VA | U.S. Department of Veterans Affairs

Re-evaluating the Use of Benzodiazepines

A Focus on High-risk Populations

VA Academic Detailing Service

Real Provider Resources
Real Patient Results

Re-evaluating the Use of Benzodiazepines

A VA Clinician's Guide

VA | U.S. Department of Veterans Affairs

VA PBM Academic Detailing Service

Real Provider Resources

Real Patient Results

Your Partner in Enhancing Veteran Health Outcomes

VA PBM Academic Detailing Service Email Group:

PharmacyAcademicDetailingProgram@va.gov

VA PBM Academic Detailing Service SharePoint Site:

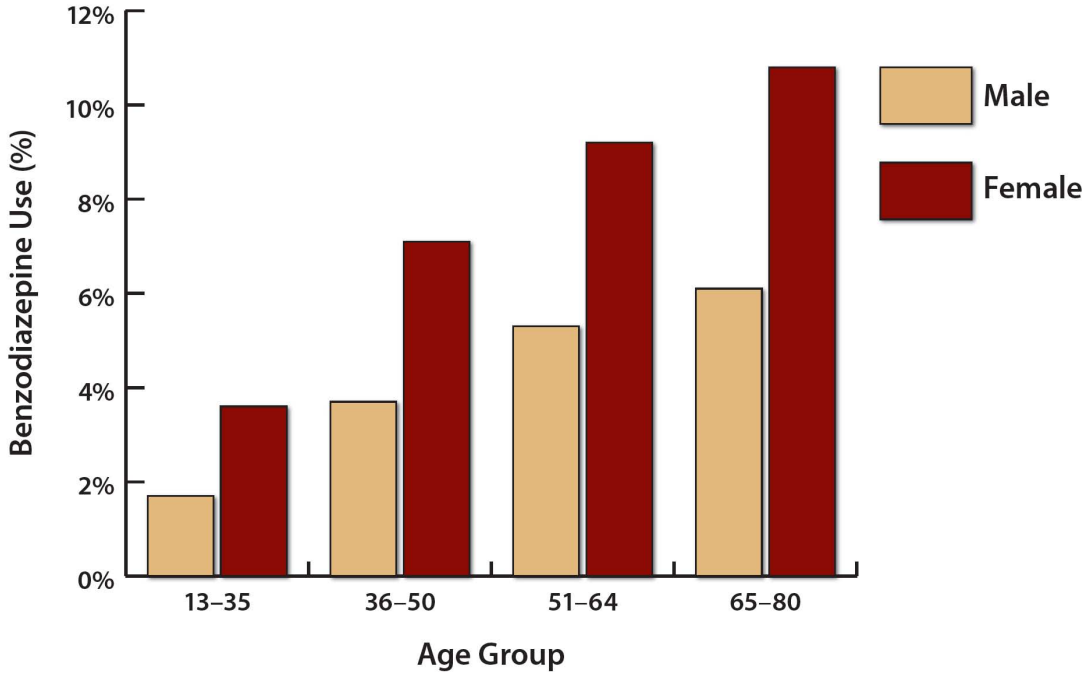
https://vaww.portal2.va.gov/sites/ad

Benzodiazepines are widely used in the treatment of anxiety, sleep, depression (as adjuvant therapy), and as muscle relaxants.[1,2] In the United States, approximately 5.6% of the adult population uses a benzodiazepine.[2,3] Although it is recommended that treatment with benzodiazepines be limited to short-term use, the prevalence of long-term use remains widespread.[3]

- ➔ Benzodiazepine use is nearly twice as prevalent in women[3,4]
- ➔ Benzodiazepines have increasing utilization with increasing age (see figure 1)[3,5,6]
- ➔ Benzodiazepines are prescribed at greater rates than antidepressants for the treatment of depression and anxiety, despite evidence that supports antidepressants as first line medications[5–7]

Between 1996 and 2013, the number of adults filling a benzodiazepine prescription increased by 67% and the total quantity filled more than tripled.[2]

Figure 1.
Prevalence of Benzodiazepine Use in the United States[3]



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]

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)

Potentially Deadly Outcomes Related to Benzodiazepines

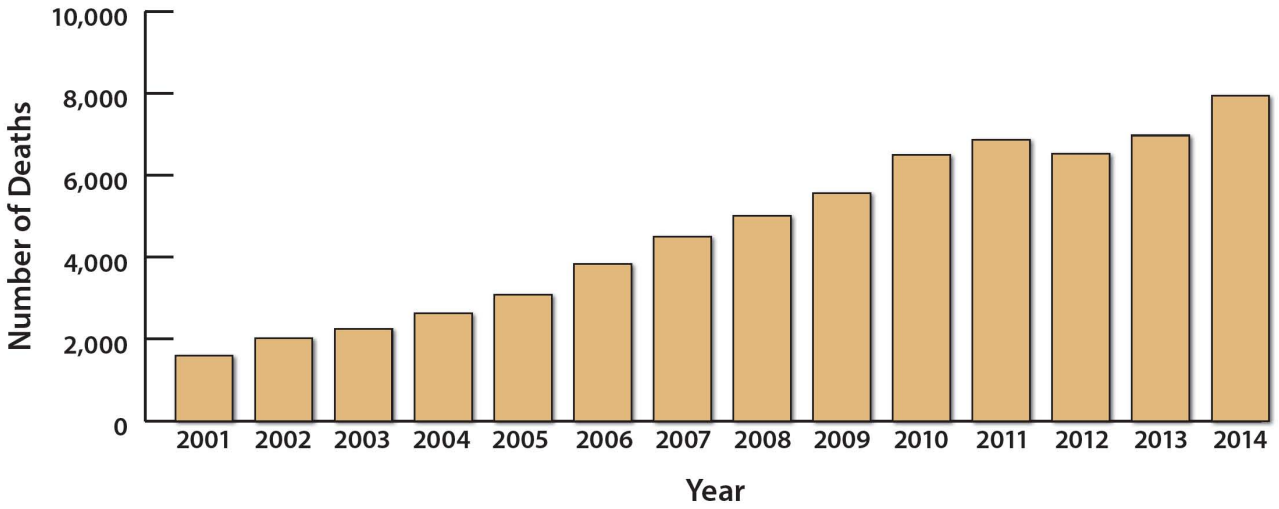
➔ Multiple epidemiologic studies have found elevated mortality risk associated with benzodiazepine utilization (odds ratio >1 in 33 studies)[11,12]

➔ Increased risk of motor vehicle accident by 60%[10]

➔ Increased risk of overdose (OD) death[2,13,14]

- 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 deaths[2,15]

Figure 2.
U.S. Overdose Deaths Involving a Benzodiazepine[15]



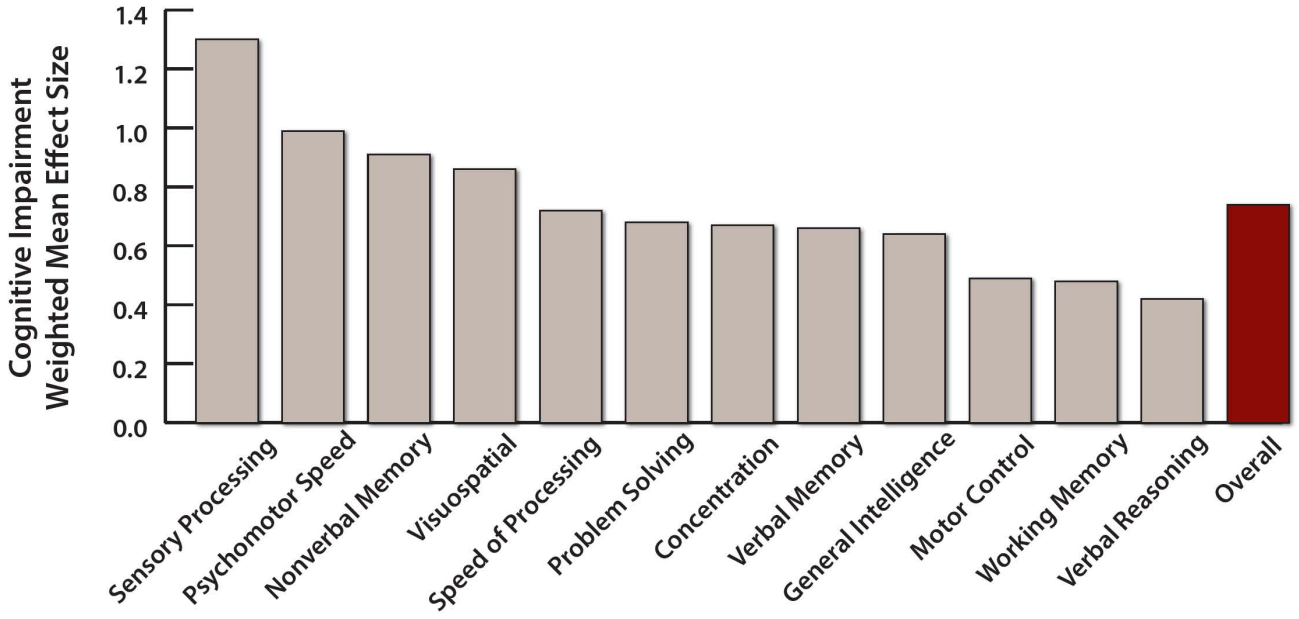
The figure above depicts the total number of U.S. overdose deaths involving a benzodiazepine.

