Patterns of Chronic Higher-Dose and Lower-Dose Opioid Use in Federal Workers' Compensation Claimants

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Introduction

According to the Centers for Disease Control and Prevention (CDC) from 1999 – 2016 more than 200,000 people have died in the United States from overdoses related to prescription opioids, with more than 11.5 million Americans misusing prescription opioids in 2016.[1,2] In response to this opioid epidemic, on October 26, 2017, the President of the United States declared a national public health emergency and directed all executive agencies to use every appropriate emergency authority to minimize the epidemic's devastation.[3] Since the President's Memorandum, the U.S. Department of Labor (DOL) has declared that combating the opioid epidemic is one of its main priorities and has dedicated significant resources and time to protecting injured federal workers from its effects.[4]

The U.S. government is the largest employer in the country with over 2.7 million employees.[5] Federal workers who are injured or become ill in the performance of duty are provided medical and other benefits by the DOL under the Federal Employees' Compensation Act (FECA).[6] FECA is administered by the Office of Workers' Compensation Program (OWCP's) Division of Federal Employees' Compensation (DFEC). DFEC does not provide medical care; it finances medical care for specific, work-related illnesses and injuries.[7] This includes payment for prescription medications including opioids. In that capacity, DFEC has implement a four-point strategic plan to combat the opioid epidemic and reduce the potential for opioid misuse and addiction among injured federal workers. The plan consists of effective controls, tailored treatment, impactful communications, and aggressive fraud detection.[8]

DOL is not alone in its efforts to stem the opioid epidemic; public, private, and legislative activities have in the aggregate produced a paradigm-shifting response to the prescribing of opioids. By 2017, the opioid prescribing rate in the U.S. had fallen to the lowest in more than 10 years, at 58.7 prescriptions per 100 persons.[9] Federal agencies have created opioid prescribing guidelines, including the joint U.S. Department of Veterans Affairs (VA) and the U.S.

[1] Seth P, Rudd R, Noonan, R, Haegerich, T. Quantifying the Epidemic of Prescription Opioid Overdose Deaths. American Journal of Public Health, March 2018; 108(4), e1-e3.
[2] Centers for Disease Control and Prevention. 2018 Annual Surveillance Report of Drug-Related Risks and Outcomes — United States. Surveillance Special Report 2. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. Published August 31, 2018.
[3] Presidential Memorandum. Combatting the National Drug Demand and Opioid Crisis. Published October 26, 2017.
[4] U.S. Department of Labor. U.S. Department of Labor FY 2018-2022 Strategic Plan.
[5] U.S. Department of Labor Bureau of Labor Statistics. Employment by Major Industry Sector.
[6] Federal Employees' Compensation Act. 5 U.S.C § 8101.
[7] 5 U.S.C. § 8103(a)("The United States shall furnish to an employee who is injured while in the performance of duty, the services, appliances, and supplies prescribed or recommended by a qualified physician, which the Secretary of Labor considers likely to cure, give relief, reduce the degree or the period of disability, or aid in lessening the amount of the monthly compensation.")
[8] U.S. Department of Labor. Office of Workers' Compensation Programs. Division of Federal Employees' Compensation. Opioid Action Plan.
[9] Centers for Disease Control and Prevention. Opioid Prescribing Rate Maps.

Department of Defense guidelines,[10] and the CDC guidelines.[11] The Centers for Medicare and Medicaid Services (CMS) has implemented fraud, waste, and abuse controls along with prescribing limits for opioids.[12] Specifically, Medicare Part D has: instituted a hard safety edit to limit initial opioid prescriptions for acute pain; performed case management for high-risk opioid users; limited at-risk opioid users to certain prescribers and pharmacies; performed safety checks for duplicate therapy or drugs which may potentiate opioid-related effects; and performed safety checks if opioid doses reach a high dose.[13] Some state legislatures have implemented controls to reduce the dose or days' supply of initial opioid prescriptions,[14] and states have mandated use of prescription drug monitoring programs (PDMPs) for prescribers and pharmacies.[15] State workers' compensation programs have been instituting opioid prescribing policies and controls as well. Ohio, for example, after implementing a series of targeted system safety controls, observed a 59% reduction in the number of opioid dependent injured workers since 2011.[16] Also, among numerous activities in the private sector, retail pharmacies have publically championed tighter controls.[17,18]

However, while guidelines and controls have reduced the number of opioid prescriptions, opioids continue to be very common drugs prescribed in workers' compensation cases.[19] In 2016, about 45% of state workers' compensation claimants with a prescription were prescribed an opioid.[20] Data from the National Council on Compensation Insurance (NCCI) shows that injured workers who were prescribed at least one prescription in 2016 received three times as many opioid prescriptions compared to the overall US opioid prescribing rate.[21]

The hazards of opioid use, especially related to workers' compensation cases, are well documented. Chronic opioid use often begins with the treatment of acute pain, such as a work-related injury. As the amount of early opioid exposure increases, the risk for long-term use becomes greater. More than just a few days of opioid exposure can lead to addiction, and each day of unnecessary opioid use increases the likelihood of physical dependence without added benefit.[11] In a study of over 9,500 workers' compensation claimants in Maryland, nearly one in 10 injured workers continued opioids beyond one year from their injury date.[22] In a large retrospective cohort study of surgical claims, the total duration of opioid use was the strongest predictor of misuse, with each refill and additional week of opioid use associated with a 44%

[10] Department of Veteran Affairs/Department of Defense. VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain. Published February 2017.
[11] Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR Recomm Rep 2016;65(No. RR-1):1–49.
[12] Centers for Medicare and Medicaid Services. Improving Utilization Review Controls in Part D. Published December 10, 2018.
[13] Centers for Medicare and Medicaid Services. Note To: Medicare Advantage Organizations, Prescription Drug Plan Sponsors, and Other Interested Parties. Announcement of Calendar Year (CY) 2019 Medicare Advantage Capitation Rates and Medicare Advantage and Part D Payment Policies and Final Call Letter. April 2, 2018.
[14] National Conference of State Legislatures. Prescribing Policies: States Confront Opioid Overdose Epidemic. Published October 31, 2018.
[15] Prescription Drug Monitoring Program Training and Technical Assistance Center. Prescription Drug Monitoring Frequently Asked Questions.
[16] Ohio Bureau of Workers' Compensation. Opioid dependence continues to fall in Ohio's work comp system. February 22, 2018. Available at: https://info.bwc.ohio.gov/.
[17] Joseph A. CVS tightens restrictions on opioid prescriptions in bid to stanch epidemic. STAT. Published September 21, 2017.
[18] Romo V. Walmart will implement new opioid prescription limits by end of summer. NPR. Published May 8, 2018.
[19] Thumula V, Wang D, Liu T. Interstate variation in use of opioids, 4th edition. Workers Compensation Research Institute. June 2017.
[20] National Council on Compensation Insurance. 2018 – State of the Line Guide.
[21] National Council on Compensation Insurance. NCCI Examines the Impact of the Opioids on the Workers' Compensation System.
[22] O'Hara NN, Pollak AN, Welsch CJ, et al. Factors associated with persistent opioid use among injured workers' compensation claimants. JAMA Network Open. 2018:1(6):e184050.

increase in the rate of misuse.[23] Additionally, in workers' compensation, the chronic use of opioids has contributed to indemnity losses[24] and longer durations of disability.[25]

