California Workers' Compensation Institute

Research Note

An Examination of Polypharmacy Claims in California Workers' Compensation

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Executive Summary

The use of pharmaceuticals is an important component of healthcare, including in the treatment of injured workers, but interactions between drugs are always a concern and should figure prominently in medication management. This is especially true given that recent research has shown that concurrent use of multiple medications (polypharmacy) to treat one or multiple medical conditions has become prevalent, with up to 10 percent of the U.S. population and up to 30 percent of older adults taking five or more drugs simultaneously.[1]

This study uses 2016 – 2017 prescription data to measure the prevalence of polypharmacy in California workers' compensation and to identify the types of drugs included in polypharmacy prescribing. For the purposes of this study, claims with five or more concurrent medications during the two-year study period were defined as polypharmacy claims. Among the key findings:

- Twenty-four percent of claims with at least one dispensed drug during calendar years 2016 and 2017 had three or more different prescription drugs concurrently dispensed.
- The likelihood that indemnity was paid on a claim increased with the number of concurrent prescriptions. About half (51.6 percent) of the claims with one to two prescription drugs were indemnity cases versus 91.3 percent of those with five or more concurrent drugs.
- Polypharmacy claims tend to be older, with 21.5 percent of polypharmacy claims being at least 10 years old, compared to 6.0 percent of the non-polypharmacy claims.
- Claims involving back conditions without spinal cord involvement (including sprain and strain injuries) account for the highest proportion of polypharmacy claims (21.3 percent).
- A high proportion of the polypharmacy claims involve older workers, with more than half (52.3 percent) of the polypharmacy claims involving injured workers who were 50 years of age or older versus 38.3 percent of the claims with fewer concurrent medications.
- Analgesic opioids and anti-inflammatories were the top two therapeutic drug groups when three or more drugs were concurrently prescribed.
- The combination of opioids, anti-inflammatories and muscle relaxants accounted for the highest proportion of three-drug combinations (4.5 percent).

1. Quinn, K. J. and Shah, N. H. Data Descriptor: A Dataset Quantifying Polypharmacy in the United States. *Scientific Data*. October 31, 2017. DOI: 10.1038/sdata.2017.167

Background

The prevalence of opioids in the U.S. and in California workers' compensation, and the negative consequences of their widespread use, have been widely discussed and researched for more than a decade. While it is important to continue to focus on measures to prevent opioid abuse and potential solutions to ensure appropriate use of these drugs, it is incumbent on all parties to be aware of other worrisome issues in pharmacotherapy.

One area of growing concern on both national[2] and international[3,4] levels is the increased prevalence of polypharmacy. Although there is no universally accepted definition for polypharmacy, it is generally defined as the simultaneous use of multiple drugs for one or more medical conditions by a patient.

Acknowledging that prescribing multiple medications for a patient may be problematic, there are also circumstances where treatment regimens that include multiple medications may be appropriate. Duerden, Avery, and Payne (2013) proposed two polypharmacy categories:

> **Appropriate polypharmacy** is defined as the prescribing of multiple medications for an individual in order to treat complex conditions or multiple conditions in circumstances where the medicine's use has been optimized and where the medicines are prescribed according to best evidence.
>
> **Problematic polypharmacy** is defined as the prescribing of multiple medications inappropriately, or where the intended benefit of the medication is not realized.[5]

While discussing problematic polypharmacy, Duerden, Avery and Payne (2013) described a 'prescribing cascade,' whereby a prescriber incrementally prescribes new medications to counter the adverse effects of other drugs, sometimes not recognizing that the symptoms could be iatrogenic (induced by the treatment). Barrett, Lucas and Alexander (2016) stated that patients may be at higher risk for adverse events associated with concurrent use of multiple medications than from the underlying illnesses the medications are designed to treat.

Dr. Glenn Wagner, Medical Examiner for San Diego noted that "prescription medications can kill either when taken in excess, or when taken appropriately but in combination with other, similar-acting medications," and that among deaths investigated by his office in 2016 "two-thirds of unintentional medication-related fatalities were caused by a mixture of more than one medication."[6]

2. Kantor, E. D., Rehm, C. D., Haas, J. S., Chan, A. T. and Giovannucci, E. L. Trends in Prescription Drug Use Among Adults in the United States From 1999-2012. JAMA. 2015;314(17):1818-1831. doi:10.1001/jama.2015.13766
3. Barrett, K., Lucas, E. and Alexander, G. C. How Polypharmacy has Become a Medical Burden Worldwide. *The Pharmaceutical Journal*. June 9, 2016. https://www.pharmaceutical-journal.com/opinion/insight/how-polypharmacy-has-become-a-medical-burden-worldwide/20201251.article
4. Duerden, M., Avery, T. and Payne, R. Polypharmacy and Medicines Optimisation: Making it Safe and Sound. *The King's Fund.* 2013. https://www.kingsfund.org.uk/sites/default/files/field/field_publication_file/polypharmacy-and-medicines-optimisation-kingsfund-nov13.pdf
5. *Ibid*, p. 1
6. Wagner, G. 2016 Annual Report. County of San Diego Department of the Medical Examiner. p. 1. https://www.sandiegocounty.gov/content/dam/sdc/me/docs/SDME%20Annual%20Report%202016.pdf

One "notable trend" reported in the San Diego Chief Medical Examiner's 2016 Annual Report states:

