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ORIGINAL RESEARCH

Benzodiazepine Use Among Patients Receiving Methadone Maintenance Treatment: A Descriptive Study

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Purpose: This study aimed to investigate the patterns and characteristics of benzodiazepine (BZD) use among patients receiving methadone maintenance treatment (MMT).

Methods: A total of 80 participants (40 with and 40 without BZD use) were recruited from the MMT clinic of the Affiliated Kangning Hospital of Ningbo University between April 2024 and March 2025. All participants were assessed using the BZD Use Questionnaire (BUQ), the Chinese version of Barratt impulsiveness scale (BIS-C), the Self-rating Anxiety Scale (SAS), the Self-rating Depression Scale (SDS), and the Quality of Life Scale for Drug Addicts (QOL-DA).

Results: Among 80 initially selected participants, 71 (BZD group: n=39; non-BZD group: n=32) were included in the final analysis after exclusions for invalid data. In univariate comparisons, the BZD group had a significantly higher prevalence of comorbid mental, sleep, and chronic disorders, higher scores on impulsivity (total, motor, and non-planning), anxiety, and depression scales, and lower scores on the total score as well as the psychological and symptoms/side effects domains of the QOL-DA (all $P < 0.05$). However, after adjusting for potential confounders, multivariate regression analyses indicated that BZD use was independently associated with higher anxiety levels ($\beta = 0.279$, $P < 0.05$) and greater total impulsivity ($\beta = 0.439$, $P < 0.001$). Regarding impulsivity subscales, BZD use was independently associated with non-planning ($\beta = 0.265$, $P < 0.05$) and motor impulsivity ($\beta = 0.345$, $P < 0.05$), but not with attentional impulsivity. No significant independent associations were found between BZD use and depression or any domain of quality of life (all $P > 0.05$).

Conclusion: BZD use was independently associated with higher levels of impulsivity and anxiety after controlling for key comorbidities, but not with depression or QOL. The causal direction between BZD use and increased impulsivity/anxiety in MMT patients remains unclear, potentially reflecting either pharmacological effects or pre-existing higher levels of impulsivity or anxiety.

Keywords: methadone maintenance treatment, benzodiazepines, impulsivity, anxiety, depression, quality of life

Introduction

Opioid use disorder (OUD) is a chronic, relapsing brain disease characterized by compulsive drug seeking and use despite harmful consequences, accompanied by profound neurochemical and molecular changes.[1] It poses a major public health challenge, being closely associated with increased morbidity, mortality, and criminal behaviour. OUD is also strongly linked to injection drug use, a major driver of blood-borne viral infections such as hepatitis C virus (HCV) and human immunodeficiency virus (HIV).[2] Methadone maintenance treatment (MMT), a substitution therapy for OUD, is one of the most widely implemented and effective interventions for preventing relapse, reducing opioid-related crime, and curbing the transmission of infectious diseases such as HIV/AIDS.[3]

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Benzodiazepines (BZDs), first introduced in the 1960s (eg, chlordiazepoxide), quickly gained clinical popularity due to their improved safety profile over barbiturates.[4] They are commonly prescribed for both psychiatric and non-psychiatric conditions, including anxiety, insomnia, seizures, and pain.[5] However, long-term use leads to the development of tolerance and dependence,[4] and continuous prescription is generally discouraged. Despite this, BZD misuse remains a global concern.[6] Individuals with a personal or family history of substance use disorders are particularly vulnerable to BZD misuse.[7] Co-use of BZDs with opioids is a major clinical risk factor for overdose.[8] Although BZDs are mild respiratory depressants when used alone, their concurrent use with opioids can lead to profound respiratory suppression.[9] Notably, individuals who filled prescriptions for a BZD in addition to an opioid had a nearly 15-fold greater risk of drug-related death than individuals not prescribed either drug.[10]

Recent data indicate a sharp rise in emergency visits and overdose fatalities linked to combined opioid–BZD use, exceeding the rates attributed to either substance alone.[11,12] Substantial evidence demonstrates that this combination heightens the risk of severe respiratory and fatal outcomes.[9,13] Patients with OUD undergoing methadone or buprenorphine maintenance therapy are especially susceptible to BZD misuse,[14] with usage rates as high as 66% in some methadone clinics.[15] In an Israeli cohort, lifetime BZD misuse among MMT patients was 66.3%, with current misuse rates at 50.8%, and approximately half of users initiated BZD use after entering the methadone program.[10]

