Benzodiazepine case based discussion

Charlie Reznikoff
ACP Pain precourse
November 1st 2012
**DAWN Report: Misused or Abused Drugs Most Commonly Involved in Emergency Department (ED) Visits: 2004 to 2010**

<table>
<thead>
<tr>
<th>Drug</th>
<th>2004 Number of ED Visits</th>
<th>2010 Number of ED Visits</th>
<th>% Change, 2004 to 2010</th>
<th>2010 ED Visits per 100,000 Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol – In Combination with Other Drugs</td>
<td>NA</td>
<td>564,796</td>
<td>NA</td>
<td>182.5</td>
</tr>
<tr>
<td>Alcohol – Underage Drinking**</td>
<td>NA</td>
<td>189,060</td>
<td>NA</td>
<td>215.4</td>
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<tr>
<td>Illicit Drugs</td>
<td>991,640</td>
<td>1,171,024</td>
<td>NC</td>
<td>378.5</td>
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<tr>
<td>Cocaine</td>
<td>NA</td>
<td>488,101</td>
<td>NA</td>
<td>157.8</td>
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<tr>
<td>Heroin</td>
<td>NA</td>
<td>224,706</td>
<td>NA</td>
<td>72.6</td>
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<tr>
<td>Marijuana</td>
<td>281,619</td>
<td>461,028</td>
<td>64</td>
<td>149.0</td>
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<tr>
<td>Pharmaceuticals</td>
<td>626,472</td>
<td>1,345,645</td>
<td>115</td>
<td>434.9</td>
</tr>
<tr>
<td>Anti-anxiety and Insomnia Drugs</td>
<td>210,711</td>
<td>472,769</td>
<td>124</td>
<td>152.8</td>
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<tr>
<td>Benzodiazepines</td>
<td><strong>170,471</strong></td>
<td><strong>408,021</strong></td>
<td><strong>139</strong></td>
<td><strong>131.9</strong></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>NA</td>
<td>105,229</td>
<td>NA</td>
<td>34.0</td>
</tr>
<tr>
<td>Pain Relievers</td>
<td>282,275</td>
<td>659,969</td>
<td>134</td>
<td>213.3</td>
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<tr>
<td>Narcotic Pain Relievers</td>
<td>166,338</td>
<td>425,247</td>
<td>156</td>
<td>137.4</td>
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<tr>
<td>Hydrocodone Products</td>
<td>46,536</td>
<td>115,739</td>
<td>149</td>
<td>37.4</td>
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<tr>
<td>Oxycodone Products</td>
<td>51,418</td>
<td>182,748</td>
<td>255</td>
<td>59.1</td>
</tr>
</tbody>
</table>

*Because a visit may involve multiple drugs, the sum of visits by drug will be greater than the total.*

**Underage drinking includes both use of alcohol in combination with other drugs and use of alcohol only for patients**
Most commonly prescribed benzo, also the benzo favored by addicts?
Alprazolam
Alprazolam’s suitable replacement?
Alprazolam’s suitable replacements

Clonazepam if in withdrawal due to structural homology and cross tolerance
Lorazepam for the psychiatric indications for the time of onset and duration
Case 1
55 year-old woman with depression and insomnia presents for an insurance evaluation after a minor car crash. Her motor vehicle crash was a minor “fender bender” one week ago. She did not fall asleep at the wheel. She didn’t see that the car had stopped in front of her. She says she had minor “whiplash”. She is pain free and has no neurologic symptoms
• She has had an episode of depression for nine weeks, characterized by poor concentration, decreased appetite, low energy, tearfulness, and difficulty getting to sleep. She is not suicidal.

• Two weeks ago another provider started fluoxetine 20 mg and clonazepam 1 mg at bedtime. Her sleep has improved but her other symptoms are unchanged. She has hypertension treated with HCTZ but no other medical issues or medications.

