Re-evaluating the Use of Benzodiazepines
A Focus on High-risk Populations
Re-evaluating the Use of Benzodiazepines
A VA Clinician’s Guide

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Benzodiazepines are widely used in the treatment of anxiety, sleep, depression (as adjuvant therapy), and as muscle relaxants. In the United States, approximately 5.6% of the adult population uses a benzodiazepine. Although it is recommended that treatment with benzodiazepines be limited to short-term use, the prevalence of long-term use remains widespread.

- Benzodiazepine use is nearly twice as prevalent in women.
- Benzodiazepines have increasing utilization with increasing age (see figure 1).
- Benzodiazepines are prescribed at greater rates than antidepressants for the treatment of depression and anxiety, despite evidence that supports antidepressants as first line medications.

Between 1996 and 2013, the number of adults filling a benzodiazepine prescription increased by 67% and the total quantity filled more than tripled.

**Figure 1. Prevalence of Benzodiazepine Use in the United States**

This retrospective analysis done in 2008 found increasing benzodiazepine use with age. The total percentage of long-term use of benzodiazepines (>120 days) also increased with age from 0.4% (18–35) to 2.7% (65–80). This is roughly one-quarter of individuals receiving a benzodiazepine in all age groups.
While there are benefits associated with the short-term utilization of benzodiazepines, these medications are associated with both short and long-term adverse consequences.¹

These adverse consequences are increased in certain populations and should not be minimized as they can sometimes result in death.²

**Potentially Deadly Outcomes Related to Benzodiazepines**

- Multiple epidemiologic studies have found elevated mortality risk associated with benzodiazepine utilization (odds ratio >1 in 33 studies)¹¹,¹²
- Increased risk of motor vehicle accident by 60%¹⁰
- Increased risk of overdose (OD) death²,¹³,¹⁴
  - After opioids, benzodiazepines are the drug class most commonly involved in intentional and unintentional pharmaceutical OD deaths (29.4%)¹⁴
  - The OD death rate involving benzodiazepine from 2001–2014 increased five fold, with opioids involved in 75% of these deaths²,¹⁵

**Figure 2.**

U.S. Overdose Deaths Involving a Benzodiazepine¹⁵

The figure above depicts the total number of U.S. overdose deaths involving a benzodiazepine.

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**Serious adverse consequences associated with benzodiazepines**⁸–¹¹

- Depressed mood
- Disinhibition
- Cognitive impairment
- Falls/hip fractures
- Traffic accidents
- Tolerance/dependence
- Accidental overdose, particularly when combined with other sedatives (e.g. alcohol, opioids)
Additional Benzodiazepine Risks

Several studies indicate that short and long-term use of benzodiazepines may lead to impairment across many cognitive domains.\textsuperscript{16–19}

In addition, the evidence, though mixed, has associated benzodiazepines use with increased risk of dementia.\textsuperscript{20–22}

![Figure 3. The Impact of Long-term Use of Benzodiazepines on Cognitive Function\textsuperscript{16}]

Thirteen studies were included in this meta-analysis in which significant, moderate-to-large weighted effect size were found across all categories of cognition with long-term (>1 year) benzodiazepine use. This suggests that long-term benzodiazepine users are potentially impaired across many cognitive domains.

Finally, benzodiazepines are widely acknowledged to cause physical dependence, with withdrawal effects possibly seen within as little as 4–6 weeks of continued therapy, and can cause addiction in some.\textsuperscript{7}
Benzodiazepines Role in Treatment

Despite benzodiazepine risks there are situations in which rapid control of symptoms (severe anxiety or panic attacks, seizures, alcohol or benzodiazepine withdrawal) is warranted. Anxiety and insomnia are common indications in which benzodiazepines are used. For these conditions, guidelines and consensus statements recommend that benzodiazepines should only be used for short-term treatment. 7,27,28
### Table 1. Treatments for Anxiety Disorders and Insomnia*

