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RESEARCH ARTICLE

An Examination of Concurrent Opioid and Benzodiazepine Prescribing in 9 States, 2015

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Introduction: Concurrent prescribing of opioids and benzodiazepines is discouraged by evidence-based clinical guidelines because of the known risks of taking these medications in combination.

Methods: This study analyzed concurrent opioid and benzodiazepine prescribing in 9 states using the 2015 Prescription Behavior Surveillance System, a multistate database of de-identified prescription drug monitoring program data. Concurrent prescribing rates were examined among individuals with both an opioid and a benzodiazepine prescription. Among patients with concurrent prescribing, total days of opioid supply, daily dosage of opioids, and total days of concurrent prescriptions were examined. Analyses were stratified by whether concurrent prescribing was from a single prescriber or multiple prescribers. Opioid prescribing and concurrent opioid and benzodiazepine prescribing rates were examined by age and sex. Analyses were conducted in 2018.

Results: Among 19,977,642 patients that were prescribed an opioid, 21.6% (4,324,092) were also prescribed a benzodiazepine, of which 54.9% (2,375,219) had concurrent prescriptions. More than half of patients with concurrent opioids and benzodiazepines received prescriptions from 2 or more distinct prescribers. Mean total opioid days, daily opioid dosage, and days of concurrent prescribing were higher among patients when multiple prescribers were involved compared with concurrent prescriptions from the same prescriber. Concurrent prescribing was more common among adults aged ≥50 years and female patients.

Conclusions: Public health interventions are needed to reduce concurrent prescribing of opioids and benzodiazepines. Evidence-based guidelines can help reduce concurrent prescribing when one prescriber is involved, and utilization of prescription drug monitoring programs and improved care coordination could help address concurrent prescribing when multiple prescribers are involved.
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INTRODUCTION

Although opioid analgesics are the most common drugs involved in prescription drug overdose deaths, benzodiazepines often play a contributing role, and are involved in approximately one third of all opioid overdose deaths in the U.S.[1] When taken together, opioids and benzodiazepines can result in synergistic respiratory depression and substantially increase the risk of drug overdose.[1–5] In an effort to decrease the use of opioids and benzodiazepines together, the U.S. Food and Drug Administration added a boxed warning to the drug labeling of prescription opioids and benzodiazepines in 2016.[6]

Despite reductions in opioid prescribing in the U.S.,[7] concurrent prescribing of opioids and benzodiazepines remains common.[4,8–10] From 2002 to 2014, the proportion of opioid recipients in the U.S. who were dispensed a benzodiazepine concurrently rose by 41%, with approximately half of patients receiving both prescriptions from the same prescriber on the same day.[8] Further, a retrospective analysis of privately insured claims data from 2001 to 2013 found that concurrent opioid

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and benzodiazepine prescribing increased from 9% in 2001 to 17% in 2013.[4] Nearly 3% of all emergency room encounters receiving an opioid prescription also received a benzodiazepine prescription.[10] In addition, a study using national laboratory test results indicated concurrent use of opioids and benzodiazepines in more than 25% of patients in 2015.[11]

The trend in concurrent opioid and benzodiazepine prescribing also parallels a rising trend in emergency department visits and drug overdose deaths in which both opioids and benzodiazepines are implicated.[1] From 2004 to 2011, the rate of emergency department visits involving nonmedical use of both opioid analgesics and benzodiazepines rose from 11.0 to 34.2 visits per 100,000, and during this same period, drug overdose deaths involving both opioids and benzodiazepines increased from 0.6 to 1.7 per 100,000.[1]

