in a virtual environment offers the potential for significant gains in cognitive function."	Random allocation crossover design. Sig. variance in time since injury (1.3 vs. 179 wks) and other data on group characteristics suggesting potential randomization failure.

Strengthening exercises are geared to produce improvements in maximum voluntary contraction. This improves ability to perform vocational and activities of daily living.

## Strengthening Exercises

### Recommended.

Strengthening exercises are recommended for use in the treatment of subacute, chronic, postoperative, moderate and severe TBI patients.

#### *Strength of Evidence – Recommended, Insufficient Evidence (I)*

#### *Level of Confidence – Low*

<i>Indications:</i>	For subacute, chronic, postoperative, moderate and severe TBI patients.
<i>Frequency/Dose/Duration:</i>	Generally prescribed on at least a daily basis. May require daily supervised treatment that transitions to home-based exercise program. Duration of supervised exercise is dependent on the severity of the deficits. Further durations should be based on ongoing improvements in function, particularly those that are not able to be sustained by a home-based program.
<i>Indications for Discontinuation:</i>	When desired improvement has been achieved, clinical plateau or failure to improve.
<i>Benefits:</i>	Improved physical fitness, mood, self esteem and motor performance.
<i>Harms:</i>	Negligible
<i>Rationale:</i>	There are no quality trials including primarily strengthening exercises. Strengthening exercises are not invasive, have low adverse effects, are relatively low cost depending on supervision requirements and duration, and are recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Strengthening, exercises, traumatic, brain, intracranial, closed, head, penetrating, craniocerebral, injury, trauma, concussion; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 3 articles in PubMed, 1 in Scopus, 2 in CINAHL, 1 in Cochrane Library, 1150 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1157 articles considered for inclusion, 0 randomized trials and 1 systematic studies met the inclusion criteria.

Stretching and flexibility exercises improve range of motion. When there is a poor range of motion, function can be significantly, adversely affected.

## Stretching and Flexibility Exercises

### Recommended.

Stretching and flexibility exercises are recommended for use in the treatment of subacute, chronic, postoperative, moderate and severe TBI patients.

#### *Strength of Evidence – Recommended, Insufficient Evidence (I)*

#### *Level of Confidence – Low*

<i>Indications:</i>	For subacute, chronic, postoperative, moderate and severe TBI patients.
<i>Frequency/Dose/Duration:</i>	Generally prescribed on at least a daily basis. May require daily supervised treatment that transitions to home-based exercise program. Duration of supervised exercise is dependent on the severity of the deficits. Further durations should be based on ongoing improvements in function, particularly those that are not able to be sustained by a home-based program.
<i>Indications for Discontinuation:</i>	When desired improvement has been achieved, clinical plateau or failure to improve.
<i>Benefits:</i>	Improved physical fitness, mood, self esteem and motor performance.
<i>Harms:</i>	Negligible
<i>Rationale:</i>	There are no studies involving primarily stretching and flexibility. There are no quality trials including primarily stretching and flexibility exercises. These exercises are not invasive, have low adverse effects, are low to moderate cost depending on supervision requirements and duration, and are recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: stretch, flexibility, stretching and flexibility, exercise, yoga, traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 91 articles in PubMed, 0 in Scopus, 5 in CINAHL, 0 in Cochrane Library, 12000 in Google Scholar, and 2 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 2 from other sources. Of the 2 articles considered for inclusion, zero randomized trials and 2 systematic studies met the inclusion criteria.

Relaxation exercises are activities that may help reduce anxiety, stress, anger, and pain. [118, 702]  
Group discussions may also be included in relaxation exercises. Relaxation is a broad topic that has many different types including physical, mental, and emotional techniques.

## Relaxation Exercises, Group Discussions

### No Recommendation.

There is no recommendation for or against relaxation exercises and group discussion for the treatment of TBI patients.

#### *Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

#### *Level of Confidence – Low*

Rationale:	There are 2 moderate quality studies involving relaxation. In [703], Qignong somewhat improved mood and self esteem and in [704], there was improved cardiovascular function which did not translate into improved psychological function or functional independence or mobility. Thus, there are no quality studies addressing relaxation exercises. Relaxation exercises are not invasive, have low adverse effects, are low cost and in the absence of quality evidence, there is no recommendation for or against relaxation exercises.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Relaxation exercises, Group Discussion, Traumatic brain injury, Intracranial injury, Closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma, closed head trauma, penetrating head trauma, penetrating craniocerebral, trauma, population groups, relaxation, group therapy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1 articles in PubMed, 0 in Scopus, 5 in CINAHL, 71 in Cochrane Library, 19800 in Google Scholar, and 1 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 1 from Cochrane Library, 1 from Google Scholar, and 2 from other sources. Of the 4 articles considered for inclusion, 2 randomized trials and 0 systematic studies met the inclusion criteria.

### Evidence for the Use of Relaxation Exercises/Group Discussion

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Bateman 2001 (5.5)	Relaxation Exercises	RCT	No mention of COI.	175 patients that sustained a single-incident brain injury either traumatic or vascular	Control Group Mean age: 44.7±13.3 years. Training group Mean age: 41.7±14.3 years. 97 males, 60 females.	Ergometer Aerobic Training (Training Group) Vs Relaxation Training Control Group (Control Group)	12 weeks following end of training	Significant improvements in exercise capacity ( $p = .05$ ) in the exercise training group ( $n = 70$ ) relative to the control group ( $n = 72$ ) were not matched by greater improvements in functional independence, mobility, or psychological function, at either 12 weeks or follow-up.	“The benefits of improved cardiovascular fitness did not appear to extend to measurable change in function or psychological state.”	Data suggest the improvements in exercise capacity (improved cardiovascular fitness) did not translate into measurable changes in terms of function or improved psychological outcomes(s).
Blake 2009 (4.5)	Relaxation Exercises	RCT	No COI.	20 individuals with brain injury	Control group mean age: 46.20±11.27 years. Exercise group±10.52 years. 15 males, 5 females.	Exercise group: received supervised Quigong instruction once per week for one hour Vs Control group: attended non-exercise social and leisure activities one hour per week for 8 weeks	Follow up at 8 weeks	Groups were comparable at baseline. After the intervention, mood was improved in the exercise group when compared with controls ( $U=22.0$ , $P=0.02$ ). Improvements in self-esteem ( $Z=2.397$ , $P=0.01$ ) and mood ( $Z=-2.032$ , $P=0.04$ ) across the study period were also evident in the exercise group only. There were no significant differences in physical functioning between groups. In view of the sample size, these findings are inconclusive.	“This study provides preliminary evidence that a brief Qigong exercise intervention programme may improve mood and self-esteem for individuals with traumatic brain injury. This needs to be tested in a large-scale randomized trial.”	Small sample size. Data suggest Quigong exercise may improve mood and self esteem but no difference in physical functioning between groups.

Aerobic exercises include brisk walking, running, swimming, and hiking. Physical activity has been suggested to “improve the learning capacity associated with long-term memory within the brain” [705]. Exercising after injuries purportedly “stimulates repair mechanisms and enhance the functional recovery after suffering a traumatic brain injury” [705]. Aerobic exercise is believed to “improve the cognitive capacity and facilitate improved physical actions and range of motion within those who suffer from cognitive impairment” [706].

## Aerobic Exercise

### Recommended.

Aerobic exercise is recommended for use in the treatment of subacute, chronic, postoperative, moderate and severe TBI patients.

#### *Strength of Evidence – Recommended, Insufficient Evidence (I)*

#### *Level of Confidence – Low*

<i>Indications:</i>	For subacute, chronic, postoperative, moderate and severe TBI patients.
<i>Frequency/Dose/Duration:</i>	Generally prescribed on at least a daily basis. May require daily supervised treatment among more severely affected patients that transitions to home-based exercise program. Duration of supervised exercise is dependent on the severity of the deficits. Further durations should be based on ongoing improvements in function, particularly those that are not able to be sustained by a home-based program.
<i>Indications for Discontinuation:</i>	When desired improvement has been achieved, clinical plateau or failure to improve.
<i>Benefits:</i>	Improved physical fitness, mood, self esteem and motor performance.
<i>Harms:</i>	Negligible
<i>Rationale:</i>	There are 4 moderate quality studies involving aerobic exercise [703, 704, 707, 708]. One trial found improvements in cardiovascular fitness, but no psychological or functional change [704]. One trial found benefits from aquatic treatment [708]. There are no sizable trials including primarily aerobic exercises. Aerobic exercises are not invasive, have low adverse effects, are low to high cost depending on supervision requirements and duration, and are recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Aerobic, exercise, exercising, physical activity, traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 19 articles in PubMed, 115 in Scopus, 7 in CINAHL, 45 in Cochrane Library, 2,570 in Google Scholar, and 0 from other sources. We considered for inclusion 3 from PubMed, 1 from Scopus, 0 from CINAHL, 1 from Cochrane Library, 6 from Google Scholar, and 0 from other sources. Of the 11 articles considered for inclusion, 5 randomized trials and 6 systematic studies met the inclusion criteria.

## Evidence for the Use of Aerobic Exercise

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Bateman 2001 (5.5)	Aerobic Exercise	RCT	No sponsors hip or conflict of interest.	N = 157 who had suffered a one-time brain injury within the past 10 to 38 weeks	Mean age for exercise group 41.7 years and for control group 44.7 years. 60 females, 97 males.	Cycle ergometer aerobic exercising group (n=70)  Vs.  Relaxation exercise group	24 weeks (12 weeks post training)	At alpha level .05 the exercising group did not have statistically significant improvements in mobility or psychologic function at weeks 12 or 24.	“The benefits of improved cardiovascular fitness did not appear to extend to measurable change in function or psychologic state.”	Data suggest the improvements in exercise capacity (improved cardiovascular fitness) did not translate into measurable changes in terms of function or improved psychological outcome.
Canning 2003 (4.5)	Aerobic Exercise	RCT	Partially funded by the Motor Accident Authority of New South Wales. No conflict of interest.	N = 24 participants who suffered a severe TBI within past 12 months and currently are attending inpatient rehabilitation	Mean age for control group 25.6 and for exercise group 24.75. 6 females, 16 males.	Experimental exercise group who had four weeks of sit-to-stand and step-up training exercises (n = 13)  Vs.  Control group with no additional training exercises (n = 11)	None	The exercise group produced a statistically higher improvement in number of repetitions of sit-to-stand movements in three minutes compared to the control group’s improvement (p < 0.05). The exercise group improved by 62% while the control group improved by 18%.	“Intensive task-specific training is recommended as an important component of rehabilitation early following severe traumatic brain injury.”	Small sample size. Data suggest intensive sit to stand training is beneficial for TBI patients in retraining motor performance. No long term follow up.
Driver 2004 (4.5)	Aerobic Exercise	RCT	No mention of sponsors hip or conflict	N = 16 who suffered a brain injury at	Mean age for study population 37.65. 8 females, 8 males.	Exercise group who completed three one-hour aquatic exercise sessions per week for 8 weeks	None	The exercise group had several measures of body movement, including elbow flexion, hip flexion, knee flexion, and body composition, which	“By providing an exercise programme that meets regularly, is safe and fun, it is possible to positively impact	Small sample size. Data suggest physical fitness improved in aquatic exercise group.

			of interest.	least one year prior		with a personal instructor (n = 8)  Vs.  Control group who participated in a vocational rehabilitation class focusing on writing and reading for 8 weeks (n = 8)		improved significantly when comparing pre- and post-scores ( $p < 0.05$ ). All comparisons were measured using paired sample t-tests.	the functional capacity of people with a brain injury. Results also indicate that people with a brain injury can respond to a training stimulus as physical work capacity, ROM and muscular strength and endurance improved. Consequently, aquatic exercise programmes can play an integral part in the rehabilitation programmes currently available to outpatients with a brain injury."	
Blake 2009 (4.5)	Aerobic Exercise	RCT	No mention of COI. Funded by the Headway House, Nottingham am.	N = 20 with chronic TBI	Mean age for exercise group 44.5 (1 female, 9 males). Mean age for control group 46.20 (4 females, 6 males)	Exercise group who underwent supervised one hour Qigong instruction sessions once a week for 8 weeks (n = 10)  Vs.  Control group who underwent one hour non-exercise activities, including group discussion, drawing, and writing, once a week for 8 weeks (n = 10)	8 weeks	The exercise group had statistically improved mood ( $p = 0.02$ ) and self-esteem ( $p = 0.01$ ) when compared to the control group. These comparisons were created using the Mann-Whitney U-test. However there was no significant difference between the two groups in regards to physical function improvement.	"This study provides preliminary evidence that a brief Qigong exercise intervention programme may improve mood and self-esteem for individuals with traumatic brain injury. This needs to be tested in a large-scale randomized trial."	Small sample size. Data suggest Qigong exercise may improve mood and self esteem but no difference in physical functioning between groups.

Aquatic therapy involves the performance of aerobic and/or flexibility and/or strengthening exercises in a pool. It is particularly used to minimize the effects of gravity, especially where reduced weight-bearing status is desirable.

## Aquatic Therapy for Select TBI Patients

### Recommended.

A trial of aquatic therapy is recommended for the treatment of subacute or chronic TBI in select patients.

#### **Strength of Evidence – Recommended, Evidence (C)**

#### **Level of Confidence – Moderate**

<i>Indications:</i>	Patient's with subacute or chronic TBI who meet criteria for referral for supervised exercise therapy and has co-morbidities (e.g., extreme obesity, significant degenerative joint disease, etc.) that preclude effective participation in weight-bearing physical activity. May also be considered when TBI impairments are sufficiently severe that removing effects of gravity improves, e.g., range of motion. Land-based exercise is generally preferable for mild TBI or for patients largely recovered, as they tend to be sustainable for most patients.
<i>Frequency/Dose/Duration:</i>	Program should generally begin with 3 to 4 visits per week. Patient should have demonstrated evidence of functional improvement within the first 2 weeks to justify additional visits. Program should include up to 4 weeks of aquatic therapy with progression towards a land-based, self-directed physical activity or self-directed aquatic therapy program by 6 weeks. Durations beyond 6 weeks should be limited to severe TBI patient injuries who are still demonstrating objective improvements at 6 weeks that cannot be achieved with land-based activities.
<i>Indications for Discontinuation:</i>	Non-tolerance, failure to progress or aggravation of pain or desired clinical outcome.
<i>Benefits:</i>	Ability to engage in exercise and rehabilitation when unable to sufficiently tolerate weight-bearing exercises in a traditional physical or occupational therapy program. More rapid improvements in range of motion in severe TBI patients.
<i>Harms:</i>	May aggravate pain in a minority.
<i>Rationale:</i>	There is one moderate quality study involving aquatic aerobic exercise [708] that suggested improved physical fitness. Aquatic therapy is not invasive, has low adverse effects, is moderate to high in cost, depending upon numbers of visits but is likely effective, thus aquatic therapy is recommended for select patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Aerobic, exercise, exercising, physical activity, traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 19 articles in PubMed, 115 in Scopus, 7 in CINAHL, 45 in Cochrane Library, 2,570 in Google Scholar, and 0 from other sources. We considered for inclusion 3 from PubMed, 1 from Scopus, 0 from CINAHL, 1 from Cochrane Library, 6 from Google Scholar, and 0 from other sources. Of the 11 articles considered for inclusion, 5 randomized trials and 6 systematic studies met the inclusion criteria.

### Evidence for the Use of Aquatic Exercise

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Driver 2004 (4.5)	Aquatic Aerobic Exercise	RCT	No mention of sponsors hip or conflict of interest.	N = 16 who suffered a brain injury at least one year prior	Mean age for study population 37.65. 8 females, 8 males.	Exercise group who completed three one-hour aquatic exercise sessions per week for 8 weeks with a personal instructor (n = 8)  Vs.  Control group who participated in a vocational rehabilitation class focusing on writing and reading for 8 weeks (n = 8)	None	The exercise group had several measures of body movement, including elbow flexion, hip flexion, knee flexion, and body composition, which improved significantly when comparing pre- and post-scores (p < 0.05). All comparisons were measured using paired sample t-tests.	“By providing an exercise programme that meets regularly, is safe and fun, it is possible to positively impact the functional capacity of people with a brain injury. Results also indicate that people with a brain injury can respond to a training stimulus as physical work capacity, ROM and muscular strength and endurance improved. Consequently, aquatic exercise programmes can play an integral part in the rehabilitation programmes currently available to outpatients with a brain injury.”	Small sample size. Data suggest physical fitness improved in aquatic exercise group.

## Activity Modification

Rest is often recommended because of a concern for reinjury during recovery from concussion [709-711]

### Rest

#### Not Recommended.

Rest is not recommended for use in the treatment of TBI patients.

*Strength of Evidence* – **Not Recommended, Evidence (C)**

*Level of Confidence* – **High**

*Rationale:*

There are quality studies assessing Rest for treatment of TBI. Rest is not invasive, has adverse effects, is low cost, has evidence of lack of efficacy, and is not recommended for treatment of TBI.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: rest, resting, traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral, trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 233 articles in PubMed, 467 in Scopus, 15 in CINAHL, 2 in Cochrane Library, 49800 in Google Scholar, and 0 from other sources. We considered for inclusion 8 from PubMed, 0 from Scopus, CINAHL, Cochrane Library, Google Scholar, and 0 from other sources. Of the 8 articles considered for inclusion, 3 randomized trials and 3 systematic studies met the inclusion criteria.

## Evidence for the Use of Rest

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Thomas 2015 (6.5)	TBI	RCT	Sponsored by Injury Research Center of the Medical College of Wisconsin. No COI.	N = 99 with mild TBI / concussion.	Aged 11 – 22 years, 65 males and 34 females.	Intervention or strict rest for 5 days (N = 50) vs Control or usual care for 1-2 days of rest, followed by stepwise return to activity (N = 49).	10 days	At 10-day period, strict rest group reported greater PCSS scores / higher total number of postconcussive symptoms / and higher daily PCSS clustered at day 4: 187.9 vs 131.9 [C], $p < 0.03$ / 79.4 [I] vs 50.2 [C], $p < 0.03$ / and 13.95 [C] vs 21.51 [I], $p < 0.03$ . Subgroup analysis; higher postconcussive symptom score at day 10 randomized to strict rest (15.2 [I] vs 7.7 [C], $p < 0.04$ ). Those who presented to ED with immediate signs of concussion and those with past history of concussion randomized to strict rest (11.0 [I] vs 14.6 [C], $p = 0.22$ and 15.1 [I] vs 5.6 [C], $p < 0.05$ ).	“Recommending strict rest for adolescents immediately after concussion offered no added benefit over the usual care.”	Data suggest strict bed rest after acute concussion not beneficial in speeding up recovery or discharge vs usual care.

Body weight support treadmill training (BWSTT) is a physical therapy technique to assist patients with limited or no walking ability to walk on a treadmill with his/her body weight supported by a harness connected to an overhead support system [712]. Those undergoing this treatment engage in high repetitions of task-oriented practices to improve motor skills and balance impairments [619]. Treadmill usage in turn allows progressive numbers of steps and increases the amount of task-specific practice a participant receives within one session [619].

## Body Weight Support Treadmill Training for TBI Patients

### Recommended.

Body weight support treadmill training is recommended for use in the treatment of TBI patients who have an inability to walk safely.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Moderate**

<i>Indications:</i>	Inability to walk, or inability to walk safely while having sufficient patient abilities to move the lower extremities.
<i>Benefits:</i>	Fosters faster return to walking ability, regain of muscle strength, and/or slower loss of strength.
<i>Harms:</i>	Negligible.
<i>Frequency/Dose/Duration:</i>	The optimum regimen needs to be tailored to the patient’s abilities and stage of recovery. The 2 comparative trials used widely differing regimens, i.e., 15min 2x/wk [713] and 45 min, 3x/wk [620].
<i>Indications for Discontinuation:</i>	Ability to walk with a walker, or to walk unassisted.
<i>Rationale:</i>	There are no sham or placebo-controlled trials. There are a few quality comparative studies assessing Body Weight Support Treadmill Training for treatment of TBI [713] [620], mostly showing comparable efficacy with other techniques. Body Weight Support Treadmill Training is not invasive, has negligible adverse effects, is high cost in aggregate, has evidence of efficacy, and thus is recommended for select treatment of TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: body weight support treadmill training, body-weight-supported treadmill training, body weight supported treadmill training, BWSTT; traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 6 articles in PubMed, 14 in Scopus, 1 in CINAHL, 10 in Cochrane Library, 329 in Google Scholar, and 1 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 1 from other sources. Of the 4 articles considered for inclusion, 3 randomized trials and 1 systematic study met the inclusion criteria.

### Evidence for the Use of Body Weight Support Treadmill Training

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Brown 2005 (5.5)	Body Weight Support Treadmill Training	RCT	No mention of COI or sponsorship.	N = 19 in postacute phase of TBI rehab	Mean age for COGT group 42.56 (3 female, 6 male). Mean age for BWSTT group 38.00 (3 female, 7 male).	Conventional over ground gait training (COGT) (n = 9)  Vs.  Body weight-supported treadmill training (BWSTT) (n = 10)	3 months after initiation of treatment	Mean increase in velocity was 0.8 cm/s for COGT and 2.8 cm/s for BWSTT. There was no significant difference in velocity overall (p=0.573). There was no between group differences in velocity changes (p=0.837). Mean stride difference was -3.6 cm for COGT and -1.0 for BWSTT. Both differences were significant (p=0.036). No significant between group differences (p=0.198). A significant difference between groups in step length change was observed (p=0.011) with COGT decreasing by 7.3 cm and BWSTT increasing by 8.9. No significant difference in function reach was observed within groups (p=0.106) or between groups (p=0.957). No significant improvement in FAC levels were observed overall (p=0.331) or between groups (p=0.641). There was no significant difference observed for mean TUG scores overall (p=0.178) or	“[T]he BWSTT was not found to be more effective than the COGT when provided more than 3 months to individuals greater than 6 years post-TBI. On the contrary, gait symmetry improved more in the COGT group. Three months of physical therapy exercises tailored to the individual’s needs, along with either the BWSTT or COGT, resulted in a narrower step width (approaching the norm) during ambulation for individuals with chronic TBI. Gait velocity and FAC did not change significantly for either group	Small sample sizes, resulting in many results likely underpowered. Pop. Is 6+yrs post-TBI. Data suggest COGT better than BWSTT for improving gait symmetry, but some findings better with treadmill.

								between groups (p=0.872).	after only 3 months of intervention.”	
Esquenazi 2012 (4.5)	Body Weight Support Treadmill Training	RCT	No COI. Study was supported by grants from MossRehab Research Fund Disclosure and Department of Defense, CDC.	N = 16 with TBI and baseline over group walking self-selected velocity of $\geq 0.2$ m/s to 0.6 m/s	Mean age for RATT $37.1 \pm 10.6$ (5 female, 3 male). Mean age for MATT $41.9 \pm 16.8$ (4 female, 4 male)	Robotic-assisted treadmill training (RATT), 45 minutes 3 times a week (n= )  Vs.  Manually assisted treadmill training, 45 minutes 3 times a week (n= )	6 to 8 weeks	All parameters produced no significant between-group differences. The average SSV increased in RATT by 49.8% (p=0.01) and by 31% (p=0.06) for MATT. RATT group average maximal velocity increased by 14.9% (p=0.06) and MATT group increased by 30.8% (p=0.01). RATT group step-length asymmetry ratio improved by 33.1% (p=0.01) and by 9.1% (p=0.73) for MATT group. RATT group distance walked increased by 11.7% (p=0.21) and MATT group increased by 19.3% (p=0.03). Mobility improvement was present for both groups (p=0.03).	“The results of this study demonstrate greater improvement in symmetry of gait (step length) for RATT and no significant differences between RATT and MATT with regard to improvement in gait velocity, endurance, and SIS. Our study provides evidence that participants with a chronic TBI can experience improvements in gait parameters with gait training with either MATT or RATT.”	Small Sample. Data suggest comparable results for both RATT and MATT on all outcome measures except greater improvement of step length (gait symmetry) from RATT was observed.

Constraint-induced movement therapy is used to help regain function of an upper extremity after traumatic brain injury has caused a deficit [714]. There are 3 aspects on constraint induced movement therapy such as, forced use of affected hand while restraining intact hand, training by shaping movements by affected hand, and doing both at the same time [715]. Often a splint or a sling are used to restrain the hand. An increasing amount of randomized controlled trials are being conducted within and outside the United States. Some studies are showing that longer CIMT sessions are showing more successful recovery.

## **Constraint-Induced Movement Therapy (CI) for TBI Patients**

### **Recommended.**

Constraint-induced movement therapy is recommended for use in the treatment of severe TBI patients who have limb function deficits.

### **Strength of Evidence – Recommended, Evidence (C)**

#### **Level of Confidence – Low**

<i>Indications:</i>	Severe TBI patients with deficits in limb function
<i>Benefits:</i>	Faster improvement in use of the more affected limb.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	14 days of 6 hrs session was more effective than a 3hr session in one trial [715]. Frequencies of an ongoing program unclear, thus individualization is recommended.
<i>Indications for Discontinuation:</i>	Reaching an acceptable plateau of performance or lack of progression of objective measures would be a reason to stop the program.
<i>Rationale:</i>	There is one moderate-quality study assessing Constraint-Induced Movement Therapy (CIMT) for treatment of TBI. CIMT is not invasive, has no adverse effects, is moderate to high cost in aggregate, has evidence of treatment efficacy, and is recommended for select treatment of TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Activity Modification, Constraint-induced movement therapy, CI, CIMT, Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury, Craniocerebral Trauma, Closed Head Trauma, Penetrating Head Trauma, Penetrating Craniocerebral Trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 5 articles in PubMed, 79 in Scopus, 4 in CINAHL, 18 in Cochrane Library, 897 in Google Scholar, and 0 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 1 randomized trial and 0 systematic studies met the inclusion criteria.

### Evidence for the Use of Constraint-Induced Movement Therapy

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Sterr, 2002 (4.0)	Traumatic Brain Injury	RCT	No mention of industry sponsorship. No COI.	N=18	11 males, 4 females. Mean age of 3h/d: 68.4±7.0 years Mean age of 6h/d: 49.9±18.5 years.	3H/D Group: (n=8) Vs. 6H/D Group: (n=7)	Weekly For 1 month	ANOVA for AOU and QOM showed treatment gain by a strong time effect respectively (p<.01, P<.01). Treatment effect was greater for 6h/d groups than for 3h/d group. Median pre-post performance time gain was 2.34 seconds for 6 h/d group, but only .64 seconds for 3 h/d group. Interaction was not significant. Beneficial effects were greater in 6 h/d group than in 3 h/d group.	"The 3-hour CIMT training schedule significantly improved motor function in chronic hemiparesis, but it was less effective than the 6-hour training schedule."	Small sample. Data suggest 6 hour training CIMT significantly improved motor function in chronic hemiparesis patients compared to 3 hour CIMT training group.

Whole body vibration is a therapeutic technique most commonly used in physical injuries to improve muscular functions by placing a patient on a vibrating platform. [716, 717]. Whole body vibration has been used to treat spinal cord injuries, knee osteoarthritis, muscle tears, and many more muscle related injuries [717, 718].

### **Whole Body Vibration (WBV) for TBI Patients**

#### **No Recommendation.**

There is no recommendation for or against the use of whole body vibration in the treatment of TBI patients.

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

There are no quality studies assessing Whole Body Vibration for treatment of TBI. Whole Body Vibration is not invasive, has minimal adverse effects, is moderately costly in aggregate, but has no quality evidence of efficacy, and so there is no recommendation for treatment of TBI.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: whole body vibration, Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury Craniocerebral Trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed zero articles in PubMed, 205 in Scopus, zero in CINAHL, zero in Cochrane Library, 60 in Google Scholar, and zero from other sources. **Zero** articles met the inclusion criteria.

Specific motor stimulation has been used to treat hand impairments from stroke or TBI [719].

## Specific Motor Stimulation

### Recommended.

Specific motor stimulation is recommended for use in the treatment of moderate to severe TBI patients who have notable impairment of at least one extremity.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

<i>Indications:</i>	Moderate to severe TBI injuries with notable impairment of at least one extremity. The quality study had entry criteria of <80% score on the Action Research Arm Test [719].
<i>Benefits:</i>	Improved functional rehabilitation of an extremity
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	One hour session daily, 5 days/wk for 6 weeks.
<i>Rationale:</i>	There is one moderate quality trial suggesting specific motor stimulation is effective for rehabilitation of patients, however, 90% of the patients were stroke patients [719]. Specific motor stimulation is not invasive, has low adverse effects, is high cost in aggregate, and while some evidence suggests it may be effective, the population was not primarily TBI, thus it is recommended by consensus (I).
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 6 articles in PubMed, 2742 in Scopus, 14 in CINAHL, 2 in Cochrane Library, 21500 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

### Evidence for the Use of Specific Motor Stimulation

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Ross 2009 (7.5)	Intensive Hand Therapy to Improve Arm Function	RCT	No COI. Supported by a Queensland Health Allied Health Research Scheme award.	N = 39 with hand impairment following stroke or TBI	18 female, 21 male. Mean age for control group 59 years, experimental group 60 years	Control (n = 19) vs Intensive Hand-training group, five 1-hour sessions for six weeks (n = 20)	6 weeks after initial treatment	<p>Mean Action Research Arm Test Score Changes: Control 17, Experimental 11, Mean between-group difference -6 (P=0.371).</p> <p>Mean Summed Manual Muscle Test Score Changes: Control 10, Experimental 14, Mean between-group difference 3 (P= 0.651).</p>	“Hand and overall arm function of all participants improved over the six-week period, however there was not a clear benefit from providing additional hand therapy.”	Population predominantly stroke patients (90%) vs (10%) TBI. Data suggest similar efficacy between intensive and conventional groups.

Systematic instruction is a multiple component system for teaching skills and other information based on a specific method. Systematic instruction has been used for rehabilitation of acquired brain injury [720, 721].

## **Systematic Instruction**

### **Recommended.**

Systematic instruction is recommended for the treatment of TBI patients with moderate to severe cognitive impairments.

*Strength of Evidence* – **Recommended, Evidence (C)**

*Level of Confidence* – **Low**

<i>Indications:</i>	TBI patients with moderate to severe cognitive impairments.
<i>Benefits:</i>	Improved learning that is better than trial-and-error learning
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	N/A
<i>Rationale:</i>	There is one moderate quality trial suggesting systematic instruction is more effective than trial-and-error learning for rehabilitation of TBI patients [720]. Systematic instruction is not invasive, has no adverse effects, is low to moderate cost in aggregate, has evidence of efficacy and is recommended for treatment of TBI patients with moderate to severe cognitive impairments.
<i>Evidence:</i>	<b>Systematic Instruction</b> – A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: <b>Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, Closed Head Trauma, Penetrating Head Trauma, Penetrating Craniocerebral Trauma,</b> controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 59 articles in PubMed, 33 in Scopus, 0 in CINAHL, 92 in Cochrane Library, 22300 in Google Scholar, and 1 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 1 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic studies met the inclusion criteria.

### Evidence for the Use of Systematic Instruction

<i>Author Year (Score):</i>	<i>Category :</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Powell, 2012 (7.0)	Systematic Instruction	RCT	No mention of COI and sponsored by the National Institutes of Health, National Center for Medical and Rehabilitation Research, Award #5R03HD054768.	N=29 persons with moderate-severe cognitive impairments due to acquired brain injury.	Mean age: 42.31±13.43 years. 17 males, 12 females.	Systematic Instruction Group: (n=15) 12, 45-minute individual training sessions on PDA Vs. Conventional Instruction Group: (n=14) 12, 45-minute individual training sessions on PDA	30 days	No significant differences were observed in either group except in the 30 day follow-up posttest. Systematic instruction participants showed better PDA skills.	“These results demonstrate that systematic instruction applied to ATC results in better skill maintenance and generalization than trial-and-error learning for individuals with moderate-severe cognitive impairments due to acquired brain injury.”	Data suggest systematic instruction training better than trial and error learning for ATC (assistive tech. for cognition) and TBI patients.

Television-assisted rehabilitation has been used for treatment of TBI patients by prompting reminders on a TV [722, 723].

## Television-Assisted Rehabilitation

### Recommended.

Television-assisted rehabilitation is recommended for use in the treatment of TBI patients.

*Strength of Evidence* – **Recommended, Evidence (C)**

*Level of Confidence* – **Low**

<i>Indications:</i>	TBI impacts that limit completion of tasks at home, for which reminders are likely helpful [722].
<i>Benefits:</i>	Improved task completion. May be usable to remind to complete exercises or cognitive exercises.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	N/A
<i>Rationale:</i>	There is one moderate quality trial of television-assisted rehabilitation for treatment of acquired brain injury patients that suggested some efficacy [722]. Television-assisted rehabilitation is not invasive, has no adverse effects, is moderate to high cost, has some evidence of efficacy and is thus recommended for treatment of TBI patients [722].
<i>Evidence:</i>	<b>Television Assisted Rehabilitation</b> – A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: <b>Television Assisted Rehabilitation; Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury</b> controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1 articles in PubMed, 3 in Scopus, 2 in CINAHL, 0 in Cochrane Library, 11 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 1 systematic studies met the inclusion criteria.

### Evidence for the Use of Television Assisted Rehabilitation

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Lemonce Ilo 2011 (5.0)	Television Assisted Prompting	RCT	Research was funded by a grant from the US department of Education, National Institute on Disability Rehabilitation & Research. No COI.	N=23	Group 1: 7 males, 5 females; Mean age 47.2±14.5. Group 2: 5 males, 6 females; Mean age 47.6±18.1.	Group 1: received Television Assisted prompt (TAP) (N=12) VS. Group 2: received typical practice (TYP) (N=11)	Follow-up at baseline, 4 and 8 wks.	Task completion was higher in TAP group (df=520, mean=0.72, SE=0.02) than with TYP (df=520, mean=0.73, SE=0.02). TAP group completed more experimental tasks compared with preferred or non-preferred tasks (p=0.01). Satisfaction survey at conclusion of study suggest that participants found TA system useful in for reminders, easy to use, and yielded greater flexibility in daily scheduling.	This study suggested that when ProM reminders are delivered automatically and via a familiar medium, the television, adults with ABI completed a greater number of tasks than when participants used self-selected or typical reminder strategies.	Crossover RCT. Data suggest TAP showed advantage for memory prompting over no prompting and higher task completion.

(Re)learning a series of actions is essential for function, both in the home and workplace. This has been used for treatment of TBI patients [724, 725].

## Action Sequences

### Recommended.

Action sequences are recommended for use in the treatment of patients with severe TBI.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – Low

<i>Indications:</i>	Severe TBI patients with requirements to (re)learn sequences of functional tasks.
<i>Benefits:</i>	Better learning of required tasks
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Modeling the activities to be taught is reportedly superior to molding, with 69% better longer-term recall of a learned sequence [724].
<i>Rationale:</i>	There is one moderate quality RCT [724] and one low quality trial [725]. The sole quality study suggests. These principles appear equally applicable to vocational rehabilitation as to activities of daily living, although there is no quality study regarding teaching occupationally relevant action sequences. Teaching action sequences is not invasive, has negligible adverse effects, is low to moderate cost and has some data suggesting some efficacy and so is recommended for treatment of select TBI patients.
<i>Evidence:</i>	Action Sequences– A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, Closed Head Trauma, Penetrating Head Trauma, Penetrating Craniocerebral Trauma, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 5 articles in PubMed, 76 in Scopus, 0 in CINAHL, 57 in Cochrane Library, 30400 in Google Scholar, and 1 from other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 1 from other sources. Of the 3 articles considered for inclusion, 1 randomized trials and 0 systematic studies met the inclusion criteria.

### Evidence for the Use of Action Sequences

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follo w-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Zlotowitz 2010  (4.0)	Action Sequences	RCT	No COI and no mention of sponsorshi p.	N=16 patients with acquired brain injury	Mean age: 38.63±14 .41 years. 11 males, 5 females.	Group A: Modelling Condition Vs. Group B: Moulding Condition	none	There was no significant difference between groups for recall of sequence after short delay. (z=1.19, P>.05) Patients were more accurate in sequence recall in modelling condition than for moulding condition after longer delay. (Group A: mean=2.63, SD=1.23; Group B: mean=1.56, SD=1.63; Z=1.91, P=0.028).	“The use of a modelling instructional technique to teach brain-injured participants an action sequence during their rehabilitation may be more effective for their longer term performance than a moulding instructional technique.”	Crossover. Small sample (n=16). Mixed patients (TBI, stroke, abscess, etc.). Data suggest brain injured patients may improve learning via modeling instead of molding technique.

Cognitive therapies have been used to rehabilitate patients with traumatic brain injuries [166, 726]. Emphases have included management of difficulties with attention and concentration [726-728]memory strategies [726, 729, 730]psychological and psychosocial functioning [731] [165, 732-737]and cognitive behavior therapy [157]. Cognitive behavior therapy has been used for treatment of TBI [738, 739]

## Cognitive Behavioral Therapies

### Recommended.

### Behavioral and Psychological Interventions

Cognitive behavioral therapies are recommended for use in the treatment of TBI patients with cognitive deficits.

#### Strength of Evidence – Recommended, Evidence (C)

#### Level of Confidence – Low

<i>Indications:</i>	Moderate to severe TBI with cognitive deficits. Rare mild TBI patients with ongoing and significant symptoms may be candidates.
<i>Benefits:</i>	Improved management of cognitive function and psychosocial factors
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Frequency is generally tailored based on individual factors of severity and need
<i>Indications for Discontinuation:</i>	Sufficient resolution, lack of progression, lack of compliance.
<i>Rationale:</i>	There are quality studies assessing Cognitive Behavioral Therapies for treatment of TBI, most of which suggest some efficacy, although there are some conflicts between the studies. Cognitive Behavioral Therapy is not invasive, has no adverse effects, is low cost, and has some evidence of efficacy and is thus recommended for treatment of select TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms Cognitive Behavioral Therapy; Traumatic brain injury, Intracranial injury, Closed Head injury ,Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 74 articles in PubMed, 371 in Scopus, 7 in CINAHL, 7 in Cochrane Library, 1800 in Google Scholar, and 0 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 2 from CINAHL, 1 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 6 articles considered for inclusion, 5 randomized trials and 1 systematic studies met the inclusion criteria.

## Evidence for the Use of Cognitive Behavioral Therapies

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Vanderploeg 2008 (8.0)	Cognitive Behavioral Therapies	RCT	Supported by the Defense and Veterans Brain Injury Center, Uniformed Services University of the Health Sciences, Bethesda, MD, the Department of Veterans Affairs, Veterans Health Administration, and a Department of Defense award administered through the Henry Jackson Foundation (grant no. MDA 905-03-2-0003).	366, 18+yo with mod- severe nonpenetrating TBI <6mo ago with GCS score $\leq 12$ , in coma for 12+ hrs, PTA for 24+ hrs, RLAS cognitive level 5-7, active duty military member or veteran, and needing 30+ of acute interdisciplinary TBI rehabilitation.	18+yo	Cognitive rehab (n=184) targeted 4 cognitive domains: attention, memory, executive functions, and pragmatic communication; 1-on-1 sessions v. functional-experiential rehab (n=182) with real-life performance situations and common tasks to compensate for functional deficits after brain injury; group sessions. All had 1.5-2.5hr/d TBI protocol-specific therapy, 2-2.5hr/d OT, PT, ST. Care continued until discharge home or to community transitional rehab program or completed 60 days specific protocol Tx.	Follow-up at 1 year.	NS between groups at 1 year for: %RTW or school (38.9 vs. 35.4%, $p=0.50$ ), and % living independently (56.3 v 61.6% ( $p=0.27$ )). Cognitive FIM post treatment: cognitive (27.3 $\pm$ 6.2) v. functional group (25.6 $\pm$ 6.0) ( $p=0.01$ ). NS between groups for motor FIM and DRS. No memory problems: cognitive 22.2% v. functional 27.6% ( $p=0.05$ ). Those with more education more often lived independently at 1 year in functional (69.1%) vs. cognitive group (47.4%) ( $p<0.02$ ). Younger more often working at 1 year in cognitive (53.3%) vs. functional group (37.8% ( $p<0.03$ )).	"...[N]o difference between cognitive-didactic and functional-experiential approaches to brain injury rehabilitation on the primary 1-year global outcome measures of the study. However, patients in the cognitive treatment arm had better posttreatment cognitive performance than patients in the functional treatment arm."	Trend to higher education level and less alcohol in cognitive rehabilitation arm may have biased in favor of CR, although baseline cognitive measures comparable. Data suggest minimal differences between groups.

Powell 2012 (7.0)	TBI	RCT	Sponsored by the National Institutes of Health, National Center for Medical and Rehabilitation Research, Award #5R03HD054768. No mention of COI.	N = 29 with acquired brain injury.	Mean age 42.31 years for the total group. 17 males, 12 females. Mean age is 42.93 years for the Systematic Instruction Group. 9 males, 6 females. Mean age is 41.64 years for the Conventional Instruction group. 2 males, 2 females.	Systematic Instruction Group – emphasized mastery, incorporating all of the previously described design and delivery elements tailored to the instruction of ATC  (N = 15)  vs  Conventional Instruction Group – emphasized exploratory learning, not mastery  (N = 4).	30 day follow-up	Pre-test performance for both the groups was not statistically significant. $p = 0.60$ . The main effect of treatment condition on post-test performance was not statistically significant. $p = 0.16$ . Accuracy at the 30-day follow-up: significant from pre to post-test. $P < .01$ . Statistically significant treatment condition. $p < 0.1$ . At fluency at post-test and 30 day follow up difference between two groups was $p = 0.81$ post-test and $p = .05$ at 30 day follow up. Fluency rates between two groups were not statistically significant at post-test, but were at follow-up. $P = .051$ .	“The results from this study suggest that systematic instruction applied to ATC results in better retention and generalization of trained skills than conventional instruction, with the potential to significantly improve client outcomes.”	Data suggest systematic instruction training better than trial and error learning for ATC (assistive tech. for cognition) and TBI patients.
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Ponsford 2016 (5.5)	Cognitive Behavioral Therapies	RCT	No COI. Funded by NHMRC grant.	N = 75, with mild to severe TBI, with Structured Clinical Interview for DSM-IV diagnosis of depression or anxiety	20 female, 55 males. Mean age 42.2 years	Non-directive counseling [NDC] + Cognitive Behavioral Therapy [CBT] (N = 26) vs Motivational Interviewing [MI] + CBT (N = 26) vs Wait-listed controls (N = 23)	30 weeks	MI+CBT and NDC+CBT groups showed greater decrease in anxiety on the Hospital and Anxiety and Depression Scale (95% CI (-2.07, -0.06)) and greater decrease in depression on the Depression Anxiety and Stress Scale (95% CI (-5.61, -0.12)) via random-effects regressions [controlled for baseline scores]. Also showed greater improvement in psychosocial functioning on Sydney Psychosocial Reintegration Scale (95% CI (0.04, 3.69))	“Findings suggest that modified CBT with booster sessions over extended periods may alleviate anxiety and depression following TBI.”	Dissimilar baseline characteristics for time since injury (4.88(11.4) vs. 3.58(5.87) vs. 2.61 (3.68) yrs and hospitalization days (57 vs. 54 vs. 79). Issues with treatment integrity in the WC group. Data suggest CBT with booster sessions may decrease anxiety and depression.
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Jean 2010 (5.5)	TBI	RCT	Sponsored by the Alzheimer Society of Canada (ASC) co-funded by the Fonds de la Recherche en Sante' du Que'bec (FRSQ) and the Canadian Institutes of Health Research (CIHR)-Institute of Aging (IA). MEB supported by doctoral grant, MS and CH supported by research grant and SW supported by doctoral training grant.	N = 22 with mild cognitive impairment of the amnesic type (MCI-A).	Aged 50 or older; 11 males and 12 females.	Experimental group learned face–name associations using a paradigm combining errorless (EL) learning and spaced retrieval or SR (N = 11)  vs Control group trained using an errorful (EF) learning Paradigm (N = 11).	10-weeks	All participants improved their capacity to learn face–name associations, ( $p < 0.001$ ).	“The absence of difference between groups on all variables might be partly explained by the high variability of scores within the experimental group.”	Data suggest comparable efficacy.
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Bédard 2013 (5.0)	Cognitive Behavioral Therapy	RCT	This study was funded by the Ontario Neurotrauma Foundation (grant ABIMIND2-476) NO COI	N = 76 individuals with depression symptoms after a TBI	Mean age: Treatment group 47.1 Control Group: 45.81  Gender (M:F): 42:34	Treatment group (N=38) received intervention based on mindfulness-based stress reduction, and the manual for MBCT by Segal and colleagues. Intervention lasted for 10 weeks. Control group (N= 38) was a wait-list control arm. The control group would not receive intervention until treatment group was finished with their 10-week treatment.	3 months	Parallel group analysis of Beck Depression Inventory-II for intervention group vs control group, 6.63 vs 2.13, (P= 0.029).  Improvements were maintained at the 3 month follow up.	“These results are consistent with those of other researchers that use mindfulness-based cognitive therapy to reduce symptoms of depression and suggest that further work to replicate these findings and improve upon the efficacy of the intervention is warranted.”	Data suggest mindfulness-based cognitive therapy may reduce depressive symptoms associated with TBI.
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Bell 2008 (score=5.0)	Cognitive Behavioral Therapies	RCT	Supported by the Centers for Disease Prevention and Control. No COI.	313 from a level I trauma center, admitted within 48 hours of the injury, injury likely a MTBI	Mean age: 32.47 years; 235 males, 78 females.	Scheduled phone contacts over first 3 months post-injury, along with standard patient instruction handout, a wallet card with the study's toll-free phone number, and CDC booklet "facts about Concussion and Brain Injury and Where to Get Help" (n = 146) vs Usual ED standard of care for MTBI – patient instruction handout and standard outpatient treatment (n = 167)	Follow up at 2 days and 2, 4, 8, and 12 weeks post-injury.	Post-traumatic symptom composite mean difference between control and treatment groups: 6.6 (95% CI: 1.2-12.0, p=0.016). General health composite mean difference between control and treatment groups: 1.5 (95% CI: -2.2-5.2, p=0.417)	"Telephone counselling, focusing on symptom management, was successful in reducing chronic symptoms after MTBI."	Significant baseline dissimilarity between groups as the treatment group had a higher baseline GCS than the control group. Also, the study design changed throughout the course of the trial as originally there were to be three groups, which were then reduced to two. Data suggest the interventional group had improved post-MTBI outcomes than the control.
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Ashman 2014 (4.5)	Cognitive Behavioral Therapy	RCT	Sponsored by National Institute for Disability and Rehabilitation research grants H133B040033 and H133B000001. NO COI.	N= 77 individuals with TBI and a diagnosis of depression	Cognitive Behavioral Therapy (CBT) group: 47.1 Supportive psychotherapy (SBT) group: 48.1  Gender (M:F) 32:42	CBT group (N=29) received 16 sessions of treatment focused on cognitive restructuring techniques to challenge and reshape automatic thoughts into more rational self-statements.  SPT group (N=26) received 16 sessions of client-centered psychotherapy treatment. Treatment focused on improving self-esteem, maximize adaptive capacities, and maintaining the individual's best possible level of functioning.	3 months	After treatment, 35% of participants in CBT group no longer met criteria for depression vs 17% of participants in SPT group. However, difference in remission rates was not statistically significant (P =.16)  Changes in the Beck Depression Inventory-II scores were not significant between CBT group and SPT group. (P=.632)	"Both forms of psychotherapy were efficacious in improving diagnoses of depression and anxiety and reducing depressive symptoms. These findings suggest that in this sample of individuals with TBI, CBT was not more effective in treating depression than SPT, though further research is needed with larger sample sizes to identify different components of these interventions that may be effective with different TBI populations."	High dropout rate, substantial intergroup variability. Data suggest comparable efficacy between groups.
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Tiersky 2005 (4.5)	Psychological Therapy	RCT	No COI. Supported by the National Institute on Disability and Rehabilitation Research and the Henry Kessler Foundation.	N = 20, mild or moderate TBI	11 female, 9 male. Mean age 46.85±10.51 years	Cognitive-behavioral psychotherapy and cognitive remediation (n = 11) vs Control (n = 9), all followed for 11 weeks	11 weeks, 1 and 3 months	Outcome measures at end of treatment: GSI – CBP+CR 0.86±0.41, control 1.74±1.00 (P=0.045), Depression – CBP+CR 1.12±0.45, control 2.11±1.14 (P=0.046), Anxiety subscale – CBP+CR 0.72±0.42, control 1.53±1.02 (P=0.066), PASAT – CBP+CR 135.55±30.71, control 110.88±60.28 (P=0.257), Problem solving – CBP+CR 13.06±2.67, control 12.58±2.21 (P=0.685), Attention Questionnaire CBP+CR 19.42±11.56, control 29.29±9.94 (P=0.082)	”Cognitive behavioral psychotherapy and cognitive remediation appear to diminish psychologic distress and improve cognitive functioning among community-living persons with mild and moderate TBI.”	Data suggest TBI patient may benefit from CBT and cognitive remediation in terms of reducing anxiety and depression.
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Fann 2015 (4.5)	Cognitive Behavioral Therapy	RCT	This study was supported by the National Institutes of Health (grant R21HD53736) and the Department of Education, National Institute on Disability and Rehabilitation Research (grant H133G070016). NO COI	N = 100 adults with Major Depression after a Traumatic Brain Injury	Mean Age: 45.8 years old  Gender (M:F) 63:37	Intervention groups received therapy adapted from Simon and Ludman's telephone care management and CBT protocol over the telephone (CBT-T, N=40) or in person (CBT-IP, (N=18)  Usual Care group (N=42) were encouraged to continue using the rehabilitation and primary care services.	24 weeks	CPT-T group had significant improvement on the patient reported Symptom Checklist-20 (SCL-20) in comparison to the UC group at follow up (treatment effect = 0.36, 95% CI: 0.01–0.70; p = 0.043)  Participants who completed more than 8 CBT sessions significantly improved SCL-20 scores compared to UC group (treatment effect = 0.43, 95% CI: 0.10–0.76; p = 0.011)	“In-person and telephone-administered CBT are acceptable and feasible in persons with TBI. Although further research is warranted, telephone CBT holds particular promise for enhancing access and adherence to effective depression treatment.”	Data suggest telephone CBT may be beneficial in decreasing depression in TBI patients.
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Radice-Neumann 2009 (4.5)	Psychological Therapy	RCT	Supported by The Mark Diamond Research Fund of the Graduate Student Association, University at Buffalo, The State University of New York.	N = 19 with acquired brain injury, minimum 1 year post-injury	8 female, 12 male. Mean age 43 years	Facial Affect Recognition "FAR" (n = 10) vs Stories of Emotional Inference "SEI" (n = 9), both treatments given for 1 hour per day, 3 times a week, each participant receiving 6 to 9 sessions total. Measured using Diagnostic Assessment of Nonverbal Affect 2 – Adult Faces and Adult Paralanguage (DANVA2-AF OR AP) emotion evaluation test (EET), levels of emotional awareness	2 weeks	Pretest scores: similar for FAR on DANVA2-AF test (P=.543) and for FAR and SEI on DANVA2-AP test (P=.758, P=.122), EET (P=.225, P=.312), LEAS-Self (P=.064, P=.732), LEAS-Other (P=.340, P=.782). SEI significant performance change from pretest I to II on DANVA2-AF (+2.79 points, P=.004). DANVA2-AF: Significant performance change found in FAR (P<.001) and SEI (P=.006). DANVA2-AP: No significant changes found (FAR P=.985, SEI P=.939). EET: No significant changes found (FAR P=.584, SEI	"Training can improve emotion perception in persons with ABI. Although further research is needed, the interventions are clinically practical and show promise for the population with ABI."	Small groups. No sham/placebo. Data suggest specific training may enhance emotion perception. FAR training improved emotion from faces & context while SEI group had improvement in ability to infer how they would feel in a given context.
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					<p>scale, both self and others (LEAS), and the Brock Adaptive Function Questionnaire (BARQ)</p>	<p><math>P=.166</math>). LEAS-Self: Both significant change over time (FAR and SEI both <math>P=0.019</math>). LEAS-Other: Significant change over time for FAR (<math>P=0.004</math>). No change in SEI (<math>P=.579</math>). BARQ: Caregivers perceived significant increase in FAR participants' behavior after intervention (<math>P = .042</math>). No change perceived in SEI (<math>P = .363</math>).</p>	
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Mittenberg 1996 (score=4.0)	Cognitive Behavioral Therapies	RCT	No mention of sponsorship or COI.	58 with mild head trauma	Mean age: 46.35 years; 40 males, 18 females.	Treatment group: given 10 page manual, "Recovering From Head Injury: A Guide for Patients", met with therapist to review expected symptoms, cognitive-behavioral model of symptom maintenance and treatment, techniques to reduce symptoms, instructions for gradual return to normal activities (n=29) vs Control group: received routine hospital treatment and discharge instructions (n=29)	Follow up at 6 months post-injury.	Postconcussion Symptoms for Control and Treatment groups, respectively: Frequency of initial symptoms – 4.38, 3.69 (p=0.42), Duration of average symptoms (days) – 51.19, 33.18 (p=0.05), Frequency of symptoms 6 months posttreatment – 3.10, 1.62 (p=0.02), Days per week symptomatic at 6 months – 1.33, 0.53 (p=0.01), Severity of average symptom at 6 months (0-10 scale) – 1.72, 0.80 (p=0.02)	"Telephone counselling, focusing on symptom management, was successful in reducing chronic symptoms after MTBI."	Standard care bias. Relatively small sample size. Data suggest interventional group achieved better outcomes (fewer symptomatic days and less severity of symptoms) vs controls.
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Ruff 1990 (3.5)	Psychological Therapy	RCT	No mention of COI. Supported by grant from the Robert Wood Johnson Foundation.	N = 24, moderate to severe head injury with at least 1 hour of coma duration	7 females, 17 males. Mean age experimental group 28.3 years, control group 31.1 years	Experimental group – cognitive retraining on attention, visuospatial abilities, learning and memory, and problem solving. Small groups of 2-4, 12 hours per week for 8 weeks, 2 hour of group therapy and 20-30 minute “wrap-up” sessions at the end of the day (n=12) vs. Control group – also received group and “wrap-up” session therapy, training focused on psychosocial functioning and activities	8 weeks after intervention began	Test—re-test correlations in Katz Adjustment Scale (KAS) subset; Social Obstreperousness: Patient rating r=0.87 (P<0.001), Relative rating r=0.88 (P<0.001), Patient vs. Relative rating r=0.01 (P>0.01). Acute Psychoticism: Patient r=0.68 (P<0.001), Relative r=0.76 (P<0.001), Patient vs Relative r=0.45 (P>0.01). Withdrawn Depression: Patient r=0.78 (P<0.001), Relative r=0.65 (P<0.1), Patient vs Relative r= -0.07 (P>0.01). Both groups did not perceive changes in emotional and psychosocial function from	“In this study, self-ratings according to the KAS proved to be reliable for both relative and patient ratings. Nonetheless, very little agreement existed between patient and relative ratings, as indicated by zero correlations for global scales of social obstreperousness and withdrawn depression. Furthermore, relatives but not patients reported significant gains.”	Baseline differences between groups for coma duration (25.5 vs. 48.3 days), otherwise data suggest potential efficacy.
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						of daily living (n=12). All participants' relatives also were involved in evaluation.		interventions (SO: U=58 P>0.10, AP: U=64 P>0.10, WD: U=62.5, P>0.10). Relatives of both groups also did not perceive changes (SO: U=55 P>0.10, AP: U=48.5 P>0.10, WD: U=36, P>0.10).		
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Patients with a TBI often experience impairment in divided attention. Divided attention is required to perform multiple cognitive and motor tasks at a given time. Divided attention is also impaired by multiple sclerosis, stroke, Alzheimer’s disease, and Parkinson’s disease. Cognitive-motor dual-tasking, or walking and talking therapy has been used for treatment of TBI patients [740].

### **Cognitive-Motor Dual-Tasking Recommended.**

Cognitive-motor dual-tasking is recommended for use in the treatment of TBI patients.

#### **Strength of Evidence – Recommended, Insufficient Evidence (I)**

*Level of Confidence – Low*

*Rationale:*

There are no quality studies of walking and talking therapy (or cognitive-motor dual-tasking). There is one trial of divided cognitive attention suggesting potential efficacy [741], but not cognitive-motor. There is one low quality study suggesting a trend towards improvement [740]. Cognitive-motor dual tasking is not invasive, has negligible adverse effects, is moderately costly, but has no quality evidence of efficacy and thus there is no recommendation.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Cognitive-Motor Dual-Tasking; Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 0 articles in PubMed, 18 in Scopus, 1 in CINAHL, 0 in Cochrane Library, 87 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 1 articles considered for inclusion, 1 randomized trials and 0 systematic studies met the inclusion criteria.

### Evidence for the Use of Cognitive-Motor Dual-Tasking

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Couillet, 2010 (5.0)	Cognitive Motor Dual-Tasking	RCT	Sponsored by grants from the Programme Hospitalier de Recherche Clinique and by Assistance Publique-Hopitaux de Paris. No mention of COI.	N = 12 patients in the stages of subacute or chronic after a severe TBI.	Mean age of AB group: 23.8 (N=5)  BA group: 26.7 (N=7)  No mention of Sexes	An AB vs. BA crossover design was used. Each phase was six weeks and consisted of four one hour training sessions a week for a total of 24 hours of training.  A phase was the control phase, consisting of cognitive tasks that did not use the patient's divided attention or working memory.  B phase consisted of specific dual attention training.	Follow up at 6 weeks, 12 weeks, and one month after the end of the trial.	Effect of time and the group x time interaction in Divided attention substest of the TAP: Mean Reaction Time: AB group: $F(3, 21) = 21.5, (p < .0001)$ ; BA group: $F(3, 21) = 20.7, (p < .0001)$  Number of Omissions: AB Group: $F(3, 18) = 22.3, (p < .0001)$ BA group: $F(3, 18) = 13.2, (p < .0001)$  Effect of time and the group x time interaction were both significant for the go-no go dual-task reaction times: AB group: $F(3, 18) = 12.3, (p < .0001)$ . BA group: $F(3, 18) = 17.5, (p < .0001)$ ,  Digit Span Dual Task: AB group: $F(3, 18) = 84.6, (p < .0001)$ ; BA group: $F(3, 18) = 28.4, (p < .0001)$	"[T] the specific rehabilitation programme for divided attention had specific effects on divided attention and was useful and helped patients to deal more rapidly and more accurately with dual-task situations."	Crossover trial. Small sample size. Data suggest training can improve dual task performance by enhancing attention.
Evans, 2009	Cognitive Motor	RCT	Sponsored by Cambridgeshi	N = 19 patients with	Treatment group:	Treatment group received 2 dual-task	A baseline assessment	Pre-training (T1) and post training (T2)	"Results suggest that	Small sample with

(3.5)	Dual-Tasking		re NHS Research and Development Support Team. No COI.	impairments in cognitive-motor dual tasking impairments due to a neurological injury.	<p>Mean age 44.4</p> <p>Control group Mean Age: 45.11</p> <p>Sex (M:F) 17:2</p>	<p>practice sessions a day, 5 days a week for 5 weeks. Practice sessions consisted of 2min walking sessions, with increasing cognitive demands.</p> <p>Control group was assessed once a week by a therapist, and patients kept a diary of their daily experiences with dual-tasking.</p>	was created before training and a follow up was conducted 5 weeks from baseline.	<p>scores among the treatment vs control groups:</p> <p>(T1, T2 for treatment vs T1,T2 control)</p> <p>Sentences and walking combined (13.9, 19.9 vs 15.44, 15.33 (p&lt;0.05))</p> <p>Tones and Walking Combined (17.2, 19.1 vs 15.33, 20.11 (p&lt;0.05))</p> <p>Memory Span &amp; Track task approached significance (93.0, 94.01 vs 84.68, 90.44 (p&lt;0.10))</p>	the intervention may lead to improvement, but that any improvement may be limited to this task and not generalize to other cognitive-motor task combinations.”	variable therapist contact time. Sparse methods Trend towards dual-tasking improvement from interventional group.
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Those who have suffered from a traumatic brain injury are vulnerable towards attention deficits [469]. Attention regulation training is designed to help an individual increase the ability to focus on certain tasks or information [469, 741-744].

## **Attention Regulation Training Recommended.**

Attention regularion training is recommended for use in the treatment of TBI patients.

*Strength of Evidence* – **Recommended, Evidence (C)**

*Level of Confidence* – **Low**

<i>Indications:</i>	Moderate to severe TBI patients with indications of impaired attention, as well as problems with dual-tasking. [741] There may be select patients with ongoing symptoms from mild TBI who may be candidates.
<i>Benefits:</i>	Improvements in sustained attention and focus.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	One regimen was 4x1hr individual training sessions/wk for 6 wks for up to 24 hours of training.
<i>Indications for Discontinuation:</i>	Sufficient recovery, ability to dual task, plateau, non-compliance with home exercises.
<i>Rationale:</i>	There are a few quality studies for the use of attention regulation training to treat TBI patients, and they mostly suggest efficacy, although the studies are heterogenous and not comparable [741] [742] [743]. Attention regulation training is not invasive, has no adverse effects, is low to moderate cost in aggregate and with evidence suggesting efficacy is recommended for treatment of TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: <b>attention regulation training, rehabilitation; traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma;</b> controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 13 articles in PubMed, 4 in Scopus, 2 in CINAHL, 2 in Cochrane Library, 29,611 in Google Scholar, and 4 from other sources. We considered for inclusion 0 from PubMed, 5 from Scopus, 0 from CINAHL, 2 from Cochrane Library, 2 from Google Scholar, and 4 from other sources. Of the 7 articles considered for inclusion, 5 randomized trials and 2 systematic studies met the inclusion criteria.

### Evidence for the Use of Attention Regulation Training

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Novakovic-Agopian, 2011 (5.0)	Attention Regulation Training	RCT	Sponsored by the Office of Research and Development Rehabilitation R&D Service Department of Veterans Affairs, and the California Pacific Medical Center Foundation. COI, Drs Novakovic-Agopian, Chen, Abrams, and McKim, and Ms Rossi are affiliated with the Veteran's Administration Medical Center, San Francisco, California.	N = 16 patients with chronic acquired brain injuries for more than 6 months.	Age range 24-63 years old, 7 males & 9 females, and mean age of 50.	Goal training (n=8) vs Education goals (n=8)	Follow-up was taken at baseline, at week 5, and at week 10 for both short-term and long-term effects.	At week 5 no significant difference between the groups for Working Memory (P<0.0001), Mental Flexibility (P = .009), Inhibition (P=0.005), and Sustained Attention (P=0.01). Significant differences were found in the Memory Domain for changes for Learning at P=0.02 and Delayed Recall at P=0.01. At week 10 significant difference between the groups for Attention and Executive Function Domain (P < .0001) and the following subdomains in Working Memory (P=0.0008), Mental Flexibility (P=0.0008), Inhibition (P=0.01), and Sustained Attention (P=0.01).	"Training in goal-oriented attentional self-regulation is theoretically driven and feasible in a research setting. Pilot results suggest improvements in cognitive and functional domains targeted by the intervention."	Pseudorandom crossover. Pilot RCT with small sample. Mixed pop., primarily TBI. Data suggest goal-oriented attentional self regulation improves attention and executive function.
Shum, 2011 (5.0)	Attention Regulation Training	RCT	Sponsored by the National Health and	N = 45 patients with moderate to severe TBI	Age range 19-57 years old, 37 males & 8 females, and	4 groups of intervention at (n=12), (n=11), &	Follow up was at week 4 and week 8	No significance between the pre-intervention rating and the change score among the 4 groups.	"The results provide evidence that prospective	Data suggest memory improvement from short duration as

			Medical Research Council Project Grant (no: 277002). No Col.		mean age of 38.	(n=11) subjected to CAMPROMPT, CAMPM, and SPRS.  CAMPROMPT= Cambridge Behavioural Prospective Memory Test; CAMPM= Comprehensive Assessment of Prospective Memory; SPRS= Sydney Psychosocial Reintegration Scale;		The self-aware S-A plus compensatory Training was tested for CAMPROMPT: Pre-inter 26.50 (19.50; 28.75) P=0.808, change 3.50 (0.25; 9.75) P=0.034, CAMPM: Pr-inter 2.03 (1.74; 2.48) P=0.664, Change -0.15 (-0.48; 0.00) P=0.692 and SPRS: Pre-inter 44.50 (37.00; 51.25) P=0.295, and Change 6.00 (0.00; 14.25) P=0.110.	memory can be improved in patients with traumatic brain injury using a compensatory approach in a relatively short duration and low intensity intervention."	well as low intensive interventions.
Niemann 1990 (3.5)	Attention Regulation Training	RCT	No mention of sponsorship or COI.	N = 29 outpatients suffering from moderate to severe traumatic brain injury.	Mean age for experiment and control groups; 28.9 and 34.3.	Experimental group or measures of attention + memory, 9 weeks for 2-hour sessions per week (N = 13) vs Control group or measures of attention, 9 weeks for 2-hour sessions per week	9 weeks after initial intervention	The attention group improved vs memory group on four measures of attention, Wilks's lambda = 64, approximated: F (4, 21) = 2.93, p < 0.02, one-tailed.	"The experimental design evaluated outcome by juxtaposing a multiple baseline procedure for a 1st set of measures of attention and memory with a pre and post group comparison that relied on 2nd set of neuropsychological tests."	No sham or control group. Results equivocal regarding efficacy.

						(N = 13). Measures of attention: d2 test, Paced Auditory Serial-addition task revision (PASAT-R), Divided Attention Test and Trail Making Test Part B test. Memory tests: Rey Auditory Verbal Learning Test-modified (RAVLT-M), and Learning Block span learning test (BSLT).				
Chen, 2011 (3.5)	Attention Regulation Training	RCT	Sponsored by the Veteran's Administration Rehabilitation Research and Development and the California Pacific Medical Centre Foundation. No Col.	N = 12 patients with chronic acquired brain injuries greater than 6 months.	Age range 24-63 years old, 5 males & 7 females, and mean age of 48.	Goals Training (n=5) Vs Education (n=7) and patients were switched at 5 weeks.	Follow-up given at the end of assessment 1 at 5 weeks, and assessment 2 at 10 weeks.	Significant improvements results were shown on behavioral measures of attention and executive control. No significant results between education and goals training at P=0.41 vs the crossover between goals training and education at P=0.40.	"[M]odulation of neural processing in extrastriate cortex was significantly enhanced by attention regulation training." "These results suggest that enhanced modulatory control over visual processing and a rebalancing of prefrontal functioning may underlie improvements in attention and executive control."	Mixed population of TBI, stroke, hemorrhage, resection or chemotherapy . Data suggest goal-directed attention regulation improves modulatory control over neural processing.

Motivational interviewing has been used for treatment of TBI patients [739].

## Motivational Interviewing

### Recommended.

Motivational interviewing is recommended for use in the treatment of patients with anxiety or depressive symptoms after TBI.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

<i>Indications:</i>	TBI patients with anxiety or depressive symptoms after TBI.
<i>Benefits:</i>	Potential to improve depressive and anxiety symptoms after TBI.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Regimens varied. They included: Four 20-minute sessions (Zatzick 2014), 10 weekly 2-hour sessions [745], to one session at 1, 2, 3, 5, 7, and 9 months post initial treatment (Bombardier 2009, Bell 2005).
<i>Rationale:</i>	There are multiple moderate quality trials evaluating the usage of motivational interviewing for patients with TBI. Multiple moderate quality trials suggested motivational interviewing was successful in reducing symptoms of anxiety and depression (Ponsford 2016, Hsieh 2012, Bombardier 2009), with two utilizing cognitive behavioral therapy (Ponsford 2016, Hsieh 2012). However, one trial had baseline differences in groups concerning for potential randomization failure (Ponsford 2016). One moderate quality study suggested motivation interviewing can improve overall function (Bell 2005). Three moderate quality studies evaluated the usage of motivation interviewing for the treatment of alcohol consumption problems (Zatzick 2014, Tweedly 2012, Ponsford 2012). Two studies suggest efficacy (Zatzick 2014, Tweedly 2012) but one suggests readiness to change influences the effectiveness of treatment (Ponsford 2012). Motivational interviewing with cognitive behavioral therapy is not invasive, has negligible adverse effects, is moderate cost in aggregate, has some potential evidence of effectiveness and so is recommended for selective treatment of TBI patients with anxiety or depressive symptoms and/or alcohol consumption problems after TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed without date limits using the following terms: motivational interviewing; brain injuries, closed head injuries, penetrating head injuries, brain concussion, concussion, craniocerebral trauma, traumatic brain, intracranial, closed head, penetrating head, craniocerebral, injury, injuries; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 16 articles in PubMed and 6 from other sources. We considered for inclusion 3 from PubMed and 6 from other sources. Of the 9 articles considered for inclusion, 9 randomized trials and 0 systematic studies met the inclusion criteria.

## Evidence for the Use of Motivational Interviewing

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Zatzick 2014 (6.5)	Motivational Interviewing	RCT	Grants supplied by National Institute on Alcohol Abuse and Alcoholism R01/AA016102 and National Institute of Mental Health K24/MH086814 were given to support this article. No declaration of interests.	N = 878	208 females, 670 males. Mean age is 36.9.	Intervention sites (n=10, patient n=469). Vs control sites (n=10, patient n=409)	Follow up after baseline at 6 and 12 months post-injury.	In the first year following injury, intervention group participants had a significant 8% reduction in Alcohol Use Disorders Identification Test (AUDIT) hazardous drinking cut-offs compared to control group. Intervention group also had a significant increase in abstinent from drinking days over the next year post-injury ( $P = 0.02$ ).	"[T]hese findings suggest that a brief trauma center intervention based upon MI (motivational interviewing) principles can yield relevant population level reductions in alcohol consumption and related hazardous drinking outcomes."	Population mixed between TBI and others. Assessment via interviews. Data suggest modest (8%) reduction in problem drinking patients, especially non-TBI patients.
Ponsford 2016 (5.5)	Motivational Interviewing	RCT	No COI. Funded by NHMRC grant.	N = 75, with mild to severe TBI, with Structured Clinical Interview for DSM-IV diagnosis of depression or anxiety	20 female, 55 males. Mean age 42.2 years	Non-directive counseling [NDC] + Cognitive Behavioral Therapy [CBT] (N = 26) vs Motivational Interviewing [MI] + CBT (N = 26) vs Wait-listed controls (N = 23)	30 weeks	MI+CBT and NDC+CBT groups showed greater decrease in anxiety on the Hospital and Anxiety and Depression Scale (95% CI (-2.07, -0.06)) and greater decrease in depression on the Depression Anxiety and Stress Scale (95% CI (-5.61, -0.12)) via random-effects regressions [controlled for baseline scores]. Also showed greater improvement in psychosocial functioning on Sydney Psychosocial Reintegration Scale (95% CI (0.04, 3.69))	"Findings suggest that modified CBT with booster sessions over extended periods may alleviate anxiety and depression following TBI."	Dissimilar baseline characteristics for time since injury (4.88(11.4) vs. 3.58(5.87) vs. 2.61 (3.68) yrs and hospitalization days (57 vs. 54 vs. 79). Issues with treatment integrity in the WC group. Data suggest CBT with booster sessions may decrease

										anxiety and depression.
Tweedy 2012 (5.5)	Motivational Interviewing	RCT	Authors declare no conflict of interest.	N= 60	45 males, 15 females. Mean age is 35 years.	Brief information (INFO, N=20) vs INFO plus motivational interviewing (MI + INFO, N= 20), vs informal discussion (ID, N= 20)	2 hours of assessment and intervention at baseline (6-9 months post-injury), and a 6 month follow up (12-15 months post-injury).	At 6 month follow up, according to the Timeline Follow-Back (TLFB), the ID group reported 7 days of drinking in month prior to follow up, compared to 3-4 days a month in the MI + INFO and INFO groups. However, these results were not statistically significant.	“There was a positive trend showing participants in both the intervention groups to be drinking less frequently and consuming fewer alcoholic drinks than those in the informal discussion (control) group. However, group differences did not reach statistical significance.... Further randomized controlled trials with larger samples are needed to establish whether brief educational and motivational interview interventions targeting alcohol use are efficacious in the traumatic brain injury population.”	Data suggest a trend in both intervention groups towards less frequent and fewer drinks over controls.
Hsieh 2012 (score=5.5)	Motivational Interviewing	RCT	This study was supported in part by grants from the National	N=27, participants with TBI in past. No	21 males, 6 females; mean age 38.0±13.2.	Group 1: received motivational interviewing and cognitive behavioral therapy. (N=9)	Baseline, week 3, week 12, week 21.	NDC+CBT group indicated significant reduction on primary outcome HADS-Anxiety (effect size: 0.24; 95%CI:	“The results provided preliminary support for the adapted CBT	Data suggest motivational interviewing or CBT may be effective for TBI

			Health and Medical Research Council and Monash University, and a scholarship from the Victorian Brain Injury Recovery Association (Australia). No COI.	current psychosis.		vs. Group 2: received non-directive counseling and cognitive behavioral therapy. (N=10) vs. Group 3: treatment as usual. (N=8)		-0.64 to 1.12); MI+CBT group also showed significant reduction on HADS-Anxiety (effect size: 0.50; 95%CI:-0.49 to 1.50). No significant reduction on DASS-Anxiety measurement in both groups (p>0.05). Female participants in NDC+CBT group showed lower HADS (p=0.00) and DASS (p=0.03), comparing with male patients.	programme, and the potential utility of MI as treatment prelude. Longer follow-up data are required to evaluate the maintenance of treatment effects."	related anxiety as both treatment groups outperformed the TAU group.
Bombardier 2009 (5.0)	Motivational Interviewing	RCT	Supported by a grant from the National Institute on Disability and Rehabilitation Research. No mention of COI.	N = 126 with TBI, discharged from inpatient rehabilitation	32 female, 94 male. Mean age 36 years	Motivational Interviewing via phone call at day 1 and again at months 1, 2, 3, 5, 7, and 9 (n = 62) vs Control group (n = 64)	1 year	Brief Symptom Inventory-Depression (BSI-D), Neurobehavioral Function Inventory-Depression subscale (NFI-D), Mental Health Index-5 (MHI-5). Pre-post changes on BSI-D subscale showed significant between group differences (Control 0.45±0.95, Telephone 0.08±0.72, P=0.019). Posttreatment BSI-D score: control 1.03±1.05, telephone 0.44±0.66 (P=0.000). Posttreatment NFI-D score: control 32.3±12.9, telephone 24.0±9.1 (P=0.000). Posttreatment MHI-5 score: control 20.2±5.9, telephone 23.4±4.8 (P=0.002). Pooled difference in treatment outcome via BSI-D score	"Telephone-based interventions using problem-solving and behavioral activation approaches may be effective in ameliorating depressive symptoms following TBI. Proactive telephone calls, motivational interviewing, and including significant others in the intervention may have contributed to its effectiveness."	High dropouts Data suggest the use of scheduled telephone interventions utilizing problem solving and behavioral activation techniques may help reduce TBI depressive symptoms.

								changes did not statistically vary by age, sex, or coma severity (P > 0.15 for all). Significant difference in white vs nonwhite participants, white reporting higher scores (P = 0.002).		
Ponsford 2012 (score=4.5)	Motivational Interviewing	RCT	Authors declare no conflict of interest.	N=60, TBI rehabilitation patients.	No mention of sex; mean age of 35.	Group 1: Motivational interview technique to limit alcohol use and supplemental information (N=18) vs. Group 2: Only received supplemental information (N=15) vs. Group 3: Informal discussion (control). (N=15)	Participants were assessed baseline and 6 months after.	No significant difference was found between intervention and control groups of overall alcohol consumption. But low relative risk of drinking (frequent or heavier drinking) was associated with action stage of readiness to change (p<0.001). Extra education (1 year) indicated to associated with higher relative risk of drinking (frequent drinking: p=0.019; heavier drinking: p=0.040).	"[R]eadiness to change and depression represent potentially important factors on which to focus efforts to minimize alcohol use following TBI. The knowledge that individuals with higher rather than lower education may be at greater risk of heavier post injury drinking is also noteworthy."	Data suggest a person's readiness to change and treatment of depression is key in treating alcohol use post TBI.
Bell 2005 (score=4.0)	Motivational Interviewing	RCT	Supported by the National Institute of Disability and Rehabilitation Research, US Department of Education No COI.	N=171 participants with primary diagnosis of TBI.	132 males, 39 females; mean age 36±15.	Group 1: received motivational interviewing through telephone. (N=85) vs Group 2: received treatment as usual. (N=86)	Baseline and 1 year.	Patients with scheduled telephone intervention indicated better primary composite outcomes (p=0.002) including perceived quality (p=0.006) and functional status (p=0.003), comparing with patients with standard follow-up care. Other measurement (GCS and EuroQol scores) indicated no significant change in both groups.	"In this study, we demonstrated the successful use of scheduled telephone counseling and education in improving outcomes for people with moderate to severe TBI and their families. Results are similar to that for other	Usual care bias. Data suggest moderate to severe TBI patients and families may benefit from scheduled telephone interventions to improve functional status and overall well-being.

									medical populations (eg, diabetes, heart disease, arthritis, depression).”	
Sander 2012 (3.5)	Motivational Interviewing	RCT	This work was supported by grants from the National Institute on Disability and Rehabilitation Research, US Department of Education (grants H133B031117, H133B090023, H133A070043, and H133A070029). No COI.	N = 104	85 males, 19 females; Mean age is 35.75 years.	Standard of Care (N = 50) Vs. Intervention group (N = 54).	Follow up period of 3 months.	History of alcohol bingeing was not significant (p=.55). There was an effect on group treatment and control on AEQ-III GP. Treatment vs control (p=.01). Group effect and binge history did not interact (p=.06). Treatment wasn’t effected by injury severity, history of binges, attribution or site (p=.25). After adjustment there was still no effect (p=.86).	“Brief intervention can be effective for educating on the negative impact of alcohol use for people with severe TBI who have emerged from posttraumatic amnesia. Attribution of the injury to alcohol use could potentially increase readiness to change in some settings, and might be used to generate discussion about the negative impact of alcohol use.”	Brief treatment (10min video) followed up by education and a motivational interview did not show efficacy to improve problem alcohol use or readiness to change.
Corrigan 2005 (3.0)	Motivational Interviewing	RCT	Funding for this project was provided by the Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration,	N= 195	138 males, 57 females. Mean age is 36.6 years.	195 participants randomly assigned into 4 groups. (1) Attention control, (2) barrier reduction, (3) motivational interview, and (4) financial incentive.	Appointments unspecified and varied by participant preference. Follow up at 3 and 6 months.	Statistically significant differences were found in the financial incentive (87%) and barrier reduction (74%) groups compared to the motivational interview (45%) and attention control (45%) groups. Significance indicated through client signing an individualized service	“Participants in the financial incentive and barrier reduction groups were at least 50% more likely to sign the ISP within 30 days compared with the motivational interview and control groups....	Data suggest financially compensated and barrier reduction groups were more likely to sign on to a substance abuse treatment program post TBI than the

			via Grant 5 KD1 T112013. No mention of COI.					plan (ISP) with a counselor within 30 days. Significance also found in fewer number of days to sign ( $M = 22.8$ days, $SD = 14.7$ ), ( $M = 44.0$ days, $SD = 35.8$ ) and fewer premature terminations (4%, 6%, 9%, 15%), respectively.	Retention in the barrier reduction and financial incentive conditions was 50% greater than in the attention control condition. If these results are replicated, they suggest that the initial intervention sets into motion a series of events that promotes later retention. These findings provide support for Newman's (1997) conception of how engagement in treatment can affect later retention."	motivational interview or attention control groups.
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Emotional training interviewing has been used for treatment of TBI patients [747].

## Emotional Training

### Recommended.

Emotional training is recommended for use in the treatment of TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

<i>Indications:</i>	TBI patients with emotional problems after TBI, able to comprehend short paragraphs, and scores at least one standard deviation below the mean on a test of facial affect recognition [747]. The sole quality study included only those more than one year after TBI, however earlier treatment may be selectively appropriate. Mild TBI patients are not expected to need emotional training due to the TBI [153], although emotional training may be needed for pre-existing reasons.
<i>Benefits:</i>	Potential to improve emotional interpretations and including understanding/reading facial expressions.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Regimens varied: regimens ranged from 9 hours over 2-3 weeks (Neumann 2015), 1-hour sessions per week for 16-20 weeks (Westerhof-Evers 2017), 1-hour sessions, 3 times per week for 2-3 weeks (Radice-Neumann 2009), and 8 two hour sessions given over 4 days (Tornås 2016a).
<i>Rationale:</i>	Multiple moderate quality trials (Tornås 2016a, Tornås 2016b, Westerhof-Evers 2017, Radice-Neumann 2009) evaluate the usage of emotional training in TBI patients. The multiple moderate quality studies suggested emotional training was successful in improving facial recognition and emotional processing (Tornås 2016a, Tornås 2016b, Westerhof-Evers 2017, Radice-Neumann 2009), however one study contained baseline differences in time from injury (Tornås 2016b). Emotional Training is not invasive, has negligible adverse effects, is moderate cost in aggregate, has some potential evidence of effectiveness and so is recommended for selective treatment of severe TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed without date limits using the following terms: emotional training, emotion training; brain injuries, closed head injuries, penetrating head injuries, brain concussion, concussion, craniocerebral trauma, traumatic brain, intracranial, closed head, penetrating head, craniocerebral, injury, injuries; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 55 articles in PubMed and 2 from other sources. We considered for inclusion 3 from PubMed and 2 from other sources. Of the 5 articles considered for inclusion, 5 randomized trials and 0 systematic studies met the inclusion criteria.

## Evidence for the Use of Emotional Training

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Tornås 2016 (score=7.0)	Emotional Training	RCT	Supported by the Norwegian Extra Foundation for Health and Rehabilitation, EXTRA funds. No mention of COI.	N=70 patients with verified acquired brain injury.	Mean age: 42.89 years; 38 males, 32 females.	Goal Management Training group (GMT) (n=33) vs. Brain Health Workshop (BHW) (n=37).	Follow-up at 6 months.	BRIEF-A scores in three index reduced significantly in both groups. Behavioral regulation index in GMT group reduced from $60.87 \pm 11.16$ to $53.87 \pm 10.54$ ( $p < 0.001$ ) vs. BHM group reduced from $62.24 \pm 11.72$ to $58.62 \pm 10.89$ ( $p < 0.05$ ). Metacognitive index in GMT group reduced from $63.68 \pm 9.65$ to $57.90 \pm 11.25$ ( $p < 0.01$ ) vs. BHM group reduced from $66.76 \pm 9.69$ to $63.74 \pm 9.88$ ( $p < 0.01$ ). Global executive composite in GMT group reduced from $63.32 \pm 9.24$ to $56.68 \pm 10.86$ ( $p < 0.001$ ) vs. BHW group reduced from $65.97 \pm 10.2$ to $62.85 \pm 10.01$ ( $p < 0.05$ ). Dysexecutive Questionnaire (DEX) score in GMT group reduced from $28.33 \pm 11.75$ to $21.7 \pm 12.02$ ( $p < 0.001$ ); in BHM group reduced from $29.06 \pm 13.32$ to $28.3 \pm 14.17$ (not statistically significant).	"[G]MT combined with external cueing is an effective metacognitive strategy training method, ameliorating executive dysfunction in daily life for patients with chronic ABI."	Data suggest GMT plus external cuing may be beneficial for chronic TBI patients to restore some executive function.
Tornås 2016 (score=6.0)	Emotional Training	RCT	Supported by the Norwegian	N=70 individuals	Mean age: 43±13 years;	Goal Management	Follow-up at baseline,	Dysexecutive Questionnaire (DEX)	"The present results have	Baseline differences

			Extra Foundation for Health and Rehabilitation through EXTRA funds. No mention of COI.	with TBI and executive dysfunction.	38 males, 32 females.	Training (GMT) (N=40) Vs Brain Health Workshop (BHW) (N=40)	post intervention (8 weeks), and 6 months.	Baseline vs Follow up, GMT: 4.55±2.69 vs 2.94±2.34 (p<0.001). Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A) baseline vs follow-up, GMT: 60.03±11.49 vs 53.97±9.75 (p<0.001). QOL Total score, baseline vs follow-up, GMT: 3.26±0.54 vs 3.57±0.53 (p<0.001). Cognitive subscale score: 2.97±0.68 vs 3.33±0.73 (p<0.01). ADL score: 3.12±0.70 vs 3.59±0.66 (p<0.001). Emotional Subscale score: 3.75±0.88 vs 4.10±0.69 (p<0.01). Physical Subscale Score: 3.50±0.76 vs 3.70±0.83 (p<0.05).	promising implications because they suggest that a relatively brief metacognitive intervention targeting sustained attention and emotional regulation is effective in improving emotional regulation and QOL even years after injury.	between groups for time in years since injury (8.9 vs. 6.8).
Westerhof-Evers 2017 (score=4.5)	Emotional Training	RCT	No mention of sponsorship. The authors declared no COI.	N=61 patients with traumatic brain injury from moderate to severe.	Mean age: 43.2±13 years; 83 males, 17 females.	T-ScEmo Intervention group (n=30) vs. Cogniplus group (n=29) vs. Healthy control group (n=42).	Follow-up at 3, and 5 months.	Primary outcome "The Awareness of Social Inferences Test" (TASIT)-Short score indicated no significant change in the two treatment groups. T-ScEmo group had TASIT-short score changed from 63.1±7 to 63.7±7 (p=0.31) vs. Cogniplus group had TASIT-short score changed from 61.4±6 to 62.3±7 (p=0.28).	"[I]mpairments in social cognition can be effectively dealt with by using a comprehensive treatment protocol, leading to improvements in everyday life social functioning."	Data suggest significant improvement in social cognition with T-ScEmo in terms of facial affect recognition, theory of mind, proxy-rated empathic behavior, societal participation and treatment

										goal attainment with gains lasting up to 5 months.
Radice-Neumann 2009 (score=4.5)	Emotional Training	RCT	Supported by The Mark Diamond Research Fund of the Graduate Student Association, University at Buffalo, The State University of New York.	N = 19 with acquired brain injury, minimum 1 year post-injury	Mean age: 43 years; 12 male, 8 female.	Facial Affect Recognition "FAR" (n = 10) vs Stories of Emotional Inference "SEI" (n = 9), both treatments given for 1 hour per day, 3 times a week, each participant receiving 6 to 9 sessions total. Measured using Diagnostic Assessment of Nonverbal Affect 2 – Adult Faces and Adult Paralanguage (DANVA2-AF OR AP) emotion evaluation test (EET), levels of emotional awareness scale, both self and others (LEAS), and the Brock Adaptive Function Questionnaire (BARQ)	2 weeks	Pretest scores: similar for FAR on DANVA2-AF test (P=.543) and for FAR and SEI on DANVA2-AP test (P=.758, P=.122), EET (P=.225, P=.312), LEAS-Self (P=.064, P=.732), LEAS-Other (P=.340, P=.782). SEI significant performance change from pretest I to II on DANVA2-AF (+2.79 points, P=.004). DANVA2-AF: Significant performance change found in FAR (P<.001) and SEI (P=.006). DANVA2-AP: No significant changes found (FAR P=.985, SEI P=.939). EET: No significant changes found (FAR P=.584, SEI P=.166). LEAS-Self: Both significant change over time (FAR and SEI both P=0.019). LEAS-Other: Significant change over time for FAR (P=0.004). No change in SEI (P=.579). BARQ: Caregivers perceived significant increase in FAR participants' behavior after intervention (P = .042).	"Training can improve emotion perception in persons with ABI. Although further research is needed, the interventions are clinically practical and show promise for the population with ABI."	Small groups. No sham/placebo. Data suggest specific training may enhance emotion perception. FAR training improved emotion from faces & context while SEI group had improvement in ability to infer how they would feel in a given context.

								No change perceived in SEI (P = .363).		
Neumann 2015 (score=3.5)	Emotional Training	RCT	No COI. Sponsored by the National Institute on Disability and Rehabilitation Research.	N = 203 with moderate to severe TBI	Mean age: 39.8 years; 151 male, 52 female.	Faces Intervention – program to teach participants to recognize emotions from facial expressions (n=24) vs. Stories Intervention – program to teach participants to decipher emotions from the context of short stories (n=23) vs. Cognitive Training Control – individual training without an emotional education component (n=24). All interventions were one-on-one computer-assisted treatments given by therapist, administered for one hour, three times per week, for three	3 and 6 months	<p>Diagnostic Assessment of Nonverbal Accuracy-2 Adult Faces mixed model MANCOVA results: Faces vs. Control interventions – Group – F1,44=5.72 (p=0.031), Effect size partial <math>\eta^2=0.11</math>, Time – F2,90=0.92 (p=0.421), Effect size partial <math>\eta^2=0.02</math>, Group x Time – F2,90=(1.14) (p=0.380), Effect size partial <math>\eta^2=0.02</math>.</p> <p>Stories vs. Control interventions – Group – F1,44=1.63 (p=0.239), Effect size partial <math>\eta^2=0.04</math>, Time – F2,88=0.58 (p=0.614), Effect size partial <math>\eta^2=0.01</math>, Group x Time – F2,88=(1.22) (p=0.350), Effect size partial <math>\eta^2=0.03</math>.</p> <p>Emotional Inference from Stories Test mixed model MANCOVA results: Faces versus Control interventions – F1,44=1.10 (p=0.349), Effect size partial <math>\eta^2=0.02</math>, Time – F2,90=4.25 (p=0.059), Effect size partial <math>\eta^2=0.09</math>, Group x Time – F2,90=(1.57) (p=0.553), Effect size partial</p>	“The Faces Intervention effectively improved facial affect recognition in participants with chronic post-traumatic brain injury, and changes were maintained for 6 months. Future work should focus on generalizing this skill to functional behaviors.”	More males randomized to faces group than females. Data suggest that the faces intervention enhanced facial affect recognition in chronic TBI patients and this improvement was sustained for 6 months suggesting faces better than either stories or control groups.

						weeks (totaling to 9 sessions).		$\eta^2=0.03$ . Stories vs. Control interventions – Group – $F_{1,44}=2.62$ ( $p=0.167$ ), Effect size partial $\eta^2=0.06$ , Time – $F_{2,88}=9.65$ ( $p=0.001$ ), Effect size partial $\eta^2=0.18$ , Group x Time – $F_{2,88}=(1.78)$ ( $p=0.253$ ), Effect size partial $\eta^2=0.04$ .		
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Goal setting has been included in the treatment of TBI patients [748-752].

## **Goal Setting Recommended.**

Goal setting is recommended for use in the treatment of TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

*Rationale:*

Two moderate quality trials both have small sample sizes, underpowering and poor reporting of results [748, 749]. Yet re-learning goal setting and attainment are important tasks. Some data suggest efficacy [753-755]. These approaches to goal setting are not invasive, have no adverse effects, are moderate to high cost in aggregate, so therefore are recommended.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Goal Setting; Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 114 articles in PubMed. We considered for inclusion 11 from PubMed and 1 from Google Scholar. Of the 12 articles considered for inclusion, 7 randomized trials and 5 systematic studies met the inclusion criteria.

## Evidence for the Use of Goal Setting

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
McPherson 2009 (6.0)	Goal setting	RCT	Sponsored by the Health Research Council of New Zealand. No COI.	N = 34 with moderate to severe traumatic brain injury.	Mean age for goal management / identity orientated / and usual care: 29 / 28 / and 40 years; 17 males and 7 females.	Goal management training (N = 12) vs Identity Orientated goal training, identity map for intervention delivery and scripted a six-step process for clinicians to aid mapping process (N = 10) vs Usual Care current rehabilitation plan (N = 12).	6 - 8 weeks	Goal attention scale, mean values: goal management vs identity oriented goal vs and usual care: base / post / follow-up; 26.38 (2.62) vs 26.15 (2.15) vs 28.34 (4.94) / 47.56 (14.11) vs 50.76 (13.71) vs 57.69 (12.25) / 43.97 (16.08) vs 48.48 (11.65) vs 51.63 (11.51).	“These theoretically informed approaches to goal setting showed promise but were time intensive and at times difficult for practitioners to utilize.”	Pilot study. No significant differences reported. Data suggest no differences between usual care and either of 2 goal setting approaches (Goal Mgt. training for structure) and (Identity oriented goal training for process). Both were time intensive and often difficult to utilize.
Tornas 2016 (6.0)	Goal Setting	RCT	Supported by the Norwegian Extra Foundation for Health and Rehabilitation through EXTRA funds. No mention of COI.	N=70 individuals with TBI and executive dysfunction.	38 males, 32 females; Mean age of 43±13.	Goal Management Training (GMT) (N=40) Vs Brain Health Workshop (BHW) (N=40)	Follow-up at baseline, post intervention (8 weeks), and 6 months.	Dysexecutive Questionnaire (DEX) Baseline vs Follow up, GMT: 4.55±2.69 vs 2.94±2.34 (p<0.001). Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A) baseline vs follow-up, GMT: 60.03±11.49 vs	“The present results have promising implications because they suggest that a relatively brief metacognitive intervention targeting sustained attention and emotional regulation is effective in improving emotional	Baseline differences between groups for time in years since injury (8.9 vs. 6.8).

								53.97±9.75 (p<0.001). QOL Total score, baseline vs follow-up, GMT: 3.26±0.54 vs 3.57±0.53 (p<0.001). Cognitive subscale score: 2.97±0.68 vs 3.33±0.73 (p<0.01). ADL score: 3.12±0.70 vs 3.59±0.66 (p<0.001). Emotional Subscale score: 3.75±0.88 vs 4.10±0.69 (p<0.01). Physical Subscale Score: 3.50±0.76 vs 3.70±0.83 (p<0.05).	regulation and QOL even years after injury.	
Owensworth 2008 (5.0)	Goal Setting	Community Life Based Goals	Sponsored by a grant from the Centre of National Research on Disability and Rehabilitation Medicine (CONROD and a National Health and Medical Research Council Public Health Fellowship. No mention of COI.	N = 35 with brain injury units and community-based rehabilitation services over 12 months	Age range 21-62 years old, 19 males & 16 females, and mean age of 43.89.	Individual Intervention (N = 10) vs Group Intervention (N = 11) vs Combined Intervention (N = 10)	3 months	Pre-post comparison and pre-follow-up comparison, PCRS: P=0.482 and P=0.150 respectively compared to P<0.025 and P=0.109 for Group and P=0.463 and P=0.114 for Combined groups.	“These findings generally support the efficacy of brief intervention formats following acquired brain injury, although further research is needed to examine clients’ suitability for particular interventions.”	Small sample sizes. Wait-list control bias. Data not well reported as compared to controls. Authors interpretations that trend towards better results with individual than group approach.

Doig 2011 (4.5)	Goal Setting	Randomized Cross over trial	Sponsored by Alexandra Hospital Foundation and the Queensland Health Community Rehabilitation Research Scheme. Principle researcher was in receipt of a University of Queensland Postgraduate Research Scholarship while conducting research.	N=14 diagnosed with TBI as evidence by loss of consciousness.	12 males, 2 females; Mean age of 24.5 (19.7-29.2)	Group 1 6 1-hour weekly sessions Home-based goal oriented therapy, followed by hospital based therapy of same amount of time (N=7) Vs Group 2 6 1-hour weekly hospital based goal oriented therapy following by home-based therapy (N=7)	1, 6, 12, and 18 weeks	Group 1, vs Group 2, Week 6, Goal Attainment Scale (GAS): 36.1 (31.7-42.8) vs 35.5 (28.9-40.9) (p<0.05). Group 1 & 2, baseline vs Wk 18: 36.1 (21-38) vs 50.0 (46.2-58) (p<0.01), & 35.0 (28.9-40.9) vs 53.6 (50-55) (p<0.01). Mayo Portland Adaptability Index (MPAI), Group 2, baseline vs week 18: 47 (37-50) vs 39 (33-48) (p<0.05). Canadian Occupational Performance Measurement (COPM) performance, Group 2, baseline vs wk 12 & 18: 4.0 (3.3-3.5) vs 7.2 (6.5-8.3) (p<0.01) & 8.6 (8.0-9.5) (p<0.05). COPM satisfaction, group 2, baseline vs wk 12 & 18: 4.0	"The results of this pilot investigation indicated that the outpatient therapy program was equally effective when carried out at home compared with a day hospital setting in terms of goal achievement, psychosocial reintegration, ability and adjustment and effect on environmental barriers."	Repeated measures crossover design small sample. Data suggest comparable efficacy between groups.
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								(2.0-4.7) VS 7.5 (6.2-7.7) (p<0.01) & 8.6 (8.0-10.0) (p<0.01).		
Gauggel 2001 (4.5)	Goal Setting	RCT	No mention of sponsorship or COI.	N=62 patients with Cerebral Vascular Accidents (CVA) and Closed Head Injury (CHI). N=47 control patients with orthopedic disorders and no TBI	No mention of gender; Mean age for Brain-Damaged groups: 41.5±13.8 and 41.7±14.4. Orthopedic Injury: 42.2±12.4 and 44.3±13.5.	High, Specific goals set for TBI patients (N=32) Vs “Do your best” goals given to TBI patients (N=30)	2 weeks after Neuropsych test and Response time blocks a few days following	Response latency, Goal by block interaction, F(1,105)=31.65 (p=0.0001). Indicating participants with high goals responded faster. Goal X Block interaction F(1,105)=9.14(p<0.01) indicating that high goals led to faster Response time. Goal Setting, chronic vs acute patients, mean personal goal (SD): -18.2% (11.1) vs -11.1% (6.0) t(23)=-2.26, (p=0.03).	“[O]ur experiment provides support for an application of the goal setting approach to the field of neuropsychology. The goal setting technique seems to be a useful tool for the investigation of motivation and self-regulation in brain-damaged patients.	Data suggest the speaker and high goal setting group responded faster than the “do your best goal” group.
Hart 2002 (3.5)	Goal Setting	Randomized Prospective Trail	Supported by grant from the National Institute on Disability and Rehabilitation Research. No mention of COI.	N=10 people with moderate to severe TBI.	8 males, 2 females; Mean age of 31.5 (19-45)	Participants got a voice organizer to remind them of goals set by clinician (N=5) Vs No voice organizer or cue recall (N=5)	Follow-Up of 1 week	Mean Recall Score, Recorded vs unrecorded cue recall groups: 5.5±1.9 vs 2.1±1.6 (p<0.001). Mean Recall Score, recorded vs unrecorded free recall group: 4.4±3.0 vs	“Portable electronic devices have the potential to assist with treatment areas beyond tasks involving prospective memory”	Small sample (n=10). Sample had variable time since injury (3mo to 18yrs). No long term F/U (only 1 week recall F/U).

								0.5±0.8 (p<0.001). All 10 patients reported liking the recall device.		
Gauggel 2002	Goal Setting	Non-RCT	No mention of sponsorship or COI.	N=87 patients with Cerebral Vascular Accidents (CVA) and Closed Head Injury (CHI).	No mention of gender; Mean age for High, Specific goal: 39.0±15.6. Self-stated goal group: 38.6±15.9. "Do your best" goal group: 47.4±13.7.	High, Specific goals set for TBI patients (N=30) Vs "Do your best" goals given to TBI patients (N=29) Vs Self-stated goals for TBI patients (N=28)	All trials done in one day.	Goal Commitment, High, Specific group, assignment of goal vs last trial: M=23.4 (4.9) vs M=24.2 (4.5) r=0.72 (p<0.001). All three groups performed very low error rates. ANCOVA, Group effect, F(2, 83)=7.57 MSE=65.9, (p=0.001). High Specific Goal performed more calculation in trial 4 vs Do you best (p<0.0001) and self-group (p<0.009).	"[B]rain-damaged patients do not necessarily have goal setting difficulties in a simple laboratory task that provides sufficient performance feedback. Moreover, it seems that brain-damaged patients can influence their own motivation quite well if they pay adequate attention to their own performance, the conditions under which they occur, and the immediate and distal effects they produce."	Exclude. Methods indicate trial not completely randomized. Rather assigned to groups and then some randomized.

Educational programs have been used in treatment of back, neck, eye and respiratory disorder treatments. However, we found no quality evidence of use of educational programs to treat traumatic brain injury patients.

## **Education Programs**

### **Recommended.**

Education programs are recommended for use in the treatment of TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

Rationale:	There are no quality studies assessing education programs for treatment of TBI. Education programs are not invasive, have no adverse effects, are low cost when education is incorporated in other rehabilitation programs, has no quality evidence of treatment efficacy, and are recommended as part of a rehabilitation plan for treatment of TBI.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Educational program; Traumatic brain injury, intracranial injury, Closed Head injury Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 35 articles in PubMed, 240 in Scopus, 6 in CINAHL, 13 in Cochrane Library, 50 in Google Scholar, and zero from other sources. Zero articles met the inclusion criteria.

Neuroplasticity is the brain's capacity to change and adapt. It refers to the physiological changes in the brain that happen as a result of our interactions with our environment. Neuroplasticity is a definite factor in recovery from brain injury. It is the basis for much of our cognitive physical rehabilitation practices.

## **Neuroplasticity**

### **No Recommendation.**

There is no recommendation for or against the use of neuroplasticity in the treatment of TBI patients.

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

<i>Rationale:</i>	There are no quality studies assessing Neuroplasticity for treatment of TBI. Neuroplasticity is not invasive has no adverse effects, is low cost, but in the absence of quality evidence of efficacy, there is no recommendation for treatment of TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Neuroplasticity, Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, Closed Head Trauma, Penetrating Head Trauma, Penetrating Craniocerebral Trauma ; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 62 articles in PubMed, 58 in Scopus, 1 in CINAHL, zero in Cochrane Library, 210 in Google Scholar, and zero from other sources. Zero articles met the inclusion criteria.

A social peer mentoring program has been included in the treatment of TBI patients [756] to address social isolation that has been reported in this population [757-760]

## Peer Mentoring Program

### No Recommendation.

There is no recommendation for or against the use of a peer mentoring program in the treatment of TBI patients.

*Strength of Evidence* – **No Recommendation, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

*Rationale:*

There are no quality trials and one low quality study of a peer mentoring program [756]. Peer-Mentoring is not invasive, have no adverse effects, are moderate to high cost in aggregate and in the absence of quality evidence of efficacy, there is no recommendation.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: mentoring, mentored, traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 5 articles in PubMed, 0 in Scopus, 0 in CINAHL, 0 in Cochrane Library, 0 in Google Scholar, and 0 from other sources. Of the 5 articles considered for inclusion, 3 randomized trials and 1 systematic study met the inclusion criteria

## Evidence for the Use of Peer-Mentoring Program

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Simpson 2011 (6.5)	Mentoring - TBI	RCT	Sponsored by a National Health and Medical Research Council Health Professional Fellowship grant. No COI.	N = 17 with severe TBI and experienced posttraumatic amnesia and moderate to severe hopelessness	Mean age: Treatment group 39.41 Wait List group 44.08  No mention of Sex	Treatment group (N = 8) received 20 hours of group based therapy, consisting of 10 weekly 2hour sessions. vs Wait List Group received standard care from Brain Injury Rehabilitation Unit. (N = 9)	3 months	Significant group-by-time interaction was found for BHS in the treatment group (F1,15 = 13.20, (p = 0.002)), At follow up 75% of patients in the treatment group retained the benefits from treatment. Suicide ideation, depression, social problem solving, self-esteem, hopefulness displayed no significant group-by-time interactions or main effects.	“This trial provides initial evidence for the efficacy of a psychological intervention in reducing hopelessness among long-term survivors with severe TBI.”	Small sample. Data suggest treatment gains maintained 3 months post-intervention for 75% of patients evidenced by reduction in mean Beck Hopelessness Scale.
Hanks 2012 (4.0)	Behavioral Programs	RCT	Sponsored by the U.S. Department of Education- National Institute of Disability Research and Rehabilitation —The Traumatic Brain Injury Model Systems Project. No COI.	N = 199 with TBI.	Mean age for control and mentoring group: 40.90 ± 17.33 / 38.46 ± 17.60 years, 136 males and 22 females.	Mentoring (N = 96) vs No mentoring (N = 62).  Outcome measures: Peer Mentoring Questionnaire; Brief Symptom Inventory-18; Family Assessment Device (FAD); Coping Inventory for Stressful Situations; Short Michigan Alcohol	2 years	Differences in subjective perception of community integration and levels of depression or anxiety, (p = 0.35). 88% in the mentoring group reported positive experience.  Those who received mentoring had better behavioral control and less chaos in the living environment / lower alcohol use / less	“Mentoring can be an effective way to benefit mood and healthy coping after TBI, and it can help to prevent maladaptive behaviors, such as substance abuse and behavioral dyscontrol, in the living situation.”	Data suggest equal in efficacy.

