Barbiturates / Sedative Hypnotic Drugs

Psychology 472: Pharmacology of Psychoactive Drugs

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Background
- Been around a long time
  - Chloral Hydrate – Used since 1880
  - Paraldehyde – Used before barbiturates
- Barbiturates
  - Primary prescription for anxiety and insomnia from 1912-1960
  - Decreased in popularity
  - Associated with
    - Overdose
    - Dangerous drug interactions
    - Dependence and abuse

Barbiturates
- Are medically used for many things
  - General anesthesia
  - Epilepsy (anticonvulsant)
  - To maintain coma in emergency situations (e.g., head trauma)
  - Bipolar disorder
  - Anxiety
  - Sleep

Non-Medical Use
- Decreases anxiety
- Sedation - Can be related to date rape
- Euphoria
- Used to come down from stimulants
- Favorite in Pharming parties

Slang Names
- Amobarbital
  - Downers, blue heavens, blue velvet, blue devils
- Phentobarbital
  - Nembies, yellow jackets, abbot, Mexican yellows
- Phenobarbital
  - Purple hearts, goof balls
- Secobarbital
  - Reds, red birds, red devils, lilly, F-40s, pinks, pink ladies, seggy
- Tuinal
  - Rainbows, reds and blues, tooies, double trouble, gorilla pills, F-66s

Barbiturates

<table>
<thead>
<tr>
<th>Name</th>
<th>Formula</th>
<th>Strength</th>
<th>Sedative</th>
<th>Rapid</th>
<th>Long</th>
<th>Depression</th>
<th>Constipation</th>
<th>Abuse</th>
<th>Overdose</th>
<th>Toxicity</th>
<th>Amnesia</th>
<th>Euphoria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amobarbital</td>
<td>Amobarbital</td>
<td>Strong</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Phentobarbital</td>
<td>Phentobarbital</td>
<td>Medium</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Phenobarbital</td>
<td>Weak</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Secobarbital</td>
<td>Secobarbital</td>
<td>Weak</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tuinal</td>
<td>Tuinal</td>
<td>Weak</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Symbols: D = Downer, E = Euphoria, T = Toxicity, L = Long-acting, R = Rapid-acting. See Table 3.1 for more information.*
Can be categorized many ways

Duration of Action
- Ultrashort acting (e.g., thiopental)
  - Extremely lipid soluble
  - Crosses the blood-brain barrier rapidly
  - Causes sleep within seconds when used intravenously.
- Longer acting (e.g., amobarbital)
  - More water soluble, slower to penetrate CNS.

Pharmacokinetics
- Half life - 3 minutes to 120 hours
- Impacts can be within seconds to 20-30 minutes
- Metabolized by the liver

Pentobarbital
- Used for short-term insomnia treatment
- Also used as an emergency treatment for seizures
- Presurgical sleep aid

Phenobarbital
- Primarily used to treat or prevent seizures.
- Also used short-term to treat insomnia
- Sleep aid before surgery

Secobarbital
- Is used to short-term to treat insomnia
- Sleep aid sedative before surgery.
Tuinal

- Combination of secobarbital sodium and amobarbital in equal proportions.
- "Toonerville trolley," or "tooners"
- High risk of overdose
- Use has decreased

GABAa Receptor

- Barbiturates bind on the Barbiturate binding site
- Causes Cl channels to open independently of GABA
- Causes other stimulatory PSE to shut down
- No signal in the stimulatory neuron

Pharmacologic Effects

- Are not analgesic
- Do not reliably produce sedation or sleep in presence of pain
- Will wake up
  - Need an opiate in surgery to help you

Sleep

- Decreases REM sleep
  - Dreaming is suppressed - restlessness
  - Become restless during continued use.
  - Sometimes not good before surgery
  - High doses –
    - Hallucinations
    - Disorientation
    - Convulsions
  - Get vivid and excessive dreaming during withdrawal.

