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Association Between Suicide Death and Concordance with Benzodiazepine Treatment Guidelines for Anxiety and Sleep Disorders

Jennifer M Boggs, PhD, MSW^{1,2}, Richard Lindrooth, PhD², Catherine Battaglia, PhD, MSHA, RN^{2,11}, Arne Beck, PhD^{1,2}, Debra P. Ritzwoller, PhD^{1,2}, Brian Ahmedani, PhD³, Rebecca C. Rossom, MD⁴, Frances Lynch, PhD⁵, Christine Y. Lu, MSc, PhD⁶, Beth E. Waitzfelder, PhD⁷, Ashli A. Owen-Smith, PhD, SM⁸, Gregory E. Simon, MD⁹, Heather D. Anderson, PhD¹⁰

¹Institute for Health Research, Kaiser Permanente Colorado Institute for Health Research, Denver, CO

²Health Systems Management and Policy Department, University of Colorado, Denver, CO

³Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, Michigan; Behavioral Health Services, Henry Ford Health System, Detroit, Michigan.

⁴HealthPartners Institute, Bloomington, Minnesota.

⁵Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon.

⁶Department of Population Medicine, Harvard Medical School, and Harvard Pilgrim Health Care Institute, Boston, Massachusetts.

⁷Kaiser Permanente Center for Health Research, Hawaii, Honolulu, Hawaii.

⁸School of Public Health, Georgia State University, Atlanta, Georgia; Center for Research and Evaluation, Kaiser Permanente Georgia, Atlanta, Georgia

⁹Kaiser Permanente Washington, Seattle, Washington.

¹⁰Department of Clinical Pharmacy, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Denver, CO

¹¹Department of Veterans Affairs (VA) Eastern Colorado Health Care System, Aurora, CO

Abstract

Objective: Guidelines for management of anxiety and sleep disorders emphasize antidepressant medications and/or psychotherapy as first/second-line and benzodiazepines as third-line treatments. We evaluated the association between suicide death and concordance with benzodiazepine guidelines.

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Data availability statement: The data supporting this work are not publicly available due to privacy and ethical restrictions.

Methods: Retrospective case-control study of patients with anxiety and/or sleep disorders from health systems across 8 U.S. states within the Mental Health Research Network. Suicide death cases were matched to controls on year and health system. Appropriate benzodiazepine prescribing defined as: no monotherapy, no long duration, and/or age <65 years. The association between guideline concordance and suicide death was evaluated, adjusting for diagnostic and treatment covariates.

Results: Sample included 6960 patients with anxiety disorders (2363 filled benzodiazepine) and 6215 with sleep disorders (1237 filled benzodiazepine). Benzodiazepine guideline concordance was associated with reduced odds for suicide in patients with anxiety disorders (OR=0.611, 95% CI=0.392-0.953, $p=.03$) and was driven by shorter duration of benzodiazepine use with concomitant psychotherapy or antidepressant medication. The association of benzodiazepine guideline concordance with suicide death did not meet statistical significance in the sleep disorder group (OR=0.413, 95% CI=0.154-1.11, $p=.08$).

Conclusions: We found reduced odds for suicide in those with anxiety disorders who filled benzodiazepines in short-moderate duration with concomitant psychotherapy or antidepressant treatment.

Keywords

Benzodiazepine; Suicide; Anxiety Disorder; Sleep Disorder

1. Introduction

Benzodiazepines were formerly considered first line treatment for patients with anxiety and sleep disorders, but the emergence of safer, more effective treatments has dramatically changed recommended guidelines. British and Canadian guidelines for pharmacological treatment of anxiety disorders, as well as the *American Academy of Family Physicians* and the *American College of Physicians* now recommend non-benzodiazepine first line treatments for anxiety and sleep disorders (Baldwin, 2005; Baldwin, 2014; Farach et al, 2012; Swinson et al, 2006; Katzman et al, 2014; Locke et al, 2015; Qaseem et al, 2016). Short-term treatment with benzodiazepines may be considered for certain types of anxiety disorders, including panic disorder and social anxiety (Baldwin, 2005; Baldwin, 2014; Farach et al, 2012; Swinson et al, 2006; Katzman et al, 2014; Locke et al, 2015). Since benzodiazepine effectiveness is restricted to short-term improvements only, guidelines recommend always combining benzodiazepines with safer long-term treatments. These include psychotherapy for both anxiety and sleep disorders – such as cognitive behavioral therapy for insomnia (Qaseem et al, 2016). For anxiety disorders, selective serotonin reuptake inhibitors (SSRI), selective norepinephrine reuptake inhibitors (SNRI) and older antidepressants, including tri-cyclic and monoamine oxidase inhibitors are recommended long-term treatments (Baldwin, 2005; Baldwin, 2014; Farach et al, 2012; Swinson et al, 2006; Katzman et al, 2014; Locke et al, 2015).

