Pain Medicine, 20(6), 2019, 1148–1155
doi: 10.1093/pm/pny179
Advance Access Publication Date: 10 September 2018
Original Research Article

Correlates of Benzodiazepine Use and Adverse Outcomes Among Patients with Chronic Pain Prescribed Long-term Opioid Therapy

Bobbi Jo H. Yarborough, PsyD,* Scott P. Stumbo, MA,* Ashley Stoneburner, MPH,* Ning Smith, PhD,* Steven K. Dobscha, MD,†,‡ Richard A. Deyo, MD, MPH,*,§ and Benjamin J. Morasco, PhD†,‡

*Kaiser Permanente Northwest Center for Health Research, Portland, Oregon; ; †Center to Improve Veteran Involvement in Care, VA Portland Health Care System, Portland, Oregon; ‡Department of Psychiatry, Oregon Health & Science University, Portland, Oregon; §Departments of Family Medicine, Internal Medicine, and the Oregon Institute for Occupational Health Sciences, Oregon Health & Science University, Portland, Oregon, USA

Correspondence to: Bobbi Jo H. Yarborough, PsyD, 3800 N Interstate Avenue, Portland, OR 97227, USA. Tel: 503-335-2400; Fax: 503-335-2424; E-mail: bobbijo.h.yarborough@kpchr.org.

Funding sources: National Institute on Drug Abuse (grant number DA034083).

Disclaimer: The content of this manuscript is solely the responsibility of the authors and does not represent the official views of the Department of Veterans Affairs or the National Institute on Drug Abuse.

Conflicts of interest: Unrelated to the current study, BJHY and SPS have received research contracts to their institution from the Industry post-marketing requirements (PMR), a consortium of companies conducting Food and Drug Administration–required postmarketing studies assessing risks related to opioid analgesics; they have also received research grants to their institution from the National Institutes of Health (NIH) and the Kaiser Permanente Community Benefit Initiative. SPS has received research funding from the Maternal and Child Health Bureau. RAD receives royalties from *UpToDate* for authoring topics on low back pain. Part of his salary has come from an endowment to Oregon Health & Science University from Kaiser Permanente. He has had support from federal grants to his university from the NIH, Centers for Disease Control and Prevention, Agency for Healthcare Research and Quality, and Patient-Centered Outcomes Research Institute. No other author reports having any potential conflict of interest with this study.

Abstract

Objective. To examine the correlates and odds of receiving overlapping benzodiazepine and opioid prescriptions and whether co-prescription was associated with greater odds of falling or visiting the emergency department. **Design**. Cross-sectional study. **Setting**. A large private integrated health system and a Veterans Health Administration integrated health system. **Subjects**. Five hundred seventeen adults with musculoskeletal pain and current prescriptions for long-term opioid therapy. **Methods.** A multivariate logistic regression model examined correlates of having overlapping benzodiazepine and opioid prescriptions in the year before enrollment in the cross-sectional study. Negative binomial models analyzed the number of falls in the past three months and past-year emergency department visits. In addition to propensity score adjustment, models controlled for demographic characteristics, psychiatric diagnoses, medications, overall comorbidity score, and opioid morphine equivalent dose. **Results**. Twenty-five percent (N = 127) of participants had co-occurring benzodiazepine and opioid prescriptions in the prior year. Odds of receiving a benzodiazepine prescription were significantly higher among patients with the following psychiatric diagnoses: anxiety disorder (adjusted odds ratio [AOR] = 4.71, 95% confidence interval [CI] = 2.67–8.32, $P < 0.001$), post-traumatic stress disorder (AOR = 2.24, 95% CI = 1.14–4.38, $P = 0.019$), and bipolar disorder (AOR = 3.82, 95% CI = 1.49–9.81, $P = 0.005$). Past-year overlapping benzodiazepine and opioid prescriptions were associated with adverse outcomes, including a greater number of falls (risk ratio [RR] = 3.27, 95% CI = 1.77–6.02, $P = 0.001$) and emergency department visits (RR = 1.66, 95% CI = 1.08–2.53, $P = 0.0194$). **Conclusions**. Among patients with chronic pain prescribed long-term opioid therapy, one-quarter of patients had co-occurring prescriptions for benzodiazepines, and dual use was associated with increased odds of falls and emergency department visits.

