Safely Tapering Benzodiazepines in Older Adults with PTSD

Ilse Wiechers, MD, MPP, MHS
National Program Director, Psychotropic Drug Safety Initiative
Office of Mental Health Operations
US Department of Veterans Affairs
Assistant Professor of Psychiatry
Yale University School of Medicine
Objectives

- Identify the risks of using benzodiazepines in elderly
- Describe evidence supporting safe & effective tapering of benzodiazepines
- Recognize benzodiazepine withdrawal
- Explain general principles of benzodiazepine tapers
- Describe alternatives to using benzodiazepines
Some basic principles

• Not recommended for > 3 weeks of use due to potential for withdrawal and abuse

• Not recommended for patients with compromised pulmonary function

• Not ideal for substance abusing patients

• Not first line treatment for anxiety or insomnia

• Generally speaking, a bad idea in the elderly
FIGURE 1—Number of Adults Filling a Benzodiazepine Prescription, Quantity Filled, and Overdose Deaths Involving Benzodiazepines: United States, 1996–2013

(Bachhuber et al., 2016)
BZD Risks: Mortality/Disinhibition

• Increases overall mortality rates with long-term use by 50% (Kripke et al, 1998; Kripke, 2000)

• Mortality hazard associated with taking prescribed sleeping pills 30 days in the past month is similar to the hazard of smoking 1-2 cigarettes a day (Kripke 2000)

• Receipt of BZDs was related to increases in aggressive behavior among patients who were aggressive at baseline (Shin et al, 2012) – often an indication for a BZD prescription

• Significantly higher risk for mortality associated with long-term BZDs for sleep (Weich et al., 2014)
High Risk Populations

• PTSD
• TBI
• Elderly
• Dementia
• Women of childbearing age
Figure 1: Total number of Veterans in VHA with a diagnosis of PTSD, by year
Cognitive Risks in PTSD Patients

Cognitive effects of BZDs are of particular concern in the veteran PTSD population:

• Cognitive dysfunction is an effect of long term BZDs (Stewart 2005)
  – Improves with discontinuation of the BZD
  – Baseline does not equalize to non-BZD control group even after 3 months without BZDs
• Geriatric patients who had received BZDs showed 50% increased risk of dementia over never users (Billioti de Gage et al 2012) and risk of Alzheimer’s (de Gage 2014)
• PTSD itself is a risk factor for dementia with rates in older veterans with PTSD as high as 2 times those without PTSD (Qureshi, 2010)
• High rates of co-occurring Traumatic Brain Injury or Post-Concussive Syndrome
PTSD Pharmacotherapy Recommendations

- **SSRI (Selective Serotonin Reuptake Inhibitor) – not all created equal**
  - **Sertraline***
  - **Paroxetine** *(though highly anticholinergic, therefore not top rec in elderly)*
  - Fluoxetine
- **SNRI (Serotonin Norepinephrine Reuptake Inhibitor)**
  - Venlafaxine*
- **Other**
  - Benzodiazepines *(harm)*
  - Mirtazapine
  - Nefazodone* *(Caution: liver injury)*
  - Tricyclic Antidepressants (TCAs)
    - Amitriptyline, imipramine

*VA/DoD Clinical Practice Guideline for the treatment of PTSD 2010

*Outperformed others in new meta-analysis – Lee et al, 2016*
Benzodiazepines – No Benefit in PTSD

• Evidence of harm has grown since PTSD CPG recommendation in 2010

• Should particularly be avoided in PTSD subgroups:
  – History of TBI or Substance Use Disorder
  – 65 years and older
  – Concurrent sedatives such as opioids
  – Pulmonary disease and sleep apnea
  – Women of child-bearing age

• Clinicians should avoid new starts and in those patients taking benzodiazepines, educate about the risk and discuss starting slow taper
Increasing use of benzos with age

Figure. Percentage of Population in the United States in 2008 With Any Benzodiazepine Use by Sex and Age

