Anxiolytic & Hypnotic Drugs

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<td>Pentobarbital NEMBUTAL</td>
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<td><strong>OTHER HYPOSTIC AGENTS</strong></td>
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<td>Zaleplon SONATA</td>
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<td>Zolpidem AMBIEN, INTERMEZZO, ZOLPIMIST</td>
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Anxiety: unpleasant state of tension, apprehension or uneasiness, characterised by, tachycardia, sweating, tumbling & palpitation, in addition to sympath. stimulation.

Episodes:
  - mild, severe, chronic, debilitating anxiety
Benzodiazepines

- Safe
- Commonly used for anxiety & insomnia
- Antidepressant with anxiolytic / SSRIs are preferred
- Nonbenzodiazepine hypnotics & antihistamine are used also
Ratio of lethal to effective dose

Benzodiazepines are relatively safe, because the lethal dose is over 1000-fold greater than the typical therapeutic dose.

\[
\text{Ratio} = \frac{\text{Lethal dose}}{\text{Effective dose}}
\]
A Receptor empty (no agonists)

Empty receptor is inactive, and the coupled chloride channel is closed.

B Receptor binding GABA

Binding of GABA causes the chloride ion channel to open, leading to hyperpolarization of the cell.

C Receptor binding GABA and benzodiazepine

Entry of Cl⁻ hyperpolarizes the cell, making it more difficult to depolarize, and therefore reduces neural excitability.

Binding of GABA is enhanced by benzodiazepine, resulting in a greater entry of chloride ion.
<table>
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<th>Long-acting</th>
<th>Intermediate-acting</th>
<th>Short-acting</th>
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<td>Days 1–3</td>
<td>10–20 Hours</td>
<td>3–8 Hours</td>
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<td>Clorazepate, Chlordiazepoxide, Diazepam, Flurazepam, Quazepam</td>
<td>Alprazolam, Estazolam, Lorazepam, Temazepam</td>
<td>Oxazepam, Triazolam</td>
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Actions of BZDs

1- Reduction of anxiety, at low doses /anxiolytic / inhibit circuits in limbic system
2- Sedative / hypnotic ($\alpha_1$-GABA$_A$)
3- Anterograde amnesia ($\alpha_1$-GABA$_A$)
4- Anticonvulsant ($\alpha_1$-GABA$_A$)
5- Muscle relaxant (presynaptic inhibition in spinal cord). (Baclofen / SkM relaxant)
Therapeutic Uses

1 - Anxiety disorders

- Anxiety secondary to Panic disorder
- Generalised anxiety disorder (GAD)
- Social anxiety
- Post traumatic stress
- Obsessive compulsive disorder
- Extreme anxiety with phobia
- Anxiety related to depression & schizophrenia

- Long acting/ clonazepam, lorazepam, diazepam/ ???
- Antianxiety effect & tolerance (tolerance???)
- Cross tolerance with ethanol
- Alprazolam / short & long term treatment of panic disorder (withdrawal reactions???)
2- **Sleep disorders**

- Hypnotic effect:
  - decrease latency to sleep
  - increase (REM) sleep
- Insomnia treatment (hangover)
- Intermed. acting (temazepam, estazolam)
- Short acting (triazolam,)
- Long acting (flurazepam, quazepam)
- Temazepam / frequent wakening (1–3hrs)
- Triazolam:
  - Difficulty in going to sleep
  - Tolerance
  - Withdrawal symptoms
3- Amnesia
  premedication for anxiety-provoking & unpleasant procedures / Midazolam

4- Seizures
  Clonazepam / adjunctive therapy
  Lorazepam & Diazepam / status epilepticus
  Clorazepate, Chlordiazepoxide, Lorazepam,
  Diazepam, Oxazepam / cross tolerance with alcohol

5- Muscular disorders
  Diazepam / muscle strain, spasticity
Pharmacokinetics

1- Absorption & distribution:

2- Duration of action:

3- Fate:
   metabolised by hep. microsomal sys. to active metabolite
   plasma $t_{1/2}$
   excreted in urine as glucor. or oxidised metabolites
   cross placenta
   CI: in pregnancy
Pharmacokinetics

4- Dependence:

- Psychological & physical
- Withdrawal symptoms: confusion, anxiety, agitation, restlessness, insomnia, tension & rarely, seizures
- BZDs with short $t_{1/2}$ (triazolam), induce more abrupt symptoms

5- Adverse effects

- Drowsiness, confusion, ataxia, cognitive impairment
- Triazolam / tolerance, daytime anxiety, amnesia & confusion
- Caution with liver disease, acute angle-closure glaucoma
- Alcohol & other CNS depressant???
- Relatively safe, overdose ???
The drugs that are more potent and rapidly eliminated (for example, triazolam) have more frequent and severe withdrawal problems.

