Role of Benzodiazepines in Treatment

Barbara J Limandri, PhD, PMHNP, BC
Portland Dialectical Behavior Therapy Institute
Portland, Oregon
blimandri@pdbti.org

Disclosures: I have no financial conflicts of interest to disclose
Learning Outcomes

- Explain the issues of prescribing patterns of benzodiazepines in the United States.
- Review the mechanisms of action of benzodiazepines in relation to treatment outcomes.
- Discuss protocols for benzodiazepine withdrawal and discontinuation.

Prescribing Patterns of Benzodiazepines

- Between 1996 and 2013 number of adults filling a BZD prescription increased 67% from 8.1 million to 13.5 million.
- In 2013 BZDs prescribed for:
  - Anxiety disorders 56.1%
  - Mood disorders 12.1%
  - Unclassified (including insomnia) 12.0%
  (Bachhuber, Hennessy, Cunningham, Starrels, 2016)
- In 2012 prescribers wrote 82.5 opioid prescriptions and 37.6 BZD prescriptions per 100 persons in US.
  (Paulozzi, Mack, Hockenberry, 2014)
Benzodiazepine Use in the US

- In 2008 5.2% of US adults aged 18-80 years used BZDs
  - Those 18-35 yrs 2.6%
  - Those 36-50 yrs 5.4%
  - Those 51-64 yrs 7.4%
  - Those 65-80 yrs 8.7%
- Nearly twice as prevalent in women as men
- About 25% of those receiving BZDs involved long-acting
  (Olfson, King, Schoenbaum, 2014)

Benzodiazepines and Opioids

- During 2004-09, 27% of veterans who received opioid analgesics also received BZDs
  - Women 33%; men 26%
  - More likely to be middle-aged, white, and live in wealthier areas
  - More likely to have had recent hospitalization for substance use disorder
- Death from drug overdose 49% with concurrent opioid and BZD prescriptions
  - Deaths were higher when BZDs prescribed regularly vs as needed
  (Park, Saitz, Ganoczy, Ilgen, Bohnert, 2015)
Long-Term Use of Benzodiazepines

• Adults 65-80 who used BZDs, 31.4% used for more than 120 days
• Adults 18-35 14.7% used for more than 120 days
• Women 65-80 yo 10% were prescribed BZDs and 30% were long term use
• Most prescriptions written by non-psychiatrists

(NIMH Press Release, Dec. 17, 2014)

Use of BZDs

• Anxiety Disorders
  • Generalized Anxiety Disorder
  • Panic Disorder
  • Social Anxiety Disorder
  • Obsessive Compulsive Disorder
• Major Depressive Disorder
• Trauma and Stress Related Disorders (PTSD, Adjustment Disorders)
• Dementia Disorders
• Cluster B Personality Disorders
Target Actions and Adverse Responses

- Sedative
- Hypnotic
- Anxiolytic
- Anticonvulsant
- Muscle relaxant

- Anterograde amnesia
- Dissociation
- Cognitive impairment
- Paradoxical anxiety
- Behavioral disinhibition
- Dependence & tolerance

Mechanism of Action of BZDs

- Gamma aminobutyric acid neurotransmitter (GABA), neuroinhibitory
- GABA receptors
  - $\text{GABA}_A$
  - $\text{GABA}_B$
- Chloride channel
GABA-A Receptor

BZD Action on GABA-A Receptor

Ashton Manual: benzo.org.uk
BZD binding to GABA

BZD Pharmacokinetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life (Active metabolite)</th>
<th>Approx Dose Equivalent to Diazepam 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Xanax)</td>
<td>6-12 hrs</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>5-30 (36-200) hrs</td>
<td>5-6 mg</td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>18-50 hrs</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Chlorazepate (Tranxene)</td>
<td>(36-200) hours</td>
<td>15 mg</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>20-100 (36-200) hrs</td>
<td>10 mg</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>10-20 hrs</td>
<td>1 mg</td>
</tr>
<tr>
<td>Oxazepam (Serax)</td>
<td>4-15 hrs</td>
<td>20 mg</td>
</tr>
<tr>
<td>Prazepam (Centrax)</td>
<td>(36-200) hrs</td>
<td>10-20 mg</td>
</tr>
</tbody>
</table>
Reasons for BZD Withdrawal

- Long term unwanted effects
  - Memory loss and impaired learning
  - Cognitive dulling
  - Emotional blunting
  - Depression
- Loss of efficacy over time

Withdrawal Process from BZDs

- Begin with detailed review of BZD use, reason for initiation, reason for continuation, change in dosage, observed effects
- Frank, non judgmental discussion of pros and cons of continuation vs withdrawal
- Commitment from both client and provider
- Adequate social and emotional support
- Discussion of use of protocol designed for slow and safe withdrawal
- Written agreement of protocol and limits of agreement (e.g., loss of prescription, limited prescriptions, appointments)
Withdrawal Principles

• Dosage tapering to avoid risk of:
  • Convulsions
  • Psychotic reactions
  • Acute anxiety exacerbation
• Switching to long-acting benzodiazepine of similar potency
• Using appropriate formulations to achieve dosage (e.g., tablet, liquid)

Designing Withdrawal Schedule

• Schedule around client’s symptoms (i.e., insomnia, morning inertia)
• Change one dose at a time, usually start with night time dose
• Less often taking dose, less focus on the drug
• The larger the initial dose, the greater the decrement (i.e., first decrease may be 25%)
• Plan first several decrements to determine tolerability of plan and permit slowing down or increasing rate of decrements
• Never go backwards in dosage taper
• Watch for compensation by increasing OTC drugs, alcohol, street drugs
• If not successful with first effort at withdrawal, try again when stress is lower
**Example Withdrawal Schedule**  
(Starting dosage alprazolam 6 mg daily. Alz = alprazolam, Dzp = diazepam.)