<table>
<thead>
<tr>
<th>Anxiety Disorders</th>
<th>Insomnia**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-drug</strong></td>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>• CBT</td>
<td>• SSRI</td>
</tr>
<tr>
<td>• Exposure therapy</td>
<td>• SNRI</td>
</tr>
</tbody>
</table>

#### 1st Line Treatment Options

- **Benzodiazepines**
  - Only use in patients with very distressing or impairing symptoms in which rapid control is necessary
  - In most cases benzodiazepine use should be limited to 4–6 weeks
  - Tolerance develops quickly to the ability to induce and prolong sleep
  - Commonly cause rebound insomnia upon discontinuation and can occur after 1–2 weeks of treatment
  - Use intermittently (e.g. <5 nights per week) and short-term

Benzodiazepines should be avoided if the patient has symptoms of:
- Posttraumatic stress disorder (PTSD)
- Chronic respiratory disease (e.g. COPD, sleep apnea)
- Receiving other CNS depressants (e.g. opioids)
- Substance use disorder (e.g. alcohol or opioid use disorder)
- History of traumatic brain injury
- Dementia
- Elderly

CBT-I = cognitive behavioral therapy for insomnia; CBT = cognitive behavioral therapy; COPD = chronic obstructive pulmonary disease; CNS = central nervous system; SSRI = selective serotonin reuptake inhibitors; SNRI = selective norepinephrine reuptake inhibitors. *Additional information on treatment can be found in Re-evaluating Benzodiazepines Quick Reference Guide. **Several comorbid conditions (e.g. alcohol use disorder, depression) can contribute to insomnia. †Doxepin 10 mg can be considered as an alternative to the FDA approved dose for insomnia (3–6 mg) based on clinical judgment.

NF = Not currently on VA National Formulary
There are several populations in which benzodiazepine use carries a larger risk. In these populations the risks of harm from a benzodiazepine may outweigh the benefits. Several of the high risk populations, as outlined below, will be highlighted later in this document.

**Highlighted High Risk Populations**

- Co-administration of opioids  Page 7
- Elderly  Page 9
- Dementia  Page 12
- PTSD  Page 14
- Chronic Respiratory Disease  Page 16
Lethal Drug Combinations: Opioids and Benzodiazepines

Benzodiazepines when co-administered with substances with sedative properties, like opioids and alcohol, can result in unintentional fatal outcomes.¹³

- Twenty-seven percent of Veterans who received opioids also received benzodiazepines¹³
- Benzodiazepines are commonly involved in opioid-related OD death (30.1%)¹⁴
- Risk of OD death increases with increasing benzodiazepine daily dose²,¹³

In our Veterans that have died of opioid overdose, 49% have concurrent benzodiazepines prescribed¹³

Figure 6.
Opioid Overdose with Co-administered Benzodiazepine¹³

This case-cohort study (2004–2009) found that of the 2,400 Veterans in the study population who died from an opioid overdose death, 1,185 (49%) died during a period in which they had been prescribed concurrent benzodiazepines. Risk of overdose increased as daily benzodiazepine dose increased.
Beyond the increased risk of accidental OD death, patients on both opioids and benzodiazepines have worse health outcomes, greater utilization of healthcare resources, and higher mental health comorbidities.\textsuperscript{32–35}

**Figure 7.** High Risk Associations with Chronic Opioid Therapy Plus Benzodiazepines\textsuperscript{32}

Prospective cohort study that compared a sample of 1,220 chronic noncancer pain patients prescribed chronic opioids and categorized them based on their benzodiazepine use patterns. The patients taking benzodiazepines daily represent a high-risk group with multiple comorbid mental health disorders.

Avoid combining benzodiazepines and opioid medications. Identify Veterans who are on this combination and safely taper one or both medications.
Benzodiazepine Risks in the Older Veteran

The 2015 American Geriatrics Society Beers Criteria recommend avoiding benzodiazepines in this population.\textsuperscript{36} Despite these consensus recommendations and known risk factors:

- Benzodiazepine use is three times more prevalent in older adults compared to younger adults\textsuperscript{3,36}
- Roughly one-quarter of long-term benzodiazepine use is in patients ≥65 years of age\textsuperscript{3}

Avoid starting benzodiazepines in older Veterans.