> The largest groups of medications and drugs represented in this data are opiates (heroin, morphine, and related compounds) and benzodiazepines, similar to in previous years. Thirty two percent of prescription opiate deaths showed a benzodiazepine present, and 83 percent of deaths with benzodiazepines had a prescription opiate present. [7]

Addressing polypharmacy in the treatment of mental health disorders, Millan (2014) differentiated counterproductive use of multiple medications which "may compromise efficacy and provoke adverse drug reactions" and positive, evidence-based polypharmacy in treatment-resistant patients who "fail to respond adequately to monotherapy."[8] Holbech, et al. (2017) reported on the benefits of combination therapy, using two drugs with different mechanisms of action, for individuals who cannot tolerate high-dose monotherapy.[9]

Polypharmacy also occurs when medications are prescribed to treat side effects caused by other medications. The use of gastrointestinal medications (laxatives and/or acid suppressants) to treat opioid-induced bowel dysfunction is not uncommon.[10,11,12] Additional side effects of long-term opioid use treated with additional medications include problems with sleep, sexual dysfunction, and dry mouth.[13] Xerostomia (dry mouth) is also a side effect of many other drugs including: antidepressants, anticonvulsants, anxiolytics, and antipsychotics, and may lead to dental decay, periodontal disease and related health problems.[14]

Use of nonsteroidal anti-inflammatory drugs (NSAIDs), especially on a chronic basis, may also result in co-prescribed medications to treat side effects.[15] Proton pump inhibitors (PPIs) or H_2-receptor antagonists (H2RAs) are prescribed concomitantly with NSAIDs to heal NSAID-associated ulcers.[16] Although PPIs have proven effective in reducing the risk of gastric ulceration, there is evidence that combining NSAIDs and PPIs may exacerbate small intestine ulceration and bleeding.[17]

7. Ibid
8. Millan, M. J. On 'Polypharmacy' and Multi-Target Agents, Complementary Strategies for Improving the Treatment of Depression: A Comparative Appraisal. International Journal of Neuropsychopharmacology. (2014), 17, 1009-1037. p. 1010. doi:10.1017/S1461145712001496.
9. Holbech, J. V., Jung, A., Jonsson, T., Wanning, M., Bredahl, C. and Bach, F. W. Combination Treatment of Neuropathic Pain: Danish Expert Recommendations Based on a Delphi Process. Journal of Pain Research. June 26, 2017. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5499948/pdf/jpr-10-1467.pdf
10. Williams, R. E., Bosnic, N., Sweeney, C. T., Duncan, A. W., Levine, K. B., Brogan, M., and Cook, S. F. Prevalence of Opioid Dispensings and Concurrent Gastointestinal Medications in Quebec. Pain Research and Mangement. 2008 Sep-Oct; 13(5): 395–400. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2799263/
11. Jehangir, A. and Parkman, H. P. Chronic Opioids in Gastroparesis: Relationship with Gastrointestinal Symptoms, Healthcare Utilization and Employment. World Journal of Gastroenterology. October 28, 2017. DOI: 10.3748/wjg.v23.i40.7310
12. Rauch, T. and Jansen, T. Gastrointestinal Side Effects of Opioid Analgesics. U. S. Pharmacist. December 19, 2012. https://www.uspharmacist.com/article/gastrointestinal-side-effects-of-opioid-analgesics
13. Sehgal, N., Colson, J. and Smith, H. S. Chronic Pain Treatment with Opioid Analgesics. Expert Review of Neurotherapeutics. 2013;13(11):1201-1220. https://www.medscape.com/viewarticle/813875_4
14. Swager, L. W. M. and Morgan, S. K. Psychotropic-Induced Dry Mouth: Don't Overlook this Potentially Serious Side Effect. Current Psychiatry. 2011 December;10(12):54-58. https://www.mdedge.com/psychiatry/article/64550/depression/psychotropic-induced-dry-mouth-dont-overlook-potentially-serious
15. Scheiman, J. M. The Use of Proton Pump Inhibitors in Treating and Preventing NSAID – Induced Mucosal Damage. Arthritis Research & Therapy. 2013. 15(Suppl3):S5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3891010/pdf/ar4177.pdf
16. Ibid
17. Wallace, J. L., et al. Proton Pump Inhibitors Exacerbate NSAID-Induced Small Intestinal Injury by Inducing Dysbiosis. Gastroenterology. October 2011. https://www.gastrojournal.org/article/S0016-5085(11)00926-7/pdf

Objective

This report expands on the topic of prescription drugs taken in combination by California injured workers, a subject that has been touched upon in previous CWCI reports.[18,19] The study focuses on four areas of interest:

- What are the most frequent drug combinations with overlapping usage?
- How prevalent are drug combinations that potentiate drug interactions or that are otherwise contraindicated?
- What proportion of injured workers who are prescribed medications receive five or more medications concurrently?
- What are the injured worker characteristics (average age, gender, medical condition) of those who are prescribed five or more concurrent medications?

Methodology

For this study, the authors extracted pharmaceutical and claim demographic data from CWCI's Industry Research Information System (IRIS) database.[20] The pharmaceutical data sample included prescriptions dispensed during the 24-month period spanning January 1, 2016 through December 31, 2017. Each drug was identified according to its National Drug Code (NDC) and descriptive detail from Medi-Span's Master Drug Data Base.[21] Medi-Span data variables used in the analysis included drug ingredient and therapeutic group.