						Screening Test; Medical Outcomes Study 12-Item Short-Form Health Survey; and Community Integration Measure.		emotion-focused / avoiding coping / and good physical quality of life: p = 0.04 / 0.01 / 0.04 / 0.03 / and 0.4.		
Struchen 2011 (3.0)	Mentoring - TBI	RCT [761]	Sponsored by grants from the National Institute on Disability and Rehabilitation Research, US Department of Education. No mention of COI.	N = 30 with TBI	Mean age of Peer Partners: 31.7 Sex (M:F) 24:6	Active peer partnering group (N=12) participants were matched with a social mentor, and received 3 months of active social mentoring. Social mentors aimed to foster social networking and social interaction with their matched peer. vs The wait list group (N=18) did not receive active mentoring and completed a weekly social activity survey (WSAS).	2 months	No statistically significant main or interaction effects were observed for social integration, as measured by the Social Integration subscale of CHART-SF, Wilks lambda F1,25 = 2.10, (p = 0.16). No statistically significant interactions or main effects of time and/or group were observed for various measures of social network size and social activity level. A significant change was observed in the CES depression scale for the active mentoring group F1,25 = 9.73, (p < 0.01), however, an increase of depressive symptoms was observed after peer mentoring. The active mentoring group showed a significant increase of perceived social support after mentoring. F1,25 = 4.66, (p < 0.05).	“Satisfaction ratings for the SPM program were uniformly high and selected positive findings encourage further investigation of social mentoring as an intervention to effect improvements in social integration.”	Sparse methods. Pilot study with small sample size and injury severity differences between groups. Data suggest increased social support after mentoring observed but depression symptoms increased as well. Trend towards increased social life satisfaction.

Video feedback on task performance has been used for treatment of TBI patients [762, 763]. Decreased self-awareness is suggested to occur due to a number of neuroanatomical as well as cognitive impairments [764, 765].

## **Video Feedback on Task Performance**

### **Recommended.**

Video feedback on task performance is recommended for use in the treatment of patients with severe TBI.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

<i>Indications:</i>	TBI patients with task performance problems after severe TBI. The quality trial used meal preparation as the outcome [762, 763], although the approach appears applicable to occupational task performance.
<i>Benefits:</i>	Potential to improve accuracy of task performance.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Meal task performance was accomplished on 4 occasions in the quality study with subsequent self- and therapist-videotape reviews and verbal feedback [762, 763],
<i>Rationale:</i>	One moderate quality trial with two reports suggested a combination of video feedback with verbal was superior to either approach alone [762, 763], Video feedback plus verbal training is not invasive, has negligible adverse effects, is moderate to high cost in aggregate, has some potential evidence of effectiveness and so is recommended for selective treatment of severe TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: feedback intervention, traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 32 articles in PubMed, 10 in Scopus, 5 in CINAHL, 4 in Cochrane Library, 90 in Google Scholar, and 3 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, CINAHL, Cochrane Library, and from Google Scholar, and 3 from other sources. Of the 5 articles considered for inclusion, 2 randomized trials and 1 systematic studies met the inclusion criteria.

## Evidence for the Use of Video Feedback

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Schmidt 2012 (7.0)	TBI	RCT	Sponsored by a partial grant from the Occupational Therapists Board of Queensland. JS supported by fellowship by the Wenkart Foundation, Australia and NAL was supported by the Balnaves Fellowship provided by the Cerebral Palsy Alliance, Australia. No COI.	N = 54 with TBI and impaired self-awareness.	Mean age 40 (13) years; 46 males and 8 females.	Video plus verbal feedback group following 4 meal preparation sessions (N = 18) vs Verbal feedback plus 4 meal sessions (N = 18) vs Experiential Feedback plus 4 meal sessions (N = 18).	Unknown	Effect of feedback intervention on online awareness (measured by number of errors); mean difference for the video feedback group vs verbal vs experimental group: mean difference = 19.7; 95% CI = 9.2-30.1 vs mean = 12.4; 95% CI = 1.8-23.0).	"The results suggest that the video plus verbal feedback approach used in this study was effective in improving self-awareness in people with TBI."	Baseline dissimilarity in yrs post injury (1.5 vs. 4.7 vs. 5.8). Data suggest combining video and verbal feedback superior to verbal or experiential alone for improving self awareness.
Schmidt 2015 (4.5)	TBI	RCT	Sponsored by a grant awarded by the Occupational Therapists Board of Queensland. NO COI.	N = 32 with TBI and impaired self-awareness.	Mean age 42.2 (13.1) years; 27 males and 5 females.	Group 1, video plus verbal feedback group following 4 meal preparation sessions (N = 10) vs Group 2, verbal feedback plus 4 meal sessions (N = 10) vs Group 3, experiential Feedback plus 4 meal sessions (N = 10).	8-10 weeks	Maintenance of gains in online awareness: group 1 vs group 2 (mean difference 20.6, 95% CI 8.8 to 32.3) vs group 3 (mean difference 14.4, 95% CI 3.1 to 25.6). Differences in number of errors group 2 vs 3 (mean difference 6.2, 95% CI -5.0 to 17.5).	"A combination of video plus verbal feedback is an effective technique for achieving maintained gains in self-awareness in people with TBI."	Same study population as Schmidt 12. Baseline dissimilarity between groups post injury (2.6 vs. 8.4 vs. 8.1). Data suggest verbal plus video feedback best for self-awareness in TBI patients by 8-10 weeks post-intervention.

Memory rehabilitation is a form of cognitive rehabilitation with the goal to improve memory retrieval. Those with traumatic brain injury may utilize memory rehabilitation to assist in restoration of normal brain function. Typically, various memory techniques are used, which include computer and non-computer-based.

## **Memory Rehabilitation Recommended.**

Memory rehabilitation is recommended for use in the treatment of TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Moderate**

<i>Indications:</i>	Memory problems post TBI. May be selectively indicated for mild TBI patients with significant memory deficits.
<i>Benefits:</i>	Improved recall and memory
<i>Harms:</i>	Negligible
<i>Rationale:</i>	There are one high-quality, 2 moderate-quality studies and one low-quality study evaluating memory rehabilitation and many studies have incorporated such exercises as part of a rehabilitation program. Memory rehabilitation is not invasive, has negligible adverse effects, has been purportedly successful for many years and thus, it is recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 342 articles in PubMed, 0 in Scopus, 0 in CINAHL, 0 in Cochrane Library, 22600 in Google Scholar, and 0 from other sources. We considered for inclusion 7 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 7 articles considered for inclusion, 4 randomized trials and 3 systematic studies met the inclusion criteria.

## Evidence for the Use of Memory Rehabilitation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Lannin 2014 (8.0)	Memory Rehabilitation	RCT	This work was supported by a grant from the Royal Rehabilitation Centre Sydney Foundation. No COI.	N = 42	33 males, 9 females; Mean age is 33.5 years.	Control Group. Non-electronic memory aids. (N = 21) vs Experimental Group. PDA. (N = 21)	1 or 2 years post intervention	From baseline to end of 8 week assessments: Control group had GAS t-score of 41.7 to 49.5. Trial had 41 to 53 (P=.0001).	"Occupational therapy training in the use of a handheld computer improved patients' daily memory function more than standard rehabilitation."	No long term follow-up. Data suggest use of handheld computerized equipment for memory aid significantly improved memory goals.
das Nair 2012 (6.0)	Memory Rehabilitation	RCT	Sponsored by grants from The Stroke Association, Remediation (2006/05), Universities UK (Overseas Research Students Award Scheme), and the University of Nottingham. No COI.	N = 72 with memory problems following traumatic brain injury, stroke or multiple sclerosis.	Mean age 47.7, (10.2) years; 32 males and 40 females.	Compensation, 10 sessions (N = 24) vs Restitution treatment programmes, 10 sessions (N = 24) vs A self-help group control 10 sessions (N = 24).	7-months	No significant effect of treatment on the Everyday Memory Questionnaire, (p = 0.97). At 7-months, mean score for compensation vs restitution vs self-help; 41.0 vs 36.6 vs 44.1. Internal memory Aids questionnaire, (p = 0.002). Treatment groups used more internal memory aids vs to self-help, (p < 0.01). Measure of mood / adjustment / and activity of daily living, (p > 0.05).	"These results show few statistically significant effects of either compensation or restitution memory group treatment as compared with a self-help group control."	Dissimilar time since diagnosis between groups. Mixed population of TBI, MS and Stroke patients. At 7 months data suggest similar efficacy between all groups for mood, memory functions and dialing living activities although the compensation and restitution groups used significantly more internal memory aids than did the self help group.
Tawmley 2014	Memory Rehabilitation	RCT	Supported by the	N = 34	32 males, 2 females; mean age	Supported Employment	No follow up	CogSMART is rated highly among the patients that use it.	"We tentatively conclude	Data suggest addition of Cog SMART may

(4.0)			DOD (award W81XWH-08-2-0193). No mention of COI.		is 31.9 years.	and CogSMART (N = 16) vs Enhanced Supported Employment (N = 18)		Cohen d effect sizes scores for group differences were .97 and .72. For supported employment and CogSMART showed small improvement.	that CogSMART may improve postconcussive symptoms and prospective memory performance. Psychoeducation regarding TBI and postconcussive symptoms and training in compensatory strategies appear to be perceived by Veterans as helpful.”	improve post concussive symptoms and prospective memory for veterans with mild-moderate TBI.
Sumowski 2014 (score=3.5)	Memory Rehabilitation	Experimental	Supported by the Kessler Foundation and Children’s Specialized Hospital. No COI.	N = 10	6 males, 4 females; mean age is 43.4 years.	Retrieval Practice (N = 10) vs Massed Restudy (N = 10) vs Spaced Restudy (N = 10).	No follow up	46.3% subjects recalled of verbal paired associates through retrieval practice, 12.5% through masses restudy, and 15% through spaced restudy (P = .00001).	“RP represents a promising memory strategy for survivors of TBI with memory impairment. In addition to the apparent effectiveness of RP, this strategy appears simple/straightforward to apply (quizzing oneself or someone else), cost-effective, safe, and noninvasive. RCTs of RP training are needed.”	Not an RCT. Data suggest RP improved memory in severe TBI patients. Very small sample size (N=10).

Reading comprehension is one of the difficulties in TBI patients [766, 767] and is one of the skillsets that has been included in TBI rehabilitation programs [767].

## Reading Comprehension Exercises

### No Recommendation.

There is no recommendation for or against the use of reading comprehension exercises in the treatment of TBI patients.

#### *Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

##### *Level of Confidence – Low*

###### *Rationale:*

There are no quality trials to address success, content, frequency or intensity of reading exercises. There is one moderate quality trial suggesting simplified emergency department discharge instructions for head injury are preferable, but this does not test rehabilitation and is in mild TBI patients [766]. Reading Comprehension exercises are not invasive, have no adverse effects, are low cost, are thought to be helpful but in the absence of quality evidence, there is no recommendation.

Higher-order reasoning training has been used for treatment of TBI patients, in large part to develop skills to determine the gist meanings of information [768, 769]. Higher-Order Reasoning Training is typically short but intense programs that target the frontal lobe which provides an integrative approach to train functionally relevant complex reasoning abilities [768, 769]. Specifically, the “Top-Down” approach has been developed by researchers to be deliberate in focusing on tasks that highlight the pre-frontal cortex in attention and task-relevant stimuli, while screening out irrelevant distractions [769]. Training frontal-mediated top-down processes in adults with TBI is theorized to be beneficial in restoring and improving higher-order cognitive functions [769].

## High-Order Reasoning Training

### Recommended.

High-order reasoning training is recommended for use in the treatment of TBI patients.

#### *Strength of Evidence – Recommended, Evidence (C)*

##### *Level of Confidence – Low*

###### *Indications:*

Moderate to severe TBI

###### *Benefits:*

Improved reasoning and better understanding gist of information

###### *Harms:*

Negligible

###### *Frequency/Dose/Duration:*

12 group sessions of 1.5hrs/session [768]. Taught SMART strategies. Reading materials used.

###### *Rationale:*

There is one moderate quality RCT suggesting some efficacy of higher-order reasoning among chronic TBI patients [768]. Higher-order reasoning training is not invasive, has not adverse effects, is

moderately costly, has evidence of efficacy and tis thus recommended.

*Evidence:*

**Higher-Order Reasoning Training** – A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: **Higher-Order Reasoning Training; Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury** controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1 articles in PubMed, 0 in Scopus, 3 in CINAHL, 5 in Cochrane Library, 975 in Google Scholar, and 1 from other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 1 from other sources. Of the 3 articles considered for inclusion, 1 randomized trials and 2 systematic studies met the inclusion criteria.

### Evidence for the Use of Higher-Order Reasoning Training

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Vas, 2011  (4.5)	TBI	Higher-Order Reasoning Training	This research was funded by the Prothro-McDermott fund of the Dallas Foundation, Wood-Hayner-Yates TBI Research Fund, Julie and EdHawes, and theDee Wyly Research fund.	N = 35 participants with TBI, at least 1-year postinjury	Age range 20-65 years old, 16 males & 12 females, and mean age of 43.	Strategic Memory and Reasoning Training (SMART) (n=18, discontinued training: n=4) Vs Brain Health Workshop (BHW, control) (n=17, discontinued training: n=3)	Follow-up given end of assessment within 3 weeks, and at 6 months post training.	Significant results found in SMART group in posttraining ( $P = .007$ ) and at 6 months posttraining ( $P = .004$ ) when compared to pretraining. No significant results found in BHW at posttesting ( $P = .44$ ), or at 6-months ( $P = .52$ ) compared to pretraining.	“First, our findings revealed that 15 to 18 hours of SMART enhanced gist-reasoning in adults with TBI. Second, the effects of SMART generalized to untrained domains such as on the working memory measure of listening span and ratings of increased participation in daily activities. Third, there appeared to be sustained benefit (6 months posttraining) of SMART as compared to the control group (BHW).”	High dropout rate in both groups. Data suggest chronic TBI patients (at least 2 yr. post injury) benefit from SMART measured by gist-reasoning and measures of executive and lifestyle functions.

## Attention

Attention deficits are one of the most frequent cognitive consequences following the TBI, [771, 772]. Common treatment models include, APT-3 (basic sustained attention and executive controls), Attention Training Technique (Time Pressure management or 7 level models of training) [771].

### Attention Process Training

#### Recommended.

Attention process training is recommended for use in the treatment of TBI patients.

#### *Strength of Evidence – Recommended, Insufficient Evidence (I)*

#### *Level of Confidence – Low*

<i>Indications:</i>	For subacute to chronic, moderate and severe TBI patients. May apply to select mild TBI patients with these cognitive deficits.
<i>Frequency/Dose/Duration:</i>	10 weeks of APT training (one hour per week) times 3 days for 10 weeks.
<i>Indications for Discontinuation:</i>	When desired improvement has been achieved, clinical plateau or failure to improve.
<i>Benefits:</i>	Improvement in performance of attention related tasks.
<i>Harms:</i>	Negligible
<i>Rationale:</i>	There are no quality studies involving APT. There is one [773] showing improvement in patient self reported attention related tasks and psychological function, although the study had a small sample size. This intervention is not invasive, has few adverse effects, is low cost, and is therefore recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: attention process training, apt, traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 20 articles in PubMed, 76 in Scopus, 5 in CINAHL, 1 in Cochrane Library, 1190 in Google Scholar, and 1 from other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, CINAHL, Cochrane Library, Google Scholar, and 1 from other sources. Of the 2 articles considered for inclusion, 1 randomized trials and 1 systematic studies met the inclusion criteria.

### Evidence for the Use of Attention Process Training [770]

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Sohlberg 2000 (3.5)	Attention Process Training [770]	RCT Cross-over	No mention of sponsorship or COI.	N = 14 with 10 weeks of brain injury.	Age range between 18-60 years of age, gender not specified.	Condition A, 24 hours of attention process training over 10 weeks (N = 7) vs Condition B, 10 hours of therapeutic support and education over 10 weeks (N = 7).	10 weeks	Greater number of changes reported in memory and attention (1.59) vs psychological functions (.59), ( $p < 0.0001$ ). The effect of intervention was significant, ( $p = 0.05$ ) with greater (Paced Serial Addition Task) or PASAT scores after APT vs brain education.	“APT influenced self-reports of cognitive function and had a stronger influence on performance of executive attention tasks than was found with the brain injury education therapy.”	Small sample. Data suggest most patients improved. APT influenced cognitive self reports and performance of attention related tasks and brain injury education improved psychological functions.

Recreational computing including micro-computer delivered attention training has been used to treat TBI patients [771, 774].

## Recreational Computing

### Recommended.

Recreational computing is recommended for the treatment of TBI patients.

#### *Strength of Evidence – Recommended, Insufficient Evidence (I)*

#### *Level of Confidence – Low*

<i>Indications:</i>	Mild, moderate or severe, subacute or chronic TBI patients.
<i>Frequency/Dose/Duration:</i>	2 x 75-minute sessions per week for 6 weeks.
<i>Indications for Discontinuation:</i>	When desired improvement has been achieved, clinical plateau or failure to improve.
<i>Benefits:</i>	Increased attentional function
<i>Harms:</i>	Negligible
<i>Rationale:</i>	There is one low quality study [774] with a small sample suggesting the experimental group performed better on tests at 6 months (PASAT and WAIS-R). This intervention is not invasive, has negligible adverse effects, is moderate to high cost and is recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: recreational computing, traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1 articles in PubMed, 45 in Scopus, 0 in CINAHL, 0 in Cochrane Library, 1280 in Google Scholar, and 2 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 2 from other sources. Of the 2 articles considered for inclusion, 1 randomized trials and 1 systematic studies met the inclusion criteria.

### Evidence for the Use of Recreational Computing

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Gray 1992 (3.5)	Recreational Computing	RCT	Sponsored by a grant from the Scottish Home and Health Department, Chief Scientist Office. No mention of COI.	N = 31 with attentional dysfunction following traumatic or non-traumatic brain damage of acute onset.	Mean age for experimental / control groups: 16.18 (7.58) / 34.14 (18.44), 24 male and 9 female.	Experimental or computerized attentional retraining group of 14 sessions of 75 minutes each (N = 17) vs Control or recreational computing group of 14 sessions of 75 minutes each (N = 14).	6 months	Post test results show, in favor of the experimental group there was difference for the WAIS-R Picture Completion (P = 0.031) and for PASAT Information Processing Rate (IPR) (P = 0.023). At follow-up, for the experimental group IPR / total score at 4 improved during intervention and at follow up phase, (p = 0.004 and 0.001 / 0.007 and 0.018). And IPR shows improvement at 6-months for control group, (p = 0.034).	"[B]y 6-month follow-up the experimental group performed better on two tests related plausibly to attentional function, namely PASAT and the arithmetic subtest of the WAIS-R."	Small sample. Data suggest that at 6 months, experimental group performed better on tests related to attentional function (PASAT) and (WAIS-R).

Computerized attention training (visual, auditory, divided training) has been used to treat TBI patients [775, 776] shows the relations of the cognitive abilities and psychiatric symptomatology with the level of functioning in the functional domains.

### **Computerized Attention Training with Visual, Auditory, and Divided Training Recommended.**

Computerized attention training is recommended for use in the treatment of patients with chronic TBI.

#### ***Strength of Evidence – Recommended, Insufficient Evidence (I)***

##### *Level of Confidence – Low*

<i>Indications:</i>	For chronic TBI patients at least 12 months post injury
<i>Frequency/Dose/Duration:</i>	Six 2-hour sessions for 9 weeks.
<i>Indications for Discontinuation:</i>	When desired improvement has been achieved, clinical plateau or failure to improve.
<i>Benefits:</i>	Improved attention measures.
<i>Harms:</i>	Negligible
<i>Rationale:</i>	There is one moderate quality study [456] suggesting Computerized Attention Training significantly improved on measures of attention. This is not invasive, has low adverse effects, is moderate to high cost and is recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion Craniocerebral Injury, Computerized Attention Training with Visual, Auditory, and Divided training; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed zero articles in PubMed, zero in Scopus, 30 in CINAHL, zero in Cochrane Library, 120 in Google Scholar, and zero from other sources. We considered for inclusion 2 from PubMed, zero from Scopus, zero from CINAHL, zero from Cochrane Library, zero from Google Scholar, and zero from other sources. Of the 2 articles considered for inclusion, 2 randomized trials and zero systematic studies met the inclusion criteria.

### Evidence for the Use of Computerized Attention Training with Visual, Auditory, and Divided Training

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Niemann 1990 (4.0)	Computerized Attention Training	RCT	No mention of sponsorship or COI.	29 outpatients suffering from moderate to severe traumatic brain injury.	Experimental group mean age: 28.9±8.2 years. Control Group: 34.3±12 years.	Experimental Group: attention training (Six 2-hr sessions) Vs. Control Group: memory training (Six 2-hr sessions)	Baseline measures taken 2 times after completion of treatments.	Attention group improved more significantly than memory group on four measures of attention: Wilks's lambda=64, approximate F(4,21) =2.93, p<.025, one-tailed. Subsequent univariate F tests revealed a significant difference between the attention group and the memory group on the TMT-B, F(1, 24) = 5.25, p < .015, one-tailed. This significance was felt acceptable despite the fact that	"The experimental design evaluated outcome by juxtaposing a multiple baseline procedure for a 1st set of measures of attention and memory with a pre and post group comparison that relied on a 2nd set of neuropsychological tests. The experimental group improved significantly in comparison with the control group on measures of attention."	Data suggest moderate-severe TBI patients in experimental group improved significantly in comparison to controls in attention measures.

								<p>the adjusted level of .013 for multiple comparisons was not met. The reversed pattern between the two groups on four memory measures was not confirmed, Wilks's lambda = .88, approximated <math>F(4, 21) = &lt; 1, p &gt; .50</math>. In contrast with the baseline measures, the tests of the SDNTB were administered only before and after the training. The result of the 2 X 2 MANOVA was nonsignificant for the group effect, Wilks's lambda = .79, approximated <math>F(3, 22) = 1.94, p &gt; .10</math>, two-tailed; the trial effect,</p>	
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								Wilks's lambda = .88; approximated $F(3, 22) = .96$ , $p > .40$ , two-tailed; and the Group X Trial interaction, Wilks's lambda = .98, approximated $F(3, 22) = .16$ ; $p > .90$ , two-tailed.		
Gray 1992 (3.5)	Computerized Attention Training	RCT	Sponsored by a grant from the Scottish Home and Health Department, Chief Scientist Office. No mention of COI.	N = 31 with attentional dysfunction following traumatic or non-traumatic brain damage of acute onset.	Mean age for experimental / control groups: 16.18 (7.58) / 34.14 (18.44), 24 male and 9 female.	Experimental or computerized attentional retraining group of 14 sessions of 75 minutes each (N = 17) vs Control or recreational computing group of 14 sessions of 75 minutes each (N = 14).	6 months	Post test results show, in favor of the experimental group there was difference for the WAIS-R Picture Completion (P = 0.031) and for PASAT Information Processing Rate (IPR) (P = 0.023). At follow-up, for the experimental group IPR / total score at 4 improved during intervention and at follow up phase, ( $p = 0.004$ and	"[B]y 6-month follow-up the experimental group performed better on two tests related plausibly to attentional function, namely PASAT and the arithmetic subtest of the WAIS-R."	Data suggest that at 6 months, experimental group performed better on tests related to attentional function (PASAT) and (WAIS_R).

								0.001 / 0.007 and 0.018). And IPR shows improvement at 6-months for control group, (p = 0.034).		
Ruff 1989 (3.5)	Computerized Attention Training	RCT	No COI	46 patients with cerebral contusions or brainstem contusions	Control group mean age: 31.7±9.2 years. Experimental group mean age: 29.9±9.9 years. 27 males, 13 females.	Control group: 4 50-min sessions focused on six areas of activity Vs. Experimental Group: 4 50-min sessions focused on four specific cognitive abilities	None	Comparing pre and posttreatment scores, both groups improved significantly [MANOVA F(1,37)=.07, P>.05 and F(1,37)=0.2, P>.05 respectively] The P plot indicated that P values of >0.065 showed areas where experimental group's performance was superior to that of the control group. Most important treatment effect was to memory skills; little significant difference in	“(T)reatment in a structured setting would improve subjects’ neuro-psychological functioning, and suggests that professional attention, psychosocial group therapy, and both general stimulation activities and cognitive remediation have positive effects on neurocognitive functioning.”	Data suggest both groups improved but experimental group gained improvement in memory and error reduction in visual selective attention.

								attention, spatial integration, and consistency of retrieval.		
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“Captain’s Log” is a computer program that is specifically designs to training users to develop attention and focus skills. There are “five modules within the program with each encompassing cognitive training tasks that include the following areas: attention, concentration, memory, visuospatial, visuomotor, and conceptualization” [777]. “Captain’s Log” has been used to help cognitive skill development among those who have suffered a traumatic brain injury as well as “those who have been diagnosed with an attention disorder like those with ADHD” [778].

### **“Captain’s Log”- Computer Training Program for Attention Skills with Tasks for Vigilance, Inattention, Prudence, Impulsivity, Focus, Variability, and Speed**

**No Recommendation.**

There is no recommendation for or against the use of “Captain’s Log” in the treatment of TBI patients.

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

There are no quality studies using the Captain’s Log for improved attention in TBI patients. This intervention is not invasive, has no adverse effects, is low to moderate cost, but there is no recommendation in the absence of quality evidence.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Captain's Log, computers, computer, software, program, training; traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 0 articles in PubMed, 1 in Scopus, 0 in CINAHL, 0 in Cochrane Library, 20 in Google Scholar, and 1 from other sources. We considered for inclusion 0 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 1 from other sources. Of the 2 articles considered for inclusion, 0 randomized trials and 2 systematic studies met the inclusion criteria.

Restorative computer and non-computer attention remediation has been used to treat TBI patients [779-781].

### **Restorative Computer and Non-Computer Attention Remediation**

**No Recommendation.**

There is no recommendation for or against the use of restorative computer and non-computer attention remediation in the treatment of TBI patients.

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

There are no quality studies involving Restorative Computer and Non-Computer Attention Remediation. This technique is not invasive, has low adverse effects, is moderate to high cost, and in the absence of quality evidence, there is no recommendation for or against Restorative Computer and Non-Computer Attention Remediation.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Attention remediation, Traumatic brain injury, Intracranial injury, Closed Head injury ,Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 9 articles in PubMed, 425 in Scopus, 4 in CINAHL, 1 in Cochrane Library, 81 in Google Scholar, and 0 from other sources. We considered for inclusion 4 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 4 articles considered for inclusion, 2 randomized trials and 1 systematic studies met the inclusion criteria.

Reaction time tests (arm movement reaction time, hand response with different levels of difficulty) have been used for saccadic deficits after severe head trauma [782-785].

## Reaction Time Training

### No Recommendation.

There is no recommendation for or against the use of reaction time training in the treatment of TBI patients.

#### *Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

#### *Level of Confidence – Low*

#### *Rationale:*

There are no quality studies using Reaction time training. These techniques are not invasive, have low adverse effects, are moderate to high cost, and in the absence of quality evidence, there is no recommendation.

#### *Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: reaction time training, traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 38 articles in PubMed, 1,709 in Scopus, 38 in CINAHL, 4 in Cochrane Library, 34,600 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 2 from other sources. Of the 4 articles considered for inclusion, 0 randomized trials and 1 systematic study met the inclusion criteria.

## Balance

Vestibular dysfunction is reportedly common in TBI patients [168]. Adults with mild traumatic brain injury may acquire some vestibular dysfunction. Vestibular dysfunction is associated with dizziness, vertigo, visual blurring, oscillopsia (a jumping of the visual field associated with movement of the head), and feeling off balance [786]. Vestibular therapy aims to decrease these symptoms and improve dynamic and static balance by utilizing exercises that target these impairments [787]. For the best outcomes, exercises should be individualized to the patient. Often, this means taking extensive amounts of information regarding history, symptoms, and tolerance to certain exercises. Studies have shown that generalized vestibular exercises are not as successful as individualized and personal ones [788].

### Vestibular Rehabilitation

#### Recommended.

Vestibular rehabilitation is selectively recommended for TBI patients.

*Strength of Evidence* – **Recommended, Evidence (C)**

*Level of Confidence* – **Low**

<i>Indications:</i>	Post TBI with vestibular symptoms thought to be peripheral and not central in origin. Generally initiated with electronystagmogram (ENG). Not indicated for concussion patients.
<i>Benefits:</i>	Faster resolution of vestibular symptoms
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	N/A
<i>Indications for Discontinuation:</i>	Sufficient recovery, resolution of symptoms.
<i>Rationale:</i>	There is one moderate quality study suggesting efficacy of Vestibular Rehab Treatment for treatment of TBI [696]. Vestibular Rehab Treatment is not invasive, has no adverse effects, is moderate cost, has some evidence of treatment efficacy, and is recommended for selective treatment of TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Vestibular Rehabilitation; Traumatic brain injury, Closed Head injury, Penetrating, Head Injury, Concussion, Craniocerebral Injury; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 31 articles in PubMed, 112 in Scopus, 4 in CINAHL, 0 in Cochrane Library, 240 in Google Scholar, and 0 from other sources. We considered for inclusion 2 from PubMed, 3 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 5 articles considered for inclusion, 1 randomized trial and 4 systematic studies met the inclusion criteria.

## Evidence for the Use of Vestibular Rehab Treatment

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Schneider 2014 (7.0)	Vestibular Therapy	RCT	This study was funded by the Alberta Centre for Child, Family and Community Research, grant number 09SM-Emery. No COI.	N=31	(18 males, 13 females); Median age of 15 (12-30).	Group 1 (N=15) received standard care for concussion from physiotherapist and also received cervical spine physiotherapy and vestibular rehabilitation. Vs. Group 2 (N=16) received the standard protocol for care by same physiotherapist.	Baseline, once a week for 8 weeks.	Greater proportion of individuals in group 1 were cleared medically to return to sport within 8 weeks, 66.2% vs <10% (95%CI 40-92.3) ( $p<0.001$ ). Group 1 10.27 time more likely to be cleared (1.51-69.56, $p<0.001$ ). Time since injury was same for both groups, and patients had zero symptoms when cleared to play.	"A greater proportion of adolescents and young adults with persistent symptoms of dizziness, neck pain and/or headache, who were treated with a combination of vestibular rehabilitation and cervical physiotherapy treatment, were medically cleared to return to sport by 8 weeks following initiation of treatment than individuals with the same kind of symptoms who continued with rest instead."	Data suggest combination therapy (cervical and vestibular PT) shortened time to medical clearance to resume sports activity.

Computer and video games have been used for cognitive rehabilitation for TBI patients [789]. Virtual Rehabilitation purportedly may be beneficial for patient engagement and motivation [790-793].

## Computer & Video Games for Balance

### Recommended.

Computer and video games for balance are recommended for use in the treatment of TBI patients.

#### *Strength of Evidence – Recommended, Insufficient Evidence (I)*

#### *Level of Confidence – Low*

<i>Indications:</i>	Hemiparetic patients > 6 months attending a rehabilitation program, absence of cognitive impairment who are able to walk 10 meters indoors without orthopedic aids and are able to follow instructions.
<i>Frequency/Dose/Duration:</i>	Two regimens have been used, either 20 hour long sessions, 3-5 times per week [792] or 15 minute stand balance training for 4 weeks [793].
<i>Indications for Discontinuation:</i>	When desired improvement has been achieved, clinical plateau or failure to improve.
<i>Benefits:</i>	Improved balance
<i>Harms:</i>	Negligible.
<i>Rationale:</i>	There are 2 moderate quality studies using video games [793, 794]. Both studies had small sample sizes. In [792], there was significant improvement in static balance and in [793], there was a weak positive trend towards increasing balance. Computer and video games are non invasive have low adverse effects, are moderate to high cost depending on supervision requirements and duration, and are recommended but larger studies need to substantiate the findings of the smaller pilot studies.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Computer and Video Games, Cognitive Rehabilitation, traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 5 articles in PubMed, 42 in Scopus, 1 in CINAHL, 6 in Cochrane Library, 2980 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 3 from other sources. Of the 3 articles considered for inclusion, 3 randomized trials and 3 systematic studies met the inclusion criteria.

## Evidence for the Use of Computer and Video Games

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Gil-Gomez 2011 (5.5)	Video & Computer Games	RCT	No Sponsorship or COI.	N=20	(11 males/6 females) Mean Age 47.3±17.8	eBaViR balance system using the Wii Balance Board (WBB) vs Control group that did normal physiotherapy.	Follow up at baseline and after 20, hour long sessions (3-5 a week)	ANOVA measurements showed significant time effect favoring WBB group for Berg Balance scale (p=0.00), Brunnel Balance assessment (p=0.048), Anterior Reach Test (p=0.005), Stepping test (paretic) (p=0.021), Stepping Test (non-paretic) (p=0.046), 1 minute walking test (p=0.007), Time "Up and Go" test (p=0.004), and 30-second Sit-to Stand Test (p=0.003). No difference in dynamic balance time effect in control and WBB group.	"[T]he study assessed the influence of a WBB-based virtual rehabilitation system (eBaViR) on standing balance rehabilitation with ABI patients and showed that virtual rehabilitation is capable of substantially improving the condition of the patients."	Small sample. Data suggest Patients who used eBaViR had a significant improvement in static balance compared to patients in traditional therapy group. Both groups showed dynamic balance improvement.
Cuthbert 2014 (5.5)	Video & Computer Games	RCT	Study funded by the Craig Hospital Foundation. No COI.	N=20	(13 males/7 females) Group 1: 31.5 (23-56) Group 2: 31.0 (19-64)	Patients received 15 minute (Extra Stand Balance Care) ESC balance training Vs VRT group which utilized games on the Wii Fit and Wii Sport interactive in addition to standard physical therapy.	Follow-up at baseline, 2, and 4 weeks.	No significant difference in Extra Standard Balance Car and VRT in Patient satisfaction. Time improvement higher in VRT group for Berg Balance Scale (0.19 pts/day, p=0.03). overall improvement in BBS between groups not significant. Both groups had comparable Dynamic Stability improvements, no adverse effects within both groups.	"[F]urthermore, these data help to provide support for the growing trend of using VR-based activities in physical rehabilitation. The VR intervention applied here utilized many of the theories of neurological and physical recovery that have driven this trend, including repetitive practice, self-observation and biofeedback."	Small sample. Data suggest slight preference for use of VR therapy for balance over traditional therapy.

Baniqued 2014 (3.0)	Video & Computer Games	Quasi rando	Study supported by grant from The Office of Naval Research And National Science Foundation Neuroengineering IGERT Fellowship grant.	N=209	(47 males/16 2 females) Group 1: 21.16±2.2 5 Group 2: 21.35±2.6 1 Group 3: 20.80±2.1 0 Group 4: 20.70±2.1 9	completed a working memory and reasoning game (WM-REAS 1 Vs. Adaptive working memory and reasoning game (WM-REAS 2) Vs. Active control casual games Vs. No-contact control group.	Total of 10, 20 minute sessions. 2-3 sessions per week. Follow up at session 1, 5, and 10.	WM-REAS 2 group vs active control group; effort ratings higher in WM-REAS 2 (p<0.017). Overall, feedback indicating three training groups. WM-REAS group higher ANOVA gain scores vs other groups (F(3,166)=5.613 p=0.001). Reduced lag blink in Wm-REAS 2 group (p<0.001). Post-experiemtnal survey showed 3 active groups, changed the way they perform daily activities in a good way.	“[N]evertheless, with the aggressive marketing of brain games and the liberal application of preliminary training results, we caution against using video games or other computer-based programs as a sole or primary approach to improving brain function, particularly if it leads to a more sedentary lifestyle or in the words of Weis and Cerankosky (2010) “displace(s) activities that might have greater educational value.”	Data suggest training games resulted in improvement which was only slightly noted on transference to untrained tasks. There was found to be better performance in attention requiring games and decreased attention blinks.
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Virtual reality utilizes computers as a way to enhance the activity of TBI patients and inspire more real life interaction [793, 795, 796].

## Virtual Reality for Balance

### Recommended.

Virtual reality for balance is recommended for use in the treatment of TBI patients.

*Strength of Evidence* – Recommended, Evidence (C)

*Level of Confidence* – Low

<i>Indications:</i>	In TBI patients physically able to use a VR system (be ambulatory), have good sitting balance and no perceptual disabilities which would prevent them from viewing the monitor where the virtual environment was displayed [797].
<i>Frequency/Dose/Duration:</i>	3 times per week for 25 minutes for a total of 4 weeks [797].
<i>Indications for Discontinuation:</i>	When desired improvement has been achieved, clinical plateau or failure to improve.
<i>Benefits:</i>	Improved memory, balance, reaction time, movement, visual and verbal learning tasks.
<i>Harms:</i>	Falls in unstable patients, dizziness, otherwise negligible
<i>Rationale:</i>	There are 7 moderate quality studies with most supporting modest efficacy [793, 797-802]. Yet, most of the studies have small sample sizes, or there are sparse methods. Larger studies are needed to clearly determine efficacy. Virtual reality games are non invasive have low adverse effects, but may be high cost if ongoing supervision is required, and are recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Virtual Reality, Virtual Reality Program; Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, Closed Head Trauma, Penetrating Head Trauma, Penetrating Craniocerebral Trauma, Virtual Reality, Virtual Reality Program; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 35 articles in PubMed, 20 in Scopus, 12 in CINAHL, 8 in Cochrane Library, 14,100 in Google Scholar, and 0 from other sources. We considered for inclusion 6 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 7 from other sources. Of the 13 articles considered for inclusion, 9 randomized trials and 3 systematic studies met the inclusion criteria.

## Evidence for the Use of Virtual Reality

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Cuthbert 2014 (5.5)	Computer and Video Games	RCT	Study funded by the Craig Hospital Foundation. No COI.	N=20 with diagnosis of TBI.	(13 males/7 females) Group 1: 31.5 (23-56) Group 2: 31.0 (19-64)	Patients received 15 minute (Extra Stand Balance Care) ESC balance training Vs VRT group which utilized games on the Wii Fit and Wii Sport interactive in addition to standard physical therapy.	Follow-up at baseline, 2, and 4 weeks.	No significant difference in Extra Standard Balance Car and VRT in Patient satisfaction. Time improvement higher in VRT group for Berg Balance Scale (0.19 pts/day, p=0.03). overall improvement in BBS between groups not significant. Both groups had comparable Dynamic Stability improvements, no adverse effects within both groups.	"[F]urthermore, these data help to provide support for the growing trend of using VR-based activities in physical rehabilitation. The VR intervention applied here utilized many of the theories of neurological and physical recovery that have driven this trend, including repetitive practice, self-observation and biofeedback."	Small sample. Data suggest slight preference for use of VR therapy for balance over traditional therapy.
Grealy 1999 (4.5)	Virtual Reality	RCT Crossover design	No mention of sponsorship or COI.	13 brain-injured patients	Mean age: 32.08 years. 7 males, 6 females.	VR exercise group vs No-exercise Control Group	None	Mean scores decreased significantly after exercise (RT: t12 = 3.21, p <.01; MT: t12 = 2.66, p < .05) while no significant changes were seen in the control condition (RT: t12 = .38,	"Exercising in a virtual environment offers the potential for significant gains in cognitive function."	Small sample. Data suggest that even while exercising in a virtual reality environment, there is significant improvement in cognitive function as experimental group performed better than controls for

								<p><math>p &gt; .05</math>; MT: <math>t_{12} = .07</math>, <math>p &gt; .05</math>). Postexercise times were also found to be significantly faster than those achieved after the control trials (RT: <math>t_{12} = 2.22</math>, <math>p &lt; .05</math>; MT: <math>t_{12} = 1.79</math>, <math>p &lt; .05</math>). However, RT and MT both remained slow after exercise.</p>		<p>reaction times, movement times and verbal and visual learning tasks.</p>
Jacoby 2013 (4.5)	Virtual Reality	RCT	No mention of sponsorship or COI.	12 people who had sustained TBI and was hospitalized in Department of Brain Injury	Mean age experimental group: $27.83 \pm 12.06$ years. Mean age of control group: $30.67 \pm 13.13$ years. 8 males, 4 females.	Experimental group (Ten 45-min VR-based treatment sessions) Vs. Control Group (10 sessions of occupational therapy cognitive training)	None	<p>No significant differences were found between the groups in total score of MET-SV before and after intervention. A larger effect was seen in participants in the experimental group improved more in their final scores on MET-SV relative to initial scores (<math>M=46.21\%</math>, <math>SD=37.06</math>, <math>median=62.28</math>), compared to control group</p>	<p>“(c)ognitive treatment in occupational therapy that focuses on mediating strategies to improve executive functions, may lead to an improvement in the ability to perform IADL activities among people following TBI.”</p>	<p>Small sample. Data suggest a trend toward VR therapy vs Cognitive retraining OT without VR results in improved complex daily activities.</p>

								(M=13.52%, SD=19.93, median=14.35) (z=-1.761, p=0.046; ES=.51)		
Yip 2013 (4.5)	Virtual Reality	RCT Single-blind	Sponsored by a General Research Grant of the Research Council, Hong Kong. No COI.	N = 37 with acquired brain injury.	18 to 55 years old, 24 male and 13 female.	Virtual reality-based prospective Memory (VRPM) group pretest and posttest, two times a week for about 30 to 45 minutes (N = 19) vs Control group regular reading and table games activities during the treatment phase (N = 18).	5-6 weeks (unclear)	VRPM showed improvement of the immediate recall PM tasks / performance of both event and time based PM tasks / ongoing tasks / and number of time checks: $p < 0.05 / 0.001 / 0.01 /$ and 0.001. No significant difference found in any outcome measure in the control group.	“The present study initially supported the positive training effect of a VR-based cognitive rehabilitation programme in PM among people with acquired brain injury.”	Small sample. Data suggest VR training resulted in improved VR based and PM outcome measures in ABI patients.
Man 2013 (4.0)	Virtual Reality	RCT	No mention of sponsorship or COI.	40 participants with mild or moderate brain injury	Ages between 18-55. No mention of gender.	Artificial intelligent virtual reality based vocational training system (AIVTS) Vs. Psycho-educational vocational training programme (PEVTS)	3 months	ANOVA measures indicated no group x time interaction effect on primary and secondary outcomes. AIVTS group performed better than PEVTS group. No group interaction effect or group difference (F=0.95, p=.33), but a difference over time (F=5.19,	“These results support the potential use of a VR-based approach in memory training in people with MCI. Further VR applications, limitations and future research are described.”	Data suggest VR based approach group performed better than therapist led group in terms of memory processes.

								<p>p=0.014). For AIVTS, pre-test (mean=79.66, SD=16.33) and post-test (mean=83.45, SD=14.32) showed differences (t=-2.59, p=0.018). For PEVTS, pre-test (mean=78.40, SD=13.52) and post-test (mean=78.55, SD=14.00) showed no differences (t=-0.058, p=0.955). Friedman's Test for individual groups of AIVTS and PEVTS over three points showed chi-squares and statistical significance were, respectively, 11.14 (p=0.04) and 8.00 (p=0.018).</p>		
Thornton 2005 (4.0)	Virtual Reality	Quasi randomization	Sponsored by the Ontario Neurotrauma Foundation and through a Premier's Research	N = 27 with TBI.	Aged 18 – 66 years, 19 male and 8 female.	An activity-based (ABE) programme, plus conventional tools of balance ( N = 12) vs	6 weeks	Activities-specific Balance Confidence Scale [360] mean score increased from 74.6 to 76.4 and 78.2 and 74.8 to	"Both exercise programmes offered benefits in addition to improved balance."	Quasi randomization, small sample. Sparse methods .Data suggest similar efficacy between group for balance

			Excellence Award (to HS). MT was supported by an Ontario Neurotrauma Foundation Student Fellowship. HS is a Career Scientist with the ministry of Health and Long-term Care of Ontario. No other COI.			Virtual reality (VR) delivered balance exercise programme (N = 15).		80.2 and 81.2 for VR group. 2 participants in each group made clinically significant improvements of nine points or more on the Lower Extremity Functional Scale (LEFS) between the baseline and post intervention testing, (p-value not given).		improvement but VR group demonstrated better quantitative improvement and expressed increased confidence and improved enjoyment.
Fong 2010 (4.0)	Virtual Reality	RCT	No mention of sponsorship or COI.	24 persons in the community with acquired brain injury	Mean age of Part I: 43.0±10.7 years. Mean age of Part II: 52.6±6.2 years. 17 males, 7 females.	Part I: Early (VR-ATM program first, followed by real ATM) Vs. Late (Real ATM first, then VR-ATM) Part II: Six 1 hour sessions over 3 weeks. VR Training Vs. Computer-assisted instruction	No	Part I: Average reaction time for real ATM was 15.5 seconds. Failed attempts with real ATM had an average reaction time of 26.5 seconds. Sensitivity of VR-ATM was 100% for cash, and 83.3% for money transfers. Part II: Mann-Whitney test indicated no significant differences in cognitive performance between participants in	"We found the VR-ATM to be usable as a valid assessment and training tool for relearning the use of ATMs prior to real-life practice in persons with ABI."	Small sample. Data suggest VR-ATM may be useful for ABI patients to relearn how to use ATMs.

								VR-ATM and CAI groups. (p=0.288-.911) No statistically significant difference was found in the post-test correct percentage scores between VR-ATM and CAI groups. (p=.059)		
Cox 2010 (3.5)	Virtual Reality	RCT	Sponsored by a grant from DARPA (Defense Advanced Research Projects Agency) through a Phase 1 SBIR (Small Business Innovation Research) Program. No mention of COI.	N = 11 male with TBI.	Mean age / range: VRDSRT and Control; 26.2 / 23-31 and 26.6 / 21-39, all male.	Virtual reality drying simulation rehabilitation training (VRDSRT) group received residential rehabilitation and VRDSRT, 4-6, 60- to 90-min rehabilitation training sessions (N = 6) vs VRDSRT control group or residential rehabilitation only (N = 5).	Unclear	The composite score improved significantly for VRDSRT group vs control, (p < 0.01). VRDSRT demonstrated a reduction in road rage / risky driving behaviors; (p = 0.01 / 0.04). Driving performance improved in VRDSRT group, (p < 0.01).	“VRDSRT showed promising results with respect to retraining driving performance and behavior among military personnel recovering from TBI.”	Small sample. Data suggest VRDSRT may be useful in retraining TBI patients in driving.
Mahajan 2011 (3.0)	Virtual Reality	RCT	No mention of sponsorship or COI.	20 participants who were at least 1 year post traumatic brain injury	Mean age: 30.62±10.91 years. 12 males, 8 females.	Isometric joystick Vs. Conventional joystick	None	The mean trial time for the MSJ was 3.4% higher than the mean trial time for the IJ, after	“The customizable isometric joystick seems to be a promising	Small sample. Data suggest participants could drive a virtual wheelchair using an IJ which may be

								controlling for wheelchair icon speed. As expected, a significant main effect of task width ( $P < .005$ , $F_{1,135} = 5968.25$ ) was found. The average trial time on wider tasks was 110.38% higher than the average trial time on narrow tasks. All other interactions were not significant. The joystick _ task-width interaction effect was significant for RMSE ( $P = .035$ , partial $\eta^2 = .109$ ) No significant differences were found in other outcome measures when compared across the 2 joystick groups. From the mixed model analysis for trial time, the interactions of joystick and task width with the covariate absolute average	interface for driving a powered wheelchair for individuals with TBI.”	useful for driving real wheelchairs.
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								<p>speed were not significant. However, a significant difference in log of trial times between the 2 joysticks (main effect: <math>P=.038</math>, <math>F_{1,135}=4.38</math>) was observed. No statistically significant differences were seen between the 2 joysticks in the following driving performance measures: boundary collisions, number of HPM violations, and number of times the wheelchair got stuck.</p>		
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## Perception and Self-Awareness and Psychological Well-Being

Perceptual deficits are common in adults with diffuse brain injury [803]. Perceptual training involves using tasks like construction of puzzles to improve functional performance [803]. Perceptual training can take place on the computer [804] or completing other functional tasks such as puzzles [803]. Perceptual training includes, basic visual scanning, somatosensory awareness and size estimation training, and complex visual perceptual organization [805].

### Perceptual Skills Training

There is no recommendation for perceptual skills training for TBI patients.

#### No Recommendation.

##### *Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

##### *Level of Confidence – Low*

##### *Rationale:*

There are no quality studies specifically addressing perceptual skills training. These techniques are not invasive, have low adverse effects, are moderate to high cost, and in the absence of quality evidence, there is no recommendation.

##### *Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Perceptual skills training, brain injuries, closed head injuries, penetrating head injuries, brain concussion, concussion, craniocerebral trauma, traumatic brain injury, intracranial injury, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1 article in PubMed, 32 in Scopus, 2 in CINAHL, 0 in Cochrane Library, 61,700 in Google Scholar, and 2 from other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 1 from other sources. Of the 5 articles considered for inclusion, 0 randomized trials and 4 systematic studies met the inclusion criteria.

In cognitive rehabilitation, verbal labeling training is used to provide feedback to TBI patients through tasks to improve performance [806]. The use of verbal and visual feedback improves self-awareness to TBI patients during occupational performances [806]. Interpersonal Process Recall (IPR) is a technique that specifically uses “videotaped interactions of participants with a professional in order to facilitate therapy” [807]. IPR is used specifically to help researchers “gain access to participants’ silent in-session experiences as remembered by the participant” [808]. These silent experiences may include “feelings, emotions, body language, and subconscious reasoning [808].” Participants are “recorded interacting with a counselor and then are exposed to that recording with the counselor present” [807]. There is a “remote control present in case the participant or the counselor wishes to pause the recording at specific moments” [807]. IPR strives to “accelerate participants’ recovery process with counseling by identifying underlying reasoning for specific actions during the interaction” [808].

## Verbal Labeling Training and Compensatory Interpersonal Process Recall Recommended.

Verbal labeling training and compensatory interpersonal process recall is selectively recommended for TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

<i>Indications:</i>	Moderate to severe chronic and post-op TBI patients with impaired self awareness and are at least one year post TBI.
<i>Frequency/Dose/Duration:</i>	Preparation of 4 meals with 2-4 days between each meal.
<i>Indications for Discontinuation:</i>	When desired improvement has been achieved, clinical plateau or failure to improve.
<i>Benefits:</i>	Improved self awareness
<i>Harms:</i>	Negligible
<i>Rationale:</i>	There is one moderate quality study [806] showing combination video plus virtual feedback was effective in TBI patients as measured by the number of errors made in meal preparation. This intervention is not invasive, has negligible adverse effects, is moderate cost, and is recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Verbal, labeling, training, traumatic, brain, injury, intracranial, closed, head, penetrating, concussion, craniocerebral, trauma controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 6 articles in PubMed, 0 in Scopus, 6 in CINAHL, 1 in Cochrane Library, 5720 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 5733 articles considered for inclusion, 1 randomized trial and 0 systematic studies met the inclusion criteria.

### Evidence for the Use of Verbal Labeling Training

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Schmidt 2012 (7.0)	Compensatory Interpersonal Process Recall (IPR), Videotape of social interaction, viewing tape, feedback, corrections and practice	Pragmatic RCT	Study was partially funded by grant from the Occupational Therapists Board of Queensland. No COI.	N = 54 participants with a TBI and also impaired self-awareness	Mean age video feedback group 42.7 years, verbal feedback group 41.6 years, and experiential feedback group 37.5. 46 males, 8 females.	Video Feedback (n=18) c Vs. Verbal Feedback (n=18) Vs. Experiential Feedback (n=18)	Meal tasks completed within 2 to 4 days. After final task no mention of long-term follow-up.	The video feedback group had statistically higher intellectual awareness compared to the verbal and experiential groups (p < 0.01). Between the verbal and experiential groups there was no statistically significant difference between intellectual awareness (mean difference = -2.4, 95% CI = (-7 – 2.1).	“In conclusion, this RCT demonstrated that the combination of video plus verbal feedback is most effective in enhancing both online and intellectual awareness compared with other feedback methods. A reassuring finding is that the intervention was not accompanied by a significant increase in emotional distress.”	Data suggest virtual feedback plus video was effective in self awareness improvement

Functionally based rehabilitation has been used to improve day-to-day life for patients with severe TBI many years after injury [775, 776].

## Psychosocial Functioning and ADLs

### Recommended.

Functionally based rehabilitation is recommended for use in the treatment of TBI patients.

#### *Strength of Evidence – Recommended, Insufficient Evidence (I)*

#### *Level of Confidence – Low*

<i>Indications:</i>	Moderate, severe, chronic and postop TBI patients 3-4 years post injury with ongoing deficits in functional independence, anxiety and depression [809].
<i>Frequency/Dose/Duration:</i>	2 sessions per week of 2-6 hours per week for 27 weeks
<i>Indications for Discontinuation:</i>	When desired improvement has been achieved, clinical plateau or failure to improve.
<i>Benefits:</i>	Self organization and psychological well being
<i>Harms:</i>	Negligible
<i>Rationale:</i>	There is one moderate quality study suggesting a multidisciplinary community outreach program post severe TBI is of benefit after the active treatment phase ended. This intervention is not invasive, has negligible adverse effects, is moderate cost, and is recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Psychosocial functioning and ADLs, Traumatic brain injury (mild, moderate, severe, acute, subacute chronic), Closed Head Penetrating Concussion, Craniocerebral Injury; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 366 articles in PubMed, 18 in Scopus, 24 in CINAHL, 1 in Cochrane Library, 120 in Google Scholar, and zero from other sources. We considered for inclusion 2 from PubMed, zero from Scopus, zero from CINAHL, zero from Cochrane Library, zero from Google Scholar, and zero from other sources. Of the 2 articles considered for inclusion, 1 randomized trial and 1 systematic studies met the inclusion criteria.

## Memory and Motor Imagery

Memory and reasoning tasks are used as cognitive rehabilitation utilizing accepted methods in TBI patients [810, 811]. Some specific methods include computer memory retaining groups, games, reasoning tasks.

### Memory/Reasoning Tasks, Games, Computer Games

Recommended.

Memory/reasoning tasks, games, computer games are selectively recommended for TBI patients.

#### *Strength of Evidence – Recommended, Insufficient Evidence (I)*

#### *Level of Confidence – Low*

<i>Indications:</i>	Moderate, severe, postoperative, chronic TBI patients with ongoing memory deficits injured at least one to seven years previously, with adequate interpersonal communication skills, 25% intact visual fields, motivated and no premorbid history of psychiatric disturbance [810].
<i>Frequency/Dose/Duration:</i>	Daily treatment for 4 days per week (5 hours per day for 20 treatment hours per week) totaling 160 hours of treatment.
<i>Indications for Discontinuation:</i>	When desired improvement has been achieved, clinical plateau or failure to improve
<i>Benefits:</i>	Memory improvement
<i>Harms:</i>	Negligible
<i>Rationale:</i>	There are 2 low quality studies, with one suggested some benefit from computer games on memory performance [810]. This intervention is not invasive, has negligible adverse effects, is moderate cost, and is recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Traumatic brain injury (mild, moderate, severe, acute, subacute chronic) Closed Head Penetrating Concussion, Craniocerebral Injury Memory/reasoning tasks, games, computer games; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed zero articles in PubMed, 77 in Scopus, zero in CINAHL, zero in Cochrane Library, 80 in Google Scholar, and zero from other sources. We considered for inclusion zero from PubMed, 2 from Scopus, zero from CINAHL, zero from Cochrane Library, 1 from Google Scholar, and 1 from other sources. Of the 4 articles considered for inclusion, 2 randomized trials and 1 systematic study met the inclusion criteria.

### Evidence for the Use of Memory/Reasoning Tasks, Games, Computer Games

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Dou 2006 (3.5)	Memory/Reasoning Tasks	Quasi-experimental design	No mention of sponsorship or COI	37 patients with TBI	Mean age: 38.067±12.32 years. 27 males, 10 females.	Computer-Assisted Memory Training Group (CAMG) with 1 month training program Vs. Therapist-administered Memory Training Group (TAMG) with 1 month training program Vs. Control Group (CG)	1 month	Test results revealed statistically significant differences between the control and the two training groups in NCSE scores (for TAMG and CG, $F=4.762$ , $p=0.015$ ; for CAMG and CG, $F=5.166$ , $p=0.02$ ). No statistically significant differences between the CAMG and TAMG ( $F=1.496$ , $p=0.256$ ). Comparing the post-training to the follow-up using a pair sample t-test, no statistically significant differences were found in each of the three groups and during the follow-up. Slight improvement in RBMT score for all groups was observed. statistically significant difference between the CAMG and CG ( $F=11.747$ , $p=0.0001$ ) and between the CAMG and CG ( $F=11.849$ , $p=$	“In conclusion, treatment efficacy has been demonstrated when using a combined EL and EE memory rehabilitation model, although there is no significant difference between CAMG and TAMG. This new development may guide improvements in memory rehabilitation in patients with TBI. Future studies should also be carried out to determine its role in Chinese people, especially those with moderate to severe TBI.”	Quasi-experimental design. Baseline differences in time post injury between groups. Data suggest CAMG performed better than CG in the NCSE and RBMT. No difference found between CAMG and TAMG. Data suggest a combination of a computerized approach and errorless learning may be best for memory improvement in TBI patients.

								0.0001) in the total RBMT score, but no statistically significant differences were found between the CAMG and TAMG (F=1.358, p=0.287). Again, no statistically significant differences were found in each of the three groups.		
Ruff 1989 (3.5)	Memory/ Reasoning Tasks	RCT	No COI	46 patients with cerebral contusions or brainstem contusions	Control group mean age: 31.7±9.2 years. Experimental group mean age: 29.9±9.9 years. 27 males, 13 females.	Control group: 4 50-min sessions focused on six areas of activity Vs. Experimental Group: 4 50-min sessions focused on four specific cognitive abilities	None	Comparing pre and posttreatment scores, both groups improved significantly [MANOVA F(1,37)=.07, P>.05 and F(1,37)=0.2, P> .05 respectively] The P plot indicated that P values of >0.065 showed areas where experimental group's performance was superior to that of the control group. Most important treatment effect was to memory skills; little significant difference in attention, spatial integration, and consistency of retrieval.	"(T)reatment in a structured setting would improve subjects' neuro-psychological functioning, and suggests that professional attention, psychosocial group therapy, and both general stimulation activities and cognitive remediation have positive effects on neurocognitive functioning."	Data suggest both groups improved but experimental group gained improvement in memory and error reduction in visual selective attention.

Computer memory retraining has been used to treat TBI patients [704, 776].

## Computer Memory Retraining Group (CMRG)

Recommended.

### Rehabilitation Programs

Computer Memory Retraining Group is recommended for use in the treatment of TBI patients.

*Strength of Evidence – Recommended, Evidence (C)*

*Level of Confidence – Low*

<i>Indications:</i>	Moderate, severe, postop, chronic TBI patients with at least one functional hand to interact with computer demands without evidence of psychiatric disorders, post injury substance abuse, no premorbid neurological disorders, sufficient vision and cognitive function
<i>Frequency/Dose/Duration:</i>	2 hour sessions per day for 20 total hours
<i>Indications for Discontinuation:</i>	When desired improvement has been achieved, clinical plateau or failure to improve
<i>Benefits:</i>	Improved memory functions.
<i>Harms:</i>	Negligible
<i>Rationale:</i>	There is one moderate quality study [812] and one low quality study [813] showing CMRG improves memory retraining. This is a non-invasive, has negligible adverse effects, moderate-high cost and with evidence suggesting efficacy is therefore recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Computer Memory Retraining Group, (CMRG); Traumatic brain, Intracranial, Closed Head, Penetrating head, Craniocerebral, injury, trauma, Concussion; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 4 articles in PubMed, 7 in Scopus, 0 in CINAHL, 0 in Cochrane Library, 4330 in Google Scholar, and 2 from other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 1 from other sources. Of the 3 articles considered for inclusion, 2 randomized trials and 1 systematic studies met the inclusion criteria.

Handheld computers have been used by TBI patients to assist in memory [814].

## Handheld Computers as Memory Aids

### Recommended.

Handheld computers are recommended for use in the treatment of TBI patients.

*Strength of Evidence* – **Moderately Recommended, Evidence (B)**

*Level of Confidence* – Moderate

<i>Indications:</i>	Moderate or Severe TBI patients who had emerged from post-traumatic amnesia, had ongoing memory problems who also had sufficient hand function to use a PDA.
<i>Benefits:</i>	Improve memory and reducing forgetfulness.
<i>Harms:</i>	Negligible.
<i>Frequency/Dose/Duration:</i>	N/A
<i>Rationale:</i>	A high quality trial suggested superior performance on memory goals after use of a handheld computer [814]. Handheld computerized aids are not invasive, have no adverse effects, are high cost, have evidence of efficacy, and thus are recommended for selective treatment of TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: attention test, sustained attention to response task or monotone counting or variables of attention test, traumatic brain injury, intracranial injury, closed head injury penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; sensitivity and specificity, predictive value of tests, gold-standard, accurate, accuracy, precision, precise, test; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed articles in 747 PubMed, 310 in Scopus, 496 in CINAHL, 4 in Cochrane Library, 25800 in Google Scholar, and 8 from other sources. We considered for inclusion 11 from PubMed, 8 from Scopus, 2 from CINAHL, 3 from Cochrane Library, 3 from Google Scholar, and 8 from other sources. Of the 35 articles considered for inclusion, 19 prognostic studies, 1 randomized trial and 5 systematic studies met the inclusion criteria.

### Evidence for the Use of Handheld Computers for Memory

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Lannin (8.0)	Memory Rehabilitation	RCT	This work was supported by a grant from the Royal Rehabilitation Centre Sydney Foundation. No COI.	N = 42 with acquired brain impairments.	33 males, 9 females; Mean age is 33.5 years.	Control Group. Non-electronic memory aids. (N = 21)  vs  Experimental Group. PDA. (N = 21)	1 or 2 years post intervention	From baseline to end of 8 week assessments: Control group had GAS t-score of 41.7 to 49.5. Trial had 41 to 53 (P=.0001).	“Occupational therapy training in the use of a handheld computer improved patients’ daily memory function more than standard rehabilitation.”	No long term follow-up. Data suggest use of handheld computerized equipment for memory aid significantly improved memory goals.

### Evidence for the Use of Computer Memory Retraining Group (CMRG)

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Ruff 1994 (4.0)	CMRG	Randomized cross-over study	Research supported by IBM. No COI.	N=15	Mean Age 26.9 (17-47). No mention of Gender.	Group A received attention training follow by memory training. Vs Group B got the reverse order of treatments stated above.	Baseline and post treatment, 3 measure administered in 7 day intervals pre and post treatment.	Both groups improved. Memory II improved (F(2)=4.52, p=0.021). Response times decreased. Attention levels, Group A performed better in 7 & 2 attention test by 0.10, Group B did not improve. Behavioral rating improved by evaluator and subjectively between groups. No depression between groups in study, and Wechsler Memory Scale test scores improved in both groups.	“The efficacy of the attention training was demonstrated on multiple levels. On the computerized measures, small but consistent gains were evident. The results of the psychometric measures were mixed.”	Small sample. Data suggests computer technology may assist TBI patients regain some attention and memory fun
Tam 2004 (3.5)	CMRG	RCT	No mention sponsorship or COI.	26 persons with brain injury (not including control group of 8 persons)	Mean Age of Self-Pace: 40.5 years. Mean age of Feedback: 33.3 years. Mean age of Personalized: 32.6 years. Mean age of Visual: 39.8 years. Mean age of Control: 45 years. 18	Completed 1 of 4 computer-assisted memory training strategies Self-paced Group (work at own pace in non-threatening environment Vs Feedback Group( immediate feedback in	No mention of follow-up.	Feedback group showed most substantial improvement within analogy memory performance. No statistical significance with memory improvement in all four groups By RBMT testing method for pre- and post-program RBMT scores. Feedback	“This attempt to develop and evaluate different computer applications for memory retraining was made and the effectiveness of applying customized computer technology in memory	Data suggest customized therapeutic computer-assisted memory retraining is key in memory skill retraining outcomes and using computers is an effective method to assist in cognitive rehab.

					<p>males, 14 females.</p> <p>clear, consistent, non-judgmental fashion) Vs Personalized Group (multimedia presentation of actual people, object, and living environment) Vs Visual Presentation Group (attractive, bright, and colorful presentation) Vs Control Group with no specified memory rehab</p>		<p>group showed statistically significant improvement in self-efficacy; self-paced, visual, and personalized groups did not show similar change.</p>	<p>rehabilitation was critically evaluated. Results of the present study showed that the unique customized therapeutic characteristics of computer-assisted memory retraining (e.g. self-paced practice, performance feedback, salient visual presentation and personalized training contents) are positive attributes of memory skill retraining outcomes.”</p>	
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Restorative imagery training has been used to treat TBI patients to facilitate independent functioning [815]. Imagery skills includes TDMI screening test, Temporal congruence stepping test, Walking trajectory test, and Hand mental rotation test [816, 817].

### Restorative Imagery Training

Restorative imagery training is selectively recommended for severe TBI patients.

#### Recommended.

*Strength of Evidence* – **Moderately Recommended, Evidence (B)**

*Level of Confidence* – Moderate

<i>Indications:</i>	Severe, postop, chronic TBI patients with ongoing deficits approximately 8 years post injury with a mean GCS of about 5
<i>Frequency/Dose/Duration:</i>	2 sessions per week 45-60 minutes long using imagery from Story Memory Technique (mSMT) for 5 weeks. [817].
<i>Indications for Discontinuation:</i>	When desired improvement has been achieved, clinical plateau or failure to improve
<i>Benefits:</i>	Improved memory and learning functions in addition to improved motor imagery [816].
<i>Harms:</i>	Negligible
<i>Rationale:</i>	There is one high quality study on Restorative Imagery training for memory improvement that [817] suggests improved memory and learning. There is one moderate quality study [816] showing some benefit in restoration of motor imagery. Restorative Imagery Training is non-invasive, has negligible adverse effects, moderate-high cost and with evidence suggesting efficacy is therefore moderately recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Restorative, imagery, training, traumatic, brain, injury, intracranial, closed, head, penetrating, concussion, craniocerebral, trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 3 articles in PubMed, 5 in Scopus, 1 in CINAHL, 0 in Cochrane Library, 3380 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 3389 articles considered for inclusion, 2 randomized trials and 2 systematic studies met the inclusion criteria.

### Evidence for the Use of Restorative Imagery Training

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Chiaravalloti 2015 (8.0)	Cognitive Rehabilitation	RCT	Sponsored by Department of Education, and endorsement by the Federal Government under the NIDRR Grant H133A070037. No COI.	N=69, Participants with moderate-severe Traumatic Brain Injury (TBI).	Participants ranged from 18 to 59 years old. Treatment Group 37.17 (11.24) and 77% male. Control Group 40.68 (11.28) and 71% male.	Treatment Group (n=35) 10 1-on-1 treatment session twice a week 45-60 mins long. Skill 1 was taught utilizing imagery to facilitate learning through reading and highly visual story from the list of words and then apply their newly acquired imagery skills to visualize. Skills applied mSMT to real-world memory-demanding tasks, utilizing both context and imagery to remember the information that story.  vs  Control Group (n=34) 10 1-on-1 treatment session twice a week 45-60 mins long. Participants received Non-training-oriented tasks consisted of reading the same stories and answering questions about their content.	Long-term follow-up 6 months after treatment completion.	The treatment group showed significant improvement when compared to the placebo group: $F(1, 69) = 4.45, P < .025$ 1-tailed, partial $\eta^2 = 0.064$ medium effect; $CI = -1.71$ to $-0.047$ ; No significant treatment results from CVLT learning slope [ $F(1, 69) = 0.686, NS, \eta^2 = 0.011$ small effect; $CI = -0.154$ to $0.373$ ]. 49% of participants in the treatment group showed an improvement compared to 18% of the control group: $\chi^2[170] = 7.42, P = .006$ , Cohen's $w = 0.33$ , medium effect. No significant difference for RBMT in everyday memory from treatment group vs control group: $\chi^2(2) = 7.36, P = .025$ , Cohen's $w = 0.43$ .	"Based on widely accepted classification systems for treatment study design, 67-69 the present results provide class I evidence supporting the efficacy of the mSMT to improve learning and memory in TBI patients with impaired learning. Thus, this study extends the evidence for efficacy of the treatment protocol to a sample of people with TBI. Future research should examine the optimal methodology for increasing the maintenance of the treatment effect over time and development of new treatment protocols that can be similarly successful in TBI patients."	Baseline comparability differences with respect to months since injury (Treatment group 119.97 (128.91) and Control group 101.97 (70.78) Data suggest mSMT improves memory and learning in TBI patients.

Oostra 2012 (4.0)	Cognitive Rehabilitation	RCT	No mention of sponsorship or COI.	N=37, Patients with moderate- severe Traumatic Brain Injury (TBI).	TBI Group 31.2_12.3 and 16:4 male: female. Control Group 32.1_14.2 and 13:4 male: female.	Rehabilitation TBI Group (n=20) targeted 4 cognitive domains: attention, memory, executive functions, and pragmatic communication; one on one sessions  vs  Healthy Control Group (n=17) with real-life performance situations and common tasks to compensate for functional deficits after brain injury; group	Follow- up time frame not mention ed	Sub-scores for MIQ- RS for kinesthetic and visual were more significant at $P<.05$ in the control group than the TBI group, with a mean total score SD of $82\pm10$ and $72\pm13$ , respectively. MIQ-RS visual ( $t_{18} = -2.92$ ; $P<.01$ ) and MIQ-RS total ( $t_{18} = -2.48$ ; $P=.024$ ) in patients with frontal brain damage [11385]. Statistically significant correlation between the number of imagined stepping movements and the duration of time periods in both groups ( $F_{1,35_153}$ , $P_{.001}$ ) by the TDMI test. TBI group showed significantly less imagined stepping movements than the control group ( $F_{1,35_15.5}$ , $P_{.001}$ ). Imagery stepping time and actual stepping time in both groups (TBI group, $r=0.82$ , $P<.001$ and control group, $R=0.80$ , $P<.001$ ).	“The present findings indicate that while TBI patients may still perform motor imagery, our cohort showed a decrease in the 3 motor imagery modalities, with a decrease of motor imagery vividness, temporal congruence, and accuracy. Our results, however, suggest that patients with TBI retain ability for motor imagery and hence may benefit from motor imagery training to improve their motor preparation and execution of movement and thus their functional ability.”	Data suggest that the TBI group exhibited decreased motor imagery modes, specifically in vividness, temporal congruence and accuracy. TBI patients retain the ability for motor imagery and may benefit from motor imagery training.
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Cognitive rehabilitation uses therapeutic activities such as restorative functional skills and memory training purportedly helps patients recover from traumatic brain injuries [818, 819].

### **Restorative Functional Skills Training**

There is no recommendation for the use of restorative functional skills training in the treatment of TBI patients.

#### **No Recommendation.**

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:* There are no quality studies on Restorative functional Skills Training. Restorative Functional Skills Training is non-invasive, has negligible adverse effects, moderate-high cost, but in the absence of evidence of efficacy there is no recommendation.

*Evidence:* A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Restorative, functional, skills, training, traumatic, brain, injury, intracranial, closed, head, penetrating, concussion, craniocerebral, trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 9 articles in PubMed, 0 in Scopus, 1 in CINAHL, 0 in Cochrane Library, 767 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 777 articles considered for inclusion, 0 randomized trials and 2 systematic studies met the inclusion criteria.

Repetition of a certain activity is used to improve recovery in patients after brain injury [820]. However repetitive training is a time consuming process and patients often report boredom [820]. Play-based interventions to stimulate enjoyment is one approach being used to overcome such difficulties [820].

### **Games, Art, and Self-Expression**

Games, art and self-expression are recommended for use in the treatment of TBI patients.

#### **Recommended.**

*Strength of Evidence – Recommended, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Indications:* TBI patients between 1 and 7 years post injury. Evidence best for mild TBI patients [821] but more severe TBI patient are thought to potentially benefit

<i>Frequency/Dose/Duration:</i>	Six weeks of 4 days per week of 5.5 hours of training (psychological and neuropsychological) for a total of 6 weeks [821].
<i>Indications for Discontinuation:</i>	When desired improvement has been achieved, clinical plateau or failure to improve
<i>Benefits:</i>	Improved memory function
<i>Harms:</i>	Negligible
<i>Rationale:</i>	There is one moderate quality study involving the use of Games, Art and Self Expression techniques which suggested modest efficacy [821]. These are non-invasive, have negligible adverse effects, low cost when self-administered, and are recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Game, puzzle, toy, art, self-expression, play, Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 937 articles in PubMed, 51 in Scopus, 61 in CINAHL, 3 in Cochrane Library, 3,240 in Google Scholar, and zero from other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 1 from other sources. Of the 2 articles considered for inclusion, 1 randomized trial and 1 systematic study met the inclusion criteria.

### Evidence for the Use of Games, Art and Self-Expression

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Ryan 1988 (4.0)	Self Expression	RCT	No mention of COI.	20 patients with head injuries with mild to moderate neuropsychological impairment	Control group mean age: 31.4 years. Experimental group mean age: 34.3 years. 14 males, 6 females.	Control Group (games, art, group discussions, relaxation exercises, self-expression) Vs. Experimental Group (retraining memory, attention and spatial integration exercises)	Immediately following the 6 week treatment.	No significant differences were observed in the T-tests, RLSE, DRS, or GOAT tests. MANOVA results revealed a significant overall effect (T (2, 36) =7.13, p<.05 indicating both groups improved over time. Experimental group did not demonstrate significant improvement over the control group. All ANOVA examinations did not reveal significant differences for either group. Results from the 2 groups x 2 severity ratings x 3 assessments MANOVA showed highly significant interaction between treatment and level of severity over the three testing conditions. (T-(2, 32) =20.13, p<.001. Subjects with mild neuropsychological impairments benefited more from memory remediation compared to more severely impaired patients.	“(t)he present data demonstrates that remediation techniques in the area of memory do not necessarily enhance memory independent of severity and that a further neurobehavioral rating of severity is required.”	Data suggest the mild TBI group received benefit from the experimental intervention but not those with moderate to severe impairments.

Cognitive rehabilitation is a type of therapy that is used to attempt to improve function within the brain after central nervous system accidents [702]. It uses multimedia to focus on similar neuropsychological processes and train the brain to do particular functions [702].

### Computer-Assisted Cognitive Rehabilitation

Computer-assisted cognitive rehabilitation is selectively recommended for the treatment of TBI patients.

#### Recommended.

*Strength of Evidence – Recommended, Evidence (C)*

*Level of Confidence – Moderate*

<i>Indications:</i>	TBI patients 3-6 months post injury with moderate cognitive dysfunction (more marked in language production, visual attention, memory span and other memory abilities such as immediate recall). Most patients showed unilateral hemispheric lesions via MRI [702].
<i>Frequency/Dose/Duration:</i>	24 sessions of pre-cognitive training 3 times per week times 8 weeks.
<i>Indications for Discontinuation:</i>	When desired improvement has been achieved, clinical plateau or failure to improve
<i>Benefits:</i>	Improved memory span and other memory functions
<i>Harms:</i>	Negligible
<i>Rationale:</i>	There are 3 moderate quality studies [166, 702, 822], all suggesting efficacy although one [166] found short term and not long term improvement in global outcomes at one year. This technique is non-invasive, has negligible adverse events and is low to moderate cost depending on self-administration and is therefore recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Computer-Assisted Cognitive Rehabilitation, Traumatic brain injury, Intracranial injury, Closed head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, Cognitive, Computer assisted; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 22 articles in PubMed, 144 in Scopus, 43 in CINAHL, 3 in Cochrane Library, 8050 in Google Scholar, and 2 from other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 2 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 3 from other sources. Of the 8 articles considered for inclusion, 8 randomized trials and 0 systematic studies met the inclusion criteria.

### Evidence for the Use of Computer Assisted Cognitive Rehabilitation

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Vanderploeg 2008 (4.5)	Computer Assisted Cognitive Therapy	RCT	No mention of sponsorship or COI	366, 18+yo with mod- severe nonpenetrating TBI <6mo ago with GCS score ≤12, in coma for 12+ hrs, PTA for 24+ hrs, RLAS cognitive level 5-7, active duty military member or veteran, and needing 30+ of acute interdisciplinary TBI rehabilitation.	Mean age cognitive 33.2±13.5 years, functional 31.7±12.9 years. 335 males, 25 females.	Cognitive rehab (n=184) targeted 4 cognitive domains: attention, memory, executive functions, and pragmatic communication; one on one sessions vs Functional-experiential rehab (n=182) with real-life performance situations and common tasks to compensate for functional deficits after brain injury; group sessions. All received 1.5-2.5hr/d TBI protocol-specific therapy, 2-2.5hr/d OT, PT, ST. Care continued until ready to discharge home or to community transitional rehabilitation program or completed 60 days specific protocol treatment.	1 year	NS between groups at 1 year for: %RTW or school (38.9 vs. 35.4%, p=0.50), and % living independently (56.3 v 61.6% (p=0.27)). Cognitive FIM post treatment: cognitive (27.3±6.2) v. functional group (25.6±6.0) (p=0.01). NS between groups for motor FIM and DRS. No memory problems: cognitive 22.2% v. functional 27.6% (p=0.05). Those with more education more often lived independently at 1 year in functional (69.1%) vs. cognitive group (47.4%) (p<0.02). Younger more often working at 1 year in cognitive (53.3%) vs. functional group (37.8% (p<0.03)).	"[N]o difference between cognitive-didactic and functional-experiential approaches to brain injury rehabilitation on the primary 1-year global outcome measures of the study. However, patients in the cognitive treatment arm had better posttreatment cognitive performance than patients in the functional treatment arm."	Data suggest both groups improved with similar long term global functional outcomes. Data suggest more improvement in short term functional cognitive outcomes for the cognitive treatment arm.

De Luca 2014 (4.0)	Com puter Assis ted  Cogni tive reha b	RCT	No mention of sponsors hip or COI	35 subjects affected by traumatic or vascular brain injury (MMSE score from 10-26 absence of severe spasticity with Ashworth Scale ≤3).	Mean age 35.97±14. 26 years. 19 males, 16 females.	Experimental treatment with 24 sessions of pc- cognitive training 3 times a week for 8 weeks including conventional rehab.  Vs.  Standard Treatment performing only conventional rehabilitation.	2 months after rehabilit ation treatme nt.	Tests at baseline in whole sample showed moderate cognitive dysfunction (MMSE 22.21± 4.79) with more impairment in language production, visual attention, memory span, and memory abilities. Functional status of entire sample was severely impair: ADL 2.88±1.97. IADL 1.97±1.45. BI 35.26±30.08. MRI showed mostly unilateral hemispheric lesions in all patients. Observed overall improvement in cognitive and functional status in both groups, with significant differences. Experimental group presented highly significant improvement in all test. Control group had significant recovery only for LCF, AC, ADL, IADL, and BI tests. At T0, no significant differences between groups. At T1, LCF score was only significant difference (p=0.009). Greater cognitive improvement for experimental than control group.	“Our data suggest that cognitive pc- training may be a promising methodology to optimize the rehabilitation outcomes following brain injury.”	Data suggest cognitive PC training may improve outcomes following brain injury. Both groups showed improvement but greater memory span was seen in experimental group.
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Lundqvist 2010 (4.0)	Cognitive Rehabilitation	RCT	No mention of sponsors hip or COI	21 individuals suffering from acquired brain injury	Mean age: 43.2 years. 10 males, 11 females.	Group I (systematic WM training for 5 wks) Vs Group II (control group-no training)	5 months	Significant difference was observed in non-trained WM tests, PASAT, Listening Span, Block Span, and CWIT. Picture Span observed significant difference after 4 wks training, but not at follow up (p=0.012). A t-test paired samples showed that the relative long-term WM training effect was significantly higher for PASAT compared to Digit Span, $t(19)=1.87$ $p<0.05$ , and for Listening Span compared to Digit span $t(19)=1.88$ , $p<0.05$ . At baseline, performance level of Digit Span was $M=8.3$ ( $SD=1.4$ )( $n=21$ ) and after 20 wks training level was $M=8.9$ ( $SD=0.89$ ) ( $n=20$ ). All 21 individuals increased their WM index when comparing the Start index (baseline) and the Max index. The Start index was $M \pm 73.7$ ( $SD \pm 9.7$ ) and the Max index was $M \pm 93.4$ ( $SD \pm 13.7$ ). The difference varied between 9.0–35.0. Best results obtained during 2 <sup>nd</sup> part of training; 74% of subjects' peak index was obtained during last 30% of training. Nine percent of subjects reached peak index already during first 50% of training. Results from the COPM interviews show a difference in estimated performance of prioritized occupations,	"Structured and intense computerized working memory training with QM improves subjects' cognitive functioning as measured by neuropsychological WM-demanding tests, WM-related activities (occupational performance, satisfaction with performance) and overall health. The training probably has an impact on the rehabilitation outcome, returning to work, as well as on daily activities for individuals with verified WM impairments."	Small sample. Data suggest that structural and intense WM training showed significant improvements in neuropsychological WM-test results at both 4 and 20 weeks post training, However, quality of life did not change but overall health quality as was rated by patients.
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								before training vs 20 weeks after training, $p < 0.05$ . An even bigger difference was found in estimated satisfaction with performance before vs 20 weeks after training, $p < 0.001$ . There was no difference ( $p > 0.05$ ) in health-related quality-of-life, as measured by the EQ-5D questionnaire, while there was a significant difference in the health self-rating VAS ( $p < 0.05$ ).		
Tam 2004 (3.5)	Cognitive Rehabilitation	RCT	No mention of sponsorship or COI	26 persons with brain injury (not including control group of 8 persons)	Mean Age of Self-Pace: 40.5 years. Mean age of Feedback: 33.3 years. Mean age of Personalized: 32.6 years. Mean age of Visual: 39.8 years. Mean age of	Completed 1 of 4 computer-assisted memory training strategies Self-paced Group (work at own pace in non-threatening environment) Vs Feedback Group (immediate feedback in clear, consistent, non-judgmental fashion) Vs Personalized Group (multimedia presentation of actual people, object, and living environment) Vs Visual Presentation Group (attractive, bright, and colorful presentation)	No mention of follow-up.	Feedback group showed most substantial improvement within analogy memory performance. No statistical significance with memory improvement in all four groups By RBMT testing method for pre- and post-program RBMT scores. Feedback group showed statistically significant improvement in self-efficacy; self-paced, visual, and personalized groups did not show similar change.	Small sample. "This attempt to develop and evaluate different computer applications for memory retraining was made and the effectiveness of applying customized computer technology in memory rehabilitation was critically evaluated. Results of the present study showed that the unique customized	Data suggest customized therapeutic computer-assisted memory retraining is key in memory skill retraining outcomes and using computers is an effective method to assist in cognitive rehab.

					Control: 45 years. 18 males, 14 females.	Vs Control Group with no specified memory rehab			therapeutic characteristics of computer-assisted memory retraining (e.g. self-paced practice, performance feedback, salient visual presentation and personalized training contents) are positive attributes of memory skill retraining outcomes.”	
Ruff 1989 (3.5)	Cogni tive Reha bilita tion	RCT	No mention of sponsors hip or COI	46 patients with cerebral contusions or brainstem contusions	Control group mean age: 31.7±9.2 years. Experime ntal group mean age: 29.9±9.9 years. 27 males, 13 females.	Control group: 4 50-min sessions focused on six areas of activity Vs. Experimental Group: 4 50-min sessions focused on four specific cognitive abilities	None	Comparing pre and posttreatment scores, both groups improved significantly [MANOVA F(1,37)=.07, P>.05 and F(1,37)=0.2, P> .05 respectively] The P plot indicated that P values of >0.065 showed areas where experimental group’s performance was superior to that of the control group. Most important treatment effect was to memory skills; little significant difference in attention, spatial integration, and consistency of retrieval.	“(T)reatment in a structured setting would improve subjects’ neuro- psychological functioning, and suggests that professional attention, psychosocial group therapy, and both general stimulation activities and cognitive remediation have positive effects on neurocognitive functioning.”	Data suggest both groups improved but experimental group gained improvement in memory and error reduction in visual selective attention.

Batchelor 1988 (3.5)	Cognitive Rehabilitation	Quasi-RCT	No mention of sponsorship or COI	34 patients with severe to extremely severe closed-head injuries	Experimental group mean age: 22.6±6.9 years. Control group mean age: 26.2±11.0 years. 27 males, 7 females.	Experimental group (computer assisted cognitive treatment) Vs Control group (non-computer cognitive treatment)	3 days after completion of treatment.	A significant difference was revealed between the number of years of education of the two groups ( $t(32) = 2.25, P < .05$ ) with the difference favoring the control subjects. Significant improvement in the level of performance of experimental and control subjects at time of posttreatment assessment compared with pretreatment assessment. Pre and posttreatment scores of the experimental and control subjects were compared using an analysis of covariance. No significant differences emerged between adjusted posttest scores between groups.	“(S)tudy failed to support hypothesis that computer-assisted cognitive therapy is any more effective in remediating disorders of memory, attention, information processing, and higher cognitive functioning in severely head-injured patients than are non-computerized techniques.”	Data suggest computer-assisted techniques no more effective than noncomputerized techniques in cognitive rehab of severely closed head injured patients.
Dou 2006 (3.0)	Cognitive Rehabilitation	Quasi-experimental design	No mention of sponsorship or COI	37 patients with TBI	Mean age: 38.067±12.32 years. 27 males, 10 females.	Computer-Assisted Memory Training Group (CAMG) with 1 month training program Vs Therapist-administered Memory Training Group (TAMG) with 1 month training program Vs. Control Group (CG)	1 month	Test results revealed statistically significant differences between the control and the two training groups in NCSE scores (for TAMG and CG, $F = 4.762, p = 0.015$ ; for CAMG and CG, $F = 5.166, p = 0.02$ ). No statistically significant differences between the CAMG and TAMG ( $F = 1.496, p = 0.256$ ). Comparing the post-training to the follow-up using a pair sample t-test, no statistically significant differences were found in each of the three groups and during the	“In conclusion, treatment efficacy has been demonstrated when using a combined EL and EE memory rehabilitation model, although there is no significant difference between CAMG and TAMG. This new development may guide improvements in memory	Quasi-experimental design. Baseline differences in time post injury between groups. Data suggest CAMG performed better than CG in the NCSE and RBMT. No difference found between CAMG and TAMG. Data suggest a combination of a computerized approach and errorless learning may be best for memory improvement in TBI patients.

							<p>follow-up. Slight improvement in RBMT score for all groups was observed. statistically significant difference between the CAMG and CG (F=11.747, p=0.0001) and between the CAMG and CG (F=11.849, p=0.0001) in the total RBMT score, but no statistically significant differences were found between the CAMG and TAMG (F=1.358, p=0.287). Again, no statistically significant differences were found in each of the three groups.</p>	<p>rehabilitation in patients with TBI. Future studies should also be carried out to determine its role in Chinese people, especially those with moderateto-severe TBI.”</p>	
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### Evidence for the Use of Psychosocial Functioning

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Powell J 2001 (7.5)	Psychosocial Functioning	RCT	No mention of COI. The research assessor was funded by a grant from the Medical Research Council, and the treatment programme was funded by the Department of Health.	N= 110 Patients who sustained severe TBI between 3 months and 20 years previously, and had no other neurological conditions.	Mean age: 34.5; (Males 71, Females 23)	Outreach group (N=54) vs. Information group (N=56) (No other description of study design and comparison groups)	Follow up for an average of 24.8 months	The outreach participants were significantly more likely to show gains on the BI (Barthel index) and the BICRO-39 (brain injury community rehabilitation outcome-39) total score and self-organization and psychological wellbeing subscales. There were likewise strong trends ( $p < 0.10$ ) for BICRO personal care and mobility, and on the FIM+FAM for personal care and cognitive functions. Differential improvements were not seen for indices of socializing, productive employment, anxiety, or depression. Median changes on individual subscales were small, reflecting the diversity of the clinical population; however, 40% of outreach but only 20% of information participants made a clinically significant improvement of 2+ points on at least one BICRO-39 scale. Time since injury was unrelated to the magnitude of gains.	This is the first RCT of multidisciplinary community rehabilitation after severe TBI, and suggests that even years after injury it can yield benefits which outlive the active treatment period.	Data suggest implementation of multidisciplinary community based outreach rehab treatment post severe TBI benefit the patient after the active treatment period. Time since injury occurrence not correlated to amount of gains.

## Problem Solving

### Group Sessions for Problem Solving, Discussion of Social Isolations and Frustrations

Recommended.

Group sessions for problem solving, discussion of social isolation and frustrations are selectively recommended for treatment of TBI patients.

*Strength of Evidence – Recommended, Evidence (C)*

*Level of Confidence – Low*

<i>Indications:</i>	TBI patients at least one year post TBI injury with documented impairments in social/vocational functions, but with cognitive functional abilities that include: taking organized notes, giving and receiving feedback, relating to others with adequate social skills, and sustaining attention for an hour long session [823].
<i>Frequency/Dose/Duration:</i>	Weekly for 12 weeks [824] to 24 weeks [823].
<i>Indications for Discontinuation:</i>	When desired improvement has been achieved, clinical plateau or failure to improve.
<i>Benefits:</i>	Improved communication, coping skills and problem solving.
<i>Harms:</i>	Negligible
<i>Rationale:</i>	There are 2 moderate quality studies involving group sessions for chronic TBI patients in comparison with either no or conventional treatment [824] and [823]. Both studies showed TBI patients improved at 6 months and one year. Group therapy is non-invasive, has negligible adverse effects and is moderate to high cost depending on duration and is thus recommended for patients with cognitive deficits.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google scholar without date limits using the following terms: group, psychotherapy, session, sessions, therapy, social support, supportive therapy; traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 5,012 articles in PubMed, 3,083 in Scopus, 458 in CINAHL, 1,453 in Cochrane Library, 8,210 in Google Scholar, and 4 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 6 from other sources. Of the 7 articles considered for inclusion, 4 randomized trials and 2 systematic studies met the inclusion criteria.

## Evidence for the Use of Group Sessions

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Dahlberg 2007 (5.5)	Group sessions for problem solving, discussion of social isolations and frustrations	RCT	Sponsored by the National Institute on Disability and Rehabilitation Research. COI.	N = 52 patients with TBI at least 1 year post-injury who had social communication deficits and received rehabilitation treatment.	Mean age group sessions 42.43, control 39.91. 44 males, 8 females.	Weekly group sessions for 12 weeks (each 1.5 hours) focused on improving communication skills (n = 26) Vs. Control group receiving no treatment (n = 26)	3, 6, and 9 months	Analysis of treatment effects via independent t tests showed significant differences between two groups in 7 out of 10 of The Profile of Functional Impairment in Communication (p values ranging from .001 - .024). There was also a statistical difference between two groups for the Social Communication Skills Questionnaire-Adapted measurement (p = .005).	"TBI subjects who received social communication skills training had improved communication skills that were maintained on follow-up. Overall life satisfaction for participants was improved."	Data suggest significant improvement in treatment group for communication skills and overall life satisfaction.
Rath 2003 (5.5)	Group sessions for problem solving, discussion of social isolations and frustrations	RCT	Funded by grant from the National Institute of Child Health and Human Development. No COI.	N = 60 outpatients with TBI who were at least 1 year post-injury and also considered higher-level (more cognitively demanding).	Mean age of entire sample 43.6. 23 males, 37 females.	Innovative Group Treatment focused on "emotional self-regulation" and "clear thinking", (N = 32) Vs Conventional Group Treatment (N = 28)	24 weeks and 6 months	The innovative group had higher self-esteem (p < .05) where the self-esteem for the conventional group was not significant at the same level (p < .08). The innovative group also showed higher problem-solving self-appraisal measures (p = .005).	"Our findings suggest that our treatment is a promising method for improving problem solving, one that may have practical applications for improving the function of people with TBI."	Data suggest treatment group (innovative group) improved problem solving compared to conventional group.

Anson 2006 (3.5)	Group sessions for problem solving, discussion of social isolations and frustrations	Non randomized	No mention of sponsorship or COI.	N = 31 participants with TBI who received outpatient therapy	Mean age of Group A 38.9, Group B 37.8. 26 males, 5 females.	Group A, receiving 10 90 minute Coping Skills Group sessions twice a week for 5 weeks, baseline phase being 5 weeks (n = 15) Vs. Group B, receiving same Coping Skills Group sessions for 5 weeks, baseline phase being 10 weeks (n=16) Vs. Control, on a waiting list	5, 10 weeks	Several ANOVA analyses were performed. Post-hoc analysis, utilizing the Bonferroni adjustment, showed a significant difference within coping skills between pre- and post-treatment ( $p < 0.05$ ). Skills did not remain stable due to a significant decrease from post-treatment to follow-up ( $p < 0.05$ ).	"The results suggest that it may be possible to modify coping strategy use following brain injury, through CBT."	Small sample. Data suggest no appreciable improvement in anxiety, depression, self esteem or psychological function but coping strategy and ability to understand emotions improved.
Ruff 1989 (3.5)	Group Sessions for Problem Solving	RCT	No COI	46 patients with cerebral contusions or brainstem contusions	Control group mean age: $31.7 \pm 9.2$ years. Experimental group mean age: $29.9 \pm 9.9$ years. 27 males, 13 females.	Control group: 4 50-min sessions focused on six areas of activity Vs. Experimental Group: 4 50-min sessions focused on four specific cognitive abilities	None	Comparing pre and posttreatment scores, both groups improved significantly [MANOVA $F(1,37)=.07$ , $P>.05$ and $F(1,37)=0.2$ , $P>.05$ respectively] The P plot indicated that P values of $>0.065$ showed areas where experimental group's performance was superior to that of the control group. Most important treatment effect was to memory skills; little significant difference in attention, spatial integration, and consistency of retrieval.	"(T)reatment in a structured setting would improve subjects' neuro-psychological functioning, and suggests that professional attention, psychosocial group therapy, and both general stimulation activities and cognitive remediation have positive effects on neurocognitive functioning."	Data suggest both groups improved but experimental group gained improvement in memory and error reduction in visual selective attention.

Compensatory (or adaptive) approaches have been used for the rehabilitation of cognitive deficits to improve memory performance [825-827].

### Compensatory Skills Training

Compensatory skills training is recommended for treatment of TBI patients.

#### Recommended.

##### *Strength of Evidence – Recommended, Insufficient Evidence (I)*

##### *Level of Confidence – Low*

<i>Indications:</i>	Moderate-severe TBI patients that includes difficult problem solving and executive dysfunction
<i>Frequency/Dose/Duration:</i>	STEP program is 9 hours per week for 12 weeks
<i>Indications for Discontinuation:</i>	When desired improvement has been achieved, clinical plateau or failure to improve.
<i>Benefits:</i>	Improved problem solving, executive function, anxiety, self concept and interpersonal communication.
<i>Harms:</i>	Negligible
<i>Rationale:</i>	There is one moderate study involving compensatory skills training [828] suggesting STEP is efficacious in self reported TBI problem solving and executive function. The other 2 low quality studies both have small samples. One study shows comparable efficacy between both groups [829] and the other study [830] reported improved anxiety, self concept, interpersonal and communication skills compared to control group. This type of intervention is non-invasive, low-moderate cost depending upon therapist time and number of sessions and has negligible adverse effects and is recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: compensatory skills training, traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 4 articles in PubMed, 19 in Scopus, 5 in CINAHL, 1 in Cochrane Library, 10,200 in Google Scholar, and 5 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 1 from CINAHL, 1 from Cochrane Library, 0 from Google Scholar, and 5 from other sources. Of the 7 articles considered for inclusion, 3 randomized trials and 4 systematic studies met the inclusion criteria.

### Evidence for the Use of Compensatory Skills Training

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Cantor 2014 (5.5)	Compensatory Skills Training	RCT	Sponsored by the Centers for Disease Control and Prevention. No COI.	N = 98 with TBI and executive dysfunction.	Mean age 45.3 ± 14.0, 37 male and 61 female.	Immediate start or IS, Short-Term Executive Plus (STEP) cognitive rehabilitation program; including problem solving, emotional regulation, individual sessions of attention and compensatory strategies training (N = 49) vs Waitlist or WL program (N = 49).	12 weeks	Intent-to-treat indicated significant treatment effect for the composite executive function measure, (p = 0.008). Secondary analysis indicated significant treatment effects for executive function scale, (p = 0.049), and the problem solving strategies, (p = 0.016).	“The STEP program is efficacious in improving self-reported post-TBI executive function and problem solving.”	Data suggest STEP efficacious in improving self reported post TBI problem solving and executive function.
Bergquist 2009 (3.5)	Compensatory Skills Training	RCT Crossover	Sponsored by a TBI Model System grant from the National Institute for Disability and Rehabilitation Research (NIDRR). No COI.	N = 14 with medically documented traumatic brain injury over an 18-month period.	Average age 48 years, 7 male and 7 female.	Baseline: Neurobehavioural Functioning Inventory (NFI), Community Integration Questionnaire (CIQ) and Compensation Techniques Questionnaire (CTQ), Followed with	Unclear	There was no significant differences in changes in functioning on any of these measures in the Calendar Condition vs the Diary Condition, (p > 0.05). Significant improvements in functioning in calendar use, (p = 0.02) and using a cue card for compensation techniques (p = 0.01) at	“These results suggest that the Internet may be an effective delivering mechanism for compensatory cognitive rehabilitation, particularly among individuals who are already utilizing some basic	Small sample Data suggest comparable efficacy.

						Intervention that included; internet-based intervention: Active condition (calendar) or control (diary) group for a total of 30 sessions of one intervention type using instant messaging with a therapist over the internet, plus 30 sessions of the alternative intervention type.		the baseline vs final assessment periods.	compensatory strategies.”	
Helffenstein 1982 (2.5)	Compensatory Skills Training	RCT	No mention of sponsorship or COI.	N = 16 with nonprogressive brain injury.	Age range from 17-35, 13 male and 3 female.	Experimental group received 20 one-hour session of Interpersonal Process Recall or IPR (N = 8) vs Control group received 20 one-hour session of 'nontherapeutic' attention (N = 8).	1 month	Experimental group demonstrated significantly greater change in a) reduction of trait anxiety, b) increase in overall self-concept, c) increase in self-concept related to 'social self, d) increase in self-concept related to 'normal' self, improvement in interpersonal and communication skills.	“[T]wenty hours of IPR treatment did facilitate growth and improvement of interpersonal and communication skills beyond that which would have been expected had there been no formal intervention.”	Small sample. Data suggest IPR group demonstrated improved anxiety, self concept, interpersonal and communication skills compared to control group.

Remediation or restorative interventions aim to improve the specific underlying cognitive deficit through cognitive exercises such as drills, worksheets, or computer-based programs [831]. CACR uses a computer platform to administer cognitive exercises that target cognitive processes such as visual perception, visual attention, working memory, and remembering written directions and visual patterns [832-834].

## **Restorative and Compensatory Computer Assisted Cognitive Remediation (CACR) and External Aids**

There is no recommendation regarding restorative and compensatory computer assisted cognitive remediation and external aids for TBI patients.

### **No Recommendation.**

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

There are no quality studies. Restorative and Compensatory CACR is not invasive, has negligible adverse effects and is low to moderate cost, and in the absence of quality evidence, there is no recommendation for or against its use.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: restorative compensatory computer assisted cognitive remediation or (CACR), traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 19 articles in PubMed, 51 in Scopus, 8 in CINAHL, 0 in Cochrane Library, 54 in Google Scholar, and 2 from other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 1 from other sources. Of the 4 articles considered for inclusion, 0 randomized trials and 4 systematic studies met the inclusion criteria.

## **Visual Training**

There is a high incidence (greater than 50%) of visual and visual-cognitive disorders in neurologically impaired patients (traumatic brain injury, cerebral vascular accidents, multiple sclerosis etc.) [488]. Visual difficulties after traumatic brain injury (TBI) are common and often difficult to recognize. Oculomotor dysfunctions are also among the most common vision problems in individuals with acquired brain injury (ABI). Visual training has been used for treatment of neurological deficits, however the randomized studies of size are mostly of stroke patients [489, 490]. One study evaluated improvements in visual search among hemianopic patients [489], while the other compared explorative saccade and flicker training in hemianopic patients [490-494].

Visual training has been used for treatment of neurological deficits; however, the randomized studies are almost solely of stroke patients [489, 490]. One study evaluated improvements in visual search among hemianopic patients [489], while the other compared explorative saccade and flicker training in hemianopic patients [490].

## **Vision Training** **Recommended.**

Vision training is recommended for use in the treatment of TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – Low

<i>Indications:</i>	Moderate and severe TBI with any of: accommodation, blurred vision, ocular motility abnormalities, difficulty with gaze, tracking difficulties, diplopia, disequilibrium in visually stimulating environments, impaired visual memory, light sensitivity, visual-spatial processing and problems with visual field integrity.
<i>Benefits:</i>	Ability to improve visual symptoms
<i>Harms:</i>	Negligible.
<i>Frequency/Dose/Duration:</i>	Dependent on severity of symptoms, and progress.
<i>Indications for Discontinuation:</i>	Resolution of visual problems from TBI.
<i>Rationale:</i>	There are no quality studies assessing Vision Training in TBI patients. There are multiple low quality studies, including studies suggesting efficacy. Vision Training is not invasive, has no adverse effects, is moderate cost, and is recommended for patients with visual impairments related to TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: visual training, oculomotor training; traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 164 articles in PubMed, 15 in Scopus, 12 in CINAHL, 281 in Cochrane Library, 63,600 in Google Scholar, and 3 from other sources. We considered for inclusion 3 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 3 from other sources. Of the 6 articles considered for inclusion, 6 randomized trials and 0 systematic studies met the inclusion criteria.

