Concurrent Utilization of Prescription Opioids and Non-opioid Controlled Substances: Rhode Island Prescription Drug Monitoring Program, 2018

ERIC P. BORRELLI, PharmD, MBA; BLAKE MORPHIS, BS; ROUBA YOUSSEF, PhD; LAURA C. CHAMBERS, PhD, MPH; BENJAMIN D. HALLOWELL, PhD; JEFFREY BRATBERG, PharmD; STEPHEN J. KOGUT, PhD, MBA, RPH

ABSTRACT

OBJECTIVE: To estimate the prevalence of concurrent prescription opioid and non-opioid controlled substance use in Rhode Island (RI).

METHODS: We conducted a cross sectional observational study using data from the RI Prescription Drug Monitoring Program on controlled substance prescriptions dispensed in 2018. We estimated the prevalence of concurrent use of other prescribed controlled substances among adults who received at least one opioid prescription.

RESULTS: In 2018, 142,692 RI adult residents received at least one opioid prescription, of whom 25.1% (99% confidence interval [CI]: 24.8-25.4) were concurrently prescribed at least one other controlled substance, including benzodiazepines (17.0%, 99% CI: 16.8–17.3), medications for insomnia (4.0%, 99% CI: 3.9–4.2), and stimulants (3.8%, 99% CI: 3.6–3.9).

CONCLUSION: The concurrent use of prescription opioids and other prescribed controlled substances is common. Our findings suggest an urgent need to implement focused initiatives to address controlled substance polypharmacy to reduce the risk of overdose.

KEYWORDS: opioids, benzodiazepines, stimulants, controlled substances, Z-drugs

INTRODUCTION

In response to a citizen's petition submitted by Drs. Leana Wen, Commissioner of Health for the Baltimore City Department of Health, and Nicole Alexander-Scott, Director of the Rhode Island Department of Health,[1] the US Food and Drug Administration (FDA) in 2016 added a black box warning to all opioid and benzodiazepine labels on the risk of respiratory depression and fatal overdose when these agents are used concurrently.[2] The FDA also noted that adverse outcomes are associated with the concurrent use of non-benzodiazepine sedative hypnotics. Despite this warning, from July 2017 through June 2018, approximately one third of all fatal opioid-involved overdoses in the US involved benzodiazepines and, when limited to prescription opioid-involved overdoses specifically, roughly half (49%) involved benzodiazepine use.[3]

RI has been significantly impacted by the overdose epidemic. Between 2009 and 2018, 1,197 fatal overdoses involving prescription opioids occurred in RI.[4] As controlled substance polypharmacy increases the risk of fatal and non-fatal opioid overdoses, the objective of our study was to estimate the prevalence of concurrent utilization of prescription opioids and non-opioid controlled substances in RI.

METHODS

We conducted a cross sectional study analyzing data from the RI Prescription Drug Monitoring Program (PDMP) from 2018. The RI PDMP includes controlled substances dispensed by all community pharmacies with a controlled substance registration in RI and includes information on controlled substances dispensed to RI-residents by pharmacies in neighboring states. More details about the RI PDMP are available at the RI Department of Health website.[5]

For this analysis we excluded patients who received lozenge and troche forms of fentanyl, and certain suppository and liquid opioid formulations of hydromorphone, meperidine, methadone, morphine, opium, and oxycodone, which are generally prescribed during end-of-life care when the risks and benefits of medication use may be weighed differently than use for acute or chronic pain relief. We also excluded prescriptions that are not known to significantly increase the risk of overdose when co-prescribed with opioids, including: antidiarrheals, anabolic steroids, human growth hormone, and testosterone. We also excluded gel forms of benzodiazepines used to treat seizures. Buprenorphine-containing products were also excluded as this medication is more often prescribed for opioid use disorder than for pain,[6-7] and we could not determine the indication for use from the available data. In addition, we excluded patients who were not RI residents because the RI PDMP would not have information about all other controlled medications that have been dispensed by pharmacies outside of RI to non-RI residents.

We identified all patients who received at least one opioid prescription during 2018, and then determined if the patient concurrently received benzodiazepines, non-benzodiazepine sedatives (the "Z-drugs" zolpidem, eszopiclone, and zaleplon), stimulants, or a non-opioid controlled substance of any type (other than the types of medications excluded).

