Benzodiazepines and Addiction: Long-Term Use and Withdrawal (Part 2)

by Jean-Marc Cloos, MD

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Benzodiazepines will continue to be used to treat patients with anxiety and insomnia until other GABAergic drugs are developed that carry no risk of dependence. Even though benzodiazepines were first marketed 40 years ago, long-term outcome studies are relatively scarce. Addiction and high-dose dependence are rare, but physiological low-dose dependence develops in many patients. Various approaches help patients cope with dependence.

A clear understanding of the particular profile of a specific benzodiazepine, identification of populations at risk, clear indications, and the courage to discontinue benzodiazepine therapy when the medication is no longer useful may help limit problems associated with these agents.

This article is the second of 2 articles on benzodiazepines, such as those of the Royal Australian College of General Practitioners or the World Health Organization, generally recommend a complete clinical evaluation and a clear diagnosis before a benzodiazepine is prescribed. For the management of anxiety and insomnia, try nonpharmacological interventions first and discuss with the patient the various treatment options (including psychotherapy).

Patients need to agree with the decision to take a benzodiazepine after being informed of potential risks of long-term use. The starting dosage should be the lowest possible and of the shortest duration—usually 1 to 3 months. Continued use should be reserved for chronic and relapsing disorders, such as anxiety, when first-line treatments have been ineffective.

The guidelines often do not reflect clinical reality. Clinicians know that benzodiazepines rapidly alleviate symptoms in several acute conditions, and—in the absence of similar rapid and safe alternative treatment options—it would be bad clinical practice not to prescribe them. Having experienced symptom relief, a number of patients tend to continue with the same treatment over the long term. This might be justified if other therapies have a lower risk to benefit ratio, are not sufficiently effective, or are contraindicated. However, benzodiazepines often continue to be prescribed because the therapeutic alternatives are more expensive, are unavailable, or are refused by the patients.

### Table 2

Characteristics of commonly used benzodiazepines in the United States

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>EDD (mg)</th>
<th>DDD (mg)</th>
<th>TDR (mg)</th>
<th>HTD (mg)</th>
<th>Receptor affinity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>0.5</td>
<td>1</td>
<td>0.25 - 4</td>
<td>10 PA</td>
<td>10.6 ± 0.4</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>25</td>
<td>30</td>
<td>10 - 100</td>
<td>300</td>
<td>684 ± 8</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.5</td>
<td>8</td>
<td>0.5 - 8</td>
<td>20 E</td>
<td>2.2 ± 0.2</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>20</td>
<td>20</td>
<td>15 - 60</td>
<td>90 E</td>
<td>190 ± 20</td>
</tr>
<tr>
<td>Diazepam</td>
<td>10</td>
<td>10</td>
<td>4 - 40</td>
<td>Variable</td>
<td>9.8 ± 0.7</td>
</tr>
<tr>
<td>Estazolam†</td>
<td>1 - 2</td>
<td>3</td>
<td>0.5 - 2</td>
<td>4</td>
<td>21.25*</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>15 - 30</td>
<td>30</td>
<td>15 - 30</td>
<td>30</td>
<td>51 ± 2</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1 - 2</td>
<td>2.5</td>
<td>1 - 6</td>
<td>10</td>
<td>3.8 ± 0.2</td>
</tr>
<tr>
<td>Midazolam (IV)</td>
<td>5 - 7.5</td>
<td>20</td>
<td>2 - 20</td>
<td>0.35 mg/kg</td>
<td>4.86 ± 0.07</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>20</td>
<td>50</td>
<td>15 - 120</td>
<td>300</td>
<td>39 ± 3</td>
</tr>
<tr>
<td>Quazepam⁺⁺</td>
<td>20</td>
<td>15</td>
<td>7.5 - 15</td>
<td>30</td>
<td>29.7⁺⁺</td>
</tr>
<tr>
<td>Temazepam</td>
<td>15 - 20</td>
<td>20</td>
<td>10 - 20</td>
<td>40</td>
<td>66 ± 1</td>
</tr>
<tr>
<td>Triazolam</td>
<td>0.25 - 0.5</td>
<td>0.25</td>
<td>0.125 - 0.25</td>
<td>0.5</td>
<td>0.54 ± 0.01</td>
</tr>
</tbody>
</table>

EDD, equivalent dose of diazepam; DDD, daily defined dose; TDR, therapeutic dose range; HTD, highest recommended therapeutic dose; PA, panic attacks; E, epilepsy.
Most clinicians would not agree to provide prescriptions of benzodiazepines if the patient were misusing the drug or using it at dosages above the therapeutic limit. However, the prolonged benzodiazepine prescription at a therapeutic dosage is often played down. Certainly, there are patients with chronic psychiatric disorders for whom benzodiazepines need to be continued long-term. With most transient anxiety and insomnia problems, however, limitations on the use of benzodiazepines seem justified.

