Benzodiazepines
Benzodiazepines: History

1950s - Invented by Swiss chemists who identified its sedative effects

1950s–60s - Chlordiazepoxide (Librium) marketed as a safer alternative to barbiturates; along with newer benzodiazepines (BZDs), promoted as having no dependence-inducing properties!

1970s–80s - BZDs most commonly prescribed drug class in the world. They remain the ‘most prescribed’ drug class in Australia

1990s on - Some decline in the number of prescriptions due to problems related to dependence and reduced therapeutic value. Generally safer than barbiturates, problems are with longer term and polydrug use

1998 - 8.89 million prescriptions dispensed.
Site and Structure of Action

- Site of action is the $\text{GABA}_A$ receptor
- Structure of $\text{GABA}_A$ receptor
  - Comprised of 5 subunits
  - $2 \alpha$ subunits (to which $\text{GABA}$ binds)
  - $2 \beta$ subunits (to which barbiturates bind)
- $1 \gamma$ subunit (to which benzodiazepines bind)
Benzodiazepines

GABA A receptor
benzodiazepine (BDZ) binding site
benzodiazepine
gamma sub-unit

synaptic cleft
GABA
Cl-

post-synaptic membrane
alpha
alpha

cytoplasm
alpha
alpha

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Benzodiazepines

- Chlordiazepoxide (Librium®)
- Diazepam (Valium®)
- Oxazepam (Serax®)
- Lorazepam (Ativan®)
- Alprazolam (Xanax®)
- Triazolam (Halcion®)
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Biol. half life (h)</th>
<th>Indication</th>
<th>Est. dose equivalents p.o. (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Xanax, Neurol)</td>
<td>6-12</td>
<td>Anxiety</td>
<td>0.5</td>
</tr>
<tr>
<td>Bromazepam (Lexaurin)</td>
<td>10-20</td>
<td>Anxiety</td>
<td>5-6</td>
</tr>
<tr>
<td>Chlordiazepoxide (Defobin)</td>
<td>5-30 [36-200]</td>
<td>Anxiety</td>
<td>25</td>
</tr>
<tr>
<td>Clobazam (Frisium)</td>
<td>12-60</td>
<td>Anxiety, convulsions</td>
<td>20</td>
</tr>
<tr>
<td>Clonazepam (Rivotril)</td>
<td>18-50</td>
<td>Anxiety, convulsions</td>
<td>0.5</td>
</tr>
<tr>
<td>Diazepam (Diazepam, Valium)</td>
<td>20-100 [36-200]</td>
<td>Anxiety</td>
<td>10</td>
</tr>
<tr>
<td>Flunitrazepam (Rohypnol)</td>
<td>18-26 [36-200]</td>
<td>Hypnosis</td>
<td>1</td>
</tr>
<tr>
<td>Midazolam (Dormicum)</td>
<td>4-6</td>
<td>Hypnosis</td>
<td>10</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>10-20</td>
<td>Anxiety</td>
<td>1</td>
</tr>
<tr>
<td>Nitrazepam (Nitrazepam)</td>
<td>15-38</td>
<td>Hypnosis</td>
<td>10</td>
</tr>
<tr>
<td>Oxazepam (Oxazepam)</td>
<td>4-15</td>
<td>Anxiety</td>
<td>20</td>
</tr>
<tr>
<td>Triazolam (Halcion)</td>
<td>2</td>
<td>Hypnosis</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Benzodiazepine receptor of GABA_A is heterogeneous

- 13 known subunits of the GABA_A receptor
- Benzodiazepine-sensitive
  - α1, α2, α3, α5
- Benzodiazepine-insensitive
  - α4 and α6
Properties of GABA\textsubscript{A} receptor

- Myorelaxant, motor-impairing, and anxiolytic-like properties thought to be mediated by α2, α3, and/or α5 subunits\textsuperscript{2}

- Benzodiazepines acting on α2, α3, and/or α5 subunits (but NOT α1) have demonstrated nonsedative, nonamnesic anxiolytic properties\textsuperscript{2}
Mechanism of action

Anticonvulsant activity and amnesic properties are thought to be mediated by α1 receptors²

- Benzodiazepines and barbiturates bind more strongly when GABA is also bound to the receptor
Properties Continued

- Benzodiazepines increase the affinity of the receptor for GABA, and thus increase Cl\(^-\) conductance and hyperpolarizing current.

