Re-evaluating the Use of Benzodiazepines

A VA Clinician's Guide

VA

U.S. Department of Veterans Affairs

Veterans Health Administration

PBM Academic Detailing Services

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Prevalence of benzodiazepine use

Millions of people are prescribed benzodiazepines for the treatment of anxiety, insomnia, depression, muscle spasms, and neurologic conditions.[1-3] Best practice guidance recommends short-term use,[4-6] but the reality is a large number of patients receive these drugs on a long-term basis.[7-9]

Older adults still have the highest prevalence of benzodiazepine use compared to younger adults.[10]

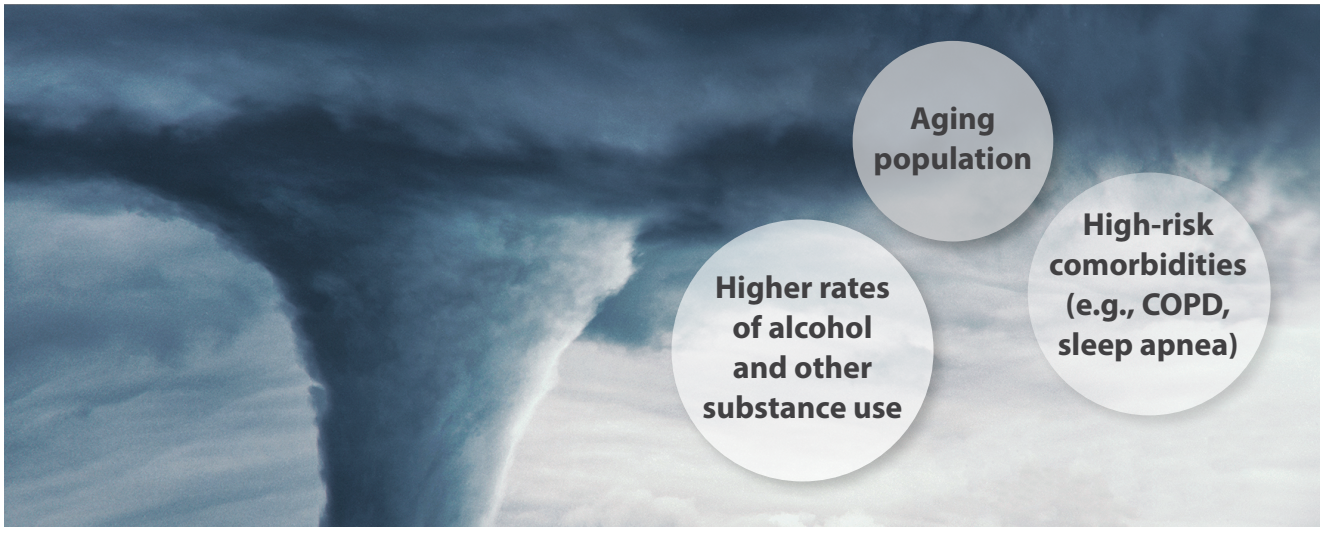
Veterans between 50-64 years-old have the highest prescribed use of benzodiazepines.[11]

Higher rates of alcohol and other substance use are also found in this aging population.[12]

The combination of advanced age, benzodiazepine use combined with alcohol and other substances, and high-risk medical comorbidities can potentially put them **at an increased risk of a fatal overdose.[12]**

Benzodiazepines are often combined with alcohol and other substances. This can have fatal consequences, particularly in aging populations.[13]

This could be the perfect storm:[13]



Serious outcomes associated with benzodiazepines

Overdose (OD) death[2,14,15]

Benzodiazepines are the second most common medication class involved in intentional and unintentional pharmaceutical OD deaths.[16] The OD death rate involving benzodiazepines rose 8-fold from 2000-2018, with opioids involved in 85% of these deaths in 2018.[2,16]

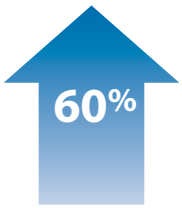
CAUTION: Overdose risk is not just with opioids! While this combination is well-known, much less attention is given to alcohol and benzodiazepines which also has a risk of overdose when combined.[12]

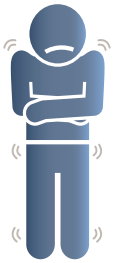
All-cause mortality

- Increases 60% in patients on benzodiazepines.[17]
- No studies (N=33) show a protective effect on mortality from benzodiazepines.[18]

Motor vehicle accident

Risk increases by 60%.[19]





Dependence and withdrawal

Dependence occurs in nearly all patients taking chronic benzodiazepines within as little as 4-6 weeks of continued therapy. In some, it can cause addiction.[20,21]

Cognitive impairment

- Short- and long-term use of benzodiazepines may lead to impairment across many cognitive domains.[22-25]
- Long-term use impacts the spectrum of domains of cognitive function, especially verbal memory.[22]

Falls risk

The risk of falls increases in older adults who use benzodiazepines and can double in those age 80 and over.[26] The risk of hip fractures also rises with benzodiazepine use.[27]

Respiratory outcomes with benzodiazepine use

- **General population:** Use has been associated with a 50% risk of community acquired pneumonia.[28]
- **Patients with COPD:** Use increases the risk of outpatient respiratory exacerbations, emergency room visits, and mortality.[29-32]
- **Patients with sleep apnea:** Use worsens respiratory outcomes and oxygen levels overnight.[33,34]

Pregnancy related outcomes

- A 2-fold increased risk of preterm birth in women using benzodiazepines during pregnancy.[35]
- Advanced levels of care may be required when benzodiazepines are prescribed, such as cesarean delivery and neonatal intensive care admission.[36,37]

There are several populations in which benzodiazepine use carries a larger risk *(see Table 1)*. In these populations, the risks of harm from a benzodiazepine may outweigh the benefits.

