Patients with Anxiety Disorders Prescribed with Benzodiazepine Are at Higher Risk of Mood Disorders and Substance Use Disorders

Ching-Fang Sun, MD[1], Yezhe Lin, MD[1-3], Akhil S. Pola, MBBS[1], Anita S. Kablinger, MD[1], PCI, Robert L. Trestman, PhD, MD[1] 1 Department of Psychiatry and Behavioral Medicine, Virginia Tech Carilion School of Medicine, Roanoke, Virginia, USA. 2 Clinical Research Center for Mental Disorders, Shanghai Pudong New Area Mental Health Center, Tongji University, Shanghai, China 3 Department of Psychiatry, Shanghai East Hospital, School of Medicine, Tongji University, Shanghai, China

Background:

- Benzodiazepines (BZDs) have been well established and widely prescribed for anxiety and related disorders.
- Safety concerns of BZD dependence, withdrawal and tolerance are well-known to clinicians.
- Potential long-term effects of BZDs on mental health are unclear.
- Considering BZD's central nervous system properties, the risk of developing a subsequent depression is in question.

Method:

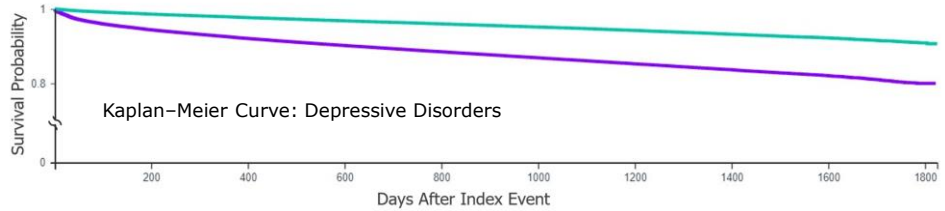
- **Study Design and Sampling:** We conducted a retrospective cohort study using TriNetX Analytics, a tool built with a real-time electronic medical record network. Data was collected from September 09, 2017 to September 09, 2022 from 60 healthcare organizations. About 80% of patients were located in the US. We included patients age 18-65 with anxiety disorder who were prescribed at least one BZD. Index event was defined by the time of anxiety diagnosis along with a prescription.
- **Exclusion Criteria:** Patients in all cohorts were excluded if they had a diagnosis of prior mood disorders (ICD-10: F30-F34), substance use disorder (ICD-10: F10-F19), psychotic disorders (ICD-10: F20-F29) and behavioral syndromes associated with physiological disturbances and physical factors (ICD-10: F50-F59).
- **Cohorts:** The study cohort was defined as patients age 18-65 with anxiety disorders (ICD-10-CM: F40-F48) prescribed with at least one BZD; the control cohort was defined as patients age 18-65 with anxiety disorders (ICD-10-CM: F40-F48) with no BZD prescription during the five-year timeframe examined.

	BZD Cohort	Control cohort	
	n (%)	n (%)	p value
Total population	705,850 (100)	1,131,153 (100)	
Gender			
Male	228,596 (32.4)	375,721 (33.2)	< 0.0001
Female	477,142 (67.6)	754,926 (66.7)	< 0.0001
Unknown	112 (0)	506 (0)	N/A
Ethnicity			
Not Hispanic or Latino	464,651 (65.8)	706,678 (62.5)	< 0.0001
Unknown Ethnicity	203,583 (28.8)	342,437 (30.3)	< 0.0001
Hispanic or Latino	37,616 (5.3)	82,038 (7.3)	< 0.0001
Race			
White	513,947 (72.8)	781,391 (69.1)	< 0.0001
Unknown	95,326 (13.5)	174,419 (15.4)	< 0.0001
Black African American	82,378 (11.7)	140,910 (12.5)	< 0.0001
Asian	11,017 (1.6)	28,867 (2.6)	< 0.0001
American Indian/Alaska	2,393 (0.3)	3,949 (0.3)	< 0.0001
Native			
Native Hawaiian/Other Pacific	789 (0.1)	1,617 (0.1)	0.257
Islander			

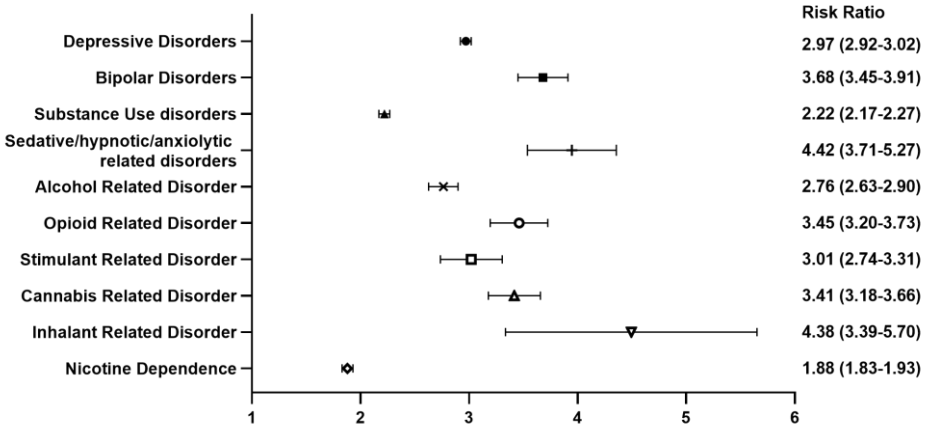
- **Statistic:** Patients in the two cohorts were matched by gender, age, race, ethnicity and common medical conditions at a 1:1 ratio by propensity scoring and then underwent Kaplan–Meier analysis and association analysis.

Results:

- A total of 652,314 patients were identified and matched for analysis. Patients in the study cohort were more likely to be female, non-Hispanic and white.
- Kaplan–Meier analysis showed the survival probability at the end of the time window was 90.4% for the control cohort and 79.9% for the study cohort (Hazard Ratio [HR] 2.97; 95% CI, 2.92-3.01; P < 0.001) in depressive disorders; 99.4% for the control cohort and 98.4% for the study cohort (HR, 3.55; 95% CI, 3.33-3.78; P < 0.001) in bipolar disorders; 94.0% for the control cohort and 88.9% for the study cohort (HR, 2.18; 95% CI, 2.13-2.22; P < 0.001) in substance use disorders.



- Patients with anxiety disorders been prescribed BZDs were at a higher risk of depressive disorders (Risk Ratio [RR], 2.97; 95% CI, 2.92-3.02), bipolar disorders (RR, 3.68; 95% CI, 3.45-3.91), substance use disorders (RR, 2.22; 95% CI, 2.17-2.27) during the five-year period following the diagnosis and prescription.



Conclusion:

- Patients with anxiety disorder prescribed BZDs are at higher risk of mood disorders and substance use disorders than a matched cohort not prescribed BZDs.
- Clinicians should carefully consider BZD prescribing and inform the patient about an increased risk of mood disorders and substance use disorders.
- Further studies are indicated to clarify the potential causal relationship between BZDs and depressive disorders.

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