BENZODIAZEPINES:
As a group, anxiety disorders are the most common mental illness in the United States, affecting 40 million adults. There is a nearly 30% lifetime prevalence of anxiety disorders in the general population. DSM-5 anxiety disorders include generalized anxiety disorder, social anxiety disorder (social phobia), panic disorder, specific phobia, and separation anxiety disorder. Although DSM-IV-TR also classified obsessive-compulsive disorder (OCD) and posttraumatic stress disorder (PTSD) as anxiety disorders, these diagnoses were reclassified in DSM-5. Anxiety also is a frequent symptom of many other psychiatric disorders, especially major depressive disorder.

For many years, benzodiazepines have been a mainstay in the treatment of anxiety. They work by enhancing the effect of γ-aminobutyric acid (GABA) by positive allosteric modulation of the GABA$_A$ receptor, which decreases neuronal excitability and produces a calming effect. Most benzodiazepines have a rapid onset of action, but their duration of action varies (Table 1, page 24). Benzodiazepines also are used to treat several nonpsychiatric conditions (Table 2, page 25).

Although benzodiazepines have many potential uses, they also carry risks that prescribers should recognize. This article reviews some of the risks of benzodiazepine use, identifies patients with higher risks of adverse effects, and presents a practical approach to prescribing these medications.

**A wide range of risks**

**Abuse and addiction.** Perhaps the most commonly recognized risk associated with benzodiazepine use is the potential for abuse and addiction. Prolonged benzodiazepine use typically results in
Prescribing benzodiazepines

Physiologic tolerance, requiring higher dosing to achieve the same initial effect. American Psychiatric Association practice guidelines recognize the potential for benzodiazepine use to result in symptoms of dependence, including cravings and withdrawal, stating that “with ongoing use, all benzodiazepines will produce physiologic dependence in most patients.” High-potency, short-acting compounds such as alprazolam have a higher risk for dependence, toxicity, and abuse. However, long-acting benzodiazepines (such as clonazepam) also can be habit-forming. Because of these properties, it is generally advisable to avoid prescribing benzodiazepines (and short-acting compounds in particular) when treating patients with current or past substance use disorders, except when treating withdrawal.

Limited efficacy for other disorders. Although benzodiazepines can help reduce anxiety in patients with anxiety disorders, they have shown less promise in treating other disorders in which anxiety is a common symptom. Treating PTSD with benzodiazepines does not appear to offer any advantage over placebo, and may even result in increased symptoms over time. There is limited evidence supporting the use of benzodiazepines to treat OCD. Patients with borderline personality disorder who are treated with benzodiazepines may experience an increase in behavioral dysregulation.

Physical ailments. Benzodiazepines can affect comorbid physical ailments. One study found that long-term benzodiazepine use among patients with comorbid pain disorders was correlated with high utilization of medical services and high disability levels. Benzodiazepine use also has been associated with an increased risk of exacerbating respiratory conditions, such as chronic obstructive pulmonary disease, and increased risk of pneumonia.

Pregnancy and breastfeeding. Benzodiazepines carry risks for women who are pregnant or breastfeeding. Benzodiazepine use during pregnancy may increase the relative risk of major malformations and oral clefts. It also may result in neonatal lethargy, sedation, and weight loss. Benzodiazepine withdrawal symptoms can occur in the neonate. Benzodiazepines are secreted in breast milk and can result in sedation among breastfed infants.

Geriatric patients. Older adults may be particularly vulnerable to the adverse effects of benzodiazepines. The Beers Criteria for Potentially Inappropriate Medication Use in Older Adults recommends against prescribing benzodiazepines to geriatric patients. Benzodiazepine use has been associated with an increased risk for falls among older adults, with an increased risk of fractures that can be fatal. Benzodiazepines also have been associated with an increased risk of cognitive dysfunction and dementia. Despite the documented risks of using benzodiazepines in geriatric patients, benzodiazepines continue to be frequently prescribed to this age group. One study found that the rate of prescribing benzodiazepines by primary care physicians increased from 2003 to 2012, primarily among older adults with no diagnosis of pain or a psychiatric disorder.

Mortality. Benzodiazepine use also carries an increased risk of mortality. Benzodiazepine users are at increased risk of motor vehicle accidents because of difficulty maintaining road position. Some research has shown that patients with schizophrenia treated with benzodiazepines have an increased risk of mortality.

Table 1

<table>
<thead>
<tr>
<th>Medication</th>
<th>Half-life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>6 to 12</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>5 to 30</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>18 to 50</td>
</tr>
<tr>
<td>Diazepam</td>
<td>20 to 100</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>10 to 20</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>4 to 15</td>
</tr>
<tr>
<td>Temazepam</td>
<td>8 to 22</td>
</tr>
<tr>
<td>Triazolam</td>
<td>2</td>
</tr>
</tbody>
</table>

Source: Reference 3
increased risk of death compared with those who are prescribed antipsychotics or anti-depressants. Another study showed that patients with schizophrenia who were prescribed benzodiazepines had a greater risk of death by suicide and accidental poisoning. Benzodiazepine use has been associated with suicidal ideation and an increased risk of suicide. Prescription opioids and benzodiazepines are the top 2 causes of overdose-related deaths (benzodiazepines are involved in approximately 31% of fatal overdoses), and from 2002 to 2015 there was a 4.3-fold increase in deaths from benzodiazepine overdose in the United States. CDC guidelines recommend against co-prescribing opioids and benzodiazepines because of the risk of death by respiratory depression. As of August 2016, the FDA required black-box warnings for opioids and benzodiazepines regarding the risk of respiratory depression and death when these agents are used in combination, noting that “If these medicines are prescribed together, limit the dosages and duration of each drug to the minimum possible while achieving the desired clinical effect.”

