Published in final edited form as:

Subst Abus. 2016 ; 37(4): 516–520. doi:10.1080/08897077.2016.1179242.

The Association Between Benzodiazepine Prescription and Aberrant Drug-related Behaviors in Primary Care Patients Receiving Opioids for Chronic Pain

Tae Woo Park, MD, MS^{a,b}, Richard Saitz, MD, MPH^{c,d}, Kerrie P. Nelson, PhD^e, Ziming Xuan, ScD, SM, MA^c, Jane M. Liebschutz, MD, MPH^d, and Karen E. Lasser, MD, MPH^{c,d}

^aDivision of General Internal Medicine, Department of Medicine, Alpert Medical School and Rhode Island Hospital, Providence, Rhode Island, USA

^bDepartment of Psychiatry and Human Behavior; Alpert Medical School and Rhode Island Hospital, Providence, Rhode Island, USA

^cDepartment of Community Health Sciences, Boston University School of Public Health, Boston, Massachusetts, USA

^dClinical Addiction Research and Education (CARE) Unit, Section of General Internal Medicine, Department of Medicine, Boston University School of Medicine and Boston Medical Center, Boston, Massachusetts, USA

^eDepartment of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, USA

Abstract

Background—Benzodiazepine use has been associated with addiction-related risks, but little is known about its association with aberrant drug-related behaviors in patients receiving opioids for chronic pain. We examined the association between receipt of a benzodiazepine prescription and two aberrant drug-related behaviors, early opioid refills and illicit drug (cocaine) use, in patients receiving opioids for non-cancer chronic pain.

Methods—This was a retrospective cohort study of 847 patients with one visit to either a hospital-based primary care clinic or one of two community health centers between 9/1/11 and 8/31/12. All patients received three opioid prescriptions written at least 21 days apart within six months, and one urine drug screen during the study period. A Cox proportional hazards model estimated the hazard of a second early opioid refill, defined as an opioid prescription written 7–25 days after the previous prescription for the same drug, as a function of time-varying

Correspondence should be addressed to Tae Woo Park, MD, Assistant Professor, Departments of Medicine and Psychiatry and Human Behavior, Alpert Medical School and Rhode Island Hospital, 593 Eddy Street, Potter 3, Providence, RI 02903. tpark1@lifespan.org.

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

All coauthors provided substantial contributions to the conception or design of the work, or acquisition, analysis, or interpretation of data for the work, and helped with drafting the work or revising it critically for important intellectual content. All coauthors approve this version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. TP is the guarantor for the study, had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

benzodiazepine prescription. A logistic regression model examined the relationship between benzodiazepine prescription and a positive urine test for cocaine. Models were adjusted for demographics, and mental/substance use disorder diagnoses.

Results—Twenty-three percent (n=196) of patients received one benzodiazepine prescription during the study period. Twenty-two percent (n=183) of patients had two early opioid refills and 11% (n=93) had one positive urine drug tests for cocaine. Receipt of benzodiazepine prescription was associated with an increased hazard of having a second early opioid refill, adjusted hazard ratio = 1.54 (95%CI, 1.09–2.18); but not associated with a positive cocaine test, adjusted odds ratio = 1.07 (95% CI, 0.55–2.23).

Conclusions—Among primary care patients receiving chronic opioid therapy, benzodiazepine prescription was associated with early opioid refills but not with cocaine use. Further research should better elucidate the risks and benefits of prescribing benzodiazepines to patients receiving opioids for chronic pain.