The potential benefit of benzodiazepines must be weighed against several risks. The primary safety concerns for benzodiazepines include addiction in all populations, and risk for falls and delirium in older adults (Beers, 2016). A recent descriptive study of prescription

patterns in the U.S. showed that benzodiazepines are frequently prescribed contrary to recommendations: for longer duration, to older adults, and to high-risk groups who should not receive these medications (Olfson, King, & Schoenbaum, 2015).

The relationship between benzodiazepines and suicide is not well understood. The odds ratios for the association of all hypnotic medications (e.g. benzodiazepines and non-benzodiazepine sleep medications) and suicide ranged from 1 to 24 in a review study, with no single study considered well-controlled for confounding mental health treatment and diagnosis factors (McCall et al, 2016). Similarly, a 2017 review of benzodiazepines and suicidal behavior indicated that nearly all studies examining the relationship between benzodiazepine and suicide showed positive associations for benzodiazepine use and suicide outcomes, but only two were well-controlled (Dodds, 2017). Benzodiazepines are not usually fatal in overdose alone (Buckley et al, 1995), but they often contribute to mortality risk in multi-drug overdoses with alcohol and opioids (Bhaskaran et al, 2015; Park et al, 2015). Benzodiazepines were present in approximately 30% of intentional overdose deaths in medical examiner studies conducted in Kentucky, Alabama, and California (Shields et al, 2006; Dhossch, Rich, & Isacso, 2001) and are present in 31% of all cause overdose deaths in the U.S. (Bhaskaran, 2015). They are also present in suicide deaths by means other than overdose, indicating that benzodiazepines may lower inhibitions, thereby facilitating suicidal action by any means in those at risk (e.g. firearm, drowning) (Shields et al, 2006; Carlsten et al, 2003; Voaklander et al, 2008; Tournier et al, 2009).

As the most common class of mental health disorders, anxiety disorders have a lifetime prevalence in the U.S. of approximately 30% (Kessler, Borges, Walters et al, 2005). Findings from the U.S. National Epidemiologic Study, an in-person clinical interview of 34,653 adults, found that 70% of people who reported suicide attempts had an anxiety disorder (Nepon et al, 2010; Sareen, Houlihan, Cox, et al, 2005). Sleep disturbances may occur as a symptom of an anxiety disorder or as an independent sleep disorder in 6-10% of the population (Qaseem et al, 2016). The relationship between sleep disorders and suicide has been most studied in the context of sleep disturbances as a mediator that increases suicide risk in those with depression, psychotic disorders, or chronic pain (Agargun et al, 1997; Agargun et al, 2007; Fawcett et al 1990; Turvey et al 2002; Fujino et al, 2005; Keshaven et al, 1994; Smith, Perlis and Haythornthwaite, 2004). A recent study from our group also found that sleep disturbances mediated the relationship between chronic pain and suicide death (Owen-Smith et al, 2019). Some have suggested sleep plays an independent role in suicide risk (Bernart & Joiner, 2007).

We examined whether suicide death, in patients with anxiety or sleep disorders, was associated with guideline discordant prescribing patterns for benzodiazepines across a large study that spans 8 U.S. states using a retrospective matched case-control design. We measured benzodiazepine dispensings or fills within closed-panel integrated health systems to measure prescribing behavior. Methods to overcome drawbacks from prior studies included examining concordance in a benzodiazepine-only sample and including a more robust set of control variables: diagnoses, prior treatment exposure and utilization of behavioral health services.