Additional Benzodiazepine Risks

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

In addition, the evidence, though mixed, has associated benzodiazepines use with increased risk of dementia.[20–22]

Figure 3.
The Impact of Long-term Use of Benzodiazepines on Cognitive Function[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.[7]

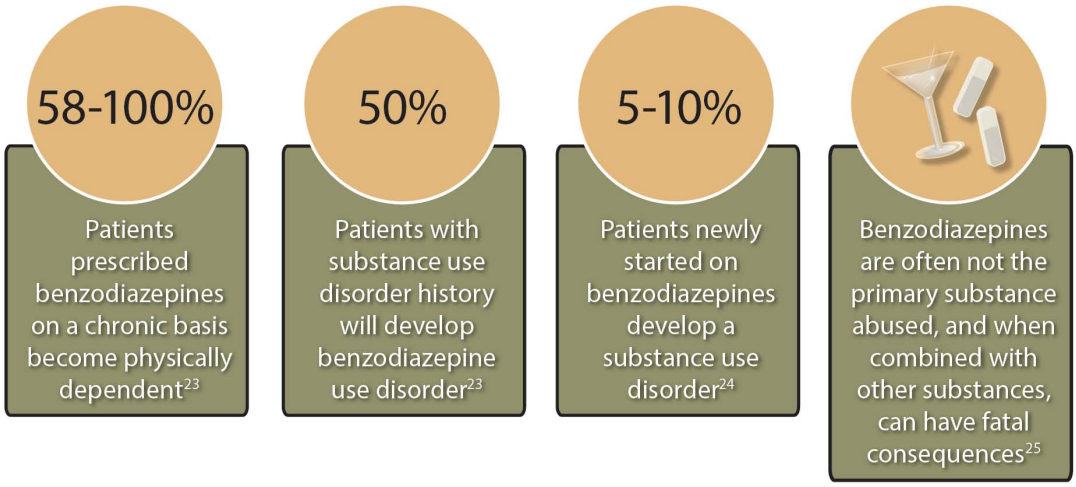
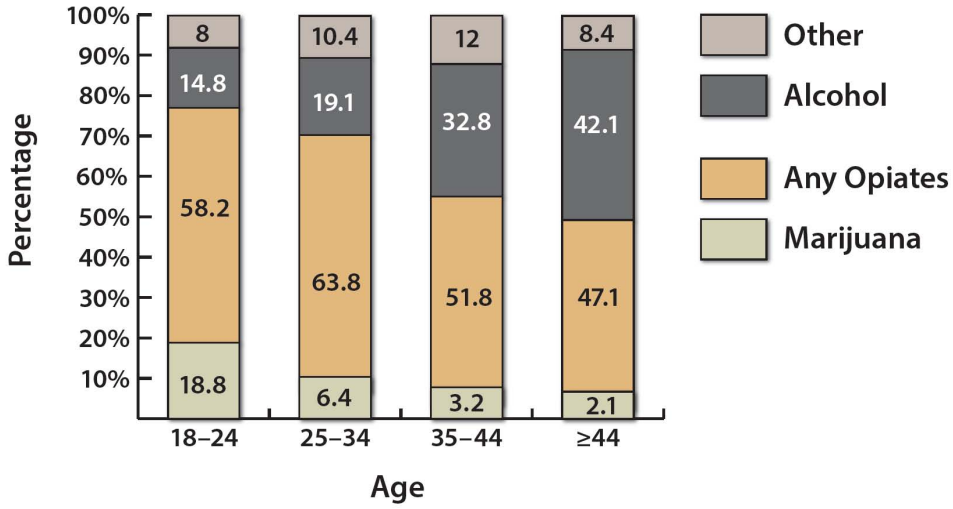


Figure 4.
Substances Abused Concurrently with Benzodiazepines[25]



Benzodiazepine abuse admission data looking at primary substance abused in combination with benzodiazepines. Report used 2008 Treatment Episode Data.

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.[26] For these conditions, guidelines and consensus statements recommend that benzodiazepines should only be used for **short-term treatment**.[7,27,28]

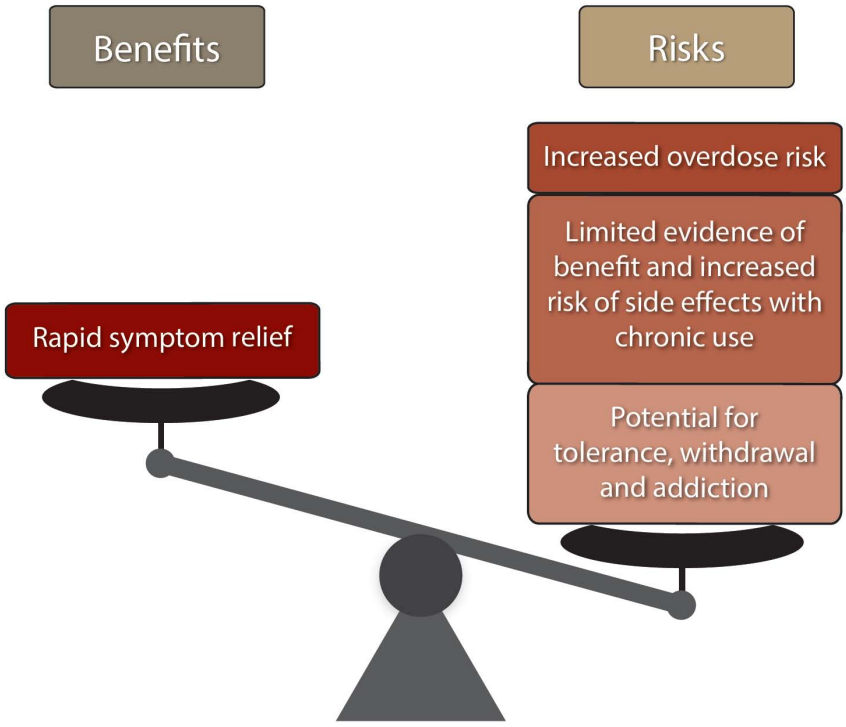
No evidence of benefit with chronic benzodiazepine use in insomnia or anxiety

Table 1. Treatments for Anxiety Disorders and Insomnia*				
	Anxiety Disorders[7,26,27]		Insomnia**[28–31]	
	Non-drug	Drug	Non-drug	Drug
1st Line Treatment Options	• CBT • Exposure therapy	• SSRI • SNRI	CBT-I (use before medications)	• Doxepin+, sedative-hypnotics, benzodiazepines, or ramelteon (NF) • Alternative options: sedating antidepressants (e.g., trazodone), hydroxyzine, melatonin
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