Women > men

Benzodiazepines are associated with increased risks in elderly

✓ Falls
✓ Hip fractures
✓ Sedation
✓ Cognitive impairment
✓ Motor vehicle crashes

Both short and long-acting benzos are listed in 2015 Beers Criteria

Ray et al. (1989); Ray (1992); Glass et al. (2005); Wang et al. (2001); Chang et al. (2008); Paterniti et al. (2002); Billotti de Gage et al. (2012); Hemmelgarn et al (1997); J Am Geriatr Soc. 2015;63(11):2227-46.
Benzo and z-drug risks in elderly

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
<th>Z-drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime sedation</td>
<td>All of the benzo risks PLUS</td>
</tr>
<tr>
<td>Delirium</td>
<td>Sleep walking/injury</td>
</tr>
<tr>
<td>Ataxia</td>
<td>Hallucinations</td>
</tr>
<tr>
<td>Memory Impairment</td>
<td></td>
</tr>
<tr>
<td>Falls and fractures</td>
<td></td>
</tr>
<tr>
<td>Motor Vehicle Accidents</td>
<td></td>
</tr>
<tr>
<td>Rebound insomnia</td>
<td></td>
</tr>
<tr>
<td>? Alzheimer’s Disease</td>
<td></td>
</tr>
</tbody>
</table>
Bottom line

• Prevention is the best strategy
  – Avoid new starts to avoid chronic use

• But even dose reduction may help minimize harms
Choosing a benzodiazepine

• Use one agent of each type (short/long-acting) regularly, you will become more familiar with tapering those agents
  - My personal preferences: lorazepam & clonazepam
  - My least favorite: alprazolam

Special considerations in the elderly

• Pick an agent with no active metabolites (i.e. no first pass metabolism in liver means less risk of toxicity)
  - Oxazepam, Temazepam, Lorazepam

• Short-acting is always preferable to long-acting
What older patients (chronic users) & physicians think about benzo tapers

### Patients
- Long-term users are psychologically dependent
- Lack of awareness, underestimate, or disregard side effects
- Less frequent daily dosing associated with willingness to taper

### Physicians
- Don’t view benzo use in the elderly as a problem
  - Minimize risks
  - Don’t see addiction as problem
  - Stable dose safe
- Anticipate resistance of patients
- Low priority
- Limited time

Cook et al. (2007a); Cook et al. (2007b), Cook et al. (2007c)
Benzodiazepines + Opioids = OD deaths

- Benzodiazepines when co-administered with substances with sedative properties, like opioids and alcohol, can result in unintentional fatal outcomes
- 27% of Veterans who received opioids also received benzodiazepines
- After opioids, benzodiazepines are the drug class most commonly involved in pharmaceutical overdose (OD) deaths (30%)
- Benzodiazepines are the class most commonly involved in an opioid-related death (30%)
- In the VA, 50% of opioid OD deaths are on concurrent benzos
  - Among opioid users risk of death goes up with benzos in a dose-response fashion

Benzodiazepine withdrawal

• Who is at risk for withdrawal?
  - Anyone taking benzodiazepines for > 2 weeks

• Symptoms of withdrawal
  - Agitation
  - Anxiety
  - Tachycardia & palpitations
  - Dysphoria
  - Insomnia & nightmares
  - Increased awareness of sensory stimuli (esp. noise & light)
  - Perceptual disturbances (aka hallucinations)
  - Depersonalization
  - Confusion
  - Delirium
  - Seizures

In the elderly, often misattributed to other medical & psych conditions, especially dementia
Benzodiazepine tapers
Some evidence to support success with combining taper and CBT

- 76 adults mean age 62, mean benzo use 19+ years
- 10-week intervention at research-based sleep clinic
- RCT with 3 arms:
  1. Supervised benzo taper
  2. CBT-I alone (weekly small group)
  3. Combination taper + CBT-I
- Key result: all 3 were successful, combo was best (85% benzo-free)
FIGURE 1. Weekly Quantity of Benzodiazepine Medication Used by Older Adults With Insomnia in a Randomized Clinical Trial of Three Interventions to Facilitate Benzodiazepine Discontinuation