2. Methods

2.1. Overall approach and considerations

There are two important challenges for evaluating the relationship of benzodiazepine use and suicide. First, anxiety and sleep disorders are both independently associated with increased risk for suicide (Agargun, Kara, Soz, 1997; Agargun et al 2007; Bernert & Joiner, 2007; Keshaven, Reynolds, Montrose, 1994; Kessler, Borges, Walters, 1999; Nepon et al, 2010). Therefore, our analysis only compares guideline concordance within diagnostic group and controls for other mental health (e.g. depression) and substance diagnoses in our models that may increase risk for suicide. The second challenge is that patients with anxiety or sleep disorders, who are treated with benzodiazepines, may be at increased risk for suicide due to more severe symptoms that lead to benzodiazepine treatment. Examples include panic attacks and nightmares which have been identified as higher risk symptoms for suicide and which may be particularly responsive to benzodiazepine treatment (Agargun et al 2007; Nepon et al, 2010; Baldwin et al, 2014). To address this challenge, we define benzodiazepine exposure according to guideline criteria and examine a group of patients with anxiety or sleep disorders who all had at least one fill for a benzodiazepine, with one exception. For the benzodiazepine duration analysis, we included all patients with anxiety and sleep disorders, including those that were not prescribed benzodiazepines as a reference group.

2.2. Data Source

We examined electronic health record (EHR) and claims information for patients with anxiety or sleep disorders, ≤ 89 years of age, who were part of the *Treatment Utilization Before Suicide* retrospective case-control study (Ahmedani, 2015). The study setting included eight learning healthcare systems within the NIMH-funded Mental Health Research Network (MHRN): Henry Ford Health System (Michigan), Health Partners (Minnesota), Harvard Pilgrim Health Care (Massachusetts), and Kaiser Permanente health systems in Colorado, Georgia, Hawaii, Oregon, and Washington (Rossom et al, 2016). Each system offers integrated medical and mental health care services with individual and group therapy, intensive outpatient programs, and psychiatric medication management.

The *Treatment Utilization Before Suicide* study includes suicide cases who died from suicide between 2001-2013 (Ahmedani, 2015). Each case was retrospectively matched by site and year of death, to 100 randomly selected control patients, who may have attempted but did not die by suicide. The only inclusion criterion was that each participant was continuously enrolled in a health plan covered at one of the eight sites, for at least 10 months during the year prior to index date, allowing for a dis-enrollment gap for 60 days prior to death. The index date was the date of suicide death for cases and same date for all matched controls. The overall TUBS sample included 2674 cases matched to 267,400 controls.

For this study, we selected all cases and controls from the TUBS sample who had at least one medical or mental health visit for anxiety or sleep disorder during the year prior to index date (based on ICD-9 code). Anxiety disorders included: anxiety disorder NOS, panic disorder with & without agoraphobia, generalized anxiety, phobias, obsessive compulsive

disorder, adjustment disorders w/ anxiety, and posttraumatic stress disorder. Sleep disorders included organic and non-organic sleep disorders: insomnia, hypersomnia, sleep apnea, parasomnias, sleep disturbances. Our guideline concordance analyses were limited to patients with at least one dispensing/fill (e.g. patient picked up from pharmacy) of a benzodiazepine during the study time frame prior to suicide. This included patients who were diagnosed with an anxiety or sleep disorder and filled a benzodiazepine between 45 – 245 days prior to their index date. The cut-off of 245 days was calculated by subtracting 120 from 365 to reach approximately month 7 in the 1-year exposure period. The 45-day criterion on the front end eliminated those who were continuously using benzodiazepines prior to the one-year exposure period. In prior studies, the absolute upper cut-off for appropriate benzodiazepine duration was 120 prescribed days per year (Olfson, King, & Schoenbaum, 2015; Pearson et al., 2006), which some consider overly generous (el-Guebaly et al, 2010). Since our period was 7 months, this would equate to 70 days. The average benzodiazepine prescription is 7-14 days, thus we set a criterion of greater than 8 fills, which would be equivalent to a cutoff range of 63 – 112 days over 7 months. We examined the 8-fill cut-off by examining a benzodiazepine duration variable independently in a secondary analysis. Additional analyses were also conducted to understand the interaction of benzodiazepine treatment with antidepressants and psychotherapy. For our analysis of benzodiazepine duration only, we included patients who did not fill any benzodiazepine prescriptions as a reference group to assist with interpretation. A supplemental duration analysis was limited to patients with at least one fill of benzodiazepines (Supplemental figure 1). All sites received Institutional Review Board approval with waivers of consent/HIPAA.