To determine information related to the concurrent use of drugs, the authors took the date a prescription was dispensed and used the days' supply for the prescription to establish the span of dates that the patient was using the specific drug ingredient.[22] When the span of dates for different drug ingredients overlapped, this was considered to be concurrent use of the two drug ingredients.

Claims with five or more concurrent medications dispensed during calendar years 2016 and 2017 were classified as polypharmaceutical claims.

Since pharmacy bills do not include diagnosis codes, the authors incorporated the IRIS database for ICD-9 and ICD-10 diagnosis codes[23] submitted by medical providers for dates of service within the 2016-2017 study period. The authors used a proprietary clinical grouping system to categorize the primary medical condition treated during the two-year study period for each injured worker in the data set.

Additional claim data included the accident year, the injured worker's gender, the injured worker's age at injury, and claim type (indemnity or medical only).

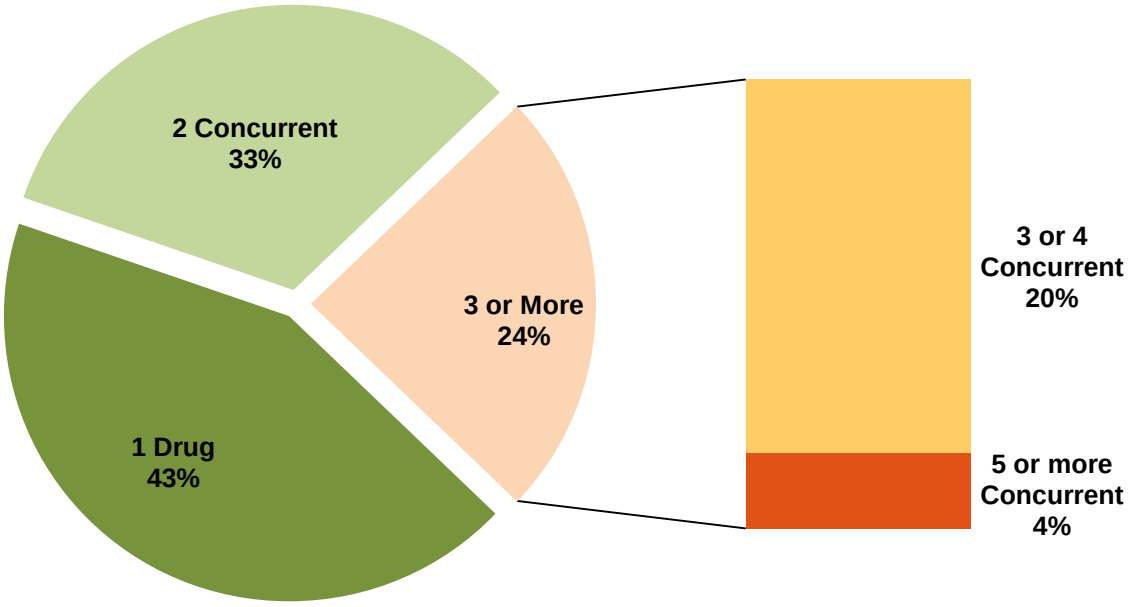
18. Swedlow, A. and Deitz, D. Opioids in Workers' Compensation Set-Asides. CWCI Report to the Industry. October 2017.
19. Jones, S. L., Hayes, S. and Young, B. Differential Use of Opioids in California Workers' Compensation Claims with Mental Health Disorders. CWCI Spotlight Report. August 2017.
20. IRIS is CWCI's proprietary database containing data on employee and employer characteristics, medical service data, benefits, and administrative costs on nearly 6.1 million California workers' compensation claims.
21. MMDB®, Version 2.5 Documentation Manual, published by Wolters Kluwer Health.
22. If days' supply was unavailable, the drug ingredient, strength, delivery form, and units supplied were used to assign a days' supply value.
23. The International Classification of Diseases, Ninth Revision (ICD-9) and the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10).

Results

Twenty-four percent of claims with at least one dispensed drug during calendar years 2016 and 2017 had three or more different prescription drugs concurrently dispensed (Exhibit 1). The authors grouped concurrent pharmaceutical usage into three categories for detailed analysis: three concurrent drugs, four concurrent drugs and five or more concurrent drugs. For the purposes of this study, polypharmacy was defined as concurrent dispensing of five or more different drugs for the same injured worker. Four percent of the claims in the study sample fell into this category (Exhibit 1).

Exhibit 1: Proportion of Claims with Concurrently Prescribed Drugs and Single Prescribed Drug

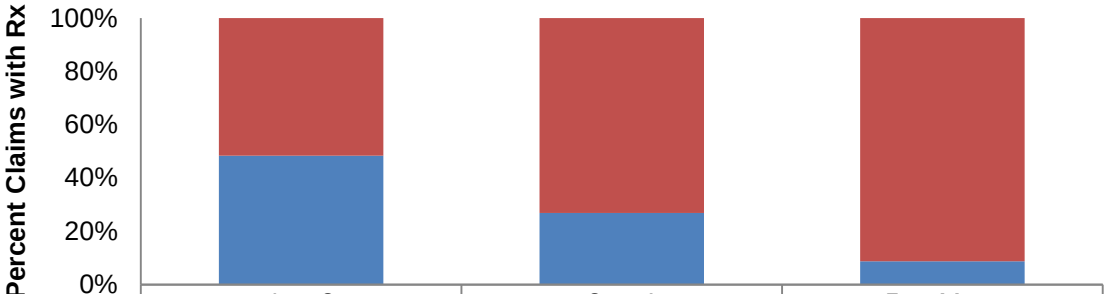
(CY 2016 & 2017 Fill Dates)



Claim and Injured Worker Characteristics

Exhibit 2 shows the distribution of the claims that had 1 or 2, 3 or 4, or 5 or more concurrent prescriptions during calendar year 2016 and 2017, broken out by claim type. Claims with just a single prescription or with only two concurrent drug prescriptions were fairly evenly divided between the two types of claims (48.4 percent were medical-only claims and 51.6 percent were indemnity claims). In contrast, 73.1 percent of the claims with three or four concurrent drugs and 91.3 percent of the claims with five or more concurrent drugs were indemnity claims.