Weighing the Benefits Versus Risks

Figure 5.
Benefits vs. Risks of Benzodiazepine Use



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

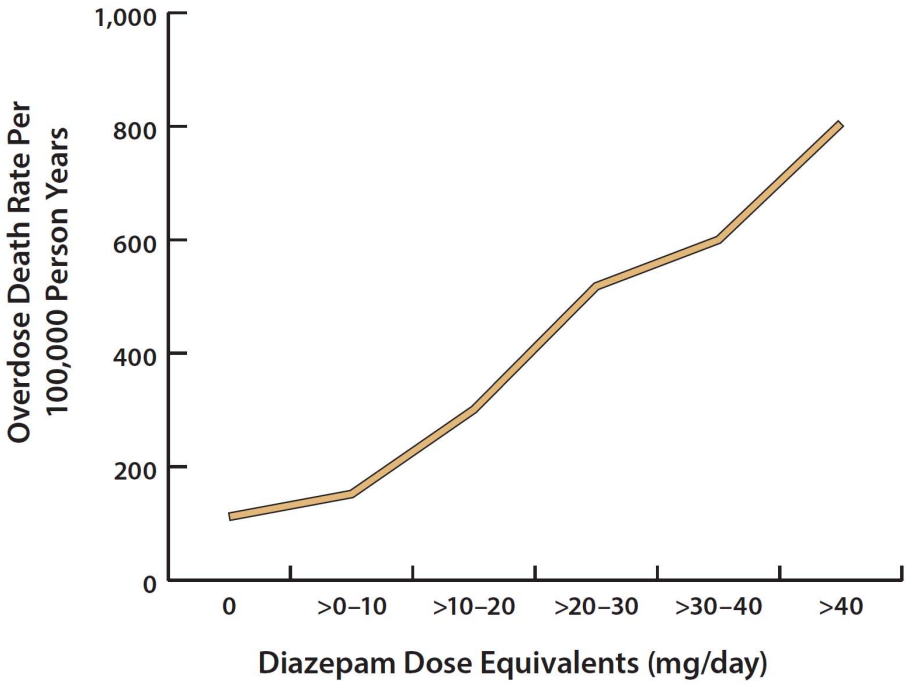
Lethal Drug Combinations: Opioids and Benzodiazepines

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 benzodiazepines[13]
- ➔ Benzodiazepines are commonly involved in opioid-related OD death (30.1%)[14]
- ➔ Risk of OD death increases with increasing benzodiazepine daily dose[2,13]

In our Veterans that have died of opioid overdose, 49% have concurrent benzodiazepines prescribed[13]

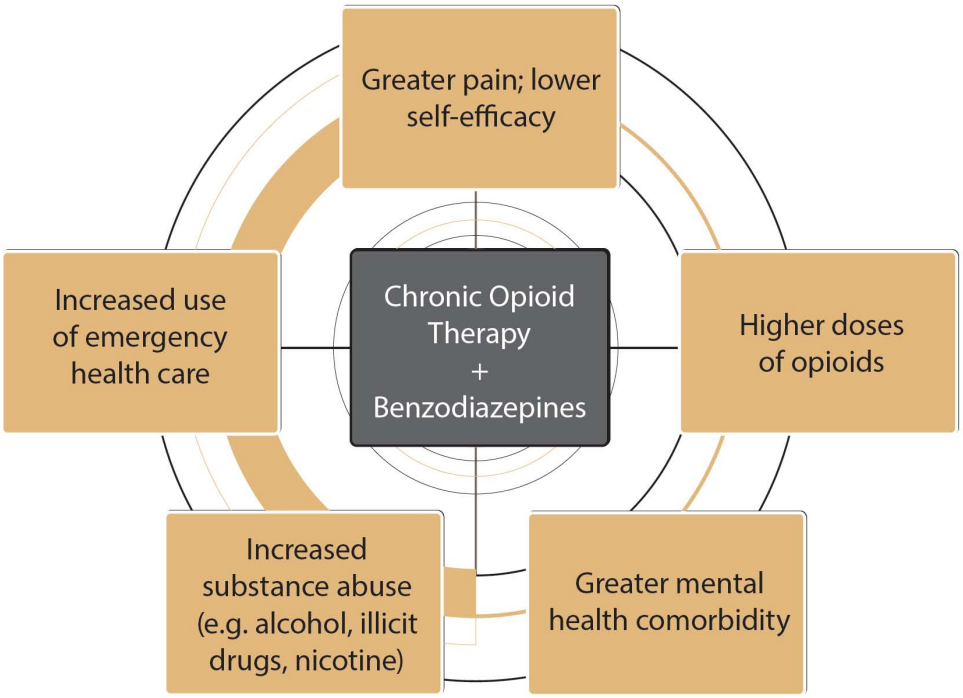
Figure 6.
Opioid Overdose with Co-administered Benzodiazepine[13]



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.[32–35]

Figure 7.
High Risk Associations with Chronic Opioid Therapy Plus Benzodiazepines[32]



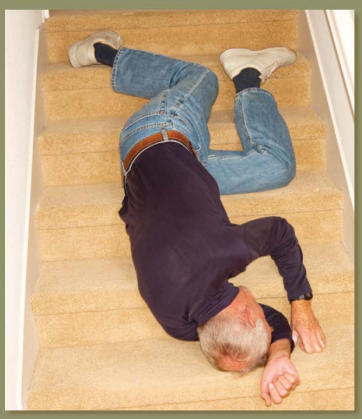
Prospective cohort study that compared a sample of 1,220 chronic noncancer pain patients prescribed chronic opioids and categorized them based on their benzodiazepine use patterns. The patients taking benzodiazepines daily represent a high-risk group with multiple comorbid mental health disorders.

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

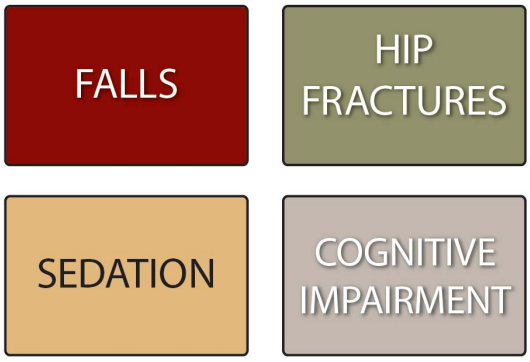
The 2015 American Geriatrics Society Beers Criteria recommend avoiding benzodiazepines in this population.[36] Despite these consensus recommendations and known risk factors:

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



Benzodiazepine use in the elderly is associated with at least a 50% increase in the risk of hip fracture[7]

Figure 8.
Benzodiazepines are Associated with Significant Risk in the Elderly[20,37–40]



Avoid starting benzodiazepines in older Veterans.

When surveyed about benzodiazepine use, prescribers underestimate the risks in their geriatric patients.[41]

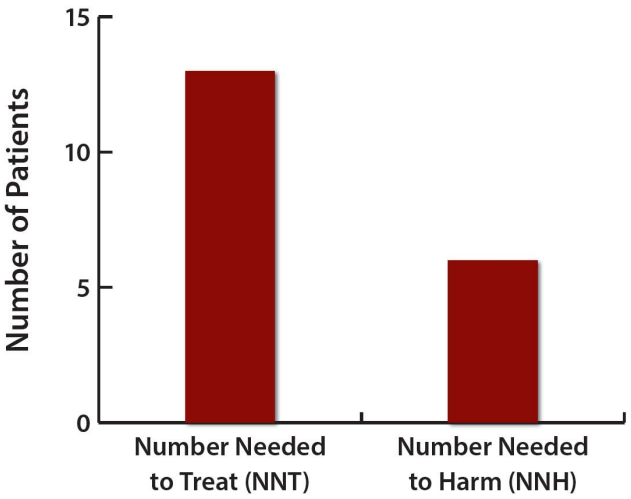
Some Provider Perceptions Include:
- **A stable dose of benzodiazepine means that it is safe and effective**[41]
- **Attempts to discontinue will fail**[41]

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]

Figure 9.
Use of Sedative Hypnotics in Older Patients with Insomnia[37]



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.

