2018

Predictors of Concomitant Use of Prescription Opiods and Benzodiazepines in Rhode Island

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PREDICTORS OF CONCOMITANT USE OF PRESCRIPTION OPIOIDS AND BENZODIAZEPINES IN RHODE ISLAND

BY

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE

REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

IN

PHARMACEUTICAL SCIENCE

UNIVERSITY OF RHODE ISLAND

2018

MASTER OF SCIENCE THESIS

OF

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2018

ABSTRACT

Objective: To determine the predictors of concomitant use of benzodiazepines with chronic opioid use in Rhode Island using pharmacy level data.

Design: Cross – sectional analysis

Setting: Rhode Island Prescription Drug Monitoring Program (PDMP) Database, 2015

Participants: Any person who filled a prescription for an opioid (>30 days' supply), a benzodiazepine or both at a licensed retail pharmacy in Rhode Island during 2015.

Main outcome measure: Concomitant use of opioid analgesics and benzodiazepines, defined as the receipt of any benzodiazepine and opioid pharmacy dispensing having a days' supply which overlaps by at least 1 day.

Results: Of 139,410 patients who were included in our analysis, 15.5% had overlapping (concomitant) opioid and benzodiazepine prescriptions during 2015. Patients who were younger than 45 years of age, and who see more than three prescribers were less likely to be prescribed both opioids and benzodiazepines, in which the days supply overlap. Additionally, each additional prescription a person receives for a controlled substance increased the odds that they were prescribed concomitant therapy.

ACKNOWLEDGMENTS

I would like to express my sincere gratitude and thanks to my major professor, Dr. Stephen Kogut. Dr. Kogut's guidance has been invaluable in the development and completion of this thesis. My confidence as a researcher has grown as a result of Dr. Kogut's patient mentorship and constructive feedback.

I would also like thank my thesis committee members, Dr. Xuerong Wen and Dr. Angela Slitt. Dr Wen provided much guidance on this project and helped me to learn the statistical software necessary to conduct the analysis for this thesis. Dr Slitt encouraged me to pursue this topic during my first semester of my graduate study.

In addition to my committee members, I would like to express my gratitude to the faculty of the Health Outcomes program and to Drs. Wu and Katenka in the Statistics and Computer Science department, for providing me with the educational foundation necessary to complete this thesis.

From the Miriam Hospital, I would like to thank Dr. Curt Beckwith and Lauri Bazerman. I have served as their research assistant for the last ten years; during that time, they fostered ethical and compassionate research practice. They were fully supportive of my decision to pursue graduate education and made accommodations so it would be possible. For this, I am grateful.

I would like to thank my family for encouraging me to pursue my interests in higher education, and providing me with a strong and loving support system.

And last, but certainly not least, I would like to thank my husband, Jared. Without his unwavering support, it would not have been possible to commit the time and effort required to complete graduate coursework, including this thesis.

PREFACE

The standard format was used in preparation of this thesis.

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CHAPTER 1

INTRODUCTION

In August, 2016, the Food and Drug Administration (FDA) published a drug safety communication warning of the serious risks associated with the concomitant use of opioids and benzodiazepines after published literature identified an increase in the combined use of these central nervous system depressant drugs. [1] Combined use of these two classes of drugs may lead to respiratory depression, coma and even death, which are all side effects that may be avoided if proper prescribing and usage guidelines are respected. [1]

Since 2014, Rhode Island has maintained a fully operational Prescription Drug Monitoring Database (PDMP), which captures medication dispensing of controlled substances, as reported by pharmacists. This study measured the extent of concomitant use of opioid and benzodiazepine medications and determined if patients prescribed both of these types of medications differ from patients using opioids solely, benzodiazepines solely, and opioids and benzodiazepines with no overlapping days of use, with regard to demographics, insurance type, and use of other controlled substances.

Hypothesis:

1. Patient demographics, number of prescribers, number of pharmacies utilized, total number of prescriptions filled, and stimulant use does not differ between those who concomitantly use opioids and benzodiazepines

and those who solely use opioids or benzodiazepines, or those who have dual, non-overlapping use of benzodiazepines and opioids.

2. Among those who concomitantly use opioids and benzodiazepines, the following factors are not predictors of increased risk: opioid type, average number of prescriptions by duration of action, average number of controlled substance prescriptions by class, average days of supply by class and number of prescribers.