When surveyed about benzodiazepine use, prescribers underestimate the risks in their geriatric patients.\textsuperscript{41}

Some Provider Perceptions Include:
- A stable dose of benzodiazepine means that it is safe and effective\textsuperscript{41}
- Attempts to discontinue will fail\textsuperscript{41}
Benzodiazepines are **NOT** safe and effective in older adults

Sedative hypnotics for the treatment of insomnia have a small magnitude of effect and substantial risk in patients ≥60 years old.\(^{37}\)

- **MORE THAN TWO TIMES** as likely to be associated with adverse events than improved sleep\(^{37}\)
- **3-FOLD** increase in dizziness, loss of balance and falls\(^{37}\)
- **4-FOLD** increase in residual morning sedation\(^{37}\)
- **5-FOLD** increase in memory loss, confusion and disorientation\(^{37}\)

**Discontinuation of benzodiazepines CAN be successful**

![Figure 9. Use of Sedative Hypnotics in Older Patients with Insomnia\(^{37}\)](image)

Meta-analysis of 24 studies with a total of 2,417 patients ≥60 years old who were prescribed a sedative hypnotic (benzodiazepines, non-benzodiazepine sedative-hypnotics, diphenhydramine) for sleep.

![Figure 10. Withdrawal of Benzodiazepines for Insomnia in an Older Adult Population\(^{42}\)](image)

In this double-blind, placebo controlled study, patients age ≥65 on chronic benzodiazepines (n = 192) for insomnia were identified, of which 101 wished to discontinue their benzodiazepine. They were compared to patients (n = 35) who chose to continue benzodiazepines. Patients were tapered over 8–9 weeks. Eighty percent successfully withdrew from their benzodiazepine. Withdrawers and continuers did not differ in sleep or benzodiazepine withdrawal symptoms and withdrawers had subtle cognitive improvements.
There may be times when benzodiazepines are appropriate in the older population (e.g. seizure disorders, alcohol withdrawal).\textsuperscript{7,36} However, if it is determined that a benzodiazepine is necessary, then it is advised to use the lowest dose for the shortest duration possible.

Figure 11. Special Considerations for Benzodiazepine Use in the Elderly\textsuperscript{7,36}

If an older Veteran is taking benzodiazepines, discuss tapering and discontinuation to reduce the risk of adverse events.
Benzodiazepines in Patients with Dementia

- Use is associated with increased risk of health-related complications and hospitalizations in patients with dementia\(^\text{36}\)
- No evidence of improvement of sleep quality in patients with dementia\(^\text{43}\)
- Benzodiazepines may cause or exacerbate:\(^\text{36,43}\)
  - Aggravated cognitive deterioration
  - Higher risk of falls
  - Aspiration
  - Death
  - Paradoxical agitation

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure12.png}
\caption*{Figure 12. Treatment Guidelines for Behavioral and Psychological Symptoms of Dementia\(^\text{44,45}\)}
\end{figure}
\end{center}

\begin{itemize}
  \item Describe the problematic behavior (via discussion with caregiver and patient, if possible)
  \item Investigate: look for triggering factors (e.g. infection (e.g. urinary tract infection), medications, drug-drug interactions, constipation, depression, pain) and eliminate
  \item Create a provider, caregiver, patient and team collaboration to create and implement treatment plan focused on psychosocial interventions (nonpharmacologic)
  \item Evaluate whether the recommended strategies were attempted and effective
\end{itemize}

Medication should be the last resort after behavioral and environmental modifications failed (exceptions: imminent risk; major depression; psychosis causing harm; aggression with potential to cause harm)
Behavioral strategies are recommended as the preferred first-line treatment approach for non-cognitive neuropsychiatric symptoms of dementia, except in emergency situations when these symptoms could lead to imminent danger or otherwise compromise safety. Consult Psychiatry or Psychology for assistance with developing behavioral strategies.