Cognitive inhibition

- Result
  - Sedation
  - Memory impairment
    - Shutting down Hippocampal formation
  - Alterations in judgment and cognitive functioning.
    - Shutting down Prefrontal Cortex
  - Produce Alzheimer-like amnesia
Behavioral Effects
- Reduces inhibitions
- Decreases motor coordination
- Get cognitive inhibitions

- Higher doses
  - General depression
  - Sleep.
  - Still higher
  - Respiratory depression
  - Death

DRINKING ALCOHOL AND TAKING BARBITURATES EQUALS DEATH

Alcohol and Barbiturates
- Combination
- Very dangerous
  - Used by users to get a better high
  - Get both accidental and intentional suicides.
  - Often used in HIV deaths

Problems
- Narrow therapeutic window TR and SF are low
  - Toxic Dose 50
  - Therapeutic Ratio = Effective Dose 50
- Certain Safety Factor = Lethal Dose 1
  - Certain Safety Factor = Lethal Dose 99
- Often lethal in overdose
- Can result in coma’s
- High potential for abuse and dependence
- Makes you feel relaxed and mellow
- Drug interactions
  - Very dangerous in combination with other drugs
  - Especially BZs and alcohol (including OTCS)

Pharmacodynamics
- Down regulation of receptors
  - Need more of the drug to get the same effect
- Liver metabolic enzymes increases
  - Faster metabolic rate

- Risk of both physical and psychological dependence.

Effects in Pregnancy
- Freely crosses placental barrier, as do all psychoactive drugs.
- Limited data, possibility of developmental abnormalities.
- Women taking drug as antiepileptic should examine the risks and take smallest effective dose.
Nonbarbiturate Sedative-Hypnotic Drugs

- Structurally resemble barbiturates
- Introduced in 1950s as anxiolytics, sedatives, and hypnotics.
- Now considered medically obsolete
- Occasionally encountered as drugs of abuse.

Meprobambate

- Miltown, Equanil, Meprospan
- Primarily used in medicine as an anxiolytic
- Was used to treat mental patients
  - Made them calmer and restored logical thinking
  - Also used to treat alcoholics
  - Was the best-selling minor tranquilizer for a time
  - Replaced by the benzodiazepines

Characteristics

- Is less sedating than traditional barbiturates but had similar symptoms
- Binds on GABA receptors
- Has impacts in the reticular formation
  - Causes sedation
  - Reduces pain
  - Creates tolerance
- Not used as much today in medicine

Paraldehyde

- Polymer of Acetaldehyde;
- Has a distinct odor
- Produces sleep for up to 12 hrs.
  - Has minimal muscle, heart, or respiratory depression.
- Used to treat DTs of alcohol withdrawal
  - Usually when having delirium tremens
- Also used to calm psychiatric patients
- Also used as a preservative, preparing leather.
  - Acetaldehyde with a small amount of sulfuric acid.

Chloral hydrate (Noctec)

- Classic "Date rape" drug, "Mickey Finn"
  - Soluble in both water and alcohol
  - Makes you unconscious
  - No amnesic properties
  - Past use as bedtime sedative for elderly
- Metabolized like alcohol
- Tolerance like other barbiturates

Methaqualone (Quaalude)

- Ludes, Lude, Panty Droppers
- Used in late 1970s and early 1980s
- Was a top-selling sedative hypnotic
  - Rivaled alcohol and marijuana in popularity for abuse.
  - "Date rape" drug; dose for anterograde amnesia lower than for incapacitation.
Barbiturate Anesthetics
- Ultrashort-acting barbiturates
  - Thiopental (Pentothal), methohexital (Brevital)
  - Propofol (Diprovan), etomidate (Amidate)
- Structurally resemble GABA.
- Have little analgesic or euphoriant activity.
- Onset is immediate.
  - Produce unconsciousness for surgery.
- Administered through inhalation or injection.

Ketamine
- Induces unconsciousness and amnesia.
- Also induces analgesia and psychedelic hallucinations.
  - Makes it unique for barbiturates
  - Often a drug of abuse
- Does not reduce blood pressure
  - Important for critically ill surgery patients.
  - Unlike other anesthetics

Pharmacokinetics
- Liquid form
- Absorbed quickly
- Peak in 30–75 minutes.
- Elimination half-life 30–60 minutes.

Adverse Effects
- Toxicity due to GABA<sub>a</sub> potentiation.
- Overdose → stupor, delirium, unconsciousness, coma, death
- Nonfatal OD = coma 1–2 hours
- Acute withdrawal symptoms in dependent person.
  - Insomnia, anxiety, tremors

Conclusions
- Are a older class of drugs
  - Been replaced by other safer drugs for most things
  - Are still effectively used in surgery
- Still are abused by users
- Have major issues with effective/lethal doses
- Get lots of overdoses when combined with other drugs
  - Can kill you when consumed with alcohol