INTRODUCTION

Benzodiazepines are commonly prescribed to treat anxiety and/or insomnia in patients receiving opioids for pain,^{1–3} common disorders in patients with pain conditions.^{4,5} But combined benzodiazepine and opioid use is increasingly implicated in emergency department visits and drug overdoses.^{6–8} And non-medical use of sedatives, including benzodiazepines, was associated with increased risk of opioid analgesic use disorder.⁹ Substance use disorder treatment admissions reporting both benzodiazepine and opioid analgesic use increased 570 percent between 2000 and 2010, while admissions that involved neither of these drugs decreased by 9.6 percent.¹⁰

The relationship between concurrent benzodiazepine and opioid analgesic use and addictive behaviors is not well understood. Concurrent benzodiazepine and opioid analgesic use may lead to opioid misuse in chronic pain patients because of euphoria caused by the combined medications. People taking methadone report that concurrent benzodiazepine use increases the euphoric effects of opioids,^{11,12} a finding replicated in laboratory settings.^{13,14} Alternatively, benzodiazepines may be a marker of unknown factors that lead to opioid misuse. Among pain patients receiving opioids, benzodiazepines are more commonly prescribed to patients with psychiatric and substance use disorders.^{6,15,16} And the presence of these co-morbidities has been associated with opioid misuse in chronic pain patients.^{17,18}

Opioid use disorders can be difficult to diagnose in patients receiving chronic opioids for pain. Aberrant drug-related behaviors have been proposed as indicators of opioid addiction.¹⁹ These behaviors can vary in severity from requests for early refills to falsifying prescriptions. In this study, we examined the association between benzodiazepine prescription and two aberrant drug-related behaviors, early opioid refills and cocaine use, in a cohort of primary care patients receiving opioids for non-cancer chronic pain. We hypothesized that benzodiazepine prescription would be associated with early refills and cocaine use in patients receiving opioids for pain.

METHODS

Study design and population

We conducted a 12-month retrospective cohort study of patients 18 to 89 years old who met the following criteria during the study period, September 1, 2011- August 31, 2012: 1) one visit to a hospital-based primary care clinic or one of two community health centers, 2) received chronic opioid therapy for chronic non-cancer pain, previously defined as receiving 3 opioid prescriptions at least 21 days apart within a 6-month period,²¹ and 3) completed at least one urine drug test. We utilized de-identified data abstracted from the electronic medical record (EMR) and housed at the Boston Medical Center Clinical Data Warehouse. The Institutional Review Board at Boston University approved this study.

Benzodiazepine and opioid prescribing

Benzodiazepine and opioid analgesic medications prescribed by a primary care clinician (physician, nurse practitioner, or physician assistant) were examined in this study. We included the following benzodiazepines: alprazolam, bromazepam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, temazepam, and triazolam. Opioid analgesics included in this study were codeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, oxymorphone, and propoxyphene. Observation for each patient started on the date of the first opioid prescription and ended on the end date of the last opioid prescription during the study period. Though some patients had gaps between opioid refills, 72% of patients had no gaps and 14% had a gap of one month or less. Thus, we decided to treat all patients as continuously exposed to opioids during the observation period. Because only one exposure to the benzodiazepine/opioid combination might lead to opioid misuse, we treated patients who received benzodiazepines as exposed to benzodiazepines on the date of the first benzodiazepine prescription until the end of the observation period.

Outcomes

We chose two measures of aberrant drug behaviors because they were available in the EMR in this study. Our primary outcome measure was time to a patient's second early opioid refill prescription. Early opioid refills were defined as an opioid prescription written 7–25 days after the previous prescription for the same drug. A lower limit of 7 days was used to exclude refills that were reprints of a prescription. An upper limit of 25 days was used because patients may have required a prescription a few days early within a typical 28-day refill cycle for personal reasons, such as a vacation. The outcome of time to a second early refill allowed for one early refill, a cutoff used in previous studies.^{20,21} We performed a medical record review of 100 individual patient records at the three sites under study. We found that 80% of early refills did not have associated medical documentation that described the prescriber's reasons for the early refill (e.g., dose escalation). This suggests that these early refills represent opioid misuse and a cutoff of two or more early refills is likely more specific for misuse. Our secondary outcome was any positive cocaine test by urine drug screen. Illicit drug use and unprescribed opioid use are common measures for aberrant drug-related behaviors.²² We limited our drug testing to cocaine because 1) cocaine and opiates were the only two illicit drugs regularly tested in our sample and 2) we were unable to

reliably distinguish between prescribed and unprescribed opioids because it is difficult to distinguish between opioid types without quantity levels (unavailable for this study) and if a separate oxycodone test isn't performed (only a portion of patients received this test).²³