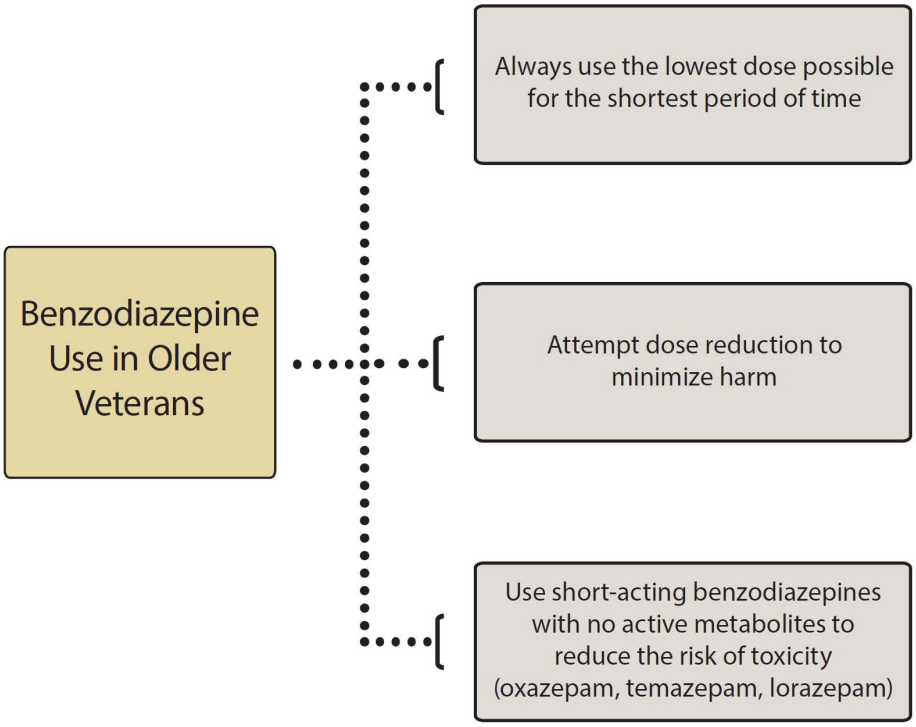
Discontinuation of benzodiazepines CAN be successful

Figure 10.
Withdrawal of Benzodiazepines for Insomnia in an Older Adult Population[42]

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).[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[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[36]

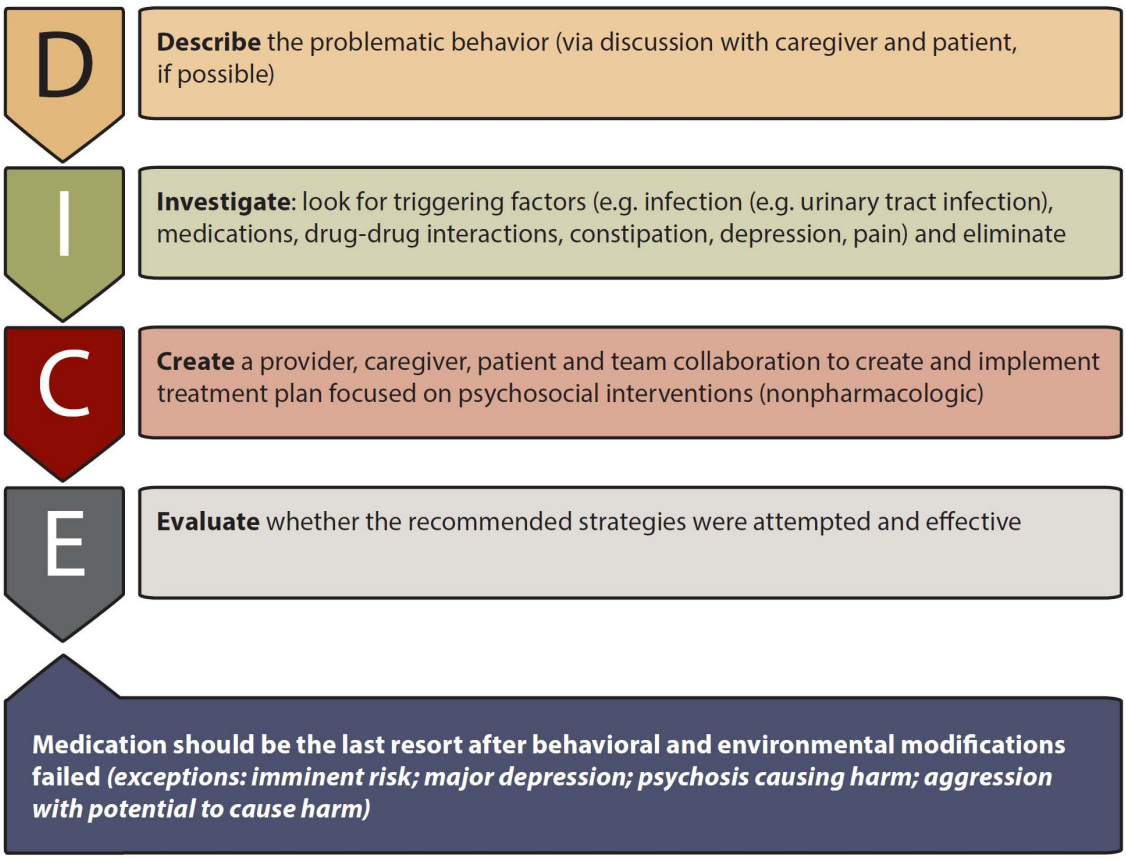
➔ No evidence of improvement of sleep quality in patients with dementia[43]

➔ Benzodiazepines may cause or exacerbate:[36,43]

- Aggravated cognitive deterioration
- Higher risk of falls
- Aspiration
- Death
- Paradoxical agitation

Benzodiazepines should be avoided in patients with dementia.

Figure 12.
Treatment Guidelines for Behavioral and Psychological Symptoms of Dementia[44,45]



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.[45] Consult Psychiatry or Psychology for assistance with developing behavioral strategies.

Table 2. Consider Non-drug Approaches in All Dementia Patients with Behavioral Symptoms[44–46]

- **Reorient:** gently remind of person, place, time
- **Calm:** offer exercise, music, massage, aromatherapy
- **Comfort:** address temperature, lighting, hunger, thirst, pain
- **Reduce Distress:** reduce noise, correct hearing/vision, provide structure, allow time to respond
- **Supervise:** provide companionship, observation, reduce choices, provide simple activities

Use nonpharmacological strategies as first-line treatment for behavioral and psychological symptoms of dementia.

Benzodiazepine Utilization in PTSD

Benzodiazepines are ineffective for the treatment and prevention of PTSD and any potential benefits are outweighed by the risks.[23,26]

Figure 13.
Specific Risks of Benzodiazepine Use in PTSD[23]

Core Symptoms

Benzodiazepines do not reduce the core symptoms of PTSD or improve PTSD-related sleep dysfunction[23,47,48]

Substance Use Disorder

Co-occurring substance use disorders are very high in PTSD, creating an increased risk of overdose and potential problems with tolerance and dependence[26]

Withdrawal Symptoms

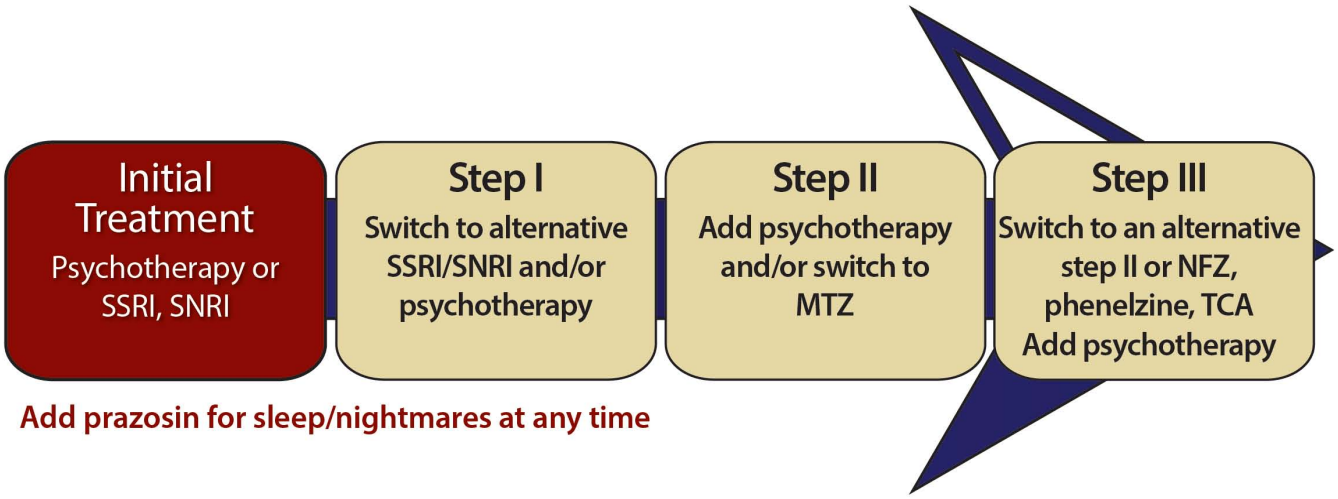
Withdrawal of benzodiazepines can worsen existing symptoms, resulting in increased anxiety, sleep disturbances, rage, hyper-alertness, increased nightmares and intrusive thoughts[48]

