Prescribed Benzodiazepines and Suicide Risk:
A Review of the Literature

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ABSTRACT

Objective: To evaluate whether prescribed benzodiazepines affect one's risk of suicide.

Data Sources: A PubMed search of English-language publications from database inception until October 11, 2016, was conducted using the terms *benzodiazepine* and *suicide*. References and related articles were also searched to yield additional publications.

Study Selection/Data Extraction: Studies were included if they addressed the relationship between suicidal behavior and the prescribed use of either specific benzodiazepines or benzodiazepines as a class. A total of 17 studies were included in this review.

Results: The majority of studies found that benzodiazepines were associated with increased suicide risk. This finding was consistent across various populations and different types of research, including a placebo-controlled crossover trial, a laboratory model of suicidal behavior, case-control studies regarding completed suicides on inpatient units, and large naturalistic studies.

Conclusions: Benzodiazepines appear to cause an overall increase in the risk of attempting or completing suicide. Possible mechanisms of prosuicidal effects may include increases in impulsivity or aggression, rebound or withdrawal symptoms, and toxicity in overdose.

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Brains of individuals who died by suicide display altered expression and regulation of genes involved in the γ-aminobutyric acid (GABA)–ergic system, including those coding for $GABA_A$ receptor subunits.[1–5] In 1 study,[6] GABA concentrations in the cerebrospinal fluid correlated with both impulsivity and prior suicidal behavior. Risk factors for suicide include the nonmedical use of $GABA_A$ receptor modulators such as alcohol and sedative-hypnotic medications.[7] In the National Comorbidity Study Replication,[8] the use of sleeping pills or other sedatives, many of which act on $GABA_A$ receptors, was associated with a 3-fold higher risk of suicide attempt even after adjusting for insomnia, substance use, anxiety, and mood disorders. Little attention has been paid, however, to the question of whether prescribing a benzodiazepine might raise a patient's suicide risk. This question is becoming increasingly important to answer: benzodiazepine prescriptions in the United States have increased considerably over the past 2 decades,[9] fatal overdoses involving benzodiazepines have become more frequent,[9] and suicides in general are steadily rising.[10]

On the other hand, prescribing clinicians may expect benzodiazepines to protect against suicide by reducing anxiety and insomnia, 2 modifiable risk factors for suicide.[11,12] Both symptoms are thought to exacerbate the psychological distress a suicidal person experiences, and insomnia may result in fatigue that then impairs emotional regulation and problem-solving abilities.[11] For people who commit suicide, anguish, a state of excruciating mental distress, can lead to desperation, an urgent need for immediate relief of that suffering.[13] If these individuals were able to obtain such relief from a rapidly calming medication, perhaps they would not resort to killing themselves. This review seeks to address the evidence regarding these 2 competing hypotheses.

METHODS

Figure 1 illustrates the strategy used to identify studies. A PubMed search of English-language publications from database inception until October 11, 2016, was conducted using the terms *benzodiazepine* and *suicide*. Additional publications were found through searching references and related articles (22 studies). Studies were included if they addressed the relationship between suicidal behavior and the prescribed use of either specific benzodiazepines or benzodiazepines as a class. Studies were not included if they addressed only suicidal ideation rather than behavior or reported only on more heterogeneous groups of medications such as sedatives, hypnotics, sedative-hypnotic medications, or sleeping pills. Three studies[14–16] were excluded because they measured only lifetime history of suicide attempts without assessing whether participants were prescribed benzodiazepines around the time of those attempts. One study[17] was excluded because too few participants were using benzodiazepines to draw any conclusions. Ultimately, 17 studies[18–35] (1 study was described in 2 articles[19,20]) were included in this review.

RESULTS

The majority of the 17 studies (Table 1) found that benzodiazepines were associated with increased suicide risk. The most striking illustration comes from

Clinical Points

- Current evidence suggests that benzodiazepines may increase the risk of suicide, particularly in patients with high baseline impulsivity or aggression.
- The suicide risks associated with benzodiazepines appear to be dose dependent.

