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Best practices in benzodiazepine prescribing and management in primary care

Abstract: Despite the lack of evidence on the long-term effectiveness of benzodiazepines and their potential harmful effects, prescriptions of the drug have significantly increased in the US over the past decade. This article reviews best practices regarding primary care benzodiazepine prescriptions and how providers can best prevent and treat benzodiazepine use disorder and other harmful effects.

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Benzodiazepines (BZDs) are a class of central nervous system (CNS) depressants with anxiolytic, hypnotic, muscle relaxant, anticonvulsant, and amnesic effects.[1] They are approved for several conditions, including anxiety, insomnia, seizures, and alcohol withdrawal.[2,3] While BZDs are relatively safe for short-term use (that is, 2 to 4 weeks) or for acute as-needed use (that is, panic attacks), their prolonged use has been associated with dependence, use disorder, and death.[2] More than half of the patients who take a BZD for over 1 month develop dependence.[4] Many are unable to discontinue use without significant withdrawal symptoms.[5]

Despite these concerns, BZD prescriptions have increased 2.5% annually between 1996 and 2013, with 5.6%

Keywords: benzodiazepines, best practices, prescription drug misuse, primary care

FDA approvals for BZDs[1,11]

BZDs	*Half-Life Duration*	Anxiety	Insomnia*	Alcohol Withdrawal	Seizures	Other
Flurazepam	*long*		+			
Chlordiazepoxide	*long*	+		+		Preoperative anxiety
Diazepam	*long*	+		+	+	Muscle spasms, preoperative sedation
Clorazepate dipotassium	*long*	+		+	+	
Clobazam	*long*					Adjunctive treatment of seizures with Lennox-Gastaut syndrome
Clonazepam	*long*				+	Panic disorder
Estazolam	*short to intermediate*		+			
Lorazepam	*short to intermediate*	+			+	Preoperative sedation
Oxazepam	*short to intermediate*	+		+		
Alprazolam	*short to intermediate*	+				Panic disorder
Temazepam	*short*		+			
Triazolam	*very short*		+			
Midazolam	*very short*					Preoperative or procedural sedation; sedation of intubated and mechanically ventilated patients

*Short-term treatment

of US adults receiving a prescription in 2013, up from 4.1% in 1996.[6] Additionally, the quantity per prescription tripled during this period.[6] "Drug overdose deaths involving BZDs rose from 1,135 in 1999 to 11,537 in 2017" in the US.[7]

The purpose of this article is to review best practices regarding BZD prescriptions in primary care and highlight how primary care providers can best prevent and treat dependence and other harmful effects associated with BZD use.

BZDs: A review

In the US, the first BZD (chlordiazepoxide) was approved in 1960. Since then, many others have entered the market and it is estimated that between 4% and 6% of the general US population uses BZDs.[3,8] Alprazolam is the most prescribed BZD with nearly 21 million prescriptions in 2018.[9] More women than men and more older adults use BZDs.[3] Additionally, patients who are prescribed opioids are more likely to also be prescribed a BZD.[10] BZD users can be divided into four groups: 1) older patients managed in primary care offices and taking many medications including BZDs, 2) patients with panic disorder or agoraphobia, 3) patients with recurrent dysphoria, and 4) patients with chronic sleep disturbances.[11] The latter two are the groups at highest risk of misusing BZDs.[11]

All BZDs bind to specific sites on the gamma-aminobutyric acid (GABA) type-A receptor, leading to an increase of the receptor's affinity for GABA (an inhibitory neurotransmitter).[1] BZDs can be divided between hypnotic and anxiolytic agents and by the duration of their half-life.[1] The FDA regulates BZD use (see *FDA approvals for BZDs*).

As second-line intervention and when taken short-term, BZDs have been found to be effective for easing symptoms of four main disorders: panic disorder, generalized anxiety disorder, social anxiety disorder, and insomnia.[1] Although often prescribed to prevent posttraumatic stress disorder (PTSD), there is no evidence that BZDs help for this indication.[11]

Even when prescribed short-term, BZDs should be used with caution. They may lead to significant adverse reactions, including drowsiness, lethargy, fatigue, stupor, difficulty concentrating, hypotonia and ataxia, rebounds of original symptoms after discontinuation,

as well as development of tolerance.[1] They may also impair individuals' ability to drive, leading to increased risk of injury.[1] Older adults taking BZDs are also at higher risk of falls, hip fractures, cognitive impairment, and hospital admissions.[12]