Covariates

Potential confounders included age, sex, race, and Medicaid insurance. We assessed for medical comorbidities using the Charlson Comorbidity Index²⁴ (Deyo modification),²⁵ pain, and mental health and substance use disorders. Diagnoses were obtained using ICD-9 (International Classification of Diseases, ninth edition) codes from the EMR problem list or through billing codes and included any anxiety disorder, any depressive disorder, any other psychiatric disorder (bipolar and psychotic disorders), any drug use disorder (opioids, cocaine, sedatives, marijuana, polysubstance and other drug abuse and dependence), and any alcohol use disorder (alcohol abuse and dependence).

Statistical analysis

We compared patient characteristics among patients who did and did not receive benzodiazepines with chi-square tests for categorical variables and t-tests for the continuous variable (age). We used survival analysis to account for censoring due to variable times of study entry, the end of the study period, or patient loss to follow-up. We used a Cox proportional hazards model for our primary outcome to calculate the hazard of time to second early opioid refill for those in receipt of benzodiazepine prescription compared to no receipt (Model 1). We treated benzodiazepine prescription as a time-varying variable, indicating that benzodiazepine prescription status was allowed to vary over time. The only situation in which patients did not contribute time to the survival analysis is when they were censored (had second opioid refill or were not being prescribed an opioid any longer). For our secondary outcome, any positive cocaine test during the study period, we used a multivariable logistic regression model (Model 2). Because the timing of drug testing was often irregular and infrequent, logistic regression was favored over a time-to-event analysis for the secondary outcome. Furthermore, because of the irregularity in the timing of drug testing, we could not reliably ascertain the timing of cocaine use and thus included all positive cocaine tests regardless of whether they occurred before or after the first benzodiazepine prescription. In a sensitivity analysis, when we excluded positive cocaine tests that occurred before the first benzodiazepine prescription, the adjusted odds ratio changed from 1.07 to 0.73 (95% CI 0.39, 1.36) but was not statistical significant. All analyses adjusted for all covariates and were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 1,285 patients received chronic opioid therapy in the 3 primary care clinics during the study period. Among these patients, 325 (25%) did not receive a drug test during the study period and thus were excluded. Of the 847 remaining patients, which constituted the final sample size, 196 (23%) received at least one benzodiazepine prescription while concurrently receiving an opioid prescription during the study period (Table 1). One hundred and eighty three (22%) patients had two or more early opioid refills and 74 (11%) had one or

more positive cocaine tests. A large proportion of the total sample, 63%, had a drug use disorder diagnosis noted in the medical record. The most common pain diagnosis was musculoskeletal in nature (82%). Patients who received benzodiazepines were more likely to be female, white, and have a diagnosis of depressive, anxiety, or other psychiatric disorder. Among pain diagnostic categories, only patients with headache were more likely to receive benzodiazepines relative to patients without headache. The number of urine drug tests or positive cocaine tests did not differ between groups.

Compared to non-receipt of a benzodiazepine prescription, receipt of a benzodiazepine prescription was associated with an increased hazard of early opioid refill (adjusted HR = 1.54; 95%CI, 1.09–2.18) (Table 2). As a sensitivity analysis, we included all 1,285 patients regardless of drug test status for Model 1 and the result was similar (adjusted HR 1.47, 95% CI 1.10, 1.98). There was no association between benzodiazepine receipt and positive cocaine test (adjusted OR = 1.07; 95%CI, 0.55–2.23).

DISCUSSION

Receipt of a benzodiazepine prescription was associated with an increased hazard of early opioid refill but not cocaine use in primary care patients who received opioids for chronic non-cancer pain, even after adjusting for the presence of psychiatric and substance use disorders. The effect size was small to medium in magnitude and may be a clinically important result.

