Risk Mitigation Strategies for Benzodiazepines and Gabapentin

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Disclosures

• Dr. Gable has nothing to disclose
• Dr. Herndon has nothing to disclose
CPE Information

- Target Audience: Pharmacists
- ACPE#: 0202-0000-19-057-L01-P
- Activity Type: Application-based
Learning Objectives

At the completion of this application-based activity, participants will be able to:

1. Explain the risks, patterns and benefits associated with the use of benzodiazepines and gabapentin.
2. Identify patients at increased risk of adverse outcomes secondary to benzodiazepines.
4. Design a protocol based on patient-specific characteristics that minimizes withdrawal symptoms.
1. Which of the following is a typical conversion ratio between gabapentin and pregabalin?
   A. 2:1
   B. 3:1
   C. 6:1
   D. 10:1
2. Which of the following has not demonstrated “desirable” or “liking” effects in clinical studies?

A. Gabapentin at normal doses
B. Pregabalin at normal doses
C. Gabapentin at high doses
D. Pregabalin at high doses
3. Karen is a 50 year-old female patient with Borderline Personality Disorder (BPD) and panic attacks presenting for a refill of her diazepam 5 mg TID and buspirone 5 mg Q12 hours. What makes the prescribing of a benzodiazepine a higher risk for this patient?

A. Her age  
B. Female gender  
C. Co-occurring BPD  
D. Co-prescribing of buspirone
4. A physician wishes to begin a benzodiazepine taper with their patient who has been taking diazepam 10 mg QID for 3 years. What taper schedule would best minimize the experience of withdrawal symptoms?

A. 75% dose reduction every 4 weeks  
B. 50% dose reduction weekly  
C. 10% dose reduction every 2 weeks  
D. Only begin taper if patient is > 65 years-old
Patient Case - Sarah

38 year old who presents to family medicine clinic for poorly controlled pain

PMHx: Generalized anxiety disorder
Fibromyalgia syndrome
Migraine without aura

Meds: Alprazolam 1 mg Q8H as needed (PRN)
Gabapentin 600mg PO Q8 hours
Sertraline 100mg PO QAM
Baclofen 10mg PO Q8 hours PRN

ROS: Endorses headache, insomnia, palpitations, diarrhea alternating with constipation
Denies chest pain, shortness of breath

SHx: Smokes 1 pack per day, drinks socially

FHx: Endorses polysubstance abuse (mother)
Why Gabapentinoids For Pain?

- Selective $\alpha_{2\delta}$ P/Q pre-synaptic calcium channel antagonist
- First reported use for pain in reflex sympathetic dystrophy
- Landmark studies in post-herpetic neuralgia and diabetic neuropathic pain solidified use as adjuvant analgesic (gabapentin)
- Level A evidence for use in diabetic neuropathic pain (pregabalin)
- Opioid sparing and synergistic effects established
- Interest in pre-emptive analgesia prior to surgery
- Increased concern with adverse effects associated with opioids and NSAIDs

Why gabapentinoids for anxiety?

- Gabapentinoids
  - Gabapentin (Neurontin®, Gralise®, Horizant®)
  - Pregabalin (Lyrica®)
- Gabapentin (GBP)/pregabalin (PGB) widely used off-label for treatment of anxiety.
- Both have been shown to decrease GABA levels, thereby increasing glutamate and promoting descending noradrenergic inhibition in locus coeruleus = decrease in anxiety.


Why gabapentinoids for anxiety?

- RCT comparing gabapentin and placebo as adjunctive therapy in social phobia, suggesting gabapentin more effective than placebo.
  - Studies with gabapentin for treatment of social phobia, panic and somatoform disorders, anxiety in breast cancer survivors, and surgery-associated anxiety with mixed results.
- Greater RCT evidence-base supporting the use of pregabalin in GAD
  - 6 short term (4–6 week) fixed-dose studies; 2 short-term (8-week) flexible-dose studies, 1 long-term (6-month) fixed dose relapse prevention study; and a short-term (8-week) flexible-dose study in patients who had not responded to previous treatment with SSRI or SNRI.