BZD users in MMT programs often differ physiologically from general BZD users, presenting with older age, multiple comorbidities (eg, HCV or HIV from previous syringe sharing), and impaired hepatic, renal, pulmonary, and immune function.[16,17] Such physiological vulnerabilities amplify the risk of adverse reactions, particularly respiratory depression and fatal overdose when opioids are concurrently used.[9] In China, national MMT guidelines explicitly prohibit the concomitant use of BZDs.[18]

Accumulating evidences suggest that impulsivity may be a behavioral marker of the propensity to take addictive drugs.[19,20] Patients with opioid, cocaine, or amphetamine use disorders exhibit significantly higher impulsivity than healthy controls.[21–23] Impulsivity also predicts treatment retention and relapse risk; higher impulsivity is associated with shorter durations in maintenance therapy.[24,25]

Unlike illicit drugs such as opioids and cocaine, BZDs are prescription medications with recognised clinical applications. However, many former opioid users in MMT programs continue to experience persistent psychological and physical distress — such as anxiety, depression, pain, and protracted withdrawal symptoms — even after opioid cessation. Consequently, some may self-medicate with BZDs to alleviate these symptoms without medical supervision.[26]

However, it remains unclear whether MMT patients using BZDs exhibit distinct patterns of impulsivity, anxiety, depression, and quality of life (QOL) compared with non-users. We hypothesized that concurrent BZD users would demonstrate higher levels of impulsivity, anxiety, and depression, along with lower QOL, than non-users. To test this hypothesis and clarify these associations, this study aimed to retrospectively examine the characteristics of MMT patients concurrently using BZDs through the administration of standardized psychological and behavioural assessments.

Materials and Methods

Participants

This study was approved by the Ethics Committee of the Affiliated Kangning Hospital of Ningbo University (Approval No.: NBKNYY-2024-LC-12) and conducted in accordance with the Declaration of Helsinki. This study was registered at the Chinese Clinical Trial Registry (ChiCTR2400086237). All participants provided written informed consent prior to enrollment. Participants were recruited from the MMT clinic of the Affiliated Kangning Hospital of Ningbo University between April 2024 and March 2025.

Inclusion Criteria

Participants were eligible if they met all of the following conditions: (1) enrollment in MMT for more than 12 months; (2) age between 18 and 60 years; (3) absence of severe physical or psychiatric disorders; (4) no impairment in verbal communication; and (5) use of BZDs within the preceding six months.

Exclusion Criteria

Participants were excluded if they (1) had severe physical or psychiatric illnesses interfering with participation; (2) exhibited intellectual disabilities or language disorders; or (3) engaged in concurrent use of other addictive substances (eg, methamphetamine, cannabis).

The source population comprised 158 patients identified from the clinic registry. Using a structured questionnaire, we classified them as 73 BZD users and 85 non-users, with a target sample size of 40 per group based on practical feasibility, available resources, and precedents from similar cross-sectional studies. To obtain two equally sized and comparable groups while minimizing selection bias, we implemented a sequential, randomization-based recruitment procedure. Separate random sequences were computer-generated for the BZD user list (n=73) and the non-user list (n=85). Based on an estimated 75–80% combined consent and eligibility rate from previous similar studies in this clinic, we planned to contact the first 50 individuals from each randomized list. Invitations were issued strictly according to this pre-generated random order; if a contacted individual was unreachable, declined, or was ineligible, the next sequentially listed individual was immediately invited. This process continued until 40 eligible participants were enrolled per group or the list was exhausted. Recruitment was completed after inviting the 48th individual in the BZD user list and the 52nd in the non-user list. Neither group exhausted its full list, resulting in a final sample of 80 participants (40 per group). Throughout the process, the research team was blinded to the allocation sequence to minimize selection bias.

Medication

All participants had received MMT for more than 12 months. Methadone doses remained stable after the induction phase, ranging from 25 mg to 140 mg daily. Dosing followed an individualized titration principle aimed at achieving optimal control of withdrawal symptoms and cravings, ensuring subjective tolerability, and preventing adverse effects on consciousness or occupational functioning.

In this study, any self-reported use of BZDs within the six months prior to assessment was operationally defined as misuse, based on Chinese MMT guidelines which prohibit concomitant BZD use due to the well-established risk of severe respiratory depression from BZD-opioid interactions.