Key Words: Opioids; Benzodiazepines; Co-Prescription; Emergency Department; Falls

Introduction

Benzodiazepines are commonly prescribed in the United States [1,2] to manage anxiety, insomnia, and muscle tension. However, their use alongside opioid analgesics, commonly prescribed for chronic pain, has caused concern, particularly as opioid prescribing peaked in the United States over the first decade of the 21st century [3]. Benzodiazepine use alone is associated with motor vehicle accidents [4] and, particularly among older adults, falls leading to fractures [4,5]. However, when taken in combination with prescription opioids, benzodiazepines can interact to cause side effects (e.g., blurred vision, confusion, dizziness, sedation) that increase risk of adverse events. Indeed, risks associated with co-use of benzodiazepines and opioids include overdose [6–9], higher use of emergency services [10,11], higher risk of serious emergency department visits (e.g., hospitalization or death rather than treatment and release) [12], and higher all-cause mortality [13]. Further, benzodiazepine and opioid co-use can cause a synergistic effect that enhances the euphoric effects of the opioids [14,15], potentially increasing risk of addiction. Chronic pain treatment guidelines from the Centers for Disease Control and Prevention [16] and the US Department of Veterans Affairs/Department of Defense [17] recommend against the co-prescription of these two medications, yet several studies have demonstrated that co-prescription of benzodiazepines among patients also prescribed opioid medications is relatively common, with rates ranging from 12% to up to 80% [2,10,18–20].

The strong association between pain and psychiatric conditions and overlapping symptoms may partly explain why these medications are frequently co-prescribed. For example, benzodiazepines and opioids are used concomitantly to treat chronic pain among people with post-traumatic stress disorder (PTSD) because of their rapid, short-term reduction of anxiety and insomnia, symptoms common to both conditions. Patients with psychiatric conditions are more likely than those without to be prescribed opioid medications for chronic pain [21], and because benzodiazepines effectively reduce overlapping psychiatric and pain symptoms in the short term, patients with chronic pain may be a particularly vulnerable group at higher risk for adverse outcomes that result from the interaction of these medications.

Although a number of studies have examined adverse risks of benzodiazepine and opioid co-use among patients with an opioid use disorder or receiving addiction treatment [22,23], relatively few studies have examined the prevalence and risks associated with co-prescription among individuals receiving routine treatment for chronic pain. Existing studies have examined the prevalence of co-prescribed benzodiazepine and opioids in US health settings, using administrative data only [10,19], or among an Australian cohort, using self-reported data [11]. Adverse outcomes studied have included aberrant drug behaviors [19], inpatient admissions for opioid overdoses [10], and emergency room visits [10,11]. One Department of Veterans Affairs (VA) study [24] examined a broad range of adverse outcomes, including alcohol-, opioid-, and nonopioid drug-related accidents and overdoses, injuries, and death. Here, among a large sample of individuals receiving long-term opioid therapy (LTOT) in two large US health systems (one private and one VA health system), using administrative and self-reported data, we examined the odds of receiving overlapping benzodiazepine and opioid prescriptions, and whether co-prescription was associated with greater odds of falling or visiting the emergency department.

Methods

Settings

Study settings included Kaiser Permanente Northwest (KPNW) and the VA Portland Health Care System (VAPORHCS). KPNW is an integrated health system with two hospitals and more than 30 medical clinics in Oregon and southwest Washington. KPNW provides a comprehensive range of medical, mental health, and addiction services to more than 575,000 members. The VAPORHCS consists of a Department of Veterans Affairs hospital, located in Portland, Oregon, and 10 outpatient clinics throughout central and northwest Oregon. The VAPORHCS provides a full range of primary, tertiary, and long-term care to more than 95,000 veterans.

Participants

Individuals with one or more past-year ICD-9 musculoskeletal pain diagnoses (712.xx, 713.xx–720.xx, 722.xx–724.xx, 729.xx, 274.00) who had received a current outpatient prescription for LTOT (stable dose of at least 90 consecutive days of opioid therapy) [25,26] were eligible for study inclusion. Diagnoses and prescription dispenses were identified using electronic medical record (EMR) data. Each potential participant's prescriptions were categorized by type and multiplied by a conversion factor to determine the average daily and monthly morphine equivalent dose (MED) (see Morasco et al. [27] for description of conversion factors). Ability to read and write in English were also criteria for inclusion. Participants were not selected for recruitment if they were $\leq$18 years old, lacked phone access, or if there was evidence in their EMR of the following: a cancer diagnosis; enrollment in an opioid substitution program in the prior year; only opioid prescriptions for tramadol, buprenorphine, or suboxone (buprenorphine/naloxone); prescriptions for naloxone, meperidine, naltrexone, or propoxyphene; or opioid dose >120 mg MED. The latter were excluded because the parent study was focused on opioid dose escalation; at the time of study enrollment, institutional policies limiting maximum opioid dose differed at the two institutions, which might have resulted in

site-specific differences in opportunities for dose escalation. Potential participants were ineligible if they had a pending litigation or disability claim related to a pain condition [27].