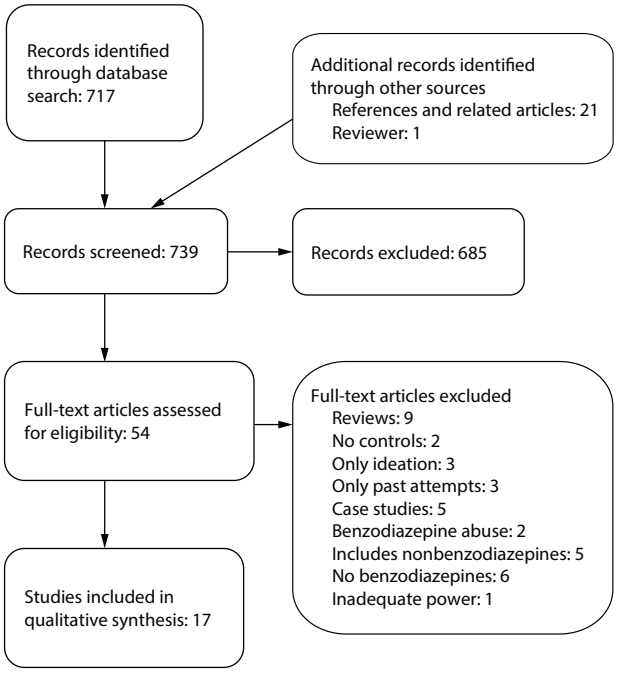
a small placebo-controlled crossover trial[19,20] comparing several classes of medications in the outpatient treatment of women with borderline personality disorder. The alprazolam arm of the study was stopped early because of a 58% rate of "severe behavioral dyscontrol" compared to a rate of 14% on placebo (7 of 12 participants vs 2 of 14, $P = .025$). Examples included overdosing, jumping in front of a car, or throwing a chair at a child. Participants in the study took alprazolam at a mean daily dose of 4.7 mg for up to 6 weeks (mean = 30 days), and the authors[19,20] were unable to identify any pattern as to when in the course of the trial these acts occurred. Those who exhibited violent or suicidal behavior generally only displayed minor evidence of dyscontrol in the preceding weeks, and, in some cases, they even reported feeling less depressed or anxious beforehand (on a modified Bunney-Hamburg Rating Scale administered weekly).[19,20]

Researchers[18] demonstrated similar effects under laboratory conditions using a measure known as the self-aggression paradigm, which has previously been shown to correlate with levels of suicidal ideation and past suicidal and self-injurious behavior. In the experiment, 46 healthy young adults were randomized to receive a single dose of either placebo or diazepam 5 mg or 10 mg and then participate in a competitive reaction time task. Each participant selected the intensity of electric shock that would be delivered if he or she "lost" the round. Those who had received diazepam 10 mg self-administered shocks of higher intensity than the control group, and they were about 6 times as likely to select an intensity that they believed would be severe. At a dosage of 5 mg, this effect was not statistically significant.[18]

Among naturalistic research, the most informative may be a 5-year longitudinal study[27] of 21,492 patients with schizophrenia, which found that high-dose benzodiazepines (eg, >15 mg/d of diazepam) were associated with roughly 2-fold increased suicide rates, even after adjusting for proxy measures of illness severity and treatment adherence. In comparison, antidepressants showed no association, and high-dose antipsychotics (eg, >7.5 mg/d of risperidone) were associated with lower suicide rates. This comparison between classes of medications helps to mitigate confounding by indication, to some degree, because antidepressants and antipsychotics also may be used to manage anxiety or insomnia.

A similar study[26] involving 2,588 patients with first-episode schizophrenia also found a strong association between benzodiazepine use and suicide (hazard ratio [HR] = 3.83; 95% CI, 1.45–10.12). Antidepressants were associated with markedly lower suicide risk (HR = 0.15; 95% CI, 0.03–0.77), and concurrent use of 2 or more antipsychotics showed no association.

Figure 1. Search Strategy[a]



[a]One study was described in 2 articles.