Table 1. Evaluating benzodiazepines in high-risk populations

Posttraumatic stress disorder (PTSD)	• Benzodiazepines have not been shown to reduce PTSD symptoms or related sleep dysfunction, and are associated with significant harm.[20,38-41]
Chronic respiratory disease (e.g., chronic obstructive pulmonary disease [COPD], sleep apnea)	**Sleep apnea** Benzodiazepines can significantly lower minimum oxygen levels during the night.[6,42,43] **COPD** Benzodiazepines increase the risk of respiratory exacerbations by 45% and emergency department visits by 92% compared to non-users.[30,44] Patients with COPD requiring help with feelings of dyspnea may benefit from:[45] • Optimizing COPD treatment • Pulmonary rehabilitation • Brief CBT and mind-body interventions (e.g., yoga, relaxation) which can help with symptoms of anxiety and depression. • Other palliative treatments of dyspnea (e.g., low dose morphine [10-30 mg per day]), neuromuscular electrical stimulation)[32,46]
Receiving other CNS depressants (e.g., opioids)	Patients taking both opioids and benzodiazepines are twice as likely to die of an overdose.[17]
Substance use disorder (e.g., alcohol or opioid use disorder)	Benzodiazepines are frequently combined with other substances. Fifteen percent of patients use heroin and benzodiazepines, with 75% using both at least weekly.[47] Up to 40% of patients used benzodiazepines and alcohol together.[47]
History of traumatic brain injury	Cognitive recovery may be delayed with use of benzodiazepines.[48]

Dementia	• Use is associated with increased risk of health-related complications and hospitalizations in patients with dementia.[49] • No evidence of improvement of sleep quality.[50] • May cause or exacerbate: cognitive deterioration; risk of falls; aspiration; death; paradoxical agitation.[49,50] • Patients with behavioral and psychological symptoms of dementia should first be managed with non-drug options that focus on changes to the environment and behaviors.[52,53]
Older age (e.g., age 65 and older)	• Benzodiazepines are associated with significant risk in the elderly (falls, hip fractures, sedation, cognitive impairment).[35,57-61] • Benzodiazepines have been associated with as high as a 40% increased risk for hip fracture in older adults.[51]

Avoid starting benzodiazepines in high-risk Veterans and review chronic use to ensure continued need.

Remember, just because a Veteran has been on a benzodiazepine for years does not mean that they are safe or still effective.

Common misperceptions of benzodiazepine use in older adults downplays risk, leading to long-term use.[52]

Misperception[52]	Reality[22-27,53,54]
A stable benzodiazepine dose is safe and effective.	Older adults are vulnerable to cognitive and psychomotor effects of benzodiazepines. Benzodiazepines are not always effective.
Attempts to discontinue benzodiazepines will fail.	Many older adults can successfully taper and discontinue benzodiazepines.

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

Benzodiazepine's role in treatment

Despite benzodiazepine risks, there are situations in which rapid control of symptoms is warranted.[21,55]

Anxiety and insomnia are two of the most common indications for benzodiazepines. Guidelines and consensus statements recommend that benzodiazepines should only be used for short-term treatment (about 4 weeks) for these conditions.[1,4,5,56]

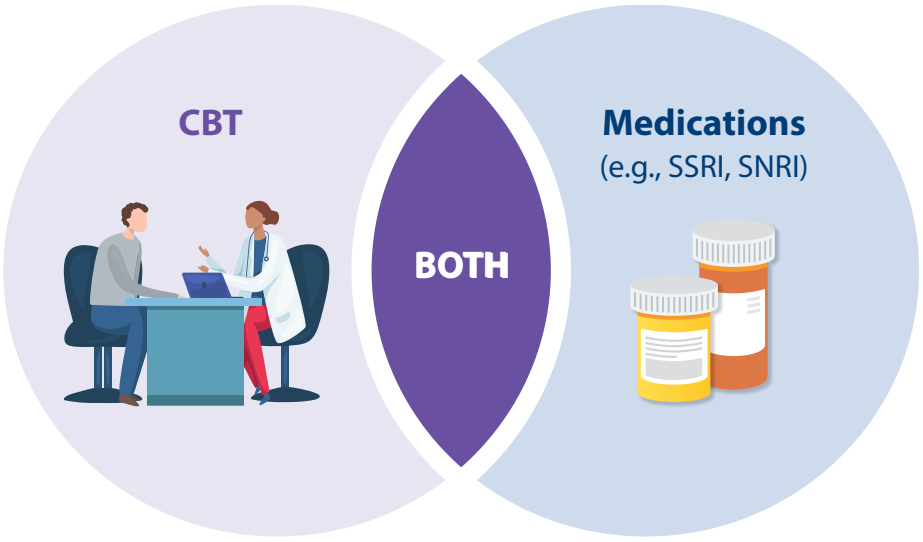
Situations where rapid control of symptoms may be needed:

- ☑ **Severe anxiety**
- ☑ **Panic attacks**
- ☑ **Seizures**
- ☑ **Alcohol or benzodiazepine withdrawal**

Relieving anxiety without relying on benzodiazepines

Management decisions for the treatment of anxiety depend on patient factors and clinical presentation. For the majority of patients, initial treatment is cognitive behavioral therapy (CBT), medication (e.g., a selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor [SNRI]), or a combination of both.[56-58]

Figure 1. Initial treatment for anxiety



Benzodiazepines should be reserved for patients with very distressing or impairing symptoms in which acute, rapid control is necessary and, in most cases, limited to 4-6 weeks while maintenance medication is being titrated.

Helping Veterans get their rest: addressing insomnia

Insomnia is a common reason for patients to receive a benzodiazepine, but alternative treatments are preferred to manage insomnia.[5,59]

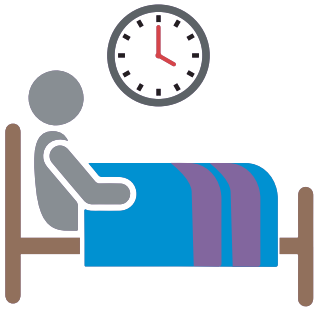


Figure 2. Mapping out a plan for managing insomnia[6,59,60]

Start with offering evidence-based behavioral therapies

- Cognitive behavioral therapy for insomnia (CBT-I) is recommended as first-line treatment for chronic insomnia.
- Brief behavioral therapy for insomnia (BBT-I) can also be encouraged but is not as effective as CBT-I.