Patient data for one year prior to index date were extracted from a Virtual Data Warehouse (VDW) that included EHR and insurance claims data from each site. The VDW is a set of tables with mutually agreed upon validated variable definitions and formats across each MHRN site (Ross et al, 2014; Tavel et al, 2012). This allows each site to retain their own private patient medical and mental health record data but overcomes the challenge of data harmonization inherent in multisite research, with the use of standardized distributed programming codes. There are routine data quality verifications for the VDW to ensure the standard variables are defined similarly across systems. Death data from the VDW are verified with mortality records from national, state, and local public health organizations by Social Security numbers or a combination of patient names, birthdates, and demographic profiles. To identify patients who died by suicide in the VDW, International Classification of Diseases, 10th revision (ICD-10) codes of X60-84 and Y87 were used. Pharmacy dispensing information for all relevant medication exposures was identified by specific national drug codes.

The number, specialty (e.g. primary care, psychiatry), and type of outpatient mental health visits (e.g. medication, psychotherapy, group) along with mental health inpatient, emergency care in the year prior to index date and diagnoses coded at each visit were collected from the VDW. International Classification of Diseases, 9th revision (ICD-9) codes were captured from health system encounters (in-patient and out-patient), to ascertain diagnoses within the year prior to the index date for all study patients. ICD-9 diagnosis codes were extracted for 12 major mental health and substance use conditions (ICD-9 codes 290-319). Demographic

information on age and sex were available from the VDW and neighborhood income and education were estimated using geocoded addresses and census block data.

2.3 Measure construction

A binary variable for guideline concordance was constructed using the following criteria for anxiety and sleep concordance: patients who filled a benzodiazepine should be younger than 65 years of age, have no more than 8 dispensings during the study time frame (defined above), and have evidence of at least 3 psychotherapy sessions (sleep and anxiety disorders) or antidepressant medication use (anxiety disorders only). While studies of brief therapies for anxiety normally include 4-6 psychotherapy sessions (Clark et al, 1999; Hofmann & Smits, 2008), good-enough-level models show improvements in symptom burden after a few sessions with diminishing returns per session thereafter (Falkenström et al, 2016; Owen, Adelson, Budge, Kopta, & Reese, 2014). In the managed care settings studied here, psychotherapy duration is typically shorter in duration. For these reasons, a cut-off of 3 sessions was considered adequate treatment duration for guideline concordance (Drake & Latimer, 2012).

2.4 Co-variate selection

All co-variables were included because they have a strong association from prior literature with suicide outcomes. Demographics were included to help reduce error in the models due to significant differences in risk for suicide death by gender, race, ethnicity, income and age (CDC, 2017). All other variables were likely confounders or variables associated with probability for benzodiazepine treatment concordance and suicide. Mental health and substance abuse disorders (Nordentoft et al, 2011) and prior suicide attempts increase the risk for suicide and influence decisions to prescribe benzodiazepines, for example patients with depression are less likely to receive benzodiazepines per treatment recommendations (Finkelstein et al, 2015; Beghi et al, 2013; Baldwin et al, 2014). Medical comorbidity increases risk for suicide and the probability of screening for mental health conditions (Ahmedani et al, 2017; Erlangsen, Stenager, & Conwell, 2015); public versus private insurance status influences care seeking and suicide outcomes (Cerel et al 2015; Masters et al, 2014); those with higher psychotherapy visits may be more likely to improve, but high levels indicate treatment resistance and increased risk for suicide (Angst et al 2002; Kornstein et al, 2001).

2.5 Statistical analysis

SAS Studio was used to extract data from the VDW, as well as develop an analytic dataset; *Stata/IC* version 15.1 was used to estimate the analytic models. For our main analysis, we predicted suicide death and evaluated the association of a binary variable for guideline concordance only in patients who filled benzodiazepines in two separate logit models for anxiety and sleep disorders. Control variables in all models included demographics (age, gender, race, ethnicity, education); prior suicide attempt; mental health diagnoses (depression, bipolar, schizophrenia); substance abuse diagnoses (alcohol & drug use disorders, which includes opioid use disorders); Charlson medical comorbidity score (0,1,2,3, 4+) – measures the number of chronic health conditions; insurance type (commercial, Medicare, Medicaid); total count of psychotherapy visits; other hypnotic use

(e.g. zolpidem), and antidepressant treatment. We applied a quadratic term to total count of psychotherapy visits to improve model fit for patients with high levels of treatment seeking.