Aggressive Behaviors

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)[49]

Benzodiazepines have been found to increase aggressive behaviors over time in Veterans with PTSD ($p < 0.05$; 95% CI [0.11–0.9]).[50]

Figure 14.
VA/DoD 2010 Guidelines
Stepped Care Treatment of PTSD[26]



SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin norepinephrine reuptake inhibitor, MTZ = mirtazapine, NFZ = nefazodone, TCA = tricyclic antidepressant

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

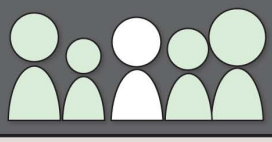
Marijuana vs. Benzodiazepines

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.[51,52] However, preliminary evidence suggests that marijuana use may worsen PTSD symptoms.[53–55]

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.[11,56,57]

Sleep Apnea[11]	Chronic Obstructive Pulmonary Diseases (COPD)*[56,57]	General Population[11]
		
Benzodiazepines can significantly lower minimum oxygen levels during the night	Benzodiazepines increase the risk of outpatient respiratory exacerbations and emergency room visits	Benzodiazepine exposure in all adults has been associated with increased risk of community-acquired pneumonia

*Brief Cognitive Behavioral Therapy can help decrease the sensation of dyspnea as well as symptoms of anxiety and depression in patients with COPD[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

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]

Figure 16.
Strategies for Benzodiazepine Discontinuation[1,61–63]

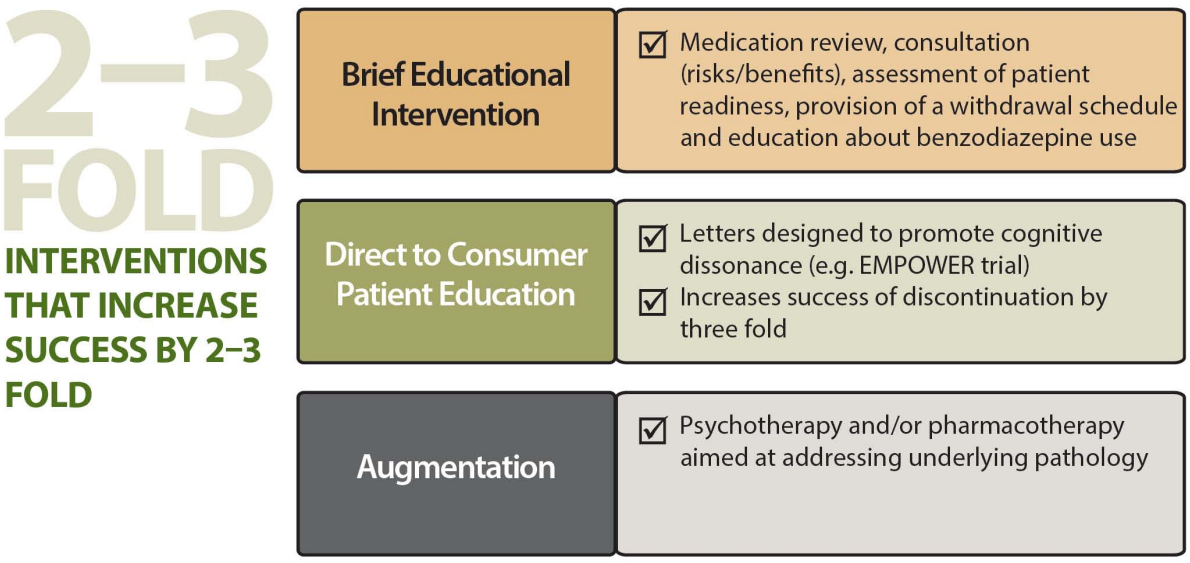
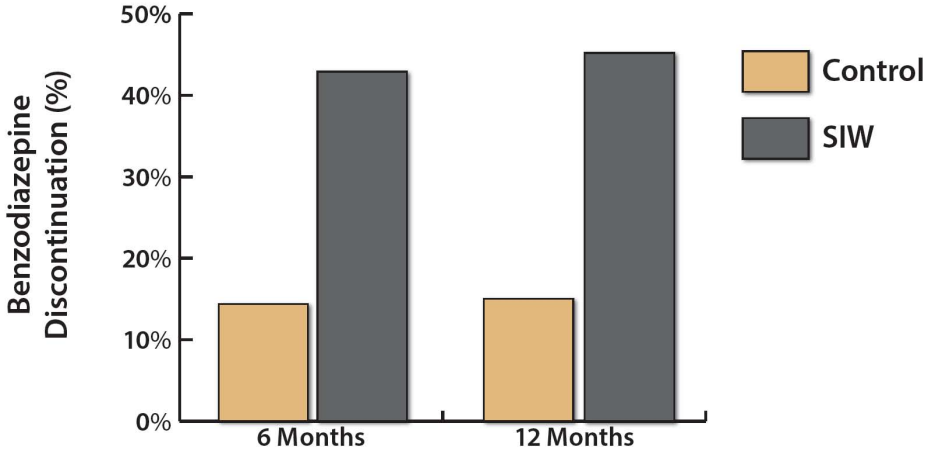
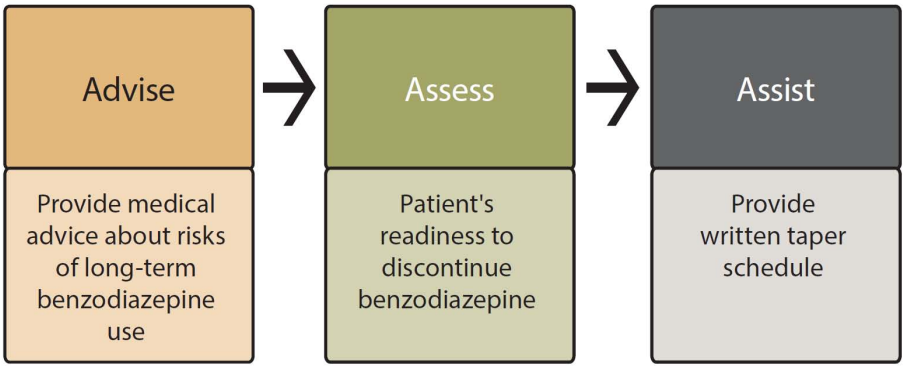


Figure 17.
Brief Intervention vs. Care as Usual: Comparison of Benzodiazepine Discontinuation at 6 and 12 Months[59]



