Benzodiazepine prescribing patterns and drug overdose mortality among individuals receiving opioid analgesics: case-cohort study

Journal:	*BMJ*
Manuscript ID:	BMJ.2014.024299
Article Type:	Research
BMJ Journal:	BMJ
Date Submitted by the Author:	10-Dec-2014
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Keywords:	Benzodiazepines, Opioid analgesics, Overdose

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Declaration of competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: financial support for the submitted work from a Veteran Affairs Health Services Research and Development Service Career Development Award (CDA-09-204; A.S.B.B.) and by the National Institutes of Health (R03 AG042899); RS has received consultant and annual travel fees from BMJ as Editor of the journal Evidence-Based Medicine; no other relationships or activities that could appear to have influenced the submitted work.

Transparency declaration

All authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Funding

This work was supported by funding from a Veteran Affairs Health Services Research and Development Service Career Development Award (CDA-09-204; A.S.B.B.) and by the National Institutes of Health (R03 AG042899). The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript of the decision to submit.

Contributors

All authors have fulfilled authorship criteria per ICMJE guidelines and have approved the manuscript and this submission. 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. The funding agencies had no role in data collection, analysis, interpretation, or the decision to submit the results.

Ethical approval

Study procedures received approval from the Ann Arbor VA human studies committee, which waived the requirement for informed consent.

Data sharing

No additional data available.

ABSTRACT

Objective: To study the association between benzodiazepine prescribing patterns including dose, type and dosing schedule and the risk of drug overdose mortality among individuals receiving opioid analgesics.

Design: Case-cohort study

Setting: Veterans Health Administration (VHA), 2004 through 2009.

Participants: For the period of 2004 to 2009, all individuals who died of a drug overdose (n = 2,400) while receiving opioid analgesics and a random sample of individuals (n = 420,386) who received VHA medical services and opioid analgesics.

Main outcome measure: Drug overdose mortality based on cause of death information from the National Death Index.

Results: 27 percent of individuals who received opioid analgesics also received benzodiazepines during the study period. Approximately half of the drug overdose deaths (n=1,185) occurred when individuals were concurrently prescribed benzodiazepines and opioids. Risk of overdose death increased based on benzodiazepine prescription history: formerly prescribed vs. not prescribed (adjusted hazard ratio [HR]=2.37, 95% confidence interval [CI]: 2.09-2.69); currently prescribed vs. not prescribed (HR=3.96, CI:3.58-4.38). Risk of overdose death increased as daily benzodiazepine dose increased. When compared to clonazepam, temazepam and lorazepam were associated with a decreased overdose risk (HRs=0.62, CI:0.47-0.80, and HR=0.78, CI: 0.62-0.99). Benzodiazepine dosing schedule was not associated with overdose risk.

Conclusions: Among individuals receiving opioid analgesics, receipt of benzodiazepines was associated with an increased risk of drug overdose death in a dose-response fashion.

The risks and benefits of benzodiazepine prescribing in this population warrant further evaluation.

Word count: 225

Word limit: 400

INTRODUCTION

Drug overdose mortality, particularly involving opioid analgesics, has increased steadily over the past two decades and is now one of the leading causes of injury mortality in the United States.[1] Of the pharmaceutical-related drug overdose deaths, which constituted 58% of total drug overdose deaths in 2010, 75% involved opioid analgesics.[2] Thirty percent of opioid analgesic-related deaths involved benzodiazepines, medications commonly prescribed concurrently for patients who receive opioid analgesics.[3-5] Although the toxicity of benzodiazepines used in isolation is generally considered mild in young and middle-aged adults, the risks from oversedation are believed to be magnified when combined with other substances with sedating properties, such as opioids.[6,7] Also, receipt of benzodiazepines may be a marker of the presence of a significant anxiety disorder, which likely carries its own risk for intentional and unintentional overdose.[8,9]

Trends in overdose mortality have been connected to patterns of opioid prescribing, an increasingly common treatment for pain.[10] On a population level, increasing rates of opioid prescribing have been linked to an increased rate of overdose[11]; on an individual level, the risk of overdose is higher among those receiving higher doses of opioids.[12, 13] One study generated the hypothesis that receipt of benzodiazepines may be associated with increased risk of overdose in patients receiving opioid analgesics.[13] To our knowledge, a large, nationwide study that focuses on overdose death and receipt of benzodiazepines and their prescribing patterns, such as the daily benzodiazepine dose, the type of benzodiazepine prescribed, or the dosing schedule of the prescription, among those receiving opioids for pain has not been performed.

