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REVIEW

Benzodiazepine Use Among Individuals with Opioid Use Disorder: A Narrative Review

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Abstract: The concomitant use of benzodiazepines (BZDs) among individuals with opioid use disorder (OUD) is highly prevalent, with a rapid annual increase in overdose-related deaths. The co-use of BZDs is a significant predictor of opioid overdose. In the absence of other drugs, BZDs are rarely the sole cause of death. Prolonged BZD use frequently results in the rapid development of tolerance and dependence. A strong association has also been established between BZD misuse and depression. Moreover, chronic BZD exposure is linked to cognitive impairments, psychomotor disturbance, delirium, and an increased risk of falls, fractures, injuries, and traffic accidents. Outpatient clinicians should routinely screen for concurrent BZD use and exercise caution in prescribing. Timely interventions—including patient education, gradual discontinuation, psychological therapies, and skills-based training—are critical to mitigating harm and improving prognosis. In addition, Traditional Chinese Medicine(TCM), including herbal prescriptions and acupuncture, may serve as promising non-addictive alternatives for the management of anxiety, insomnia, and withdrawal-related symptoms. Strengthening multifaceted efforts will be crucial for reducing the burden of BZD use and improving treatment outcomes in OUD.

Keywords: benzodiazepines, opioids, abuse, overdose

Introduction

Opioid use disorder (OUD) is a chronic, relapsing disease characterized by compulsive drug seeking and use despite harmful consequences, accompanied by profound neurochemical and molecular changes in the brain.[1] It represents a substantial public health burden, being strongly associated with substantial morbidity, mortality, and elevated rates of criminal behavior. Furthermore, OUD is closely linked to injection drug use, which remains a key driver of blood-borne viral infections such as hepatitis C virus (HCV) and human immunodeficiency virus (HIV).[2]

Benzodiazepines (BZDs), first introduced in the 1960s with agents such as chlordiazepoxide, rapidly became widely used due to their relatively favorable safety profile compared with barbiturates, particularly with respect to respiratory depression.[3] Owing to their broad therapeutic efficacy, BZDs are frequently prescribed for both psychiatric and non-psychiatric conditions, including anxiety, insomnia, seizures, and pain.[4] These drugs play an irreplaceable role in the treatment of mental illness, pain management, and other areas. However, prolonged use of BZDs can lead to tolerance and dependence. More importantly, tolerance and dependence can develop rapidly.[3] Abrupt discontinuation may precipitate withdrawal syndromes of varying severity, significantly impairing patients' quality of life and social functioning.[5]

Over the past 20 years, the non-medical use of narcotic and psychotropic drugs, represented respectively by opioids and BZDs, has emerged as a pressing global public health concern, accompanied by a sharp increase in overdose-related mortality.[4,6–8] Currently, unbeknownst to many patients and prescribers, when BZDs are prescribed in combination with opioids, there is a much greater danger of harm compared to either taken in isolation.[9] The number of emergency department visits and overdose deaths involving combined opioid–BZD use has increased more rapidly in recent years than those attributed to either drug alone.[10,11]

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Given these trends, this review aims to summarize the prevalence, mechanisms, causes of abuse, characteristics, hazards and intervention strategies related to BZDs abuse among individuals with OUD, drawing upon both domestic and international literature. To this end, a PubMed search was conducted in May 2024 using the following MeSH terms: "benzodiazepines and opioid", "benzodiazepines and overdose", "benzodiazepine and abuse", and "opioid and overdose", without date restrictions.

Prevalence

At present, many countries are experiencing not only an increase in opioid use and abuse but also a parallel rise in BZDs consumption.[4] Although continuous use of BZDs is generally not recommended, their misuse has long been widespread.[5] The non-medical use and abuse of BZDs represent a growing global problem. In the United States, BZDs prescribing has risen sharply over the past several decades, with an estimated 3% of the general population receiving long-term prescriptions.[12,13] Similarly, a large claims-based cohort study in Japan involving 84,412 patients with newly initiated BZDs prescriptions found that 35.8% continued BZD use for three months, 15.2% for one year, and 4.9% for eight years without achieving even a three-month drug-free interval.[14]

