BENZODIAZEPINES: the good, the bad, and the alternatives

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Indications

- Generalized anxiety disorder
- Panic disorder
- Anxiety associated with depression
- Other anxiety disorders
Pharmacology

- Modulate gamma-aminobutyric acid A (GABA-A) receptors
- GABA is the primary inhibitory neurotransmitter of CNS
- Locks receptor into configuration with higher GABA affinity
- Increases frequency at which the GABA channel opens
- Influx of chloride ions leads to reduced rate of muscle and neuronal firing
Intoxication and Overdose

• Intoxication
  • Somnolence
  • Slurred speech
  • Ataxia
  • Irritability
  • Elevated or labile mood

• Overdose
  • Alcohol increases risk of respiratory suppression
  • Flumazenil for acute reversal, but a/w risk of inducing withdrawal seizure in chronic users
Short-Acting Benzos

• Half-life <12 hrs
• Triazolam, Oxazepam, Midazolam
Long-acting benzos

• Half-life >24 hrs
• Diazepam, Chlordiazepoxide
Intermediate-acting benzos

- Half-life between 12-24 hrs
- Lorazepam, Temazepam, Alprazolam, Clonazepam
## Benzodiazepine and nonbenzodiazepine hypnotic pharmacokinetics

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
<th>Generic name</th>
<th>Trade name</th>
<th>Usual single adult dose (oral)</th>
<th>Oral peak (hours)</th>
<th>Half-life (hours) parent</th>
<th>Metabolite activity*</th>
<th>CYP3A4 interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>Alprazolam</td>
<td>Xanax</td>
<td>0.25-0.5 mg</td>
<td>1-2</td>
<td>6-27</td>
<td>Inactive</td>
<td>Yes</td>
</tr>
<tr>
<td>Bromazepam</td>
<td>Bromazepam</td>
<td>Lectapam</td>
<td>2-6 mg</td>
<td>1-2</td>
<td>8-20</td>
<td>Inactive</td>
<td>Limited</td>
</tr>
<tr>
<td>Clorazepoxide</td>
<td>Clorazepoxide</td>
<td>Librium</td>
<td>5-25 mg</td>
<td>0.5-4</td>
<td>7-10</td>
<td>Active</td>
<td>Yes</td>
</tr>
<tr>
<td>Clorazepm</td>
<td>Clorazepm</td>
<td>Onfi</td>
<td>10-20 mg</td>
<td>0.5-4</td>
<td>30-42</td>
<td>Active (half-life 71-82 hours)</td>
<td>Limited (interacts via CYP2C19)</td>
</tr>
<tr>
<td>Clorazepam</td>
<td>Clorazepam</td>
<td>Klonopin</td>
<td>0.25-0.5 mg</td>
<td>1-2</td>
<td>18-50</td>
<td>Inactive</td>
<td>Limited</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>Clorazepate</td>
<td>Tranxene</td>
<td>7-15 mg</td>
<td>1-2</td>
<td>20-50</td>
<td>Active</td>
<td>No</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Diazepam</td>
<td>Vallium</td>
<td>2-10 mg</td>
<td>0.5-1</td>
<td>10-24</td>
<td>Active</td>
<td>Limited</td>
</tr>
<tr>
<td>Estazolam</td>
<td>Estazolam</td>
<td>Proxim</td>
<td>0.5-2 mg</td>
<td>0.5-6</td>
<td>8-10</td>
<td>Inactive</td>
<td>Limited</td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>Flunitrazepam</td>
<td>Rohypinol</td>
<td>0.5-2 mg</td>
<td>1-2</td>
<td>16-35</td>
<td>Active</td>
<td>Limited</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>Flurazepam</td>
<td>Dalmane</td>
<td>15-30 mg</td>
<td>0.5-1</td>
<td>2-4</td>
<td>Active</td>
<td>Limited</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Lorazepam</td>
<td>Ativan</td>
<td>0.5-2 mg</td>
<td>2-4</td>
<td>10-20</td>
<td>Inactive</td>
<td>No</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Midazolam</td>
<td>Versed</td>
<td>0.25 to 1 mg/kg maximum 20 mg (oral syrup for pediatric sedation)</td>
<td>1.2</td>
<td>1.5-3</td>
<td>Active</td>
<td>Yes</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>Oxazepam</td>
<td>Serax</td>
<td>10-30 mg</td>
<td>2-4</td>
<td>5-20</td>
<td>Inactive</td>
<td>No</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Temazepam</td>
<td>Restoril</td>
<td>7.5-30 mg</td>
<td>1-2</td>
<td>3-19</td>
<td>Inactive</td>
<td>No</td>
</tr>
<tr>
<td>Triazolam</td>
<td>Triazolam</td>
<td>Halcion</td>
<td>0.125-0.25 mg</td>
<td>0.7-2</td>
<td>2-3</td>
<td>Inactive</td>
<td>Yes</td>
</tr>
<tr>
<td>Drug</td>
<td>Adult oral total daily dose (mg)*</td>
<td>Comparative potency (mg)†</td>
<td>Onset after oral dose (hours)</td>
<td>Metabolism</td>
<td>Elimination half-life (hours)Δ</td>
<td></td>
<td></td>
</tr>
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<td>---------------------</td>
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<td>---------------------------------------------------------------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.5 to 6</td>
<td>0.5</td>
<td>1</td>
<td>CYP3A4 to minimally active metabolites.</td>
<td>11 to 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam extended release</td>
<td>0.5 to 6 once daily</td>
<td>0.5</td>
<td>1</td>
<td></td>
<td>16 (older adults)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bromazepam⁰</td>
<td>6 to 30</td>
<td>7.5</td>
<td>1</td>
<td>CYP1A2. No active metabolite.</td>
<td>8 to 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>5 to 100</td>
<td>10</td>
<td>1</td>
<td>CYP3A4 to active metabolites.</td>
<td>30 to 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.5 to 4</td>
<td>0.25 to 0.5</td>
<td>0.5 to 1</td>
<td>CYP3A4. No active metabolite.</td>
<td>18 to 50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clorazepate</td>
<td>15 to 60</td>
<td>7.5</td>
<td>0.5 to 1</td>
<td>CYP3A4 to active metabolite.</td>
<td>36 to 200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>4 to 40</td>
<td>5</td>
<td>0.25 to 0.5</td>
<td>CYP2C19 and 3A4 to active metabolites.</td>
<td>50 to 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.5 to 6</td>
<td>1</td>
<td>0.5 to 1</td>
<td>Non-CYP glucuronidation in liver. No active metabolite.</td>
<td>10 to 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxazepam</td>
<td>30 to 120</td>
<td>15 to 30</td>
<td>1 to 2</td>
<td>Non-CYP glucuronidation in liver. No active metabolite.</td>
<td>5 to 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prazepam⁰</td>
<td>15 to 60</td>
<td>15</td>
<td>2 to 3</td>
<td>CYP3A4 to active metabolites.</td>
<td>30 to 200</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Dosage ranges vary. †Comparative potency may vary. ΔHalf-life may be extended in certain conditions.
Metabolism