If patient still suffers from insomnia, or if CBT-I is not a good option

Consider medication for chronic insomnia

- Intermittent (e.g., 3 or 5 days/week) dosing for a period of < 2 weeks may help.
- Preferred options include low-dose doxepin (3 or 6 mg) and non-benzodiazepine receptor agonist (e.g., zolpidem).
- Continue to offer CBT-I, if not already completed.

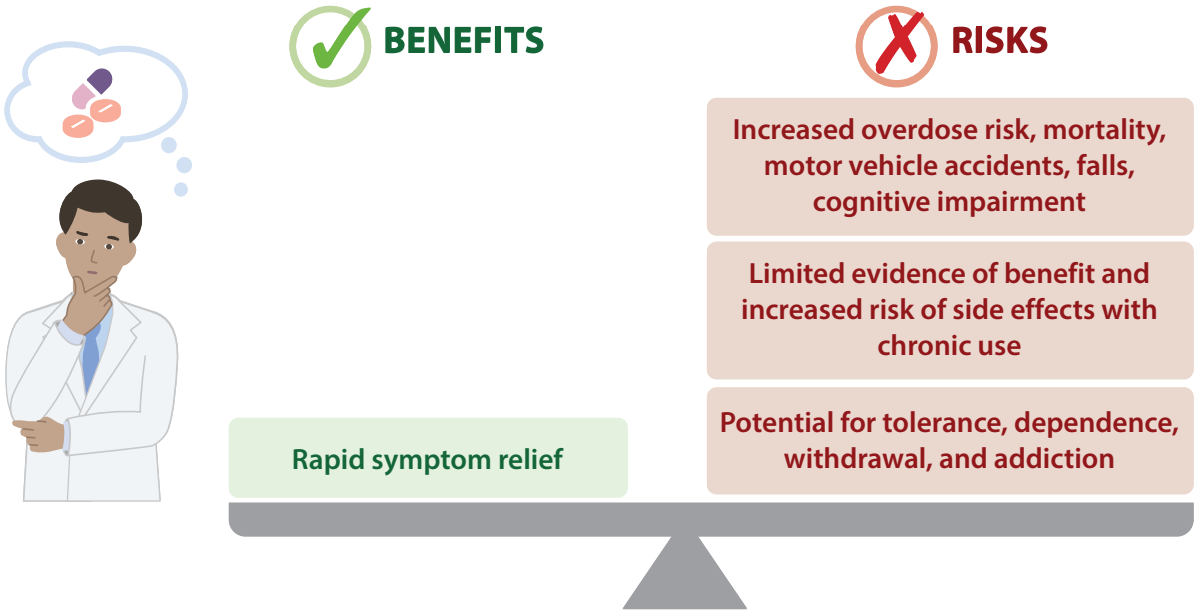
Avoid benzodiazepines

- In most cases the harm of benzodiazepines (e.g., triazolam, temazepam) outweigh the benefits.
- Benzodiazepines may negatively affect sleep architecture, and have significant interactions with alcohol and other medications (e.g., opioids).n
- Tolerance quickly develops to the ability to induce and prolong sleep. Rebound insomnia can occur 1-2 weeks after treatment discontinuation.

Weighing the benefits and risks of benzodiazepines

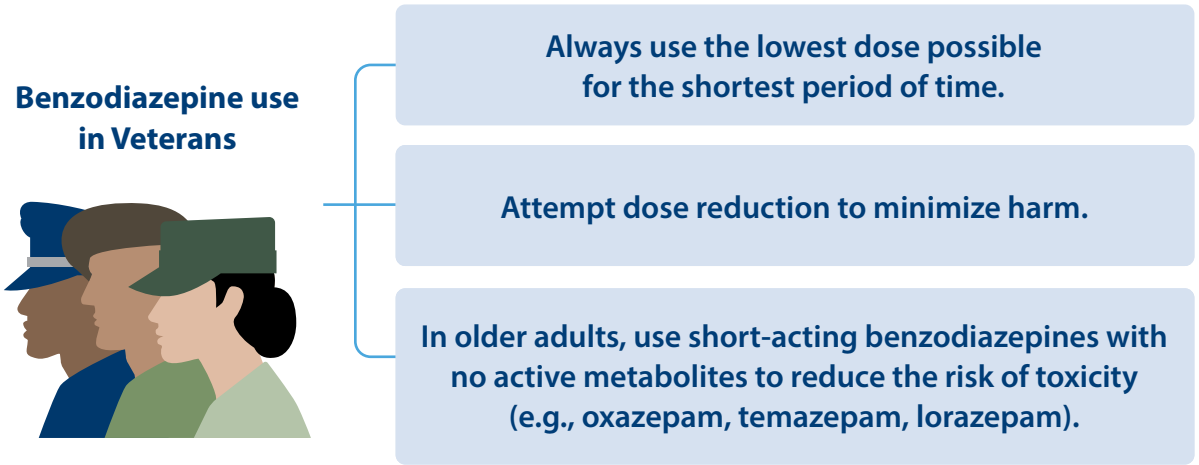
The benefit of benzodiazepines must be weighed against the risks to determine if they are the right treatment option for a Veteran.

Figure 3. Benzodiazepines are quick to improve symptoms, but have significant risks.



If a benzodiazepine is deemed necessary, use the lowest dose possible and plan for the shortest duration possible.