Exhibit 2: Distribution of Claims with 1-2, 3-4 or 5 or More Concurrent Drugs by Claim Type, CY 2016 and 2017 Fill Dates



	1 or 2	3 or 4	5 or More
Indemnity	51.6%	73.1%	91.3%
Medical Only	48.4%	26.9%	8.7%

Polypharmacy is more prevalent among older claims. Exhibit 3 shows the distribution of CY 2016-2017 polypharmacy and non-polypharmacy claims by claim age (based on accident year). As noted below, claims with more than two years of development account for 71.1 percent of the polypharmacy claims, with 21.5 percent of the claims with five or more concurrent prescriptions being at least 10 years old. In contrast, only 33.0 percent of the non-polypharmacy claims had more than two years of development, and only 6.0 percent involved claims that were at least 10 years old.

Exhibit 3: Claim Age Comparison - Polypharmacy vs Non-Polypharmacy Claims, AY 2000 - 2017

Accident Year	Polypharmacy Claims	Non-Polypharmacy Claims
2000 - 2006	17.8%	5.0%
2007	3.7%	1.0%
2008	3.9%	1.0%
2009	3.9%	1.1%
2010	3.4%	1.3%
2011	4.6%	1.6%
2012	5.3%	2.2%
2013	5.8%	3.2%
2014	9.0%	5.5%
2015	13.6%	11.2%
2016	20.4%	37.3%
2017	8.5%	29.7%
Total	**100.0%**	**100.0%**

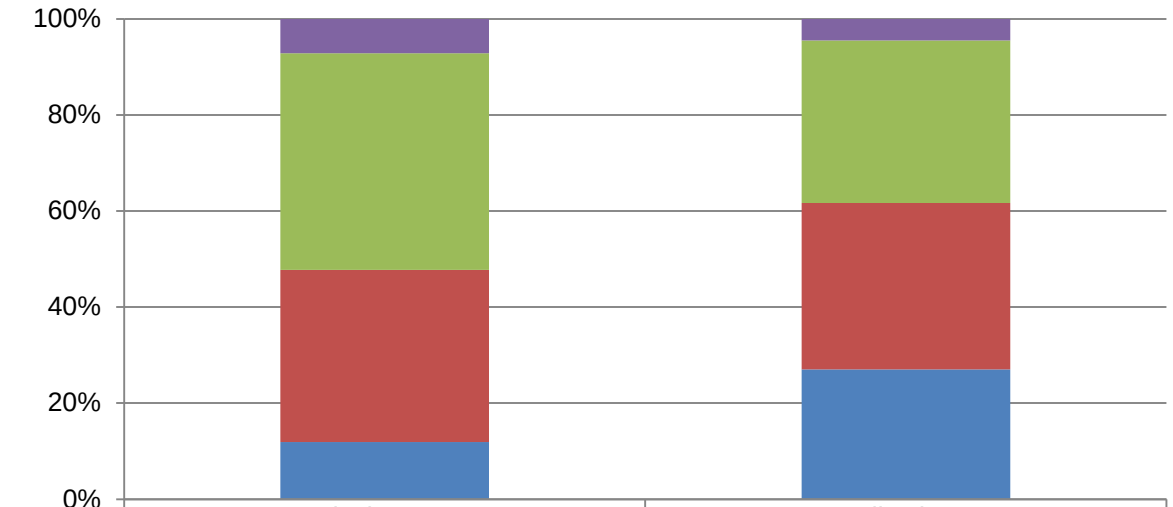
Using the ICD-10 diagnosis codes submitted by treating physicians during 2016 and 2017, the authors grouped the medical conditions treated during the study period into diagnostic categories focusing on newer claims (AY 2016 and AY 2017), then produced separate distributions for the polypharmacy and non-polypharmacy claims. Among the polypharmacy claims, medical back conditions (including sprains and strains, spinal stenosis and spondylosis) that did not involve the spinal cord were the top diagnostic category, accounting for 21.3 percent of the claims compared to 14.2 percent of the non-polypharmacy claims (Exhibit 4). Multiple drugs were used concurrently to treat pain, inflammation and nerve irritation associated with medical back conditions. Not surprisingly, minor wounds and contusions were the top diagnostic category for non-polypharmacy claims, noted in in 15.9 percent of these claims versus only 6.9 percent of the polypharmacy claims.