Recruitment

A personalized invitation card describing the study was mailed to each prospective participant; study contact information and a prepaid postcard were included for participants to indicate interest or decline participation. Research staff followed up by phone to answer questions and conduct a brief preliminary screening assessment. Those interested and who met inclusion criteria were scheduled for an in-person study visit, unless phone was preferred.

During the study visit, participants provided written informed consent, completed interviewer-administered questionnaires, and received a $50 gift card for their participation. The enrollment period, during which both self-reported and EMR-derived data were collected, spanned December 2013 to September 2015. All study procedures were reviewed, approved, and monitored by the KPNW and VAPORHCS Institutional Review Boards.

Measures

In addition to past-year musculoskeletal pain diagnoses and opioid prescriptions, other data extracted from the EMR included past-year psychiatric diagnoses (e.g., depression, PTSD, other anxiety disorders, bipolar disorder, alcohol and substance use disorders), overall medical comorbidity (Selim index [28]), other medications known to interact with opioids (sedatives/hypnotics, antidepressants), and past-year emergency room visits. Past-year benzodiazepine use (dichotomized as 0 or $\geq$1 benzodiazepine dispense) was measured by evidence of any prior 12-month dispense in the EMR that overlapped at least one day with an opioid prescription, consistent with previous studies [9,10]. Emergency department visits were likewise derived from the EMR as a continuous variable. Demographic characteristics and falls were self-reported: "Have you had any falls in the last three months (yes/no)?" "If yes, how many?"

Analysis

To compare demographic characteristics and diagnostic factors between patients who had prior-year overlapping co-prescriptions for benzodiazepines and opioids vs those who only were prescribed LTOT (with no period of overlap), *t* tests were used for normally distributed continuous measures, and Mann-Whitney tests were used for non-normal data distribution; chi-square tests were used for categorical measures, and Fisher exact tests were used when small cell counts were encountered. Multivariate logistic regression analysis was conducted to identify factors associated with overlapping benzodiazepine prescription (yes/no) in the prior year. Negative binomial models were used to evaluate the association of overlapping benzodiazepine use with the number of self-reported falls in the three months before study enrollment and the number of EMR-documented past-year emergency department (ED) visits. As those who received benzodiazepine prescriptions may be different from those who did not receive benzodiazepine prescriptions in terms of demographic or clinical factors, a propensity score was created for receiving benzodiazepine prescription using logistic regression including all baseline demographic and diagnostic variables. This propensity score was adjusted for in all the subsequent models to account for confounding. Additional covariates such as age, sex, race, ethnicity, education, mental health diagnoses (depression, PTSD, and bipolar disorder) and substance/alcohol use disorder diagnoses, antidepressant and other sedative/hypnotic prescriptions, comorbidity score, and opioid morphine equivalent dose were also included in the models; all models were adjusted for health system. Data analysis was conducted using SAS 9.4 software (SAS Institute Inc, Cary, NC, USA).

Results

We mailed recruitment letters to 2,320 individuals and reached 1,747 (75.3%) potential recruits; 915 (52.3%) refused, commonly because they were uninterested or did not have time, and 315 (18.0%) were found to be ineligible. Our final sample included 517 (22% of mailed letters, 29% of individuals reached for contact) participants with prior-year musculoskeletal pain diagnoses and current prescriptions for long-term opioid therapy [27]; 80.1% (N = 414) of interviews were conducted in person, 19.3% (N = 110) were conducted by phone, and 0.6% (N = 3) were unspecified.

In the study sample, 24.6% of participants had evidence of past-year concurrent prescriptions for opioids and benzodiazepines; the mean number of polypharmacy months was 7.6. Bivariate analyses based on prescription benzodiazepine status indicated that, compared with participants not prescribed a benzodiazepine, individuals co-prescribed benzodiazepines in the past year were primarily female (57.5% vs 44.1%, $P = 0.009$), had higher overall comorbidity scores (5.1 ± 2.6 vs 4.2 ± 2.6, $P < 0.001$), and were more likely to have anxiety disorder (40.2% vs 10.3%, $P < 0.001$), post-traumatic stress disorder (24.4% vs 12.1%, $P < 0.001$), bipolar disorder (11.0% vs 2.6%, $P < 0.001$), or depression (48.8% vs 31.0%, $P < 0.001$) diagnoses. Finally, they were more likely to be prescribed additional sedative/hypnotic medications (27.6% vs 12.6%, $P < 0.001$), antidepressants (57.5% vs 43.3%, $P = 0.006$), and to have more documented emergency department (0.82 ± 1.7 vs 0.45 ± 1.1, $P = 0.004$) and primary care visits (4.5 ± 3.3 vs 3.2 ± 2.2, $P < 0.001$) than individuals without

overlapping benzodiazepine prescriptions (see Table 1 for additional details).

