Sedatives and Hypnotics

Sedatives

The agents that lower tension and excitement and produce a state of drowsiness are called Sedatives.

Hypnotics

The agents that produce normal sleep and act as anesthetic at high doses are called Hypnotics.

A hypnotic drug should produce drowsiness and encourage the onset and maintenance of a state of sleep that as far as possible resembles the natural sleep state.

A sedative can become a hypnotic if it is given in large enough doses →dose dependent

Progressive dose related effects

Sedation ——›Hypnosis ——›Anesthesia ——›Coma ——›Stupor (a state of near-unconsciousness or insensibility) ——›Death.

Types of sleep disorder

According to the Sleep Disorder Classification Committee (1979), there are 4 major categories of sleep disorders:

1. Insomnias:

Not enough sleep or sleep of poor quality. Problems of falling asleep (initial insomnias) or staying asleep (maintenance insomnias), or waking too early, by far the most common sleep disturbances.

2. Hypersomnia's:

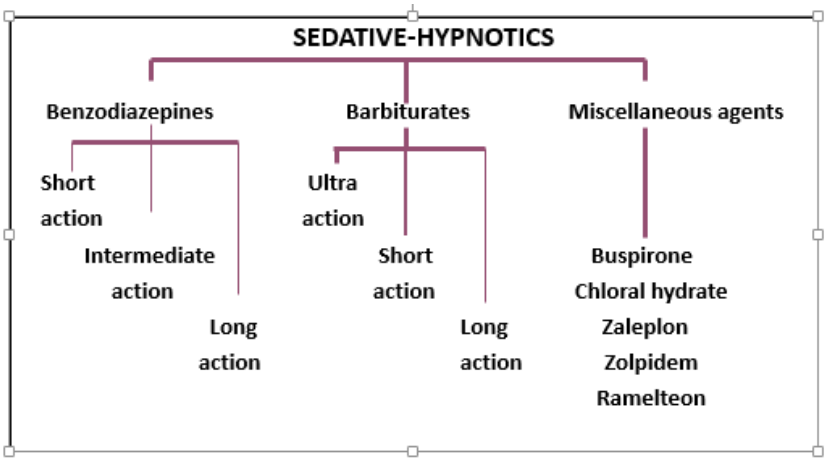
Sleeping for excessive lengths of time.

3. Parasomnias:

An abnormal event that occurs during sleep (e.g. Nightmares, night terrors)

4. Disorders of sleep-wake schedule.

Sedative and Hypnotic drugs are as follows:



GABA System:

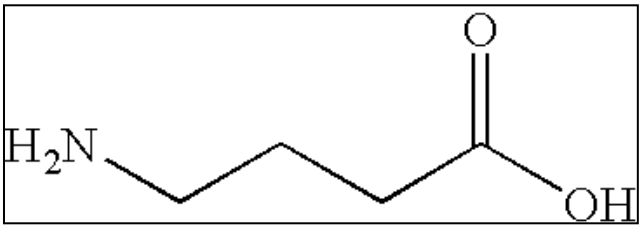
Major inhibitory neurotransmitter in the brain.

Discovered in 1950

About 20% of CNC neurons are GABAergic.

It has specific receptors in chloride channels present on the membrane of post synaptic neurons.

→ Regulates the entrance of chloride into the postsynaptic cells.



GABA receptor:

Two types of GABA receptors.