Although previous studies provide information on the trends and frequency of concurrent opioid and benzodiazepine prescribing,[8] limited information exists on how frequently these overlapping episodes result from a single provider versus multiple providers. In addition, limited information exists on the patient characteristics, frequency, dosage, and duration of concurrent prescribing.[12] Such information could be helpful in understanding the patterns of concurrent prescribing of opioids and benzodiazepines and help inform prevention efforts. Implications for prevention efforts could be different based on the number of prescribers involved in overlapping opioid/benzodiazepine episodes. For example, evidence-based guidelines, such as the "CDC Guideline for Prescribing Opioids for Chronic Pain" (Centers for Disease Control [CDC] Prescribing Guideline),[13] which recommends a high degree of caution when prescribing an opioid in combination with a benzodiazepine, could be more helpful in reducing concurrent prescribing when one prescriber is involved, as opposed to multiple providers unaware of each other's prescriptions. Meanwhile, prescription drug monitoring programs (PDMPs), electronic databases used to monitor the prescribing and dispensing of controlled substance, and care coordination may be more effective when concurrent prescribing is the result of multiple prescribers. Understanding the characteristics of patients with an overlapping episode can help identify effective interventions and better target efforts to reduce the concurrent prescribing of opioids and benzodiazepines. The objectives of this study are the following: (1) to examine the number of distinct prescribers involved in concurrent opioid and benzodiazepine prescribing episodes; (2) to investigate the days of opioid use, daily dosage of opioids, and duration of concurrent prescribing; and (3) to analyze the demographic characteristics of patients with concurrent prescriptions.

METHODS

Data from PDMPs were obtained through the Prescription Behavior Surveillance System (PBSS) at Brandeis University. PBSS is a longitudinal database of de-identified PDMP data from multiple states that have collected statewide PDMP data. PBSS was created to serve as an early warning public health surveillance tool and a database for evaluation of state and local policies and interventions aimed at improving the prescribing of controlled substances. CDC determined this study to be exempt from human subject regulations and IRB approval.

The PBSS contains information regarding all in-state filled controlled substance prescriptions that are received by a state PDMP. Information includes de-identified patient ID, de-identified prescriber ID, de-identified pharmacy ID, dispensing date, days of supply, quantity dispensed, drug name, National Drug Code, patient birthday, patient sex, and geographic information of the patient and the pharmacy. Availability of this information varies by state. Brandeis University calculated the total dosage and daily dosage of all opioid prescriptions as morphine milligram equivalents (MMEs). MME conversion factors have been published elsewhere.[14]

Study Population

The current study includes 2015 PDMP data from 9 of the 11 states participating in PBSS: California, Delaware, Florida, Idaho, Kentucky, Maine, Ohio, Virginia, and West Virginia. Two states were excluded because prescription information needed (e.g., prescriber ID) for the analysis was not available. Data from 2015 were used, as they were the most current data available for analysis. Out-of-state residents who filled opioid or benzodiazepine prescriptions in 1 of the 9 states were excluded from the analysis.

Measures

Individuals with at least one opioid prescription were identified. Overall opioid prescribing rates were calculated using 2015 population estimates from the U.S. Census Bureau for each of the 9 states. Among individuals with an opioid prescription, the percentage with at least one benzodiazepine prescription in 2015 was examined. Opioid and benzodiazepine prescriptions were identified using their National Drug Code codes. Buprenorphine products, typically used for substance use disorder treatment, were excluded from the analysis.[7] Methadone used for the treatment of opioid use disorder at methadone clinics is not available in PDMP data.

The rate of concurrent prescribing was examined among individuals who had both an opioid and a benzodiazepine prescription. Concurrent prescribing was defined as having any opioid and benzodiazepine prescriptions, which overlapped for at least 7 consecutive days.[8,15–17] Concurrent prescriptions did not have to be dispensed on the same day. De-identified prescriber ID was used to identify the source of prescriptions. If an individual had concurrent prescriptions from the same prescriber during the year, the source of concurrent prescriptions was defined as one

prescriber; otherwise, the source of concurrent prescriptions was defined as multiple prescribers (i.e., different prescribers).

Three characteristics of concurrent opioid and benzodiazepine prescriptions were examined among individuals who had concurrent opioid and benzodiazepine prescriptions: total days of opioid supply, daily dosage of opioids, and total days of concurrent prescribing. Total days of opioid supply were calculated as the total number of calendar days during the year that an individual had an opioid supply. Individuals with overlapping opioid prescriptions were assumed to take them concurrently. Thus, given the definition, total days of opioid supply could only be equal to or greater than the total days of concurrent prescribing, and it could not exceed 365 days. Daily dosage of opioids was defined as the total dosage of opioid prescriptions of an individual divided by total days of opioid supply. High daily dosage of opioids was defined as daily dosage ≥90 MMEs per day.[13] Total days of concurrent prescribing was defined as total days of overlapping opioid and benzodiazepine prescriptions. When an individual had more than one occurrence of concurrent prescribing during the year, total days of concurrent prescribing was obtained by adding up each occurrence. If multiple opioid prescriptions overlapped with a single benzodiazepine or multiple benzodiazepines prescriptions overlapped with a single opioid, an overlapping day was only counted once to avoid double counting.