Veterans were more likely to have diagnoses of depression (VA 47.3% vs KPNW 28.7%, $\chi^2 = 18.0$, $P < 0.001$), PTSD (VA 31.2% vs KPNW 6.0%, $\chi^2 = 58.8$, $P < 0.001$), and substance use disorder (VA 16.1% vs KPNW 3.6%, $\chi^2 = 24.9$, $P < 0.001$). The prevalence of bipolar and anxiety disorder diagnoses did not differ by site. Veterans also had a higher Selim comorbidity score than KPNW participants (VA mean = 4.85 vs KPNW mean = 4.16, F = 8.1, $P = 0.005$).

Prescribing practices appeared to differ between the two sites based on mental health comorbidity. Among the subset of participants with overlapping benzodiazepine and opioid prescriptions (N = 127), 67.5% of veterans with depression had benzodiazepine prescriptions compared with 40.2% of KPNW participants with depression ($\chi^2 = 8.2$, $P = 0.004$). Of veterans with PTSD, 47.5% were co-prescribed compared with 13.8% of KPNW participants with PTSD ($\chi^2 = 16.9$, $P < 0.001$). The likelihood of benzodiazepine prescribing did not differ for bipolar, anxiety, or substance use disorders. The Selim comorbidity score among individuals taking benzodiazepines did not differ by site.

In a multivariate logistic model, after controlling for covariates (age, sex, race, ethnicity, education, substance/alcohol use disorder diagnosis, comorbidity score, antidepressant and sedative/hypnotic prescriptions, and opioid morphine equivalent dose), the only variables associated with receiving an overlapping past-year opioid and benzodiazepine prescription were psychiatric diagnoses: anxiety disorder (adjusted odds ratio [AOR] = 4.71, 95% confidence interval [CI] = 2.67–8.32, $P < 0.001$), post-traumatic stress disorder (AOR = 2.24, 95% CI = 1.14–4.38, $P = 0.019$), and bipolar disorder (AOR = 3.82, 95% CI = 1.49–9.81, $P = 0.005$). No other variables were significant (see Table 2 for additional details).

Our final models (Table 3) assessed associations of overlapping benzodiazepine and opioid prescriptions with two outcome variables: self-reported falls and EMR-derived emergency department visits. After controlling for the covariates described above, individuals with co-prescribed benzodiazepine use experienced 3.27 times the number of self-reported falls in the prior three months (95% CI = 1.77–6.02, $P < 0.001$). Additionally, being a patient of the VA (risk ratio [RR] = 1.98, 95% CI = 1.04–3.78, $P = 0.039$), being female (RR = 1.93, 95% CI = 1.07–3.50, $P = 0.029$), and co-prescription for another sedative/hypnotic medication (not including benzodiazepine; AOR = 3.57, 95% CI = 1.73–7.35, $P = 0.001$) were also associated with increased falls. Age, race, ethnicity, education, baseline morphine equivalent dose, comorbidity score, substance use disorders, and antidepressant medication use were not associated with falls.

Individuals with co-prescribed benzodiazepines and opioids also experienced 1.66 times more emergency department visits in the past year (95% CI = 1.08–2.53, $P = 0.0194$). Being a patient at the VA (RR = 3.82, 95% CI = 2.27–6.45, $P < 0.001$), having higher medical comorbidity scores (RR = 1.38, 95% CI = 1.28–1.48, $P < 0.001$), and being female (RR = 1.64, 95% CI = 1.00–2.68, $P = 0.0483$) were associated with increased ED use. Being older was associated with lower ED use (RR = 0.91, 95% CI = 0.84–0.99, $P = 0.033$). Race, ethnicity, education, baseline morphine equivalent dose, depression, post-traumatic stress disorder, bipolar disorder, substance use disorder, and antidepressant or sedative/hypnotic medication use were not associated with ED use.

Discussion

In a large cross-sectional cohort of individuals prescribed LTOT for chronic pain, one-quarter (24.6%) had a past-year, overlapping benzodiazepine prescription. Individuals with evidence of these overlapping prescriptions experienced more falls and had higher emergency department use compared with individuals prescribed opioids without overlapping benzodiazepine prescriptions. These findings are similar to those described elsewhere [10,11], confirming that opioid and benzodiazepine co-prescription is associated with adverse outcomes in a large, diverse sample of outpatients being treated for chronic pain.

Our study adds to growing evidence that individuals prescribed LTOT not only commonly receive co-prescribed benzodiazepines, but also have additional comorbidities and significant risk factors [29]. We found that individuals prescribed both LTOT and benzodiazepine medications concurrently were more likely to be diagnosed with depression, post-traumatic stress disorder, and bipolar disorder and were more likely to be prescribed additional sedatives/hypnotics and antidepressants. Other studies have documented the co-occurring use of benzodiazepines, antidepressants, and antipsychotics in patients prescribed LTOT [11,30,31] and the associated risks [32]. Interestingly, we did not find greater benzodiazepine co-prescribing for patients with substance use disorder diagnoses, as others have [10,23]. Nor did we find greater benzodiazepine prescribing for those with higher opioid morphine equivalent doses.