There is also a strong dose response relationship to opioid-related problems and overdose deaths. Results from a number of studies have confirmed that opioids are associated with dose-dependent increases in abuse,[26] death and overdose,[27,28] fractures,[29] myocardial infarction,[30] motor vehicle accidents,[31] and endocrinological effects.[32] In 2010, a study from a large health maintenance organization found that patients receiving opioids in over 100 morphine milligram equivalency (MME) per day were at nearly nine times the risk of overdosing compared to those on 20 MME per day. Approximately one in nine of those overdoses resulted in death.[27] In 2016, a prospective cohort study of over two million patients taking opioids determined that rates of overdose death among those prescribed opioid doses of 500 – 5,000 MME per day were over 60 times higher (80 per 10,000 person-years (95% CI 56.7-113.0)) than those prescribed opioid doses of up to 39.9 MME per day (1.3 per 10,000 person-years (95% CI 1.0 – 1.5)).[33] Thus, in 2016, the CDC released guidelines for prescribing opioids for chronic pain and stated that clinicians should avoid or justify a decision to titrate dosages of 90 MME per day or more due to these dose-related adverse events.[11]

Beyond dose and duration, the specific opioid formulation also impacts risk. A cohort study from the VA observed that those patients receiving long-acting or extended-release opioids had a 2.3 times greater risk of overdose than those patients taking short-acting opioids, with the risk greatest during the first two weeks of therapy.[34] The CDC and the Food and Drug Administration (FDA) have also strengthened their recommendations for extended-release formulations. The CDC chronic pain guidelines recommend clinicians should prescribe immediate-release opioids instead of extended-release opioids when starting opioid therapy,[11] and the FDA has instituted similar recommendations through their prescription drug labeling. The FDA recommends reserving extended-release opioids to use in patients for whom alternative treatment options, including immediate-release opioids, are ineffective, not tolerated, or would otherwise be inadequate. Additionally, in June of 2017, as recommended by the FDA, Endo Pharmaceuticals removed an extended-release opioid product from the market due to

[23] Brat GA, Agniel D, Beam A, et al. Postsurgical prescriptions for opioid naïve patients and association with overdose and misuse: retrospective cohort study. BMJ 2018;360:j5790.
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[34] Miller M, Barber CW, Leatherman S, et al. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. JAMA Intern Med. 2015;175(4):608-15.

abuse concerns (Opana ER (oxymorphone extended-release tablets)).[35] This was the first time the FDA requested an opioid pain medication be removed from the market.

Concurrent opioid use with other medications, such as benzodiazepine use, can also increase risk. In August of 2016, the FDA released a drug safety communication to the public, warning that taking opioids with benzodiazepines or other Central Nervous System depressants had resulted in serious side effects, including slowed or difficult breathing and death. The FDA added this as a boxed warning to all prescription opioid pain and prescription opioid cough medicines. Specifically, the FDA described increases in misuse, abuse, overdose, and death when taking opioids and benzodiazepines concomitantly.[36] Also noteworthy is that some specific subgroups are more commonly associated with receiving concomitant prescriptions of benzodiazepines and opioids, including women, those older than 65, and chronic users of opioids.[37]

Other drugs, such as muscle relaxants, sedative hypnotics, and gabapentinoids, can potentiate the adverse effects of opioids. The combination of an opioid, benzodiazepine, and carisoprodol, a muscle relaxant, is commonly referred to by the street name of 'Holy Trinity' due to the synergistic-like effects on euphoria.[38] This combination is associated with more than 12 times the risk of overdose death as compared to just taking opioids alone (aHR 12.6 (95% CI 8.9-17.9). Sedative hypnotics (including benzodiazepines, muscle relaxants, barbiturates, and nonbarbiturate hypnotics) when combined with opioids at lower doses are associated with greater than five times the risk of overdose death compared to those receiving no sedative hypnotics (aHR 5.6 (95% CI 1.6-19.3).[39] Further, gabapentin has been identified as an independent risk factor for opioid-related deaths due to its potential respiratory depressive effects and is reportedly misused due to its euphoric effects at high doses.[40,41] As the gabapentin dose increases so does the increase in opioid related deaths, and it should be noted that gabapentin concentrations increase by 44% when co-administered with morphine.[40,42] Also, pregabalin (another gabapentinoid), has been associated with increases in opioid-related deaths especially at increased doses.[43] The opioid epidemic has led prescribers to seek alternatives to opioids, and this has led to increases in gabapentinoid (gabapentin and pregabalin) prescriptions across the country.[44] However, this may have unintended consequences if these products potentially lead to abuse, misuse, and even opioid-related

[35] U.S. Food and Drug Administration. FDA requests removal of Opana ER for risks related to abuse. June 8, 2017.
[36] U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. August 31, 2016.
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[44] Goodman CW, Brett AS. Gabapentin and pregabalin for pain – is increased prescribing a cause for concern? N Engl J Med. 2017;377:411-4.

deaths. Overall, those prescribers who seek to reduce opioid use by coprescribing alternative medications may inadvertently be introducing new risks.[45]

Additionally, comorbid conditions can have an effect on opioid-related outcomes. Mental health conditions may have a synergistic effect with opioid-related overdoses and deaths. For example, a one percent increase in state-level depression diagnoses was associated with a 26% increase in opioid-related deaths.[46] Also, those with opioid-related toxicity were more likely to be diagnosed with anxiety, post-traumatic stress disorder, and bipolar disorder according to one study.[47]

Overall, the complexities to chronic opioid use have created significant challenges for patients, prescribers, pharmacies, and payers. In a survey from two large health plans of over 1,200 patients taking sustained high-dose opioids, nearly half (49%) of the patients agreed or strongly agreed to cut down or stop taking opioids, yet 80% continued taking high-dose opioids one year later.[48] A retrospective cohort from a large health plan showed that nearly all patients (91%) that had a nonfatal opioid overdose continued to receive opioids at a median follow-up of 299 days.[49]

In the workers' compensation context, opioid use may not stop after a workers' compensation case is closed, especially for those at higher doses. For example, according to a retrospective database study from Canada, those injured workers that received less than 10 Morphine Equivalent Dose (MED) at the end of their claim were likely to have post-claim opioid use in less than 15% of cases, while those with 120 MED or more at the end of their claim were likely to have post-claim opioid use in approximately 80% of cases.[50] This may be due to the difficulty prescribers and patients have in finding effective tapering methods to minimize withdrawal but also continue to provide effective pain relief. The rate at which opioids may be effectively tapered takes into account many factors including dose, formulation, and individual risk factors, which often results in a tailored tapering approach.

Objective

Due to the complexities of chronic opioid use, an examination of the FECA-specific population was warranted. A greater understanding of the dose level, concurrent drug use, and comorbid conditions affecting the federal injured worker would hopefully lead to the development of policies that can assist at-risk claimants, reduce chronic use, identify additional areas of study, and ultimately strive for measurable progress. Accordingly, this descriptive study aims to identify claimant-specific attributes that are associated with either lower (<90 MED) or higher (≥ 90 MED) dose chronic noncancer opioid utilization in the FECA population. This study focused on

[45] Throckmorton DC, Woodcock J. Combined gabapentinoid and opioid use: the consequences of shifting prescribing trends. Ann Intern Med. 2018;169:727-8.
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chronic opioid use at either a higher or lower dose, as initial research into FECA's opioid population has shown that a large portion have been taking opioids chronically at varying doses for years.[51] Studying this chronic opioid population more closely may also assist other programs, as payers, administrators, and prescribers often find this population is among the most challenging for optimizing drug therapy. Finally, the 90 MED threshold was utilized because it is a CDC-recommended threshold above which clinicians should avoid or justify a decision to further increase the dose. As explained above, dose is an indicator for increased risk which may further delineate the needs of these chronic opioid users.

