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# Benzodiazepine use for anxiety disorders is associated with increased long-term risk of mood and substance use disorders: A large-scale retrospective cohort study

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## HIGHLIGHTS

- Benzodiazepine prescriptions have risen over the last two decades.
- This 5-year retrospective study investigates the risks of long-term benzodiazepine use.
- Long-term benzodiazepine use is associated with mood and substance use disorders.
- Clinicians should be cautious about the risks of long-term benzodiazepine prescription.

## ARTICLE INFO

*Keywords:*
Benzodiazepines
Anxiety disorders
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## ABSTRACT

*Background:* Benzodiazepines (BZDs) are widely prescribed for anxiety disorders. However, the long-term implications on mental health remain uncertain, especially the potential association between chronic BZD use and subsequent diagnosis of mood and substance use disorders (SUDs).

*Method:* We conducted a 5-year retrospective cohort study by analyzing the TriNetX database, a real-time electronic medical record network. The study population was defined as patients aged 18–65 with anxiety disorders (ICD-10-CM: F40-F48). We employed propensity score matching to pair a BZD-exposed cohort (≥12 BZD prescriptions) with a BZD-unexposed control cohort. The outcomes were defined as depressive disorders, bipolar disorders, and SUDs. We employed Kaplan-Meier analyses to assess the survival probability over five years following diagnosis and BZD exposure; log-rank test to obtain the hazard ratio (HR) with 95 % confidence interval (CI).

*Results:* We identified and matched 76,137 patients in the study and control cohorts. Compared to the control cohort, the BZD-exposed group exhibited significantly higher risks of being diagnosed with depressive disorders (HR, 2.64; 95 % CI, 2.59–2.68), bipolar disorders (HR, 4.39; 95 % CI, 4.15–4.64), overall substance use disorders (HR, 3.00; 95 % CI, 2.92–3.08), alcohol use disorder (HR, 3.38; 95 % CI, 3.20–3.57), stimulant use disorder (HR, 3.24; 95 % CI, 2.95, 3.55), cannabis use disorder (HR, 2.93; 95 % CI, 2.75–3.11), inhalant use disorder (HR, 4.14; 95 % CI, 3.38–5.06), and nicotine use disorder (HR, 2.72; 95 % CI, 2.63–2.81).

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*Conclusion:* Our findings demonstrate a concerning association between BZD use and an increased risk of being diagnosed with various mood disorders and SUDs.

## 1. Introduction

Benzodiazepines (BZDs) are prescribed for anxiety and a variety of conditions including alcohol withdrawal, insomnia, seizures, panic disorder, and more (Wick, 2013). Despite the effectiveness, BZDs carry the potential for misuse. Furthermore, their ability to intensify euphoria when combined with opioids and stimulants could potentially lead individuals towards substance use disorders and increased mortality rates (Lader, 2014; Patorno et al., 2017). Given the frequent coexistence of anxiety disorders with substance use and mood disorders, the safety profile of BZD prescriptions in patients with anxiety disorders is therefore in question (Grant et al., 2004) (Saha et al., 2021).

Despite the concerns, the rate of BZD prescription has surged over the past two decades. Alprazolam, clonazepam, and lorazepam were among the top ten prescriptions for psychiatric medications (Moore and Mattison, 2017) with more than 1 in 20 people filling a prescription in the United States (Bachhuber et al., 2016). Between the mid-1990s and 2013, the prescription rate escalated by 67 %, accompanied by a three-fold increase in prescription quantity (Bachhuber et al., 2016). A similar pattern was observed in one study examining the pattern of BZD prescriptions in the ambulatory setting. (Agarwal and Landon, 2019). Of note, BZDs rank as the third most common illicit or prescription medicine misused among adults and adolescents in the U.S., coinciding with a rise in overdose mortality rates (Votaw et al., 2019). (Bachhuber et al., 2016). Although recent evidence suggested that overall BZD prescription slightly decreased in the period between January 2018 and March 2021, the overall picture of frequent prescription is still concerning. (Milani et al., 2021).

Although evidence outlines the potential association between BZD prescription and the subsequent diagnosis of substance use disorders other than BZD misuse, the correlation is yet to be determined. Likewise, there is ambiguity regarding the correlation between BZD prescriptions and the risk of future mood disorders. In this study, we aim to investigate the association between BZD prescriptions, mood disorders, and substance use disorders through a retrospective cohort study analysis of large-scale de-identified patient data.