Measurements

We assessed BZD use characteristics, impulsivity, anxiety, depression, and QOL in 80 MMT patients using validated instruments administered by trained psychologists.

BZD Use Questionnaire (BUQ)

The BUQ, an interviewer-administered tool utilizing open-ended questions, documented BZD use characteristics and patterns. Data collection covered (1) demographic information (eg, gender, age) and (2) use characteristics (eg, route of administration, reasons for use); complete data are shown in Tables 1 and 2.

The diagnosis of comorbid conditions—primarily including mental disorders, sleep disorders, and chronic diseases—was based on participant self-report and clinical records from methadone maintenance clinics. To enhance the reliability of the data, electronic health records from these clinics were used, with participants' informed consent, to cross-verify and supplement self-reported diagnoses for specific conditions.

Chinese Version of Barratt Impulsiveness Scale-11 (BIS-11-C)

The Barratt Impulsiveness Scale (BIS) is a self-report instrument measuring impulsive personality traits.[27] The Chinese version, adapted by Zhou Liang et al,[28] demonstrates strong reliability and validity in Chinese populations. BIS-11-C includes 30 items forming three dimensions—attentional, non-planning, and motor impulsiveness. Higher scores indicate greater impulsivity.[29]

Table 1 Demographic Characteristics of the Study Participants

Characteristics	BZD (n=39)	Non-BZD (n=32)	P-Value
Age (years)	37.33 ± 6.92	34.56 ± 7.10	0.101
Gender (n,%)			0.585
Male	32 (82.1%)	26 (81.3%)	
Female	7 (17.9%)	6 (18.7%)	
Marital (n,%)			0.846
Married	21 (53.8%)	17 (53.1%)	
Unmarried	9 (23.1%)	6 (18.8%)	
Divorced	9 (23.1%)	9 (28.1%)	
Occupation (n,%)			0.941
Full-time	7 (17.9%)	5 (15.6%)	
Part-time	18 (46.2%)	16 (50.0%)	
Unemployed	14 (35.9%)	11 (34.4%)	
Years of education (years)	9.26 ± 1.80	8.98 ± 1.69	0.494
Family relation (n,%)			0.897
Harmonious	5 (12.8%)	3 (9.3%)	
General	18 (46.2%)	15 (46.9%)	
Inharmonious	16 (41.0%)	14 (43.8%)	
Medical conditions (n,%)			
Sleep disorder	27 (69.2%)	15 (46.9%)	0.048*
Mental disorder	22 (56.4%)	10 (31.3%)	0.029*
Chronic disease	23 (59.0%)	11 (34.4%)	0.033*
HIV/AIDS	2 (5.1%)	1 (3.1%)	0.575
Age of initial opioid use (years)	23.92 ± 5.78	25.13 ± 5.88	0.389
Duration in MMT (months)	52.31 ± 20.87	54.00 ± 29.39	0.778

Notes: Data are presented as mean ± SD or n (%). Continuous variables were compared using the Student's *t*-test, and categorical variables were compared using the Chi-square test. *P < 0.05 for the BZD group vs the non-BZD group.

Self-Rating Anxiety Scale (SAS)

Developed by Zung in 1971,[30] the SAS comprises 20 items rated on a four-point Likert scale (1–4), reflecting symptom frequency over the preceding week. The raw score is multiplied by 1.25 to obtain a standardized score: <50 indicates no anxiety; 50–59 mild; 60–69 moderate; ≥70 severe anxiety. The Chinese version has shown good psychometric properties.[31,32]

Self-Rating Depression Scale (SDS)

The SDS is a 20-item self-report measure of depressive symptoms.[33,34] Each item is rated from 1 to 4, with the raw score multiplied by 1.25 to yield a standard score: <53 indicates no depression; 53–62 mild; 63–72 moderate; ≥73 severe depression. The Chinese version demonstrates good reliability and validity.[31,32]

Table 2 Characteristics of BZD Use among Study Participants

Characteristics	BZD (n=39)
Route of administration (n,%)	
Oral	31 (79.5%)
Intravenous injection	8 (20.5%)
Reason for BZD use (n,%)	
Recreational purposes	11 (28.2%)
Improve insomnia	13 (33.3%)
Improve anxiety (or depression) symptoms	10 (25.6%)
Withdrawal of opioid	5 (12.8%)
Original BZD use	
Before MMT	12 (30.8%)
After MMT	27 (69.2%)
Attitude to use of BZDs	
Danger	17 (43.6%)
No danger	22 (56.4%)
Drug source (n,%)	
Prescription drugs	7 (17.9%)
Family member or friend	13 (33.3%)
Illicit market	19 (48.8%)
Place of use (n,%)	
Own home	32 (82.1%)
Other locations	7 (17.9%)
Duration for BZD use (months)	25.08 ± 18.96
Interval of BZD use (days)	5.54 ± 3.94

Notes: Continuous variables are presented as mean ± SD; categorical variables are presented as n (%). Since participants were allowed to select multiple reasons for BZD use, the percentages sum to more than 100%.