The aim of this study is to describe the relationship between the receipt of concurrent benzodiazepines and opioid analgesics and drug overdose mortality in patients receiving prescription opioids for the treatment of acute, chronic and cancer pain. Quantifying the magnitude of risk associated with these patterns might help identify individuals at particularly high risk for overdose and could potentially inform risk-reduction approaches in this population. We hypothesized that receipt of concurrent benzodiazepines and opioid analgesics would be associated with overdose death and that this relationship would be dose-dependent and vary by benzodiazepine type and dosing schedule. We used a case-cohort study design to examine the relationship of benzodiazepine prescription history, dose, type and schedule with risk of drug overdose death over a 6-year period among a nationwide sample of patients who received treatment with opioid analgesics in the Veterans Health Administration (VHA).

METHODS

Study design and population

This study utilized a case-cohort study design.[14] Similar to a nested case-control study, cases and controls are sampled from the same source population. Controls in the case-cohort design are randomly sampled and, unlike a nested case-control study, matching typically does not occur. Cases and controls in this study were sampled from a source population that consisted of individuals who received Veterans Health Administration (VHA) medical services and opioid analgesic medications as an outpatient between fiscal years (FY) 2004-2009. The VHA is the largest integrated health care system in the United States, serving nearly nine million individuals across over 150

hospitals and over 800 community-based outpatient centers throughout the US. There were 2,400 cases which included all drug overdose deaths that occurred while receiving opioid analgesics and 420,386 controls which included 5% annual random samples of the source population during the study period. We attempted to limit the analysis to individuals receiving prescription opioids for the treatment of acute, chronic and non-terminal cancer pain by excluding 221 individuals who received methadone prescriptions received for maintenance purposes and 5,816 individuals with indicators of palliative care consultations or hospice care. The final sample size for this study was 422,786. In order to avoid potential immortal time bias, the start of observation for both cases and controls was the date of the first opioid analgesic fill after the first medical visit of the year within the study period.[15] Observation for controls ended either when the individual died of any cause or at the end of FY09, whichever occurred first.

Data sources

We used data abstracted from the electronic medical records of VHA patients. This included demographic and clinical encounter data from the VHA's National Patient Care Database. Outpatient prescription data was collected from the VHA's Pharmacy Benefits Management (PBM) Services and consisted of records of filled prescriptions (which included the fill date, days supply, and schedule). Cause of death information was obtained from the National Death Index (NDI).[16] Matching with the NDI for our sample used two methods: 1) a full match on the 9-digit Social Security number (SSN) and sex and match on at least 2 of the 3 parts (day, month, year) of date of birth; or 2) match on at least 7 digits of the SSN plus full match on date of birth, sex, first name, and last name

and middle initial when present. Study procedures received approval from the Ann Arbor VA human studies committee, which waived the requirement for informed consent.

Drug overdose deaths

The NDI reports cause of death using codes from the International Statistical Classification of Diseases, Tenth Revision (ICD-10). Cause of overdose death can be classified as unintentional (X40-45), intentional (X60-65) or indeterminate (Y10-15) and specific drugs involved may be listed with a T-code.[17] Because intent is often difficult to determine, particularly in poisoning deaths[18], and a significant proportion of death certificates do not specify the drug(s) involved,[2] we defined our drug overdose outcome as any intentional, unintentional or indeterminate overdose death caused by any medication or drug (X40-45, X60-65, Y10-15, without T-code specified).

