

# Benzodiazepine and Z-hypnotic stewardship

These agents are not first-line treatments for many of the conditions for which they are used. When they are used, there should be a plan in place for deprescribing.

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The author reported no potential conflict of interest relevant to this article.

doi: 10.12788/jfp.0381

## PRACTICE RECOMMENDATIONS

➤ *Recommend cognitive behavioral therapy as first-line treatment for anxiety and insomnia.* (A)

➤ *Limit benzodiazepine prescribing to ≤ 2 to 4 weeks for anxiety and insomnia.* (B)

➤ *Taper benzodiazepines slowly and flexibly.* (A)

### Strength of recommendation (SOR)

- (A) Good-quality patient-oriented evidence
- (B) Inconsistent or limited-quality patient-oriented evidence
- (C) Consensus, usual practice, opinion, disease-oriented evidence, case series

**B**enzodiazepines (BZDs) and Z-hypnotics have been available for decades, yet uncertainties about their use remain. They are prescribed and overprescribed most often for anxiety and insomnia, for which they have value but also the potential for significant adverse consequences, notably physiologic dependence. Use of these agents should be limited, and planned deprescribing is a fundamental aspect of prescribing.

**A brief history.** BZDs are a subset of benzodiazepine receptor agonists (BZRAs), which enhance the inhibitory effect of centrally acting  $\gamma$ -amino butyric acid (GABA) at the GABA<sub>A</sub> receptor through allosteric modulation. In 1960, the first BZD, chlordiazepoxide, was marketed for clinical use, and as other agents in the class became available, BZDs supplanted the more toxic barbiturates, another BZRA subset (TABLE 1). By the late 1970s, BZDs had risen to the top of most prescribed medications, with one agent in particular—diazepam (Valium)—earning a reputation as “mother’s little helper,” a phrase derived from a Rolling Stones’ song with that title produced in 1966.<sup>1</sup>

With recognition of the problems associated with BZDs, their popularity diminished somewhat but remained high. BZDs were listed under Schedule IV by the Drug Enforcement Administration in 1975 due to the risk for addiction, and on the American Geriatrics Society Beers Criteria list in 1991 because of significant adverse consequences in the elderly. Researchers began to question their use as early as the 1970s, and the landmark *Ashton Manual*, guidance for patients and clinicians alike, was published in 2002.<sup>2</sup>

Currently, there are 14 BZDs approved by the Food and Drug Administration (FDA) as well as 3 Z-hypnotics, termed such as they include the letter “z” in their generic names (TABLE 1). In recent years, BZD prescribing has risen; a 2019 study found that 1 of 8 American adults reported using a BZD in the previous year.<sup>3</sup>

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TABLE 1

## FDA-approved benzodiazepine receptor agonists

Benzodiazepines		Z-hypnotics	Barbiturates	Other
Alprazolam	Flurazepam	Eszopiclone	Butalbital	Carisoprodol
Chlordiazepoxide	Lorazepam	Zaleplon	Butabarbital	Propofol
Clobazam	Midazolam	Zolpidem	Methohexital	
Clonazepam	Oxazepam		Pentobarbital	
Clorazepate	Quazepam		Phenobarbital	
Diazepam	Temazepam		Primidone	
Estazolam	Triazolam			

### Limited benefits of benzodiazepine receptor agonists

BZRAs can be of benefit in a limited range of medical conditions, including some for which they are first-line considerations. (See TABLE 2 for a list of indications for BZDs.) They are most often prescribed for anxiety and insomnia, although they are not first-line treatments for these conditions and should be prescribed only when symptoms limit a patient's daily functioning.

■ **BZRAs are not intended for long-term use.** In recent decades, the percentage of patients prescribed BZRAs has doubled, and more than 80% of these patients indicate usage for more than 6 months.<sup>4</sup> Evidence, however, does not support long-term daily use.

Observation periods in most studies are far shorter than the number of years over which BZDs are actually prescribed, and flawed research methodology has introduced the risk of bias. Specifically, the generalizability of reported outcomes must be qualified, since efficacy trials performed under ideal study conditions (eg, exclusion criteria to minimize confounders) differ from circumstances seen in clinical practice. Conclusions are also limited by the inherent bias of pharmaceutical industry sponsorship and unavailability of unpublished trials that may have demonstrated unfavorable results.