Exhibit 4: Top Ten Diagnosis Categories for Polypharmacy Claims Compared to All Claims for Treatment Years 2016 and 2017 (AY 2016 and 2017)

Diagnosis Category Description	Polypharmacy Claims	Non-Polypharmacy Claims
Medical Back Problems w/o Spinal Cord Involvement	21.3%	14.2%
Ruptured Tendon, Tendonitis, Myositis & Bursitis	10.2%	11.0%
Sprain of Shoulder, Arm, Knee, Lower Leg	9.5%	14.7%
Other Heart & Circulatory Disorders	9.1%	7.4%
Other Diagnoses of Musculoskeletal System	8.7%	8.3%
Degenerative, Infective & Metabolic Joint Disorder	8.6%	6.2%
Minor Wounds & Contusions	6.9%	15.9%
Wound, Fracture of Shoulder, Arm, Knee, Lower Leg	4.7%	3.4%
Spine Disorders w/ Spinal Cord or Root Involvement	4.0%	2.1%
Other Injuries, Poisonings & Toxic Effects	2.5%	4.7%
Total Percentage for the Top 10 Diagnoses	**85.4%**	**88.0%**

In addition to exhibiting a different injury mix, injured workers using five or more concurrent medications were older on average than injured workers taking fewer medications. As noted in Exhibit 5, more than half (52.3 percent) of injured workers in the polypharmacy category were 50 years of age or older compared to 38.3 percent of injured workers with fewer concurrent medications.

Exhibit 5: Injured Worker Average Age at Injury - Polypharmacy Claims Compared to Non-Polypharmacy Claims (AY 2000 - 2017)



	Polypharmacy	All Other
> 64	7.2%	4.5%
50 - 64	45.1%	33.8%
35 - 49	35.9%	34.7%
< 35	11.9%	27.0%

Concurrent Therapeutic Drugs

Analgesic anti-inflammatories and opioids were the most prevalent drugs dispensed (22.7 percent and 18.4 percent, respectively) when three or more drugs were used concurrently. Exhibit 6 compares the top ten therapeutic drug groups found in polypharmacy claims (concurrent use of five or more drugs) to the top ten drugs found in claims in which there was concurrent use of three drugs and claims in which there was concurrent use of four drugs. Analgesic opioids and anti-inflammatories were the top two therapeutic groups in each of the three claim categories, but gastrointestinal agents[24] were more prevalent in the claims in which there was concurrent use of four drugs and in the polypharmacy claims than in the claims in which there was concurrent use of three drugs, while muscle relaxants were less prevalent.

Drugs used to treat anxiety and depression also were more prevalent in the claims in which four or more drugs were concurrently used, while analgesics were less prevalent. There are multiple reasons why antidepressants represent increased proportions when greater numbers of drugs are used concurrently. Antidepressants are used for neuropathic pain management[25] as well as treating depression. Treatment plans addressing major depression often involve concurrent use of different types of antidepressants with different therapeutic properties.[26]

Exhibit 6: Top 10 Therapeutic Groups - Percentages by Therapeutic Group and Concurrent Drug Count

Therapeutic Group	3	4	5+
Analgesics – Opioid	18.8%	18.1%	16.7%
Analgesics - Anti-Inflammatory	24.3%	19.3%	14.4%
Gastrointestinal Agents - Misc.	9.6%	11.3%	12.3%
Muscle Relaxants	13.8%	12.0%	9.9%
Antidepressants	4.7%	6.8%	7.9%
Anticonvulsants	6.3%	7.5%	7.6%
Dermatologicals*	5.8%	6.2%	6.3%
Hypnotics/Sedatives/Sleep Disorder Agents	1.4%	2.0%	2.9%
Antianxiety Agents	1.2%	1.7%	2.2%
Corticosteroids	1.8%	1.7%	1.5%
Total Percentage for the Top 10 Therapeutic Groups	87.6%	86.6%	81.6%

* Dermatologicals include topical corticosteroids, topical anti-inflammatories, and topical analgesics.

24. Gastrointestinal agents include ulcer medications, laxatives and opioid receptor antagonists (used to treat opioid induced constipation).
25. Sansone, R. A. and Sansone, L. A. Pain, Pain, Go Away: Antidepressants and Pain Management. *Psychiatry*. 2008:5(12):16-19. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2729622/pdf/PE_5_12_16.pdf
26. Millan, M. J. On 'Polypharmacy' and Multi-Target Agents, Complementary Strategies for Improving the Treatment of Depression: A Comparative Appraisal. *International Journal of Neuropsychopharmacology*. 2014, 17, 1009-1037. doi:10.1017/S1461145712001496

Exhibit 7 lists the top 20 therapeutic three-drug combinations found in claims in which three or more drugs were dispensed concurrently. Together, the top 20 combinations represent 33 percent of the three-drug combinations found in the sample. Anti-inflammatory drugs were in 14 out of the top 20 combinations and were dispensed along with opioids in seven of the top 20 combinations. Opioids were found in 13 of the top 20 combinations, and muscle relaxants (antispasmodics and antispastics) were found in eight of the top 20 combinations. Twenty percent of the claims with three or more concurrent drugs had three-drug combinations of an opioid, an anti-inflammatory, and a muscle relaxant.