CHAPTER 2

REVIEW OF LITERATURE

It has been widely publicized that the United States is experiencing an opioid addiction and overdose epidemic. In a NCHS data brief from 2014, it was noted that opioid analgesic poisoning (intentional and unintentional) accounted for 41% of drug poisoning deaths in 2011. This number represents 16,917 deaths, a 300% increase from 1999.[2] As of 2009, drug poisoning deaths surpassed traffic accidents as the leading cause of injury related deaths for the first time since 1980.[3]

Opioids are used to treat a wide range of pain experiences, from severe pain associated with cancer to moderate to severe pain associated with neuropathy, fibromyalgia, headaches, and musculoskeletal disorders. Opioids are, therefore, prescribed to a wide range of individuals. From 2000 to 2010, there was 104% increase in the number of opioid analgesic prescriptions written: 89.2 million prescriptions. The number of patients receiving opioid prescriptions increased 80% in this same time period, to 27.5 million individuals.[4] While there has been an increase in both the number of patients receiving prescriptions for opioids and the total number of prescriptions written, there is evidence to suggest being prescribed opioids did little to improve the health and disability status of the patient, as health status remained unchanged or actually decreased.[4]

Safely and effectively managing acute and chronic pain in a patient with comorbid conditions presents challenges. While it may inappropriate to use opioids in

conjunction with a variety of medication classes, combined use with benzodiazepines is particularly perilous. Jones, et al, analyzed 2010 overdose data for the United States, and found that among overdose deaths involving an opioid analgesic, benzodiazepines were also involved in 30% of cases.[5] In another study, conducted by Yarbourgh, et al, the researchers analyzed interviews with survivors of opioid overdoses and found that most events involved the use of multiple drugs (83%), and often benzodiazepines (32%).[6] Reisfield, et al, noted that opioids and benzodiazepines are the most commonly co-abused drugs; estimates ranging from 20-50% of patients who are prescribed long term opioid therapy, also received prescriptions for a benzodiazepine.[7]

The concomitant use of opioids with benzodiazepines is discouraged in prescribing guidelines,[8] but co-prescribing these drugs by both a single prescriber or simultaneously by multiple prescribers is not uncommon, nor is prescribing for a longer duration than is recommended.[9] This may be due to the fact that benzodiazepines are characterized as relatively safe while having a high therapeutic index,[10] and less likely than opioids to be the sole drug involved in an accidental overdose.[11] Benzodiazepines are recommended as a second-line treatment for some common conditions such as insomnia, and anxiety, and when they are prescribed it is recommended that they are used for a short time period and not in conjunction with certain other classes of medicines, including opioids. Benzodiazepines alter the pharmacodynamic effects of opioids. Studies have shown that the concomitant use amplifies the central nervous system effects of opioids.[12] Additionally, opioids and benzodiazepines have different mechanisms of action which is problematic because both opioids and benzodiazepines are central nervous system depressants; these drugs

have the effect of depressing the central nervous system through two different mechanisms when the two classes of drugs are administered together.[11] This can lead to overdose; chronic use of both opioids and benzodiazepines has been associated with "additive effects in sleep disordered breathing."[13] Finally, when benzodiazepines are prescribed for a longer period than is recommended, the patient may experience an increased tolerance to the dose of the drug[10] and dependency.[14] Risk for dependency may also be linked to the type of first benzodiazepine used and dose escalation schedule.[14]

Reports such as these have led the FDA to announce extensive changes to the requirements for the package labeling and medication guide of nearly four hundred products which contain opioid analgesics, including cough products or benzodiazepines. The new materials will contain the FDA's most serious warning – the boxed warning, to indicate the serious risks associated with the use of these medications. In addition to the packaging changes, this announcement was accompanied by the publication of a drug safety communication with the intention of warning prescribers and those taking these medications about the dangers of concomitant use of these classes of medications.[1]

The Rhode Island Prescription Drug Monitoring Program affords physicians and pharmacists alike the ability to actively manage their patients, and make prescribing decisions based on a comprehensive look at the patient's prescription history. The focus of this study was to quantify the number of patients in Rhode Island who were prescribed concomitant therapy with opioids and benzodiazepines in 2015 and determine if there were patient level or prescription level predicators that

indicated a patient was more likely to be prescribed concomitant therapy.

CHAPTER 3

METHODOLOGY

Study design

A cross sectional observational study was conducted using de-identified pharmacy-level data obtained from the Rhode Island Prescription Drug Monitoring Program (PDMP). For all patients who received benzodiazepine or opioid medications in 2015, the percentage who received a dispensing for both categories of drugs was determined, and characteristics associated with use of both opioid and benzodiazepine medications were identified.

Data Source

The Rhode Island PDMP database includes pharmacy-level data for all prescriptions filled for schedule II to IV medications at Rhode Island based pharmacies who hold a controlled substance registration number. As mandated by state law, all pharmacies that dispense schedule II-IV medications to individuals who are "not an inpatient of a hospital, correctional institution or nursing facility" are required to electronically report 19 data elements to the PDMP within 72 hours of filling the prescription. The data set does not include medications dispensed to patients of outpatient methadone maintenance programs. A de-identified subset of PDMP data was used, which included the following variables: age, gender, payer, date of prescription fill, the number of days covered by the prescription, medication name, and a de-identified prescriber drug enforcement administration identification number.

Study population:

The study population was comprised of patients of any age who filled a prescription for an opioid medication, a benzodiazepine, or both in Rhode Island, during 2015.

Patient identification:

Inclusion/exclusion criteria

The following patients were included: A.) Patients, of any age, who filled at least one prescription for oxycodone, hydrocodone, morphine, oxymorphone, hydromorphone, tapentadol, methadone, pentazocine, butorphanol, meperidine, levorphanol or codeine tablets, or fentanyl patches, totaling at least a 30 days' supply during 2015. Patients who filled prescriptions for buprenorphine or dose forms of opioids which suggest cancer treatment (such as fentanyl lozenges) were excluded; and B. Patients who filled at least one prescription for any benzodiazepine drug.