Other naturalistic studies of outpatient prescribing consistently confirm this association between benzodiazepines and suicidal behavior in a variety of populations, including patients with schizophrenia,[22] adolescents with major depressive disorder,[21] and the general population of Saskatchewan, Canada.[23] In a case-control study[25] of adults with deliberate self-poisoning, these risks were consistent between acute benzodiazepine treatment (eg, less than a week) or longer-term use (eg, 6–12 months). A study[28] of suicides among seniors found increased risk with benzodiazepine types and dosages that conformed to Beers Criteria recommendations and with those that did not. US veterans receiving opioid analgesics have also shown higher rates of fatal drug overdoses when concurrently prescribed benzodiazepines, although the authors[24] did not distinguish between intentional and accidental overdoses.

Case-control studies comparing inpatients who completed suicide during hospitalization to matched controls have yielded similar results. Two[30,32] of 4[29,30,32,33] such studies found that benzodiazepines were prescribed to more of the patients in the suicide groups than in the control groups, and the other 2 studies[29,33] showed nonsignificant trends in that direction. In comparison, antipsychotics displayed either a negative correlation with suicide[32,33] or no overall association.[29,30] However, 1 additional related study,[31] a retrospective chart review involving patients hospitalized on an inpatient unit, found no association between the use of alprazolam or clonazepam and self-injurious or assaultive behavior.