Both therapeutic and recreational BZD use have been increasing in recent years, contributing to a higher prevalence of BZD use disorder among individuals with opioid dependence. There is a subset of individuals at greater risk for BZDs abuse, particularly those with a personal or family history of a substance use disorder.[15] For example, Stein reported that 40% of patients seeking inpatient opioid detoxification had used BZDs in the past month.[16] In Europe, a retrospective cross-sectional analysis of postmortem toxicology from 2002 to 2013 revealed that 51.17% of drug-related deaths were attributed to heroin overdose, while 11.72% were linked to combination of opioids and BZDs.[7] Patients with OUD receiving methadone or buprenorphine maintenance therapy are particularly vulnerable to BZDs misuse and abuse.[17] And rates of BZD use in some methadone clinic are reported to be as high as 66%.[18] The prevalence of lifetime BZDs abuse is about 66.3% and current abuse is at 50.8% among patients at a methadone clinic in Israel. Notably, about half of the BZD users do not start using a BZD until after entering into the methadone program.[19] A study from China similarly found that 20% of 288 patients enrolled in methadone maintenance programs also reported BZD use.[20] (Selected studies are summarized in Table 1).

Table 1 Selected Studies on the Concomitant Use of BZDs and Opioids

Author, Year	Study Location	Participants	Objectives	Study Design	Findings
Avik Chatterjee[21] (2021)	The United States	29 adults with recent opioid use	Explore the practice of combining non-opioid substances with opioid drugs, and analyze the potential risks.	Qualitative study using semi-structured interviews	Polysubstance use involving opioids is prevalent, with common co-used substances including BZDs, promethazine, and amphetamine salts.
Tae Woo Park[22] (2021)	The United States	26 opioid agonist treatment patients using BZDs	Explore patient motivations for and understanding of BZD risks, along with contexts of use and prescribing.	Qualitative study using semi-structured interviews	Patients in opioid agonist treatment often perceive the benefits of BZDs as outweighing the risks.
Albright, David L[23] (2020)	The United States	311 adults (electronic health records from consenting medical facilities)	Determine the relationship between various drugs (eg, BZDs, alcohol, marijuana) and opioid use.	Cross-sectional study	Methamphetamine, hallucinogens, and BZDs were the most common substances used concomitantly with opioids.

(*Continued*)

Table 1 (Continued).

Author, Year	Study Location	Participants	Objectives	Study Design	Findings
Xing-xiao Huang[15] (2020)	China	288 patients in MMT	Investigate BZD misuse and its associated factors in MMT patients.	Qualitative study using semi-structured interviews	High-dose methadone and injecting opioids were significantly associated with BZD misuse.
Martijn Boon[9] (2020)	Netherlands	29 manuscripts	Evaluate and summarize current clinical evidence of the combined use of opioids and BZDs on mortality and adverse respiratory outcomes.	Review	Concomitant use of opioids and BZDs was associated with an increased risk of mortality and severe adverse respiratory events across most settings.
Michael D. Stein[24] (2017)	The United States	245 persons initiating inpatient opioid detoxification who reported BZDs use in the past 30 days	Beliefs of opioid users regarding risks associated with BZD use.	Qualitative study using semi-structured interviews	Relative to non-users, BZD users were significantly more likely to deny or minimize the adverse consequences of BZD use.
Nozomi Takeshima[14] (2016)	Japan	A total 84,412 patients with new BZDs prescriptions were included in the cohort	Frequency and predictors of long-term BZD use among new users with extended follow-up.	A cohort study based on a large claims database	Predictors for long-term BZDs use were older age, high dose of BZDs, any psychiatric disorders, and concomitant prescription of psychotropic drugs.
Tatjana Petrushevska[7] (2015)	Europe	165 DRD cases between 2002 and 2013	Trends in drug overdose and drug-related mortality in North Macedonia (2009–2019).	Cross-sectional retrospective survey	51.17% of DRD cases were due to heroin overdose; 11.72% of cases were attributed to a combination of methadone and benzodiazepines (BZDs).
Kevin W Chen[25] (2011)	The United States	205 Patients	Prevalence of BZD misuse in MMT and characteristics associated with use.	Qualitative study using semi-structured interviews	47% of respondents had a history of BZD use. A majority of these users (54%) initiated use after entering MMT. Most methadone programs do not address co-occurring anxiety disorders.

Abbreviations: BZDs, benzodiazepines; MMT, methadone maintenance therapy; DRD, drug-related deaths.