1. $GABA_A$ receptor → Postsynaptic neuron
2. $GABA_B$ receptor → Both presynaptic and postsynaptic

Site of action of GABA is the $GABA_A$ receptor

Structure of $GABA_A$ receptor

- ✓ Pentameric structure
- ✓ Consists of 5 subunits

  2 α_1 subunits

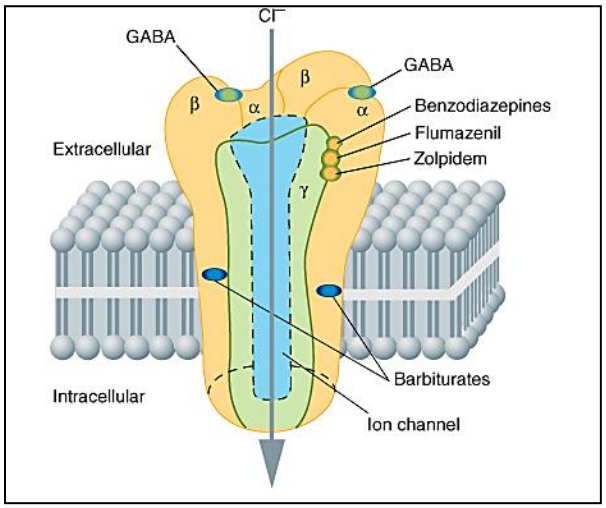
2 β_2 subunits

1 γ_2 subunit

GABA binding site: located between α_1 and β_2 subunits.

Benzodiazepine binding site: located between α_1 and γ_2 subunits

$GABA_A$ receptor is directly coupled to Cl^- channel, together are called $GABA_A$ receptor Cl^- ion channel macromolecular complex.

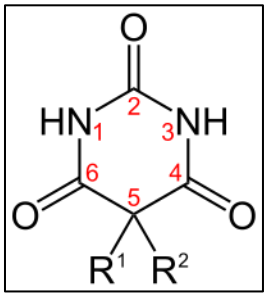


Barbiturates

Barbiturates were extensively used as sedative and hypnotic drugs. However, except for a few specialized uses, they have been largely replaced by the much safer benzodiazepines.

Chemistry

Barbiturates are the derivatives of barbituric acid which has no hypnotic activity. It becomes active when both the H- atoms at C_5 are replaced by either alkyl or aryl group. Barbiturates with oxygen at C_2 are known as oxybarbiturates or simply barbiturates. But barbiturates where O_2 at C_2 is replaced by S are known as thiobarbiturates. These compounds are more lipid soluble than the corresponding oxybarbiturates.



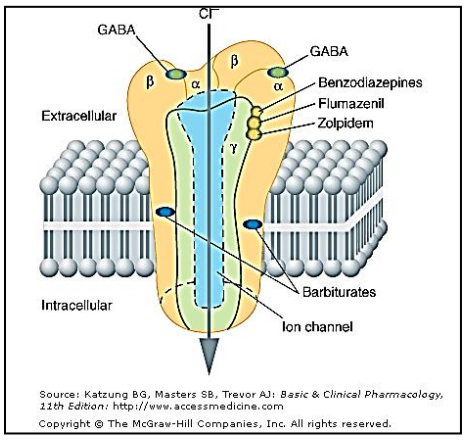
Classification

Barbiturates are classified by their **duration of action** into four groups.