Methods

To identify workers' compensation opioid drug claims and the primary cohort of chronic opioid users with either a lower or higher dose, we linked DFEC pharmacy claims paid for and provided from fiscal years 2017 and 2018 (10/1/2016 to 9/30/2018), based on National Drug Codes (NDCs) to First Data Bank's MedKnowledge database for specific hierarchical ingredient code descriptions (HIC_DESC).[52] The HIC_DESC is a 50-character alphanumeric column that provides the text description of generic drug names which then links brand and generic drugs. Applicable drug names for this study were first identified and compiled through a review of American Hospital Formulary Service Drug Information (AHFS-DI) drug classes, and through the U.S. National Library of Medicine's DailyMed database which were then linked to HIC_DESC and NDCs. Extended-release opioid products were identified through their dosage form description (GCDF_DESC). Methadone, fentanyl patches, and buprenorphine patches were all considered extended-release products. A list of abuse-deterrent extended-release opioid products was obtained from the FDA, and was used to identify such products.[53] Certain opioids that are only FDA-approved for opioid use disorder were excluded from the analysis if an opioid use disorder diagnosis was also recorded, including buprenorphine, methadone dispersible tablets, and buprenorphine/naloxone combination products. The supplementary material provides a listing of HIC_DESC and GCDF_DESC targets used in this study.

Chronic opioid users were defined based on methods previously described through the CONSORT (CONsortium to Study Opioid Risks and Trends) Study from the National Institute of Drug Abuse (NIDA) and Hooten WM et al.[54,55] For purposes of this study, claimants were defined as chronic opioid users if they had a total days' supply of ≥ 120 days, or ≥ 10 prescription opioid fills and > 90 total days' supply, over the two-year period. All claimants with an industrial cancer diagnosis were identified using International Classification of Diseases (ICD) codes listed from the Office of Inspector General's (OIG) Toolkit: Using Data Analysis to Calculate Opioid Levels and Identify Patients at Risk of Misuse or Overdose.[56] All claimants with an industrial cancer diagnosis were then excluded from any analysis.

Once characterized for purposes of this study a chronic noncancer opioid user, MME conversion factors were utilized from the CDC,[57] and methods from the OIG toolkit[56] were used

[51] U.S. Department of Labor. Office of Workers' Compensation Programs. Opioids Data and Charts..
[52] First Data Bank. FDB Medknowledge.
[53] U.S. Food and Drug Administration. Abuse-Deterrent Opioid Analgesics. April 23, 2018.
[54] Hooten WM, Stauver JL, Mcgree ME, et al. Incidence and risk factors for progression from acute to long-term opioid prescribing: A population-based study. Mayo Clin Proc. 2015;90(7):850-6.
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[56] U.S. Department of Health and Human Services. Office of Inspector General. Toolkit: Using data analysis to calculate opioid levels and identify patients at risk of misuse or overdose.
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to calculate the average daily MED in individual claimants. The average daily MED was calculated over the entire two-year time period. Claimants were then categorized into two groups: those claimants where the average MED was less than 90 MED were deemed lower-dose, and those claimants where the average MED was 90 MED or more were deemed higher-dose.

Concurrent use of opioids and other drugs was identified based on overlapping days' supply of 30 or more cumulative days. Additionally, naloxone specifically was considered concurrent if at least one day supply was overlapping, as naloxone is prescribed for preventative measures and not on a continuous basis as like other drugs.

Accepted mental health conditions, total accepted conditions, total surgeries, and urine drug screens were also compiled. Accepted conditions may have occurred prior to fiscal year 2017 if the accepted condition was still active during the study period. An active (accepted) condition is one in which the condition has not resolved. See the supplementary material for a further description of ICD codes utilized for the identification of other diagnoses relevant to the primary cohorts. Surgeries and urine drug tests were counted if the date of service was within the study's two-year period. Specifically surgical procedures were identified if current procedural terminology (CPT) codes fell within a range of 10021-69990. Certain demographics such as claimant age and sex were also captured.

Unique pharmacy and provider national provider identifiers (NPIs) where opioids were dispensed or prescribed were documented. Further, the claimant's first opioid prescription was captured, and duration and dose was assessed if it occurred during the study period (fiscal years 2017 and 2018). Finally, a time series analysis was computed from the proportion of opioid prescriptions per chronic noncancer opioid claimant monthly from October 2017 through September 2018.

Between-group comparisons were made statistically using Pearson's Chi-square test for categorical data and an independent t-test for continuous data using STATA 13.1 and verified by SAS Enterprise Guide. Mean and 95% confidence intervals were calculated for continuous data, and two-sided *P* values reflect statistical significance at an alpha level of 0.05. Figures were created from SAS Enterprise Guide, and time series data of opioid prescriptions was computed using R and visually inspected for any significance in trends. All claimants were de-identified and the study met agency exceptions under 45 CFR 46.104(4)(ii) and 45 CFR 46.104(4)(iv).