Gabapentinoid risks

- Edema
- Potential bone mineral density changes
- Sedation
- Neurocognitive changes
- Fall risk
- Abuse
- Withdrawal syndrome
- Respiratory depression / overdose-related mortality

Abuse liability of gabapentinoids

- Rewarding behavior via conditioned place preference
  - GBP negligible
  - PGB minimal effects
- Meeting dependence criteria (PGB > GBP)
- Durability of self-administration / dopamine impact
- Conversion from prescribed dosing to self-escalation / non-medical
- Overdose risk (based on case reports)
  - Polypharm versus GBP or PGB alone
  - GBP resulted in nausea and sedation
  - PGB resulted in coma and respiratory depression

Drug Liking of GBP and PGB

Zacny et al.
• N = 16
• Healthy volunteers receiving PGB monotherapy, with oxycodone, or placebo
• Doses of 75-150mg equal to placebo in drug liking

PGB Package Insert
• N = 15
• Recreational drug users receiving multiple sedative / hypnotic drugs, including PGB 450mg as a single dose
• Subjective ratings similar to diazepam 30mg as a single dose

Lile et al.
• N = 8
• Current cannabis users receiving GBP as 600mg and 1200mg dose
• Similar drug liking to THC and increased drug-liking to THC when co-administered

Abuse and Dependence of PGB

• French pharmacovigilance database (1/1/10 through 12/31/15)
• 184,310 reports resulted in 521 abuse or dependence cases
  • Opioids 68.1%
  • Anxiolytics 27.8%
  • Triptans 4.4%
  • Baclofen 1.5%
  • Pregabalin 1.5%

• Risk compared to positive control and negative control
  • Pregabalin OR 1.1 (95% CI 0.6-2.3)
  • Clonazepam OR 5.7 (95% CI 3.5-9.2)
  • Amitriptyline 0 cases

OR: odds ratio; CI: confidence interval

Abuse and dependence of GBP & PGB

European Medicines Agency Database

Opioid + Gabapentinoid

• Increased risk of fatal overdose
  • Mechanism of slowed gastrointestinal peristalsis?
  • True respiratory depressant effects vs. reversal of tolerance?
• Enhanced euphoria from opioid, including med assisted therapy
• Decreased withdrawal symptoms from opioid
• Abuse / misuse more common in opioid use disorder compared to population

Current Pharmacovigilance Measures

Mandatory PDMP reporting

Rescheduled as controlled substance

GBP / PGB Withdrawal Symptoms

Timing
• Onset 12 to 168 hours
• Most commonly 24-48 hours

Symptoms
• Agitation (up to 50%)
• Anxiety
• Confusion
• Delirium
• Delirium tremens
• Diaphoresis
• Hyperalgesia
• Insomnia
• Nausea
• Seizure

## GBP / PGB taper strategies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Current Dose (daily)</th>
<th>Reduce to (daily)</th>
<th>Reduce to (daily)</th>
<th>Reduce to (daily)</th>
<th>7 days**</th>
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</thead>
<tbody>
<tr>
<td>Pregabalin</td>
<td>600mg</td>
<td>450mg X 2 days</td>
<td>300mg X 2 days</td>
<td>150mg / day X 2 days</td>
<td>75mg X 1 day, then stop</td>
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<td></td>
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</tr>
<tr>
<td>Gabapentin*</td>
<td>3600mg</td>
<td>2700mg X 2 days</td>
<td>1800mg X 2 days</td>
<td>900mg / day X 2 days</td>
<td>600mg X 1 day, then stop</td>
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<tr>
<td>Pregabalin</td>
<td>450mg</td>
<td>300mg X 3 days</td>
<td>150mg X 3 days</td>
<td>75mg X 1 day, then stop</td>
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<td>Gabapentin*</td>
<td>2,700mg</td>
<td>1800mg X 3 days</td>
<td>900mg X 3 days</td>
<td>600mg X 1 day, then stop</td>
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<tr>
<td>Gabapentin*</td>
<td>1,800mg</td>
<td>900mg X 4 days</td>
<td>600mg X 3 days, then stop</td>
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<td>Pregabalin</td>
<td>150mg</td>
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<tr>
<td>Gabapentin*</td>
<td>900mg</td>
<td>600mg X 7 days, then stop</td>
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</tbody>
</table>