Overall, our findings suggest a need for better risk screening before initiating either benzodiazepines or opioids, and for clinically addressing overlapping areas of risk associated with pain and mental health. Prescribing alerts or prescription drug monitoring programs may be an effective way to reduce co-prescription, but use of the latter remains voluntary in many states (including Oregon), and self-reported use remains relatively low [33–35]. The recent Centers for Disease Control and VA guidelines on opioid prescribing discourage co-prescribing benzodiazepines [16,17], but the impact of these recommendations is not yet known.

Table 1. Demographic characteristics, falls, psychiatric comorbidity, and emergency department visits among individuals with past-year co-prescribed opioid and benzodiazepine use vs no co-prescribed use (N = 517)

	Total Sample	Overlapping Prescriptions for Benzodiazepines and Opioids (N = 127, 24.6%), No. (%) or Mean ± SD	No Past-Year Overlapping Benzodiazepine and Opioid Use (N = 390, 75.4%), No. (%) or Mean ± SD	*P* Value
KPNW	331 (64.0)	87 (68.5)	244 (62.6)	0.226
VAPORHCS	186 (36.0)	40 (31.5)	146 (37.4)	—
Characteristics derived from questionnaire				
Female	245 (47.4)	73 (57.5)	172 (44.1)	0.009
White race	428 (82.8)	109 (87.2)	328 (84.8)	0.501
Hispanic ethnicity	23 (4.5)	6 (4.7)	17 (4.4)	0.867
Age, y	59.4 ± 11.3	57.7 ± 11.9	59.9 ± 11.1	0.059
Education				
Up to and including high school diploma or GED	106 (20.5)	27 (21.3)	79 (20.3)	0.848
Some college or technical school	284 (54.9)	67 (52.8)	217 (55.6)	—
College degree or higher	127 (24.6)	33 (26.0)	94 (24.1)	—
Any self-reported fall	143 (27.7)	43 (33.9)	100 (25.6)	0.072
Variables derived from electronic medical record				
Anxiety disorder	91 (17.6)	51 (40.2)	40 (10.3)	<0.0001
Depression	183 (35.4)	62 (48.8)	121 (31.0)	0.0003
Post-traumatic stress disorder	78 (15.1)	31 (24.4)	47 (12.1)	0.0007
Bipolar disorder	24 (4.6)	14 (11.0)	10 (2.6)	<0.0001
Substance/alcohol use disorder	42 (8.1)	10 (7.9)	32 (8.2)	0.906
Selim comorbidity index	4.4 ± 2.7	5.1 ± 2.6	4.2 ± 2.6	0.0009
Current daily morphine equivalent dose	36.3 ± 27.9	37.8 ± 30.5	35.7 ± 26.6	0.461
Months prescribed benzodiazepine	NA	7.6 ± 6.4	NA	NA
Sedative/hypnotic prescription medication use	84 (16.3)	35 (27.6)	49 (12.6)	<0.0001
Antidepressant prescription medication use	242 (46.8)	73 (57.5)	169 (43.3)	0.006
Emergency department visits	0.54 ± 1.2	0.82 ± 1.7	0.45 ± 1.07	0.004

GED = General Equivalency Diploma; KPNW= Kaiser Permanente Northwest; VAPORHCS = VA Portland Health Care System.

Table 2. Odds of receiving overlapping benzodiazepine and opioid prescriptions in year before baseline

	AOR	95% CI	*P* Value
VAPORHCS	0.741	0.392–1.401	0.357
Age (per 5-y increase)	0.989	0.968–1.011	0.339
Female	1.375	0.800–2.361	0.249
White race	1.290	0.647–2.571	0.469
Hispanic ethnicity	0.969	0.284–3.309	0.959
Up to and including high school diploma or GED*	0.976	0.496–1.918	0.943
Some college or technical school*	0.858	0.498–1.478	0.581
Morphine equivalent opioid dose	1.000	0.992–1.008	0.923
Anxiety disorder	4.713	2.670–8.319	<0.0001
Depression	1.430	0.861–2.376	0.167
Post-traumatic stress disorder	2.239	1.143–4.383	0.019
Bipolar disorder	3.819	1.487–9.805	0.005
Comorbidity index	1.022	0.923–1.131	0.679
Substance/alcohol use disorder	0.423	0.169–1.063	0.067

This table presents the results of a multivariate logistic regression on the odds of being given a co-prescription of benzodiazepines and opioids in the past year. The AOR represents the odds of receiving a co-prescription, adjusting for all other covariates in the model.