Exhibit 7: Top 20 Combinations of 3 Therapeutic Drugs

1	Opioid/Anti-Inflammatory/Muscle Relaxants	4.5%
2	Opioid/Anti-Inflammatory/Gastrointestinal	3.1%
3	Anti-Inflammatory/Gastrointestinal/Muscle Relaxants	3.0%
4	Anti-Inflammatory/Anti-Inflammatory/Muscle Relaxants	2.0%
5	Opioid/Anti-Inflammatory/Anticonvulsants	1.8%
6	Opioid/Opioid/Anti-Inflammatory	1.6%
7	Opioid/Gastrointestinal/Muscle Relaxants	1.6%
8	Anti-Inflammatory/Muscle Relaxants/Dermatologicals	1.5%
9	Opioid/Anti-Inflammatory/Anti-Inflammatory	1.4%
10	Opioid/Muscle Relaxants/Anticonvulsants	1.4%
11	Opioid/Anti-Inflammatory/Dermatologicals	1.3%
12	Anti-Inflammatory/Gastrointestinal/Dermatologicals	1.3%
13	Anti-Inflammatory/Gastrointestinal/Anticonvulsants	1.3%
14	Anti-Inflammatory/Muscle Relaxants/Anticonvulsants	1.2%
15	Opioid/Gastrointestinal/Anticonvulsants	1.1%
16	Opioid/Opioid/Muscle Relaxants	1.1%
17	Anti-Inflammatory/Anti-Inflammatory/Gastrointestinal	1.0%
18	Opioid/Anti-Inflammatory/Antidepressants	1.0%
19	Opioid/Antidepressants/Anticonvulsants	0.9%
20	Opioid/Opioid/Gastrointestinal	0.9%
	Total Percentage for the Top 20 3-Drug Combinations	**33.0%**

The authors also examined different four-drug combinations. As was the case with the three-drug combinations, opioids, anti-inflammatories, and muscle relaxants were the most common drug categories found in the top 20 four-drug combinations, with gastrointestinal agents and anticonvulsants frequently added as fourth drugs (Exhibit 8). The presence of multiple opioids (short- and long-acting) or different anti-inflammatories (*e.g.*, ibuprofen and diclofenac sodium) also created four-drug combinations.

Gastrointestinal agents (primarily laxatives and proton pump inhibitors) were found in more than half of the top 20 four-drug combinations. Co-prescribing of gastrointestinal medications with opioids and/or anti-inflammatories may be prophylactic or in reaction to gastrointestinal disorders (*e.g.*, constipation and small intestinal injury) that result from the use of the analgesic drugs.

Proton pump inhibitors are often prescribed with nonsteroidal anti-inflammatory drugs (NSAIDs) to inhibit acid secretion and protect against gastrointestinal damage.[27,28,29] Although used to treat side effects of NSAIDs, there is evidence that proton pump inhibitors may actually exacerbate the NSAID-induced small intestinal injury.[30]

Opioid induced constipation (OIC) is a common side effect and may be treated with medications including laxatives and prescription drugs (*i.e.*, lubiprostone, methylnaltrexone, naloxegol, and naldemedine) that are specifically designed to counteract OIC.[31] Opioids were part of the drug regimen in 16 of the top 20 four-drug combinations and gastrointestinal agents were included in more than half of those combinations.

Exhibit 8: Top 20 Combinations of 4 Therapeutic Drugs

1	Opioid/Anti-Inflammatory/Muscle Relaxants/Gastrointestinal	1.8%
2	Opioid/Anti-Inflammatory/Muscle Relaxants/Anticonvulsant	1.1%
3	Opioid/Anti-Inflammatory/Gastrointestinal/Anticonvulsant	1.0%
4	Opioid/Anti-Inflammatory/Anti-Inflammatory/Muscle Relaxants	1.0%
5	Opioid/Opioid/Anti-Inflammatory/Muscle Relaxants	0.9%
6	Opioid/Opioid/Anti-Inflammatory/Gastrointestinal	0.8%
7	Opioid/Anti-Inflammatory/Gastrointestinal/Dermatologicals	0.8%
8	Opioid/Muscle Relaxants/Gastrointestinal/Anticonvulsants	0.8%
9	Anti-Inflammatory/Muscle Relaxants/Gastrointestinal/Anticonvulsant	0.7%
10	Opioid/Anti-Inflammatory/Muscle Relaxants/Dermatologicals	0.7%
11	Anti-Inflammatory/Gastrointestinal/Muscle Relaxants/Dermatologicals	0.7%
12	Anti-Inflammatory/Anti-Inflammatory/Gastrointestinal/Muscle Relaxants	0.7%
13	Opioid/Anti-Inflammatory/Anti-Inflammatory/Gastrointestinal	0.6%
14	Opioid/Anti-Inflammatory/Gastrointestinal/Antidepressants	0.6%
15	Opioid/Anti-Inflammatory/Antidepressants/Anticonvulsants	0.6%
16	Opioid/Gastrointestinal/Antidepressants/Anticonvulsants	0.6%
17	Opioid/Opioid/Anti-Inflammatory/Anticonvulsants	0.6%
18	Opioid/Opioid/Muscle Relaxants/Anticonvulsants	0.5%
19	Opioid/Opioid/Gastrointestinal/Muscle Relaxants	0.5%
20	Anti-Inflammatory/Gastrointestinal/Antidepressants/Anticonvulsants	0.5%
	Total Percentage for the Top 20 4-Drug Combinations	**15.8%**