<table>
<thead>
<tr>
<th>Table 2. Consider Non-drug Approaches in All Dementia Patients with Behavioral Symptoms(^{44-46})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reorient:</strong> gently remind of person, place, time</td>
</tr>
<tr>
<td><strong>Calm:</strong> offer exercise, music, massage, aromatherapy</td>
</tr>
<tr>
<td><strong>Comfort:</strong> address temperature, lighting, hunger, thirst, pain</td>
</tr>
<tr>
<td><strong>Reduce Distress:</strong> reduce noise, correct hearing/vision, provide structure, allow time to respond</td>
</tr>
<tr>
<td><strong>Supervise:</strong> provide companionship, observation, reduce choices, provide simple activities</td>
</tr>
</tbody>
</table>

Use nonpharmacological strategies as first-line treatment for behavioral and psychological symptoms of dementia.
Benzodiazepines are ineffective for the treatment and prevention of PTSD and any potential benefits are outweighed by the risks.\textsuperscript{23,26}

Figure 13. Specific Risks of Benzodiazepine Use in PTSD\textsuperscript{23}

<table>
<thead>
<tr>
<th>Core Symptoms</th>
<th>Benzodiazepines do not reduce the core symptoms of PTSD or improve PTSD-related sleep dysfunction\textsuperscript{23,47,48}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance Use Disorder</td>
<td>Co-occurring substance use disorders are very high in PTSD, creating an increased risk of overdose and potential problems with tolerance and dependence\textsuperscript{29}</td>
</tr>
<tr>
<td>Withdrawal Symptoms</td>
<td>Withdrawal of benzodiazepines can worsen existing symptoms, resulting in increased anxiety, sleep disturbances, rage, hyper-alertness, increased nightmares and intrusive thoughts\textsuperscript{48}</td>
</tr>
<tr>
<td>Aggressive Behaviors</td>
<td>Although aggressive behaviors are not commonly observed with PTSD, they are more likely to occur with disinhibiting substances (alcohol, benzodiazepines), particularly if other aggravating situations are present (e.g. financial stressors, homelessness)\textsuperscript{49}</td>
</tr>
</tbody>
</table>
Benzodiazepines have been found to increase aggressive behaviors over time in Veterans with PTSD (p <0.05; 95% CI [0.11–0.9]).

Avoid starting benzodiazepines in patients with PTSD and discuss discontinuation with Veterans currently on these high risk/low benefit medications.

Marijuana vs. Benzodiazepines

Some Veterans may turn to marijuana to replace their benzodiazepine as it is being touted as a safer, less sedating, more effective alternative. Marijuana’s role in the treatment of PTSD is largely unknown. However, preliminary evidence suggests that marijuana use may worsen PTSD symptoms.

It is important to discuss marijuana’s potential effects on PTSD.
Benzodiazepines and Negative Respiratory Outcomes

Several studies confirm that benzodiazepines may adversely impact respiration through a variety of mechanisms.\textsuperscript{11,56,57} 

*Brief Cognitive Behavioral Therapy can help decrease the sensation of dyspnea as well as symptoms of anxiety and depression in patients with COPD.\textsuperscript{58} 

The potential for negative respiratory outcomes needs to be taken into consideration, especially for vulnerable subgroups like individuals with sleep apnea and COPD.

In Veterans with chronic respiratory diseases avoid starting benzodiazepines and consider safely tapering if the Veteran is currently taking a benzodiazepine.
Reducing Long-term Benzodiazepine Use

What Can We Do to Prevent Long-term Benzodiazepine Use?

Many patients may experience difficulties with discontinuing benzodiazepines at the end of an acute treatment period. To avoid this, do not initiate benzodiazepines. If benzodiazepines are started, a clearly defined exit plan should be determined and then communicated to the Veteran.