Quality of Life Scale for Drug Addicts (QOL-DA)

The QOL-DA assesses quality of life in patients with substance use disorders.[35] It contains 41 items across four domains —physical function, psychological function, symptoms/side effects, and social function—rated on a five-point Likert scale (from 1 to 5). Higher scores indicate better QOL.

Data Analysis

Statistical analyses were conducted using SPSS version 26.0. Descriptive analyses were performed to determine proportions of BZD use characteristics. The normality of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed data were compared between groups using independent-sample t-tests, while the Mann–Whitney *U*-test was applied for variables that violated the normality assumption, specifically years of education, age of initial opioid use, and duration in MMT. Categorical variables were analyzed using the chi-square test. A p-value < 0.05 was considered statistically significant.

To assess the independent relationships between BZD use and various outcomes, we conducted separate multiple linear regression analyses for the following: anxiety (SAS), depression (SDS), impulsivity (BIS-11), and quality of life (QOL-DA). In each model, BZD use (yes/no) served as the primary predictor. Based on clinical relevance, all models were adjusted for the following potential confounders: sex, age, duration in MMT, and the presence of mental disorders, sleep disorders, and chronic diseases. Model fit was assessed using adjusted R^2 and omnibus F-tests. The significance of individual predictors was evaluated with t-tests, applying a two-sided alpha level of 0.05.

Results

Demographic Characteristics

A total of 80 participants were recruited; 71 provided valid data (39 in the BZD group, 32 in the non-BZD group). Four cases were excluded due to coding errors, and five due to logical inconsistencies or >15% missing data. No significant differences were observed between groups in age, gender, marital status, education, or other demographic characteristics ($P > 0.05$). The sample was predominantly male (81.7%). Nearly half were unmarried or divorced (46.5%), and 35.2% were unemployed (Table 1).

No significant between-group differences were found for age at initial opioid use, duration in MMT, or HIV co-infection ($P > 0.05$). However, participants in the BZD group showed a significantly higher prevalence of mental disorders ($P = 0.029$), sleep disorders ($P = 0.048$), and chronic conditions such as hepatitis B/C, cardiovascular/cerebrovascular diseases ($P = 0.033$) (Table 1).

BZD Use Characteristics

Among BZD users, 71.8% reported self-medicating for opioid withdrawal-related symptoms (eg, anxiety, depression, insomnia), while 28.2% reported recreational use for euphoria. Oral and intravenous routes were both reported, with intravenous use accounting for 20.5%. Drug sources included medical prescriptions (17.9%), friends/family, and the illicit market. The mean interval between BZD uses was 5.54 ± 3.94 days (Table 2).

Comparison of Impulsivity, SAS and SDS

In the overall sample, 52.1% and 40.9% of participants met the criteria for clinically significant anxiety (defined as an SAS score ≥50) and depression (defined as an SDS score ≥53), respectively.[31,32] Group comparisons using independent-samples t-tests indicated that the BZD group scored significantly higher than the non-BZD group in impulsivity: total BIS score (77.87 ± 11.49 vs 68.06 ± 10.72, $P = 0.004$), non-planning impulsivity (25.97 ± 7.68 vs 21.94 ± 5.7, $P = 0.017$), and motor impulsivity (28.95 ± 7.04 vs 24.81 ± 7.45, $P = 0.019$). Similarly, SAS scores (54.36 ± 13.99 vs 47.81 ± 13.13, $P = 0.047$) and SDS scores (47.67 ± 14.29 vs 40.00 ± 13.94, $P= 0.026$) were significantly higher in the BZD group (Table 3).