Medication prescribing patterns

Benzodiazepine and opioid analgesic prescriptions filled on an outpatient basis were examined in this study. Since individuals with indications for benzodiazepines may be at higher risk of overdose death[8], we distinguished periods during which individuals were currently receiving benzodiazepines from periods when they had formerly received them in order to help address unmeasured confounding.[19] Every person-day was classified according to each individual's benzodiazepine prescription history, categorized as current, former, or none. "Current" receipt time accumulated starting with a benzodiazepine prescription fill and continued through the end of the fill as determined by the days supply. If another fill was received, current receipt time continued to accumulate. "Former" receipt time accumulated starting at the end of a current

benzodiazepine prescription fill and continued through to the end of the study period, unless another benzodiazepine prescription was filled, at which time the fill again contributed to current receipt time. Periods prior to an individual's first benzodiazepine fill or periods for those who never received a benzodiazepine were labeled "none". With regards to each individual's opioid prescription history, every person-day was classified as "current" or "none." Only days classified as current opioid receipt were included in this study.

Benzodiazepine types included in the study were alprazolam, chlordiazepoxide, clonazepam, diazepam, lorazepam, temazepam, estazolam, flurazepam, oxazepam, quazepam, and triazolam. Benzodiazepine dose was calculated as diazepam equivalents, according to previously published conversion tables. [20] Benzodiazepine schedule was classified as regularly scheduled, as-needed or simultaneous regularly scheduled and as-needed. Opioid analgesics included in this study were codeine, morphine, oxycodone, hydrocodone, oxymorphone, hydromorphone, fentanyl, propoxyphene and methadone. Methadone prescriptions in this study were limited to those prescribed to treat pain by excluding prescriptions in which 1) dosing instructions indicated the methadone was prescribed for maintenance, 2) oral or effervescent methadone formulations were prescribed unless the dosing schedule indicated more than once a day dosing, or 3) the dosing schedule was once a day unless the instructions indicated the methadone was prescribed for pain. Buprenorphine is not currently indicated for pain treatment in the VHA and was not included in this analysis. Opioid analgesic dose was calculated as morphine equivalents.[21, 22]

Both benzodiazepine and opioid analgesic dose were measured using an "as-prescribed" approach, which assumes that patients took their medications according to the prescribers' instructions.[23] Dose was calculated by adding all diazepam or morphine milligram (mg) equivalents in each prescription and dividing by the number of days supply. This represented the daily dose. If there was an overlap between two prescriptions of the same drug at the same dose and schedule, it was assumed that the first prescription was finished before the second prescription was started rather than assuming a higher amount of medication was taken during the overlap. If the overlapping drugs were of a different type, dose or schedule, than the second fill was assumed to have started on the date it was filled. Both benzodiazepine and opioid analgesic dose were treated as time-varying.

Covariates

We obtained demographic and diagnostic data from patient records. Demographic data included age, sex, and race. Race was classified as white, black, other, and missing/not recorded. Additionally, each individual's zip code of residence was linked to US Census data to obtain the percentage of people living below the federal poverty line in that zip code as a proxy measure for socioeconomic status.[24] Zip code data was missing in 4.3% of the sample and was imputed using simple imputation. The socioeconomic status variable was categorized into quintiles. All diagnoses were made during the year prior to each individual's start of observation. Diagnoses were categorized into substance use disorders, PTSD, other anxiety disorders, depressive disorders, and bipolar or psychotic disorders. Additionally, we measured medical comorbidity using the Charlson comorbidity score.[25] In order to assess mental health and

substance use disorder acuity, the number of mental health and substance use disorder-related hospitalizations determined by VHA bed section codes in the year prior to start of observation was also measured.

Statistical analysis

We compared baseline patient characteristics between those who received benzodiazepines during the study period and those who did not receive benzodiazepines with chi-square tests (Table 1).

We calculated overdose mortality rates for individuals' benzodiazepine prescription history, dose, type and schedule (Table 2). The denominator for all rates (person-years) was adjusted to account for the case-cohort design by multiplying the observation time accumulated for the cohort by the inverse of the sampling fraction. Consequently, all rates are estimates for the entire source population.