There are several potential explanations for our findings. Benzodiazepine prescription is associated with addictive behaviors in this patient population. One prior study categorized chronic pain patients receiving opioids into three groups: “typical”, “addictive behaviors” and “pain dysfunction”.²⁶ Patients in the “addictive behaviors” and “pain dysfunction” group were more likely to receive benzodiazepine prescriptions. In a cross-sectional study of pain patients receiving opioids, benzodiazepine use was associated with having a substance use disorder and ever injecting drugs.¹⁵ In another study of pain patients receiving opioids, those with a substance use disorder were more likely to be prescribed concurrent sedatives, which included benzodiazepines.¹⁶ Thus, it is possible that those who receive benzodiazepines are more likely to exhibit addictive behavior, which might lead to opioid misuse.

Another interpretation of our findings is that the effect of combining benzodiazepines and opioids leads to opioid misuse. Benzodiazepines can produce a euphoric effect, especially when combined with opioids. In a small study, 72% of methadone maintenance patients reported that diazepam increased or “boosts” the effect of methadone.¹¹ In another study, 33% of benzodiazepine users in one methadone maintenance program reported using benzodiazepines “to feel good” and 22% used them “to get high”.¹² Human laboratory experiments have demonstrated that when combined with methadone, diazepam produces greater subjective opioid effects and drug high than methadone alone or methadone plus placebo^{14,27} and produces a greater effect on subjective measures, such as drug liking and euphoria, than placebo.¹³ It is possible that benzodiazepines increased “drug liking” and

euphoria of opioid analgesics in our study, which may have led to enhanced opioid craving and repeated requests for early refills.

Alternatively, receipt of a benzodiazepine prescription may be a marker for more severe pain. Concurrent sedative use has been associated with having more than one pain condition in patients receiving opioids.¹⁶ The presence of baseline anxiety symptoms is associated with greater pain severity at 12-month follow-up in primary care patients with chronic musculoskeletal pain and depression.²⁸ In a human laboratory study, participants with “high” trait anxiety were the least pain-tolerant.²⁹ Thus, benzodiazepine receipt, particularly for the treatment of anxiety, may be a marker for more severe pain or low pain tolerance. Though data demonstrating an association between pain severity and aberrant drug-related behaviors is weak,^{30–32} patients with more severe pain or low pain tolerance may be similar to the “pain dysfunction” group in the study described above.²⁶ That group had higher levels of pain, mental health problems, and opioid misuse and were more likely to be prescribed benzodiazepines. Patients with more pain and anxiety may be more likely to take opioids for self-medication purposes as an anxiolytic, which combined with potential disinhibition from benzodiazepines, leads to early refill requests.

Possible neurobiological explanations of our results include incentive sensitization and priming. Incentive sensitization is a hypersensitivity of brain circuits through repeated drug administration that results in an increased incentive salience towards drugs.³³ It is possible that the addition of a benzodiazepine to a patient’s opioid regimen may trigger this sensitization process. Another possibility involves priming. Priming mice with nicotine enhances the effects of cocaine.³⁴ Similarly, benzodiazepine use in opioid users may enhance the effects of opioids and lead to greater opioid use.

In our study, benzodiazepine prescription was unrelated to cocaine use. It is possible that chronic pain patients receiving benzodiazepines have higher levels of anxiety and are more likely to seek drugs through licit rather than illicit sources. Receipt of a drug test has been previously associated with having a drug use disorder.^{21,35} Prescribers in our study who suspected drug use disorder (and hence ordered urine drug testing) in some patients might have been hesitant to prescribe them benzodiazepines.

