

Sedative and Hypnotic Drugs

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In this article, we will study in detail about the various sedative and hypnotic drugs, their mechanism of action, adverse effects/toxicity, contraindications, drug interactions, and drugs of choice. Other important pharmacological and therapeutic aspects of individual drugs will also be studied.



Definitions

Sedation: state of **decreased responsiveness** to any level of stimulation; associated with some decrease in motor activity and ideation.

Sedatives: these are the drugs which subdue excitement (anxiolytic) and **calm the subject** without inducing sleep, though drowsiness may be produced.

Hypnotic: These are the drugs which induce and/or **maintain sleep**, similar to normal arousable sleep.

“Hypnotic” and “Hypnosis” are totally different terms (hypnosis refers to trans like state).

- A hypnotic drug is more depressant on CNS than a sedative drug.
- Some sedative drugs can act as hypnotic if given in higher doses.

Classification of Sedative and Hypnotic Drugs

Benzodiazepines	Barbiturates	Atypical
Short-acting: • Triazolam • Lorazepam (Ativan ^R) • Diazepam (Valium ^R)	Ultrashort acting: • Thiopental	• Zopiclone (Imovane ^R) • Eszopiclone • Zaleplon (Starnoc ^R) • Zolpidem (Ambien ^R)
Intermediate-acting: • Alprazolam	Short-acting: • Secobarbital	• Chloral Hydrate • Buspirone (BuSpar ^R)
Long-acting: • Flurazepam	Long-acting: • Phenobarbital	• Ramelteon, tasimlton • Suvorexant

Overview/Introduction of Sedative and Hypnotic Drugs

Sedative and hypnotic drugs are used in the treatment of insomnia and anxiety.

It is important to understand the sleep cycle first to understand the pharmacology of sedative and hypnotic drugs.

There are two main phases of sleep:

1. Non-REM (rapid eye movement) Sleep (70-80%):

Stages	Status	On EEG
0	Awake, 1-2%	α activity with eyes closed and β activity with eyes open
1	Dozing, 3-6%	$\alpha + \theta$ waves
2	Unequivocal sleep, 40-50%	θ waves
3	Deep sleep transition, 5-8%	θ , δ and spindle activity, K complexes can be evoked with strong stimuli
4	Cerebral sleep, 10-20%	δ activity predominated, K complexes cannot be evoked

2. REM Sleep (20-30%):

- Marked by irregular, **darting eye movements**.
- **Dreams and nightmares** occur in this stage only, which can be remembered after arousal.
- There is marked fluctuation in **heart rate and blood pressure**.
- Muscles are relaxed.

Important Points:

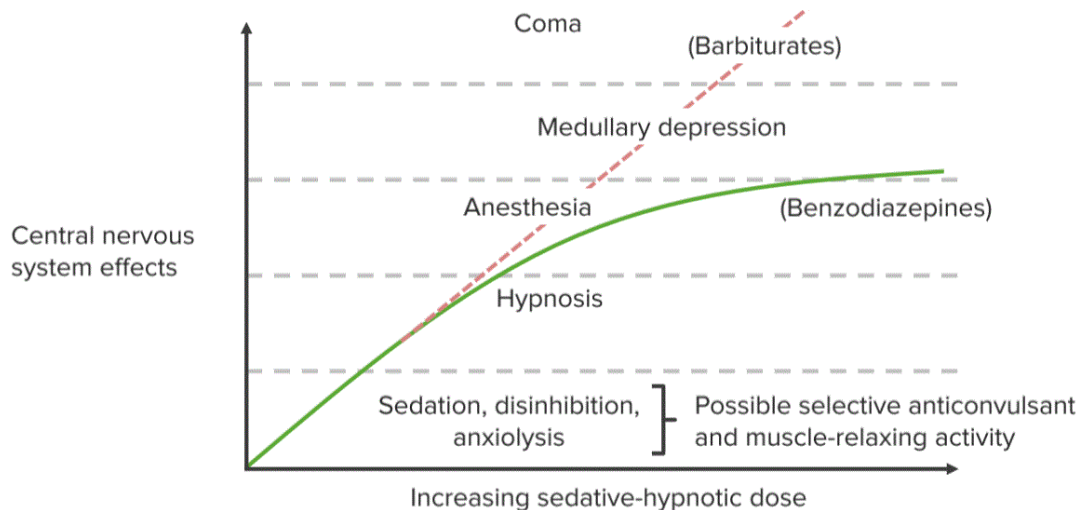
- One sleep cycle is about 80-100 minutes long.
- It repeats with the sequence of 1-4 REM.