BZD contraindications include "myasthenia gravis, ataxia, sleep apnea syndrome, chronic respiratory insufficiency, spinal and cerebral ataxia, angle-closure glaucoma, or acute CNS-depressant intoxication."[1] BZDs are not recommended for use in patients with bipolar disorder, depression, suicidal ideation, psychosis, substance use disorders, or neurocognitive disorders.[11] In 2016, the FDA required the addition of a boxed warning to drug labels of BZDs and prescription opioids about BZD risks, including death, when they are combined with opioid pain or cough medicines.[13] In September 2020, the boxed warning was updated to include "potential for abuse, addiction, and other serious risks".[14] When prescribing BZDs, providers also ought to assess for any drug-drug interactions, especially with opioids or CNS depressants, as interactions may lead to severe respiratory depression and death.[11]

BZD misuse and BZD-related disorders

There is a lack of evidence on the efficacy of taking BZDs for more than 4 weeks. Long-term use might even trigger counteracting effects. For example, BZD use by patients with PTSD over a long period was shown to interfere with fear extinction and, as such, tended to worsen symptoms.[15-17] Increased symptoms of anxiety and phobia, including rebound anxiety, have also been reported.[16]

Another disadvantage of using BZDs long-term is the relatively fast development of tolerance to their therapeutic effects while adverse reactions persist.[18] "Tolerance develops to hypnotic effects within days to weeks, to myorelaxant effects within weeks, to anticonvulsant effects within weeks to months, and to anxiolytic effects within months,"[11] often leading patients to gradually increase doses or take more than one type of BZD.[11,18]

Three BZD-related disorders (that is, use disorder, intoxication, and withdrawal) are defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) under sedative, hypnotic, and anxiolytic disorders. Risk factors to develop a BZD-related disorder include "preexisting or active substance use disorders (especially alcohol, sedative hypnotics, cannabis, opioids, and stimulants), family history, medical availability, early onset of use, chronic medical conditions, chronic insomnia, chronic dysphoria, impulsivity, and borderline or dependent personality disorders."[11] Those disorders tend to be iatrogenic, that is, associated with medical overprescriptions.[11]

Half of the patients on BZDs for more than 1 month will develop dependence, even when taking medication as prescribed.[4] Dependence and use disorder may develop in the absence of tolerance.[4] Risk factors include a history of mental illness and prescription of large doses of BZDs. Signs of dependence and/or use disorder include doctor-shopping, buying from different pharmacies, overlapping prescriptions, and withdrawal symptoms.[19,20]

Dependence will lead to symptoms of withdrawal upon BZD cessation or dose reduction. Symptoms tend to develop faster with shorter-acting agents (that is, within 2 or 3 days) compared with longer-acting agents (that is, within 5 to 10 days).[1] They vary per patient and can be divided into physical, psychological, and sensory symptoms. Most common physical symptoms include flulike symptoms and muscle cramps.[20] Rebound of prior symptoms is also often associated with stopping BZDs that were used for sleep disorders.[1] Psychological withdrawal symptoms include "anxiety and panic disorders, restlessness and agitation, depression and mood swings, psycho-vegetative symptoms (for example, tremor), reduced concentration, and sleep disturbances and nightmares."[1] They can last for weeks and may be challenging to distinguish from underlying anxiety disorders.[20] Lastly, in the most severe cases, patients may have seizures, paranoid thoughts, hallucinations, depersonalization, and withdrawal delirium.[1] Symptom severity increases with duration of use and/or the concurrent development of a use disorder.

Risks for fatal BZD intoxication are low when BZDs are used as a single drug.[21] However, they increase significantly when BZDs are used intranasally, rather than by mouth, or used with alcohol or opioids.[21]

Finally, BZD-associated disorders may lead to hazardous uses. BZDs sourced over the internet or on the streets are often of unknown origin, strength, and quality, and may lead to serious adverse reactions and death.[20] I.V. injection of temazepam has been reported as leading to emboli and gangrene.[20]

Special attention to vulnerable populations

Extra caution is recommended when prescribing BZDs to vulnerable populations such as older individuals,

pregnant women, and women of childbearing age, as well as patients with polysubstance use.