In secondary analyses, we deconstructed the guideline concordance variable using additional logit models which included all the control variables. First, we examined the impact of benzodiazepine duration by constructing a categorical variable (0,1-2, 3-5, 6-8,9-11,12-14,15+ dispensings). We included all patients with an anxiety and sleep disorder including those who did not fill a benzodiazepine, who served as a reference group. Second, we examined persons with anxiety disorders who were <65 years of age who used different levels of benzodiazepines (1-2, 3-8, 9+ fills) either in monotherapy or with other treatments (antidepressants or psychotherapy). Monotherapy was defined as evidence of benzodiazepine treatment only, without any indication of antidepressant use and <3 visits for psychotherapy.

3 Results

Of the 6960 patients with any anxiety disorder diagnosis at a visit during the study timeframe, 2363 had at least one dispensing of a benzodiazepine (Table 1). Of the 6215 with sleep disorders, 1237 had at least one dispensing of a benzodiazepine. Histories of benzodiazepine, antidepressant, and psychotherapy treatments in the prior year were more common in the anxiety disorder group than the sleep disorder group. The sleep disorder group tended to be older (mean age = 52 years vs. 44 years for anxiety disorders) with higher Charlson medical comorbidity score. When comparing unadjusted characteristics of patients who filled at least one benzodiazepine versus none, we also observed higher rates of comorbid mental health and substance use conditions, psychotherapy and antidepressant treatment in those who filled at least one benzodiazepine (Supplemental Table 1). Table 1 shows several notable differences across demographic, treatment and diagnostic variables between those who are concordant/discordant with guidelines, showing the importance of controlling for these in adjusted analyses. Table 2 highlights the reasons for discordance among those with anxiety and sleep disorders in the full sample and conditional on benzodiazepine use. This illustrates that monotherapy is the largest contributor to discordance, particularly for sleep disorders, indicating low rates of psychotherapy in the sleep disorder group.

The unadjusted odd for suicide death were 54% lower in those who were concordant with benzodiazepine guidelines in the anxiety disorder group (N = 2363) (OR = .456, 95% CI = .314 - .673, $p < .0001$). In adjusted models, examining patients with anxiety disorders who used benzodiazepines (N = 2363), we observed odds that were 39% lower for suicide death in those who met guidelines (OR = 0.611, 95% CI = 0.392 - 0.953, $p = .03$) (Full model results in Supplemental Table 2). Similar reductions were noted in the sleep disorder group among patients who met guidelines (N = 1237), but neither unadjusted (OR = .432, 95% CI = .185 - 1.011, $p = .053$) or adjusted (OR = 0.413, 95% CI = 0.154 - 1.11, $p = .08$) models reached statistical significance (Full model results in Supplemental Table 3).

For the benzodiazepine duration analysis, we examined a categorical variable of multiple levels of benzodiazepine dispensings among all patients (N = 12108) with anxiety or sleep

disorders (0,1-2, 3-5, 6-8, 9-11, 12-14, 15+) (Figure 1). We observe slightly increased odds ratios of suicide death from 1-2 benzodiazepine fills versus none (OR = 1.656, $p < .01$, 95% CI = 1.209 - 2.269) and larger ORs starting at 3-5 fills (OR = 3.172, $p < .01$, 95% CI = 2.279 - 4.415). Interestingly, the ORs remain steady from 3 to 14 fills and then begin to increase again for 15+ fills (OR = 5.639, $p < .01$, 95% CI = 3.01 - 10.539). Supplemental Figure 1 shows a similar pattern when limiting the duration analysis to those with at least one benzodiazepine dispensing, using a reference of 1-2 dispensings.

We also examined the impact of concomitant antidepressant or psychotherapy treatments with benzodiazepines versus monotherapy at multiple fill levels (1-2, 3-8, 9+). This analysis was limited to those with anxiety disorders who were < 65 years of age. A categorical variable of treatments at 5 levels was implemented (Figure 2). Those with 3-8 benzodiazepine fills in monotherapy (OR = 2.75, $p < .01$, 1.325 - 5.7) and those with long benzodiazepine duration (9+ fills) (1.67, $p = .05$, 1.0 - 2.78) had higher odds of suicide death compared to persons with 1-2 benzodiazepine fills plus evidence of other treatments (reference). Compared to reference, the other two groups were not significantly different (3-8 benzodiazepine fills with other treatments and 1-2 benzodiazepine fills in monotherapy). This would indicate that moderate amounts of benzodiazepines used in monotherapy and long benzodiazepine duration are likely contributing to the association we observe above in the overall guideline concordance model.