<table>
<thead>
<tr>
<th></th>
<th>MORNING</th>
<th>MID DAY</th>
<th>EVENING</th>
<th>DAILY DIAZEPAM EQUIVALENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>Alz 2 mg</td>
<td>Alz 2 mg</td>
<td>Alz 1.5 mg + Dzp 10 mg</td>
<td>120 mg</td>
</tr>
<tr>
<td>Week 2</td>
<td>Alz 2 mg</td>
<td>Alz 2 mg</td>
<td>Alz 1 mg + Dzp 20 mg</td>
<td>120 mg</td>
</tr>
<tr>
<td>Week 3</td>
<td>Alz 1.5 mg + Dzp 10 mg</td>
<td>Alz 2 mg</td>
<td>Alz 1 mg + Dzp 20 mg</td>
<td>120 mg</td>
</tr>
<tr>
<td>Week 4</td>
<td>Alz 1 mg + Dzp 20 mg</td>
<td>Alz 2 mg</td>
<td>Alz 1 mg + Dzp 20 mg</td>
<td>120 mg</td>
</tr>
<tr>
<td>Week 5-6</td>
<td>Alz 1 mg + Dzp 20 mg</td>
<td>Alz 1 mg + Dzp 10 mg</td>
<td>Alz 1 mg + Dzp 20 mg</td>
<td>110 mg</td>
</tr>
</tbody>
</table>

**Example Withdrawal Schedule**  
(Starting dosage alprazolam 6 mg daily. Alz = alprazolam, Dzp = diazepam.)

<table>
<thead>
<tr>
<th></th>
<th>MORNING</th>
<th>MID DAY</th>
<th>EVENING</th>
<th>DAILY DIAZEPAM EQUIVALENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 7-8</td>
<td>Alz 1 mg + Dzp 20 mg</td>
<td>Alz 1 mg + Dzp 10 mg</td>
<td>Alz 0.5 mg + Dzp 20 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>Weeks 9-10</td>
<td>Alz 1 mg + Dzp 20 mg</td>
<td>Alz 1 mg + Dzp 10 mg</td>
<td>D/C alz Dzp 20 mg</td>
<td>90 mg</td>
</tr>
<tr>
<td>Weeks 11-12</td>
<td>Alz 0.5 mg + Dzp 20 mg</td>
<td>Alz 1 mg + Dzp 10 mg</td>
<td>Dzp 20 mg</td>
<td>80 mg</td>
</tr>
<tr>
<td>Weeks 13-14</td>
<td>Alz 0.5 mg + Dzp 20 mg</td>
<td>Alz 1 mg + Dzp 10 mg</td>
<td>Dzp 20 mg</td>
<td>80 mg</td>
</tr>
<tr>
<td>Weeks 15-16</td>
<td>Alz 0.5 mg + Dzp 20 mg</td>
<td>D/C alz Dzp 10 mg</td>
<td>Dzp 20 mg</td>
<td>60 mg</td>
</tr>
</tbody>
</table>
Example Withdrawal Schedule
(Starting dosage alprazolam 6 mg daily. Alz = alprazolam, Dzp = diazepam.)

<table>
<thead>
<tr>
<th></th>
<th>MORNING</th>
<th>MID DAY</th>
<th>EVENING</th>
<th>DAILY DIAZEPAM EQUIVALENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 17-18</td>
<td>D/C alz Dzp 20 mg</td>
<td>Dzp 10 mg</td>
<td>Dzp 20 mg</td>
<td>50 mg</td>
</tr>
<tr>
<td>Weeks 19-20</td>
<td>Dzp 25 mg</td>
<td>D/C dzp</td>
<td>Dzp 25 mg</td>
<td>50 mg</td>
</tr>
<tr>
<td>Weeks 21-22</td>
<td>Dzp 20 mg</td>
<td>--</td>
<td>Dzp 25 mg</td>
<td>45 mg</td>
</tr>
<tr>
<td>Weeks 23-24</td>
<td>Dzp 20 mg</td>
<td>--</td>
<td>Dzp 20 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Weeks 25-26</td>
<td>Dzp 18 mg</td>
<td>--</td>
<td>Dzp 20 mg</td>
<td>38 mg</td>
</tr>
<tr>
<td>Weeks 27</td>
<td>Dzp 18 mg</td>
<td>--</td>
<td>Dzp 18 mg</td>
<td>36 mg</td>
</tr>
</tbody>
</table>

Continue decreasing by 2 mg daily until down to 14 mg daily then decrease by 1 mg daily

Alternative Anxiolytics

• Serotonin reuptake inhibitors
• Serotonin norepinephrine reuptake inhibitors
• Augmentation with buspirone
• Other gaba-ergics (e.g., lamotrigine)
• Alpha or beta blockers
Alternative Anxiety Reduction Strategies

- Progressive relaxation
- Mindfulness practice
- Distress tolerance skills

Summary

- Benzodiazepines used for short term only (2-4 wks)
- Avoid use with older clients, esp with mobility problems
- Can be used as interim while other medications initiated (e.g., SRIs)
- Require careful and crystal clear explanation to client with specific limitations
- Withdrawal should be slow and using established written protocol that client agrees to adhere to
- Non adherence needs to have consequences established initially in writing
References


References