The Mechanism of BZDs Dependence

BZDs can be administered orally, intravenously, or intramuscularly.[26] Once absorbed into the bloodstream, BZDs are distributed to various tissues and organs via circulatory system. BZDs act by binding to specific sites on the γ-aminobutyric acid-A (GABA-A) receptor, enhancing the receptor's affinity for GABA, the primary inhibitory neurotransmitter in the central nervous system. This interaction increases chloride ion influx through ligand-gated channels, resulting in neuronal hyperpolarization and enhanced inhibitory tone. With long-term BZD exposure, the efficiency of GABA-A receptor function diminishes, leading to the development of tolerance. When BZDs administration is abruptly discontinued, this down-regulated inhibitory state is unmasked, giving rise to withdrawal symptoms of varying severity.[27–29]

The abuse potential of different BZDs varies and is closely linked to their pharmacokinetic properties. Lipophilicity, in particular, plays a critical role in determining onset of action, with highly lipophilic agents generally exhibiting greater abuse liability. Diazepam, for instance, possesses the highest abuse potential, followed by alprazolam and lorazepam, all of which receive the strongest subjective ratings for euphoria among drug abusers. In contrast, drugs such as oxazepam, clorazepate, and chlordiazepoxide are associated with lower abuse potential.[19]

Causes of BZDs Abuse

A primary reason is that OUD is a chronic, relapsing brain disease. And it also leaves the patients at heightened risk for additional substance misuse.[23] Some experts classify BZDs abuse into two categories: unintentional misuse, which begins with legitimate medical use but progresses to inappropriate consumption, and intentional or recreational misuse, driven by the pursuit of euphoria.[5,19,21]

The former is for self-treatment. Even after opioid withdrawal, many patients with OUD continue to experience persistent psychological and physical distress, such as anxiety, depression, insomnia, pain and other protracted withdrawal symptoms. Instead of seeking medical guidance, these individuals may turn to BZDs to relieve discomfort.[22] In contrast, intentional misuse is more commonly associated with recreational purposes, particularly among patients with OUD enrolled in Mthadone Maintenance Programs. (the reason is, methadone, unlike heroin, does not induce euphoria).[19,25] For instance, they often report a "heroin-like" euphoria when methadone is combined with a BZD. Among the general opioid users, BZDs are often used to enhance the euphoria effect of opioids. They often report a more intense and prolonged effect when concomitantly using a BZD.[9] Whether used for self-treatment, recreational purposes, or both, BZDs abuse nearly always results in adverse outcomes and contributes to a further deterioration of the user's condition.

Characteristics of BZDs Abuse

The most common routes of BZD administration include oral, intramuscular injection and intravenous use. In some cases, individuals with OUD combine BDZs with heroin and administer them intramuscularly or intravenously to achieve a more intense euphoric effect.[26]

Patterns of BZDs abuse can generally be divided into two categories: a lower dose continuous use, with a stable course and a high-dose dose with an addictive profile and an irregular course, with lifetime comorbidity with substance use of different kinds.[30] Importantly, BZD use has a dose-response relationship with an increased mortality risk. Prolonged use of high doses of BZDs is associated with a 70–80% increase in mortality.[31] Moreover, individuals who combine BZDs with other drugs tend to consume significantly higher doses compared with those who abuse BZDs alone.[19]

Hazards of the Co-Use of BZDs and Opioids

Respiratory Depression and Risk of Death

Multiple studies have highlighted the adverse health consequences of concomitant BZDs and opioid use.[9,32–35] There is abundant evidence on the effects of the combined use of opioids and BZDs on mortality and severe respiratory adverse events.[9,32] Indeed, opioids and BZDs are the two most common classes of prescription drugs involved in overdose deaths. In the absence of other drugs or illegal drugs, BZDs is rarely the sole cause of death. 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.[19]

