CNS Depressants

Dr. Mohd Nazam Ansari
What is Misuse?

- **Misuse** = “Non-medical use” or any use that is outside of a medically prescribed regimen

- Examples can include:
  - Taking for *psychoactive “high” effects*
  - Taking in *extreme doses*
  - **Mixing** pills
  - Using with *alcohol or other illicit substances*
  - Obtaining from *non-medical sources*
Commonly Misused Rx Drugs

Classified in 3 classes

• CNS Stimulants: ADHD, weight loss
  – E.g. Ritalin,

• CNS Depressants (Sedatives - Hypnotics): treat anxiety and sleep disorders
  – E.g. Xanax (Alprazolam), Ativan (Lorazepam), Valium (Diazepam)

• Opiates: pain-killers
  – E.g. Morphine, Codeine
CNS depressants

• CNS depressants are antagonists of the behavioral stimulants.

• CNS Depressants are drugs that can slow down normal brain functions.

• Depressants are used to induce sedation, muscle relaxation and drowsiness.

• CNS depressants are additive with each other and with the behavioral state of the user. Supra-additive = synergistic.

• Psychological dependence, and tolerance do occur to CNS depressants.
Sedative-Hypnotics

**Sedative**: Drugs that have an inhibitory effect on the CNS to the degree that they reduce:
- Nervousness (العصبية)
- Excitability (الاهتياجية)
- Irritability (التهيج) without causing sleep

- Drugs causes calmness, relaxation, reduction of anxiety (nervousness, feeling of apprehension, fear, or worry).
- Sedatives may be referred to as *tranquilizers*, depressants, anxiolytics.

**Hypnotics**: Calm or soothe the CNS to the point that they cause sleep
- used in the treatment of severe insomnia
- A sedative can become a hypnotic if it is given in large enough doses
Mechanisms of action

- **Reversible depression of excitable tissue:** E.g. Barbiturates and non-barbiturates, ethyl alcohol, and general anesthetics.

- **Greater depression of polysynaptic pathways, such as the reticular activating system (RAS).**

- **Potentiating the GABA$_A$ receptor complex:** E.g. Barbiturates prolong Cl$^-$ access 4 to 5 times.

The GABA receptor is a pentameric structure. The receptor complex includes distinct binding sites for benzodiazepines, barbiturates and GABA-like substances. GABA transmission exerts an inhibitory effect on norepinephrine (NE), dopamine (DA), serotonin (5-HT), and acetylcholine (ACh) pathways.
GABA is the principal inhibitory neurotransmitter in the mammalian CNS → ↑ opening time of chloride channels → ↑conductance of chloride ions → hyperpolarization
Sedative-Hypnotic Effects

- Sedation
- Slurred speech
- Incoordination
- Unsteady gait
- Impaired attention or memory
- Stupor or coma
- Overdose risk increased with opioids or in combination with other sedatives, including alcohol
Classification:

- **Barbiturates**
  - **Ultra short:** Thiopental, Mephobexital, Thiamylal
  - **Short:** Pentobarbital, Secobarbital
  - **Intermediate:** Butabarbital
  - **Long:** Phenobarbital, Mephobarbital

- **Benzodiazepines**
  - **Short acting:** Triazolam, Oxazepam
  - **Intermediate acting:** Lorazepam, Alprazolam, Midazolam
  - **Long acting:** Clonazepam, Chlordizepoxide, Diazepam

- **Non-benzodiazepines hypnotics**
  - Zolpidem (Ambien )
  - Zaleplon (Sonata )
Barbiturates

- Derivatives of barbituric acid
- First synthesized in 1868
- Used as anticonvulsants and sedative hypnotics
- High abuse liability
- Used with other analgesic combinations (aspirin, codeine) for treatment of tension and migraine headaches
- Phenobarbital and belladonna alkaloid combinations used to treat peptic ulcers and irritable bowel syndrome
Barbiturates: Mechanism of Action

- Site of action: Brainstem (reticular formation)
- Barbiturates are GABA (gamma-aminobutyric acid) agonists, acting on the GABA$_A$ receptor. GABA is the principal inhibitory neurotransmitter in the mammalian CNS → ↑ opening time of chloride channels → ↑ conductance of chloride ions → hyperpolarization
Barbiturates: Drug Effects

- Low doses: sedative effects
- High doses: hypnotic effects (also lowers respiratory rate)
- Notorious enzyme inducers
  - Stimulate liver enzymes that cause the metabolism or breakdown of many drugs

Barbiturates: Indications

- Hypnotic
- Sedative
- Anticonvulsant
- Anesthesia for surgical procedures
## Barbiturates: Side Effects