Table 1. Studies Assessing Prescribed Benzodiazepines and Suicide Risk

Study	Subjects[a]	Methods	Relevant Findings[b]
Placebo-controlled studies			
Berman et al[18]	46 healthy volunteers (mean age = 23 y, range not listed, 59% male)	Laboratory measure of self-aggression following single-dose placebo (n = 15), diazepam 5 mg (n = 16), diazepam 10 mg (n = 15)	Diazepam10 mg ↑ intensity of self-administered shocks, ↑ rates of selecting "severe" voltage (40% vs 6.7%, $P < .05$); diazepam 5 mg NS but trended in same direction
Cowdry and Gardner,[19] Gardner and Cowdry[20]	16 patients with borderline personality disorder (mean age = 32 y; range, 23–42 y; 100% female; 12 with prior overdoses; 10 with prior wrist cutting)	"Behavioral dyscontrol" during 6-wk crossover trials of placebo, alprazolam (mean daily dosage = 4.7 mg), carbamazepine (820 mg), trifluoperazine (7.8 mg), tranylcypromine (40 mg)	Alprazolam ↑ rates of severe behavioral dyscontrol (7/12 [58%] vs 2/14 [14%]; $P = .025$; eg, overdoses, deep neck cuts); carbamazepine ↓ severity of dyscontrol, others NS on measures of dyscontrol
Naturalistic outpatient studies			
Brent et al[21]	334 MDD patients (age range, 12–18 y; mean age and sexes not listed; all with prior nonresponse to 1 SSRI)	Suicidal adverse events (attempt or new/worsening ideation) and nonsuicidal self-injury during 12-wk antidepressant trial; BZDs (n = 10) were used at clinicians' discretion	BZDs ↑ rates of suicidal adverse events (60% vs 13%, $P < .001$) and nonsuicidal self-injury (40% vs 8%, $P = .009$)
Fontanella et al[22]	18,953 schizophrenia patients (mean age = 42 y; range, 18–58 y; 58% male)	Prescriptions and suicides over 6.5-y follow-up, adjusted for comorbidities	BZDs alone ↑ risk (HR = 2.80; 95% CI, 1.45–5.42), BZDs plus antipsychotics ↑ risk (HR = 3.96; 95% CI, 2.06–7.63)
Neutel and Patten[23]	225,796 new BZD prescriptions; 97,862 controls (aged > 20 y, mean age and sexes not listed)	Suicide attempts/completion within 60 days of starting BZD, stratified by antidepressant use (mostly TCAs), did not adjust for diagnosis	BZDs alone ↑ risk (adjusted OR = 6.2; 95% CI, 2.6–15.4), BZDs plus antidepressants NS (adjusted OR = 2.4; 95% CI, 0.6–10.2)
Park et al[24]	2,400 drug overdose deaths; 420,386 controls (aged ≥ 18 y, > 90% male); all US veterans on opioid analgesics	BZD prescriptions at time of death; adjusted for demographics, diagnosis, opioid dose; did not distinguish intentional vs unintentional overdose	BZD ↑ risk (adjusted HR = 3.86; 95% CI, 3.49–4.26), risk was dose dependent; temazepam ↓ risk vs clonazepam (adjusted HR = 0.63; 95% CI, 0.48–0.82)
Shih et al[25]	629 deliberate self-poisonings, 6,290 controls (mean age = 42 y; range, 20–? y; 67% female)	BZD prescriptions at time of suicide; adjusted for diagnoses of sleep, anxiety, mood, and psychotic disorders but not substance use	BZD ↑ risk (adjusted OR = 2.47; 95% CI, 1.93–3.17), regardless of whether recently initiated (< 1 wk) or longer term (up to 1 y)
Tiihonen et al[26]	2,588 first-episode schizophrenia patients (mean age = 38 y; range, 16–65 y; 62% male)	Prescriptions and suicides over mean 4.2-y follow-up; adjusted for other medications, age at diagnosis, and duration of first hospitalization	BZD ↑ risk (HR = 3.83; 95% CI, 1.45–10.12), antidepressants ↓ risk (HR = 0.15; 95% CI, 0.03–0.77), ≥ 2 antipsychotics NS (HR = 0.87; 95% CI, 0.32–2.34)
Tiihonen et al[27]	21,492 schizophrenia patients (mean age = 46 y; range, 16–65 y; 61% male)	Prescriptions and suicides over 5-y follow-up; adjusted for number of clinic visits attended, number of days in hospital, and illness duration	High-dose BZDs (eg, diazepam >15 mg/d) ↑ risk (adjusted HR = 2.16; 95% CI, 1.29–3.64), "high-dose" antipsychotics (eg, risperidone >7.5 mg/d) ↓ risk (adjusted HR = 0.43; 95% CI, 0.24–0.78), antidepressant NS
Voaklander et al[28]	602 suicides, 2,999 controls (mean age = 76 y; range, 66–? y; 72% male)	BZD prescriptions during 30 days preceding suicide; adjusted for demographics, comorbidities, other medications	BZDs ↑ risk (adjusted OR = 4.46; 95% CI, 3.25–6.11), both for all suicides and nonpoisoning suicides, whether or not BZD types/dosages conformed to Beers Criteria
Suicides or self-injury in hospital			
Gaertner et al[29]	61 inpatient suicides, 61 controls (median age = 40 y; range, 19–76 y; 51% male), matched for diagnosis	Medications during 10 days preceding suicide; the only BZD used was lorazepam	Lorazepam NS but reportedly trended toward ↑ in suicides, results were not clearly stated
Neuner et al[30]	118 inpatient suicides, 120 controls (mean age = 47 y, range not listed, 58% males), matched for diagnosis	Medications at the time of suicide	Reported separately by diagnosis; when combined, ↑ BZDs in suicides (63/118 [53%] vs 46/120 [38%], $P = .027$), ↑ FGAs in suicides (68/118 [58%] vs 52/120 [43%], $P = .029$), SGAs NS
Rothschild et al[31]	108 inpatients on alprazolam (mean age = 45 y; range, 19–82 y; 65% female), 111 on clonazepam (mean age = 47 y; range, 18–79 y; 65% female), 104 controls (mean age = 42 y; range, 19–80 y; 65% female), matched for diagnosis and hospitalization length	Rates of self-injury, assaults, loss of privileges, seclusion/restraints, need for increased observation (median daily dosages: alprazolam 2–2.9 mg and clonazepam 1–1.9 mg)	NS for self-injury (alprazolam 1.9%, clonazepam 1.8%, no BZD 2.9%), assaults (alprazolam 0%, clonazepam 0.9%, no BZD 1.0%), or other measures