Study variables:

Outcome variables:

The primary outcome measure was the concomitant use of opioid medications and benzodiazepines. This variable was defined as the receipt of any benzodiazepine and opioid pharmacy dispensing having a days' supply which overlapped by at least 1 day.

Independent variables:

Demographic variables included age (and age group), gender, payment type (including cash and insurance), number of unique opioid and/or benzodiazepine prescribers, if the patient received any prescriptions from the top five, ten and twenty five percent of opioid prescribers in Rhode Island (percentage was determined by the total number of opioid prescriptions written in 2015 by the prescriber in relation to the total number of

opioid prescriptions in 2015), type of opioid medication(s) prescribed (short acting versus long acting, and also chemical type (oxycodone, hydrocodone, morphine, oxymorphone, hydromorphone, tapentadol, methadone, pentazocine, butorphanol, meperidine, levorphanol, codeine and fentanyl), total days' supply, total number of dispensings for controlled substances of any type (CII-CIV), whether the drugs of interest were prescribed by the same or different prescribers, if the patient was a high utilizer of multiple pharmacies or prescribers, and the concurrent use of stimulants.

Statistical analysis:

A descriptive analysis was conducted to identify the overall frequency and percentage of each variable included in the study. Each independent variable was compared with concomitant use, sole use of opioids, sole use of benzodiazepines and non-concomitant use of both opioids and benzodiazepines. We conducted a student t-test for continuous variables, and a Chi-square test for categorical variables to determine the statistical significance of differences between the four outcome groups.

After the initial descriptive analysis, the outcome groups were collapsed into one dichotomous variable: concomitant use (sole use of opioids, sole use of benzodiazepines and non-concomitant use of both opioids and benzodiazepines groups were combined to represent non-concomitant use.)

Univariate logistic regression analysis was conducted to evaluate the association between each independent variable with the dependent variable and identify the significant risk factors of concomitant use of opioid and benzodiazepine medication. A predictive multivariate logistic regression model was then built using a backward stepwise approach with all significant independent variables identified from

the univariate logistic regression. Independent variables associated with combined use of opioid and benzodiazepine drugs at $P<0.2$ (for any strata) were retained in the model. Diagnostic tests for collinearity were performed between independent variables, 2-way interactions were assessed, and diagnostics of model fit were examined, as guided by Akaike information criterion and the Hosmer Lemeshow test. The measure of association between outcome and each independent variable was determined by computing the odds ratio with a 95% confidence interval. Bonferroni Correction was applied for multiple or pairwise comparisons for independent variables with multiple levels.

A sensitivity analyses was conducted. Specifically, the definition of concomitant use of opioid and benzodiazepine medications was expanded to include 0, ≥ 2, or ≥ 3 concomitant days of opioid and benzodiazepine prescriptions. For zero concomitant days, the gap between prescriptions was not greater than one day.

Finally, a subgroup analyses was conducted to examine whether the significant risk factors for concomitant use of opioids and benzodiazepines differed by gender.

Statistical analyses were conducted in SAS 9.4 (SAS software Inc., Cary, NC). The statistical significance level was set at $P<0.05$. This protocol was submitted to the University of Rhode Island Institutional Review Board for review, and classified as not human subjects research.

CHAPTER 4

FINDINGS

Hypothesis 1:

The PDMP database that we analyzed was comprised of 2,516,314 claims for 409,740 unique individuals, from 2015 and 2016. To identify our population of interest, we first reduced the database to claims from 2015 only, identifying 1,289,651 claims for 364,128 unique individuals. We then limited the database to include prescriptions for opioids and benzodiazepines of any duration. The data were then arranged at the patient level only, in order to tally days' supply of each drug class and identify additional patients for exclusion; this yielded 326,785 unique individuals who had opioid use of any duration and/or benzodiazepine use. We then removed any patient who had missing prescription information data, including drug NDC, date of fill, or days' supply. We also identified individuals who we presumed to be receiving opioids to manage cancer pain, based on the type of fentanyl prescriptions (e.g. lozenge). This further reduced our database to 297,594 unique individuals. Finally, we excluded individuals who did not meet the threshold of 30 days of opioid use in 2015. Our resulting database included 139,410 unique individuals. Of those included, 34,825 (25%) patients filled opioid prescriptions totaling at least 30 days and no benzodiazepine prescriptions, 81,062 (58.1%) patients filled a benzodiazepine prescription and no opioid prescriptions, 1,871 (1.3%) patients filled opioid prescriptions totaling at least 30 days and a benzodiazepine prescription which did not

overlap with the opioid prescription. These three groups of patients were combined to represent the non-concomitant use level of the dichotomized concomitant use outcome variable. Additionally, 21,652 (15.5%) patients filled opioid prescriptions totaling at least 30 days, and a benzodiazepine prescription which overlapped the opioid prescription by at least one day. This group was labeled the concomitant use group. See Figure 1.