Barbiturates

Act at GABA_A: BZD receptor-Cl⁻ Channels → Keeps the GABA induced opening of the channel for **longer duration** → Increase the ionic flow across the membrane → produces an inhibitory effect

Important: As compared to benzodiazepines, barbiturates **increase the duration** of opening instead of the frequency of opening.

The binding site is α and β subunits. If the concentration of barbiturate is increased, it produces **GABA mimetic action**. It depresses the glutamate-induced neural depolarization through **AMPA receptors**. At high concentrations, it also inhibits **sodium and potassium channels**. Benzodiazepines are frequently prescribed as sedatives and anxiolytics that are positive modulators of GABA_A receptors and CNS depressants. Their depressant effects are potentiated by marijuana, opioids, and antipsychotics. Barbiturates are largely replaced by benzodiazepines in medical practice, although are still used as **anticonvulsants**.



"Dose-response" Image created by Lecturio

Pharmacodynamics

- The effect of the drug becomes less marked with continuous use (**tolerance**).
- **Physical dependence** can be seen following long term use.
- **Withdrawal syndrome** is also observed following discontinuation.
- **Rebound** increase (**rebound phenomenon**) in REM sleep and increased nightmares seen after discontinuation.
- Respiration is depressed at high doses.
- **BP and heart rate** are decreased.
- Reduces **skeletal muscle contraction**.
- **Tone and motility of intestine** are decreased.
- **Urine output** is decreased.

Pharmacokinetics

- Most of the drugs in this category are mainly metabolized by the liver.
- **Redistribution** is observed before final disposal.
- **Secobarbital and Pentobarbital** can have a **cumulative effect** upon multiple doses. Excretion of Phenobarbital can be increased by **alkalization of urine**.

Adverse effects

- Hangover

- Tolerance
- Dependence
- Mental confusion
- Precipitates porphyria
- Hypersensitivity

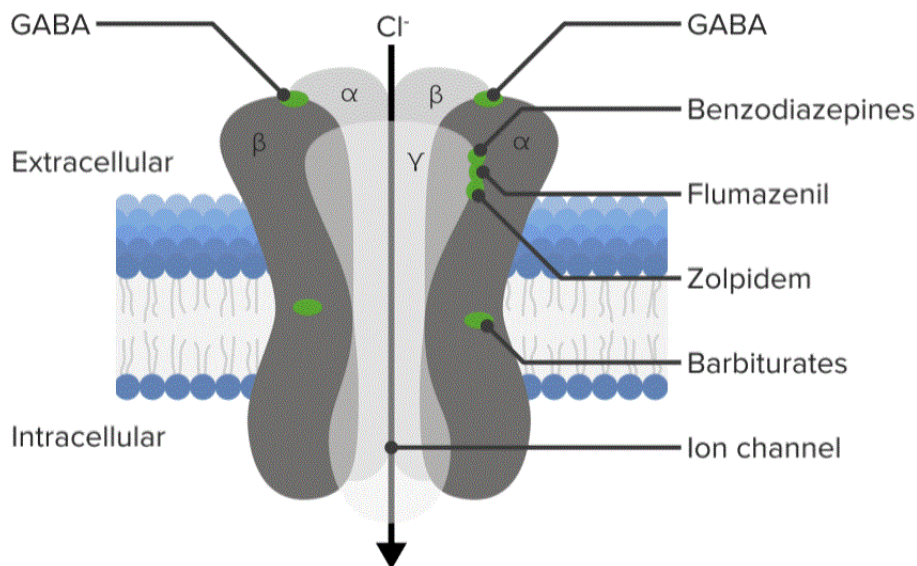
Benzodiazepines (BZD)

They bind to **α/γ interface** of GABA_A receptor - Cl⁻ Channel Complex. They increase the **frequency of opening** of GABA_A: BZD receptor-Cl⁻ Channels. They also enhance the binding of GABA with GABA_A receptor. They **don't have the GABA mimetic action**. They have a higher therapeutic index. Even after 20 times higher hypnotic doses, respiration will not be depressed and death won't occur.

They decrease BP. Diazepam and Lorazepam decrease cardiac output, while Midazolam decreases peripheral resistance. **Rebound phenomenon** is less marked.