A sensible approach to prescribing
Given the risks posed by benzodiazepines, what would constitute a sensible approach to their use? Clearly, there are some patients for whom benzodiazepine use should be minimized or avoided (Table 3). In a patient who is deemed a good candidate for benzodiazepines, a long-acting agent may be preferable because of the increased risk of dependence associated with short-acting compounds. Start with a low dose, and use the lowest dose that adequately treats the patient’s symptoms. Using scheduled rather than “as-needed” dosing may help reduce behavioral escape patterns that reinforce anxiety and dependence in the long term.

Before starting a patient on a benzodiazepine, discuss with him (her) the risks of use and an exit plan to discontinue the medication. For example, a benzodiazepine may be prescribed at the same time as a selective serotonin reuptake inhibitor (SSRI), with the goal of weaning off the benzodiazepine once the SSRI has achieved efficacy. Inform the patient that prescribing or treatment may be terminated if it is discovered that the patient is abusing or diverting the medication.

### Table 2

**Uses for benzodiazepines**

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th>Psychiatric symptoms</th>
<th>Nonpsychiatric uses</th>
<th>Rescue medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety disorders</td>
<td>Anxiety</td>
<td>Anticonvulsants</td>
<td>Alcohol or benzodiazepine withdrawal</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Insomnia</td>
<td>Muscle relaxants</td>
<td>Psychotropic adverse effects, such as akathisia</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>Agitation/aggression</td>
<td>Anti-vertigo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Catatonia</td>
<td>Sedative</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3

**Benzodiazepine treatment: High-risk patients**

<table>
<thead>
<tr>
<th>Group</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant or breastfeeding women</td>
<td>Increased risk of fetal malformations; sedation in breastfed infants</td>
</tr>
<tr>
<td>Geriatric patients</td>
<td>Increased risk of falls and cognitive impairment</td>
</tr>
<tr>
<td>Patients with current or past substance use disorders</td>
<td>Risk of abuse or dependence</td>
</tr>
<tr>
<td>Patients using prescribed opioids</td>
<td>Increased risk of respiratory depression and death</td>
</tr>
<tr>
<td>Patients with COPD</td>
<td>Increased risk of adverse respiratory outcomes</td>
</tr>
<tr>
<td>Patients with comorbid PTSD or OCD</td>
<td>No proven efficacy in treating PTSD or OCD</td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease; OCD: obsessive-compulsive disorder; PTSD: posttraumatic stress disorder
Prescribing benzodiazepines

Inform the patient that prescribing or treatment may be terminated if it is discovered that the patient is abusing the medication.

Table 4

<table>
<thead>
<tr>
<th>Non-benzodiazepine treatments for anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacologic</strong></td>
</tr>
<tr>
<td>SSRIs/SNRIs</td>
</tr>
<tr>
<td>Buspirone</td>
</tr>
<tr>
<td>Atypical antipsychotics*</td>
</tr>
<tr>
<td>Mirtazapine*</td>
</tr>
<tr>
<td>TCAs</td>
</tr>
<tr>
<td>MAOIs</td>
</tr>
<tr>
<td>Gabapentin/pregabalin*</td>
</tr>
<tr>
<td>Antihistamines (diphenhydramine,* hydroxyzine)</td>
</tr>
<tr>
<td>Propranolol*</td>
</tr>
<tr>
<td>Anticonvulsants (lamotrigine, topiramate)*</td>
</tr>
</tbody>
</table>

*Off-label use

MAOIs: monamine oxidase inhibitors; SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants

Source: Reference 41

(regularly reviewing the state prescription monitoring program database can help determine if this has occurred). Strongly consider using non-benzodiazepine treatments for anxiety with (or eventually in place of) benzodiazepines (Table 4).

Reducing or stopping benzodiazepines can be challenging. Patients often are reluctant to stop such medications, and abrupt cessation can cause severe withdrawal. Benzodiazepine withdrawal symptoms can be severe or even fatal. Therefore, a safe and collaborative approach to reducing or stopping benzodiazepines is necessary. A starting point might be to review the risks associated with benzodiazepine use with the patient and ask about the frequency of use. Discuss with the patient a slow taper, perhaps reducing the dose by 10% to 25% increments weekly to biweekly. Less motivated patients may require a slower taper, more time, or repeated discussions. When starting a dose reduction, notify the patient that some rebound anxiety or insomnia are to be expected. With any progress the patient makes toward reducing his usage, congratulate him on such progress.

References


### Related Resources


### Drug Brand Names

- Alprazolam - Xanax
- Buspirone - BuSpar
- Clonazapamide - Librium
- Diazepam - Valium
- Diphenhydramine - Benadryl
- Gabapentin - Neurontin
- Hydroxyzine - Vistaril
- Lamotrigine - Lamictal
- Lorazepam - Ativan
- Mirtazapine - Remeron
- Oxazepam - Serax
- Pregabalin - Lyrica
- Praproanol - Inderal
- Temazepam - Restoril
- Topiramate - Topamax
- Triazolam - Halcion

### Clinical Point

When starting a dose reduction, notify the patient that some rebound anxiety or insomnia are to be expected.