Continuation of benzodiazepines not only may prevent patients from finding alternative solutions to their problems but also may dull affect and mask certain mental disorders, such as depression.

### Benzodiazepine withdrawal: general guidelines

Before discontinuing benzodiazepine treatment, make sure that the patient is in good general health and that he or she is informed about symptomatic rebound that frequently occurs during tapering.

The Benzodiazepine Withdrawal Symptom Questionnaire or the 35-item or 20-item version of the Physician Withdrawal Checklist can be used to gauge withdrawal symptoms.

It is important to address any underlying medical or psychiatric condition before discontinuing benzodiazepine treatment. Alternative treatments of anxiety, such as antidepressants, should be initiated several weeks before benzodiazepine discontinuation and maintained throughout the withdrawal process. Also, a nonbenzodiazepine substitute may be useful for patients with sleep disorders.

Gradual dosage reduction combined with psychological interventions (often cognitive-behavioral) appears to be the most effective withdrawal method. A switch from a short–half-life to a long–half-life benzodiazepine (eg, diazepam) will avoid high plasma level variations during tapering, but the tapering can be done with any benzodiazepine given at fixed intervals throughout the day (eg, 2 to 4 times per day).

With higher dosages or with multiple benzodiazepines, a switch to an equivalent diazepam dosage for 1 month before discontinuation may be beneficial. The general recommendation is to reduce the dosage by 10% to 25% every week. If withdrawal symptoms become particularly severe toward the end of treatment, tapering can be slowed.

There is no clear evidence about the optimum rate of tapering. The speed may be adapted according to the withdrawal symptoms; however, the general recommendation is to withdraw the drug in 4 to 6 weeks in patients taking low therapeutic doses. Withdrawal should take no longer than 6 months. Slow withdrawal may diminish the occurrence of withdrawal symptoms. When possible, however, a quicker withdrawal regimen is preferable.

An example of (slow) diazepam tapering is given in Table 1. The initial dose of diazepam can be calculated via an equivalence table, particularly helpful in patients consuming different kinds of benzodiazepines. Table 2 summarizes the characteristics of benzodiazepines commonly used in the United States.

### Table 1

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Rate of reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 20 mg</td>
<td>10 mg/wk</td>
</tr>
<tr>
<td>&gt; 10 mg and ≤20 mg</td>
<td>5 mg/wk</td>
</tr>
<tr>
<td>≤10 mg</td>
<td>Reduce by 2.5 mg/wk as follows: Week 1: 4 × 2.5 mg/d; Week 2: 2.5 mg/d; Week 3: 2.5 mg/d; Week 4: 0 mg; 2.5 mg; 0 mg; 0 mg</td>
</tr>
</tbody>
</table>

This activity will provide participants with education on benzodiazepines, their uses, and safety aspects.

**GOAL STATEMENT**
This activity will provide participants with education on benzodiazepines, their uses, and safety aspects.

**TARGET AUDIENCE**
This continuing medical education activity is intended for psychiatrists, psychologists, primary care physicians, nurse practitioners, and other health care professionals who seek to improve their care for patients with mental health disorders.

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**FACULTY DISCLOSURES**
Dr. Cloos reports no conflicts of interest concerning the subject matter of this article.

This activity has been independently reviewed for balance.

**EXPIRATION DATE:** August 20, 2010
**RELEASE DATE:** August 20, 2011

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**Category 1 Posttest**

1. Prevalence rates of benzodiazepine use in the general population vary because of different study criteria, but they range
   A. Approximately up to 10%
   B. Approximately up to 20%
   C. Approximately up to 30%
   D. Approximately up to 40%

2. In which of the following groups is benzodiazepine use most common?
   A. Males
   B. Adolescents
   C. Middle-aged women
   D. Older adults

3. The clinical reality is that contrary to most guidelines for benzodiazepine use for the treatment of acute symptoms, many patients continue with the treatment over the long term.
   A. True
   B. False

4. Long-term use of benzodiazepines is likely to result in which of the following?
   A. Repeated dose escalation
   B. Recreational abuse
   C. High-dose dependence
   D. All of the above
   E. None of the above

5. Which of the following is recommended to avoid withdrawal symptoms on discontinuation of a benzodiazepine?
   A. Gradual dosage reduction
   B. Psychological intervention
   C. Switching from an agent with a short half-life to one with a long half-life
   D. All of the above
   E. None of the above

**CREDITS:** 1.5
**RELEASE DATE:** August 20, 2010
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**LEARNING OBJECTIVES**
After completing this activity, participants should be able to:
- Discuss the prevalence rates of benzodiazepines in the general population and identify groups at high risk for long-term use
- Identify issues associated with long-term use of benzodiazepines
- Explain withdrawal principles as they pertain to benzodiazepines

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