We used Cox proportional hazards models to calculate hazard ratios (HRs) for current and former receipt of benzodiazepines, compared to no receipt. All HRs were adjusted for all covariates, including time-varying opioid analgesic dose. We used a risk-set approach and a robust variance estimator for all multivariable modeling.[26] We calculated approximated absolute risk differences for significant associations by estimating the overall rate of overdose among individuals receiving opioid analgesics, next multiplying this rate by the hazard ratio (HR), and then taking the difference between these 2 estimated rates.

Our primary analysis (Model 1, Table 3) studied the association between benzodiazepine prescription history and overdose mortality. Secondarily, we studied the association between benzodiazepine dose, type and schedule and overdose only during

times when individuals were currently receiving benzodiazepines and opioid analgesics concurrently (Model 2, Table 3). We also studied the association between benzodiazepine prescription history and overdose stratified by opioid dose categories (Table 4). Separate models were created for each opioid dose category.

Several sensitivity analyses were conducted. We examined the association between benzodiazepine prescription history and overdose mortality not known to be intentional, by defining a modified overdose outcome that excluded overdoses coded as intentional. We also examined the association between benzodiazepine prescription history and opioid/benzodiazepine-attributable overdose mortality by defining a modified overdose outcome that included only deaths attributed to opioids and/or benzodiazepines (ICD-10 codes X41, X42, X44, X61, X62, X64, Y11, Y12, Y14 in combination with T40.2, T40.3, T40.4, T40.6 or T42.4). Finally, we examined the association between benzodiazepine prescription history and overdose mortality in a cohort that excluded patients with a cancer diagnosis in the year prior to observation (except for non-melanoma skin cancer).

Analyses were conducted using SAS version 9.3 (SAS Institute, Cary, North Carolina).

RESULTS

Sample

Of the 422,786 individuals in the study population, 112,069 (27%) had filled at least one benzodiazepine prescription during the study period (Table 1). Those who received benzodiazepines were more likely to be female, middle-aged, white, and reside

in wealthier areas. Additionally, they were more likely to have had a recent mental health or substance use disorder-related hospitalization, a diagnosis of a substance use disorder or a number of mental disorders including PTSD, other anxiety disorders, depression, and bipolar or psychotic disorders.

Unadjusted rates of overdose

Of the 2,400 individuals in the study population who died of a drug overdose while receiving opioid analgesics, 1,185 (49%) died during a period in which they had been prescribed concurrent benzodiazepines (Table 2). Unadjusted rates of drug overdose death were higher during periods when individuals currently received benzodiazepines, than in those when individuals formerly received them or had not received them at all. Unadjusted overdose rates increased at consecutively higher daily benzodiazepine dose categories. Periods during which individuals received lorazepam and temazepam had lower overdose rates than periods involving the other benzodiazepine types. Overdose rates were higher in periods in which benzodiazepines were simultaneously prescribed regularly scheduled and as-needed medications compared to the other schedules. When the overdose rates were stratified by daily opioid dose categories (Figure 1), the difference in rates between periods of current and former benzodiazepine receipt was not significant at the lowest opioid dose category but was significant at higher opioid dose categories.

Adjusted analyses

Compared to periods in which individuals had not received benzodiazepines, periods of current benzodiazepine receipt (hazard ratio = 3.96; 95% confidence interval [CI], 3.58–4.38) and former benzodiazepine receipt (HR = 2.37; 95%CI, 2.09-2.69) were associated with an increased risk of overdose death (Table 3). Higher benzodiazepine dose categories were associated with greater risk of overdose death. Temazapam (HR = 0.62; 95%CI, 0.47-0.80) and lorazepam (HR = 0.78; 95%CI, 0.62-0.99) were found to have an association with decreased overdose risk compared to the most commonly prescribed benzodiazepine, clonazepam. All other benzodiazepines had similar risk when compared to clonazepam. No association between benzodiazepine dosing schedule with overdose death was found after adjustment. After stratifying by daily opioid dose, periods of current and former benzodiazepine receipt were associated with an increased risk of overdose death in each opioid dose category compared to no receipt, but current and former benzodiazepine receipt differed from each other only during periods when the daily opioid dose was greater than 20 mg (Table 4).