- Patients receiving cognitive behavior therapy (N=24)
- Patients receiving medication taper (N=25)
- Patients receiving cognitive behavior therapy combined with medication taper (N=27)
More evidence to support success with combining taper and CBT

- 65 adults, mean age 67, mean benzo use 12+ years

- 8-week intervention

- RCT with 2 arms:
  1. Taper alone (25% q1-2 weeks)
  2. Combination taper + CBT (weekly small groups)

- Key result: combined was better (77% vs 38% completely stopped benzo use), persisted at 12-month follow up

Direct patient education works too

- **EMPOWER (Eliminating Medications Through Patient Ownership of End Results) cluster randomized trial**
  - Community pharmacies randomized to intervention
  - Participants: 65+ yo, receiving long-term benzo therapy (3 mo of Rx fills prior to study)

- Intervention: distributed patient education booklet about dangers of benzos with taper recommendations & instructions to talk to a pharmacist or physicians

- Key result: 62% of intervention group initiated conversation about taper; more had discontinued benzos at 6 mo f/up (27% vs 5% of the control group)

Before you begin a taper

- A team-based approach will be most effective in efforts to taper a patient from benzodiazepines
- Build a stable relationship with your patient
- Evaluate and treat any co-occurring conditions
- Obtain complete drug and alcohol history and random drug screen
- Review recent medical notes (ER visits) and coordinate care with other providers
- If available, query prescription drug monitoring database

General principles for tapers

• Switch from short-acting to long-acting for taper
  - **Exception**: for older patients already on a short-acting benzo, try tapering on that agent first

• Never taper more than one agent at the same time!!!

• Set clear goals **with the patient**

• Need more frequent follow up visits

• Chronic users require **slow taper** over several months
General principles for tapers

- Scheduled, not PRN dosing
- Decrease total *original* dose 25% q 1-2 weeks
- Consider holding dose at 50% total original dose for several weeks to a month
- Decrease 10-25% *current* dose q 1-2 weeks thereafter

Hardest part is the last 25%

May not be able to taper off entirely, but less is better (harm reduction)
Example Taper

**Milestone Suggestions**

<table>
<thead>
<tr>
<th>Week</th>
<th>Example: Alprazolam 2 mg bid Convert to 40 mg diazepam daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>35 mg/day</td>
</tr>
<tr>
<td>Week 2</td>
<td>Total dose decrease by 25%</td>
</tr>
<tr>
<td></td>
<td>30 mg/day (25%)</td>
</tr>
<tr>
<td>Week 3</td>
<td>25 mg/day</td>
</tr>
<tr>
<td>Week 4</td>
<td>Total dose decrease by 50%</td>
</tr>
<tr>
<td></td>
<td>20 mg/day (50%)</td>
</tr>
<tr>
<td>Week 5-8</td>
<td>Hold dose</td>
</tr>
<tr>
<td></td>
<td>Continue at 20 mg/day for 1 month</td>
</tr>
<tr>
<td>Week 9-10</td>
<td>Current dose reduction of 25% every two weeks</td>
</tr>
<tr>
<td></td>
<td>15 mg/day</td>
</tr>
<tr>
<td>Week 11-12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg/day</td>
</tr>
<tr>
<td>Week 13-14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 mg/day</td>
</tr>
<tr>
<td>Week 15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>discontinue</td>
</tr>
</tbody>
</table>

