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Margaret Gnegy
Professor of Pharmacology

Antianxiety Drugs:
Benzodiazepines
The bottom line

- Benzodiazepines (BDZ) bind to GABA$_A$ receptors and enhance the action of GABA.

- BDZs are useful for a wide variety of indications but have limited CNS depressant activity.

- Principles important in onset and half-life of BDZs are lipophilicity, redistribution and metabolism.

- Unwanted effects include a withdrawal syndrome and ‘hangover’.

- The pharmacological and anatomical specificity of the GABA$_A$ receptor subunits has been exploited to develop drugs with sedative but not anxiolytic effects.
Antianxiety Drugs

• Benzodiazepines
• Buspirone
• Antidepressant medications
  – Selective serotonin reuptake inhibitors
  – Tricyclic antidepressants
  – Monoamine oxidase inhibitors
Pharmacological actions of benzodiazepines

- Relief of anxiety
- Drowsiness and sedation
- Skeletal muscle relaxation
- Anticonvulsive activity
- Anterograde amnesia

All due to actions in CNS at GABA_A receptors
GABA

$\gamma$-aminobutyric acid

$H_2N$-$CH_2$-$CH_2$-$CH_2$-$COOH$
GABA_A Receptor

Adapted from The Biochemical basis of Neuropahrmacology, by Jack Cooper, Floyd Bloom and Robert Roth, 8th Ed. Oxford Pr., 2003 p. 117
Benzodiazepine structure

Temazepam
BDZ-induced shift in GABA Dose Response Curve
Absorption, metabolism and excretion

• Relative rates of absorption, metabolism and excretion differ markedly
• Drugs are prescribed for their pharmacokinetics
• Greater lipid solubility leads to greater absorption and more rapid onset of action
• Elimination half-life determined by metabolism
Representative of **Diazepam**, a highly lipophilic drug.
Metabolism of benzodiazepines

Chlordiazepoxide → Desmethylichlordiazepoxide* → Demoxepam* → Desmethyl Diazepam* → Oxazepam* → Hydroxyethylflurazepam* → Desalkylflurazepam* → Cyp 3A4, 2C19 → Long-acting active metabolite → Conjugation → Urinary Excretion

Diazepam → Desmethyl Diazepam* → Oxazepam* → Hydroxyethylflurazepam* → Desalkylflurazepam* → Cyp 3A4, 2C19 → Long-acting active metabolite → Conjugation → Urinary Excretion

Prazepam → Clorazepate (inactive) → Alprazolam and triazolam → Alpha-hydroxy metabolites* → Conjugation → Urinary Excretion

Dalmane → Flurazepam → Hydroxyethylflurazepam* → Desalkylflurazepam* → Cyp 3A4 → Long-acting active metabolite → Conjugation → Urinary Excretion

Pharmacokinetic characteristics of some benzodiazepines

<table>
<thead>
<tr>
<th>Agonist</th>
<th>Trade name</th>
<th>Time to [peak plasma] (hr)</th>
<th>Elim. Half-life (hr)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>Valium</td>
<td>0.5-2.0</td>
<td>30-60</td>
<td>Very lipid soluble, anxiety, status, preanesthetic, muscle relaxant</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Ativan</td>
<td>1-6</td>
<td>10-18</td>
<td>More H₂O soluble, anxiety</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Restoril</td>
<td>2-3</td>
<td>8-15</td>
<td>Slower oral absorption, insomnia</td>
</tr>
<tr>
<td>Triazolam</td>
<td>Halcion</td>
<td>1-2</td>
<td>1.5-4</td>
<td>Rapidly inactivated, insomnia, disturbances</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Versed</td>
<td>I.V., I.M.</td>
<td>2-5</td>
<td>Rapidly inactiv., pre-anesthetic, amnesia</td>
</tr>
</tbody>
</table>

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Half-life advantages to benzodiazepines

• Therapeutic uses of a benzodiazepine depend on half life

• BDZs used as anticonvulsants have a long half life; rapid entry into brain needed for status epilepticus (diazepam or lorazepam)

• Want a short elimination half-life for hypnotics, ex. temazepam

• Anti-anxiety agents should have longer half life, ex. lorazepam
Drug interactions with benzodiazepines