Sensitivity analyses

We conducted several sensitivity analyses in order to test the robustness of the results of our primary analysis. We found that the exclusion of intentional overdose deaths, overdose deaths not related to opioids or benzodiazepines, and people with cancer resulted in only minor differences in the degree of association between benzodiazepine prescription history and overdose death, and no substantive differences in the inferences drawn from analyses.

DISCUSSION

Although the observational design of this study cannot determine whether benzodiazepine prescribing patterns are the direct cause of overdose, we found that receipt of concurrent benzodiazepines was associated with an increased risk of overdose death in this large, national sample of individuals who received opioid analgesics. Notably, approximately half of the overdose deaths occurred while individuals were receiving concurrent benzodiazepines and opioids. Benzodiazepine dose was also found to be associated with an increased risk of overdose in a dose-response fashion. Temazepam and lorazepam were associated with a decreased risk of overdose compared to clonazepam. Current receipt of benzodiazepines was associated with a greater magnitude of risk than former receipt. These associations remained significant in analyses adjusting for potential confounders.

The strengths of this study included the large size of the study cohort and the ability to study a national sample of patients from the largest health system in the United States. Additionally, we were able to adjust for a range of potential confounders including demographic, socioeconomic and medical and mental health diagnostic data. Though we studied a large, national cohort, all study participants were mostly male, older US Veterans, who have been found to have higher rates of accidental poisoning mortality.[27] This may limit the generalizability of the study. Because we only examined treatment received within the VHA in this study, we may not have captured encounters that could affect overdose risk, such as medications received from non-VHA prescribers. Additionally, since our daily dose calculations for benzodiazepines and opioid analgesics assume that individuals take medications exactly as prescribed, we may not have

accurately measured the amount of medications taken on any given day. Individuals may have retained medications beyond the period they were prescribed for or received additional medications from non-VHA prescribers and subsequently took larger doses than indicated by the prescribers' instructions. If this behavior is associated with receiving benzodiazepines and with overdose death, then our effect estimates may have been inflated.

The findings of this study were largely consistent with studies that have suggested that there are risks associated with concurrent benzodiazepine and opioid use. Dunn et al[13] found an association between receipt of sedative-hypnotic medications and increased risk of combined fatal and non-fatal overdoses. Other studies have looked at smaller subgroups of individuals taking opioid analgesics. In a study limited to individuals with severe respiratory disease, receipt of concurrent benzodiazepines and opioid analgesics was associated with increased risk of total mortality.[28] In a study of individuals with post-traumatic stress disorder, receipt of concurrent benzodiazepines and opioid analgesics, combined with antidepressants, was found to be associated with increased risk of adverse events.[29] Our study extends this literature in several ways. We studied a much larger, nationwide sample focusing exclusively on benzodiazepine prescribing patterns and their association with fatal overdoses. We found a dose-dependent relationship between benzodiazepine dose and overdose death. And we more rigorously addressed issues of confounding in our analysis.

Because benzodiazepines were more likely to be prescribed to those with substance use and mental disorders, conditions which carry their own risk for overdose death,[8] the association between receipt of benzodiazepines and overdose death may be

partially explained by these underlying conditions or the severity of those conditions.[30] We attempted to address this possibility in two ways. Baseline patient characteristics, including demographic information, medical and mental health diagnoses, and the daily opioid dose were adjusted for in a multivariable model. Additionally, by distinguishing between periods of current and former receipt of benzodiazepines, we addressed some unmeasured confounding. Nonetheless, because those with current receipt of benzodiazepines may have had more severe conditions for which benzodiazepines were prescribed than those with former receipt, some residual confounding may exist. It is important to note that within the present study, benzodiazepines might be better conceptualized as a marker of risk with unknown direct causal links to overdose.