• Vitals and physical exam are unremarkable other than a decreased mood and psychomotor retardation.
• 55 year-old woman recently started on clonazepam and fluoxetine with a minor car accident, still appearing depressed. You should

1. Add methylphenidate for neurovegetative symptoms
2. Change clonazepam to temazepam
3. Do nothing at this point, follow up in 2 weeks for fluoxetine effect
4. Ask her to surrender her car keys, and arrange a ride home from clinic
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Commonly used benzos and why

• Clonazepam for **GAD/adjustment disorder**
  – Longer action, less euphoria
• Lorazepam for **panic/specific phobia**
  – More rapid onset, shorter half life, less euphoria
• Diazepam for **detoxification**
  – Self tapering, rapid onset, long half life
• Midazolam for **anesthesia**
  – Very short half life, easy to titrate IV
• Temazepam for **sleep**
  – Half life appropriate for 8 hour sleep, less euphoria
<table>
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<tbody>
<tr>
<td><strong>Long Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlordiazepoxide (Librium®)</td>
<td>Int. (po)</td>
<td>2-4 (po)</td>
<td>5-30</td>
<td>3-100</td>
<td>10 mg</td>
</tr>
<tr>
<td>Diazepam¹ (Valium®)</td>
<td>Rapid (po, IV)</td>
<td>1 (po)</td>
<td>20-50</td>
<td>3-100</td>
<td>5 mg</td>
</tr>
<tr>
<td>Flurazepam (Dalmane®)</td>
<td>Rapid</td>
<td>0.5-2</td>
<td>inactive</td>
<td>47-100</td>
<td>30 mg</td>
</tr>
<tr>
<td><strong>Intermediate Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam¹ (Xanax®)</td>
<td>Int.</td>
<td>0.7-1.6</td>
<td>6-20</td>
<td>-</td>
<td>0.5mg</td>
</tr>
<tr>
<td>Clonazepam¹ (Rivotril®)</td>
<td>Int.</td>
<td>1-4</td>
<td>18-39</td>
<td>-</td>
<td>0.25mg</td>
</tr>
<tr>
<td>Lorazepam¹ (Ativan®)</td>
<td>Int. (po), Rapid (sl, IV)</td>
<td>1-1.5 (po)</td>
<td>10-20</td>
<td>-</td>
<td>1mg</td>
</tr>
<tr>
<td>Oxazepam¹ (Serax®)</td>
<td>Slow</td>
<td>2-3</td>
<td>3-21</td>
<td>-</td>
<td>15mg</td>
</tr>
<tr>
<td>Temazepam¹ (Restoril®)</td>
<td>Slow</td>
<td>0.75-1.5</td>
<td>10-20</td>
<td>-</td>
<td>30mg</td>
</tr>
<tr>
<td><strong>Short Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam¹ (Versed®)</td>
<td>Most Rapid IV</td>
<td>0.5-1 (IV)</td>
<td>1-4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Triazolam (Halcion®)</td>
<td>Int.</td>
<td>0.75-2</td>
<td>1.6-5.5</td>
<td>-</td>
<td>0.5mg</td>
</tr>
</tbody>
</table>

¹ formulary at VHHSC

² Rapid onset = within 15 minutes. Intermediate = 15-30 minutes. Slow = 30-60 minutes
Benzos and driving

• Strong evidence that any benzo use is associated with motor vehicle crashes
• Impairment related to long half life of benzos
• Coingestion of alcohol very high risk
• Of the antidepressants, tricyclics are the most problematic (in elderly)

Prohibited Behaviors

Minnesota’s DWI law stipulates that it is a crime:

1) to drive, operate, or be in control of any motor vehicle anywhere in the state while:

- under the influence of alcohol, a controlled substance, or (knowingly) a hazardous substance, or any combination of these;

- having an alcohol concentration (AC) of .08 (.08 means .08 percent alcohol concentration, which is 8/10,000ths by volume) or more at the time or within two hours of doing so;

- having any amount or the metabolites of a schedule I or II controlled substance, other than marijuana, in the body; or

- if the vehicle is a commercial motor vehicle, having an alcohol concentration of .04 or more at the time or within two hours of doing so; or

2) to refuse to submit to a chemical test of the person’s blood, breath, or urine under Minnesota Statutes, section 169A.52 (implied consent law).