## 2. Method

### 2.1. Study design and data source

We performed a retrospective cohort study using TriNetX Research Network, which provides access to de-identified electronic medical records including diagnoses, procedures, medications, and laboratory values. TriNetX Networks are composed of healthcare organizations across 25 countries, including, but not limited to, the United States, Brazil, Germany, Italy, the United Arab Emirates, Japan, Taiwan, Malaysia. Data came from academic medical centers, including their affiliated or owned ambulatory physician practices, clinics, main and satellite hospitals, specialized treatment centers, and more. Most healthcare organizations refresh their data with an average interval of 2–4 weeks. We obtained data from July 23, 2019, to July 23, 2024, including patient demographics and comorbidities. Upon the time of conducting the analysis, we obtained this data from approximately 117 million patients across 83 healthcare organizations. about 90 % of our patients were in the US. The Carilion Clinic Institutional Review Board (IRB) determined that this study does not meet the definition of human subject research, and therefore did not require IRB approval.

### 2.2. Cohorts and statistic

The BZD cohort (study cohort) was defined as patients aged 18–65 with anxiety disorders (ICD-10-CM: F40-F48) prescribed at least one BZD; the control cohort was defined as patients aged 18–65 with anxiety disorders (ICD-10-CM: F40-F48) without any BZD prescription history. The first incidence of BZD prescription must happen within a month of the anxiety disorder diagnosis. Patients in the BZD cohort must have at least 12 prescriptions on file.

We excluded patients with pre-existing mood disorders (ICD-10-CM: F30-F34), substance use disorder (ICD-10-CM: F10-F19), psychotic disorders (ICD-10-CM: F20-F29) and behavioral syndromes associated with physiological disturbances and physical factors (ICD-10-CM: F50-F59). Patients in the two cohorts were matched by gender, age, race, ethnicity, and 10 common medical conditions including family history of mental illness at a 1:1 ratio by propensity scoring, and then underwent Kaplan–Meier analysis and Cox proportional hazards model with association analysis.

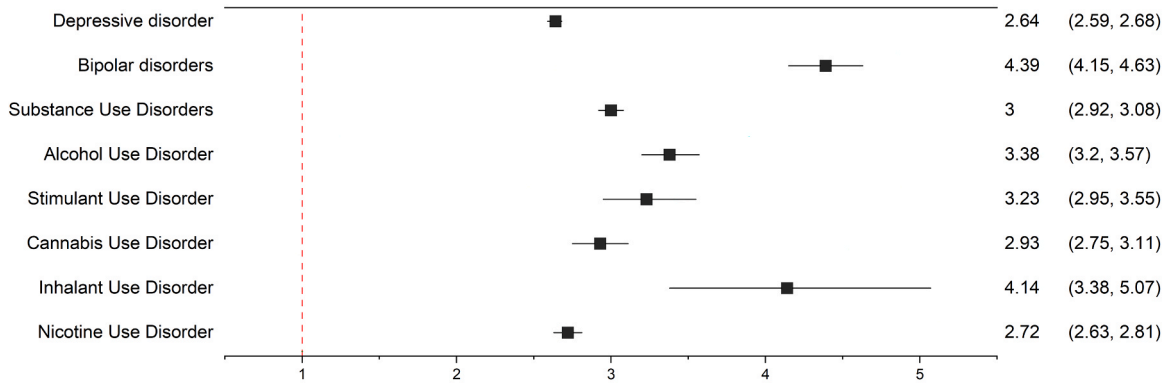


**Fig. 1.** Hazard ratio significance of depressive disorders, bipolar disorders, and substance use disorders difference in the BZD cohort versus the control cohort. Depressive disorders were defined as diagnoses including depressive episode (F32), major depressive disorder, recurrent (F33), and dysthymic disorder (F34.1). Bipolar disorders were defined as diagnoses including manic episode (F30), bipolar disorder (F31), and cyclothymic disorder (F34.0). Substance use disorders were defined as mental and behavioral disorders due to psychoactive substance use (F10-F19). Base rates of participants developing each disorder were provided in supplement 1.

The index event was defined as the time subjects were diagnosed with anxiety; identified outcomes included diagnoses of depressive disorders, bipolar disorders, and substance use disorders within 5 years after the index event. Depressive disorders included a depressive episode (ICD-10-CM: F32), major depressive disorder, recurrent (ICD-10-CM: F33), and dysthymic disorder (ICD-10-CM: F34.1). Bipolar disorders included a manic episode (ICD-10-CM: F30), bipolar disorder (ICD-10-CM: F31), and cyclothymic disorder (ICD-10-CM: F34.0). We defined the significance level as $p<0.05$. Statistical analysis was performed using TriNetX Analytics, an analytic tool embedded within the TriNetX platform. This study followed the STROBE cohort reporting guideline.