• Benzodiazepines are safe, but are CNS depressants
• Have potentiative effects with other CNS depressants: antipsychotics, opioids, alcohol, antihistamines, MAO inhibitors, tricyclic antidepressants, anticonvulsants
• Inhibitors or activators of CYP3A4:
  – inhibitors: erythromycin, ritonavir, grapefruit juice
  – activator: carbamazepine, phenobarbital
Side effects of benzodiazepines

- Lightheadedness, increased reaction time
- Hangovers: drowsiness and confusion, especially with drugs with long $t_{1/2}$
- Rebound withdrawal effects: rebound anxiety or wakefulness, especially with drugs with short $t_{1/2}$ or abrupt discontinuation of the drug
- Ataxia and nystagmus
- Anterograde amnesia
- Paradoxical excitement: uninhibited behavior, hostility rage, hypomanic behavior
Contraindications to benzodiazepine use

• Benzodiazepines may decrease muscular tone in upper airway
  – Avoid in COPD and obstructive sleep apnea
• Alcoholics and older patients with liver problems
  – Older patients can use a benzodiazepine not metabolized by a P450
Tolerance, abuse, dependence

• Some risk for dependence and abuse but much less than for other drugs like barbiturates
• Abuse may be more prevalent in people that also abuse other substances
• May be no abstinence syndrome following gradual withdrawal of drug
• May be physical dependence after long-term use
Therapeutic uses for benzodiazepines

- Anxiety (lorazepam)
- Sleep disorders (lorazepam, triazolam, flurazepam, temazepam)
- Seizures (clonazepam, diazepam, lorazepam)
- Skeletal muscle spasms (diazepam)
- Alcohol withdrawal (diazepam, lorazepam)
- Preanesthetic medication (midazolam - good for injecting; diazepam, then lorazepam)
Flumazenil

- Benzodiazepine receptor antagonist
- Reverses the effects of benzodiazepines
- Hastening recovery from benzodiazepine sedation or anesthesia after diagnostic procedures or minor surgery
- Only available for IV administration
\( \text{GABA}_A \) receptor subtypes and their location matter in therapeutics

Adapted from The Biochemical basis of Neuropahrmacology, by Jack Cooper, Floyd Bloom and Robert Roth, 8th Ed. Oxford Pr., 2003 p. 117
## Role and location of $\text{GABA}_A$ receptor subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$</td>
<td>Widespread, cerebral cortex</td>
<td>Sedation, amnesia, seizure protection</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>Limbic region, striatum, cortex</td>
<td>Anxiolytic</td>
</tr>
<tr>
<td>$\alpha_5$</td>
<td>Hippocampus</td>
<td>Associative learning &amp; memory</td>
</tr>
<tr>
<td>$\beta_2, \beta_3$</td>
<td>Widespread</td>
<td>Consciousness (required for iv anesthetic action)</td>
</tr>
</tbody>
</table>
**GABA<sub>A</sub> receptor subtype selective drugs**

- **Zolpidem (Ambien): α1-selective, hypnotic**
  - Imidazopyridine, nonbenzodiazepine
  - Shortens sleep latency, prolongs sleep time
  - Readily absorbed from GI tract, completely metabolized in liver
  - Plasma half-life = 2 hrs
  - Wakeful behavior and amnesia
  - New zolpidem extended release

- **Other subtype-selective drugs:**
  - **Zaleplon (Sonata): α1-selective, hypnotic, t<sub>½</sub> = 1 hr**
  - **Eszopiclone (Lunesta): α1-selective, hypnotic, t<sub>½</sub> = 6 hr**
  - Not limited to short term use
  - Used primarily to shorten onset to sleep
Safety and Adverse effects

- Risk of abuse and tolerance low when used as directed

- Few withdrawal reactions, although some have been reported

- No tolerance to therapeutic effect
Buspirone (Buspar)

- Used to treat generalized anxiety with limited severity
- Partial agonist at 5-HT$_{1A}$ receptors
- Lacks CNS depressant properties
- Minimal sedation
- Slow onset of action
Chloral hydrate

- Rapidly converted to ethanol in liver
- Irritating to GI tract
- Useful for sedation in children or elderly undergoing uncomfortable procedures
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