4 Discussion

In a large sample of patients across 8 different health systems in the U.S., we found that patients who received benzodiazepine treatments in concordance with treatment guidelines for anxiety disorders had a reduced likelihood for suicide death using a case-control design. Our results were robust in a population who filled benzodiazepines, which helps address issues of confounding by indication. Interestingly, we found that the safest duration of benzodiazepine use across the whole sample was 1-2 fills, with higher amounts indicating increased association for suicide. This association was significantly mitigated in those with moderate benzodiazepine use (3-8 fills) by adding concomitant antidepressant or psychotherapy treatments. Our results for sleep disorders showed similar associations to anxiety but were not statistically significant.

Our benzodiazepine duration analysis showed significant associations with suicide death starting with 1-2 dispensings, with a sharp increase beyond 2 dispensings (Figure 1). This is expected due to confounding by indication for patients who receive any amount of benzodiazepines, since the reference group for the duration analysis included patients who did not use benzodiazepines as a reference group. Longer exposure to benzodiazepines certainly increases the risk for benzodiazepine drug dependency, which would likely increase the risk for suicide. Past studies have defined long-term benzodiazepine duration in terms of risk for addiction, not suicide, as more than 120 days per year, equivalent to our 8-dispensing cut-off (Olfson, King, & Schoenbaum, 2015). Our duration analysis indicates that there is little difference in the association for suicide death between 3 and 14 dispensings (Figure 2), indicating that 3 dispensings, not 8, could be considered long-duration for suicide risk. Interestingly, Lorazepam has guidance for duration of 2-4 weeks,

which would be equivalent to our 1-2 fills category, while other common benzodiazepine medications have no recommended duration other than “short.”

Our guideline concordance analysis showed that antidepressant and/or psychotherapy treatments mitigated the odds for suicide death among those with 3-8 benzodiazepine dispensings compared to those who used benzodiazepines in monotherapy (Figure 2). Therefore, prescribing more than 2 dispensings of a benzodiazepine does not change the association for suicide death versus 1-2 dispensings, as long as monotherapy was avoided. When considering the appropriateness of benzodiazepine use, duration may be less important concomitant long-term therapies, consistent with guideline recommended prescribing practices. FDA-approved labeling on common benzodiazepines do not incorporate any recommendations from anxiety and sleep disorder guidelines, specifically that benzodiazepines should not be first line treatment or used in monotherapy (Ativan, 2007; Klonopin, 2013; Valium, 2008; Xanax, 2011).

We are not suggesting that benzodiazepines be avoided all together, particularly since antidepressants do not have a fast mechanism of action for severe anxiety symptoms. The *American Academy of Family Physicians* indicates that benzodiazepines may be effective in handling short term crisis and/or during initial treatment before antidepressants have reached therapeutic benefit. Compared to placebo, antidepressants show reductions in anxiety symptoms in several randomized control trials, without risk for addiction (Batelaan, Van Balkom & Stein, 2012). Importantly, guidelines indicate that benzodiazepines offer no improvement in long-term outcomes, highlighting the importance of avoiding benzodiazepine monotherapy, which our findings support (Locke et al, 2015).

A recommendation to consider is that anyone treated with benzodiazepines should be considered at increased risk for suicide and therefore screened. Our results clearly show a significant positive correlation in adjusted models between duration of benzodiazepine treatment and suicide death starting with just 1-2 dispensings. This may be due to higher disease severity associated with benzodiazepine prescribing and/or increased risk for benzodiazepine overdose. While we cannot distinguish between these two suicide risk factors from our analyses, the cause may be less important than the signal that benzodiazepine treatment gives to screen for suicide risk.

Future work should explore the benefit of suicide risk screening in patients with anxiety disorders who are treated with benzodiazepines, particularly those who are treated by Primary Care Providers (PCPs). PCPs prescribed 55% of benzodiazepines in the U.S. and are twice as likely to prescribe in conflict with treatment guidelines compared to psychiatrists, specifically prescribing in monotherapy for treatment of anxiety disorders (Cascade & Kalali, 2008). There are recommendations for depression screening with measures such as the Patient Health Questionnaire-9, which includes suicide risk assessment in those with depression disorders in primary care settings (USPSTF, 2015). There are currently no equivalent recommendations for suicide screening in those with anxiety disorders.