This study had several limitations. It is a retrospective study of EMR data. Patients may have received medications from health care settings outside of primary care (or the affiliated hospital system), which would not have been captured with the EMR that provided the data for this study. This could have biased the analyses in either direction. We did not measure pain severity. Because more severe pain may be associated with benzodiazepine prescription and early opioid refills, pain severity may have been an unmeasured confounder in our study. We only studied patients that had a urine drug test during the study period. A quarter of patients receiving chronic opioid therapy in the 3 clinics studied did not receive a drug test during the study period. It is possible that only those patients with suspicion of substance misuse were tested. This might limit the findings of this study to pain patients receiving opioids with suspicion of substance misuse. Approximately 14% of patients had gaps of greater than 1 month between opioid prescriptions and thus may not have been exposed to opioids and benzodiazepines concurrently. As a sensitivity analysis, we excluded patients

with gaps of greater than 1 month between opioid prescriptions and our results did not change.

In conclusion, we found that benzodiazepine prescription was associated with early opioid refills but not cocaine use in patients prescribed opioids for pain. Benzodiazepine prescription may best be conceived of as a marker for addictive behaviors, low pain tolerance or higher pain severity in this population. Because alternative therapies exist for the primary indications for benzodiazepine prescription, further research should better elucidate the risks and benefits of prescribing benzodiazepines to patients receiving opioids for pain.

Acknowledgments

FUNDING

This research was supported by a grant from the National Institute on Drug Abuse (R01DA034252). The funding agencies had no role in data collection, analysis, interpretation, or the decision to submit the results.

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Table 1

Baseline characteristics of primary care patients who received opioids for chronic pain by receipt of benzodiazepine prescription^a

	Any benzodiazepine prescription during study period		
Characteristic	Yes (n=196)	No (n=651)	p-value
Female, % (n)	58 (114)	38 (250)	<0.001
Age, mean (SD)	51 (11)	53 (11)	0.09
Race			
White, % (n)	50 (98)	32 (207)	<0.001
Insurance			
Medicaid, % (n)	71 (140)	72 (471)	0.80
Charlson Comorbidity Index			
1, % (n)	73 (143)	69 (447)	0.28
Pain diagnosis			
Headache, % (n)	45 (89)	28 (183)	<0.001
Neuropathy, % (n)	18 (360)	20 (128)	0.73
Musculoskeletal, % (n)	78 (153)	82 (538)	0.22
Any depressive disorder ^b , % (n)	73 (144)	47 (307)	<0.001
Any anxiety disorder, % (n)	61 (120)	30 (197)	<0.001
Any other psychiatric disorder ^c , % (n)	13 (26)	8 (49)	0.01
Any drug use disorder ^d , % (n)	67 (131)	62 (406)	0.25
Any alcohol use disorder ^e , % (n)	12 (24)	18 (118)	0.053
Number of urine drug tests, mean (SD)	2.66 (1.91)	2.76 (1.84)	0.49
Number of positive cocaine tests, mean (SD)	0.11 (0.43)	0.14 (0.46)	0.40

SD: standard deviation

^aPatients received 3 or more opioid prescriptions at least 21 days apart within a 6-month period

^bAll mental health and substance use disorder diagnoses were based on ICD-9 codes as noted in the electronic medical record

^cIncludes any bipolar disorder and any psychotic disorder

^dIncludes opioids, cocaine, sedatives, marijuana, polysubstance and other drug abuse or dependence

^eIncludes alcohol abuse or dependence

Table 2

Risk estimates of aberrant drug behaviors by benzodiazepine prescription

Model 1^a	Hazard ratio			
	Second early opioid refill			
	Unadjusted	95% CI	Adjusted	95% CI
No benzodiazepine prescription	1.00 (reference)	-	1.00 (reference)	-
Received benzodiazepine prescription	1.73	1.26–2.38	1.54	1.09–2.18
Model 2^a	Odds Ratio			
	Positive cocaine test			
	Unadjusted	95% CI	Adjusted	95% CI
No benzodiazepine prescription	1.00 (reference)	-	1.00 (reference)	-
Received benzodiazepine prescription	0.80	0.48–1.34	1.07	0.62–2.23

CI: confidence interval

^aBoth models adjusted for sex, age, race, Medicaid insurance, Charlson Comorbidity Index, any depressive disorder, any anxiety disorder, any other psychiatric disorder, any drug use disorder, or any alcohol use disorder