## Evidence for Vision Training

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Keller 2010 (3.5)	TBI	RCT	No mention of sponsorship or COI.	N = 20 with visual field deficits.	Mean 59, Range 16 – 85, 8 females 12 Males	Audiovisual Stimulation Training, 20 training sessions (30 minutes) over 3 weeks (N = 10) vs Visual only stimulation training using the same apparatus, 20 training sessions (30 minutes) over 3 weeks (N = 10).	Assessed before and after 3 week training	Audiovisual stimulation training had statistically significantly better outcomes for visual exploration (85.3% v 64.1%, p = 0.001), reading time (75 seconds v 178 seconds, p = 0.003), search time per object (2.9 seconds v 4.9 seconds, p = 0.009), and activities of daily living total score (1.5 v 5.0 p = 0.036) outcomes as well as differences in number and amplitude of saccades from electro-oculography evaluations	“Audiovisual exploration training in patients with visual field defects resulting from occipital lobe lesions after recent stroke improves performance in a variety of activities of everyday life”	All stroke patients. Data suggest multimodal audiovisual training appears more effective for recovery of function compared to visual training alone.
Roth 2009 (3.5)	TBI	RCT	No COI. Study was funded by Adolf Messer foundation.	N = 30 with postchiasmatic lesions	Mean 60, range 34-76, 11 females, 19 males	Explorative saccade training, 2 sessions of 30 minutes per day, 5 days a week (N = 15) vs Flicker-stimulation training, 2 sessions of 30 minutes per day, 5 days a week (N = 15).	Assessed before, immediately after initial training and after 6 week training	No significant differences between two primary treatments for any outcomes at the 6-week follow-up. Significant differences were seen between blind and seeing side assessments.	“[I]n patients with hemianopic orientation disorder, compensatory EST selectively improves exploration behavior on the blind side in everyday tasks.”	Mixed population that is mostly stroke. Data suggest compensatory EST improves daily life activity performance.

Thiagarajan 2013 (3.0)	Visual Training	Experimental	No COI. Sponsored by the U.S. Army, Department of Defense, College of Optometrists in Vision Development, and SUNY College of Optometry Graduate Program.	N = 12 with documented mTBI, injury onset of greater than 1 year	Mean age: 29; 4 males and 8 females.	6 weeks of oculomotor training, 2 60 minute sessions per week (N = 12) vs 6 weeks of placebo treatment (N = 12). Each participant underwent both treatment with a 1 week washout period between.	Follow-up at 1 week post-intervention for each treatment	Mean of laboratory-based objective measure of symmetric vergence (baseline vs. after OMT): Peak velocity – Convergence (C) 13.0±1.9, 18.0±0.9 (p=0.01) / Divergence (D) 11.6±1.1, 13.5±0.8 (p<0.01), Time Constant – C 399±68, 228±14 (p=0.01), D 378±35, 312.22 (p<0.01), Steady-state Variability – C 0.90±0.07, 0.75±0.04 (p=0.04), D 0.81±0.05, 0.78±0.02 (p=0.54), Response Amplitude C 3.93±0.07, 3.96±0.08 (p=0.43), D 3.93±0.06, 3.93±0.08, (p=1.00)	“The significant improvement in most aspects of vergence eye movements following OMT demonstrates considerable residual brain plasticity via oculomotor learning.”	Small sample crossover study. Sparse method, significant dropouts and compliance to protocol issues.
Thiagarajan 2014 (2.5)	Visual Training	Experimental	No COI. Sponsored by the US Army, DOD.	N = 12 with documented mTBI, injury onset of greater than 1 year	Mean age: 29; 4 males and 8 females.	6 weeks of oculomotor training, 2 60 minute sessions per week (N = 12) vs 6 weeks of placebo treatment (N = 12). Each participant underwent both treatment with a 1 week washout period between.	Follow-up at 1 week post-intervention for each treatment	Mean visagraph parameters (at baseline, at post-OMT, p-value): Reading rate [wpm] (142, 17, p<0.01), Comprehension [%] (81, 85, p=0.31), Fixations/100 words (164, 135, p=0.02), Regressions/100 words (30, 23, p=0.11), Fixation duration [seconds] (0.27, 0.27, p=0.91), Grade level efficacy (4.1, 6.3, p=0.01)	“OBVR had a strong positive effect on oculomotor control, reading rate, and overall reading ability. This oculomotor learning effect suggests considerable residual neuroplasticity following mTBI.	Small sample crossover study, sparse methods.

Thiagarajan 2014 (2.0)	Visual Training	Experimental	No COI. Sponsored by the US Army, DOD.	N = 12 with documented mTBI, injury onset of greater than 1 year	Mean age: 29±3;	6 weeks of oculomotor training, 2 60 minute sessions per week (N = 12) vs 6 weeks of placebo treatment (N = 12). Each participant underwent both treatment with a 1 week washout period between.	Follow-up at 1 week post-intervention for each treatment	Mean saccade ratio for SRML reduced after OMT (t(11)=3.83, p=0.002). Mean SRSL did not reduce (t(11)=2.06, p=0.06). Mean increase in peak velocity ±2.5° horizontal after OMT (t(11)=2.35, p=0.03). Saccadic gain (SG) increased for ±2.5° horizontal (t(11)=2.4, p=0.03) and ±2.5° vertical (t(11)=3.54, p=0.004). SG increased for ±5° vertical saccades (t(11)=2.16, p=0.05). Saccadic latency did not change for horizontal (t(11)=1.65, p=0.12) or vertical (t(11)=1.06, p=0.30) random saccades	“The versional-based OMT had a significant, positive effect on most aspects of versional tracking. These findings are suggestive of improved rhythmicity, accuracy and sequencing of saccades following OMT in mTBI as a result of oculomotor learning.”	Small sample, sparse methods.
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Oculomotor training has been used, especially in military settings, for rehabilitation from TBI [495].

## Oculomotor Training Recommended.

Oculomotor training is recommended for the treatment of TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – Low

<i>Indications:</i>	TBI with accommodative dysfunction of at least 6 months duration.
<i>Benefits:</i>	Identification and treatment of accommodative dysfunction related to TBI.
<i>Harms:</i>	Negligible.
<i>Frequency/Dose/Duration:</i>	Two 60minute sessions/week for 9 sessions total [495].
<i>Indications for Discontinuation:</i>	Resolution, completion of a course of treatment.
<i>Rationale:</i>	There is one moderate-quality trial in the military suggesting efficacy of Oculomotor Training for rehabilitation of TIB [495]. Oculomotor Training is not invasive, has negligible adverse effects, is low to moderate cost in aggregate, has some evidence of efficacy in military settings, and thus is recommended for select treatment of TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: visual training, oculomotor training; traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 164 articles in PubMed, 15 in Scopus, 12 in CINAHL, 281 in Cochrane Library, 63,600 in Google Scholar, and 3 from other sources. We considered for inclusion 3 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 3 from other sources. Of the 6 articles considered for inclusion, 1 randomized trial and 0 systematic studies met the inclusion criteria.

## Evidence for Oculomotor Training

Thiagarajan 2014 (4.5)	Vision, Speech, Swallowing, Balance, and Hearing	RCT crossover	No COI. Supported by U.S. Department of Defense (DoD) grant, the College of Optometrists in Vision Development, and SUNY graduate program.	N = 12 with mild TBI, injury onset of over 1 year, displayed at least one clinical sign of accommodative dysfunction	8 female, 4 male Mean age overall 29 ± 3 years	Oculomotor training (OMT)  Vs.  Placebo training (P)  Each session 60 minutes, two sessions per week, 9 hours for one treatment total	15 weeks	Placebo training produced no significantly different measures ( $p > 0.05$ ). OMT produced an increase of about 30% in peak velocity for increasing ( $t(11) = 3.61, p = 0.01$ ) and decrease ( $t(11) = 3.65, p = 0.01$ ) steps of accommodation.	“These results provide evidence for a significant positive effect of the accommodatively based OMT on accommodative responsivity. Such improvement is suggestive of oculomotor learning, demonstrating considerable residual brain-visual system plasticity in the adult compromised brain.	Small sample, crossover design. Data suggest OMT improved most measures related to accommodation on responsivity which may be the result of oculomotor learning.
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## Medication Recommendations

### Non-Steroidal Anti-Inflammatory Medications

Non-steroidal anti-inflammatory (NSAIDs) have been used for treatment of traumatic brain injuries, although mostly for febrile control [835-837]. A few studies reviewed potential NSAID use for intracerebral pressure control [837, 838]. Some have theorized that NSAIDs may be helpful in neuroregenerative processes [839], and one trial in mice found evidence of reduced inflammatory responses among those mice treated with ibuprofen although no differences in their cognitive-maze test [840].

#### NSAIDs for TBI Patients

##### No Recommendation.

There is no recommendation for or against NSAIDs for treatment of TBI. There are other indications for TBI patients such as headache, febrile control and musculoskeletal pain.

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

There are no quality placebo-controlled trials evaluating the use of NSAIDs for treatment of TBI.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: Traumatic brain injury, intracranial injury, closed Head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral Trauma, anti-Inflammatory Agent, pharmacological action, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed 123 articles in PubMed, 13 in Scopus, 5 in CINAHL, 5 in Cochrane Library and 0 in other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library and 0 from other sources. Of the 2 articles considered for inclusion, 0 randomized trials and 2 systematic studies met the inclusion criteria. There is 1 moderate-quality randomized controlled trial.

#### NSAIDs for Febrile Control

##### Recommended.

NSAIDs are recommended for treatment of fever in TBI patients, with preference for continuous IV infusion over boluses [835].

*Strength of Evidence – Recommended, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Indications:*

Moderate-severe TBI with fever.

<i>Frequency/Dose/Duration:</i>	Diclofenac low-dose infusion: initial IV bolus 0.2 mg/kg diluted in 100 ml NS then a continuous infusion of 75 mg in 50 ml normal saline until internal temperature was lower than 38°C for at least 12 hours [835].
<i>Indications for Discontinuation:</i>	Satisfactory temperature control
<i>Benefits:</i>	Improved febrile control. May improve CNS outcomes
<i>Harms:</i>	Hemorrhage, especially GI or CNS.
<i>Rationale:</i>	There are no quality trials of NSAIDs compared with placebo for treatment of TBI patients. One moderate quality trial for treatment of fever found continuous NSAID infusion superior to boluses for control of fevers in comatose patients [835]. NSAIDs are not invasive, have low adverse effects in employed populations although somewhat higher in ICU settings, and are low cost. There is moderate quality evidence of efficacy for febrile suppression among patients treated with continuous IV NSAID infusion.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: Traumatic brain injury, intracranial injury, closed Head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral Trauma, anti-Inflammatory Agent, pharmacological action, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed 123 articles in PubMed, 13 in Scopus, 5 in CINAHL, 5 in Cochrane Library and 0 in other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library and 0 from other sources. Of the 2 articles considered for inclusion, 0 randomized trials and 2 systematic studies met the inclusion criteria. There is 1 moderate-quality randomized controlled trial.

### Evidence for the Use of NSAIDs

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Cormio 2007 (score = 4.5)	[Previous table header, if any]	RCT	No mention of sponsorship or COI.	N=23 febrile comatose, GCS≤8, at least one reactive pupil, Temp≥38C, 12 with severe TBI and 10 with SAH.	ages 14-75yo.	Diclofenac low-dose infusion: initial IV bolus 0.2 mg/kg diluted in 100 ml NS then a continuous infusion of 75 mg in 50 ml normal saline until internal temperature was lower than 38°C for at least 12 hours (N=10) vs. boluses of NSAIDs: 0.2 mg/kg diclofenac sodium infusion, 100 mg ketoprofene, and 1000 mg paracetamol all diluted in 100 ml normal saline (N=12).	Follow-up 24 hours following the stop of antipyretic therapy.	Percentage of time >38°C was 4% vs. 34% (p<0.0001). Maximum temperatures also lower with continuous infusion. Favorable outcomes (good result, moderate disability): 70% DCF vs. 83% controls (NS) at 6mo.	“Low dose DCF infusion is a potential useful strategy for a successful control temperature better than intermittent NSAIDs dosing, minimizing potentially brain-damaging effects of fever.”	Data suggest considerably better febrile control with continuous IV NSAID infusion vs. NSAID boluses. However, not powered to detect differences in other endpoints.

## Dextromethorphan (Nuedexta®) for TBI Patients

Dextromethorphan/quinidine has been used for treatment of pseudobulbar affect in adults with underlying neurological conditions [841] [842, 843].

### Dextromethorphan for TBI Patients

#### No Recommendation.

There is no recommendation for the use of dextromethorphan in the treatment of TBI patients.

#### *Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

#### *Level of Confidence – Low*

<i>Indications:</i>	Has been used for emotional dyscontrol accompanying TBI. Also has been used to treat pseudobulbar palsy.
<i>Benefits:</i>	Purported improvement of control of emotions associated with TBI
<i>Harms:</i>	Sedation, fatigue, nausea, vomiting, constipation, diarrhea, dizziness, confusion
<i>Frequency/Dose/Duration:</i>	As per manufacturer's recommendation.
<i>Rationale:</i>	Dextromethorphan is not invasive has some adverse effects, is low to moderate cost. There are no quality studies addressing the use of dextromethorphan for TBI patients and thus there is no recommendation. Dextromethorphan also has other potential indications.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Nuedexta, Dextromethorphan, Quinidine, traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed zero articles in PubMed, 0 in Scopus, 1 in CINAHL, 2 in Cochrane Library, 27 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the one article considered for inclusion, zero randomized trials and 1 systematic study met the inclusion criteria.

## Evidence for the Use of Dextromethorphan

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Pioro 2010 (Score=6.0)	Dextromethorphan	RCT	Supported by Avanir Pharmaceuticals. Pioro received research support and compensation for consulting from Avanir Pharmaceuticals. Other authors also received compensation for work on this project.	N = 326 with clinically significant pseudobulbar affect (PBA), a score $\geq 13$ on the Center for Neurological Study—Lability Scale (CNS-LS), and either an amyotrophic lateral sclerosis (ALS) diagnosis within the last 30 months or a multiple sclerosis (MS) or probable MS diagnosis	Mean age = 51.41 years; 149 males, 117 females.	30mg dextromethorphan plus 10mg quinidine (DM 30mg + Q 10mg, DMq-30) (N = 110) vs DM 20mg + Q 10mg (DMq-20) (N = 107) vs placebo (N = 109). Each patient took one capsule each morning during week 1. For weeks 2-12 patients took one capsule each morning and another at night.	Weeks 2, 4, 8, and 12.	Mean change in daily episode rate for DMq-30, DMq-20, and placebo, respectively: -4.1, -3.9, -3.0 ( $p = 0.0099$ , $p = 0.0048$ , respectively). Via longitudinal negative binomial model, reduction in PBA episode rate for DMq-30 vs. placebo was 46.9% ( $p < 0.0001$ ) and for DMq-20 vs. placebo was 49.0% ( $p < 0.0001$ ).	“DMq markedly reduced PBA frequency and severity, decreasing the condition’s detrimental impact on a patient’s life, with satisfactory safety and high tolerability. The findings expand the clinical evidence that DMq may be an important treatment for patients suffering from the socially debilitating symptoms of PBA.”	Results determined from patient diary entries. Only a 12 week time period. Placebo controlled RCT. Data suggest DMq reduced the frequency and severity of PBA.
Pope 2012 (Score=2.0)	Dextromethorphan	RCT	Supported by Avanir Pharmaceuticals, Inc. Pope is an employee of Avanir Pharmaceuticals, Inc. Other authors were also employees of this company.	N = 52 healthy test subjects with body weight $\geq 60$ kg for males, $\geq 52$ kg for females, BMI 19-20 kg/m <sup>2</sup> , non-smoker, and could abstain from alcohol for the length of the trial	Mean age = 36.1 years; 39 males, 24 females.	Group 1 – given a dose of 5 mg memantine once daily, which was titrate over 3 weeks to 10 mg twice daily for 11 days, DMQ 30 mg (dextromethorphan 30mg/quinidine 30mg) twice	No long-term follow-up.	Only 17 patients from each group were evaluated (total n included 34). Ratio of AUC12 values 90% confidence intervals for memantine (group 1, day 40 vs. day 32), dextromethorphan (DM) (group 2, day 40 vs. day 8), dextrophan (DX)	“Minimal pharmacokinetic and pharmacodynamic interactions were observed between memantine and DMQ, suggesting they can be coadministered without dose adjustment.	Open label RCT. Small sample. Significant AEs in group I (78.3%) and in group II (92.9%).

						<p>daily was also given for another 8 days (N = 23) vs Group 2 – given DMQ 30mg twice daily for 8 days, then administered memantine, titrated like group 1, for 11 additional days (N = 29)</p>		<p>(group 2, day 40 vs. day 8), and quinidine (group 2, day 40 vs. day 8), respectively: 0.850-1.036, 1.041-1.160, 1.020-1.167, 1.153-1.349. To be pharmacokinetically similar, the 90% CI had to fall within predefined range of 0.8—1.25.</p>	
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## Cytoprotective Drugs for TBI Patients

There are two main reasons for using cytoprotective drugs in TBI patients: (1) prevention of stress ulcers, and to (2) counteract NSAID-related effects on the GI tract. There are four commonly used cytoprotective classes of drugs – proton pump inhibitors (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole), misoprostol, sucralfate, and histamine Type 2 receptor blockers (famotidine, ranitidine, cimetidine, etc.). There is not generally believed to be substantial differences in efficacy for prevention of gastrointestinal bleeding, [844, 845].

### Proton Pump Inhibitors (PPIs)

#### Strongly Recommended.

Proton pump inhibitors are strongly recommended for use with NSAIDs for select TBI patients.

*Strength of Evidence – Strongly Recommended, Evidence (A)*

*Level of Confidence – High*

<i>Indications:</i>	NSAID use with either risk factors for GI bleeding (e.g., elderly, diabetes mellitus, rheumatoid arthritis), or ICU stay and concerns for gastric ulcers.
<i>Benefits:</i>	Eliminates increased risk of GI bleeding from NSAIDs. May reduce risk of stress ulcers.
<i>Harms:</i>	Adverse effects of the proton pump inhibitor. Concerns for higher bacterial burden in the stomach with lack of low pH and thus increased risk of bacterial pneumonia from aspiration, making suggestions sucralfate or possibly H2 blockers may be preferable for that indication [846, 847].
<i>Frequency/Dose/Duration:</i>	Dose and frequency for proton pump inhibitors, sucralfate, and H2 blockers are as recommended by manufacturer. Duration is the extent of the NSAID therapy; use is at times permanent for those with recurrent bleeds or other complications.
<i>Rationale:</i>	Risks of gastrointestinal events are also recommended for assessment, particularly including prior history of gastrointestinal bleeding and source, length of treatment, age, smoking, diabetes mellitus and other medical factors. Those with greater risk should be considered for treatment with acetaminophen, NSAID plus misoprostol, proton pump inhibitors (see below), or a COX-2 selective agent (see NSAIDs/acetaminophen evidence table). (306, 307, 342, 346, 354, 355) [848-853]. Gastrointestinal adverse events are generally considered the most significant of the risks of NSAIDs. A large volume of high- and moderate-quality evidence consistently shows proton pump inhibitors are effective for prevention and or treatment of gastric and duodenal ulcers and erosions. (356-365) [854-863]. There is only one quality head-to-head trial, and it found no difference in efficacy between pantoprazole and omeprazole (358) [855]. Misoprostol has also been consistently shown to be effective compared with placebo. (366-375) [845, 864] [865-867]; [868] [869] [870, 871] Relatively fewer studies have shown sucralfate to be effective compared with placebo; (376) [872] H2 blockers appear more effective for treatment of duodenal than gastric mucosa. (319-321) [873] [874] [875]. There are relatively

few quality trials comparing efficacy of the different classes of agents. Pantoprazole but not lansoprazole has been found modestly superior to misoprostol.(315, 377) [876] [845]. No difference was found between famotidine and lansoprazole.(378) [877] Misoprostol has been reported superior to ranitidine,(379, 380) [859] [864] cimetidine, (381) [867] and sucralfate.(371, 382) [878] [867]. In short, while the evidence is not definitive, available quality evidence suggests proton pump inhibitors and misoprostol appear superior to H-2 blockers and sucralfate. While COX-2 selective agents have generally been recommended as either third- or fourth-line medications for routine use in osteoarthritis patients, when there is a risk of gastrointestinal complications, they are often preferred. For patients at high risk of gastrointestinal bleeding, there is evidence that a combination of proton pump inhibitor plus COX-2 selective agent is efficacious (383) [879].

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Proton pump inhibitors, PPIs, critical care, intensive care unit, ICU, emergency room, ER; traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; systematic, systematic review. We found and reviewed 1 article in PubMed, 16 in Scopus, 0 in CINAHL, 63 in Cochrane Library, 653 in Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

## Evidence for the Use of Proton Pump Inhibitors

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Chan 2002 (9.5)	Proton Pump Inhibitors (PPIs)	RCT	No mention of sponsorship. No COI.	N = 102 patients with RA, OA, and other forms of arthritis with ulcer bleeding. 2 participants withdrew after randomization.	Mean age 62.5. 33 males, 67 females.	Omeprazole 20mg plus amoxicillin 1g plus clarithromycin 500mg vs. omeprazole 20mg and placebo antibiotics each BID for 1 week	Every 8 weeks for a period of 6 months.	H pylori eradicated in 90% vs. 6% controls. 6-month probability of ulcers 12.1% (95% CI 3.1-21.1) in eradication group vs. 34.4% (21.1-47.7) in controls (p = 0.0085); 6-month probabilities of complicated ulcers 4.2% (1.3-9.7) vs. 27.1% (14.7-39.5), p = 0.0026.	"Screening and treatment for H pylori infection significantly reduces the risk of ulcers for patients starting long-term NSAID treatment."	One week treatment 6 months diclofenac SR. Data suggests antibiotics plus omeprazole effective.
Labenz 2002 (9.0)	Proton Pump Inhibitors (PPIs)	RCT	No mention of sponsorship or COI.	N = 832 patients who tested positive for H pylori. Mean age 55. 660 participants included in intention to treat analysis.	Mean age 55. 252 males, 408 females.	Omeprazole 20mg BID vs. amoxicillin 1g BID vs. clarithromycin 500mg BID for 1 week (OAC), plus 4 weeks of placebo QD (OAC-P); OAC for 1 week plus 4 weeks omeprazole 20mg QD (OAC-O); omeprazole 20mg QD for 1 plus 4 weeks [532]; or placebo for 5 weeks (P-P)	Follow up at Week 1 and Week 5.	Relative risk reduction (%) (95% CI) and absolute risk reduction (%) (95% CI) for the treatment groups was as follows: OAC-P: 79 (4.5-95), 4.6 (0.7-8.5); OAC-O: 80 (11.1-96), 4.7 (0.8-8.6); O-O: 100, 5.8 (2.1-9.5).	"In H pylori infected patients, all three active therapies reduced the occurrence of NSAID associated peptic ulcer and dyspeptic symptoms requiring therapy."	All diclofenac 50mg twice a day for 5 weeks. Other arms treatment for 1 week. Three treatment arms all reduced risk comparably. Results may not be generalized beyond H pylori infected patients.

Scheiman 2006 (9.0)	Proton Pump Inhibitors (PPIs)	RCT	Sponsored by AstraZeneca R&D. No mention of COI.	VENUS study: N = 805; PLUTO study: N = 573 for at-risk patients (≥60 years and/or ulcer history).	Mean age 65.4. Venus study: 266 males, 539 females. Pluto study: 130 males, 443 females.	Esomeprazole 20mg vs. Esomeprazole 40mg vs. Placebo QD for 6 months.	No follow up.	16.5% (95% CI: 9.7–23.4) on COX-2s or placebo developed ulcers over 6 months vs. 0.9% (95% CI: 0–2.6) esomeprazole 20mg and 4.1% (95% CI: 0.6–7.6) esomeprazole 40mg (p < 0.001, p = 0.002) vs. placebo, respectively.	“For at-risk patients, esomeprazole was effective in preventing ulcers in long-term users of NSAIDs, including COX-2 inhibitors.”	Two RCTs with large sample size. Study suggests efficacy.
Regula 2006 (9.0)	Proton Pump Inhibitors (PPIs)	RCT	Sponsored by ALTANA Pharama AG. COI, Regula Jaroslaw, Butruk Eugeniusz, Dekkers Cornelius PM, de Boer Sybrand Y, Raps Dieter, Simon Laszlo, have in the past received grants from ALTANA. Terjung Andreas, Thomas Kathy B., Luhmann Reinhold, and Fischer Renate are employees of ALTANA.	N = 595 rheumatic patients on continual NSAIDs with at least 1 more recognized risk factor that contributes to GI injury.	Mean age 66. 172 males, 423 females.	Pantoprazole 20mg vs. pantoprazole 40mg vs. omeprazole 20mg QD for 6 months	Follow up at 3 and 6 months after treatment.	At 6 months, probability of therapeutic remission 90% pantoprazole 20mg QD, 93% pantoprazole 40 mg QD, and 89% omeprazole 20mg QD. Probabilities of endoscopic failure 9% vs. 5% vs. 7% respectively (NS).	“For patients taking NSAIDs continually, pantoprazole 20 mg o.d., pantoprazole 40 mg o.d., or omeprazole 20 mg o.d. provide equivalent, effective, and well-tolerated prophylaxis against GI lesions, including peptic ulcers.”	Large population of rheumatoid arthritis, osteoarthritis, multiple conditions and spine for 6 months of treatment. Suggests equal efficacy.
Yeomans 2008 (9.0)	Proton Pump Inhibitors (PPIs)	RCT	Sponsored by AstraZeneca. COI, Neville Yeomans is an advisor for	N = 991 participants ≥60 years without baseline	Mean age 69.5 ± 6.5. 566 males, 425 females.	Esomeprazole 20mg QD vs. Placebo for 26 weeks.	No follow up.	Twenty-seven (5.4%) in placebo group with gastric or duodenal ulcer during 26-week treatment vs. 8 (1.6%)	“Esomeprazole 20 mg once daily reduces the risk of developing gastric and/or duodenal	Large population. Suggests efficacy.

			AstraZeneca, and previously to Merck Sharp & Dohme and Pfizer. Angel Lanas, Sander Veldhuyen van Zanten, Konstantin Tchernev, Dimitrios Karamanolis, and Chris Hawkey have received financial support from AstraZeneca. Emma Naucner and Lars-Erik Svedberg are employees of AstraZeneca.	gastro-duodenal ulcer receiving aspirin 75-325mg daily.				esomeprazole group (life-table estimates: 6.2%vs 1.8%; p = 0.0007). At 26 weeks, cumulative proportion with erosive esophagitis lower for esomeprazole vs. placebo (4.4% vs. 18.3%, respectively; p <0.0001).	ulcers and symptoms associated with the continuous use of low-dose aspirin in patients aged > or =60 yr without preexisting gastroduodenal ulcers."	
Dorta 2000 (8.5)	Proton Pump Inhibitors (PPIs)	RCT	Sponsored by the Swiss Cancer League/Cancer Research Switzerland and Astra Hassle AB.	N = 12 healthy volunteers.	Median age 29. 7 males, 5 females.	Two-week course of omeprazole (40mg) plus "separate 2-week course of an identical looking placebo." Water-soluble diclofenac (50mg) taken 2nd week.	No follow up time.	No differences in healing scores after administration of placebo/diclofenac (median = 6; range 0-6) and omeprazole/diclofenac (median = 9; range 0-6; p = 0.17) were found.	"In healthy subjects, omeprazole does not accelerate the healing of pre-existing mucosal lesions or prevent the development of small diclofenac-induced mucosal lesions."	Crossover study with small sample size. Short-term treatments of unclear clinical significance.
Bianchi Porro	Proton Pump	RCT	No mention of	N = 104 with RA or OA.	Mean age 59.5. 18 males, 86 females.	40mg pantoprazole Vs.	Weeks 4 and 12	Difference in probability of remaining free of	"Pantoprazole 40mg once daily was well tolerated	RA or OA 12 week treatment.

2000 (8.5)	Inhibitors (PPIs)		sponsorship or COI.			Placebo QD for 12 weeks		peptic ulcer 5% (95% CI-13%, = 23%) at 4 weeks and 13% (-9%, = 33%) at 12 weeks.	and is more effective than placebo in the prevention of peptic ulcers in patients with rheumatic diseases who require continuous, long-term, treatment with NSAIDs.”	Suggests efficacy.
Hawkey 2005 (7.5)	Proton Pump Inhibitors (PPIs)	RCT	All but one author were employees or consultants to AstraZeneca. Study was funded by a grant from AstraZeneca R&D, Mölndal, Sweden.	2 RCTs: N = 608 and N = 556 (NASAI, SPACE 1)  Con-tinuous NSAID users free of gastro-duodenal ulcers, erosive esophag-itis, and H pylori	Sell 2004 (7.5)	Proton Pump Inhibitors (PPIs)	RCT	Sponsored by Novartis Pharma. No mention of COI.	N = 245 THA	Mean age 63 years. 110 men, 135 women.
Sell 2004 (7.5)	Proton Pump Inhibitors (PPIs)	RCT	Sponsored by Novartis Pharma. No mention of COI.	N = 245 THA	Mean age 63 years. 110 men, 135 women.	Cholestyramine-bound diclofenac 75mg QD  vs.  BID for 14 days post op	6 months.	In diclofenac 150mg, 19% slight heterotopic ossification (Booker 1, none more severe) vs. 75mg which had 17% grade 1 and 4% grade 2 Booker. No clinical difference after 6 months.	“Although the two doses displayed similar efficacy the author recommends the lower dose because of the lower instance of adverse gastrointestinal	Co-administrati on of proton pump inhibitors likely resulted in lower side effect

									event (23% vs. 38%, p=0.02)."	profile. No placebo control.
Stupnicki 2003 (6.5)	Proton Pump Inhibitors (PPIs)	RCT	Supported by ALTANA Pharma AG, Konstanz, Germany. No mention of COI.	N = 515 Rheumatic patients likely to take NSAIDs continuously for at least 6 months	376 female, 139 male  Median age pantoprazole group 64 years, misoprostol group 64 years	Pantoprazole 20mg plus placebo vs. misoprostol 200µg	3 and 6 months	Pantoprazole superior to misoprostol (p = 0.005) for endoscopic failure. Estimated remission rates 3 and 6 months, 98 and 95% (pantoprazole); 95 and 86% (misoprostol). Discontinuations for likely/definitely drug-related adverse effects: 13/257 (5%) pantoprazole vs. 33/258 (13%) misoprostol.	"Pantoprazole 20 mg o.d. is superior to misoprostol 200 microg b.i.d. in the prevention of NSAID-induced gastrointestinal lesions and symptoms in patients on continuous long-term treatment with NSAIDs due to rheumatic diseases and at risk to develop such lesions or symptoms."	Six-month treatment. Study suggests pantoprazole superior to misoprostol.
Desai 2008 (6.5)	Proton Pump Inhibitors (PPIs)	RCT	No mention of COI. Supported by an Independent Investigator Research Grant from Pfizer, Inc., and by grant from the Digestive Disease Research Foundation.	N = 70 Healthy adults aged 50-75 not taking chronic NSAIDs	37 female, 33 male  Mean age NPX 500mg BID plus omerprazole 58.2 years, placebo 58.9 years	Naproxen 500mg BID plus omeprazole 20mg QD vs. naproxen 500mg BID plus placebo for a 6.5-day treatment	14 days	Less gastroduodenal ulcers in naproxen plus omeprazole vs. naproxen plus placebo [11.8% (4 ulcers/34 subjects) vs. 46.9% (15/32), RR = 0.25, p = 0.002]. NPX plus OMP associated with decreased risk of ulceration and erosion [5 erosions [38.2% (13/34) vs. 81.3% (26/32), RR = 0.47, P B 0.001].	"[O]MP at the U.S. OTC dosage of 20 mg daily begun on Day 1 of NSAID treatment reduces both GDUs and dyspepsia with OMP. Therefore, in view of the relatively low cost, availability, and good safety profile of OTC OMP, co-prescription of a PPI in relatively healthy older patients requiring short-term non-specific NSAID	"Pilot Study"; unclear whether endoscopy data translate to clinical outcomes to support conclusion.

									therapy may be reasonable.”	
Bianchi Porro 1998 (6.0)	Proton Pump Inhibitors (PPIs)	RCT	No mention of COI or sponsorship.	N = 114 Arthritic disorders requiring indomethacin, diclofenac, or ketoprofen	87 female, 16 male  Mean age omeprazole group 53.1±12 years, placebo group 51.6±9.2 years	Omeprazole 20mg QD vs.  Placebo for 3 weeks. All patients given indomethacin 100mg, ketoprofen 150mg, and diclofenac 150mg	7 days	26/57 (46%) of omeprazole vs. 20/57 (35%) of placebo group with normal gastroduodenal mucosa (score = 0). Clinically significant gastric lesions (score 3-4) in 6/57 (11%) omeprazole vs. 11/57 (19%) on placebo.	“Omeprazole 20mg once daily is significantly more effective than placebo in the prevention of gastric and duodenal ulcers due to chronic NSAIDs treatment and may provide clinical advantages, in terms of tolerability, over currently available prophylactic therapies.”	Three weeks of treatment added to NSAID. Data support treatment.
Graham 2002 (6.0)	Proton Pump Inhibitors (PPIs)	RCT	Graham’s research is supported by Abbott Laboratories, Astra USA, Astra-Merck, Enteric Products Inc, Glaxo Wellcome Inc, Meretek Diagnostics, Merck Sharp & Dohme, Merck, Proctor & Gamble, SmithKline Diagnostics, and TAP Pharmaceutic	N = 535 Patients without H pylori and long-term users of NSAIDs with history of gastric ulcer	348 female, 187 male  Mean age of placebo group 60.5±11.8 years, misoprostol group 59.4±12.0, lansoprazole 15mg group 61.6±12.1, lansoprazole 30mg group 60.2±11.8	Placebo plus Misoprostol 200µg QID vs. 15 or 30mg of lansoprazole QD for 12 weeks	Months 1, 2 and 3	Patients on NSAIDs. Either dose lansoprazole remained free from gastric ulcer longer vs. placebo (p <0.001). Misoprostol group remained free of gastric ulcers longer than placebo (p <0.001), 15mg lansoprazole (p = 0.01), or 30mg lansoprazole (p = 0.04).	“Proton pump inhibitors such as lansoprazole are superior to placebo for the prevention of NSAID-induced gastric ulcers but not superior to misoprostol, 800 microg/d. When the poor compliance and potential adverse effects associated with misoprostol are considered, proton pump inhibitors and full-dose misoprostol are clinically equivalent.”	Not blinded to misoprostol . H pylori negative.

			<p>al Products Inc. Agrawal's research is supported by Pharmacia, Pfizer Inc, and TAP Pharmaceutical.</p> <p>Campbell's research is supported by AstraZenica, Merck, TAP Pharmaceuticals, Wyeth-Ayerst, and Janssen Pharmaceutica. Overall study supported by grant from TAP Pharmaceutical Products Inc.</p>							
Bergman 1992 (6.0)	Proton Pump Inhibitors (PPIs)	RCT	No mention of COI. Supported by grant from Houde Laboratories Paris La Defense.	N = 12 Healthy volunteers	5 female, 7 male  Age range 22-32 years	Lansoprazole 30mg QD vs. placebo plus aspirin for 1 week	1 week	Mean Lanza scores 0.67±0.98 with lansoprazole vs. 2.25±1.1 with placebo (p <0.005).	"[I]t is possible to distinguish the functional and morphologic effects of a gastrototoxic drug such as aspirin during experimental studies in humans. Lansoprazole prevents hemorrhagic lesions without	Crossover study with small sample size (n = 12). Short experimental design of 1 week.

									reinforcing the mucosal barrier.”	
Niwa 2008 5.5	Proton Pump Inhibitors (PPIs)	RCT	No mention of COI or sponsorship.	N = 10 Healthy subjects	0 female, 10 male  Age range 20 to 40 years	Rebamipide 300mg plus diclofenac 75mg plus omeprazole 20mg vs. placebo plus diclofenac 75mg plus omeprazole 20mg QD for 1 week	4 weeks	Number of subjects with small-intestinal mucosal injuries significantly higher in placebo group (8/10) than rebamipide group (2.10) (p = 0.023).	“Rebamipide had significantly higher efficacy than placebo in preventing NSAID-induced small-intestinal mucosal injury.”	Crossover trial with small sample size (n = 10). Evaluation of small intestine. 7 day treatment. Data suggests efficacy for small intestine.
Miyake 2005 5.0	Proton Pump Inhibitors (PPIs)	RCT	No mention of COI or sponsorship.	N = 26 RA in patients treated over a long term with NSAIDs	14 female, 12 male  Mean age famotidine group 65.6 years, lansoprazole group 62.6 years	Famotidine 20mg BID vs. lansoprazole 15mg QD for 24 weeks	24 weeks	8% (1/13) peptic ulcer onset rate infamotidine vs. 2/13 (15%) lansoprazole (NS).	“In Japan, normal-dose H2RA is expected to be a new PU preventive treatment strategy in patients requiring long-term NSAID therapy.”	RA patients on NSAIDs with peptic ulcers scars 24-week treatment; small sample (n = 26). Under-reported study.
Scheiman 1994 (4.5)	Proton Pump Inhibitors (PPIs)	RCT	No COI. Supported by NIH grant and by Merck Sharpe and Dohme Research Laboratories.	N = 20 Healthy volunteers	9 female, 11 male  Mean age 27±6 years	Omeprazole 40mg QD vs. placebo plus aspirin 650mg QID for 2 weeks	2 weeks	Omeprazole reduced PUD 55% vs. 10% (p <0.01). Endoscopic evidence of intraluminal bleeding or ulceration in 70% of placebo vs. 15% of omeprazole (p <0.001).	“Omeprazole 40mg/day significantly prevented both gastric and duodenal injury due to 2600mg aspirin/day over the two-week period of our study...Omeprazole 40mg/day prevented 95% of subjects from	Crossover, short 2 week study.

									developing ulceration, 85% from having >15 erosions (all ≤3mm in size), and 55% from having >5 erosions. In the subjects given placebo, 25% developed gastric ulcers, 70% had grade 3 injury or worse, and all 95% had at least grade 2 injury.”	
Pilotto 2000 (4.0)	Proton Pump Inhibitors (PPIs)	RCT	No mention of COI. Supported by the host institutions.	N = 69 H pylori positive patients with no severe gastro-duodenal lesions	40 female, 29 male Mean age PAC group 74 years, P group 76.9 years	Pantoprazole 40mg QD plus amoxicillin 1g BID and clarithromycin 250mg BID for 1 week vs. pantoprazole 40mg QD for 1 month	1 month	Higher incidence of severe gastroduodenal damage in Group PAC vs. Group P (29% vs. 9%, p <0.05). Percent of patients worsened, unchanged, improved after 1 month Group PAC: 46%, 46%, and 9% vs. Group P: 7%, 65%, 29% (p <0.0008).	“One month of pantoprazole was more effective than a proton pump inhibitor-based triple therapy in the prevention of gastroduodenal damage in elderly H. pylori-positive NSAID users.”	Triple therapy for 1 week pantoprazole for 1 month reduces strength of conclusion regarding what is efficacious vs. efficacy of 1 month when 1 arm still actively treated.

## Sucralfate

### Recommended.

Group sessions for problem solving, discussion of social isolation and frustrations are selectively recommended for treatment of TBI patients.

#### *Strength of Evidence – Moderately Recommended, Evidence (B)*

*Level of Confidence – Moderate*

<i>Indications:</i>	NSAID use with either risk factors for GI bleeding (e.g., past history of GI bleeding, elderly, diabetes mellitus, rheumatoid arthritis), or ICU stay and concerns for gastric ulcers.
<i>Benefits:</i>	Eliminates increased risk of GI bleeding from NSAIDs. May reduce risk of stress ulcers.
<i>Harms:</i>	Adverse effects of the proton pump inhibitor. Concerns for higher bacterial burden in the stomach with lack of low pH and thus increased risk of bacterial pneumonia from aspiration, making suggestions sucralfate or possibly H2 blockers may be preferable for that indication [846] [847].
<i>Frequency/Dose/Duration:</i>	Dose and frequency for proton pump inhibitors, sucralfate, and H2 blockers are as recommended by manufacturer. Duration is the extent of the NSAID therapy; use is at times permanent for those with recurrent bleeds or other complications.
<i>Rationale:</i>	<p>Risks of gastrointestinal events are also recommended for assessment, particularly including prior history of gastrointestinal bleeding and source, length of treatment, age, smoking, diabetes mellitus and other medical factors. Those with greater risk should be considered for treatment with acetaminophen, NSAID plus misoprostol, proton pump inhibitors (see below), or a COX-2 selective agent (see NSAIDs/acetaminophen evidence table) (306, 307, 342, 346, 354, 355) [848] [849] [850, 851] [852] [853].</p> <p>Gastrointestinal adverse events are generally considered the most significant of the risks of NSAIDs. A large volume of high- and moderate-quality evidence consistently shows proton pump inhibitors are effective for prevention and or treatment of gastric and duodenal ulcers and erosions.(356-365) [854], [855] [856] [857] [858] [859] [860, 861] [862] [863]) There is only one quality head-to-head trial, and it found no difference in efficacy between pantoprazole and omeprazole.(358) [855] Misoprostol has also been consistently shown to be effective compared with placebo.(366-375) [880] [864-867] [868] [869] [870] [871]. Relatively fewer studies have shown sucralfate to be effective compared with placebo (376) [872] H2 blockers appear more effective for treatment of duodenal than gastric mucosa (319-321) [873] [874] [875]. There are relatively few quality trials comparing efficacy of the different classes of agents. Pantoprazole but not lansoprazole has been found modestly superior to misoprostol (315, 377) [876] [845]. No difference was found between famotidine and lansoprazole (378) [877] Misoprostol has been reported superior to ranitidine, (379, 380) ([859] [864] cimetidine,(381) [867] and sucralfate.(371, 382) [878] [867]. In short, while the evidence is not</p>

definitive, available quality evidence suggests proton pump inhibitors and misoprostol appear superior to H-2 blockers and sucralfate. While COX-2 selective agents have generally been recommended as either third- or fourth-line medications for routine use in osteoarthritis patients, when there is a risk of gastrointestinal complications, they are often preferred. For patients at high risk of gastrointestinal bleeding, there is evidence that a combination of proton pump inhibitor plus COX-2 selective agent is efficacious (383) [879].

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: sucralfate, critical care, intensive care unit, ICU, emergency room, ER; traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1 article in PubMed, 26 in Scopus, 0 in CINAHL, 3 in Cochrane Library, 2,185 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 0 randomized trials and 1 systematic study met the inclusion criteria.

## Evidence for the Use of Sucralfate

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Agrawal 1991 (6.5)	Sucralfate	RCT	Supported by grant from G. D. Searle & Company. This company provided study design and data analyses.	N = 356 OA patients receiving ibuprofen, piroxicam or naproxen with abdominal pain	115 female, 241 male  Median age misoprostol group 60 years, sucralfate group 60 years	Misoprostol 200µg  vs.  Sucralfate 1g QID	3 months	Gastric ulcer developed in 2/122 (1.6%, 95% CI, 0.3% to 6.4%) on misoprostol vs. 21/131 on sucralfate (16%, CI, 10.4% to 23.7%). Difference in ulcer rates: 14.4% (CI, 10.4% to 19.5%.	“In patients receiving chronic NSAID therapy for osteoarthritis, treatment with misoprostol for 3 months was associated with a significantly lower frequency of gastric ulcer formation, compared with treatment with sucralfate (P less than 0.001).”	OA patients. Study suggests misoprostol is effective compared with sucralfate.
Lanza 1988 (5.5)	Sucralfate	RCT	No COI or sponsorship mentioned.	N = 30 Healthy volunteers	No gender distribution described.  Age range 18-47.	Misoprostol 200µg vs. sucralfate 1g vs. placebo, co-administered with 650mg of aspirin 4 times a day 7 days	2 hours after medication administration	Misoprostol superior to sucralfate (p = 0.0001) and placebo (p = 0.00001). Differences in success rates between misoprostol and sucralfate and misoprostol and placebo (44%; 100%) and (61%; 100%), respectively.	“[M]isoprostol at a dose of 200µg, 4 times a day, when dosed concurrently with aspirin, was highly effective in protecting the gastroduodenal mucosae from aspirin-induced injury.”	Suggests misoprostol is superior to placebo and sucralfate. Sucralfate not blinded.
Miglioli 1996 (5.0)	Sucralfate	RCT	No COI or sponsorship mentioned.	N = 107  With arthritis	89 female, 18 male  Mean age 55.2±9.7 years	Diclofenac 200mg a day vs. naproxen 1g a day plus sucralfate gel 1gm BID  vs.  Placebo for 14 days	Repeated assessments after administration.	More GU/DU ulcers in placebo group (p <0.05). More on placebo had heartburn and epigastric pain at final evaluation (51 vs. 30% and 49 vs. 28%; p <0.05).	“Sucralfate gel reduces both the incidence of acute gastroduodenal mucosal lesions and symptoms in patients with arthritis receiving short-term nonsteroidal anti-inflammatory drugs.”	Data support efficacy in prevention.

## H2 Blockers

### Recommended.

H2-blockers are selectively recommended for treatment of TBI patients.

*Strength of Evidence* – **Recommended, Evidence (C)**

*Level of Confidence* – **Moderate**

<i>Indications:</i>	NSAID use with either risk factors for GI bleeding (e.g., elderly, diabetes mellitus, rheumatoid arthritis), or ICU stay and concerns for gastric ulcers.
<i>Benefits:</i>	Eliminates increased risk of GI bleeding from NSAIDs. May reduce risk of stress ulcers.
<i>Harms:</i>	Adverse effects of the proton pump inhibitor. Concerns for higher bacterial burden in the stomach with lack of low pH and thus increased risk of bacterial pneumonia from aspiration, making suggestions sucralfate or possibly H2 blockers may be preferable for that indication [846] [847].
<i>Frequency/Dose/Duration:</i>	Dose and frequency for proton pump inhibitors, sucralfate, and H2 blockers are as recommended by manufacturer. Duration is the extent of the NSAID therapy; use is at times permanent for those with recurrent bleeds or other complications.
<i>Rationale:</i>	<p>Risks of gastrointestinal events are also recommended for assessment, particularly including prior history of gastrointestinal bleeding and source, length of treatment, age, smoking, diabetes mellitus and other medical factors. Those with greater risk should be considered for treatment with acetaminophen, NSAID plus misoprostol, proton pump inhibitors (see below), or a COX-2 selective agent (see NSAIDs/acetaminophen evidence table) (306, 307, 342, 346, 354, 355) [848] [849-851] [852] [853].</p> <p>Gastrointestinal adverse events are generally considered the most significant of the risks of NSAIDs. A large volume of high- and moderate-quality evidence consistently shows proton pump inhibitors are effective for prevention and or treatment of gastric and duodenal ulcers and erosions.(356-365) [854], [855] [856] [857] [858] [859] [861, 881] [862] [863]) There is only one quality head-to-head trial, and it found no difference in efficacy between pantoprazole and omeprazole.(358) [855] Misoprostol has also been consistently shown to be effective compared with placebo.(366-375) [880] [815] [865] [866, 867]; [868] [869] [870] [871] Relatively fewer studies have shown sucralfate to be effective compared with placebo;(376) [882] H2 blockers appear more effective for treatment of duodenal than gastric mucosa [873] [874] [875]. There are relatively few quality trials comparing efficacy of the different classes of agents. Pantoprazole but not lansoprazole has been found modestly superior to misoprostol (315, 377) [876] [845]. No difference was found between famotidine and lansoprazole (378) [877] Misoprostol has been reported superior to ranitidine, (379, 380) [859] [864] cimetidine, [867] and sucralfate [878] [867]. In short, while the evidence is not definitive, available quality evidence suggests proton pump inhibitors and misoprostol</p>

appear superior to H-2 blockers and sucralfate. While COX-2 selective agents have generally been recommended as either third- or fourth-line medications for routine use in osteoarthritis patients, when there is a risk of gastrointestinal complications, they are often preferred. For patients at high risk of gastrointestinal bleeding, there is evidence that a combination of proton pump inhibitor plus COX-2 selective agent is efficacious [879].

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: sucralfate, critical care, intensive care unit, ICU, emergency room, ER; traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1 article in PubMed, 26 in Scopus, 0 in CINAHL, 3 in Cochrane Library, 2,185 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 1 article considered for inclusion, 0 randomized trials and 1 systematic study met the inclusion criteria.

## Evidence for the Use of H2 Blockers

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Rixen 1996 ( 7.5)	H2 Blockers	RCT	No mention of COI or sponsorship.	N = 20 with severe head injury and GCS <10	Mean age: 36 years. 8 male, 7 female	Continuous infusion of ranitidine at 6.25 mg/hr (n = 9) vs. Placebo (n = 11)	Not reported	Ranitidine increased CD4+ lymphocytes (33% to 49%; p < 0.05) and decreased CD8+ lymphocytes (41% to 27%; p < 0.05).	This study demonstrates an immunostimulatory effect of the histamine2receptor antagonist, ranitidine, both at the cellular and mediator levels in patients after head injury.”	Small sample. Data suggest ranitidine improved lymphocyte function post severe head injury pointing to an immunostimulatory effect of ranitidine.
Ehsanullah 1988 (6.0)	H2 Blockers	RCT	No mention of COI or sponsorship.	N = 297 RA or OA without lesions in the stomach and duodenum	158 female, 139 male  Mean age ranitidine group 57 years, placebo group 60 years	Ranitidine 150mg twice a day  vs.  Placebo twice a day.  NSAID drug treatment: naproxen 750mg a day; piroxicam 20mg a day; diclofenac 100mg a day; indomethacin 100mg a day.	4 and 8 weeks	Cumulative incidence of peptic ulceration at 8 weeks 10.3% (27/263); 2/135 (1.5%) developed duodenal ulceration in the ranitidine group vs. 10/126 (8%) taking placebo. Frequency of gastric ulceration same (6%) for the 2 groups at 8 weeks. Fewer gastric lesions in ranitidine group.	“Ranitidine 150 mg twice daily significantly reduced the incidence of duodenal ulceration but not gastric ulceration when prescribed concomitantly with one of four commonly used non-steroidal anti-inflammatory drugs.”	RA or OA. Also treatments with naproxen, diclofenac, indomethacin or piroxicam. Suggests ranitidine prevents DU, not GU.
Robinson 1989 (5.5)	H2 Blockers	RCT	No mention of COI. Supported partially by grant from Glaxo Inc., Research Triangle Park,	N = 144 Patients with normal endoscopic findings requiring NSAIDs	93 female, 51 male  Mean age ranitidine male 50.1±3.1 years/female 47.0±2.5, placebo male	Ranitidine 150mg twice a day  vs.  Placebo plus ibuprofen, indomethacin	Week 8	47/57 (82%) of ranitidine had no mucosal damage in the duodenum by study end vs. 32/49 (65%) on placebo.	“[R]anitidine therapy (150mg bid) was effective in preventing duodenal, but not gastric injury resulting from eight weeks of NSAID treatment.”	8 weeks treatment also included with NSAID (ibuprofen, naproxen, sulindac, indomethacin, piroxicam).

			North Carolina		45.9±3.2/female 43.1±2.0	, naproxen, sulindac, or piroxicam for 8 weeks				
Robinson 1991 (4.5)	H2 Blockers	RCT	No mention of COI or sponsorship.	N = 673 Patients receiving NSAIDs for arthritic or musculo-skeletal conditions	412 female, 261 male  Mean age 51.2 for ranitidine group, 50.7 for placebo	Ranitidine 150mg twice daily  vs.  Placebo for 4 weeks or 8 weeks.	4 and 8 weeks	Protective effect against duodenal mucosal lesions including duodenal ulcers (3 studies) and gastric mucosal lesions including gastric ulcers (1 study) observed vs. placebo.	"[R]anitidine is effective in preventing NSAID-associated duodenal ulcers and may be appropriate prophylaxis for certain high-risk patients."	4 RCTs for 4 weeks or 8 weeks treatment. Data suggests protective for DU not GU.

Magnesium is a cofactor in cellular energy metabolism and protein synthesis and is a calcium channel blocker. Magnesium increases cardiac output and cerebral blood flow. It has been used for treatment of TBI patients [883].

## Other Medications

### Magnesium for TBI Patients

**Not Recommended.**

**Magnesium is not recommended for TBI patients** [884, 885], other than magnesium-deficient patients.

*Strength of Evidence* – Acute TBI – **Moderately Not Recommended, Evidence (B)**

*Strength of Evidence* – Subacute, Chronic, pre/peri/post-operative– **Not Recommended,**

**Insufficient Evidence (I)**

*Level of Confidence* – Low

*Rationale:*

There is one high-quality trial among acute TBI patients suggesting lack of efficacy for treatment of moderate to severe TBI patients [884]. The other trial was only partially completed and was low quality [885]. With one high-quality trial suggesting lack of efficacy, magnesium is moderately not recommended for treatment of acute TBI patients. It is not recommended (insufficient evidence) for treatment of other TBI patients absent evidence of Mg nutritional deficiency.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: magnesium, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed 118 articles in PubMed, 387 in Scopus, 20 in CINAHL, 48 in Cochrane Library and 1 in other sources. We considered for inclusion 11 from PubMed, zero from Scopus, zero from CINAHL, zero from Cochrane Library, and one from other sources. Of the 12 articles considered for inclusion, 2 randomized trials and zero systematic studies met the inclusion criteria. There is 1 high-quality and 1 low-quality RCT incorporated into this analysis.

## Evidence for the Use of Magnesium

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Temkin 2007 (Score = 9.0)	Magnesium	RCT	Sponsored by the NINDS/NIH. No COI.	N = 499 Age 14 and older admitted with moderate or severe traumatic brain injury.	Mean age magnesium 34.3±16.6 years, placebo 34.4±17.8 years.	(N = 250) Magnesium sulfate 1.0-1.85 mmol/L or 1.25-2.5 mmol/L vs. (N=249) Placebo 1.0-1.85 mmol/L or 1.25-2.5 mmol/L for 5 days.	Follow-up at 1, 3, and 6 months.	No significant results for higher doses of magnesium than placebo -7 to 14; p=0.70; No significant results for lower doses of magnesium than placebo - 10.5 to -2; p=0.007; Both at 95% CI	"[W]e undertook a double-blind, single institution trial designed to test the hypothesis that magnesium supplementation given within 8 h of significant head injury would attenuate mortality and improve functioning. By using a broad array of measures, we did not prove our hypothesis."	Moderate to severe TBI. Large sample size. Data suggest lack of efficacy.

Van Norden 2005 (Score = 3.5)	Magnesium	RCT	Sponsored by the Netherlands Heart Foundation. No mention of COI.	N = 186 patients age > 18 using magnesium therapy.	Mean age magnesium 57 years, placebo 56 years.	(N = 94) Magnesium sulfate 1.0-2.0 mmol/L Vs. (N = 92) Placebo 1.0-2.0 mmol/L for 14-18 days.	Follow-up for 18 days.	64 mmol magnesium sulfate a day, serum magnesium levels of 1.0–2.0 mmol/L can easily be maintained without severe side effects (nausea, headache, and muscle weakness).	"With an intravenous dosage schedule of 64 mmol magnesium sulphate a day, serum magnesium levels of 1.0–2.0 mmol/L can easily be maintained without severe side effects for an extended period in a vast majority of patients with SAH."	Study described as partially completed trial. Sparse details
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Progesterone has been thought to have neuroprotective effects and has been used for treatment of TBI patients [886-891].

## **Progesterone for TBI Patients**

**Not Recommended.**

**Progesterone is not recommended for TBI patients.**

*Strength of Evidence (Acute, Moderate to severe) – Strongly Not Recommended, Evidence (A)*

*Strength of Evidence (Subacute, Chronic and/or Mild, pre/peri/postoperative) – Not*

**Recommended, Insufficient Evidence (I)**

*Level of Confidence – High*

*Rationale:*

There are 2 high-quality, sizable trials of progesterone for moderate to severe, acute TBI patients with neither showing benefits [892] [888] and one showing increased risk of phlebitis [892]. Two smaller-sized trials had suggested some potential benefits [889] [887]. Progesterone is either not invasive or minimally invasive, has apparent risks of phlebitis, and thrombophlebitis, is low cost, but is not shown to be effective and is thus not recommended.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: progesterone, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed 118 articles in PubMed, 387 in Scopus, 20 in CINAHL, 48 in Cochrane Library and 1 in other sources. We considered for inclusion 11 from PubMed, zero from Scopus, zero from CINAHL, zero from Cochrane Library, and one from other sources. Of the 12 articles considered for inclusion, 6 randomized trials and zero systematic studies met the inclusion criteria.

## Evidence for the Use of Progesterone

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Skolnick 2014 (Score = 9.5)	Progesterone	RCT, multinational, prospective, double-blind, parallel-group	Sponsored by BHR Pharma, a division of Besins Healthcare. No mention of COI.	N = 1179 with severe TBI. Patients had Glasgow Coma Score $\leq 8$ .	Age range 16 to 70 years.	Progesterone group (N = 591) vs. Placebo group (N = 588). Treatments were given intravenously.	Follow-up for 90 days, 180 days, and 6 months.	The primary outcome: at 6 months, the GOS score was not statistically significant between both groups [OR 95% CI: 0.96 (0.77–1.18)]. 50.4% patients in the progesterone group had favorable GOS score and 50.5% in the placebo group. 22.2% patients in the progesterone group and 22.3% in the placebo group, were in vegetable state or died.	“Primary and secondary efficacy analyses showed no clinical benefit of progesterone in patients with severe TBI. These data stand in contrast to the robust preclinical data and results of early single-center trials that provided the impetus to initiate phase 3 trials.”	Data suggest lack of efficacy.

<p>Wright 2014 (Score = 8.5)</p>	<p>Progesterone</p>	<p>RCT Double-blinded, multicenter</p>	<p>Sponsored by the National Institute of Neurological Disorders and Stroke, the National Center for Advancing Translational Sciences of the National Institutes of Health, and the Emory Emergency Neurosciences Laboratory in the Department of Emergency Medicine. COI, Dr. Wright reports receiving royalties from a patent related to progesterone for the treatment of traumatic brain injury (U.S. patents 7,473,687, 7,915,244, and 8,455,468), which is licensed to BHR Pharma.</p>	<p>N = 882 with severe, moderate to severe, or moderate acute TBI (Glasgow Coma Scale score of 4 to 12, on a scale from 3 to 15, with lower scores indicating a lower level of consciousness). Patients started with the study within 4 hours after blunt injury.</p>	<p>Age range 17 – 94 years.</p>	<p>Intravenous progesterone (N = 442) vs. Placebo group (N = 440). Treatments were administered for 96 hours.</p>	<p>Follow-up for 6 months.</p>	<p>Primary outcome: 51.0% of the progesterone group had favorable outcomes vs. 55.5% of the placebo group [-4.5 (95% CI: -11.1 to 2.1)]. Progesterone group had fewer favorable outcomes vs. placebo group according to a relative benefit of 0.95 (95% confidence interval [CI], 0.85 to 1.06; p = 0.35). At 6 months, the mortality was 17.2% in the study population, ranging from 13.0% in the moderate-injury group to 27.6% in the severe-injury group.</p>	<p>“This clinical trial did not show a benefit of progesterone over placebo in the improvement of outcomes in patients with acute TBI.”</p>	<p>Data suggest lack of efficacy and increased phlebitis</p>
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Xiao 2008 (Score = 8.5)	Progesterone	RCT, prospective	Sponsored by the Scientific Research Fund of Zhejiang Provincial Education Department, China. No COI.	N = 159 with Patients entered the study within 8 hours of injury with a Glasgow Coma Score ≤ 8.	Mean age 30 (11) years in the progesterone group and 31 (9) years in the placebo group.	Progesterone group: 1.0 mg/kg via intramuscular injection and then once per 12 hours for 5 consecutive days (N = 82)vs. Placebo group (N = 77).	Follow-up for 3 and 6 months.	At 3 mo., progesterone group had better recovery rate vs. placebo [21 (25) vs. 10 (12)], (p = 0.044). Dichotomization of GOS scores showed favorable outcomes for 47% in progesterone group vs. 31% placebo group (p = 0.034). At 6 mos., dichotomization of GOS scores showed favorable outcomes for 58% in progesterone group vs. 42% placebo (p = 0.048). At 3 and 6 mos., mean modified FIM scores were significant between progesterone group (8.02 ± 1.73 and 9.87 ± 1.17) vs. placebo group (7.35 ± 1.89 and 8.95 ± 1.05), (p	“[The] data suggest that acute severe TBI patients with administration of progesterone hold improved neurologic outcomes for up to 6 months. These results provide information important for further large and multicenter clinical trials on progesterone as a promising neuroprotective drug.”	Data suggest better outcomes with progesterone with death and disability.
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								< 0.05 and p < 0.01).		
Wright 2005 (Score = 7.0)	Progesterone	RCT	Sponsored by the National Institute for Neurological Disorders and Stroke, National Institutes of Health, and the General Clinical Research Center at Emory University and Grady Memorial Hospital. No mention of COI.	N = 36 with a closed head injury arising from blunt trauma, or a moderate to severe brain injury (Index Glasgow Coma Score [GCS] 4-12). Patients arrived in the emergency department in less than 11 hours post injury.		Progesterone infusion (N = 32, 11 females and 21 males) vs. Placebo infusion (N = 4). The treatments were administered over 12 hours and repeated every 12 hours.	Follow-up at 30 days.	The mean value for CL was found to be $1.73 \pm 0.72$ L/kg/h and was not different in men ( $1.66 \pm 0.67$ L/kg/h) and women ( $1.88 \pm 0.81$ L/kg/h). The mean value for terminal half-life was found to be $1.78 \pm 1.0$ hour.	“Using the results from this study coupled with future findings from a dose-response efficacy trial, investigators should be able to adjust infusion rates of progesterone to achieve optimal steady-state concentrations.”	Pharmacokinetic Study. No outcomes data.

Wright 2007 (Score = 6.5)	Progesterone	RCT, double-blind	Sponsored by the National Institute for Neurological Disorders and Stroke, National Institutes of Health, and the General Clinical Research Center at Emory University and Grady Memorial Hospital. No mention of COI.	N = 100 with blunt trauma. Patients arrived within 11 hours of injury with a Glasgow Coma Scale score of 4 to 12.	Mean age 35.8 (15.0) years.	Intravenous progesterone group (N = 77) vs. Placebo group (N = 23).	Follow-up for day 1, 2, 3, 4, and 30.	At day 3, the progesterone group had a lower increase in temperature vs. control group [slope= -0.0055 (95% CI: -0.010 to -0.001)]. Severe TBI patients in the progesterone group remained in a longer comma vs. the placebo group (10.1 days [95% CI: 7.7 to 12.5 days] vs. 3.9 [95% CI: 2.5 to 5.4]). 7 patients (30.4%) in the placebo group died within 30 days of the injury. Patients who enrolled with GCS score of 9 – 12, 10 of 18 (55.6%) patients in the progesterone group had a moderate good recovery vs. none of 7 in the placebo group (p = 0.0202).	“In this small study, progesterone caused no discernible harm and showed possible signs of benefit.”	Phase 2 trial. Some baseline differences. Higher death in 30d with placebo (30 vs. 13%).
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<p>Shakeri 2013 (Score = 3.5)</p>	<p>Progesterone</p>	<p>RCT</p>	<p>Sponsored by Research Deputy of Tabriz University of Medical Sciences. No COI.</p>	<p>N =76 with diffuse axonal injury. Patients had Glasgow Coma Score <math>\leq 8</math>. Patients were admitted to the hospital within 8 hours after head trauma. Mean age was <math>33.97 \pm 12.48</math> years in the case group and <math>34.68 \pm 12.87</math> years in the control group.</p>		<p>Progesterone (case group: Medroxyprogesterone tablets (every 12 hours) (N = 38) vs. Control group (N = 38).</p>	<p>Follow-up for 3 months.</p>	<p>29 patients died during hospitalization, 12 (31.6%) out of case group and 17 (44.7%) out of control group. The recovery rate was higher in the case group [10 (26.3)] vs. the control group [6 (15.8)]. The GOS score was 50% higher in the case group vs. the control group (29%). Patients with <math>5 \leq \text{GCS} \leq 8</math> in the case group had significantly higher rates of GOS score vs. the control group (<math>p = 0.03</math>).</p>	<p>“The use of progesterone may significantly improve neurologic outcome of patients suffering severe TBI up to 3 months after injury, especially those with <math>5 \leq \text{GCS} \leq 8</math>, providing a potential benefit to the treatment of acute severe TBI patients. Considering this drug had no significant side effects, so progesterone could be used in patients with severe TBI as a neuro-protective drug.”</p>	<p>Data suggest modest efficacy but sparse methodological details.</p>
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## Bromocriptine

Bromocriptine is a dopamine receptor agonist that affects D2 and partially affects D1 receptors. D2 sites reportedly are involved in head injured patients in controlling NP and NBH problems, and D2 sites affect the nigrostriatal region. When head injuries are severe and diffuse in nature, bromocriptine is purportedly beneficial [893-895] and [896].

### Bromocriptine for TBI Patients

#### No Recommendation.

**There is no recommendation for or against bromocriptine for treatment of TBI patients.**

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

There are 3 small, moderate-quality crossover trials with conflicting results regarding efficacy [893-895] and thus there is no recommendation for or against bromocriptine.

*Evidence:*

A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: bromocriptine, traumatic brain injury, brain injuries, intracranial injury, closed head injury, penetrating head injury, brain concussion, concussion, craniocerebral trauma, craniocerebral injury, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 52 articles, and considered 14 for inclusion. In Scopus, we found and reviewed 103 articles, and considered zero for inclusion. In CINAHL, we found and reviewed 22 articles, and considered zero for inclusion. In Cochrane Library, we found and reviewed 4 articles, and considered zero for inclusion. We also considered for inclusion zero articles from other sources. Of the 14 articles considered for inclusion, 3 randomized trials and 1 systematic studies met the inclusion criteria. There are 3 moderate-quality RCTs incorporated into this analysis.

### Evidence for the Use of Bromocriptine

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Se x:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Whyte 2008 (score = 5.0)	Bromocriptine vs Placebo	RCT/Crossover	Sponsored by the National Institute on Neurological Diseases and Stroke, the National Center for Medical Rehabilitation Research, and the National Institute on Child Health and Human Development. No mention of COI.	N = 22 participants with a history of TBI of at least moderate severity for at least 3 months before the study. Participants need to be able to perform tasks for 10-15 minutes semi independently.	Mean age 35.75 years.	Bromocriptine (with upward titration starting at 1.25 mg twice a day to the target dose of 5 mg twice a day during the first 3 days and then tapered for 1 week after 3 weeks of data collection)/placebo (for 3 days before data collection started for 3 weeks) (N=6) Vs. Placebo (titration of placebo to match other group with 3 weeks of data collection)/bromocriptine (titrated and tapered) (N=6) for 8 consecutive weeks with the first 4 weeks dedicated to the first treatment and the second 4 weeks dedicated to the second treatment.	Follow-up for 8 weeks	There was no significant difference between groups.	"[W]e failed to find evidence of positive effects of bromocriptine (5 mg, twice a day) on a range of measures of attentional function after moderate and severe TBI."	Moderate to severe TBI crossover. Data suggest lack of efficacy on attentional skills.

McDowell 1998 (score = 5.0)	Bromocriptine vs Placebo	RCT/Crossover	Sponsored by NIH, the McDonnell-Pew Program in Cognitive Neuroscience, and the Moss Rehabilitation Research Institute. No mention of COI.	N = 24 patients who had suffered a TBI causing concussion with a loss of consciousness more than 4 weeks before testing.	Median age 32.5 years.	2.5 mg bromocriptine followed by cognitive testing 90 minutes after pill administration Vs. Placebo followed by cognitive testing 90 minutes after pill administration. There was a separate control group from a different study that was not taking medication.	Follow-up 90-120 minutes post pill administration.	Mean dual task: counting in msec: placebo 198 v. drug 96, (p=0.028). Mean dual task: digit span in msec: placebo 539 v. drug 400, (p=0.016). Mean trail making test: 83s v. 64s, (p=0.013). Mean stroop interference test: 23s v. 38s, (p=0.05). Mean FAS test (words produced): 23 v. 31, (p=0.02). Mean Wisconsin card sorting: 2.9 v. 1.7, (p=0.041). NS between treatments for spatial delayed response task, reading span, dual task: baseline, stroop color control, trail making A, and letter cancellation test.	"[O]ur empirical findings have shown that dopamine appears to modulate executive processes which are impaired after damage to the prefrontal cortex."	Crossover. Experimental study of executive function with single dose suggests some cognition efficacy.
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McAllister 2011 (score = 4.5)	Bromocriptine vs Placebo	RCT, Prospective, double-blind, crossover	Sponsored by NIDRR and NIH. No mention of COI.	N = 26 with mild TBI and N = 31 healthy controls (HC).	The mean age was 31.8 (9.7) years in the HC group and 28.3 (11.3) years in the mTBI group.	Healthy controls (N = 31) Vs. MTBI (N = 26) 1 month after surgery, patients received bromocriptine or placebo.	Follow-up for 1, 2, 3, and 4 hours after medication ingestion.	MTBI group showed poorer 0-back (p = 0.004), 3-back (p = 0.047), and mean-back (p = 0.009) performance on bromocriptine vs. placebo. A main effect of drug was found on 0-back (p = 0.039). Drug effect both HCs and MTBI patients showing improved performance on bromocriptine (p = 0.027).	"[T]he current results remain most consistent with the conclusion that MTBI is associated with subtle dysregulation of frontal dopaminergic systems in the first 4–6 weeks after injury and that simple augmentation strategies with a dopamine agonist that affects predominantly D2 receptors may not improve cognitive functioning"	Crossover trial. Suggests bromocriptine 30days post mild TBI ineffective in improving working memory.
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Cyclosporine has been used for treatment of TBI patients [897-901]. It has been suggested that Cyclosporine is an immunosuppressant which attenuates mitochondrial dysfunction following TBI thus acting as a neuroprotective agent [901].

## Cyclosporine for TBI Patients

### No Recommendation.

**There is no recommendation for or against cyclosporine for treatment of TBI patients.**

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

There are few trials of cyclosporine for purposes of treating acute, severe TBI. Most studies are dosing or pharmacokinetic studies. There is one moderate quality trial for treatment of TBI patients and found a non-significant trend suggesting improved functional outcomes [897]. However, without clear evidence of efficacy, there is no recommendation until additional studies with sufficient power are available.

*Evidence:*

A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: cyclosporine, brain injuries, head injuries closed, head injuries penetrating, brain concussion, concussion, craniocerebral trauma, traumatic brain, intracranial, closed head, penetrating head or craniocerebral, injury, injuries, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 25 articles, and considered 6 for inclusion. In Scopus, we found and reviewed 80 articles, and considered 1 for inclusion. In CINAHL, we found and reviewed zero articles, and considered zero for inclusion. In Cochrane Library, we found and reviewed 9 articles, and considered zero for inclusion. We also considered for inclusion zero articles from other sources. Of the 7 articles considered for inclusion, 5 randomized trials and zero systematic studies met the inclusion criteria. There are 4 moderate-quality RCTs incorporated into this analysis. There is 1 low-quality RCT. There are zero systematic reviews.

### Evidence for the Use of Cyclosporine

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Hatton 2008 (score = 7.0)	Cyclosporine	RCT	Supported by National Institutes of Health Grant No. R01 NS41239-02, General Clinical Research Center US Public Health Service Grant No. M01RR02602, and Kentucky Spinal Cord and Head Injury Research Trust Grant No. 1R01NS 41239-01 (all to Drs. Young and Hatton). No COI.	N = 40 with acute severe non-penetrating TBI admitted to the Medical Center.	Mean Age was 29.5 years. 80% male.	4 Cyclosporine groups of (N = 8) vs. Placebo (N = 8). Any cyclosporine value of > 300 ng/ml in cohorts I to III and 750 ng/ml in cohort IV. Including, 50% increase in serum creatinine concentration and 50% reduction in dose for the next dosing day.	Follow-up for 6 months	No significant difference in the mortality rate between cyclosporine-treated patients (18.8% of 32 patients) and placebo-treated patients (25% of 8 patients). Outcome scores improved in 7% patients from poor to good at the 6-months assessment with no improvement in the placebo group, (p = 0.15).	“In patients with acute TBI who received cyclosporine at doses up to 5 mg/kg/day, administered intravenously, with treatment initiated within 8 hours of injury, the rate of mortality or other adverse events was not significantly different from that of the placebo group.”	Severe TBI. No differences in deaths but trend to better improvement in status with cyclosporine (p=0.15).
Empey 2006 (score = 5.0)	Cyclosporine	RCT	Supported by NIH 5R01NS041239, NIH M01 RR02602, and the Kentucky Spinal Cord and Head Injury Research Trust 1R01NS41239-01. No COI.	N= 30 patients with traumatic brain injury with a Glasgow score between 4 and 8.	Age was between 16-65 years.	Group 1- 0.625 mg/kg/dose of cyclosporine and identical amount for placebo. (N=8 CsA, 2 placebo) Group 2- 1.25 mg/kg/dose of cyclosporine and identical amount for placebo (N= 8 CsA, 2 placebo) Vs. Group 3- 2.5 mg/kg/dose of	Follow-up for 72 h.	Whole blood level concentration increased as a function of dose. Mean AUC (h* µg/L) was significantly higher in cohort 3 vs. 1 and 2; 32500 vs. 9840 and 18300 (p<0.05). The predicted maximum concentration (µg/L) of whole blood was also significantly higher in group 3 vs. group 1 and 2; 1300	“These data show patients with acute severe TBI demonstrate a more rapid clearance and a larger distribution volume of CsA. Pharmacokinetic parameters derived from this study will guide dosing strategies for future prospective clinical trials	Severe TBI. Small samples. Pharmacokinetic study. Patients not well described. No outcomes data.

						cyclosporine and identical amount for placebo (N=8 CsA and 2 placebo). All doses administered for 2 h bouts at 12 h intervals for 72 h		vs. 398 and 645 (p<0.05).	evaluating CsA therapy following acute TBI.”	
Mazzeo 2009 (score = 4.5)	Cyclosporine	RCT	Supported by the NIH-NINDS as part of project grant no. NS12587 to M.R.B. (the primary investigator), and by the Lind-Lawrence Foundation and the Reynolds Foundation. No COI.	N = 50 after traumatic injury (TBI). Mean age was 32.7 years.		Within 12 h of the injury patients received either: Cyclosporine A (CsA) 5 mg/kg over 24 h as a slow continuous infusion diluted in 250 mL of 5% dextrose (N = 37) vs. Placebo was 250 mL of 5% dextrose alone (N = 13).	Follow-up over 22-month period.	There is no statistical significance between the groups in total alkaline or bilirubin phosphatase levels. Significance difference was seen in WBC counts only at 24 h, (p = 0.02). Fisher’s exact test demonstrated that the differences between two groups was not statistically significant, at 3 and 6 months, (p = 0.7 and 0.3), respectively.	“This study demonstrates the good safety and tolerability profile of CsA when it is administered early after severe TBI with the goal of neuroprotection.”	Some baseline differences with worse GCS in cyclosporine A group. Data suggest no difference in deaths.
Brophy 2013 (score = 4.5)	Cyclosporine	RCT	Supported by NIH NINDS grant N. P50 NS 12587-27. No COI.	N= 50 patients with traumatic brain injury and a Glasgow score of 3-8. Mean age was 34 years.		Cyclosporine group- 5 mg/kg cyclosporine diluted in 250 mL DW for a 24 h continuous infusion (N=37) Vs. Control group- matching placebo with 250 mL of DW (N=10)	Follow-up for 72 hours.	Results of this study were only reported for cyclosporine group. The exposure characteristics were Cerebrospinal Fluid (CSF) and Extracellular fluid (ECF). CSF exposure achieved 0.37% of whole blood AUC, whereas ECF exposure achieved	“The exposure characteristics of CsA in TBI patients in this study were as expected based on its biochemical properties. The total blood clearance reflects that of a low extraction ratio	Secondary report of Mazzeo 2009. Severe TBI. Study of adverse effects and does not have comparative outcomes data.

								0.04% if ECF. There was correlation between ECF and CSF of (r2= 0.651).	drug, as previously reported in the literature.”	
Aminmansour 2014 (score = 3.0)	Cyclosporine	RCT	No mention of sponsorship. No COI.	N = 100 patients with diffuse axonal injury after traumatic brain injury; Mean age was 30.5 years.		Intervention Group- 5 mg/kg.24 h cyclosporine as solution in 250 mL of dextrose water. Administered 8 h after injury. (N=50) Vs. Control Group- received placebo as 250 ml DW started at the same time and continued for 24 h. (N=50)	Follow-up at 3 and 6 months .	The Glasgow outcome scale was used to assess neural improvement at follow-up. No significant differences between groups for Glasgow scores at 3 or 6 months (p>0.05). All participants showed MMSE results in either the moderate (10-19) or severe (0-9) ranges. No significant differences between groups for MMSE scores at either time point. Complete blood results showed significantly higher white blood cells in the cyclosporine group at 12 h (p<0.001).	“Our results suggest that CsA administration to patients with DAI during first 8 h after damage with the dose of 5 mg/kg for 24 h is safe and no clinically important side-effect may ensue. However, it may not bring about desired effects in terms of neuroprotection and cognitive outcome.”	Study described as RCT but methods describe matched prospective case control. Data suggest lack of efficacy.

Donepezil has been used for treatment of TBI, particularly for targeting cognitive function such as memory [902-906].

## Donepezil for TBI Patients

**Recommended.**

**Donepezil is recommended for TBI patients.**

*Strength of Evidence (Subacute, Chronic) – Recommended, Evidence (C)*

*Strength of Evidence (Acute, Pre/Peri/Postoperative) – Recommended, Insufficient Evidence (I)*

*Level of Confidence – Low*

<i>Indications:</i>	Particularly for subacute or chronic TBI with attention and/or short-term memory impairments [905].
<i>Frequency/Dose/Duration:</i>	Trial was of 10 weeks duration [905]. It is unclear if longer duration has any added benefits.
<i>Indications for Discontinuation:</i>	Adverse effects, satisfactory recovery.
<i>Benefits:</i>	Improvements in memory and attention
<i>Harms:</i>	Bowel frequency and incontinence [905].
<i>Rationale:</i>	There is one moderate-quality trial suggesting modest efficacy among subacute or chronic TBI patients for memory impairments [905]. A second trial lacked placebo control and reported comparable efficacy between Donepezil, Galantamine, and Rivastigmine [904]. Donepezil is not invasive, has low adverse effects and is thus recommended for cognitive function.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms Traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma, Aricept, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed 12 articles in PubMed, 56 in Scopus, 11 in CINAHL, 3 in Cochrane Library and 0 in other sources. We considered for inclusion 4 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library and 1 from other sources. Of the 5 articles considered for inclusion, 2 randomized trials and 2 systematic studies met the inclusion criteria. There are 2 moderate-quality RCTs incorporated into this analysis. There are 2 systematic reviews.

## Evidence for the Use of Donepezil

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Zhang 2004 (score = 6.5)	Donepezil	RCT	Sponsored by the University of Pennsylvania School of Medicine and Texas Health Science Center at San Antonio. No COI.	N = 20 with TBI mean 4mo previously to examine effect of donepezil on short-term memory and sustained attention in post-acute patients using Wechsler Memory-Scale-III (WMS-III), Paced Auditory Serial Addition Test (PASAT), Auditory or Visual Immediate Index (VII or All).	Mean ( $\pm$ SD) age 33 ( $\pm$ 2) for Group A and 31 ( $\pm$ 2) for Group B.	Group A received donepezil 5mg/d for 2 and 10mg/d for 8 weeks by mouth for the first 10 weeks, plus washout period of 4 weeks. (N = 10) vs. Group B received placebo visually identical tables, in the first 10 weeks, plus washout period, plus donepezil (N = 10).	Follow-up for 24-weeks, cross-over at 10-week.	At baseline, no significant statistical difference was observed in scores of neuropsychological testing. Patients with donepezil in group A after all treatments for All and VII, $p = 0.002$ and $p < 0.000$ . In group B, scores increased after receiving donepezil treatment. No statistically significant difference between the two groups at the week-24 assessment on either the All or VII, $p = 0.588$ or $0.397$ .	"Donepezil increased neuropsychological testing scores in short-term memory and sustained attention in post-acute TBI patients."	Post-acute TBI (subacute-chronic), mean 4mo out. Crossover trial. Data suggest modest efficacy.
Tenovuo 2005 (score = 4.5)	Rivastigmine vs Galantamine vs Donepezil	RCT	No mention of sponsorship or COI.	N=111 with clinically definitive TBI (Kay et al., 1993) with chronic sequels; fairly stable phase after trauma, at least one of the four target symptoms (fatigue, poor memory,	Mean age $40 \pm 1.3$ years	Donepezil started at 5 mg od in the morning (N=27) vs. Galantamine started at 4 mg bid morning and afternoon	No mention of study duration or follow-up time.	Mean maintenance dose: 7.2 mg od donepezil, 5.0 mg bid galantamine, 2.3 mg bid for rivastigmine. Positive response (%); 41%	"CAIs show a very promising therapeutic potential in the treatment of chronic TBI. There were no significant differences	Quasi-Randomizati onData suggest comparable efficacy between all 3 drug groups.

				diminished attention).	(N=30) vs. Rivastigmine started at 1.5 mg bid morning and afternoon (N=54). Doses raised after 1 week if no therapeutic response with good tolerability or if there was partial response and good tolerability.	donepezil, 60% galantamine, 59% rivastigmine. No differences between these drugs were found.	between the three drugs. Large-scale randomised double-blinded placebo-controlled studies are clearly needed."	
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Methylphenidate (MP) has been used to treat complications associated with traumatic brain injury (TBI) such as arousal, initiation, and attention problems. [907], as well as cognitive and behavioral impairments in some TBI patients [908-910].

## **Methylphenidate for TBI Patients**

**Recommended.**

### **Medications (including topical creams)**

**Methylphenidate is recommended for TBI patients with cognitive deficits.**

*Strength of Evidence (Subacute) – Moderately Recommended, Evidence (B)*

*Strength of Evidence (Acute, Chronic) – Recommended, Insufficient Evidence (I)*

*Level of Confidence – Moderate*

<i>Indications:</i>	Acute to subacute TBI with impaired cognitive functioning. May be reasonable to trial in those with chronic TBI who exhibit cognitive problems.
<i>Frequency/Dose/Duration:</i>	Six weeks [911]. Longer duration may be indicated for ongoing deficits, provided there are also ongoing cognitive improvements.
<i>Indications for Discontinuation:</i>	tachycardia, hypertension, excessive or intolerable harms including difficulty sleeping, decreased appetite, blunted affect, nervous habits and mannerisms, and obsessive thinking
<i>Benefits:</i>	Improved memory, attention, cognition
<i>Harms:</i>	Difficulty sleeping, decreased appetite, blunted affect, nervous habits and mannerisms, and obsessive thinking. Infrequent hypertension and tachycardia [912]
<i>Rationale:</i>	There are multiple quality trials, most suggesting benefits. One study of 2-week duration showed improved information processing speed [913, 914]. A 6-week, moderate quality treatment trial suggested improved cognitive processing and attention [911]. One study showed some benefit with even a single dose although this study had a small sample size. [102]. Methylphenidate is not invasive, has relatively low adverse effects, is not costly and is recommended for treatment of TBI patients with cognitive and attentional deficits.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: Methylphenidate, brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed dead or penetrating head or craniocerebral; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, retrospective studies, or prospective studies. We found and reviewed 54 articles in PubMed, 76 in Scopus, 29 in CINAHL, 2 in Cochrane Library and 0 from other sources. We considered for inclusion 19 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from

Cochrane Library and 1 from other sources. Of the 20 articles considered for inclusion, 15 randomized trials and 5 systematic studies met the inclusion criteria. There are 1 high- and 11 moderate-quality RCTs incorporated into this analysis. There are 2 low-quality RCTs. There are 5 systematic reviews.

### Evidence for the Use of Methylphenidate

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Willmott 2009 (score = 8.5)	Methylphenidate vs Placebo	RCT/ Cross over	Sponsored by the Victorian Neurotrauma Initiative and the Wenkart Foundation. No COI.	N = 40 with moderate to severe TBI,	between the ages of 16 and 60. Mean age 26.33±9.14 years.	Methylphenidate 0.3 mg/kg pills twice daily at 8 am and noon Vs. Placebo pills. 6 sessions over 2 weeks. Sessions were blocked in 3s. One session of each block was assigned methylphenidate and the other placebo.	Follow-up for 2 weeks	Speed measures (mean±SD) 2 & 7 automatic speed raw score (ASRS): methylphenidate 134.80±41.76 v. placebo 131.05±42.34, p=0.003. Selection attention task (SAT) reaction time (RT) simple selective attention task RT (SSAT): methylphenidate 762.18±176.33 v. placebo 800.07±200.08, (p=0.001). Four choice reaction time task (4CRT RT) dissimilar compatible RT (DC): methylphenidate 838.70±174.06 v. placebo 881.45±202.77, (p=0.003). 4CRT RT dissimilar incompatible RT (DI): methylphenidate 934.26±223.16 v. placebo 959.17±238.95, p=0.034. 4CRT RT	“[T]his study has clearly demonstrated the efficacy of methylphenidate in facilitating speed of information processing in TBI rehabilitation inpatients.”	Crossover trial. Mean 68 days since injury. Data suggest methylphenidate associated with better information processing speed. No long term results.

								similar compatible RT (SC): methylphenidate 864.55±193.79 v. placebo 911.50±231.72, (p=0.002). Symbol digit modalities task (SDMT) no correct: methylphenidate 51.80±13.45 v. placebo 50.18±12.69, (p=0.017). NS between groups for all other measures and outcomes.		
Whyte 2004 (score = 7.5)	Methylphenidate vs Placebo	RCT/Crossover	Sponsored in part, by grant R01NS39163 from the National Institute on Neurological Diseases and Stroke, National Institutes of Health, and grant R24HD39621 from the National Center for Medical Rehabilitation Research, National Institute on Child Health	N = 39 with a history of TBI for at least 3 months	between the ages of 16 and 60. Mean age 37 years.	Methylphenidate (MP) 0.3 mg/kg/dose twice a day (8:30 am and noon) Monday through Saturday with Sunday being a washout day before crossover followed by placebo alternating weekly MPPMPPMP, (N = 18) vs Placebo followed by MP (PMPMPMP, 5 days a week for 6 weeks (N = 21).	Follow-up for 6 weeks.	Initial speed – perceptually simple visual go/no-go (50% targets) median reaction time (RT), first 32 trials: p=0.03. Initial response bias – perceptually simple visual go/no-go (50% targets) response rate, first 32 trials: p=0.04. Family ratings – cognitive failures questionnaire total score: p=0.04. NS for all other measures.	“MP, in a dose of 0.3 mg/kg twice a day, seems to have clear and consistent positive effects on speed of processing and caregiver ratings of attentiveness in a highly selected sample of individuals with moderate to severe TBI.”	Repeated crossover trial. Subjects complained of attention problems. Most results negative but efficacy for cognitive processing and attention is suggested.

			and Human Development, National Institutes of Health. No mention of COI.							
Willmott 2013 (score = 7.5)	Methylphenidate vs Placebo	RCT/ Crossover	Sponsored by the Victorian Neurotrauma Initiative Pty Ltd and the Wenkart Foundation. No COI.	N = 32 moderate-to-severe TBI and N = 40 healthy controls.	Aged between 16–60 years.	Methylphenidate (MP) trial at 0.3 mg/kg twice daily for six sessions (N = 32) Vs. Placebo controls for six sessions (N = 40)	Follow-up for 2 weeks.	TBI participants performed more poorly on: SDMT / 2&7 ASRS / 2&7 CSRS / DC RT / and SI RT: (p < 0.0005 / p = 0.001 / p < 0.0005 / p = 0.005 / and p = 0.002). Performances of Val allele homozygotes: TBI performed more poorly on 7/8 measures: LNS / SDMT / 2&7 ASRS / 2&7 CSRS / SSAT RT / DC RT / and SI RT; (p = 0.044 / p < 0.001 / p < 0.001/ p = 0.002 / p = 0.030 / p < 0.001 / and p = 0.004).	“COMT allele status was not strongly associated with attentional performance or response to MP in the TBI sample.”	Crossover RCT. Experimental study. Median 47 days since injury. Genetic influences appear minor.
Kim 2006 (score = 6.5)	Methylphenidate vs Placebo	RCT	Sponsored by a grant to YHK from the Brain Research Center of the 21 <sup>st</sup> Century Frontier Research Program funded by the Ministry of Science and	N = 18 with chronic TBI, mild cognitive impairment (MMSE score 20-29), and no previous brain disorders.	Mean age 34 years.	Methylphenidate 20 mg (N=9) Vs. Placebo (N=9). Assessments at baseline, 2 hours after treatment was administered and follow-up 2 days later which was also the washout	Follow-up for 2 days.	Improvement ratio for reaction time (%) for working memory task: post drug administration test methylphenidate 13.74±13.22 v placebo 4.02±9.48 (p<0.05); post drug washout test, NS between groups.	“[M]ethylphenidate was beneficial for improving cognitive performance in patients with chronic TBI even with a single dose, as was shown from the results of this study.”	Experimental with single dose. Small sample. Chronic TBI. Data suggest efficacy though no long term data.

			Technology of Republic of Korea. No mention of COI.			period for the drugs.		Improvement ratio for accuracy (%) for working memory task: NS between groups. Improvement ratio for reaction time (%) for visuospatial attention task: NS between groups. Improvement ratio for accuracy (%) for visuospatial attention task: NS between groups.		
Alban 2004 (score = 6.0)	Methylphenidate vs Placebo	RCT/ Cross over	Sponsored in part, by grant from the National Institute on Neurological Diseases and Stroke. No mention of COI.	N = 36 with a history of traumatic brain injury for at least 3 months before enrollment between the ages of 16-60 years with a GCS score of less than N = 12 and posttraumatic amnesia for more than 1 hour.	Mean age 36 years.	Methylphenidate (MPH) (M) and placebo (P) in alternating weeks, (MPMPMP) or (PMPMPM) for 6 weeks. MPH BID at 0.3 mg/kg/dose rounded to nearest 2.5 mg. Both MPH and placebo were given orally. MPH or placebo for 6 days/week with one day (Sundays) used as washout day. All also attended an activity program 5 d/wk, Monday through Friday.	Follow-up for 6 weeks.	NS between MPH and placebo for adverse effects. Mean arterial pressure (mean±SD): MPH 95.12±10.14 v. placebo 92.63±9.411 (p=0.046). Systolic pressure: MPH 122.81±16.16 v. placebo 119.14±14.59 (p=0.024). Diastolic pressure: NS. Pulse: MPH 83.22±14.11 v. placebo 76.23±12.16 (p<0.001).	“Our findings show MPH to have few adverse effects, although our sample size of 34 participants cannot rule out uncommon adverse effects or small differences in common adverse effects between MPH and placebo.”	Methylphenidate associated with increased blood pressure and pulse. One subject discharged for hypertension.

Speech 1993 (score = 6.0)	Methylphenidate vs Placebo	RCT/ Crossover	No mention of sponsorship or COI.	N = 12 ambulatory patients with moderate to severe TBI, at least 21 years of age, high school graduate, no history of learning problems, no history of sensitivity to methylphenidate, and no history of treatment for psychiatric or neurological disorders.	Mean age 27.6 year	Methylphenidate 0.3 mg/kg bid. (8 am and noon) for 1 week followed by placebo for 1 week Vs. Placebo followed by treatment.	Follow-up at the end of the first and second weeks.	Neuropsychological test of attention / learning / cognitive processing speed and social/personality/ functioning: no statistical significance, and none of the drug/placebo comparisons approached significance, (p = NS).	"[W]hile stimulant medications are relatively safe with regard to side-effects and are well tolerated by patients, our results do not provide support for the clinical use of stimulant medications to treat the chronic neurobehavioural sequelae of closed head injury."	Crossover trial. All early post TBI. Data suggest no significant improvements on cognitive tests.
Gualtieri 1988 (score = 4.5)	Methylphenidate vs Placebo	RCT/ Crossover	No mention of sponsorship or COI.	N = 15 closed head injury (CHI) patients with a GCS <8 past the initial recovery phase.	Mean age 24.1±9.41 years.	Methylphenidate (MPH) 0.15 mg/kg bid. 8 am and noon v. MPH 0.30 mg/kg b.i.d. 8 am and noon vs. Placebo.	Patients spent 2 weeks in each condition with a 2 day washout period between conditions. MPH responders continued on the drug and had follow-ups monthly. Those that made it to 1 year on MPH (n=3)	Selective reminding test (SRT) CLTR (least square means): placebo 0.25 v. low dose MPH 0.50, p<0.024. SRT Delay CLTR: placebo 1.4 v. low dose MPH 4.8, p<0.03. SRT Sum recall: NS. SRT intrusions: placebo 9.38 v. low dose MPH 3.7, p<0.0044. SRT average trial sum: placebo 6.05 v. low dose MPH 7.17, p<0.024. SRT sum slope: placebo 0.13 v. low dose MPH	"There is some evidence, then, for short-term stimulant effects on the behavioural symptoms and cognitive deficits that occur in many CHI patients."	Crossover. Mean 47 months since injury. Data suggest most patients with favorable results, but not long term differences.

							enrolled in a reversal study.	0.38, p<0.035. SRT sums Ss linear: placebo 1.38 v. low dose MPH 4.26, p<0.029. Verbal fluency test (VFT) Perseverance A & B: placebo 3.2 v. 0.7, p<0.026. VFT Perseverance B: placebo 2.89 v. low dose MPH -0.19, p<0.0004. VFT Total correct B: NS. Continuous performance test (CPT) Omission errors: NS.		
Lee 2005 (score = 4.0)	Methylphenidate vs Sertraline vs Placebo	RCT	No mention of sponsorship or COI.	N = 30 with TBI for 2 weeks to 1 year	between the ages of 18-55.	Methylphenidate or MPD, started at 5 mg/day and increased by 2.5 mg every day until it reached 20 mg/day (N = 10) Vs. Sertraline or SER, started at 25 mg/day and was increased by 25 mg every 2 days until it reached 100 mg/day (N = 10) Vs. Placebo for 4 weeks (N = 10).	Follow-up for 4 weeks.	Hamilton Rating Scale for Depression (HAM-D) score (baseline/4 week): MPD 25.2/15.7 v. SER 27.6/20.0 v. placebo 25.7/22.3, post hoc MPD>placebo, (p=0.005), SER>placebo, (p=0.050). Recognition reaction time (ms) baseline/4 week: MPD 399.2/340.2 v. SER 405.8/389.5 v. placebo 443.8/377.3, post hoc MPD >SER, (p=0.045), placebo >SER, (p=0.026). Adverse events	“[I]t is concluded that in patients with mild to moderate TBI, both methylphenidate and sertraline had significant effects on the depressive symptoms compared with the placebo, while methylphenidate seemed to have more beneficial effects on cognitive function and daytime alertness than sertraline, at least in the 4 week treatment	Mild to moderate TBI. Dropouts unclear. Data suggest methylphenidate outperformed sertraline for attention and cognition. Both medications comparable for depression and

								were higher in the SER group compared to the MPD group, (p = 0.010).	of patients with TBI.”	superior to placebo.
Moein 2006 (score = 4.0)	Methylphenidate vs Placebo	RCT	Sponsored by a grant from Isfahan University of Medical Sciences, Department of Research. No mention of COI.	N = 40 with severe TBI (GCS 5-8) and 40 moderately TBI patients (GCS 9-12).	Mean age for treatment and control groups: 35 (17.9) / 33.7 (13.1).	Methylphenidate 0.3 mg/kg per dose (max 20 mg per dose) twice a day orally on the second day of admissions (N = 46) Vs. Control who received placebo starch pills orally twice daily (N = 39).	Follow-up with the mean hospital stay up to 13.72 days in control vs 11.12 days in treatment group.	Severe head injury ICU stay (days±SD): treatment 9.85±4.66 v. control 12.95±7.59, (p=0.06). Hospital stay (days±SD): treatment 14.1±5.99 v. control 18.35±7.75, (p=0.029). GCS on discharge: NS. Moderate head injury ICU stays: treatment 4.09±1.34 v. control 5.58±3.81, (p=0.05). Hospital stay: NS. GCS on discharge: NS. Total ICU stay: treatment 6.90±4.44 v. control 9.36±7.04, (p=0.031). Hospital stay: treatment 11.12±5.43 v. control 13.72±7.83, (p=0.043). GCS on discharge: NS.	“Methylphenidate was associated with reductions in ICU and hospital length of stay by 23% in severely TBI patients (P=0.06 for ICU and P=0.029 for hospital stay time). However, in the moderately TBI patients who received methylphenidate, there was 26% fall (p=0.05) only in ICU length of stay.”	Quasi-randomized (MRN) replaced unknown number of dropouts. Data trended towards shorter ICU stay, but significantly shorter hospital stays.
Mooney 1993 (score = 4.0)	Methylphenidate vs Placebo	RCT	No mention of sponsorship or COI.	N = 38 adult males with severe TBI that were 6	Mean age 29.45 years.	Methylphenidate building up over the first 4 weeks of the study to	Follow-up for 6 weeks.	Repeated measure univariate ANOVA (MS between/ MS within): KAS	“[T]reatment with methylphenidate was found to	Mean 27 months post injury. Some

				months or further out from their injury.	30 mg per day for the last 2 weeks (N = 19) vs. Placebo for 6 weeks total (N = 19).	<p>Belligerence 17.05/1.86, (p=0.005); STAS Trait Anger 666.12/28.96, (p=0.000); STAS State Anger 76.00/20.22, (p=0.06); POMS Anger-Hostility 320.21/24.03, (p=0.001). Mean scores on general psychopathology outcome measures pre/post treatment with methylphenidate [pre915]: OSSI-P placebo 262.91±101.76/258.94±93.28 v. treatment 331.53±101.88/260.74±106.61; OSSI-I placebo 306.81±78.50/305.19±80.09 v. treatment 342.63±85.86/269.26±70.97; KAS-General Psychopathology placebo 41.69±9.57/41.38±8.76 v. treatment 46.37±7.88/38.05±3.95. Repeated measures univariate ANOVA for each general psychopathology</p>	significantly reduce anger in brain-injured men as reflected by changes in scores on the anger outcome measures used in the study.”	baseline differences. Data suggest improvement in memory but not attention or anger.
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								outcome measure (MS between/MS within): OSSI-P 81664.79/2268.47, (p=0.003); OSSI-I 76125.79/2114.61, (p=0.001); KAS-General Psychopathology 278.17/17.08, (p=0.000).		
Plenger 1996 (score = 4.0)	Methylphenidate vs Placebo	RCT	Sponsored by the Centers for Disease Control grant. No COI.	N = 23 with moderate to moderately severe TBI or complicated mild TBI,	between the ages of 16 to 65.	Methylphenidate 30 mg/kg daily at 8 am and noon (N = 10 acute phase, N = 6 30-day and N = 5 at 90-day) vs. Placebo for 30 days with follow-up 90 days after first day of drug treatment. (N = 13 / 6 / and 4).	Follow-up at 30 and 90 days.	Disability rating scale: 30 days, (p<0.007); 90 day, NS. Continuous performance test (CPT) (Hits and Del): 30 days, (p<0.038); 90 days, NS. CPT (commissions): NS. Attention (CPT + paced auditory serial addition test (PASAT) + 2&7 + Attn/Conc from Wms-R): 30 days, (p<0.03); 90 days, NS. Declarative memory (VSR + WMS-R, Del., Gen., Vis. & Ver.): NS. Motor performance and memory (Porteus Mazes & Pursuit Rotor): 30 days, (p<0.050); 90 days, (p=0.07).	“[A]lthough early treatment of moderately severe traumatic brain injury with methylphenidate appears to hold promise, specific parameters regarding treatment need to be further identified to validate this as a viable clinical treatment.”	High dropout rate.
Whyte 1997 (score = 4.0)	Methylphenidate vs Placebo	RCT/ Cross over	No mention of sponsorship or COI.	N = 19 with TBI,	with a mean of 30.8 years	Methylphenidate or MP 0.25 mg/kg, 2 doses	Follow-up for 6 days.	Performance decrement (mean±SD): MP -	“These data suggest that MP can be a useful	Repeated crossover trial.

						per day vs. Placebo 90 minutes before task performance for 6 tasks on 6 different days.		0.07±0.56 v. placebo - 0.51±0.48, (p=0.01). Baseline: reaction time (RT): MP 634±249 v. placebo 700±279, (p=0.00). Slope of speed function: MP 94±59 v. placebo 136±71, (p=0.01). Sorting productivity (items sorted): 426±218 v. 399±205, (p=0.00). Optimal warning (ms): NS. Vigilance decrement yes rate: 0.01±0.02 v. 0.03±0.03, (p=0.01). Vigilance level RT: NS. Duration of each off-task behavior (s): 2.19±1.69 v. 3.40±2.96, (p=0.05). Minimum score RT: 540±246 v. 570±217, (p=0.05). All other performance measures: NS.	medication in TBI, by acting primarily to increase mental processing speed.”	Appears possibly related to Alban 2004, but N=19 vs. 35.
Johansson 2017 (score = 3.5)	Methylphenidate	Randomized (not placebo control)	No COI. No mention of industry sponsorship.	N= 30 participants, who suffered from long-term post-concussion	Mean age: 39.7 years; 18 females, 12 males	Participants were randomized into 3 groups: No medication (methylphenidate) Vs.	Follow up at 6 months	After six-month follow-up, effects on Mental Fatigue Scale (MFS), depression, anxiety, and cognitive	“Individuals suffering from prolonged symptoms after TBI reported reduced mental fatigue and	Small sample, not placebo controlled . Data suggest long-term

		rolle d)		symptoms after a mild TBI or moderate TBI		Low dose (5mg x 3/day) Vs. Normal dose(20 mg x 3/day) Data not given on number of participants.		function (processing speed, attention, working memory) were significantly improved compared to baseline data (P < 0.001, respectively). Heart rate was significantly increased (P = 0.01), while blood pressure was not changed.	improved cognitive functions with long-term methylphenidat e treatment. It is suggested that methylphenidat e can be a treatment option for long- term mental fatigue and cognitive impairment after a TBI, but further randomized control research is warranted."	methylph enidate use may improve post TBI fatigue but working ability did not change from baseline to 6 months post interventi on.
Johansson 2013 (score = 2.5)	Methylphe nidate	RCT	No mention of sponsorship. No COI.	N = 29 with a mild TBI and with TBI and also with pain in the neck, shoulders. Physically- well rehabilitated TBI.	Mean age for study patients was 38.6 ± 11.1.	Methylphenidate no medication, Vs. Low dose (5mg x 3) Week 1: 5mg x 1; week 2: 5mg x 2; weeks 3 5mg x 3 Vs. Normal dose (20mg x3) Week 1: 10 mg x 2; week 2: 20 mg + 10 mg + 10 mg; week 3: 20 mg + 20 mg + 10 mg and week 4: 20 mg x 3 Vs. No medication	Follow-up for 4 weeks.	Treatment significantly improved mental fatigue measured by the MFS (F = 21.7, p < 0.001). CPRS depression (F = 8.6, p = 0.001) and anxiety (F = 4.9, p = 0.010) scales also improved significantly. Pain was not significantly changed due to treatment (F = 0.127, p = 0.881).	"Methylphenidat e was well- tolerated by TBI subjects. No major adverse effects and no cardiovascular effects were detected in the present study."	Open label. Data suggest less mental fatigue with higher dose.

					short-acting Ritalin®.				
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Modafinil is primarily used for treatment of narcolepsy and hypersomnolence [916], although it has been used for other causes of somnolence including TBI.