<table>
<thead>
<tr>
<th>Body System</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>agitation, confusion, ataxia, CNS depression, nervousness, hallucination, insomnia, anxiety, dizziness, thinking abnormalities, Drowsiness, vertigo, coma</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Respiratory depression, apnea, bronchospasms, cough</td>
</tr>
<tr>
<td>Digestive System</td>
<td>Nausea, vomiting, diarrhea, constipation</td>
</tr>
<tr>
<td>Reproductive System</td>
<td>cross the placental barrier and cause fetal abnormalities</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>bradycardia, hypertension</td>
</tr>
<tr>
<td>Other</td>
<td>Agranulocytosis, vasodilatation, hypotension, headache, fever, liver damage,</td>
</tr>
</tbody>
</table>
Barbiturates: Toxicity and Overdose

- Overdose frequently leads to respiratory depression, and subsequently, respiratory arrest
- Overdose produces CNS depression (sleep to coma and death)
- Can be therapeutic
  - Anesthesia induction
  - Uncontrollable seizures

Barbiturates: Drug Interaction

- Additive effects
  - ETOH, antihistamines, benzodiazepines, narcotics, tranquilizers
- Inhibited metabolism
  - MAOIs will prolong effects of barbiturates
- Increased metabolism
  - Reduces anticoagulant response, leading to possible clot formation
Benzodiazepines

Most commonly prescribed drug classes

Do not increase metabolism of other drugs

- **Short acting**: Triazolam, Oxazepam
- **Intermediate acting**: Lorazepam, Alprazolam, Midazolam, Temazepam, Estazolam
- **Long acting**: Clonazepam, Clordizepoxide, Diazepam, Flurazepam, Quazepam
Benzodiazepines: Mechanism of Action

- Affect hypothalamic, thalamic, and limbic systems of the brain
- Benzodiazepines (BZDs) bind to the gamma sub-unit of the GABA-A receptor. Their binding causes an allosteric (structural) modification of the receptor that results in an increase in GABA A receptor activity. BZDs do not substitute for GABA, which bind at the alpha sub-unit, but increase the frequency of channel opening events which leads to an increase in chloride ion conductance and inhibition of the action potential.
## Benzodiazepines:

<table>
<thead>
<tr>
<th>Indications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>Mild and infrequent</td>
</tr>
<tr>
<td>Sleep induction</td>
<td>Headache</td>
</tr>
<tr>
<td>Skeletal muscle relaxation</td>
<td>Drowsiness</td>
</tr>
<tr>
<td>Anxiety relief</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Treatment of alcohol</td>
<td>Vertigo</td>
</tr>
<tr>
<td>withdrawal</td>
<td>Lethargy</td>
</tr>
<tr>
<td>Agitation</td>
<td>Nervousness</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
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<tr>
<td>Epilepsy</td>
<td></td>
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<tr>
<td>Balanced anesthesia</td>
<td></td>
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</tbody>
</table>
Non-benzodiazepine Hypnotics

5-HT agonist e.g. buspirone (5-HT_{A1})

Zaleplon (Sonata) and zolpidem (Ambien)

• Share many characteristics of benzodiazepines
Buspirone (BuSpar)

- Anxiolytic, not structurally related to the benzodiazepines
- Does not have anticonvulsant, hypnotic, muscle relaxant, ataxic, and dependence-producing properties
- Similar level of efficacy as an anxiolytic compared to the benzodiazepines
- Relief of anxiety may take several weeks for a noticeable response and 3-4 weeks for optimal response
Zolpidem (Ambien)

• Non-benzodiazepine
• Commonly used to treat both anxiety and insomniac patients
• **MOA**: acts on the subdivision of benzodiazepines receptors in CNS.
• It produces hypnotic effects, accompanied by strong sedation. However, the duration of action is short
• Similar to benzodiazepines in its hypnotic efficacy
Zaleplon (Sonata)

• New hypnotic

• **MOA**: Interact with GABA sub-complex type A by binding selectively with benzodiazepine-1 receptor to produce sedative and hypnotic effects

• Has sedative, anxiolytic, muscle relaxant, and anticonvulsant effects
Sedative-Hypnotic Withdrawal

- Within 6-8 hours of last dose
- Must be monitored closely due to potential fatalities
- Can be life threatening if breathing and blood pressure problems untreated
- Increased heart rate, blood pressure, excessive sweating, abdominal cramps, tremors
- Withdrawal deaths more frequent than overdose deaths.
- Nausea or vomiting
- Transient hallucinations or illusions
- Agitation
- Anxiety
- Seizures
Medications for Sedative-Hypnotic Dependence

- Taper: slowly decrease dose to minimize withdrawal symptoms
- May first convert to longer-acting agent
- Use non-addictive medications for residual anxiety symptoms
  - SSRIs and other antidepressants
  - Other anti-anxiety agents
THANQ...