Table 1 provides the frequency and percentage of the independent variables by each of the four groups outlined above. The majority of our study population was female (63%) and the average age was 55 years (SD 18.7). Most had commercial insurance (65%), filled prescriptions at fewer than 4 pharmacies (94.2%) and had fewer than 4 prescribers (89.4%). The average number of prescriptions for controlled substances per patient during 2015 was 6.7 (SD 7.3). Each independent variable was compared with each outcome of interest; all variables were statistically significantly associated with differences among the four outcomes groups, with the exception of gender. Subsequent multivariable analysis was performed using the dichotomized concomitant use outcome variable.

For the multivariate analysis, the continuous variable age was not included, since both age variables were significant in the univariate analysis. Gender was not included since it was insignificant in the univariate analysis. Overall, the covariates included in the multivariate model remained statistically significant.

A diagnostic test for collinearity did not reveal any collinear covariates. We also assessed for 2-way interactions between age and all covariates, and total number of prescriptions and all covariates. Significant interaction was seen between age and

total number of controlled substance prescriptions, number of prescribers and stimulant use, and also between total number of prescriptions and pharmacy utilization, payment type and stimulant use. These interactions were then entered in the model. After running subsequent models, pharmacy utilization was removed as it was no longer significant. The model fit was not improved by the inclusion of the interaction terms, according to the Hosmer and Lemeshow test ($p < .0001$), therefore the model findings without the interaction terms is presented in Table 2.

Results from the multivariable model revealed that patients who were 45-64 years of age (OR 1.326, 95% CI 1.259-1.398) or greater than 64 years of age (OR 1.85, 95% CI 1.75-1.96) were more likely to be prescribed concomitant opioid and benzodiazepine prescriptions than younger patients. Those who received controlled substance prescriptions from less than or equal to three prescribers (OR 0.257, 95% CI 0.246-0.268) were less likely to be prescribed concomitant opioid and benzodiazepine prescriptions than those who received controlled substance prescriptions from greater than 3 prescribers. However, patients who paid for the most recent prescription using health insurance (commercial health insurance OR 1.003, 95% CI 0.943-1.067; public health insurance OR 1.108, 95% CI 1.035-1.185; other health insurance OR 3.684, 95% CI 3.249-4.177), and did not have a least one prescription filled for a stimulant (OR 3.285, 95% CI 3.021-3.572), had increased odds of being prescribed benzodiazepines and opioids concomitantly. Additionally, each additional prescription for a controlled substance that a person was prescribed increased the odds that they were prescribed concomitant therapy by 12 percent (OR 1.12, 95% CI 1.118-1.122.

Hypothesis 2:

Of those individuals who were prescribed at least one instance of concomitant prescriptions, the average number of opioid, benzodiazepine and controlled substance prescriptions and the most commonly prescribed opioid and benzodiazepine medications were identified. The most commonly prescribed opioids were oxycodone and hydrocodone, with roughly 50% of the concomitant use group being prescribed at least one of these medications (54% and 49%, respectively). On average, individuals who received concomitant opioid and benzodiazepine prescriptions, received 10 prescriptions for opioids (SD 7) and 7 prescriptions for benzodiazepines (SD 5). See Table 3.

We analyzed prescribers by de-identified DEA number, and determined the top 25%, 10% and 5% of opioid prescribers, by prescription volume. In the concomitant use group, 21,595 (99.7% of the concomitant use group) individuals filled at least one opioid prescription by a provider who was in the top 25%, 7,359 (34%) filled at least one opioid prescription by a provider who was in the top 10% and 4,073 (18.8%) filled at least one opioid prescription by a provider who was in the top 5%. See Table 4.

We conducted a sub group analysis of those receiving concomitant opioids and benzodiazepines, stratifying by gender. Women, who represented 66% the concomitant use group, were generally older (36.6% of women were older than 64 years of age versus 29.1% of men, $p < 0.0001$), more likely to pay for prescriptions using public insurance (28.9% vs 24.3%, $p < 0.0001$), have >3 prescribers (38.7% vs 36.3%, p 0.0007) and fill a greater number of prescriptions for at least one stimulant (7.5% vs 5.8%, $p < .0001$). See Table 5.

Table 6 highlights the significant differences in the type of opioids used among men and women, and differences in prescribing patterns. Of the most commonly prescribed opioids, previously mentioned, men filled a greater percentage of prescriptions than women for oxycodone (59.3% vs 51.3%, p <.0001), morphine (16% vs 13.8%, p <0.0001) and methadone (2.4% vs 1.7%, p 0.0004). Men also filled more prescriptions for opioids overall than women (mean 10 prescriptions vs 7 prescriptions, p <.0001). Men were prescribed a greater number of days of opioids (mean 178.7 days' vs 172.7 days' supply, p 0.0025). However, women received a greater number of days of benzodiazepines (mean 174 days' supply vs 161.3 days' supply, p <.0001) and were prescribed concomitant therapy by different prescribers more frequently than men (60.7% vs 56.9%, p <.0001).