## **Modafinil for TBI Patients**

### **No Recommendation.**

**There is no recommendation for or against modafinil for TBI patients. It is primarily used for treatment of narcolepsy and hypersomnolence [916].**

*Strength of Evidence* – No Recommendation, Insufficient Evidence (I)

*Level of Confidence* – Low

*Rationale:*

There are 3 moderate quality studies on Modafinil. One study, [917] showed some improvement in EDS and ability to stay awake but not in post-traumatic fatigue and [918] showed no benefit when compared to placebo. Thus, there is no recommendation for or against modafinil or armodafinil for TBI patients.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: Modafinil and Armodafinil, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed 11 articles in PubMed, 16 in Scopus, 0 in CINAHL, 4 in Cochrane Library and 0 in other sources. We considered for inclusion 10 from PubMed, 0 from Scopus, CINAHL, Cochrane Library and other sources. Of the 10 articles considered for inclusion, 3 randomized trials and 7 systematic studies met the inclusion criteria. There are 3 moderate-quality RCTs incorporated into this analysis. There are 7 systematic reviews.

### Evidence for the Use of Modafinil (Provigil), Armodafinil

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Kaiser 2010 (score = 7.0)	Modafinil vs Placebo	RCT-Pilot Study	No sponsorship. No mention of COI	N=20 patients with TBI who had fatigue or EDS or both.	Ages, 37 ± 9 for treatment group and 43±19 for placebo group	Modafinil group Received 1 oral capsule (100 mg per day) (N=10) Vs. Placebo (N=10)	Follow-up for every 2 weeks, and after 6 weeks.	After 6 weeks, the decrease in ESS scores was higher in the modafinil group (2.3 ± 2.3 compared with 0.7 ± 1.8 placebo group, p = 0.005 The objective measurement of the ability to remain awake at daytime under nonstimulating conditions revealed Significant increase in the ability to remain awake at daytime compared with baseline of	“[M]odafinil is effective and well tolerated in the treatment of posttraumatic EDS but not of fatigue”.	Pilot study with placebo group. Posttraumatic fatigue not improved with modafinil but EDS improved as well as ability to stay awake.

								the mean sleep latency on MWT in the treatment group (8.4±9.6 minutes) compared with the placebo group (0.4 ± 6.2 minutes) (p=0.04) Patients treated with modafinil had no change in sleep latencies compared with baseline (2.7 ± 14.7 minutes), and decreased sleep pressure compared with the placebo group (p =0.03).		
Jha 2008 (score = 7.0)	Modafinil vs Placebo	RCT/Crossover	Sponsored by the US Department of Education, Office of Special Education and	N=51 who received inpatient rehabilitation	Mean age 38.25±12.20 years.	Modafinil 100 mg 1 tablet QD at noon for 3 days	Follow-up for at least 24 weeks.	Before crossover mean±SD baseline/w	"In this randomized controlled study of	Crossover trial showed comparable efficacy between

		Rehabilitation Services, National Institute on Disability and rehabilitation Research, and Cephalon. No mention of COI.	for TBI and at least 1 year post injury.	then increased to 1 tablet BID for 11 days followed by maintenance dose of 2 tabs QAM and 2 tabs at noon for 8 weeks. Four wk washout, then crossover to placebo on same schedule (N=27) vs. placebo tabs then modafinil (n=24). All offered 4 week open label period of modafinil.	week 4 ImPACT visual motor speed composite: modafinil 23.92±5.5 2/23.49±5.36 vs. placebo 21.44±8.93/25.22±7.19 (p=0.0354) . After crossover mean±SD baseline/w eek 4 Modified Fatigue Impact: baseline/w eek 4 modafinil 39.73±20.82/28.91±19.06 vs. placebo 36.27±17.67/37.74±17.51, - 10.9±15.93 (p=0.0323) . After crossover mean±SD baseline/w eek 4/week 10	fatigue in individuals with moderate to severe TBI, there was no significant difference between treatment with modafinil and placebo over a 10-week period.”	Modafinil to placebo. Baseline comparability differences.
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								ImPACT Verbal Memory Composite : modafinil 80.26±12.95/76.58±18.18/77.41±16.52 vs. placebo 78.07±11.96/85.36±11/84/87.09±12.01 (p=0.0057 week 4, p=0.0038 week 10).		
Menn 2014 (score = 4.0)	Modafinil, (Armodafinil) vs Placebo	RCT	Sponsored by Teva Pharmaceutical Industries Ltd. COI, Menn received research funding from Teva Pharmaceutical Industries Ltd; Yang is employee of Cephalon/Teva Pharmaceutical Industries Ltd; Lankford has received research funding from Actelion, Apnicure, Arena, Cephalon, Evotec, Fisher Paykel, GlaxoSmith- Kline, Lilly, Merck, Neurim, Neurocrine, Neurogen, Organon, Pfizer, Respiroics, Sanofi-Aventis, Schering-Plough, Sepracor, Somaxon, Sunovion,	N=117 with a history of mild or moderate closed TBI (Glasgow Coma Scale score >8) in the last 1-10 years and complaint of excessive sleepiness for ≥3 months within 12 months of TBI.	Mean age 31.3±10.54 years.	Armodafinil 50 mg/day (N=30) Vs. Armodafinil 150 mg/day (N=29) Vs. Armodafinil 250 mg/day (N=29) Vs. Placebo (N=29) 12 week study.	Follow-up at weeks 2, 4, 8, and 12. There was an optional 12 month open-label extension with 150 or 250 mg/day armodafinil.	Mean sleep latency baseline to final visit: armodafinil 150 mg 2.6±4.35, 150 mg 5.0±4.95, 250 mg 7.2±6.35 min vs. placebo (p=0.0010, 250 mg vs. placebo). Clinical Global Impression of Change (CHI-C): week 4 150 mg	“Significant objective improvement in sleep latency was demonstrated for patients receiving armodafinil 250 mg/day in patients with mostly mild closed TBI.”	Sponsor terminated study early due to low enrollment. Study terminated early. Poor compliance and high dropout rate (>50%).

		<p>Takeda, Transcept, UBC, Ventus, and Vanda; Lankford is a consultant for Actelion, Apnicure, Cephalon, Cereve, Pfizer, and Somaxon and has participated in speaking engagements for Jazz Pharmaceuticals, Purdue, Sanofi-Aventis, and Somaxon. Manuscript preparation was provided by Teva Pharmaceutical Industries Ltd.</p>				<p>50% responders vs. 250 mg 50% vs. placebo 22% (p=0.0350, and 0.0469 respectively).</p>	
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## Anti-spasticity Medications (Not Including Botox)

Anti-spasticity medications are typically administered to relieve muscle pain and muscle spasms. Patients may experience post-TBI spasticity events, or side effects, that can be reduced by these agents [919-929]. Certain muscle relaxants, such as suxamethonium, offer sedative and relaxing properties without increasing intracranial pressure or reducing cerebral perfusion pressure [930].

### Anti-spasticity Medications for TBI Patients

Recommended.

**Anti-spasticity medications are recommended for treatment of TBI patients.**

*Strength of Evidence – Recommended, Evidence (C)*

*Level of Confidence – Low*

<i>Indications:</i>	For treatment of discrete indications of muscle spasticity and dystonia associated with TBI. Otherwise, can be impairing and result in slowed mentation and potentially slowed recovery.
<i>Frequency/Dose/Duration:</i>	Medications typically used for this purpose include tizanidine, dantrium, baclofen. Per manufacturer's recommendations depending upon medication
<i>Indications for Discontinuation:</i>	Drowsiness, somnolence, bradycardia, hypertension, elevated liver enzymes, constipation
<i>Rationale:</i>	There is 1 moderate RCT [931] comparing Tizanidine to placebo. It suggested improvements in spasticity and hypertonia. There are 2 moderate quality studies showing comparable efficacy. Thus, muscle relaxants are recommended for treatment of spasticity and hypertonia. They have separate indications for other sequelae of accidents (e.g., see Low Back Disorders Guideline).
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: muscle relaxants, baclofen, carisoprodol, chlorzoxazone, chlorphenesin, cyclobenzaprine, dantrolene, diazepam, medazepam, mephenesin, meprobamate, metaxalone, methocarbamol, orphenadrine, quinine, tizanidine, tolperisone, xylazine, zoxazolamine, traumatic brain injury, closed head injury, penetrating head injury, concussion, craniocerebral injury, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed 118 articles in PubMed, 423 in Scopus, 0 in CINAHL, 15 in Cochrane Library and 12 in other sources. We considered for inclusion 8 from PubMed, 3 from Scopus, 0 from CINAHL, 0 from Cochrane Library and 0 from other sources. Of the 11 articles considered for inclusion, 10 randomized trials and 1 systematic studies met the inclusion criteria. There are 3 moderate-quality RCTs incorporated into this analysis. There is 1 low-quality RCT.

### Evidence for the Use of Muscle Relaxants (not including Botox)

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Brown 1996 (score = 5.5)	Suxamethonium vs Saline	Double Blind Crossover	No mention of sponsorship or COI.	N=11 patients who obtained a severe head injury and had a Glasgow Coma score less than 8.	Mean Age 36 (17-70) years	Group 1 Received injection i.v. with 1 mg/kg of suxamethonium at a concentration of 50 mg/mL Vs. Group 2 Received injection i.v. with normal saline 0.02 ml/kg.	Follow-Up time baseline, 1, 2, 4, 6, 8, and 10 minutes after injection.	No statistical significance comparing baseline Intracranial Pressure as well as Cerebral Perfusion Pressure.	“[O]n average the administration of suxamethonium to head injured patients who are sedated with propofol and morphine infusions and are being hyperventilated does not cause an increase in ICP or a fall in CPP.”	Small sample cross-over. Data suggest suxamethonium did not lead to increased intracranial pressure or cerebral perfusion pressure compared to NS control.
Meythaler 2001 (score = 5.5)	Tizanidine vs Placebo	RCT/Crossover	Sponsored by Elan Pharmaceuticals, under and investigational drug treatment protocol. No COI.	N=17 with acquired brain injury either from stroke (N=9) or from Traumatic Brain Injury (N=8);	Mean Age 44 (19-67)	N=17 All patients received 6 weeks of either tizanidine or placebo administered orally every 3 to 4 days slightly increasing the dose until they reached 36 mg/day. After the first trial they allowed 1 week for medication tapering then the second arm	Follow-up at Baseline, 2, 4, 6, 8 weeks.	Tizanidine Phase: Lower Extremity Ashworth score baseline vs week 4; $2.3 \pm 1.4$ to $1.7 \pm 1.1$ ( $p < 0.0001$ ). Spasm score baseline vs week 4; $1.0 \pm 0.9$ to $0.5 \pm 0.8$ ( $p = 0.0464$ ). Muscle tone vs Placebo at week 6 ( $p = 0.0006$ ). Upper extremity Ashworth score baseline vs week 4; $1.9 \pm 1.1$ to $1.5 \pm 0.9$ ( $p < 0.001$ ). motor tone at	“[T]izanidine was effective in decreasing the spastic hyper-tonia associated with acquired brain injury relative to placebo. Due to side effects related to drowsiness and somnolence, there were limitations on the therapeutic dosage levels attainable in the study.”	Small sample, crossover trial. Mistake on Motor Strength Statistics p values don't line up. Data suggest tizanidine superior to placebo for spasticity/hypertonia. Increases drowsiness.

						would start the other medication.		<p>week 6; <math>1.8 \pm 1.2</math> increase (<math>p &lt; 0.0.117</math>).</p> <p>Motor Strength baseline vs week 6; <math>3.55 \pm 1.3</math> to <math>3.73 \pm 1.3</math> (<math>p = 0.0089</math>).</p> <p>Placebo Phase: Lower Extremity motor tone baseline vs week 4; <math>2.6 \pm 1.5</math> to <math>2.1 \pm 1.4</math> (<math>p = 0.0007</math>).</p> <p>Upper extremity motor tone baseline vs 4 weeks; <math>2.2 \pm 1.3</math> to <math>1.9 \pm 1.3</math> (<math>p = 0.0038</math>).</p> <p>Motor strength baseline vs week 6; <math>3.55 \pm 1.3</math> to <math>3.74 \pm 1.3</math> (<math>p = 0.0246</math>)</p>		
Bourgoin 2005 (score = 4.5)	Sufentanil vs Ketamine	RCT, Prospective	No mention of sponsorship or COI.	N = 30 with severe brain injury.	Mean age $29 \pm 12$ years in the Sufentanil group and $29 \pm 11$ years in the Ketamine group.	Sufentanil group (N = 15) vs Ketamine group (N = 15).	Follow-up for 24 hours.	ICP was $17.7 \pm 6.5$ mm Hg in sufentanil group vs. $16.2 \pm 6.4$ mm Hg in ketamine group. VMCAM value was higher in sufentanil group ( $77 \pm 21$ cm/sec) vs. ketamine group ( $60 \pm 33$ cm/sec, $p = 0.03$ ). At 6, 7, and 13 min, there was difference in BIS value	“The present study shows that the increase in sufentanil or ketamine plasma concentrations using a target controlled infusion is not associated with adverse effects on cerebral hemodynamics in patients with severe brain	Small sample. Data suggest doubling sufentanil or ketamine showed similar results and did not significantly change intracranial pressure, cerebral perfusion pressure or mean MCA velocity.

								between groups (p < 0.05).	injury. The use of target-controlled infusion could be of interest in the management of severely brain-injured patients. However, there is a need for specific pharmacokinetic models designed for intensive care unit patients.”	
Kolenda 1996 (score = 1.5)	Ketamine/Midazolam vs Fentanyl/Midazolam	RCT	No mention of sponsorship and COI.	N=35 patients who suffered a moderate or severe head injury;	Mean Age: Group 1 38 (18-72) yrs.; Group 2 29 (16-59) yrs.	Group 1 Received analgesedative therapy with 6.5 mg/kg and 65 mg/kg ketamine per day Vs. Group 2 Received analgesedative therapy with 6.5 mg/kg and 65 mg/kg fentanyl per day.	Follow-Up baseline and day 14 (final dosage) and day 1, 3, and 7 after termination of the analgesedative therapy.	Tube feeding, group 1 vs group 2, 14 day average: 824 mL/day vs 579 mL/day statistical difference at day 3, 4, 5; (p<0.05). Mean Arterial pressure (MAP) group 1 vs Group 2, day 3 and 7: 91 (76-107) vs 81 (73-107) and 95 (88-107) vs 77 (76-90); (p<0.05). Mean pulse rate group 1 vs group 2, day 2, 3, and 7: 80 (64-104) vs 56 (44-92), 74 (62-104) vs 62 (48-80), 84 (68-96) vs 68 (64-76), respectively;	“We conclude that on the one hand ketamine/midazolam analgesedation in head-injured patients is more expensive than a comparable anaesthetic therapy using fentanyl/midazolam, and this disadvantage is not countered by the earlier restitution of consciousness in the ketamine group. But with regard to risk patients for intensive therapy such as	High dropout rate due to multiple complications. Baseline differences in treatment groups. Data suggest comparable (in) efficacy.

								<p>(p&lt;0.005). Intracranial Pressure, group 1 vs group 2, day 8 and 10: 16 (14-22) vs 11 (6-18), 18 (14-22) vs 10 (6-22); (p&lt;0.05).</p>	<p>those presenting severe cardiovascular, pulmonary or gastro-intestinal problems requiring intensive medication, ketamine offers an alternative anaesthetic concept [13, 18, 30, and 34]. Its bronchodilating action as well as its stabilizing effect on circulation and gastro-intestinal motility may be of great beneficial value for these patients.”</p>
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## Migraine Headache Medications

There are other classes of migraine headache medications that are FDA-approved for treatment of migraine headaches. These include triptans and ergot alkaloids.

### Triptans and Ergot Alkaloids for Post-TBI Migraine Headaches

Recommended.

**Migraine headache medications, including triptans and ergot alkaloids, are recommended for treatment of post-TBI migraine headaches.**

*Strength of Evidence* – Recommended, Insufficient Evidence (I)

*Level of Confidence* – Moderate

<i>Indications:</i>	Post-TBI migraine headaches or post-concussive headaches.
<i>Frequency/Dose/Duration:</i>	Per manufacturer's recommendations
<i>Indications for Discontinuation:</i>	Adverse effects, intolerance, adverse effects, resolution of headaches
<i>Rationale:</i>	There are no quality trials for treating TBI patients. However, these medications have approved indications for treatment of migraines (Holland 12; Silberstein 12) and thus they are recommended for treatment of post-TBI patients.

## Antiseizure Prophylaxis (Anticonvulsants)

Posttraumatic seizures are a frequent complication accompanying traumatic brain injuries [396, 932] [933]. Antiseizure prophylactic medications have been administered following TBI to both prevent development of seizures, as well as to reduce risk of second seizures after an initial seizure occurs after TBI [396, 932-934].

### Antiseizure Prophylaxis (Anticonvulsants) for TBI Patients

**There is no recommendation for or against anti-seizure prophylaxis for severe or postoperative traumatic brain injury. Anti-seizure prophylaxis is not recommended for routine use in mild or moderate TBI patients.**

*Strength of Evidence* – **No Recommendation, Insufficient Evidence (I)** Severe TBI, Post-operative

*Strength of Evidence* – **Not Recommended, Insufficient Evidence (I)** Mild, moderate TBI

*Level of Confidence* – Low

<i>Rationale:</i>	There are no quality trials of efficacy in mild or moderate TBI patients. There is one moderate –quality study [933] suggests phenytoin prevents seizures through the first week post TBI [933]. A trial without placebo group had a trend towards more mortality in the valproate arm (13.4% vs. 7.2%, p=0.07) [935]. Another trial lacked a placebo group and suggested comparable efficacy [936]. Seizure prophylaxis is not invasive, has minimal short-term adverse effects but significant management issues over intermediate to long term and thus there is no recommendation for or against use in severe or post-operative TBI patients. Use is not recommended in mild and moderate TBI patients.
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*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed head or penetrating head or craniocerebral; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, retrospective studies, or prospective studies. We found and reviewed 8 articles in PubMed, 53 in Scopus, 2 in CINAHL, 0 in Cochrane Library and 2 in other sources. We considered for inclusion 3 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library and 1 from other sources. Of the 5 articles considered for inclusion, 3 randomized trials and 1 systematic studies met the inclusion criteria. There are 3 moderate-quality RCTs incorporated into this analysis. There is 1 low-quality RCT.

### Evidence for the Use of Antiseizure Prophylaxis

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Temkin 1999 (score = 7.0)	Seizure( Prophylaxis Phenytoin vs Valproic Acid	RCT	No mention of sponsorship or COI.	N = 379 patients admitted to a hospital with traumatic brain injury within 24 hours of injury.	Mean age; 37.3 years	1-Week course of Phenytoin (20 mg/kg) (N = 132) Vs. 1-month course of Valproate (20 mg/kg) (N = 120) Vs. 6-month course of Valproate (20 mg/kg) (N=127)	Follow-up for two years.	Levels of ALT were significantly higher in the Phenytoin group compared to either Valproate group at 1 month follow-up (p<0.02). There was no significant difference between groups for early seizures (p=0.14), however, the valproate groups showed a larger risk ratio (RR=2.9). There was also no significant differences for late seizures (p=0.27). The RR for mortality over 2 years was higher the valproate group, and it approached significance;	“Valproate therapy shows no benefit over short-term phenytoin therapy for prevention of early seizures and neither treatment prevents late seizures. There was a trend toward a higher mortality rate among valproate-treated patients.”	Data suggest comparable efficacy to prevent early seizures, though no placebo group. Valproate trended towards greater mortality (13.4% vs. 7.2%, p=0.07).

								2.0 (0.9-4.1) (p=0.07).		
Temkin 1990 (score = 6.5)	Seizure Prophylaxis Phenytoin vs Placebo	RCT	Sponsored by a grant from the National Institutes of Health (RO1-NS-19643) and the Warner-Lambert/Parke-Davis. No mention of COI.	N = 404 with a severe head injury admitted to a level I trauma center with a diagnosis of cortical contusion, subdural, epidural, or intracerebral hematoma, depressed skull fracture, penetrating head wound, seizure within 24 hours of injury, or a GCS ≤ 10;	Mean (±SD) age 34 (±18) for phenytoin group and 34 (±17) for placebo group.	Phenytoin (20 mg per kg of body weight intravenously initially, but switched to oral administration ranging from 200mg to 1200mg) group (N=208) Vs. Placebo group (N=196); Both groups received allocated treatment within 24 hours of injury.	Follow-up 1, 3, 6, 9, 12 and 24 months .	Phenytoin group had a significantly lower cumulative seizure rate (± SE) at the end of the first week compared to placebo group: 3.6%±1.3% vs. 14.2%±2.6%, (p<0.001). No significant differences reported between groups for late seizures occurring between day 8 and 2 years.	“[P]henytoin reduces the incidence of seizures in the first week after injury, but not thereafter.”	Data suggest phenytoin may prevent seizures only in first week after severe head injury.
McQueen 1983 (score=6.5)	Seizure Prophylaxis	RCT	No mention of COI. Sponsored by	N = 164 with a head injury	Total patients in each age range: 5-15 years – 43, 16-29 years – 67, 30-49 years – 34, 50-65 years – 20; 130 males, 34 females	Phenytoin group: received either 50 or 100 mg phenytoin on day of admission to trial, then children (5-15 years) received 5 mg/kg body weight, adults received 300 mg/day either in one or two doses (n=84) vs Placebo: matched with same amount as phenytoin subjects (n=80)	2 weeks, 6, 12, 15, 18, and 24 months	Only half of patients entering the trial continued medication usage for one full year. 7 patients died during this study. 11 developed post-traumatic epilepsy within one year (6 taking phenytoin, 5	“These results imply that all randomised clinical trials of prophylaxis of late onset post-traumatic epilepsy conducted to date are too small (by a factor of at least six).	Data suggest low incidence of late post-traumatic seizures following TBI but study may be underpowered to observe effects.

								taking placebo). Four patients developed seizures between 1-2 year post-injury.		
Haltiner, 1999 (score=5.5)	Seizure Prophylaxis	RCT	No COI. Sponsored by National Institutes of Health (NIH) Grant, an NIH training grant, a Clinician Investigator Development Award, and NIH Program project in head injury grant. Parke-Davis Cooperation provided partial funding to complete original study.	N=404 patients with early or late posttraumatic seizures	Age and Gender not provided.	Phenytoin Group: (n=208) received 20 mg/kg of body weight of phenytoin vs Placebo Group: (n=196) received same dose as phenytoin group with placebo	2 weeks, 2 years	Overall incidence for delayed early seizures lower in phenytoin group compared to placebo (3.6±1.3% vs. 14.2±2.6%, p<0.001). Incidence of late seizures (seizures occurring after 7 days post-treatment) did not differ between phenytoin and placebo groups (27.5±4%, 21.1±3.7%, p>0.2)	“The results of this study indicate that the incidence of early posttraumatic seizure can be effectively reduced by prophylactic administration of phenytoin for 1 or 2 weeks without a significant increase in drug-related side effects. Reduction in posttraumatic seizure during the 1st week, however, was not associated with a reduction in the mortality rate.”	Short follow-up time. Data suggest phenytoin prophylaxis reduced early seizures but did not decrease mortality.
Dikmen 2000 (score = 5.0)	Phenytoin vs Valproic Acid	RCT	No mention of sponsorship or COI.	N = 279 adult subjects who were admitted to a hospital	Mean age was 36.5 years.	1 month of Valproate (40 to 100 mg/mL) (VPA) followed by 5 months of placebo	Follow-up for 12 months	Trend for higher mortality rate in VPA groups vs. phenytoin	“Valproate (VPA) appears to have a benign neuropsycholo	No true placebo arm. Intention-to-treat was secondary analysis. Analyses

				within 24 hours of traumatic brain injury.		(N= 94) Vs. 6 months of VPA (N=91) Vs. 1 week of phenytoin (10 to 20 mg/mL) - followed by 6 months of placebo. (N=94)		group (p=0.07). No significant differences for drug effect for motor functions, attention/concentration and memory (p>0.05). The COWAT verbal skills test did show a significantly higher odds ratio (95% CI) for the drug effect; 4 (1, 8) (p=0.02). There were no other significant adverse or neuropsychological effects of VPA compared to phenytoin.	gical side effects profile, making it a cognitively safe antiepileptic drug to use for controlling established seizures or stabilizing mood.”	suggest no difference between treatments.
Manaka, 1992 (score=4.5)	Seizure Prophylaxis	RCT	No mention of sponsorship or COI.	N = 191 Patients with fresh head injuries.	Mean age: 38 ± 19.9 years for group I, 29.3 ± 19.6 years for group II; Gender not specified.	Group I: Severe head injury (N = 126) (Group IA: anticonvulsant administered (N = 50) vs group IB: control (N = 76)) vs group II: mild head injury (N = 65)	Follow-up for a duration of 5 years. Follow-up data reported at first month after injury and annually.	12.7% of group I, broken into 16% for group IA and 10.5% for group IB, and 0% of group II developed epileptic attacks. Statistically significant risk factors for epilepsy: disturbance of consciousness	“1. Phenobarbital does not have a prophylactic effect on posttraumatic epilepsy. 2. Severity of cerebral injury is proportional to incidence for posttraumatic epilepsy. 3. Consciousness,	Data suggest (in) efficacy of phenobarbital for seizure prophylaxis.

								(Relative risk or RR = 5.36, p < 0.01), neurological sign (RR = 4.79, p < 0.01), abnormal CT findings (p < 0.05), intracerebral hematoma (RR = 3.74, p < 0.05)	abnormal CT finding, neurological sequelae and/or intracerebral hematoma were potential factors for attack and, above all, multiplicity of risks was an important risk for posttraumatic epilepsy."	
Dikmen 1991 (score=4.0)	Seizure Prophylaxis	RCT	Sponsored by the National Institutes of Health, Bethesda, MD, the National Center for Health Services Research Office of the Assistant Secretary of Health, Rockville, MD, and Warner-Lamber/Parke-Davis, Morris Plains, NJ. Warner-Lamber/Parke-Davis provided the drug treatments used.	N = 244 with moderate to severe head injuries	Mean age: 30.9 for phenytoin group, 32.9 for placebo group; 152 males, 92 females.	Phenytoin group: received phenytoin for one year, 15% received <3 µmol/L, 36% received 3-6 µmol/L, and 48% received >6 µmol/L (n=208) vs Placebo group: received placebo for one year (n=196)	1, 12, and 24 months	Phenytoin group performed more poorly across most neuropsychological Measures (Overall rank-sum-type test, p<0.05) at 1 month.	"Our findings do not negate phenytoin's proven efficacy in controlling established seizures nor do they indicate that its cognitive effects are worse than other anticonvulsant drugs."	Data suggest cessation of phenytoin resulted in improved cognition in all groups and prevented posttraumatic seizures in severe TBI patients but moderate and mild TBI patients had unclear benefit from phenytoin.

Murri, 1980 (score=4.0)	Seizure Prophylaxis	RCT	No mention of sponsorship or COI.	N=90 patients with seizures from serious head injury	Mean age: 63 years; 64 males, 26 females	Group 1: (n=) received 0.5-1.5 mg/kg/day of phenobarbital vs Group 2: (n=) received 1.6-2.5 mg/kg/day of phenobarbital	Baseline, and every 6 months for 2 years	Lower incidence of PTE in participants showed efficient prophylactic effect. Lower dosage of PB showed a favorable effect with only 2 patients having seizures. Twenty-three percent of 88 patients that did not develop seizures showed anomalies even 2 years after trauma.	"In conclusion, our data support the validity for of PB prophylaxis for PTE. However our follow-up was limited to 2 years and it is known that in this period seizures may occur in 70-80% of patients [3, 10, 18]. Thus, the possibility observed of a delayed onset of epilepsy in these patients, and observed in one subject, cannot be excluded."	Data difficult to interpret due to the variable doses of phenobarbital administered. However, there appears to be some benefit from phenytoin prophylaxis 2 years post injury.
Bertch, 1985 (score=3.5)	Seizure Prophylaxis	RCT	No mention of sponsorship or COI.	N = 267 head injury patients.	Mean Age: Not specified, age range from 18 months to 81 years; Gender not specified.	Phenyton (N = 151) vs placebo (N = 116)	Follow up at baseline, 1 week, 1,3,6,9, 12,15,18,21, and 24 months	Difference in serum calcium levels statistically significant at visit 8 (p = 0.04) and visit 9 (p = 0.02) for control vs phenytoin patients. No significant difference for phosphorus or folate levels.	"Further studies considering the effects of longterm phenytoin therapy on laboratory indices are suggested."	Data suggest phenytoin infusion for seizure prophylaxis does not negatively impact laboratory values.

Young 1983 (score = 3.0)	Phenytoin vs Phenobarbital	RCT	No mention of sponsorship or COI.	N=214 patients with traumatic brain injury.	Mean age; 25.1 years.	Phenytoin Group (10 to 20 µg/ml) (N=98) Vs. Phenobarbital Group-If patients did not react well with phenytoin they were switched to this group (N=21) Vs. Placebo Group (N=95)	Follow- up for 18 months .	No significant difference between phenytoin and phenobarbital groups for patients having late seizures (p=0.48). Drug group as a whole did not show lower risk for late seizures vs. placebo (p=0.75). Median time to death was 16 days in drug group and 14.5 days in placebo group, (p=0.30).	“It cannot be concluded that higher phenytoin plasma concentrations and higher compliance rates than obtained in this study would not have significantly decreased the occurrence of late post- traumatic epilepsy.”	Sparse methods. Data suggest phenytoin not effective compared with placebo to prevent seizures.
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## Antidepressants

Antidepressants treat depressive disorders and conditions by inhibiting the uptake of certain molecules in the brain. Many studies have shown an association between this kind of head injury and depression [937-943] [944]. Antidepressants include SSRIs, MAOIs, SNRIs, rMAO-A-inhibitors, TeCAs, NaSSAs and TCAs. When addressing TBI and depression, certain drugs, such as Sertraline, have shown benefit in addressing neurobehavioral and emotional problems, but has little effect on behavioral and cognitive issues [937]. Another study addressing depression after TBI with sertraline found improved recent verbal memory, visual memory, psychomotor speed and general cognitive efficiency [942]. Evidence remains conflicted for recommendation as other investigators have found sertraline not as effective as methylphenidate for improving cognitive function [941]. Another study aimed to reduce the incidence of depression within the first year of traumatic brain injury showed no beneficial results when Sertraline was discontinued [939].

### Antidepressants for TBI Patients

**Recommended.**

**Anti-depressants are recommended for treatment of TBI patients with depressive symptoms or depression.**

*Strength of Evidence – Recommended, Insufficient Evidence (I)*

*Level of Confidence – Low*

<i>Indications:</i>	For the treatment of depression in TBI patients
<i>Benefits:</i>	Improvement in depressive symptoms in TBI patients.
<i>Harms:</i>	Intolerance, nausea, increased appetite, weight gain, fatigue, drowsiness, insomnia, dry mouth, blurred vision, drug-drug interactions
<i>Frequency/Dose/Duration:</i>	Per manufacturer's recommendations
<i>Indications for Discontinuation:</i>	Resolution of or significant improvement in depressive symptoms.
<i>Rationale:</i>	There are 6 moderate quality studies with mixed results; 2 suggesting efficacy [943],[938]) and 3 suggesting lack efficacy [940, 945], [946]. Thus, evidence specific to TBI is limited. Anti-depressants are not invasive, have some adverse effects and are low to moderate cost. They are indicated for treatment of depression or depressive symptoms.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: antidepressants, traumatic brain injury, closed head injury, penetrating head injury, concussion, craniocerebral injury, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed 47 articles in PubMed, 69 in Scopus, 6 in CINAHL, 27 in Cochrane Library and 5 in other sources. We considered for inclusion 12 from PubMed, 2 from Scopus, 0 from CINAHL, 0 from Cochrane Library and 2 from other sources. Of the 12 articles considered for inclusion, 8 randomized trials and 4 systematic studies met the inclusion criteria. There are 6 moderate-quality RCTs incorporated into this analysis. There is 1 low-quality RCT.

## Evidence for the Use of Antidepressants

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Rappoport 2010 (score = 7.0)	Citalopram vs Placebo	Double Blind RCT	Sponsored by Ontario Neurotrauma Foundation and Ontario Mental Health Foundation.	N=21 subjects were randomized after completing an open label citalopram treatment for major depression from TBI;	Mean Age 46.67 ± 19.9	Group 1 (N=10) patients who were given the active drug citalopram Vs. Group 2 (N=11) patients who were given placebo treatment	Follow-up every month for 40 weeks.	Group 1 vs 2, relapse rates during 40 week intervention: 5 (50%) vs 6 (54.5%) no significant difference between groups. No significant difference between groups for time of relapse.	“This study highlights the relatively high risk of relapse within depression after TBI and raises questions about the effectiveness and potential limitations of citalopram continuing treatment in preventing relapse of major depression.”	Similar relapse rates between citalopram vs. placebo, suggesting lack of efficacy.
Ashman 2009 (score = 6.5)	Sertraline vs Placebo	Double Blind RCT	Sponsored by the National Institute of Disability and Rehabilitation Research, United States Department of Education, and Pfizer Pharmaceutical Company. No COI.	N = 41 6 month post injury TBI patients also diagnosed with depression;	Mean Age 49.1 ± 10.9	Group 1 (N =22) patients who were given Sertraline. Dosage determined by physicians vs. Group 2 (N =19) patients given a placebo.	Follow-up at wk 2, 4, 6, 8, and 10.	Group 1 vs 2, Depression prevalence after 10 wk intervention: 18% vs 37%. Group 1 vs 2, percent of treatment respondents (HAM-D score decrease by 50%): 59% vs 32% (p=0.15). Group 1 and 2, pre vs post intervention, Depression: 26.4 ± 7.5 vs 14.9 ± 9.6 (p<0.001). Anxiety: 21.9 ± 14.9 vs 11.9 ± 11.6 (p<0.001). Quality of Life (QOL): 2.8 ± 0.9 vs 5.7 ± 6.7 (p<0.01).	“Both groups showed improvements in mood, anxiety, and QOL, with 59% of the experimental group and 32% of the placebo group responding to the treatment, defined as a reduction of a person’s HAM-D score by 50%.	High drop-out rate. Both groups showed improvements in mood and QOL. Trend toward better HAM-D response than placebo (50% reductions 59% vs. 32%), but not

								Group 1 vs 2, HAM-D scores (HamGScale): 8.16 ± 0.48 vs 9.62 ± 0.52 (p=0.04).		significant (p=0.08).
Novack 2009 (score = 5.0)	Sertraline vs Placebo	Double Blinded RCT	Sponsored by the national institute of Disability and Rehabilitation Research Grant. No COI.	N=99 patients who had TBI and GCS score below 12;	Mean Age: Group 1 35.3 ± 16.7; Group 2 34.5 ± 15.6	Group 1 (N=49) Treatment group Sertraline 50mg QD Vs. Group 2 (N=50) Placebo group	Follow-up on phone weekly for 3 months, monthly after for another 9 months. In hospital visits at 3, 6, and 12 months.	Group 1 vs 2, diagnosis of depression during 90 day intervention: 0 new cases vs 5 (10%) new cases X <sup>2</sup> =5.16, (p=0.023). No significant difference in depression diagnosis throughout the year between groups. Group 1 vs 2, Hamilton Depression Rating Scale (HDRS) >6 prevalence: 6.7% vs 25% X <sup>2</sup> =4.1, (p=0.04). Group 1 vs 2, Neurobehavioral Functioning Inventory, 3 months: 89.0 ± 11.4 vs 96.0 ± 14.0 (p<0.05).	“Sertraline is effective in diminishing depressive symptoms even among those not clinically depressed while the medication is being taken. However, the results do not support the idea that administration early in recovery diminishes the expression of depressive symptoms after the drug is stopped. There is no basis from this study to assume that sertraline administered early in recovery after TBI, when neurotransmitter functioning is often altered, has ongoing effects on the serotonin system after sertraline is discontinued.”	Data suggest lack of efficacy between groups.

Banos 2010 (score = 4.5)	Sertraline vs Placebo	Double Blind RCT	Sponsored by the national Institute on Disability and Rehabilitation Research Grant.	N=99 patients with moderate to severe TBI; Mean Age: Group 1 35.3 ± 16.7; Group 2 34.5 ± 15.6		Group 1 (N=49) Sertraline 50 mg QD. Vs. Group 2 (N=50) given placebo.	Follow-up at 3, 6, and 12 months.	Group 1 vs Group 2, Wisconsin Card Sorting Test-64 results at month 3: 78.25 ± 18.7 vs 92.7 ± 15.4 (p<0.006). No other significant differences between sertraline and placebo group throughout study.	"Sertraline does not appear to prevent development of cognitive and behavioral problems following TBI, although this does not negate evidence for the treatment (as opposed to prophylactic) role of sertraline to address emotional and neurobehavioral problems in individuals with TBI."	High drop outs in sertraline group. Data suggest early administration of sertraline does not prevent cognitive and behavioral problems for moderate to severe TBI in the first year post-injury.
Wroblewski 1996 (score = 4.0)	Desipramine vs Placebo	RCT	No mention of sponsorship or COI.	N=10 patients with severe traumatic brain injury who were suspected of having depression; Mean Age: Group 1 30; Group 2 33		Group 1 (N=6) Desipramine Vs. Group 2 (N=4) patients treated for placebo for 1 month, if no improvement, they crossed over to desipramine.	Follow-up at 1 month and 2 months.	6 patients (60%) showed a complete resolution from depression after 1 month of desipramine. Group 1 vs 2, improvement over time: Group 1 recovered faster (p=0.001). Side effects: 1 patient had a seizure, 1 had mania, and 2 had minor seizures that were resolved by lowering the dosage.	"Results ... demonstrate the clinically significant effectiveness of desipramine in treating long-standing depression in a series of patients with severe traumatic brain injury, as rated with DSM-III-R criteria; show statistically significant improvement on affect/mood scale data, favoring the treated versus	Very small samples. Data suggest desipramine may be of modest benefit for longstanding depression associated with TBI.

									untreated(Placebo lead-in) group.”	
Lee 2005 (score = 4.0)	Sertraline vs Methylphenidate vs Placebo	Double Blind RCT	No mention of sponsorship or COI.	N=30 patients with mild to moderate TBI; Mean Age: Group 1 35.3 ± 8.0; Group 2 33.6 ± 12.3; Group 3 35.5 ± 7.2		Group 1 (N=10) patients that were given 5 mg/day Methylphenidate (MPD), increase to 20 mg/day after 1 week; Group 2 (N=10) Patients that were given Sertraline (SER) (25mg/day increased to 100 mg/day); Group 3 (N=10) patients that were given placebo treatment	Follow-up at baseline and 4 weeks.	Significant improvement in all groups for HAM-D, Beck Depression Inventory (BDI) and Quality of Life scale, (p<0.05). Group 1 vs 2 vs 3, Rivermead Postconcussion Symptoms Questionnaire (RPQ) baseline/4 weeks: 38.0 ± 7.8/24.8 ± 10.0 (p<0.001) vs 32.0 ± 10.2/30.3 ± 9.4 (NS) vs 39.4 ± 8.8/30.4 ± 10.7 (p<0.05). Group 1 vs Group 3, post hoc analysis group x time of Hamilton Rating scale for Depression (HAM-D): (p=0.005). Group 2 vs Group 3, post hoc analyses group x time HAM-D: (p=0.05). Group 1 vs Group 2, adverse effects: 6 vs 13 (p<0.01). Cognitive function tests revealed Group 1 and 3 were superior to group 2. (p<0.045). Group 1 vs 2 vs 3, Recognition	“At the present stage, it is concluded that in patients with mild to moderate TBI, both methylphenidate and sertraline had significant effects on the depressive symptoms compared with the placebo, while methylphenidate seemed to have more beneficial effects on cognitive function and daytime alertness than sertraline, at least in the 4 week treatment of patients with TBI.”	Mild to mod. TBI. Dropouts unclear. Data suggest MP outperformed sertraline for attention and cognition.

								Reaction Time (RRT) baseline/4 wks.: 399.2 ± 51.2/340.2 ± 34.5 vs 405.8 ± 56.7/389.5 ± 61.3 vs 443.8 ± 60.7/377.3 ± 37.3 (p<0.021) group x time effect.		
Meythaler 2000 (score = 2.0)	Sertraline vs Placebo	Prospective Cross-Over RCT	Sponsored by grants from the UAB Injury Control and Research Center and Pfizer.	N=9 subjects with GCS score less than 7 after TBI injury (motor vehicle accident induced TBI); Mean Age N/A (14-65)		Group 1 (N=6) patients who were given the active drug Sertraline (50 mg/day increased to 100 mg/day). Vs. Group 2 (N=3) patients who were given placebo treatment.	Follow-up after 2 weeks.	Group 1 vs 2, Orientation Log score, baseline/2 wks.: 8.6/12.2 vs 7.7/21.7 placebo group recovered faster (p<0.0042). Agitated behavior Scale did not significantly improve for either group. No significant difference in improvement for Galveston orientation and amnesia test [252].	“This pilot study fails to establish whether the early use of sertraline may improve alertness, decrease agitation or improve cognitive recall of material. This may be due to the small size of the study group, the brief duration of treatment or by a skewed placebo group. Larger studies will be required to prove any efficacy. There were no complications with its use and sertraline did not demonstrate a detrimental effect on recovery. This indicates that sertraline may be safe to use in the treatment of psychiatric or behavioral	Small sample, pilot study. Most subjects could not be followed for cross over so it was analyzed with regard to rate of recovery. Data suggest sertraline did not improve arousal/alertness.

									complications attributable to TBI.”	
Saran 1985 (score = 2.0)	Amytryptiline vs Phenezine	Prospective RCT	No mention of sponsorship or COI.	N=22 patients who either had secondary or primary depression; Mean Age: Group 1 42 (36-58); Group 2 44.2 (26-58)		Group 1 (N=10) patients who had secondary depression due to a minor traumatic brain injury Vs. Group 2 (N=12) control group whom had depression primarily and did not acquire a closed head injury	Follow-up Patients were evaluated every week for 8 weeks. First four weeks amitriptyline was given, if no improvement then patients were given phenelzine.	Group 1 vs 2, Dexamethasone suppression Test failure rate: 10% vs 91% (p<0.001). Group 1 vs Group 2, Hamilton Depression rating Scale (HAM-D) during amitriptyline: Group 2 improved, none of Group 1 did not (p<0.001). Group 1 and 2, Phenezine treatment, wk 1-4 HAM-D score change: Not significant.	“In summary, our results suggest that DST nonsuppression may be useful biologic marker in disguising primary depression with melancholia from depression with melancholia after closed head injury, and amitriptyline and phenezine have limited use in patients with depression after minor closed head injury.”	No placebo comparison. Small sample sizes. Data suggest both amitriptyline and phenytoin have limited benefit in depression with melancholia post TBI and not different between them.

## Atypical Antipsychotics

Atypical antipsychotics have been used to treat psychotic disorders [947]. These drugs are classified as atypical due to an association with lower risk of causing extrapyramidal signs and symptoms (EPS) [948, 949]. Controversy surrounds the usage of these drugs for TBI treatment [950].

### Atypical Antipsychotics for TBI Patients

#### Recommended.

**Atypical antipsychotics are selectively recommended for treatment of TBI patients with agitation from mood disorders.**

#### *Strength of Evidence – Recommended, Insufficient Evidence (I)*

#### *Level of Confidence – Low*

<i>Indications:</i>	For the treatment of agitation in TBI patients with mood disorders
<i>Benefits:</i>	Improvement in agitation and mood disorder symptoms in TBI patients.
<i>Harms:</i>	Intolerance, weight gain, fatigue, drowsiness, insomnia, dry mouth, blurred vision, drug-drug interactions. Caution is warranted in those with hypothalamic pituitary dysfunction.
<i>Frequency/Dose/Duration:</i>	Per manufacturer's recommendations
<i>Indications for Discontinuation:</i>	Resolution of or significant improvement in agitation. Development of hypothalamic pituitary dysfunction.
<i>Rationale:</i>	There are no quality studies for the use of atypical antipsychotics to treat agitation in TBI patients. Some data suggest efficacy [951-954]. Atypical antipsychotics are not invasive, have some adverse effects and are low to moderate cost. Thus, these medications are recommended but lack sufficient evidence.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Valporic Acid, Depakote, Atypical Antipsychotic, Agitation; Traumatic brain injury, Intracranial injury, Closed Head injury Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma; Sensitivity, Specificity, Predictive Value of Tests, Gold-standard, accurate, accuracy, precision, precise, test controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 0 articles in PubMed, 1 in Scopus, 0 in CINAHL, 1 in Cochrane Library, 6 in Google Scholar, and 0 from other sources. Zero Articles met the inclusion criteria.

## Mood Stabilizers

Structural brain changes, cognitive and functional decline, and poor treatment response are all characteristics of neuropsychiatric disorders. Mood stabilizers such as lithium are theorized to upregulate numerous neuroprotective pathways in order to inhibit the functional and structural decline of the brain [955].

### Mood Stabilizers for TBI Patients

There is no recommendation regarding mood stabilizers for treatment of TBI patients. There may be other indications for treatment with these agents.

#### No Recommendation.

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

There are no quality studies for the use of mood stabilizers to treat TBI patients. Lithium may be indicated for treatment of mania and bipolar disorders that are beyond the scope of this guideline. Thus, there is no recommendation for or against the use of lithium for treatment of TBI patients.

*Evidence:*

Mood stabilizers – A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Mood Stabilizers, Lithium; Traumatic Brain Injury, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2 articles in PubMed, 7 in Scopus, 1 in CINAHL, 0 in Cochrane Library, 5,170 in Google Scholar, and 0 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 4 articles considered for inclusion, 0 randomized trials and 4 systematic studies met the inclusion criteria.

## Benzodiazepines

Benzodiazepines are typically used to treat anxiety, depression, panic attacks, nausea, seizures, vomiting and muscle spasms, but can also be used for sedation [956-959]. After experiencing a traumatic brain injury, benzodiazepines have been used to provide sedation before procedures, but effectiveness over other sedative agents is purportedly unclear [956-960].

### Benzodiazepines for TBI Patients Sometimes Recommended.

**Benzodiazepines are not indicated for treatment of TBI patients. Benzodiazepines are selectively recommended for treatment of TBI patients with discrete indications including anxiety, spasticity secondary to TBI and persistent vestibular dysfunction.**

*Strength of Evidence – Recommended, Insufficient Evidence (I)*

*Level of Confidence – Low*

<i>Indications:</i>	Not for use solely for TBI. Uses include discrete issues with anxiety, panic attacks, agitation, insomnia, alcohol withdrawal. As benzodiazepines impair memory and cognitive recovery, those TBI patients requiring a course of benzodiazepines after TBI (e.g., alcohol withdrawal) should be tapered as soon as practical.
<i>Benefits:</i>	Reduction in anxiety, panic attacks, hysteria. Reduced risk of seizures with alcohol withdrawal
<i>Harms:</i>	Respiratory sedation, CNS depression, confusion, dizziness, addiction, dependency.
<i>Frequency/Dose/Duration:</i>	As per manufacturer's recommendations
<i>Indications for Discontinuation:</i>	Sufficient resolution of the symptoms that necessitated treatment.
<i>Rationale:</i>	There are few quality studies evaluating benzodiazepines in TBI patients. There is only 1 moderate quality study [958] finding comparable efficacy between midazolam and propofol. No studies are compared to placebo. Thus, evidence specific to TBI is limited. Benzodiazepines are not invasive, have some adverse effects and are low to moderate cost. They are not indicated for treatment of TBI. However, they may have discrete indications for treatment of anxiety, agitation, panic attacks, insomnia or alcohol withdrawal symptoms.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed head or penetrating head or craniocerebral; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, retrospective studies, or prospective studies. We found and reviewed 37 articles in PubMed, 14 in Scopus, 1 in CINAHL, 1 in Cochrane Library and zero in other sources. We considered for inclusion 5 from PubMed, zero from Scopus, zero from CINAHL, zero from Cochrane Library and zero from other sources. Of the 5 articles considered for inclusion, 3 randomized trials and 2 systematic studies met the inclusion criteria. There is 1 moderate-quality RCT incorporated into this analysis. There are 2 low-quality RCTs.

## Evidence for the Use of Benzodiazepines

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Ghori 2007 (score = 4.5)	Midazolam vs Propofol	RCT	Sponsored by the Dept. of Anaesthesia and Intensive Care Medicine, Cork University Hospital. COI, George D Shorten employed by Dept. of Anaesthesia and Intensive Care Medicine at Cork University.	N = 28 TBI patients with GCS score < 9;	Age range 18-65 years.	Midazolam 0.1–0.3mg/kg/h (N = 15); Propofol 1.5–5mg/Kg/h (N = 13); Both groups received morphine sulfate (0.1–0.2mg/kg/h)	Follow-up at baseline, day 1-5, and month 3.	Midazolam vs propofol Serum s100β concentrations (Mean, [SD]); Day 1, (0.99 ± 0.81) vs (0.41 ± 0.4)μg/L; Day 2, (0.80 ± 0.81) vs (0.41 ± 0.24) μg/L; Day 3, (0.52 ± 0.55) vs (0.24 ± 0.25) μg/L; and Day 4, (0.54 ± 0.43) vs (0.24 ± 0.35) μg/L; (p < 0.05)	“Plasma concentrations of neurological injury markers were similar in patients who received midazolam and propofol. Patients with poor neurological outcomes had consistently higher serum s100β.”	Methodological details sparse. Small sample size. Many medications given.
Tanguy 2012 (score = 3.5)	Midazolam vs Propofol	RCT	Sponsored by Programme Hospitalier de Recherche Clinique (PHRC) of Rennes. No COI.	N = 36 with severe TBI.	Mean age 35 – 18 years.	Propofol (N = 15) vs. Midazolam (N = 14)	Follow-up for 72 hours and 12 months.	No difference between propofol and midazolam in the cerebral L: P ratio (time effect p = 0.201, treatment effect p = 0.401, time x treatment interaction p = 0.101).	“[The] results indicate that there is no difference between the effects of propofol and midazolam sedation on the cerebral metabolic profile during the acute phase of severe TBI. Accordingly, the use of propofol as a sedative agent in	Small sample size. Methodological details sparse. Relatively invasive monitoring using cerebral microdialysis catheter. High complication rate.

									TBI and its neuroprotective effects warrant further investigation."	
Sanchez-Izquierdo-Riera 1998 (score = 3.0)	Midazolam vs Propofol vs Combination	RCT	No mention of sponsorship or COI	N = 100 with TBI requiring mechanical ventilation for at least 48 hours;	mean age 35.4 ± 16.6 years.	Group A midazolam 0.1 mg/kg/ hr with max. dose of 0.35 mg/kg/hr. (N = 34); Group B propofol 1.5 mg/kg/hr with max. dose 6 mg/kg/hr. (N = 33); Group C combination of midazolam and propofol in doses similar to above groups. (N = 33)	Follow-up at baseline, hour 3, 6, 12, and 24 after sedation stoppage.	Wake-up time significantly increased in Pf groups. Group A (660 ± 400 min) vs Group B (110 ± 50 min) vs. Group C (190 ± 200 min), (p < 0.01).	"...Mz and Pf, used alone or in combination, are safe and effective in the sedation of critically ill trauma patients.	Methodological details sparse. Large number of therapeutic failures.

## Corticosteroids

Corticosteroids has been used for treatment of acute TBI. The effect of corticosteroids on the risk of death has been reported in a past [961].

### Corticosteroids for TBI Patients

**Moderately Not Recommended.**

**Glucocorticosteroids are moderately not recommended for treatment of TBI.**

*Strength of Evidence – Moderately Not Recommended, Evidence (B)*

*Level of Confidence – Moderate*

*Rationale:*

There are 6 moderate quality studies involving glucocorticosteroids and 5 of these report lack of efficacy [962] [963, 964] [965] and [966]. Neither morbidity nor mortality was improved by the steroid. Steroids have evidence of efficacy for traumatic hyphema (see Eye Guideline). Glucocorticosteroids are either not invasive or minimally invasive depending on route of administration, have adverse effects, are low cost, but are not effective and thus are not indicated for treatment of TBI.

*Evidence:*

A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: corticosteroids, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 390 articles, and considered 5 for inclusion. In Scopus, we found and reviewed 39 articles, and considered 1 for inclusion. In CINAHL, we found and reviewed 5 articles, and considered zero for inclusion. In Cochrane Library, we found and reviewed 75 articles, and considered zero for inclusion. We also considered for inclusion zero articles from other sources. Of the 6 articles considered for inclusion, 6 randomized trials and zero systematic studies met the inclusion criteria. There are 5 moderate-quality RCTs incorporated into this analysis.

## Evidence for the Use of Corticosteroids

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Roberts 2004 (score = 7.5)	Methylprednisolone vs Placebo	RCT	Sponsored by the UK Medical Research Council, Pharmacia and Upjohn. No COI.	N= 10,008 Adults with head injury a Glasgow coma score (GCS) of 14 or less within 8 h of injury	Mean age= 37 years (SD 17)	48 h infusion of corticosteroids (methylprednisolone) (N=5007) Vs. Placebo (N=5001)	Follow up period was 6 months. Primary outcomes were death within 2 weeks of injury and death or disability at 6 months.	Compared with placebo, the risk of death from all causes within 2 weeks was higher in the group allocated corticosteroids (1052 [21.1%] vs 893 [17.9%] deaths; relative risk 1.18 [95% CI 1.09–1.27]; p=0.0001). The relative increase in deaths due to corticosteroids did not differ by injury severity (p=0.22) or time since injury (p=0.05).	“[O]ur results show there is no reduction in mortality with methylprednisolone in the 2 weeks after head injury. The cause of the rise in risk of death within 2 weeks is unclear.”	Data suggest IV corticosteroids did not reduce mortality 2 wks.after TBI.
Braakman 1983 (score = 6.0)	Dexamethasone vs Placebo	RCT	No mention of industry sponsorship or COI.	N = 161 patients after a non-missile-related head injury.	Mean age not reported	High-dose dexamethasone phosphate group (N =81) Vs. Placebo group (N =80) The regimen for administration of dexamethasone* in adults was as follows: initial dose:	Follow-up for 6 months.	A sequential test was used for analyses, using survival at 1 month as basic effectiveness criterion. No difference in 1-month survival rate or in distribution of outcome after 6 months, either within group as whole, or in subgroups with varying severity of	“[D]examethasone in high doses has no statistically significant effect on morbidity or mortality in head-injured patients who are comatose on admission.”	Patients all comatose. Data suggest lack of efficacy.

						100 mg intravenously; Days 1 to 4:100 mg/day IV; Days 5 to 7:16 mg/day IV or IM; and Days 8, 9, and 10:12 mg, 8 mg, and 4 mg/day, respectively, IV or IM. Children 10-14 years were given half adult dose, and those <10 years received 25% of adult dose.		brain damage on admission.		
Cooper 1979 (score = 5.5)	Dexamethasone vs Placebo	RCT	No mention of industry sponsorship or COI.	N= 76 patients with severe head injuries.	Mean Age= 25.6 years.	Low-dose dexamethasone (16 mg/day) (N=25) Vs. High-dose dexamethasone (96mg/day) (N=24) Vs. Placebo (N=27)	Follow up period was 6 months following injury.	Of the 76 patients available for analysis, a good outcome was achieved in 37% of placebo-treated patients, 44% of low-dose-treated patients, and 29% of high-dose-treated patients. These differences are not statistically significant. Similarly dexamethasone administration had no statistically	"[N]o previous study has shown a significant improvement in outcome following severe head injury as a result of treatment with corticosteroids. A decrease in mortality rate achieved by increasing the number of vegetative survivors is not a desirable result. Our results	Sparse methods. Data suggest neither low nor high dose dexamethasone affected morbidity of mortality in severe TBI patients.

								significant effect on intracranial pressure patterns or serial neurological examinations during hospitalization. Gastrointestinal bleeding occurred in only one patient. Good outcome was associated with age under 10 years, lighter depth of coma on admission, and the preservation of brain-stem reflexes upon admission.	show no difference in outcome when either higher low-dose corticosteroid treatment is compared with placebo. This series shows that most patients do not survive because of "diffuse injuries" and other causes of death not amenable to steroid treatment".	
Dearden 1986 (score = 4.5)	Dexamethasone vs Placebo	RCT	No mention of industry sponsorship or COI.	N=130 patients with severe head injuries admitted to intensive care during a 3-year period.	Age range (yrs.): for steroid group 7-79 and for placebo group 2-74.	Dexamethasone (50mg, intravenously) (N=68) Vs. Placebo group (N=62). Adults in the steroid group received dexamethasone as a bolus on admission to the neurosurgical unit, then 100 mg on Days 1, 2, and 3, 50 mg on Day 4, and 25 mg	Follow-up for 6 months.	Outcome appeared worse in the steroid-treated group, with 33 (49%) patients dead or vegetative compared to 22 (35.5%) in the placebo group, although this difference did not reach statistical significance.	"[I]n the light of these two studies, the administration of glucocorticoids in the treatment of severe head injury is no longer indicated and, based on the observations of this study, may even be contraindicated in the presence of an elevated ICP."	Sparse methods. High dropouts due to mortality. Data suggest lack of efficacy at 6mo.

						on Day 5 on continuous intravenous infusion. Children received proportionate intravenous dosages calculated on a weight basis.				
Saul 1981 (score = 4.0)	Methylprednisolone vs Placebo	RCT	No mention of industry sponsorship or COI.	N= 100 patients with severe craniocerebral trauma, hospital admittance within 6 hours of injury, GCS ≤7;	Mean age 32 for steroid group and 30 for nonsteroid group.	Steroid group receiving 250mg methylprednisolone intravenously, followed by 125mg every 6 hours (N=50) Vs. Nonsteroid control group (N=50)	Follow up at 6 months.	No statistically significant differences reported between groups for clinical outcome.	“The variable response to steroids observed in different patient groups may partially account for the differences in steroid efficacy reported previously. In order to establish the efficacy of steroids in head injuries, one must conduct studies in which the patient’s ongoing response to the entire regimen can be precisely assessed. Based on the data, our regimen for steroid therapy in patients with severe head injuries is as follows: we begin steroid treatment in all such patients (either dexamethasone 1	Data suggest lack of efficacy at 6mo.



## NMDA Receptor Antagonists (Excitatory Amino Acid Inhibitors)

Excitatory amino acid inhibitors prevent the reuptake of excitatory neurotransmitters, aspartate and glutamate, by interfering with excitatory amino acid transporters [967-972]. After experiencing a TBI, ionic imbalances in brain tissue purportedly result in excitotoxic episodes that are thought to potentially lead to neuronal death [967, 970]. Amantadine is also considered an NMDA Receptor Antagonist and is considered separately below. Some inhibitory drugs, such as Ketamine and Dexanabinol, have also been included in this class and have been suggested to reduce mean arterial pressure, without resulting in increased intracranial pressure [969, 971].

### Excitatory Amino Acid Inhibitors for TBI Patients

#### No Recommendation.

**There is no recommendation for or against excitatory amino acid inhibitors.**

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

There are 4 moderate quality trials [970, 973, 974]. One pilot study suggested gacyclidine may be beneficial at high doses [973]. These medications are not invasive, have adverse effects, but lack evidence of efficacy other than a potentially promising pilot study of gacyclidine, thus there is no recommendation for or against these medications.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, craniocerebral injury, craniocerebral trauma, excitatory amino acid antagonists, excitatory amino acid inhibitors, n-methyl-d-aspartate, neuroprotective agent, ampa/kainate receptor blockers, metabotropic receptor blockers, antagon, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed 203 articles in PubMed, 43 in Scopus, 24 in CINAHL, 24 in Cochrane Library and zero in other sources. We considered for inclusion 19 from PubMed, zero from Scopus, zero from CINAHL, zero from Cochrane Library and zero from other sources. Of the 14 articles considered for inclusion, 10 randomized trials and 4 systematic studies met the inclusion criteria. There are 4 moderate-quality RCTs incorporated into this analysis. There is 1 low-quality RCT.

### Evidence for the Use of Excitatory Amino Acid Inhibitors

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Lepeintre 2004 (score = 6.5)	Gacyclidine vs Placebo	RCT, multicenter, prospective, double-blind	Sponsored by BEAUFOUR-IPSEN PHARMA. No mention of COI.	N =48 with acute TBI (GCS 4 – 8).	Age range 18 – 64 years.	Four parallel groups: placebo (N = 12), gacyclidine 0.01mg/kg (N = 11), 0.02mg/kg (N = 13), or 0.04mg/kg (N = 12). The first dose was given within 2 hours following the injury, and the second dose 4 hours after the first.	Follow-up for day 1, 3, 7, 14, 21, 30, 90, 180 and 365.	20 patients died before 1 year, which were no related to the treatment. During the study, 44 patients (91.7%) experienced at least one adverse effect. No significant differences between groups in the GOS scale at any follow-up.	"[B]ased on the available evidence, noncompetitive NMDA receptor antagonists i.e. gacyclidine, appear to be an essential component in their elaboration. Data obtained in this clinical trial appear sufficient to warrant a European multicenter study using the same evaluation criteria."	Pilot study. Small sample with 4 groups. Data suggest gacyclidine may be beneficial esp. at highest dose (0.04mg/kg) for TBI vs. placebo. However, requires a full trial.

Yurkewicz 2005 (score = 5.5)	Traxoprodil vs Placebo	RCT, multi-center, double-blind	No mention of sponsorship or COI	N = 404 with severe TBI (GCS 4–8). Patients were injured within 8 hours of treatment.	Age range 16–66 years.	Traxoprodil (CP-101,606) group: 72 hours intravenous infusion (N = 198) vs. Placebo group (N = 206)	Follow-up for 1, 3, and 6 months.	39 (19.7%) patients died in traxoprodil group vs. 55 (26.7%) in placebo group. Primary outcome: traxoprodil group (41.2%) had more favorable outcomes on dGOS vs. placebo (35.7%) at 6 months (p = 0.21, OR 95% CI: [0.85, 2.06]).	“Traxoprodil was well tolerated. Although these results are intriguing, no definitive claim of efficacy can be made for traxoprodil for the treatment of severe TBI.”	Data suggest lack of efficacy. Weak trend favored traxoprodil for Glasgow score (p=0.21).
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Morris 1999 (score=5.0)	Selfotel vs Placebo	RCT prospective	No mention of industry sponsorship or COI	693 patients with severe head injury in two multicenter double-blind studies done simultaneously (one in Europe, Canada, Australia and Argentina and one in U.S.) 99 medical centers participated in study	Mean age = 32 for Selfotel group and 31 for Placebo group with 77.5% male and 22.5% female.	Selfotel IV 5mg/kg qd for 4 days (N=339) vs. Placebo: 5 mg/kg qd for 4 days (N=354)	Follow-up at 1, 3 and 6 months.	A favorable outcome was defined as “good” or “moderate” score on Glasgow outcome scale (GOS). At 6 mos., favorable outcomes in 185/338 (55%) in Selfotel group vs. 204/352 (58%) in placebo group (p>0.25). 74 vs. 68 deaths in Selfotel vs. placebo (p>0.25). No difference in percentage of time in which patients’ ICPs were >20 mm Hg between placebo (23%) and Selfotel (20.6%)	“...no statistically significant difference in mortality rates in all cases between the two treatment groups in the head injury trials.”	Trial stopped prematurely due to safety concerns over apparent excessive stroke and mortality incidents associated with study drug although both groups showed similar adverse outcomes in the final analyses.
Bourgoin 2005 (score = 4.5)	Sufentanil vs Ketamine	RCT, prospective	No mention of sponsorship or COI.	N = 30 with severe brain injury.	Mean age 29 ± 12 years in the Sufentanil group and	Sufentanil group (N = 15) vs. Ketamine group (N = 15).	Follow-up for 24 hours.	ICP was 17.7 ± 6.5 mm Hg in the sufentanil group vs. 16.2 ± 6.4 mm Hg in	“The present study shows that the increase in sufentanil or ketamine plasma	Small sample. Data suggest doubling sufentanil or ketamine

					29 ± 11 years in the Ketamine group.			the ketamine group. VMCAM value was significantly higher in the sufentanil group (77 ± 21 cm/sec) vs. the ketamine group (60 ± 33 cm/sec, p = 0.03). At 6, 7, and 13 min, there was statistical difference in the BIS value between groups (p < 0.05).	concentrations using a target controlled infusion is not associated with adverse effects on cerebral hemodynamics in patients with severe brain injury. The use of target-controlled infusion could be of interest in the management of severely brain-injured patients. However, there is a need for specific pharmacokinetic models designed for intensive care unit patients."	showed similar results and did not significantly change intracranial pressure, cerebral perfusion pressure or mean MCA velocity.
Merchant 1999 (score = 3.0)	CP-101,606 vs Placebo	RCT, double-blind	No mention of sponsorship or COI.	N = 53 with moderate TBI (GCS 13–14) or mild TBI (GCS 9 – 14) (n = 45) or hemorrhagic stroke (n = 8).	Age range 15–78 years.	Patients received CP-101,606 or placebo within 12 hours of injury. First series of patients had drug/placebo dosed IV 0.75 mg/kg/hr. for 2 hours and then stopped (n = 25). For next two series of patients, after 2-hour infusion,	Follow-up for 0, 1, 2, 12, 24, 48, and 96 hours.	There were improvements in the GCS in the patients receiving treatment; however, there were no differences in the speed of the improvement.	"At all three doses tested in this double-blind placebo-controlled study, CP- 101,606 was well-tolerated and there were no clinically significant cardiovascular or hematological abnormalities. ... The results of this study suggest that unlike other NMDA receptor antagonists, CP-101,606 had no	Data suggest lack of efficacy of CP-101,606 in mild-moderate TBI patients.

					subjects had their treatment continued at 0.37 mg/kg/hr. for 22 hours (n = 4) or 70 hours (n = 24) for total dosing time of 24 and 72 hours, respectively.		psychotropic effects and was well-tolerated in patients who had sustained either a mild or moderate TBI or an atraumatic hemorrhagic stroke.”	
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## Amantadine

Amantadine is a dopamine agonist and an *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist [975, 976]. Amantadine has been used for treatment of TBI patients [893, 896, 976-985].

### Amantadine for Mild TBI Patients, Pre/Peri/Post-Operative

**No Recommendation.**

**There is no recommendation for or against amantadine for mild TBI patients and pre/peri/post-operative.**

*Strength of Evidence (Mild TBI, Pre/Peri/Post-operative) – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Moderate*

### Amantadine for Moderate and Severe, Subacute TBI Patients

**Recommended.**

**Amantadine is moderately recommended for moderate and severe TBI patients.**

*Strength of Evidence (Subacute to early Chronic Phases, Severe TBI) – Moderately Recommended, Evidence (B)*

*Strength of Evidence (Subacute to early Chronic Phases, Moderate TBI) – Recommended, Insufficient Evidence (I)*

*Level of Confidence – Moderate*

<i>Indications:</i>	Moderate-severe TBI, including penetrating injuries. Treatment in the highest quality trial was initiated from 4 to 16 weeks post TBI for treatment of functional deficits. [980]. Another trial enrolled TBI patients with irritability at 6 months after TBI and found efficacy for irritability [981].
<i>Frequency/Dose/Duration:</i>	Amantadine 100 mg 2x/day, then 150 mg 2x/day at 14 days, and 200 mg 2x/day at week 4 [980]. Another quality trial used 100mg QAM and at noon (BID) for 28 days [981].
<i>Indications for Discontinuation:</i>	Intolerance, adverse effects (see harms)
<i>Benefits:</i>	Earlier resolution of disabilities
<i>Harms:</i>	Vomiting, agitation, hypertonia, spasticity, insomnia, psychosis, hyperactivity, disorganization, vivid dreams, anorexia, aggression, delirium, and depression [980] [975] [976].
<i>Rationale:</i>	A high-quality RCT suggested amantadine is successful for treating functional deficits among subacute to chronic severe TBI patients [980]. The next highest quality trial suggested success to decrease irritability among those with chronic TBI and irritability among patients over 6 months beyond TBI [981]. Amantadine is not invasive or minimally invasive, has low adverse effects is low to moderate cost depending on route of administration, has evidence of efficacy and is thus recommended for these select patients. It is recommended by inference for treatment of subacute or chronic moderate TBI patients with functional deficits or irritability. There is no recommendation for

treatment of other TBI patients including mild, pre/peri/postoperative TBI patients.

*Evidence:*

A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: amantadine, traumatic brain injury, brain injuries, intracranial injury, closed head injury, penetrating head injury, brain concussion, concussion, craniocerebral trauma, craniocerebral injury, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. In PubMed we found and reviewed 52 articles, and considered 14 for inclusion. In Scopus, we found and reviewed 103 articles, and considered zero for inclusion. In CINAHL, we found and reviewed 22 articles, and considered zero for inclusion. In Cochrane Library, we found and reviewed 4 articles, and considered zero for inclusion. We also considered for inclusion zero articles from other sources. Of the 14 articles considered for inclusion, 3 randomized trials and 1 systematic studies met the inclusion criteria. There are 2 high- and 3 moderate-quality RCTs incorporated into this analysis. There is 1 low-quality RCT. There are 2 systematic reviews.

## Evidence for the Use of Amantadine

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Giacino 2012 (score = 9.0)	Amantadine vs Placebo	RCT	Sponsored by the National Institute on Disability and Rehabilitation Research. No mention of COI.	N = 184 with non-penetrating traumatic brain injury.	Mean age amantadine 35.5±15.3 years, placebo 37.2±15.4 years.	Amantadine 100 mg 2x/day, then 150 mg 2x/day at 14 days, and 200 mg 2x/day at week 4 (N = 87) vs. Placebo 100 mg 2x/day, then 150 mg 2x/day at 14 days, and 200 mg 2x/day at week 4 (N = 97).	Follow-up at weeks 4 and 6.	Significant recovery time in amantadine group than placebo group at week 4. (p=0.007) at 0.24 points. Overall no significant differences between baseline and week 6 in DRS score. Amantadine was lower in week 2 than placebo at 0.30 points and (p=0.02).	"Amantadine accelerated the pace of functional recovery during active treatment in patients with post-traumatic disorders of consciousness."	Data suggest amantadine successful for severe TBI at 4-16 weeks out.
Whyte 2013 (score = 9.0)	Amantadine vs Placebo	RCT	Sponsored by the National Institute on Disability and Rehabilitation Research. No COI.	N = 184 with nonpenetrating TBI enrolled from acute inpatient rehabilitation programs between 4 and 16 weeks post injury.	Age range 16 – 65 years.	Amantadine hydrochloride (200 to 400mg) vs. Placebo. Treatments were administered daily for 4 weeks.	Follow-up for 2 weeks.	During the 6-week trial, 468 adverse events were reported with an average rate of about 0.40 events per week per patient. The median number of medical complications experienced per patient	"Patients with DOCs have a high rate of medical complications early after injury. Many of these complications require brain injury expertise for optimal management. Active medical management appears to contribute to the reduction in new complications. An optimal system of	Large sample. Trial of amantadine but report of all hospital complications. Second report of Giacino 2012.

								was 2 (mean, 2.85), but the rate of complications for individual patients ranged from 0 to 9. 32 (17.4%) patients did not present new medical events, and 152 (82.6%) experienced at least 1 medical complication. There were 135 (29%) mild medical complications, 270 (58%) moderate, and 61 (13%) severe.	care for DOC patients must provide expert medical management in the early weeks after injury.”	
Hammond 2014 (score = 7.5)	Amantadine vs Placebo	RCT	Sponsored by US Department of Education, Office of Special Education and Rehabilitative Services, National Institute on Disability and Rehabilitation Research. No COI.	N = 76 with a sustained closed head injury due to trauma at least 6 months prior to enrollment;	Age range 16 – 65 years.	Amantadine hydrochloride 100 mg every morning and noon (N = 38) vs. Placebo (N = 38) for 28 days.	Follow-up for 28 ± 3 days.	Amantadine group improved 80.56% in NPI irritability vs. 44.44% placebo (p = 0.0016). NPI-I mean change in amantadine group was -4.3 vs. -2.6 in placebo (p = 0.0085). Significant difference	“Amantadine 100 mg every morning and at noon appears an effective and safe means of reducing frequency and severity of irritability and aggression among individuals with TBI and sufficient creatinine clearance.	Data suggest amantadine improved irritability and aggression associated with chronic TBI.

								between groups in mean change in both frequency (p = 0.0156) and severity of irritability (p = 0.0055). Mean change NPI-aggression -4.65 amantadine vs. -2.46 placebo (p = 0.046).		
McMahon 2009 (score = 5.0)	Amantadine vs Placebo	RCT Crossover	Sponsored by the NICHD and NINDS. No mention of COI.	N = 7 with acquired brain injury	Age 5-18	Placebo 4mg/kg/day for 7 days followed by 6 mg/kg/day for 14 days Vs. Amantadine 4 mg/kg/day (or maximum of 300 mg Amantadine) for 7 days followed by 6 mg/kg/day (or maximum of 400 mg of Amantadine) for 14 days.	Follow-up for 8 weeks	No significant results in recovery in arm from coma. Average CNCS scores P=0.24, P=0.28, and P=0.33	"This study suggests that amantadine facilitates recovery of consciousness in pediatric acquired brain injury and provides important information necessary to design future more definitive studies."	Study in children. Pilot. Only 5 completers.
Meythaler 2002 (score = 4.0)	Amantadine vs Placebo	RCT, Double-blind crossover	Sponsored by NIDRR. No mention of COI.	N = 35 with TBI in a transportation accident; age range 16–75 years.		Group 1: amantadine (200 mg) the first 6 weeks after injury (N = 15) vs. Group 2: placebo the	Follow-up for 6 weeks.	At 6 weeks, group 1 had improvement in MMSE scores of 14.3 points from 8.1 ± 10.4 to	"There was a consistent trend toward a more rapid functional improvement regardless of when a patient with DAI-	Crossover. Data suggest no efficacy over natural history.

					<p>first 6 weeks and amantadine the second 6 weeks (N = 20).</p>	<p>22.5 ± 8.4 (p = 0.0185) vs. 2.4 from 22.5 ± 8.4 to 24.8 ± 6.1 points in placebo (p&gt;0.05). Group 1 had improvement in DRS scores of 9.8 points from 15.5 ± SD to 5.7 ± SD 4.2 (p = 0.0022) vs. 0.15 points from 5.7 ± 4.12 to 5.5 ± 4.6 in group 2 (p&gt;0.05). Group 1 had improvement in GOS score of 0.8 points from 3.0 ± 0 to 3.8 ± 0.6 (p = 0.0077) vs. 0.1 points from 3.8 ± 0.6 to 3.9 ± 1.2 in 2<sup>nd</sup> 6-week period (p&gt;0.05). Group 1 had improvement in FIM-cog scores of 15.1 points from 11.6 ± 8.6 to 26.7 ± 8.7 (p = 0.0033) vs. 11.3 points</p>	<p>associated TBI was started on amantadine in the first 3 months after injury.”</p>
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								from 8.4 ± 5.5 to 19.7 ± 12.9 in group 2 (p = 0.0030).		
Schneider 1999 (score = 3.0)	Amantadine vs Placebo	RCT, Crossover	No mention of sponsorship or COI.	N = 10 Age 18-55 with closed head injury		Amantadine 50 mg to 150 mg for 2 weeks followed by 2 week withdrawal followed by 2 week placebo (N = 5) vs. Placebo for 2 weeks followed by 2 week withdrawal followed by 2 week (N= 5) Amantadine 50 mg to 150 mg.	Follow-up for 8 week	No significant results for amantadine P=0.773 verses placebo group P=0.405 for comparable variables.	"[A]lthough patients generally improved, this initial exploratory study found no differences in rate of cognitive improvement between subjects given amantadine versus those given placebo."	Crossover. Small sample (10). Only reports data on 10 after 8 dropouts. Data suggest lack of efficacy.

## Cannabinoids

Dexanabinol (HU-211) is a synthetic, nonpsychotropic cannabinoid that has been suggested as a neuroprotective drug. This drug purportedly differs from other neuroprotective drugs because it targets various pathophysiological mechanisms, which include glutamate excitotoxicity, free radical damage, and inflammatory response. Dexanabinol is suggested to be most protective against the breakdown of the blood-brain barrier, reduces edema formation, decreases the number and severity of neurological problems and has been used for treatment of TBI patients [968] [971]. Endocannabinoids have also been used to treat TBI patients [986].

### Cannabinoids for TBI Patients

#### No Recommendation.

**There is no recommendation for or against cannabinoids for TBI patients.**

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

The overall breadth and depth of literature on these related subjects is sparse. A high quality trial of dexanabinol suggested no benefits of a single early dose on 6-month outcomes [968]. A moderate quality trial suggested lower intracranial pressures and a trend but no clear evidence of better long-term survival [971]. A moderate quality trial of a cannabinoid CB1/CB2 receptor agonist suggested potential modest short-term efficacy with lower intracranial pressures and short term survival but no evidence of long-term benefits [986]. With a lack of clear evidence of efficacy and the highest quality study being negative, there is no recommendation for or against dexanabinol or endocannabinoids for TBI patients.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: HU-211, brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed head or penetrating head or craniocerebral; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, retrospective studies, or prospective studies. We found and reviewed 5 articles in PubMed, 42 in Scopus, 0 in CINAHL, 6 in Cochrane Library and 0 from other sources. We considered for inclusion 3 from PubMed, 0 from Scopus, CINAHL, Cochrane Library and other sources. Of the 3 articles considered for inclusion, 2 randomized trials and 1 systematic studies met the inclusion criteria. There is 1 high- and 2 moderate-quality RCTs incorporated into this analysis.

## Evidence for the Use of Cannabinoids

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Maas 2006 (score = 8.5)	Dexanabinol	RCT	Sponsored by Pharmos Corporation. HH, NK, and MM were employed by Pharmos Corporation.	N = 846 with traumatic brain injury. Median age dexanabinol 33 years, placebo 32 years.	Study group age 33 years, Placebo group age 32 years	Dexanabinol group 150mg diluted dissolved into cosolvent mixture of ethanol, Cremophor, and 0.9% sodium chloride single dose within 6 hours of surgery (N = 428) vs. Placebo group 150mg of cosolvent mixture single dose within 6 hours of surgery (N = 418).	Follow-up at 3 and 6 months.	There were no significant differences between groups.	"The results of this trial show the safety of dexanabinol in the treatment of traumatic brain injury, but do not show efficacy."	Large sample size. Assessed efficacy of one early dose on 6 month outcomes and showed no efficacy.
Knoller 2002 (score = 7.0)	Dexanabinol	RCT	No mention of sponsorship or COI.	N = 67 with a GCS score of 4-8, phase 1 demonstrated that dexanabinol (HU-211) was safe and well tolerated in healthy volunteers at doses up to 200 mg per	Mean age dexanabinol 29±12 years, placebo 31±13 years.	Dexanabinol 150mg, 20 patients; 48mg, 10 patients (study drug). (N = 30) vs. Placebo, 13 with low dose, 24 with high dose (N = 37).	Follow-up for 10 days or until discharge.	Mean percentage time ICP above 25 mm Hg: reduced in dexanabinol group by 67%, 82%, and 97% on first, second (p<0.02) and	"Dexanabinol was safe and well tolerated in severe head injury. The treated patients achieved significantly better intracranial pressure/cerebral perfusion	Severe TBI. Modest sample size. Data suggest lower ICP with dexanabinol. Trend to better long term outcomes.

				subject; phase 2 evaluated the safety of this agent in severe brain injury patients.				third day (p<0.005).	pressure control without jeopardizing blood pressure."	
Firsching 2012 (score = 7.0)	Endocannabinoids	RCT	Sponsored by Key Neurotek Pharmaceuticals AG, Magdeburg, Germany. R.F. was the European coordinator, .F. and J.P. were intensively involved in the study design.	N = 97 with severe TBI, addressing acute neurodegeneration.	Age groups: 18–58 for high dose / 19–63 low dose / 18–64 and placebo.	High dose high dose: IV infusion of KN38-7271, 80 µm as accelerated infusion (1 hour) þ 920 µm as constant-rate infusion over 23 hours (N = 31) vs. Low dose IV infusion of KN38-7271, 40 µm as accelerated infusion (1 hour) þ 460 µm as constant-rate infusion over 23 hours (N = 33) vs. Placebo without KN38-7271, given as 1-hr accelerated infusion followed by constant infusion over 23 hours (N = 33).	Follow-up for 1, 3 and 6 months.	Survival rates showed significant difference between either or both KN38-7271-treated groups and placebo (p = 0.026). Highest and lowest CPP values recorded were highest in high-dose group and lowest in placebo with, (p = 0.0582, actual highest CPP, days 0 to 7) and 0.0456 (actual lowest CPP, days 2 to 7, not shown).	"KN38-7271 appeared beneficial in the acute early phase of the comatose patient after a head injury."	Phase 2 trial. Data suggest lower ICPs and short term survival but no long term survival advantage and placebo group had more injury, procedure complications raising question of confounding.

## Cerebrolysin

Cerebrolysin is a neuropeptide preparation, which mimics endogenous neurotropic factor action on the brain and is thought to decrease amyloid production. It has also been used in dementia and Parkinson's disease patients [987].

### Cerebrolysin for TBI Patients (not currently approved for use in U.S.)

#### No Recommendation.

**There is no recommendation for or against cerebrolysin for treatment of TBI patients.**

#### *Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

#### *Level of Confidence – Low*

#### *Rationale:*

There are 2 RCTs of Cerebrolysin. [988] is a pilot study and [989] performed an exploratory RCT on 208 ischemic stroke patients with promising results although a phase III trial is needed to confirm these results. Neither study clearly defined the dose, instead both identified volume of the drug (mL). While preliminary data suggest efficacy, Phase 3 trials are needed prior to a potential recommendation for TBI patients.

#### *Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed dead or penetrating head or craniocerebral; Sedatives, sedative hypnotics (zolpidem, propofol) and analgesics, narcotics (morphine sulfate, fentanyl, sufentanil), controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, retrospective studies, or prospective studies. We found and reviewed 265 articles in PubMed, 22 in Scopus, 12 in CINAHL, 1 in Cochrane Library and 2 in other sources. We considered for inclusion 8 from PubMed, zero from Scopus, zero from CINAHL, zero from Cochrane Library and zero from other sources. Of the 8 articles considered for inclusion, 6 randomized trials and 2 systematic studies met the inclusion criteria. There is 1 high- and 1 moderate-quality RCTs incorporated into this analysis.

#### *Comments:*

This medication has not been approved for use in the US.

## Evidence for the Cerebrolysin

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Muresanu 2016 Score = 9.5	Cerebrolysin Vs Placebo	RCT Double blind parallel group study	Sponsored by EVER Neuro Pharma GmbH, Austria. COI, Dr Muresanu is a coordinating investigator of the Cerebrolysin and Recovery After Stroke (CARS) trial and a member of the Cerebrolysin Asian Pacific Trial in Acute Brain Injury and Neurorecovery (CAPTAIN) trial scientific advisory board. Dr Muresanu reports receipt of grants/research supports from EVER Neuro Pharma.	N=208 ischemic supratentorial strokes with a volume of >4 cm <sup>3</sup>	Mean age = 64.0, 63.9% male, 36.1% female	30 mL Cerebrolysin (diluted with physiological saline to 100 mL) (n=104) Vs. Placebo (physiological saline (100 mL)) (n=104) administered once daily. (Ed., dose not clearly defined in the study, only volume defined).	Follow-up at 7, 14, and 21 days after baseline and on days 42 and 90 post stroke.	Mean±SD Action Research Arm Test score baseline vs day 90: 10.1±15.9 vs. 40.7±20.2 Cerebrolysin. 10.7±16.5 vs. 26.5±21.0 placebo. Effect size on the ARAT score on day 90 Cerebrolysin vs. placebo (Mann–Whitney estimator, 0.71; 95% CI: 0.63–0.79; p<0.0001)	"Cerebrolysin had a beneficial effect on function and global outcome in early rehabilitation patients after stroke. Its safety was comparable with that of the placebo, suggesting a favorable benefit/risk ratio. Because this study was exploratory and had a relatively small sample size, the results should be confirmed in a large-scale, randomized clinical trial."	Data suggest cerebrolysin superior to placebo for ARAT score and global outcome after stroke at 90 days. However, results need confirmation on a larger Phase III trial.
Chen 2013 (score = 7.0 )	Cerebrolysin	RCT, Double-Blind Pilot Study	No mention of sponsorship. No COI.	N = 32 with mTBI.	Mean age 44.8 ± 16.36 years (range, 30 – 75 years).	Group A: Cerebrolysin (once daily intravenous infusion of 30 mL Cerebrolysin over a 60-min period for 5 days) (N = 17) vs. Group B:	Follow-up for week 1, 4, and 12.	At week 12, the CASI score was greater in group A vs. group B (21.0 ± 20.4 vs. 7.6 ± 12.1; p = 0.0461). Group A had greater difference vs.	"[The] results indicated that Cerebrolysin therapy started within 24 h after the onset of MTBI with intracranial contusion haemorrhage can improve	Phase 2 pilot study. Data suggest cerebrolysin improves cognitive function of MTBI patients at 3rd month post-injury esp. regarding

					<p>placebo (N = 15). (Ed., dose not clearly defined in the study, only volume defined).</p>	<p>group B in drawing subscale at week 4 (<math>1.79 \pm 1.42</math> vs. <math>0.20 \pm 1.47</math>) and week 12 (<math>2.14 \pm 2.54</math> vs. <math>0.57 \pm 1.74</math>), (<math>p = 0.0066</math> and <math>p = 0.0472</math>). Group A had greater difference in the long-term memory vs. group B at week 12 (<math>1.79 \pm 3.91</math> vs. <math>-0.57 \pm 1.87</math>), (<math>p = 0.0256</math>).</p>	<p>patients' CASI scores; this finding suggests that Cerebrolysin may enhance cognitive recovery after MTBI. We believe that MTBI with intracranial contusion haemorrhage patients can benefit from supplementary treatment with Cerebrolysin in addition to the usual medical treatment for this condition."</p>	<p>memory and drawing.</p>
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## Tranexamic Acid

Tranexamic acid aids in reducing blood loss, or intracranial bleeding, associated with traumatic brain injury without increased occlusive events [990-993].

### Tranexamic Acid for TBI Patients

#### Recommended.

**Tranexamic acid is selectively recommended for treatment of TBI patients.**

*Strength of Evidence* – Recommended, Evidence (C)

*Level of Confidence* – Moderate

<i>Indications:</i>	For selective use in TBI patients immediately post injury (1-3 hours) with either 1) evidence of intracranial hemorrhage or 2) strong suspicion of hemorrhage. The purpose is to reduce mortality risk and rebleeding and need for transfusion. [991]
<i>Benefits:</i>	Prevent further bleeding post TBI. Reduce risk of death. [991]
<i>Harms:</i>	Thromboembolic complications including hemorrhage and potential death.
<i>Frequency/Dose/Duration:</i>	Loading doses range from 2.5 mg/kg to 100 mg/kg and maintenance doses range from 0.25 mg/kg/hr. to 4 mg/kg/hr. delivered over 1-12 hours [991]
<i>Indications for Discontinuation:</i>	When patient is stable or complications arise from treatment with TXA.
<i>Rationale:</i>	(See also Eye Guideline for use of tranexamic acid for traumatic hyphema.) One quite large, high-quality study suggested TXA reduced risk of death by an absolute value of 1.5% (14.5% vs. 16.0%) if given within 3 hours [991]. There are 2 other studies of much smaller sample sizes, one of which is borderline significant. [993, 994]. TXA is minimally invasive, has adverse effects, and is costly, but has some evidence of efficacy in a highly select, at-risk population and is thus selectively recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: tranexamic acid, amikapron, amstat, anvitoff, carxamin, cylcocapron, cyklokapron, emorhalt, frenolyse, mastop, rikavarin, tamcha, tranexamsaeure, tranexan, tranhexamic, transamin, trasamlon, ugurol, brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed dead or penetrating head or craniocerebral; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, retrospective studies, or prospective studies. We found and reviewed 30 articles in PubMed, 18 in Scopus, 7 in CINAHL, 3 in Cochrane Library and 0 in other sources. We considered for inclusion 9 from PubMed, 0

from Scopus, 0 from CINAHL, 0 from Cochrane Library and 0 from other sources. Of the 9 articles considered for inclusion, 4 randomized trials and 5 systematic studies met the inclusion criteria. There are 2 high- and 1 moderate-quality RCTs incorporated into this analysis.

## Evidence for the Use of Tranexamic Acid

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Roberts 2013 (score = 8.5)	Tranexamic Acid vs Placebo	RCT	Sponsored by the London School of Hygiene & Tropical Medicine and the World Health Organization. No COI.	N = 20,211 adult trauma patients with, or at risk of, significant bleeding.	Mean age: 35 years.	Tranexamic acid (TXA) (N = 10,115) vs. Placebo (N = 10,115).	No long-term follow-up.	Death (Any cause) – 1463 (14.5%) TXA vs 1613 (16.0%) Placebo; RR 0.91 (95%CI 0.85-0.97; p=0.0035); Death (vascular occlusion) – 489 (4.9%) TXA vs 575 (5.7%) Placebo; RR 0.69 (95%CI 0.44-1.07; p=0.096). Any vascular occlusive event – 168 (1.7%) TXA vs 201 (2.0%) Placebo; RR 0.84 (95%CI 0.68-1.02; p=0.084). Blood product transfused – 5067 (50.4%) TXA vs 5160 (51.3%) Placebo; RR 0.98 (95%CI 0.96-1.01; p=0.21)	“Tranexamic acid safely reduced the risk of death in bleeding trauma patients in this study.	Data suggest TXA reduced risk of death in bleeding trauma patients when given within 3 hours compared with placebo.
Yutthakamsunt 2013 (score = 8.0)	Tranexamic Acid vs Placebo	RCT	No mention of sponsorship. No COI.	N = 240 patients with moderate to severe TBI.	Mean age: 40 years.	Tranexamic acid (TXA) (N = 120) vs. Placebo (N = 120).	Follow-up not reported.	TXA vs Placebo: Progressive intracranial haemorrhage – Relative Risk (RR) = 0.65 (95%CI 0.40-1.05); Increase in pressure effect – RR = 0.91 (95%CI 0.42-1.97); Improved GCS motor score – RR = 0.98 (95%CI 0.67-1.44); Death –	“We have not shown that TXA improves clinical outcomes and this information would be required in order to make any recommendation about the use of TXA in clinical practice.”	Data suggest TXA did not significantly reduce progressive intracranial hemorrhage compared with placebo (18% vs. 27%, p= 0.65). Study may be underpowered.

								RR = 0.69 (95%CI 0.35-1.39).		
Perel 2011 (score = 6.5)	Tranexamic Acid vs Placebo	RCT	Part of CRASH-2 study (Lancet 2010). Sponsored by the UK Health Technology Assessment Programme. No COI.	N = 270 trauma patients with, or at risk of, significant extracranial bleeding and traumatic brain injury	Mean age: 36+14years Tranexamic Acid group; 37+14years Placebo group.	Tranexamic acid (N = 133) vs. Placebo (N = 137).	Follow-up time uncertain.	Difference in haemorrhage growth (ml) between Tranexamic acid and Placebo patients –All patients (unadjusted): -2.1 (-9.8 to 5.6; p=0.33); All patients (adjusted*): -3.79 (-11.5 to 3.9; p=0.33). Deaths – Tranexamic acid vs. Placebo: 11% vs. 18% (95%CI 0.21 to 1.04; p=0.06). *Adjusted for Glasgow coma score, age, time from injury to the scans, and initial haemorrhage volume.	“The CRASH-2 trial has shown reliably that early administration of tranexamic acid in trauma patients with, or at risk of, significant bleeding reduces the risk of all cause mortality.”	Nested placebo-controlled of Crash-2 study. Data suggest comparable efficacy of TXA vs. placebo for bleeding reduction among TBI and TXA trended towards less mortality (p=0.06)

## Sedatives, Sedative Hypnotics, and Opioids

A variety of agents in this classification have been used to treat TBI patients primarily for purposes of inducing and/or controlling sedation, including propofol [957-959, 995], ketamine [969, 996], midazolam [957-959, 996], fentanyl [996-999], remifentanyl [998], sufentanyl [969] [999], alfentanil [999], dexmedetomidine [995], morphine [997] [998]. These have been used in hospital settings, and thus they are beyond the scope of this Guideline.

For guidance on Opioids Use, see Opioids Guideline.

### Sedatives, Sedative Hypnotics, and Opioids for TBI Patients

#### No Recommendation.

**Because these agents are used in hospital settings, there is no recommendation for or against sedatives, sedative hypnotics, and opioids for TBI patients.**

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed dead or penetrating head or craniocerebral; Sedatives, sedative hypnotics (zolpidem, propofol) and analgesics, narcotics (morphine sulfate, fentanyl, sufentanyl), controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, retrospective studies, or prospective studies. We found and reviewed 265 articles in PubMed, 22 in Scopus, 12 in CINAHL, 1 in Cochrane Library and 2 in other sources. We considered for inclusion 8 from PubMed, zero from Scopus, zero from CINAHL, zero from Cochrane Library and zero from other sources. Of the 8 articles considered for inclusion, 6 randomized trials and 2 systematic studies met the inclusion criteria. There are 3 moderate-quality RCTs incorporated into this analysis. There are 6 low-quality RCTs.

## Evidence for the Use of Sedatives, Sedative Hypnotics, Analgesics, & Narcotics

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
James 2012 (score = 5.5)	Dexmedetomidine vs Propofol	RCT Crossover Design	Sponsored by the Hospira Worldwide, Inc. and the American Heart Association Scientist Development Grant. COI, Dr. M. L. James serves as a speaking consultant for Hospira Worldwide, Inc.	N = 8 with TBI;	Age range ≥ 18 years old.	0.54 µg/kg/h of dexmedetomidine administered to patients and 25.5 µg/kg/min of propofol administered to patients over a 12 hour crossover design (N = 8)	Follow-up at baseline and hours 2, 6, 8, and 12.	No significant statistics reported. Differences in cerebral substrates (lactate/pyruvate ratio) were noted. DEX group L/P ratio before testing (45.9 ± 39.5, ( p = .398 )) Post testing (33.8 ± 10.7, (p = .328) )	"[D]exmedetomidine and propofol appear equally effective in sedating patients with TBI and neither is associated with adverse physiological effects.	Pilot study. Small sample size. Data suggest similar efficacy between dexmedetomidine vs propofol. Excluded as n<10.
Ghori 2007 (score = 4.5)	Midazolam vs Propofol	RCT	Sponsored by the Department of Anaesthesia and Intensive Care Medicine, Cork University Hospital. COI, George D Shorten employed by the	N = 28 TBI patients with GCS score < 9;	Age range 18-65 years.	Midazolam 0.1–0.3mg/kg/h (N = 15); Propofol 1.5–5mg/Kg/h (N = 13); Both groups received morphine sulfate (0.1–0.2mg/kg/h)	Follow-up at baseline, day 1-5, and month 3.	Midazolam vs propofol Serum s100β concentrations (Mean, [SD]): Day 1, (0.99 ± 0.81) vs (0.41 ± 0.4)µg/L; Day 2, (0.80 ± 0.81) vs (0.41 ± 0.24) µg/L; Day 3, (0.52 ± 0.55) vs (0.24 ± 0.25) µg/L; and Day 4, (0.54 ± 0.43) vs (0.24 ± 0.35) µg/L; (p < 0.05)	"Plasma concentrations of neurological injury markers were similar in patients who received midazolam and propofol. Patients with poor neurological outcomes had consistently higher serum s100β."	Methodological details sparse. Small sample size. Many medications given.

			Department of Anaesthesia and Intensive Care Medicine at Cork University.							
Bourgoin 2005 (score = 4.5)	NMDA receptor antagonist Sufentanil vs Ketamine	RCT, prospective	No mention of sponsorship or COI.	N = 30 with severe brain injury.	Mean age 29 ± 12 years in the Sufentanil group and 29 ± 11 years in the Ketamine group.	Sufentanil group (N = 15) vs. Ketamine group (N = 15).	Follow-up for 24 hours.	ICP was 17.7 ± 6.5 mm Hg in the sufentanil group vs. 16.2 ± 6.4 mm Hg in the ketamine group. VMCAM value was significantly higher in the sufentanil group (77 ± 21 cm/sec) vs. the ketamine group (60 ± 33 cm/sec, p = 0.03). At 6, 7, and 13 min, there was statistical difference in the BIS value between groups (p < 0.05).	"The present study shows that the increase in sufentanil or ketamine plasma concentrations using a target controlled infusion is not associated with adverse effects on cerebral hemodynamics in patients with severe brain injury. The use of target-controlled infusion could be of interest in the management of severely brain-injured patients. However, there is a need for specific pharmacokinetic models designed for	Small sample. Data suggest doubling sufentanil or ketamine showed similar results and did not significantly change intracranial pressure, cerebral perfusion pressure or mean MCA velocity.

									intensive care unit patients.”	
Nadal 2000 (score = 3.5)	Fentanyl vs Morphine	RCT, Crossover design	Sponsored by the Fondo de Investigaciones Sanitarias de la Seguridad Social, Madrid, Spain and the Marato TV3, Barcelona, Spain. No mention of COI	N = 30 patients with severe closed-head injury during the first 3 days of admission into the ICU;	Mean age 30 ± 13 years.	2.0 µg/kg fentanyl was administered intravenously over 1 minute to group 1. 0.2 mg/kg morphine was administered intravenously over 1 minute to the group again 24 hours later. (N = 30)	Follow-up at baseline, minute 5 and 60, and day 1 and 2.	MABP decreased significantly after 5 minutes; Morphine (p = 0.002); Fentanyl (p = 0.016); ICP increased after 5 minutes: Morphine (p = 0.008) Fentanyl (p = 0.044). Cerebral perfusion pressure at 5 minutes had minimum values of 64 ± 15 mmHg after morphine (p = 0.001) and 65 ± 18 mmHg after fentanyl (p < 0.0001)	“[M]orphine and fentanyl increased intracranial pressure and decreased mean arterial blood pressure and cerebral perfusion pressure. No significant effect was shown on arteriovenous oxygen levels and middle cerebral artery mean flow velocity in TBI patients.”	Small sample size. Methodological details sparse.
Tanguy 2012 (score = 3.5)	Propofol vs Midazolam	RCT, prospective, single-blind	Sponsored by Programme Hospitalier de Recherche Clinique (PHRC) of Rennes. No COI.	N = 36 with severe TBI.	Mean age 35 – 18 years.	Propofol (N = 15) vs. Midazolam (N = 14)	Follow-up for 72 hours and 12 months.	There was no difference between propofol and midazolam in the cerebral L: P ratio (time effect p = 0.201, treatment effect p = 0.401, time x treatment interaction p = 0.101).	“[The] results indicate that there is no difference between the effects of propofol and midazolam sedation on the cerebral metabolic profile during the acute phase of severe TBI. Accordingly, the use of propofol as a sedative agent in TBI and its neuroprotective	Small sample size. Methodological details sparse. Relatively invasive monitoring using cerebral microdialysis catheter. High complication rate. Data suggests similar efficacy between propofol and midazolam.

									effects warrant further investigation.	
Karabinis 2004 (score = 3.0)	Remifentanyl vs Fentanyl vs Morphine	RCT	No mention of sponsorship. COI, Andreas Karabinis, Kostas Mandragos, Spiros Stergiopoulos, Apostolos Komnos, Jens Soukup and Ben Speelberg received payment from Glaxo-SmithKline according to the number of patients recruited. Andrew JT Kirkham is an employee of GlaxoSmithKline.	N = 161 patients with acute TBI or had undergone intracranial surgery;	Age range 18-80 years.	Remifentanyl was given at 9 µg kg <sup>-1</sup> h <sup>-1</sup> and increased to a maximum of 18 µg kg <sup>-1</sup> h <sup>-1</sup> before administering propofol at 0.5 mg kg <sup>-1</sup> h <sup>-1</sup> during days 1-3. Midazolam was administered in doses of 0.03 mg kg <sup>-1</sup> h <sup>-1</sup> during days 4 and 5. (N = 84). vs. Fentanyl & morphine were administered at recommended doses along with the same dosage/timing of propofol and midazolam as seen in group 1. (N = 77).	Follow-up at baseline and day 1, 3, and 5.	Between-patient variability at the time of neurological assessment was significantly smaller when using remifentanyl (remifentanyl = 0.44 vs. fentanyl = 0.86 (p = 0.024) vs. morphine = 0.98 (p = 0.006)). Mean neurological assessment times were significantly shorter when using remifentanyl (remifentanyl = 0.41 hour vs. fentanyl = 0.71 hour (p = 0.001) vs. morphine = 0.82 hour (p <0.001)).	"Analgesia-based sedation with remifentanyl permitted significantly faster and more predictable awakening for neurological assessment."	Methodological details sparse. Data suggest remifentanyl superior for measured outcomes.
Sanchez-Izquierdo-Riera 1998 (score = 3.0)	Midazolam (Mz) vs Propofol (Pf)	RCT	No mention of sponsorship or COI	N = 100 with acute TBI requiring mechanic	Mean age 35.4 ± 16.6 years.	Group A received midazolam at a rate of 0.1 mg / kg <sup>-1</sup> / h <sup>-1</sup> with a	Follow-up at baseline, hour 3, 6, 12, and 24 after	Wake-up time significantly decreased in Pf groups. Group A (660 ± 400 min) vs	"In summary, the results indicate that Mz and Pf, used alone or in	Methodological details sparse. Large number of therapeutic failures.

	vs Combo Mz- Pf			al ventilatio n for at least 48 hours;		maximum dose of 0.35 mg / kg- 1 / h-1. (N = 34); Group B received propofol at a rate of 1.5 mg / kg-1 / h-1 with a maximum dose of 6 mg / kg-1 / h-l. (N = 33); Group C received a combination of midazolam and propofol in doses similar to the previous groups. (N = 33)	sedation stoppage.	Group B (110 ± 50 min) vs. Group C (190 ± 200 min), (p < 0.01).	combination, are safe and effective in the sedation of critically ill trauma patients.	Data suggest propofol either alone or in combination with midazolam resulted in shorter wake-up times.
Kolenda 1996 (score = 1.5)	Ketamine/ Midazolam vs Fentanyl/M idazolam	RCT	No mention of sponsorshi p and COI.	N=35 patients who suffered a moderate or severe head injury;	Mean Age: Group 1 38 (18- 72) yrs.; Group 2 29 (16- 59) yrs.	Group 1 Received analgesedative therapy with 6.5 mg/kg and 65 mg/kg ketamine per day Vs. Group 2 Received analgesedative therapy with 6.5 mg/kg and 65 mg/kg fentanyl per day.	Follow-Up baseline and day 14 (final dosage) and day 1, 3, and 7 after terminatio n of the analgeseda tive therapy.	Tube feeding, group 1 vs group 2, 14 day average: 824 mL/day vs 579 mL/day statistical difference at day 3, 4, 5; (p<0.05). Mean Arterial pressure (MAP) group 1 vs Group 2, day 3 and 7: 91 (76-107) vs 81 (73-107) and 95 (88- 107) vs 77 (76-90); (p<0.05). Mean pulse rate group 1 vs group 2, day 2, 3, and 7: 80 (64-104) vs 56 (44-92), 74 (62-104) vs 62 (48- 80), 84 (68-96) vs 68 (64-76), respectively; (p<0.005).	"... [K]etamine/mid azolam analgesedation in head-injured patients is more expensive than a comparable anaesthetic therapy using fentanyl/midazo lam, and this disadvantage is not countered by the earlier restitution of consciousness in the ketamine group. But with regard to risk patients for intensive therapy such as	High dropout rate due to multiple complications. Baseline differences in treatment groups. Data suggest comparable (in) efficacy.