Multicollinearity diagnostics, conducted prior to regression analysis, showed no concerns with all variance inflation factors below 2 (Table 4), supporting the inclusion of all predictors in the models. The overall regression models for anxiety (SAS), depression (SDS), impulsivity (BIS-11), and quality of life (QOL-DA) were statistically significant ($P < 0.05$). As detailed in Table 5, multivariate regression analysis revealed that BZD use was independently associated with higher levels of anxiety ($\beta = 0.279$, $P < 0.05$) and greater total impulsivity ($\beta = 0.439$, $P < 0.001$). Analysis of impulsivity subscales revealed positive associations with non-planning impulsivity ($\beta = 0.265$, $P < 0.05$) and motor impulsivity ($\beta = 0.345$, $P < 0.05$), but not with attentional impulsivity. No significant associations were observed between BZD use and depression or any domain of QOL (all $P > 0.05$).

Comparison of QOL-DA

Group comparisons using independent-samples t-tests indicated that, compared with the non-BZD group, the BZD group reported significantly lower QOL-DA total scores (134.31 ± 20.44 vs 145.19 ± 22.72, $P = 0.037$), as well as lower

Table 3 Comparison of BIS, SAS, and SDS Scores Between the Two Groups

Group	Total Score	Attentional	Nonplanning	Motor	SAS	SDS
BZD (n=39)	77.87 ± 11.49	22.95 ± 5.64	25.97 ± 7.68	28.95 ± 7.04	54.36 ± 13.99	47.67 ± 14.29
Non-BZD (n=32)	68.06 ± 10.72	21.31 ± 5.22	21.94 ± 5.78	24.81 ± 7.45	47.81 ± 13.13	40.00 ± 13.94
P-value	0.004*	0.213	0.017*	0.019*	0.047*	0.0261*

Notes: Variables are presented as mean ± SD. Comparisons were made using the Student's *t*-test, with *P < 0.05 for the BZD group vs the non-BZD group.

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Table 4 Multicollinearity Diagnostics: Tolerance and Variance Inflation Factor (VIF)

Variable	Tolerance	VIF
BZD use	0.794	1.259
Mental disorder	0.871	1.148
Sleep disorder	0.767	1.303
Chronic disease	0.798	1.254
Gender	0.957	1.045
Age	0.512	1.952
Duration in MMT	0.517	1.936

Notes: VIF > 10 denotes severe multicollinearity; VIF > 5 indicates moderate multicollinearity.

psychological function (P = 0.014) and symptoms/side effects (P = 0.022) subscale scores. No significant differences were found in physical or social function (P > 0.05) (Table 6). However, subsequent multivariate regression analysis, adjusting for potential confounders, revealed no significant independent association between BZD use and any domain of QOL (all P > 0.05) (Table 5).

Table 5 Multiple Regression Analyses Examining Associations Between BZD Use and Various Outcomes (Standardized Coefficients, β)

Predictor	SAS	SDS	Total BIS Score	Attentional	Nonplanning	Motor	Total QOL Score	Physical Function	Psychological Function	Symptoms/Side Effects	Social Function
BZD use	0.279*	0.091	0.439***	0.162	0.265*	0.345*	−0.117	0.068	−0.111	−0.174	−0.153
Mental disorder	−0.345**	−0.589***	0.126	0.171	0.021	0.060	0.116	−0.163	0.342**	0.041	0.073
Sleep disorder	−0.158	−0.071	−0.039	−0.072	0.031	−0.041	0.212	0.204	0.154	0.227	0.001
Chronic disease	−0.131	−0.226*	−0.156	−0.119	−0.203	0.027	0.072	−0.075	0.245*	0.024	−0.038
Gender	−0.078	−0.076	−0.141	−0.267*	0.015	−0.049	0.020	−0.130	0.107	0.037	0.047
Age	0.014	−0.239	−0.249	−0.110	−0.086	−0.243	−0.157	−0.183	0.020	−0.113	−0.214
Duration in MMT	−0.218	0.019	0.128	−0.114	0.063	0.232	0.148	0.048	0.053	0.233	0.133

Notes: *P < 0.05, ** P < 0.01, *** P < 0.001. All models were adjusted for all other variables listed in the table.

Table 6 Comparison of QOL-DA Scores Between the Two Groups

Variable	BZD (n=39)	Non-BZD (n=32)	P-Value
Physical function	33.21 ± 9.48	32.43 ± 7.29	0.708
Psychological function	30.13 ± 8.76	35.59 ± 9.43	0.014*
Symptoms/side effects	33.62 ± 6.39	37.13 ± 6.08	0.022*
Social function	37.36 ± 6.88	40.03 ± 5.52	0.079
Total quality of life	134.31 ± 20.44	145.19 ± 22.72	0.037*

Notes: Variables are presented as mean ± SD. Comparisons were made using the Student's *t*-test, with *P < 0.05 for the BZD group vs the non-BZD group.