■ **Insomnia**, a current (past 30 days) complaint in more than 40% of US adults, is associated with a variety of symptoms.<sup>5</sup> About 20% of adults have an insomnia disorder, defined as a predominant problem for at least 1 month involving sleep initiation, maintenance, or nonrestorative sleep along with day-

time function-limiting fatigue.<sup>5</sup> Meta-analyses indicate BZRAs can reduce sleep latency (BZDs, by 4 minutes; Z-hypnotics, 22 minutes) and may increase sleep duration (BZDs, 62 minutes per limited data; Z-hypnotics, data insufficient).<sup>6,7</sup> Definitive evidence for long-term (> 2-4 weeks) BZD benefit is lacking, and cognitive behavioral therapy for insomnia (CBT-I) is well established as first-line treatment yielding improvements that may last at least 18 months after completion of therapy.<sup>8,9</sup>

Although CBT-I is generally provided by behavioral health specialists, elements of CBT-I and sleep hygiene measures can be effectively used by primary care clinicians.<sup>10</sup> Data indicate other nonpharmacologic interventions are also effective,<sup>11</sup> including acceptance and commitment therapy,<sup>12</sup> meditation,<sup>13</sup> and acupuncture.<sup>14</sup>

■ **Episodic fear and anxiety** are universal and essential for survival. Fear is an alarm warning of an immediate hazard. Anxiety (the emotion) paired with worry (the thought) relate to a perceived future threat. Transient (state) anxiety should not be suppressed altogether if self-management can curb its intensity and thereby allow effective problem engagement. However, when individuals are incapacitated by crisis anxiety or sporadic specific phobias such as flight anxiety, episodic BZDs do have a role.

■ **Ongoing anxiety** is a more complex treatment situation. Obsessive-compulsive disorder and posttraumatic stress disorder are no longer categorized as anxiety disorders, but they often involve anxiety. Here, BZDs have no indication aside from exceptional acute crisis presentations. Anxiety dis-

orders are defined by a core persistent (trait) anxiety disproportionate to the actual threat, limited daily functioning, and more than 6 months' duration. One of 3 Americans older than 13 years meet the criteria for anxiety in their lifetime; 1 of 5 meet the criteria in any single year.<sup>15</sup>

BZDs are effective in treating anxiety disorders in the short term (2-4 weeks)<sup>2,16,17</sup>; however, benefit may fade over time.<sup>18-21</sup> For some individuals, data suggest BZDs themselves might actually *generate* anxiety, as evidenced by reduced symptom intensity following discontinuation.<sup>22,23</sup> Recommended first-line medications for anxiety disorders include certain antidepressants and pregabalin, which exhibit efficacy similar to that of BZDs.<sup>24</sup> Mindfulness and various psychotherapies have value, as well.<sup>16</sup> Among the latter, CBT is considered first line with benefit comparable to BZDs in the short term; yet unlike BZDs, CBT gains can last 12 months or longer after the conclusion of therapy.<sup>25,26</sup> Because there may be a delay between the start of CBT and the onset of benefit, BZDs, which work quickly, may be used to bridge functionally impaired patients in the short term.

### Risks with benzodiazepine receptor agonists

Harms from BZRA use are common, tempering their utility. Sedation, dyscognition, and psychomotor impairments are often seen upon initiation of BZRA use. These adverse effects can—although not always—improve with continuous BZRA exposure, an effect known as tolerance, which is due to neuropharmacologic adaptation.

Cognitive issues include problems with memory, judgment, and decision making. These may be unrecognized or, if noted, attributed to other issues such as aging, and may become clear only when BZRAs are discontinued. Anterograde amnesia and parasomnias occur less often.

Psychomotor impairment can result in falls, fractures, and other injuries, especially in the elderly. Decrements in mood, including emergent depression and paradoxical anxiety, can occur. Some individuals experience disinhibition that is expressed

TABLE 2

### Indications for benzodiazepine use

<b>First-line treatment</b>
Anesthesia for procedures
Benzodiazepine withdrawal
Burning mouth syndrome (clonazepam)
Crisis anxiety without psychotic features
Moderate-to-severe alcohol withdrawal
Movement disorders: stiff person syndrome, status dystonicus, catatonia
Status epilepticus
<b>Second-line treatment</b>
Anxiety disorders
Certain treatment-resistant seizure disorders (clonazepam, clobazam)
Insomnia
Muscle spasm

through irritability, agitation, aggression, and violence.