								Intracranial Pressure, group 1 vs group 2, day 8 and 10: 16 (14-22) vs 11 (6-18), 18 (14-22) vs 10 (6-22); (p<0.05).	those presenting severe cardiovascular, pulmonary or gastro-intestinal problems requiring intensive medication, ketamine offers an alternative anaesthetic concept [13, 18, 30, and 34]. Its bronchodilating action as well as its stabilizing effect on circulation and gastro-intestinal motility may be of great beneficial value for these patients."	
Albanese 1999 (score = 1.5)	[Previous table header, if any]	RCT Crossover	No mention of sponsorship or COI	N = 6 males with TBI and GCS score ≤ 8;	Age range 20-45 years.	6-min injection of either sufentanil (1 µg/kg), alfentanil (100 µg/kg), or fentanyl (10 µg/kg) followed by an infusion of 0.005, 0.7, and 0.075 µg/kg/min, for 1 hr. The three opioids were given to each	Follow-up at baseline, 10, 30, and 60 minutes after opioid administration, and at 3, 24 hour intervals.	Significant increases in ICP were associated with infusions. (Minute 3/5/10 in mm Hg) Sufentanil (25 ± 5 / 27 ± 6 / 24 ± 6), fentanyl ( 21 ± 2 / 25 ± 4 / 21 ± 4 ), alfentanil ( 22 ± 7 / 21 ± 5 / 20 ± 6 ) Overall ICP increase (9 ± 2 mm Hg, 8 ± 2 mm Hg, and 5.5 ± 1.0 mm Hg, (p < 0.05).	"[S]ignificant, but transient, equal increases in ICP were observed after bolus injections of alfentanil, sufentanil, and fentanyl in patients with head trauma and increased intracranial pressure."	Small sample size. Methodological details sparse. Study excluded as sample size too small (<10) as well as quality score low.

					patient at 24-hr intervals. (N = 6)				
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## Barbiturates

Barbiturates serve as central nervous system depressants. After traumatic brain injury, certain barbiturates, such as pentobarbital, have been used to attempt to control refractory intracranial hypertension that can result from surgery or medical treatment [934, 1000-1005].

### Barbiturates for TBI Patients

#### Not Recommended.

**Barbiturates are not recommended for treatment of TBI.**

*Strength of Evidence – Not Recommended, Evidence (C)*

*Level of Confidence – Low*

*Rationale:*

There are 2 moderate quality studies. In one study, mannitol was considerably superior to pentobarbital for reducing mortality (41% vs. 77%) [542]. The other trial used a control arm that is no longer substantially used [1003]. As there is moderate quality evidence that mannitol is superior to pentobarbital, use of barbiturates is not recommended.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed dead or penetrating head or craniocerebral; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, retrospective studies, or prospective studies. We found and reviewed 75 articles in PubMed, 24 in Scopus, 2 in CINAHL, 9 in Cochrane Library and 1 in other sources. We considered for inclusion 4 from PubMed, 2 from Scopus, zero from CINAHL, zero from Cochrane Library and 1 from other sources. Of the 5 articles considered for inclusion, 4 randomized trials and 3 systematic studies met the inclusion criteria. There are 2 moderate-quality RCTs incorporated into this analysis. There are 3 low-quality RCTs.

## Evidence for the Use of Barbiturates

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Schwartz 1984 (score = 4.5)	Pentobarbital vs Mannitol	RCT	Sponsored by the Sunnybrook Medical Center grant. No mention of COI.	N = 59 with elevated intracranial pressure from severe head injury. Glasgow Coma Scale scores <8.	Mean age mannitol 30.1 years, pentobarbital 28.9 years.	Mannitol 20% 1g/kg with a serum osmolality of 320mOs/L (N = 31) vs. Pentobarbital IV bolus of 10mg/kg and continuous infusion at 0.5-3mg/kg/hr. (N = 28).	All patients given CT scan.	Scores on the GCS correlated with survival rates at 3 months 16/28 patients had dies in the pentobarbital group and at 1-year 6/12 remained hospitalized. For mannitol 13/31 had died and at 1-year 8/16 were hospitalized. Twice as many patients starting with pentobarbital had to use mannitol as rescue medicine, making pentobarbital not 25% better (p=0.04) than mannitol.	“There is no evidence that pentobarbital is 25 percent better than mannitol, either for the control of raised intracranial pressure or for improving survival in patients with intracranial hypertension due to head injury.”	For patients experiencing elevated episodes of ICP they were given rescue medicine, making the study a cross-over, unblinded study. Severe TBI. Data suggest mannitol superior for mortality (41% Mannitol vs 77% Pentobarbital)
Eisenberg 1988 (score = 4.5)	Pentobarbital vs	RCT	Sponsored by National Institutes of	N = 73 patients with TBI	Age range between 15-50 years old.	Barbiturate treatment group. 10 mg/kg	Follow-up at baseline,	ICP control in barbiturate group had	“High dose pentobarbital treatment in	Failed conventional treatment,

	Conventional Treatment		Health. No mention of COI	and a GCS score $\leq 7$ ;		pentobarbital administered over 30 minutes followed by 5 mg/kg/hr. for three hours. A maintenance dose of 1 mg/kg/hr. was used to keep serum levels at 3-4 mg % (N = 37) Vs. Conventional treatment group. 1 mg/hr. morphine administered, hyperventilation, elevation of head, and $\geq .25$ g/kg bolus Mannitol administered (N = 36 )	hours 3, 12, 24, 48, day 1, and month 6.	success in 12 (32.4%) patients vs. 6 (16.7%) in the conventional treatment group, (p = 0.12).	addition to conventional treatment can assist in managing elevated ICP in TBI patients.”	could be crossed over to barbiturate treatment. Did not meet enrollment target. Very specific population; generalizability questionable. Control treatment no longer typically used.
Pérez-Bárcena 2008 (score = 3.0)	Pentobarbital vs Thiopental	RCT	Sponsored by the Spanish government's Fondo de Investigación Sanitaria. No COI.	N = 44 with TBI and a GCS score $\leq 8$ ;	age range between 15-76 years old	10 mg/kg of pentobarbital administered over 30 minutes followed by 5 mg/kg per hour for 3 hours (N = 22) Vs. 2 mg/kg bolus thiopental administered over 20 seconds followed by 3 mg/kg per hour. (N = 22).	Follow-up at baseline, day 1, 2, 3, and month 6.	Uncontrollable ICP in 11 cases in thiopental group and 18 cases in pentobarbital group, (p = 0.03). Thiopental ICP control vs pentobarbital, (odds ratio = 5.1) and 95% CI, (1.2 to 21.9) (p = 0.027).	“Thiopental appeared to be more effective than pentobarbital in controlling intracranial hypertension refractory to first-tier measures.”	Possible randomization failure. Data suggest thiopental may be superior to pentobarbital for reducing intracranial pressure, but with possible randomization failure, the results are questionable.

Young 1983 (score = 3.0)	[Previous table header, if any]	RCT	No mention of sponsorship or COI.	N=214 patients with traumatic brain injury.	Mean age; 25.1 years.	Phenytoin Group (10 to 20 µg/ml) (N=98) Vs. Phenobarbital Group-If patients did not react well with phenytoin they were switched to this group (N=21) Vs. Placebo Group(N=95)	Follow- up for 18 months.	No difference between phenytoin and phenobarbital groups for having late seizures (p=0.48). Drug group as whole did not show lower risk for late seizures vs. placebo (p=0.75). Median time to death was 16 days in the drug vs. 14.5 days in placebo, (p=0.30).	“It cannot be concluded that higher phenytoin plasma concentrations and higher compliance rates than obtained in this study would not have significantly decreased the occurrence of late post- traumatic epilepsy.”	Sparse methods. Data suggest phenytoin not effective compared with placebo to prevent seizures.
Ward 1985 (score = 3.0)	Pentobarbital	RCT	Sponsored by the National Institutes of Health. No mention of COI	N = 53 with an acute intradural hematoma;	Age range above 12 years old.	Pentobarbital administered at 5-10 mg/kg initially, followed by 1-3 mg/kg per hour. (N = 27) Vs. Control group (N = 26)	Follow- up at baseline, day 4, and weeks 1 and 2.	ICP (mean, SD) of pentobarbital group (19.5 mm Hg, ±13.0 mm Hg) vs control group (18.5 mm Hg, ±12.1 mm Hg) showed no significant difference. Arteriole hypotension occurred in 14% of the treated patients and 7% of the control group.	“Results show the prophylactic use of pentobarbital in TBI patients has no significant effect, thus its use is not recommended.”	Methodological details sparse. Many complications in both groups.

## Beta Blockers

Beta blockers prevent the stimulation of the adrenergic receptors. After experiencing a traumatic brain injury, catecholamines form in response to excitatory neurotransmitters. This surge purportedly results in poor neurological outcomes and secondary injury [1006-1009]. Beta blockers are believed to assist in controlling the effects of intracranial hemorrhaging, tachycardia, hypertension and intensity of agitation [977, 1006, 1007, 1009-1017]

### Beta Blockers for TBI Patients

#### Recommended.

**Beta-blockers are selectively recommended for treatment of TBI patients.**

*Strength of Evidence* –Acute, moderate & severe, pre/peri/post-operative: **Recommended, Evidence (C)**

*Strength of Evidence* –Subacute, Chronic, mild: **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – Moderate

*Indications:*

Selectively recommended for management of tachycardia in TBI patients. May be used as an option for hypertensive management.

*Benefits:*

Cessation of tachycardia and/or normalization of blood pressure

*Harms:*

Bradycardia, syncope, dizziness, drowsiness, fatigue, dry mouth.

*Frequency/Dose/Duration:*

Per manufacturer's recommendations.

*Indications for Discontinuation:*

When tachycardia symptoms resolve or other adverse events.

*Rationale:*

There are no quality trials of the general use of beta-blockers for management of TBI patients, thus there is no recommendation for general use among TBI patients. There are 2 moderate quality studies regarding beta blockers. One trial showed that atenolol reduced supraventricular tachycardia and ST-segment and T wave changes as well as appearance of less necrosis at autopsy [1018]. One trial found landiol effective for controlling tachycardia [1010]. A third trial addressed intubation and is thus not included here [1012]. Beta-blockers are either not invasive or minimally invasive, have modest risks, are low to moderate cost and have evidence of efficacy. They are recommended for selective treatment of patients with TBI. Benefits of ongoing treatment after the acute phase have not been shown specifically for TBI patients, but may be inferred based on treatment of either tachycardia and/or hypertension and thus are recommended by expert consensus.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: beta blockers, propranolol, pindolol, acebutolol, atenolol, bisoprolol, metoprolol, nadolol, propranolol, beta-adrenergic blocking agents, brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed dead or penetrating head or craniocerebral; controlled clinical trial, controlled trials, randomized

controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, retrospective studies, or prospective studies. We found and reviewed 40 articles in PubMed, 13 in Scopus, 10 in CINAHL, 9 in Cochrane Library and 0 in other sources. We considered for inclusion 9 from PubMed, 5 from Scopus, 1 from CINAHL, 2 from Cochrane Library and 0 from other sources. Of the 17 articles considered for inclusion, 4 randomized trials and 7 systematic studies met the inclusion criteria. There are 3 moderate-quality RCTs incorporated into this analysis. There is 1 low-quality RCT.

### Evidence for the Use of Beta Blockers

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Levitt 2001 (score = 7.5)	Beta Blockers (Landiolol for intubation vs Lidocaine)	RCT, double blind	No mention of sponsorship or COI.	N = 30 with isolated blunt injury to the head and required intubation.	Mean age 44.1 ± 16.7	Given 0.14 ± 0.06 mg/kg esmolol. (N = 16) vs. Given 0.15 ± 0.11mg/kg lidocaine. (N = 14). Measurements were recorded at one minute intervals for a total of eight minutes.	Follow-up at 8 minutes, not long term.	No difference between groups for changes in HR, (p = 0.68). No difference between groups for changes in DBP, (p = 0.56). No difference between groups for changes in SBP, (p = 0.23).	“Esmolol and lidocaine have similar efficacies to attenuate moderate hemodynamic response to intubation of patients with isolated head trauma.”	Small sample. Data suggest comparable efficacy for reducing response to intubation.
Kawaguchi 2010 (score = 7.0)	Beta Blockers (Landiolol vs Placebo)	RCT Multicenter	Supported by the Department of Anesthesiology, Nara medical University, the Department of Anesthesiology – Resuscitology, Yamaguchi University Graduate School of Medicine, and the Department of Anesthesiology, Hachioji medical Center Tokyo Medical University. No mention of COI.	N = 56 with undergoing intracranial aneurysm surgery with tachycardia	Age 20-75.	Landiolol, given a bolus of (50µg/kg) followed by a continuous infusion at (20µ/kg/min) (N = 28) vs. No Landiolol administrated (N = 28).	Follow-up at 24, 72 hours and at 3 months post operation.	No significant differences in BNP and troponin T values at all-time points between the groups. Serum S-100β values 24 hours after operation were significantly lower in the landiolol treated group, (p = 0.0409).	“[C]ontinuous administration of landiolol can be effectively used for the treatment of tachycardia during intracranial aneurysm surgery in patients with SAH without affecting on arterial blood pressure.”	Data suggest landiolol reduced serum S-100 β levels 24 hours post-op compared with controls. However, landiolol associated with more bradycardia (57% vs. 18%).

Cruickshank 1987 (score = 4.0)	Beta Blockers (Atenolol vs Placebo)	RCT	No mention of sponsorship or COI.	N = 114 with acute head injury.	Aged 11-70 years.	Atenolol 10 mg every 6 hours for 3 and further 4 days (N = 56) vs. Placebo 10 mg every 6 hours for 3 and 4 more days (N = 58).	7 day follow-up.	There was a significant positive correlation between arterial noradrenaline and creatine kinase. 30% vs 7.4% of atenolol group ( $p < 0.05$ ) showed CKMB levels $>3\%$ of total CK.	"Atenolol appeared to reduce significantly the likelihood of supraventricular tachycardia and ST-segment and T-wave changes and prevented cardiac necrosis seen at necropsy."	Data suggest atenolol reduces risk of SVT, ST-segment and T-wave changes. Among those who died, there were fewer cardiac changes at necropsy.
Brooke 1992 (score = 3.5)	Beta Blockers (Propranolol vs Placebo)	RCT	Supported by the National Institute on Disability and Rehabilitation Research grant G00830076, Department of Education, Washington DC and Harborview Injury Prevention and Research Center, Center for Disease control grant CCR49-002570. No mention of COI.	N = 21 with severe, traumatic, closed-head injuries with more than one hour unconsciousness less than an 8 on Glasgow Coma Scale upon admission and any agitation severe enough to be scored on the Overt Aggression Scale.	No age reported.	Treated with increasing dose of propranolol beginning with 60mg a day increasing by 60mg every third day to a maximum of 420mg and tapering off after 3 weeks. (N = 11) vs. Given a placebo dose increasing and tapering in pattern with treated group. (N = 10).	Follow up on a weekly basis for seven weeks.	Intensities for agitation by week higher for placebo. ( $z = -2.028$ , $p < .05$ ) and patterns of increase and decrease between groups not similar, ( $r = 0.491$ ). Number of agitation episodes by week for placebo not greater ( $z = -1.5213$ ) and decrease patterns for N of episodes was similar ( $r = .892$ , $p > 0.05$ ).	"The intensity of agitation was significantly lower in the treatment group although the number of episodes were similar. The use of restraints was also significantly lower in the treatment group."	Small sample with sparse methods. Data suggest propranolol reduced intensity of agitation compared with placebo.

## Aminosteroids

Aminosteroids have been shown to inhibit lipid peroxidation in animals and further randomized controlled trials have attempted to evaluate the effectiveness of tirilazad, an aminosteroid, in humans with head injuries. [1019].

### Aminosteroids for TBI Patients

#### Not Recommended.

**Aminosteroids are not recommended for TBI patients.**

*Strength of Evidence – Not Recommended, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

Few studies have been performed evaluating efficacy of aminosteroids. Of these, there is one showing that the mortality rate is almost identical in both the placebo and study group. A Cochrane review represented a RCT purportedly with 1,156 subjects was to be imminently published, but extensive literature searching has failed to reveal such a study [1019]. In [1020] results cannot be accurately interpreted due to potential randomization failure due to baseline “dissimilarity of prognostic variables.” Thus in the absence of quality evidence, along with strong reason to believe a negative study went unpublished, aminosteroids are not recommended for use in treating TBI patients.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: aminosteroids, traumatic brain Injury, closed head injury, penetrating head injury, concussion, craniocerebral injury, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed 8 articles in PubMed, 2 in Scopus, 0 in CINAHL, 1 in Cochrane Library and 0 in other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 1 from Cochrane Library and 0 from other sources. Of the 2 articles considered for inclusion, 1 randomized trials and 1 systematic studies met the inclusion criteria. There is 1 moderate-quality RCTs incorporated into this analysis. There is 1 systematic review.

### Evidence for the Use of Aminosteroids

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Marshall 1998 (score = NA)	Aminosteroids	RCT	Sponsored by UpJohn Co. No mention of COI.	N = 1120 patients with severe head injury or moderate head injury exhibiting CT scan abnormalities, Glasgow Coma Score (GCS) of 4-8 or 9-12; Eighty-five percent (957) of the patients had suffered a severe head injury (Glasgow Coma Scale [GCS] score 4-8) and 15% (163) had sustained a moderate head injury (GCS score 9-12).	Mean age= 33.6 years.	10 mg/kg tirilazad mesylate group (N =562) vs. 10 mg/kg placebo group (N= 558). Both groups received treatment by intravenous infusion through a central venous line every 6 hours for 5 days.	Follow up at 3 and 6 months.	Six-month outcomes for tirilazad-and placebo groups for Glasgow Outcome Scale categories of both good recovery and death showed no differences. In a subgroup analysis, those with moderate injury at 6mo had lower mortality with tirilazad vs. placebo: 6% vs. 24%, (p=0.042). Among severe head injury group, borderline significance in mortality rates between tirilazad and placebo: 33% vs. 43%, (p=0.071).	"[O]verall efficacy of the use of tirilazad mesylate in patients with moderate and severe head injury could not be demonstrated. A potential positive effect may exist in male patients with traumatic SAH. The reported study emphasizes potential problems occurring within trials of severe head injury."	Appears to be a randomization failure as there were "striking imbalances between baseline prognostic variables", therefore this study cannot be scored.

## Citicoline

Choline is an intermediary of acetylcholine, a neurotransmitter that helps in central and peripheral nervous system functions such as arousal, motor functioning, cognitive functioning, and memory. Cytidine 5'-diphosphocholine (CDP-choline or citicoline) is a naturally occurring source of choline supplementation that may provide neuroprotection and repair as well as improve cognitive symptoms months to years after injury. In the US, CDP-choline is considered a supplement whereas in other countries, such as Europe and Japan, it is considered a pharmaceutical drug that is prescribed [1021]. In TBI, CDP-choline purportedly may be beneficial for neuroprotection during the secondary injury phase and for neurofacilitation for improving recovery throughout rehabilitation [1021-1027].

### Citicoline for TBI Patients

#### No Recommendation.

**There is no recommendation for or against citicholine for TBI patients.**

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

There are 2 moderate quality trials involving Citicholine. One study was terminated early for lack of utility [1028]. The other study suggested a slight benefit [1029] but sample size was small. In the absence of evidence of efficacy, there is no recommendation.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: Citicoline, cytidine diphosphate choline, citicholine, CDP choline, INN, brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed dead or penetrating head or craniocerebral; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, retrospective studies, or prospective studies. We found and reviewed 36 articles in PubMed, 108 in Scopus, 3 in CINAHL, 2 in Cochrane Library and 0 from other sources. We considered for inclusion 7 from PubMed, 1 from Scopus, 1 from CINAHL, 1 from Cochrane Library and 0 from other sources. Of the 3 articles considered for inclusion, 1 randomized trials and 1 systematic studies met the inclusion criteria. There are 2 moderate-quality RCTs incorporated into this analysis. There are 3 low-quality RCTs. There are 4 systematic reviews.

## Evidence for the Use of Citicoline

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Zafonte 2012 (score = 6.5)	Citicoline	RCT	Sponsored by the National Institute of Child Health and Human Development and Ferrer Grupo. No COI.	N= 1213 receiving an acute inpatient hospitalization at a trauma center for non-penetrating TBI;	Ages 18 to 70 years.	Citicoline (2000 mg/d) group (N=607) Vs. Placebo group (N=606). Both groups received treatment via enteral route for 90 days beginning within 24 hours of injury	Assessments at baseline, every 12 hours for 7 days, 14, 30, 58, 90, 135 and 180 days.	Trial was stopped for futility. Patients with complicated mild TBI in the placebo group did better than those given citicoline (global OR 0.72, 95% CI 0.56-0.91, p=0.004). No other significant differences between groups.	“[T]his large, randomized, blinded study showed that acute and subacute treatment with citicoline did not result in improvement in functional and cognitive status. These findings call into question the use of citicoline for patients with TBI.”	Data suggest citicoline comparable to placebo for cognitive status at 90 days out from TBI.
Levin 1991 (score = 5.0)	Citicoline	RCT	No mention of sponsorship or COI.	N =14 hospitalized patients with mild to moderate head injury	Between the ages of 16 to 70; Median age 25 for CDP-choline group and 20 for placebo group.	One gram oral CDP-choline group (n=7) Vs. Placebo group (n=7)	Assessments at baseline and 1 month.	Neuropsychological findings (baseline/follow-up/percent change). Recall of words: CDP-choline (76/111/147), placebo (117/106/8). Recall of locations: CDP-choline (67/94/40), placebo (95/95/-1). Recall of designs: CDP-choline (25/38/104, (p<0.05)), placebo (40/45/29, (p<0.05)). Verbal fluency: CDP-choline	“[I]t appears that CDP-choline is well tolerated, although the patients who were treated did complain more of gastrointestinal distress at one month than the non-treated patients.”	Very small samples. Baseline characteristics sparse. Data from preliminary results suggest improved recognition memory for CDP-choline group.

								(22/41/8), placebo (35/37/13). Designs-free: CDP-choline (18/16/-9), placebo (13/20/25). Designs-fixed: CDP-choline (14/11, p<0.05/0), placebo (13/19, p<0.05/77). CPT (msec): CDP-choline 1527/1225/-9), placebo (1444/1108/-15). PASAT (correct/time): CDP-choline (0.315/0.344/25), placebo (0.398/0.479/27).		
Shokouhi 2014 (score = 3.5)	Citicoline	RCT	Sponsored by Iran's National Elites Foundation and the Neuroscience Research Center. No COI.	N = 58 with diffuse axonal injuries, GCS ≤8, no presence of lesions on the chest, abdomen or focal brain, and who were admitted to affiliated trauma departments;	Mean (±SD) age 30.94 (±8.6) for participants.	Citicoline treatment group receiving 500mg every 6 hours (N =29) vs. Control group (N =29)	Assessments at baseline, 1 day, 6, 12 and 15 days.	On 12th day assessment, Citicoline group exhibited significantly higher Matrix Gla Protein (MGP) values compared with control group; 44.86±21.58 vs. 31.11±17.65, (p=0.01). No statistically significant differences reported between groups for average GCS scores or Fetuin-A levels.	"[C]iticoline, having neutral effects on levels of consciousness, may have a protective role against inflammation and, following vascular calcification, in secondary-TBI through increasing serum levels of fetuin-A and MGP."	Sparse methods. Data suggest citicholine may have protective effect for inflammatory damage and calcification secondary to TBI. But no functional benefit demonstrated.
Maldonado 1991 (score = 3.0)	Citicoline	RCT	No mention of sponsorship or COI.	N =216 with a head injury, initial GCS between 5 and 10;	Mean ages not reported.	CDP-Choline treatment group (receiving 1 g IV Q 6	Assessments at baseline, ICU discharge	Percentage of patients improved at 3 months: headache – NS, dizziness – NS,	"[O]ur results and those of other authors indicate that CDP-choline is effective and safe in	Sparse methods. Data suggest trend in motor, cognitive and psychic improvement in

						hours for 1st and 2nd day, 1 g every 8 hours for 3rd and 4th day. Participants with a phleboclysis got same dose until discharge, and those without received 1g Q 12 hours. After discharge, 200mg Q 8h) (N=115) Vs. Control group (N=101). Both groups received conventional plus allocated treatment.	and 3 months.	motor dysfunction – NS, memory problems – NS, superior neurological dysfunction (SND) – NS, changes in character CDP-choline 91.83 v. control 75, (p<0.05). Distribution of patients by GOS score at 3 months: I- CDP-choline 77 v. control 51, (p<0.05), II – NS, III – NS, IV – NS, V – NS.	the treatment of patients with moderate or severe head injuries.”	CDP-Choline group among severe TBI patients.
Leõn-Carriõn 2000 (score = 2.5)	Citicoline	RCT	Sponsored by the University of Seville and Ferrer Internaciõnal. No mention of COI.	N = 7 with severe memory deficits due to traumatic brain injury;	Ages 18 to 40.	CDPc (1 g/d v.o.) (N=X) Vs. Placebo group (N=X)	Both underwent a memory rehabilitation program for 3 months and received treatment concurrently.	Before and after within group results were gathered. Placebo (before/after): attention (95.60±5.73/97.60±2.19), vigilance (88.40±8.65/96.80±1.79), verbal fluency (22.40±9.91/23.60±11.01), Benton visual retention test	“[P]atients who underwent concurrent neuropsychological + CDPc treatment showed significant improvement in memory volume and verbal fluency.”	Small sample size and sparse methods.

								<p>– number of errors (8.20±3.63/9.40±6.95), Luria’s memory words (62.80±13.24/62.00±11.58). CDPc: attention (82±33.79/90.80±20.57), vigilance (89.60±17.74/98.90±1.79), verbal fluency (24.80±14.65/31.80±9.36, (p&lt;0.05)), Benton visual retention test – number of errors (8.80±5.45/7.20±3.70), Luria’s memory words (63.20±17.31/71.00±12.98, (p&lt;0.05)).</p>	
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## Physostigmine (Eserine)

Physostigmine interrupts acetylcholine metabolism and inhibits acetylcholinesterase. It has been used as an aid in memory retention and cognitive function after traumatic brain injury [1030, 1031]. Scopolamine alternatively has been associated with memory impairments in some experimental studies [1032-1034], providing some rationale for physostigmine.

### Physostigmine (Eserine) for TBI Patients

#### No Recommendation.

**There is no recommendation for physostigmine for treatment of TBI patients.**

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

There are 2 moderate quality studies from over 20 years ago with neither showing clear benefit of physostigmine [1030, 1031]. Thus, there is no recommendation for physostigmine.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: Physostigmine, brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed dead or penetrating head or craniocerebral; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, retrospective studies, or prospective studies. We found and reviewed 11 articles in PubMed, 26 in Scopus, 4 in CINAHL, 2 in Cochrane Library and zero in other sources. We considered for inclusion 6 from PubMed, zero from Scopus, zero from CINAHL, zero from Cochrane Library and zero from other sources. Of the articles considered for inclusion, 6 randomized trials and 1 systematic studies met the inclusion criteria. There are 2 moderate-quality RCTs incorporated into this analysis.

## Evidence for the Use of Physostigmine (Eserine)

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Levin 1986 (score = 5.5)	Physostigmine vs Placebo	RCT, Double-blind, placebo-controlled crossover design	Sponsored by the Moody Foundation, the Javits Neuroscience Investigator Award, and the Del Oro Hospital. No COI	N= 16 men undergoing inpatient rehab for TBIs;	Age range 18-38 years	Group 1: oral physotigmine (N = 8) Vs. Group 2: placebo (N = 8) Patients received either 1 mg or 1.5 mg of oral physotigmine or placebo three times a day during two, seven day testing periods. Two 8 g servings of phosphatidylcholine (lecithin) were administered daily for 21 days.	Follow-up at baseline and day 7, 15, and 21.	Patients showed improvement in sustained attention after receiving physotigmine ( $p = 0.008$ ). Patients who received oral physotigmine in treatment 1 showed more significant improvements in the performance testing than patients in treatment 2 ( $p = 0.02$ ).	“Although the results generally indicated no difference in the effects of the physotigmine- lecithin combination as compared to lecithin alone, sustained attention on the continuous performance test was more efficient under physotigmine than placebo when the drug condition occurred first in the crossover design.”	Crossover. Data suggest physostigmine of no additive benefit above the placebo (lecithin).
Cardenas 1994 (score = 5.0)	Physostigmine vs Placebo	RCT, Double-blind, placebo-controlled	Sponsored by the National Institute on Disability and Rehabilitation Research,	N = 36 men with at least 3 months post-TBI;	Mean age 29±5	Responders (N = 16) and Non-responders (N =20). Each group received both placebo and	Follow-up at baseline, 8 and 16 days,	16 (44%) of patients who took physotigmine improved in their memory	“Results support the potential benefit of cholinergic agonists on	Crossover design. Sparse results reported with mostly reporting of

		crossover design	Department of Education. No COI.		physostigmine with scopolamine. 2 treatment phases scopolamine 5 µg/hr. for 8 days by transdermal patch. Subsequent subjects received a transdermal patch behind each ear for 4-12 hours. Initial physotigmine 2.0 mg and then increased to a maximum dose of 4.0 mg over 7 days.	and 1 month.	test performances (p = 0.384). Responders who took physotigmine improved their standing time when standing tandem with eyes closed vs. non-responders (p < 0.05).	memory after TBI and the need for further research of possible clinical markers for the drug.”	data by “responders.” Follow-up only short term (8 days)
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## Rivastigmine

The most common neurobehavioral consequences of TBI are cognitive impairments. Rivastigmine is a cholinesterase inhibitor that has been suggested to improve cholinergic function in patients with TBI [1035].

### Rivastigmine for TBI Patients

#### Recommended.

**Rivastigmine is recommended for treatment of TBI patients.**

*Strength of Evidence – Recommended, Insufficient Evidence (I)*

*Level of Confidence – Low*

<i>Indications:</i>	For TBI patients with moderate to severe memory deficits.
<i>Benefits:</i>	Improved cognitive function
<i>Harms:</i>	Nausea, vomiting, upper respiratory tract infection, vomiting, diarrhea, tremor, dizziness, drowsiness, anxiety, arthralgia, weakness.
<i>Frequency/Dose/Duration:</i>	Rivastigmine 1.5mg BID with food. Increased to 3.0mg BID at 4 wks. Increased to highest tolerated dose, up to 6 mg/day [1036].
<i>Indications for Discontinuation:</i>	Intolerance, adverse drug events or sufficient resolution of symptoms. The longest trial lasted 26 weeks as an open label [1035].
<i>Rationale:</i>	There are 3 studies using Rivastigmine for TBI. One trial with two reports suggests those with moderate to severe TBI showed improvements [1036] [1035] although the overall study trial was negative suggesting lack of benefit in mild TBI patients. Another trial has also suggested modest benefits [1037], although a third study found no advantage over Donepezil or Galantamine [904]. Adverse drug reactions are high [1037]. Rivastigmine is not invasive, has considerable adverse effects, is moderately costly and has some evidence of efficacy in moderate to severe TBI patients and is thus recommended.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: Rivastigmine, brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed dead or penetrating head or craniocerebral; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, retrospective studies, or prospective studies. We found and reviewed 11 articles in PubMed, 26 in Scopus, 4 in CINAHL, 2 in Cochrane Library and zero in other sources. We considered for inclusion 6 from PubMed, zero from Scopus, zero from CINAHL, zero from Cochrane Library and zero from other sources. Of the articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria. There are 4 moderate-quality RCTs incorporated into this analysis.

## Evidence for the Use of Rivastigmine (Exelon)

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Tenovuo 2009 (score = 7.5)	Rivastigmine vs Placebo	RCT Double blind crossover	Sponsored by Novartis Finland. No COI.	N=102 with TBI, at least two of the following target symptoms: fatigue, decreased stress tolerance, difficulties in concentration, decrease of initiative ability, poor short-term memory, cognitive slowness and changes in behaviour or personality.	18 years or older	N=51 Sequence A (rivastigmine–wash-out–placebo) vs. =51 sequence B (placebo–wash-out–rivastigmine for 8 weeks with 4 week wash-out period. Dose raised every 2 weeks. Max dose equaled 12mg rivastigmine.	Follow-up at 8 weeks.	Primary outcome: rivastigmine group had higher right answers in Subtraction test (OR 2.81; 95% CI: 0.22–5.39; p = 0.034) and Vigilance test (OR 0.08; 95% CI: 0.001–0.17; p = 0.048) vs. placebo group.	"A weak trend favouring rivastigmine for chronic symptoms of TBI was observed. The clinical significance of the results and the problems in conducting drug trials for chronic TBI symptoms are discussed"	High dropout rate (32% dropped out due to ADRs). Data suggest weak trend for rivastigmine for chronic TBI symptoms.
Silver 2006 (score = 6.0)	Rivastigmine vs Placebo	Multicenter RCT	Sponsored Novartis Pharmaceuticals Corporation. COI, J. Silver has received honoraria from Novartis. B. Koumaras is an employee of Novartis and owns equity interest. M. Chen is an employee of Novartis. D. Mirski is a	N = 157 with mild TBI, based on the International Classification of Diseases, Ninth Revision, Clinical Modification 854.0 head injury, and met or exceeded the American Congress of Rehabilitation Medicine criteria.	Aged 18 to 50 years.	Rivastigmine 3 to 6 mg/day (N = 80) Vs. Matching placebo (N = 77).	Follow-up at 12 weeks.	Mean duration of treatment (81.0±23.0 days and 79.6±22.7 days for rivastigmine vs. placebo, respectively; p = 0.712). No differences were found between the groups.	"Rivastigmine was safe and well tolerated in patients with traumatic brain injury with cognitive deficits. Rivastigmine shows promising results in the subgroup of patients with traumatic	Overall study data do not support efficacy. However, post-hoc analyses of moderate to severe TBI patients suggest rivastigmine may be effective for cognitive function in those more

		<p>former employee of Novartis, owns equity interest, and has received honoraria from Novartis. S. Potkin has received grants and honoraria (in excess of \$10,000) from Novartis. P. Reyes has received grants (in excess of \$10,000) and honoraria (in excess of \$10,000) from Novartis. D. Warden has nothing to disclose. P. Harvey has received honoraria from Novartis. D. Arciniegas has received educational grants (in excess of \$10,000) and honoraria (in excess of \$10,000) from Novartis and has given expert testimony related to the</p>					<p>brain injury with moderate to severe memory deficits. "</p>	<p>severely affected.</p>
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			subject of the study. D. Katz has nothing to disclose. I. Gunay is an employee of Novartis.							
Tenovuo 2005 (score = 4.5)	Rivastigmine vs Galantamine vs Donepezil	RCT	No mention of sponsorship or COI.	N=111 with clinically definitive TBI (Kay et al., 1993) with chronic sequels; fairly stable phase after trauma, at least one of the four target symptoms (fatigue, poor memory, diminished attention).	Mean age 40±1.3 years	Donepezil started at 5 mg od in the morning (N=27) vs. Galantamine started at 4 mg bid morning and afternoon (N=30) vs. Rivastigmine started at 1.5 mg bid morning and afternoon (N=54). Doses raised after 1 week if no therapeutic response with good tolerability or if there was partial response and good tolerability.	No mention of study duration or follow-up time.	Mean maintenance dose: 7.2 mg od donepezil, 5.0 mg bid galantamine, 2.3 mg bid for rivastigmine. Positive response (%); 41% donepezil, 60% galantamine, 59% rivastigmine. No differences between these drugs were found.	"CAIs show a very promising therapeutic potential in the treatment of chronic TBI. There were no significant differences between the three drugs. Large-scale randomised double-blinded placebo-controlled studies are clearly needed."	Quasi-randomization Data suggest comparable efficacy between all 3 drug groups.
Silver 2009 (score = 4.0)  Second report,	Rivastigmine vs Placebo	Multicenter RCT	Sponsored by Novartis Pharmaceuticals Corporation. COI, B. Koumaras, X. Meng and I.	N=127 ICD-9, Clinical Modification 854.0 head injury criteria (nonpenetrating) and met or	Aged 18 to 50 years.	Rivastigmine 3 to 6 mg/day (N=65) vs. matching placebo (N=62).	Follow-up at 38 weeks.	At week 38, differences from baseline (week 0) were seen for the	"Treatment with rivastigmine for up to 38 weeks was safe in patients with	Open-label extension study to Silver 2006. 2 <sup>nd</sup> report. Data suggest approximately

<p>see Silver 2006.</p>			<p>Gunay are all employees of Novartis Pharmaceuticals Corporation. Dr. Harvey was compensated by Novartis Pharmaceuticals during the clinical trial for research assistance. He received no compensation for the preparation of this paper.</p>	<p>exceeded the American Congress of Rehabilitation Medicine criteria for mild TBI. Current cognitive deficits which started to occur at least 12 months earlier.</p>		<p>following efficacy measures: CANTAB RVIP A' (P&lt;0.001); CANTAB RVIP mean latency (P&lt;0.001); CANTAB-RT simple reaction time (P=0.002); HVLt total word recall (P&lt;0.001); CANTAB-SWM total errors (P&lt;0.001); COWA-semantic association fluency (P=0.008); Trail A (P&lt;0.001); and Trail B (P&lt;0.001).</p>	<p>TBI and cognitive impairment."</p>	<p>40% had significant improvement from baseline in CANTAB RVIPA and HVLt total word recall for ex-placebo subgroup from week 12-38. However, lack of placebo group limits conclusions on efficacy.</p>
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## Cabergoline

Cabergoline is an ergot derivative, dopamine receptor agonist, lowers prolactin levels, and has a similar use profile as bromocriptine. Deamino arginine vasopressin is used to treat diabetes insipidus, as well as hypernatremia [1038, 1039]. Memantine has been studied in rat models and thought to have neuroprotective potential for TBI patients [1040, 1041]. Substance P is proposed to have an important role in edema, and thus antagonists are proposed as neuroprotective [1042, 1043].

### Cabergoline for TBI Patients

#### No Recommendation.

**There is no recommendation for or against cabergoline for TBI patients.**

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

There is no quality studies of cabergoline and thus there is no recommendation.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: cabergoline; brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed dead or penetrating head or craniocerebral; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, retrospective studies, or prospective studies. We found and reviewed 0 articles in PubMed, Scopus, CINAHL, Cochrane Library and other sources. We considered for inclusion 0 from PubMed, Scopus, CINAHL, Cochrane Library and other sources. No articles met the inclusion criteria. There no quality studies for cabergoline for TBI patients.

## Deamino Arginine Vasopressin (DDAVP) (Desmopressin)

Desmopressin is an ADH analog aimed at decreasing urine output by increasing the activity of ADH [1044]

### Deamino Arginine Vasopressin (DDAVP) for TBI Patients

Recommended.(For treatment of diabetes insipidus)

**DDAVP is recommended for treatment of diabetes insipidus. Otherwise, there is no recommendation for or against DDAVP for TBI patients.**

*Strength of Evidence (Diabetes Insipidus) – Recommended, Insufficient Evidence (I)*

*Strength of Evidence (Lacking DI) – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

<i>Indications:</i>	DDAVP (Cabergoline) is recommended for treatment of diabetes insipidus [1044] but there is no recommendation for use in TBI patients.
<i>Frequency/Dose/Duration:</i>	Per manufacturer’s recommendation
<i>Indications for Discontinuation:</i>	Until not needed for treatment of diabetes insipidus.
<i>Rationale:</i>	There are no quality studies of cabergoline and thus there is no recommendation for general treatment of TBI patients. However, some patients do have indications for treatment of diabetes insipidus.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: Deamino arginine vasopressin, brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed dead or penetrating head or craniocerebral; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, retrospective studies, or prospective studies. We found and reviewed 4 articles in PubMed, 2 in Scopus, 0 in CINAHL, 1 in Cochrane Library and 0 in other sources. We considered for inclusion 0 articles from the databases and other sources. Zero randomized trials and systematic studies met the inclusion criteria. There are no quality studies on DDAVP for TBI patients.

## Memantine

Memantine is an N-methyl-D-aspartate (NMDA)-receptor antagonist. It works by blocking excess activity from glutamate and “may” reduce symptoms associated with Alzheimer’s disease [1045] or Parkinson’s disease or other types of dementia [1046].

### Memantine for TBI Patients

**No Recommendation.**

#### Medications (including topical creams)

**There is no recommendation for or against memantine for the treatment of TBI patients.**

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

There are no quality studies of memantine and thus there is no recommendation.

*Evidence:*

A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: memantine, traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, craniocerebral injury, craniocerebral trauma, penetrating head trauma, closed head trauma, brain concussion, penetrating craniocerebral trauma, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed zero articles in PubMed, zero in Scopus, zero in CINAHL, zero in Cochrane Library and zero in other sources. We considered for inclusion zero from PubMed, zero from Scopus, zero from CINAHL, zero from Cochrane Library and zero from other sources. Of the zero articles considered for inclusion, zero randomized trials and zero systematic studies met the inclusion criteria. There are no quality studies on memantine for TBI patients.

## Substance P Antagonists (Neurokinin 1 Receptors)

Substance P antagonists are non-peptidic antagonists which have recently emerged as a class of drugs with antidepressant activity but potentially less adverse effects [1047, 1048]. Substance P has been determined to directly result in neuronal death. Limiting the release of Substance P has been linked to a decrease in cerebral edema and increased functional outcomes post TBI [1043].

### Substance P Antagonists for TBI Patients

#### No Recommendation.

**There is no recommendation for or against substance P antagonists for the treatment of TBI patients.**

*Strength of Evidence* – No Recommendation, Insufficient Evidence (I)

*Level of Confidence* – Low

*Rationale:*

There are no quality studies of substance P antagonists and thus there is no recommendation.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: Traumatic brain injury, intracranial injury, closed Head injury, penetrating head injury, concussion, brain concussion, craniocerebral Injury, craniocerebral Trauma, and neurokinin-1 Receptor Antagonists, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed 2 articles in PubMed, 39 in Scopus, 0 in CINAHL, 0 in Cochrane Library and 0 in other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library and 0 from other sources. Of the 1 articles considered for inclusion, 0 randomized trials and 1 systematic studies met the inclusion criteria. There are no quality studies on Substance P antagonists for TBI patients.

## Piracetam

Piracetam is a derivative of gamma-aminobutyric acid (GABA) and has been suggested to restore cellular membrane fluidity. At the neuronal level, Piracetam modulates cholinergic and glutamatergic transmitter systems and is thought to have neuroprotective and anticonvulsant properties. It has been used to treat cognitive disorders and dementia [1049].

### Piracetam for TBI Patients

#### No Recommendation.

There is no recommendation for or against use of piracetam for treatment of TBI patients.

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

There are no quality studies of Piracetam and thus there is no recommendation.

*Evidence:*

**Piracetam** – A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Google Scholar and Cochrane Library without date limits using the following terms: piracetum, brain injuries, head injury or closed, penetrating, brain concussion or concussion, craniocerebral trauma, traumatic brain, intracranial or closed dead or penetrating head or craniocerebral; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, retrospective studies, or prospective studies. We found and reviewed zero articles in PubMed, zero in Scopus, zero in CINAHL, zero in Cochrane Library and zero in other sources. We considered for inclusion zero from PubMed, zero from Scopus, zero from CINAHL, zero from Cochrane Library and zero from other sources. Zero articles met the inclusion criteria.

## Complementary and Alternative Medicine

Complementary and alternative medications and homeopathy have been used for treatment of TBI patients [1050-1052].

### Boswellia Serrata for TBI Patients

No Recommendation.

**There is no recommendation for or against *Boswellia Serrata* for TBI patients.**

*Strength of Evidence* – No Recommendation, Insufficient Evidence (I)

*Level of Confidence* – Low

*Rationale:*

There is one moderate quality pilot study of *Boswellia Serrata* reporting a non-significant trend [1052], thus there is no recommendation for or against *Boswellia Serrata*.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: complementary therapies, complementary and alternative medicine, integrative medicine, alternative therapies, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed 118 articles in PubMed, 387 in Scopus, 20 in CINAHL, 48 in Cochrane Library and 1 in other sources. We considered for inclusion 11 from PubMed, zero from Scopus, zero from CINAHL, zero from Cochrane Library, and one from other sources. Of the 12 articles considered for inclusion, 3 randomized trials and zero systematic studies met the inclusion criteria.

### Other Alternative, Complementary, Homeopathic Treatments for TBI Patients

No Recommendation.

**There is no recommendation for or against other alternative, complementary, or homeopathic treatments for TBI patients.**

*Strength of Evidence* – No Recommendation, Insufficient Evidence (I)

*Level of Confidence* – Low

*Rationale:*

Homeopathic treatments were evaluated in two low quality studies [1050, 1051]. among patients 3 years after injury [1051], thus there is no quality evidence and no recommendation for or against other complementary, alternative or homeopathic treatments for TBI.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: complementary therapies, complementary and alternative medicine, integrative medicine, alternative therapies, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*,

randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed 118 articles in PubMed, 387 in Scopus, 20 in CINAHL, 48 in Cochrane Library and 1 in other sources. We considered for inclusion 11 from PubMed, zero from Scopus, zero from CINAHL, zero from Cochrane Library, and one from other sources. Of the 12 articles considered for inclusion, 3 randomized trials and zero systematic studies met the inclusion criteria.

There is one moderate-quality RCTs incorporated into this analysis.  
There are nosystematic reviews.

## Evidence for the Use of Complementary/Alternative Medicine

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Moein 2013 (Score = 5.0)	Complementary/Alternative Medicine	RCT, double-blind, crossover	Sponsored by Isfahan University of Medical Sciences, Medical School, Isfahan, Iran. No COI.	N = 38 with diffuse axonal injury, coma >6hrs. GCS≤12 within first 24 hrs.	Age range 15–65 years.	Group A: Placebo (N = 20) vs. Group B: Boswellia Serrata capsules (3 times per day) (N = 18) for 6 weeks and then switched to the other intervention for another 6 weeks.	Follow-up for 2, 6, and 12 weeks.	Both groups showed improvements in the DRS (p = 0.15), but there was not statistically difference. After taking Boswellia Serrata capsules, patients had higher improvement on cognitive ability for self-care activities.	“These results suggest that BS resin does not significantly affect general outcome, but may enhance the cognitive outcome of patients with DAI.”	Pilot. Crossover. High dropouts. Data suggest treatment may have efficacy and need full size trials.
Chapman 1999 (Score = 3.0)	Complementary/Alternative Medicine	RCT, double-blind	Sponsored by the National Institutes of Health, Office of Alternative Medicine, Laboratoires Boiron, and the Boiron Research Foundation. No mention of COI.	N = 50 with MTBI (mean 2.93 years since injury, SD 3.1).	Mean age in the treatment group was 42.7 (11.3) years and 43.5 (12.3) in the placebo group.	Treatment group: homeopathic medicines. Each patient received a medication (from 18 homeopathic medicines) according to his/her symptoms. (N = 27) vs. Placebo control (N = 23).	Follow-up for 4 months.	The DSS was statistically improved in the treatment group vs. the placebo group [95% CI: – 0.895 to – 0.15], (p = 0.009). Additionally, the treatment group had greater improvements in the SRS vs. the placebo group [95% CI: – 0.548 to 0.01], which was almost statistically significant (p = 0.058). The treatment group showed significant reduction on the main symptoms in	“This study suggests that homeopathy may have a role in treating persistent MTBI. Our findings require large-scale, independent replication.”	Pilot study. Various treatments used. Baseline differences concerning (e.g. alternative med. experiences 17 vs. 41%). DSS was stat. improved in treatment group vs. placebo [95% CI: – 0.895 to – 0.15], (p = 0.009). Treatment group had greater improvements in SRS vs. placebo [95% CI: – 0.548 to 0.01], which was almost significant (p = 0.058). Treatment

								the SRS-10 vs. the placebo group [95% CI – 0.766 to – 0.048]], (p = 0.027).		group showed significant reduction in main symptoms in SRS-10 vs. placebo [95% CI – 0.766 to – 0.048]], (p = 0.027).
Sun 2009 (Score = 2.0)	Complementary /Alternative Medicine	RCT	No mention of sponsorship or COI.	N = 80 with traumatic intracranial hematoma (TICH). Patients had Glasgow Coma Score (GCS) ≤8.	Age range 16 – 64 years.	Trial group: Danhong Injection (herbal TCM product from Radix Salviae miltiorrhizae and Flos Carthami tinctorii) (N = 40) Vs. Control group (N = 40).	Follow-up for day 7, day 14 and at 3 months.	GCS was statistically significant difference in the trial group (11.88 ± 0.97) vs. the control group (11.10±1.15) after treatment (p < 0.01). There was a significant difference between groups in the reduction of hematoma volume (p < 0.05). The trial group (4.48 ± 1.11) had a superior GOS vs. the control group (4.02 ± 0.91), (p < 0.05).	“No obvious adverse reaction occurred during the whole therapeutic course. No abnormal intracranial hematoma expansion or rehemorrhage was detected during the therapeutic course. No abnormality was found in the dynamic observation of the patients’ coagulation spectrum, indicating DHI was effective and safe in treatment of TICH, with no possibility of hemorrhage. These results indicate that DHI may be considered as an effective agent in the treatment of TICH.”	Sparse details.

## Infusion Therapy

### Intrathecal Baclofen (ITB) Pump for TBI Patients

Recommended.

Intrathecal baclofen is recommended for highly selective use among TBI patients.

*Strength of Evidence – Recommended, Insufficient Evidence (I)*

*Level of Confidence – Low*

<i>Indications:</i>	For treatment of severe, chronic muscle spasticity and dystonia associated with TBI that is unable to be sufficiently controlled through non-invasive means that included other pharmaceutical, including baclofen at 80-160mg/day. Also should have considered and tried at least one of: diazepam, clonidine and/or dantrolene [1053]. Should have severe hypertonia sufficient to interfere with activities of daily living [1053]. That single quality trial required at least one year with these indications prior to inclusion in the trial, as well as Ashworth score at least 3, and average spasm score at least 2.
<i>Benefits:</i>	Reduced muscle spasticity and ability to better accomplish normal activities.
<i>Harms:</i>	Drowsiness, weakness, dizziness, headache, seizures, nausea, vomiting, constipation, hypotension, confusion, fatigue, respiratory depression, insomnia, increased urinary frequency, urinary retention, adverse events, infections, paralysis, and death.
<i>Frequency/Dose/Duration:</i>	Intrathecal test dose of 50 mcg in a volume of 1 mL injected into the intrathecal space by barbotage over at least one minute. Generally at least 2 trials of saline and intrathecal dose of baclofen to confirm efficacy before consideration of implantation of an intrathecal pump.
<i>Indications for Discontinuation:</i>	Sufficient resolution of symptoms, often after a trial of turning the device off. Infections, complications, intolerance.
<i>Rationale:</i>	There is 1 moderate quality study [1053] and one lower quality study showing some efficacy in reducing spasticity and dystonia in bilateral extremities [929]. Both studies were compared to placebo and both with small sample sizes. Neither involved implantation of a pump system. Baclofen administered intrathecally, especially by a pump, is invasive, has considerable adverse effects, is costly, but data suggest it is likely effective for a highly select TBI patient group.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: muscle relaxants, baclofen, carisoprodol, chlorzoxazone, chlorphenesin, cyclobenzaprine, dantrolene, diazepam, medazepam, mephenesin, meprobamate, metaxalone, methocarbamol, orphenadrine, quinine, tizanidine, tolperisone, xylazine, zoxazolamine, traumatic brain injury, closed head injury, penetrating head injury, concussion, craniocerebral injury, controlled clinical trial, controlled trials, randomized controlled trial, randomized

controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Nonexperimental Studies. We found and reviewed 118 articles in PubMed, 423 in Scopus, 0 in CINAHL, 15 in Cochrane Library and 12 in other sources. We considered for inclusion 8 from PubMed, 3 from Scopus, 0 from CINAHL, 0 from Cochrane Library and 0 from other sources. Of the 11 articles considered for inclusion, 10 randomized trials and 1 systematic studies met the inclusion criteria. There is 1 moderate RCT incorporated into this analysis. There is 1 low-quality RCT.

### Evidence for the Use of Intrathecal Baclofen (ITB) Pump

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Meythaler 1996 (score = 6.5)	Intrathecal Baclofen vs Placebo	RCT/Crossover	Sponsored in part by grant from the United States Department of Health and Human Services, Centers for Disease Control and Prevention – National Center for Injury Prevention and Control to the University of Alabama Injury Control Research Center. No COI.	N=11 adults who had an acquired brain injury (9 Motor vehicle crash (MVC) 1 Gunshot wound (GSW) and 1 Anoxic episode; Mean	Age 25 (20-37)	N=11 All patients were randomized to receive a bolus injection of either intrathecal, preservative-free normal saline or 50 ug of baclofen diluted with preservative saline. Crossover phase at 48 hours.	Follow-up for baseline 1, 2, 4, and 6 hours post injection.	Lower extremity (LE) Ashworth baseline vs 4 hours; $4.2 \pm 0.8$ vs $2.2 \pm 0.6$ ( $p=0.0033$ ). LE Ashworth score Placeo (PLC) vs active drug (ACT) at hour 4 and 6; hr. 4 ( $p=0.0084$ ) hr. 6 ( $p=0.0163$ ). LE spasm score baseline vs 4 hours; $3.1 \pm 1.0$ vs $1.0 \pm 0.7$ ( $p=0.0032$ ). LE Muscle spasm score Placeo (PLC) vs active drug (ACT) at hour 4 and 6; hr. 4 ( $p=0.0073$ ) hr. 6 ( $p=0.0049$ ). LE reflex score baseline vs 4 hours; $3.2 \pm 0.5$ vs $1.0 \pm 1.3$ ( $p=0.0033$ ). LE Reflex score Placeo (PLC) vs active drug (ACT) at hour 4 and 6; hr. 4 ( $p=0.0086$ ) hr. 6 ( $p=0.0085$ ). Upper extremity (UE) Ashworth score baseline vs 4 hours; $3.3 \pm 1.3$ vs	“Intrathecal baclofen has the potential for improving, significantly, The quality of life in patients with acquired BI. The issue is whether there is a reduction in tone, and whether the dosage required to produce this change in spastic hypertonia may negatively affect the patient's cognitive function or have other untoward effects. Particular attention must be given to evaluating patients for cognitive changes and functional improvements, as well as the long-term costs of the system.”	Small sample crossover trial. Intrathecal baclofen associated with reduced spastic hypertonia compared with placebo.

								1.9 ± 0.8 (p=0.0033). UE spasm score baseline vs 4 hours; 1.8 ± 1.3 vs 0.6 ± 1.0 (p=0.007). UE biceps reflex score baseline vs 4 hours; 2.7 ± 0.5 vs 1.7 ± 0.6 (p=0.0111).		
Meythaler 1999 (score = 3.5)	Intrathecal Baclofen vs Placebo	RCT	Sponsored by Medtronic, Inc. Commercial party with a direct financial interest in the results of the research supporting this article has conferred or will confer a financial benefit upon one or more of the authors.	N = 17 patients with TBI and intractable spasticity and dystonia for more than 6 months' duration recruited in a consecutive manner.	Mean age: 29± 11 yrs.)	Patients were randomized to receive a bolus intrathecal injection of either preservative-free normal saline (N=not mentioned) Vs. 50 µg of baclofen. (N=not mentioned) A lumbar puncture was performed at either the L3-L4 or the L2-L3 interspace, and 1 cc was injected.	Follow-up for data collection every 1 month, 3 months, 6 months, 9 months, and 1 year after pump placement.	After 1 year of continuous ITB treatment the average LE Ashworth score decreased from 3.5 ±1.3 (SD) to 1.7 ± 0.9 (p < .0001), spasm score from 1.8 to 1.3 to 0.2 ± 0.5 (p < .0001), and reflex score from 2.5 ± 1.1 to 0.1 ±0.3 (p < .0001). The average UE Ashworth score decreased from 2.9 ± 1.5 to 1.6 ± 1.0 (p < .0001), spasm score from 1.2 ± 1.5 to 0.2 ± 0.6 (p < .0001), and reflex score from 2.2 ± 0.5 to 1.0 ±0.8 (p < .0001). The average ITB dose required to attain these effects at 1 year was 302pg continuously infused per day.	"Continuous intrathecal infusion of baclofen is capable of maintaining a reduction in spasticity and dystonia in both the upper and lower extremities of TBI patients."	Small sample size. Data suggest that at one year, continuous infusion of Baclofen reduces spasticity and dystonia in both the upper and lower extremities.

## Injection Therapy

### Nerve Blocks

Diagnostic and therapeutic nerve blocks involve a percutaneous needle filled with lidocaine or another local anesthetic and are used to target specific nerves. Most commonly in TBI patients, these are to target one or both of the occipital nerve branches. Nerve blocks trialed also include supraorbital, supratrochlear and auriculotemporal. These are used to attempt to determine and evaluate headaches, spasticity, ROM and/or dystonia. Generally, these blocks are performed simultaneously for both diagnostic and therapeutic purposes. There also are nerve blocks commonly administered for cervical nerve roots to address neck-related pain.

### Radiofrequency Neurotomy, Neurotomy, or Facet Rhizotomy for Chronic Cervicothoracic Pain No Recommendation.

There is no recommendation for or against the use of radiofrequency neurotomy, neurotomy, or facet rhizotomy for the treatment of chronic cervicothoracic pain confirmed with diagnostic blocks, but who do not have radiculopathy and who have failed conservative treatment.

*Strength of Evidence* – **No Recommendation, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

<i>Indications:</i>	Chronic cervicothoracic pain patients without radiculopathy who failed conservative treatments and who have had a confirmed diagnosis by medial branch blocks.[1054]
<i>Indications for Discontinuation:</i>	Resolution of symptoms. If there is no response to the first procedure, there is no evidence that a second lesion will be beneficial.
<i>Frequency/Dose/Duration:</i>	One procedure might be tried after failure of non-invasive treatments including NSAIDs and a quality exercise program or as a means to help with participation in an active rehabilitation program. There is no recommendation for repeated procedures. It is reasonable to attempt a second lesion after 26 weeks in patients who had greater than 50% improvement in pain from first procedure for the first 8 weeks with a late return of pain.[1055] There is no recommendation for a third or for additional procedures. There is logically a limit as to how many times it is possible to permanently destroy the same nerve.

### Radiofrequency Neurotomy for Cervicogenic Headache

#### Moderately Not Recommended.

**Radiofrequency neurotomy is moderately not recommended for the treatment of cervicogenic headache.**

*Strength of Evidence* – **Moderately Not Recommended, Evidence (B)**

*Level of Confidence* – **Low**

Occipital nerve blocks have been used to treat migraine and cervicogenic headaches [1056-1059]. Greater occipital nerve blockade has been used to treat episodic cluster headache [1060] and for migraines [1061].

## Occipital Nerve Blocks

### Recommended.

Occipital nerve blocks are recommended for the treatment of cervicogenic headache. There is no recommendation for or against occipital nerve blocks for the treatment of migraine headache.

### **For Cervicogenic Headache: Strength of Evidence – Recommended, Evidence (C)**

*Level of Confidence – Low*

### **For Migraine Headache: Strength of Evidence – No Recommendation, Insufficient Evidence (I)**

*Level of Confidence – Low*

<i>Indications:</i>	Unilateral cervicogenic headaches, with headache precipitated by neck movement or pressure over the greater occipital nerve, reduced neck range of motion [1056]. Post-traumatic migraine headaches are another potential indication. Whiplash injury was excluded from the Naja study. Headaches should be resistant to other forms of treatment (e.g., NSAID, acetaminophen, stress reduction, exercise etc.).
<i>Benefits:</i>	Potential for reduced headache intensity, frequency and duration. Potential for reductions in use of other medications.
<i>Harms:</i>	Medicalization of the case, especially as average pain relief of 3.67 days vs. 1.52 days for normal saline [1056]. Rare procedure complications.
<i>Frequency/Dose/Duration:</i>	The highest quality study showing limited short-term efficacy for cervicogenic headaches used 10mL (3mL 2% lidocaine, 3mL 2% lidocaine with epinephrine 1:200,000, 2.5mL 0.5% bupivacaine, 0.5mL fentanyl 50µg/mL and 1mL clonidine 150 µg /mL).
<i>Rationale:</i>	There are 2 high quality trials with conflicting results, one suggesting efficacy for cervicogenic headache [1056] and one suggesting a lack of efficacy for migraines [1057], resulting in questions regarding whether efficacy may differ based on the diagnosis. Two moderate quality trials suggested efficacy for migraines [1058] [1059]. Thus, the overall quantity of quality literature is small and conflicts for migraine headaches. There is no long-term study showing efficacy for treatment of cervicogenic headaches, and there is one trial without placebo control suggesting comparable efficacy with a transcutaneous stimulation device [1062]. Nerve blocks are invasive, have some adverse effects, are moderate to high cost over time, and have some evidence of short-term efficacy and thus are selectively recommended for treatment of cervicogenic and migraine headaches thought to be related to the TBI event that are resistant to other forms of treatment.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: migraine disorders, Migraines, Tension-Type Headache, neuralgia, cluster headache, post-traumatic headache, cervicogenic headache, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies.

We found and reviewed 22 articles in PubMed, 7 in Cochrane Library, 4550 in Google Scholar, and 1 from other sources. We considered for inclusion 3 from PubMed, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 4 articles considered for inclusion, 3 randomized trials and 1 systematic studies met the inclusion criteria.

### Evidence for the Use of Occipital Nerve Blocks

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Naja, 2006 (8.0)	Occipital Nerve Block	RCT	Sponsored by the Makassed General Hospital and the suggestions of the peer-reviewers in the preparation of this article. No mention of COI.	N = 50 patients with cervicogenic headache.	The mean age of the block group is 46.44 years. 3 males, 19 females. The mean age of the placebo group is 47.36 years. 7 males, 18 females.	Block Group (N =25): received either both GON and LON blocks, or GON and LON with facial nerve blockade, depending on the extension of the headache.  Vs.  Placebo Group (N =25): received injections of an equivalent volume of preservative-free normal saline.	Two weeks.	At the two-week follow up the Block and Placebo group depicted the following data, respectively. Duration of pain relief (days): 3.67, 1.52, p=0.0001. Frequency of headaches/2 weeks: 5.50, 7.04, p=0.026. Number of analgesics consumed/2 weeks: Paracetamol (tablet 500mg) – 48, 70.96, p=0.0001; Dextropropoxyphene (capsule 30mg) – 18.33, 40.17, p=0.0001; Tramadol hydrochloride (tablet 50 mg) – 2.33, 5.56, p=0.006; Ketoprofen (tablet 100 mg) – 0.50, 4.30, p=0.01. Total Pain Index: 194.25, 329.96, p=0.0001.	“In conclusion, the nerve stimulator-guided occipital nerve blockade is a treatment that provides relief of CGH and accompanying symptoms for up to two weeks. This simple technique merits further investigation for patients suffering from CGH.”	Some also injected with facial nerve blocks. Data suggest at 2 weeks post injection, block group had sig. reduction in cervicogenic headache and symptoms c/w controls. However, only 3.67 days vs. 1.52 days relief from NS injection. Analgesic use also decreased and return to functional activities better in block group.

Dilli 2015 (8.0)	ONB	RCT	Sponsored by CTSA grant number UL1 TR000135 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH). No COI.	N = 70 with ICHD (International Classification of Headache Disorders, second edition) II defined episodic	Aged 18 and 75 years; 20 females and 55 females.	Active intervention, 2.5 ml 0.5% bupivacaine plus 0.5 ml 20 mg methylprednisolone over the ipsilateral (N = 35)  vs  Placebo intervention, bilateral (bilateral headache) occipital nerve or 2.75 ml normal saline plus 0.25 ml 1% lidocaine without epinephrine (N = 35).	About 15-days	Those with at least 50% reduction in the frequency of moderate or severe migraine headache was 30% for both groups; 10/33  vs 9/30, $\Delta$ 0.00, 95% CI -0.22 to 0.23.  Mean frequency of at least moderate (mean 9.8 versus 9.5) and severe (3.6 versus 4.3) migraine days / acute medication days (7.9 versus 10.0) not different at baseline.	“Greater ONB does not reduce the frequency of moderate to severe migraine days in patients with episodic or chronic migraine compared to placebo.”	Data suggest occipital nerve blocks did not decrease frequency of moderate to severe headache days in patients with either episodic or chronic migraines c/w placebo.
Lauretti 2014 (7.5)	Occipital Nerve Block	RCT	No mention of sponsorship or COI.	N = 30 with refractory cervicogenic headache	Mean age: 43 years. 8 males, 20 females.	Group 5: GON subcompartmental technique, 10 mg dexamethasone, 40 mg lidocaine, nonionic	2 and 24 weeks	Significant decrease in VAS ( $p < 0.01$ ) was observed in all subcompartmental groups during 24 weeks compared to only 2 weeks of effective analgesia after classic GON technique ( $p < 0.01$ ).	“[T]he suboccipital compartmental GON technique resulted in at least 24 compared to 2 weeks of analgesia when the same dosage of dexamethasone and	No placebo control. Randomization only involved an evaluation of different volumes of injectate (5, 10 or 15mL).

						<p>iodine contrast and saline, 5 mL final volume)</p> <p>(N = 10)</p> <p>vs</p> <p>Group 10 GON subcompartmental technique, 10 mg dexamethasone, 40 mg lidocaine, nonionic iodine contrast and saline, 10 mL final volume</p> <p>(N = 10)</p> <p>vs</p> <p>VS Group 15 GON subcompartmental technique, 10 mg dexamethasone, 40 mg lidocaine, nonionic iodine contrast and saline 15 mL final volume</p>	<p>Rescue analgesics were reduced during first 2 weeks under GON and for at least 24 weeks for all groups. Analgesic effect persisted similarly for all 3 groups regardless of final volume.</p>	<p>lidocaine was applied by the classical technique, suggesting that the administration of the drugs near to the dorsal ganglion was more efficacious to counteract CH."</p>	<p>Data suggest no differences. All groups reported sig. pain reductions last 24 wks, although pain levels gradually rose.</p>
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						(N = 10).				
Cuadrado 2016 (7.5)	Occipital Nerve Block	RCT	No sponsorship or COI.	N = 36 women with chronic migraines (CM).	Mean age: 35.8 ±11.1 years.	Occipital nerve (GON) blocks with bupivacaine 0.5%  (N = 18)  vs  Sham procedure with saline  (N = 18).	At 1 hour, 1 week after and 1 week following treatment .	The GON block had significant results compared to the placebo in decreasing the amount of days per week with moderate- or-severe  headache (MANOVA; p= 0.027), or any headache (p= 0.04). Pressure pain thresholds  (PPT) differences at baseline (T=0) compared to treatment (T1) and follow up (T2) among groups were statistically  significant for the supraorbital (T0–T1, p= 0.022; T0–T2, p= 0.031) and infraorbital sites (T0– T1, p= 0.013; T0– T2, p= 0.005).	“GON anaesthetic blocks appear to be effective in the short term in CM, as measured by a reduction in  the number of days with moderate-to- severe headache or any headache during the week following injection.”	Data suggest greater occip. nerve blocks had short term efficacy for chronic migraine attributed to decrease in moderate to severe headache days. Blocks also resulted in increase in pressure pain thresholds.
Inan 2015 (7.5)	ONB	RCT	No mention of sponsorship. No COI.	N = 84 with chronic migraine (CM).	Mean age 37.0 ± 9.1 group A and 37.3 ± 8.8 group B; 7 males, 65 females.	Group A, injections of bupivacaine  GON blockade  (N = 37)	4-weeks	1 <sup>st</sup> month;  Post-treatment values group B, (p < 0.001) vs placebo, (p = 0.223).	“[G]ON blockade with bupivacaine was superior to placebo and was found to be effective,	Data suggest greater occip. nerve blocks plus bupivacaine superior to placebo for decreasing number,

						vs Group B, injections of placebo  GON blockade  (N = 37).		2 <sup>nd</sup> month;  Headache duration for group A vs B; p < 0.001 vs p < 0.05.  Both group's values 2 <sup>nd</sup> and 3 <sup>rd</sup> month values, (p < 0.001).  Headache durations, at all follow-up periods, (p > 0.005).	safe, and cost-effective for the treatment of CM.”	duration and severity of headache pain.
Gabrhelik 2011 (4.0)	ONB	Pilot RCT	No mention of sponsorship or COI.	N = 30 with refractory cervicogenic headache.	Mean age 45.90 (12.8) group A and 43.60 (9.2) group B; 13 males and 17 females.	Group A, greater occipital nerve block with steroid  (N = 15) vs Pulsed radiofrequency treatment  (N = 15).	Evaluated parameters were recorded before the procedures, and at 3 and 9 months after the treatment	Median VAS before treatment; 5.5 in group A vs 5.9 group B.  At 9-months;  VAS of 4.3, (p < 0.05) in group A vs 3.1 group B, (p < 0.001).  Before treatment / and 3 months after treatment; the median index MQS – III. 9.2 in both groups / 4.8 in group A vs 3.2 in group B, (p < 0.001).	“Greater occipital nerve blockade with a mixture of local anaesthetic and steroid  and pulsed radiofrequency to the greater occipital nerve are both effective  intervention techniques in the treatment of refractory cervicogenic headaches.”	Pilot study. Claims blind, but likelihood seems low as one arm was an injection. Data suggest comparable results, with improved pain at 3mo, but then worsening pain at 9mo.

## Occipital Nerve Stimulation (ONS)

Occipital nerve stimulation has been attempted both transcutaneously (non-invasive) [1063] and by implanted stimulator [1064-1067].

### Non-Invasive Occipital and Supraorbital Nerve Stimulation (ONS)

#### Recommended.

Non-invasive occipital and supraorbital nerve stimulation is recommended for the treatment of TBI patients.

#### *Strength of Evidence – Recommended, Evidence (C)*

#### *Level of Confidence – Low*

<i>Indications:</i>	Non-allodynia pain (i.e., not overly sensitive to pain on palpation of neck/scalp or other stimulation; may be assessed with 12-item allodynia symptoms checklist, ASC-12 [1068]). Chronic migraine or tension headaches [1069] thought to be related to the TBI event. Headaches should be resistant to other forms of treatment (e.g., NSAID, acetaminophen, stress reduction, exercise etc.) [1064]. At least 2 months of medication withdrawal for medication overuse headaches [1064].
<i>Benefits:</i>	Potential for reduced headache intensity, frequency and duration. Potential for reductions in use of other medications.
<i>Harms:</i>	Medicalization of the case.
<i>Frequency/Dose/Duration:</i>	Sessions of 30min./day for 2 weeks.
<i>Rationale:</i>	A few moderate quality RCTs found headache reductions compared with sham [1063]. One trial found the reductions lasted beyond the 2wks of treatment to the duration of the trial of 60 days with 86% v. 4% of non-allodynic patients achieving at least 50% reduction in headache days [1063]. Cutaneous nerve stimulation administered in sessions is not invasive, has minimal adverse effects, is high cost, and have some evidence of short- to intermediate-term efficacy and thus are selectively recommended for treatment of cervicogenic and migraine headaches thought to be related to the TBI event that are resistant to other forms of treatment.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, Peripheral Nerve Stimulation, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 93 articles in PubMed, 756 in Scopus, 13 in CINAHL, 11 in Cochrane Library, 3770 in Google Scholar, and 4 from other sources. We considered for inclusion 0 from PubMed, 5 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 3 from Google Scholar, and 4 from other sources. Of the 13 articles considered for inclusion, 2 randomized trials and 8 systematic studies met the inclusion criteria

### Evidence for Occipital Nerve Stimulation (ONS)

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Gabrhelik 2011 (4.0)	ONB	Pilot  RCT	No mention of sponsorship or COI.	N = 30 with refractory cervicogenic headache.	Mean age 45.90 (12.8) group A and 43.60 (9.2) group B; 13 males and 17 females.	Group A, greater occipital nerve block with steroid (N = 15)  vs  Pulsed radiofrequency treatment (N = 15).		Median VAS before treatment; 5.5 in group A vs 5.9 group B.  At 9-months;  VAS of 4.3, ( $p < 0.05$ ) in group A vs 3.1 group B, ( $p < 0.001$ ).  Before treatment / and 3 months after treatment; the median index MQS – III. 9.2 in both groups / 4.8 in group A vs 3.2 in group B, ( $p < 0.001$ ).	“Greater occipital nerve blockade with a mixture of local anaesthetic and steroid  and pulsed radiofrequency to the greater occipital nerve are both effective  intervention techniques in the treatment of refractory cervicogenic headaches.”	Pilot study. Claims blind, but likelihood seems low as one arm was an injection. Data suggest comparable results, with improved pain at 3mo, but then worsening pain at 9mo.

## Implantable Occipital Nerve Stimulation (ONS) Devices Not Recommended.

Implantable occipital nerve stimulation (ONS) devices are not recommended for use in the treatment of TBI patients.

**Strength of Evidence – Not Recommended, Insufficient Evidence (I)**

**Level of Confidence – Low**

*Rationale:*

There is one moderate quality trial suggesting lack of efficacy [1070]. There is one report of some efficacy in a longer-term, but open label trial for treatment of migraine headaches [1071]. The same trial reported high rates of adverse events with 20/177 (11.3%) having unsuccessful trials, 9/105 (8.6%) having explanation in the active device group in the first year, and an overall experience of adverse events affecting 70.7% of the patients. Implantable devices are invasive, have significant adverse effects, are high cost and with the only quality trial suggesting lack of efficacy, there is a need for further quality trials to establish efficacy. Additionally, the only quality trial of size is on migraine headaches, which is of questionable use for treatment of TBI patients. These devices may be a consideration for limited use in those with normal psychological profiles, no evidence of malingering, and with headaches refractory to numerous treatments and preventives including, but not limited to, multiple classes of pharmaceuticals, and botulinum.

*Evidence:*

*A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, Peripheral Nerve Stimulation, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 93 articles in PubMed, 756 in Scopus, 13 in CINAHL, 11 in Cochrane Library, 3770 in Google Scholar, and 4 from other sources. We considered for inclusion 0 from PubMed, 5 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 3 from Google Scholar, and 4 from other sources. Of the 13 articles considered for inclusion, 2 randomized trials and 8 systematic studies met the inclusion criteria*

### Evidence for the Use of Occipital Nerve Blocks (ONS)

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Silberstein 2012 (9.0)	ONS	RCT	Sponsored by St. Jude medical Neuromodulator Division. No conflict of interest for authors, SN, KR, JV, JO, JG, NM and PW. For all other authors there was COI.	N = 157 With Chronic Migraine.	Mean age 44.6(±12) 32 males, 124 females.	(N = 105) Received implantation of peripheral nerve stimulation (PNS) device. The device was St Jude Medical Neuromodulation . Connected to the implantable pulse generator(IPG). These patients received programing for appropriate stimulation.  vs  (N = 52) Received implantation of peripheral nerve stimulation (PNS) device. The device was St Jude Medical Neuromodulation . Connected to	12 weeks	Percentage of responders in the active compared with the control group. (95% lower confidence bound (LCB) of -0.06; p=0.55). patients that achieved a 30 % reduction (p = 0.01). Active compared to control reduction of headache days (Active = 6.1), baseline = 22.4, Control = 3.0, Baseline = 20.1 (p = 0.008). reduction in migrated related disability (p = 0.001). direct report of pain relief (p = 0.001).	“Study failed to meet its primary endpoint, this is the first large-scale study of PNS of the occipital nerves in CM patients that showed significant reductions in pain, headache days, and migraine-related disability.”	Data suggest lack of efficacy. As well, only 17% vs. 13% considered responders.

						the implantable pulse generator(IPG). Connected to a sham and did not receive stimulation programming.				
Slotty 2014 (5.5)	ONS	RCT	No sponsorship. JV and PJS are consultants for SJM, receiving payment for preparing and giving educational presentations, as well as reimbursement for travel expenses. CW and SS are consultants for SJM and Spinal Modulation Inc,	N = 8 with ONS.	Ages 18 or older, gender not specified.	Group 1, effective Stimulation (N = 8) vs Group 2, subthreshold Stimulation (N = 8) vs Group 3, no Stimulation (N = 8).	Unknown	At baseline, group differences; VAS and MPQ, $p < 0.0001$ and SF-36, $p = 0.012$ .  Subthreshold stimulation (Group 2) vs with no stimulation (Group 3), with a VAS score of $5.65 \pm 2.11$ and $8.45 \pm 0.99$ , ( $p = 0.0031$ ).  Difference observed between pre-study and Group 1, ( $p = 0.091$ ).	“ONS delivers consistent and reproducible results in the treatment of distinct medically intractable migraine.”	Sample too small for reliable conclusions (n=8). Data suggest paresthesia not needed for pain reduction but supra threshold stimulation led to better results.

			receiving payment for preparing and giving educational presentations, as well as reimbursement for travel expenses. AG is a consultant for Allergan, MSD, Bayer, Teva, Pfizer, Weber und Weber.							
Dodick, 2015 (5.0)	ONS	RCT	Drs Mekhail, Vaisman, Reed, Trentman, Goldstein, Narouze and Ordia, report no	N= 157 patients with chronic migraines.	Mean age: 44.6 ±10.3 years. 91 females, 66 males.	All participants were implanted with a neurostimulation system. For 52 weeks the active group (N= 105) received appropriate stimulation of	Follow-up at 12, 24, and 52 weeks.	Significant results in reduction of headache days by 6.7 (±8.4) in the Intent-to-treat (ITT) group (p<0.001), and by 7.7 (±8.7)	“Our results support the 12-month efficacy of PNS [peripheral nerve stimulation] of the occipital nerves for headache pain and disability	Open label phase, then DB-RCT. Data suggest peripheral nerve stimulation at 12mo decreased HA pain and intensity but sig. adverse events. High rates of adverse events

			conflicts of interest, all other authors report a COI.			their implantable pulse generator (IPG). Control group (N= 52) had a sham program with no IPG stimulation. Control group received stimulation for 12 weeks, then received appropriate IPG stimulation for 40 weeks.		days in the intractable chronic migraine (ICM) group (p<0.001).  Significant results in both migraine disability assessment (MIDAS) and Zung Pain and Distress (PAD) in both ITT and ICM groups at 24 and 52 weeks (p<0.001).	associated with chronic migraine.”	and explanation within 12 mo.
Saper, 2010 (4.5)	ONS	RCT	Sponsored by GlaxoSmithKline (GSK), Johnson & Johnson, Eli Lilly, Merck, St. Jude Medical, Map Pharma, Nupathe, Zogenix, Neura Axon and Boston Scientific	N=66 patients with intractable chronic migraine.	Mean age: 43±10.6 years. 13 males, 53 females.	AS Group: (n=28) adjustable stimulation VS PS Group: (n=16) preset stimulation VS MM Group: (n=17) medical management VS Ancillary Group: (n=5)	1 and 3 months	For AS group headache days per month reduced by 27.0±44.8%, 8.8±28.6% for PS, 4.4±19.1% for MM, and 39.9±51.0% for ancillary group. Actual headache days reduction corresponds to 6.7±10 for AS, 1.5±4.6 for PS, 1.0±4.2 for MM, and 9.1±12.3 for ancillary group. Pain reduction was 1.5±1.6 for AS, 0.5±1.3 for PS, 0.6±1 for MM, and 1.9±3.5 for ancillary group. Responder rate was 39% for AS group, 6% for PS group, 0% in the MM group. These	“The results of this feasibility study offer promise and should prompt further controlled studies of ONS in CM.”	Feasibility study, which is underpowered. Data not sig., but trend towards reduced pain in adjustable stim group.

			and Medtronic , Advanced Neuromodulation Systems, St. Jude Medical, the National Institute of Neurological Disorders and Stroke and Mayo Clinic. SDS has consulted for Novartis. No mention of COI.					differences are significant.		
Bono 2014 (4.0)	ONS	RCT	No sponsorship or COI.	N = 160 with chronic migraines or chronic tension-	Mean age: 41±12 years. 33 males, 127 females.	Real occipital transcutaneous electrical stimulation or OTES, pulse width 250 ms,	3 months	% of responders in the real OTES vs with sham OTES, (p < 0.001).	“Severe CA is associated with decreased response to treatment with OTES in patients with CM and CTTH.”	Data suggest the Occipital transcutaneous electric stimulation group had sig. more responders than sham. But severe

				type headache.		frequency 40 Hz, intensity 20 mA (N = 108)  vs Sham OTES, pulse width 250 ms, frequency 40 Hz, intensity 20 mA (N = 52).		Multivariate analysis; CA / OTES treatment / and CA and OTES interaction;  $p = 0.00016 / p = 0.003 /$ and $p = 0.004$ .  Anxiety and mood between real vs sham, ( $p = 0.6$ and $0.21$ ).		cutaneous allodynia associated with reduced response to the stimulation treatment in chronic migraine and chronic tension-type headache patients.
Serra, 2012 (3.5)	ONS	RCT	No sponsorship or COI.	N=34 patients with chronic migraines.	The mean age is 46 years. Author reported 76% women, 34% men.	Internal Neurostimulator On – Arm A: Vs. Internal Neurostimulator Off – Arm B: patients could switch stimulation on if their headache attacks increased in severity or frequency by 30% or more.	1 month, 3 month, 6 month, and 12 month follow ups.	Migraine Disability Assessment (MIDAS) at baseline, 1-month FU, 3-month FU, 6-month FU, and 12-month FU for Arm A are 70, 25, 20, 19, 14, $p < 0.001$ ; Arm B scores are 8, 6, 6, 6, 5, $p < 0.001$ respectively.	“According to the results obtained, ONS appears to be a safe and effective treatment for carefully selected CM and MOH patients.”	Crossover. But trial apparently unblinded as one arm of the trial could turn device on, and did so on average 4.9 days. Variable lengths of followup. Data suggest occipital nerve stimulation for chronic migraine and medication overuse headache may be of benefit for decreasing intensity and frequency of HAs and improving quality of life and reducing medication use at 1yr.

Botulinum toxin has been used for treatment of spasticity related to TBI [920, 922, 928, 1072-1075].

## Botulinum Toxin

### Recommended.

Botulinum toxin is recommended for use in the treatment of spasticity related to TBI. Indications for cervical spine related conditions are in the Cervical and Thoracic Spine Guideline.

*Strength of Evidence* – **Recommended, Evidence (C)**

*Level of Confidence* – **Low**

<i>Indications:</i>	Spasticity related to TBI. Also is used for treatment of chronic migraine.
<i>Benefits:</i>	Reduction in spasticity
<i>Harms:</i>	Muscle weakness. May result in death if over-dosed.
<i>Frequency/Dose/Duration:</i>	The highest quality placebo-controlled trial used Botulinum 100U in 5mL/2mL NS injection (above/below elbow diluant). 50U injected into each of FCR and FCU. Other muscles from shoulder to hand injected up to 500U [1074].
<i>Indications for Discontinuation:</i>	Sufficient resolution of spasticity, adverse effects.
<i>Rationale:</i>	Both moderate quality placebo-controlled trials suggested botulinum is superior for management of spasticity [1074, 1075], and one of the trials found comparable results to physiotherapy [1075]. Benefit durations of 18-22 weeks in the higher quality trial [1074]. Botulinum Toxin is invasive, has significant adverse effects especially if over-dosed, is high cost, but has evidence of treatment efficacy, and is recommended for treatment of spasticity related to TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Traumatic, brain, injury, Intracranial, Closed, Head, Penetrating, Concussion, Concussion, Craniocerebral, Trauma, Penetrating, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 70 articles in PubMed, 4 in Scopus, 32 in CINAHL, 1 in Cochrane Library, 4100 in Google Scholar, and 0 from other sources. We considered for inclusion 12 from PubMed, 0 from Scopus, 5 from CINAHL, 1 from Cochrane Library, 2 from Google Scholar, and 5 from other sources. Of the 24 articles considered for inclusion, 5 randomized trials and 19 systematic studies met the inclusion criteria.

## Evidence for the Use of Botulinum Toxin

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Barnes 2010 (7.0)	Neurotoxin vs Neurotoxin	RCT	Sponsored by Merz Pharmaceuticals GmbH, Germany Authors received lecture fees and honoraria for serving on advisory boards for the sponsor, Compensation for the conduct of the study and honoraria for serving on advisory boards for the sponsor, compensation for the conduct of the study, some are employees of the study sponsor.	N=192 adults who had suffered a stroke, brain injury, multiple sclerosis or cerebral palsy wrist focal wrist and elbow flexor spasticity;	Mean Age 55.4 ± 14.3 with 81 females and 111 males	Group 1 (N=96) Was given NT 201 injection of a more dilute concentration (20 U/ml) with a maximum dose of 400 units at investigators discretion. Vs Group 2 (N=96) Patients were given the same treatment and duration of treatment with a more concentrated NT 201 solution (50 U/ml).	Follow-up at baseline, 4 and 12 weeks. Safety follow up at 20 weeks.	Treatment response at week 4; 95 of the pre-protocol patients (57.6%; n=165). 20 U/ml group: 51 (63%) 50 U/ml group 44 patients (52.4%). Week 12 Pre-protocol response: 44.6% Full Analysis Set difference between responds from Group 1 vs 2 at 4 weeks; 11.2% (95% Confidence interval (CI): -2.9, 24.6). Week 4 Ashworth 1-point improvement prevalence; 62.2% Week 12 Responses in all muscle group prevalence; 44%-56.8% Global Assessment of Treatment response (GATR) at week 4 improvement prevalence in both groups; patients 80.2% investigators 89.0%	“[T]he administration of one set of NT 201 injections resulted in substantial improvements in functional disability and muscle tone. This study supports the treatment of upper limb spasticity with NT 201 regardless of etiology.”	88% of sample stroke patients. Data suggest whether 20 u/ml had similar efficacy for improving functional disability and muscle tone in a diverse population of patients with upper limb spasticity at 4 weeks after injection.

Simpson 2009 (6.0)	Botulinum neurotoxin vs Placebo vs Combination	RCT	Sponsored by Mount Sinai School of Medicine, and unrestricted grants by Allergen Inc. No COI.	N=60 adults who had a prior stroke (N=49) or traumatic brain injury (N=11);	Mean Age: Group 1 52.4 ± 14.5, Group 2 51.9 ± 17.3, Group 3 51.3 ± 14.7. There are 33 men and 27 women in this study.	Group 1 (N= 20) Botulinum neurotoxin (BoNT) IM 100 units of BoNT-A, 0.5 mg human albumin, and 0.9 mg sodium chloride with oral placebo Vs. Group 2 (N=21) Placebo IM plus oral dose of Tizanidine (TZD) 4 mg tablets. Dose were taken twice per day and initiated at 2 mg/day to a maximum of 36 mg/day. Vs. Group 3 (N=19) Received both intramuscular injection and oral placebo. Study duration was 22-24 weeks.	Follow-up at baseline, week 3, 6, 12, 18, 22.	Modified Ashworth Score (MAS) reduction in wrist flexor tone baseline minus week 3 - score (Mean change from baseline MAS); Group 1: -1.55 (1.19) Group 2: -0.25(0.64) Group 3: -0.67(0.91); (p=0.001). At week 6 - score (Mean change from baseline MAS); Group 1: -1.32 (0.89), Group 2: -0.22(0.88), Group 3: -0.68(1.00); (p=0.01). MAS reduction in finger flexor tone baseline minus week 3 - score (Mean change from baseline MAS); Group 1: -1.45(1.19), Group 2: -0.65(0.75), Group 3: -0.17(0.71); (p=0.001). At week 6 - score (Mean change from baseline MAS); Group 1: -1.37(1.46), Group 2: -0.39(0.98), Group 3: -0.26(0.93); (p<0.02). Finger	“[I]njections of BoNT alone to treat focal or multifocal spasticity decrease muscle tone with few systemic effects and should be considered as the primary treatment before oral medications.”	High dropout rate. Study suggests Botulinum more effective than tizanidine or placebo in reducing muscle tone in upper extremity from stroke or TBI.
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								Flexor tone in varying doses of BoNT vs all groups at week 3 and week 6 – improvement (MAS change from baseline); Any dose: 1.63(1.20) and 1.53(1.41) 100 unit dose improvement: 2.00 wk 3, (p=0.001 vs group 2 and p<0.001 vs Group 3), 1.62 (p=0.01 vs Group 2 and p<0.02 vs Group 3). 200 unit MAS reduction: 2.75 wk 3 (p=0.03 vs Group 2, p=0.01 vs Group 3), 2.75 wk 6 (p<0.02 vs Group 3). Adverse events BoNT vs TZD throughout trial – number (percentage); 8(40% vs 19 (90.5%)) (p=0.0007).		
Verplancke 2004 (6.0)	Botulinum Toxin vs Saline	RCT	Sponsored by Allergan Inc. No COI.	N=35 Patients who had acquired an acute sever brain injury (N=20 for TBI) and (N=15 for neurosurgery /anoxia);	Mean Age N/A (17-70) with 10 women and 25 male patients.	Group 1 N=11 Control group that underwent standard program of physiotherapy. Vs Group 2 N=12 Received injections of saline as well as casting. Vs Group 3 N=12 Received injections of botulinum as well as casting.	Follow-up at baseline and 12 weeks.	Modified Ashworth Scale scores baseline vs 12 weeks, Group 2; 2.2 ± 1.056 vs 1.0 ± 1.297 (p<0.03). Group 3; 2.3 ± 0.77 vs 1.3 ± 1.619 (p=0.04). Range of Motion increase (Dorsal Ankle Flexion), baseline vs	“[T]his study has shown that early active intervention is not only safe but probably has value. Active intervention with casting with and without botulinum toxin A is valuable for	Blinding unclear between groups. Data suggest physiotherapy comparable to botulinum and both

								12 weeks -Mean (Range), Group 1; 4.59° (-18° to +26°). Group 2; 11.65° (-22° to +28°). Group 3; 13.56° (-22° to 30°).	patients who are losing range of ankle movement following severe brain injury.”	superior to placebo.
Smith 2000 (5.5)	Botulinum Toxin	RCT	This study was supported by an educational grant from Ipsen Limited UK who supplied the botulinum toxin used in this study.	N=21 hemiplegic patients with troublesome upper limb spasticity. N=19 with stroke and two with head injury.	Mean age placebo: 45 years, 500Mu 39 years, 1000 Mu 67 years, 1500 Mu 54 years.  10 males, 15 females.	Placebo injection (N=6) vs. 500 Mu (N=6) vs. 1000 Mu (N=7) dose of botulinum toxin.	Assessments at baseline (week 0) and at 2, 6 and 12 weeks post dosing.	Mean (SD) modified Ashworth (median range) for the fingers: Changes at 6 weeks: placebo 2 (-3,3), 500Mu -3 (-4,-1), 1000Mu 0 (-3,1), 1500Mu -1 (-4,-1), Combined dose-2 (-4,1)***; p<0.01.	“Botulinum toxin produced beneficial effects in spasticity and passive range of movement in the hemiplegic upper limb. Increasing the dose increased the magnitude of response for impairments in some muscle groups but had little effect on duration of response.”	Baseline comparability dissimilar re. ages (45 vs. 39 vs. 67 vs. 54yrs). at 6 weeks, data suggest botulinum associated with improved passive ROM in hemiplegic upper limb and reduced spasticity and dose increases response but not response durations.
Francisco 2002 (5.0)	High volume Botox vs low volume Botox	RCT-Pilot Study	Sponsored by grant from the national Institution on disability and Rehabilitation Research, U.S Dept. of Education,	N = 13 adults whom had modified Ashworth scale scores of 3 both wrist and finger flexors;	Mean Age 44.5 (27-70) with 9 males and 4 female patients.	Group 1 (N = 6) (N= 1 for TBI, 5 for Stroke) Group received High-Volume Botulinum Toxin-A (BTX-A) solution of 50 units per 1 ml of preservative saline. Vs Group 2 (N = 7) (N=2 for TBI 5 for Stroke) Group	Follow-up for 4, 8, and 12 weeks.	Modified Ashworth score (MAS) baseline vs.4 weeks, 8 weeks, and 12 weeks. Group 1 decreased 1.8 ± 0.7, 1.9 ± 0.9, and 1.7 ± 1.2 at 4, 8, and 12 weeks	“At the doses used in this study, wrist and flexor spasticity secondary to stroke or traumatic brain injury was significantly	Study methods sparse. No placebo control.

			Washington, DC. No COI.			received Low-Volumes BTX-A solution containing 100 units per 1 ml of preservative free saline.		respectively vs group 2 decreased $1.3 \pm 0.4$ , $1.4 \pm 0.7$ . and $0.9 \pm 0.6$ as same post injection periods. ( $p < 0.05$ ) decrease for all groups and follows ups. MAS wrist flexor score 4 weeks vs 12 week significantly higher for both groups at 12 weeks ( $p = 0.045$ ) (weakening of treatment) Group 1 vs group 2 Global Rating Scale (patient) at 8 weeks, $2.0 \pm 0.6$ vs $3.3 \pm 1.1$ ( $p = 0.041$ ) Group 1 vs Group 2 Global Ratings Score (investigator scores) at 8 weeks; $1.7 \pm 0.8$ vs $3.9 \pm$ $0.7$ ( $p = 0.003$ ) at 12 weeks; $3.0 \pm 1.3$ vs $4.6 \pm 1.0$ ( $p = 0.045$ )	reduced, as demonstrated by decreases of at least one point in the MAS. This improvement was maintained up to 12 wk after BTX-A administration. The decrease in MAS scores was also consistent with the perceived clinical improvement by the patient (or caregiver) and by a blinded investigator. When two different volume preparations of the same BTX-A dose were compared, there was a trend in favor of the high- volume preparation, although this difference did not reach statistical Significance.”	
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## Allied Health

A Meniett device is a device that is used for treating Meniere's disease [1076-1080]. Meniere's is a reported complication of trauma [1081].

### Meniett Device

#### No Recommendation.

A Meniett device is recommended for use in the treatment of select TBI patients with Meniere's disease.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

<i>Indications:</i>	Unilateral Meniere's with disruptive levels of vertigo, low frequency sensorineural hearing loss on audiometry, functional level of 2-4 (Otolaryngol Head Neck Surg 1995;113:181-185), abnormal cochleogram in the affected ear (SP/AP click ratio >0.39 or toneburst SP of $\geq 2.0\mu V$ ) [1082].
<i>Benefits:</i>	Improved control of vertiginous symptoms, although differences at 4 months compared with sham relatively modest [1082].
<i>Harms:</i>	Intolerance of device, lack of sufficient control of symptoms, ear infection.
<i>Indications for Discontinuation:</i>	Sufficient recovery to not need device, intolerance, non-use of device.
<i>Rationale:</i>	A sham-controlled trial found the Meniett device effective, although by 4 months there were relatively modest differences compared with sham [1082] [1083]. There are no quality studies assessing Meniett Device for treatment of TBI. Meniett Device is invasive, has some adverse effects, is high cost, has some evidence of efficacy in Meniere's patients and thus is selectively recommended (I) for treatment of vertigo both resistant to other treatment and passage of time from TBI, as well as of sufficient severity.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Meniett Device; Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, Closed Head Trauma, Penetrating Head Trauma, Penetrating Craniocerebral Trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 0 articles in PubMed, 0 in Scopus, 0 in CINAHL, 0 in Cochrane Library, 24 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 3 from Google Scholar, and 0 from other sources. Out of the 3 articles considered for inclusion, 3 randomized trails and 0 systematic reviews met the inclusion criteria.

## Evidence for the Use of Meniett Device

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Gates 2004 (7.0)	TBI	RCT	Sponsored by Medtronic Xomed as an unrestricted grant to each of the 4 study centers. No mention of COI.	N = 77 with clinical diagnosis of active, definite, unilateral cochleovestibular Meniere's disease causing disruptive levels of vertigo.	Aged 33 to 71 years; 35 males and 42 females.	Treatment group, with an active Meniett device (N = 34) vs Control group, an identical device to treatment group that did not generate pressure (N = 33).	4-months	During 2 weeks; median proportion of vertigo days was 0.13 (0.07-0.36) for pre-tube placement vs 0.21 (0.07-0.36) for post-tube placement, (p = 0.34). Vertigo score per month as the dependent variable and treatment group and treatment month as the predictor variables was (p = 0.03 for treatment group vs treatment month (p = 0.053).	"The Meniett device is a minimally invasive, safe, and efficacious intermediate treatment for people with substantial vertigo uncontrolled by medical therapy."	Data suggest Meniett device appears helpful for controlling vertigo.
Gates 2006 (4.5)	Meniett Device	RCT	Supported by an unrestricted grant from Medtronic Xomed, Inc. No COI.	N = 58 with active, unilateral cochleovestibular disease.	Mean Age: 48.9 ± 9.3 years. 20 males, 38 females.	Meniett Device Group: (N =29) low sodium diet using meniett device 3 times per day and maintain tympanostomy tube in affected ear vs Placebo Group (N =29) low sodium diet, placebo	2 years	Thirty-nine of 58 patients had remission or greatly improved results, 14 dropped to receive surgery. Of the 43 patients with active vertigo, 20 went in remission. On average, achieved remission in 2.8±3.7 months. Of remaining participants, 8 improved and 2 worsened. Only 7 of 35 had relapse with Ménière's disease.	"Use of the Meniett device was associated with a significant reduction in vertigo frequency in about two thirds of the participants, and this improvement was maintained long term."	2-year follow-up of Gates 2004. Suggest Meniett device associated with reduction in vertiginous symptoms.

						meniett device				
Ödkvist, 2000 (4.5)	Meniett Device	RCT	No mention of sponsorship or COI.	N = 56 patients with Meniere's disease.	Age range 20-65. No mention of sex.	Treatment group (N =31) received 2 weeks of treatment consisting of repeated pressure pulses applied to the middle of the ear via ear canal. vs Placebo group (N =25) was set up to a similar device, but did not receive any stimulation.	2 weeks from baseline	Hearing threshold levels before and after treatment with active Meniett were significantly different from 0 at the frequencies 500 Hz (p<0.03) and 1 kHz (p<0.01)  A significant improvement in frequency and intensity of vertigo, dizziness, aural pressure and tinnitus was found in the active group	"The study showed an improvement in the inner ear symptoms after Meniett treatment."	Data suggest improvement at 500Hz and 1000Hz for pure tone audiometry in Meniett group.

## Transcranial Magnetic Stimulation (TMS)

Transcranial magnetic stimulation uses an electromagnetic coil that is placed against a patient's forehead. It attempts to stimulate or inhibit nerve cells in the brain. TMS has a few different methods of procedure and has been used to treat depression [1084]. There have been attempts to use TMS for neurological conditions including TBI [1085-1090].

## Transcranial Magnetic Stimulation (TMS)

### No Recommendation.

There is no recommendation for or against the use of transcranial magnetic stimulation in the treatment of TBI patients.

*Strength of Evidence* – **No Recommendation, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

*Rationale:*

There are no quality studies assessing Transcranial Magnetic Stimulation for treatment of TBI. Transcranial Magnetic Stimulation is not invasive, has no adverse effects, is high cost, but in the absence of quality evidence of effectiveness, there is no recommendation. There are other approved indications, including headache and depression.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Transcranial Magnetic Stimulation, Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, Closed Head Trauma, Penetrating Head Trauma, Penetrating Craniocerebral Trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 43 articles in PubMed, 229 in Scopus, 2 in CINAHL, 7 in Cochrane Library, 3870 in Google Scholar, and 4 from other sources. We considered for inclusion 4 from PubMed, 5 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 4 from other sources. Of the 13 articles considered for inclusion, 1 randomized trial and 7 systematic studies met the inclusion criteria.

TBI often leads to cognitive and emotional impairments such as attention deficit and memory loss. Transcranial direct current stimulation (tDCS) is a noninvasive neuro-modulatory modality that is increasingly being used to improve cognitive function [1091] [1092, 1093]. tDCS involves the application of a weak DC electric current to the scalp to modulate the neurons in the brain [1093] [1094]. tDCS applied on the motor cortex has been reported to increase the pain threshold and provide relief from neuropathic pain [1094].

## **Transcranial Direct Current Stimulation (TCDS)**

### **No Recommendation.**

#### **Allied Health Interventions**

There is no recommendation for or against the use of transcranial direct current stimulation in the treatment of TBI patients.

*Strength of Evidence* – **No Recommendation, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

*Rationale:*

There are no quality studies assessing the utility of Transcranial Direct Current Stimulation for treatment of TBI. There are a few mechanistic studies suggesting potential utility, but they lack meaningful clinical followup and outcomes [1095] [1094]. Transcranial Direct Current Stimulation is not invasive has no adverse effects, is high cost, but with the lack of quality evidence of clinical efficacy, there is no recommendation.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 15 articles in PubMed, 60 in Scopus, 2 in CINAHL, 31 in Cochrane Library, 40 in Google Scholar, and 0 from other sources. We considered for inclusion 3 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 4 articles considered for inclusion, 2 randomized trials and 0 systematic studies met the inclusion criteria.

### Evidence for the Use of Transcranial Direct Current Stimulation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Ulam 2015 (4.5)	TDCS	RCT	No sponsorship or COI.	N = 26 recovering from TBI.	Mean age of 33.52 years; 22 males and 4 females.	Active tDCS group, 20 minutes session of 1mA anodal stimulation to the left dorsolateral prefrontal cortex, on 10 consecutive days (N = 13) vs Sham TDCS group, electrodes placed in the same locations as treatment (N = 13)	10-day treatment	Delta yielded a significant difference between active and sham TDCS groups at F3, ( $p = 0.043$ ). Decreases in delta were correlated with improved performance on neuropsychological tests for the active group.	"Results suggest that 10 anodal TDCS sessions may beneficially modulate regulation of cortical excitability for patients with TBI."	Data suggest TDCS may modulate cortical excitability in TBI patients. No meaningful clinical measures, as the study was about potential mechanisms.
Yoon 2014 (3.0)	TDCS	Sham-controlled trial.  Non-RCT	Sponsored by National Research Foundation of Korea and SNUBH Research Fund. No COI.	N = 16 with chronic neuropathic pain.	Mean age of 27.5 years; 12 males and 4 females.	Active TDCS (N = 10) vs Sham TDCS (N = 6)	No mention of follow up.	There was significant decrease in NRS for pain in the active TDCS group ( $P = 0.016$ ) but not the sham group ( $P = 0.102$ ). The active TDCS group alleviated pain interference with daily life while there was no effect on pain interference with mood or sleep ( $P = 0.380$ , $P = 0.135$ ). Also, TDCS efficacy in the active group was found to correlate with metabolic changes in the cerebellum and left medulla.	"[F]indings suggest that, similar to invasive MCS, noninvasive TDCS has a potential role in alleviating neuropathic pain."	Data suggest increased metabolism in the medulla and decreased metabolism in the left DLPFC post TDCS compared to sham.

## Manipulation and Mobilization

Manipulation and mobilization are two types of manual therapy. These include wide arrays of different techniques and schools of thought. Some consider these two interventions to be on a spectrum of velocity and applied force. In general, mobilization involves assisted, low-force, low-velocity movement within or at the limit of joint range of motion. Manipulation involves higher-force, higher-velocity, and low-amplitude action with a focus on moving a target joint.

From the standpoint of evidence-based practice guidelines development, there are numerous types of manipulation utilized in many different studies [1096-1104]. These issues result in difficulties comparing methods, techniques, or results across the available literature. Differences between techniques appear to be largely unstated in the available systematic reviews, which have aggregated all studies together. Adjustment is generally a synonym for manipulation in the chiropractic profession. There are studies evaluating thoracic manipulation for cervical pain without cervical manipulation [1105].