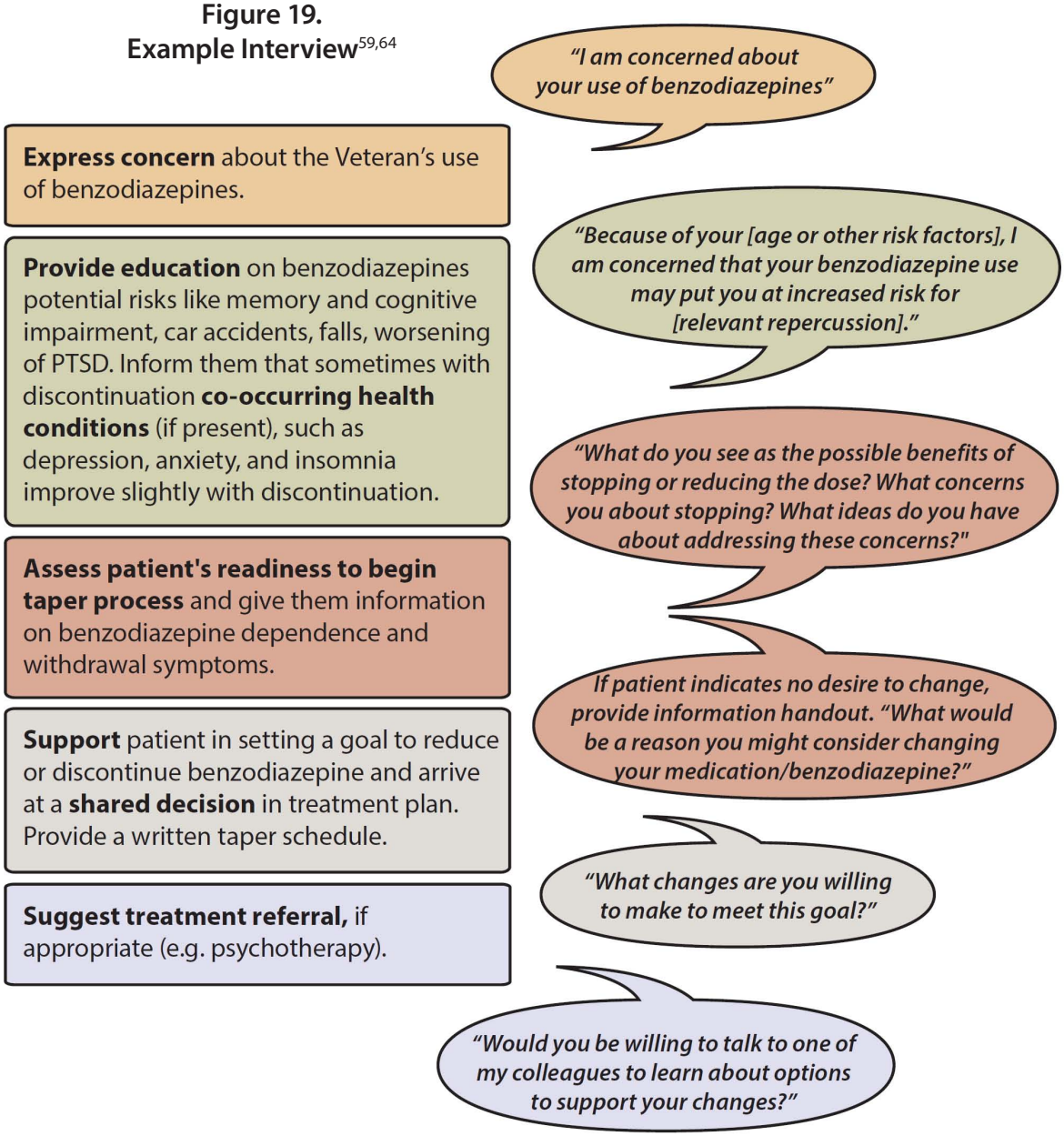
SIW = study intervention group with written instructions. A total of 75 general practitioners (532 patients) were randomized to provide care as usual or a brief educational intervention (information on benzodiazepine dependence, abstinence and withdrawal symptoms; risks of long-term use, memory and cognitive 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.

Figure 18.
Structure of a Brief Educational Intervention[64]



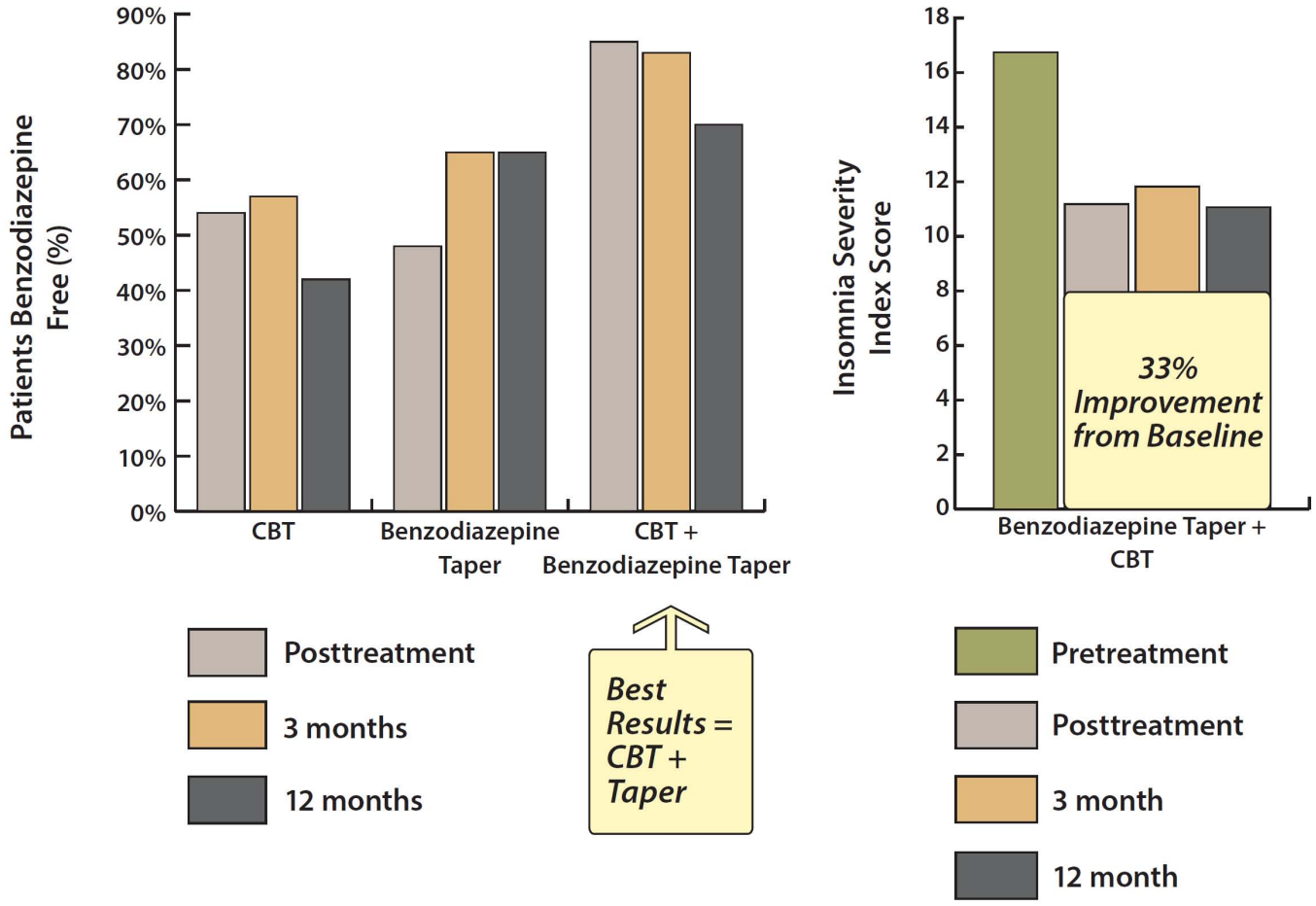
Explore and acknowledge perceived benefits and harms and allow Veteran to express his/her concerns.[64]

Figure 19.
Example Interview[59,64]



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

Figure 20.
Benzodiazepine Taper and Cognitive Behavior Therapy[65]