Results

Figure 1: Flow Chart of Study Group Inclusion and Exclusion FY17-FY18

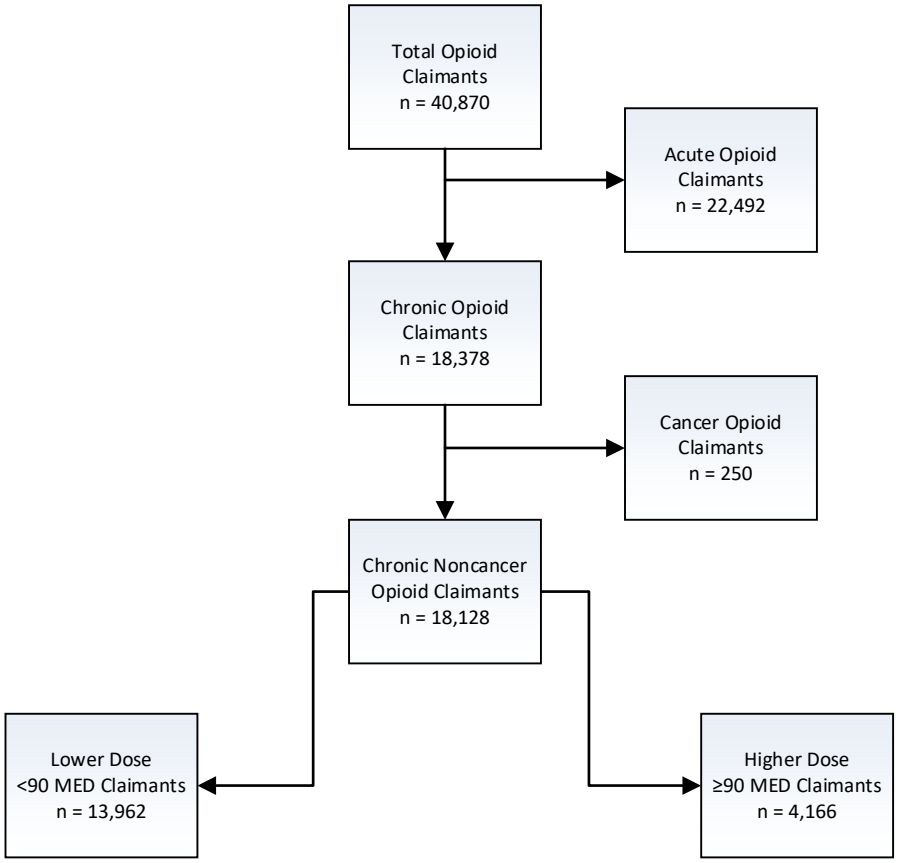


Table 1: Group Characteristics: FY17-FY18 Chronic, Noncancer, Opioid Claimants

Characteristic	**Lower Dose <90 MED (n = 13962) [77%]**	**Higher Dose ≥90 MED (n = 4166) [23%]**	***P* value***
Age, mean (SD)	60.1 (10.2)	61.1 (9.1)	<0.0001
Age > 65, n (%)	4601 (33)	1483 (35.6)	0.0015
Sex, n (%) Male Female	 6433 (46.1) 7529 (53.9)	 2267 (54.4) 1899 (45.6)	<0.0001
Accepted Diagnoses, mean (SD)	7.95 (4.96)	7.67 (4.60)	0.0012
Depression, n (%)	564 (4.0)	306 (7.4)	<0.0001
Bipolar, n (%)	498 (3.6)	251 (6.0)	<0.0001
PTSD, n (%)	231 (1.7)	63 (1.5)	0.5235
Substance Use Disorder, n (%)	35 (0.25)	40 (0.96)	<0.0001
Opioid Use Disorder, n (%)	29 (0.21)	30 (0.72)	<0.0001
Anxiety, n (%)	547 (3.9)	209 (5.0)	0.0018
Surgery, n (%)	6249 (44.8)	1692 (40.6)	<0.0001
Urine Drug Tests ≥ 2, n (%)	4388 (31.4)	1793 (43.0)	<0.0001
Number of opioid prescriptions, mean (SD)	18.7 (11.4)	37.0 (16.8)	<0.0001
Generic Opioid Prescriptions, mean (SD)	16.7 (11.1)	26.7 (16.7)	<0.0001
Brand Opioid Prescriptions, mean (SD)	1.45 (4.83)	8.45 (11.6)	<0.0001
Opioid duration in days, mean (SD)	436.6 (199.2)	593.7 (161.9)	<0.0001

Characteristic	Lower Dose <90 MED (n = 13962) [77%]	Higher Dose ≥90 MED (n = 4166) [23%]	*P* value*
Morphine Equivalency Dose (MED), mean (SD)	35.1 (20.1)	227.8 (202.2)	<0.0001
Extended-Release Opioids, n (%)	2852 (20.4)	3258 (78.2)	<0.0001
Extended-Release Abuse Deterrent Opioid, n (%)	884 (6.3)	1528 (36.7)	<0.0001
2 or more Extended-Release Opioids, n (%)	24 (0.17)	69 (1.66)	<0.0001
Acetaminophen, including acetaminophen/opioid combinations, n (%)	10,300 (73.8)	1902 (45.7)	<0.0001
Benzodiazepine, n (%)	1553 (11.1)	901 (21.6)	<0.0001
Gabapentinoid, n (%)	5348 (38.3)	1855 (44.5)	<0.0001
Muscle Relaxant, n (%)	6419 (46.0)	2080 (50.0)	<0.0001
Carisoprodol, n (%)	802 (5.7)	366 (8.7)	<0.0001
Serotonin-norepinephrine reuptake inhibitors (SNRIs), n (%)	1399 (10.0)	791 (19.0)	<0.0001
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), n (%)	6940 (49.7)	1709 (41.0)	<0.0001
Tricyclic Antidepressants, n (%)	490 (3.5)	289 (6.9)	<0.0001
Z-hypnotic, n (%)	1791 (12.8)	766 (18.4)	<0.0001
Naloxone, n (%)	509 (3.7)	601 (14.4)	<0.0001
Testosterone, n (%)	16 (0.11)	23 (0.55)	<0.0001
Opioids Only, n (%)	792 (5.7)	206 (4.9)	0.0707
Opioid, Benzodiazepine, and Carisoprodol, n (%)	143 (1.0)	96 (2.3)	<0.0001
Opioid, Benzodiazepine, Carisoprodol, and Gabapentinoid, n (%)	60 (0.43)	48 (1.15)	<0.0001
Opioid, Benzodiazepine, Carisoprodol, Gabapentinoid, and Z-hypnotic, n (%)	23 (0.16)	15 (0.36)	0.016
Number of Opioid Prescribers, mean (SD)	2.41 (1.61)	2.69 (1.79)	<0.0001
Number of Opioid Pharmacies, mean (SD)	1.75 (1.11)	1.99 (1.38)	<0.0001
≥ 4 Prescribers AND ≥ 4 Pharmacies, n (%)	350 (2.5)	180 (4.3)	<0.0001

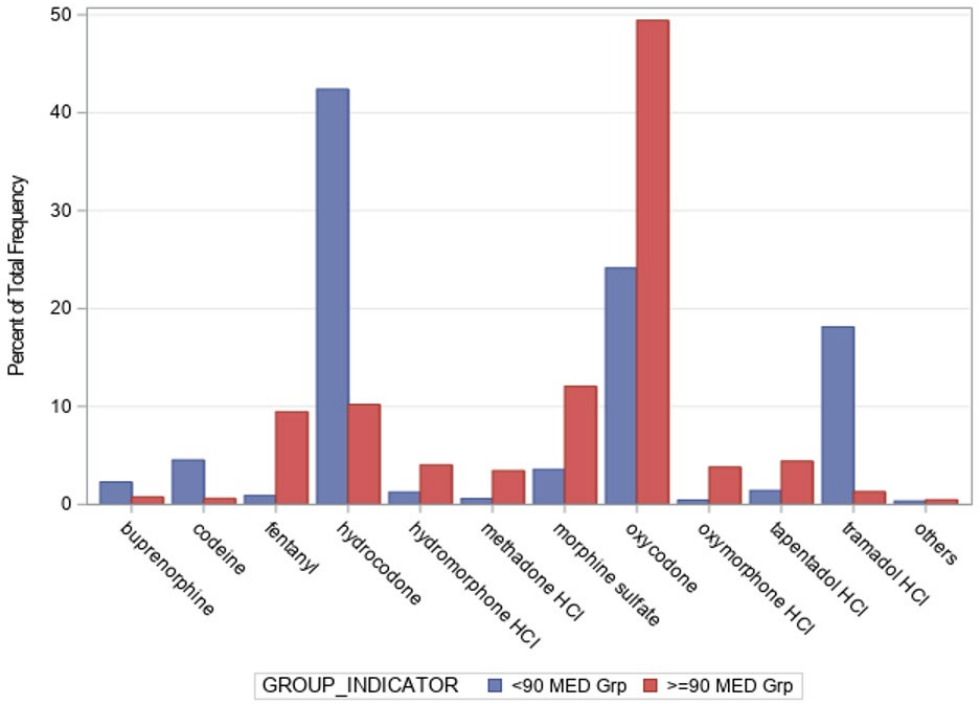
**P* values <0.05 denote statistical significance

Table 2: Chronic, Noncancer, Opioid Claimants Receiving a First Opioid Prescription During FY17 or FY18

Characteristic	Lower Dose <90 MED (n = 515) [93.6%]	Higher Dose ≥90 MED (n = 35) [6.4%]	*P* value*
First Opioid Prescription in Days, mean (SD)	22.0 (12.6)	35.3 (21.2)	<0.0001
First Opioid Prescription Morphine Equivalency Dose (MED), mean (SD)	29.2 (24.0)	103.7 (82.7)	<0.0001
First Opioid Prescription as Extended-Release, n (%)	34 (0.24)	13 (0.31)	0.445