Many practitioners begin with lower force manipulation or mobilization techniques, and reserve higher force manipulation techniques for those who do not respond to lower force techniques to limit adverse effects and complications. Manipulation is generally considered a safe procedure, but like all other treatments is not without risks. For example, reported fatal outcomes have occurred and are particularly attributed to cervical manipulation [1106]. Reports of more severe but rare adverse effects include vertebral artery dissection, carotid artery injury, and disc herniation or spinal cord compression myelopathy, although these reports need to be considered in the context of natural progressions of cervical pain without any intervention [1107]. The mean age of patients experiencing vertebral artery dissection in the case reports is 38 and the risk has been reportedly due to cervical manipulation with a rotary component [1106]. However, more recent population based studies have questioned the incidence of vascular injury from manipulation, suggesting instead that this may more often be an acceleration or natural progression of an event in progress [1108]. Mobilization is less likely to lead to side effects than is manipulation.

The most common adverse response to neck manipulation is local discomfort that resolves within 24 to 48 hours [1106] [1106]. There have been reports of vertebral artery dissection that result in posterior circulation stroke purportedly following cervical manipulation [1098]. There has been much debate on the frequency of these events and multiple reports suggest low risk [1109]. Population-based case control study of all patients who seek chiropractic care in Ontario revealed a frequency of 8 cases occurred within 7 days of receiving chiropractic care in 109 million person years of observation in Ontario [1108]. Of particular interest was the observation that the odds ratio of a stroke occurring after a primary physician visit for cervical pain was the same as that noted following a chiropractic office visits, raising doubt as to whether there is any relationship between the manipulation and stroke. Vertebral artery dissections are heralded by cervical pain and frequently headache that can bring a patient to either a chiropractor or general physician's office, and if not recognized can progress to stroke that can be fatal. This should be considered in the differential diagnosis of cervical pain.

## Manipulation/Mobilization for Acute, Subacute, or Chronic Cervicothoracic Pain Recommended.

Manipulation/mobilization of the cervical and/or thoracic spine is recommended for short-term relief of cervical pain or as a component of an active treatment program focusing on active exercises for acute cervicothoracic pain. However, high amplitude, high velocity manipulation is not recommended.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

<i>Benefits:</i>	Potential for faster resolution of pain and improved function.
<i>Harms:</i>	Worsening of neck pain, especially immediately after manipulation.
<i>Frequency/Dose/Duration:</i>	Dependent on severity. Most patients with more severe spine conditions may receive up to 12 visits over 6 to 8 weeks, typically one to 3 times a week;[1110-1112] total treatments dependent on response to therapy. Substantial progression (e.g., return to work or activities, increasing ability to tolerate exercise, reduced medication use) should be documented at each follow-up visit. Treatment plan should be reassessed after each 2-week interval. Most guidelines suggest that if there is significant response in the above outcomes, it is worth considering another 2 weeks of treatment. If no response to 2 weeks of application of a particular manipulation treatment, it should be discontinued and 2 weeks of a different method of manipulation/mobilization or other treatment should be considered. If there is no response after 4 weeks and two 2-week trials of different manipulation/mobilization techniques, it is unlikely that further manipulation/mobilization will be helpful.
<i>Indications for Discontinuation:</i>	Lack of demonstrated continued functional response after 6 manipulation/mobilization sessions (2 trials of 2 or more different methods), resolution of symptoms, or failure to participate in an active rehabilitation program.
<i>Rationale:</i>	Multiple studies evaluate thoracic and cervical spine manipulation, [1106, 1113] whereas other studies evaluated one or the other.[1100, 1111, 1114-1117] Other studies do not delineate between the two different types of therapies.[1097, 1118-1122]

There are no quality trials comparing mobilization to sham or placebo for treatment of acute cervical pain. The closest study appears to be that of Cleland et al (2007), but it was impaired by methodological limitations. Most studies compare mobilization to manipulation, or use mobilization as a component of other interventions, significantly weakening the ability to infer efficacy of manipulation.[1123] Most studies had small samples sizes with most <70.[1111, 1112, 1124, 1125] A moderate-quality trial evaluating mobilization suggested greater benefit compared with directed exercise and continued care by a general practitioner. However, this study included acute, subacute, and chronic pain without delineation between duration in the results, and the general practitioner care appeared to fail to include treatments thought to be efficacious.[1126] A moderate-quality trial comparing cervical manipulation to mobilization suggested improvement in pain and range of motion in both groups after a single

treatment, but manipulation was reportedly associated with overall better pain improvement on the NRS-101 and larger gains in range of motion [1127]. Thus, the available quality evidence conflicts on treatment of cervicothoracic pain.[1128] Having suggested mobilization is a favorable treatment option for patients with cervical pain compared with directed exercise or continued care by a general practitioner, although the general medical care may have been suboptimal.[1126]

There are no sham-controlled trials of manipulation. Only a few RCTs evaluated subacute cervicothoracic pain and did so in combination with chronic cervicothoracic pain without reporting findings based on duration of symptoms. [1112] A moderate-quality study comparing a single episode of cervical manipulation versus mobilization in subacute and chronic patients reported manipulation to have greater improvement in cervicothoracic pain at rest and active range of motion.[1114] A moderate-quality study that did not describe well the duration of symptoms found an increase in range of motion after a single thoracic spine manipulation compared to no intervention.[1129] (Krauss 08) Where another study compared manipulation and exercises alone and in combination and reported no significant clinical differences at 12-month follow up in chronic pain patients.[1113]

A moderate-quality study of patients with chronic pain examined manipulation, manipulation and exercise and an exercise only group. They found that the manipulation alone group had less improvement compared to manipulation with exercise and exercises alone at 16 months after 11 weeks of treatment.[1113] One study of 119 patients with cervicothoracic pain greater than 3 months duration reported improvement in all groups, but did not find any difference in the manipulation group when compared to physiotherapy and intensive training of cervical musculature for 6 weeks.[1130] A moderate-quality study suggested acupuncture was more effective than manipulation or medications in treating chronic cervical pain.[1097] Another moderate-quality study compared manipulation with sham ultrasound to sham ultrasound alone and suggested an improvement in pain in the manipulation group at 12 weeks.[1131] While the RCTs show that other interventions are equally beneficial, the manipulation groups also experienced significant improvement in pain control and range of motion. Manipulation in subacute and chronic cervicothoracic pain is recommended and is best utilized in combination with an active exercise program.[1113, 1132] It was not possible to determine which technique was beneficial for which patient populations. There was also insufficient evidence for cervicothoracic pain with radicular findings.

A study evaluated a Clinical Prediction Rule for cervicothoracic pain using thoracic manipulation that is somewhat analogous to those for the lumbar spine (see Low Back Disorders guideline). They reported predictors for increasing the likelihood of a positive outcome with thoracic manipulation.[1133, 1134] These 6 variables were symptoms <30 days, no symptoms distal to the shoulder, neck extension does not aggravate pain, FABQPA score <12, diminished upper thoracic spine

kyphosis, and cervical extension ROM <30 degrees. Once this information has been reproduced and validated there may be a group of patients identified where thoracic manipulation may be recommended with greater specificity. However, a recent RCT reported that the above CPR was not able to be validated.[1135] Another group assessed a clinical prediction rule and noted better response to treatment if: initial Neck Disability Index <11.5, bilateral involvement pattern, no sedentary work >5 hours a day, feeling better while moving the neck, not worse while extending the neck, and a diagnosis of spondylosis without radiculopathy.[1136]

Evidence:

There are 4 high-[1099, 1118, 1137, 1138] and 76 moderate-quality RCTs or crossover trials (one with two reports) incorporated into this analysis.[487, 1096, 1097, 1100, 1101, 1106, 1110, 1111, 1113-1116, 1119-1131, 1139-1189] There are 25 low-quality [1190-1216] RCTs and 5 other studies [1117, 1214, 1216-1218] in Appendix 1.

A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: manipulation and mobilization, disorder terms-cervicalgia, neck pain, cervical pain, neck, cervical, vertebrae, vertebral, spine, radiculopathy, radiculopathies, radicular pain, intervertebral disc displacement, herniated, herniat\*, displacement, displacements, displaced, disk, disc, disks, discs, pain, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Non-experimental Studies. In PubMed we found and reviewed 756 articles, and considered 130 for inclusion. In Scopus, we found and reviewed 1,436 articles, and considered 5 for inclusion. In CINAHL, we found and reviewed 134 articles, and considered 8 for inclusion. In Cochrane Library, we found and reviewed 32 articles, and considered 0 for inclusion. We also considered for inclusion 0 articles from other sources. Of the 143 articles considered for inclusion, 104 randomized trials and 13 systematic studies met the inclusion criteria.

## Manipulation for Chronic Cervicogenic Headache Pain

### Recommended.

Spinal manipulation of the cervical and/or thoracic spine is recommended for treatment of chronic cervicogenic headache pain.

*Strength of Evidence* – **Recommended, Evidence (C)**

*Level of Confidence* – **Low**

<i>Frequency/Dose/Duration:</i>	Once or twice a week for 4 to 5 appointments, up to 8 total appointments recommended if there is benefit after 4 to 5 appointments.[487, 1219]
<i>Indications for Discontinuation:</i>	Resolution of symptoms, adverse effects from treatment, lack of demonstrated positive effect on headache intensity and/or frequency, or non-participation in an active rehabilitation therapy program.[1143]
<i>Evidence:</i>	<p>There are 4 high-[1099, 1118, 1137, 1138] and 76 moderate-quality RCTs or crossover trials (one with two reports) incorporated into this analysis.[487, 1096, 1097, 1100, 1101, 1106, 1110, 1111, 1113-1116, 1119-1131, 1139-1189] There are 25 low-quality [1190-1216] RCTs and 5 other studies [1117, 1214, 1216-1218] in Appendix 1.</p> <p>A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: manipulation and mobilization, disorder terms-cervicalgia, neck pain, cervical pain, neck, cervical, vertebrae, vertebral, spine, radiculopathy, radiculopathies, radicular pain, intervertebral disc displacement, herniated, herniat*, displacement, displacements, displaced, disk, disc, disks, discs, pain, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Non-experimental Studies. In PubMed we found and reviewed 756 articles, and considered 130 for inclusion. In Scopus, we found and reviewed 1,436 articles, and considered 5 for inclusion. In CINAHL, we found and reviewed 134 articles, and considered 8 for inclusion. In Cochrane Library, we found and reviewed 32 articles, and considered 0 for inclusion. We also considered for inclusion 0 articles from other sources. Of the 143 articles considered for inclusion, 104 randomized trials and 13 systematic studies met the inclusion criteria.</p>

## Manipulation for Cervical Spine Conditions

### Not Recommended.

High-amplitude, high-velocity spinal manipulation of the cervical and/or thoracic spine is not recommended for treatment of cervical spine conditions.

*Strength of Evidence – Not Recommended, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

A moderate-quality study evaluated 80 patients with chronic cervicogenic headache randomized to either 8 or 16 spinal manipulation sessions in 8 weeks as the intervention group, and 8 or 16 sessions of “light massage” as the control group. The authors reported both clinical and statistical benefit of manipulation lasting up to 24 weeks with decreased reported pain and decreased reported analgesic use. There was no clear benefit of 16 versus 8 visits.[487] A moderate-quality study evaluated cervical manipulation with sham manipulation in a modified crossover study design suggested improvement with cervical range of motion, but did not find improvement in headache pain.[1152] Another moderate-quality study in headache patients evaluated cervical manipulation compared to low level laser treatment and massage and failed to find a difference in cervical range of motion, analgesic use per day, headache intensity per episode and number of headaches per day.[1143, 1220] A moderate-quality study that was a continuation of an earlier study evaluated high velocity low amplitude manipulation with laser and massage as placebo. They reported significant improvement in cervicogenic headache.[1151] A moderate-quality study evaluated manipulation versus exercise and found that exercise groups produced better long term outcomes than placebo or manipulation alone.[1219] High-amplitude, high-velocity manipulation is not recommended due to concerns it may increase risk of adverse effects such as arterial dissection.

*Evidence:*

There are 4 high-[1099, 1118, 1137, 1138] and 76 moderate-quality RCTs or crossover trials (one with two reports) incorporated into this analysis.[487, 1096, 1097, 1100, 1101, 1106, 1110, 1111, 1113-1116, 1119-1131, 1139-1189] There are 25 low-quality [1190-1216] RCTs and 5 other studies [1117, 1214, 1216-1218] in Appendix 1.

A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: manipulation and mobilization, disorder terms-cervicalgia, neck pain, cervical pain, neck, cervical, vertebrae, vertebral, spine, radiculopathy, radiculopathies, radicular pain, intervertebral disc displacement, herniated, herniat\*, displacement, displacements, displaced, disk, disc, disks, discs, pain, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Non-experimental Studies. In PubMed we found and reviewed 756 articles,

and considered 130 for inclusion. In Scopus, we found and reviewed 1,436 articles, and considered 5 for inclusion. In CINAHL, we found and reviewed 134 articles, and considered 8 for inclusion. In Cochrane Library, we found and reviewed 32 articles, and considered 0 for inclusion. We also considered for inclusion 0 articles from other sources. Of the 143 articles considered for inclusion, 104 randomized trials and 13 systematic studies met the inclusion criteria.

## **Cervical Manipulation for Tension Headaches**

### **Not Recommended.**

**Cervical manipulation is not recommended for tension headaches.[1140, 1145, 1149]**

*Strength of Evidence* – **Not Recommended, Evidence (C)**

*Level of Confidence* – **Low**

*Rationale:*

There is a moderate-quality study of 75 patients evaluating cervical manipulation versus laser light therapy and soft tissue massage as placebo. The authors did not find any benefit of manipulation after 19 weeks of follow up.[1140] Another moderate-quality study evaluated manipulation compared to amitriptyline for tension headaches. They found after discontinuation of treatment, manipulation had positive outcomes over amitriptyline; however, they did not address possible withdrawal headaches from amitriptyline.[1145]

*Evidence:*

There are 4 high-[1099, 1118, 1137, 1138] and 76 moderate-quality RCTs or crossover trials (one with two reports) incorporated into this analysis.[487, 1096, 1097, 1100, 1101, 1106, 1110, 1111, 1113-1116, 1119-1131, 1139-1189] There are 25 low-quality [1190-1216] RCTs and 5 other studies [1117, 1214, 1216-1218] in Appendix 1.

A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: manipulation and mobilization, disorder terms-cervicalgia, neck pain, cervical pain, neck, cervical, vertebrae, vertebral, spine, radiculopathy, radiculopathies, radicular pain, intervertebral disc displacement, herniated, herniat\*, displacement, displacements, displaced, disk, disc, disks, discs, pain, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Non-experimental Studies. In PubMed we found and reviewed 756 articles, and considered 130 for inclusion. In Scopus, we found and reviewed 1,436 articles, and considered 5 for inclusion. In CINAHL, we found and reviewed 134 articles, and considered 8 for inclusion. In Cochrane Library, we found and reviewed 32 articles, and considered 0 for inclusion. We also considered for inclusion 0 articles from other sources. Of the 143 articles considered for inclusion, 104 randomized trials and 13 systematic studies met the inclusion criteria.

## Regular or Routine Manipulation or Mobilization

### Not Recommended.

Regular or routine manipulation or mobilization, prolonged treatment (manipulation several times a month for years), and prophylactic treatment is not recommended.

*Strength of Evidence* – **Not Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **High**

*Rationale:*

There is no quality evidence of efficacy for prolonged treatment (manipulation several times a month for years). There is no quality evidence that prophylactic treatment is effective for primary prevention (before first episode of pain) or for secondary prevention (after recovery from an episode of cervicothoracic pain), and prophylactic treatment is not recommended. There is also no evidence that manipulation on a regular or routine basis is beneficial.

*Evidence:*

There are 4 high-[1099, 1118, 1137, 1138] and 76 moderate-quality RCTs or crossover trials (one with two reports) incorporated into this analysis.[487, 1096, 1097, 1100, 1101, 1106, 1110, 1111, 1113-1116, 1119-1131, 1139-1189] There are 25 low-quality [1190-1216] RCTs and 5 other studies [1117, 1214, 1216-1218] in Appendix 1.

A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: manipulation and mobilization, disorder terms-cervicalgia, neck pain, cervical pain, neck, cervical, vertebrae, vertebral, spine, radiculopathy, radiculopathies, radicular pain, intervertebral disc displacement, herniated, herniat\*, displacement, displacements, displaced, disk, disc, disks, discs, pain, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Non-experimental Studies. In PubMed we found and reviewed 756 articles, and considered 130 for inclusion. In Scopus, we found and reviewed 1,436 articles, and considered 5 for inclusion. In CINAHL, we found and reviewed 134 articles, and considered 8 for inclusion. In Cochrane Library, we found and reviewed 32 articles, and considered 0 for inclusion. We also considered for inclusion 0 articles from other sources. Of the 143 articles considered for inclusion, 104 randomized trials and 13 systematic studies met the inclusion criteria.

## Manipulation for Radicular Pain Syndromes with Acute Neurological Deficits Not Recommended.

Manipulation is not recommended for the treatment of radicular pain syndromes with acute neurological deficits, especially with progressive neurological loss.

*Strength of Evidence* – **Not Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Moderate**

*Rationale:*

There is no quality evidence to address manipulation with neurological deficits; however, there are concerns about the use of manipulation in the presence of acute or progressive neurological deficits. Young et al. conducted an RCT evaluating cervical traction for radicular pain. Each group received manual therapy consisting of HLVA of the cervical and thoracic spine in addition to exercise. They reported improvement in both groups; however the study was not designed to evaluate the effects of manipulation of cervical radiculopathy.[1099] Another study compared cervical lateral glide mobilization to ultrasound and reported benefits for manipulation. The evaluations were taken immediately following the single intervention without long-term follow up.[1141]

*Evidence:*

There are 4 high-[1099, 1118, 1137, 1138] and 76 moderate-quality RCTs or crossover trials (one with two reports) incorporated into this analysis.[487, 1096, 1097, 1100, 1101, 1106, 1110, 1111, 1113-1116, 1119-1131, 1139-1189] There are 25 low-quality [1190-1216] RCTs and 5 other studies [1117, 1214, 1216-1218] in Appendix 1.

A comprehensive literature search was conducted using multiple search engines including PubMed, Scopus, CINAHL and Cochrane Library without date limits using the following terms: manipulation and mobilization, disorder terms-cervicalgia, neck pain, cervical pain, neck, cervical, vertebrae, vertebral, spine, radiculopathy, radiculopathies, radicular pain, intervertebral disc displacement, herniated, herniat\*, displacement, displacements, displaced, disk, disc, disks, discs, pain, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective studies, prospective studies, epidemiological studies, epidemiological research, and Non-experimental Studies. In PubMed we found and reviewed 756 articles, and considered 130 for inclusion. In Scopus, we found and reviewed 1,436 articles, and considered 5 for inclusion. In CINAHL, we found and reviewed 134 articles, and considered 8 for inclusion. In Cochrane Library, we found and reviewed 32 articles, and considered 0 for inclusion. We also considered for inclusion 0 articles from other sources. Of the 143 articles considered for inclusion, 104 randomized trials and 13 systematic studies met the inclusion criteria.

## Manipulation for Radicular Pain Syndromes without Neurologic Deficits

### No Recommendation.

There is no recommendation for or against manipulation for the treatment of radicular pain syndromes without neurologic deficits.

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

There is no quality evidence to address manipulation with neurological deficits; however, there are concerns about the use of manipulation in the presence of acute or progressive neurological deficits. Young et al. conducted an RCT evaluating cervical traction for radicular pain. Each group received manual therapy consisting of HLVA of the cervical and thoracic spine in addition to exercise. They reported improvement in both groups; however the study was not designed to evaluate the effects of manipulation of cervical radiculopathy.[1099] Another study compared cervical lateral glide mobilization to ultrasound and reported benefits for manipulation. The evaluations were taken immediately following the single intervention without long-term follow up.[1141]

*Evidence:*

There are 4 high-[1099, 1118, 1137, 1138] and 76 moderate-quality RCTs or crossover trials (one with two reports) incorporated into this analysis.[487, 1096, 1097, 1100, 1101, 1106, 1110, 1111, 1113-1116, 1119-1131, 1139-1189] There are 25 low-quality [1190-1216] RCTs and 5 other studies [1117, 1214, 1216-1218] in Appendix 1.

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The main function of the thalamus is arousal and regulation [980, 1221]. Deep brain stimulation (DBS) attempts to stimulate the deep brain and thus arouse the patient and help the thalamus recover [980, 1222, 1223].

## Deep Thalamic Stimulation

### No Recommendation.

There is no recommendation for or against the use of deep thalamic stimulation in the treatment of TBI patients.

*Strength of Evidence* – **No Recommendation, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

*Rationale:*

There are no quality studies assessing Deep Thalamic Stimulation for treatment of TBI. Deep Thalamic Stimulation is not invasive, has no adverse effects, is low cost, has no quality evidence of treatment efficacy, and thus there is no recommendation for treatment of TBI.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: ((Deep Thalamic Stimulation) OR (Thalamic Deep Brain Stimulation)); Traumatic brain injury OR Closed Head injury OR Penetrating Head Injury OR Concussion OR Craniocerebral Injury; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 12 articles in PubMed, 16 in Scopus, 5 in CINAHL, 1 in Cochrane Library, 2640 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 4 from Google Scholar, and 0 from other sources. Of the 5 articles considered for inclusion, 0 randomized trials and 4 systematic studies met the inclusion criteria.

## Acupuncture

Acupuncture has been used to treat some patients with traumatic brain injury [1224, 1225]. It has been used to treat headache related symptoms in TBI patients [1225], muscle spasticity [1224], insomnia [1226] and cervical disorders. Cervical spine disorders are likely the most common indication for acupuncture among TBI patients.

Acupuncture is based in part on the theory that many diseases are manifestations of an imbalance between yin and yang, as reflected by disruption of normal vital energy flow (qi) in specific locations, referred to as meridians. Needling along one of the 361 classical acupuncture points on these meridians is believed to restore balance. This stimulation is classically done with thin, solid, metallic needles, which are frequently manipulated (or turned) manually or stimulated electrically (electroacupuncture). In addition to needling, acupuncture frequently involves moxibustion and cupping. Besides traditional Chinese acupuncture, there are many other types of acupuncture that have arisen, including accessing non-traditional acupuncture points.[1150, 1227-1231]

### Acupuncture for Chronic Cervicothoracic Pain Recommended.

Acupuncture is recommended for select use in chronic cervicothoracic pain with or without radicular symptoms as an adjunct to facilitate more effective treatments.

*Strength of Evidence* – **Recommended, Evidence (C)**

*Level of Confidence* – **Low**

*Indications:*

As an adjunct treatment option for chronic cervicothoracic pain as a limited course during which time there are clear objective and functional goals that are to be achieved. Considerations include time-limited use in chronic cervicothoracic pain patients without underlying serious pathology as an adjunct to a conditioning program that has both graded aerobic exercise and strengthening exercises.

Acupuncture is recommended to assist in increasing functional activity levels more rapidly, and, if it is recommended, the primary attention should remain on the conditioning program. In those not involved in a conditioning program, or who are non-compliant with graded increases in activity levels, this intervention is not recommended.

*Benefits:*

Modest reduction in pain.

*Harms:*

Rare needling of deep tissue, such as artery, lung, etc. and resultant complications. Use of acupuncture may theoretically increase reliance on passive modality(ies) for chronic pain.

*Frequency/Dose/Duration:*

Different frequencies and numbers of treatments used in quality studies ranged from weekly for 1 month to 20 appointments over 3 months. Usual program is 10 sessions over 3 to 4 weeks.[1232] An initial trial of 5 to 6 appointments is recommended in combination with a conditioning program of aerobic and strengthening exercises. Future appointments should be tied to improvements in objective measures to justify an additional 6 sessions, for a total of 12 sessions.

*Indications for Discontinuation:*

Resolution, intolerance, or non-compliance including non-compliance with aerobic and strengthening exercises.

## Acupuncture for Acute or Subacute Cervicothoracic Pain Not Recommended.

Routine use of acupuncture is not recommended for treatment of acute or subacute cervicothoracic pain or for acute radicular pain.

*Strength of Evidence – Not Recommended, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

There are quality studies evaluating the utility of acupuncture for treatment of chronic cervicothoracic pain, although they conflict to some extent regarding whether it is efficacious and which type of acupuncture to perform. [1118, 1233-1235] One issue is the benefit of acupuncture versus electroacupuncture. A moderate-quality study showed that electroacupuncture was more effective than acupuncture alone.[1236] Quality trials compared to sham demonstrated a short term improvement in range of motion and pain[1233, 1234, 1237] and one of these moderate quality trials showed acupuncture was associated with improvements in pain-related activity, sleep, anxiety, depression, and satisfaction with life.[1232] Trials comparing acupuncture with no treatment have shown a decrease in pain of up to 40% over baseline after 12 weeks.[1238] The highest scored study (see evidence table) showed improvement in motion-related pain 1 hour after acupuncture above that seen for dry needling and sham acupuncture.[1233] Benefits beyond the duration of treatment of up to 3 years have been suggested.[1232] However, studies generally fail to control for attention bias, and also suggest that needling in locations other than traditional acupuncture points can provide equal benefit,[1232, 1239, 1240] which leads to questions regarding whether it is the needling rather than the acupuncture that was beneficial. Other quality trials have compared acupuncture with physiotherapy and medications and other treatments, with some failing to find differences in outcomes. A moderate-quality study of acupoint electrical stimulation did not find improvement in patients with variable duration of pain ranging from acute to chronic.[1241] Other studies found less of an effect or no effect, when compared to other treatments and placebo.[1118, 1237, 1242] One moderate-quality study looked at acupuncture compared to sham acupuncture; both treatment groups improved without a significant difference between the two up to 16 weeks after intervention.[1235]

There is no high quality evidence for treatment of acute cervicothoracic pain, radicular pain syndromes, or other cervical pain-related conditions. Acupuncture would not be expected to improve on the history of acute cervicothoracic pain treated with more effective treatments reviewed elsewhere.

Despite reservations regarding its true mechanism of action, the overall presence of quality trials demonstrating superiority of acupuncture to sham acupuncture provides quality evidence of efficacy, although the magnitude of benefits is modest and the treatment is passive. Acupuncture is minimally invasive, has relatively

low adverse effects in experienced hands, and is moderate cost depending on numbers of treatments.

There are no sham-controlled studies, but there is one quality study assessing use of acupuncture for treatment of spasticity related to TBI [1224] which suggested efficacy of electroacupuncture at 100Hz. Acupuncture is not invasive, generally has negligible adverse effects, is moderate cost, and has some potential evidence of treatment efficacy for spasticity. There is no recommendation for treatment of spasticity related to TBI until there is a sufficient body of quality evidence.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Acupuncture; Traumatic brain injury AND Closed Head injury AND Penetrating Head Injury AND Concussion AND Craniocerebral Injury; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 36 articles in PubMed, 30 in Scopus, 6 in CINAHL, 2 in Cochrane Library, 5460 in Google Scholar, and 1 from other sources. We considered for inclusion 5 from PubMed, 2 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 8 articles considered for inclusion, 2 randomized trials and 3 systematic studies met the inclusion criteria.

## Evidence for the Use of Acupuncture

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Zhao, 2015 (8.0)	Functional Electrical Stimulation	RCT	Sponsored by the Science Foundation on Traditional Chinese Medicine (TCM)/Integrative Medicine of the Tianjin Administration of TCM (grant no. 11031). No COI.	N=60 patients with muscle spasticity after brain injury.	The mean age for the 100 Hz group was 62 years. 15 males, 5 females. The mean age for the 2 Hz group was 63.5 years. 16 males, 4 females. The mean age for the Sham group was 62.45 years. 15 males, 5 females.	100 Hz group – received 100 Hz transcutaneous electrical acupoint stimulation (TEAS). N=20.  Vs.  2 Hz group – received 2 Hz transcutaneous electrical acupoint stimulation. N=20.  Vs.  Sham group – received 0 Hz transcutaneous electrical acupoint stimulation. N=20.	After 1 month and 2 months.	The MAS score for the wrist at Week 2, 3, 4, and Month 1 depicts a significant difference between the 100 Hz and sham, $p<0.05$ . Week 2 depicted a significant difference between the 100 Hz and 2 Hz, $p<0.05$ . Week 4 depicted a significant difference between the 2Hz and the sham. The MAS scores for the elbow, shoulder, knee, and ankle were changed with 100 Hz or 2 Hz treatments.	“TEAS appears to be a safe and effective therapy to relieve muscle spasticity after brain injury, although large-scale studies are required to further verify the findings.”	Data suggest that at one month post intervention muscle spasticity was significantly decreased in the TEAS 100 Hz group compared to both the TEAS 2 Hz and control groups.
Jonas 2016 (7.0)	Acupuncture	RCT	Funded by a grant from the Department of Defense Telemedicine and Advanced Technology	N=43	40 males, 5 females; Mean age 34.	(N=15) Auricular Acupuncture (AA). (N=14) Traditional Chinese Acupuncture [1196]. (N=14) Usual Care (UC)	Week 6, 12	Headache Impact test (HIT) improved in TCA and AA but not UC. AA, -10.2% [-6.4	“In this small exploratory study, AA and TCA acupuncture improved headache-	Data suggest both AA and TCA decreased headache scores via

			Research Center. No COI.			for 6 weeks than 6 weeks AA treatment.		points]; TCA, -4.6% [-2.9 points]; UC, +0.8% [+0.6 points]. AA significantly improved vs UC, (p=0.0079). Global pain score decreased substantially in both TCA and AA vs UC, (p=0.0036, p=0.0155, respectively). Usual pain decreased more in TCA group vs UC (p=0.0008). TCS & AA vs UC in Numerical rating scale (NRS), Pain now (p=0.0021), Pain Usual (p=0.0153), Pain Best (p=0.0004).	related QoL more than UC in Service members with TBI and resulted in only a few minor adverse effects.”	HIT when compared to UC.
Zolloman 2012 (3.5)	Acupuncture	Randomized Pilot Study	Work supported by US Army Medical Research and Materiel Command (CDMRP). No COI.	N=24	Group 1: 7 males, 5 females; Mean age 44.5±15.2. Group 2: 2 males, 6 females; Mean age 43.5±16.1.	Group 1: control group received no acupuncture, only prescribed medical history and prescribed sleep aid by study physician. Group 2: received same treatment but also 20 minutes of acupuncture twice weekly.	Follow up at baseline and twice weekly for 5 weeks.	Baseline vs post treatment: group 2 showed improvement (Z=-3.07, p<0.01), same decrease from baseline line to 1 month. Group 1 did not improve significantly post-treatment	“This pilot intervention study, although not conclusive, supports the contention that acupuncture has a beneficial effect on perception of	Dropouts before study enrollment /completion results in substantially unequal groups (n=8 v 12) and trends towards many



The effectiveness of the Flaxy Neurotherapy System, which combines biofeedback and photic stimulation (using glasses with light emitting diodes) in an attempt to affect EEG patterns that are known to be associated with cognitive dysfunction after TBI. In a randomized wait-list control design of 12 subjects, significant improvements in depression, fatigue, memory and learning were found [1243].

## **Biofeedback for TBI Patients**

### **No Recommendation.**

There is no recommendation for or against the use of biofeedback in the treatment of TBI patients.

*Strength of Evidence* – **No Recommendation, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

<i>Rationale:</i>	There are no quality studies assessing Biofeedback for treatment of TBI. Biofeedback is not invasive has no adverse effects, is low cost, has no quality evidence of treatment efficacy, and thus there is no recommendation for treatment of TBI. There may be other indications for biofeedback.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Biofeedback OR neurofeedback; Traumatic brain injury, Closed Head injury, Penetrating, Head Injury, Concussion, Craniocerebral Injury; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 17 articles in PubMed, 26 in Scopus, 4 in CINAHL, 3 in Cochrane Library, 3210 in Google Scholar, and 2 from other sources. We considered for inclusion 2 from PubMed, 1 from Scopus, 1 from CINAHL, 1 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 7 articles considered for inclusion, 1 randomized trials and 5 systematic studies met the inclusion criteria.

Laser therapy or low-level laser therapy has been used for treating pain, inflammation, neurological disorders, and promoting healing of tissues [915, 1244-1249]. LLLT uses red and NIR light rather than hotter light that is used for cutting and heating tissue. LLLT has been raising interest for treating traumatic brain injury because of purported abilities to inhibit apoptosis, stimulate growth, and increase neurogenesis [1244]. See Cervical and Thoracic Spine Disorders Guideline for indications for treatment of the cervical spine.

### **Laser Therapy/Low-Level Laser Therapy (LLLT)**

#### **No Recommendation.**

There is no recommendation for or against the use of laser therapy in the treatment of TBI patients.

*Strength of Evidence* – **No Recommendation, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

*Rationale:*

There are no quality studies assessing Low Level Laser Therapy for treatment of TBI. Low Level Laser Therapy is not invasive, has negligible adverse effects, is high cost, but has no evidence of treatment efficacy for TBI and thus there is no recommendation.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, Closed Head Trauma, Penetrating Head Trauma, Penetrating Craniocerebral Trauma, Low level light therapy, low level laser therapy, Laser therapy, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 120 articles in PubMed, 57 in Scopus, 1 in CINAHL, 0 in Cochrane Library, 1 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 0 randomized trials and 1 systematic study met the inclusion criteria.

Functional electrical stimulation [1182] uses a stimulator to activate skeletal muscle to accomplish a functional goal [1250]. FES bypasses the injured spinal cord and applies electrical pulses to peripheral motor neurons that elicit or, in part, mimic action potentials to induce distal muscles to contract [1251].

## Functional Electrical Stimulation

### No Recommendation.

There is no recommendation for or against the use of functional electrical stimulation in the treatment of TBI patients.

*Strength of Evidence* – **No Recommendation, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

*Rationale:*

There are only two quality and one low quality study assessing Functional Electrical Stimulation for treatment of TBI [1252] [1253] [587] and only the low quality study showed trends towards efficacy without statistical significance. Functional Electrical Stimulation is not invasive or minimally invasive, has negligible adverse effects, is moderate to high cost in aggregate, but as it is lacking evidence of efficacy, there is no recommendation for treatment of TBI. As the low quality study was underpowered but suggested a trend towards meaningful differences, this rating is no recommendation rather than not recommended pending reports of further investigations of quality.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Functional electrical stimulation [1182]; Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 33 articles in PubMed, 93 in Scopus, 5 in CINAHL, 11 in Cochrane Library, 14,000 in Google Scholar, and 0 from other sources. We considered for inclusion 3 from PubMed, 3 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 7 articles considered for inclusion, 4 randomized trials and 2 systematic studies met the inclusion criteria.

## Evidence for the Use of Functional Electrical Stimulation

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments :</i>
Leung, 2014 (7.0)	Functional Electrical Stimulation	RCT	Sponsored by The Rehabilitation and Disability Research Grants of the Royal Rehabilitation Centre Sydney, and the Research Infrastructure Block Grants of the University of Sydney. No COI.	N=36 patients with severe traumatic brain injury and ankle plantarflexion contractures.	Experimental Group mean age was 38 years. 14 males, 3 females. Control group mean age was 38 years. 15 males, 3 females.	Experimental Group - tilt table standing, electrical stimulation and ankle Splinting. N=17.  Vs.  Control Group - tilt table standing only. N=18.	Week 10.	Passive Ankle Dorsiflexion (PAD) for experimental minus control group for week 6 minus week 0 and week 10 minus week 0, respectively at 12 Nm (deg) was -3(-8 to 2) and -1(-6 to 4). At 9 Nm (deg) was -1(-5 to 3) and -1(-6 to 4). At 7 Nm (deg) 1(-3 to 5) and 0(-5 to 5). At 5 Nm (deg) was 2(-2 to 6) and 1(-3 to 6). At 3 Nm (deg) was 2(-3 to 7) and 0(-6 to 5).	"Contrary to expectations, the present study showed that 6 weeks of regular standing on a tilt table combined with electrical stimulation and ankle splinting did not provide added benefits when compared to a less-intensive program of tilt table standing alone, for people with severe traumatic brain injury and ankle contractures."	Experimental study without clinical outcomes. Baseline differences between groups for time from injury to baseline assessment. Data suggest similar efficacy between groups.
Lairamore , 2014 (6.0)	Functional Electrical Stimulation	RCT	No mention of sponsorship or COI.	N=32 patients with stroke or brain injury.	The mean age for the experimental group was 54.8 year. 10 males, 3 females. The mean age for the control group was 47.8 years. 6	Experimental Group – received Functional Electrical Stimulation. N=13.  vs.  Control Group – received sensory stimulation. N=13	No follow up mentioned.	Differences between the experimental and control group have a p values of p=0.83 in change in gait speed, p=0.77 FIM locomotion scores, p=0.79 EMG activity of the TA muscle during the swing phase of gait, and p=0.71 in loading phase of gait.	"The current results with this small sample suggest a low dose of gait training with single channel FES did not augment gait nor EMG activity beyond gait training with sensory stimulation; therefore, clinicians will likely be better served using a larger dose of FES or multichannel FES in this clinical population."	Data suggest lack of efficacy of functional ES on gait recovery post-neurological injury.

					males, 7 females.					
Peri, 2001 (6.0)	Functional Electrical Stimulation	RCT	No mention of sponsorship or COI.	N=10 coma patients	The mean age of the patients was 40 years. 8 males, 2 females.	ES – received 300 $\mu$ s pulses at 40 Hz electrical stimulation to the median nerve via 'Respond Select' by EMPI. N=6.  Vs.  Control - received a "sham" stimulation. N=4.	3 months.	The ES treatment group emerged from coma an average of 2 days earlier than the control group, p=0.31. The FIM/FAM results depict that the ES patients had a better functional status with a mean score 114 than the control patients with a mean score of 64.5. The difference is not statistically significant.	"These data show an interesting trend, although statistical power was limited in this small pilot study, suggesting the need for a larger trial."	Small sample. Pilot Study. Data suggest a trend towards ES group awakening from coma 2 days sooner than controls.

Neuromuscular electrical stimulation (NMES) is a therapeutic procedure used to strengthen muscle groups with preserved motor innervation [1254-1257]. NMES refers to the electrical stimulation of an intact lower motor neuron (LMN) to stimulate paralyzed or paretic muscles, providing a functional or therapeutic benefit [1258].

## Neuromuscular Electrical Stimulation (NMES)

### No Recommendation.

There is no recommendation for or against the use of neuromuscular electrical stimulation in the treatment of TBI patients.

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

There are two quality studies assessing Neuromuscular Electrical Stimulation for treatment of TBI and they conflict, with one showing improved swallowing function [1259], while another showed no improvement [1260]. A low quality trial suggested efficacy [1261]. Neuromuscular Electrical Stimulation is not invasive, has low adverse effects, is moderate to high cost in aggregate, but as it is lacking quality evidence of treatment efficacy, there is no recommendation for treatment of TBI.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Neuromuscular Electrical Stimulation; Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 5 articles in PubMed, 31 in Scopus, 2 in CINAHL, 5 in Cochrane Library, 23 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from PubMed, 3 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 4 articles considered for inclusion, 3 randomized trials and 1 systematic studies met the inclusion criteria.

## Evidence for the Use of Neuromuscular Electrical Stimulation

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Terre, 2015 (7.0)	Neuromuscular Electrical Stimulation	Allied Health	Sponsored by a grant of the FUNDACIÓN MAPFRE. No COI.	N=20. 14 stroke patients and 6 patients with severe traumatic brain injury.	The mean age of patients in the NMES group is 46 years. 6 males, 4 females. The mean age of the patients in the SES group is 51 years. 6 males, 4 females.	NMES group - Patients underwent NMES and conventional swallowing therapy. N=10. Vs. SES group - patients underwent sham electrical stimulation (SES) and conventional swallowing therapy. N=10.	3 months.	The Functional Oral Intake Scale (FOIS) score prior treatment for the NMES group was 2, SES group was 2.1. After treatment score was 4.9 NMES group and 3.1 SES group. The difference is p=0.0005. At 3-month follow-up, FOIS score is 5.3 NMES and 4.6 in SES group. Not statistically significant.	“Neuromuscular electrical stimulation significantly accelerated swallowing function in patients with oropharyngeal dysphagia secondary to acquired brain injury.”	Data suggest NMES therapy accelerate the swallowing function in patients with oropharyngeal dysphagia resulting from an acquired brain injury.
Beom, 2015 (5.0)	Neuromuscular Electrical Stimulation	Allied Health	Sponsored by Cyber-medic Corp., Iksan, Republic of Korea. No COI.	N=132	The mean age of the SM group was 64.4 years. 33 males, 33 females. The mean age of the SI group was 59.8	SM group - received hyolaryngeal NMES of the suprahyoid muscles only with Stimplus. N=66. Vs.	No follow-up.	The Functional Dysphagia Scale score report a decrease in scores $42.0 \pm 19.1$ to $32.3 \pm 17.8$ in the SM group and from $44.8 \pm 17.4$ to $32.9 \pm 18.8$ in the SI group, after electrical	“In conclusion, electrical stimulation of the suprahyoid muscle showed no	Data suggest similar efficacy between groups. (ES to suprahyoid muscles similar to ES to

					years. 42 males, 22 females.	SI group - received electrical stimulation of the suprahyoid muscle with one pair of electrodes and of the infrahyoid muscle with another pair of them. N=66.		stimulation, p<0.001, respectively. The Swallow Function Score increased from 3.3 ± 1.8 to 4.2 ± 1.6 in the SM group and from 2.8 ± 1.8 to 4.0 ± 1.8 in the SI group, after electrical stimulation, p<0.001, respectively.	significant differences in FDS scores and SFSSs from that of the infrahyoid muscle. The results of this study suggest that both SM and SI therapies induced similar improvements in swallowing function in brain-injured patients.	infrahyoid muscles) Significant number of dropouts in both groups.
Alon, 1998 (3.5)	Neuromuscular Electrical Stimulation	Allied Health	No mention of sponsorship or COI.	N=20. 13 patients who survived a cerebrovascular accident and 7 with TBI.	The mean age of the patients is 51.65 years. 14 males, 6 females.	No comparison group.	No follow-up.	ANOVA test scores from flexion at rest to flexion immediately after a 10-meter walk for the elbow are 14.3 ± 3.5 to 15.5 ± 0.5, respectively. P<.001. For the	“Application of the NESS system for three to four hours daily improves	Small sample. Data suggest use of NESS improved some functions in TBI and

								<p>wrist are <math>11.5 \pm 3.1</math> to <math>8.6 \pm 0.9</math>, respectively, <math>p &lt; .001</math>. Active wrist extension and flexion increased by <math>12.7 \pm 0.5</math> and <math>9.0 \pm 3.3</math> degrees, respectively. <math>P &lt; 0.01</math>.</p>	<p>selected impairments and may help to restore partial hand functions of patients with chronic stroke or head injury.”</p>	<p>stroke patients as 80% [16385] patients were able to hold a 1 kg weight with an active NESS system vs only 3 patients without active NESS.</p>
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## Non-Operative Therapeutic Procedures

Traumatic brain injuries lead to neurobehavioral impairments such as physical, psychological, and behavioral challenges [1262]. For survivors of serious brain injury, behavioral symptoms, including marked irritability, aggression, and various forms of regressed social functioning, commonly increase over time as other indicators of functional disability decrease [419, 802, 1262-1267].

### Behavioral Programs

#### Recommended.

Behavioral programs are recommended for use in the treatment of TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Moderate**

<i>Indications:</i>	Moderate to severe TBI with behavioral issues, especially if not trending towards resolution.
<i>Benefits:</i>	Improved awareness and function. Resolution of functional and impairing difficulties, especially those that may inhibit return to quality life and work.
<i>Harms:</i>	Medicalization
<i>Frequency/Dose/Duration:</i>	The highest quality study included social skills training program of 12 weekly 3-hour group sessions with therapist plus 1 weekly individual session with clinical psychologist [1267], while another study used web-based approaches [1266].
<i>Indications for Discontinuation:</i>	Resolution of symptoms, sufficient recovery to function, lack of compliance, reaching a clinical plateau.
<i>Rationale:</i>	There are no quality sham-controlled trials. The overall literature base has much heterogeneity in methods and interventions which preclude an evidence-based treatment recommendation. Yet, these programs have some empirical evidence of efficacy. Behavioral Programs are not invasive, have negligible adverse effects, are moderate cost, have no quality evidence of treatment efficacy, are thought to be effective and necessary for recovery from some sequelae and thus are recommended for treatment of TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: behavioral programs, traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 136 articles in PubMed, 288 in Scopus, 5 in CINAHL, 8 in Cochrane Library, 16400 in Google Scholar, and 2 from other sources. We considered for inclusion 5 from PubMed, 1 from Scopus, 2 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 2 from other sources. Of the 10 articles considered for inclusion, 6 randomized trials and 1 systematic study met the inclusion criteria.

### Evidence for the Use of Behavioral Programs

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
McDonald 2008 (6.0)	Behavioral Programs	RCT	Sponsored by the Australian National Health and Medical Research Council. McDonald is an author of The Awareness of Social Inference Test, which is used as an outcome measure in this study, and receives royalties for its sale. No COI.	N = 51 with traumatic brain injury and social skills deficits.	Mean age for Skills training / Social / and Waitlist groups: 36.3 ± 10.7 / 33.1 ± 11.7 / and 35.2 ± 11.3 years, 40 males and 11 females.	Social skills training program of 12 weekly 3-hour group sessions with therapist plus 1 weekly individual session with clinical psychologist (N = 18) vs Social group program of 12 weekly sessions focused on group activities for companionship (N = 17) vs Waitlist group (N = 16).	12-weeks	No sig. difference between groups in any of the outcomes variables assessed, except on Partner Directed Behavioral Skill (PDBS) scores improved significantly across all three groups (p=0.004).	"[D]espite the small numbers and the severe, chronic nature of disability experienced by the participants, improvements in social behavior were apparent especially in a reduction in self-centered behavior and greater effort to involve the conversational partner."	Data suggests limited positive effects from social skills training in patients with severe or chronic brain injuries.
McLaughlin 2013 (5.0)	Behavioral Programs	RCT	Sponsored the National Institute of Child Health and Human Development. No COI.	N = 201 with TBI.	Age range 18 – 61 years, 140 males and 62 females.	Intervention, an online screening tool on the BIAUSA Web site (N = 97) vs Controls used the Web site for a minimum of 30 minutes (N = 104).  Outcome measures: caregiver knowledge, skill application, behavioral intention, and overall life satisfaction.	3-months	(51%) had 1 visit to the program Web site, 24% 2 visits, 18% 3 or more visits, and 7% did not visit the Web site. The knowledge item posttest change score, (r = 0.24, p = 0.016).	"This study demonstrated the effectiveness of a Web-based intervention in teaching effective skills to caregivers advocating for a family member with brain injury."	Data suggest use of a web-based training intervention may be of benefit to teach the necessary skills to caregivers caring for TBI family members.

Brown 2015 (5.0)	Behavioral Programs	RCT	Sponsored by the Department of Education, National Institute on Disability and Rehabilitation Research, Mayo Clinic TBI Model System Center Grant. No COI.	N = 257 with moderate–severe TBI 1 or more years post-injury.	18 years of age or older, 97 males and 160 females.	Curriculum group, 6-hour sessions, consistent with the design of a community-based practical behavioral trial and REAIMS framework (N = 129) vs Allocated to Usual Care group (N = 128).  Outcome measure; advocacy Behaviour Rating Scale (ABRS).	4-months	Between groups, ABRS scores increased after intervention in both groups, p = 0.4447 and 0.1282.  ABRS ratings significantly greater after an intervention for both letters, (p < 50.001) and videos (p < 50.001).	“Curriculum-based advocacy training was not superior to a self-directed approach in improving ABRS scores.”	Data suggest equal in efficacy.
Hanks 2012 (4.0)	Behavioral Programs	RCT	Sponsored by the U.S. Department of Education-National Institute of Disability Research and Rehabilitation—The Traumatic Brain Injury Model Systems Project. No COI.	N = 199 with TBI.	Mean age for control and mentoring group: 40.90 ± 17.33 / 38.46 ± 17.60 years, 136 males and 22 females.	Mentoring (N = 96) vs No mentoring (N = 62).  Outcome measures: Peer Mentoring Questionnaire; Brief Symptom Inventory-18; Family Assessment Device (FAD); Coping Inventory for Stressful Situations; Short Michigan Alcohol Screening Test; Medical Outcomes Study 12-Item Short-	2 years	Differences in subjective perception of community integration and levels of depression or anxiety, (p = 0.35). 88% in the mentoring group reported positive experience.  Those who received mentoring had better	“Mentoring can be an effective way to benefit mood and healthy coping after TBI, and it can help to prevent maladaptive behaviors, such as substance abuse and behavioral dyscontrol, in the living situation.”	Data suggest mentoring may increase coping post TBI.

						Form Health Survey; and Community Integration Measure.		behavioral control and less chaos in the living environment / lower alcohol use / less emotion-focused / avoiding coping / and good physical quality of life: p = 0.04 / 0.01 / 0.04 / 0.03 / and 0.4.		
Carnevale 2006 (4.0)	Behavioral Programs	RCT	Sponsored by the National Institute on Disability and Rehabilitation Research, U.S. Department of Education and the Henry H. Kessler Foundation. No COI.	N = 47 with a diagnosis of TBI.	Mean age 40.5 ± 12.2, 56 males and 18 females.	Control group, no education (N = 17) vs Education only: full education from the Natural Setting Behavior Management (NSBM) staff (N = 14) vs Full NSBM: personalized education from NSBM staff (N = 16).	Follow-ups were at 7, 16, and 30 weeks.	No significant differences in ANOVA at 7 and 16 weeks, and at 30 weeks (F = 3.32, p = 0.05). The NSBM and the education only groups (Tukey honestly significant difference, P < 0.04). Average frequency at baseline correlated	"A program of caregiver education and individualized behavior management in natural settings can decrease the frequency of disruptive behavioral challenges."	Data suggest the rate of disruptive behavior in the NSBM group declined.

								<p>with frequency at 7, 16, and 30 weeks post baseline (<math>r = 0.81</math>, <math>r = 0.76</math>, <math>r = 0.75</math>; all <math>P &lt; 0.001</math>). When controlling for baseline emotional exhaustion, treatment effects did not reach significance at 7 and 16 weeks, but did at 30 weeks (<math>F = 4.26</math>, <math>P &lt; 0.03</math>).</p>	
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## Inpatient and Outpatient Rehabilitation Programs

There are numerous and diverse rehabilitation programs that have been developed. Some are inpatient, while some are outpatient [1268-1270]. Some are based in acute care facilities, while others rehabilitation facilities and still others specialize in TBI patients. Some programs have a single or few components (e.g., physical therapy and medical services), while others are integrated/multidisciplinary and include many other services (e.g., psychology/mental health, vocational rehabilitation, occupational therapy, substances abuse treatment/prevention, social work). Not all patients need all program components, so regardless of the setting, tailoring of the program to the specific patient's needs is required. Multidisciplinary programs are generally more comprehensive and may be more indicated with more severe injuries with greater degrees of various impairments. Selective and integrated rehabilitation programs are designed to help the individual work on specific tasks in order to “retrain” the body to accomplish said task [1271]. Some programs focus on TBI while others may focus on an array of neurological and orthopedic conditions [1272]. This section will classify these heterogenous programs into only the two categories of inpatient and outpatient for ease of use.

For those with TBI rehabilitation typically consists of an individualized program of rehabilitation therapies delivered most often by an integrated interdisciplinary team with at least two components (e.g., medical and therapy). Most programs have many more components, especially those targeting the TBI patient population and some are multi-disciplinary [1268, 1269, 1273].

### Outpatient: Home and Community-Based Rehabilitation

#### Recommended.

Outpatient home and community-based rehabilitation is selectively recommended for TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Moderate**

<i>Indications:</i>	Sufficient residual symptoms and/or signs of post TBI to necessitate ongoing treatment, be it medical, physical therapy, occupational therapy, or other. These programs are generally more helpful for those with greater numbers and magnitudes of mismatch between current abilities and job cognitive and physical demands. There may be select cases with mild TBI with ongoing symptoms who may be candidates.
<i>Benefits:</i>	Ongoing treatment targeting functional outcomes to improve the patient's overall prognosis. Improved likelihood of achieving goals including RTW.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Highly variable and depends on the clinical status, including symptoms, signs, functional deficits, rate of progress, need for individualized care (e.g., coaching), etc. Outpatient appointments are generally at least 2-3 times/week. With outpatient physical therapy services needs, appointments may be daily.
<i>Indications for Discontinuation:</i>	Sufficient recovery, end of healing, reaching a plateau, non-compliance, substances use recalcitrant recidivism.

*Rationale:*

The overall literature base is weak, as there are quality studies assessing components of rehabilitation programs, but no quality studies assessing whether these programs are superior to no treatment or to sham. Outpatient home and Community-Based Rehabilitation is not invasive, has negligible adverse effects, is high cost, is thought to be quite effective and so is recommended for selective treatment of TBI.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: home and community based rehabilitation, traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 25 articles in PubMed, 69 in Scopus, 35 in CINAHL, 6 in Cochrane Library, 17400 in Google Scholar, and 0 from other sources. We considered for inclusion 5 from PubMed, 2 from Scopus, 2 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 9 articles considered for inclusion, 4 randomized trials and 1 systematic study met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Outpatient rehabilitation, services, traumatic, brain, injury, intracranial, closed, head, penetrating, concussion, craniocerebral, trauma, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 35 articles in PubMed, 13 in Scopus, 17 in CINAHL, 5 in Cochrane Library, 7340 in Google Scholar, and 0 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 7410 articles considered for inclusion, 0 randomized trials and 2 systematic studies met the inclusion criteria.

## **Inpatient: Comprehensive Integrated Interdisciplinary Rehabilitation**

Inpatient comprehensive integrated interdisciplinary rehabilitation is selectively recommended for treatment of TBI patients.

### **Recommended.**

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

<i>Indications:</i>	Sufficient residual symptoms and/or signs of mostly acute TBI to necessitate ongoing and daily treatment, be it medical, physical therapy, occupational therapy, or other. Most programs are multidisciplinary and generally TBI inpatients are sufficiently severely affected to require multidisciplinary services. Most patients will have incurred severe TBI, but occasionally, patients with moderate TBI may also be benefited by these programs. Generally not used for chronic patients unless the TBI was severe and the patient is making functional gains not possible or substantially less likely in an outpatient setting.
<i>Benefits:</i>	Ongoing treatment targeting functional outcomes to improve the patient's overall prognosis. Improved likelihood of achieving goals including RTW.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Highly variable and depends on the clinical status, including symptoms, signs, functional deficits, rate of progress, need for individualized care (e.g., coaching), etc.
<i>Indications for Discontinuation:</i>	Sufficient recovery to be able to be discharged to outpatient facilities.
<i>Rationale:</i>	The overall literature base is weak, as there are quality studies assessing components of inpatient rehabilitation programs, but naturally no quality studies assessing whether these programs are superior to no treatment or to sham. Inpatient Comprehensive Integrated Rehabilitation is not invasive, has negligible adverse effects, is high cost, is thought to be quite effective and so is recommended for selective treatment of TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: multidisciplinary rehabilitation program, traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 78 articles in PubMed, 52 in Scopus, 9 in CINAHL, 4 in Cochrane Library, 8490 in Google Scholar, and 2 from other sources. We considered for inclusion 8 from PubMed, 0 from Scopus, CINAHL, Cochrane Library, and Google Scholar, and 2 from other sources. Of the 10 articles considered for inclusion, 4 randomized trials and 2 systematic studies met the inclusion criteria.

## Evidence for the Use of Comprehensive Integrated Inpatient Interdisciplinary Rehabilitation Programs

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Vanderploeg 2008 (4.5)	Comprehensive Integrated Inpatient Interdisciplinary Rehabilitation Programs	RCT	Sponsored by the Defense and Veterans Brain Injury Center, Uniformed Services University of the Health Sciences, Bethesda, MD, the Department of Veterans Affairs, Veterans Health Administration, and a Department of Defense award administered through the Henry Jackson Foundation. No COI.	N = 366 with moderate to severe nonpenetrating TBI within the last 6 months with a Glasgow Coma Scale score of $\leq 12$ , in a coma for 12+ hours, PTA for 24+ hours, RLAS cognitive level of 5 to 7, 18 years old or older, active duty military member or veteran, and need of 30 days or more of acute interdisciplinary TBI rehabilitation.	Mean age for cognitive and functional rehabilitation groups: $33.2 \pm 13.5$ / $31.7 \pm 12.9$ , 340 males and 26 females.	Cognitive-didactic treatment targeted 4 cognitive domains impaired by TBI: attention, memory, executive functions, and pragmatic communication; one on one sessions (N = 184) vs Functional-experiential treatment with the use of real-life performance situations and common tasks to compensate for functional deficits after brain injury; group sessions (N = 182).	1-year	NS between groups at 1 year for: percent who returned to work or school and percent living independently. Cognitive FIM at end of treatment: cognitive group ( $27.3 \pm 6.2$ ) vs functional group ( $25.6 \pm 6.0$ ), $p = 0.01$ . NS between groups for motor FIM and DRS. Memory problems [1274]: cognitive 22.2% v. functional 27.6%, $p = 0.05$ . Those with more education more often lived independently at 1 year in the functional group (69.1%) compared to	“The results from this trial, with the largest sample ever treated in a randomized controlled rehabilitation trial of TBI, indicated no difference between cognitive-didactic and functional-experiential approaches to brain injury rehabilitation on the primary 1-year global outcome measures of the study. However, patients in the cognitive treatment arm had better posttreatment cognitive performance than patients in the functional treatment arm.”	Data suggest both groups improved with similar long term global functional outcomes. Data suggest more improvement in short term functional cognition

								the cognitive group (47.4%), p < 0.02. Younger participants were more often working at 1 year in the cognitive group (53.3%) compared to the functional group (37.8%, p<0.03).		
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### Evidence for the Use of Multidisciplinary Rehabilitation Programs

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Powell J 2001 (7.5)	Multidisciplinary Rehabilitation Programs	RCT	No mention of COI. The research assessor was funded by a grant from the Medical Research Council, and the treatment programme was funded by the Department of Health.	N= 110 Patients who sustained severe TBI between 3 months and 20 years previously, and had no other neurological conditions.	Mean age: 34.5; (Males 71, Females 23)	Outreach group (N=54) vs. Information group (N=56) (No other description of study design and comparison groups)	Follow up for an average of 24.8 months	The outreach participants were significantly more likely to show gains on the BI (Barthel index) and the BICRO-39 (brain injury community rehabilitation outcome-39) total score and self-organization and psychological wellbeing subscales.	This is the first RCT of multidisciplinary community rehabilitation after severe TBI, and suggests that even years after injury it can yield benefits which outlive the active treatment period.	Data suggest implementation of multidisciplinary community based outreach rehab treatment post severe TBI benefit the patient after the active treatment period. Time since injury

							<p>There were likewise strong trends (<math>p &lt; 0.10</math>) for BICRO personal care and mobility, and on the FIM+FAM for personal care and cognitive functions. Differential improvements were not seen for indices of socializing, productive employment, anxiety, or depression. Median changes on individual subscales were small, reflecting the diversity of the clinical population; however, 40% of outreach but only 20% of information participants made a clinically significant improvement of 2+ points on at least one BICRO-39</p>	<p>occurrence not correlated to amount of gains.</p>
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								scale. Time since injury was unrelated to the magnitude of gains.		
Cicerone 2008 (7.0)	Multidisciplinary Rehabilitation Programs	RCT	Sponsored by the National Institute on Disability and Rehabilitation Research. No COI.	N = 68 with traumatic brain injury (TBI) recruited from clinical referrals and the community.	Standard Neurorehabilitation group 34.5 ± 12.4  Intensive cognitive rehabilitation group 38.7 ± 11.1  Gender (M:F) 46:22	Standard neurorehabilitation, includes physical, occupational and speech therapies (N = 34) vs. Intensive Cognitive Rehabilitation, includes communication group, cognitive group and life skills group (N = 34). Both groups received 15 hours of treatment for week for 16 weeks. Primary/Secondary outcomes; Community integration (CIQ), Life satisfaction (PQOL) / NP functioning, Perceived self-efficacy, community based-employment.	6 months	There were no significant main effects for treatment or condition on the CIQ / PQOL / NP scores / Self – efficacy scores. 74% participant after completion of the study required follow - up treatment. Participants showed improvement on CIQ scores from post treatment to follow – up (p = 0.04).	“Improvements seen after intensive cognitive rehabilitation may be related to interventions directed at the self-regulation of cognitive and emotional processes and the integrated treatment of cognitive, interpersonal, and functional skills.”	Data suggest a comprehensive NP rehab plan post TBI improves self perceived quality of life and community functions. as measured by CIQ and PQOL.

Browne 2013 (4.5)	Multidisciplinary Rehabilitation	RCT	Sponsored by the Australian and New Zealand College Of Anaesthetists and the State Health Research and Advisory Council of Western Australia. No COI.	N = 142 non-severe head injured trauma inpatients.	Mean age of 37 years, 106 male and 36 female.	Intervention Multidisciplinary Intervention or MI (N = 69) vs Control, usual care or UC (N = 73).	1, 3, and 6 months	Intervention group reported significantly greater relief from pain vs the control, (p < 0.05). At 6 months, alcohol use predicted a significant 26%, 49%, 56%, and 30% of the variance in pain, depressive, and PTSD severity, and physical mobility, respectively. 24% of the UC group below the cut-off for being at risk of developing PTSD/Depression received new clinical diagnoses at 6 months vs none of the 'not at risk' MI group.	"[T]he multidisciplinary intervention was not superior to usual care in reducing pain and psychological symptom severity, and improving functional outcomes within the first 6 months when overall group outcomes were compared."	Significant loss to follow-up for 6 month outcome analysis. Data suggest importance of early multidisciplinary programs to decrease and prevent traumatic injury disability.
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Barreca 2003 (4.0)	Multidisciplinary Rehabilitation	RCT	Sponsored by the Ontario Neurotrauma Foundation. No mention of COI.	N = 12 with acquired brain injury.	Mean age 41.3 (1.5) ranging from 17 to 66 years, 10 male and 3 female.	Treatment A received an enriched stimulus environment, collaborative multidisciplinary interventions and additional yes/no response training (N = 7) vs Treatment B received the standard hospital environment and interventions (N = 6).	8 weeks	No order effect AB vs BA, ( $p = 0.60$ ), but a trend towards statistical significance for increased responsiveness with treatment A, ( $p = 0.07$ ). Inter-rater reliability ( $n =$ 10) ranged from fair-to- good, intra class correlation (ICC) 0.51; 95% (CI) (0.29– 0.93). Post- hoc analyses showed statistically significant increased responsiveness for 4 participants with treatment A, ( $p < 0.001$ ).	“Evidence is provided that enhanced communication strategies can improve responsiveness in a sub-group of participants with severe acquired brain injuries.”	Randomize d crossover study design. Data suggest enhanced communica tion may improve responsive ness in acquired brain injury patients.
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## Evidence for the Use of Home and Community-Based Rehabilitation

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Powell 2002 (7.5)  RCT	Home and Community Based Program	RCT	Sponsored by the Medical Research Council and Department of Health. No mention of COI.	N = 110 with sustained severe traumatic brain injury (TBI) between 3 months and 20 years previously.	Age 16 – 65.	Information group received assessment and limited treatment, with pursuing referrals to patient services (N = 56) vs Outreach treatment for 2 – 6 hours a week, plus goal planning framework for 27.3 weeks (N = 54).  Primary outcomes: Barthel Index, brain injury community rehabilitation outcome-39 scales (BICRO-39). Secondary; functional independence/assessment Measures (FIM+FAM). Outcome measures; Barthel Index, brain injury community rehabilitation outcome-39	24.8-months	Barthel Index (BI) / Functional Independence Assessment Measure (FIM+FAM) / and Brain Injury Community Rehabilitation Outcome-39 (BICRO-39): 35% vs 20%, $p < 0.05$ / median score change on the BICRO-39 were greater for those in the outreach vs the information group for the total score / and mean rank 53.2 vs 40.4, ( $p < 0.03$ ).  Clinically significant improvement / high success rates; 71% compared 40% in the outreach group / 2.0 points compared to 1.0 success scores.	“In patients with severe traumatic brain injury, a multidisciplinary community-based outreach rehabilitation program improved social functioning.”	Data suggest implementation of multidisciplinary community based outreach rehab treatment post severe TBI benefit the patient after the active treatment period. Time since injury occurrence not correlated to amount of gains.

## Residential Rehabilitation

Residential rehabilitation facilities are used for treatment of TBI patients [1275]. Residential Rehabilitation has been used as a treatment option for those who have had a traumatic brain injury and are seeking treatment. It is a program that is separate from home and inpatient care.

### Residential Rehabilitation

Residential rehabilitation is selectively recommended for treatment of TBI patients.

#### Recommended.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Moderate**

<i>Indications:</i>	Sufficient residual symptoms and/or signs of post TBI to necessitate ongoing outpatient treatment, be it medical, physical therapy, occupational therapy, or other. Generally these programs are used for those with more numerous impairments, an inability to return to home unassisted, and/or greater numbers and magnitudes of mismatch between current abilities and ADLs, job cognitive, and physical demands.
<i>Benefits:</i>	Ongoing treatment targeting functional outcomes to improve the patient's overall prognosis. Improved likelihood of achieving goals including ADLs and RTW.
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	Highly variable and depends on the clinical status, including symptoms, signs, functional deficits, rate of progress, need for individualized care (e.g., coaching), etc. Daily unskilled or skilled care is generally needed.
<i>Indications for Discontinuation:</i>	Sufficient recovery, end of healing, reaching a plateau, non-compliance.
<i>Rationale:</i>	There are no quality studies assessing residential rehabilitation programs. These programs are not invasive, have negligible adverse effects, are high cost, are thought to be effective and so are recommended for selective treatment of TBI.
<i>Rationale:</i>	There are quality studies assessing Residential Rehabilitation for treatment of TBI. Residential Rehabilitation is not invasive have no adverse effects, are low cost, have evidence of treatment efficacy, and are/not recommended for treatment of TBI.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Residential Rehabilitation, Brain Injuries, Head Injuries, Closed, Penetrating, Brain Concussion, Craniocerebral Trauma, Traumatic Brain, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 28 articles in PubMed, 32 in Scopus, 10 in CINAHL, 6 in Cochrane Library, 2500 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from

PubMed, 4 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 6 articles considered for inclusion, 0 randomized trials and 2 systematic studies met the inclusion criteria.

Supported living programs or long-term care residential services are used for patients that require long-term care or rehabilitation [1276, 1277]. These are generally less intensive than skilled nursing facilities.

## Supported Living Programs

Supported living programs are selectively recommended for treatment of TBI patients.

### Recommended.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Moderate**

<i>Indications:</i>	Severe TBI with sufficient impairments and inability to, e.g., perform ADLs, but insufficient for a skilled nursing facility that assisted living is required. Most patients needing supported living programs will have incurred severe TBI, but occasionally, select patients with moderate TBI with significant impairments and incapacity may also be benefited by these programs.
<i>Benefits:</i>	Ability to receive tailored assistance. May be able to receive sufficient care to achieve independence and discharge to either home or a lower level of skilled care.
<i>Harms:</i>	Potential for nosocomial infections. May also be in a facility that does not sufficiently accelerate the rehabilitative process, thus impairing achievement of treatment goals.
<i>Indications for Discontinuation:</i>	Recovery sufficient to not require
<i>Rationale:</i>	There are no quality studies assessing Supported Living Programs (SLP) for treatment of TBI. SLP is not invasive, has significant risks of problems such as nosocomial infections, and is high cost. For select severe TBI patients, there may be no other practical alternative and thus skilled care SLPs are selectively recommended for some severe TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Supported Living Programs, SLP, Long-Term Care Residential Services, Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, Closed Head Trauma, Penetrating Head Trauma, Penetrating Craniocerebral Trauma, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 3 articles in PubMed, 0 in Scopus, 14 in CINAHL, 97 in Cochrane Library, 33760 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

There are many options for treatment facilities for someone with a severe TBI. One of these is a nursing care facility. These facilities are also known as nursing homes or skilled nursing facilities (SNF). These facilities provide medical care to patients 24 hours a day and can treat those suffering acute or chronic conditions [1278].

### Skilled Nursing Facilities

Skilled nursing facilities are selectively recommended for treatment of TBI patients.

#### Recommended.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Moderate**

<i>Indications:</i>	Severe TBI with sufficient impairments and inabilities to perform ADLs that a skilled nursing facility if needed.
<i>Benefits:</i>	Ability to receive tailored assistance. May be able to receive sufficient care to achieve independence and discharge to either home or a lower level of skilled care.
<i>Harms:</i>	Potential for nosocomial infections. May also be in a facility that does not sufficiently accelerate the rehabilitative Process, thus impairing achievement of treatment goals.
<i>Frequency/Dose/Duration:</i>	N/A
<i>Indications for Discontinuation:</i>	Recovery sufficient to not require
<i>Rationale:</i>	There are no quality studies assessing Nursing Care Facilities for treatment of TBI. Nursing Care Facility treatment is not invasive, has significant risks of problems such as nosocomial infections, and is high cost. For select severe TBI patients, there may be no other practical alternative and thus skilled care facilities are selectively recommended for some severe TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: nursing care facility, facilities, skilled nursing facilities, nursing care; traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 5 articles in PubMed, 0 in Scopus, 4 in CINAHL, 7 in Cochrane Library, 23 in Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

With TBI, rehabilitation may be helpful particularly for rehabilitating the patient toward the goal of return to work (RTW).

## Occupational Rehabilitation

Occupational rehabilitation is selectively recommended for treatment of TBI patients.

### Recommended.

*Strength of Evidence* – **Recommended, Evidence (C)**

*Level of Confidence* – **Low**

<i>Indications:</i>	There are many indications. These include sufficient impairments to provide for mismatch between the patient's current capabilities and future job requirements. Also helpful for mismatches in ADLs. In some practice settings, occupational therapy rehabilitation concentrates on the distal limbs while physical therapy concentrates on torso and proximal limbs; if so, those are additional indications.
<i>Benefits:</i>	Improved functional recovery, recovery at a faster pace. Ability to RTW. RTW at a higher job function.
<i>Harms:</i>	Return home with greater ability to perform ADLs.
<i>Frequency/Dose/Duration:</i>	Negligible. Medicalization is possible.
<i>Indications for Discontinuation:</i>	Frequency is dependent on the individual status, including degrees of deficits, and degrees of mismatches between capabilities and ADLs and/or job tasks. In general, inpatient or outpatient intensive services requirements are often daily, while outpatient care with fewer mismatches may be as little as every week or two to start.
<i>Rationale:</i>	Recovery, plateau, lack of further functional gain, exhaustion of treatment options with quality efficacy.
<i>Evidence:</i>	There are no quality studies assessing the utility of Occupational Rehabilitation for treatment of TBI, although there are many studies of individual treatment components. Occupational Rehabilitation is not invasive, has negligible adverse effects, is moderate to high cost, has evidence of treatment efficacy for many component parts, and thus is recommended for treatment of TBI.
	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Occupational, rehabilitation, traumatic, brain, injury, intracranial, closed, head, penetrating, concussion, craniocerebral, trauma, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 239 articles in PubMed, 10 in Scopus, 7 in CINAHL, 2 in Cochrane Library, 21800 in Google Scholar, and 0 from other sources. We considered for inclusion 4 from PubMed, 1 from Scopus, 0 from CINAHL, 1 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 22058 articles considered for inclusion, 0 randomized trials and 5 systematic studies met the inclusion criteria.

Opioid/Chemical treatment programs have been used for treatment of substances use patients [1279-1281]. They are a heterogenous group of treatment programs ranging from detoxification to 24-hr. residential treatment facilities. There is one study suggesting potential efficacy for purposes of prevention [1282].

## Opioid/Chemical Treatment Programs

Opioid/chemical treatment programs are selectively recommended for treatment of TBI patients.

### Recommended.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Moderate**

<i>Indications:</i>	Substances abuse sufficient to require opioid and/or chemical treatment programs, including withdrawal, anticipated high-risk withdrawal, medical condition, emotional factors, behavioral factors, cognitive aspects, recurrences, and degrees of addictions.
<i>Benefits:</i>	Avoidance of substances use, managed withdrawal to reduce fatalities and other severe effects of withdrawal.
<i>Harms:</i>	Negligible. May incur complications from treatment especially with medications.
<i>Indications for Discontinuation:</i>	Completion of treatment.
<i>Rationale:</i>	There are no quality studies assessing Opioid/Chemical Treatment Program for treatment of TBI patients. Opioid/Chemical Treatment Programs are not invasive, may not have significant adverse effects (other than medication treatment complications), are high cost, do not have evidence of treatment efficacy for TBI patients, but are likely effective for select patients with substances abuse and are thus recommended for treatment of select TBI patients.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Opioid or Chemical treatment programs, Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 101 articles in PubMed, 121 in Scopus, 11 in CINAHL, zero in Cochrane Library, 180 in Google Scholar, and zero from other sources. Zero articles met the inclusion criteria.

### Evidence for the Use of Opioid/Chemical Treatment Programs

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Tweedy 2012 (5.5)	TBI	Treatment	Authors declare no conflict of interest.	N= 60	45 males, 15 females. Mean age is 35 years.	Brief information (INFO, N=20) vs INFO plus motivational interviewing (MI + INFO, N= 20), vs informal discussion (ID, N= 20)	2 hours of assessment and intervention at baseline (6-9 months post-injury), and a 6 month follow up (12-15 months post-injury).	At 6 month follow up, according to the Timeline Follow-Back (TLFB), the ID group reported 7 days of drinking in month prior to follow up, compared to 3-4 days a month in the MI + INFO and INFO groups. However, these results were not statistically significant.	“There was a positive trend showing participants in both the intervention groups to be drinking less frequently and consuming fewer alcoholic drinks than those in the informal discussion (control) group. However, group differences did not reach statistical significance.... Further randomized controlled trials with larger samples are needed to establish whether brief educational and motivational interview interventions targeting alcohol use are efficacious in the traumatic brain injury population.”	Data suggest a trend in both intervention groups towards less frequent and fewer drinks over controls.

Corrigan 2005 (3.0)	TBI	Treatment	Funding for this project was provided by the Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, via Grant 5 KD1 TI12013. No mention of COI.	N= 195	138 males, 57 females. Mean age is 36.6 years.	195 participants randomly assigned into 4 groups. [170] Attention control, (2) barrier reduction, (3) motivational interview, and (4) financial incentive.	Appointments unspecified and varied by participant preference. Follow up at 3 and 6 months.	Statistically significant differences were found in the financial incentive (87%) and barrier reduction (74%) groups compared to the motivational interview (45%) and attention control (45%) groups. Significance indicated through client signing an individualized service plan (ISP) with a counselor within 30 days. Significance also found in fewer number of days to sign ( $M = 22.8$ days, $SD = 14.7$ ), ( $M = 44.0$ days, $SD = 35.8$ ) and fewer premature terminations (4%, 6%, 9%, 15%), respectively.	“Participants in the financial incentive and barrier reduction groups were at least 50% more likely to sign the ISP within 30 days compared with the motivational interview and control groups.... Retention in the barrier reduction and financial incentive conditions was 50% greater than in the attention control condition. If these results are replicated, they suggest that the initial intervention sets into motion a series of events that promotes later retention. These findings provide support for Newman’s (1997) conception of how engagement in treatment can affect later retention.”	Data suggest financially compensated and barrier reduction groups were more likely to sign on to a substance abuse treatment program post TBI than the motivational interview or attention control groups.
Vungkhanching 2007 (3.0)	TBI	Treatment	Funded by US Department of Education,	N = 117	83 males, 34 females.	Intervention (N = 36) vs Comparison (N = 81)	There were 12	Intervention group participants	A skills-based intervention	Differences in baseline between

			Office of Special Education and Rehabilitation Services, National Institute on Disability and Rehabilitation Research (NIDRR; H133P980014) to A.W.H. No mention of COI.		Mean age is 35 years.		systematic sessions of motivational counseling aimed at alcohol or drug abuse. There was a 3 month and 9 month follow up.	more likely to be employed (89.7% vs 35.1%), abstain from alcohol (24.1% vs 9.4%) than comparison group. A higher proportion of participants remained abstinent of drug use.	provides a promising approach to promoting abstinence from all substances and increasing readiness for employment for adults with traumatic brain injuries in outpatient settings.	groups particularly in GOAT scores and time post injury. Data suggest skills based intervention appears to result in a sig. reduction of drug and alcohol abuse and increased employment likeliness at 9mo.
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## Outpatient Rehabilitation Services

See physical therapy, occupational therapy, vocational rehabilitation, outpatient treatment programs, etc.

Music therapy is clinical use of music intended to be a therapeutic intervention. Music therapy has been used in rehabilitation to stimulate brain functions involved in movement, cognition, speech, emotions, and sensory perceptions [1283, 1284].

### Music Therapy

There is no recommendation for or against the use of music therapy in the treatment of TBI patients.

#### No Recommendation.

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

There is one moderate quality study assessing Music Therapy for treatment of TBI [1284], however the sample sizes are so small at 4-5 per group that with non-significant results, the overall evidence base is inadequate. Music Therapy is not invasive, has no adverse effects, is low to moderate cost in aggregate, but has no quality evidence of efficacy, and thus there is no recommendation for treatment of TBI.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, Closed Head Trauma, Penetrating Head Trauma, Penetrating Craniocerebral Trauma, Music Therapy, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 11 articles in PubMed, 6 in Scopus, 0 in CINAHL, 2 in Cochrane Library, 24000 in Google Scholar, and 2 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 2 from other sources. Of the 4 articles considered for inclusion, 1 randomized trial and 1 systematic studies met the inclusion criteria.

### Evidence for the Use of Music Therapy

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Lynch, 2016 (4.5)	Music Therapy	RCT	No mention of COI or sponsorship.	N=14	Mean age: 43.93 years. 9 males, 5 females.	MT group: received music therapy (n=5) Vs. Singing group: (n=5) Vs. Control group: (n=4)	None	One-way ANOVA of the and pre- and posttest group differences showed a trend toward improvement in the Music therapy group over the singing group.	"Feasibility and effect size data support a larger trial of the MEFT protocol."	Small sample. Data suggest a trend towards MEFT group being better than SG group.

## Adaptive Devices

Orthotics, especially ankle-foot orthotics (AFOs) have been used for treatment of foot drop [1285].

### Ankle-foot Orthotics for Treatment of Foot Drop

Ankle-foot orthotics are selectively recommended for treatment of foot drop associated with TBI injuries.

#### Recommended.

**Strength of Evidence – Recommended, Insufficient Evidence (I)**

*Level of Confidence – Moderate*

<i>Rationale:</i>	Although there are no quality trials, ankle-foot orthotics for foot drop have been used successfully for many years and thus they are recommended since they facilitate walking ability. Evaluation for orthotics should include evaluation of the footwear that is to be worn by the patient, including the nature of the fore-soles. Fronts of shoes and boots can catch on carpets and low-lying irregular surfaces, and modifications of shoes and boots may mitigate slip, trip, and fall risks posed by footwear.
<i>Evidence:</i>	There is 1 low-quality RCT in Appendix 1 [1285].

Adaptive devices, casting, and orthotics have long been used for treatment of impairments, including those related to TBI. This prominently includes AFOs for the foot and wrist/hand supports for the distal upper extremity.

### Adaptive Devices, Casting, and Orthotics

#### Recommended.

Adaptive devices, casting, and orthotics are selectively recommended for treatment of TBI patients.

**Strength of Evidence – Recommended, Insufficient Evidence (I)**

*Level of Confidence – Moderate*

<i>Indications:</i>	Sufficient impairment to need a device to position the extremity for function, e.g., sufficient foot drop that a device may foster better walking and avoid stumbling; sufficient wrist drop that a device positions the extremity for better grasp. Some manufactured devices suffice, but some custom-made orthotics and casts are required to be made for specific circumstances or injury/patient characteristics.
<i>Benefits:</i>	Better able to use the extremity. May help maintain, or reduce losses of, extremity strength through greater use of the extremity.
<i>Harms:</i>	May use the device beyond that required, i.e., pseudo-dependent on it.
<i>Indications for Discontinuation:</i>	Sufficient recovery to no longer require a device
<i>Rationale:</i>	There are no quality studies assessing Adaptive Devices for treatment of TBI. See also Ankle/Foot Guideline regarding foot drop. Adaptive Devices, casts and orthotics are not invasive, have minimal adverse effects, are moderate cost, have been found to be helpful for

treatment including ambulation, and thus are recommended for select treatment of TBI.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Adaptive devices (beds, standing frames, wheelchair cushions, lower extremity bracing); Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed zero articles in PubMed, 533 in Scopus, zero in CINAHL, zero in Cochrane Library, 5 in Google Scholar, and zero from other sources. Zero articles met the inclusion criteria.

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: muscle tone and joint restriction management, spasticity, orthotics, casting, postural control; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 101 articles in PubMed, 71 in Scopus, 8 in CINAHL, 2 in Cochrane Library, 180 in Google Scholar, and 7 from other sources. We considered for inclusion 5 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 7 from other sources. Of the 12 articles considered for inclusion, 3 randomized trials and 1 systematic study met the inclusion criteria.

Neuromuscular re-education is a therapy used to restore normal movement and function. The therapy uses simple repetitive movements of joints, weight bearing, resistance, and variable speed and length of therapy. (North American Spine Society) The application of neuromuscular reeducation for treatment of traumatic brain injury is unknown.

## **Neuromuscular Re-Education**

### **No Recommendation.**

There is no recommendation for or against the use of neuromuscular re-education in the treatment of TBI patients.

*Strength of Evidence* – **No Recommendation, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

*Rationale:*

There are no quality studies assessing Neuromuscular Re-Education for treatment of TBI. Neuromuscular Re-Education is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, but has no quality evidence of treatment efficacy, and thus there is no recommendation for treatment of TBI.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 0 articles in PubMed, 0 in Scopus, 2 in CINAHL, 11 in Cochrane Library, 359 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

Severe damage to the central nervous system, of various origin, often causes severe spasticity [1286-1293].

## **Muscle Tone and Joint Restriction Management**

There is no recommendation for muscle tone and joint restriction management in TBI patients.

### **No Recommendation.**

*Strength of Evidence* – **No Recommendation, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

*Rationale:*

There are no quality studies assessing Muscle Tone and Joint Restriction Management (Including Spasticity) for treatment of TBI. There are other evidence-based recommendations for management of spasticity, occupational therapy, exercise, physical therapy, etc. Muscle Tone and Joint Restriction Management (Including Spasticity) is not invasive, has negligible adverse effects, is moderate to high cost in aggregate, but absent quality evidence, there is no recommendation for this specific approach for treatment of TBI.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: postural balance, balance, balancing, visual, orthoptics, neurotology, neuro-otologic, communication, swallowing, therapy, treatment; traumatic brain injury, intracranial injury, closed head injury, penetrating head injury, concussion, brain concussion, craniocerebral injury, craniocerebral trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random\*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2,088 articles in PubMed, 2,265 in Scopus, 106 in CINAHL, 862 in Cochrane Library, 149,518 in Google Scholar, and 0 from other sources. We considered for inclusion 6 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 7 articles considered for inclusion, 3 randomized trials and 4 systematic studies met the inclusion criteria.

## Evidence for the Use of Non-Operative Therapeutic Procedures

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Terre, 2015 (7.0)	Vision, Speech, Swallowing, Balance, and Hearing	RCT	Sponsored by a grant of the FUNDACIÓN MAPFRE. No COI.	N=20. 14 stroke patients and 6 patients with severe traumatic brain injury.	The mean age of patients in the NMES group is 46 years. 6 males, 4 females. The mean age of the patients in the SES group is 51 years. 6 males, 4 females.	NMES group - Patients underwent NMES and conventional swallowing therapy. N=10. Vs. SES group - patients underwent sham electrical stimulation (SES) and conventional swallowing therapy. N=10.	3 months.	The Functional Oral Intake Scale (FOIS) score prior treatment for the NMES group was 2, SES group was 2.1. After treatment score was 4.9 NMES group and 3.1 SES group. The difference is $p=0.0005$ . At 3-month follow-up, FOIS score is 5.3 NMES and 4.6 in SES group. Not statistically significant.	“Neuromuscular electrical stimulation significantly accelerated swallowing function improvement in patients with oropharyngeal dysphagia secondary to acquired brain injury.”	Data suggest NMES therapy accelerate the swallowing function in patients with oropharyngeal dysphagia resulting from an acquired brain injury.
Dahlberg 2007 (5.5)	Vision, Speech, Swallowing, Balance, and Hearing	RCT	Sponsored by the National Institute on Disability and Rehabilitation Research. COI.	N = 52 patients with TBI at least 1 year post-injury who had social communication deficits	Mean age group sessions 42.43, control 39.91. 44 males, 8 females.	Weekly group sessions for 12 weeks (each 1.5 hours) focused on improving communication skills	3, 6, and 9 months	Analysis of treatment effects via independent t tests showed significant differences between two groups in 7	“TBI subjects who received social communication skills training had improved communication skills that were maintained on follow-up. Overall	Volunteer basis for subjects. Data suggest group sessions improve communication skills

				and received rehabilitation treatment.		(n = 26) Vs. Control group receiving no treatment (n = 26)		out of 10 of The Profile of Functional Impairment in Communication (p values ranging from .001 - .024). There was also a statistical difference between two groups for the Social Communication Skills Questionnaire-Adapted measurement (p = .005).	life satisfaction for participants was improved.”	within subjects, even during the follow-up months.
Thiagarajan 2014 (4.5)	Vision, Speech, Swallowing, Balance, and Hearing	RCT crossover	No COI. Supported by U.S. Department of Defense (DoD) grant, the College of Optometrists in Vision Development, and SUNY graduate program.	N = 12 with mild TBI, injury onset of over 1 year, displayed at least one clinical sign of accommodative dysfunction	8 female, 4 male  Mean age overall 29 ± 3 years	Oculomotor training (OMT)  Vs.  Placebo training (P)  Each session 60 minutes, two sessions per week, 9 hours for one treatment total	15 weeks	Placebo training produced no significantly different measures (p > 0.05). OMT produced an increase of about 30% in peak velocity for increasing (t(11) = 3.61, p = 0.01) and decrease (t(11) = 3.65, p = 0.01) steps of accommodation.	“These results provide evidence for a significant positive effect of the accommodatively based OMT on accommodative responsiveness. Such improvement is suggestive of oculomotor learning, demonstrating considerable residual brain-visual system plasticity in the adult compromised brain.	Small sample, crossover design. Data suggest OMT improved most measures related to accommodation responsiveness which may be the result of oculomotor learning.

## Anger Management Therapy

Anger sometimes occurs either to have caused the TBI, or as a consequence of it. Anger management therapy has been used to treat anger issues in TBI patients [1294]. As with many cases of traumatic brain injuries (TBI), the recovery and treatment phase to improve the lifestyle of the patient. One particular area that patients are overcoming is anger management. It was observed that more family support and participation help patients deal with anger management [1295]. Patients with anger after undergoing TBI is complex, multifaceted problem that should be under estimated and should be observed as psychological adjustment in difficulty [1296].

### Anger Management Therapy

Anger management therapy is selectively recommended for treatment of TBI patients.

#### Recommended.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Low**

<i>Indications:</i>	TBI patients with anger management needs, either as an underlying cause of the TBI or as a consequence of it.
<i>Benefits:</i>	Better anger management
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	One low quality trial utilized 5 to 8 weekly individual therapy sessions [1294].
<i>Rationale:</i>	There are no quality studies. Anger management therapy is not invasive, has negligible adverse effects, is moderate cost in aggregate and while there is not quality evidence of efficacy, it is recommended for selective treatment of TBI patients with anger issues as there is little else to manage these problems.
<i>Evidence:</i>	<b>Anger Management</b> – A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: <b>anger, management, traumatic, brain, injury, intracranial, closed, head, penetrating, concussion, craniocerebral, trauma</b> controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 6 articles in PubMed, 0 in Scopus, 3 in CINAHL, 3 in Cochrane Library, 24600 in Google Scholar, and 0 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 1 from CINAHL, 1 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 24612 articles considered for inclusion, 1 randomized trials and 6 systematic studies met the inclusion criteria.

### Evidence for the Use of Anger Management

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Medd 2000 (3.5)	TBI	RCT	No mention of sponsorship or COI.	N = 16 with brain injuries	14 males 2 females, aged 16 to 60 years old. Mean of 35.88 for Treatment and 34.0 for Waiting List	Treatment Group (TREAT) (N = 8) vs Waiting List Group (WAIT) (N = 8)	Follow-up at week 8	The pre-intervention TREAT group had significantly higher levels of AX-O than WAIT group [F(1,14) = 12.18, P = .004]. There was a significant interaction between Group and Time for the variable AX-O [F(1,14) = 10.50, P = .006]. This indicates that TREAT group showed a decrease in AX-O between Pre- and Post-intervention than the WAIT group.	“Repeated-measures analyses for TREAT showed significant improvements between pre-treatment and post-treatment measures (immediate and 2-month follow-up) on the STAXI. No significant generalisation of treatment effects to self-esteem, anxiety, depression, or degree of self-awareness were found.”	Baseline differences in time in months post injury (37.3 vs. 74.3) as well as dissimilar number of amnesia days. Data suggest no sig. differences between groups in terms of self-esteem, depression, anxiety or self awareness.

## Suicide Prevention

TBI patients are susceptible to depression and suicide, thus suicide prevention has been included in some programs [745]. Scheduled telephone interventions have also been used for TBI patients with depressive symptoms [1297]. Neuropsychological impairments such as dysfunction of memory and speed of information processing are post-concussion symptoms that can cause significant psychosocial problems following TBI [567, 1298-1301].

### Suicide Prevention

Suicide prevention is selectively recommended for treatment of TBI patients.

#### Recommended.

#### *Strength of Evidence – Recommended, Evidence (C)*

*Level of Confidence – Low*

<i>Indications:</i>	TBI patients with depressive symptoms, depression, with or without suicidal ideation.
<i>Benefits:</i>	Potential to prevent suicides
<i>Harms:</i>	Negligible
<i>Frequency/Dose/Duration:</i>	One moderate quality trial utilized 10 weekly 2-hour sessions [745]. A trial also used a scheduled telephone intervention [1297].
<i>Rationale:</i>	One moderate quality trial suggested psychological treatment was successful in producing improvement in hope that persisted for 3 months. Suicide prevention training is not invasive, has negligible adverse effects, is moderate cost in aggregate, has evidence of effectiveness to reduce hopelessness and so is recommended for selective treatment of TBI patients with depressive symptoms, depression, with or without suicidal ideation.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed and Google Scholar without date limits using the following terms: psychological therapy, psychological rehabilitation, suicide, depressive disorder, depression; Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 105 articles in PubMed, 1,250 in Google Scholar, and 6 from other sources. We considered for inclusion 6 from PubMed, 4 from Google Scholar, and 6 from other sources. Of the 16 articles considered for inclusion, 7 randomized trials and 9 systematic studies met the inclusion criteria.

## Evidence for the Use of Suicide Prevention

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Simpson 2011 (6.5)	Psychological Therapy	RCT	No COI. Funded by grant from the National Health and Medical Research Council Health Professional Fellowship.	N = 17, severe TBI with posttraumatic amnesia > 1 day, suffered from moderate to severe hopelessness (Beck Hopelessness Scale [BHS]) and/or suicide ideation	No gender distribution described. Mean age treatment group 39.41 years, wait-list 44.08 years	20 hour manualized group cognitive behavior therapy (n = 8) vs wait-listed controls (n = 9)	3 months	Within treatment group, a group-by-time interaction found for Beck Hopelessness Scale (F1,15=13.2, P=0.002). Indicates reduction in mean score between time 1 and 2 without group or time main effects. At follow-up 75% of treatment group maintained improvement. Suicide ideation, depression, social problem solving, self-esteem, and hopefulness showed no statistically significant group-by time interactions or main effects.	"This trial provides initial evidence for the efficacy of a psychological intervention in reducing hopelessness among long-term survivors with severe TBI."	Small sample. Data suggest treatment gains maintained 3 months post-intervention for 75% of patients evidenced by reduction in mean Beck Hopelessness Scale.
Ponsford 2016 (5.5)	Psychological Therapy	RCT	No COI. Funded by NHMRC grant.	N = 75, with mild to severe TBI, with Structured Clinical Interview for DSM-IV diagnosis of depression or anxiety	20 female, 55 males. Mean age 42.2 years	Non-directive counseling [NDC] + Cognitive Behavioral Therapy [CBT] (N = 26) vs Motivational Interviewing [MI] + CBT (N = 26) vs Wait-listed controls (N = 23)	30 weeks	MI+CBT and NDC+CBT groups showed greater decrease in anxiety on the Hospital and Anxiety and Depression Scale (95% CI (-2.07, -0.06)) and greater decrease in depression on the Depression Anxiety and Stress Scale (95% CI (-5.61, -0.12)) via random-effects regressions [controlled for	"Findings suggest that modified CBT with booster sessions over extended periods may alleviate anxiety and depression following TBI."	Dissimilar baseline characteristics for time since injury (4.88(11.4) vs. 3.58(5.87) vs. 2.61 (3.68) yrs and hospitalization days (57 vs. 54

								baseline scores]. Also showed greater improvement in psychosocial functioning on Sydney Psychosocial Reintegration Scale (95% CI (0.04, 3.69))		vs. 79). Issues with treatment integrity in the WC group. Data suggest CBT with booster sessions may decrease anxiety and depression.
Bombardier 2009 (5.0)	Psychological Therapy	RCT	Supported by a grant from the National Institute on Disability and Rehabilitation Research. No mention of COI.	N = 126 with TBI, discharged from inpatient rehabilitation	32 female, 94 male. Mean age 36 years	Motivational Interviewing via phone call at day 1 and again at months 1, 2, 3, 5, 7, and 9 (n = 62) vs Control group (n = 64)	1 year	Brief Symptom Inventory-Depression (BSI-D), Neurobehavioral Function Inventory-Depression subscale (NFI-D), Mental Health Index-5 (MHI-5). Pre-post changes on BSI-D subscale showed significant between group differences (Control 0.45±0.95, Telephone 0.08±0.72, P=0.019). Posttreatment BSI-D score: control 1.03±1.05, telephone 0.44±0.66 (P=0.000). Posttreatment NFI-D score: control 32.3±12.9, telephone 24.0±9.1 (P=0.000). Posttreatment MHI-5 score: control 20.2±5.9, telephone 23.4±4.8 (P=0.002). Pooled difference in	“Telephone-based interventions using problem-solving and behavioral activation approaches may be effective in ameliorating depressive symptoms following TBI. Proactive telephone calls, motivational interviewing, and including others in the intervention may have contributed to its	High dropouts Data suggest the use of scheduled telephone interventions utilizing problem solving and behavioral activation techniques may help reduce TBI depressive symptoms.

								treatment outcome via BSI-D score changes did not statistically vary by age, sex, or coma severity (P > 0.15 for all). Significant difference in white vs nonwhite participants, white reporting higher scores (P = 0.002).	effectiveness.”	
Tiersky 2005 (4.5)	Psychological Therapy	RCT	No COI. Supported by the National Institute on Disability and Rehabilitation Research and the Henry Kessler Foundation.	N = 20, mild or moderate TBI	11 female, 9 male. Mean age 46.85±10.51 years	Cognitive-behavioral psychotherapy and cognitive remediation (n = 11) vs Control (n = 9), all followed for 11 weeks	11 weeks, 1 and 3 months	Outcome measures at end of treatment: GSI – CBP+CR 0.86±0.41, control 1.74±1.00 (P=0.045), Depression – CBP+CR 1.12±0.45, control 2.11±1.14 (P=0.046), Anxiety subscale – CBP+CR 0.72±0.42, control 1.53±1.02 (P=0.066), PASAT – CBP+CR 135.55±30.71, control 110.88±60.28 (P=0.257), Problem solving – CBP+CR 13.06±2.67, control 12.58±2.21 (P=0.685), Attention Questionnaire CBP+CR 19.42±11.56, control 29.29±9.94 (P=0.082)	“Cognitive behavioral psychotherapy and cognitive remediation appear to diminish psychological distress and improve cognitive functioning among community-living persons with mild and moderate TBI.”	Data suggest TBI patient may benefit from CBT and cognitive remediation in terms of reducing anxiety and depression.
Radice-Neumann 2009 (4.5)	Psychological Therapy	RCT	Supported by The Mark Diamond Research Fund of the Graduate Student Association, University at Buffalo, The State	N = 19 with acquired brain injury, minimum 1 year post-injury	8 female, 12 male. Mean age 43 years	Facial Affect Recognition “FAR” (n = 10) vs Stories of Emotional Inference “SEI” (n = 9), both treatments given	2 weeks	Pretest scores: similar for FAR on DANVA2-AF test (P=.543) and for FAR and SEI on DANVA2-AP test (P=.758, P=.122), EET (P=.225, P=.312), LEAS-Self (P=.064,	“Training can improve emotion perception in persons with ABI. Although further research is	Small groups. No sham/placebo. Data suggest specific training may

			University of New York.			for 1 hour per day, 3 times a week, each participant receiving 6 to 9 sessions total. Measured using Diagnostic Assessment of Nonverbal Affect 2 – Adult Faces and Adult Paralanguage (DANVA2-AF OR AP) emotion evaluation test (EET), levels of emotional awareness scale, both self and others (LEAS), and the Brock Adaptive Function Questionnaire (BARQ)		P=.732), LEAS-Other (P=.340, P=.782). SEI significant performance change from pretest I to II on DANVA2-AF (+2.79 points, P=.004). DANVA2-AF: Significant performance change found in FAR (P<.001) and SEI (P=.006). DANVA2-AP: No significant changes found (FAR P=.985, SEI P=.939). EET: No significant changes found (FAR P=.584, SEI P=.166). LEAS-Self: Both significant change over time (FAR and SEI both P=0.019). LEAS-Other: Significant change over time for FAR (P=0.004). No change in SEI (P=.579). BARQ: Caregivers perceived significant increase in FAR participants' behavior after intervention (P = .042). No change perceived in SEI (P = .363).	needed, the interventions are clinically practical and show promise for the population with ABI.”	enhance emotion perception. FAR training improved emotion from faces & context while SEI group had improvement in ability to infer how they would feel in a given context.
Ashman 2014 (4.5)	Psychological Therapy	RCT	Sponsored by National Institute for Disability and Rehabilitation research grants H133B040033	N = 77 individuals with TBI and a diagnosis of depression	Cognitive Behavioral Therapy (CBT) group: 47.1. Supportive	CBT group (N=29) received 16 sessions of treatment focused on cognitive restructuring	3 months	After treatment, 35% of participants in CBT group no longer met criteria for depression vs 17% of participants in SPT group. However, difference in	“Both forms of psychotherapy were efficacious in improving diagnoses of	High dropout rate, substantial intergroup variability. Data

			and H133B000001. NO COI.		e psychotherapy (SBT) group: 48.1. Gender (M:F) 32:42	techniques to challenge and reshape automatic thoughts into more rational self-statements. SPT group (N=26) received 16 sessions of client-centered psychotherapy treatment. Treatment focused on improving self-esteem, maximize adaptive capacities, and maintaining the individual's best possible level of functioning.		remission rates was not statistically significant (P =.16). Changes in the Beck Depression Inventory-II scores were not significant between CBT group and SPT group. (P=.632)	depression and anxiety and reducing depressive symptoms. These findings suggest that in this sample of individuals with TBI, CBT was not more effective in treating depression than SPT, though further research is needed with larger sample sizes to identify different components of these interventions that may be effective with different TBI populations."	suggest comparable efficacy between groups.
Ruff 1990 (3.5)	Psychological Therapy	RCT	No mention of COI. Supported by grant from the Robert Wood Johnson Foundation.	N = 24, moderate to severe head injury with at least 1 hour of coma duration	7 females, 17 males. Mean age experimental group 28.3 years, control group 31.1 years	Experimental group – cognitive retraining on attention, visuospatial abilities, learning and memory, and problem solving. Small groups of 2-4, 12 hours per week for 8	8 weeks after intervention began	Test—re-test correlations in Katz Adjustment Scale (KAS) subset; Social Obstreperousness: Patient rating r=0.87 (P<0.001), Relative rating r=0.88 (P<0.001), Patient vs. Relative rating r=0.01 (P>0.01). Acute	"In this study, self-ratings according to the KAS proved to be reliable for both relative and patient ratings. Nonetheless, very little	

					<p>weeks, 2 hour of group therapy and 20-30 minute “wrap-up” sessions at the end of the day (n=12) vs. Control group – also received group and “wrap-up” session therapy, training focused on psychosocial functioning and activities of daily living (n=12). All participants’ relatives also were involved in evaluation.</p>	<p>Psychoticism: Patient <math>r=0.68</math> (<math>P&lt;0.001</math>), Relative <math>r=0.76</math> (<math>P&lt;0.001</math>), Patient vs Relative <math>r=0.45</math> (<math>P&gt;0.01</math>). Withdrawn Depression: Patient <math>r=0.78</math> (<math>P&lt;0.001</math>), Relative <math>r=0.65</math> (<math>P&lt;0.1</math>), Patient vs Relative <math>r= -0.07</math> (<math>P&gt;0.01</math>). Both groups did not perceive changes in emotional and psychosocial function from interventions (SO: <math>U=58</math> <math>P&gt;0.10</math>, AP: <math>U=64</math> <math>P&gt;0.10</math>, WD: <math>U=62.5</math>, <math>P&gt;0.10</math>). Relatives of both groups also did not perceive changes (SO: <math>U=55</math> <math>P&gt;0.10</math>, AP: <math>U=48.5</math> <math>P&gt;0.10</math>, WD: <math>U=36</math>, <math>P&gt;0.10</math>).</p>	<p>agreement existed between patient and relative ratings, as indicated by zero correlations for global scales of social obstreperous ness and withdrawn depression. Furthermore, relatives but not patients reported significant gains.”</p>
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## Substance Abuse Counseling

Substance abuse counseling has been used as a preventive action to minimize substance abuse following a traumatic brain injury (TBI) [1282, 1302].

### Substance Abuse Counseling

#### Recommended.

Substance abuse counseling is recommended for use in the treatment of TBI patients.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Moderate**

<i>Indications:</i>	Illicit substance(s) use, substance(s) abuse, substance(s) involved in TBI event, and/or problematic substances use.
<i>Benefits:</i>	Potential for reduced risk of future injury, reduced adverse health risks.
<i>Harms:</i>	Negligible
<i>Rationale:</i>	There are no quality studies with sufficient data reporting to support an evidence-based recommendation. Community based life goals are not invasive, have negligible adverse effects, but in the absence of quality evidence, there is no recommendation.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed and Google Scholar without date limits using the following terms: Substance abuse counseling, Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, Closed Head Trauma, Penetrating Head Trauma, Penetrating Craniocerebral Trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 11 articles in PubMed, 22700 in Google Scholar, and 14 from other sources. We considered for inclusion 3 from PubMed, 1 from Google Scholar, and 1 from other sources. Of the 5 articles considered for inclusion, 4 randomized trials and 1 systematic studies met the inclusion criteria.