Figure 4. A framework for benzodiazepine use[21,55]

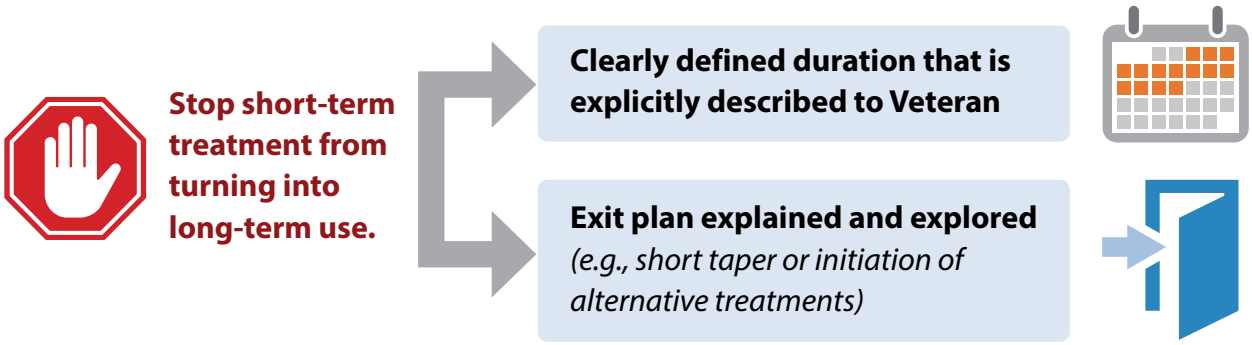


Acute benzodiazepine use

Preventing long-term use of benzodiazepines

Many patients may experience difficulties with discontinuing benzodiazepines at the end of an acute treatment period. **If benzodiazepines are started, a clearly defined exit plan should be determined and then communicated to the Veteran.**

Figure 5. Have a benzodiazepine exit plan.



A maximum of 4-6 weeks duration is recommended.

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

Chronic benzodiazepine use

Patients on chronic benzodiazepines should be reviewed to ensure:

- ✓ Proper safety monitoring and risk mitigation
- ✓ Continued need for ongoing use

Table 2. Suggested safety monitoring for benzodiazepines

PDMP	UDT
At least annually*	At least annually

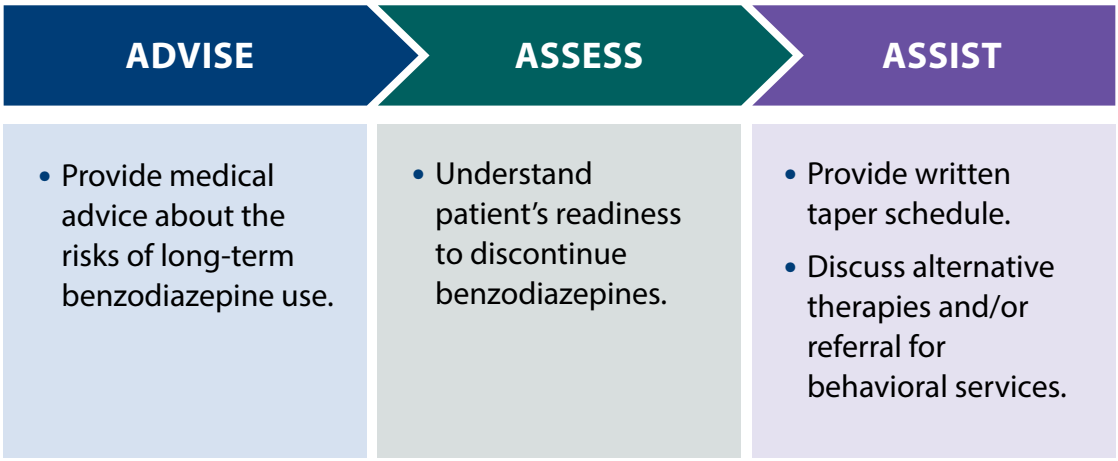
*Querying frequency and potential exclusions must adhere to the most stringent of VHA or the state PDMP regulations, as applicable, including the regulations from the state of facility where prescriber is practicing, state of the licensure of the prescriber, and location of the patient's residence. PDMP = prescription drug monitoring program; UDT = urine drug testing.

If it is determined that the risks of the benzodiazepine outweigh the benefits, engage the patient and develop a plan to taper and discontinue the medication.

Strategies for successful benzodiazepine discontinuation

Minimal educational interventions are effective strategies to assist patients with decreasing or stopping benzodiazepines, such as:[61-63]

- **Brief educational intervention:** medication review, consultation (risk/benefits), assessment of patient readiness, provision of a withdrawal schedule, and education about benzodiazepine use
- **Direct to consumer education:** letters designed to promote cognitive dissonance (e.g., EMPOWER trial), which increased success of discontinuation by 8-fold
- **Augmentation:** psychotherapy and/or pharmacotherapy aimed at addressing underlying condition



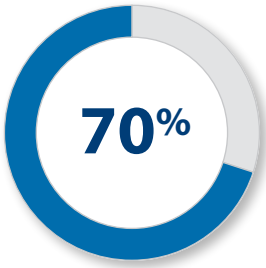
Framework of a brief educational intervention[64]

Provide information on benzodiazepine dependence, abstinence, and withdrawal symptoms; risks of long-term use, memory and cognitive impairment, accidents, falls, and reassurance about reducing medication.

Patients receiving a brief intervention were 3 times more likely to discontinue benzodiazepine use after 12 months vs. controls.[65]

Figure 6. Patients are more likely to discontinue benzodiazepines after receiving brief intervention with taper instructions.[62,66]

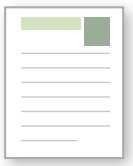
30% more patients discontinued benzodiazepines at 12 months.



70% of patients remained benzodiazepine free at 36 months.

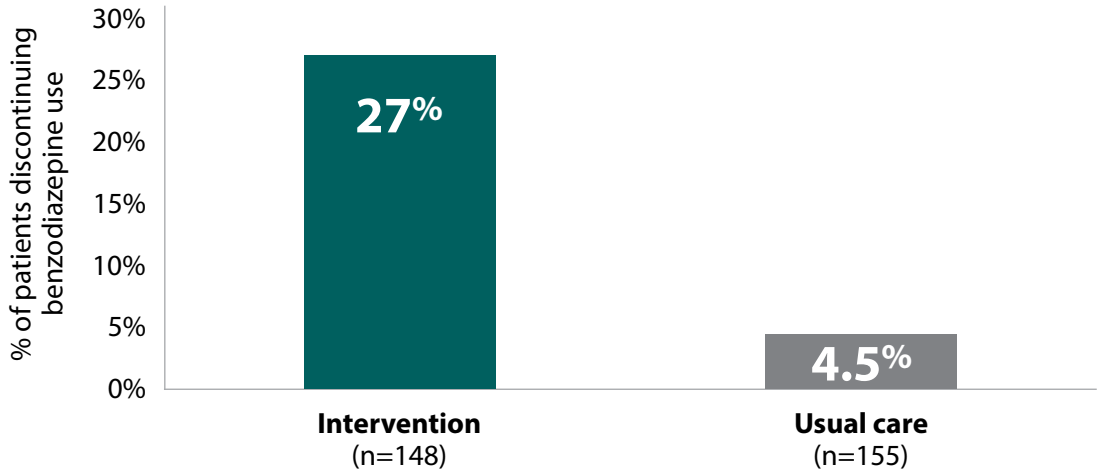
75 general practitioners were randomized to provide usual care or a brief educational and a self-help leaflet to improve sleep. Benzodiazepine withdrawal effects (i.e., anxiety, irritability, insomnia) worsened in the intervention group at 6 months but was not different by 12 months. There was no increase in anxiety, depression, insomnia, or alcohol consumption.[62]