27. Scheiman, J. M. The Use of Proton Pump Inhibitors in Treating and Preventing NSAID-Induced Mucosal Damage. *Arthritis Research & Therapy*. 2013, 15(Suppl 3):55.
28. Sostres, C., Gargallo, C. J. and Lanas, A. Nonsteroidal Anti-Inflammatory Drugs and Upper and Lower Gastrointestinal Mucosal Damage. *Arthritis Research & Therapy*. 2013. 15(Suppl 3):53.
29. Wallace, J. L., et al. Proton Pump Inhibitors Exacerbate NSAID-Induced Small Intestinal Injury by Inducing Dysbiosis. Gastroenterology. October 2011.
30. *Ibid*
31. Gregorian, T., Lewis, J. and Tsu, L. Opioid-Induced Constipation: Clinical Guidance and Approved Therapies. U. S. Pharmacist. December 15, 2017. https://www.uspharmacist.com/article/opioidinduced-constipation-clinical-guidance-and-approved-therapies

Some of the concurrent drugs found in the data may be cause for concern due to their combined cumulative effects. Opioids and muscle relaxants such as cyclobenzaprine are present in 14.8 percent of all claims where there are two or more drugs. Both of these drug categories have sedative and respiratory depression effects, so using them concurrently is associated with increased risk for opioid-induced respiratory depression.[32]

As shown in Exhibits 7 and 8, opioids, muscle relaxants, and anticonvulsants such as gabapentin were often prescribed concurrently (present in 6.2 percent of all claims that include three or more drugs), and given the potentially dangerous interactions of these drugs, their concurrent use warrants caution and close physician monitoring. Research has revealed that there is an increased risk of a "life-threatening drug-drug interaction between gabapentin and opioids in routine clinical practice."[33]

The authors also analyzed drug combinations that included other central nervous system depressants, including benzodiazepines and non-benzodiazepines.[34] The two-year sample data showed concurrent use of these drugs was relatively infrequent, but not insignificant, as these combinations were found in nearly 2 percent of the claims with 2 or more concurrent drugs.

Exhibit 9: Prevalence of Opioid & Central Nervous System Depressant Combinations Among Concurrent Drug Claims

Concurrent Drugs	Percent of Claims with 2 or More Concurrent Drugs
Opioid/Hypnotic-Sedative/Muscle Relaxants	0.6%
Opioid/Hypnotic-Sedative/Muscle Relaxants /Anticonvulsant	0.2%
Opioid/Benzodiazepine	1.1%

Although impacting a small proportion of claims, benzodiazepines and other types of sedative-hypnotic drugs also depress the central nervous system, further increasing the risk of respiratory depression when used in combination with opioids. That risk is further increased when opioids, muscle relaxants and benzodiazepines are all prescribed together.[35]

32. Fudin, J. Reassessing Routine Refills for Cyclobenzaprine. *Pharmacy Times*. June 28, 2016. https://www.pharmacytimes.com/contributor/jeffrey-fudin/2016/06/reassessing-routine-refills-for-cyclobenzaprine
33. Gomes, T., Juurlink, D. N., Antoniou, T., Mamdani, M. M., Paterson, J. M. and van den Brink, W. Gabapentin, Opioids, and the Risk of Opioid-Related Death: A Population-Based Nested Case-Control Study. *PLOS Medicine*. October, 3, 2017. https://doi.org/10.1371/journal.pmed.1002396
34. A partial list of central nervous depressants is included in Appendix 1 for examples of drugs.
35. Horsfall, J. T. and Sprague, J. E. The Pharmacology and Toxicology of the 'Holy Trinity'. Basic & Clinical Pharmacology & Toxicology. 2017, 120, 115 – 119. Doi: 10.1111/bcpt.12655

Discussion

Studies of pharmaceutical usage in the general population have shown increases in the concurrent use of multiple prescription drugs, with 2017 research by Quinn and Shah finding that as much as 10 percent of the U.S. population (and 30 percent of older adults) were taking five or more drugs simultaneously.[36] Thus, in reviewing the results of this study, it is important to note that the presence of polypharmacy in an industrial injury claim may be further compounded if the injured worker is simultaneously prescribed medications for their general health by a group health provider or any other physician outside the workers' compensation system.

This study found that almost a quarter of the California workers' compensation claims that had at least one drug dispensed in 2016 and 2017 had concurrent use of three or more drugs at some point during the two-year study period, while four percent fell into the polypharmacy claim category with five or more concurrent drugs. The likelihood that indemnity was paid on a claim increased with the number of concurrent prescriptions, as the study found that indemnity was paid on just over half of the claims with 1 to 2 prescriptions, while nearly three quarters of the claims with three or more concurrent drugs involved indemnity payments, and that percentage increased to more than 91 percent for the polypharmacy claims. The results also show polypharmacy claims tend to be older, as 21.5 percent of the claims with five or more concurrent prescriptions involved injuries that were at least 10 years old – more than triple the proportion noted for non-polypharmacy claims; and conversely, two-thirds of the non-polypharmacy claims were less than two years old compared to less than 29 percent of the polypharmacy claims.

The importance of examining polypharmacy is underscored by the following 3 examples from the data set:

Example 1: Newer Injury

Although more likely to be found on older claims, polypharmacy also occurred in association with the treatment of new injuries as shown in the example below.