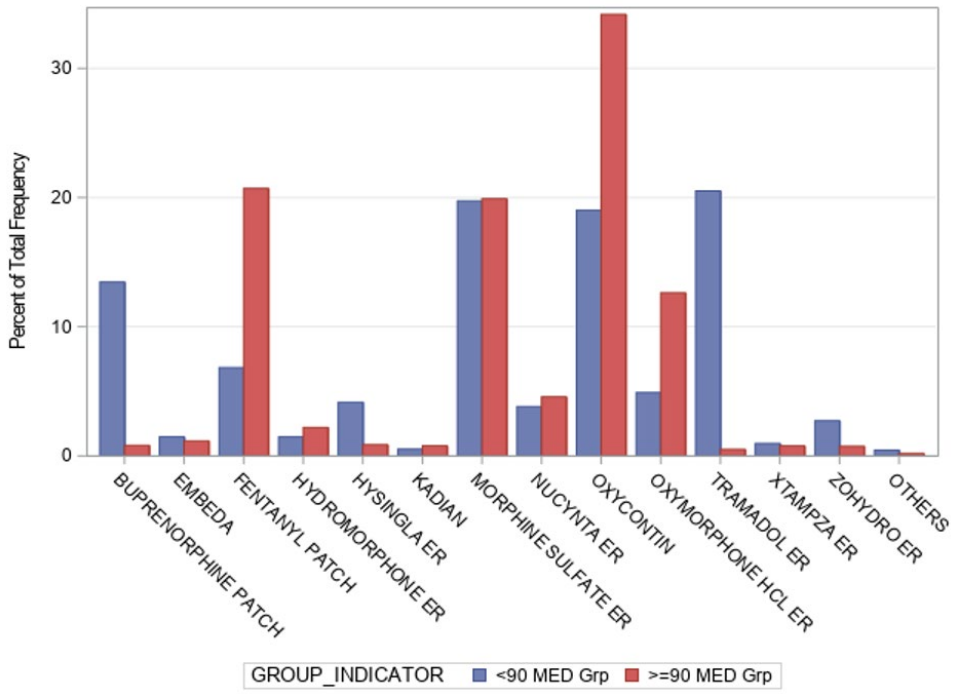
**P* values <0.05 denote statistical significance

Figure 2: Percentage of Opioid Prescriptions in Lower (<90 MED) or Higher (≥90 MED) Dose Cohort (FY17-18)*



***All individual drugs are statistically significant between each group (p<0.0001)**

Figure 3: Percentage of Extended-Release Opioid Prescriptions in Lower (<90 MED) or Higher (≥90 MED) Dose Cohort (FY17-18)*



***Morphine Sulfate ER (p=0.5184), Xtampza ER (p = 0.0016), all other individual drugs are statistically significant between each group (p<0.0001)**

Figure 4. Monthly Opioid Prescriptions per Claimant by MED Group FY17-18

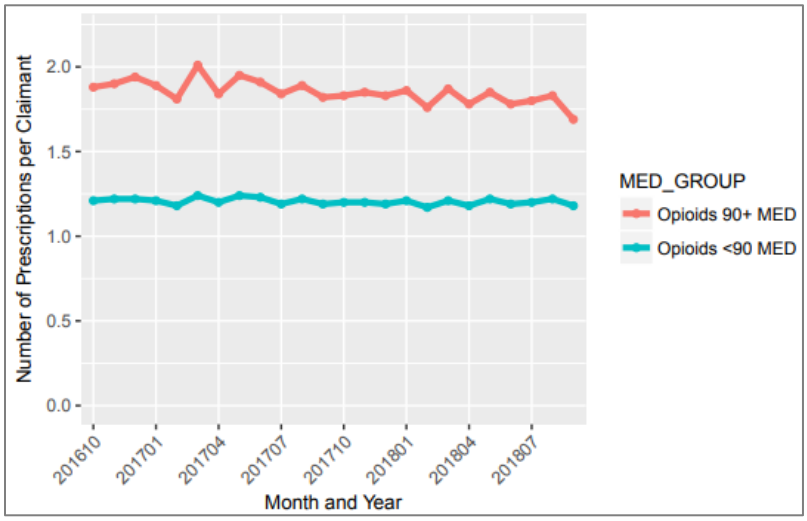


Figure 5. Monthly Oxycontin Prescriptions per Claimant by MED Group FY17-18

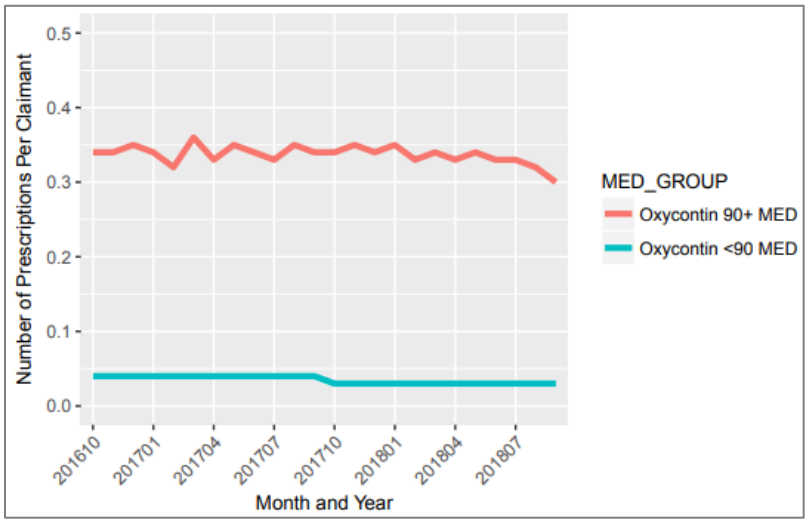
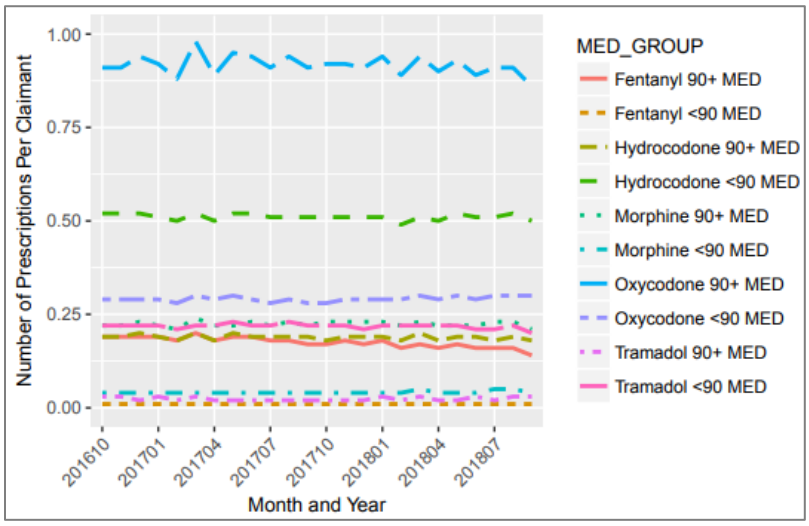


Figure 6. Monthly Five Opioid Prescriptions per Claimant by MED Group FY17-18



Discussion

This is the first known study to compare chronic, noncancer, opioid claimants that were prescribed higher (≥ 90 MED) or lower (< 90 MED) dose among federal workers with accepted work-related injuries under the FECA. A total of 40,870 unique claimants were identified as taking opioids over the studied two-year period with 18,128 non-cancer claimants receiving opioids on a chronic basis. These claimants averaged 436 opioid days in the lower-dose group and 593 opioid days in the higher-dose group.