■ **Misuse of BZRAs is not unusual** and can be related to dosing errors or attempts to ease intrusive symptoms. Nonmedical use almost always occurs in the context of an underlying use disorder, whereby BZRAs serve to amplify euphoria or ameliorate withdrawal from opioids or alcohol. Addiction *per se*, which entails BZRA craving and compulsive use leading to adverse consequences, is unusual.

BZRAs are associated with increased mortality, including all-cause mortality and suicide. They are respiratory depressants, although when taken alone in excess rarely result in death. They are, however, strongly implicated in opioid-related overdose fatalities, as their presence has been identified in 1 of 3 such decedents.<sup>27</sup>

### Physiologic dependence with BZRAs

Among the more important adverse outcomes with ongoing BZRA exposure is physiologic dependence. This occurs primarily because of neuroadaptation of GABA<sub>A</sub> and glutamatergic receptors, but dependence probably also involves changes in the adenosine A<sub>2A</sub>, serotonergic, and peripheral benzodiazepine receptors, the latter being

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Physiologic dependence with benzodiazepine receptor agonists has been seen in those exposed for as little as 1 week and at usual or even low dosages.

present on mitochondrial membranes. The hypothalamic-pituitary-adrenal axis also appears to be involved.

Physiologic dependence is expressed through BZRA tolerance and characteristic physical and psychological symptoms upon withdrawal. Tolerance refers to a reduced effect with continued substance exposure or the need for an increased dose to get the same effect. Drug withdrawal can result in manifestations distinctive to addiction-prone substances, as well as to some medications without addiction liability, such as corticosteroids and antidepressants. Tolerance and withdrawal are not applicable criteria in the diagnosis of sedative-hypnotic use disorder when BZRAs are prescribed.<sup>28</sup>

■ **Withdrawal.** Reported prevalence of BZRA physiologic dependence differs according to populations studied, criteria used, and the deprescribing process employed. Some researchers have found rates of one-third and others exceeding one-half among individuals using BZRAs for longer than a month.<sup>23,29</sup> Physiologic dependence has also been seen in those exposed for as little as 1 week and at usual or even low dosages.<sup>30,31</sup> Moderate-to-severe withdrawal symptoms occur in 10% to 44% of BZRA users, and an estimated 10% to 15% have protracted (months, years, indefinite) symptoms that may fluctuate unpredictably and seem peculiar, bizarre, or unrelated to BZRA neuropharmacology.<sup>2,32,33</sup> The extent and severity of withdrawal can be striking, as highlighted in qualitative research of individuals seeking support and assistance in online communities.<sup>34</sup>

## Deprescribing BZRAs

Because benefits are limited and adverse outcomes including physiologic dependence are common, it is recommended that clinicians urge deprescribing of BZRAs for any patient taking them consistently for more than 1 month. Published deprescribing investigations and guidance are insufficient, heterogeneous, and confusing. Still, some approaches can work well, and success rates as high as 80% have been achieved among the elderly, for example.<sup>35</sup> Brief interventions such as providing individualized advice, support,

and management are effective.<sup>36,37</sup> Abrupt discontinuation is inappropriate and can be life threatening.<sup>38</sup> Forced cessation is also inappropriate unless significant respiratory depression is identified.

The *Ashton Manual* is a useful guide, readable by patients. Proceed with tapering slowly at a rate led by the patient's response.<sup>2,39</sup> Avoid discrediting patients' reports of unusual withdrawal symptoms, as this can lead to misdiagnosis (eg, somatic symptom disorder) or ineffective treatment (eg, addiction recovery approaches). Adding CBT to tapering improves outcomes, and adjunctive medications may be helpful, although not without their own problems.<sup>29</sup> Consistent support of patients by others involved in treatment (prescriber, pharmacist, behavioral health specialists, peer coach, significant others) is essential. Complex challenges generally resolve through authentic listening and response but may require referral to others with necessary skills and experience. Complete cessation may take 12 to 18 months (or longer). Even if complete cessation is not possible, the least dose necessary can be achieved.

JFP

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