We sought to identify all patients with recent access to both opioid and non-opioid controlled medications, irrespective of the number of days of overlap. Therefore, consistent with other work,[8] concurrent utilization was defined as at least one day of medication overlap according to the prescription fill dates and days' supply of medication, for any quantity dispensed. We calculated 99% confidence intervals (CIs) for prevalence estimates and used a significance threshold of p<0.01 for Chi-square tests of subgroup comparisons. Multivariable logistic regression was performed to estimate the odds of concurrent use of prescription opioid and non-opioid controlled substances, adjusted for patient sex, age group, payment method, and county of residence. Because it appeared that Medicare Advantage plans were often misclassified as "commercial insurance" in the RI PDMP dataset, a payment type of "commercial insurance" was reclassified as "Medicare" if the patient was age 65 or older. In addition, we dichotomized Medicare payment type by age to determine rates of concurrent use among Medicare beneficiaries under 65 years of age who qualify based on having a long-term disability or end stage renal disease (ESRD). Payment method and county were assigned according to the most recently dispensed opioid prescription. Analyses were performed using SAS version 9.4. The study was approved by the Institutional Review Boards at the RI Department of Health and the University of Rhode Island.

RESULTS

In 2018, there were 142,692 adult RI residents who received at least one opioid prescription dispensed by a RI licensed pharmacy [**Table 1**]. Women comprised 59% of these residents, and the most frequent payment type was commercial insurance (43.0%), followed by Medicare (27.8%), Medicaid (13.6%) and cash (12.3%). Approximately 30% of subjects were age 65 or older and more than half of patients (56.8%) lived in Providence County.

One in four patients who received an opioid prescription also received an overlapping prescription for a non-opioid controlled substance (38,150/142,692; 25.1%; 99% CI: 24.8–25.4). Women had a higher prevalence of concurrent use than men: 27.9% (99% CI: 27.5–28.3) versus 21.0% (99% CI: 20.5–21.4), respectively. Patients aged 50 to 64 years of age had the highest prevalence of concurrent utilization of opioids and other controlled substances when compared to other age groups (29.1%, 99% CI: 28.6–29.7). Concurrent use was particularly high among patients younger than 65 years who paid with Medicare insurance at 41.3% (99% CI: 40.0–42.6, n = 3,747). The non-opioid class with the highest prevalence of concurrent utilization was benzodiazepines, with 17.0% (99% CI: 16.8–17.3) having at least one day overlap with a benzodiazepine and opioid prescription [**Table 2**]. The

Table 1. Concurrent Use of Prescription Opioid and Non-Opioid Controlled Substances, Overall and by Patient Characteristics

Demographics	Patients with at Least 1 Opioid Dispensing n	Patients with Overlapping Dispensings for Opioid and Non-Opioid Controlled Substance n (%), [99% CI]	Adjusted Odds of Concurrent Use of Prescription Opioid and Non-Opioid Controlled Substances*^ aOR (95% CI)
Overall	142,692	35,744 (25.1%), [24.8%–25.4%]	
Age, years			
18–34	20,239	2,743 (13.6%), [12.9%–14.2%]	**0.47 (0.45–0.50)**
35–49	28,960	7,356 (25.4%), [24.7%–26.1%]	Reference
50–64	49,385	14,384 (29.1%), [28.6%–29.7%]	**1.20 (1.16–1.24)**
65–74	25,385	7,011 (27.6%), [26.9%–28.3%]	**1.12 (1.05–1.20)**
75+	18,723	4,250 (22.7%), [21.9%–23.5%]	**0.82 (0.77–0.88)**
Sex			
Men	59,174	12,405 (21.0%), [20.5%–21.4%]	Reference
Women	83,478	23,319 (27.9%), [27.5%–28.3%]	**1.54 (1.50–1.58)**
Payment Method			
Commercial Insurance	61,361	13,683 (22.3%), [21.9%–22.7%]	Reference
Medicaid	19,352	5,135 (26.5%), [25.7%–27.4%]	**1.31 (1.26–1.36)**
Medicare<65	9,072	3,747 (41.3%), [40.0%–42.6%]	**2.13 (2.04–2.24)**
Medicare≥65	30,561	8,181 (26.8%), [26.1%–27.4%]	**1.25 (1.16–1.33)**
Cash	17,503	3,775 (21.6%), [20.8%–22.4%]	0.98 (0.92–1.03)
Other	4,843	1,223 (25.3%), [23.6%–26.9%]	**1.30 (1.21–1.41)**
County of Residence			
Providence	81,066	19,610 (24.2%), [23.8%–24.6%]	Reference
Kent	27,459	7,488 (27.3%), [26.6%–28.0%]	**1.17 (1.13–1.21)**
Washington	18,239	4,565 (25.0%), [24.2%–25.9%]	**1.06 (1.02–1.10)**
Bristol	5,857	1,505 (25.7%), [24.2%–27.2%]	**1.10 (1.03–1.17)**
Newport	10,071	2,576 (25.6%), [24.5%–26.7%]	1.05 (1.00–1.11)