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Discussion

The use and misuse of BZDs are highly prevalent among individuals receiving MMT. Previous studies have reported prevalence rates of up to 50% among this population.[15] Furthermore, more than half of BZD users undergoing MMT reportedly began using BZDs only after entering the program.[10] In our MMT clinic, the prevalence of BZD misuse was 54.7%, with 69.2% of BZD users initiating use after starting MMT. These findings are consistent with previous research. We propose that the physical and psychological discomfort associated with opioid withdrawal may serve as a primary motivation for initiating BZD use following enrollment in MMT. This underscores the critical need for timely interventions to manage post-withdrawal symptoms and prevent secondary substance misuse.

A particularly noteworthy finding of this study was that 28.2% of participants reported current recreational BZD misuse, despite having initially used them for symptom relief. Several factors may explain the high prevalence of recreational misuse among MMT patients. First, unlike heroin, methadone lacks euphoric effects; thus, some individuals may combine it with BZDs to alleviate cravings or achieve a "high."[10] Second, there remains a common misconception that BZDs are relatively safe or non-addictive. Third, unintentional misuse often begins with self-medication for sleep disturbances, withdrawal symptoms, or psychological distress (eg, anxiety, depression) but can evolve into habitual recreational use over time.

Association Between BZDs and Impulsivity

Impulsivity is a multidimensional neuropsychological construct commonly defined as the tendency to act prematurely without adequate consideration of consequences.[21,36] While prior research on impulsivity and addiction has largely focused on cocaine, opioids, and amphetamines, the misuse of prescription drugs—particularly BZDs—has attracted increasing attention in recent years. Evidence suggests that individuals with a history of heroin use receiving opioid substitution therapy (eg, methadone or buprenorphine) are especially vulnerable to BZD misuse.[37]

A central finding of this study is that BZD use maintained an independent association with higher levels of overall impulsivity, non-planning impulsivity, and motor impulsivity, even after controlling for key confounders including comorbid conditions such as mental disorders, sleep disorders, and chronic diseases. Two potential explanations can be considered. First, individuals with higher baseline impulsivity may be more susceptible to co-using BZDs, as impulsivity is a well-established risk factor for substance misuse. Alternatively, BZD use itself may exacerbate impulsivity through its neurochemical effects on inhibitory control. However, this hypothesis requires longitudinal investigation to determine causality.

Associations Between BZDs, Anxiety, and Depression

Anxiety and depression are highly prevalent among individuals with OUD undergoing MMT. In our study, the prevalence rates of anxiety and depression were 52.1% and 40.9%, respectively—figures consistent with prior literature.[38,39]

Although BZDs have been widely prescribed for their anxiolytic properties,[40] our study revealed that BZD use was independently associated with higher anxiety levels, even after accounting for key comorbidities including mental, sleep, and chronic disorders. This seemingly paradoxical result may be explained by two factors. First, BZDs may be used in an addictive manner (at high doses and irregularly) in non-medical contexts, which can cause adverse physiological effects and thereby limit the manifestation of their anti-anxiety properties. Second, concurrent polysubstance use can exacerbate both physical and psychological distress, impair quality of life, and disrupt social and familial support systems, all of which may aggravate pre-existing anxiety symptoms. Alternatively, the observed association could reflect reverse causality: individuals with more severe anxiety symptoms may be more likely to initiate or escalate BZD use as a form of self-medication. This explanation does not preclude the aforementioned mechanisms, since maladaptive use patterns could develop over time. Longitudinal studies are needed to disentangle the temporal and causal relationships between BZD use and anxiety symptomatology in this clinical population.

Furthermore, our results revealed an important finding: the significant difference in depression scores between BZD users and non-users observed in unadjusted analyses was no longer present after controlling for relevant comorbidities and other confounding factors, indicating no independent association between BZD use and depression levels. This

contrasts with some previous reports that identify BZD use as a risk factor for depression and link its cessation to symptomatic improvement in MMT patients.[41,42] Several considerations may explain these discrepant findings. Methodological variations, particularly in the selection of adjusted confounders, likely play a role. Additionally, residual confounding by unmeasured factors (eg, disease severity, social support) or limited statistical power due to our sample size may have obscured a more complex association.