## 3. Result

We identified and matched 76,137 individuals in the BZD cohort and the control cohort during the examined timeframe. Compared with the control cohort before matching, subjects included in the BZD cohort were more likely to be non-Hispanic or Latino (65.2 % v.s. 63.8 %, $P < 0.001$) and white race (67.1 % v.s. 65.4 %, $p<0.001$) (Supplement 1).

We found patients prescribed BZDs were more likely to be diagnosed with depressive disorders (Hazard Ratio [HR], 2.64; 95 % CI, 2.59–2.68), bipolar disorders (HR, 4.39; 95 % CI, 4.15–4.64), overall substance use disorders (HR, 3.00; 95 % CI, 2.92–3.08), alcohol use disorder (HR, 3.38; 95 % CI, 3.20–3.57), stimulant use disorder (HR, 3.24; 95 % CI, 2.95, 3.55), cannabis use disorder (HR, 2.93; 95 % CI, 2.75–3.11), inhalant use disorder (HR, 4.14; 95 % CI, 3.38–5.06), and nicotine use disorder (HR, 2.72; 95 % CI, 2.63–2.81) during the five-year period following the diagnosis and initial BZD prescription. The hazard ratio of all the outcomes is illustrated in Fig. 1 and Supplement 2. We could not draw any conclusion on sedative/hypnotic/anxiolytic use disorders and opioid use disorder since the hazard ratio was not valid with a $p>0.05$. Kaplan–Meier analysis showed the survival probability at the end of the time window was 36.4 % for the study cohort and 66.4 % for the control cohort in depressive disorders; 88.4 % for the study cohort and 97.1 % for the study cohort in bipolar disorders; 63.6 % for the study cohort and 85.6 % for the control cohort in substance use disorders. (Supplement 3)

## 4. Discussion

Patients with anxiety disorders prescribed benzodiazepines were more likely to be diagnosed with depressive disorders, bipolar disorders, and substance use disorders during the 5-year follow-up period compared to their control counterparts. Our study highlights that long-term BZD use is related to substance use disorders including stimulants, cannabis, alcohol, inhalants, and nicotine-related conditions. We did not obtain a valid conclusion on sedative/hypnotic/anxiolytic use disorders or opioid use disorders due to the limited number of patients with the designed outcome. We believe patients chronically on BZDs might be less likely to be diagnosed with a sedative/hypnotic/anxiolytic use disorder because they are obtaining the BZDs from a prescriber. Regarding the demographics, we found patients prescribed BZDs were more likely to be middle-aged Caucasian individuals who were older than their control cohort counterparts. BZD prescription differences in race and age are unclear, but discrimination against racial minorities and avoiding BZD in racial minorities are possible explanations. (Cook et al., 2018)

Limited literature explains the correlation between BZDs, alcohol, and opioid use disorders. We assume the correlation might be a result of their shared mechanism: central nerve system (CNS) depression. BZDs act as allosteric modulators of gamma-aminobutyric acid (GABA)-A receptors. BZDs upregulate chloride channels opening frequency across the neuronal membrane, causing negatively charged ion influx resulting in hyperpolarization. (Crocetti and Guerrini, 2020). In a similar manner, alcohol acts as an agonist at GABA-A receptors, which leads to hyperpolarization via the influx of chloride ions. (Lobo and Harris, 2008). Opioids work differently and increase potassium efflux and decrease calcium influx causing hyperpolarization and CNS depression. (Pathan and Williams, 2012). Patients who misuse BZDs might seek an alternative substance for the same effect, which explains the increased risk of alcohol use disorder and opioid use disorder in our study. Though the underlying mechanism above is based on our assumption, the fatal combination of BZDs and opioids has been well studied. Concomitant prescriptions of BZDs and opioids have grown over the last few years leading to an increased risk of overdose from opioids (Sun et al., 2017) (Dasgupta et al., 2016) (Park et al., 2015), which solidifies the correlation between CNS depressants. In our study, results on opioid use disorder did not show statistical significance. We assumed that it could be a result of clinicians avoiding prescribing an opioid to patients who are taking a BZD.