First, starting with older adults, BZD use has been associated with higher risks of delirium upon hospital admission, hip fractures, disability, and neurocognitive disorders.[22-27] This may be explained by pharmacokinetic changes associated with aging, polypharmacy, and increased prevalence of (even minimal) brain damage.[11] Paradoxical reactions to BZDs, as well as psychomotor retardation and cognitive dysfunction, may occur in older patients.[1] Based on those risks, BZDs have been added to the list of medications to be avoided in older adults under the American Geriatrics Society's Beers Criteria®, with the exception of cases of alcohol withdrawal and periprocedural anesthesia.[28] If BZDs must be prescribed for older adults, providers might opt for BZDs that do not require oxidative hepatic metabolism, namely lorazepam, oxazepam, and temazepam.[11] Lastly, BZDs have been associated with substance use disorder in older adults, along with smoking and alcohol.[29]

Secondly, another vulnerable group includes pregnant women and women of childbearing age. BZDs are class D teratogens and are contraindicated in breastfeeding mothers.[30] However, the risk to this population is not entirely clear and as such, clinicians should weigh BZD benefits and risks during pregnancy and breastfeeding, compared with the risk of an untreated mental illness.[11]

Third, BZD use by patients with a substance use disorder puts them at significantly increased risk of toxicity, overdose, and (suicidal and accidental) death and should be avoided, if possible.[31,32]

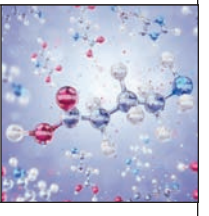
Despite those warnings, BZDs are prescribed more frequently to patients who are already at risk for BZD-related adverse events, including patients with depression, substance use, alcohol misuse, sleep apnea, and chronic obstructive pulmonary disease.[33] BZD-related primary care visits by older adults grew from 5.6% in 2003 to 8.7% in 2012 in the US, the largest increase among CNS depressants.[34] There is therefore an urgent need to strengthen primary care providers' knowledge about BZD risks for those populations.

Assessment and treatment in primary care

Primary care providers, as primary prescribers of BZDs, have a special role to play in assessing risk factors for BZD misuse.[35] This assessment should include evaluating proper BZD indication, effectiveness, adverse reactions, and, if needed, considering alternatives.[35] Providers should consider key points before analyzing and discussing BZD risks, benefits, and possible alternatives with their patients (see *BZD risks, benefits, and alternatives*).

If both clinicians and patients opt for continuation, close monitoring should be established.[35] The provider should also consider changing to a longer-acting BZD to reduce potential risks. Adding psychotherapy, pharmacotherapy (such as selective serotonin reuptake inhibitors, adrenergic inhibitors, or antihistamines), and lifestyle changes might be recommended.[35]

Providers should consider key points before analyzing and discussing BZD risks, benefits, and possible alternatives with their patients.



If the provider and patient decide in favor of discontinuation, the patient will need extra support and education.[35] As a first critical step, providers will need to engage the patient in a discussion about the benefits and challenges of BZD discontinuation (including, in the case of sudden discontinuation, the risk of seizures), with possibly the use of motivational interviewing.[36,37] Education tools such as the Eliminating Medications through Patient Ownership of End Results (EMPOWER) intervention for older adults have been found to help foster strong patient engagement and a good therapeutic relationship with the primary care provider.[38]

Then, priority should be given to gradual tapering and managing withdrawal symptoms.[37,39] BZDs ought to be discontinued over 4 to 6 weeks or more for diazepam doses over 30 mg per day or the equivalent dose of another BZD.[1] The dose may be reduced by 50% every week, or between 10% and 25% every 2 weeks, depending on the patient's tolerance to symptoms.[1,40,41] It is, however, recommended that tapering last less than 8 weeks to prevent withdrawal treatment from becoming the patient's "morbid focus."[1,42] A fixed withdrawal schedule may be discussed and agreed upon with the patient.[1] Most patients can go through withdrawal as outpatients. Some with specific health risks or those taking large amounts of BZDs (for example, 100 mg or more of diazepam daily or

an equivalent dose of another BZD) may have to be hospitalized for withdrawal.[1] Switching to longer-acting agents such as diazepam for the purpose of discontinuation or tapering does not lead to better outcomes.[1]

No gold standard intervention exists for the management of withdrawal symptoms.[43] Possible options explored in a recent preprint metanalysis include mood stabilizers, flumazenil, propranolol, melatonin, and buspirone, the latter two being the safest ones, although all are off-label for this purpose.[43] Some evidence exists for the use of melatonin (to improve sleep during withdrawal) and slow subcutaneous infusion of flumazenil in an inpatient setting (given its risks).[1] Flumazenil should be used with caution as it carries significant risks of seizure and psychosis.[1] When the patient presents with a coexisting psychological disorder, an integrative program to also address this disorder ought to be included.[1] Patients on opioid maintenance therapy should be kept on a high enough dose to prevent withdrawal from opioids.[1] Lastly, buprenorphine is often preferred over methadone for patients on opioid maintenance therapy who are concurrently taking BZDs.[44] BZDs with methadone have indeed been associated with higher hospitalization rates, greater ICU utilization rates, and worse medical outcomes compared with BZDs with buprenorphine.[45]