GED = General Equivalency Diploma; OR = odds ratio; CI = confidence interval; VAPORHCS = VA Portland Health Care System.

*Educational categories are compared with individuals with college degree or higher.

Physicians also need additional tools for tapering individuals off opioids, benzodiazepines, or both, as they often encounter difficulties or do not know where and how to start [36]. For example, patients may be reluctant to taper if they perceive a low risk of adverse events from their current medication regimen and if potential future adverse events are less salient than the risk of increased symptoms that could result from tapering [37]. The decision to taper or discontinue use of these medications in patients with comorbid chronic pain and mental illness is not an easy one. Further, though opioid tapering studies have been conducted [38] and a recent systematic review concluded that strategies that incorporated a psychosocial component were often effective in reducing opioid doses [39], no comprehensive evidence-based opioid tapering protocol yet exists. A recent review of psychosocial interventions aimed at reducing problematic benzodiazepine use found weak evidence for most strategies [40]. Though clinicians often endorse the need to reduce co-prescriptions, they report barriers to doing so, including a belief that their own patients appear to be stably taking both medications or that discontinuing either medication is too difficult [41]. Providers have also described the emotional burden of having tapering discussions with patients, inadequate resources and training, a lack of patient–clinician trust, and the potential conflict between their efforts to safely prescribe medications while maintaining patient satisfaction as barriers [42]. Structural strategies, including an intervention using a pharmacy prior authorization consult aimed at reducing co-prescribing in a veteran population, have shown some success [43].

Table 3. Risk ratios for number of falls in the prior 3 months and prior-year emergency department visits among individuals with overlapping opioid and benzodiazepine prescriptions

	Falls*			Emergency Department Visits†		
	RR	95% CI	*P* Value	RR	95% CI	*P* Value
Overlapping benzodiazepine prescription	3.27	1.77–6.02	0.0001	1.66	1.08–2.53	0.0194
VAPORHCS	1.98	1.04–3.78	0.039	3.82	2.27–6.45	<0.0001
Age (per 5-y increase)	0.99	0.88–1.13	0.934	0.91	0.84–0.99	0.033
Female	1.93	1.07–3.50	0.029	1.64	1.00–2.68	0.048
White race	0.73	0.34–1.53	0.401	0.91	0.54–1.51	0.713
Hispanic ethnicity	0.87	0.22–3.37	0.840	0.56	0.21–1.50	0.251
Up to or including high school diploma/GED‡	1.29	0.56–2.56	0.644	1.10	0.63–1.91	0.742
Some college or technical school‡	0.74	0.41–1.33	0.312	1.11	0.70–1.74	0.658
Morphine equivalent dose	1.01	1.00–1.02	0.120	1.00	1.00–1.01	0.185
Depression diagnosis	—	—	—	0.87	0.58-1.33	0.538
PTSD diagnosis	—	—	—	0.76	0.45–1.28	0.307
Bipolar diagnosis	—	—	—	1.19	0.49–2.84	0.704
Comorbidity index	1.09	0.99–1.20	0.066	1.38	1.28–1.48	<0.0001
Substance/alcohol use disorder diagnosis	0.41	0.16–1.09	0.075	0.78	0.42–1.44	0.430
Antidepressant prescription	1.31	0.79–2.18	0.295	0.74	0.50–1.10	0.138
Sedative/hypnotic prescription	3.57	1.73–7.35	0.001	0.92	0.56–1.52	0.750

This table presents the results of two separate multivariate negative binomial regressions on the risk of falling and emergency department visits comparing individuals with a co-prescription of benzodiazepines and opioids in the past year with individuals without those co-prescriptions. The RR represents the risks associated with the co-prescription of benzodiazepines and opioids, adjusting for all other covariates in the model. A propensity score derived from analyses presented in Table 2 was added to the outcome models to control for confounding. Depression, PTSD, and bipolar diagnoses were not included in the multivariate risk model for predicting falls as we had no a priori hypothesis about why these diagnoses would be associated with falling.

GED = General Equivalency Diploma; PTSD = post-traumatic stress disorder; RR = risk ratio; CI = confidence interval; VAPORHCS = VA Portland Health Care System.

*Falls are continuous, self-reported (mean = 1.35, SD = 9.35).

†Emergency department visits are a continuous measure derived from the electronic medical record.

‡Educational categories are compared with individuals with a college degree or higher.