aOR: Adjusted Odds Ratio; CI= confidence interval; 40 patients had missing information for gender

* Multivariable analysis including patient sex, age group, payment type and RI county of residence.

^Statistically significant results in bold font

Table 2. Prescription Controlled Substance Classes with the Highest Prevalence of Concurrent Utilization with Prescription Opioids

	Patients with Use of Prescription Opioids (N =142,692) and Concurrent Use of:			
	Any non–opioid type of prescribed controlled substance	Benzodiazepines	Z–Drugs	Stimulants
Number of Patients with Concurrent Utilization Overall (%)	35,744 (25.1%)	24,279 (17.0%)	5,731 (4.0%)	5,356 (3.8%)
Age group				
18–34 (N=20,239)	13.6%	7.1%	1.1%	**5.9%**
35–49 (N=28,960)	25.4%	15.8%	3.5%	**6.7%**
50–64 (N=49,385)	**29.1%**	**20.1%**	**5.3%**	3.4%
65–74 (N=25,385)	**27.6%**	**19.9%**	**5.2%**	1.7%
75+ (N=18,723)	22.7%	17.6%	3.2%	0.6%
Gender				
Male (N=59,174)	21.0%	13.5%	3.6%	3.0%
Female (N=83,478)	**27.9%**	**19.5%**	**4.3%**	**4.3%**

* Bold indicates a statistically significant higher percentage of concurrent utilization for the subgroup compared with all others, p<0.01

prevalence of concurrent use of opioids and non-opioid controlled substances was lower for Z-drugs for insomnia (4.0%, 99% CI: 3.9–4.2) and stimulants (3.8%, 99% CI: 3.6–3.9).

The multivariable logistic regression analysis identified several factors associated with increased odds of concurrent use of opioid and non-opioid prescribed controlled substances. Patients who paid for their prescription with Medicaid insurance had 31% higher odds of concurrent use, as compared with patients using commercial insurance (adjusted OR [aOR]: 1.31, 95% CI 1.26–1.36), adjusting for sex, age group, and county of residence. People under 65 years of age who paid with Medicare insurance had more than twice the odds of those using commercial insurance to concurrently utilize prescription opioids and non-opioid controlled substances (aOR: 2.13, 95% CI: 2.04–2.24). Women had 54% higher odds of concurrent use of opioids and other prescribed controlled substances as compared to men (aOR: 1.54, 95% CI: 1.50–1.58).

DISCUSSION

One in four adult RI residents (25%) who received a prescription for an opioid medication in 2018 also concurrently received at least one pharmacy-dispensed non-opioid controlled substance, most frequently a benzodiazepine (17%). Even though a smaller percentage of patients concurrently received a sedative-hypnotic "Z-drug" or a stimulant medication (roughly 4% for each category), this represents a substantial number of RI residents utilizing each of these combinations (5,731 and 5,356 patients, respectively). The concurrent utilization observed in our study occurred even with warnings built into electronic prescribing and dispensing systems, and the widespread availability of the PDMP for reviewing patients' controlled substance prescription history.