The study revealed that nearly one in four chronic, noncancer, opioid claimants within the FECA population averaged a higher dose (4,166). Those claimants were more likely to be male (54.4% vs. 46.1%), have a diagnosis of depression (7.4% vs. 4.0%), anxiety (5.0% vs. 3.9%), and bipolar disorder (6.0% vs. 3.6%), than those claimants taking a lower dose. The higher-dose population also demonstrated higher usage of extended-release opioids (78.2% vs. 20.4%) and in particular oxycodone extended-release (34.2% vs. 19.0%), more concomitant use of interacting drugs including benzodiazepines (21.6% vs. 11.1%), and fewer first-line pain treatments such as acetaminophen (45.7% vs. 73.8%) or non-steroidal anti-inflammatory drugs (NSAIDs) (41.0% vs. 49.7%) than their lower-dose counterparts. More than half (57%) of this higher-dose population received less than two urine drug test over a two-year period, and only 14.4% received a prescription for naloxone despite an average MED above 200. They were also more likely to go to more pharmacies and more prescribers, and they received more opioid prescriptions over the two year period. (Table 1, Figures 2-6).

The higher-dose group also was consuming a large portion of extended-release opioid products. More than three out of four higher-dose opioid claimants (78.2%) were on an extended-release opioid in some form (Table 1). Extended-release opioids contain large opioid doses that are released into the body slowly over time to alleviate pill burden, but have not been adequately proven to provide more effective pain relief over immediate-release opioid formulations for chronic, noncancer pain.[58] These products have also been linked to higher rates of overdose and death.

Specifically, oxycontin, an extended-release formulation of oxycodone, was more prominent in the higher-dose group (Figure 2 and 5). Oxycontin has a long history of abuse in the United States, and some suggest it was the main culprit in starting the nation's current opioid crisis.[59] In the late 1990s and early 2000s, Oxycontin's manufacturer created aggressive marketing campaigns misrepresenting the risk of addiction to persuade doctors to prescribe it, despite the product offering no proven advantages over appropriate doses of other opioids. In fact, the FDA's medical review officer concluded that Oxycontin had not been shown to have a significant advantage over conventional, immediate-release oxycodone taken four times a day other than a reduction in the frequency of dosing. [60] The company engaged in unlawful marketing practices, which misrepresented the risk of addiction. They subsequently pled guilty to misbranding and

[58] Chou R, Clark E, Helfand M. Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: a systematic review. J Pain Symptom Mange. 2003;26(5):1026-48.
[59] Mettler K. Oxycontin – How misleading marketing got America addicted. The Washington Post. February 21, 2019.
[60] Van Zee A. The promotion and marketing of OxyContin: commercial triumph, public health tragedy. Am J Public Health. 2009;99(2):221-7.

was required to pay $600 million in fines in 2007.[61] However, marketing actions, even if later debunked or exposed, can have long lasting effects in medical practice.

Patients themselves also have a preference towards oxycodone products, likely for the wrong reasons. Even without its extended-release properties, oxycodone has an elevated abuse liability profile due to its high likability and fewer negative subjective effects than other opioids (morphine and hydrocodone), according to a systematic literature review of nine studies.[62] Other workers' compensation programs have had success in reducing Oxycontin usage in chronic users through the adoption of workers' compensation guidelines and moving Oxycontin off formulary.[63,64]

Due to various extended-release formulation concerns, in 2011, the FDA began to require a risk evaluation and mitigation strategy (REMS) for extended-release opioids, which is a drug safety program to help ensure the benefits of a medication outweigh its risks. The central component of the Opioid REMS is to provide education to prescribers.[65] This has had a small impact at the national level. One national audit of prescription claims showed a 4.3% reduction in extended-release opioids after the REMS was initiated.[66] Other educational efforts, such as academic detailing to prescribers, have resulted in changing prescribing patterns in atrial fibrillation and chronic obstructive pulmonary disease, may also produce promising results to address opioid overuse.[67] Further, in a number of workers' compensation programs, tighter controls have been instituted on extended-release products, such as requiring prior authorization, removing them from the formulary, and adopting guideline based prescribing.[63] Abuse-deterrent extended-release opioids were also more frequent in the higher-dose group (36.7%) versus the lower-dose group (6.3%). These products are newer extended-release products that may deter some aspects of abuse, such as overdose by injection or alternative routes of administration. However, none of the current abuse-deterrent formulations prevent overdose by consuming a large number of tablets or capsules, which is the most common method of abuse.[68]

As noted the higher-dose group also demonstrated more concomitant use of interacting drugs. Polypharmacy is the practice of prescribing multiple drugs to treat a single condition, such as chronic lower-back pain. Claimants with lower-back pain frequently present with muscle spasms, neuropathic pain, and difficulty sleeping. These symptoms may result in the prescribing of additional drugs, including muscle relaxants, gabapentinoids (gabapentin and pregabalin), z-hypnotics (zolpidem, zopiclone, and zaleplon), and benzodiazepines, the combination of which with opioids may increase the risk of overdose and death. The higher-dose group had nearly double the amount of claimants taking benzodiazepines (21.6% vs 11.1%). This is concerning because the dose-dependent relationship of opioid overdose mortality and respiratory depression is strongly influenced by concurrent benzodiazepine exposure, and especially in the

[61] United States of America vs. The Purdue Frederick Company, Inc., et al. Case No. 1:07CR00029 Available at: http://www.vawd.uscourts.gov/OPINIONS/JONES/107CR00029.PDF. July 23, 2007.
[62] Wightman R, Perrone J, Portelli I, et al. Likeability and abuse liability of commonly prescribed opioids. J Med Toxicol. 2012;8(4):335-40.
[63] Thumula V, Wang D, Liu T. Interstate variations in use of opioids, 3rd edition. Workers Compensation Research Institute. June 2016.
[64] Williams M. Ohio injured-worker fund to stop covering OxyContin prescriptions. The Columbus Dispatch. 2/22/2019. Available at: https://www.dispatch.com/business/20190222/ohio-injured-worker-fund-to-stop-covering-oxycontin-prescriptions.
[65] U.S. Food and Drug Administration. Opioid analgesic risk evaluation and mitigation strategy (REMS). December 17, 2018.
[66] Divino V, Capedea MS, Coplan P, et al. Assessing the impact of the extended-release/long-acting opioid an-algesics risk evaluation and mitigation strategies on opioid prescrip-tion volume. J Opioid Mang. 2017;13(3):157-168.
[67] Trotter Davis M, Bateman B, Avorn J. Educational outreach to opioid prescribers: the case for academic detailing. Pain Physician. 2017;20(2S):S147-51.
[68] U.S. Food and Drug Administration. Abuse-deterrent opioid analgesics. April 23, 2018.

presence of higher opioid doses, according to one study.[69] Other drugs such as z-hypnotics, gabapentin, and muscle relaxants, including carisoprodol, were all increased in the higher-dose group, and all have the ability to potentiate opioid adverse events. Z-hypnotics are some of the most common agents used for the treatment of insomnia. They have similarities to benzodiazepine mechanisms of action and sedative effects and are recommended by the FDA to be limited when used with opioids.[36] Opioids with zolpidem or other z-hypnotics have CNS respiratory depressant effects which may increase the risk of death. Gabapentinoids are classified as antiepileptic drugs, but are commonly used off-label for chronic neuropathic pain conditions. Gabapentin and pregabalin (gabapentinoids) have been shown to potentially be an independent risk factor for opioid-related overdose, and were utilized more in the higher-dose group, with 44.5% of those claimants taking a gabapentinoid versus 38.3% in the lower-dose group. Muscle relaxants can also be problematic when concomitantly prescribed with opioids. For example, carisoprodol, and its metabolite, meprobamate, can cause abuse, dependence, and respiratory depression, and when combined with opioids and benzodiazepines the effects can be additive, producing higher risks for death.[39] A handful of claimants were concurrently taking an opioid, carisoprodol, benzodiazepine, gabapentinoid, and a z-hypnotic in both groups, likely representing the highest risk subset.