The less potent and more slowly eliminated drugs (for example, flurazepam) continue to improve sleep even after discontinuation.
Benzodiazepine Antagonists

- Flumazenil / GABA R antag.
- IV only, rapid onset, short duration, t1/2 1hr
- Frequent admin. is required
- May precipitate withdrawal in dependent patients
- Seizure may occur/ mixed ingestion with TCA
- SE: dizziness, NV & agitation
Other Anxiolytic Agents

• Antidepressants
  ◆ 1st line / avoiding dependence
  ◆ SSRIs (escitalopram or paroxetine)
  ◆ SNRIs (venlafaxine, duloxetine)
  ◆ SSRIs & SNRIs have lower potential for dependence

• Buspirone
  ◆ Chronic GAD
  ◆ Slow onset
  ◆ 5-HT1A, 5-HT2A, D2
  ◆ No anticonvulsant, M relaxant
  ◆ Few SE
  ◆ Doesn’t potentiate CNS depressants
Differentiating Tolerance, Dependence, and Addiction

Tolerance occurs when larger doses of drug are required to produce the same effect. Tolerance can occur for numerous reasons: innate tolerance is genetically determined, pharmacokinetic tolerance results from changes in drug metabolism, and pharmacodynamic tolerance is caused by adaptive changes in receptor density or second messenger characteristics. Cross-tolerance is sometimes used pharmacologically during detoxification to allow one drug to substitute for another.

Dependence can be either physical or psychologic. Psychologic dependence is manifested by cravings for a drug—probably the major cause of relapse. Physical dependence is virtually synonymous with withdrawal. Cessation of use of drugs that cause physical dependence will result in withdrawal symptoms. Importantly, tolerance and dependence are biologic phenomena and do not imply drug abuse.

Abuse or addiction denotes an overwhelming compulsion and preoccupation with obtaining and using a drug. Not all drugs of abuse are associated with the same propensity to cause tolerance or dependence.
Barbiturates

- Used to induce & maintain sleep
- Replaced by BZDs because they induce tolerance & physical dependence & associated with very severe withdrawal symptoms
- All are controlled sub.
- Thiopental (very short-acting) used to induce anaesthesia
- Prolong duration of Cl⁻ channel opening
- Block excitatory glutamate receptors
- Anesthetic conc. of pent. block high-frequency Na⁺ channel
Classification of Barbiturates

Long-acting
- Phenobarbital

Short-acting
- Pentobarbital
- Secobarbital
- Amobarbital
- 3–8 Hours

Ultra-short-acting
- Thiopental
- 20 Minutes
Actions of Barbiturates

- **CNS depression**
  - low doses (sedation)
  - higher doses (hypnosis, anaesthesia???, coma & death)
  - Don’t raise pain threshold
  - chronic use lead to tolerance

- **Respiratory depression**
  - Suppress hypoxic & chemoreceptor response to CO2
Therapeutic uses of Barbiturates

- Anaesthesia, thiopental
- Anticonvulsant, phenobarbital (tonic-clonic seizure)
- Sedative / hypnotic (Butalbital, acetaminophen & caffeine or aspirin & caffeine)
Potential for addiction

Vertigo

Drowsiness

Tremors

Nausea

Enzyme induction
Zolpidem

- Non-BZD compound, bind BZD-R subtype selectively
- No anticonvulsant or muscle-relaxant effect
- Few withdrawal, minimal rebound insomnia, little tolerance
- Rapidly abs., rapid onset, short $t_{1/2}$
**Zalpelon**
Non BZDs, few residual effects, rapid elimination

**Eszopicone**
Non BZD, effective in insomnia, rapid abs., & metabolism

**Ramelton**
Selective MT1 & MT2, used for insomnia, No dependence, SE: ———, prolactin ???
### Therapeutic Disadvantages

**Benzodiazepines**
- The benzodiazepines may disturb intellectual functioning and motor dexterity.
- The benzodiazepines have the potential for dependence, and withdrawal seizures may occur.
- Withdrawal of drug often results in rebound insomnia.

**Other agents**
- Slower onset of action than benzodiazepines.
- No muscle relaxation nor anticonvulsant activity.
- Have no anticonvulsant or muscle-relaxing properties.
- Has only marginal effects on objective measures of sleep efficacy.

**Barbiturates**
- The barbiturates induce tolerance, drug-metabolizing enzymes, and physical dependence, and they show severe withdrawal symptoms.

### Therapeutic Advantages

**Benzodiazepines**
- Potential use in chronic therapy for seizures.
- These less potent and more slowly eliminated drugs show no rebound insomnia on discontinuation of treatment.
- Agent of choice in treating panic disorders.
- Do not require Phase I metabolism and, therefore, show fewer drug interactions and are safer in patients with hepatic impairment.
- Useful in long-term therapy for chronic anxiety with symptoms of irritability and hostility.
- Does not potentiate the CNS depression of alcohol.
- Low potential for addiction.
- Effective for up to 6 months.
- Show minimal withdrawal effects.
- Exhibit minimal rebound insomnia.
- Little or no tolerance occurs with pronged use.
- The potential for abuse is minimal with minimal dependence or withdrawal effects.
- The drug can be administered long-term.

**Other agents**
- Effective for up to 6 months.
- Show minimal withdrawal effects.

**Barbiturates**
- Rapid onset of action.