Our study had several strengths and limitations. Suicide death is a rare event, which means that it is difficult to implement stronger designs such as a randomized trial or a retrospective cohort design. It is possible that concomitant use of opioids increased risk for suicide death in those who were discordant with benzodiazepine prescribing guidelines. While we controlled for opioid use disorders, opioid dispensing information was not available. We did not have data on potency or types of benzodiazepines prescribed, which may have been informative considering short versus long acting benzodiazepines could have differential effects (Dodds, 2017). Furthermore, we could not precisely measure timing of benzodiazepine and antidepressant medication use or the specific indication for the prescriptions (e.g. anxiety, sleep, depression etc.). We did not have measures of sleep disturbance symptoms or know whether evidence-based therapies were received (Rybarczyk et al, 2013), which may partially explain our lack of significant association in the sleep disorder group, along with the smaller associations for suicide in those with sleep disorders compared to anxiety. A strength of our study is a more robust set of control variables than former studies of benzodiazepines and suicide because we included mental health diagnoses, prior behavioral health utilization and treatments. However, we did not have symptom severity measures, which means our study may still suffer from confounding by indication. Examining a sample who filled at least one benzodiazepine is a strength to reduce bias because the entire group received treatment. Interestingly, we found that adding more treatment (e.g. antidepressant or psychotherapy) resulted in reduced likelihood for suicide in those with moderate benzodiazepine use, which shows we have overcome confounding by indication to some degree. Studies with more detailed cause of death information that go beyond ICD-10 cause of death codes (e.g. studies using coroner's reports) are needed to precisely measure the interaction of benzodiazepine duration and use as a lethal mean in suicide attempt/death. A study that included non-fatal suicide attempts by benzodiazepine overdose would help increase the sample size and offer more precise assessment of benzodiazepines as a lethal means.

5 Conclusion

This study shows that about one fifth of individuals filled benzodiazepines for sleep and anxiety outside recommended guidelines and this discordance is associated with suicide death. There are several possible reasons for discordance: providers may not be aware of the guidelines, they may not believe the guidelines to be accurate and/or compelling in their evidence, or patients may pressure providers to prescribe benzodiazepines, due to the beneficial short-term effects. We hope that this study provides an impetus to physicians and health systems to carefully monitor benzodiazepine prescribing practices that are discordant per anxiety and sleep disorder guidelines and to consider screening patients who are treated with benzodiazepines for suicide risk. Specifically, we found reduced odds for suicide in those with anxiety disorders who filled benzodiazepines in short to moderate duration with concomitant psychotherapy or antidepressant treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
Association of benzodiazepine duration with suicide death among all patients

Figure 2:
Association of suicide by treatments received in younger persons (<65 yrs.) with anxiety disorders who received any level of benzodiazepine treatment

Table 1.