Several study limitations should be considered when interpreting these results. Our recruitment rate was under 30%. Participants who did not enroll were slightly older, more often male, and more likely to identify as nonwhite; there were no significant differences in average daily opioid dose or rate of pain-related diagnoses between patients who did or did not enroll in the study [27]. The study findings may not be generalizable outside of integrated care or VA settings, or outside the Pacific Northwest. This study reports cross-sectional data, and thus we cannot address associations between overlapping benzodiazepine and opioid use over time. Self-reported data (e.g., falls) are subject to recall bias, though the lookback window of three months was relatively recent. We did not verify that the outcomes occurred before the exposure to overlapping prescribed opioids and benzodiazepines. Other adverse outcomes would be important to explore (e.g., opioid-related overdoses) but were too infrequent in our data to be analyzed.

Conclusions

Results from this study showed that one-quarter of patients from a large, diverse sample being treated with opioids for chronic noncancer pain had overlapping benzodiazepine co-prescriptions in the past year. Co-occurring prescription opioids and benzodiazepines were significantly associated with increased risks of falls and emergency department use. Clinicians need additional tools and strategies to treat their patients' pain and psychiatric conditions while simultaneously keeping their patients safe from harm.

Acknowledgments

The authors express their gratitude to Julie Cavese, MA, and Stephanie Hyde, MA, who conducted recruitment and data collection for this study.

References

1. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. JAMA Psychiatry 2015; 72(2):136–142.
2. Paulozzi LJ, Strickler GK, Kreiner PW, et al. Controlled substance prescribing patterns—prescription behavior surveillance system, eight states, 2013. MMWR Surveill Summ 2015;64(9):1–14.
3. Guy GP, Zhang K, Bohm MK Jr, et al. Vital signs: Changes in opioid prescribing in the United States, 2006-2015. MMWR Morb Mortal Wkly Rep 2017; 66(26):697–704.

4. Brandt J, Leong C. Benzodiazepines and Z-drugs: An updated review of major adverse outcomes reported on in epidemiologic research. Drugs R D 2017;17 (4):493–507.
5. Skinner BW, Johnston EV, Saum LM. Benzodiazepine initiation and dose escalation: A risk factor for inpatient falls. Ann Pharmacother 2017;51 (4):281–5.
6. Chen LH, Hedegaard H, Warner M. Drug-poisoning deaths involving opioid analgesics: United States, 1999-2011. NCHS Data Brief 2014;166:1–8.
7. Sharp MJ, Melnik TA. Poisoning deaths involving opioid analgesics—New York State, 2003-2012. MMWR Morb Mortal Wkly Rep 2015;64 (29):377–80.
8. Turner BJ, Liang Y. Drug overdose in a retrospective cohort with non-cancer pain treated with opioids, antidepressants, and/or sedative-hypnotics: Interactions with mental health disorders. J Gen Intern Med. 2015;30:1081.
9. Park TW, Saitz R, Ganoczy D, et al. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: Case-cohort study. BMJ 2015;350:h2698.
10. Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S. Association between concurrent use of prescription opioids and benzodiazepines and overdose: Retrospective analysis. BMJ 2017;356:j760.
11. Nielsen S, Lintzeris N, Bruno R, et al. Benzodiazepine use among chronic pain patients prescribed opioids: Associations with pain, physical and mental health, and health service utilization. Pain Med 2015;16 (2):356–66.
12. Day C. Benzodiazepines in Combination with Opioid Pain Relievers or Alcohol: Greater Risk of More Serious ED Visit Outcomes, in the CBHSQ Report. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.
13. Gaither JR, Goulet JL, Becker WC, et al. The association between receipt of guideline-concordant long-term opioid therapy and all-cause mortality. J Gen Intern Med 2016;31(5):492–501.
14. Jones JD, Mogali S, Comer SD. Polydrug abuse: A review of opioid and benzodiazepine combination use. Drug Alcohol Depend 2012;125(1–2):8–18.
15. Weed PF, France CP, Gerak LR. Preference for an opioid/benzodiazepine mixture over an opioid alone using a concurrent choice procedure in rhesus monkeys. J Pharmacol Exp Ther 2017;362(1):59–66.
16. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. MMWR Recomm Rep 2016;65 (1):1–49.
17. Department of Veterans Affairs, Department of Defense. Clinical Practice Guideline for Opioid Therapy for Chronic Pain. Washington, DC: U.S. Department of Veterans Affairs; 2017.
18. Paulozzi LJ, Mack KA, Hockenberry JM. Vital signs: Variation among states in prescribing of opioid pain relievers and benzodiazepines—United States, 2012. MMWR Morb Mortal Wkly Rep 2014;63 (26):563–8.
19. Park TW, Saitz R, Nelson KP, et al. The association between benzodiazepine prescription and aberrant drug-related behaviors in primary care patients receiving opioids for chronic pain. Subst Abus 2016;37 (4):516–20.
20. Dasgupta N, Funk MJ, Proescholdbell S, et al. Cohort study of the impact of high-dose opioid analgesics on overdose mortality. Pain Med 2016;17(1):85–98.
21. Sullivan MD, Edlund MJ, Zhang L, et al. Association between mental health disorders, problem drug use, and regular prescription opioid use. Arch Intern Med 2006;166(19):2087–93.
22. Abrahamsson T, Berge J, Öjehagen A, et al. Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment—a nation-wide register-based open cohort study. Drug Alcohol Depend 2017;174:58–64.
23. Stein BD, Mendelsohn J, Gordon AJ, et al. Opioid analgesic and benzodiazepine prescribing among Medicaid-enrollees with opioid use disorders: The influence of provider communities. J Addict Dis 2017; 36(1):14–22.
24. Gressler LE, Martin BC, Hudson TJ, Painter JT. Relationship between concomitant benzodiazepine-opioid use and adverse outcomes among US veterans. Pain 2018;159(3):451–9.
25. Edlund MJ, Steffick D, Hudson T, et al. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. Pain 2007;129(3):355–62.
26. Von Korff M, Korff MV, Saunders K, et al. De facto long-term opioid therapy for noncancer pain. Clin J Pain 2008;24(6):521–7.
27. Morasco BJ, Yarborough BJ, Smith NX, et al. Higher prescription opioid dose is associated with worse patient-reported pain outcomes and more health care utilization. J Pain 2017;18(4):437–45.
28. Selim AJ, Fincke BG, Ren XS, et al. Comorbidity assessments based on patient report: Results from the Veterans Health Study. J Ambul Care Manage 2004; 27(3):281–95.
29. Quinn PD, Hur K, Chang Z, et al. Incident and long-term opioid therapy among patients with psychiatric conditions and medications: A national study of commercial health care claims. Pain 2017;158(1): 140–8.
30. Mosher HJ, Richardson KK, Lund BC. Sedative prescriptions are common at opioid initiation: An observational study in the Veterans Health Administration. Pain Med 2017.
31. Zin CS, Ismail F. Co-prescription of opioids with benzodiazepine and other co-medications among opioid