Risk profiling programs, such as the VA's stratification tool for opioid risk mitigation,[70] can assist in targeting potentially at-risk claimants for pharmacotherapy interventions, including retrospective drug utilization reviews. These types of activities have shown substantial benefits in other programs. For example, once potentially at-risk claimants have been identified, retrospective drug utilization review by pharmacists can identify problem areas to be communicated with providers. One study from a commercial health plan showed a 28% reduction in potentially unsafe opioid and central nervous system combination therapy after targeting high-risk opioid users.[71]

Initial opioid prescription dose and duration are also quite important at outlining future risks associated with long-term opioid use. In this study, a smaller cohort of claimants (Table 2) started opioids during the study period of fiscal years 2017 and 2018, the higher-dose group was more likely to have a higher MED and a longer duration on the first opioid prescription than the lower-dose group. It appears the results are similar to what other studies are finding when considering the dose and duration of the initial opioid prescription.[23]

The higher-dose group was also more likely to go to four or more pharmacies and four or more prescribers than the lower-dose group (4.3% vs. 2.5%).The Centers for Medicare and Medicaid Services (CMS) along with their Part D sponsors measure and track beneficiaries that obtain opioids at four or more pharmacies and four or more prescribers. CMS then allows their Part D sponsors to perform drug utilization reviews, implement real-time safety edits, and restrict potential at-risk beneficiaries to selected pharmacies or providers to improve opioid safety and minimize fraud, waste, and abuse. Since implementing these controls in 2011, CMS has seen a

[69] Dasgupta N, Jonsson M, Proescholdbell S, et al. Cohort study of the impact of high-dose opioid analgesics on overdose mortality. Pain Med. 2016;17:85-98.
[70] Olivia EM, Bowe T, Tavakoli S, et al. Development and applications of the Veterans Health Administration's stratification tool for opioid risk mitigation (STORM) to improve opioid safety and prevent overdose and suicide. Psychol Serv. 2017;14(1):34-49.
[71] Qureshi N, Wesolowicz LA, Liu C, et al. Effectiveness of a retrospective drug utilization review on potentially unsafe opioid and central nervous system combination therapy. J Manag Care Spec Pharm. 2015;21(10): 938-44.

76% decrease in their beneficiaries taking 120 MME and in those going to four or more pharmacies and four or more prescribers.[13]

The lower-dose group also had unique factors that should be examined further. Overall, the lower-dose group was taking different opioids than the higher-dose group, with many in the lower-dose group taking less potent opioid products (Figure 2 and 3). Tramadol (18.1% vs. 1.3%) and hydrocodone (42.4% vs. 10.2%), in particular, were much more common in the lower-dose group than the higher-dose group (Figure 2). This would be expected as these products have a lesser opioid potency (MME equivalent) than products such as oxycodone. Both drugs have been commonly prescribed in and outside of workers' compensation for years and are inexpensive options for both prescribers and claimants. Due to their potential for abuse, both underwent controlled substance rescheduling in 2014. This prevented hydrocodone combination products from being refilled, and dropped the national prescription rate from 120 million in 2014 to 93.5 million prescriptions in 2015.[72] As a result, tramadol prescriptions increased as prescribers turned from hydrocodone to tramadol and other non-Schedule II controlled substances for pain.[73] It should be noted that tramadol is often considered a safer alternative to opioids; however, a 50 milligram tablet of tramadol has the same morphine equivalency as a five milligram tablet of hydrocodone. Tramadol has a similar adverse event profile as opioids, plus the risk for seizures.[74]

Buprenorphine patch was also more common in the lower-dose group than the higher-dose group (13.5% vs. 0.8%) (Figure 3). Buprenorphine patch, unlike other extended-release opioids that are a Schedule II controlled substance, is a Schedule III controlled substance. Meaning that it has a lower expected abuse or dependency potential than other extended-release opioids. Buprenorphine is a partial opioid agonist that has a respiratory depressive ceiling effect, yet no apparent ceiling effect for analgesia at therapeutic doses. This improves buprenorphine's safety profile versus other opioids. For example, in a 24 month cohort study of the National Poison Data System, buprenorphine patch was associated with only five calls of abuse, 11 calls for suspected suicidal intent, and no deaths out of 1,073,812 prescriptions dispensed. These rates were less than any other extended-release opioid.[75] Note though, the buprenorphine patch still caries warnings that it may lead to a fatal arrhythmia and has a high discontinue rate due to its lack of efficacy.[76]

One aspect of each cohort that cannot be over looked is the age of the claimants. In both the higher-dose and lower-dose groups, over a third of patients were over the age of 65. This is concerning because older patients are normally more sensitive to drug products and have a more difficult time metabolizing and eliminating drugs from the body. The American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults recommends avoiding many drugs and drug classes listed in this study, including benzodiazepines, muscle

[72] Burke J. Hydrocodone prescribing and quotas. Pharmacy Times. January 16, 2017. Available at: https://www.pharmacytimes.com/publications/issue/2017/january2017/hydrocodone-prescribing-and-quotas.
[73] Varisco TJ, Ogunsanya ME, Barner JC, et al. Pharmacists' perceptions regarding the impact of hydrocodone rescheduling on prescription volume, workflow management, and patient outcomes. J Am Pharm Assoc. 2017;57(2S):S51-62.
[74] Professional Product Label – Ultram (tramadol hydrochloride tablet, coated). Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=45f59e6f-1794-40a4-8f8b-3a9415924468.
[75] Coplan PM, Sessler NE, Harikrishnan V, et al. Comparison of abuse, suspected suicidal intent, and fatalities related to the 7-day buprenorphine transdermal patch versus other opioid analgesics in the National Poison Data System. Postgrad Med. 2017;129(1):55-61.
[76] Butrans (buprenorphine patch, extended-release). Professional Product Label. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=794aa355-66de-41b8-aedf-f2c40f6bc664.

relaxants, and z-hypnotics.[77] The older adult population also tends to be reluctant to speak up and question their doctor's decisions and are much more passive in communicating about their health care than younger generations.[78] The National Poll on Healthy Aging shows that only about one in three older Americans who take prescription drugs have talked to anyone about possible drug interactions in the past two years.[79] Simply discussing and communicating the risk of opioids with patients can help prevent abuse,[80] and ensuring patients are provided FDA-approved Medication Guides can help patients avoid serious adverse events.[81]

Like this study of the FECA program, others have shown that adult chronic opioid users, irrespective of dose level, are more likely to receive potentially unsafe medications that deviate significantly from nationally-accepted guidelines and FDA recommendations.[82] It may be that prescribers struggle to control pain in their population due to the lack of beneficial drug-related pain therapies, run out of options, and care for their patients by unintentionally exposing patients to significant risks through various drugs and drug combinations. As prescribers explore new pain management options, switching from one product to another should not be seen as a panacea, especially with opioids. This may result in new patterns of abuse or adverse events as larger portions of the population are affected and now can be monitored using effective data sources.