Unadjusted characteristics of full patient sample

Factor	Level	Anxiety Disorders (N = 6960)			Sleep Disorders (N = 6215)		
		Guideline Discordant	Guideline Concordant	P-val	Guideline Discordant	Guideline Concordant	P-val
N		1203 (17.3%)	5757 (82.7%)		1105 (17.8%)	5110 (82.2%)	
Suicide death		110 (9.1%)	220 (3.8%)	<0.001	96 (8.7%)	110 (2.2%)	<0.001
Any benzodiazepine		1203 (100.0%)	1160 (20.1%)	<0.001	1105 (100.0%)	132 (2.6%)	<0.001
Benzodiazepine duration, mean (SD)		6.0 (5.53)	0.57 (1.47)	<0.001	4.44 (4.71)	0.11 (0.8)	<0.001
Both anxiety and sleep disorders		232 (19.3%)	835 (14.5%)	<0.001	393 (35.6%)	674 (13.2%)	<0.001
Age, mean (SD)		54.58 (17.52)	42.47 (18.56)	<0.001	56.3 (15.32)	51.45 (18.62)	<0.001
Gender	F	774 (64.3%)	3743 (65.0%)	0.65	640 (57.9%)	2518 (49.3%)	<0.001
	M	429 (35.7%)	2014 (35.0%)		465 (42.1%)	2592 (50.7%)	
Hispanic	No	569 (47.3%)	2417 (42.0%)	0.001	638 (57.7%)	2519 (49.3%)	<0.001
	Unknown	591 (49.1%)	3052 (53.0%)		431 (39.0%)	2346 (45.9%)	
	Yes	43 (3.6%)	288 (5.0%)		36 (3.3%)	245 (4.8%)	
Race	Non-White	135 (11.2%)	539 (9.4%)	0.072	101 (9.1%)	601 (11.8%)	<0.001
	Unknown	346 (28.8%)	1787 (31.0%)		225 (20.4%)	1338 (26.2%)	
	White	722 (60.0%)	3431 (59.6%)		779 (70.5%)	3171 (62.1%)	
Lower education (census determined)	No	727 (60.4%)	3666 (63.7%)	0.098	644 (58.3%)	3144 (61.5%)	0.032
	Yes	438 (36.4%)	1913 (33.2%)		429 (38.8%)	1782 (34.9%)	
	Unknown	38 (3.2%)	178 (3.1%)		32 (2.9%)	184 (3.6%)	
Insurance	Medicaid	74 (6.2%)	308 (5.4%)	<0.001	84 (7.6%)	248 (4.9%)	<0.001
	Medicare	367 (30.5%)	604 (10.5%)		314 (28.4%)	1108 (21.7%)	
	Private	762 (63.3%)	4845 (84.2%)		707 (64.0%)	3754 (73.5%)	
Suicide attempt		26 (2.2%)	55 (1.0%)	<0.001	31 (2.8%)	27 (0.5%)	<0.001
Depression		464 (38.6%)	2688 (46.7%)	<0.001	461 (41.7%)	1361 (26.6%)	<0.001
Bipolar		64 (5.3%)	248 (4.3%)	0.12	53 (4.8%)	105 (2.1%)	<0.001
Schizophrenia		47 (3.9%)	117 (2.0%)	<0.001	35 (3.2%)	53 (1.0%)	<0.001
Drug use disorder		62 (5.2%)	293 (5.1%)	0.93	55 (5.0%)	118 (2.3%)	<0.001
Alcohol use disorder		80 (6.7%)	362 (6.3%)	0.64	68 (6.2%)	172 (3.4%)	<0.001
Charlson	0	704 (58.5%)	4258 (74.0%)	<0.001	570 (51.6%)	3110 (60.9%)	<0.001
	1	219 (18.2%)	888 (15.4%)		223 (20.2%)	951 (18.6%)	
	2	107 (8.9%)	303 (5.3%)		124 (11.2%)	462 (9.0%)	
	3	64 (5.3%)	115 (2.0%)		63 (5.7%)	206 (4.0%)	
	4	109 (9.1%)	193 (3.4%)		125 (11.3%)	381 (7.5%)	
New antidepressant (SSRI, SNRI)		419 (34.8%)	2618 (45.5%)	<0.001	516 (46.7%)	1086 (21.3%)	<0.001
Old antidepressant (TCA, MAOI)		258 (21.4%)	1149 (20.0%)	0.24	463 (41.9%)	1153 (22.6%)	<0.001
Non-benzodiazepine hypnotic		132 (11.0%)	291 (5.1%)	<0.001	231 (20.9%)	634 (12.4%)	<0.001

		Anxiety Disorders (N = 6960)			Sleep Disorders (N = 6215)		
Factor	Level	Guideline Discordant	Guideline Concordant	P-val	Guideline Discordant	Guideline Concordant	P-val
Long benzodiazepine duration (9+ fills in past year)		396 (32.9%)	0 (0.0%)	<0.001	214 (19.4%)	0 (0.0%)	<0.001
Total psychotherapy visit count, mean (SD)		1.1 (3.66)	2.02 (4.77)	<0.001	0.66 (2.82)	0.67 (3.14)	0.97

Table 2.

Frequency of anxiety and sleep guideline concordance criteria

Criteria	Number Discordant	% Discordant			
		Anxiety Disorder (N = 6960)	Anxiety Disorder and Filled Benzodiazepine (N = 2363)	Sleep Disorder (N = 6215)	Sleep Disorder and Filled Benzodiazepine (N = 1237)
>65 years and benzo use	207	3%	8.76%	0.3%	1.54%
Long benzo duration (9+ fills)	396	5.7%	16.76%	3.4%	17.3%
Short benzo duration and no evidence of antidepressant or psychotherapy (anxiety disorders)	600	8.6%	25.39%	n/a	n/a
Short benzo duration and no evidence of psychotherapy (sleep disorders)	872	n/a	n/a	14%	70.5%
Total discordance		17.3%	51%	17.8%	89%

Notes. Guideline criteria are not mutually exclusive