## Evidence for the Use of Substance Abuse Counseling

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/ Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Zatzick 2014 (6.5)	TBI	Treatment	Grants supplied by National Institute on Alcohol Abuse and Alcoholism R01/AA016102 and National Institute of Mental Health K24/MH086814 were given to support this article. No declaration of interests.	N= 878	208 females, 670 males. Mean age is 36.9.	Intervention sites (n=10, patient n=469). Vs control sites (n=10, patient n=409)	Follow up after baseline at 6 and 12 months post-injury.	In the first year following injury, intervention group participants had a significant 8% reduction in Alcohol Use Disorders Identification Test (AUDIT) hazardous drinking cut-offs compared to control group. Intervention group also had a significant increase in abstinent from drinking days over the next year post-injury ( $P = 0.02$ ).	"[T]hese findings suggest that a brief trauma center intervention based upon MI (motivational interviewing) principles can yield relevant population level reductions in alcohol consumption and related hazardous drinking outcomes."	Population mixed between TBI and others. Assessment via interviews. Data suggest modest (8%) reduction in problem drinking patients, especially non-TBI patients.
Tweedley 2012 (5.5)	TBI	Treatment	Authors declare no conflict of interest.	N= 60	45 males, 15 females. Mean age is 35 years.	Brief information (INFO, N=20) vs INFO plus motivational interviewing (MI + INFO, N= 20), vs informal discussion (ID, N= 20)	2 hours of assessment and intervention at baseline (6-9 months post-injury), and a 6 month follow up (12-15 months post-injury).	At 6 month follow up, according to the Timeline Follow-Back (TLFB), the ID group reported 7 days of drinking in month prior to follow up, compared to 3-4 days a month in the MI + INFO and INFO groups. However, these results were not statistically significant.	"There was a positive trend showing participants in both the intervention groups to be drinking less frequently and consuming fewer alcoholic drinks than those in the informal discussion (control) group. However, group differences did not reach	Data suggest a trend in both intervention groups towards less frequent and fewer drinks over controls.

									statistical significance.... Further randomized controlled trials with larger samples are needed to establish whether brief educational and motivational interview interventions targeting alcohol use are efficacious in the traumatic brain injury population."	
Sander 2012 (3.5)	TBI	Treatment	This work was supported by grants from the National Institute on Disability and Rehabilitation Research, US Department of Education (grants H133B031117, H133B090023, H133A070043, and H133A070029). No COI.	N = 104	85 males, 19 females; Mean age is 35.75 years.	Standard of Care (N = 50) Vs. Intervention group (N = 54).	Follow up period of 3 months.	History of alcohol bingeing was not significant (P=.55). There was an effect on group treatment and control on AEQ-III GP. Treatment vs control (P=.01). Group effect and binge history did not interact (P=.06). Treatment wasn't effected by injury severity, history of binges, attribution or site (P=.25). After adjustment there was still no effect (P=.86).	"Brief intervention can be effective for educating on the negative impact of alcohol use for people with severe TBI who have emerged from posttraumatic amnesia. Attribution of the injury to alcohol use could potentially increase readiness to change in some settings, and might be used to generate discussion about the negative impact of alcohol use."	Brief treatment (10min video) followed up by education and a motivational interview did not show efficacy to improve problem alcohol use or readiness to change.
Corrigan 2005 (3.0)	TBI	Treatment	Funding for this project was provided by the Center for Substance	N = 195	138 males, 57 females. Mean age	195 participants randomly assigned into 4 groups. [170]	Appointments unspecified and varied by participant preference. Follow up at 3 and 6 months.	Statistically significant differences were found in the financial incentive (87%) and barrier reduction (74%) groups compared to the motivational interview	"Participants in the financial incentive and barrier reduction groups were at least 50% more likely to sign the ISP within 30 days compared with the motivational	Data suggest financially compensated and barrier reduction groups were more likely to sign on to a substance abuse

			Abuse Treatment, Substance Abuse and Mental Health Services Administration, via Grant 5 KD1 TI12013. No mention of COI.		is 36.6 years .	Attention control, (2) barrier reduction, (3) motivational interview, and (4) financial incentive.		(45%) and attention control (45%) groups. Significance indicated through client signing an individualized service plan (ISP) with a counselor within 30 days. Significance also found in fewer number of days to sign ( $M = 22.8$ days, $SD = 14.7$ ), ( $M = 44.0$ days, $SD = 35.8$ ) and fewer premature terminations (4%, 6%, 9%, 15%), respectively.	interview and control groups.... Retention in the barrier reduction and financial incentive conditions was 50% greater than in the attention control condition. If these results are replicated, they suggest that the initial intervention sets into motion a series of events that promotes later retention. These findings provide support for Newman's (1997) conception of how engagement in treatment can affect later retention."	treatment program post TBI than the motivational interview or attention control groups.
Vungkhanching 2007 (3.0)	TBI	Treatment	Funded by US Department of Education, Office of Special Education and Rehabilitation Services, National Institute on Disability and Rehabilitation Research (NIDRR; H133P980014) to A.W.H. No mention of COI.	N = 117	83 males, 34 females. Mean age is 35 years .	Intervention (N = 36) vs Comparison (N = 81)	There were 12 systematic sessions of motivational counseling aimed at alcohol or drug abuse. There was a 3 month and 9 month follow up.	Intervention group participants more likely to be employed (89.7% vs 35.1%), abstain from alcohol (24.1% vs 9.4%) than comparison group. A higher proportion of participants remained abstinent of drug use.	A skills-based intervention provides a promising approach to promoting abstinence from all substances and increasing readiness for employment for adults with traumatic brain injuries in outpatient settings.	Differences in baseline between groups particularly in GOAT scores and time post injury. Data suggest skills based intervention appears to result in a sig. reduction of drug and alcohol abuse and increased employment likelihood at 9mo.

## Community Based Life Goals

Acquired brain injury is a significant health problem, which often has considerable consequences for societal participation of those affected. Those with severe psychosocial problems may experience difficulties with community reintegration [1303]. Community-based rehabilitation programs for people with a brain injury are diverse [1304]. The results of the perspective study indicate that the improvements of independent living and societal participation are not achieved at the expense of emotional stability [1303].

### Community-Based Life Goals

#### No Recommendation.

There is no recommendation for or against the use of community-based life goals in the treatment of TBI patients.

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

<i>Rationale:</i>	There are no quality studies with sufficient data reporting to support an evidence-based recommendation. Community based life goals are not invasive, have negligible adverse effects, but in the absence of quality evidence, there is no recommendation.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: community based life goals, Traumatic brain injury, Closed Head injury, Penetrating Head Injury, Concussion, Craniocerebral Injury, controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 9 articles in PubMed, zero in Scopus, 11 in CINAHL, zero in Cochrane Library, 60 in Google Scholar, and zero from other sources. We considered for inclusion 9 from PubMed, zero from Scopus, zero from CINAHL, zero from Cochrane Library, 1 from Google Scholar, and zero from other sources. Of the 10 articles considered for inclusion, 1 randomized trials and 9 systematic studies met the inclusion criteria.

### Evidence for the Use of Community Based Life Goals

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Ownsworth 2008 (5.0)	TBI	Community Life Based Goals	Sponsored by a grant from the Centre of National Research on Disability and Rehabilitation Medicine (CONROD) and a National Health and Medical Research Council Public Health Fellowship. No mention of COI.	N = 35 with brain injury units and community-based rehabilitation services over 12 months	Age range 21-62 years old, 19 males & 16 females, and mean age of 43.89.	Individual Intervention (N = 10) vs Group Intervention (N = 11) vs Combined Intervention (N = 10)	3 months	Pre-post comparison and pre-follow-up comparison, PCRS: P=0.482 and P=0.150 respectively compared to P<0.025 and P=0.109 for Group and P=0.463 and P=0.114 for Combined groups.	“These findings generally support the efficacy of brief intervention formats following acquired brain injury, although further research is needed to examine clients’ suitability for particular interventions.”	Small sample sizes. Wait-list control bias. Data not well reported as compared to controls. Authors interpretations that trend towards better results with individual than group approach not able to verify because of data reporting limitations.

## Distance-based Healthcare (Telehealth; Telemedicine)

See Initial Approaches to Treatment Guideline.

## Home Healthcare

See Initial Approaches to Treatment Guideline.

## Return to Work and Assessments

Return to work (RTW) is considered a major challenge for TBI affected patients [152, 570, 1305-1311], as it is for return to sports [351, 1312-1315] [308, 309, 1316, 1317] [1318] [570]. Most estimates are that less than 50% of moderate to severely affected patients achieve employment [1306, 1319], and one estimate was under 10% [1320]. Thus, return to work is considered an important part of rehabilitation after TBI since being employed is typically associated with better quality of life and self-worth for TBI survivors [1305]. Factors associated with higher RTW rates are unclear, but generally thought to include shorter hospital stay, and shorter rehabilitation stays [1321-1323] which would also appear likely confounded by injury severity, [1311], younger age, multiple body injuries and increased severity of TBI (Waljas 2014) yet, Glasgow Coma Scale Scores have not been found predictive [1323-1326] nor have anxiety or depression [1311, 1321, 1326-1328].

Decision-making may be difficult as there are reported problems with reliability of the history and physical examination for decision-making that may impact return to work determinations [103, 105, 108, 109, 117]. Chief among these is likely under-reporting of pre-injury symptoms, psychological conditions, alcohol use, and drug use that is problematic in studies that independently assessed pre-morbid medical records [105] [109].

Decision-making may also be potentially difficult as there are reported problems with effort on physical examination and/or neuropsychological evaluation [176] [125, 128]. It has been suggested that this is addressable through: [170] optimize expectations, (2) treat depression and anxiety, (3) minimize stereotype threat, (4) addressing anger and revenge, (5) address loss aversion, and (6) consider possible effects of compensation on behavior. [176]

### Return to Work

It is recommended workers are returned to work, generally earlier than later. [460]

#### Recommended.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Moderate**

#### *Indications:*

All TBI patients. The speed of return to usual work activities, if possible, is based on the patient's current cognitive and physical status as compared with the job's cognitive and physical demands. Mild TBI patients may generally be returned to work in some capacity immediately. Close follow-up can be utilized to adjust work activities

as tolerated. RTW for those with safety critical jobs requirement exercising of judgment and/or executive demands beyond the current capacity may require added cautions about the speed of RTW.

Yet, especially with progressively more severe TBI, decision-making may be difficult as there are reported problems with reliability for decision-making that may impact diagnosis, treatment and return to work [103] [105, 109]. Under-reporting of pre-injury symptoms is reportedly problematic [105, 109]. Additionally, pre-injury conditions such as alcohol and drug use and the preexistence of psychological conditions and pre-existing pain have been shown to be recalled at significantly lower rates in comparison with preinjury medical records [109].

Among more severely affected workers, graded transitional programs (cognitive and/or physical, as indicated) and gradually increasing hours of work should be strongly considered. Tailoring of the limitations and lengths of shifts with consideration of graded transitional work positions are strong considerations.

*Benefits:*

Potential to improve faster based on return to work earlier

*Harms:*

May result in some frustration if the job demands substantially exceed the patient's capabilities. Mismatches may require re-addressing.

*Rationale:*

There are no RCTs comparing early vs. delayed return to work. A trial in pediatric patients found worse outcomes among those assigned to strict rest compared with the usual care group, suggesting strict rest is not helpful.

There is one moderate-quality trial assessing whether the use of resource facilitation is helpful for RTW and found efficacy of those services; please see vocational rehabilitation section below [1305]. That trial may provide some indirect evidence that earlier RTW may be effective. There are no trials for any disorder in any of the ACOEM Guidelines showing superiority of delayed return to work, thus the earlier a worker can RTW, generally the better and return to work is recommended.

Return to work is non-invasive, has few adverse effects, is low cost, is likely quite effective and thus is recommended. RTW often requires tailoring to the specific worker and their limitations.

*Evidence:*

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Traumatic Brain Injury, Return to work, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury, Craniocerebral Trauma, Closed Head Trauma, Penetrating Head Trauma, Penetrating Craniocerebral Trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 130 articles in PubMed, 205 in Scopus, 20 in CINAHL, 6 in Cochrane Library, 47,100 in Google Scholar, and 5 from other sources. We considered for inclusion 7 from PubMed, 4 from Scopus, 9 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 5 from other sources. Of the 25 articles considered for inclusion, 2 randomized trials and 5 systematic studies met the inclusion criteria.

### Evidence for the Use of Return to Work

Author Year Score	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Thomas 2015 (6.5)	TBI	RCT	Sponsored by Injury Research Center of the Medical College of Wisconsin. No COI.	N = 99 with mild TBI / concussion.	Aged 11 – 22 years, 65 males and 34 females.	Intervention or strict rest for 5 days (N = 50) vs Control or usual care for 1-2 days of rest, followed by stepwise return to activity (N = 49).	10 days	At 10-day period, strict rest group reported greater PCSS scores / higher total number of postconcussive symptoms / and higher daily PCSS clustered at day 4: 187.9 vs 131.9 [C], $p < 0.03$ / 79.4 [I] vs 50.2 [C], $p < 0.03$ / and 13.95 [C] vs 21.51 [I], $p < 0.03$ . Subgroup analysis; higher postconcussive symptom score at day 10 randomized to strict rest (15.2 [I] vs 7.7 [C], $p < 0.04$ ). Those who presented to ED with immediate signs of concussion and those with past history of concussion randomized to strict rest (11.0 [I] vs 14.6 [C], $p = 0.22$ and 15.1 [I] vs 5.6 [C], $p < 0.05$ .	“Recommending strict rest for adolescents immediately after concussion offered no added benefit over the usual care.”	Data suggest strict rest after acute concussion not beneficial in speeding up recovery or discharge vs usual care in pediatrics patient group.
Salazar, 2000 (5.5)	Return-to-work	RCT	No mention of COI. Sponsored by Defense and Veterans Head Injury Program and by the	N = 120	Mean age: 25.44 years. 113 males,	Hospital Group (N=67) vs Home Group (N=53).	Follow-up for 1 year.	Return to work was 90% for the hospital group and 94% for the home group ( $P=.51$ ). Among patients working at 1 year, 91% of hospital group and	“In this study, the overall benefit of in-hospital cognitive rehabilitation for patients with moderate-to-	Data suggest similar efficacy between in hospital cognitive rehab and home cognitive rehab for TBI patients.

			Medical Research Service of the Department of Veterans Affairs.		7 females.			93% of home group were working full time (P>.99). No significant difference between groups in quality of life. No significant differences between groups in verbal and visual memory or attention, general measures of cognitive or psychiatric function. Most patients showed cognitive improvement, but there was a self-reported increase in aggression for both groups. In a post-hoc subset analysis of patients unconscious for more than 1 hour following TBI (n=75), in-hospital group had a greater return-to-duty rate (80% vs 58%; P=.05).	severe TBI was similar to that of home rehabilitation. These findings emphasize the importance of conducting randomized trials to evaluate TBI rehabilitation interventions.”	
Twamley 2014 (4.0)	Return-to-work	RCT	Sponsorship by DOD. Dr. Delis receives royalties from the sale of the CVLT-II and D-KEFS could be a potential COI.	N=34	Mean age: 31.99 years. 32 males, 2 females.	Supported Employment + CogSMART (N=16) Vs Enhanced Supported Employment (N=18)	No follow-up.	Significant improvements in CogSMART postconcussive symptoms and prospective memory performance were observed (p=.01; p=.05 respectively). No statistical difference were observed in neuropsychological, k symptom severity, quality of life, or work outcome comparisons.	“In this study, the overall benefit of in-hospital cognitive rehabilitation for patients with moderate-to-severe TBI was similar to that of home rehabilitation. These findings emphasize the importance of conducting	Pilot RCT. Data suggest Cog SMART “may” improve post concussive symptoms and Veterans with TBI.

								Supported employment plus CogSMART group showed small to medium effect size improvements in psychiatric symptom severity (CAPS: d=.43 and HAM-D: d=.37). relative to the enhanced supported employment group. Five participants in enhanced group obtained competitive work within the first 14-wks of the study compared to 8 participants in the supported plus CogSMART group (d=.49).	randomized trials to evaluate TBI rehabilitation interventions.”	
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As return to work (RTW) is problematic, many different vocational rehabilitation (VR) programs have been utilized. These are thought to have been effective in assisting TBI patients in the recovery and RTW processes [152, 1305, 1308, 1329, 1330]. The components of VR programs utilized vary, but usually include elements sometimes classified as: case-coordination-based, program-based and supported employment [1329]. Case-coordination involves assessing job requirements and referring for services including job training and vocational counseling [1331]. Program-based includes intensive individualized work skills rehabilitation, guided work trials and assisted placement with transitional job support [1329] [1320]. Supported employment includes job placement, on-the-job training and long-term support for job skills with on the-job coaching Wehman [1329, 1332-1335].

### Vocational Rehabilitation Programs

Vocational rehabilitation programs are selectively recommended for treatment of TBI patients.

#### Recommended.

*Strength of Evidence – Recommended, Insufficient Evidence (I)*

*Level of Confidence – Moderate*

<i>Indications:</i>	Many severe TBI patients and occasional moderate TBI patients. Vocational rehabilitation programs are generally more helpful for those with greater mismatch between current abilities and job cognitive and physical demands. See also Return to Work above.
<i>Benefits:</i>	Potential to improve faster based on earlier return to work
<i>Harms:</i>	Negligible other than program cost.
<i>Frequency/Dose/Duration:</i>	N/A
<i>Rationale:</i>	There are no quality RCTs comparing vocational rehabilitation programs to those treated without VR programs. There is one moderate-quality trial assessing whether the use of resource facilitation is helpful for RTW and found efficacy of those services. [1305]. Vocational rehabilitation programs are non-invasive, have negligible effects, are moderate cost, and are likely effective and thus are recommended. They often require tailoring to the specific worker and their limitations.
<i>Evidence:</i>	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: vocational rehabilitation; Traumatic brain injury, Intracranial injury, Closed Head injury, Penetrating head injury, Concussion, Brain Concussion, Craniocerebral Injury ,Craniocerebral Trauma; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 71 articles in PubMed, 1565 in Scopus, 42 in CINAHL, 49 in Cochrane Library, 50 in Google Scholar, and 1 from other sources. We considered for inclusion 2 from PubMed, 6 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 1 from other sources. Of the 12 articles considered for inclusion, 1 randomized trial and 8 systematic studies met the inclusion criteria.

### Evidence for the Use of Vocational Rehabilitation Programs

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Radford 2013 (5.5)	Vocational Rehabilitation Programs	RCT	Sponsored by the College of Occupational Therapists. No COI.	N = 94 participants with TBI hospitalizations	Mean age of 34.3 yrs, 72 males, 22 females	TBI-VR Group (N =40 ) vs Usual Care Group (N = 54)	Follow up by questionnaire at 3, 6, 12 months	15% more individuals in the TBI-VR group (27/36, 75%) started working 13 months post hospital discharge than the UC group (27/45, 50%). Those with moderate or severe TBI had greater outcomes in the TBI-VR group than the UC group: 16/23 (75%) vs 9/21 (43%). This was also the case for minor TBI: 13/14 (93%) vs 14/25 (56%). Mean cost per person in the TBI-VR group was only £75.23 more than the UC group (£2106.94 ± 1542.86 vs £2031.71 ± 2352.24).	“Returning TBI people to work following early targeted TBI specialist vocational rehabilitation is likely to be cost-effective and may result in improved work outcomes.”	Data suggest TBI patients trend towards benefit from vocational rehab for early return to work compared to usual care group. Moderate-severe TBI patients experienced the most benefit.

Trexler 2010 (4.0)	Vocational Rehabilitation Programs	RCT	This research was in part funded by a US Department of Health and Human Services, Health Resources and Services Administration, Traumatic Brain Injury Planning and Implementation Partnership Grant and by the Dr Lisa Thompson Center for Family Education at the Rehabilitation Hospital of Indiana. No mention of COI.	23, with acquired TBI and caregivers with injury <1yr ago, had been employed and/or attended school 2 years pre-injury with RTW/school goal.	ages 18-60	Resource facilitation (RF, n=12) with contact from RF facilitator Q2Wks to assist in RTW median 8hr. vs. regular follow-up control conditions (n=11).	no contact during 6 months with 6 month follow-up.	Mayo-Portland Adaptability Inventory (M2PI): increased in both groups over treatment period (F=60.65 (p<0.0001)) with greater improvement in RF group vs. controls (F=9.11 (p=0.007)). M2PI employment item: RF group – 64% employed at follow-up vs. 36% of controls. PHQ-9 scores: NS between groups.	“...RF may have a significant impact not only on return to work but also on participation in the community and at home.”	Small sample size. Time since injury in controls vs. RF group (124 vs. 64d, p=0.11) but median 85 vs. 52 d suggests highly skewed distribution(s) and caution in evaluating mean values. Data suggest FR 78% more employed than among CR controls.
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## Functional Capacity Evaluations

While most commonly used for evaluation of spine and extremity disorders, functional capacity evaluations have been used to assess TBI patients [1336]. Functional capacity evaluations are a set of tests, observations and practices that are combined to attempt to ascertain the ability of the patient to function most commonly either in one discrete job (e.g., return to work after injury) or potentially in a wide variety of different employment settings without targeting one in particular. A functional capacity evaluation is used to infer the work capacity [1337]. A FCE may also be used to ascertain a baseline from which to develop a treatment program, to target specific work return to work needs.[1338-1340] The goals of FCEs include:

- Determine individual's readiness to work after injury or illness at Maximum Medical Improvement (MMI),
- Assist with goal-setting and treatment planning for rehabilitation or to monitor the progress of a patient in a rehabilitation program,
- Estimate potential vocational status and provide a foundation for effective vocational rehabilitation,
- Provide information to assist in disability determinations,
- Provide information for hiring decisions (post-offer or fit-for-duty testing),
- Assess the extent of disability in litigation cases, and
- Provide information regarding a patient's level of effort and consistency of performance.

### FCEs for Traumatic Brain Injury Patients

#### Recommended.

**FCEs are a recommended option for evaluation of disabling TBI sequelae where the information may be helpful to attempt to objectify worker capability, function, motivation and effort vis-à-vis either a specific job or general job requirements.** There are circumstances where a patient with moderate to moderately-severe TBI is not progressing as anticipated at 6 to 8 weeks and an FCE can evaluate functional status and patient performance in order to match performance to specific job demands, particularly in instances where those demands are medium to heavy. If a provider is comfortable describing work ability without an FCE, there is no requirement to do this testing.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Moderate**

*Benefits:*

Assess functional abilities and may facilitate greater confidence in return to work.

*Harms:*

Medicalization, worsening of pain with testing. May have misleading results that understate capabilities. May be particularly misleading if the FCE does not assess job-specific cognitive aspects, yet those are the patients primary difficulties.

## FCEs for Chronic Disabling Cervical or Thoracic Pain

### Recommended.

**FCEs are a recommended option for evaluation of disabling chronic cervical or thoracic pain where the information may be helpful to attempt to objectify worker capability, function, motivation and effort vis-à-vis either a specific job or general job requirements.** There are circumstances where a patient is not progressing as anticipated at 6 to 8 weeks and an FCE can evaluate functional status and patient performance in order to match performance to specific job demands, particularly in instances where those demands are medium to heavy. If a provider is comfortable describing work ability without an FCE, there is no requirement to do this testing.

*Strength of Evidence* – **Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **Moderate**

<i>Benefits:</i>	Assess functional abilities and may facilitate greater confidence in return to work.
<i>Harms:</i>	Medicalization, worsening of pain with testing. May have misleading results that understate capabilities.
<i>Rationale:</i>	FCEs are one of the few means to attempt to objectify limitations and are frequently used in workers' compensation systems, particularly as the correlation between pain ratings and functional abilities appears weak.[1341-1347] Yet, obtaining objective data regarding either TBI or spine problems is somewhat more challenging than for extremity-related impairments due to the degree of reliance on the patient's subjective willingness to exert or sustain major activities (e.g., standing, walking, sitting) that are critical for job performance. As FCEs typically emphasize physical over cognitive performance, FCEs are also typically somewhat limited in their ability to assess most TBI patients. Those that combine job-specific cognitive with physical assessments may be better able evaluate, assess and guide the return to work and rehabilitative processes. Because their reliability and validity have not been proven, FCEs should be utilized to evaluate work ability about what a patient was willing to do on a given day. They should not be used to override the judgment about the work ability of a patient with a TBI or spine problem.

Many commercial FCE models are available. There is research regarding inter-and intra-rater reliability for some of the models (complete discussion is beyond the scope of this guideline). The validity of FCEs, particularly predictive validity, is more difficult to determine, since factors other than physical performance may affect return to work.[1348, 1349] An FCE may be done for one or more reasons, including identifying an individual's ability to perform specific job tasks associated with a job (job-specific FCE) and physical activities associated with any job (general FCE), or to assist in the objectification of the degree(s) of impairment(s). The type of FCE needed, and any other issues the FCE evaluator needs to address, should be specified when requesting a FCE.

The term "capacity" used in FCE may be misleading, since an FCE generally measures an individual's voluntary performance rather than

his or her capacity. Physical performance is affected by psychosocial as well as physical factors. The extent of an individual's performance should be evaluated as part of the FCE process through analysis of his or her level of physical effort (based on physiological and biomechanical changes during activity) and consistency of performance. Perhaps more importantly, the objective findings identified in the musculoskeletal evaluation should correlate with any identified functional deficits. The individual's performance level, especially as it relates to stated levels of performance, should be discussed in the FCE report. A properly performed and well-reported FCE will highlight such discrepancies. This is particularly important in TBI and cervicothoracic evaluations where there may be greater degrees of impairments at stake and where there are somewhat fewer metrics available than for the distal upper extremity.

FCE test components may vary depending on the model used, but most contain the following:

- Patient interview including:
  - Informed consent
  - Injury/illness and medical history
  - Current symptoms, activities and stated limitations
  - Pain ratings/disability questionnaires
  - Musculoskeletal examination (e.g., including Waddell's non-organic signs)
  - Observations throughout the session (e.g., demonstrated sitting tolerance, pain modifying behaviors)
  - Material handling tests (lifting, carrying, pushing, pulling)
  - Movement tests (walking, crouching, kneeling, reaching, etc.)
  - Positional tolerance tests
  - Dexterity/hand function
  - Static strength (varies among models)
  - Aerobic fitness (usually submaximal test-also variable among models)
  - Job specific activities as relevant
  - Reliability of client reporting (e.g., non-organic signs, pain questionnaires, placebo tests, etc.)
  - Physical effort testing (e.g., Jamar Dynamometer maximum voluntary effort, bell curve analysis, rapid exchange grip, competitive test performance, heart rate, observation of clinical inconsistencies, etc.)

FCE test length may vary between FCE models, although most 1-day FCEs are completed in 3 to 4 hours. Two-day tests, where the patient is seen on 2 consecutive days, may be recommended when there are problems with fatigue (e.g., chronic fatigue syndrome), delayed onset of symptoms, unusually complex job demands to simulate, and questions about symptom validity. Test length for 2-day tests is generally 3 to 4 hours on the first day, and 2 to 3 hours on second day.

Interpretation of FCE results is complicated in that it is a measure of voluntary performance. Before beginning testing, the patient is counseled to avoid doing anything to knowingly reinjure him or

herself. Thus “fear avoidance” may cause testing to seriously underestimate actual ability and result in a report that the patient had “self-limited performance due to pain,” suggesting a low pain tolerance, when in reality the patient was doing what he or she was instructed.

The best studies on the ability of FCEs to predict safe re-entry to the workplace following rehabilitation of work-related back pain/injury suggest that FCEs are not able to predict safe return to work (concurrent validity).[1350-1352] In a prospective cohort study of 1,438 consecutive work-related back patients, all underwent a FCE prior to return to work. In the control group, the FCE was used to write return-to-work guidelines, while in the study group it was ignored and the worker was returned usually to full duty. Ignoring the FCE reportedly improved outcomes in a 1994 study, although the results have not been duplicated[1353] and the quality of an FCE is believed to be heavily dependent on the skill, knowledge and experience of the FCE evaluator.[1354]

## **FCEs for Chronic Stable Cervicothoracic Pain or Post-operative Recovery**

### **No Recommendation.**

**There is no recommendation for or against FCEs for chronic stable cervicothoracic pain or after completion of post-operative recovery among those able to return to work.**

*Strength of Evidence – No Recommendation, Insufficient Evidence (I)*

*Level of Confidence – Low*

*Rationale:*

FCEs are one of the few means to attempt to objectify limitations and are frequently used in workers’ compensation systems, particularly as the correlation between pain ratings and functional abilities appears weak.[1341-1347] Yet, obtaining objective data regarding either TBI or spine problems is somewhat more challenging than for extremity-related impairments due to the degree of reliance on the patient’s subjective willingness to exert or sustain major activities (e.g., standing, walking, sitting) that are critical for job performance. As FCEs typically emphasize physical over cognitive performance, FCEs are also typically somewhat limited in their ability to assess most TBI patients. Those that combine job-specific cognitive with physical assessments may be better able evaluate, assess and guide the return to work and rehabilitative processes. Because their reliability and validity have not been proven, FCEs should be utilized to evaluate work ability about what a patient was willing to do on a given day. They should not be used to override the judgment about the work ability of a patient with a TBI or spine problem.

Many commercial FCE models are available. There is research regarding inter-and intra-rater reliability for some of the models (complete discussion is beyond the scope of this guideline). The validity of FCEs, particularly predictive validity, is more difficult to determine, since factors other than physical performance may affect

return to work.[1348, 1349] An FCE may be done for one or more reasons, including identifying an individual's ability to perform specific job tasks associated with a job (job-specific FCE) and physical activities associated with any job (general FCE), or to assist in the objectification of the degree(s) of impairment(s). The type of FCE needed, and any other issues the FCE evaluator needs to address, should be specified when requesting a FCE.

The term "capacity" used in FCE may be misleading, since an FCE generally measures an individual's voluntary performance rather than his or her capacity. Physical performance is affected by psychosocial as well as physical factors. The extent of an individual's performance should be evaluated as part of the FCE process through analysis of his or her level of physical effort (based on physiological and biomechanical changes during activity) and consistency of performance. Perhaps more importantly, the objective findings identified in the musculoskeletal evaluation should correlate with any identified functional deficits. The individual's performance level, especially as it relates to stated levels of performance, should be discussed in the FCE report. A properly performed and well-reported FCE will highlight such discrepancies. This is particularly important in TBI and cervicothoracic evaluations where there may be greater degrees of impairments at stake and where there are somewhat fewer metrics available than for the distal upper extremity.

FCE test components may vary depending on the model used, but most contain the following:

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- Pain ratings/disability questionnaires
- Musculoskeletal examination (e.g., including Waddell's non-organic signs)
- Observations throughout the session (e.g., demonstrated sitting tolerance, pain modifying behaviors)
- Material handling tests (lifting, carrying, pushing, pulling)
- Movement tests (walking, crouching, kneeling, reaching, etc.)
- Positional tolerance tests
- Dexterity/hand function
- Static strength (varies among models)
- Aerobic fitness (usually submaximal test-also variable among models)
- Job specific activities as relevant
- Reliability of client reporting (e.g., non-organic signs, pain questionnaires, placebo tests, etc.)
- Physical effort testing (e.g., Jamar Dynamometer maximum voluntary effort, bell curve analysis, rapid exchange grip, competitive test performance, heart rate, observation of clinical inconsistencies, etc.)

FCE test length may vary between FCE models, although most 1-day FCEs are completed in 3 to 4 hours. Two-day tests, where the patient is seen on 2 consecutive days, may be recommended when there are problems with fatigue (e.g., chronic fatigue syndrome), delayed onset of symptoms, unusually complex job demands to simulate, and questions about symptom validity. Test length for 2-day tests is generally 3 to 4 hours on the first day, and 2 to 3 hours on second day.

Interpretation of FCE results is complicated in that it is a measure of voluntary performance. Before beginning testing, the patient is counseled to avoid doing anything to knowingly reinjure him or herself. Thus “fear avoidance” may cause testing to seriously underestimate actual ability and result in a report that the patient had “self-limited performance due to pain,” suggesting a low pain tolerance, when in reality the patient was doing what he or she was instructed.

The best studies on the ability of FCEs to predict safe re-entry to the workplace following rehabilitation of work-related back pain/injury suggest that FCEs are not able to predict safe return to work (concurrent validity).[1350-1352] In a prospective cohort study of 1,438 consecutive work-related back patients, all underwent a FCE prior to return to work. In the control group, the FCE was used to write return-to-work guidelines, while in the study group it was ignored and the worker was returned usually to full duty. Ignoring the FCE reportedly improved outcomes in a 1994 study, although the results have not been duplicated[1353] and the quality of an FCE is believed to be heavily dependent on the skill, knowledge and experience of the FCE evaluator.[1354]

**FCEs for Acute Cervicothoracic Pain, Acute or Subacute Radicular Syndromes, or Post-Surgical Cervical or Thoracic Pain**  
**Not Recommended.**

**FCEs are not recommended for evaluation of acute cervicothoracic pain, acute or subacute radicular syndromes, or post-surgical cervicothoracic pain problems within the first 12 weeks of the post-operative period.**

*Strength of Evidence* – **Not Recommended, Insufficient Evidence (I)**

*Level of Confidence* – **High**

*Rationale:*

FCEs are one of the few means to attempt to objectify limitations and are frequently used in workers' compensation systems, particularly as the correlation between pain ratings and functional abilities appears weak.[1341-1347] Yet, obtaining objective data regarding either TBI or spine problems is somewhat more challenging than for extremity-related impairments due to the degree of reliance on the patient's subjective willingness to exert or sustain major activities (e.g., standing, walking, sitting) that are critical for job performance. As FCEs typically emphasize physical over cognitive performance, FCEs are also typically somewhat limited in their ability to assess most TBI patients. Those that combine job-specific cognitive with physical assessments may be better able evaluate, assess and guide the return to work and rehabilitative processes. Because their reliability and validity have not been proven, FCEs should be utilized to evaluate work ability about what a patient was willing to do on a given day. They should not be used to override the judgment about the work ability of a patient with a TBI or spine problem.

Many commercial FCE models are available. There is research regarding inter-and intra-rater reliability for some of the models (complete discussion is beyond the scope of this guideline). The validity of FCEs, particularly predictive validity, is more difficult to determine, since factors other than physical performance may affect return to work.[1348, 1349] An FCE may be done for one or more reasons, including identifying an individual's ability to perform specific job tasks associated with a job (job-specific FCE) and physical activities associated with any job (general FCE), or to assist in the objectification of the degree(s) of impairment(s). The type of FCE needed, and any other issues the FCE evaluator needs to address, should be specified when requesting a FCE.

The term "capacity" used in FCE may be misleading, since an FCE generally measures an individual's voluntary performance rather than his or her capacity. Physical performance is affected by psychosocial as well as physical factors. The extent of an individual's performance should be evaluated as part of the FCE process through analysis of his or her level of physical effort (based on physiological and biomechanical changes during activity) and consistency of performance. Perhaps more importantly, the objective findings identified in the musculoskeletal evaluation should correlate with any

identified functional deficits. The individual's performance level, especially as it relates to stated levels of performance, should be discussed in the FCE report. A properly performed and well-reported FCE will highlight such discrepancies. This is particularly important in TBI and cervicothoracic evaluations where there may be greater degrees of impairments at stake and where there are somewhat fewer metrics available than for the distal upper extremity.

FCE test components may vary depending on the model used, but most contain the following:

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  - Informed consent
  - Injury/illness and medical history
  - Current symptoms, activities and stated limitations
  - Pain ratings/disability questionnaires
  - Musculoskeletal examination (e.g., including Waddell's non-organic signs)
- Observations throughout the session (e.g., demonstrated sitting tolerance, pain modifying behaviors)
- Material handling tests (lifting, carrying, pushing, pulling)
- Movement tests (walking, crouching, kneeling, reaching, etc.)
- Positional tolerance tests
- Dexterity/hand function
- Static strength (varies among models)
- Aerobic fitness (usually submaximal test-also variable among models)
- Job specific activities as relevant
- Reliability of client reporting (e.g., non-organic signs, pain questionnaires, placebo tests, etc.)
- Physical effort testing (e.g., Jamar Dynamometer maximum voluntary effort, bell curve analysis, rapid exchange grip, competitive test performance, heart rate, observation of clinical inconsistencies, etc.)

FCE test length may vary between FCE models, although most 1-day FCEs are completed in 3 to 4 hours. Two-day tests, where the patient is seen on 2 consecutive days, may be recommended when there are problems with fatigue (e.g., chronic fatigue syndrome), delayed onset of symptoms, unusually complex job demands to simulate, and questions about symptom validity. Test length for 2-day tests is generally 3 to 4 hours on the first day, and 2 to 3 hours on second day.

Interpretation of FCE results is complicated in that it is a measure of voluntary performance. Before beginning testing, the patient is counseled to avoid doing anything to knowingly reinjure him or herself. Thus "fear avoidance" may cause testing to seriously underestimate actual ability and result in a report that the patient had "self-limited performance due to pain," suggesting a low pain tolerance, when in reality the patient was doing what he or she was instructed.

The best studies on the ability of FCEs to predict safe re-entry to the workplace following rehabilitation of work-related back pain/injury

suggest that FCEs are not able to predict safe return to work (concurrent validity).[1350-1352] In a prospective cohort study of 1,438 consecutive work-related back patients, all underwent a FCE prior to return to work. In the control group, the FCE was used to write return-to-work guidelines, while in the study group it was ignored and the worker was returned usually to full duty. Ignoring the FCE reportedly improved outcomes in a 1994 study, although the results have not been duplicated[1353] and the quality of an FCE is believed to be heavily dependent on the skill, knowledge and experience of the FCE evaluator.[1354]

*Evidence:*

*Comments:*

## Job Site Evaluations

Job site evaluations are used for many purposes that include ascertainment of job requirements (as job descriptions are typically inadequate for job-specific return to work analyses), measurement of specific exposures, measurement of job performance abilities, analyses of potential movement to another position, ability to reduce job limitations on the job, planning rehabilitation program targets and components, and prevention of secondary injuries. Any of these are appropriate uses of job site evaluations.

## Prognosis

The prognosis for TBI patients is naturally correlated with the severity of the TBI event [126, 453, 1355-1357] [429]. Markers for prognosis include durations of loss of consciousness and post-traumatic amnesia [453]. Military and civilian populations have been found to have few long-term sequella of TBI after accounting for PTSD [100, 133, 1358].

Psychological factors, psychiatric history, anxiety, depression, low social support, perception of adverse consequences of TBI, stress and low intelligence are widely reported risks for persistence of TBI symptoms, especially mild TBI [104, 127, 130, 132-135, 1359] [110, 131]. There is a reported propensity for a sizable proportion of those with mild TBI to exaggerate the duration and severity of symptoms, especially with secondary gain considerations that include workers compensation or litigation [126, 427]. Assessment of effort has been reported to be a major problem in evaluation of subacute to chronic TBI cases, especially when the TBI was mild [124-126, 128].

Full recovery is expected after mild TBI [117, 126, 350, 1360] [114, 135, 349, 1357, 1361], with expected full recovery in 1 to 3 months [429] [106, 349, 427, 436, 1317, 1362]. By contrast, most improvements in moderate to severe TBI occur over the first 1 to 2 years, but may persist beyond and indefinitely particularly with severe injuries [95, 429, 449, 1355]. There is far less quality literature on repeated TBI events, nearly all of which involves athletes; quality data substantially conflict regarding whether there are worse cognitive or degenerative outcomes and prognoses with multiple TBIs [1363-1365] despite the attention this is receiving in the lay press.

## Follow-up Visits

It is recommended that patients with work-related mild to moderate TBI should follow-up in person or by phone every 1 to 5 days with a health care provider who can offer subsequent assessments and counseling regarding assessments for complications (e.g., subdural hematomas), advancing cognitive

activity levels, advancing physical activities, avoiding inactivity, medication use, anticipated favorable prognosis, and other concerns [**Recommended Insufficient Evidence (I)**]. Those with moderate to severe TBI may require hospitalization and some will require intensive care monitoring and treatments [**Recommended Insufficient Evidence (I)**].

Interactive sessions should typically actively involve the patient in his or her recovery. If the patient has returned to work, these interactions may be conducted on site or by telephone to avoid interfering with work activities. Subsequent follow-up can occur when there is need for: 1) altered treatment; 2) release to modified, increased, or full duty; or 3) after appreciable healing or recovery can be expected. Typically, this will be no later than 1 week into the acute pain period.

When a patient has residual and stable sequellae of TBI, less frequent followup is needed. Achievement of stability generally takes a minimum of 2 years. Regardless of apparent stability, more frequent follow-up may be needed when there is a move to the next level of functioning, e.g., when an individual is ready to re-enter the work force well down the line post-injury. In that context of re-integrating into the work force, follow-up is frequently of benefit and more frequent follow-up during that transitioning period may be of benefit to work through transitioning, accommodations, and fear avoidant beliefs.

After 2 years, and when there is complete stability, follow-up may be infrequent, such as every 6 months, unless there is functional transitioning noted above. Depending upon the complexity of the case and the TBI complications, outpatient follow-up visits may be needed more frequently, approximately every 3-6 months. Mostly stable patients may generally be seen 4-6 times per year due to their TBI co-morbidities, with more frequent and individualized followups needed for complex and/or less stable patients.

## Appendix 1: Low-Quality Studies

### Evidence for the Use of Computed Tomography (CT)

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Area of Body:	Diagnoses:	Type of CT used:	Surgery Performed:	Clinical Outcomes Assessed:	Results:	Conclusion:	Comments:
De Reuck J 2011 (3.5)	CT	Diagnostic	No COI mentioned	N= 39	14 females, 25 males  Median age for those with seizures 64, median age for those without seizures 59	Brain	Moderately severe traumatic brain injury and cerebral contusions	Not specified	None	Those admitted to the neurological department between 2002 and 2005, all patients had a CT scan of the brain and x-rays of bone fractures; 14 patients developed seizures and 25 did not; the CT/ MRI scans were compared to between patients who developed late onset seizures and those that did not	The average GCS score for the group that did not develop seizures was 12 (IQR 10-15), the average score for the group that did develop seizures was 14 (IQR 12-15) (p=0.992). The average late-onset of seizures was 7 (IQR 6-22) months after TBI.	“Seizures after non-complicated cerebral contusions are difficult to treat. Vascular risk factors and alcohol abuse may also predispose to their occurrence. The EEG findings after the TBI are highly predictive.”	Data suggest late onset seizures are a treatment challenge which may be correlated to vascular risk factors and alcohol abuse.
Egea-Guerro JJ 2012 (3.5)	CT	Prospective Observational Study	No COI mentioned	N= 61	8 females, 53 males  Mean age overall 37.69 ± 16.44 years	Brain	Severe traumatic brain injury patients admitted to the intensive care unit, GCS ≤8, between October 2009 any May 2011	Not specified	None	Usage of clinical variables (gender, age, reference GCS, papillary reactivity, prehospital hypotension, desaturation, ISS) and neuromonitoring data for predicting brain death after severe TBI	Patients at risk to be brain dead (BD) with mass lesion: (OR 33.6; 95% CI: 3.75–300.30; P = .002),	“Clinical variables and neuromonitoring information may identify TBI patients at risk of deterioration to BD.”	Data suggest specific clinical variables may assist in predicting patients developing brain death post severe TBI, specifically low brain tissue oxygenation levels.

Englander J 2003 (3.5)	CT	Prospective Longitudinal Study	No COI. Supported partially by the National Institute on Disability and Rehabilitation Research, US Department of Education	N= 1839	478 females, 1361 males  Greatest percentage between ages 16 and 25 (33%)	Brain	Adults with traumatic brain injury admitted to trauma centers with acute rehabilitation	Compilation of all dictated radiographic reports covering first seven days post-injury	None	CT scan pathology during first week post-injury, FIM scores (functional mobility, self-care, communication, and cognitive status), Disability Rating Scale, Supervision Rating Scale	The association of subdural hematoma with ambulation, self-care, and supervision needs was related to the degree of midline shift but not to the presence of subdural hematoma.	“These findings may aid health care professionals and potential caregivers in planning for rehabilitation and supervision needs after rehabilitation discharge and, to a lesser extent, at 1 year after TBI.”	Data suggest presence of midline shift greater than 5 mm or a CT reflected subcortical contusion is associated with a greater need for ambulation/rehab.
Maas 2005 (3.5)	CT	Observational Study	Supported by grant from the National Institutes of Health	N= 2269	No gender distribution specified.  No mean age listed. Ages ranged from 15 and 65	Brain	Severe, moderate or closed traumatic brain injury, participants of the International and North American TIRILAZAD trials	The Marshall computed tomographic classification, alternative CT models	None	Mass lesions, signs of raised intracranial pressure (compressed or absent basal cisterns, midline shift), TBI outcome	90% had abnormal CT readings; 84% showed parenchymal or extracerebral lesions; 45% had abnormal brain cisterns; 53% tSAH (subdural mass lesion) and 21% had intraventricular blood	“It is preferable to use combinations of individual CT predictors rather than the Marshall CT classification for prognostic purposes in TBI. Such models should include at least the following parameters: status of basal cisterns, shift, traumatic subarachnoid or intraventricular hemorrhage, and presence of different types of mass lesions.”	Data suggest a combination of CT predictive models and no one model is superior for predicting outcomes.

Wilde MC, 2000 (3.5)	CT	Observational Study	Partially supported by grant from the Department of Education. No other COI.	N= 50	15 females, 35 males  Mean age 33.33 years for left side group, 37.07 for right side group, and 31.98 for diffuse group	Brain	Moderate and severe nonpenetrating traumatic brain injury patient, emerged from posttraumatic amnesia	Not specified	None	CT scan of left hemisphere of brain (n = 15) vs Right hemisphere (n = 19) vs Diffuse or negative brain CT scan and no neurosurgery (n = 16)	The percentage of final broken configuration errors was higher in the patients with right craniotomies than in the left or no craniotomy groups, which did not differ.	“The percentage of final broken configuration errors was higher in the patients with right craniotomies than in the left or no craniotomy groups, which did not differ. Broken configuration errors did not occur more frequently on designs without an embedded grid pattern. Right craniotomy patients did not show a greater percentage of broken configuration errors on nongrid designs as compared to grid designs.”	Data suggest the relation between injury severity and broken configurations as measured by the GCS was modest but statistically significant.
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## Evidence for the Use of Magnetic Resonance Imaging (MRI)

Author Year (Score):	Cat egor y:	Stu dy type :	Samp le size:	Age/Sex:	Spons orship /COI:	Area of Body:	Diagnoses:	Type of MRI used:	Ty pe of CT used:	T1 W eig ht ed Im ag es:	T2 we igh te d Im ag es:	X - r a y :	Mye logr aphy:	M or e th an one rater:	Sur gery Performed:	Cli nic al Out come s As ses sed:	Lon g term follo w-up: (me an whe n not ed)	Results:	Conclusion:	Comments:
Hou 2007 (3.5)	MRI	Retr osp ective	N = 47	28 males, 8 females; Mean age 30 ± 16.8.	Partial support of this study was provided by the UC Neuro trauma Research Fund to A.O.	Left and right hemisphere	Traumatic brain injury and presume diffuse axonal injury (DAI).	1.5 Tesla	No	Yes	Yes	No	No	No	No	Yes	No	Apparent diffusion coefficient (ADC) values were significantly higher in the favorable outcome group (GOS scores 4-5) compared to unfavorable outcome group (GOS 1-3) (p<0.0001).	“This study suggests that there are subtle DAI lesions not visibly detectable by DWI.”	Data suggest ADC maps are correlated to TBI outcomes and there maps may be used to detect non-visible DAI lesions.

Gerber 2004 (3.5)	MRI	Comparative Analysis	N = 43	31 males, 12 females; Mean age of 32.	Research supported by the US Department of Education's National Institute on Disability and Rehabilitation Research.	Frontal, temporal, parietal, occipital	Traumatic brain injury	1.5 Tesla	No	Yes	Yes	No	No	No	No	No	Yes	1 year	T2* GE weighted MRI sequence detected significantly more lesions in the cortical, white matter, central grey, and brainstem regions and in each of the frontal, temporal, parietal, and occipital lobes at 1-year post-injury (p<0.001) compared to T2 SE.	"Therefore, clinicians must consider other factors beyond neurological injury severity, even when detected by the most sensitive imaging criteria, when estimating outcome."	Data suggest long term outcomes are related to T2 SE and T2*GE imaging which deficit injury severity and T2*GE has better sensitivity for detecting TBI hemorrhage than does T2 SE.
Firsching 1998 (3.5)	MRI	Prospective	N = 61	38 males, 23 females; Mean age of 23.	No mention of sponsorship or COI.	Midline and Brainstem	Comatose after severe head injury	1.5 Tesla magnet	Yes	Yes	Yes	No	No	No	No	No	Yes	7 days	In 39/61 had brainstem lesions and 24/61 unilateral lesion of brainstem, cerebellum, or supratentorial lesions. 17/61 (28%) died (13 with bilateral pontine lesion, 4 with bilateral brainstem). Total incidence of brainstem lesions was found in 64% of patients.	"This incidence is much higher than findings from earlier series based on CT scanning or neuropathological data. Because these brainstem lesions, which were undetected by CT scanning, apparently	Data suggest MRI detected more brainstem lesions post severe head injury than did CT making MRI a valuable predictive tool.

																			have great predictive value, early MR imaging should be required for future studies on the effect of drugs or different regimens of treatment in head injury to ensure that subgroups are comparable."	
Scheid 2007 (3.5)	MRI	Prospective	N = 14	11 males, 3 females; Median age 28 (22-62)	No mention of sponsorship or COI.	Axial	Traumatic microbleeds	1.5 Tesla and 3.0 Tesla	No	Yes	Yes	No	Yes	No	No	Yes	61 months	Traumatic microbleeds (TMBs) were found on 1.5 T and 3.0 T images. There was a negative correlation between the number of TMBs and the time interval between traumatic brain injury and MRI scans, the median 61 months (range 15 to 116 months). 239 TMBs were found for 1.5T	"MRI at high-field strengths might also be recommended in rare cases where clinical data and injury mechanism suggest a diagnosis of DAI, despite normal findings on routine MRI."	Small sample (N=14). Data suggest an MRI of 1.5 T is appropriate for detection of most TMBs unless there is a high index of suspicion for DAI.

																		and 470 for 3.0T (p=0.001).		
Brandstak 2006 (3.5)	MRI	Prospective	N = 36	25 males, 11 females; Mean age 42 ± 17.	No mention of sponsorship or COI.	Corpus callosum, coronaradiata, dorsolateral upper brain stem.	Closed head traumatic brain injury	1.5 Tesla	No	Yes	Yes	No	No	No	No	No	1 year	Normal MRI was found in 16/36 and abnormal MRI on 20/36. Lesions suggestive of diffuse axonal injury (DAI) was seen in 12/20.	“As a conclusion, early MRI with conventional imaging techniques is important for the detection of traumatic lesions. Both the number and extent of lesions diminish significantly with time.”	Data suggest late MRI studies when compared to early MRI studies show fewer lesions at one year at one year there was marked reduction in contusion size with DAI disappearance.

Luccichenti 2010 (3.5)	MRI	Prospective	N = 18	14 males, 4 females; Mean age 31.6 ± 8.9	No mention of sponsorship or COI.	Whole brain, frontal, temporal, parietal, occipital, basal ganglia, corpus callosum, cerebellum, brain stem	Traumatic brain injury	3.0 Tesla or 1.5 Tesla	No	Yes	Yes	No	No	No	No	Yes	60 days	Comparing 1.5T to 3.0T was significant in all areas of the brain except in occipital, cerebellum, and brainstem.	"In conclusion, this study showed that 3T MRI is almost twice as sensitive as 1.5T MRI in assessing DAI with haemosiderin in terms of number and volume of lesions."	Small sample (N=18). Data suggest high field MRI enhances visualization of DAI which may help in the understanding of chronic and subacute cognitive and behavioral changes in the TBI patient.
Pasco 2006 (3.0)	MRI	Prospective	N = 12	10 males, 2 females; Mean age of 27 ± 2.8.	No mention of sponsorship or COI.	All images from axial anterior commissure-posterior commissure plane (AC/PC).	Severe traumatic brain injury	1.5 Tesla	Yes	Yes	Yes	No	Yes	No	No	Yes	No	Patients received initial CT scan within the first hours of post-TBI. 5/12 had focal lesions, 4/12 diffuse axonal, and 3/12 with mixed lesions. For the first MRI 4/12 had focal lesions, 3/12 had diffuse axonal injury, and 5/12 had mixed lesions.	"Cerebral edema development is a critical event after severe head injury that can be characterized over time using noninvasive quantitative diffusion MRI."	Small sample (N=12). Data suggest ICE is a more relevant marker than is ECE in STBI and correlates with MRI.

Liu 1999 (3.0)	MRI	Prospective	N = 9	8 males, 1 female; Mean age 39.	Support by a grant from NIH. No COI.	Splenium of corpus callosum, left parietooccipital, body of corpus callosum, right posterior frontal, right caudate. Use echo-planar technique.	Traumatic brain injury	1.5 Tesla	Yes	No	No	No	Yes	No	No	Yes	Images done 1-18 days after injury	MRI scans were done on all 9 patients. Diffuse axonal injury (DAI) was found in all 9 patients and was predictive of apparent diffusion coefficient (ADC), which was greater than 2 SD below normal-appearing white matter (in the same patients).	“Significant decreases in ADC values can be found in the presence of DAI well into the subacute period in humans. While cytotoxic edema may be a contributor, the decreased ADC extends beyond that described for cytotoxic edema with infarcts, suggesting alternative mechanisms at work in DAI.”	Small sample (N=9). Data suggest there is a significant decrease in ADC for TBI patients in the acute period which may persist into the subacute phase.
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Inglese 2005 (3.0)	MRI	Prospective	N = 75	29 males, 17 females; Mean age 36 (18-58)	Supported by grants from the National Institutes of Health, and the General Clinical Research Center.	Corpus callosum genu, corpus callosum, internal capsule posterior limb, centrum semiovale	Mild traumatic brain injury. (late imaging 0.6 to 31 years and early imaging 1-10 days).	1.5 Tesla	Yes	Yes	Yes	No	Yes	No	No	Yes	5.7 years (0.6 to 31 years)	On healthy volunteers there was no abnormalities on MR imaging. For late imaging corpus callosum splenium and internal capsule posterior limb showed significant abnormalities compared to controls (p<0.05).	"Although in patients with mild TBI, DTI changes of normal-appearing white matter are too subtle to be detected with the whole-brain histogram analysis; mean diffusivity and fractional anisotropy abnormalities are present in areas which are predilection sites of DAI."	Data suggest in mild TBI, DTI changes are often subtle but since they are present both during early and late time points they may indicate permanent brain damage and be of utility for outcome.
Voller 1999 (2.5)	MRI	Prospective	N = 12	7 males, 5 females; mean age 24.1 ± 6.0	No mention of sponsorship or COI.	Sagittal, coronal, and axial positions.	Mild traumatic brain injury	1.5 Tesla		Yes	Yes	No	Yes	No	No	Yes	6 Weeks	3/12 had abnormal scans via MRI. All scans of control participants were normal. Authors found that the most sensitive method for detecting brain damage was through neuropsychological examination. EEG recordings no slowing or	"The use of combined early neuropsychological evaluation and MRI should be more emphasized in MTBI regarding structural and/or functional impairment	Data suggest MRI and neuropsychological exams can detect both structural and functional dysfunction in mild TBI patients.

																		focal change was found.	and also possible aspects of neurorehabilitation.”	
Datta 2009 (2.5)	MRI	Prospective	N = 20	15 males, 5 females; Mean age 35 (23-70).	Study sponsored by Nil. No COI.	Frontal and temporal lobes .	Mild traumatic brain injury with possible concussion	Yes	No	Yes	Yes	No	No	No	No	No	No	MRI scans were normal in 9/20 and abnormal in 11/20. On T1 images the lesions were hypointense in 8/11 and isointense in 3/11. On T2 weighted images the lesions hypointense in 1/11 and hyperintense in 10/11 cases. There was no correlation between lesion intensity on MRI and neuropsychological deficits.	“Prefrontal dysfunction is invariably associated with PCS following MTBI. Structural lesions on MRI may not always be present but when present may influence the degree or severity of the symptoms.”	Data suggest prefrontal lesions seen on MRI likely associated with PCS although not always visible on MRI.

Langfitt 1986 (2.5)	MRI	Preliminary Observations, case studies.	N = 3	All males; Ages are 22, 25, 46.	No mention of sponsorship or COI.	Superior, middle, inferior	Post-traumatic intracranial hemorrhage	0.12 Tesla Signa	9800	Yes	Yes	No	No	No	No	Yes	6 months	Unilateral lesions had reduced metabolism in anterior temporal lobes shown by MRI and CT scan. MRI showed several lesions not seen on CT scan.	"Position emission tomography showed disturbances of glucose metabolism that extended beyond the structural abnormalities demonstrated by MRI and CT; anterior temporal lobe dysfunction was particularly evident in all three patients."	Small sample (N=3)
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## Evidence for the Use of Magnetic Resonance (MR) Spectroscopy (MRS)

Author /Year Study Type	Category	Study type	Conflict of Interest	Sample Size	Age/Sex	Area of Head	Diagnoses	Type of MRS used	Type of imaging used	CT	T1 weighted images	T2 weighted images	X-ray	Myelography	More than one rater	Surgery Performed	Clinical outcomes assessed	Long term follow-up (mean when noted)	Results	Conclusion	Comments
Friedman 1998 (3.5)	MR Spectroscopy	Diagnostic	Sponsored by the European Community project Human Capital and A. van den Boogaart, Katholieke Universiteit, Leuven, Belgium. No mention of COI.	N = 26	Mean age was 32.5 24 males and 2 females.	Occipital lobe	TBI TBI group (n=12) Healthy controls (n=14)	MRS	MRI 1.5T	-	+	+	-	-	-	-	+	-	Glasgow Coma Scale scores and choline levels were not significantly related to neuropsychological outcomes. NAA and creatine levels in gray matter and white matter were significantly correlated to neuropsychological	“MR Spectroscopy may prove valuable in predicting recovery from TBI. H-MRS tends to yield more information when examining milder brain injuries than other diagnostic tests.”	Data suggest diffuse axonal injury from TBI correlates to neurometabolic concentrations and behavior.

																			al function (p=0.02 and p=0.03). Proton MRS provides noninvasive assessment of extent of injury after head trauma and in evaluating neuropsychological dysfunction.		
Chen 2012 (3.5)	MRS Spectroscopy	Diagnostic	Sponsored by the Science Foundation of Haiku Health Bureau (2010-SWY-13-058)	N = 19	Age range: 12-51  No mention of gender.	L/R hemisphere	mTBI group (n=19) Healthy control (n=0)	MRS, DTI	CT and MRI 3.0T	+	+	+	-	-	-	-	+	-	CT scans showed no significant abnormalities (without fracture or hemorrhage). The conventional MRI revealed swelling (89.5%),	“MRS might be more useful than other methods, such as Computed Tomography or Conventional MRI in the diagnosis of mTBI. “	Data suggest MRI and DTI may detect more changes associated with mild TBI compared to CT and MRI.

			and Haiku u Scienc e Techn ology Inform ation No COI.															skull fracture (10.5%), and extracranial hemorrhage (15.8%). MRS revealed a significant decrease in NAA/Cr (1.07 +/- 0.30; p<0.05), NAA/Choline (0.83 +/- 0.28; p<0.05), and Lac/Cr (0.31 +/- 0.25; p<0.05) compared to control. Because H-MRS is noninvasive and provides quantitative data on injury it is helpful		
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																			in determining mechanism of injury.		
Sivak 2014 (3.5)	MRS spectroscopy	Diagnostic	Sponsored by the EU resource and European social fund – ITMS 26110 23006 7 and 2012/31-UKMA-8. No COI.	N = 43	Mean age was 32.4 39 males and 4 females	Frontal lobes and upper brainstem	mTBI within previous 3 days. mTBI group (n=21) Healthy control (n=22)	H-MRS	MRI-FLAIR	-	+	+	-	-	+	-	-	-	Significant decrease in NAA were found in both frontal Lobes and in NAA/Cr ratio in right frontal lobe (p<0.05). Correlations were found between NAA in the left frontal lobe with Backward Digit Span (p=0.022) and Stroop test A (p=0.0034).	“Results show a correlation of H-MRS metabolite changes with cognitive decline and presence or absence of LOC in the acute phase after mTBI. MRS diagnostics are sensitive enough to detect post-traumatic metabolic changes in brain tissue that standard MRI detects as normal.”	Data suggest proton magnetic resonance spectroscopy detects post traumatic metabolic changes in mild TBI patients which routine MRI cannot.

Garnett 2000 (3.0)	MRS spectroscopy	Diagnostic	Sponsored by the Medical Research Council. No mention of COI.	N = 46	Mean age was 37.5 TBI Group: 22 males and 4 females. Control Group: No data given.	Frontal lobes	TBI group (n=26) Healthy controls (n=20)	H-MRS	MRI	-	+	+	-	-	-	-	+	6.2 months for MRI and 6.7 months for MRS	From time of brain injury to follow-up (6.2 months) 10/26 still had significant decrease in NAA/Cr ratios (p=0.02). NAA/Cr was significantly correlated to Glasgow Coma Scale scores (p=0.005) and Disability Rating Scale (p<0.005). Areas of frontal white matter that appeared normal on MRI, were	"MRI examinations of frontal lobe white matter appeared normal, yet proton MRS show abnormalities. Proton MRS can provide a more relevant understanding of the extent of disabilities following TBI."	Data suggest TBI results in altered NAA and Cho levels which is not seen via conventional imaging techniques.
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																		actually abnormal on MRS. The findings provide evidence for potential mechanism of injury for cellular and neuroaxonal damage not visible by conventional imaging.			
Brooks 2000 (3.0)	MRS Spectroscopy	Diagnostic	Sponsored by the European community project "Human Capital and Mobility/Networks" and by grants	N = 47	Mean age was 29.4. 35 males and 12 females.	L/R hemisphere	TBI group (n=19). Healthy controls (n=28).	H-MRS	-	-	+	+	-	-	-	-	+	6 months	Compared to controls TBI patients had significantly less white matter NAA (p<0.01), grey matter NAA (p<0.01), and Choline (p<0.01)	"H-MRS provides a noninvasive approach to assessing neuronal injury and inflammation following TBI. This diagnostic test may provide insight into outcome predictions, determining effectiveness of therapy, and clinical management."	Data suggest H-MRS may be useful in the quantification of neuronal integrity post TBI. Age was negatively associated with outcome.

		<p>from the State of New Mexico, the National Institutes of Health (NS35708), (NS39123), and the National Foundation for Functional Brain Imaging (Department of Energy grant DE-FG03-99ER62764-A000). No mention of COI.</p>																<p>at every time point. Correlation between concurrent measures of GM NAA and cognitive function were observed with a range of 0.45-0.67. GM NAA predicted cognitive outcome at 1.5 and 3 months (r=.63 and 0.7). Proton MRS provides noninvasive technique to show and study neuronal injury and</p>		
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																			inflammation from TBI.		
Vagnozzi 2010 (3.0)	MRSpectroscopy	Diagnostic	Sponsored by the Italian Ministry of University and Research (PRIN 2007J BHZ5F). No mention of COI.	N = 70	Mean age was 27. 54 males and 16 females	Frontal lobes	mTBI group (n=40) Healthy controls (n=30)	MRS 1.5 Tesla 3.0 Tesla	MRI 1.5 Tesla 3.0 Tesla	-	+	+	-	-	-	-	+	1 month	By 3-days post injury there was a significant alteration in NAA/Cr (17.6%) and NAA/Cho (21.4%) was observed in all 40 athletes (p<0.001) compared to controls.	"The results indicate H-MRS is an accurate and noninvasive tool to measure changes in cerebral energy metabolism caused by mTBI."	Data suggest H-MRS is a useful non-invasive tool for detecting NAA and measure metabolic transient changes in the mild traumatic brain injured patient post-TBI.
Kirov 2013 (3.0)	MRSpectroscopy	Diagnostic	Sponsored by NIH Grants EB01015, NS39135, NS290	N = 39	Mean age: 33.3 TBI gender: 21 males and 5 females. Control gender	Whole brain	mTBI group (n=26) Healthy control (n=13)	3T MR Scanner H-MRSI	MRI	-	+	+	-	-	-	-	+	-	PCS-negative (n=11) and the appropriate control (n=8) groups did not	"H-MRS is capable of detecting changes in neural metabolite levels following a TBI. These (PCS-positive) changes	Data suggest WM NAA levels were lower in PCS + patients and



			Health . No mention of COI.															splenium (p<0.01). There was no significant correlation between abnormal MTR and normal-appearing white matter and NAA/Cr. The proton MR spectroscopy revealed NAA/Cr (1.53 +/- 0.37) ratios related to good neurological outcome .		assist in predicting clinical outcomes.	
Cohen 2007 (2.5)	MRSpectroscopy	Diagnostic	No mention of COI. Sponsored by Nation	N = 39	Mean age was 35 22 males and 17 females	Whole brain	TBI mTBI group (n=20) Healthy controls (n=19)	MRS	MRI	-	+	+	-	-	-	-	+	4.6 years	Whole brain NAA levels were significantly lower in	"MRS diagnostics can detect neuronal/axonal injury via metabolite analysis beyond the	WBNAAMay detect post TBI neuronal injury.





### Evidence for the Use of Functional MRI

Author Year (Score):	Cat egor y:	Stud y type:	Sam ple size:	Age/ Sex:	Sponso rship/COI:	Area of Body:	Diag nose s:	Type of MRI used:	Type of CT used:	T1 Wei ghte d Imag es:	T2 Wei ghte d Imag es:	X-ray:	My elog rap hy:	Mo re tha n one rat er:	Surge ry Perfor med:	Clinic al Outco mes Asses sed:	Long Term Follow-up (mean when noted):	Results:	Conclusion:	Comment s:
Jantzen 2004 (3.5)	fMRI	Pros pecti ve	N=8	8 male s; Mea n age of 20 (19-23)	No mentio n of Sponso rship or COI.	Medial frontal gyrus, left middle frontal gyrus, contralateral precentral gyrus, left inferior frontal gyrus, bilateral superior parietal lobe, and ipsilateral cerebellum	Conc ussi on	fMRI 1.5 Tesla	No	No	No	No	No	No	No	Yes	None	Three sequencing tasks demonstrated similar patterns of activities in all areas sequenced. For control subject there was small change in activity. Concussed individuals had intensive increases in areas associated with functioning .	“fMRI shows promise as a valuable diagnostic and research tool in the assessment of concussion injuries in athletes. The data presented here represent the initial stages in developing a comprehensive research protocol for detecting, assessing, and tracking sportsrelated MTBI.”	Very small sample (n=8). Preliminary study. Data suggest fMRI may detect some post-TBI changes c/w controls.

Czerniak 2014 (3.5)	fMRI	Diagnostic	N=21 (9 concussed, 12 unconcussed)	13 males, 8 females; Mean age of 20.2 ± 0.4	Sponsored by grants from the National Institute of Mental Health to CMM. No COI.	Location not specified	concussion	3.0 Tesla Phillips Achieva whole body MR	No	Yes	No	No	No	No	No	Yes	None	No significant differences between concussion and non-concussion group in neurocognitive assessment. Significant differences in Resting state functional connectivity in regions: Anterior Cingulate Cortex, Left Dorsolateral Prefrontal Cortex, Right Dorsolateral Prefrontal Cortex (more connected in concussed group).	“Resting State Functional connectivity may therefore represent a more sensitive long-term measure of recovery after a concussion, and may be a useful aide for clinical assessment and follow-up care if investigated further longitudinally.”	Small Sample. Data suggest that the resting state brain connectivity may be a more precise and quantitative way of detecting prolonged differences in college athletes with concussion.
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### Evidence for the Use of Diffusion Tensor Imaging (DTI)

Author Year (Score):	Category :	Study type :	Sample size:	Age/Sex:	Sponsorship/COI:	Area of body:	Diagnoses:	SP EC T or SP ET:	MRI or CT:	T1 weight ed images:	T2 weight ed images:	More than one rater:	Clinical outcomes assessed:	Long term follow-up: (mean when noted)	Results:	Conclusions:	Comments:
Mayer 2010 (3.5)	DTI	Prospective	N = 43 (20 females, 7 males)	Mean age 27.45 ±7.39. Control group : No gender mentioned; Mean age 26.81 ±6.68.	Authors have received funding from the National Institutes of Health. No COI.	Corpus callosum (CC), splenium [48], left superior corona radiate [1366], left uncinate fasciculus (UF), left internal capsule (IC), left corona radiate (CR), genu (GNU).	Closed-head traumatic brain injury (n=22) and healthy controls (n=21).	DTI 3 Tesla	MRI 3 Tesla	Yes	Yes	No	Fractional anisotropy (FA), apparent diffusion coefficient (ADC), axial diffusivity (AD), radial diffusivity (RD)	No	FA levels in the right hemisphere were positively correlated with attention deficits (p<0.01) for the TBI group. Traditional neuropsychological tests classification of injury had 65% accuracy for controls and 66.7% for TBI. Left and right hemisphere FA had a classification accuracy of 70% for controls and 81% for TBI.	“Our preliminary longitudinal data suggest a partial normalization of FA (i.e., a decrease toward levels observed in HC) within several ROI in our mTBI group”	

Watts 2014 (3.5)	DTI	Prospective	N=36	18 males, 18 females; Group 1	This research was supported by the National Institutes of Health. No COI.	Anterior and posterior commissure	(N=20) patients with TBI (N=16) healthy controls BI	3.0 T MRI	3.0 T MRI and CT	Yes	Yes	Yes	acute head injury, Glasgow Coma Scale score of 13–15, and two or more concussive symptoms (loss of consciousness, blurred vision, confusion, dizziness, memory problems, or poor balance)	No	There was a large difference in Fractional Anisotropy (FA) potholes in mTBI vs control (102.5±34.3 vs 50.6±28.9 (p<0.001).	“In summary, the pothole and molehill approach to the analysis of DTI data is a potentially useful method that can be used to avoid many of the problems of traditional region of interest-based methods, which improves the detection effectiveness for any disease process with a heterogeneous spatial
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																	distributi on of pathologi c findings.”
Ilvesmaki 2014 (3.5)	DTI	Diag nost ic	N= 11 5	TBI: 45 males , 30 femal es; Mean age 37.2± 12.0. Contr ol: 20 males 20 femal es; mean age 40.6± 12.2.	This work was supported by a grant by the Emil Aaltonen foundation to T.I. One author has been reimbursed by government, professional scientific bodies, and commercial organization for work in mTBI.	All planes of the brain.	75 individuals with mTBI within the Ed. 40 healthy controls.	spi n ec ho- bas ed an d diff usi on- we igh ted ec ho pla nar im agi ng seq ue nc e.	64- row Ct sca nne r, 3 T MRI	Yes	Yes	Yes	Loss oc conscious longer than 5 min, post – trauma amnesia, lesion on CT or MRI, Glasgow Coma Score, Sports Concussion analysis Tool (SCAT).	None	No significant differences between control and patients in fractional anisotropy, apparent diffusion coefficient, axial diffusivity or radial diffusivity. No significant difference between different levels of TBI. Only significant between age groups in both control and patients. Factional anisotropy values (p<0.01).	“In conclusio n, in this large homogen eous, premorbi dly healthy sample, acute mild TBI was not associate d with obvious DTI abnormal ities detectabl e with TBSS. Clear differenc es in DTI findings were associate d with age, even in healthy subjects in their 40 s. Therefore , age	

																	should always be considered a potential confounder in DTI studies."
Li 2016 (3.5)	DTI	Prospective	N=65	29 males, 36 females; Mean age Group 1: 35.8±7.58 Group 2: 36.7±7.09 Group 3: 36.11±7.11	This work was supported by a grant from the Jinan Military General Hospital. No COI.	corpus callosum (CC), inferior fronto-occipital fasciculus (IFF), uncinate fasciculus (UF), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), anterior thalamic radiation (ATR), and corticospinal tract (CT).	Patients with successful recovery (SR) of PTSD after mTBI (N=22) Patients with poor recovery (PR) of PTSD after mTBI (N=21) Control (N=22)	TBSST - Wisconsin analysis	3.0T MRI	Yes	Yes	No.	The evaluation included the psychometric measures for PTSD diagnosis, which is based on Diagnostic and Statistical Manual of Mental Disorders-V criteria, and symptom severity using the clinician-administered PTSD scale (CAPS).	6 months	The application of the MD values in subacute phase allowed discrimination between PR and SR groups with a sensitivity of 73% and a specificity of 78%, resulting in an accuracy of 75.56%, using the threshold as P = 0.50.	"The present study revealed a significant alteration in the DTI metrics for a group of patients with mTBI, spanning the acute to chronic phases. These changes were highly correlated with PTSD."	
Kraus 2007 (3.5)	DTI	Prospective	N = 55	23 males, 32 females;	Sponsored by the national Institute of	Anterior/posterior corona radiate (ACR/PCR), cortico-	Mild traumatic brain injury (n=20), moderate	3.0 Tesla	No	No	Yes	No	Neuropsychological tests: (executive measures executive	No	Those with mild brain injury compared to moderate to	"The data presented here demonstrate that	

				Mean age 34.85 ±2.82	Health. No COI>	spinal tracts (CST), cingulum (CG) fibres, forceps minor (fMin), forceps major (fMaj), the body, genu and splenium of corpus callosum (bCC, gCC, and sCC), inferior fronto-occipital [1367], superior longitudinal fasciculus (SLF), external capsule (ExCap), and sagittal stratum and optic radiations.	to severe injury (n=17), and healthy controls (n=18).					domain tests) Tower of London, Stroop Colour Test, Paced Auditory Serial Addition Test (PASAT), Trail Making Test (TMT), Controlled Oral Word Association (COWA), Wechsler Test of Adult Reading (TAR), California Verbal Learning Test Memory Measures: (CVLT-II), Brief Visual Spatial Memory Test (BVMT-R) Attention measures: Digit Span and Spatial Span Other: Grooved Pegboard, and Test of Memory Malingering (TOMM)	severe brain injury performed significantly better on the executive measures executive domain tests (p<0.01), CVLT trials 1-5 (p<0.05), BVMT trials 1-3 (p<0.05), and the grooved pegboard (p<0.01). Fractional anisotropy (FA) was significantly greater in those with severe to moderate injury compared to mild or control in the corpus callosum regions of interest body, genu, and splenium (p<0.01). DTI	DTI allows for a more sensitive delineation of severity and mechanism of white matter pathology, and may help to explain apparent discrepancies between clinically diagnosed injury severity and cognitive outcomes across the spectrum of TBI.”
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Marquez de la Plata 2011 (3.5)	DTI	Prospective	N = 49	34 males, 15 females; Manage	Supported C. Marquez de la Plata & Co. Author. No COI.	Interhemispheric commissural: corpus callosum; Limbic: fornix, perforant pathway L/R (PPL/PPR), cingulum L/R (CIL/CIR); Association fibers: uncinata fasciculus L/R (UNCL/UNCR), inferior longitudinal fasciculus L/R (ILFL/ILFR), inferior fronto-occipital fasciculus L/R [IFOL1367]	Traumatic axonal injury (TAI) (n=30) and healthy controls (n=19)	DTI	MRI 3.0 Tesla	Yes	Yes	No	Glasgow Outcome Scale-Extended (GOSE), Trail Making Test (TMT) A/B, Controlled Oral Word Association Test (COWAT), Stroop, CVLT-II, fractional anisotropy (FA)	8 months	There was no association between FA voxel-based lesion load and all outcome measures. Between group differences (control vs. TBI) in FA was statistically significant in the corpus callosum and association fibers- UNCL, UNCR, ILFR, IFOL, IFOR (p<0.005). Group differences in mean diffusivity was significant across all regions (interhemispheric commissural p<0.005; Association fibers p<0.005; UNCR and CIL p<0.05) of interest except for limbic fornix (p>0.05).	“While diffusion tensor tractography can detect compromise to commissural, limbic, and association fibers after TAI, the association between tractography-derived measures of integrity within limbic and association fibers and cognitive outcome is nonspecific. Given their sensitivity to microstructural WM
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																	(white matter) compromise and relation to clinical outcome, all three analysis techniques show promise as markers to assist with selecting appropriate candidates for TAI directed therapies or as potential markers of treatment outcome."
Palacios 2011 (3.0)	DTI	Prospective	N = 31	20 males, 11 females; Mean Age 23.6±4.8	Supported by grants from the Spanish Ministry of Science and Innovation, Generalitat de	Corpus callosum (CC), fornix, superior longitudinal fascicule (SLF), inferior longitudinal fascicule (ILF), inferior	Severe or diffuse traumatic brain injury (n=15) and healthy controls (n=16).	DTI	MRI	Yes	Yes	No	Glasgow Coma Scale (GCS), Wechsler Adult Intelligence Scale (WAIS-III), Digit span and Letter-	No	RBMT scores correlated with the fornix and the corpus callosum (p<0.05). There no correlations between GCS	"This DTI study suggests that declarative and working memory deficits in diffuse	

					Catalunya. No COI.	fronto-occipital fascicule [1367].							Number Sequencing (LNS), Rivermead Behavioral Memory Test (RBMT), fractional anisotropy (FA), apparent diffusion coefficient (ADC)		scores and mean FA values. LNS scores were significantly lower for the TBI compared to control (p=0.02).	TBI patients are related to differential patterns of FA reduction."	
Rutgers 2008 (N=3.0)	DTI	Prospective	N = 32	20 males, 12 females; Mean age 32±9	This study was supported by the Institut pour la Recherche sur la Moelle e'pine're et l'Ence'phale. No COI.	Cerebral lobar white matter: centrum semivale, frontal, parietal, temporal, and occipital lobes.	Corpus callosum/cingulum	Internal capsule: anterior/posterior limb.	Mesencephalon, brain stem, and cerebellum.	Mild traumatic brain injury (n=21) and healthy controls (n=11).	DTI 1.5T	MRI 1.5T	Yes	Yes		"The present study shows that patients with mild TBI have multiple white matter regions with abnormally reduced FA, predominantly in cerebral lobar white matter, cingulum, and	

																	corpus callosum.
Greenberg 2008 (3.0)	DTI	Prospective	N = 13	10 males, 3 females; Mean Age 34.46	Supported by the Provincial Rehabilitation Institute. No COI.	Anterior and posterior corpus callosum, deep frontal white matter, deep temporal white matter	Moderate to severe traumatic brain injury	DTI 1.5	MRI 1.5 Tesla	Yes	Yes	No	Glasgow Coma Scale (GCS), Fractional anisotropy (FA)	29 +/- 4 months	FA significantly decreased in the right frontal lobes at time 1 (immediately after injury) .38 +/- 0.6 and time 2 (29 months post injury) .30 +/- .06 (p<0.05). Left frontal lobes for time 1 .37 +/- and time 2 .32 +/- 0.6 (p<0.013). DTI was sensitive to diffuse axonal injury.	“Our results show that interval decline in diffusion anisotropy in frontal and temporal lobes was present in a group of patients with moderate-severe, subacute TBI.”	
Gu 2012 (2.5)	DTI	Prospective	N = 30	24 males, 6 females; Mean age of TBI 34.8± 11.27 vs control	This study was supported by the Research Foundation of Shanghai Health Bureau and the Shanghai Committee of	Posterior limb of internal capsule (PLIC), uncinate fasciculus (UF), anterior corona radiata (ACR), superior	Closed-head injury (n=15) and healthy controls (n=15).	DTI 1.5 T	DTI 1.5 T	Yes	Yes	No	Fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), mean diffusivity, and neuropsychological tests	No	FA and AD levels were significantly different between controls and TBI patients in all regions of interest (p<0.05). Controls scored significantly	“We found widespread primary changes in FA, MD, AD, and RD measurements during the acute	

				33.8±11.9.	Science and Technology. No COI.	longitudinal fascicule (SLF), interior longitudinal fascicule (ILF), corpus callosum: genu, body, and cingulum bundle.									higher in working memory scores (p<0.01) compared to DAI patients and was inversely correlated with RD values for the cingulum bundle (p=0.017), SLF (p=0.001), ILF (p=0.012). Attention test scores had a positive correlation with RD values in the ACR (p=0.012), SLF (p=0.008), and ILF (p=0.008).	phase of injury and differences between patients with DAI and healthy controls.”	
Kumar 2010 (2.5)	DTI	Prospective	N = 33	18 males, 15 females; TBI Mean age 35.25 ±10.28 vs 37.35 ±9.34 for	This study was supported by the Indian Council of medical Research. No COI.	Corpus callosum: genu, midbody, splenium.	Traumatic brain injury (n=16) and healthy controls (n=17)	DTI 1.5 T	MRI 1.5 T	Yes	Yes	No	Fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), mean diffusivity (MD), neuropsychological tests	6 months and 24 months	At 6 months FA values in the midbody of the corpus callosum had a positive correlation to picture completion test (PCT) for those with head trauma (p=0.022). AD values in midbody were	“IN conclusion, our study suggests that FA and RD indices are surrogate markers of microstructural alteration	

				control.											inversely correlated with block design test (BDT) (p=0.014). At 24 months RD values in the genu were positively correlated with numbers connection test [940] (p=0.047).	s in patients with TBI over time and correlate significantly with some NPT scores.”
Jang 2009 (2.5)	DTI	Prospective	N = 26	(14 males, 12 females; Mean age 32 (20-72))	This work was supported by National Research Foundation of Korea funded by the Korean Government. No COI.	Corona radiate (CR), posterior limb of internal capsule (PL), cerebral peduncle (CP), pons, medulla.	Diffuse axonal injury (n=14) and healthy controls (n=12).	DTI 1.5 T	MRI	Yes	Yes	No	Fractional anisotropy (FA), apparent diffusion coefficient (ADC)	No	FA values 2 SD below control was considered a corticospinal tract injury (CST). FA values revealed 51 lesions in 14 patients head injury. The pons and cerebral peduncle had the most lesions found.	“In conclusion, we have demonstrated that all patients who showed motor weakness without specific lesions along the CST pathway on conventional brain MRI had CST injuries, and found that the

																	locations of the lesions causing the CST injury were distributed in the following order: the pons, the midbrain, the CR, the medulla, and the PL."	
Bazarian 2012 (2.5)	DTI	Prospective	N= 15	14 males, 1 female; No mean age, age range 16-35.	Support for this study was provided by National Institutes of Health grant and by a grant from the University of Rochester Health Sciences Center For Computational Innovation. No mention of COI.	Whole body scan. Parts of brain interested in: external capsule, posterior and anterior corpus callosum, posterior and anterior limb of the internal capsule	10 high school athletes that could potentially receive concussion throughout the season and 5 controls.	3-T Trio Scanner	No	No	No	No	Computerized cognitive testing with ImPACT, Standardized Assessment of Concussion (SAC), ANOVA testing.	3 months	Concussed athlete had largest proportion of White Matter (WM) baseline to post Wm voxel FA change of 3.19%. and Mean Diffusivity (MD) of 3.44%. Controls vs. Athletes WM voxel Functional Acuity (FA Change): 1.05%±0.15% vs	"WB analysis detected significantly changed WM in a single concussed athlete. Athletes with multiple SHB had significant changes in a percentage of their WM that was over three		

															0.28%±0.01% (p=0.002). Mean diffusivity change: 1.48%±0.17% vs 0.48%±0.05% (p=0.002).	times higher than controls.”	
Tisserand 2006 (2.0)	DTI	Prospective	N= 14	No mention of gender; Age range (20-40)	No mention of sponsorship or COI.	manual tracing was carried out within the genu, splenium, and body of the corpus callosum (CC).	Severe or moderate TBI.	Not specified	Not specified	Yes	Yes	No	None	No	fractional anisotropy (FA) values were lower in TBI patients (p=0.002) in the middle-posterior brain region bilaterally and the splenium (p=0.015).	“Overall, our findings seem to suggest that abnormalities in anisotropy in TBI patients are subtle and regionally specific. Interestingly, we found that the splenium of the CC was for the largest part contained in the middle-posterior region of normal	

																		appearin g white matter.”	
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### Evidence for the Use of Diffusion Tensor Imaging (DTI)

Author Year (Score):	Category:	Study type:	Sample size:	Age/SEX:	Sponsorship/COI:	Area of body:	Diagnoses:	SP EC T or SP ET:	MRI or CT:	T1 weight ed ima ges:	T2 weig hted imag es:	More tha n one rate r:	Clinical outcomes assessed:	Long term follo w-up: (mean when noted )	Results:	Conclusio n:	Comment s:
Mayer 2010 (3.5)	DTI	Prospective	N = 43 (20 females, 7 males)	Mean age 27.45 ±7.39. Control group: No gender mentioned; Mean age 26.81 ±6.68.	Authors have received funding from the National Institutes of Health. No COI.	Corpus callosum (CC), splenium [48], left superior corona radiate [1366], left uncinate fasciculus (UF), left internal capsule (IC), left corona radiate (CR), genu (GNU).	Closed-head traumatic brain injury (n=22) and healthy controls (n=21).	DTI 3 Tesla	MRI 3 Tesla	Yes	Yes	No	Fractional anisotropy (FA), apparent diffusion coefficient (ADC), axial diffusivity (AD), radial diffusivity (RD)	No	FA levels in the right hemisphere were positively correlated with attention deficits (p<0.01) for the TBI group. Traditional neuropsychological tests classification of injury had 65% accuracy for controls and 66.7% for TBI. Left and right hemisphere FA had a classification accuracy of	“Our preliminary longitudinal data suggest a partial normalization of FA (i.e., a decrease toward levels observed in HC) within several ROI in our mTBI group”	Data suggest DTI may be useful for classifying mild TBI and may then be a recovery biomarker.

															70% for controls and 81% for TBI.		
Watts 2014 (3.5)	DTI	Prospective	N=36	18 males, 18 females; Group 1	This research was supported by the National Institutes of Health. No COI.	Anterior and posterior commissure	(N=20) patients with TBI (N=16) healthy controls BI	3.0 T MRI	3.0 T MRI and CT	Yes	Yes	Yes	acute head injury, Glasgow Coma Scale score of 13–15, and two or more concussive symptoms (loss of consciousness, blurred vision, confusion, dizziness, memory problems, or poor balance)	No	There was a large difference in Fractional Anisotropy (FA) potholes in mTBI vs control (102.5±34.3 vs 50.6±28.9 (p<0.001).	“In summary, the pothole and molehill approach to the analysis of DTI data is a potentially useful method that can be used to avoid many of the problems of traditional region of interest-based methods, which improves the detection effectiveness for any disease	Data suggests bias may be introduced in the pothole approach which may need cross validation and independent training to minimize.

																	process with a heterogeneous spatial distribution of pathological findings.”	
Ilvesmaki 2014 (3.5)	DTI	Diagnostic	N=115	TBI: 45 males, 30 females; Mean age 37.2±12.0. Control: 20 males 20 females; mean age 40.6±12.2.	This work was supported by a grant by the Emil Aaltonen foundation to T.I. One author has been reimbursed by government, professional scientific bodies, and commercial organization for work in mTBI.	All planes of the brain.	75 individuals with mTBI within the Ed. 40 healthy controls.	spin ec ho-based and diffusion-weighted ec ho planar imaging sequence.	64-row Ct scanner, 3 T MRI	Yes	Yes	Yes	Loss of consciousness longer than 5 min, post-trauma amnesia, lesion on CT or MRI, Glasgow Coma Score, Sports Concussion analysis Tool (SCAT).	None	No significant differences between control and patients in fractional anisotropy, apparent diffusion coefficient, axial diffusivity or radial diffusivity. No significant difference between different levels of TBI. Only significant between age groups in both control and patients. Fractional anisotropy values (p<0.01).	“In conclusion, in this large homogeneous, premorbidly healthy sample, acute mild TBI was not associated with obvious DTI abnormalities detectable with TBSS. Clear differences in DTI findings were associated with age, even in healthy	Data suggest mild TBI not associated with DTI changes.	

																subjects in their 40s. Therefore, age should always be considered a potential confounder in DTI studies."	
Li 2016 (3.5)	DTI	Prospective	N=65	29 males, 36 females; Mean age Group 1: 35.8±7.58 Group 2: 36.7±7.09 Group 3: 36.11±7.11	This work was supported by a grant from the Jinan Military General Hospital. No COI.	corpus callosum (CC), inferior fronto-occipital fasciculus (IFF), uncinate fasciculus (UF), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), anterior thalamic radiation (ATR), and corticospinal tract (CT).	Patients with successful recovery (SR) of PTSD after mTBI (N=22) Patients with poor recovery (PR) of PTSD after mTBI (N=21) Control (N=22)	TBSST - Wisconsin analysis	3.0T MRI	Yes	Yes	No.	The evaluation included the psychometric measures for PTSD diagnosis, which is based on Diagnostic and Statistical Manual of Mental Disorders-V criteria, and symptom severity using the clinician-administered PTSD scale (CAPS).	6 months	The application of the MD values in subacute phase allowed discrimination between PR and SR groups with a sensitivity of 73% and a specificity of 78%, resulting in an accuracy of 75.56%, using the threshold as P = 0.50.	"The present study revealed a significant alteration in the DTI metrics for a group of patients with mTBI, spanning the acute to chronic phases. These changes were highly correlated with PTSD."	Data suggest WM abnormalities in mild TBI patients are common. DTI changes overtime (Acute---chronic) and there changes correlate to PTSD.

Kraus 2007 (3.5)	DTI	Prospective	N = 55	23 males, 32 females; Mean age 34.85 ±2.82	Sponsored by the national Institute of Health. No COI>	Anterior/posterior corona radiate (ACR/PCR), cortico-spinal tracts (CST), cingulum (CG) fibres, forceps minor (fMin), forceps major (fMaj), the body, genu and splenium of corpus callosum (bCC, gCC, and sCC), inferior fronto-occipital [1367], superior longitudinal fasciculus (SLF), external capsule (ExCap), and sagittal stratum and optic radiations.	Mild traumatic brain injury (n=20), moderate to severe injury (n=17), and healthy controls (n=18).	3.0 Tesla	No	No	Yes	No	Neuropsychological tests: (executive measures executive domain tests) Tower of London, Stroop Colour Test, Paced Auditory Serial Addition Test (PASAT), Trail Making Test (TMT), Controlled Oral Word Association (COWA), Wechsler Test of Adult Reading (TAR), California Verbal Learning Test Memory Measures: (CVLT-II), Brief Visual Spatial Memory Test (BVM-T-R) Attention measures: Digit Span and Spatial Span Other: Grooved Pegboard,	No	Those with mild brain injury compared to moderate to severe brain injury performed significantly better on the executive measures executive domain tests (p<0.01), CVLT trials 1-5 (p<0.05), BVM-T trials 1-3 (p<0.05), and the grooved pegboard (p<0.01). Fractional anisotropy (FA) was significantly greater in those with severe to moderate injury compared to mild or control in the corpus callosum regions of interest body, genu, and splenium (p<0.01). DTI	“The data presented here demonstrate that DTI allows for a more sensitive delineation of severity and mechanism of white matter pathology, and may help to explain apparent discrepancies between clinically diagnosed injury severity and cognitive outcomes across the spectrum of TBI.”	Data suggests DTI relates cognitive dysfunction to TBI even if the injury occurred years prior to the study.
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													and Test of Memory Malingering (TOMM)				
Marquez de la Plata 2011 (3.5)	DTI	Prospective	N = 49	34 males, 15 females; Manange	Supported C. Marquez de la Plata & Co. Author. No COI.	Interhemispheric commissural: corpus callosum; Limbic: fornix, perforant pathway L/R (PPL/PPR), cingulum L/R (CIL/CIR); Association fibers: uncinate fasciculus L/R (UNCL/UNCR), inferior longitudinal fasciculus L/R (ILFL/ILFR), inferior fronto-occipital fasciculus L/R [IFOL1367]	Traumatic axonal injury (TAI) (n=30) and healthy controls (n=19)	DTI	MRI 3.0 Tesla	Yes	Yes	No	Glasgow Outcome Scale-Extended (GOSE), Trail Making Test (TMT) A/B, Controlled Oral Word Association Test (COWAT), Stroop, CVLT-II, fractional anisotropy (FA)	8 months	There was no association between FA voxel-based lesion load and all outcome measures. Between group differences (control vs. TBI) in FA was statistically significant in the corpus callosum and association fibers- UNCL, UNCR, ILFR, IFOL, IFOR (p<0.005). Group differences in mean diffusivity was significant across all regions (interhemispheric commissural p<0.005; Association fibers p<0.005; UNCR and CIL	“While diffusion tensor tractography can detect compromise to commissural, limbic, and association fibers after TAI, the association between tractography-derived measures of integrity within limbic and association fibers and cognitive outcome is nonspecific. Given their	Data suggest DTI is sensitive to WM changes and thus clinical outcome.

															p<0.05) of interest except for limbic fornix (p>0.05).	sensitivity to microstructural WM (white matter) compromise and relation to clinical outcome, all three analysis techniques show promise as markers to assist with selecting appropriate candidates for TAI directed therapies or as potential markers of treatment outcome.	
Palacios 2011 (3.0)	DTI	Prospective	N = 31	20 males, 11 females;	Supported by grants from the Spanish Ministry of	Corpus callosum (CC), fornix, superior longitudinal	Severe or diffuse traumatic brain injury (n=15) and	DTI	MRI	Yes	Yes	No	Glasgow Coma Scale (GCS), Wechsler Adult	No	RBMT scores correlated with the fornix and the corpus	"This DTI study suggests that declarativ	Data suggest a decrease of white matter

				Mean Age 23.6±4.8	Science and Innovation, Generalitat de Catalunya. No COI.	fascicule (SLF), interior longitudinal fascicule (ILF), inferior fronto-occipital fascicule [1367].	healthy controls (n=16).						Intelligence Scale (WAIS-III), Digit span and Letter-Number Sequencing (LNS), Rivermead Behavioral Memory Test (RBMT), fractional anisotropy (FA), apparent diffusion coefficient (ADC)		callosum (p<0.05). There no correlations between GCS scores and mean FA values. LNS scores were significantly lower for the TBI compared to control (p=0.02).	e and working memory deficits in diffuse TBI patients are related to differential patterns of FA reduction."	integrity in associate with diffuse TBI.
Rutgers 2008 (N=3.0)	DTI	Prospective	N = 32	20 males, 12 females; Mean age 32±9	This study was supported by the Institut pour la Recherche sur la Moelle e'pine`re et l'Ence`phale. No COI.	Cerebral lobar white matter: centrum semivale, frontal, parietal, temporal, and occipital lobes.	Corpus callosum/cingulum	Internal capsule: anterior/posterior limb.	Mild traumatic brain injury (n=21) and healthy controls (n=11).	DTI 1.5T	MRI 1.5T	Yes	Yes		"The present study shows that patients with mild TBI have multiple white matter regions with abnormally reduced FA, predominantly in cerebral lobar white	Data suggest in mild TBI patients there are multiple regions of reduced FA in the white matter.	

																	matter, cingulum, and corpus callosum.”	
Greenberg 2008 (3.0)	DTI	Prospective	N = 13	10 males, 3 females; Mean Age 34.46	Supported by the Provincial Rehabilitation Institute. No COI.	Anterior and posterior corpus callosum, deep frontal white matter, deep temporal white matter	Moderate to severe traumatic brain injury	DTI 1.5	MRI 1.5 Tesla	Yes	Yes	No	Glasgow Coma Scale (GCS), Fractional anisotropy (FA)	29 +/- 4 months	FA significantly decreased in the right frontal lobes at time 1 (immediately after injury) .38+/- 0.6 and time 2 (29 months post injury) .30 +/- .06 (p<0.05). Left frontal lobes for time 1 .37 +/- and time 2 .32+/- 0.6 (p<0.013). DTI was sensitive to diffuse axonal injury.	“Our results show that interval decline in diffusion anisotropy in frontal and temporal lobes was present in a group of patients with moderate-severe, subacute TBI.”	Small sample. Data suggest WM injury progression correlate to changes in diffusion anisotropy.	
Gu 2012 (2.5)	DTI	Prospective	N = 30	24 males, 6 females; Mean age of TBI 34.8± 11.27 vs contr	This study was supported by the Research Foundation of Shanghai Health Bureau and the Shanghai Committee of	Posterior limb of internal capsule (PLIC), uncinate fasciculus (UF), anterior corona radiata (ACR),	Closed-head injury (n=15) and healthy controls (n=15).	DTI 1.5 T	DTI 1.5 T	Yes	Yes	No	Fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), mean diffusivity, and neuropsychological tests	No	FA and AD levels were significantly different between controls and TBI patients in all regions of interest (p<0.05). Controls scored	“We found widespread primary changes in FA, MD, AD, and RD measurements during	Data suggest while matter changes in early DAI may be predictive for cognitive	

				ol 33.8± 11.9.	Science and Technology. No COI.	superior longitudinal fascicule (SLF), interior longitudinal fascicule (ILF), corpus callosum: genu, body, and cingulum bundle.									significantly higher in working memory scores (p<0.01) compared to DAI patients and was inversely correlated with RD values for the cingulum bundle (p=0.017), SLF (p=0.001), ILF (p=0.012). Attention test scores had a positive correlation with RD values in the ACR (p=0.012), SLF (p=0.008), and ILF (p=0.008).	the acute phase of injury and differenc es between patients with DAI and healthy controls.”	dysfuncti on.
Kumar 2010 (2.5)	DTI	Pros pect ive	N = 33	18 males , 15 femal es; TBI Mean age 35.25 ±10.2 8 vs 37.35 ±9.34 for	This study was supported by the Indian Council of medical Research. No COI.	Corpus callosum: genu, midbody, splenium.	Traumatic brain injury (n=16) and healthy controls (n=17)	DTI 1.5 T	MRI 1.5 T	Yes	Yes	No	Fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), mean diffusivity (MD), neuropsychol ogical tests	6 mont hs and 24 mont hs	At 6 months FA values in the midbody of the corpus callosum had a positive correlation to picture completion test (PCT) for those with head trauma (p=0.022). AD values in	“IN conclusio n, our study suggests that FA and RD indices are surrogate markers of microstru ctural	Data suggest FA and RD all measures for structural changes and correlate with NPT scores which may mark

				control.											midbody were inversely correlated with block design test (BDT) (p=0.014). At 24 months RD values in the genu were positively correlated with numbers connection test [940] (p=0.047).	alterations in patients with TBI over time and correlate significantly with some NPT scores.”	residual injury for moderate TBI patients.
Jang 2009 (2.5)	DTI	Prospective	N = 26	(14 males, 12 females; Mean age 32 (20-72))	This work was supported by National Research Foundation of Korea funded by the Korean Government. No COI.	Corona radiate (CR), posterior limb of internal capsule (PL), cerebral peduncle (CP), pons, medulla.	Diffuse axonal injury (n=14) and healthy controls (n=12).	DTI 1.5 T	MRI	Yes	Yes	No	Fractional anisotropy (FA), apparent diffusion coefficient (ADC)	No	FA values 2 SD below control was considered a corticospinal tract injury (CST). FA values revealed 51 lesions in 14 patients head injury. The pons and cerebral peduncle had the most lesions found.	“In conclusion, we have demonstrated that all patients who showed motor weakness without specific lesions along the CST pathway on conventional brain MRI had CST injuries, and found	Data suggest pons is most prevalent area of CST injury in patients with diffuse axonal injury.

																	that the locations of the lesions causing the CST injury were distributed in the following order: the pons, the midbrain, the CR, the medulla, and the PL.”	
Bazarian 2012 (2.5)	DTI	Prospective	N= 15	14 males, 1 female; No mean age, age range 16-35.	Support for this study was provided by National Institutes of Health grant and by a grant from the University of Rochester Health Sciences Center For Computational Innovation. No mention of COI.	Whole body scan. Parts of brain interested in: external capsule, posterior and anterior corpus callosum, posterior and anterior limb of the internal capsule	10 high school athletes that could potentially receive concussion throughout the season and 5 controls.	3-T Trio Scanner	No	No	No	No	Computerized cognitive testing with ImPACT, Standardized Assessment of Concussion (SAC), ANOVA testing.	3 months	Concussed athlete had largest proportion of White Matter (WM) baseline to post Wm voxel FA change of 3.19%. and Mean Diffusivity (MD) of 3.44%. Controls vs. Athletes WM voxel Functional Acuity (FA Change): 1.05%±0.15%	“WB analysis detected significantly changed WM in a single concussed athlete. Athletes with multiple SHB had significant changes in a percentage of their WM that was	Small sample. Data suggests even a single concussion causes changes of WM in athletes and those with multiple concussive event had more than 3 times the WM changes	

															vs 0.28%±0.01% (p=0.002). Mean diffusivity change: 1.48%±0.17% vs 0.48%±0.05% (p=0.002).	over three times higher than controls.”	of controls.
Tisserand 2006 (2.0)	DTI	Prospect ive	N= 14	No menti on of gende r; Age range (20- 40)	No mention of sponsorship or COI.	manual tracing was carried out within the genu, splenium, and body of the corpus callosum (CC).	Severe or moderate TBI.	No t spe cifi ed	Not spe cifie d	Yes	Yes	No	None	No	fractional anisotropy (FA) values were lower in TBI patients (p=0.002) in the middle- posterior brain region bilaterally and the splenium (p=0.015).	“Overall, our findings seem to suggest that abnormal ities in anisotrop y in TBI patients are subtle and regionally specific. Interestin gly, we found that the splenium of the CC was for the largest part containe d in the middle- posterior region of normal	Small sample (N=8). Data suggests FA is lower in TBI patients as compare d with controls.

																	appearing white matter."	
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**Evidence for the Use of Single-Photon Emission Computerized Tomography (SPECT) or Single-Photon Emission Tomographic (SPET)**

<i>Author Year (Score):</i>	<i>Cate gory:</i>	<i>Study type:</i>	<i>Sample size:</i>	<i>Age/Sex :</i>	<i>Spons orship /COI</i>	<i>Area of head:</i>	<i>Diagn oses:</i>	<i>SPEC T or SPET:</i>	<i>MRI or CT:</i>	<i>More than one rater :</i>	<i>Surger y Perfor med:</i>	<i>Clinical outcom es asse ssed:</i>	<i>Long term follo w-up: (mean when noted)</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Wiedmann 1989 (3.5)	SPECT	Pros pecti ve	N = 24 with brain trauma	Mean age of 44.7 years old. 6 Females , 18 Males	Spons ored by Medic al Resea rch Council of Great Britai n. No menti on of COI.	Oribit ofront al left/right, fronta l L/R, pariet al L/R, occipi tal L/R, anteri or/posterio r temp	Traum atic brain injury. Split patien ts into two group s by injury: diffus e (n=16) and focal (n=8).	SPEC T 99m-Tc HMP AO	MRI 1.5 Tesla , T1 and T2 weig hted	No	No	Yes	6 mont hs	For the diffuse group MRI showed 12/16 and 14/16 had abnormal SPECT. Only 1/16 had normal MRI and SPECT scans. SPECT detected more abnormalitie s in the parietal	"The authors conclude that patterns of CBF abnormalities were different for the focal and diffuse groups; SPECT was able to identify abnormalities not demonstrated on MRI and vice versa	Small Sample. Data suggest SPECT identified abnormalities

						oral L/R								lobes and MRI detected more in the orbitofrontal and anterior temporal regions. All patients 8/8 with focal injury had abnormal MRI and SPECT scans.	and abnormal regional CBF was related to neuropsychological defects.”	
Umile 2002 (3.5)	SPECT	Retropective	N = 20 patients with head trauma	Mean age of 37.2 years old. 9 Females, 11 Males	Sponsored by the National Institutes of Health. No COI.	Brain	TBI	SPECT – Picker Prism 3000 triple detector	Both	No	No	No	Not mentioned	15 patients had normal static imaging (MRI/CT). Dynamic imaging revealed 18 patients with abnormalities on the PET or SPECT. 13 or the 15 normal patients had an abnormal PET or SPECT.	“The abnormal temporal lobe findings on PET and SPECT in humans may be analogous to the neuropathologic evidence of medial temporal injury provided by animal studies after mild TBI.”	Data suggest there is a high incidence of temporal lobe injury perhaps explaining memory dysfunction in mild TBI patients. PET and SPECT images may correlate to the injured brain areas.