• Most are metabolized via hepatic CYP450 enzymes
• Exception: Oxazepam, Temazepam, Lorazepam
The Good

• When used short-term, often results in immediate and noticeable relief of anxiety

• Candidates for long-term, low-dose benzo treatment:
  • Failed trials on alternative agents
  • Do not develop tolerance
  • Experience only mild/tolerable withdrawal symptoms if tapered off
The Bad

• Psychological and physiological tolerance
• Side effects: sedation, memory impairment, cognitive dulling
• In elderly: dizziness, unsteady gait and falls
The Bad, continued...

- In withdrawal: rebound anxiety, restlessness, insomnia, seizure, death
  - Taper to prevent withdrawal
  - Approximately 10-25% reduction weekly or every other week
  - Shorter-acting benzo = more difficult taper
  - Consider switch to longer-acting benzo (ie. Klonopin)
- Long-term use: more susceptible to anxiety
The Bad, continued...

• In combination with:
  • Alcohol: increased respiratory suppression
  • Opioids: extreme sleepiness, respiratory depression, coma, death
  • Note that benzos can lower the pain threshold
The Alternatives

• Anti-depressants (ie. SSRI/SNRI)
  • SE of increased anxiety/agitation during first few weeks of tx is common
  • As such, sometimes co-administer with a benzo during first month
  • Bupropion (NDRI) may exacerbate anxiety, however, can be effective tx of the anxiety that accompanies depression

• Buspirone
  • 5HT-1A partial agonist
  • Similar to anti-depressants: may take several weeks to take effect
  • Dosing: 15 mg PO bid, increase by 5 mg every 2-3 days, max dose 60
The Alternatives

• Propranolol
  • For somatic symptoms of anxiety (tachycardia, tremor, flushing, diaphoresis, SOB)
  • Performance anxiety, 10-40 mg hour prior
  • Dosing: 10 mg PO TID PRN, increase as tolerated

• Hydroxyzine
  • Sedation is common
  • Generally effective within 30 minutes
  • Dosing: 25-50 mg PO TID or QID PRN, up to 100 mg in one dose
The Alternatives

• Gabapentin
  • Sedation also common, also useful for etoh withdrawals & cravings
  • Dosing: initial 300 mg PO bid, titrate up as necessary
  • Pregabalin

• Prazosin
  • Helps with nightmares/insomnia associated with PTSD, can also dose BID to help with hyperarousal features of PTSD
  • Dosing: initial 1 mg PO qhs, typical dosing range: 1-16
Key Points for Patients

• Some degree of stress and anxiety is a common part of normal, daily life
• Limit or restrict caffeine use altogether
• Regular exercise is an effective, natural tool to lower anxiety
• If prescribed, ensure pt is aware this is for short-term use only