Since July 2018, pharmacists and prescribers are required to check patients' controlled substance prescription history in the PDMP prior to prescribing/dispensing an opioid for the first time and every 3-months for chronic opioid therapy.[5] It is also recommended that the PDMP is checked prior to prescribing/dispensing a benzodiazepine or sedating medication.[5] Our findings suggest that either prescribers and/or pharmacists did not check the PDMP before prescribing/dispensing these controlled substances (i.e., were unaware of the concurrent use), or they considered the benefit of the combination to exceed the substantial risk of morbidity and mortality. The 2018 regulations, which were made aware to all controlled substance prescribers in July of that year, required documentation of this benefit-risk calculation for opioid-benzodiazepine combinations. This documentation, if extant, is retained only within prescriber written or electronic notes, and is not transmitted to the PDMP. Yet a 2019 survey of RI prescribers and pharmacists indicated suboptimal awareness of these requirements.[9]

Several other studies have examined the concurrent utilization of prescription opioids and benzodiazepines, albeit using varied definitions of concurrent use. One analysis using 2015 data from PDMPs in nine states found that 21.6% of patients who received at least one opioid prescription also received a prescription for a benzodiazepine during the calendar year, with 54.9% (11.9% of the study population) having at least 7 days overlap of opioids and benzodiazepines.[10] A cross-sectional study using data from the North Carolina Medicaid program from 2017–2018 found that 19.7% of patients with at least one opioid prescription had at least one day overlap with a benzodiazepine prescription.[11] The concurrent use of prescription opioids and benzodiazepines is also common among older adults. In a study of enrollees of a commercial Medicare supplement plan in 2017, Musich et al. found that 18.4% of patients who received at least two prescriptions for opioids had concurrent use of benzodiazepines for at least 30 days.[12]

While the thresholds for defining prescription overlap differ across published studies, our analysis aligns with other research in finding that prescription opioids and benzodiazepines are often prescribed concurrently despite the increased

risk of drug-related harm. Among unintentional opioid overdose deaths in RI occurring from July through December 2016, 24.1% had a positive toxicology report for benzodiazepines.[13] Moreover, an analysis of Medicare Part D claims for 2013–2014 found that patients who were concurrently prescribed opioids and benzodiazepines were more than five times more likely to experience an opioid overdose compared to patients without concurrent use, after adjusting for demographic and clinical characteristics (adjusted hazard ratio: 5.05, 95% CI: 3.68–6.93).[14] It is encouraging that following the FDA's alert there was an estimated 18% relative reduction nationally in the concurrent use of prescription opioids and benzodiazepines during the subsequent 16 months,[15] while in RI, the number of patients who received a prescription for both an opioid and benzodiazepine within a 30- day period declined by 41% from the first quarter of 2017 to the first quarter of 2020, potentially as a result of the July 2018 regulation changes.[16]

There are fewer published studies regarding the concurrent use of prescription opioids and other types of prescribed controlled substances, such as sedative hypnotics, stimulants and other CNS depressant medications. In the aforementioned study by Musich *et al.*, approximately 6.81% of patients receiving prescription opioids concurrently used non-benzodiazepine sedative hypnotics, which is slightly higher than what we observed in RI in 2018.[12] Moreover, they reported that among patients with depression or anxiety, the concurrent use of prescription opioids and two or more central nervous system agents resulted in an 18% increased risk of injurious falls or fractures.[12] Additionally, a retrospective analysis of patients receiving opioid prescriptions in the Washington Medicaid program found that patients who also received non-benzodiazepine CNS depressants (predominantly Z drugs) had more than a 3 fold increase in the risk of opioid-related death (adjusted hazard ratio: 3.1, 95% CI: 1.6–6.2).[17]

We also found that 3.8% of RI adults who received a prescription for an opioid had concurrent utilization of stimulants. Prescription opioid use is not an absolute contraindication among patients who are prescribed stimulants, yet both medication classes have a high risk of physical and psychological dependence[18,19] and the combination may lead to euphoric effects.[20] A cross-sectional study of pharmacy data from 29 state Medicaid plans found that 5.4% of adults with attention deficit hyperactivity disorder had concurrently used stimulants and opioids,[18] while a case-control study conducted of residents of British Columbia for the years 2015–2016 found that patients who were prescribed opioids and experienced an overdose had significantly higher odds of prescription stimulant utilization compared to their controls (OR: 3.63, 95% CI: 2.99–4.39).[19]