Benzodiazepines is present in many regions of the brain:

- Cerebral cortex (confusion, amnesia)
- Thalamus (disinhibition, sedation, motor inhibition)
- Limbic structures (anxiolysis, sedation)



"Benzodiazepines. GABA receptor-chloride ion channel macromolecular complex" Image created by Lecturio

Pharmacodynamics

- Selective anxiolytic, sedative, muscle relaxant and **anticonvulsant action**.
- All BZD reduce the duration of REM except
- Clonazepam and diazepam have higher **muscle relaxant**
- **Anterograde amnesia** is observed.

Pharmacokinetics

- Redistribution is seen following administration.

- **Hepatic metabolism** is the main pathway of disposal.
- Metabolized into more active metabolites.

Adverse Effects

- Dizziness
- Vertigo
- Ataxia
- Disorientation
- Amnesia
- Impaired psychomotor skills

Drug abuse and Toxicity

- **Flunitrazepam** has been used in “**date rape**”; **chloral hydrate** is also used with alcohol for the **same purpose**.
- **Symptoms of benzodiazepine poisoning** are **similar to ethanol poisoning**, with tachycardia and dilated pupils.
- **Flumazenil** is the **antidote for acute benzodiazepine poisoning**. It binds at the same BZP site.

Pharmacology of Individual Drugs

Barbiturates

Phenobarbital

Mechanism of Action: Act at GABA_A: BZD receptor-Cl⁻ Channels. Furthermore, it has anti-glutamate and calcium ion entry reducing activity.

Clinical use: It has specific anticonvulsant action (used for **generalized tonic-clonic seizures**, simple partial and complex partial seizures and **status epilepticus, febrile seizures**), treatment of **congenital non-hemolytic anemia** and **kernicterus**.

Note: It has a half-life of 50-140 hr.

Adverse Effects: Behavioral abnormalities, learning and memory impairments, decreased intelligence, hyperactivity among children, mental confusion among geriatric persons, **rashes, megaloblastic anemia, and osteomalacia**.

Interactions: Being an enzyme inducer, it reduces the effect of many drugs.

Contraindications: Acute intermittent porphyria, **liver and kidney diseases**, obstructive sleep apnea, and pulmonary insufficiency.

Secobarbital

Mechanism of Action: Act at GABA_A: BZD receptor-Cl⁻ Channels

Clinical use: Used for the treatment of insomnia, and for preoperative sedation.

Adverse Effects: Impairs driving skills. Multiple doses produce cumulative effects.

Interactions: Similar to other barbiturates.

Contraindications: Similar to other barbiturates.

Thiopentone

Mechanism of Action: Act at GABA_A: BZD receptor-Cl⁻ Channels

Clinical use: Used as anesthesia because of its rapid action (for induction); however, it has been largely replaced by propofol in medical practice. It can be used for the treatment of refractive cases of **status epilepticus**. It is also used for the treatment of elevated intracranial pressure.

Adverse Effects: Extravasation of the drug from i.v. route can cause intense pain, necrosis, and gangrene of the limb. It produces poor analgesia, significant nausea, very little muscle relaxation, and **laryngospasm**.

Interactions: It should not be mixed with succinylcholine in single syringe, alcohol and CNS depressants, antihypertensive, other barbiturate anesthetics, and ketamine.

Contraindications: Same as other barbiturates.

Benzodiazepines

Flurazepam

Mechanism of Action: Increase the **frequency** of opening of GABA_A: BZD receptor-Cl⁻ Channels

Clinical Use: Useful for patients with frequent nocturnal awakening, generalized anxiety disorders, panic attacks, and the night before surgery.

No rebound insomnia after discontinuation.

Adverse Effects: Paradoxical stimulation, irritability, and sweating. Other adverse effects are dizziness, vertigo, disorientation, amnesia, ataxia, and impaired psychomotor skills.

Interactions: Alcohol and other CNS depressants, sodium valproate, cimetidine, isoniazid, oral contraceptives.

Contraindications: Hypersensitivity and pregnancy. Other contraindications are same as other BZDs.

Alprazolam

Mechanism of Action: Increase the **frequency** of opening of GABA_A: BZD receptor-Cl⁻ Channels

Clinical Use: It is a drug of choice for treatment of **panic disorders and agoraphobia**. It is mainly used as **anxiolytic**, but can be used as nighttime hypnotic.

Adverse Effects: Marked withdrawal syndrome after discontinuation. It is more toxic on overdose compared to other BZDs.

Contraindications: Hypersensitivity and pregnancy. Other contraindications are the same as other BZDs.

Triazolam

Mechanism of Action: Increase the **frequency** of opening of GABA_A: BZD receptor-Cl⁻ Channels

It has a rapid onset of action with peak effect in less than 1 hour.

Clinical uses: Good for inducing sleep, but poor for maintaining it.