The bad news: you **MUST** sit down and calculate out a detailed taper regimen
<table>
<thead>
<tr>
<th>Benzodiazepine Equivalency</th>
<th>Dosage Equivalency (mg)</th>
<th>Elimination Half-Life (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Xanax)</td>
<td>0.5</td>
<td>6-20</td>
</tr>
<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>25</td>
<td>30-100</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>0.25-0.5</td>
<td>18-50</td>
</tr>
<tr>
<td>Clorazepate (Tranxene)</td>
<td>7.5</td>
<td>30-100</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>5</td>
<td>30-100</td>
</tr>
<tr>
<td>Flurazepam (Dalmame)</td>
<td>15-30</td>
<td>50-160</td>
</tr>
<tr>
<td>Halazepam (Paxipam)</td>
<td>20</td>
<td>30-100</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>1</td>
<td>10-20</td>
</tr>
<tr>
<td>Midazolam (Versed)</td>
<td>N/A</td>
<td>2-3</td>
</tr>
<tr>
<td>Oxazepam (Serax)</td>
<td>15</td>
<td>8-12</td>
</tr>
<tr>
<td>Prazepam (Centrax)</td>
<td>10</td>
<td>30-100</td>
</tr>
<tr>
<td>Quazepam (Doral)</td>
<td>15</td>
<td>50-160</td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td>15-30</td>
<td>8-20</td>
</tr>
<tr>
<td>Triazolam (Halcion)</td>
<td>0.25</td>
<td>1.5-5</td>
</tr>
</tbody>
</table>
A Few Clinical Pearls

• Consider starting SSRI/SNRI before taper
• Refer for CBT-I when symptoms of insomnia rebound
• BE FLEXIBLE!
• Take your time (esp. with chronic users)
Alternatives to benzodiazepines in the elderly: **Anxiety**
Managing Anxiety: evaluation

• Thoroughly evaluate anxiety complaint
  – Are symptoms of medical illness getting attributed to anxiety?
  – Is anxiety a reaction to disabilities that result from medical condition? (i.e., an adjustment disorder)
  – Is patient open to possibility that symptoms are related to “anxiety”? If PTSD diagnosis, are they related to hyperarousal?
    • (Are they psychologically-minded?)
  – What is the diagnosis?

• Identify and modify contributing factors
  – Manage medical/mental health comorbidities that may be contributing to anxiety complaints
Non-pharmacologic treatments

• Relaxation training, CBT, supportive therapy, and cognitive therapy all have demonstrated efficacy\(^1\)

• As is generally the case for everything, most evidence is for CBT

• While you are waiting on therapy referral:
  – Work with patient to identify thoughts accompanying physical symptoms
  – Work with patient to de-catastrophize physical symptoms
  – Address key underlying schema/fears

In older adults, if evidence for pharm = nonpharm nonpharm goes first

Wolitzky-Taylor KB, et al. Depression and Anxiety. 2010;27:190-211
Pharmacologic treatments

• If you choose to augment psychotherapy, primary benzodiazepine alternatives are:

  – Antidepressants

  – Buspirone
Antidepressants

• SSRIs/SNRIs
  – Citalopram, sertraline, venlafaxine ER
  – For somatically-preoccupied, LOTS of education re: potential side effects ahead of time (esp. GI)
  – Start at very small dose with equally small increases every 2 wks
    • Venlafaxine (immediate release) 25mg tablet
      – go up by 12.5-25 mg

• Mirtazapine: limited evidence
• Bupropion: limited evidence of benefit for anxiety
  – No need to avoid for MDD in anxious patients

Buspirone

• Partial serotonin agonist (5-HT$_{1A}$ receptor)
• One of earliest trials (1979): “as effective an antianxiety agent as diazepam”$^1$
  – Generally performs well relative to benzo with fewer side effects$^{1,2}$
• Start 5mg tid
  – Standard range 20-30mg total daily; max 60mg daily
• Generally well-tolerated
  – CNS > GI symptoms
• Almost the only psychotropic not on Beers list

Which med to choose?