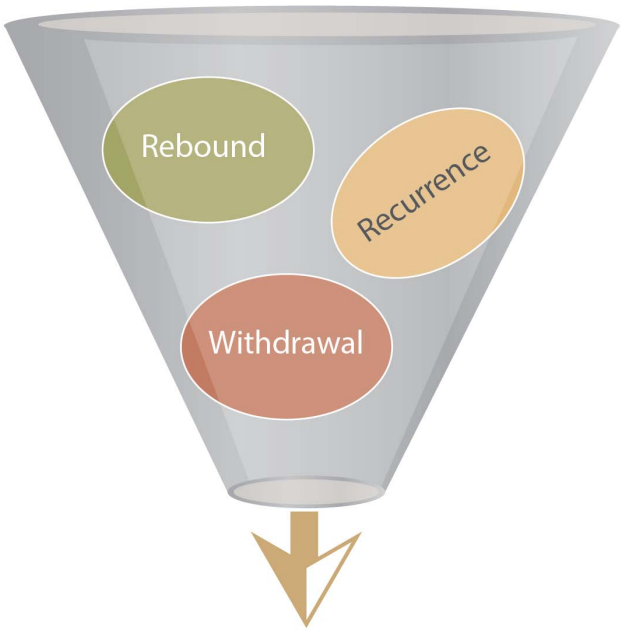
Seventy-six older adult outpatients with chronic insomnia and prolonged use (mean duration of 19.3 years) of a benzodiazepine for sleep were randomly assigned for a 10-week intervention consisting of a supervised benzodiazepine withdrawal program (n = 25), cognitive behavior therapy (CBT) for insomnia (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 ($p < 0.0001$).

Benzodiazepine Reduction or Discontinuation

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]

Figure 21.
Triad of Benzodiazepine Discontinuation Symptoms[66]



Slow withdrawal can lessen symptoms and promote successful discontinuation

Benzodiazepine Tapering Strategies:

- ➔ Gradually taper the original benzodiazepine[66]
  OR
- ➔ Substitute with a longer-acting benzodiazepine then gradually taper[66]
  OR
- ➔ Taper to lower dose of original benzodiazepine then switch to a longer-acting benzodiazepine

Table 3. Benzodiazepine Withdrawal Symptoms[7]

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

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[7,66]			
Benzodiazepine Agent	**Approximate Dosage Equivalents**	**Elimination Half-Life (may include active metabolites)**	**Example Taper Schedules**
Chlordiazepoxide	25 mg	>100 hours	Shorter Taper (e.g. 3 months) • Reduce dose by 50% the first 2–4 weeks (e.g. 25% decrease every 2 weeks) • Maintain on that dose 1–2 months Then • Reduce dose by 25% every two weeks Longer Taper (e.g. 6 months) • 10–25% every 4 weeks
Diazepam	10 mg	>100 hours	
Clonazepam	1 mg	20–50 hours	
Lorazepam	2 mg	10–20 hours	
Alprazolam	1 mg	12–15 hours	
Temazepam	15 mg	10–20 hours	
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[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[1]

- ☑ 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[1]

- 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

This summary was written by:

Sarah J. Popish, Pharm.D., BCPP
Daina L. Wells, Pharm.D., BCPS, BCPP

We thank our expert reviewers:

Anna White, Pharm D., BCPP — Academic Detailing Clinical Pharmacy Specialist, VISN 12;
Bruce P. Capehart, MD, OEF/OIF — Program Medical Director, Mental Health Service Line, VA Medical Center Durham
Karen Drexler, MD — National Mental Health Program Director – Addictive Disorders, Mental Health Services, Office of Patient Care Services, VA Central Office
Karla E. Mallo, Pharm.D. — Pharmacy Benefits Executive, VISN 19
Todd Semla, MS, Pharm.D. — National PBM Clinical Pharmacy Program Manager – Mental Health & Geriatrics, National Pharmacy Benefits Management Services
Albert Shaw, MD, Psychiatrist — Harry S. Truman Memorial Veterans' Hospital
Matthew A. Schreiber, MD, PhD, Psychiatrist — VA Puget Sound Health Care System

REFERENCES

1. *Discontinuation Strategies for Patients with Long-term Benzodiazepine Use: A Review of Clinical Evidence and Guidelines*. 2015, Ottawa ON: 2015 Canadian Agency for Drugs and Technologies in Health.
2. Bachhuber, M.A., et al., *Increasing Benzodiazepine Prescriptions and Overdose Mortality in the United States, 1996-2013.* Am J Public Health, 2016: p. e1–e3.
3. Olfson, M., M. King, and M. Schoenbaum, *Benzodiazepine use in the United States.* JAMA Psychiatry, 2015. 72(2): p. 136–42.
4. Bernardy, N.C., et al., *Gender differences in prescribing among veterans diagnosed with posttraumatic stress disorder.* J Gen Intern Med, 2013. 28 Suppl 2: p. S542–8.
5. Demyttenaere, K., et al., *Clinical factors influencing the prescription of antidepressants and benzodiazepines: results from the European study of the epidemiology of mental disorders (ESEMeD).* J Affect Disord, 2008. 110(1-2): p. 84–93.
6. Benitez, C.I., et al., *Use of benzodiazepines and selective serotonin reuptake inhibitors in middle-aged and older adults with anxiety disorders: a longitudinal and prospective study.* Am J Geriatr Psychiatry, 2008. 16(1): p. 5–13.
7. Taylor D, C. Paton, and S. Kapur, *The Maudsley Prescribing Guidelines in Psychiatry 12th Edition*. 2015, West Suseex: Wiley Blackwell.
8. Lugoboni, F., et al., *Quality of life in a cohort of high-dose benzodiazepine dependent patients.* Drug Alcohol Depend, 2014. 142: p. 105–9.
9. Gray, S.L., et al., *Benzodiazepine use and physical performance in community-dwelling older women.* J Am Geriatr Soc, 2003. 51(11): p. 1563–70.

10. Rapoport, M.J., et al., *Benzodiazepine use and driving: a meta-analysis.* J Clin Psychiatry, 2009. 70(5): p. 663–73.
11. Obiora, E., et al., *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): p. 163–70.
12. Kripke, D.F., *Mortality Risk of Hypnotics: Strengths and Limits of Evidence.* Drug Saf, 2015.
13. Park, T.W., et al., *Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study.* BMJ, 2015. 350: p. h2698.
14. Jones, C.M., K.A. Mack, and L.J. Paulozzi, *Pharmaceutical overdose deaths, United States, 2010.* JAMA, 2013. 309(7): p. 657–9.
15. National Institute on Drug Abuse. National Center for Health Statistics, CDC Wonder. National Overdose Deaths.
16. Barker, M.J., et al., *Cognitive effects of long-term benzodiazepine use: a meta-analysis.* CNS Drugs, 2004. 18(1): p. 37–48.
17. Bierman, E.J., 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): p. 1194–200.
18. Boeuf-Cazou, O., et al., *Impact of long-term benzodiazepine use on cognitive functioning in young adults: the VISAT cohort.* Eur J Clin Pharmacol, 2011. 67(10): p. 1045–52.
19. Tannenbaum, C., 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): p. 639–58.
20. Billioti de Gage, S., et al., *Benzodiazepine use and risk of dementia: prospective population based study.* BMJ, 2012. 345: p. e6231.
21. Shash, D., et al., *Benzodiazepine, psychotropic medication, and dementia: A population-based cohort study.* Alzheimers Dement, 2015.
22. Gray, S.L., et al., *Benzodiazepine use and risk of incident dementia or cognitive decline: prospective population based study.* BMJ, 2016. 352: p. i90.
23. Guina, J., et al., *Benzodiazepines for PTSD: A Systematic Review and Meta-Analysis.* J Psychiatr Pract, 2015. 21(4): p. 281–303.
24. Wesson DR et al. in JH Lowinson, P Ruiz, RB Millman, JG Langrod (Eds.). Substance Abuse: A Comprehensive Textbook (4th ed.). Baltimore. MD: Lippincott. Williams & Wilkins. 2004. pp. 302–312.
25. Substance Abuse and Mental Health Services Administration, *The TEDS Report: Substance Abuse Treatment Admissions for Abuse of Benzodiazepines.* Rockville, MD., June 2, 2011.
26. Management of Post-Traumatic Stress. Washington, DC: Office of Quality and Performance and the Veterans Affairs and Department of Defense Development Work Group, Veterans Health Administration, Department of Veterans Affairs. October 2010.
27. Katzman, M.A., et al., *Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders.* BMC Psychiatry, 2014. 14 Suppl 1: p. S1.
28. Schutte-Rodin, S., et al., *Clinical guideline for the evaluation and management of chronic insomnia in adults.* J Clin Sleep Med, 2008. 4(5): p. 487–504.
29. Bhat, A., F. Shafi, and A.A. El Solh, *Pharmacotherapy of insomnia.* Expert Opin Pharmacother, 2008. 9(3): p. 351–62.