  - Therefore, benzodiazepines are *indirect agonists* of the GABA receptor.
Medical Indications for Use

- Anxiolytic – chronic / phobic anxiety & panic attacks
- Sedative and hypnotic – sleep disturbance & anaesthesia / premed
- Anticonvulsant – status epilepticus, myoclonic & photic epilepsy
- Muscle relaxant – muscle spasm / spasticity
- Alcohol withdrawal.
Prescribing BZD

- Usually not a solution to presenting problems
- Limited long-term efficacy with potential for dependence
- Short-acting night sedation can lead to daytime use (i.e. when taken to avoid withdrawal)
- Similarly, continuance of use avoids withdrawal
- Long-term use is common and associated with:
  - excessive sedation
  - cognitive impairment
  - increased risk of accidents
  - adverse sleep effects
  - dependence and withdrawal (even at therapeutic doses)
- When used with alcohol and other CNS depressants, BZDs have an additive effect, increasing the risk of harm.
Benzodiazepines

Patterns of Use

• BZDs are one of the most prescribed drugs
• 4% of all prescriptions from General Practitioners are for benzodiazepines (BZDs)
• Predictors for BZD prescription include:
  – being female
  – being elderly
  – being an established patient
  – attending a busy doctor, or a doctor in inner urban area
• Over 40% of prescriptions given to people ≥70 years
• Night time use tends to increase with age
• 58% of current users report daily use for ≥6 months.
BZD and Long-term Use

• Long-term use is common and associated with:
  – altered use patterns (from night time to daytime use)
  – excessive sedation
  – cognitive impairment
  – increased risk of accidents
  – adverse sleep effects
  – dependence and withdrawal (even at therapeutic doses)

• BZDs have an additive effect with alcohol / other CNS depressants, increasing the risk of harm

• BZDs have limited long-term efficacy.
BZD and Illicit Drug Use

• Illicit BZD use is usually oral, although around 5% are likely to inject (usually males)

• Often 2\textsuperscript{nd} drug of choice for illicit drug users, as BZDs assist withdrawal from opioids, stimulants and alcohol

• Estimated around 70% of people using $\geq 50$ mg per day are polydrug users, who tend to:
  – be younger
  – have higher daily doses and higher lifetime exposure
  – use in combination with other CNS depressants to increase intoxication
  – prefer fast-acting BZDs (diazepam, flunitrazepam)
  – may convert form to enable injection.
Pharmacodynamics

- Rapidly absorbed orally (slower rate of absorption IM)
- Lipid soluble - differences determine rate of passage through blood brain barrier i.e.
  \[ \uparrow \text{lipophilic} \rightarrow \uparrow \text{speed of onset} \]
- Duration of action variable –
  \[ \uparrow \text{lipophilic} \rightarrow \downarrow \text{duration of action due to distribution in adipose tissue.} \]
Metabolism

• Metabolised in the liver – mostly oxidative transformation prior to conjugation with glucuronic acid for urinary excretion

• Elimination half life (drug & active metabolites) ranges from 8 – >60 hours, if short half life & no active metabolites rapidly attains steady state with minimal accumulation.
Neurotransmission

- Potentiate neurotransmission mediated by GABA (main inhibitory neurotransmitter), therefore neurons are more difficult to excite.

- Specific neuronal membrane receptors for BZD closely associated with synaptic GABA receptors.

- Receptors distributed through CNS, concentrated in reticular formation & limbic systems, also peripheral binding sites.

- Further understanding of the effects of BZDs on receptor subgroups may lead to the development of non-sedating anxiolytic BZDs.
Effects: Low Dose

**Short term:**
- Sedation
- Anxiety relief
- Anticonvulsant properties
- Can usually attend daily business (though should not drive in first 2 weeks of treatment).