• Comorbid depression
  – SSRI/SNRI as first choice over buspirone

• No depression
  – Toss-up
  – If ++ GI symptoms, consider buspirone first
Alternatives to benzodiazepines in the elderly: **Insomnia**
Managing Insomnia

• Thoroughly evaluate sleep complaint
  – Insomnia Severity Index (ISI): used to assess the nature, severity and impact of insomnia on the patient as well as to monitor response to treatment
  • 7 items intended to assess the patient’s insomnia over the past 2 weeks; patients rank their responses on a scale of 0-4

<table>
<thead>
<tr>
<th>Insomnia Severity Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Difficulty falling asleep</td>
</tr>
<tr>
<td>2. Difficulty staying asleep</td>
</tr>
<tr>
<td>3. Problem waking up to early</td>
</tr>
<tr>
<td>4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?</td>
</tr>
<tr>
<td>5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?</td>
</tr>
<tr>
<td>6. How WORRIED/DISTRESSED are you about your current sleep problem?</td>
</tr>
<tr>
<td>7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?</td>
</tr>
</tbody>
</table>

Total score categories:
0–7 = No clinically significant insomnia
8–14 = Subthreshold insomnia
15–21 = Clinical insomnia (moderate severity)
22–28 = Clinical insomnia (severe)
Identify and modify contributing factors

- Switch to non-stimulating medications
- Adjust dosing schedule of stimulating medications (example: bupropion)
- Reduce/eliminate caffeine, alcohol and illicit drug use
- Manage medical/mental health comorbidities that may be contributing to sleep complaints
  - Sleep apnea, arthritis/pain, GERD, CHF, depression
Non-pharm first

• Implement non-pharmacologic treatments
  – Cognitive Behavioral Therapy for Insomnia (CBT-I)
  – Sleep hygiene
  – Education about changes in sleep with aging
    • Changes in sleep architecture can lead to more frequent awakenings, less restful or satisfying sleep
    • Advanced sleep phase syndrome (early to bed, early to rise)

• Then and only then do we pull out the prescription pad
CBT-i Coach

Features:

• Interactive sleep diary
• Insomnia Severity Index (ISI)
• Psychoeducation
• Automatic calculation of the sleep prescription with therapist adjustment options
• Tools to improve sleep, including relaxation exercises
• Customizable reminders to alert user to sleep hygiene, to record sleep habits, and to take sleep assessments

http://www ptsd.va.gov/professional/materials/apps/cbticoach_app_pro.asp
Pharmacotherapy

• If patient offered CBT-I and basic principles of sleep hygiene but is still suffering from insomnia, medications may be an option

• FDA Approved Agents for Insomnia
  – Doxepin, Temazepam, Zolpidem, Zolpidem CR, Diphenhydramine, Doxylamine, Ramelteon, Zaleplon, Eszopiclone

• Off-label Agents for Insomnia
  – Amitriptyline, Gabapentin, Hydroxyzine, Mirtazapine, Trazodone, Prazosin (nightmares in PTSD)
Pharmacotherapy

• If patient offered CBT-I and basic principles of sleep hygiene but is still suffering from insomnia, medications may be an option

• FDA Approved Agents for Insomnia
  – Doxepin, Temazepam, Zolpidem, Zolpidem CR, Diphenhydramine, Doxylamine, Ramelteon, Zaleplon, Eszopiclone

• Off-label Agents for Insomnia
  – Amitriptyline, Gapabentin, Hydroxyzine, Mirtazapine, Trazodone, Prazosin (nightmares in PTSD)
Doxepin

• Tricyclic antidepressant (TCA) recently FDA approved (Silenor ®) at low doses for treatment of insomnia (sleep maintenance)

• Acts primarily as an H1 antagonist and has a side effect profile comparable to placebo at low doses
  – Does not appear to cause tolerance or rebound insomnia

• Caution is advised in patients who are high risk of suicide due to risk of toxicity in overdose

• TCAs are on Beers Criteria List as inappropriate for use in elderly, EXCEPT for doxepine ≤ 6mg

Low dose doxepin is a reasonable treatment option for patients with insomnia. Use caution with elderly patients.