users: Differential in opioid doses. J Pain Res 2017; 10:249–57.
32. Hawkins EJ, Malte CA, Grossbard J, et al. Comparative safety of benzodiazepines and opioids among Veterans Affairs patients with posttraumatic stress disorder. J Addict Med 2013;7(5): 354–62.
33. Delcher, PhD C, Wang, MS Y, Young, MD HW, et al. Trends in Florida's prescription drug monitoring program registration and utilization: Implications for increasing voluntary use. J Opioid Manag 2017;13 (5):283–9.
34. Finnell JT, Twillman RK, Breslan SA, et al. The role of continuing medical education in increasing enrollment in prescription drug monitoring programs. Clin Ther 2017;39(9):1896–902.e2.
35. Irvine JM, Hallvik SE, Hildebran C, et al. Who uses a prescription drug monitoring program and how? Insights from a statewide survey of Oregon clinicians. J Pain 2014;15(7):747–55.
36. Merlin JS, Young SR, Starrels JL, et al. Managing concerning behaviors in patients prescribed opioids for chronic pain: A Delphi study. J Gen Intern Med 2018;33(2):166–76.
37. Frank JW, Levy C, Matlock DD, et al. Patients' perspectives on tapering of chronic opioid therapy: A qualitative study. Pain Med 2016;17(10): 1838–47.
38. Sullivan MD, Turner JA, DiLodovico C, et al. Prescription opioid taper support for outpatients with chronic pain: A randomized controlled trial. J Pain 2017;18(3):308–18.
39. Frank JW, Lovejoy TI, Becker WC, et al. Patient outcomes in dose reduction or discontinuation of long-term opioid therapy: A systematic review. Ann Intern Med 2017;167(3):181–91.
40. Darker CD, Sweeney BP, Barry JM, Farrell MF, Donnelly-Swift E. Psychosocial interventions for benzodiazepine harmful use, abuse or dependence. Cochrane Database Syst Rev 2015;5:CD009652.
41. Hawkins EJ, Malte CA, Hagedorn HJ, Berger D, Frank A, Lott A, Achtmeyer CE, Mariano AJ, Saxon AJ. Survey of primary care and mental health prescribers' perspectives on reducing opioid and benzodiazepine co-prescribing among veterans. Pain Med 2017;18(3):454–67.
42. Kennedy LC, Binswanger IA, Mueller SR, Levy C, Matlock DD, Calcaterra SL, Koester S, Frank JW. "Those conversations in my experience don't go well": A qualitative study of primary care provider experiences tapering long-term opioid medications. Pain Med 2017.
43. Pardo D, Miller L, Chiulli D. Implementation of a pharmacy consult to reduce co-prescribing of opioids and benzodiazepines in a Veteran population. Subst Abus 2017;38(2):157–60.