Concurrent use of BZDs is a significant predictor of opioid overdose for the following reasons.[33,34] First, although BZDs are relatively weak respiratory depressants, they can exert potent respiratory depression when used in combination with opioids.[9] Complex opioid - BZD drug interactions (via CYP system metabolism) and hepatic dysfunction can produce increased opioid serum concentrations, exacerbating risk for overdose.[35] Second, tolerance to opioid-induced respiratory depression does not confer cross-tolerance to the effects of BZDs, This causes a high risk of overdose even among experienced opioid abusers.[9] Third, the risk arises because individuals with OUD often have physiological profiles distinct from those of general BZD users, characterized by older age, more comorbidities (eg, HCV and HIV from past syringe sharing), and poorer hepatorenal, pulmonary, and immune function.[36,37] Adverse drug reactions are closely linked to specific physiological traits. Therefore, concomitant opioid and BZD use amplifies the risk of severe complications such as respiratory depression and fatal overdose.[9]

Association Between BZDs and Depression

Depression is highly prevalent among individuals with OUD, with clinical estimates suggesting a prevalence exceeding 50% in certain populations.[38,39] BZD use and misuse are recognized as significant risk factors for depressive disorders.[24,40] Chronic BZD exposure induces neuroadaptive changes—including reduced GABAergic activity, impaired monoaminergic function, diminished neurogenesis, and cognitive disruption- all of which may worsen depressive symptoms and hinder recovery.[41]

Shaul Schreiber's research also indicates that BZD abuse is clearly correlated with depression, and that discontinuing BZDs is associated with an improvement in depressive symptoms. BZD abuse not only fails to alleviate depression but may also induce or exacerbate it.[25] For this reason, clinical guidelines generally discourage long-term prescribing of BZDs in patients with depression, despite their anxiolytic and hypnotic properties.[5]

Among former heroin misuser in the methadone maintenance program, where BZDs co-use is common, depression assessment should be an integral component of routine care, and antidepressant pharmacotherapy should be considered alongside interventions to reduce BZDs misuse.[25]

BZDs and Cognitive Impairment

Since the 1970s, numerous studies have documented detrimental effects of BZDs on cognitive function.[42] Long-term BZD use is associated with impairments in attention, memory, and learning, as well as an increased risk of delirium and cognitive decline.[43] The impact of BZDs on cognitive function may be long-lasting, leading to persistent impairments in working memory, language, and processing speed.[44,45] High-dose abuse further exacerbates these deficits, with pronounced impairments in verbal and visuospatial memory, attention, and executive functioning.[43,46]

Furthermore, the impact of BZDs on cognitive function is related to the age of the subjects. The anticholinergic activity of BZDs is particularly detrimental among individuals aged 55 years and older, predisposing them to more pronounced cognitive dysfunction.[47] A 2020 meta-analysis reported that in elderly populations, BZD users showed significantly reduced processing speed (digit symbol test scores), while BZD abusers exhibited declines in global cognition (Mini-Mental State Examination scores).[45] Given that OUD itself is associated with cognitive impairment,1 the concurrent use of BZDs may exacerbate cognitive decline— a question warranting further investigation in future research.

Other Hazards of Co-Use of BZDs and Opioids

Beyond respiratory, psychiatric, and cognitive consequences, BZD use in combination with opioids is associated with additional adverse outcomes. In patients undergoing methadone or buprenorphine maintenance treatment, BZD co-use contributes to poor treatment retention and higher rates of program failure, particularly among individuals with untreated psychiatric comorbidities.[24] Furthermore, BZD use has been linked to psychomotor disturbances, delirium, and increased risks of falls, fractures, injuries, and traffic accidents.[43] Collectively, these hazards underscore the serious health burden of concurrent opioid–BZD use.

Intervention

The co-use of BZDs and opioids is associated with poorer treatment outcomes and a worse long-term prognosis among individuals with OUD.[30] Early and targeted interventions are therefore essential for both unintentional and recreational BZD misuse. Current literature describes several strategies aimed at reducing concomitant BZD use and alleviating related psychological distress, which can be broadly divided into the following categories. Current literature describes several strategies aimed at reducing concomitant BZD use and alleviating related psychological distress, which can be broadly divided into the following categories.