(continued)

Table 1 (continued). Studies Assessing Prescribed Benzodiazepines and Suicide Risk

Study	Subjects[a]	Methods	Relevant Findings[b]
Taiminen[32]	25 inpatient suicides, 25 controls (mean age = 38 y; range, 19–62 y; 60% female), matched for diagnosis	Medications at the time of suicide	↑ BZDs in suicides (72% vs 44%, $P < .05$); antidepressant and antipsychotic rates NS; ↓ antipsychotic dosages in suicides (137 vs 197 chlorpromazine equivalents/d, on average, $P < .05$)
Taiminen and Kujari[33]	28 inpatient suicides, 28 controls (mean age = 33 y; range, 19–63 y; 57% female), all with psychotic disorders	Medications at the time of suicide, 14 of these suicides were also included in previous study[32]	BZDs NS but trend toward ↑ BZDs in suicides (64% vs 39%), all were taking antipsychotics, ↓ antipsychotic dosages in suicides (183 vs 279 chlorpromazine equivalents/d, on average, $P < .05$)
Suicide attempts just prior to hospitalization			
Barak et al[34]	101 suicide attempts, 101 controls (mean age = 77 y, all "elderly," 58% female), all with MDD	Preadmission medications, did not control for whether patient was in any form of psychiatric treatment	↓ BZDs in suicide attempts (14% vs 27%, $P = .026$), ↓ antidepressants (42% vs 57%, $P = .02$)
Raja et al[35]	129 suicide attempts (mean age = 45 y, 55% female); 1,233 admitted for other reasons (mean age = 42 y, age ranges not listed, 56% female)	Preadmission medications; did not match by or adjust for diagnosis, age, sex, or other variables	↑ BZDs in suicide attempts (43% vs 23%, $P < .001$), ↑ antidepressants (39% vs 16%, $P < .001$), ↓ antipsychotics (33% vs 50%, $P < .001$), ↓ antiepileptic mood stabilizers (23% vs 35%, $P = .006$), ↓ lithium (2% vs 11%, $P = .005$)

[a]Unless otherwise stated, populations are diagnostically heterogeneous.
[b]Unless otherwise stated, HR, OR, or rates are comparing BZD vs no BZD, medication vs placebo, or suicide vs no suicide.
Abbreviations: BZD = benzodiazepine, FGA = first-generation antipsychotic, HR = hazard ratio, MDD = major depressive disorder, NS = no significant association, OR = odds ratio, SGA = second-generation antipsychotic, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.
Symbols: ↑ = increased, ↓ = decreased.

Case-control studies comparing the medications of inpatients who either had or had not attempted suicide just prior to admission yielded mixed results. One such study[35] found greater benzodiazepine use among the suicide attempt group, and the other[34] found the opposite. Both studies were considerably limited, however, by not controlling for diagnosis[35] or not controlling for rates of outpatient psychiatric treatment as a whole.[34]

CONCLUSIONS

Benzodiazepines have been shown to increase aggression[36] and impair behavioral inhibition.[37,38] In particular, benzodiazepines may promote a dissociated type of aggression in which users view themselves as friendlier and less hostile but then respond in more aggressive ways to provocation.[39] Alcohol, another $GABA_A$ receptor modulator, has also been well established to enhance aggression,[40] and 1 animal study[41] found that benzodiazepine receptor antagonists such as flumazenil can block alcohol's proaggressive effects.