A sensitivity analysis did not reveal any statistically significant differences among patients who filled concomitant benzodiazepine and opioid prescriptions with varying degrees of overlapping days. See Appendix 1.

CHAPTER 5

CONCLUSION

In this state-level analysis of 139,410 individuals we found that overall 15.5% (21,652) of individuals were prescribed opioid and benzodiazepine prescriptions concomitantly, which overlapped by at least one day, at least once during 2015. This figure represents 2.1% of Rhode Islanders during that time. Of those who were prescribed concomitant therapy, roughly twice as many women (66% to 34%) received these medication types concomitantly as compared with men. Our results agree with published findings from the analysis of 2013-2014 data obtained from the Texas PDMP and a national data sample which mimicked the data available in a PDMP for 2015. These analyses presented similar trends of potentially inappropriate concurrent prescribing of opioids and benzodiazepines (among other potentially inappropriate drug combinations.)

In analyzing data from the Texas PDMP, researchers found that 15.99% of controlled substance users were prescribed at least one instance of potentially inappropriate concurrent combinations of drugs. Their analysis included a greater number of inappropriate drug combinations than our analysis, however they found that opioids were the most prevalent drug class involved in potentially inappropriate concurrent use combinations (96% of individuals who were prescribed at least one instance of potentially inappropriate concurrent combinations of drugs). They determined that risk factors for concurrent use of inappropriate drug combinations

included having a prescription for opioids, being greater than 18 years old, and using a controlled substance for greater than 30 days.[15]

Another study which found similar results, compared laboratory drug screening test result data to provider supplied prescription information, for both prescriptions written by the clinician who order the drug screening, and other drugs that the patient was prescribed, which were obtained from the PDMP. All subjects included in this study were prescribed either a benzodiazepine and/or an opioid. This study concluded that concomitant use of benzodiazepines and opioids were more common in women ($P<0.01$), and that this result was driven by the increased number of benzodiazepine prescriptions which women received (32.7% vs 23.5%). They also found that the use of benzodiazepines, opioids and the concomitant use of both drugs increased with age.[16]

We also found that older age increases risk for concomitant opioid and benzodiazepine use, which is supported by findings that older adults may suffer from more chronic pain,[17] and are prescribed benzodiazepines for a range of maladies including, insomnia and anxiety.[18] We theorized that an individual who was prescribed concomitant opioid and benzodiazepine drugs was more likely to have a greater number of prescribers; this theory was confirmed by our findings. Patients who saw greater than two prescribers were more likely to receive concomitant therapy. These patients may have more complicated medical conditions requiring them to see more physicians, but the care may not be well coordinated. Another potential explanation of this finding is timing of the implementation of the PDMP with relation to our study year. One goal of implementation is to encourage prescribers to consult

the database prior to prescribing medications, however through the end of 2015 (the year of the study), only about 40% of prescribers had registered with the PDMP. Further analysis with subsequent years of data may find different results; as of September, 2016, 100% of Rhode Island prescribers were registered with the PDMP.[19] Lastly, patients who were prescribed stimulant medications were less likely to be prescribed opioids and benzodiazepines as concomitant therapy. We included stimulant use as a covariate due to its potential for abuse. While stimulant use (and subsequent abuse) has been historically seen in younger populations,[20] stimulant dependence and abuse has been reported in older adult populations as well.[21]

Much of the published literature surrounding concomitant use of benzodiazepines and opioids discusses changes in prescribing patterns over time,[22] the detrimental effects of concomitant use of these drugs, including death,[5,11,23,24] and socio-economic factors that predict concomitancy.[13,22,25] While these topics are important and relevant to the current climate of pharmaceutical prescribing, these are not factors that we can consider with the data utilized in our study. In addition to its primary purpose as a real-time tool to aid prescribers and pharmacists in making the best decisions for their patients with timely information about patients' prescription history, PDMP data provide opportunity for state-wide evaluation of patterns of controlled substance use, such as our study, that inform public health efforts to promote safe and evidence-based use of higher-risk medications.

Limitations:

While the PDMP dataset lacks certain basic demographic information, such as

race/ethnicity, other variables which are captured in the database have been reported as predictors in published literature and were consistent with our findings, including age, and a single provider who writes concomitant prescriptions.[22]

This study has several limitations in its current state, some of which can be addressed in future analysis, and others that are limitations of the dataset. Limitations which will be addressed in subsequent analysis are identifying and determining the significance of other prescribed scheduled medications, identifying prescribers who write the most prescriptions for opioids, benzodiazepines, and the concomitant use of these medications. It is possible that some providers are unaware of their patient's concomitant therapy while others may be prescribing it knowingly. Further sub-group analyses will provide more insight into these factors.

Limitations that we cannot address through a more thorough analysis include a lack of diagnosis information, use of non-scheduled drugs, race, socio-economic status attributes including income, education, transportation, housing status, marital status – all which may be of interest but are beyond the scope of this research and database. We excluded patients who we determined to be receiving end-of-life care or cancer treatment, without diagnosis code this determination was based on the type of prescription that a patient filled. It is possible that we over or under-estimated the number of patients with these conditions.