In a separate trial, **more than half of patients** who met with their primary care provider, discussed benzodiazepine use, and received a detailed, written, guided taper had **stopped benzodiazepines** at 24 months, regardless of benzodiazepine indication.[67]



Another successful strategy is **direct to consumer education**, which is often an informative pamphlet that is mailed directly to the patient. This intervention has been shown to be effective in Veterans and has been shown to improve patient willingness and ability to taper or discontinue benzodiazepine use.[68]

Figure 7. Direct to patient education improved likelihood of discontinuing benzodiazepines 8-fold.[63]

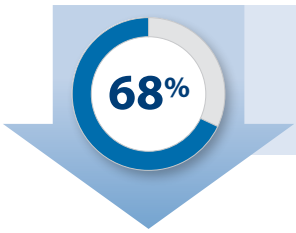


After 6-month follow-up, patients (median age 64) in the intervention group (education pamphlet) were more likely to discontinue benzodiazepines as shown above (adjusted OR 8.33; 95% CI: 3.32-20.93). Over the 6-month period, 56 patients (37.8%) in the intervention group and 17 patients (11%) of the usual care group either discontinued or reduced benzodiazepine doses (OR 5.49; 95% CI: 2.78-10.84).[63]

Augmentation

Using an evidence-based treatment to address the benzodiazepine indication assists in tapering benzodiazepine doses.

Adding cognitive behavioral therapy for insomnia (CBT-i) reduces benzodiazepine use

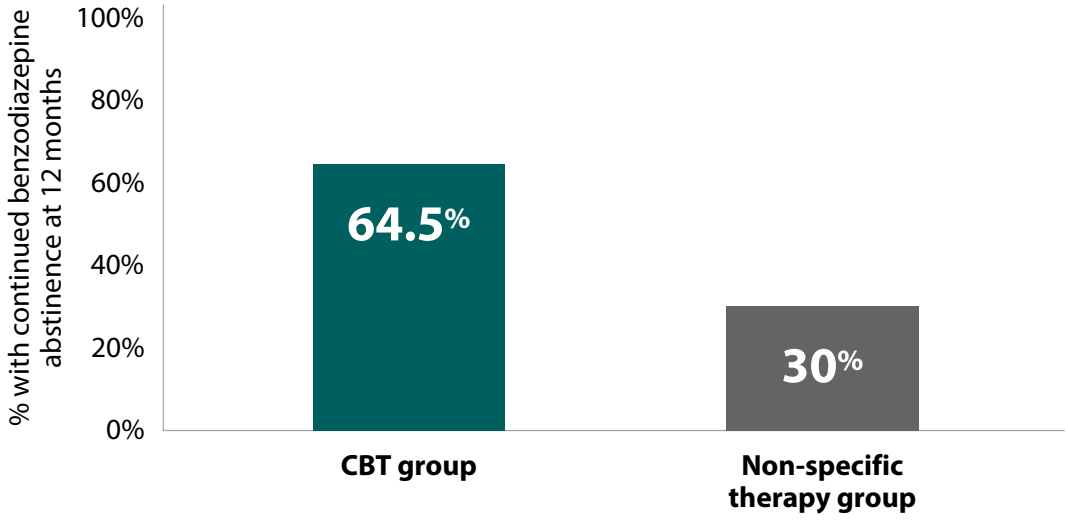


CBT-i plus taper reduced benzodiazepine use by 68% vs. taper alone.[69]

In a meta-analysis of eight randomized, controlled trials of 508 adults with insomnia, patients receiving CBT-I plus taper were more likely to stop using benzodiazepines than those who were tapered alone (RR 1.68; 95% CI: 1.19-2.39; p=0.003) at 3 months. At 12 months, the results from four studies were similar but not statistically significant (RR 1.67; 95% CI: 0.91-3.07; p=0.10).[69]

Cognitive behavioral therapy combined with gradual benzodiazepine tapers in patients with anxiety disorders (panic and generalized anxiety) has also been shown to contribute to greater success with short- and long-term benzodiazepine reduction and discontinuation (NNT = 3).[70]

Figure 8. More patients with anxiety successfully stopped taking benzodiazepines with a CBT augmented taper.[71]



Forty-eight adults with over seven years of benzodiazepine use for anxiety randomly received a guided benzodiazepine taper with either CBT (n=28) or non-specific therapy (n=28). Assessment points at the end of therapy found 74% of patients in the CBT group withdrew from benzodiazepines vs. 37% in the non-standard therapy group. No serious side effects were reported.[71]

Advise Veterans on the benefits of stopping benzodiazepines and work with them to develop a discontinuation strategy.

Benzodiazepine dose reduction or discontinuation plans

After the decision has been made to taper the benzodiazepine, provide education on the possible withdrawal and rebound symptoms and maintain open lines of communication with the patient.

- Consider alternative treatment options, if needed.
- Design a **SLOW** taper to the lowest dose necessary to maintain function and good symptom control.
- Provide education about safe tapering and risks of alcohol and other substances during taper.

Slowly tapering can lessen withdrawal and rebound symptoms and promote successful discontinuation.