In this study, concurrent benzodiazepine prescribing was more common among those who died of an overdose. Benzodiazepines are often prescribed for individuals also receiving high doses of opioid analgesics[4, 5], a risk factor for overdose death[12, 13]. We found that the difference in overdose risk between current and former periods of benzodiazepine receipt was widest at the highest opioid dose category and narrowest at the lowest opioid dose category, suggesting that any potential effect of benzodiazepines on overdose may be greatest for those patients at higher opioid doses.

Though receipt of benzodiazepines and the benzodiazepine dose were associated with increased overdose risk, the type of benzodiazepine and dosing schedule were found to be largely unrelated after adjusting for potential confounders. Temazepam[31] and alprazolam[32] have been associated with increased toxicity compared to other benzodiazepines in studies of deliberate self-poisonings involving benzodiazepines. We found that when compared to clonazepam, temazepam and lorazepam were associated

with a decreased overdose risk. Possible explanations are the pharmacokinetics of the medications and selection factors related to their use, but differentiating between these two was beyond the scope of the present study. More research is needed to understand why specific benzodiazepines are associated with a lower risk of overdose. Though there is limited evidence that an as-needed benzodiazepine dosing schedule may pose risks for individuals, particularly in the elderly and those with substance use disorders[33, 34], no association was found between as-needed dosing and overdose risk when compared to regularly scheduled dosing after adjusting for potential confounders.

Though the design of this study does not allow for the determination of the extent to which benzodiazepines cause overdoses, it does indicate a need for clinicians to be aware of the increased risk of overdose among individuals currently receiving benzodiazepines and opioids and that the risk may be higher among those receiving higher doses of either or both medications. This risk may be due to risks inherent to those prescribed benzodiazepines, such as the presence of an anxiety condition, and/or to the benzodiazepine itself. Thus, clinicians might take caution when prescribing benzodiazepines to this group. Though it is unknown whether patients with comorbid pain and anxiety who use opioids and benzodiazepines would benefit from the same interventions to reduce overdose risk as patients using opioids alone, clinicians might consider including this group in overdose prevention efforts, such as naloxone training for caregivers.[35]

CONCLUSIONS

In this observational study of a large, national cohort of individuals who received opioid analgesics, receipt of concurrent benzodiazepines was associated with increased risk of drug overdose death. The risks and benefits of benzodiazepine prescribing in this population warrant both caution and further evaluation.

What is already known on this topic

- Benzodiazepines are commonly involved in opioid analgesic-related overdose deaths, a steadily increasing cause of injury mortality in the United States.
- No study has focused specifically on the relationship between prescribing patterns of concurrent benzodiazepine and opioid analgesics and overdose death in a large, nationwide sample.

What this study adds

- Receipt of benzodiazepines was associated with an increased risk of overdose death among individuals receiving opioid analgesics in this large, nationwide sample.
- The relationship between receipt of benzodiazepines and overdose death was dose-dependent: increasing benzodiazepine dose was associated with an increasing risk of overdose death.
- Lorazepam and temazepam were associated with a decreased risk of overdose death when compared to clonazepam.