An Overview of Minnesota’s DWI Laws

This information brief provides a brief overview of DWI laws, which are mainly codified in Minnesota Statutes, chapter 169A.
Bottom line Case 1

• Long acting benzodiazepines for sleep are associated with MVCs the next day
• Be aware of the different times of onset, half life, and indications for benzos
• Intoxicated patients should be asked to surrender their car keys
• Patients on controlled substances should be educated about driving laws
Case 2
• A 57 year-old man with alcohol-related cirrhosis is admitted to the hospital for alcohol detoxification. He has had two previous episodes of delirium tremens and at least one alcohol-related seizures. He is 12 hours from his last drink. He feels “shaky” but otherwise reports no symptoms. He would like detox and admission to an addiction treatment program.
Vital signs are normal. The patient is anxious but has clear mentation. He has slight jaundice and stigmata of cirrhosis. Extremities wasted and a slightly protuberant abdomen.

AST 170; ALT 100; Creatinine 0.5; Bili 2.3; INR 1.3; Blood alcohol level is 0.03%. Platelets are 89, and sodium is 135, other labs are normal.

Abdominal ultrasound is consistent with cirrhosis and minimal ascites.
• 57 year-old man with stable alcoholic cirrhosis and a history of DTs and seizures presents for Alcohol detoxification. You should use:

1. Alcohol withdrawal protocol (symptom driven) using diazepam
2. Alcohol withdrawal protocol (symptom driven) using lorazepam
3. Scheduled diazepam
4. Scheduled lorazepam
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4. **Scheduled lorazepam**
Alcohol Withdrawal
(mayo clinic proceedings, 1995)

Diagram showing the progression of minor and major withdrawal symptoms over 6 days, including disorientation, tremors, irritability, seizures, hallucinations, and autonomic activity.
Delirium Tremens

• Risk factors for DTs:
  – Previous DTs
    
    History predicts future
  – Age >30
  – Concurrent illness
  – Sustained drinking
  – Poor nutrition
Alcohol WD Seizures

- Occur early after alcohol cessation
  - Often the first sign of W/D
- 3 % of alcohol dependent patients
- Generalized convulsions
- Brief often isolated episodes
- *Suppressed easily with benzodiazepines*
Individualized treatment for alcohol withdrawal. A randomized double-blind controlled trial.[see comment].


The library owns this title from 1962 to the present.

OBJECTIVE--To assess the effect of an individualized treatment regimen on the intensity and duration of medication treatment for alcohol withdrawal. DESIGN--A randomized double-blind, controlled trial. SETTING--An inpatient detoxification unit in a Veterans Affairs medical center. PATIENTS--One hundred one patients admitted for the treatment of alcohol withdrawal who could give informed consent and had no history of seizures or medication use that might alter the clinical course of withdrawal. INTERVENTION--Patients were randomized to either a standard course of chlordiazepoxide four times daily with additional medication as needed (fixed-schedule therapy) or to a treatment regimen that provided chlordiazepoxide only in response to the development of the signs and symptoms of alcohol withdrawal (symptom-triggered therapy). The need for administration of "as-needed" medication was determined using a validated measure of the severity of alcohol withdrawal. MAIN OUTCOME MEASURES--Duration of medication treatment and total chlordiazepoxide administered. RESULTS--The median duration of treatment in the symptom-triggered group was 9 hours, compared with 68 hours in the fixed-schedule group (P < .001). The symptom-triggered group received 100 mg of chlordiazepoxide, and the fixed-schedule group received 425 mg (P < .001). There were no significant differences in the severity of withdrawal during treatment or in the incidence of seizures or delirium tremens. CONCLUSIONS--Symptom-triggered therapy individualizes treatment, decreases both treatment duration and the amount of benzodiazepine used, and is as efficacious as standard fixed-schedule therapy for alcohol withdrawal.
The Biochemical Basis of Neuropharmacology
Cooper, Bloom & Roth
Bottom line case 2

- Choose lorazepam for elderly, cirrhosis, or renal insufficiency—no active metabolites
- Unlike diazepam, lorazepam is not self tapering, and requires a scheduled taper
- Symptom driven alcohol protocols are appropriate for mild to moderate withdrawal
- If high risk for DTs or seizure, schedule benzodiazepines for withdrawal
Case 3
A 45 year-old woman with generalized anxiety disorder is on clonazepam 1 mg TID and Sertraline 150 mg daily. She presents to you wishing to taper off clonazepam because of side effects. She feels “dopey” and reports forgetting things. Also she dislikes being on a potentially addictive controlled substance
• She has been on this dose of clonazepam for 10 months uninterrupted, and prior to that she was not on another sedative. She has no history of addiction including no alcohol use. She does not have a seizure disorder. Other than her psychiatric illness she has no medical issues and is on no other medications.