30. Tariq, S.H. and S. Pulisetty, *Pharmacotherapy for insomnia.* Clin Geriatr Med, 2008. 24(1): p. 93–105, vii.
31. Ferracioli-Oda, E., A. Qawasmi, and M.H. Bloch, *Meta-analysis: melatonin for the treatment of primary sleep disorders.* PLoS One, 2013. 8(5): p. e63773.
32. Nielsen, S., et al., *Benzodiazepine use among chronic pain patients prescribed opioids: associations with pain, physical and mental health, and health service utilization.* Pain Med, 2015. 16(2): p. 356–66.
33. Pakulska, W. and E. Czarnecka, *Effect of diazepam and midazolam on the antinociceptive effect of morphine, metamizol and indomethacin in mice.* Pharmazie, 2001. 56(1): p. 89–91.
34. Brotz, D., et al., *Is there a role for benzodiazepines in the management of lumbar disc prolapse with acute sciatica?* Pain, 2010. 149(3): p. 470–5.
35. Ciccone, D.S., et al., *Psychological correlates of opioid use in patients with chronic nonmalignant pain: a preliminary test of the downhill spiral hypothesis.* J Pain Symptom Manage, 2000. 20(3): p. 180–92.
36. *American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.* J Am Geriatr Soc, 2015. 63(11): p. 2227–46.
37. Glass, J., et al., *Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits.* BMJ, 2005. 331(7526): p. 1169.
38. Wang, P.S., et al., *Hazardous benzodiazepine regimens in the elderly: effects of half-life, dosage, and duration on risk of hip fracture.* Am J Psychiatry, 2001. 158(6): p. 892–8.
39. Tamblyn, R., et al., *A 5-year prospective assessment of the risk associated with individual benzodiazepines and doses in new elderly users.* J Am Geriatr Soc, 2005. 53(2): p. 233–41.
40. Paterniti, S., C. Dufouil, and A. Alperovitch, *Long-term benzodiazepine use and cognitive decline in the elderly: the Epidemiology of Vascular Aging Study.* J Clin Psychopharmacol, 2002. 22(3): p. 285–93.
41. Cook, J.M., et al., *Physicians' perspectives on prescribing benzodiazepines for older adults: a qualitative study.* J Gen Intern Med, 2007. 22(3): p. 303–7.
42. Curran, H.V., 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): p. 1223–37.
43. Defrancesco, M., et al., *Use of Benzodiazepines in Alzheimer's Disease: A Systematic Review of Literature.* Int J Neuropsychopharmacol, 2015. 18(10): p. pyv055.
44. Kapusta, P., et al., *Behaviour management in dementia.* Can Fam Physician, 2011. 57(12): p. 1420–2.
45. Kales, H.C., L.N. Gitlin, and C.G. Lyketsos, *Management of neuropsychiatric symptoms of dementia in clinical settings: recommendations from a multidisciplinary expert panel.* J Am Geriatr Soc, 2014. 62(4): p. 762–9.
46. Gitlin, L.N., H.C. Kales, and C.G. Lyketsos, *Nonpharmacologic management of behavioral symptoms in dementia.* JAMA, 2012. 308(19): p. 2020–9.
47. Braun, P., et al., *Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment.* J Clin Psychiatry, 1990. 51(6): p. 236–8.
48. Risse, S.C., et al., *Severe withdrawal symptoms after discontinuation of alprazolam in eight patients with combat-induced posttraumatic stress disorder.* J Clin Psychiatry, 1990. 51(5): p. 206–9.

49. Elbogen, E.B., et al., *Violent behaviour and post-traumatic stress disorder in US Iraq and Afghanistan veterans.* Br J Psychiatry, 2014. 204: p. 368–75.
50. Shin, H.J., et al., *Longitudinal correlates of aggressive behavior in help-seeking U.S. veterans with PTSD.* J Trauma Stress, 2012. 25(6): p. 649–56.
51. Yarnell, S., *The Use of Medicinal Marijuana for Posttraumatic Stress Disorder: A Review of the Current Literature.* Prim Care Companion CNS Disord, 2015. 17(3).
52. Betthauser, K., J. Pilz, and L.E. Vollmer, *Use and effects of cannabinoids in military veterans with posttraumatic stress disorder.* Am J Health Syst Pharm, 2015. 72(15): p. 1279–84.
53. Wilkinson, S.T., E. Stefanovics, and R.A. Rosenheck, *Marijuana use is associated with worse outcomes in symptom severity and violent behavior in patients with posttraumatic stress disorder.* J Clin Psychiatry, 2015. 76(9): p. 1174–80.
54. Bonn-Miller, M.O., A.A. Vujanovic, and K.D. Drescher, *Cannabis use among military veterans after residential treatment for posttraumatic stress disorder.* Psychol Addict Behav, 2011. 25(3): p. 485–91.
55. Bremner, J.D., et al., *Chronic PTSD in Vietnam combat veterans: course of illness and substance abuse.* Am J Psychiatry, 1996. 153(3): p. 369–75.
56. Vozoris, N.T., *Do benzodiazepines contribute to respiratory problems?* Expert Rev Respir Med, 2014. 8(6): p. 661–3.
57. Rodriguez-Roisin, R. and J. Garcia-Aymerich, *Should we exercise caution with benzodiazepine use in patients with COPD?* Eur Respir J, 2014. 44(2): p. 284–6.
58. Maurer, J., et al., *Anxiety and depression in COPD: current understanding, unanswered questions, and research needs.* Chest, 2008. 134(4 Suppl): p. 43S–56S.
59. Vicens, C., 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): p. 471–9.
60. Mugunthan, K., T. McGuire, and P. Glasziou, *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): p. e573–8.
61. Tannenbaum, C., et al., *Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: the EMPOWER cluster randomized trial.* JAMA Intern Med, 2014. 174(6): p. 890–8.
62. Gould, R.L., et al., *Interventions for reducing benzodiazepine use in older people: meta-analysis of randomised controlled trials.* Br J Psychiatry, 2014. 204(2): p. 98–107.
63. Pollmann, A.S., et al., *Deprescribing benzodiazepines and Z-drugs in community-dwelling adults: a scoping review.* BMC Pharmacol Toxicol, 2015. 16: p. 19.
64. *Screening for Drug Use in General Medical Settings Resource Guide.* National Institute on Drug Abuse, 2010.
65. Morin, C.M., et al., *Randomized clinical trial of supervised tapering and cognitive behavior therapy to facilitate benzodiazepine discontinuation in older adults with chronic insomnia.* Am J Psychiatry, 2004. 161(2): p. 332–42.
66. Management of Substance Use Disorders. Washington, DC: Office of Quality and Performance and the Veterans Affairs and Department of Defense Development Work Group, Veterans Health Administration, Department of Veterans Affairs. 2015.

67. Perry, P.J., *Psychotropic drug handbook*. eighth ed. 2007, Philadephia, PA: Lippincott Williams & Wilkins.
68. Guaiana, G. and C. Barbui, *Discontinuing benzodiazepines: best practices.* Epidemiol Psychiatr Sci, 2016: p. 1–3.
69. Lader, M. and A. Kyriacou, *Withdrawing Benzodiazepines in Patients With Anxiety Disorders.* Curr Psychiatry Rep, 2016. 18(1): p. 8.

Notes

VA Academic Detailing Service

Real Provider Resources
Real Patient Results

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.

VA PBM Academic Detailing Service Email Group
PharmacyAcademicDetailingProgram@va.gov

VA PBM Academic Detailing Service SharePoint Site
https://vaww.portal2.va.gov/sites/ad

August 2016

IB 10-928, P96810