Strengthening Medication Management

At the Policy Level

Having recognized these threats, some countries have implemented regulatory measures to mitigate the risks associated with the co-use of BZDs and opioids. For example, the US Centers for Disease Control and Prevention (CDC) 2016 guideline urged clinicians to avoid concurrent prescription of opioids and BZDs whenever possible.[48] Similarly, the US Food and Drug Administration (FDA) issued a black box warning emphasizing the dangers of co-use.[49] In China, comprehensive control measures for narcotic and psychotropic drugs have been established, including full-process supervision and strict enforcement against illegal diversion. The National Medical Products Administration (NMPA) governs this through the Catalog of Narcotic Drugs and the Catalog of Psychotropic Drugs. As of July 2024, a total of 509 substances are strictly regulated, comprising 123 narcotic drugs, 166 psychotropic drugs, and 220 non-medicinal narcotic and psychotropic substances.[50]

At the Institutional Level

It is crucial to ensure that BZDs are properly managed, taking into account issues such as addiction and overdose. For patients with OUD who attempt to self-medicate symptoms such as insomnia or anxiety with BZDs, outpatient clinicians should prioritize safer alternatives without abuse potential, including options from Traditional Chinese Medicine (TCM).[19,51,52] Close monitoring is necessary during BZD tapering, as withdrawal symptoms occur in 30–100% of patients.[31] In China, the community-based methadone maintenance programs, established nationwide since 2004, has covered almost all areas. Consequently, the vast majority of patients with OUD in China are enrolled in this program.[53] This extensive coverage provides a crucial opportunity for the early detection of BZD misuse. Furthermore, the standardized methadone maintenance programs manual explicitly prohibits concurrent BZD use, enabling outpatient physicians to identify and intervene promptly.[54]

Identification and Risk Education

Routine screening for BZD use should be integrated into OUD management, particularly within methadone programs. Accurate identification of BZD co-use is essential for safe dosing of methadone, as unrecognized misuse increases the risk of overdose.[23,55] Once misuse is suspected or confirmed, clinicians should provide comprehensive education regarding the heightened dangers of opioid–BZD combinations.[21] Since many BZDs are obtained from peers or family members, patient education should also emphasize the risks of sharing medications.[19,51]

Alternative Pharmacological and Non-Pharmacological Treatments

For patients who rely on BZDs primarily for anxiety and insomnia, safer non-addictive alternatives should be considered. Non-pharmacological approaches and TCM-based therapies show particular promise.[56,57] A study from China reported that acupuncture improved sleep quality and alleviated withdrawal-related symptoms in patients with BZD dependence.[56] Similarly, herbal medicines with detoxifying, heat-clearing, and sedative properties have demonstrated efficacy in reducing insomnia linked to BZD withdrawal.[57]

Psychological Interventions

Psychological therapies have long been central to the treatment of substance use disorders, targeting both the underlying causes and relapse-related psychosocial factors.[58] Cognitive Behavioral Therapy (CBT), Dialectical Behavior Therapy (DBT), Contingency Management (CM), and Family Behavior Therapy (FBT) have all shown efficacy in treating drug dependence.[59] Many individuals who combine opioids with other substances also suffer from comorbid psychiatric conditions such as depression, bipolar disorder, post-traumatic stress disorder, anxiety disorders, schizophrenia, or attention deficit/hyperactivity disorder, with a significant proportion meeting criteria for multiple diagnoses.[21] Timely psychological interventions can mitigate distress, raise awareness of polydrug-related risks, strengthen motivation for behavioral change, and improve prognosis.[4,24,60]

Skills Training and Coping Strategies

Individuals with concurrent BZD and opioid use often exhibit poor coping skills when faced with psychological distress, insomnia, or cravings, leaving them vulnerable to impulsive drug use.[33] Skills-based interventions that enhance emotion regulation, reduce impulsive behaviors, and provide strategies for resisting drug-related cues are particularly beneficial.[61] Such programs can equip patients with healthier coping mechanisms, thereby reducing the risk of relapse and improving treatment adherence.

Conclusion

The concomitant use of BZDs and opioids remains highly prevalent among individuals with OUD and poses serious health risks. Various intervention strategies have been implemented to mitigate these harms. Timely interventions—including patient education, gradual discontinuation, psychological therapies, and skills-based training—are critical to mitigating harm and improving prognosis. TCM, including herbal prescriptions and acupuncture, may serve as promising

non-addictive alternatives for the management of anxiety, insomnia, and withdrawal-related symptoms. A comprehensive strategy that integrates policy regulation, clinical supervision, early identification, patient education, pharmacological and non-pharmacological alternatives, and psychological support is essential to address the hazards of BZD misuse in OUD populations. Strengthening such multifaceted efforts will be crucial for reducing the burden of BZD use and improving treatment outcomes in OUD.

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 no conflicts of interest in this work.

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