Statistical Analysis

Means were calculated for total days of opioid supply, daily dosage of opioids, and total days of concurrent prescriptions stratified by prescriber sources of concurrent opioid and benzodiazepine prescriptions (one prescriber versus multiple prescribers). To test for differences across the measures, *t*-tests were used. Rates of opioid prescribing and concurrent opioid and benzodiazepine prescribing were examined by age and sex. All analyses were conducted in SAS, version 9.4, and Stata, version 14.2. Analyses were conducted in 2018.

RESULTS

In 2015, across the 9 states, 20.0 million patients (22.3% of their total population) were dispensed an opioid (Table 1). The rate of opioid prescriptions varied at the state level from 20.8% in Delaware to 24.9% in Virginia and West Virginia. In 2015, among patients prescribed an opioid, 21.6% were also prescribed at least one benzodiazepine. The rate of benzodiazepine prescriptions among opioid patients ranged from 19.5% in Virginia to 26.5% in West Virginia. Among patients prescribed both an opioid and a benzodiazepine, 54.9% had concurrent prescriptions. The rate of concurrent prescribing varied at the state level from 46.1% in Idaho to 65.1% in West Virginia.

In each of the 9 examined states, more than half of patients with concurrent opioids and benzodiazepines received prescriptions from 2 or more distinct prescribers (Figure 1). The involvement of 2 or more prescribers in a concurrent episode was most common in Delaware (66.9%), Maine (64.8%), and Ohio (64.1%), and least common in West Virginia (52.4%) and California (53.2%).

Table 1. Rate of Opioid and Benzodiazepine Prescriptions by State, 2015

Variable	California	Delaware	Florida	Idaho	Kentucky	Maine	Ohio	Virginia	West Virginia	9 states
State population	39,144,818	945,934	20,271,272	1,654,930	4,425,092	1,329,328	11,613,423	8,382,993	1,844,128	89,611,918
Population with at least one opioid prescription										
Number	8,153,894	197,234	4,728,318	356,806	1,070,725	298,516	2,680,067	2,089,185	402,888	19,977,642
Percentage	21.5	20.8	23.3	21.5	24.2	22.4	23.1	24.9	24.9	22.3
Patients prescribed an opioid, population with at least one benzodiazepine										
Number	1,677,950	41,553	1,143,916	73,749	234,021	66,996	572,275	406,814	106,818	4,324,092
Percentage	20.6	21.1	24.2	20.7	21.9	22.4	21.4	19.5	26.5	21.6
Patients prescribed both, population with concurrent prescriptions										
Number	948,189	20,652	635,356	33,976	144,909	32,532	289,546	200,563	69,496	2,375,219
Percentage with concurrent prescriptions, %	56.5	49.7	55.5	46.1	61.9	48.6	50.6	49.3	65.1	54.9

Note: State population estimates were obtained from the U.S. Census Bureau.