We conclude that there are predictive factors that can be observed in pharmacy level data to determine if a patient is at a higher risk for being prescribed concomitant benzodiazepine and opioid therapy. These factors are age greater than or equal to 45 years, using health insurance to pay for controlled substance prescriptions (rather than

cash) and receiving controlled substance prescriptions from greater than two prescribers.

APPENDICES

Table 1. Characteristics of 139,410 patients who received opioid and/or benzodiazepine prescriptions from RI pharmacies in 2015

Characteristic	Concomitant Use (% of Total)	Opioid Only (% of Total)	Benzodiazepine Only (% of Total)	Dual use no overlap (% of Total)	Total	p value
	n = 21652 (15.5)	n = 34825 (25)	n = 81062 (58.1)	n = 1871 (1.3)	N = 139410	
Age						
Age Mean, (SD)	59.2 (15.7)	59.4 (17.2)	51.4 (19.3)	57.6 (17.1)	54.8 (18.7)	<0.0001[1]
Age Group, N (%)						
<19	47 (<1)	491 (1.4)	3705 (4.6)	9 (<1)	4253 (3)	<0.0001
19 -24	117 (<1)	350 (1)	3910 (4.8)	32 (<1)	4413 (3.2)	
25 – 44	3474 (16)	5313 (15.3)	20287 (25)	389 (20.1)	29539 (21.1)	
45 – 64	10642 (49.2)	15773 (45.3)	32462 (40.1)	801 (42.8)	59909 (42.8)	
> 64	7372 (34.1)	12898 (37)	20698 (25.5)	640 (34.21)	41780 (29.9)	
Gender, N (%)						
Male	7363 (34)	16304 (46.8)	27062 (33.4)	660 (35.3)	51598 (36.9)	<0.0001
Female	14288 (66)	18515 (53.2)	53977 (66.6)	1211 (64.7)	88266 (63.1)	
Payment type, N (%)						
Cash	1881 (8.7)	3570 (10.2)	11302 (13.9)	204 (10.9)	16916 (12.1)	<0.0001
Public	5914 (27.3)	10255 (29.2)	13298 (16.4)	457 (24.4)	30018 (21.5)	
Commercial	13152 (60.7)	20456 (58.2)	56007 (69.1)	1163 (62.2)	90877 (65)	
Other	705 (3.3)	888 (2.5)	454 (<1)	47 (2.5)	862 (2.5)	
Total Number of prescribers (all opioids and/benzodiazepines) N (%)						
<= 3	13456 (62.2)	33867 (96.3)	80283 (99)	1348 (72)	125118 (89.4)	<0.0001
> 3	8196 (37.8)	1301 (3.7)	779 (1)	1523 (28)	14776 (10.6)	
Total Number of pharmacies used to fill opioid and/or benzodiazepine prescriptions, N (%)						
<= 3	17572 (81.2)	31882 (91.6)	80184 (98.9)	1673 (89.4)	131727 (94.2)	<0.0001
> 3	4080 (18.8)	2943 (8.4)	878 (1.1)	198 (10.6)	8168 (5.8)	
Total Prescriptions for controlled substances, Mean (SD)						
	24.2 (15.7)	10.5 (9.9)	6.2 (7.0)	9.8 (7.7)	6.7(7.3)	<0.0001[1]
Stimulant Use, Filled at least one prescription in 2015, N (%)						
	1498 (6.9)	950 (2.7)	5205 (6.4)	125 (6.7)	7794 (5.6)	<0.0001

[1]Performed Student t-test using Concomitant use compared to all other categories combined

Table 2. Adjusted odds of receiving concomitant opioid and benzodiazepine prescriptions, and compared with using either medication separately (N = 139,410).

Characteristic	Odds Ratio	95% CI[1]		p Value
Age (Ref = 25-44)				
<= 18	0.231	0.17	0.32	<.0001
19 – 24	0.343	0.28	0.43	<.0001
45 – 64	1.326	1.259	1.398	<.0001
>= 65	1.85	1.75	1.96	<.0001
Payment Type (Ref = Cash)				
Commercial Insurance	1.003	0.943	1.067	0.9268
Public Insurance	1.108	1.035	1.185	0.003
Other	3.684	3.249	4.177	<.0001
Unique Prescribers (Ref = > 3 Prescribers)				
<= 3 Prescribers	0.257	0.246	0.268	<.0001
Total Number of Prescriptions	1.119	1.117	1.121	<.0001
Stimulant Use (Ref = None)	3.226	2.967	3.509	<.0001

Table 3. Opioid and Benzodiazepine Use in the Concomitant Use Group: Medication Type, [1] Number of Prescriptions, Total Days' Supply and Patients receiving Medication from Different Prescribers