*Gabapentin dosing recommendations based on extrapolated doses of 1:6 potency ratio and bioavailability

**Day 7 recommendations based on clinical experience in a chronic pain and substance use disorder population
Back to Sarah

• 3 early refill requests for gabapentin over past 12 months
• Admits to using a “4th dose” on days with migraine or fibromyalgia flare
• PDMP shows no other prescribers, no opioids filled

Should we begin to taper?
Should we switch to pregabalin?
How does uncontrolled anxiety impact pain outcomes?

PDMP: prescription drug monitoring program
Benzodiazepines (BZDs)

1959- chlordiazepoxide introduced

1963- diazepam introduced
BZD started replacing chloral hydrate / barbiturate use

1975- BZDs placed on FDA restricted drug list due to abuse concerns

1980s- BZD use declined in favor of SSRI and psychotherapy use

FDA: Food and Drug Administration
SSRI: Selective serotonin reuptake inhibitor

Parks, J. Safe & Effective Use of Benzodiazepines in Clinical Practice.
### Anxiolytics
- Clonazepam (Klonopin®)
- Alprazolam (Xanax®)
- Lorazepam (Ativan®)
- Diazepam (Valium®)
- Clorazepate (Tranxene®)
- Chlordiazepoxide (Librium®)
- Oxazepam (Serax®)

### Sedative-Hypnotics
- Triazolam (Halcion®)
- Estazolam (ProSom®)
- Flurazepam (Dalmane®)
- Quazepam (Doral®)
- Temazepam (Restoril®)
Benzodiazepines

- **Mechanism of action:** bind to GABA-A receptors → opens Cl- ion channels → influx of Cl- into neuron causing inhibition of neuronal firing (i.e.- facilitates GABA- an inhibitory NT)
  - 4 types of GABA-A receptors that are BZD sensitive:
    - $\alpha_1$ (produces sedative effects), $\alpha_2$ (produces anxiolytic effects), $\alpha_3$, $\alpha_5$
    - **BZD are NOT selective to $\alpha$ receptors** (*zolpidem/zaleplon are selective to $\alpha_1$ – GABA-A*)
- **Pharmacologic Properties:**
  - Anxiolytic
  - Sedative-hypnotic
  - Muscle relaxant
  - Anticonvulsant

Current Benzodiazepine Prescribing

- ~1 in 20 US adults filled a BZD prescription during the course of a year in 2008
- BZD use substantially higher among women
- BZD seeking is common in primary care settings
  - 9 of 10 older adults who use benzodiazepines on a long-term basis have their Rx’s written exclusively by PCPs (for tx of anxiety / insomnia)
- From 1996 to 2013, the number of adults that obtained a BZD increased by 67%
  - The amount of BZD dispensed more than tripled during that same time period

Olson M, King M, Schoenbaum M. Benzodiazepine Use in the United States. JAMA Psychiatry. 2015;72(2):136-142
Kroll DS, Nieva HR, Barsky AJ, Linder JA. Benzodiazepines are Prescribed More Frequently to Patients Already at Risk for Benzodiazepine-Related Adverse Events in Primary Care. J Gen Intern Med 31(9):1027–34
BZD Clinical Applications

- Pre-operative anesthesia
- Acute alcohol withdrawal
- Acute seizure control
- Catatonia
- Acute agitation associated with mania or psychosis
- Akathisia
- Specific anxiety disorders - panic disorder, SAD, GAD
- Specific phobia (infrequent, predictable inciting stimuli - fear of air travel, public speaking, dental procedures)
- Insomnia (short-term, 2 – 4 weeks)

SAD: social anxiety disorder; GAD: generalized anxiety disorder
Benzodiazepines for Pain