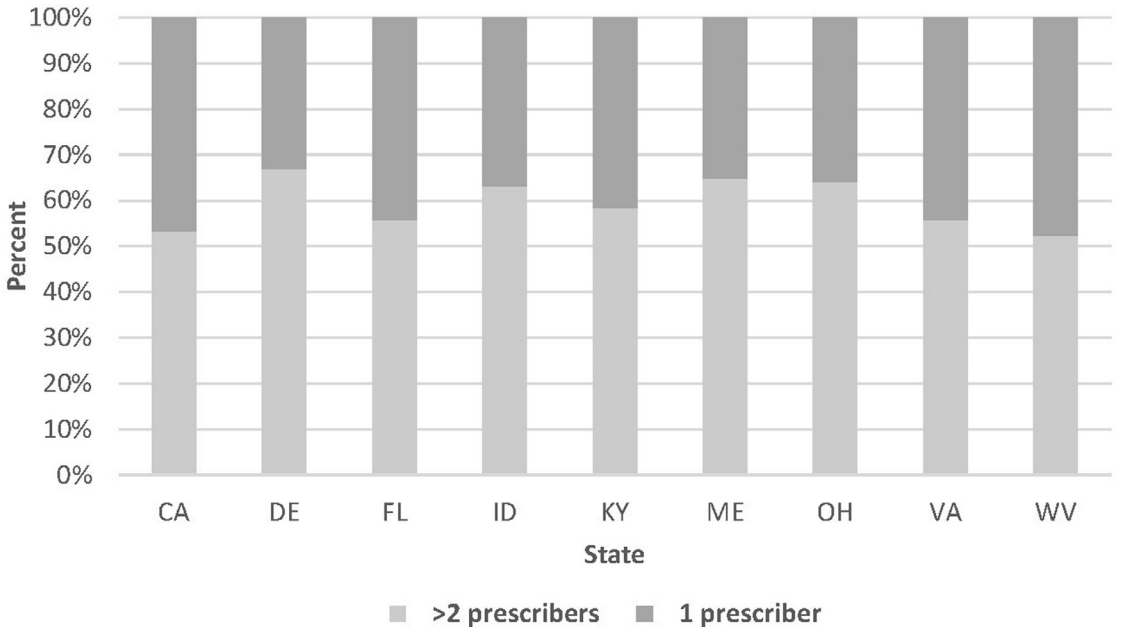

Figure 1. Distribution of concurrent opioid and benzodiazepine prescribing by the number of prescribers involved.
CA, California; DE, Delaware; FL, Florida; ID, Idaho; KY, Kentucky; ME, Maine; OH, Ohio; VA, Virginia; WV, West Virginia.

The characteristics of concurrent opioid and benzodiazepine prescriptions varied by state and the number of prescribers involved. Across the 9 states, mean total days of opioid supply were higher when the concurrent prescriptions were from 2 or more prescribers (153.1 days) compared with when 1 prescriber was involved (118.8 days, $p<0.001$). Kentucky had the highest number of mean total days of opioid supply across both categories, an average of 218.8 days when the concurrent prescriptions were from 2 or more prescribers and 201.9 days when 1 prescriber was involved.

The mean daily dosage of opioids was higher among patients when the concurrent prescriptions were from 2 or more prescribers (71.4 MMEs/day) compared with concurrent prescriptions from the same prescriber (63.9 MMEs/day, $p<0.001$) (Table 2). The mean daily dosage of opioids was highest in Maine when the concurrent prescriptions were from multiple prescribers (83.1 MMEs/day) and highest in California when 1 prescriber was involved (70.5 MMEs/day).

The mean total days of concurrent prescribing was higher among patients when the concurrent prescriptions were from multiple prescribers (101.2 days) compared with concurrent prescriptions involving one prescriber (77.6 days, $p<0.001$). Kentucky had the highest mean days of concurrent prescribing across both categories, an average of 157.0 days when the concurrent prescriptions were from multiple prescribers and 148.7 days when the concurrent prescriptions were from the same prescriber.

The rates of opioid prescribing and concurrent prescribing of opioids and benzodiazepines varied by age and sex (Table 3). The greatest percentages of patients with opioid prescriptions were aged 50–64 years (28.4%) and ≥65 years (25.9%). Similarly, the greatest share of patients with concurrent opioid and benzodiazepine prescriptions were aged 50–64 years (37.6%) and ≥65 years (34.6%).

DISCUSSION

Concurrent prescribing of opioids and benzodiazepines puts individuals at greater risk for overdose.[1–5] This study shows that among individuals prescribed an opioid in 2015 in 9 PBSS states, nearly 1 in 4 were also prescribed a benzodiazepine during the year. Among those prescribed both medications during the year, 55% were prescribed opioids and benzodiazepines concurrently.