It is difficult to explain the correlation between BZDs and substance use disorders that do not involve a shared mechanism. However, the common neurobiology behind addiction might provide a possible explanation. When BZDs bind to the alpha-1 subunit on GABA-A receptors, they activate the dopaminergic neurons in the ventral tegmental area (VTA). Dopaminergic neuron activation leads to disinhibition and other neurobiological changes central to the mechanism of addiction in general (Tan et al., 2010) (Riegel and Kalivas, 2010). Underdiagnosing other substance use disorders at the time of BZD prescriptions may be another explanation since BZD misuse customarily occurs in coexistence with other drugs, primarily with opioids and alcohol. Patients with substance use disorders may use BZDs to elevate the effects of other drugs, curb the excitation from stimulants, or ameliorate withdrawal symptoms from CNS depressants. (Edinoff et al., 2021)

The correlation between BZD prescriptions and depressive disorders has not been studied at a biochemical level, but the phenomenon is well-documented. Evidence suggests that BZDs trigger the onset and worsening of depressive symptoms (Lydiard et al., 1987; Vankova et al., 2021). Additionally, both chronic BZD use and BZD withdrawal can cause or intensify depression (Ashton, 1991) (Cosci and Chouinard, 2020). While there is no distinct explanation behind the exacerbation or onset of depressive symptoms in patients treated with BZDs, there are several hypotheses: 1) BZDs decrease the turnover of serotonin, norepinephrine, and other amines causing their depletion which contributes to depressive symptoms, (Wise et al., 1972), 2) BZD use is associated with rebound insomnia which is a known risk factor of depression (Li et al., 2016;Margareten, 2011), 3) BZDs could potentially stimulate the production of IL-6, a pro-inflammatory cytokine, which is involved in the pathophysiology of depression (Roohi et al., 2021) (Cornwell et al., 2023). According to our results, patients with BZD use are at risk of substance use disorders, which may indirectly increase the risk of mood disorders. Individuals with severe anxiety may use substances to cope with their symptoms that can predispose to the development of a substance use disorder (Arunogiri, Lubman, 2015; Hides et al., 2008). There is a possibility that BZDs were more likely to be prescribed to individuals with severe anxiety who could subsequently develop substance use disorders as strong associations exist between substance use disorders and anxiety disorders (Grant et al., 2004)

Another outcome highlighted in our study is that the risk of bipolar disorders in patients prescribed BZDs was about four times higher compared to their control cohort counterparts. Cognitive deficits from BZD use could worsen bipolar symptoms and delay the recovery process (Gruber et al., 2008; Clark and Sahakian, 2008; Otheman et al., 2018). Studies further show that BZD use was associated with a higher risk of recurrence of either depressive, hypomanic, manic, or mixed states amongst patients with bipolar 1 and 2 disorders. (Perlis et al., 2010). BZD's detrimental effects including sedation and memory difficulties could compromise medication adherence, thereby increasing the risk of recurrence of manic episodes (Perlis et al., 2010). An alternative explanation to our study result is the possibility of underlying undiagnosed bipolar disorder in patients prescribed BZDs. Since sleep disturbance is a part of bipolar symptomology, clinicians might start the BZD

**Table 1**
Baseline characteristics: demographic data of the patients with anxiety disorders prescribed at least one BZD compared with a matched control cohort of patients with anxiety disorders without a BZD prescription.