Claim with polypharmacy within 30 days of neck strain injury

Generic Name	Therapeutic Drug Group
Etodolac Tab SR 24HR 500 MG	Analgesics - Anti-Inflammatory
Omeprazole Cap Delayed Release 20 MG	Ulcer Drugs
Lidocaine Patch 5%	Dermatologicals
Orphenadrine Citrate Tab SR 12HR 100 MG	Muscle Relaxants
Ketoprofen Cap 50 MG	Analgesics - Anti-Inflammatory
Tramadol-Acetaminophen Tab 37.5-325 MG	Analgesics - Opioid

36. Quinn, K. J. and Shah, N. H. Data Descriptor: A Dataset Quantifying Polypharmacy in the United States. *Scientific Data*. October 31, 2017. DOI: 10.1038/sdata.2017.167

Example 2: Older Injury

Below is an example of an older injury (AY 2000 claim) with polypharmacy treatment during the two-year study period. In this example, the antidepressants were included in pain management treatment, though the data did not show a diagnosis related to depression.

Claim with initial injury diagnosis of displaced disk and subsequent surgeries to back, elbow, and foot over a 16-year period

Generic Name	Therapeutic Drug Group
Hydrocodone-Acetaminophen Tab 10-325 MG	Analgesics - Opioid
Morphine Sulfate Tab CR 15 MG	Analgesics - Opioid
Trazodone HCl Tab 50 MG	Antidepressants
Ranitidine HCl Tab 150 MG	Ulcer Drugs
Bupropion HCl Tab SR 24HR 150 MG	Antidepressants
Gabapentin Tab 600 MG	Anticonvulsants

The above polypharmacy examples reflect combinations of drugs that are representative of claims with five or more drugs concurrently prescribed. Neither of these two claims represented a catastrophic injury involving multiple body systems for which multiple medications might be expected. When assessing the potential benefits of individual drugs and co-prescribed drugs, physicians must also consider the potential drug-drug interactions that may yield harm or diminish the efficacy of a given drug for the specific patient. This may be particularly challenging when a physician develops a treatment plan that involves multiple drugs for an injured worker and there are other physicians simultaneously treating the individual for the industrial injury or for non-industrial conditions.

Example 3: Lack of Patient-Specific Prescribing

While most physicians develop and revise drug treatment plans to assist their patients with recovery and symptom management, there are some physicians who may be dispensing multiple medications to their patients for economic rather than clinical reasons. Data from our two-year study period showed a medical provider group that prescribed the same four oral suspensions (generic Zantac, generic Benadryl, gabapentin, and cyclobenzaprine) for all of their injured workers who were treated with medications, submitting charges of $380 and $440 for each prescription.

It is common knowledge that there are risks associated with certain drugs, some of which can be mitigated by the addition of another drug to treat side effects, and some of which may be exacerbated by the addition of another drug to treat side effects. Other health risks result from drug-drug interactions, as is the case with opioids, muscle relaxants, and hypnotic-sedatives, possibly leading to excess sedation or respiratory depression.

This study found that while workers' compensation polypharmacy claims involve many different types of drugs, opioids were the most prevalent therapeutic drug category found in claims with five or more concurrent prescriptions, present in one out of every six of these claims. In addition, the results showed that among claims with three or more concurrent prescriptions, opioids were present in 13 of the top 20 drug combinations; while among claims with four or more concurrent prescriptions, opioids were present in 16 of the top 20 drug combinations.

Given that the national opioid epidemic has placed a spotlight on the overuse of prescription opioids and the need to more closely monitor pharmaceutical therapy, these findings point to a continued need for vigilance in regard to the types of medications that are concurrently prescribed to injured workers as well as to other patients.

Several of the statutory and regulatory reforms to the California workers' compensation enacted in recent years have had (or soon will have) an impact on both the types and quantity of prescription drugs dispensed to injured workers. These include the statutory requirements for utilization review and the adoption of a Medical Treatment Utilization Schedule (MTUS) based on evidence-based medicine; the adoption of independent medical review by a physician to resolve disputes over treatment requests, including requests for prescription drugs; and the January 1, 2018 implementation of the drug formulary as a component of the MTUS, which has added a new level of oversight for pharmaceutical therapy. In addition, as of October 2, 2018, California medical providers must consult the Controlled Substance Utilization Review and Evaluation System (CURES) prior to prescribing, ordering, administering, or furnishing a Schedule II – IV controlled substance, including opioids and many of the other drugs which this study found are commonly found in polypharmacy claims. This statewide requirement should help physicians avoid unknowingly prescribing a drug that is contraindicated with another drug.

These public policy changes should lead to reductions in the use of opioids, which in turn should help alleviate the need for ancillary medications used to treat opioid-induced constipation and other side effects. The reductions in opioid usage, as well as heightened attention to drug combinations that include an opioid (*e.g.*, opioids and benzodiazepines or opioids and muscle relaxants) should also improve injured workers' overall treatment and facilitate their return to work. At the same time, to the extent that these changes lead to increased use of opioid alternatives such as NSAIDs, they could result in fewer medications being used to treat injured workers and/or a change in the mix of drugs used in pharmaceutical therapy.

Appendix

Examples of Benzodiazepines and Other Central Nervous System Depressants	
Generic Name	**Brand Name(s)**
Benzodiazepines	
Alprazolam	Xanax
Clonazepam	Klonopin
Diazepam	Valium
Non-Benzodiazepine Hypnotics	
Eszopiclone	Lunesta
Zalepion	Sonata
Zolpidem	Ambien, Intermezzo
Muscle Relaxants	
Baclofen	Gablofen, Lioresal
Carisoprodol	Soma
Cyclobenzaprine	Flexeril, Amrix
Antipsychotics	
Aripiprazole	Abilify
Lurasidone	Latuda
Quetiapine	Seroquel

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