- Randomized, placebo controlled, comparative efficacy trial
- N = 114 subjects with non-radicular acute low back pain
- Randomized to naproxen, naproxen + diazepam, naproxen + placebo
  - No between group differences noted (0.3, 95% CI: -2.8, 3.5)
  - No between group differences of adverse effects noted (6%, 95% CI: -9, 20%)
- Positive data for clonazepam in burning mouth syndrome only

Benzodiazepines for Anxiety

• Current data supports short-term use (4 – 6 weeks)
• Despite many clinicians intending to taper/discontinue BZDs after the 4–6 weeks it takes SSRIs to have their therapeutic effect, 12% of patients receiving this regiment continue BZDs for > 6 months
• No data to support BZD for post traumatic stress disorder
• BZDs may interfere with fear extinction & cause fear-sensitizing effects in response to stress

How Do You Select a Benzodiazepine?
• Metabolism: hepatic oxidation (catalyzed by CYP3A4) & glucuronidation
  • EXCEPT- LOT- lorazepam, oxazepam, & temazepam which are conjugated only & do not have active metabolites
  • Clonazepam undergoes nitroreduction with no active metabolites
• N-desmethyldiazepam (DMDZ)- active metabolite ~ 20 – 100 hour half-life (t ½)
  • Chlordiazepoxide, clorazepate, diazepam
  • Diazepam demethylation mediated by CYP3A4 & 2C19
Benzodiazepine Half-life

• **Short t ½: 5 – 14 hours**
  - Oxazepam
  - No accumulation, severe withdrawal symptoms if discontinued abruptly

• **Intermediate t ½: 10 – 40 hours**
  - Alprazolam, lorazepam, temazepam
  - No accumulation, Q12 – Q8 dosing
  - Clonazepam ~40 hrs = Daily dosing

• **Long t ½: up to 100 + hours**
  - Diazepam, clorazepate, chlordiazepoxide
  - Accumulation of metabolites
    - Less severe withdrawal symptoms
    - Avoid in elderly

Benzodiazepine Onset of Action

• High lipophilicity (onset 30-60 min)
  • Diazepam, clorazepate, alprazolam
  • Absorbed rapidly & distributed quickly
  • Increased abuse potential
• Moderate lipophilicity
  • Chlordiazepoxide, lorazepam, clonazepam, temazepam
• Low lipophilicity
  • Oxazepam
  • Absorbed slowly

BZD Treatment Tips

• **Alprazolam**: high incidence of rebound anxiety due to short half-life; higher abuse potential

• **Lorazepam**: preferred BZD in hepatic impairment; predictable absorption via intramuscular delivery

• **Clonazepam**: appears to exhibit less abuse potential and less anterograde amnesia

• **Diazepam**: provides myorelaxation at higher doses, discourage use in elderly due to long half-life and accumulation; higher abuse potential
• 38 year old who presents back at family medicine clinic 1 week after an acute hospitalization. She is slurring her words and nodding off during your session.

• PMHx: Generalized anxiety disorder
  Post-traumatic stress disorder
  Fibromyalgia syndrome
  Migraine without aura

• Meds: Alprazolam 2 mg TID
  Gabapentin 600mg PO Q8 hours
  Sertraline 150mg PO QAM
  Hydrocodone / acetaminophen 5/325 mg q 4 – 6 hours

• Sarah informs you that she went to the emergency department last week because she thought she was having a “heart attack.” They diagnosed her with panic attacks and treated her pain with hydrocodone / acetaminophen. She informs the clinic social worker that she has been drinking 2 – 3 glasses of wine every night.
Discuss With Your Neighbor...

• Are there any drug-drug interactions?
• What safety concerns do you have?
• How does Sarah’s alcohol use influence treatment?
• Discuss any concerns specifically surrounding the benzodiazepine use
BZD Tolerability Concerns

- Sedation
- Ataxia
- Psychomotor slowed
- Cognitive impairment
- Anterograde amnesia
- **Respiratory depression**
- Impaired coordination
- Slurred speech
- Paradoxical excitation
BZD Use Complications

- Tolerance, dependence, withdrawal
- BZD use disorder
- Tolerability concerns - ataxia/falls, cognitive impairment/anterograde amnesia
- Street use / value (diversion)
- Central nervous system (CNS) depression
- Overdose risk when combined with other CNS depressants
National Drug Overdose Deaths Involving Benzodiazepines

Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018
Discuss With Your Neighbor…

• How has the opioid overdose epidemic impacted your practice?
• Do you have concerns about benzodiazepine prescribing patterns in your region?
• How should pharmacies approach the co-prescribing of opioids and benzodiazepines?
Features of BZD Dependence

- Need the BZD to carry out normal daily activities
- Extreme difficulty stopping or tapering the BZD
- Crave the next dose / increase anxiety between doses
- Regularly contact prescriber for refills
- Occasionally or frequently lose prescriptions / doctor shop
- Pay cash instead of using prescription insurance
- Carry extra doses with them in the event that anxiety were to occur
- Self increase BZD dose when more anxious
- Continue to experience anxiety, insomnia, depression despite taking the BZD

High Risk Populations

• Elderly (impaired cognition, ataxia/falls)
• Patients taking a concurrent opioid
• Active substance use disorder
• PTSD
• Borderline Personality Disorder
• Respiratory disorders
• Sleep disordered breathing
• Traumatic brain injury
Chronic Opioid + BZD Use

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam (Klonopin®)</td>
<td>1 mg</td>
</tr>
<tr>
<td>Alprazolam (Xanax®)</td>
<td>1 mg</td>
</tr>
<tr>
<td>Lorazepam (Ativan®)</td>
<td>2 mg</td>
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<tr>
<td>Diazepam (Valium®)</td>
<td>10 mg</td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td>15 mg</td>
</tr>
<tr>
<td>Chlordiazepoxide (Librium®)</td>
<td>25 mg</td>
</tr>
</tbody>
</table>

Benzodiazepine Withdrawal

- Of those prescribed therapeutic doses of BZDs long-term, 58–100% inadvertently become physically dependent (therapeutic dose dependence).
- If BZD is taken regularly for ≥ 8 weeks, it should be gradually tapered to reduce withdrawal risk.
- High dose and long-term use are associated with a greater chance of developing BZD withdrawal.
  - 90% of long-term BZD users (> 1 year) experience significant withdrawal.
- Acute BZD withdrawal syndrome may persist from 5 - 28 days (peaking after ~ 14 days).
- Protracted withdrawal phase: symptoms of withdrawal may persist 6 to 12 months after discontinuation.

Benzodiazepine Withdrawal

- Anxiety, depression, insomnia, restlessness
- Agitation / irritability
- Muscle tension / weakness
- Diaphoresis, nightmares
- Weight / appetite changes
- Depersonalization, hallucinations (visual/auditory)
- Tingling, numbness, sensory hypersensitivity (light/sound)

**Seizures**

BZD Withdrawal Syndromes

- Relapse = recurrence of the original anxiety symptoms that follow d/c of treatment
- Rebound = anxiety symptoms are more intense
- Withdrawal implies a degree a physical dependence
  - Short half-life BZDs: 1 – 2 day onset
  - Long half-life BZDs: 4 – 7 day onset (lasts for weeks)

Tapering a Benzodiazepine

- **Concern:** fear of return of symptoms (anxiety, insomnia)
- **Strategy:** slow taper to avoid withdrawal symptoms, provide education advising that anxiety and insomnia can be part of withdrawal but will improve with time, offer alternative treatments such as psychotherapy
  - BZD taper: reduce dose by 25% every 1 – 2 weeks
  - **Slower taper:** reduce dose by 10-25% every 1 – 4 weeks over 6 months
    - May convert from shorter- to longer-t ½ BZD in order to decrease potential withdrawal symptoms; data on this practice is lacking
- Review taper progress frequently and provide emotional support/encouragement
- Do not concurrently taper opioid treatments

The Severity of Dependence Scale (SDS) was created to provide a short and easily administered self-report scale to measure the degree of dependence for different types of drugs.

- Sarah is currently taking alprazolam 2 mg Q8 hours
- Would you switch her to another benzodiazepine?
- Which one?