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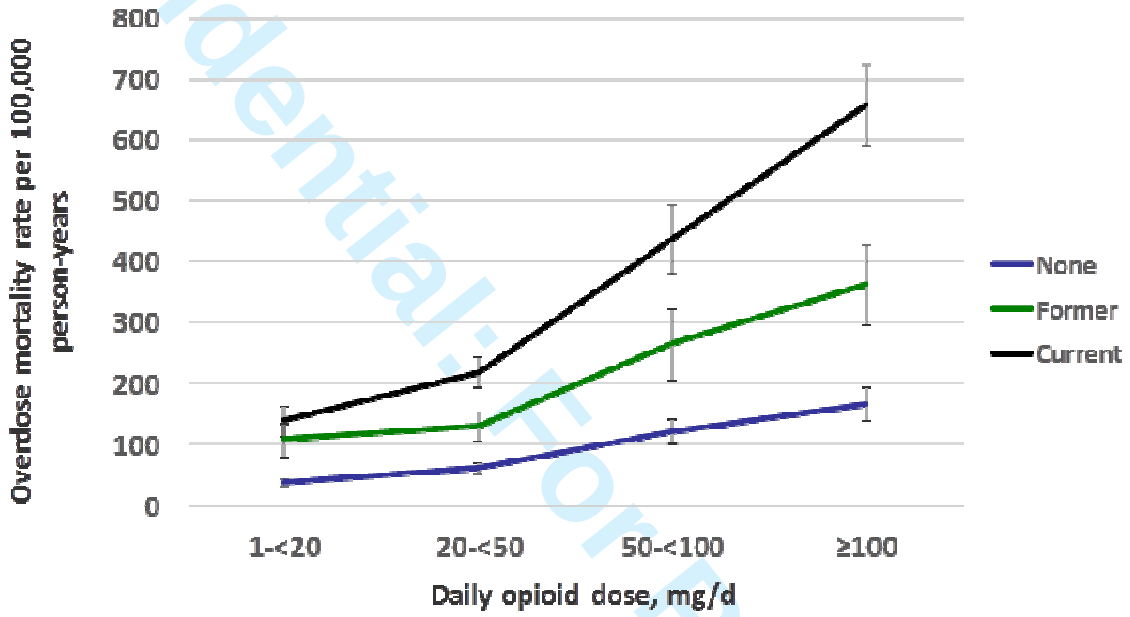
FIGURE LEGEND

Figure 1. Unadjusted overdose mortality rates by benzodiazepine prescription history and daily opioid dose

Abbreviations: mg, milligram; d, day
Error bars represent 95% confidence intervals
Unadjusted overdose rates are estimates for the entire source population



TABLES

Table 1. Characteristics of the Sample of Veterans Health Administration Patients Who Received Opioid Analgesics Between Fiscal Year 2004-2009 by Receipt of Benzodiazepine

Characteristic	Receipt of Benzodiazepine[a]	
	No (n=310,717 n (%)	Yes (n=112,069 n (%)
Male	291,070 (94)	102,252 (91)
Age		
18-29	9,256 (3)	2,639 (2)
30-39	15,053 (5)	5,791 (5)
40-49	35,961 (12)	15,841 (14)
50-59	83,772 (27)	38,471 (34)
60-69	77,147 (25)	25,366 (23)
≥70	89,528 (29)	23,961 (21)
Race		
Black	57,286 (18)	12,600 (11)
White	217,663 (70)	89,764 (80)
Other/missing	35,768 (12)	9,705 (9)
Hispanic ethnicity	14,285 (5)	5,470 (5)
Area level poverty by quintiles		
1 (Wealthiest)	61,992 (20)	22,565 (20)
2	61,741 (20)	22,853 (20)
3	61,377 (20)	23,140 (21)
4	61,465 (20)	23,113 (21)
5 (Poorest)	64,142 (21)	20,398 (18)
Substance use disorder (SUD)[b]	29,544 (10)	14,712 (13)
Recent mental health or SUD-related hospitalization[b]	4,607 (1)	4,798 (4)
Post-traumatic stress disorder[b]	27,995 (9)	24,759 (22)
Other anxiety disorder[b]	15,266 (5)	22,369 (20)
Depression[b]	58,627 (19)	42,827 (38)
Bipolar/psychotic disorder[b]	13,587 (4)	11,795 (11)
Cancer[b]	73,929 (24)	25,821 (23)
Charlson comorbidity index[b]		
0	129,358 (42)	44,003 (39)
1	73,260 (24)	27,448 (24)
≥2	108,099 (35)	40,618 (36)

[a]$p<0.001$ for all between-group comparisons

[b]All conditions were measured in the year up to and including the day of the first opioid fill during the observation period and are not mutually exclusive

Table 2. Unadjusted overdose mortality rates by benzodiazepine prescription history, daily benzodiazepine dose, benzodiazepine type, and benzodiazepine schedule