Figure 9. Triad of benzodiazepine discontinuation symptoms[72]

Figure 10. Benzodiazepine withdrawal symptoms[21]

Psychological	Physical
• Anxiety/irritability • Insomnia/ nightmares • Depersonalization • Decreased memory and concentration • Delusion and hallucinations • Depression	• Stiffness • Weakness • Gastrointestinal disturbance • Flu-like symptoms • Paresthesia • Visual disturbances • Seizures

Withdrawal symptoms can occur after about 4 weeks of continuous use. All patients taking benzodiazepines on a regular basis for more than 4 weeks should be tapered. ***A slow taper is associated with total cessation of benzodiazepine use in about two-thirds of patients.[72]***

The use of medications to treat benzodiazepine withdrawal is limited and conflicting.[73-76] **Rebound symptoms**, which may also manifest as withdrawal, will resolve over time, though can be protracted. **Recurrence of symptoms** (e.g., insomnia, anxiety) can be managed with alternative evidence-based treatments for that indication. See ***Re-evaluating the Use of Benzodiazepines: A Quick Reference Guide*** for more information about rebound symptoms and managing recurrence.

Set the Veteran up for success

There is no one-size-fits-all approach to tapering benzodiazepines. **Each patient may require a different rate of taper.** A proper benzodiazepine taper can take many months or even years.

- Patients who have been on low doses of benzodiazepines for a relatively short time (less than a year) can often tolerate a faster taper.[77]
- Patients on high doses of benzodiazepines or those who have been taking the medication consistently for many years may need a slower taper.

The rate of taper should ultimately be determined by the patient's symptoms.

TIPS FOR TAPERING

- Go slow!
- Provide written instructions for the taper schedule.
- Document taper schedule in electronic medical record.
- Schedule follow-up with the Veteran to assess tolerability of the taper. This can be done by various health care team members (e.g., nurse, clinical pharmacy practitioner) and provided via clinic visit, telehealth, and/or telephone.
- Be flexible! Adjust schedule to accommodate issues that may arise.
- If withdrawal is experienced, hold or slow down the taper schedule.
- Substitute a longer-acting benzodiazepine if the patient is on a short-acting form and experiencing withdrawal.

SHORTER TAPER[21,72,76,78,79]

- Gradually reduce total dose by 50% over the first 4 weeks (e.g., 10–15% decrease weekly)
- Maintain on that dose (50% original dose) 1–2 months, *then*
- Reduce dose by 25% every 2 weeks

LONGER TAPER[21,72,76,79]

- 10–25% every 2-4 weeks

Remember if discontinuation cannot be achieved, reduction in dose is still valuable.

Summary of strategies to discontinue benzodiazepines

1 Determine benefit vs. harm of benzodiazepine therapy.

- Is there still an indication for the benzodiazepine?
- 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.[73]

- Recommend gradual dose reduction and discontinuation.
- Use educational interventions to achieve better discontinuation outcomes.
- Offer psychotherapy interventions (e.g., cognitive behavioral therapy for insomnia).

3 Perform slow taper over months.

- Provide written instructions and document taper recommendations in the medical record.
- Educate patient on signs and symptoms of withdrawal.

References

1. Agarwal SD, Landon BE. Patterns in Outpatient Benzodiazepine Prescribing in the United States. *JAMA Netw Open.* 2019;2(1):e187399.
2. Bachhuber MA, Hennessy S, Cunningham CO, Starrels JL. Increasing Benzodiazepine Prescriptions and Overdose Mortality in the United States, 1996-2013. *Am J Public Health.* 2016:e1-e3.
3. Blanco C, Han B, Jones CM, et al. Prevalence and Correlates of Benzodiazepine Use, Misuse, and Use Disorders Among Adults in the United States. *J Clin Psychiatry.* 2018;79(6).
4. National Institute for Health and Care Excellence. Generalised anxiety disorder and panic disorder in adults: management. https://www.nice.org.uk/guidance/cg113. Published July 2020. Accessed Dec 7, 2020.
5. Sateia MJ, Buysse DJ, Krystal AD, et al. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med.* 2017;13(2):307-349.
6. Veterans Health Administration, Department of Defense. *VA/DoD Clinical Practice Guideline for the Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea. Version 1.0 - 2019.*
7. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. *JAMA Psychiatry.* 2015;72(2):136-142.
8. Kaufmann CN, Spira AP, Depp CA, Mojtabai R. Long-Term Use of Benzodiazepines and Nonbenzodiazepine Hypnotics, 1999-2014. *Psychiatr Serv.* 2018;69(2):235-238.
9. Taipale H, Särkilä H, Tanskanen A, et al. Incidence of and Characteristics Associated With Long-term Benzodiazepine Use in Finland. *JAMA Netw Open.* 2020;3(10):e2019029-e2019029.
10. Substance Abuse and Mental Health Services Administration. 2019 National Survey of Drug Use and Health (NSDUH) Releases. https://www.samhsa.gov/data/release/2019-national-survey-drug-use-and-health-nsduh-releases. Accessed December 15, 2020.
11. Maust DT, Kim HM, Wiechers IR, et al. Benzodiazepine Use among Medicare, Commercially Insured, and Veteran Older Adults, 2013-2017. *J Am Geriatr Soc.* 2021;69(1):98-105.
12. Maust DT, Lin LA, Blow FC. Benzodiazepine Use and Misuse Among Adults in the United States. *Psychiatr Serv.* 2019;70(2):97-106.
13. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. *The TEDS Report: Substance Abuse Treatment Admissions for Abuse of Benzodiazepines.* June 2, 2011.
14. Park TW, Saitz R, Ganoczy D, et al. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. *BMJ.* 2015;350:h2698.
15. Jones CM, Mack KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. *JAMA.* 2013;309(7):657-659.
16. National Institute on Drug Abuse. Overdose death rates. https://www.drugabuse.gov/drug-topics/trends-statistics/overdose-death-rates. Published March 10, 2020. Accessed December 15, 2020.
17. Xu KY, Hartz SM, Borodovsky JT, et al. Association Between Benzodiazepine Use With or Without Opioid Use and All-Cause Mortality in the United States, 1999-2015. *JAMA Netw Open*. 2020;3(12):e2028557.
18. Kripke DF. Mortality Risk of Hypnotics: Strengths and Limits of Evidence. *Drug Saf.* 2016;39(2):93-107.