Antihistamines

• Diphenhydramine, doxylamine, hydroxyzine
• Short-term use recommended
• May consider in patients with substance use disorders
• Associated with anticholinergic side effects
  – Dry mouth, dizziness, drowsiness, impaired coordination, hypotension, confusion, urinary retention, worsening of narrow angle glaucoma

Not in elderly

Educate everyone about the “PM” OTC meds

Ramelteon (Rozerem®)

- Melatonin agonist
- FDA approved for “chronic and transient insomnia characterized by difficulty with sleep onset”
  - Helps decrease sleep latency but has not been shown to have significant effects on sleep maintenance
- Recommended as 1st line treatment of insomnia by The American Academy of Sleep Medicine
- Not a controlled substance
- Does not appear to produce rebound insomnia or symptoms of withdrawal with prolonged use

Sedative-hypnotics

Benzodiazepines

Nonbenzodiazepines

– Eszopiclone (Lunesta®)
– Zaleplon (Sonata®)
– Zolpidem and Zolpidem extended-release (Ambien® & Ambien CR®)
Sedative-hypnotics

- Recommended by The American Academy of Sleep Medicine as first line agents with evaluation of agent 2-4 weeks after initiation
  - Use at the lowest effective dose then taper and discontinue when possible
  - If long-term treatment is required, follow-up visits should be scheduled at least every 6 months to assess safety and efficacy

- Tolerance often quickly develops to the sleep inducing and prolonging effects

- Rebound insomnia can occur upon discontinuation after only 1-2 weeks of treatment

All on Beer Criteria – avoid use in older patients

If you choose to prescribe a sedative-hypnotic

<table>
<thead>
<tr>
<th>General Guidelines for Prescribing Sedative-hypnotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Use the lowest effective dose</td>
</tr>
<tr>
<td>2. Consider intermittent dosing (alternate nights or less) if possible*</td>
</tr>
<tr>
<td>3. Prescribe for short-term use (≤ 4 weeks) in the majority of cases</td>
</tr>
<tr>
<td>4. Consider tapering when discontinuing as dependence may have developed</td>
</tr>
<tr>
<td>5. Be alert for rebound insomnia and other withdrawal symptoms</td>
</tr>
<tr>
<td>6. Advise patients of the interaction with alcohol and other sedating drugs</td>
</tr>
</tbody>
</table>

*Only zolpidem has been studied with intermittent dosing at this time

Sedating Antidepressants

Trazodone
- Low doses primarily act at alpha-1, H1, and serotonin-2A & -2C receptors\(^1\)
- Most effective when used with an antidepressant in patients with depressive disorders\(^2,3\)
- Priapism risk 1/6000

Mirtazapine
- Low doses (3.25-15 mg) cause sedation acting as an H1 antagonist\(^4\)
- Therapeutic doses (15-45 mg) also block serotonin-2 receptors\(^5\)
- Most effective when used with an antidepressant in patients with depressive disorders\(^6\)
- Often used in older patients with poor PO intake/failure to thrive due to side effect of increased appetite and weight gain
  - Increased appetite and weight gain occurs in first 6 weeks

Gabapentin

• Has been shown to increase slow-wave sleep (deep sleep), reduce sleep latency and reduce arousals\(^1\)

• May help reduce drinking, promote abstinence and improve sleep in patients with alcohol use disorders\(^2-5\)

• Little evidence in elderly

Prazosin

• A generic lipid-soluble alpha-1 adrenoreceptor (AR) antagonist introduced in 1973 as “Minipress” for treatment of hypertension

• Recommended for Veterans with PTSD-related nightmares

• Doses studied range from 1-15 mg with an average of 9-13 mg nightly, 2-4 mg nightly in geriatric patients
  – Start at 1mg at bedtime and titrate up every 4-7 days, re-evaluate symptoms and monitor blood pressure and heart rate at each step

Studies show safe & effective in elderly combat vets!

Melatonin

• Neurohormone primarily produced by the pineal gland

• Indications:
  - **Delayed sleep phase disorder** - Acts as a phase re-setter rather than as a hypnotic
  - **Jet lag** - Improves daytime fatigue

• Dosing: 1-3 mg QHS
• t ½: < 1 hour
• Side effects: drowsiness, headache, dizziness and nausea
• Avoid use with other hypnotics
PTSD Consultation Program
FOR PROVIDERS WHO TREAT VETERANS

PTSDconsult@va.gov
(866) 948-7880
www.ptsd.va.gov/consult