	Overdose Deaths, No.	Person-Years	Overdose Mortality Rate per 100,000 Person-Years (95% CI)[a]
Benzodiazepine prescription history			
None	794	1,116,346	71 (66, 76)
Former	421	225,171	187 (170, 205)
Current	1185	375,332	316 (298, 334)
Daily benzodiazepine dose, mg/d			
0	421	376,645	112 (101, 123)
>0-10	241	158,676	152 (133, 172)
>10-20	366	121,411	301 (271, 333)
>20-30	237	45,718	518 (454, 586)
>30-40	169	28,170	600 (513, 694)
>40	172	21,357	805 (689, 930)
Benzodiazepine type			
Clonazepam	288	76,017	379 (336, 424)
Diazepam	276	72,444	381 (337, 427)
Alprazolam	182	63,155	288 (248, 332)
Lorazepam	110	64,587	170 (140, 204)
Temazepam	88	57,301	154 (123, 187)
Other	20	6,464	309 (189, 459)
Multiple	221	35,365	625 (545, 710)
Benzodiazepine schedule			
Regularly scheduled only	449	169,515	265 (241, 290)
As needed only	638	190,933	334 (309, 361)
Simultaneous as needed and regularly scheduled	98	14,884	658 (535, 795)

Abbreviation: CI, confidence interval

[a]Unadjusted overdose rates are estimates for the entire source population

Table 3. Adjusted hazard ratios of overdose deaths by benzodiazepine prescription history, daily benzodiazepine dose, benzodiazepine type, and benzodiazepine schedule

	Hazard ratio	95% CI
	Model 1[a]	
Benzodiazepine prescription history		
None	1.00 (reference)	-
Former	2.37	2.09-2.69
Current	3.96	3.58-4.38
	Model 2[b]	
Daily benzodiazepine dose, mg/d		
>0-10	1.00 (reference)	-
>10-20	1.71	1.44-2.03
>20-30	2.37	1.93-2.90
>30-40	2.70	2.14-3.39
>40	3.10	2.42-3.97
Benzodiazepine type		
Clonazepam	1.00 (reference)	-
Alprazolam	0.91	0.74-1.12
Diazepam	0.92	0.76-1.11
Lorazepam	0.78	0.62-0.99
Temazepam	0.62	0.47-0.80
Other	1.09	0.67-1.77
Multiple	1.04	0.82-1.32
Benzodiazepine schedule		
Regularly scheduled	1.00 (reference)	-
As needed only	0.99	0.87-1.13
Simultaneous as needed and regularly scheduled	1.07	0.80-1.43

Abbreviations: CI, confidence interval
[a]Model 1 adjusted for sex, age, race, ethnicity, area level poverty, time-varying daily opioid dose, recent SUD-related hospitalization, Charlson comorbidity index, and diagnosis of substance use disorder, post-traumatic stress disorder, other anxiety disorder, depression, bipolar/psychotic disorder, and cancer
[b]Model 2 adjusted for same variables as Model 1 but included only periods when individuals were currently receiving benzodiazepines

Table 4. Adjusted hazard ratios of overdose deaths by benzodiazepine prescription history, stratified by daily opioid dose[a]

	Hazard ratio	95% CI
	Daily opioid dose = >0-<20 mg	
Benzodiazepine prescription history		
None	1.00 (reference)	-
Former	2.62	1.90-3.60
Current	3.50	2.69-4.55
	Daily opioid dose = 20-<50 mg	
Benzodiazepine prescription history		
None	1.00 (reference)	-
Former	2.16	1.74-2.70
Current	3.66	3.07-4.35
	Daily opioid dose = 50-<100 mg	
Benzodiazepine prescription history		
None	1.00 (reference)	-
Former	2.26	1.76-2.91
Current	3.75	3.08-4.57
	Daily opioid dose = ≥100 mg	
Benzodiazepine prescription history		
None	1.00 (reference)	-
Former	2.57	2.02-3.28
Current	4.68	3.84-5.71

Abbreviations: CI, confidence interval

[a]Separate models were created for each daily opioid dose category adjusting for sex, age, race, ethnicity, area level poverty, time-varying daily opioid dose, recent SUD-related hospitalization, Charlson comorbidity index, and diagnosis of substance use disorder, post-traumatic stress disorder, other anxiety disorder, depression, bipolar/psychotic disorder, and cancer