Impulsivity and aggression both appear to mediate suicide risk.[42] While many completed suicides involve planning and preparation, impulsivity may distinguish those individuals who carry out suicidal plans from those who plan for suicide but then decide against it.[42] A propensity toward impulsive aggression, which can be passed down between generations, may also be one factor in the intrafamilial transmission of suicidal behavior.[43]

The majority of studies identified in this review report a positive correlation between prescribed benzodiazepines and attempted or completed suicide. One possible interpretation is that anxiety and insomnia themselves (rather than the medications used to treat these symptoms) are responsible. Several factors, however, suggest that benzodiazepines may play a causal role[44]: the consistency across different studies and populations, the coherence between diverse lines of evidence (epidemiologic, clinical, laboratory-based, neurobiologic), the availability of experimental evidence,[18–20] the plausibility of the proposed mechanisms, and the analogy between prescribed use of benzodiazepines and nonmedical substance use, which is considered an important risk factor for suicide.[45] Moreover, some of the same studies linking benzodiazepines and suicide found that antidepressants and antipsychotics, which also may be used to manage anxiety and insomnia, either did not correlate with suicide or were associated with lower suicide rates.[26,27]

In some cases, benzodiazepines are used as an instrument of suicide. Taken in overdose, they can cause lethal respiratory suppression, particularly when combined with other depressants such as alcohol or opioids.[46] In 2013, for example, benzodiazepines were involved in 31% of all fatal prescription drug overdoses in the United States.[9] The US Food and Drug Administration[47] has since issued a black box warning regarding concurrent prescribing of opioids and benzodiazepines.

Rebound or withdrawal symptoms also may contribute to suicide risk. While benzodiazepines are intended to treat anxiety and insomnia, discontinuation, reduction in dosage, or missed doses may lead to emergence or exacerbation of these same symptoms. Abruptly stopping alprazolam, for example, has been shown to impair sleep onset and quality in healthy volunteers after as little as 2 weeks of daily use.[48] More research is needed to clarify the safest manner in which to taper benzodiazepines in patients at risk of suicide.

Several notes of caution are warranted in applying the results of this review to clinical practice. The prescribing of medications requires weighing possible risks against potential benefits for each individual patient. The results

of this review also do not rule out the possibility that benzodiazepines may be safe or perhaps even protective for certain patients at certain dosages.

Indeed, effects of benzodiazepines on aggression,[36] impulsivity,[49] and suicide[18,24,27] do appear to be dose dependent. In 1 study,[27] for example, increased suicide risk in patients with schizophrenia was only statistically significant at daily dosages equivalent to more than 15 mg of diazepam.

Effects on impulsivity and aggression also vary on the basis of individual characteristics, with greater risk in those patients with low anxiety and high baseline impulsivity or aggression.[36,49] Particular care should be used in those with histories of suicide attempts or violence. Disinhibition also may be more likely in children, seniors, those with degenerative central nervous system diseases such as dementia, and those with borderline or antisocial personality disorders compared to other groups.[20,49] Of note, clinical impressions of individuals' responses to benzodiazepines may be misleading, with some patients reporting benefit but then going on to behave more aggressively toward themselves or others.[19,20,39]

In theory, different benzodiazepines may vary in their level of risk, but the available evidence does not allow for clear comparisons. Most studies included in this review analyzed benzodiazepines as a class rather than separately. While Paton[49] suggests greater risk of disinhibition from high-potency benzodiazepines with shorter half-lives (eg, alprazolam), increased aggression is also well documented in response to the longer-acting, lower-potency diazepam.[36] The closely related "Z-drugs" (zolpidem, zaleplon, and eszopiclone) were not included in this review, but another recent article[50] examines the interplay between insomnia, the use of such hypnotics, and suicide.

Nonpharmacologic approaches, such as attending to sleep hygiene,[51] are important for clinicians to consider. Future research should also seek to identify safer medications for the acute management of insomnia and anxious distress in suicidal patients. Although a full review of the research regarding other classes of medications is beyond the scope of this article, several of the studies[27,32,33] cited here point to atypical antipsychotics as potential candidates to alleviate these symptoms without increasing the likelihood of suicide.

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Drug names: alprazolam (Xanax, Niravam, and others), carbamazepine (Tegretol, Epitol, and others), clonazepam (Klonopin and others), diazepam (Valium and others), eszopiclone (Lunesta), lorazepam (Ativan and others), risperidone (Risperdal and others), temazepam (Restoril and others), tranylcypromine (Parnate and others), zaleplon (Sonata and others), zolpidem (Ambien, Edluar, and others).

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