Medication N (%)	
Oxycodone	11,694 (54)
Hydrocodone	10617 (49)
Morphine	3143 (14.5)
Codeine	1905 (8.8)
Fentanyl	1159 (5.4)
Hydromorphone	955 (4.4)
Methadone	426 (2)
Oxymorphone	116 (<1)
Tapentadol	93 (<1)
Pentazoncine	23 (<1)
Buterophanol	23 (<1)
Meperidine	20 (<1)
Levorphanol	1 (<1)
Benzodiazepine Type, N (%)	
Alprazolam	6518 (28.2)
Lorazepam	5618 (24.3)
Clonazepam	5602 (24.2)
Diazepam	4663 (20.2)
Temazepam	515 (2.2)
Clorazepate	91 (<1)
Chlordiazepoxide	53 (<1)
Triazolam	46 1)
Oxazepam	18 (<1)
Flurazepam	12 (<1)
Estrazolam	3 (<1)
Average number of opioid prescriptions by duration of action, Mean (SD)	
Short Acting	9.3 (6.7)
Long Acting	1.7 (4.5)
Average Number of Prescriptions, Mean (SD)	
Opioids	10 (7)
Benzodiazepines	7 (5)
Average Days of Supply, Mean (SD)	
Opioids	174.8 (117.2)
Benzodiazepines	169.7 (125)
Overlapping days	10.2(10.2)
Different Prescribers, N (%)	
At least one instance of concomitant opioid and benzodiazepine prescriptions were prescribed by different prescribers	12861 (59.4)

Table 4. Receipt of an Opioid Prescription by a top 25%, 10% and 5% Opioid Prescriber by Total Prescription Volume, in the Concomitant Use Group.

Patient filled at least one prescription written by a prescriber who was in the top	
25% of opioid prescribers	21595 (99.7)
10% of opioid prescribers	7359 (34)
5% of opioid prescribers	4073 (18.8)

Table 5. Opioid and Benzodiazepine Use in the Concomitant Use Group, Stratified by Gender: Medication Type,[1] Number of Prescriptions, Total Days' Supply.

	Male	Female	p Value
	n = 7363	n = 14288	
Age			
Age Mean, Mean (SD)	57.7 (14.3)	60.04 (16.3)	<0.0001
Age Group, N (%)			
<19	19 (<1)	28 (<1)	<0.0001
19 -24	45 (<1)	72 (<1)	
25 – 44	1190 (16.2)	2283 (16)	
45 – 64	3968 (53.9)	6674 (46.7)	
> 64	2141 (29.1)	5231 (36.6)	
Payer, N (%)			
Cash	626 (8.5)	1255 (8.8)	<0.0001
Public	1792 (24.3)	4122 (28.9)	
Commercial	4691 (63.7)	8460 (59.2)	
Other	254 (3.5	451 (3.2)	
Number of Prescribers, N (%)			
<= 3	4691 (63.7)	8764 (61.3)	0.0007
> 3	2672 (36.3)	5524 (38.7)	
Number of Unique Pharmacies, N (%)			
<= 3	5924 (80.5)	11648 (81.5)	0.0572
> 3	1439 (19.5)	2640 (18.5)	
Total Prescriptions, Mean (SD)			
Any prescriptions reported in the PDMP	24.2 (15.7)	24.0 (15.6)	0.0015
Stimulant Use, N (%)			
Filled at least one prescription in 2015	424 (5.8)	1074 (7.5)	<0.0001
Total Prescriptions, Mean (SD)			
	23.6 (15.4)	24.5 (15.8)	<0.0001

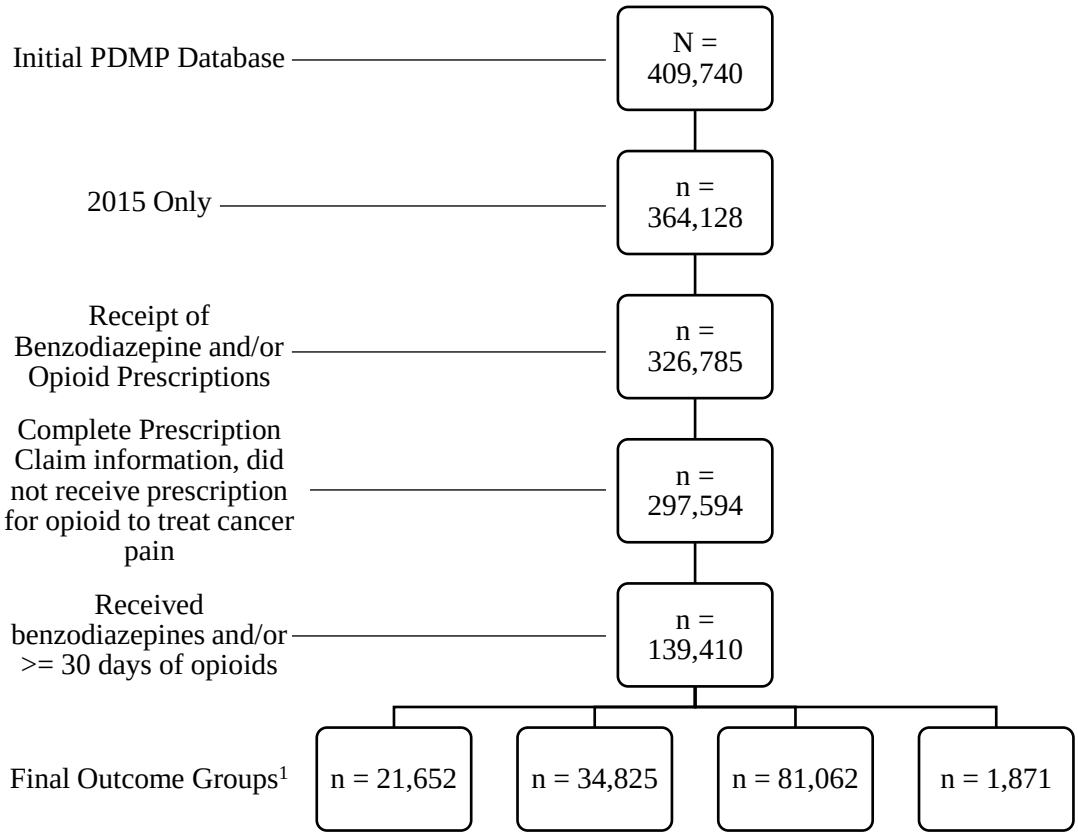
[1] One case was removed for gender variable not recorded