Let’s Discuss Sarah’s Taper

Strategies for Tapering

• Provide patient with clear written instructions for taper
  • Discuss how prescription will be written, quantity provided, and refill date
  • Consider having patient sign a treatment agreement
• Consider converting to a long-acting agent to ease withdrawal symptoms
• Do NOT increase the dose once a taper has started
• Avoid “as needed” use of benzodiazepines during the taper
• Provide a limited day supply of medication
• Ensure only one prescriber of BZD
• Primary care settings – refer to behavioral health consultant
  • Consider use of Motivational Interviewing & cognitive behavioral therapy

Strategies for Tapering

• Obtain urine drug testing prior to starting taper and periodically thereafter
• Monitor for use of other substances to replace benzodiazepine or manage withdrawal symptoms
• Monitor Gamma-Glutamyl Transferase (GGT) for alcohol use
• Use of the urine drug testing to monitor adherence with benzodiazepine is limited
  • Alprazolam, lorazepam and clonazepam may not be detected
  • Short-acting agents may only be detected in urine for 1 to 3 days
Treatment of BZD Withdrawal

• Seizure Prevention:
  • Carbamazepine 200 – 400 mg BID x 2 to 4 weeks post BZD
  • Divalproex 500 mg to 2000 mg BID x 2 – 4 weeks post BZD

• Hypertension, sweating, tremor, restlessness:
  • Propranolol 10 mg TID
  • Clonidine 0.1 mg TID
  • Hydroxyzine 25 – 50 mg q 6 hour PRN

• Insomnia:
  • Trazodone 25 to 150 mg at bedtime
  • Melatonin 3 to 5 mg at bedtime

• Pain:
  • Acetaminophen 500 mg q 4 hour PRN
  • Ibuprofen 600 – 800 mg q 8 hour PRN

Alternative Treatments for Anxiety

- Antidepressants (SSRIs, SNRIs)
- Buspirone
- Pregabalin / gabapentin
- Hydroxyzine
- Beta-blockers (propranolol)
- Cognitive behavioral therapy
- Trauma-based therapy

SNRI: serotonin norepinephrine reuptake inhibitor
Now Back to Sarah

• Hydrocodone / APAP was discontinued
• Alprazolam decreased to 1 mg TID x 1 week, then 1 mg BID x 1 week, then stopped
• Sarah ended up back at the ED and was prescribed quetiapine 25 mg TID
• She tested positive for heroin/fentanyl
• What could have been done differently?
Wrap-Up Questions

• Have your thoughts regarding the use of gabapentin changed?
• What did you learn about benzodiazepine use that you will take back to your practice?
• How does harm reduction fit into the practice of pharmacy?
Use of gabapentinoids for pain management and anxiety must be weighed against abuse and overdose risk.

Prescribing and dispensing of gabapentinoids and benzodiazepines, along with opioid treatments, has steadily increased.

When overdose risk is recognized, treatments should be thoughtfully tapered.

Non-benzodiazepine treatments, such as psychotherapy and antidepressants can be readily utilized for the treatment of anxiety.
1. Which of the following is a typical conversion ratio between gabapentin and pregabalin?
   A. 2:1
   B. 3:1
   C. 6:1
   D. 10:1
2. Which of the following has not demonstrated “desirable” or ”liking” in clinical studies?

A. Gabapentin at normal doses
B. Pregabalin at normal doses
C. Gabapentin at high doses
D. Pregabalin at high doses
3. Karen is a 50 year-old female patient with Borderline Personality Disorder (BPD) and panic attacks presenting for a refill of her diazepam 5 mg TID and buspirone 5 mg BID. What makes the prescribing of a benzodiazepine a higher risk for this patient?

A. Her age  
B. Female gender  
C. Co-occurring BPD  
D. Co-prescribing of buspirone
Assessment Questions

4. A physician wishes to begin a benzodiazepine taper with their patient who has been taking diazepam 10 mg QID for 3 years. What taper schedule would best minimize the experience of withdrawal symptoms?
   A. 75% dose reduction every 4 weeks
   B. 50% dose reduction weekly
   C. 10% dose reduction every 2 weeks
   D. Only begin taper if patient is > 65 years-old