Adverse Effects: Tolerance and withdrawal syndrome are common (rebound insomnia). Paranoia, psychiatric disorders

Contraindications: Hypersensitivity and pregnancy. Other contraindications are the same as other BZDs.

Lorazepam

Mechanism of Action: Increase the **frequency** of opening of GABA_A: BZD receptor-Cl⁻ Channels

Clinical uses: Second-line choice for treatment of **status epilepticus**. Useful for preventing convulsions (delirium tremens) in alcohol withdrawal, **cocaine toxicity**, and amphetamine overdose. It is also useful before initiating chemotherapy for **cancer** to prevent anxiety.

Other important points:

- It is the only BZD which is recommended for intramuscular use.
- It shows about 90% plasma protein binding.
- It has fewer drug interactions.
- Preferred in **hepatic impairment**.

Diazepam

- It shows about **99% plasma protein binding**.
- It is a potent muscle relaxant. Useful for treatment of tetanus and spinal injuries.
- It can dilate coronary arteries when given intravenously
- Acts as a good analgesic if given intravenously
- Likely to cause rebound insomnia.

Atypical Hypnotics

Zopiclone

Eszopiclone is the enantiomer of Zopiclone.

Mechanism of Action: They act on the same receptor as BZDs. The effect is similar to BZDs but it does not alter REM sleep.

Clinical Uses: They don't have anticonvulsive activity. They can be used for short term treatment of insomnia.

Adverse Effects: Metallic taste, impaired judgment, dry mouth, psychological disturbances

Contraindications: Respiratory insufficiency, sleep apnea, hepatic dysfunction

Zaleplon

- Shortest acting
- Do not prolong sleep
- **Mechanism of Action:** It acts on the same receptor as BZDs
- **Clinical uses:** short-term treatment for insomnia
- Don't have anticonvulsive effect.
- **Interactions:** Alcohol and other CNS depressants

Zolpidem

- **Mechanism of Action:** It acts on the same receptor as BZDs
- **Clinical uses:**
 - Shortens sleep latency
 - Sleep duration is not prolonged
 - No anticonvulsant, anxiolytic and muscle relaxant effect
 - No effect on sleep pattern
 - Minimal daytime sedation
 - No rebound insomnia
 - No tolerance, dependence and low abuse potential
- **Adverse Effects:** Dependence liability.
- **Interactions:** Alcohol and other CNS depressants.

Chloral Hydrate

No longer used.

Buspirone

Mechanism of Action: Partial agonist at brain **5-HT_{1A} Receptors** with some affinity to Dopamine D₂ receptor.

Clinical use

- **Generalized anxiety disorder.**
- Selective anxiolytic with no sedative, hypnotic, muscle relaxant activity. It has a **slow onset** of action (10 days).
- Withdrawal doesn't produce rebound anxiety.
- Unsuitable for acute anxiety because it takes about a week to show effect.

Adverse Effects: Tachycardia, palpitation, chest pain, nervousness, tinnitus, dizziness, GI distress, paresthesia, and pupillary constriction

Contraindications: Hypersensitive

Interactions: CYP3A4 inducers and inhibitors

Ramelteon

Mechanism of Action: Agonist at **MT₁ and MT₂ melatonin receptors** at **suprachiasmatic nucleus** in brain.

Clinical use

- For regularizing sleep-wake cycle
- Decreases the time required for falling asleep

Note: No rebound insomnia/ withdrawal syndrome with use of ramelteon

Adverse Effects: Dizziness, somnolence, fatigue, decrease in testosterone and prolactin

Interactions: Alcohol and fluvoxamine

Contraindications: Hypersensitivity

Tasimelteon

Mechanism of Action:

- It is a melatonin receptor (MT₁ & MT₂) agonist.
- More affinity for MT₂
- No withdrawal syndrome, abuse potential or physical dependence observed.

Clinical use: It is used in the treatment of **Non-24-Hour Sleep-Wake Disorder (Non-24)**.

Adverse Effects: Headache, nightmares, upper respiratory or urinary tract infections

Interactions: Fluvoxamine, rifampicin

Contraindications: **Hepatic impairment** and pregnancy.

Suvorexant

Mechanism of Action: Antagonist at orexin receptors

Clinical uses: Useful in sleep onset difficulty and/ or maintenance.

Adverse Effects: Daytime impairment, behavioral changes, sleep paralysis, hallucinations, cataplexy.

Contraindications: Narcolepsy

Interactions: Alcohol

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Correct answers: 1D; 2A; 3C

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