Figure 15.
Have a Benzodiazepine Exit Plan

Clearly defined duration that is explicitly described to Veteran

Stop Short-term Treatment from Turning into Long-term Use
A maximum of 4–6 weeks duration is recommended

Exit plan explained and explored (e.g. short taper or initiation of alternative treatments)

If determined that a benzodiazepine is necessary, use it for the shortest duration possible (e.g. 14 days) and have a clearly defined and explained exit plan.

Strategies for Successful Benzodiazepine Discontinuation

Several studies have found that minimal educational interventions, like letter campaigns or brief interventions, are effective strategies to assist patients with decreasing or stopping their benzodiazepines.59–61
SIW = study intervention group with written instructions. A total of 75 general practitioners (532 patients) were randomized to provide care as usual or a brief educational intervention (information on benzodiazepine dependence, abstinence and withdrawal symptoms; risks of long-term use, memory and cognitive impairment, accidents and falls; reassurance about reducing medication) and a self-help leaflet to improve sleep. The number needed to treat was 4 (95% CI 3–5). There was no increase in anxiety, depression, insomnia or alcohol consumption and slight improvements in anxiety and depression symptoms were noted in intervention group. Most frequently reported withdrawal symptoms were insomnia, anxiety and irritability.
Explore and acknowledge perceived benefits and harms and allow Veteran to express his/her concerns.64

Figure 18.
Structure of a Brief Educational Intervention

Figure 19.
Example Interview

Express concern about the Veteran’s use of benzodiazepines.

Provide education on benzodiazepines potential risks like memory and cognitive impairment, car accidents, falls, worsening of PTSD. Inform them that sometimes with discontinuation co-occurring health conditions (if present), such as depression, anxiety, and insomnia improve slightly with discontinuation.

Assess patient’s readiness to begin taper process and give them information on benzodiazepine dependence and withdrawal symptoms.

Support patient in setting a goal to reduce or discontinue benzodiazepine and arrive at a shared decision in treatment plan. Provide a written taper schedule.

Suggest treatment referral, if appropriate (e.g. psychotherapy).

“I am concerned about your use of benzodiazepines”

“Because of your [age or other risk factors], I am concerned that your benzodiazepine use may put you at increased risk for [relevant repercussion].”

“What do you see as the possible benefits of stopping or reducing the dose? What concerns you about stopping? What ideas do you have about addressing these concerns?”

If patient indicates no desire to change, provide information handout. “What would be a reason you might consider changing your medication/benzodiazepine?”

“What changes are you willing to make to meet this goal?”

“Would you be willing to talk to one of my colleagues to learn about options to support your changes?”
Advise Veterans on the benefits of stopping their benzodiazepines and work with them to develop a discontinuation strategy.

Seventy-six older adult outpatients with chronic insomnia and prolonged use (mean duration of 19.3 years) of a benzodiazepine for sleep were randomly assigned for a 10-week intervention consisting of a supervised benzodiazepine withdrawal program (n = 25), cognitive behavior therapy (CBT) for insomnia (n = 24), or supervised withdrawal plus cognitive behavior therapy (n = 27). All three interventions produced significant reductions in both the quantity (90% reduction) and frequency (80% reduction) of benzodiazepine use (p <0.0001).
After the decision has been made to taper the benzodiazepine make sure that the Veteran is aware of and provided education on the possible withdrawal and rebound symptoms and maintain open lines of communication with the patient.