Little evidence exists for the use of psychotherapy to help with BZD dependence and/or use disorder. Motivational interviewing has been successfully used for mild to moderate dependence with other substance use disorders, but there is little evidence with regard to its impact for BZDs.[1] Cognitive behavioral therapy may also be helpful. At the primary care level, practitioners may decide to implement a minimal, brief intervention, as this may facilitate an initial reduction of BZD consumption.[1] Dose reduction may indeed be a valuable initial harm-reduction strategy that providers decide to implement in the short term while they work on building a more solid therapeutic relationship with the patient.[5]

If withdrawal is too challenging or if the patient's condition is not well managed with alternatives, the patient may have to be maintained on BZDs.[37] In these cases, the provider, in dialogue with patients, may explore ways to progressively reduce consumption to the lowest possible level as a harm-reduction strategy.[37] However, patients with certain conditions such as depression will not benefit from using BZDs. As such, tapering is highly recommended in these cases, especially as patients get older.[37]

BZD risks, benefits, and alternatives[35]

Risks	Benefits	Alternatives*
• Physical adverse reactions (for example, dizziness, slurred speech, and psychomotor impairment; most seriously: overdose, withdrawal, falls, autonomic instability, seizures, hepatotoxicity, respiratory depression, and death). • Cognitive adverse reactions (for example, drowsiness, inattention; most seriously: confusion, amnesia, hallucinations, delirium, and coma). • Emotional adverse reactions (for example, depression, irritability, anxiety; most seriously: lability). • Behavioral adverse reactions (for example, disinhibition, insomnia, and avoidance; most seriously: suicidality, violence, and abuse). • Others (for example, teratogenicity, breastfeeding risks, drug-drug interactions).	• Short-term anxiolytic effects • Short-term hypnotic effects • Fast-acting • Can be prescribed as needed	Acute/Fast-Acting Treatment • Behavioral techniques • Psychotherapy • Sedating antidepressants (for example, trazodone, mirtazapine, tricyclics) • Adrenergic inhibitors (for example, prazosin, propranolol) • Antihistamines (for example, hydroxyzine) • Antiepileptic drugs (for example, gabapentin, pregabalin) • Antipsychotics (for example, quetiapine, olanzapine, risperidone) Chronic Treatment • Behavioral techniques • Psychotherapy • Serotonergic agents (for example, antidepressants, buspirone) • Antipsychotics • Antiepileptic drugs (for example, lamotrigine)

*Use of some of these medications for anxiety or insomnia is off-label.

Prevention: Best practices in primary care

When considering initiating a BZD, several aspects should be taken into account and discussed with the patient. Those may include limiting duration of BZD use to less than 2 to 3 months, setting up intervals of treatment within that period (especially for sleep disorders) to decrease risk of rebound, and conducting a careful evaluation for treatment indication(s) and available alternatives, with special consideration for vulnerable populations.[1,21]

Providers should also access their state's Prescription Drug Monitoring Program (PDMP) and look for BZDs and other CNS depressants prescribed by other providers.[37] PDMPs have been shown to decrease quantity of BZDs dispensed.[46] However, while red flags from PDMPs provide information to take into account, they are not always a reason for strict refusal to prescribe BZDs as taking such a position may lead to acute withdrawal symptoms and create unintended harm to the patient in some situations.[47] Urine drug screening might also be used for monitoring purposes.

Successful interventions have been implemented in primary care to reduce BZD prescriptions. For example, at a midwestern university outpatient clinic, providers participated in a brief educational session including "academic detailing" (current evidence about BZDs) and "pharmaceutical detailing" (a sales technique borrowed from pharmaceutical companies).[5] Thirty days into the intervention, the clinic reported an 80% decrease in BZD prescriptions, a reduction maintained for months after the intervention.[5] Projects implemented for other substances in primary care may also offer insights. The use of a Schedule II patient agreement for opioids and stimulants (including urine screens, PDMP checks, and no prescriptions written outside of the 3-month mandatory visit) has been shown to increase adherence to urine screens from 5.3% to 71.1% and PDMP checks from 11.3% to 99.0%.[48]

Conclusion

In light of the increased use of BZDs by not only the general population but also the most-at-risk individuals, it is urgent to call the attention of the medical and nursing community and address this problem. A growing number of alternatives to BZDs exist for both anxiety and sleep that should be used as first-line treatments. Patients who have been taking BZDs for more than 2 to 3 months can be supported in decreasing or discontinuing their use. This process should however be managed carefully and in close collaboration with patients (and their families) as this can be a challenging and terrifying undertaking for them. NP

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