References *(continued)*

19. Rapoport MJ, Lanctot KL, Streiner DL, et al. Benzodiazepine use and driving: a meta-analysis. *J Clin Psychiatry.* 2009;70(5):663-673.
20. Guina J, Rossetter SR, De RB, et al. Benzodiazepines for PTSD: A Systematic Review and Meta-Analysis. *J Psychiatr Pract.* 2015;21(4):281-303.
21. Taylor D, Paton C, Kapur S. *The Maudsley Prescribing Guidelines in Psychiatry 12th Edition*. West Sussex: Wiley Blackwell; 2015.
22. Barker MJ, Greenwood KM, Jackson M, Crowe SF. Cognitive effects of long-term benzodiazepine use: a meta-analysis. *CNS Drugs.* 2004;18(1):37-48.
23. Bierman EJ, Comijs HC, Gundy CM, et al. The effect of chronic benzodiazepine use on cognitive functioning in older persons: good, bad or indifferent? *Int J Geriatr Psychiatry.* 2007;22(12):1194-1200.
24. Boeuf-Cazou O, Bongue B, Ansiau D, et al. Impact of long-term benzodiazepine use on cognitive functioning in young adults: the VISAT cohort. *Eur J Clin Pharmacol.* 2011;67(10):1045-1052.
25. Tannenbaum C, Paquette A, Hilmer S, et al. A systematic review of amnestic and non-amnestic mild cognitive impairment induced by anticholinergic, antihistamine, GABAergic and opioid drugs. *Drugs Aging.* 2012;29(8):639-658.
26. Díaz-Gutiérrez MJ, Martínez-Cengotitabengoa M, Sáez de Adana E, et al. Relationship between the use of benzodiazepines and falls in older adults: A systematic review. *Maturitas.* 2017;101:17-22.
27. Donnelly K, Bracchi R, Hewitt J, et al. Benzodiazepines, Z-drugs and the risk of hip fracture: A systematic review and meta-analysis. *PLoS One.* 2017;12(4):e0174730.
28. Obiora E, Hubbard R, Sanders RD, Myles PR. The impact of benzodiazepines on occurrence of pneumonia and mortality from pneumonia: a nested case-control and survival analysis in a population-based cohort. *Thorax.* 2013;68(2):163-170.
29. Baillargeon J, Singh G, Kuo YF, et al. Association of Opioid and Benzodiazepine Use with Adverse Respiratory Events in Older Adults with Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc.* 2019;16(10):1245-1251.
30. Rodriguez-Roisin R, Garcia-Aymerich J. Should we exercise caution with benzodiazepine use in patients with COPD? *Eur Respir J.* 2014;44(2):284-286.
31. Vozoris NT. Do benzodiazepines contribute to respiratory problems? *Expert Rev Respir Med.* 2014;8(6):661-663.
32. Ekström MP, Bornefalk-Hermansson A, Abernethy AP, Currow DC. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *BMJ.* 2014;348:g445.
33. Berry RB, Kouchi K, Bower J, et al. Triazolam in patients with obstructive sleep apnea. *Am J Respir Crit Care Med.* 1995;151(2 Pt 1):450-454.
34. Wang PS, Bohn RL, Glynn RJ, Mogun H, Avorn J. Hazardous benzodiazepine regimens in the elderly: effects of half-life, dosage, and duration on risk of hip fracture. *Am J Psychiatry.* 2001;158(6):892-898.
35. Shyken JM, Babbar S, Babbar S, Forinash A. Benzodiazepines in Pregnancy. *Clin Obstet Gynecol.* 2019;62(1):156-167.
36. Freeman MP, Góez-Mogollón L, McInerney KA, et al. Obstetrical and neonatal outcomes after benzodiazepine exposure during pregnancy: Results from a prospective registry of women with psychiatric disorders. *Gen Hosp Psychiatry.* 2018;53:73-79.
37. Yonkers KA, Gilstad-Hayden K, Forray A, Lipkind HS. Association of Panic Disorder, Generalized Anxiety Disorder, and Benzodiazepine Treatment During Pregnancy With Risk of Adverse Birth Outcomes. *JAMA Psychiatry.* 2017;74(11):1145-1152.
38. Braun P, Greenberg D, Dasberg H, Lerer B. Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment. *J Clin Psychiatry.* 1990;51(6):236-238.
39. Cates ME, Bishop MH, Davis LL, et al. Clonazepam for treatment of sleep disturbances associated with combat-related posttraumatic stress disorder. *Ann Pharmacother.* 2004;38(9):1395-1399.
40. Veterans Health Administration, Department of Defense. *VA/DoD Clinical Practice Guideline for the Management of Post-Traumatic Stress. Version 2.0–2010*.
41. Deka R, Bryan CJ, LaFleur J, et al. Benzodiazepines, Health Care Utilization, and Suicidal Behavior in Veterans With Posttraumatic Stress Disorder. *J Clin Psychiatry.* 2018;79(6).
42. Gonçalves M, Oliveira A, Leão A, et al. The impact of benzodiazepine use in nocturnal O2 saturation of OSAS patients. *Sleep Medicine.* 2013;14:e141-e142.
43. Wang S, Chen W, Tang S, et al. Benzodiazepines Associated With Acute Respiratory Failure in Patients With Obstructive Sleep Apnea. *Front Pharmacol.* 2019 Jan 7;9:1513.
44. Vozoris NT, Fischer HD, Wang X, et al. Benzodiazepine drug use and adverse respiratory outcomes among older adults with COPD. *Eur Respir J.* 2014;44(2):332-340.
45. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf. Published 2021. Accessed May 11, 2021.
46. Currow DC, Quinn S, Greene A, et al. The longitudinal pattern of response when morphine is used to treat chronic refractory dyspnea. *J Palliat Med.* 2013;16(8):881-886.
47. Longo LP, Johnson B. Addiction: Part I. Benzodiazepines—side effects, abuse risk and alternatives. *Am Fam Physician.* 2000;61(7):2121-2128.
48. Larson EB, Zollman FS. The effect of sleep medications on cognitive recovery from traumatic brain injury. *J Head Trauma Rehabil.* 2010;25(1):61-67.