| | BZD Cohort | Control cohort | |
|---|---|---|---|
| | n (%) | n (%) | p-value |
| Total population | 76,137 (100) | 76,137 (100) | - |
| Mean Age at Index (Year+/-SD) | 44.2 +/- 12.5 | 43.6 +/- 13.7 | <0.001 |
| **Gender** | | | |
| Male | 22,925 (30.1) | 23,172 (30.4) | 0.168 |
| Female | 46,677 (61.3) | 46,648 (61.3) | 0.879 |
| Unknown | 6535 (8.6) | 6317 (8.3) | 0.044 |
| **Ethnicity** | | | |
| Not Hispanic or Latino | 49,600 (65.1) | 50,893 (66.8) | <0.001 |
| Unknown Ethnicity | 22,905 (30.1) | 21,347 (28.1) | <0.001 |
| Hispanic or Latino | 3632 (4.8) | 3897 (5.1) | 0.002 |
| **Race** | | | |
| White | 51,079 (67.1) | 51,355 (67.5) | 0.132 |
| Other | 2358 (3.1) | 2250 (3.0) | 0.106 |
| Black African American | 4374 (5.7) | 4385 (5.8) | 0.904 |
| Asian | 1698 (2.2) | 1752 (2.3) | 0.352 |
| American Indian or Alaska Native | 224 (0.2) | 242 (0.2) | 0.404 |
| Native Hawaiian or Other Pacific Islander | 145 (0.2) | 137 (0.2) | <0.001 |
| Common conditions (ICD−10-CM code) | | | |
| Disorders of thyroid gland (E00-E07) | 8642 (11.4) | 9010 (11.8) | 0.003 |
| Diabetes mellitus (E08-E13) | 6520 (8.6) | 6666 (8.8) | 0.007 |
| Asthma (J45) | 8157 (10.7) | 9071 (11.9) | <0.001 |
| Chronic kidney disease (N18) | 2042 (2.7) | 2154 (2.8) | 0.080 |
| Diseases of liver (K70-K77) | 4194 (5.5) | 4452 (5.8) | 0.004 |
| Family history of other mental and behavioral disorders (Z81.8) | 422 (0.6) | 487 (0.6) | 0.031 |
| Migraine (G43) | 7947 (10.4) | 8711 (11.4) | <0.001 |
| Sleep apnea (G47.3) | 4936 (6.5) | 5355 (7.0) | <0.001 |
| Insomnia (G47.0) | 8724 (11.5) | 9827 (12.9) | <0.001 |
| Overweight and obesity (E66) | 9819 (12.9) | 10,288 (13.5) | <0.001 |
| Neoplasms (C00-D49) | 15,144 (19.9) | 16,322 (21.4) | <0.001 |
| Generalized anxiety disorder (F41.1) | 15,500 (20.4) | 15,651 (20.6) | 0.337 |
| Panic disorder [episodic paroxysmal anxiety] (F41.0) | 5275 (6.9) | 5147 (6.8) | 0.194 |
| Phobic anxiety disorders (F40) | 2201 (2.9) | 2162 (2.8) | 0.549 |
| Post-traumatic stress disorder (F43.1) | 4370 (5.7) | 3904 (5.1) | <0.001 |
| Adjustment disorders (F43.2) | 4029 (5.3) | 4427 (5.8) | <0.001 |
| Obsessive-compulsive disorder (F42) | 1857 (2.4) | 1970 (2.6) | 0.064 |

prescription for sleep management before the patient is determined to have bipolar disorder.

### 4.1. Limitations

There are limitations in this study. First, due to the nature of retrospective cohort studies, the causality of BZD prescription and subsequent mood disorders and substance use disorders is unclear. Anxiety disorders are highly comorbid with mood disorders (Tiller, 2013, Yang et al., 2019). Mood disorders could be secondary to anxiety disorders instead of the consequence of BZD use. Patients with undiagnosed substance use disorders and drug-seeking behavior could have a pre-existing condition at the time of initial BZD prescription. On the other hand, BZDs might be prescribed for conditions other than anxiety, such as insomnia. Despite the propensity match, there might be participants with undocumented insomnia, which could be comorbid with substance use disorder. Second, the selection of participants might contribute to bias. Due to the analytic tool limitations, we could not provide information on how many participants were excluded due to pre-existing conditions defined in the methodology. Third, we did not assess the severity of anxiety and the categories of anxiety diagnosis as the inclusion criteria, which could be a potential confounding factor. Third, our study results may not apply to other countries since 90 % of the patient information was obtained in the United States.

## 5. Conclusion

Our study suggests patients with anxiety disorders prescribed BZDs are at a higher risk for mood disorders and substance use disorders. It is important for clinicians to exercise caution before prescribing BZDs. Further studies in a clinical setting are warranted to clarify the causality of BZDs, in the development of mood disorders and substance use disorders.

## Author disclosures

Ching-Fang Sun and Binx Y. Lin are American Psychiatric Association (APA) Fellows at the time of publication. This manuscript is solely the responsibility of the author, not necessarily represent the official views of APA.

## CRediT authorship contribution statement

**Ching-Fang Sun:** Writing – original draft, Project administration, Investigation, Formal analysis, Conceptualization. **Robert L. Trestman:** Writing – review & editing, Supervision, Resources. **Binx Y. Lin:** Writing – review & editing. **Anita S. Kablinger:** Writing – review & editing, Supervision, Resources. **Akhil S. Pola:** Writing – original draft, Project administration. **Kuan-Pin Su:** Writing – review & editing.

## Declaration of Competing Interest

We declare no conflict of interest by any authors.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dadr.2024.100270.

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