Almost half of patients with concurrent prescriptions for opioids and benzodiazepines obtained both medications from the same prescriber. When one prescriber is involved, evidence-based guidelines, such as the CDC Prescribing Guideline, which discourages the concurrent prescribing of opioids and benzodiazepines,[18] may be effective in reducing this prescribing behavior. In fact, research has shown that the release of the CDC Prescribing Guideline was associated with a reduction in the percentage of patients receiving overlapping opioid and benzodiazepine prescriptions.[18] Given the greater risks of benzodiazepine withdrawal relative to opioid withdrawal,

Table 2. Characteristics of Concurrent Opioid and Benzodiazepine Prescriptions by State

Variable	Mean total opioid days			Mean daily dose of opioids (MME)			Mean days of overlap		
	One prescriber	Two+ prescribers	*p*-value	One prescriber	Two+ prescribers	*p*-value	One prescriber	Two+ prescribers	*p*-value
Total	118.8	153.1	**<0.0001**	63.9	71.4	**<0.0001**	77.6	101.2	**<0.0001**
State									
California	91.3	127.8	**<0.0001**	70.5	80.2	**<0.0001**	56.5	81.0	**<0.0001**
Delaware	138.8	179.4	**<0.0001**	66.4	77.8	**<0.0001**	80.2	114.1	**<0.0001**
Florida	125.9	154.7	**<0.0001**	62.9	68.8	**<0.0001**	85.0	104.3	**<0.0001**
Idaho	147.8	186.6	**<0.0001**	69.3	75.7	**<0.0001**	80.1	114.8	**<0.0001**
Kentucky	201.9	218.8	**<0.0001**	52.1	75.7	**<0.0001**	148.7	157.0	**<0.0001**
Maine	129.7	174.0	**<0.0001**	69.4	83.1	**<0.0001**	72.8	115.0	**<0.0001**
Ohio	156.1	181.2	**<0.0001**	49.0	57.7	**<0.0001**	99.6	120.7	**<0.0001**
Virginia	112.3	147.6	**<0.0001**	61.4	66.2	**<0.0001**	71.7	95.0	**<0.0001**
West Virginia	155.2	163.0	**<0.0001**	55.0	59.4	**<0.0001**	112.2	115.0	**0.001**

Note: Boldface indicates statistical significance ($p<0.05$).
MME, morphine milligram equivalent.

Table 3. Demographic Characteristics Among Patients With Opioids and Patients With Concurrent Opioid and Benzodiazepine Prescriptions

Variable	Patients with an opioid, %	Patients with concurrent prescriptions, %
Age, years		
<18	3.1	0.3
18–34	20.5	7.4
35–49	22.1	20.1
50–64	28.4	37.6
≥65	25.9	34.6
Sex		
Male	41.2	34.1
Female	58.8	65.9

when patients receiving both benzodiazepines and opioids require tapering to reduce overdose risk, it might be safer and more practical to taper opioids first.[13] Therefore, clinicians should communicate with mental health professionals managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care.[13] Despite the lower risk of opioid withdrawal, it is important to avoid abrupt tapering or sudden discontinuation of opioids, as these practices can result in severe opioid withdrawal symptoms and some patients seeking other sources of opioids.[19]

More than half of concurrent opioid and benzodiazepine prescribing instances resulted from prescriptions involving 2 or more distinct prescribers. Furthermore, when patients obtained concurrent prescriptions from 2 or more prescribers, they tended to have more total days of opioid supply, higher daily dosages of opioids, and more total days of concurrent prescriptions, compared with patients who obtained concurrent prescriptions from one prescriber. These findings have several important implications. First, among patients prescribed opioids, higher opioid doses are associated with an increased risk of opioid overdose death.[20–22] Second, patients receiving opioids for longer durations are at higher risk for long-term use and developing opioid use disorder.[23,24] Third, higher daily dosage and longer duration of concurrent prescriptions might indicate that prescribers were not aware of all other opioids or benzodiazepines that their patients were prescribed, thus reducing the likelihood of engaging in risk mitigation strategies. The concurrent prescribing of opioids and benzodiazepines by multiple prescribers highlights the importance of PDMPs in avoiding concurrent prescribing, and the importance of reviewing PDMPs before prescribing controlled substances to mitigate risk and improve coordination of care. PDMPs allow prescribers to view a patient's prescribing history to determine if a

patient has a current prescription from a different prescriber. Some states, including California in October 2018, have mandated checking the PDMP before prescribing any controlled substance. Evidence has shown that PDMPs, particularly those mandating provider review before prescribing opioids, are associated with lower rates of opioid prescribing and lower opioid overdose rates.[25–27]