**Other effects:**
- Drowsiness, lethargy, fatigue
- Impaired concentration, coordination, memory
- Reduced ability to think and learn
- Emotional anaesthesia
- Clumsiness, ataxia
- Depression
- Mood swings
- Blurred vision and/or vertigo
- Light-headedness
- Nausea, constipation, dry mouth, loss of appetite.
Effects: High Dose

**Short term**
- Sedation
- Intoxication
- Drowsiness.

**Other effects**
- Paradoxical excitement
- Mood swings
- Hostile and erratic behaviour.

**Toxicity**
- Performance deficits
- Emotional blunting
- Muscle weakness
- Sensitivity
- Potentiates other drugs
- Euphoria, hypomania.
Overdose

• Benzodiazepines are the most commonly implicated drug in overdose cases

• On their own, unlikely to cause death despite causing respiratory depression

• Serious / potentially fatal implications when used in combination with other CNS depressants.
Overdose Response

• Overdose depresses the conscious state and respiratory system

Flumazenil®

• a BZD antagonist which reverses BZD overdose, though contraindicated outside the Emergency Department

• precipitates seizures in:
  – chronic BZD users
  – pre-existing epilepsy
  – tricyclic antidepressant users
  – concurrent amphetamine or cocaine users.
Benzodiazepine Therapy

Fig. 7 Schematic
Dependence

Two groups of patients are especially likely to develop dependence.

1. Low dose dependence occurs among women and elderly prescribed low doses over long time periods (up to 40% experience withdrawal symptoms)

2. High dose dependence occurs among polydrug users.
Withdrawal

- 40% of people on long-term therapeutic BZD doses, will experience withdrawal if abruptly ceased.
- Symptoms occur within 2 ‘short-acting’ to 7 days ‘long-acting’ forms.
- BZD withdrawal:
  - is not life-threatening & usually protracted.
  - initial symptoms/problems re-emerge on cessation.
  - issues usually more complicated on cessation.
- Seizures uncommon (unless high dose use or abrupt withdrawal, + alcohol use).
- Two main groups of ‘dedicated’ users:
  - prescribed (older women).
  - high level, erratic polydrug use.
Withdrawal Severity

Severity of withdrawal is dependent on:

- pattern and extent of use (duration, quantity, type (half-life))
- withdrawal experience (prior symptoms, success, complications)
- coexisting physical / mental health problems.
3 Areas of BZD Withdrawal

Anxiety and anxiety-related symptoms
- anxiety, panic attacks, hyperventilation, tremor
- sleep disturbance, muscle spasms, anorexia, weight loss
- visual disturbance, sweating
- dysphoria.

Perceptual distortions
- hypersensitivity to stimuli
- abnormal body sensations
- depersonalisation/derealisation.

Major events
- seizures (grand mal type)
- precipitation of psychosis.
Second-Generation Hypnotics

- **Zolpidem**

  **General:**
  Nonbenzodiazepine
  - Structurally unrelated to benzo’s, but acts in much the same manner
  - Binds to (subtype 1) GABA$_{A1}$ receptors
  - Useful for the short-term treatment of insomnia
  - Primarily a sedative (rather than an anxiolytic)
Pharmacokinetics and Dynamics and Adverse Effects

Pharmacokinetics
- Rapidly absorbed in the GI tract following oral administration (75% reaches plasma)
- Only approx. 20% is metabolized in first-pass metabolism
- Metabolized in the liver and excreted by the kidney’s
- Peak plasma levels reached in approx. 1 hour

Pharmacodynamics
- Produces sedation and promotes good sleep (w/o anxiolytic, anticonvulsant, or muscle-relaxant effects)
- Memory is affected
- Flumazenil reported to reverse memory impairments and overdoses
  Flumazenil also reported to improve memory and learning, thus suggesting a possible role of endogenous benzo’s in memory function

Adverse Effects
- Drowsiness, dizziness, and nausea at therapeutic doses
- Severe nausea and vomiting greatly limit overdoses
Agonists of Benzo Receptors

- **Zaleplon & Zopiclone**
  - Nonbenzodiazepine agonist that acts at the GABA$_{A_1}$ receptors to exert actions similar to benzo’s
  - Short half-life
  - Only approx. 30% of an orally administered dose reaches the plasma, and most of that undergoes first-pass elimination

Half as potent as zolpidem
- Improves sleep quality w/o rebound insomnia, and little chance of developing dependency