Consistent with the published literature,[12, 21-23] women in our study had a higher odds of receiving concurrent therapy with opioid and non-opioid prescribed controlled substances when compared to men, which was particularly higher for benzodiazepines (19.5% vs 13.5%, p<0.01). However, this finding is not unexpected as women have a higher prevalence of diagnosed anxiety disorder as compared with men.[22] The highest prevalence of concurrent utilization of opioids and non-opioid controlled medications was among Medicare patients under the age of 65 (41.3%). The high prevalence of controlled substance polypharmacy in this subgroup merits concern given that these patients have chronic disability or ESRD; however, this finding aligns with prior research. One analysis of Medicare data from 2007 through 2011 found that more than 40% of non-senior beneficiaries received at least one opioid prescription annually.[24] Another analysis of Medicare Part D claims data from 2015 found that 41.4% of enrollees under the age of 65 who had at least one opioid prescription also had concurrent utilization of either a benzodiazepine or sedative hypnotic, compared to under 24% for enrollees age 65 or older.[8] Additionally, an analysis of the U.S. Renal Data System (USRDS) database for the calendar year 2014 found that 52.2% of patients had at least one opioid prescription annually, and 17% of patients with an opioid prescription received a benzodiazepine prescription within 1 week of the opioid dispensing.[25]

There were several limitations to our study. Foremost, the PDMP data contains pharmacy-level information only, and we were unable to determine the indications for medication use. Also, we were unable to assess controlled substance use without prescription, or medication received from outlets other than pharmacies with a RI retail pharmacy license. An additional limitation is that pharmacy dispensing records do not confirm that the medication was consumed by the patient whose name is on the prescription captured within the PDMP data. Patients may have been nonadherent, may have been advised by their provider to stop taking a medication when a concurrent controlled substance was added to their regimen, and/or may have shared their medications with someone else. We also did not determine whether the concurrently used medications were issued from the same prescriber; however, all providers have access to the PDMP to review a patient's use of other controlled medications before a new prescription is issued. Last, we applied a liberal definition of concurrent use, requiring only 1-day overlap between opioid and non-opioid controlled substance dispensing. This likely resulted in a higher rate of concurrent utilization than what may have been observed if we used a 7-day or 30-day overlap definition.

Further research is needed to determine adverse health outcomes and health care utilization resulting from the combined use of these high-risk medications, to evaluate the prevalence and impact of naloxone co-prescribing to mitigate risk, and to determine if the regulations of 2018 had further impact into 2019 and beyond in reducing controlled substance polypharmacy.

CONCLUSION

Approximately 1 in 4 adult RI residents who received a pharmacy dispensing for an opioid also received a concurrent non-opioid prescription controlled substance, while 1 in 6 had concurrent utilization of prescription opioids and benzodiazepines despite the evidence-based risk of this combination. Our findings suggest an urgent need to implement focused initiatives to address controlled substance polypharmacy to reduce the risk of opioid overdose.

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Disclaimer

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Authors

Eric P. Borrelli, PharmD, MBA, PhD Candidate in Pharmaceutical Sciences, Department of Pharmacy Practice, College of Pharmacy, University of Rhode Island.

Blake Morphis, BS, Director of Analytic Services, Healthcentric Advisors.

Rouba Youssef, PhD, Health Information Analyst, Healthcentric Advisors. (during time of study)

Laura C. Chambers, PhD, MPH, Epidemiologist, Rhode Island Department of Health.

Benjamin D. Hallowell, PhD, Biostatistician, Rhode Island Department of Health.

Jeffrey Bratberg, PharmD, Clinical Professor, Department of Pharmacy Practice, College of Pharmacy, University of Rhode Island.

Stephen J. Kogut, PhD, MBA, RPh, Professor of Pharmacy Practice; Department of Pharmacy Practice, College of Pharmacy, University of Rhode Island.

Correspondence

Eric Borrelli, PharmD, MBA
University of Rhode Island College of Pharmacy
7 Greenhouse Rd
Kingston, RI 02881
401-864-9681
EricBorrelli@my.uri.edu