Although there was little variation across the states in opioid prescribing rates and patients receiving both opioids and benzodiazepines, more variation was observed in the rate of concurrent prescribing and the characteristics of concurrent prescriptions. For instance, the rate of concurrent prescribing varied from 65% in West Virginia to 46% in Idaho. The number of prescribers involved in concurrent prescribing also varied substantially across states. For example, in Delaware, 67% of patients concurrently prescribed opioid and benzodiazepines obtained them from 2 or more prescribers, compared with 52% in West Virginia. Among patients with concurrent prescriptions, the mean total days of opioid supply and mean days of concurrent prescribing in Kentucky were twice that of California. However, although California had the lowest mean days of concurrent prescribing, it had the second highest mean daily dosage of opioids among patients with concurrent prescribing. These variations indicate that, in addition to national efforts to address the high-risk concurrent prescribing of opioids and benzodiazepines, tailored and targeted intervention efforts, such as educational outreach to opioid prescribers (academic detailing), could be impactful given the heterogeneous patterns of concurrent prescribing at the state level.

Female patients were more likely to be prescribed opioids, as well as concurrent opioid and benzodiazepine prescriptions, than male patients. These findings are consistent with evidence showing that female patients seek medical care more often than male patients and have a higher prevalence of chronic pain, mental health conditions, and anxiety—conditions for which these medications are commonly prescribed.[8,28–31] The largest percentage of individuals with concurrent opioid and benzodiazepine prescriptions were older adults, aged 50–64 years (37.6%) and ≥65 years (34.6%). This finding is consistent with previous research showing that benzodiazepine prescribing increases with age.[32] Although drug overdose rates tend to be lowest among older adults, the concurrent use of opioids and benzodiazepines among older adults is associated with other risk factors, including falls and injuries.[33–36]

Though this study provides important insights into the concurrent prescribing of opioids and benzodiazepines, it also highlights important areas for future research. Given the association between PDMP characteristics and prescribing behaviors,[25,26] future research is needed to examine how PDMP characteristics, such as mandatory use, are associated with the concurrent prescribing of opioid and benzodiazepines. In addition, future research could examine patient characteristics associated with the concurrent prescribing of opioid and benzodiazepines. Together, this information could help identify effective interventions and target efforts to reduce the number of individuals concurrently prescribed an opioid and a benzodiazepine.

Limitations

This study is subject to several limitations. First, the clinical context and indications for the concurrent prescribing of opioids and benzodiazepines cannot be determined. Second, the data used in this study represent dispensed prescriptions, and information is not available on actual medication use. Third, data are not available on medication use without a prescription. Previous research has indicated that in more than half of patients with positive laboratory test results for concurrent opioid and benzodiazepine use, one drug was prescribed, whereas the other was nonprescribed.[11] Fourth, prescriptions dispensed outside of the state are not captured. Fifth, the cross-sectional nature of the study limits the ability to examine factors associated with cross-state variation in concurrent prescribing rates. Lastly, the data used in the present study examine prescribing behaviors occurring before the release of the CDC Prescribing Guideline in March 2016. Although the percentage of patients with overlapping opioid and benzodiazepine prescriptions has been declining in recent years, particularly after the release of the CDC Prescribing Guideline,[18] it is important to continue monitoring changes in concurrent prescribing.

CONCLUSIONS

Concurrent prescribing of opioids and benzodiazepines is common, despite the known risks of taking these medications in combination. The findings in this study highlight the need for public health actions to reduce concurrent prescribing. Evidence-based guidelines, such as the CDC Prescribing Guideline, could be helpful in reducing this prescribing behavior when one prescriber is involved. Meanwhile, the utilization of PDMPs and care coordination could help address concurrent prescribing when multiple prescribers are involved.

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