Prescribers may want to tailor specific plans, in conjunction with their patients, seeking noninvasive nonpharmacological treatments for chronic pain where evidence displays beneficial results.[83] Medicare Part D has been successful in using a tailored approach to care of its chronic opioid user population,[13] and DFEC has been working with claimants and their treating providers to assist claimants with opioid-specific issues, discuss medication-assisted treatment, provide second medical opinions to optimize drug and non-drug therapy for pain, and assist in the opioid tapering process for those on higher-opioid doses. This may explain some of the drop seen in the higher-dose group over time (figure 4).

Tapering opioids can specifically be challenging and stressful for prescribers, patients, and family members involved, as there is no one fits all approach to tapering. For example, the VA, with its published opioid taper decision tool, has multiple suggestions on the approach to tapering.[84] The reductions in dose and the frequency of those dose reductions can vary from weekly to monthly or even longer. Also, patients may fail potentially multiple tapering trials prior to being free of opioids, and some may never be able to be tapered off completely. Some may require medication-assisted treatment with buprenorphine or methadone, for example, if opioid use disorder manifests itself as a concern.

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[77] Fick DM, Semia TP, Beizer J, et al. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. 2015;63(100):2227-46.

[78] Kahana E, Kanaha B. Baby Boomers' expectations of health and medicine. Virtual Mentor. 2014;16(5):380-4.

[79] Malani P, Singer D, Clark S, et al. Drug interactions: how to avoid them. National Poll on Healthy Aging. University of Michigan. December 2017. Available at: https://www.healthyagingpoll.org/sites/default/files/2017-11/NPHA_Drug-Interactions-Report_111417.pdf.

[80] Hero JO, McMurtry C, Benson J, et al. Discussing opioid risks with patients to reduce misuse and abuse: evidence form 2 surveys. Ann Fam Med. 2016;14(6):575-7.

[81] U.S. Food and Drug Administration. Medication Guides. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm085729.htm.

[82] Silva Arlmodovar A, Nahata MC. Potentially unsafe chronic medication use among older chronic opioid users. Pharmacotherapy. 2019 Jan 13. Doi: 10.1002/phar.2218. [Epub ahead of print]

[83] Skelly AC, Chou R, Dettori JR, et al. Noninvasive nonpharmacological treatment for chronic pain: a systematic review. Comparative Effectiveness Review No. 209. AHRQ Publication No 18-EHC013-EF. June 2018.

[84] U.S. Department of Veterans Affairs. PBM Academic Detailing Service. Opioid Taper Decision Tool.

Overall, there is limited evidence of the benefit of opioids for chronic noncancer pain, regardless of dose, despite substantial evidence of harms.[85] This study detailed characteristic differences among those claimants taking higher- or lower-dose opioids chronically, and showed that some claimants may even be at greater risk than others. DOL will continue its efforts to assist claimants receiving chronic opioids, especially in working with claimants and prescribers to reduce or discontinue opioid use. Discontinuing or reducing opioids may in fact improve pain, function, and the quality of life of those chronically receiving opioids.[86] DOL will also continue its close and continuous examination of the data to find effective sustainable solutions.

Limitations

There are limitations to this study that should be noted. The CDC defines long-term opioid therapy as the use of opioids on most days for > 3 months.[11] For purposes of this study, claimants were defined as chronic opioid users if they had a total days' supply of ≥ 120 days, or ≥ 10 prescription opioid fills and > 90 total days' supply, over the two-year period. This may have identified claimants over the two year period that were not taking opioids consistently over a 3 month period as defined by the CDC. However, the identified claimants in this study averaged 436 opioid days in the lower-dose group and 593 opioid days in the higher-dose group over the studied two-year period. This is well over most days during the two year period. This study only identified claimant characteristics that were documented within DFEC's billing systems. The claimant's comorbid diagnoses outside of workers' compensation (non-employment-related conditions) were not considered as they are not documented in the billing system. Further, as the study focused on ICD 10 accepted conditions, it was difficult to determine the severity of the injuries or the severity of pain between the groups. Certain claimants in either group may have a greater need for pain control and higher doses may be medically justified and may have failed certain first-line treatments. This study did not assess any variances between injury diagnoses. A recent analysis of workers' compensation claimants in Maryland found that opioid use was significantly associated with strain, sprain injuries, and crush injuries.[22] Further, opioid prescribing practices (quantity, dose, and duration) vary by geographic location, which was not studied here. One study showed that the wide variation of opioid prescribing does not reflect differences in the prevalence of injuries, surgeries, or conditions, but rather indicates the lack of consistency among providers when prescribing opioids. The variation is likely a result of a number of dynamics from local medical subcultures to how medical practices are organized.[87] Our study also did not address variability among medical specialties. A study of over 80,000 Medicaid patients found significant difference among various medical specialties, and that all medical specialties, except internal medicine, had higher odds of prescribing an opioid than general practitioners for chronic noncancer pain.[88] The aspects and limitations above have been found to be additional measurement points to pursue in the future to further detail any additional variations among claimants receiving opioids on a chronic basis.

Conclusion

[85] Chou R, Deyo R, Devine B, et al. The effectiveness and risks of long-term opioid treatment of chronic pain. Evidence Report/Technology Assessment No. 218. AHRQ Publication No. 14-E005-EF. September 2014.
[86] Frank JW, Lovejoy TI, Becker WC, et al. Patient outcomes in dose reduction or discontinuation of long-term opioid therapy: a systematic review. Ann Intern Med. 2017;167(3):181-91.
[87] McDonald DC, Carlson K, Izrael D. Geographic variation in opioid prescribing in the U.S. J Pain. 2012;13(10):988-96.
[88] Ringwalt C, Gugelmann H, Garrettson M, et al. Differential prescribing of opioid analgesics according to physician specialty for Medicaid patients with chronic noncancer pain diagnoses. Pain Res Manag. 2014;19(4):179-85.

The opioid epidemic has far-reaching effects which can be seen in injured federal workers. This is the first known study involving 18,128 injured federal workers to compare characteristics of chronic, noncancer, opioid claimants that were prescribed higher (≥ 90 MED) or lower (< 90 MED) dose. This study revealed that these claimants were not only differentiated by dose, but also by specific attributes that may compound the risk of overdose and death even further. A higher opioid dose is a risk factor for overdose and death by itself, but the higher-dose group was also more likely to use potentially unsafe medications, such as extended-release opioids, as well as potentially unsafe combinations, including benzodiazepines, muscle relaxants, gabapentinoids, and z-hypnotics, than their chronic lower-dose counterparts, which may potentially compound these risks. This was all in a setting where evidence to support the effectiveness of chronic opioid use is lacking, and points to areas where risks may outweigh benefits. Overall, this study provided much needed insight into areas where improvements can be made to assist potential at-risk claimants, and reduce chronic opioid use. Additionally, there are identified areas for further study. The Office of Workers' Compensation Programs' (OWCP) will be striving to make measurable progress based on this study and others through its four-point strategic plan to combat the opioid epidemic and reduce the potential for opioid misuse and addiction among injured federal workers.