• She is clearly anxious about withdrawal otherwise her exam is totally normal
• 45 year-old woman wishing to taper off clonazepam after eight months. Your plan for her is:

1. Discontinue clonazepam at any time. She is not at risk of withdrawal
2. Discontinue Clonazepam and add amitriptyline 50 mg QHS to treat symptoms clonazepam withdrawal
3. Taper clonazepam slowly over 30 days with no additional medication change
4. Switch clonazepam to phenobarbitol and taper slowly over 30 days
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3. **Taper clonazepam slowly over 30 days with no additional medication change**
4. Switch clonazepam to phenobarbital and taper slowly over 30 days
Benzo Cessation Syndromes

- Recurrence
- Rebound
- Withdrawal
Recurrence

• You were anxious before you started benzos, you’ll be anxious when you stop
Recurrence

- Recurrence of the underlying disorder
- Usually insomnia or anxiety
- Universal after cessation of benzos
- Educate and reassure the patient
- Find appropriate alternative to benzos
Rebound
“recurrence with a vengeance”

• Whatever anxiety (or insomnia) you had before you started benzos is amplified for 1-2 weeks after stopping
Rebound

• Heightening of underlying condition the benzo was suppressing
• Classically insomnia, panic, and anxiety
• Self limited, <2 weeks
• No autonomic discharge, seizure, or delirium
• Reassure, educate and find alternatives
• Benzo taper optional for comfort only
(True) Withdrawal

• Delirium, psychosis, autonomic arousal, seizure, death
(True) Withdrawal

- Akin to alcohol withdrawal
- Autonomic discharge
- Seizures
- Psychosis
- Delirium
- Mortality on the order of DTs
- Variable severity and time course
Risk assessment for withdrawal

• Benzo exposure sufficient for physiologic dependence is highly variable!
  
  – 6 months daily use moderate dose
  – 3 months daily use 3X normal dose
  – Any duration in an alcohol/barbiturate dependent patient

Lowinson “Substance abuse” 4-15-2011
Benzo users are notoriously poor historians, and unreliable pill takers
Likelihood of withdrawal

• Short acting meds
• No metabolites
• High dose
• Concomitant alcohol use cessation
• Concomitant medical illness
Timing of Withdrawal

• Timing of onset of withdrawal is characteristic to the half life of the benzo used
  – Midaz (<24 hours)
  – Loraz (48 hours)
  – Diaz (up to seven days)
Principles of Tapering

• Find symptom suppressing dose
• Replace short acting with long acting
  – chlordiazepox phenobarb diazepam clonazepam
• Taper with 10% steps daily (fastest!) to weekly
• Halt or reverse taper if recurrence of symptoms
Tapers

- Uncomplicated outpatient
- Complicated outpatient
- Complicated inpatient
Uncomplicated Outpatient Taper

• Non-addicted patient
• No aberrant behavior
• No previous serious withdrawal
• Physiologic dependence

• Leave medication the same and taper over 30 days
Complicated Outpatient Taper

• Failed uncomplicated taper
• Addiction history or aberrant behavior
• No previous serious withdrawal
• Physiologic dependence

• Change to long acting and taper over 30 days
Inpatient Taper

• Multiple failed tapers
• Serious addictive behavior
• Serious withdrawal history

• Change to long acting, 30-60 day taper inpatient facility or highly structured outpatient, possible commitment
Find The Suppressing Dose

• In serious withdrawal, the commonest reason for a failed taper is insufficient dose
• Never begin to taper before the symptom suppressing dose is found
• Titrate benzos until the patient is calm and autonomic storm resolved
Medical Complications of Chronic Use: Risks of nonsterile injections and infectious complications may occur with intravenous use. Episodes of drug-induced sleep or coma may result in respiratory problems, nerve compression injuries, and accidents. Multiple medical problems may develop in chronic alcoholics, including nutritional deficiencies, megaloblastic anemia, psoriasis, gastritis, peptic ulcer, cirrhosis, pancreatitis, peripheral neuropathy, endocrinopathy, elevated triglycerides, and infectious diseases.