Fumeya 1990 (3.5)	SPECT	Prospective	N = 24 patients with head injury	No mention of age or sex.	No mention of sponsorship or COI	Left and right frontal lobes	Acute traumatic brain injury	SPECT <sup>99m</sup> Tc-DTPA - human serum albumin	CT and T2-weighted 1.5 Tesla MRI	No	No	No	No	All patients underwent SPECT, which found 51 contusional lesions on 24 patients. 38/51 lesions were seen on CT and MRI. 13/58 were seen on MRI, but not on CT scanning (using window techniques).	“The results suggest that the former may include a mixture of brain oedema and hyperemia and the latter may imply brain oedema. MR imaging can reveal the minor oedema which CT fails to show in patients with acute head injury.”	Data suggests MRI detects edema which CT does not in acute head injury patient.
Atighechi 2009 (3.5)	SPECT	Prospective	N = 40 with head trauma	N = 21 fulfilled requirements completely. Mean age of 27.6 years old. 2 Females, 19 Males	No mention of sponsorship or COI.	L/R Frontal, parietal, and temporal lobes. Olfactory bulb	Traumatic head injury with anosmia (n=21) Traumatic head injury without anosmia (n=19)	SPET <sup>99m</sup> Tc ethyl cysteinate dime r	MRI	No	No	Yes	No	18/21 (85.7%) with anosmia head trauma had abnormal SPECT. Frontal abnormalities in SPECT had a 0.81 correlation with MRI (p=0.309). When MRI and SPECT	“ The findings of this study suggest that damage to the frontal lobes and olfactory bulbs as shown in the brain MRI and hypoperfusion in the frontal, left parietal, and left temporal	Data suggest SPECT imagery corresponds to post-traumatic anosmia.

														are together there was a 90.4% of finding an abnormality .	lobes in the semiquantitative SPECT corresponds to post-traumatic anosmia. Further neurophysiological and imaging studies are definitely needed to set the idea completely”	
Umile 1998 (2.5)	SPECT	Retropective	N = 4 with mTBI	Mean age of 41.5 years old. 1 female, 3 males.	No mention of sponsorship or COI.	Left and right frontal, right and left temporal, right and left occipital	Mild traumatic brain injury (mTBI).	SPECT	Neither	No	No	Yes	91 months	Performance on the neuropsychological (NP) tests predicted cerebral blood flow patterns on SPECT. However, SPECT findings did not predict NP test performance.	“Statistical analysis of composite data from all four patients showed that test performance predicted SPECT findings, but SPECT findings did not predict test performance.”	Very small sample.

### Evidence for the Use of Positron Emission Test (PET)

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnosis:	Comparison:	Results:	Conclusion:	Comments
Vespa P, 2005 (3.5)	PET	Case Control	Sponsored by NINDS 03039, NS02089, and the State of California Neurotrauma Initiative Grant. No mention of COI.	N = 19 patients with TBI.	No mention of age or sex.	TBI	Patients had severe TBI with either GCSr8 or evidence of traumatic mass lesion on computerized tomographic scan and GCSr12	Longitudinal MD data showed a 25% incidence rate of metabolic crisis (elevated lactate/pyruvate ratio (LPR) 440) but only a 2.4% incidence rate of ischemia. LPR was negatively correlated with CMRO2 (r= -0.44, P<0.001). Increased LPR most tightly corresponds to nonischemic reduction in the CMRO2	"The primary findings of the current study were that the injured brain has persistent impairments in metabolism that can be reflected by cerebral microdialysis. Specifically, the LPR best reflects impaired oxidative metabolism, but is not specific for brain ischemia. Moreover, the metabolic crisis was not primarily a result on persistent brain ischemia, and hence	Data suggests TBI results in a series of metabolic changes reflected by abnormal cerebral microdialysis LPR unrelated to ischemia.

									elevations in LPR are not specific for brain ischemia. Moreover, these findings suggest that the use of microdialysis monitoring of various metabolites to determine the overall state of energy balance between supply and demand might be the most appropriate monitoring tool in TBI."	
Chen SH, 2003 (3.0)	PET	Case Control	Sponsored by the Physiologic Imaging Research Center of the Indiana University	N= 10	Mean age was 34.3 years. Mean age of 34.3 years old. 6 Females, 4 Males	TBI	(n= ) 5 five patients with mild head trauma vs.  (n=) 5 matched healthy controls	There was no significant difference in normalized FDG uptake between patients and controls during resting state. Patients scored slightly lower than controls on memory task: 24.0 (1.9) vs 26.6 (3.1), (p=.09). There	"During the resting state, normalized regional cerebral glucose metabolism was similar between patients and controls, but differences	Very small sample. Data suggests lack of efficacy.

			School of Medicine, the American Psychological Association Division 40 and American Psychological Foundation, and the American Psychological Association Science Directorate. No COI.					was no statistical difference in perception condition reaction times between patients and controls (0.32 (0.59) s v 0.39 (0.44), p = 0.23), nor was there a between group difference in reaction times for the memory condition (patients: 0.32 (0.50) s; controls: 0.25 (0.69), p =0.20).	emerged in rCBF increases during a spatial working memory task in the inferior right frontal gyrus. Post hoc analysis of this area in the resting state study did not differentiate the groups. In simplistic terms, it is likely that during a more passive state the brain is not using resources required in accomplishing a specific cognitive task. ". "	
Spadoni 2015 (2.5)	PET	Case-Control	No mention of sponsorship or COI.	45 Operation Iraqi Freedom and Opera	Mean age of 30 years old. 0 Females, 45 Males	mTBI	Poor TOMM Score (N = 10)  Vs  Good TOMM Score	There was no significance in the prevalence of PTSD, STAI or BDI-II and the Neuropsychological measures between the two groups. There was a	"These findings have important implications for the disentangling of feigned versus actual	Data suggest in individuals with mTBI from combat trauma decreased TOMM performance

				tion Endur ing Freed om Veter an volun teers			(N = 35)  TOMM is the Test of Memory Malingering	significant difference between the severity of PTSD (P<0.05). With PET scanning, a voxel-based multiple regression with Group predicting FDG uptake revealed that only the right anterior cortex produced a significant cluster of greater uptake in the Good TOMM group than the Poor TOMM Group.	memory impairment, where the latter may be secondary to neural mechanisms not consistent with forgetting or deception.”	may be related to ventromedial prefrontal cortical dysfunction.
Levine B, 2002 (2.0)	PET	Case Control	Sponsor ed by Canadia n Institute s of Health Researc h, the Ontario Mental Health Foundat ion and the Rotman Researc h Institute . No COI.	N = 17 subje ct	Mean age was 27.5 years old.Mean age of 27.5 years old.  6 Males in TBI group. No mention of other sex distributi on.	TBI	Moderate to severe TBI (N=6) vs Matched healthy controls (N=11)	Both TBI patients and control group engaged frontal, temporal, and parietal regions known to be involved in memory retrieval, although the TBI patients showed slight increases in frontal, anterior cingulate, and occipital activity. The hemispheric asymmetry characteristic of controls was attenuated in patients with TBI. The TBI patients’ performance was below that of the	”In contrast with neuroimaging studies of TBI effects emphasizing structural or functional metabolic deficits, activation functional neuroimaging paradigms can reveal effects in intact or altered tissue in relation to focal or diffuse brain injury.	Very small sample. Data suggests TBI patients used altered neuroanatom ical networks while performing memory tasks.

								controls, although this difference did not reach significance, $t(5.77)=2.09$	Consistent with prior work in patients with TBI and other etiologies, we documented a reduction in focus of cortical activation in patients with moderate to severe TBI in response to a memory retrieval task with known functional neuroanatomical properties."	
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### Evidence for the Use of Quantitative Electroencephalograph (QEEG) and Electroencephalography (EEG)

Author Year (Score)	Category:	Study type:	Sponsorship and COI	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Leon-Carrion 2008 (3.5)	EEG/QEEG	Diagnostic	Supported by the Ministry of Science and Education as part of the National Plan for Scientific Research,	N = 81	(50 males, 31 females). Mean age is 42.21 years.	TBI	QEEG Vs EEG Discriminant Analysis	The correlation between QEEG and FIM/FAM reached significance with $R=8.85$ ( $p<0.0001$ ) Discriminant analysis showed 100% specificity and 100% sensitivity.	"The discriminant function may be a useful tool in objective evaluations of patients seeking a diagnosis of	Data suggest that use of discriminant function may assist in diagnosis of dependence levels for ABI.

			Development and Technological Innovation (2004-2007) and co-funded by the European Regional Development Fund (ERDF): FIT-300100-2006-77.						their level of dependence and that it could be included in current functionality assessment protocols."	
Naunheim 2010 (3.5)	EEG/QEEG	Diagnostic	Teya Casner, MPH, is funded by BrainScope and responsible for collection of data and data transfer to New York University. Robert Chabot is a scientific consultant to BrainScope, Co. However, BrainScope did not participate in the data analysis or writing of the manuscript.	N = 105	(60 males, 45 females). Mean age is 41.0 years.	TBI	CT + Vs. CT -	CT+ patients had a mean TBI-DC of 80.4, CT- patients a value of 38.9 and control patients a mean index of 24.5. sensitivity for CT+ is 92.45% and the specificity for normal controls is 90.00%. The negative predictive value was 91.8% and the positive predictive value was 90.7%.	"The TBI discriminant index appears to be a sensitive index of brain function. It may be used to suggest whether or not a patient presenting with altered mental status requires a CT scan. This index may aid in the triage of such patients in the ED. Such an easy to use, automated system may greatly enhance the clinical utility of EEG in the ED."	Data suggests TBI index appears sensitive for brain function and may aid in determining which patients require CT scan.

Alvarez 2008 (3.0)	EEG/QEEG	Diagnostic	Supported by grants from EB-EWE Pharma (Austria) and the EuroEspes Compnay (Spain).	N = 20	(14 males, 6 females). Mean age 29.6 years.	TBI	SKT scores Vs. PR scores	A significant reduction in the slow EEG delta activity was observed in postacute TBI patients after 1 year (P<0.05). Also a reduction of PR scores with respect to baseline (1.51+/- 0.24 vs 1.90 +/- 0.30; P<0.05). With cognitive evaluation baseline PR scores correlated positively with SKT total score (r=0.549; P<0.05).	"According to the results of the present study, it is concluded that EEG slowing seems to decrease during the first 3 years after braing injury regardless of severity. Improvements of cognitive performance in attention, and memory related tasks, which correlated positively with reductions of qEEG slowing. Results of this exploratory study encourage the conduction of controlled clinical trials to evaluate the effects of CERE on functional recovery patients with traumatic brain injury."	Data suggest cerebrolysin "may" improve recovery post TBI as measured by improved cognitive performance and observed increased EEG activity.
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Ronne-Engstrom 2006 (3.0)	EEG/QEEG	Diagnostic	Financial support was provided by The Hjärnfonden foundation, Selander Foundation and the Swedish Society of Medicine. No mention of COI.	N = 70	(45 males, 25 females). Mean age is 47.2 years.	TBI	EEG seizure pattern Vs. Delta pattern	A significant reduction in the slow EEG delta activity was observed in postacute TBI patients after 1 year (P<0.05). Also a reduction of PR scores with respect to baseline (1.51+/- 0.24 vs 1.90 +/- 0.30; P<0.05). With cognitive evaluation baseline PR scores correlated positively with SKT total score (r=0.549; P<0.05). 23 patients developed seizures (33%). Twelve of the patients with focal high-frequency activity developed epileptiform activity of which eight patients had seizures (44%).	"Moderate and severe brain injury carries a high risk of epileptic seizures occurring after a time lag (74 +/- 47 h in this study) after trauma. This supports the theory that the epileptogenesis is tied to the post-traumatic neurochemical changes and offers a time window for intervention. There is an age-related difference in the EEG pattern after TBI, with older patients being more prone to seizures and younger patients more often having paroxysmal delta pattern."	Data suggest TBI carries risk of epileptic activity with a time lag between the traumatic event and presence of seizures.
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Thompson 2005 (3.0)	EEG/QEEG	Diagnostic	Supported by the Hershey Medical Center, and College of Health and Human Development, PSU. No mention of COI.	N = 24	(24 males, 0 females). Mean age is 20.95 years.	TBI	EEG spectrum includes: delta, theta, alpha, alpha2, beta, beta2.	The general EEG finding from this study is that there was an overall decrease of amplitude across spectrum (delta,theta, alpha, alpha2, beta, and beta2) in TMBI subjects, especially during standing postures.	"Overall, the results from this study are at odds with currently accepted conventional wisdom that mild traumatic brain injury (MTBI) is a transient injury with a temporary fluctuation in consciousness that fully resolves over a matter of days. Our results show that the lingering effects of MTBI are detectable in individuals for at least a matter of months post-injury. We have confirmed the potential of EEG in conjunction with postural tasks to identify an underlying functional abnormality in concussed	Data suggests there are lingering effects from mild TBI.
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									individuals who were cleared for sport participation based upon standard clinical symptoms resolution."	
Jiang 2011 (2.5)	EEG/QEEG	Diagnostic	Supported by National Science Foundation of China (approval number: 30973087). No COI.	N = 118	(67 males, 51 females). Mean age is 36.15 years.	TBI	APOE polymorphism Vs. EEG	No significant difference was found between APOEε4 carriers and non-carriers among the normal control group in terms of age, sex, smoking and alcohol drinking. In the normal control group, both APOEε4 carriers and non-carriers had normal EEG, and no significant difference of QEEG data was found between APOEε4 carriers and non-carriers. In the TBI group, APOEε4 carriers had more focal or global irregular slow wave activities than APOEε4 non-carriers.	"To conclude, although many studies have demonstrated the influence and prediction potential of APOE genotype on EEG parameters in AD patients, the influence of APOE genotype on EEG at the early stage of TBI has not been reported yet. Our present work is the first study of investigating the relationship between EEG alterations and APOE gene at the early stage of TBI. Our study revealed that, APOE polymorphism	Data suggest TBI may induce different abnormalities of the EEG among different APOE genotypes especially APOEε4 early in TBI individuals.

									did not cause different changes of QEEG among normal subjects; however, TBI can induce different alterations of QEEG among different APOE carriers, and especially the APOE4 increased the EEG abnormalities at the early stage of TBI."	
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### Evidence for the Use of Neurocognitive Testing

Author Year (Score)	Category:	Study type:	Conflict of Interest	Sample size:	Age/Sex:	Diagnosis:	Comparison:	Results:	Conclusion:	Comments
Cole 2013 (3.5)	Computerized neurocognitive assessment	Diagnostic-Computerized neurocognitive assessment (NCAT)	This research was supported by the Defense and Veterans Brain Injury Center and conducted with the oversight and support of the Henry M. Jacson Foundation and Womack Army	N=419 military population	Mean age: 29 years (from time1) 34 from time 1 and 2. 191 men, 10 women. 177	Concussions	ANAM4 (Automated Neuropsychological Assessment Metrics, n=50) Vs CNS-Vital Signs (n=39) Vs.	The data from the current study reveal a wide range of test-retest reliabilities within and across NCATs, with coefficients ranging from	"[A] highly reliable test is clinically useless if it is not also valid. In addition to establishing either adequate test-retest	Data suggest that the reliability of these 4 computerized assessment tools are consistent with previously

			Medical Center. No COI.		men, 41 women for time1 and 2.		CogState (n=53) Vs. ImpACT (n=44)	the low range (0.22) to the high range (0.83) Overall, test– retest reliabilities reported in the literature and the current study suggest that computerized NCATs are less reliable than suggested for clinical use. If treatment algorithms required ServiceMemb ersto return to baseline levels of performance, there is increased risk for false positives or false negatives. Specifically, some individuals could be returned to	reliability or methods of assessing stability that account for testing error, NCATs need to be evaluated for the degree they measure the cognitive domain claimed to measure or adequately identify individuals at risk for mTBI-related problems. Thus, validity studies comparing NCATs to traditional neuropsych logical assessments with healthy controls and acutely injured participants are needed.”	reported literature, they are not optimal for clinical decision making.
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								duty prior to full recovery, and conversely, some fully recovered individuals may be unnecessarily held out of duty. Clinicians using these tests should carefully consider the impact of lower-than-desired test-retest reliability.		
Lau 2011 (3.5)	Neurocognitive Testing	Diagnostic	One or more of the authors has declared the following potential conflict of interest or source of funding: M.W.C. and M.R.L. are cofounders and part owners of ImPACT Applications, the company that distributes the	N = 108	(108 males, 0 females) Mean age is 16.01 years.	Concussion	Protracted Recovery (N=50)  Short-Recovery (N = 58)	A combination of 4 symptom clusters and 4 neurocognitive composite scores had the highest sensitivity (65.22%), specificity (80.36%), positive predictive value (73.17%), and	The use of computerized neurocognitive testing in conjunction with symptom clusters results improves sensitivity, specificity, positive predictive value, and	Data suggest there is improvement in sensitivity, specificity, PPV and NPV for predictive purposes when computerized tests are used in conjunction

			ImPACT program. B.C.L. is not a shareholder or employee of ImPACT Applications and has no financial interests in the company.					negative predictive value (73.80%) in predicting protracted recovery.	negative predictive value of predicting protracted recovery compared with each used alone. Net increase in sensitivity of 24.41%.	with symptom clusters.
Barr 2001 (2.5)	Neurocognitive testing: The Standardized Assessment of Concussion (SAC)	Diagnostic	No mention of sponsorship or COI.	N= 1313 male athletes	The mean age of the 68 controls was 18.1 years Mean age of the injured athletes was 17.2 years	Concussions resulting sports injuries	Test- retest controls (N=68) Vs. Athletes with concussion (N=50)	The results of this study demonstrate that the Standardized Assessment of Concussion (SAC) is a reliable and valid measure for evaluating the early neurocognitive effects of sports-related head injury. High school and college athletes tested within minutes of sustaining a concussion exhibited	"[I]n summary, neuropsychology is likely to have a continuing impact on the development of methods for assessing Sports-related head injury. Future research will need to address the empirical basis of return to play criteria. Attention	Data suggest SAC appears to be a reasonable tool for evaluating the immediate effects of mild TBI (sensitivity= 94%, specificity= 76%)

								<p>an average decrease of 4 points on a 30-point scale, while controls showed an average increase of less than 1 point when retested with the SAC. The decrease in test scores by injured participants indicates the presence of measurable Neurocognitive impairment immediately following MTBI. These differences were not the result of age effects or differences in the interval between baseline and repeat testing.</p>	<p>will also need to focus on the use of multiple baselines to prevent practice effects following injury, the role that learning disability and prior concussions may have on the recovery of function, and the nature of practice effects resulting from repeated test administration during recovery (Collins et al., 1999; Hinton-Bayre et al., 1999). Future studies using</p>	
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									<p>athletes with orthopedic injuries as controls is also recommended to examine the more general effects of injury on neuropsychological status (Satz et al., 1999). Maintaining the scientist-practitioner model of neuropsychology will help us to extend findings obtained from the study of sports injury to the larger arena of clinical and forensic assessment</p>	
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									of MTBI in the general population.”	
Register-Mihalik 2012 (2.5)	ImPACT	Diagnostic	No mention of sponsorship or COI.	N = 40	(20 males, 20 females) . Mean age is 18 years.	Concussion	N = 20 College Athletes N = 20 High school athletes.	Collegiate student-athletes performed better than high school student-athletes on ImPACT processing speed composite score.	Processing speed may need to be reassessed as an athlete ages to ensure the most accurate representation of proper cognitive function due to continued brain development, among other factors.	Data suggest SAC appears to be a reasonable tool for evaluating the immediate effects of mild TBI (sensitivity= 94%, specificity= 76%)

### Evidence for the Use of Neuropsychological Assessment

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Lange 2012 (3.5)	Neuropsychological Assessment	Case control Study	Sponsored by several test publishing companies. No mention of COI.	158 patients with TBI	Mean age of 27.9 years old. 11 Females, 147 Males	TBI	Mild TBI-Pass (N = 87)  Vs  Mild TBI-Fail (N = 42)  Vs	MTBI-Fail group were significantly worse on Omissions T and Hit Reaction Time compared to the other groups. When comparing MTBI-Fail and MTBI-Pass, the indices EI-RAW-100	“[T]he CPT-II can only be used as a test to rule in poor effort, but not as a test to rule out poor effort.”	Data suggest CPT-II measures may be useful in the detection of suspected

							Severe TBI-Pass (N = 29)  All participant took the Conners' Continuous Performance Test (CPT-II)	(sensitivity = .29, specificity = 1.0, PPP = 1.0, NPP = 0.72). When comparing MTBI-Fail and STBI-Pass,, the highest classification values were EI-RAW-100 (Sensitivity = 0.45, specificity = 1.0, PPP = 1.0, NPP = 0.77)		individuals having poor effort.
Baker 2015 (3.0)	Neuropsychological Assessment	Case-Control Study	Sponsored by La Trobe University Physical Activity and Rehabilitation Group and La Trobe University Post Graduate Research Scholarship. No mention of COI.	120 patients with mTBI or trauma to one or more bones.	Mean age of 38.85 years old. 30 Females, 90 Males	TBI	mTBI Group  Vs  Orthopaedic group  All patients participated in multiple test and examinations.	There was no significant difference on the Mini Mental State Examination (P = 0.83), road law road craft test (P=0.26), HPT-RT and HPT-HR (P=0.12 and P = 0.10) between mTBI and orthopaedic group. There was a significant difference in on the simple spatial reaction time (P=0.04).	"This research supports existing guidelines which suggest that patients with a mTBI should not drive for 24h; however, further research required to map factors which facilitate timely return to driving."	Quasi experimental diagnostic test. Data suggest mild TBI patients should not drive at least 24 hours post-surgery.
Spadoni 2015 (2.5)	Neuropsychological Assessment	Case-Control	No mention of sponsorship or COI.	45 Operation Iraqi Freedom and Operation Enduring Freedom Veteran volunteers	Mean age of 30 years old. 0 Females, 45 Males	mTBI	Poor TOMM Score (N = 10)  Vs  Good TOMM Score (N = 35)	There was no significance in the prevalence of PTSD, STAI or BDI-II and the Neuropsychological measures between the two groups. There was a significant difference between the severity of PTSD (P<0.05). A voxel-based multiple	"These findings have important implications for the disentanglement of feigned versus actual memory impairment, where the latter may be secondary to neural mechanisms not	Data suggest in individuals with mTBI from combat trauma decreased TOMM performance may be related to

							TOMM is the Test of Memory Malingering	regression with Group predicting FDG uptake revealed that only the right anterior cortex produced a significant cluster of greater uptake in the Good TOMM group than the Poor TOMM Group.	consistent with forgetting or deception.”	ventromedial prefrontal cortical dysfunction .
Cullen 2014 (2.0)	Neuropsychological Assessment	Retrospective Study	Sponsored by the Canada Foundation for Innovation and the Province of Ontario. No COI.	60 participants with TBI	Mean age of 48.74 years old. 8 Females, 30 Males	TBI	Drivers (N = 19)  Vs  Non-Drivers (N=19)  Both groups were tested with Trail-making A and B, Digital Span forward, and digital span backward.	Those who were returning to driving had a significantly better score in Trial-making A and Trial making B (P < 0.01, P <0.01) than those who were not.	“The results suggest that neuropsychological measures of processing speed and cognitive flexibility may predict return to driving after TBI.”	Time of administration of questionnaire different between drivers and non-drivers. So results are inconclusive.

### Evidence for the Use of Automated Neuropsychological Assessment Metrics [1]

Author Year (Score)	Category:	Study type:	Conflict of Interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Kabat M 2001 (3.5)	ANAM	Retrospective Study	No mention of sponsorship or COI.	N=191 Outpatients	Aged 22-77 with mean age of 41 years. 170 males and 21 females.	Outpatients with suspected neurocognitive dysfunction.	Backward Digit span (N=132) vs WAIS-R Arithmetic (N=132) vs Trail Making Part B (N=139) vs WAIS-R Digit Symbol (N=137)	PCA showed accuracy in scores were sensitive to different cognitive demands while time-based showed consistency in speed and efficiency.	"The present study represents the first step in understanding the factor structure of a group of ANAM measures. The results of such a study will be particularly useful in clinical settings to assist in battery selection and to assess the efficacy of a brief, cost-effective, repeated measures battery for screening, monitoring, and triage."	Data suggest use of ANAM may assess neurocognitive function.

Bleiberg 2000 (3.5)	ANAM	Retrospective Study	No mention of sponsorship or COI.	N=122, high school and college aged 15-27 years old, 78 males and 44 females	Aged 15-27 years old, with mean age of 28.78	Mild brain injury	Trials B with test N=119 vs Trigrams total Score (N=118) vs PASA T total (N=118) vs HVTL 3 trial total (N=119) vs STROOP Color-Word (N=119).	Scores from the ANAM mathematical processing (MTH) and the Sternberg memory [396] tests showed the highest correlations with traditional neuropsychological measures.	"In the present sample of healthy older adolescents and young adults, ANAM subtests and traditional neuropsychological measures appear to be assessing similar underlying constructs in the areas of cognitive efficiency, working memory, and resistance to interference."	Data suggest computerized traditional tests correlate to ANAM.
Segalowitz 2007 (3.5)	ANAM	Retrospective Study	Sponsored by a grant Ontario Ministry of Health Promotion (to BW and SJS) and from the Natural Sciences and Engineering Research Council of Canada (to	N= 29, 15 girls, 14 boys	Aged 15-16.8 years with mean of 15.4 years.	Concussion Study with patients with no concussion history.	The following tests were compared to each other using the same population; CDD vs CDS vs MSP vs MTH vs CPT vs SRT. N= 29	"While our data reflect retest reliability specifically on the ANAM, our results address more general issues in the clinical neuropsychology of concussion. Depending on their psychometric properties neuropsychological test scores can	"While neuropsychological testing has been useful for research purposes it has not been useful for differentiating those with persistent symptoms (post-concussion syndrome)	Data suggest ANAM aggregate score is useful for cognitive measures involving memory and processing.

			SJS). No COI.					be useful only for screening, only for group studies, or for clinical assessment of individuals."	from those who are fully recovered."	
Levinson DM 1997 (3.0)	ANAM	Retrospective Study	No mention of sponsorship or COI.	N= 24, 18-64 years old, three groups: 8 in marginally mild (GP1), 7 in mild moderate (GP2), and 7 in moderate injuries (GP3). Group 1 6 females: 2 males, Group 2 3 females: 4 males, Group 1 2 females: 5 males.	18-64 years old with mean of 38 years.	Traumatic brain injury	(N = 8) Group 1 vs. (N= 7) Group 2 vs. (N= 7) Group 3.	GPI showed a significant impairment on only one task, Sternberg Memory search; GPIs 2 and 3 showed significant impairments on 3 tasks, Sternberg Memory Search (ST 2 and ST4), Running Memory and 4 tasks Sternberg Memory Search (ST2 and ST4), Mathematic Processing, Running Memory.	"The results of the analyses of efficiency of performance indicate that it possesses much utility both as a measure of assessing severity of trauma to the brain and as a method of tracking progress of recovery from TBI."	Data suggest the ANAM composite dependent variable "may" be an indicator of general brain function.

Armstrong 2013 (2.5)	ANAM	Prospective observational study	Funded by Telemedicine and Advanced Technology Research Center (TATRC). No COI.	N = 49 Active duty military personnel 46 males, 3 females	Aged 18-64 with mean age of 28.78	Head injury with loss of consciousness greater than 15 min.	VRST (N = 49) vs. ANAM (N= 49) vs. D-KEFS (N= 49). All patients subject to same tests from the initial population.	Participants who were older responded more slowly on computerized tests of word reading and color naming.	"Valid virtual reality cognitive assessments open new lines of inquiry into the impact of environmental stimuli on performance and offer promise for the future of neuropsychological assessments used with military personnel."	Data suggests VRST may be of use in neurological treatment.
Coldren 2012 (2.5)	ANAM	Case Control Study	Sponsored by U.S. Army Medical Research Acquisition Activity, Fort Detrick, Maryland W81XWH-09-2-0057. No COI.	N = 155, deployed soldiers from Iraq between January to April 2009, neurocognitive functioning of U.S. Army Soldiers presenting for medical care within 72 hours of a concussion , using an ANAM device and comparing to controls.	Ages 18 to 55, 137 males to 18 females. No average given.	Mild traumatic brain injury known as concussions	(N =47 concussed) , but only 26 were used for ANAM testing vs. (N= 108 non-concussed ) but only 34 were used for ANAM testing	CDS median scores were lower in concussed participants than in controls at both baseline and follow-up.	The current study adds to the body of literature indicating that neurocognitive testing, and in particular the ANAM, does not have a role as a screening instrument for detection of concussion by approximately 10 days post injury.	Data suggests ANAM lacks diagnostic ability 10 days post injury.

Warden DL 2013 (2.5)	ANAM	Retrospective Study	Sponsored by the Defense and Veterans Head Injury Program and the Uniformed Services University of the Health Sciences. No COI.	N=483 cadets from the United States Military Academy	Mean age of cadets 18.95 years with all male population	Sports concussion	(N = 254) SRT vs. (N= 110) CPT vs. (N= 28) MTH vs. (N= 34) MSP vs. (N= 70) STN vs. (N= 47) CDD.	There were no significant differences on MTH, MSP, STN, and CDD. "The central finding in this study is that no cadet had returned to his baseline SRT on the day he returned to contact sports, despite being in a careful and systematic concussion surveillance and care system."	"Computerized neuropsychological tests such as ANAM, when combined with the computer classrooms available at many schools, make it possible to do baseline testing of large numbers of athletes rapidly and inexpensively."	Data suggest reaction time post sports concussion is prolonged at 4 days.
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### Evidence for the Use of Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT)

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Lau 2011 (3.5)	ImPACT	Diagnostic	One or more of the authors has declared the following potential conflict of interest or source of funding: M.W.C. and M.R.L. are	N = 108	(108 males, 0 females). Mean age is 16.01 years.	Concussion	Post-Concussion Symptom Scale Vs. 4 symptom cluster Vs. 4 neurocognitive scores Vs.	Symptom Scale had a sensitivity of 40.81%; specificity 79.31%. Combined had a sensitivity of 65.22%; specificity 80.36%; classified 73.53%. Post-Concussion Neurocognitive composite scores had a sensitivity of 53.20%;	"The use of computerized neurocognitive testing in conjunction with symptom clusters results improves sensitivity, specificity, positive predictive	Data suggest that reliability of these 4 computerized assessment tools are consistent with previously reported literature, and they are

			cofounders and part owners of ImPACT Applications, the company that distributes the ImPACT program. B.C.L. is not a shareholder or employee of ImPACT Applications and has no financial interests in the company.				Combined neurocognitive and symptom cluster.	specificity, 75.44%; classified 65.38%. Symptom cluster had a sensitivity of 46.94%; specificity, 77.20%; classified 63.21%.	value, and negative predictive value of predicting protracted recovery compared with each used alone. Net increase in sensitivity of 24.41%.”	not optimal for clinical decision making.
Register-Mihalik 2012 (2.5)	ImPACT	Diagnostic	No mention of sponsorship or COI.	N = 40	(20 males, 20 females). Mean age is 18 years.	Concussion	Main outcome measures include: Hopkins Verbal Learning Test, Brief Visual-Spatial Memory Test, Trail Making Test B, Symbol digit Modalities Test, Stroop Test, and ImPACT.	There were no significant interaction effects noted from computerized or paper-and-pencil batteries. No statistical differences observed for the effect of age. ImPACT processing speed score (F = 5.03, P = .031). TMT-B (F = 73.43%, P<.001). Stroop Test (F = 96.85, p < .001 ImPACT (F = 5.81, P = .005). SDMT, Stroop Test, and ImPACT had highest reliability values.	“An athlete's neurocognitive performance may vary across sessions. It is important for clinicians to know the reliability and precision of these tests in order to properly interpret test scores.”	Data suggest SAC appears to be a reasonable tool for evaluating the immediate effects of mild TBI (sensitivity=94%, specificity=76%)

## Evidence for the Use of Memory Tests

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Baird 2005 (3.5)	Memory Test	Pilot study	No mention of sponsorship or COI.	N = 37 with post-traumatic amnesia (PTA).	Mean age 39 (15) years; 27 males and 10 females.	PTA	Severe global memory impairment (N = 20) vs Mild memory impairment (N = 7) vs Severe selective memory impairment (N = 6) vs Mild selective memory impairment (N = 4).  Recognition Memory Test (RMT), Glasgow Coma Scale (GCS).	Difference between memory groups in clinical variables such as age ( $p = 0.08$ ) or sex distribution ( $p = 0.93$ ). No significant difference between memory groups in injury severity as measured by GCS score, ( $p = 0.26$ ). Those with a global memory impairment (Groups 1 and 2) were more cognitively impaired vs those with selective memory impairment.	"These findings suggest that reliance on memory performance as a measure of PTA is not ideal and highlight the need for further research of this issue."	Pilot study. Data suggest memory performance does not necessarily measure PTA.
Livengood 2010 (3.5)	Memory Test	Diagnostic	Sponsored by grant #R01 NS47690 from NINDS. No COI.	N = 46 with moderate to severe TBI.	Aged 15 to 53 years; 26 males and 20 females.	Moderate to severe TBI	TBI individuals (N = 23) vs Matched controls (N = 23).  the Everyday Memory Questionnaire (EMQ), Rey Auditory	EMQ total score for either the group with TBI (self-ratings: $r = -0.26$ ; KI ratings: $r = -0.08$ ) and the control participants (self-ratings: $r = 0.23$ ).  EMQ total score for individuals with TBI (M = 6.28, SD = 2.42) endorsed a greater number of everyday memory vs controls (M = 5.09, SD =	"These findings suggest intact memory self-awareness following moderate-to-severe TBI during the early stages of recovery (2–10 months post-injury)."	Small sample and all participants were compensate rushing malingering. Data suggest at 2- 10 months post moderate to severe TBI, memory self-

							Verbal Learning Test (RAVLT), and the 7/24 Spatial Recall Test	1.83), $t(44) = 1.88$ , $p < 0.05$ , $d = 0.57$ .		awareness is present.
Schretlen D 1991 (3.0)	Rey 15-item Memory test	Diagnostic	No mention of COI or sponsorship.	N= 304	200 males, 102females  Mean age: 35.8 years	Malingered Amnesia, dementia, severe mental illness, or another neuropsychiatric disorder		Performance was found to correlate highly with IQ ( $r = .55$ , $n=193$ , $p<.001$ ) and Mini-Mental State Examination scores ( $r = .81$ , $n = 97$ , $p < .001$ ). Fewer than 15% of subjects faking mental disorders were identified by this procedure, and 27% of patients scored in the "malingering" range.	"The results of this study suggest that patients with mild brain injuries, especially in persons whose premorbid IQ was at least borderline, on the other hand, are not likely to impair performance on Rey's 15-Item Memory Test. Although the results of this study do not support the uncritical application of any given cutoff score for Rey's 15-Item Memory Test, the test can provide useful data concerning the probability of malingering in some cases."	Data suggest the detection of malingering amnesia is highly correlated with IQ and the MMPI.

### Evidence for the Use of Burr Holes, External Ventricular Drains, and Ventriculostomy

<i>Author Year (Score)</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Griesdale 2010 (3.5)	Ventriculostomy	Retrospective Cohort, Vancouver, BC	Sponsored by the National Institutes of Health and Merck. Dr. Kurth is a consultant to i3 Drug Safety and World Health Information Science Consultations, LLC. No mention of COI.	N = 171 with severe TBI. Methods suggest may have been consecutive ICU admit cases. Excluded those obeying commands w/ 12hr, and those died w/i 12 hrs of ICU admit.	Mean age for EVD inserted and no EVD group: 35 (15.4) and 42 (18.0) years, 132 male and 39 female.	Compared Glasgow Coma Score of > vs. < 6. All treated with HOB elevated >30deg; neck in neutral; MAP≥70mmHg, norepi IV if needed, PaO2≥70mmHg, acetaminophen 650Q4hr, cooling blankets and core<38degC. Treated with EVD to try to keep ICP<20mmHg.	28-day	Among those with EVD, Median ICU stay of 14 vs. 6days, p<0.001; Mortality in hospital of 28.6% vs. 1.3%, p<0.001 and 28-day mortality of 22.4 vs. 12.3%, p=0.07. EVD associated with in-hospital mortality (OR=2.8, 95% CI 1.1-7.1) and 28-day mortality (OR=2.1, 95% CI 0.8-5.6).	“The association of EVD with 28-day mortality was only apparent among patients with GCS score of ≥6.” “EVD use was associated with increased mortality; however, this was driven entirely by those patients with a best GCS ≥ 6.”	Data suggest use of an EVD was associated with increased mortality.

### Evidence for the Use of Vocational Rehabilitation Programs

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Schmidt 1995 (2.0)	Vocational Rehabilitation Programs	RCT	Sponsored by the General Disablement Benefits Fund, Disablement Insurance Fund, and the Fund of Applied Social Research of the University of Amsterdam. No COI.	N = 395 patients receiving multidisciplinary treatment.	Mean age of 40 yrs, 231 males, 164 females	VR Participation (N = 197) Vs No VR Participation (N = 198) AND Working (N=87) Vs Not working (N=308) AND Paid work after rehab (N=154) Vs No paid work (N=241)	No follow up mentioned	Participating in VR depends on age, gender, work experience, and disorder (P<0.05). Working on trial is more common for men who participated in VR and suffering for brain injury (P<0.05).	“The findings suggest that rehabilitation programs that aim specifically at promoting employment for people with disabilities are effective, in particular when they take place in both a laboratory and a natural setting.”	Only 20% of population studied had brain injury. Sparse data on compliance and dropout.

### Evidence for the Use of Rest

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Moser 2012 (3.5)	TBI	RCT	No mention of sponsorship or COI.	N = 49 who sustained a concussion.	Aged 14 – 13 years, 33 males and 16 females.	Group one, 1-7 days between sustaining a concussion and onset of rest (N = 14) vs	At least 1 week	28 differed vs 21 who did not receive additional rest on pre-test measure on: verbal memory / processing speed /	“[A] period of cognitive and physical rest may be a useful	Data suggest periods of cognitive and physical rest may be helpful for treating

						Group 2, 3-30 days between concussion and onset of rest vs (N = 22) Group 3, 31+ days between concussion and onset of rest (N = 13).		reaction time / visual memory / total symptoms scored: F (1,47) = 7.69; p = 0.008 / F (1,47) = 15.94; p = 0.001 / F (1,47) = 20.02; p = 0.002 / p = 0.11 / and p 0.016. At 1 week, of the 28 who received additional rest time differed only on processing speed, F (1, 47) = 9.44, p (0.004).	means of treating concussion-related symptoms, whether applied soon after a concussion or weeks to months later."	sports concussion regardless of timing.
de Kruijk 2002 (3.0)	TBI	RCT	No mention of sponsorship or COI.	N = 107 with mild traumatic brain injury (mTBI).	Aged 15-72 and 17 – 76 years for Full group, 60 males and 47 females.	Full, 6 days of full bed rest (N = 53) vs No, no bed rest group (N = 54).	6 months	Those in Full group rested on average of 57 hours during the first 10 days after the trauma, reporting more difficulty to comply with advice vs those in No rest group, and using more oral analgesics vs No group (p = 0.47).  After 6 months, those in Full group reported higher VAS score on 12 of 16 PTC (post-traumatic complaints) after adjusting for baseline differences.	"As a means of speeding up recovery of patients with PTC after MTBI, bed rest is no more effective than no bed rest at all."	High dropout rate. Data suggest lack of efficacy for bed rest after mild TBI.

### Evidence for the Use of Body Weight Support Treadmill Training

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Wilson 2006 (3.5)	Body Weight Support Treadmill Training	RCT	No COI. Partially supported by grant from National Institute on Disability and Rehabilitation Research, United States Department of Education, under the Office of Special Education and Rehabilitation Services.	N = 38 with TBI and significant gait abnormalities	Mean age for PWB group 32.8 ± 14.3 (1 female, 18 male). Mean age for control group 26.4 ± 8.7 (2 female, 17 male)	Standard physical therapy (control), twice daily for <1 hour, for 8 weeks (n=19)  Vs.  Physical therapy with partial weight-bearing gait training, twice daily for <1 hour, for 8 weeks (n=19)	8 weeks of intervention, immediate post-treatment	Improvements in functional ambulation, standing balance, Rivermead Mobility Index, and FIM scores were detected in both groups via Wilcoxon's signed-ranks tests (p=0.05). There were no significant between-group differences detected.	"Results did not support the hypothesis that 8 wks of partial weight-bearing gait retraining improves functional ambulation to a greater extent than traditional physical therapy in individuals after traumatic brain injury based on common clinical measures."	An open label randomized study. Age difference. Data suggest similar efficacy between groups.

### Evidence for the Use of Cognitive Behavioral Therapies

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Pastore 2010 (2.5)	Cognitive Behavioral Therapy	RCT	NO COI. No mention of Sponsorship.	Patients aged 4-18 years with TBI (N=40)	Clinical group mean age at assessment 10.9  Control group mean age at assessment 8.94  Gender (M:F) 31:9	Clinical Group (N=28) received intervention focused on the modification of problem behaviors according to the ABC model.  Control group did not receive any interventions.	12 months	The clinical group had Significant differences from baseline to follow compared to the control group in the following Child Behavior Checklist scales: Withdrawn (-10.68 vs -4.58, (p=0.046)); Somatic complaints (-9.28 vs -0.83 (p=0.033)); Anxiety/Depression (-10.71 vs -2.25 (p=0.006)); Social Problems (-8.78 vs -4.17 (p=0.015)); Internalising (-10.18 vs -2.50 (p=0.032)); Total Problems (-8.53 vs -1.75 (p=0.023))	"Our results suggest that CBT is an effective intervention for young patients with psychological problems after TBI."	Data suggest CBT may provide benefit for improving psychological symptoms post TBI.

### Evidence for the Use of Biofeedback

<i>Author Year Score</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Wong 1997 (3.5 )	Biofeedback	RCT	No mention of sponsorship or COI.	N = 60 with unilateral hemiparesis or hemiplegia from first acute stroke (CVA) or traumatic brain injury (TBI) were recruited for this study.	Mean age was 51.3 years, 43 males and 17 females.	Group A trained by the new biofeedback trainer (N = 30) vs. Group B trained by the conventional standing table 60 min per session (N = 30)	Follow-up time of 3 to 4 weeks.	After 4 weeks postural syndromme in Group A and B was reduced from 17.2±10.8 percent and 17±10.00 percent to 3.5±2.2 and 10.1±6.4 percent. Learning effect after first day of training in group A (p = 0.013) was better compared to Group B (p = 0.166).	"There are no significant differences between in these two kinds of evaluation modalities (p > 0.05)."	Data suggest biofeedback device was of some benefit in stance symmetry in hemiplegic patients.

### Evidence for the Use of Botulinum Toxin

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Mayer 2008 (3.5)	Botox injection techniques	RCT	Sponsored in part by the National Institute on Disability and Rehabilitation Research and an education grant from Allergan Inc. No COI.	N=31 with acquired brain injury (21 Traumatic Brain Injury (TBI) 8 with stroke and 2 with hypoxic encephalopathy);	Mean Age: Group 1 34.7 ± 21.9; Group 2 37.9 ± 19.9, with 17 males and 1 female.	Group 1 (N=18) Botulinum Toxin-A (BTX-A) injections that were given via motor point injection technique Vs. Group 1 (N=18) BTX-A injection via an distributed injection technique. Both injection techniques were on the Brachioradialis, Brachialis, and Biceps Brachii Muscle.	Follow up a baseline and 3 weeks.	Three clinicophysiological variables studies: Tardieu catch angle [1196], Asworth Scale, and root mean square test (RMS) of electromyographic activity (EMG). Group 1 vs Group 2 at 3 weeks gave no statistical significance for any variables studied. Group 1 TCA, baseline vs 3 weeks 102.9 ± 11.9 vs 76.8 ± 21.1 (p<0.001). RMS EMG (Biceps) 0.119 ± 0.106 vs 0.050 ± 0.043 (p=0.007), (Brachioradialis) 0.132 ± 0.077 vs 0.048 ± 0.028 (p<0.001). Ashworth score baseline vs 3 weeks, 3 (3) VS 2 (0-2) (p<0.001). Group 2 TCA, baseline vs 3 weeks 105.1 ± 9.6 vs 74.4 ± 28.7 (p<0.001). RMS EMG (Biceps) 0.158 ± 0.136 vs 0.051 ± 0.041 (p=0.004), (Brachialis) 0.091 ± 0.068 vs 0.056 ± 0.058 (p=0.02), (Brachioradialis) 0.197 ± 0.166 vs 0.059 ± 0.048 (p=0.002). Ashworth score baseline vs 3 weeks, 3 (3) VS 2 (0-3) (p<0.001).	“The impacts of 2 different injection techniques on elbow flexor hypertonia were compared, using low-dose (60U in the biceps, 30U in the brachioradialis), high-volume (2.4mL in the biceps, 1.2mL in the brachioradialis) injections of BTX-A. Single motor point and multisite distributed injections were found to have similar impact at these doses and volumes. Findings suggest that low-dose, high-volume strategies may have a potential role in reducing drug cost and helping clinicians stay within accepted limits for total body dose in patients with UMNS requiring many injections.”	Sparse methodological details. Mentions no COI however Allergan is a pharmaceutical company that produces botulinum.

## Evidence for the Use of Transcranial Magnetic Stimulation (TMS)

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Leung, 2015 (3.5)	Transcranial Magnetic Stimulation	RCT	No COI. Sponsored by VA Rehabilitation and Research Development Award.	N=24	Mean age of Group 1: 41.2±14 years. Mean age of Group 2: 41.4±11.6 years. 21 males, 3 females.	Group 1: real treatment group received 3 neuronavigated rTMS with intertreatment interval at least 24 hrs no more than 72 hrs. (n=12) Vs. Group 2: sham treatment group could visualize and hear the sound of the coil 180 degrees away from scalp (n=12)	1 week and 4 week headache and neuropsychological assessments conducted.	The real treatment group resulted in significantly higher percentage of persistent headache intensity reduction than the sham group (p=.0041; F=4.73; df=1; 56.3% vs. 15.4% respectively). Overall composite score of functionally debilitating headache exacerbation is significantly reduced in real group at posttreatment 4 week assessment comparing to the sham group (p=.017).	“The current study demonstrates that three sessions of rTMS given within a week at least 24 hours apart at the LMC can reduce MTBI-HA symptoms up to one month without any significant persistent neuropsychological side effects. This rTMS protocol provides a feasible noninvasive means of therapy for managing MTBI-HA. Future studies correlated with structural and functional neuroimaging studies, and posttreatment motor cortex excitability assessment may further reveal the physiological bases of the treatment effect.”	Small sample size high dropout rate. Minimal differences between treatments for most outcomes.

### Evidence for the Use of Transcranial Direct Current Stimulation

<i>Author Year (Score) :</i>	<i>Catego ry:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Kang 2012 (3.5)	TDCS	RCT Cross-over Double-blind	Sponsored by a grant from the Korean Health Technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea and by Handok and Daewoong Pharmaceuticals Co., Ltd and SK Chemicals Ltd. No mention of COI.	N = 9 with attention deficit after a TBI.	Mean age of 50.4 years;, 8 males and 1 Female.	Transcranial direct current stimulation TDCS, 2 mA for 20 minutes (N = unknown) vs Sham transcranial direct current stimulation or TDCS, 2 mA for 1 min (N = unknown).	3 and 24 hours	The levels of attention, fatigue, task difficulty, or sleep quality had no significant differences between the TDCS and sham group. Reaction time was shorter than baseline after TDCS, ( $p = 0.056$ ) while there was no change in the sham group. The change was not noted 3 or 24 hours after stimulation, ( $p > 0.05$ ).	“Anodal transcranial direct current stimulation applied to the left dorsolateral prefrontal cortex improves attention compared with sham stimulation in patients with traumatic brain injury, which suggests a potential role for this intervention in improving attention during cognitive training after traumatic brain injury.”	Small sample. Crossover design. Data mostly suggest lack of efficacy.

### Evidence for the Use of Hyperbaric Oxygen Therapy (HBO or HBOT)

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Shi 2003 (3.0)	Hyperbaric Oxygen Therapy	RCT	No mention of sponsorship or COI.	N = 320 with post brain injury neural status.	Mean age of 38.5 years; 215 males and 105 females.	Medication and hyperbaric oxygen or HBO, 0.1 Mpa of pressure, inspired oxygen of 96% for 90 minutes daily for 10 days, during therapy patients received 20 ml cerebrolysin mixed with 250 ml glucose (10%) given intravenously daily for 7-10 days (N = 195) vs Medication only, non-HBO, same treatment except HBO for 2-4 courses (N = 125).	6-18 months	Total success rate of headache, dizziness, and poor memory: HBO 100% v. non-HBO 24.5%, p=0. Total success rate of epilepsy: HBO 82.6% v. non-HBO, not controlled after 30 days, p=0. Total success rate of rCBF as assessed by SPECT: HBO 93.4% v. non-HBO, no patients regained normal rCBF after 30 days of treatment, p=0. Long term outcomes: HBO - 181/195 resumed pretrauma function levels, 14/195 partially disabled; non-HBO - 21/125 resumed pretrauma function levels, 68/125 partially disabled, 36/125 totally disabled, p=0.	"HBO therapy has specific curative effects on patients with postbrain injury neural status, and 99mTc-ECD SPECT could play an important role in diagnosing postbrain injury neural status and monitoring the therapeutic effects of HBO."	Sparse methodological details. Data suggest HBO therapy beneficial to post brain injury patients in symptom improvement compared to medication.
Boussi-Gross 2013 (3.0)	Hyperbaric Oxygen Therapy	RCT Crossover	Sponsored by Assaf-Harofeh Medical Center, Tauber Family Foundation and the Physics Complex System at Tel Aviv University. No COI.	N = 56 with mTBI.	Mean age of 44 years; 24 males 32 and females.	Treated group, evaluated at baseline and following 40 HBOT sessions (N = 45) vs Crossover group evaluated 3 times: at	2-months	Significant improvement was observed after HBOT in the treated group in all cognitive measures (p < 0.005). No significant improvement was noted in the crossover group. The EQ-5D significantly improved after HBOT in the treated and cross	"HBOT can induce neuroplasticity leading to repair of chronically impaired brain functions and improved quality of life in mTBI patients with prolonged PCS at late chronic stage."	A randomized crossover. Significant dropouts.

						baseline, following a 2-month control period of no treatment, and following subsequent 2-months of 40 HBOT sessions (N = 45).		over group ( $p < 0.0001$ for both).		
Artru 1976 (2.5)	Hyperbaric Oxygen Therapy	RCT	No mention of sponsorship or COI.	N = 60 with head injuries and in a coma.	Mean age of 29.8 years. Gender not given.	Oxygen at high pressure or OHP 10 daily sessions followed by no session for 4 days and then another set of 10 daily sessions, until recovery, consciousness or death (N = 31) vs Standard therapy for 14 months and 12-month follow-up (N = 29).	12 months	At 1-month the OHP patients had significantly higher rate of recovered consciousness and lower rate of persistent coma, ( $p < 0.03$ and $0.03$ ). Average survivor duration of coma in the OHP group 28.2 days vs 32.7 in the control.	"At this point, our study does not reveal any difference in the overall mortality rate of OHP-treated and untreated patients."	Data suggest somparable mortality and coma duration in both groups. There was a trend towards restored consciousness at 1 month in OHP group.

## Evidence for the Use of Induced Hypothermia

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Jiang 2006 (3.5)	Induced hypothermia	RCT	Funded by grants from the National Key Basic Research Project, Science and Technology Committee of Shanghai, and the Program for Shanghai Outstanding Medical Academic Leader. No COI.	N = 215 with severe traumatic brain injury.	48 females, 167 males  Mean age for long-term group 22.7 years, mean age for short-term group 32.1 years	Long term hypothermia group used mild hypothermia for $5 \pm 1.3$ days (N = 108)  vs.  Short-term hypothermia group used mild hypothermia for $2 \pm 0.6$ days (N = 107).	The last follow-up was at 6 months.	The ICP significantly rebounded after rewarming in the short term hypothermia group and was significantly higher than that of the long-term mild hypothermia (P < 0.05). Forty-seven cases (43.5%) had a favorable outcome and 61 cases (56.5%) in the long-term mild hypothermia group. Thirty-one (29.0%) had a favorable outcome and 76 (71.0%) had an unfavorable outcome in the short-term mild hypothermia group.	"[Five] days of longterm cooling is more efficacious than 2 days of short-term cooling when mild hypothermia is used to control refractory intracranial hypertension in patients with severe traumatic brain injury."	Data suggest long term cooling for 5 days better than short term cooling for 2 days in severe TBI patients with intracranial hypertension.
Polderman, 2001 (3.5)	Induced hypothermia	RCT	No mention of COI or sponsorship.	N = 41 with severe head injury.	No gender distribution described  Mean age group 1 $36.2 \pm 28.1$ years, group 2 $39.1 \pm 26.2$ years	Group 1 treated using hypothermia with a body temperature of $32^{\circ}\text{C}$ and pentobarbital administration (N = 21)  vs. Group 2 treated	Electrolyte measurements were taken 3 times before and 3 times during cooling in the hypothermia group and 3 times before and after normalization of ICP.	Mg levels decreased in all Group 1 patients from $0.98 \pm 0.15$ to $0.58 \pm 0.13$ mmol/L (P < 0.01). Phosphate levels decreased in all Group 1 patients, from $1.09 \pm 0.19$ to $0.51 \pm 0.18$ mmol/L	"[I]nduction of hypothermia in patients with severe head injury is associated with severe electrolyte depletion, which is at	Poor replication. Data suggest management of electrolytes is important for treating severely injured head patients when hypothermia

						with pentobarbital administration alone (N = 20).		(P < 0.01). Calcium levels decreased in 16 (76%) of 21 patients in Group 1 , from 2.13 ± 0.25 to 1.94 ± 0.14 mmol/L (P < 0.01). Potassium levels decreased in 15 patients, the mean serum levels decreased from 4.2 ± 0.59 to 3.6 ± 0.7 mmol/L during the cooling period (P < 0.01). No variations in electrolyte levels were seen in Group 2.	least partly due to increased urinary excretion through hypothermia-induced polyuria."	is administered.
Polderman 2002 (3.5)	Induced hypothermia	RCT	No mention of COI or sponsorship.	N = 136 with severe head injury and a Glasgow Coma Scale (GCS) ≤ 8.	37 female, 99 male  Mean age hypothermia group 39.2 ± 24.2 years, control group 34.2 ± 29.6 years	Control group patients who responded to the barbiturate coma (N = 72)  vs.  Moderate hypothermia group, with core temperatures of 32-34°C, consisting of patients who did not respond to the barbiturate coma (N = 64).	The last follow-up was at 6 months.	Sodium levels remained normal in both groups. ICP values of 20 or less were achieved within 2 hrs in 39/64 patients, within 3 hrs in 55/64 patients and within 4 hrs in 62/64 patients. ICP levels remained above 20 but below 25 mm Hg in 2/64 patients. Hospital mortality was lower (62.5 vs 72.2%, P < 0.05) and the number of patients with good neurological outcome higher	"[M]ortality was significantly lower and neurological outcome significantly better in patients treated with hypothermia and barbiturate coma compared to barbiturate coma alone. Moreover, the results of our study confirm that artificial	Data suggest therapeutic hypothermia may improve outcomes including survival if used in a protocol which includes management of adverse outcomes.

								(15.6 vs 9.7%, P < 0.02) in the hypothermia group vs. the control group.	cooling is a highly effective method to control high ICP in all categories of patients with severe head injury."	
Qiu 2005 (3.5)	Induced hypothermia	RCT	No mention of COI or sponsorship.	N = 86 with severe traumatic brain injury.	30 female, 56 male  Mean age 40.0 ± 11.2 years	Hypothermia group with core temperatures kept at 33-35°C using at cooling blanket and rewarming began after 3-5 days (N = 43)  vs.  Normothermia group with no hypothermia treatment (N = 43).	The last follow-up was at 2 years after the injury.	EDP values of the patients in the hypothermia group at 24, 48, and 72 hrs after injury were significantly lower vs control (p < 0.05) Highest EDP was observed at 48 hrs after injury in both groups. The mild or no disability rate in the hypothermia group was significantly higher than that in the control group (53.5% vs. 27.9%, P < 0.05) and the mortality in the hypothermia group was much lower than that in the control group (25.6% vs. 51.2%, P < 0.05). For patients with decompression, the mortality rate in the hypothermia group was much	"Mild hypothermia is a safe and effective therapeutic method, which can lower the extradural pressure, increase the serum superoxide dismutase and improve the neurological outcomes without severe complication in the patients with severe traumatic brain injury."	Data suggest mild hypothermia may improve outcomes in TBI patients.

								lower than that in the control group (18.2% vs. 43.8%, $P < 0.05$ , $\chi^2 = 5.32$ and $\chi^2 = 2.75$ , respectively), and for those without an operation, it was 55.5% in the hypothermia group and 72.7% in the control group.		
Qiu 2006 (3.5)	Induced hypothermia	RCT	No mention of COI or sponsorship.	N = 96 with severe brain injury.	32 female, 64 male  Mean age $41.3 \pm 11.7$ years	Selective brain cooling (SBC) group was treated using a cooling cap around the head in which 4°C water was circulating keeping the brain temperature at 33-35°C (N = 24)  vs.  Mild systemic hypothermia (MSH) group was treated using a cooling blanket and kept a rectal temperature between 34.5-36°C (N = 30)  vs.  Control group	The last follow-up was at 1 year after injury.	Thrombocytopenia was present in 18, 23, and 15 patients in SBC, MSH, and control groups respectively ( $\chi^2 = 15.73$ , $P < 0.01$ ). No differences were seen between SBC and MSH groups after hypothermia in thrombocytopenia. Good recovery (GOS score 4-5) in SBC, MSH, and control group were 39% (7/18), 35% (8/23) and 80% (12/15), respectively ( $P < 0.01$ ).	"Therapeutic hypothermia increases the incidence of thrombocytopenia in severe TBI, and patients with thrombocytopenia after therapeutic hypothermia are associated with unfavorable neurological prognosis."	Data suggest hypothermia increases the risk of thrombocytopenia in TBI patients.

						was treated with the same therapies except hypothermia (N = 42).				
Shiozaki 1993 (3.5)	Induced hypothermia	RCT	No mention of COI or sponsorship.	N = 33 with a severe head injury and a persistent intracranial pressure (ICP) greater than 20 mm Hg.	17 female, 16 male  Mean age for control group 35.4 ± 12.6 years, for hypothermia group 35.3 ± 15.3 years	Mild hypothermia group induced by water-circulating blankets above and below the patient for 2 days or until it was considered not to be effective at a temperature of 33.5-34.5°C (N = 16) Vs. Control group (N = 17).	2, 4, 7, and 14 days post admission, 6 months	Twelve out of 17 patients in the control group were classified as neurologically dead because of uncontrollable ICP within 48 hrs in 8 and within 9 days in 4. The other 5, ICP > 20 mm Hg persisted for 4-7 days and then slowly decreased. Compared to the control group, the hypothermia group declined in ICP by a mean of 10.4 mm Hg (P < 0.01), but the Cerebral perfusion pressure (CPP) rose by a mean of 14.0 mm Hg (P < 0.01) in 12/16 patients. The other 4 showed little change in both ICP and CPP.	"[M]ild hypothermia is a safe and effective method to control traumatic intracranial hypertension and to improve mortality and morbidity rates."	Data suggest use of mild hypothermia for refractory ICH post TBI may improve morbidity and mortality.
Zhi 2003 (3.5)	Induced hypothermia	RCT	No mention of COI or sponsorship.	N = 396 with severe head injury.	105 female, 291 male  Mean age for hypothermia group 43 ± 17 years, for	Hypothermic group with rectal temperatures kept at 32-35.0°C and rewarming at a rate of 1°C every 4 hrs	24 hours, day 3, and day 7 post treatment	The mortality rate in the hypothermia group than in the control group and the good recovery rate was higher in the hypothermia	"Mild hypothermia is safe and effective for preventing brain damage in patients	Data suggest mild hypothermia may reduce mortality and improve

					control 42 ± 19 years	(N = 198)  Vs.  Control group (N = 198).		group (P < 0.05). The ICP of patients was lower in the hypothermia group at 3 and 7 days after trauma (P < 0.05). Blood glucose and lactic acid levels were lower in the hypothermia group on days 3 and 7 (P < 0.05). No difference in average blood pressure, heart rate, blood gas, electrolytes, and complications between the groups.	with severe head injury, as well as reducing mortality and improving the prognosis. It is important to monitor PbtO2, BT, CBF, and SjvO2 in hypothermic therapy."	prognostic outcomes.
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### Evidence for the Use of Neuromuscular Electrical Stimulation

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Alon, 1998 (3.5)	Neuromuscular Electrical Stimulation	Allied Health	No mention of sponsorship or COI.	N=20. 13 patients who survived a cerebrovascular accident and 7 with TBI.	The mean age of the patients is 51.65 years. 14 males, 6 females.	No comparison group.	No follow-up.	ANOVA test scores from flexion at rest to flexion immediately after a 10-meter walk for the elbow are $14.3 \pm 3.5$ to $15.5 \pm 0.5$ , respectively. $P < .001$ . For the wrist are $11.5 \pm 3.1$ to $8.6 \pm 0.9$ , respectively, $p < .001$ . Active wrist extension and flexion increased by $12.7 \pm 0.5$ and $9.0 \pm 3.3$ degrees, respectively. $P < 0.01$ .	"Application of the NESS system for three to four hours daily improves selected impairments and may help to restore partial hand functions of patients with chronic stroke or head injury."	Small sample. Data suggest use of NESS improved some functions in TBI and stroke patients as 80% [16385] patients were able to hold a 1 kg weight with an active NESS system vs only 3 patients without active NESS.

### Evidence for the Use of Hyperventilation

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Shiozaki 1993 (3.5)	Hyperventilation	RCT	No mention of COI or sponsorship.	N = 33 with a severe head injury and a persistent intracranial pressure	Mean age for control group $35.4 \pm 12.6$ years, for hypothermia group $35.3 \pm$	Mild hypothermia group induced by water-circulating blankets above and below the patient for 2 days	2, 4, 7, and 14 days post admission, 6 months	Twelve out of 17 patients in the control group were classified as neurologically dead because of uncontrollable ICP	"[M]ild hypothermia is a safe and effective method to control traumatic intracranial	Data suggest use of mild hypothermia for refractory ICH post TBI may improve

				(ICP) greater than 20 mm Hg.	15.3 years, 16 males and 17 females.	or until it was considered not to be effective at a temperature of 33.5-34.5°C (N = 16) vs Control group (N = 17).		within 48 hrs in 8 and within 9 days in 4. The other 5, ICP > 20 mm Hg persisted for 4-7 days and then slowly decreased. Compared to the control group, the hypothermia group declined in ICP by a mean of 10.4 mm Hg (P < 0.01), but the Cerebral perfusion pressure (CPP) rose by a mean of 14.0 mm Hg (P < 0.01) in 12/16 patients. The other 4 showed little change in both ICP and CPP.	hypertension and to improve mortality and morbidity rates."	morbidity and mortality.
Previgliano 2002 (3.5)	Hyperventilation	RCT	No mention of sponsorship or COI.	N = 34 with severe closed head injury.	Mean age in CPP and HV groups: 39 (12) and 39 (22), 30 males and 4 females.	Cerebral Perfusion Pressure or CPP group (N = 16) vs Hyperventilation or HV group (N = 18).	1-year	Statistical differences were found for PCO2 B and A, p < 0.01 and < 0.01, minor in HV group. ICP A, (p < 0.01) minor in HV group, ICP (B-A) minor in HV, (p < 0.01).	"[M]aintaining a CPP above 75 mmHg during FB is enough to make it a safe procedure, since no changes are shown with HV."	Data suggest HV had no impact on preventing the ICP peak during FB.

### Evidence for the Use of Behavioral Programs

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Fong 2010 (3.5)	Behavioral Programs	RCT	No mention of sponsorship COI.	N = 24 persons in the community with acquired brain injury	Mean age of Part I: 43.0±10.7 years. Mean age of Part II: 52.6±6.2 years. 17 males, 7 females.	Two behavioral check lists: Part I: Early virtual reality or VR-ATM program first, followed by real ATM (N = 14) vs Part II;	3 weeks	Part I: Average reaction time for real ATM was 15.5 seconds. Failed attempts with real ATM had an average reaction time of 26.5 seconds. Sensitivity of VR-ATM was 100%	"We found the VR-ATM to be usable as a valid assessment and training tool for relearning the use of ATMs prior to real-life practice in persons with ABI."	Small sample sizes. Data suggest VR-ATM may be used to relieve ATM use.

						<p>Late (Real ATM first, then VR-ATM)  Part II: Six 1 hour sessions over 3 weeks  VR Training (N = 5)  vs  Computer-assisted instruction (N = 5).</p>		<p>for cash, and 83.3% for money transfers.  Part II: Mann-Whitney test indicated no significant differences in cognitive performance between participants in VR-ATM and CAI groups. (p = 0.288-0.911) No statistically significant difference found in the post-test correct percentage scores between VR-ATM and CAI groups. (p = 0.059)</p>	
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### Evidence for the Use of Home and Community-Based Rehabilitation

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Bellon 2014 (3.5)	Home and Community Based Program	RCT Crossover	Sponsored by grants from the National Institute on Disability and Rehabilitation Research, Office of Special Education and Rehabilitative Services, US Department of Education, TBI	N = 69 with a TBI.	Mean age 43.7 (15.8) years, 41 males and 28 females.	Walking intervention HiMAT scale of 13 items (N = 69) vs Controls or nutrition education module identify eating habits they felt they needed to improve (N = 69).	12-weeks	A significant interaction for Time of Assessment and Treatment Order (F (2,134) = 5.274, p = 0.006, partial $\eta^2$ = 0.073), with larger declines during the walking phases of each group. At 24 weeks, significant	“Increased walking may be a successful, affordable and easily accessible treatment option for TBI survivors with symptoms of depression and stress who would rather avoid medications and who may not truly benefit from	Crossover design. Nearly 50% of all study participants dropped out. Results are self reported measures.

			Model Systems grant to Santa Clara Valley Medical Center. No mention of COI.					effect for Assessment Time (F (2,134) = 5.304, p = 0.006, partial n <sup>2</sup> = 0.073), with scores decreasing (less stress).	psychotherapy alone."	
Carnevale 2002 (3.5)	Home and Community Based Program	RCT	Sponsored by the National Institute on Disability and Rehabilitation Research (NIDRR), US Department of Education to the Northern New Jersey Traumatic Brain Injury Model System. No mention of COI.	N = 27 with TBI and their caregivers. Participants had a behavioral impairment related to TBI.	Patients mean age 38.9 (11.5) and caregivers' mean age 47.5 (14.4), 18 males and 9 females.	Group 1: control (N = 10) vs Group 2: education regarding common neurobehavioral sequelae of TBI (N = 8) vs Group 3: education + intervention in practical behavior management techniques (N = 9).	Follow-up at 1, 5, and 14 weeks.	Most ANCOVA subscales, the covariate was statistically significant: QRS scale limits on family opportunities/ QRS scale pessimism/QRS scale personal burden/MBI scale emotional exhaustion/MBI scale depersonalization (DP)/MBI scale personal accomplishment (PA) at 5 and 14 weeks: F (20.660); p < 0.000 and F (10.609); p < 0.004/F (5.733); p < 0.027 and F (5.373); p < 0.032/F (8.355); p < 0.009/F (51.269); p < 0.000 and F (64.383); p < 0.000/F (32.455); p < 0.000 and F	"The results are discussed in terms of the potential modifiability of caregiver burden, the small sample size, and the sensitivity of current measures of caregiver stress and burden to detect clinically meaningful change."	Data suggest comparable in efficacy.

								(31.494); p < 0.000/F (31.872); p < 0.000.		
Cusick 2003 (2.5)	Home and Community Based Program	RCT	No mention of sponsored or COI.	N = 132 with TBI.	Age range 16-65 years, 84 males and 48 females.	<p>Medicaid Waiver group (N = 66) vs Control group, matched recipients (N = 66).</p> <p>Follow-up interview which included: The Craig Handicap Assessment and Reporting Technique or CHART, the Sickness Impact Profiles, Satisfaction with Life Scale, the SF-12 and questions on symptoms and services use.</p>	4-year	<p>Waiver group showed significant outcomes: SF-12 mental health (p = 0.006), SF-12 mental health sub-scale (p = 0.032), alcohol use (p = 0:003) and risk of using alcohol (p &lt; 0.001) vs controls.</p> <p>The waiver group used more of the 4 services: case management / physical therapy / second rehabilitation admission / and group home stay; p = 0.005 / 0.038 / 0.013 / and 0.008.</p> <p>Waiver group Scored significantly lower on the CHART-SF Physical Independence sub-scale (p &lt;</p>	<p>“[T]his research, provides a clear mandate for more, desperately needed research to understand not only Medicaid Waivers, but outcomes for persons with disabilities who may have been disadvantaged in some way prior to injury and certainly are disadvantaged as they enter into their new lives with disabilities.”</p>	A non-randomized telephone survey. Baseline comparability differences due to the waiver recipient group having experienced more case management services, physical therapy, group home services and more second rehab admissions than control group.

								0.05), Cognitive Independence sub-scale (p < 0.001), Mobility sub-scale (p < 0.05), occupational sub-scale (p < 0.01) and the Total CHART-SF score, (p < 0.01)		
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## Evidence for the Use of Residential Rehabilitation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Willer 1998 (3.5)	TBI	Treatment	Supported by the Ontario Ministry of Health and the Ontario Brain Injury Association. No COI.	N = 46	(20 males, 3 females). Mean age is 34.09 years.	Residential Rehabilitation Program N=23 Vs. Control Group (Home or long-term care facility) N=23	Residential Rehabilitation program follow up had a range of three years.	The residential rehabilitation group had a disability score of 23.9 SD(6.019). Control group had a disability score of 20.30 SD(6.098). t=.38. p<.05. Patients who received residential rehabilitative care, showed an increase in functional ability that compared with a home based service.	“Postacute rehabilitation appears to be effective in improving function for individuals with severe brain injury. Residential-based services appear to produce greater functional improvement, whereas home-based services are more effective at maintaining community integration.”	A 1:1 Matched case control study. Data suggest TBI individuals receiving residential based post-acute rehab displayed statistically significant gains in functional abilities compared to the traditional group.
Warden 2000 (3.5)	TBI	Treatment	Funded by the Defense and Veterans Head Injury Program through the Henry M. Jackson Foundation for the Advancement of Military Medicine and the Uniformed Services University of the Health Sciences, and by a grant from the Medical Research Service of the Department	N = 53	(51 males, 2 females). Mean age is 26 years.	Treatment N = 28 Vs. Control N = 35	Patients were followed up over the course of 7 weeks. Home patients were called weekly for updates. Nurses would also ask the treatment patients for updates.	There wasn't any significant statistical relationship between fitness for military duty or and specific elements like mental and physical exercises, medication compliance, shopping, etc. Patients who were compliant with treatment recommendations	“A home-based program, including weekly telephone calls by a trained psychiatric nurse, is a viable treatment option, when combined with multidisciplinary evaluation and medical treatment in this population. A home based rehabilitation program may provide effective care at a lower cost	Data suggest a home based rehab program may provide benefit for moderate to severe TBI patients.

			of Veterans Affairs. No mention of COI.						than inpatient rehabilitation.”	
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### Evidence for the Use of Muscle Tone and Joint Restriction Management, Including Spasticity

<i>Author Year (Score):</i>	<i>Category:</i>	<i>Study type:</i>	<i>Conflict of Interest:</i>	<i>Sample size:</i>	<i>Age/Sex:</i>	<i>Comparison:</i>	<i>Follow-up:</i>	<i>Results:</i>	<i>Conclusion:</i>	<i>Comments:</i>
Mosley 1997 (3.5)	Muscle tone and joint restriction management	RCT	No mention of sponsorship or COI.	N = 9 with sustained traumatic closed head injuries and had limited dorsiflexion motion	Mean age 29.1 (11.0); 8 males and 1 female.	Group one, casted first (N = 4) vs Group two, casted second (N = 5).	Day 1, 7, and 14	Passive ankle dorsiflexion increased by a mean of 13.5 degrees (SD=9.3) during the experimental condition vs a mean decrease of 1.9 degrees (SD=10.2) during the control condition.	“The use of this treatment regimen, therefore, can improve rehabilitation outcomes.”	Small sample crossover study. Data suggest casting plus stretching in TBI patients may increase the ROM in dorsiflexion.
Hill 1994 (3.0)	Muscle tone and joint restriction management	RCT	Sponsored by NIHR Grant and The Rehabilitation Institute of Chicago. No mention of COI.	N = 15 with brain injury.	Aged 9 – 48 years and mean age for groups 1 and 2, 24.9 and 32.1 years; 13 males and 2 females.	Group 1, a month of casting plus 1 month of traditional therapy including passive and active range of motion, neurophysiological treatment techniques (N = 8) vs Group 2, a month of traditional therapy plus casting (N = 7).	1-month	Group 1 showed significantly greater improvement in point of stretch reflex elicitation with casting, (p = 0.001). 11 showed improvements in clinical measures of spasticity with casting.	“These findings suggest that casting is more effective than traditional techniques in reducing contracture and in decreasing hypertonicity in some cases.	Small sample (N=15). Preliminary results suggest casting may be beneficial in reducing contractures and hypertonicity post TBI.

Ring 2009 (3.0)	Muscle tone and joint restriction management	RCT	Sponsored in part by Ness Ltd, Ra'anana, Israel.	N = 15 with prior chronic hemiparesis resulting from stroke or traumatic brain injury.	Mean age: 52.2 ± 6 3.6 years;	After 4-week adaptation period, gait was measured under two conditions [170] while using the neuroprosthesis; and (2) while using the AFO. Patients under each condition: walked on level ground up and down a 50-m hallway.	8-weeks	No significant difference in gait speed, stride time improved from 1.48 6 0.21 seconds with the AFO to 1.41 6 0.16 seconds with the neuroprosthesis, (p = 0.02). Swing time variability decreased from 5.3 ± 1.6% with the AFO to 4.3 ± 1.4% with the neuroprosthesis, (p = 0.01). A gait asymmetry index improved by 15%, from 0.20 ± 0.09 with the AFO to 0.17 ± 0.08 with the neuroprosthesis, (p = 0.05).	"Compared with AFO, the studied neuroprosthesis appears to enhance balance control during walking and, thus, more effectively manage footdrop."	Small sample (N=15). Data suggest the study prosthetic may increase balance during walking perhaps controlling footdrop compared to AFO. Not an RCT.
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## Appendix 2: PICO Questions

1. **P**—Workers and/or patients with TBI  
**I**—Skull x-rays  
**C**—Is there evidence that skull x-rays are superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
2. **P**—Workers and/or patients with TBI  
**I**—Computerized tomography (CT)  
**C**—Is there evidence that CT is superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
3. **P**—Workers and/or patients with TBI  
**I**—Magnetic resonance imaging (MRI)  
**C**—Is there evidence that MRI is superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
4. **P**—Workers and/or patients with TBI  
**I**—Magnetic resonance spectroscopy (MRS)  
**C**—Is there evidence that MRS is superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
5. **P**—Workers and/or patients with TBI  
**I**—Functional magnetic resonance imaging (fMRI)  
**C**—Is there evidence that fMRI is superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
6. **P**—Workers and/or patients with TBI  
**I**—Diffusor tension imaging (DTI)  
**C**—Is there evidence that DTI is superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
7. **P**—Workers and/or patients with TBI  
**I**—Single photon emission computerized tomography (SPECT)  
**C**—Is there evidence that SPECT is superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
8. **P**—Workers and/or patients with TBI  
**I**—Positron emission testing (PET)  
**C**—Is there evidence that PET is superior to other diagnostic tools?

- O**—Identification/diagnosis of TBI
- 9. **P**—Workers and/or patients with TBI
  - I**—Vascular imaging tests
  - C**—Are vascular imaging tests superior to other diagnostic tools?
  - O**—Identification/diagnosis of TBI
- 10. **P**—Workers and/or patients with TBI
  - I**—Brain acoustic monitoring (BAM)
  - C**—Is BAM superior to other diagnostic tools?
  - O**—Identification/diagnosis of TBI
- 11. **P**—Workers and/or patients with TBI
  - I**—Electroencephalography (EEG)
  - C**—Is EEG superior to other diagnostic tools?
  - O**—Identification/diagnosis of TBI
- 12. **P**—Workers and/or patients with TBI
  - I**—Quantitative electroencephalography (qEEG)
  - C**—Is qEEG superior to EEG or other diagnostic tools?
  - O**—Identification/diagnosis of TBI
- 13. **P**—Workers and/or patient with TBI
  - I**—Somatosensory evoked potential (SSEP)
  - C**—Is SSEP superior to other diagnostic tools?
  - O**—Identification/diagnosis of TBI
- 14. **P**—Workers and/or patients with TBI
  - I**—Vestibular evoked myogenic potentials
  - C**—Are vestibular evoked myogenic potentials superior to other diagnostic tools?
  - O**—Identification/diagnosis of TBI
- 15. **P**—Workers and/or patients with TBI
  - I**—Electromyography (EMG)
  - C**—Is EMG superior to other diagnostic tools?
  - O**—Identification/diagnosis of TBI
- 16. **P**—Workers and/or patients with TBI
  - I**—Nerve conduction studies
  - C**—Are nerve conduction studies superior to other diagnostic tools?

- O**—Identification/diagnosis of TBI
- 17. **P**—Workers and/or patients with TBI
  - I**—Electroneuronography (EnoG)
  - C**—Is EnoG superior to other diagnostic tools?
  - O**—Identification/diagnosis of TBI
- 18. **P**—Workers and/or patients with TBI
  - I**—Ultrasonography (US)
  - C**—Is US superior to other diagnostic tools?
  - O**—Identification/diagnosis of TBI
- 19. **P**—Workers and/or patients with TBI
  - I**—Neurocognitive testing
  - C**—Is neurocognitive testing superior to other diagnostic tools?
  - O**—Identification/diagnosis of TBI
- 20. **P**—Workers and/or patients with TBI
  - I**—Neurological assessment
  - C**—Is neurological assessment superior to other diagnostic tools?
  - O**—Identification/diagnosis of TBI
- 21. **P**—Workers and/or patients with TBI
  - I**—Automated neuropsychological assessment metrics [1]
  - C**—Is ANAM superior to other diagnostic tools?
  - O**—Identification/diagnosis of TBI
- 22. **P**—Workers and/or patients with TBI
  - I**—Cognitive event related potential
  - C**—Is the use of cognitive event related potential superior to other diagnostic tools?
  - O**—Identification/diagnosis of TBI
- 23. **P**—Workers and/or patients with TBI
  - I**—Immediate Post-Concussion Assessment and Cognitive Testing (ImpACT)
  - C**—Is ImpACT superior to other post-concussion tools?
  - O**—Identification/diagnosis of TBI
- 24. **P**—Workers and/or patients with TBI
  - I**—King Devick testing

- C—Is King Devick testing superior to other post-concussion tools?
- O—Identification/diagnosis of TBI
- 25. P—Workers and/or patients with TBI
- I—Military Acute Concussion Evaluation [318]
- C—Is the MACE superior to other concussion evaluations?
- O—Identification/diagnosis of TBI
- 26. P—Workers and/or patients with TBI
- I—Sport Concussion Assessment Tool (SCAT)
- C—Is the SCAT superior to other concussion evaluation
- O—Identification/diagnosis of TBI
- 27. P—Workers and/or patients with TBI
- I—Standardized Assessment of Concussion (SAC)
- C—Is the SAC superior to other concussion evaluation
- O—Identification/diagnosis of TBI
- 28. P—Workers and/or patients with TBI
- I—Attention tests
- C—Are Attention tests superior to other diagnostic tools?
- O—Identification/diagnosis of TBI
- 29. P—Workers and/or patients with TBI
- I—Executive function tests
- C—Are executive function tests superior to other diagnostic tools?
- O—Identification/diagnosis of TBI
- 30. P—Workers and/or patients with TBI
- I—Memory tests
- C—Are memory tests superior to other diagnostic tools?
- O—Identification/diagnosis of TBI
- 31. P—Workers and/or patients with TBI
- I—Minnesota Multiphasic Personality Inventory (MMPI)
- C—Is the MMPI superior to other diagnostic tools?
- O—Identification/diagnosis of TBI
- 32. P—Workers and/or patients with TBI
- I—Wechsler Adult Intelligence Scale (WAIS, WAIS-III)

- C**—Are the WAIS or WAIS-III superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
33. **P**—Workers and/or patients with TBI  
**I**—Wechsler Memory Scale III (WMS-III)  
**C**—Is the WMS-III superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
34. **P**—Workers and/or patients with TBI  
**I**—Tests of memory malingering  
**C**—Are memory malingering tests superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
35. **P**—Workers and/or patients with TBI  
**I**—Visual acuity testing  
**C**—Is visual acuity testing superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
36. **P**—Workers and/or patients with TBI  
**I**—Visual evoked potential (VEP)  
**C**—Is VEP superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
37. **P**—Workers and/or patients with TBI  
**I**—Visual field testing  
**C**—Is visual field testing superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
38. **P**—Workers and/or patients with TBI  
**I**—Visual perceptual testing  
**C**—Is visual perceptual testing superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
39. **P**—Workers and/or patients with TBI  
**I**—Electroretinogram (REG)  
**C**—Is ERG superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
40. **P**—Workers and/or patients with TBI  
**I**—Fluorescein antibody

- C**—Is fluorescein antibody superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
41. **P**—Workers and/or patients with TBI  
**I**—Optical coherence tomography  
**C**—Is optical coherence tomography superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
42. **P**—Workers and/or patients with TBI  
**I**—Audiometry  
**C**—Is audiometry superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
43. **P**—Workers and/or patients with TBI  
**I**—Brainstem audiometry evoked response  
**C**—Is brainstem audiometry evoked response superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
44. **P**—Workers and/or patients with TBI  
**I**—Tympanometry  
**C**—Is tympanometry superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
45. **P**—Workers and/or patients with TBI  
**I**—Vestibular function testing  
**C**—Is vestibular function testing superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
46. **P**—Workers and/or patients with TBI  
**I**—Computerized dynamic platform posturography  
**C**—Is computerized dynamic platform posturography superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
47. **P**—Workers and/or patients with TBI  
**I**—Electronystagmography (ENG) or video nystagmography (VNG)  
**C**—Are either ENG or VNG superior to other diagnostic tools?  
**O**—Identification/diagnosis of TBI
48. **P**—Workers and/or patients with TBI

- I—Rotary chair testing
  - C—Is rotary chair testing superior to other diagnostic tools?
  - O—Identification/diagnosis of TBI
49. P—Workers and/or patients with TBI
- I—Cognitive-motor dual testing
  - C—Is cognitive-motor dual testing superior to other diagnostic tools?
  - O—Identification/diagnosis of TBI
50. P—Workers and/or patients with TBI
- I—Family visits
  - C—Are family visits equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
51. P—Workers and/or patients with TBI
- I—Multimodal and unimodal coma stimulation
  - C—Are multimodal or unimodal coma stimulation equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
52. P—Workers and/or patients with TBI
- I—Action sequences
  - C—Are action sequences equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
53. P—Workers and/or patients with TBI
- I—High order reasoning training
  - C—Is high order reasoning training equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
54. P—Workers and/or patients with TBI
- I—Vision training
  - C—Is vision training equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
55. P—Workers and/or patients with TBI
- I—Reading comprehension

- C**—Is reading comprehension equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
56. **P**—Workers and/or patients with TBI
- I**—Specific motor comprehension
- C**—Is specific motor comprehension equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
57. **P**—Workers and/or patients with TBI
- I**—Systematic instruction
- C**—Is systematic instruction equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
58. **P**—Workers and/or patients with TBI
- I**—Television assisted rehabilitation
- C**—Is television assisted rehabilitation equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
59. **P**—Workers and/or patients with TBI
- I**—Handheld computers for memory aids
- C**—Are handheld computers equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
60. **P**—Workers and/or patients with TBI
- I**—Physical therapy
- C**—Is physical therapy equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
61. **P**—Workers and/or patients with TBI
- I**—Occupational therapy
- C**—Is occupational therapy equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
62. **P**—Workers and/or patients with TBI
- I**—Strengthening exercises

- C**—Are strengthening exercises equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
63. **P**—Workers and/or patients with TBI
- I**—Stretching and flexibility exercises
- C**—Are stretching and flexibility exercises equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
64. **P**—Workers and/or patients with TBI
- I**—Relaxation exercises and group discussion
- C**—Are relaxation exercises and group discussion equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
65. **P**—Workers and/or patients with TBI
- I**—Aerobic exercises
- C**—Are aerobic exercises equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
66. **P**—Workers and/or patients with TBI
- I**—Aquatic therapy
- C**—Is aquatic therapy equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
67. **P**—Workers and/or patients with TBI
- I**—Computer and video games
- C**—Are computer and video games equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
68. **P**—Workers and/or patients with TBI
- I**—Virtual reality
- C**—Is virtual reality equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
69. **P**—Workers and/or patients with TBI
- I**—Compensatory skills training

- C**—Is compensatory skills training equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
70. **P**—Workers and/or patients with TBI
- I**—Restorative and compensatory computer assisted cognitive remediation (CACR) and external aids
- C**—Are CACR and external aids equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
71. **P**—Workers and/or patients with TBI
- I**—Attention process training [770]
- C**—Is APT equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
72. **P**—Workers and/or patients with TBI
- I**—Recreational computing
- C**—Is recreational computing equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
73. **P**—Workers and/or patients with TBI
- I**—Computerized attention training with visual, auditory and divided training
- C**—Is computerized attention training with visual, auditory and divided training equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
74. **P**—Workers and/or patients with TBI
- I**—Captain’s Log
- C**—Is Captain’s Log equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
75. **P**—Workers and/or patients with TBI
- I**—Restorative computer and non-computer attention remediation
- C**—Are restorative computer and non-computer attention remediation equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms

76. **P**—Workers and/or patients with TBI  
**I**—Reaction time training  
**C**—Is reaction time training equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
77. **P**—Workers and/or patients with TBI  
**I**—Perceptual skills training  
**C**—Is perceptual skills training equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
78. **P**—Workers and/or patients with TBI  
**I**—Verbal labeling training and compensatory interpersonal process recall  
**C**—Are verbal labeling training and compensatory interpersonal process recall equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
79. **P**—Workers and/or patients with TBI  
**I**—Psychological functioning and activities of daily living (ADLs)  
**C**—Are psychological functioning and ADLs equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
80. **P**—Workers and/or patients with TBI  
**I**—Memory/reasoning tasks, games and computer games  
**C**—Memory/reasoning tasks, games and computer games equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
81. **P**—Workers and/or patients with TBI  
**I**—Computer memory retraining group (CMRG)  
**C**—Is CMRG equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
82. **P**—Workers and/or patients with TBI  
**I**—Restorative imagery training  
**C**—Is restorative imagery training equivalent or superior to other effective treatments?

- O**—Treatment of TBI and/or symptoms
83. **P**—Workers and/or patients with TBI  
**I**—Restorative functional skills training  
**C**—Is restorative functional skills training equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
84. **P**—Workers and/or patients with TBI  
**I**—Games, art, and other types of self-expression  
**C**—Are games, art, and other types of self-expression equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
85. **P**—Workers and/or patients with TBI  
**I**—Computer-assisted cognitive rehabilitation  
**C**—Is computer-assisted cognitive rehabilitation equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
86. **P**—Workers and/or patients with TBI  
**I**—Induced hypothermia  
**C**—Is induced hypothermia equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
87. **P**—Workers and/or patients with TBI  
**I**—Intracranial pressure monitoring and thresholds  
**C**—Are intracranial pressure monitoring and thresholds equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
88. **P**—Workers and/or patients with TBI  
**I**—Oxygen monitoring and thresholds  
**C**—Are oxygen monitoring and thresholds equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
89. **P**—Workers and/or patients with TBI  
**I**—Return to work

- C**—Is Return to work equivalent or superior to other effective treatments?
  - O**—Treatment of TBI and/or symptoms
90. **P**—Workers and/or patients with TBI
- I**—Vocational rehabilitation programs
  - C**—Are vocational rehabilitation programs equivalent or superior to other effective treatments?
  - O**—Treatment of TBI and/or symptoms
91. **P**—Workers and/or patients with TBI
- I**—Functional capacity evaluations (FCEs)
  - C**—Are FCEs equivalent or superior to other TBI assessment tools?
  - O**—Treatment of TBI and/or symptoms
92. **P**—Workers and/or patients with TBI
- I**—FCEs for chronic disabling cervical or thoracic pain
  - C**—Are FCEs recommended assessments for chronic disabling cervical or thoracic pain?
  - O**—Treatment of TBI and/or symptoms
93. **P**—Workers and/or patients with TBI
- I**—FCEs for chronic stable cervicothoracic pain or post-operative recovery
  - C**—Are FCEs recommended for assessment of chronic stable cervicothoracic pain or post-operative recovery?
  - O**—Treatment of TBI and/or symptoms
94. **P**—Workers and/or patients with TBI
- I**—FCEs for acute cervicothoracic pain, acute or subacute radicular syndromes, or post-surgical cervical or thoracic pain
  - C**—Are FCEs recommended for acute cervicothoracic pain, acute or subacute radicular syndromes, or post-surgical cervical or thoracic pain?
  - O**—Treatment of TBI and/or symptoms
95. **P**—Workers and/or patients with TBI
- I**—Proton pump inhibitors (PPIs)
  - C**—Are PPIs equivalent or superior to other effective treatments?
  - O**—Treatment of TBI and/or symptoms
96. **P**—Workers and/or patients with TBI

- I—Sucralfate
  - C—Is sucralfate equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
97. P—Workers and/or patients with TBI
- I—H2 blockers
  - C—Are H2 blockers equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
98. P—Workers and/or patients with TBI
- I—Nonsteroidal anti-inflammatory agents (NSAIDs)
  - C—Are NSAIDs equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
99. P—Workers and/or patients with TBI
- I—NSAIDs for febrile control
  - C—Are NSAIDs for febrile control equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
100. P—Workers and/or patients with TBI
- I—*Boswellia Serrata*
  - C—Is *Boswellia Serrata* equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
101. P—Workers and/or patients with TBI
- I—Other alternative, complementary, or homeopathic treatments
  - C—Are other alternative, complementary, or homeopathic treatments equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
102. P—Workers and/or patients with TBI
- I—Magnesium
  - C—Is magnesium equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
103. P—Workers and/or patients with TBI
- I—Progesterone
  - C—Is progesterone equivalent or superior to other effective treatments?

- O**—Treatment of TBI and/or symptoms
- 104. **P**—Workers and/or patients with TBI
  - I**—Bromocriptine
  - C**—Is bromocriptine equivalent or superior to other effective treatments?
  - O**—Treatment of TBI and/or symptoms
- 105. **P**—Workers and/or patients with TBI
  - I**—Cyclosporine
  - C**—Is cyclosporine equivalent or superior to other effective treatments?
  - O**—Treatment of TBI and/or symptoms
- 106. **P**—Workers and/or patients with TBI
  - I**—Donepezil
  - C**—Is donepezil equivalent or superior to other effective treatments?
  - O**—Treatment of TBI and/or symptoms
- 107. **P**—Workers and/or patients with TBI
  - I**—Mannitol for intracranial pressure
  - C**—Is Mannitol for intracranial pressure equivalent or superior to other effective treatments?
  - O**—Treatment of TBI and/or symptoms
- 108. **P**—Workers and/or patients with TBI
  - I**—Hypertonic saline for intracranial pressure
  - C**—Is hypertonic saline for intracranial pressure equivalent or superior to other effective treatments?
  - O**—Treatment of TBI and/or symptoms
- 109. **P**—Workers and/or patients with TBI
  - I**—Ringers lactate for intracranial pressure
  - C**—Is Ringers lactate for intracranial pressure equivalent or superior to other effective treatments?
  - O**—Treatment of TBI and/or symptoms
- 110. **P**—Workers and/or patients with TBI
  - I**—Methylphenidate
  - C**—Is methylphenidate equivalent or superior to other effective treatments?
  - O**—Treatment of TBI and/or symptoms

111. **P**—Workers and/or patients with TBI  
**I**—Modafinil  
**C**—Is modafinil equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
112. **P**—Workers and/or patients with TBI  
**I**—Anti-spasticity medications  
**C**—Are anti-spasticity medications equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
113. **P**—Workers and/or patients with TBI  
**I**—Antiseizure prophylaxis (anticonvulsants)  
**C**—Is antiseizure prophylaxis (anticonvulsants) equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
114. **P**—Workers and/or patients with TBI  
**I**—Antidepressants  
**C**—Are antidepressants equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
115. **P**—Workers and/or patients with TBI  
**I**—Benzodiazepines  
**C**—Are benzodiazepines equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
116. **P**—Workers and/or patients with TBI  
**I**—Corticosteroids  
**C**—Are corticosteroids equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
117. **P**—Workers and/or patients with TBI  
**I**—Excitatory amino acid inhibitors  
**C**—Are excitatory amino acid inhibitors equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
118. **P**—Workers and/or patients with TBI

- I—Amantadine
  - C—Is amantadine equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
119. P—Workers and/or patients with TBI
- I—Cannabinoids
  - C—Are cannabinoids equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
120. P—Workers and/or patients with TBI
- I—Cerebrolysin
  - C—Is cerebrolysin equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
121. P—Workers and/or patients with TBI
- I—Tranexamic acid
  - C—Is tranexamic acid equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
122. P—Workers and/or patients with TBI
- I—Sedatives, sedative hypnotics, and opioids
  - C—Are sedatives, sedative hypnotics, and opioids equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
123. P—Workers and/or patients with TBI
- I—Barbiturates
  - C—Are barbiturates equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
124. P—Workers and/or patients with TBI
- I—Beta blockers
  - C—Are beta blockers equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
125. P—Workers and/or patients with TBI
- I—Aminosteroids
  - C—Are aminosteroids equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms

126. **P**—Workers and/or patients with TBI  
**I**—Citicoline  
**C**—Is citicoline equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
127. **P**—Workers and/or patients with TBI  
**I**—Physostigmine (eserine)  
**C**—Is physostigmine (eserine) equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
128. **P**—Workers and/or patients with TBI  
**I**—Rivastigmine  
**C**—Is rivastigmine equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
129. **P**—Workers and/or patients with TBI  
**I**—Cabergoline  
**C**—Is cabergoline equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
130. **P**—Workers and/or patients with TBI  
**I**—Deamino arginine vasopressin (DDAVP)  
**C**—Is deamino arginine vasopressin (DDAVP) equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
131. **P**—Workers and/or patients with TBI  
**I**—Memantine  
**C**—Is memantine equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
132. **P**—Workers and/or patients with TBI  
**I**—Substance P antagonists  
**C**—Are substance P Antagonists equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
133. **P**—Workers and/or patients with TBI

- I—Piracetam
  - C—Is piracetam equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
134. P—Workers and/or patients with TBI
- I—Intrathecal baclofen pumps
  - C—Are intrathecal baclofen pumps equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
135. P—Workers and/or patients with TBI
- I—Nutritional support
  - C—Is Nutritional support equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
136. P—Workers and/or patients with TBI
- I—Rest
  - C—Is rest equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
137. P—Workers and/or patients with TBI
- I—Body weight support treadmill
  - C—Is a body weight support treadmill equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
138. P—Workers and/or patients with TBI
- I—Constraint-induced movement therapy
  - C—Is constraint-induced movement therapy equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
139. P—Workers and/or patients with TBI
- I—Whole body vibration (WBV)
  - C—Is WBV equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
140. P—Workers and/or patients with TBI
- I—Cognitive behavioral therapy (CBT)

- C**—Is CBT equivalent or superior to other effective treatments?
  - O**—Treatment of TBI and/or symptoms
141. **P**—Workers and/or patients with TBI
- I**—Education programs
  - C**—Are education programs equivalent or superior to other effective treatments?
  - O**—Treatment of TBI and/or symptoms
142. **P**—Workers and/or patients with TBI
- I**—Neuroplasticity
  - C**—Is neuroplasticity equivalent or superior to other effective treatments?
  - O**—Treatment of TBI and/or symptoms
143. **P**—Workers and/or patients with TBI
- I**—Robotics
  - C**—Are robotics equivalent or superior to other effective treatments?
  - O**—Treatment of TBI and/or symptoms
144. **P**—Workers and/or patients with TBI
- I**—Vestibular rehabilitation treatment
  - C**—Is vestibular rehabilitation treatment equivalent or superior to other effective treatments?
  - O**—Treatment of TBI and/or symptoms
145. **P**—Workers and/or patients with TBI
- I**—Radiofrequency neurotomy, neurotomy, and facet rhizotomy
  - C**—Are radiofrequency neurotomy, neurotomy, and facet rhizotomy equivalent or superior to other effective treatments?
  - O**—Treatment of TBI and/or symptoms
146. **P**—Workers and/or patients with TBI
- I**—Radiofrequency neurotomy for cervicogenic headache
  - C**—Is radiofrequency for cervicogenic headache equivalent or superior to other effective treatments?
  - O**—Treatment of TBI and/or symptoms
147. **P**—Workers and/or patients with TBI
- I**—Occipital nerve blocks

- C**—Are occipital nerve blocks equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
148. **P**—Workers and/or patients with TBI
- I**—Non-invasive occipital nerve stimulation (ONS)
- C**—Is ONS equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
149. **P**—Workers and/or patients with TBI
- I**—Implantable occipital nerve stimulation devices
- C**—Are implantable ONS devices equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
150. **P**—Workers and/or patients with TBI
- I**—Botulinum toxin
- C**—Is botulinum toxin equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
151. **P**—Workers and/or patients with TBI
- I**—Meniett device
- C**—Is the Meniett device equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
152. **P**—Workers and/or patients with TBI
- I**—Transcranial magnetic stimulation (TMS)
- C**—Is TMS equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
153. **P**—Workers and/or patients with TBI
- I**—Transcranial direct current stimulation (TDCS)
- C**—Is TDCS equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
154. **P**—Workers and/or patients with TBI
- I**—Hyperbaric oxygen therapy (HBO or HBOT)
- C**—Is HBO or HBOT equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms

155. **P**—Workers and/or patients with TBI  
**I**—Manipulation / mobilization for cervicothoracic pain  
**C**—Is manipulation / mobilization for cervicothoracic pain equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
156. **P**—Workers and/or patients with TBI  
**I**—Manipulation for chronic cervicogenic headache pain  
**C**—Is manipulation for chronic cervicogenic headache pain equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
157. **P**—Workers and/or patients with TBI  
**I**—Manipulation of cervical spine  
**C**—Is manipulation of cervical spine equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
158. **P**—Workers and/or patients with TBI  
**I**—Cervical manipulation for tension headaches  
**C**—Is cervical manipulation for tension headaches equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
159. **P**—Workers and/or patients with TBI  
**I**—Routine manipulation / mobilization  
**C**—Is routine manipulation / mobilization equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
160. **P**—Workers and/or patients with TBI  
**I**—Manipulation for radicular pain syndromes with acute neurological deficits  
**C**—Is manipulation for radicular pain syndromes with acute neurological deficits equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
161. **P**—Workers and/or patients with TBI  
**I**—Manipulation for radicular pain without neurological deficits

- C**—Is manipulation for radicular pain without neurological deficits equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
162. **P**—Workers and/or patients with TBI  
**I**—Deep thalamic stimulation  
**C**—Is deep thalamic stimulation equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
163. **P**—Workers and/or patients with TBI  
**I**—Acupuncture for cervicothoracic pain  
**C**—Is acupuncture for cervicothoracic pain equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
164. **P**—Workers and/or patients with TBI  
**I**—Induced hypothermia  
**C**—Is induced hypothermia equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
165. **P**—Workers and/or patients with TBI  
**I**—Laser therapy/low-level laser therapy  
**C**—Is laser therapy or low-level laser therapy equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
166. **P**—Workers and/or patients with TBI  
**I**—Functional electrical stimulation [1182]  
**C**—Is FES equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
167. **P**—Workers and/or patients with TBI  
**I**—Neuromuscular electrical stimulation (NMES)  
**C**—Is NMES equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
168. **P**—Workers and/or patients with TBI  
**I**—Hyperventilation

- C**—Is hyperventilation equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
169. **P**—Workers and/or patients with TBI  
**I**—Behavioral programs  
**C**—Are behavioral programs equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
170. **P**—Workers and/or patients with TBI  
**I**—Outpatient home and community-based rehabilitation  
**C**—Is outpatient home and community-based rehabilitation equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
171. **P**—Workers and/or patients with TBI  
**I**—Comprehensive integrated interdisciplinary rehabilitation  
**C**—Is comprehensive integrated interdisciplinary rehabilitation equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
172. **P**—Workers and/or patients with TBI  
**I**—Residential rehabilitation  
**C**—Is residential rehabilitation equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
173. **P**—Workers and/or patients with TBI  
**I**—Supported living programs  
**C**—Are supported living programs equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
174. **P**—Workers and/or patients with TBI  
**I**—Skilled nursing facilities (SNFs)  
**C**—Are SNFs equivalent or superior to other effective treatments?  
**O**—Treatment of TBI and/or symptoms
175. **P**—Workers and/or patients with TBI  
**I**—Occupational rehabilitation

- C**—Is occupational rehabilitation equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
176. **P**—Workers and/or patients with TBI
- I**—Opioid/chemical treatment programs
- C**—Are opioid/chemical treatment programs equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
177. **P**—Workers and/or patients with TBI
- I**—Music therapy
- C**—Is music therapy equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
178. **P**—Workers and/or patients with TBI
- I**—Ankle-foot orthotics
- C**—Are ankle-foot orthotics equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
179. **P**—Workers and/or patients with TBI
- I**—Adaptive devices, casting, and orthotics
- C**—Are adaptive devices, casting and orthotics equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
180. **P**—Workers and/or patients with TBI
- I**—Neuromuscular re-education
- C**—Is neuromuscular re-education equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
181. **P**—Workers and/or patients with TBI
- I**—Muscle tone and joint restriction management
- C**—Is muscle tone and joint restriction management equivalent or superior to other effective treatments?
- O**—Treatment of TBI and/or symptoms
182. **P**—Workers and/or patients with TBI

- I—Mood stabilizers
  - C—Are mood stabilizers equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
183. P—Workers and/or patients with TBI
- I—Attention regulation training
  - C—Is attention regulation training equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
184. P—Workers and/or patients with TBI
- I—Anger management training
  - C—Is anger management training equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
185. P—Workers and/or patients with TBI
- I—Suicide prevention
  - C—Is suicide prevention equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
186. P—Workers and/or patients with TBI
- I—Motivational interviewing
  - C—Is motivational interviewing equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
187. P—Workers and/or patients with TBI
- I—Emotional training
  - C—Is emotional training equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
188. P—Workers and/or patients with TBI
- I—Goal setting
  - C—Is goal setting equivalent or superior to other effective treatments?
  - O—Treatment of TBI and/or symptoms
189. P—Workers and/or patients with TBI
- I—Peer monitoring program

C—Is a peer monitoring program equivalent or superior to other effective treatments?

O—Treatment of TBI and/or symptoms

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