Nevertheless, our analysis suggests that among this highly comorbid MMT population, comorbidities—including mental disorders, sleep disorders, and chronic somatic diseases—act as significant confounders in the relationship between BZD use and depression. The elevated symptom burden observed among BZD users appears to be largely attributable to their greater baseline psychiatric and somatic comorbidity, rather than to a direct effect of BZD use. These findings highlight the necessity of rigorously adjusting for such comorbidities in similar research.

Association Between BZDs and QOL

QOL encompasses both physical and psychological well-being.[43] Although initial unadjusted analysis indicated lower QOL scores among BZD users, this association was not independent of confounding factors. The link appears to be driven by a greater baseline burden of comorbidities—such as mental and chronic somatic disorders—in BZD users, rather than by a direct pharmacological effect. Consequently, interventions aimed at enhancing QOL in this clinically complex population should focus on the integrated management of these underlying medical and mental conditions.

External Validity and Generalizability

The findings of this study must be interpreted within the context of its specific population, as all participants were recruited from a Chinese clinical setting. Substantial inter-individual variability in drug metabolism is well-documented across different ethnic and ancestral groups, with pronounced differences frequently observed between populations of European and East Asian descent.[44] Such ethnic disparities in pharmacokinetics and pharmacogenomics can directly influence drug exposure, therapeutic efficacy, and safety profiles.[45] Therefore, these factors may limit the broader extrapolation of our clinical findings to other populations, implying that when designing multi-regional trials or considering generalizability, it is imperative to account for these variations.

Future Prospects

At present, the psychiatric mechanisms underlying drug-related addictive behaviors remain incompletely characterized. It has often been implicitly assumed that the same symptomatic domains targeted by the therapeutic use of BZDs also contribute to the development of dependence.[46] Given this complexity, early identification and intervention are essential for addressing both unintentional and recreational BZD use within the MMT population.

To translate these insights into practice, several pragmatic measures are recommended for MMT settings. First, implementing routine screening for BZD use and comorbid mental health conditions in MMT clinics is a critical step for early detection. Second, delivering structured psychoeducation regarding the risks of BZD misuse is warranted. Finally, skills-based interventions should be introduced to enhance patients' emotion regulation, reduce impulsivity, and equip them with strategies to manage drug-related cues.

The present study provides empirical evidence to inform the development of effective clinical and behavioral strategies aimed at improving treatment outcomes. Future research should focus on designing and evaluating targeted interventions that reduce impulsivity, alleviate anxiety and depression, and enhance quality of life. Furthermore, longitudinal studies are warranted to determine whether such interventions can decrease concurrent BZD misuse, improve treatment adherence, and ultimately enhance the long-term prognosis of patients receiving MMT.

Limitations

Several limitations of this study should be acknowledged. First, as a cross-sectional study based on self-reported data, the findings may be influenced by recall bias or social desirability bias, particularly for stigmatized behaviors such as illicit substance use. Second, the relatively small sample size may limit the statistical power and generalizability of the results. Future studies with larger samples are needed to confirm these findings. Third, methodological constraints prevented us

from examining the potential effects of BZD dosage and specific drug types, both of which may differentially influence clinical outcomes. Further research incorporating these variables is warranted to provide a more comprehensive understanding of BZD use among MMT patients.

Conclusion

Even after adjustment for key comorbidities (including mental, sleep, and chronic somatic disorders), BZD use maintained independent associations with elevated levels of overall, non-planning, and motor impulsivity, as well as with higher anxiety. In contrast, the apparent links between BZD use and worse depression or QOL were attenuated and became statistically non-significant after accounting for relevant confounders. These findings suggest that BZD use was independently associated with higher levels of impulsivity and anxiety after controlling for key comorbidities, whereas the apparent links with depression and QOL are largely confounded by coexisting clinical conditions.

Notably, the causal direction between BZD use and elevated impulsivity/anxiety in MMT patients remains unclear. This association may be driven either by the pharmacological effects of BZDs directly exacerbating these symptoms, or by pre-existing higher levels of impulsivity or anxiety increasing the propensity to initiate or continue BZD use.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Ethical Approval and Informed Consent

This study was approved by the ethics committee of Affiliated Kangning Hospital of Ningbo University in accordance with the Declaration of Helsinki. The ethics trial no. is NBKNYY-2024-LC-12. Informed consent was obtained from all subjects.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest regarding this manuscript.

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