References *(continued)*

49. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.* 2019;67(4):674-694.
50. Defrancesco M, Marksteiner J, Fleischhacker WW, Blasko I. Use of Benzodiazepines in Alzheimer's Disease: A Systematic Review of Literature. *Int J Neuropsychopharmacol.* 2015;18(10):pyv055.
51. Saarelainen L, Tolppanen AM, Koponen M, et al. Risk of Hip Fracture in Benzodiazepine Users With and Without Alzheimer Disease. *J Am Med Dir Assoc.* 2017;18(1):87.e15-87.e21.
52. Cook JM, Marshall R, Masci C, Coyne JC. Physicians' perspectives on prescribing benzodiazepines for older adults: a qualitative study. *J Gen Intern Med.* 2007;22(3):303-307.
53. Curran HV, Collins R, Fletcher S, et al. Older adults and withdrawal from benzodiazepine hypnotics in general practice: effects on cognitive function, sleep, mood and quality of life. *Psychol Med.* 2003;33(7):1223-1237.
54. Glass J, Lanctot KL, Herrmann N, et al. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ.* 2005;331(7526):1169.
55. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.* 2015;63(11):2227-2246.
56. Pollack MH. Refractory generalized anxiety disorder. *J Clin Psychiatry.* 2009;70 Suppl 2:32-38.
57. DeMartini J, Patel G, Fancher TL. Generalized Anxiety Disorder. *Ann Intern Med.* 2019;170(7):Itc49-itc64.
58. Katzman MA, Bleau P, Blier P, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry.* 2014;14 Suppl 1:S1.
59. Qaseem A, Kansagara D, Forciea MA, et al. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. *Ann Intern Med.* 2016;165(2):125-133.
60. Schutte-Rodin S, Broch L, Buysse D, et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med.* 2008;4(5):487-504.
61. Mugunthan K, McGuire T, Glasziou P. Minimal interventions to decrease long-term use of benzodiazepines in primary care: a systematic review and meta-analysis. *Br J Gen Pract.* 2011;61(590):e573-578.
62. Vicens C, Bejarano F, Sempere E, et al. Comparative efficacy of two interventions to discontinue long-term benzodiazepine use: cluster randomised controlled trial in primary care. *Br J Psychiatry.* 2014;204(6):471-479.
63. Tannenbaum C, Martin P, Tamblyn R, Benedetti A, Ahmed S. Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: the EMPOWER cluster randomized trial. *JAMA Intern Med.* 2014;174(6):890-898.
64. Screening for Drug Use in General Medical Settings Resource Guide. National Institute on Drug Abuse. 2010.
65. Lynch T, Ryan C, Hughes CM, et al. Brief interventions targeting long-term benzodiazepine and Z-drug use in primary care: a systematic review and meta-analysis. *Addiction.* 2020;115(9):1618-1639.
66. Vicens C, Sempere E, Bejarano F, et al. Efficacy of two interventions on the discontinuation of benzodiazepines in long-term users: 36-month follow-up of a cluster randomised trial in primary care. *Br J Gen Pract.* 2016;66(643):e85-91.
67. Davidson S, Thomson C, Prescott G. A Durable Minimal Intervention Strategy to Reduce Benzodiazepine Use in a Primary Care Population. *Korean J Fam Med.* 2020;41(2):126-132.
68. Erwin WJ, Goodman C, Smith T. Effectiveness of a direct-to-consumer written health education program in the reduction of benzodiazepine and sedative-hypnotic use in an elderly population at a single Veterans Affairs medical center. *Ment Health Clin.* 2018;8(3):100-104.
69. Takaesu Y, Utsumi T, Okajima I, et al. Psychosocial intervention for discontinuing benzodiazepine hypnotics in patients with chronic insomnia: A systematic review and meta-analysis. *Sleep Med Rev.* 2019;48:101214.
70. Takeshima M, Otsubo T, Funada D, et al. Does cognitive behavioral therapy for anxiety disorders assist the discontinuation of benzodiazepines among patients with anxiety disorders? A systematic review and meta-analysis. *Psychiatry Clin Neurosci.* 2021 Apr;75(4):119-127.
71. Gosselin P, Ladouceur R, Morin CM, et al. Benzodiazepine discontinuation among adults with GAD: A randomized trial of cognitive-behavioral therapy. *J Consult Clin Psychol.* 2006;74(5):908-919.
72. Veterans Health Administration, Department of Defense. *VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders (SUD). Version 4.0–2021*.
73. *Discontinuation Strategies for Patients with Long-term Benzodiazepine Use: A Review of Clinical Evidence and Guidelines*. Ottawa ON: Canadian Agency for Drugs and Technologies in Health. 2015.
74. Baandrup L, Ebdrup BH, Rasmussen J, Lindschou J, Gluud C, Glenthøj BY. Pharmacological interventions for benzodiazepine discontinuation in chronic benzodiazepine users. *Cochrane Database Syst Rev.* 2018;3(3):Cd011481.
75. Guaiana G, Barbui C. Discontinuing benzodiazepines: best practices. *Epidemiol Psychiatr Sci.* 2016:1-3.
76. Lader M, Kyriacou A. Withdrawing Benzodiazepines in Patients With Anxiety Disorders. *Curr Psychiatry Rep.* 2016;18(1):8.
77. Ashton CH. Benzodiazepines: how they work and how to withdraw. Newcastle University. https://benzo.org.uk/manual. Published 2002. Accessed March 15, 2021.
78. Risse SC, Whitters A, Burke J, Chen S, Scurfield RM, Raskind MA. Severe withdrawal symptoms after discontinuation of alprazolam in eight patients with combat-induced posttraumatic stress disorder. *J Clin Psychiatry.* 1990;51(5):206-209.
79. Perry PJ, Alexander B, Liskow B, et al. *Psychotropic Drug Handbook, Eighth Edition*. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.

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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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