Table 6. Opioid and Benzodiazepine Use in the Concomitant Use Group, Stratified by Gender: Chemical Type, Number of Prescriptions, Total Days Supply[1] and Inconsistent Prescribers.

Chemical Type, N (%)			
	Male	Female	p Value
Oxycodone	4363 (59.3)	7330 (51.3)	<0.0001
Morphine	1175 (16)	1968 (13.8)	<0.0001
Codeine	476 (6.5)	1429 (10)	<0.0001
Methadone	179 (2.4)	247 (1.7)	0.0004
Average number of prescriptions by duration of Action, Mean (SD)			
Long Acting	2.0 (4.8)	1.6 (4.3)	<0.0001
Average Number of Prescriptions, Mean (SD)			
Opioids	10 (7)	7.4 (4)	<0.0001
Benzodiazepines	6.6 (5)	7.1 (5.1)	<0.0001
Average Days of Supply, Mean (SD)			
For Opioids	178.7 (119.5)	172.7 (115.9)	0.0025
For Benzodiazepines	161.3 (126.9)	174 (123.8)	<0.0001
Different Prescribers, N (%)			
At least one instance of concomitant opioid and benzodiazepine prescriptions were prescribed by different prescribers	4188 (56.9)	8673 (60.7)	<0.0001

[1]Significant independent variables included

Figure 1. Flow chart for selection criteria of study participants



[1]From left to right: Concomitant use of opioids and benzodiazepines, opioid use only, benzodiazepine use only, non-concomitant use of opioids and benzodiazepines.

Appendix 1. Sensitivity Analysis of Number of Days of Overlapping Benzodiazepine and Opioid Prescriptions Dispensed in RI pharmacies in 2015, in the Concomitant Use Group

	Concomitant Use[1]	No Overlap[2]	At least 2 days of overlap	At least 3 days of overlap	p Value
	n = 21652	n = 22136	n = 21276	n = 20890	
Age*					
Age Mean	59.2 (15.7)	59.2 (15.7)	59.4 (17.2)	51.4 (19.3)	0.96
Age Group					
<19	47 (<1)	48 (<1)	46 (<1)	44 (<1)	>.99
19 -24	117 (<1)	121 (<1)	113 (<1)	108 (<1)	
25 – 44	3474 (16)	3550 (16)	3397 (16)	3314 (15.9)	
45 – 64	10642 (49.2)	10873 (49.1)	10457 (49.2)	10286 (49.2)	
> 64	7372 (34.1)	7544 (34.1)	7263 (34.1)	7138 (34.2)	
Gender					
Male	7363 (34)	7572 (34.2)	7213 (33.9)	7046 (33.7)	0.98
Female	14288 (66)	14563 (65.8)	14062 (66.1)	13843 (66.3)	
Payer					
Cash	1881 (8.7)	1924 (8.7)	1851 (8.7)	1819 (8.7)	>.99
Public	5914 (27.3)	6058 (27.4)	5819 (27.4)	5746 (27.5)	
Commercial	13152 (60.7)	13435 (60.7)	12915 (60.7)	12650 (60.6)	
Other	705 (3.3)	719 (3.3)	691 (3.3)	675 (3.2)	
Number of prescribers					
<= 3	13456 (62.2)	13758 (62.1)	13248 (62.3)	13025 (62.4)	0.97
> 3	8196 (37.8)	8378 (37.9)	8028 (37.7)	7865 (37.7)	
Pharmacy Utilization					
<= 3	17572 (81.2)	17988 (81.3)	17252 (81.1)	16929 (81)	0.94
> 3	4080 (18.8)	4148 (18.7)	4024 (18.9)	3961 (19)	
Total Prescriptions*					
	24.2 (15.7)	24.0 (15.6)	24.4 (15.7)	24.6 (15.7)	>.99
Stimulant Use					
Filled at least one prescription in 2015	1498 (6.9)	1514 (6.8)	1482 (7)	1460 (7)	0.93

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