PENTOBARBITAL CHALLENGE TEST

Procedure should be performed only on inpatients with respiratory support staff and equipment available. Give 200 mg of pentobarbital orally to a fasting patient in resting state. The patient should be showing slight signs of withdrawal; do not give pentobarbital if the patient may have recently taken sedative agents.

<table>
<thead>
<tr>
<th>Patient's condition</th>
<th>Degree of tolerance</th>
<th>Estimated 24-hour pentobarbital requirement (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asleep, but arousable</td>
<td>Little or no tolerance</td>
<td>None</td>
</tr>
<tr>
<td>Drowsy, slurred speech, coarse nystagmus, Rombergian</td>
<td>Definite tolerance</td>
<td>300-600</td>
</tr>
<tr>
<td>Comfortable, fine nystagmus only drug effect</td>
<td>Marked tolerance</td>
<td>800</td>
</tr>
<tr>
<td>No signs of drug effects, perhaps signs of abstinence persisting</td>
<td>Extreme tolerance</td>
<td>1,000-1,200 or more</td>
</tr>
</tbody>
</table>

Using Alcohol Protocols

• Safe for moderate withdrawal
• Not helpful for severe withdrawal
  – Physician should schedule large doses
• Use longer acting sedatives if possible
Case 3 bottom line

- Understand benzo rebound phenomenon
- Be able to assess the risk of true withdrawal
- Construct an appropriate taper based on your patient’s demographics
- Find the symptom suppressing dose and taper slowly
Case 4
• A 76 year-old woman with COPD and osteoporosis requests a medication for sleep. She is unable to sleep, due to the recent loss of her spouse—who died one week ago unexpectedly. She is tearful and she blames herself as she describes to you finding her husband’s deceased body. She is not suicidal. She has slept less than 2 hours nightly since this event.
• She has on average two COPD exacerbations per year. She takes an inhaled short-acting beta agonist, long-acting anticholinergic, and an inhaled glucocorticoid. She is not on home oxygen. She takes phosphodiesterase inhibitors for osteoporosis. She is formerly tobacco dependent and alcohol dependent with 2 years abstinence from both.

• She is willing to see a grief counselor, but would also like a sleeping aid.
• 76 year-old woman with copd, osteoporosis and acute insomnia. The most important contraindication to using a benzodiazepine is:
1. Benzodiazepines interfere with talk therapy due to their amnestic effect
2. Benzodiazepines cause respiratory suppression increasing the severity of COPD exacerbations
3. Benzodiazepines at night in older patients are associated with falls and hip fractures
4. Benzodiazepines in recovering alcoholics are associated with alcohol relapse
5. Benzodiazepines are not indicated for acute insomnia
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5. Benzodiazepines are not indicated for acute insomnia
Benzos and hip fractures

• All benzos (and Z-drugs) associated with increased risk of falls and hip fractures
• Rate ratios of hip fracture were > 2.2
• Polypharmacy and alcohol magnify the risk

Benzos and alcoholism

• Benzo use is not consistently associated with relapse to alcohol consumption
• Those with an addiction or first degree relative with an addiction prefer benzos to placebo, and escalate doses over time
• Those without an addiction prefer placebo to benzos, and self moderate use over time
• Benzos are rarely the primary addictive substance

Woods, katz, winger Jama dec 16 vol 260 no 23 1988 p3476
Case 5
A 50 year-old man presents to the emergency room with alcohol on his breath and a variety of pills in his possession. Your nurse identifies two of the pills as alprazolam and oxymorphone. He has a respiratory rate of 4 breaths per minute and an oxygen saturation of 84%. His heart rate is 50 and his systolic blood pressure is 95 mm hg. He is responsive to noxious stimulus only. His pupils are small but not pinpoint. He appears cyanotic. You have no medical records on this man.
This is a 50 year-old man with an apparent overdose of alcohol, benzos, and opioids. Your next step is:

1. Give IV naloxone
2. Give IV flumazenil
3. Give both Flumazenil and Naloxone IV
4. Intubate
This is a 50 year-old man with an apparent overdose of alcohol, benzos, and opioids. Your next step is:

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2. Give IV flumazenil
3. Give both Flumazenil and Naloxone IV
4. Intubate
When to use flumazenil?
Limited use of flumazenil

- Reversal of brief procedural sedation
- Not in patients dependent on benzos, barbs or alcohol
- Not a diagnostic test!

- May precipitate seizures
Thank You!