Slow tapering protocol (3–6 months) is preferred and is associated with total cessation of benzodiazepine use in about two-thirds of patients.66

**Benzodiazepine Tapering Strategies:**

- Gradually taper the original benzodiazepine66 OR
- Substitute with a longer-acting benzodiazepine then gradually taper66 OR
- Taper to lower dose of original benzodiazepine then switch to a longer-acting benzodiazepine

### Table 3. Benzodiazepine Withdrawal Symptoms7

<table>
<thead>
<tr>
<th>Psychological</th>
<th>Physical</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anxiety/irritability</td>
<td>• Stiffness</td>
</tr>
<tr>
<td>• Insomnia/nightmares</td>
<td>• Weakness</td>
</tr>
<tr>
<td>• Depersonalization</td>
<td>• Gastrointestinal disturbance</td>
</tr>
<tr>
<td>• Decreased memory and concentration</td>
<td>• Flu like symptoms</td>
</tr>
<tr>
<td>• Delusion and hallucinations</td>
<td>• Paresthesia</td>
</tr>
<tr>
<td>• Depression</td>
<td>• Visual disturbances</td>
</tr>
<tr>
<td></td>
<td>• Seizures</td>
</tr>
</tbody>
</table>

Almost all patients report withdrawal symptoms upon discontinuation of a therapeutic dose of benzodiazepines.67 Withdrawal symptoms can occur after 4–6 weeks of continuous use.
Table 4. Benzodiazepine Dosage Equivalents and Taper Schedules

<table>
<thead>
<tr>
<th>Benzodiazepine Agent</th>
<th>Approximate Dosage Equivalents</th>
<th>Elimination Half-Life (may include active metabolites)</th>
<th>Example Taper Schedules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlordiazepoxide</td>
<td>25 mg</td>
<td>&gt;100 hours</td>
<td>Shorter Taper (e.g. 3 months)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>10 mg</td>
<td>&gt;100 hours</td>
<td>• Reduce dose by 50% the first 2–4 weeks (e.g. 25% decrease every 2 weeks)</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>1 mg</td>
<td>20–50 hours</td>
<td>• Maintain on that dose 1–2 months Then</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2 mg</td>
<td>10–20 hours</td>
<td>• Reduce dose by 25% every two weeks</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>1 mg</td>
<td>12–15 hours</td>
<td>Longer Taper (e.g. 6 months)</td>
</tr>
<tr>
<td>Temazepam</td>
<td>15 mg</td>
<td>10–20 hours</td>
<td>• 10–25% every 4 weeks</td>
</tr>
</tbody>
</table>

Switching to a longer acting benzodiazepine may be considered if clinically appropriate; in geriatric patients consider tapering the short acting agent until withdrawal symptoms are seen then switch to a longer acting agent; high dose alprazolam may not have complete cross tolerance, and a gradual switch to diazepam or clonazepam before taper may be appropriate; other treatment modalities should be considered (e.g. antidepressants for anxiety) if clinically appropriate.

- Provide written instructions for the taper schedule
- Allow for flexibility of taper schedule to accommodate issues that may arise
- Remember if discontinuation cannot be achieved, reduction in dose is still valuable
- There is limited and conflicting information on medications used to treat benzodiazepine withdrawal\textsuperscript{1,68,69}
- If withdrawal is experienced hold or slow down the taper schedule
Summary of Strategies to Discontinue Benzodiazepines

1. Determine Benefit vs. Harm of Benzodiazepine Therapy
   - Does the benzodiazepine therapy continue to be indicated?
   - What specific risk factors does the Veteran have?
   - Does the benefit of the benzodiazepine outweigh the risk?

2. Employ Strategies that Help with Long-term Benzodiazepine Discontinuation
   - Recommend gradual dose reduction and discontinuation
   - Use educational interventions to achieve better discontinuation outcomes
   - Offer psychotherapy interventions (e.g. cognitive behavioral therapy for insomnia)

   Minimal Educational Interventions
   - Discontinuation education letter/pamphlet
   - Consultation with clinician to discuss risks of long-term benzodiazepine use and benefits of discontinuation
   - Self-help instructions (e.g. sleep hygiene)

3. Perform Slow Taper Over Months
   - Provide written instructions
   - Educate patient on signs and symptoms of withdrawal
REFERENCES


U.S. Department of Veterans Affairs

This reference guide was created to be used as a tool for VA providers and is available to use from the Academic Detailing Service SharePoint.

These are general recommendations only; specific clinical decisions should be made by the treating provider based on an individual patient’s clinical condition.

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