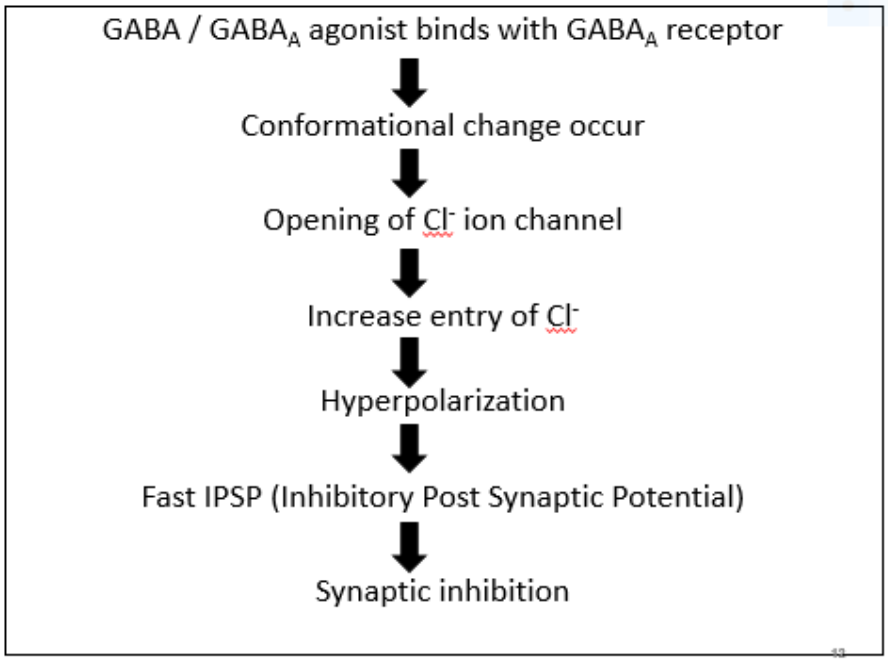
1. Long acting (8-12 hours) -Phenobarbitone
2. Intermediate acting (6-8 hours) -Amobarbital and butabarbital.
3. Short-acting (3-6 hours) - Secobarbital and pentobarbital.
4. Ultra-short acting (less than 1 hour) -Thiopental.

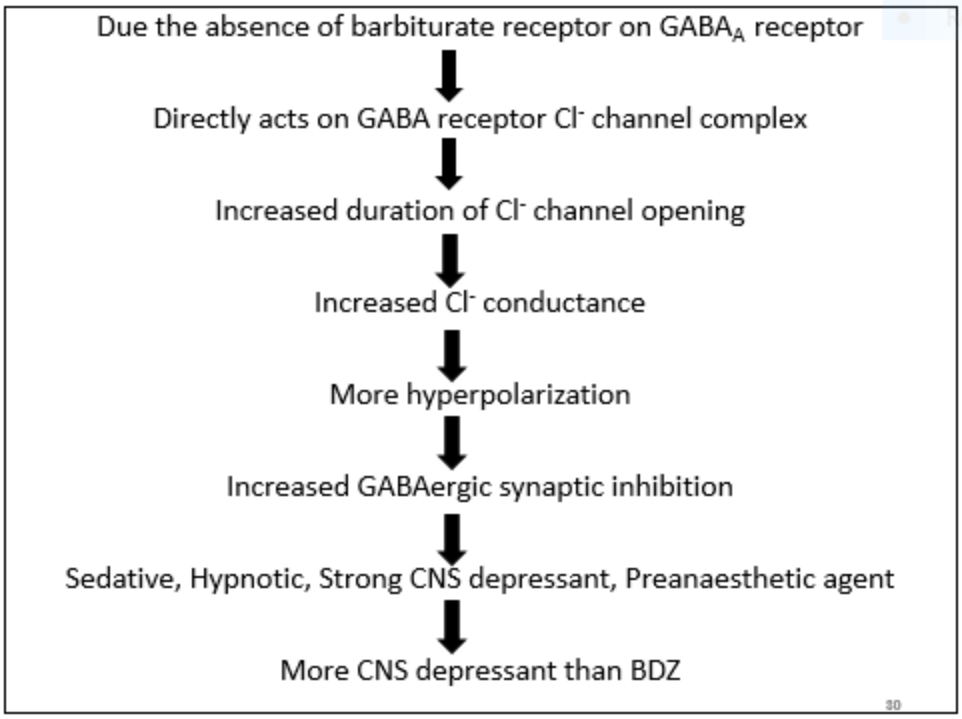
Mechanism of action:

Barbiturates act throughout the CNS. The mesencephalic **(regulating wakefulness and sleep-wake transitions)** reticular activity system is much more sensitive to these drugs. Barbiturates activate both presynaptic and post-synaptic inhibition that is mediated by GABA. Besides these, they have some GABA like action.



Function and effector M/C of $GABA_A$ receptor





Pharmacological action

Barbiturates reversibly depress the activity of all excitable tissues specially CNS. In hypnotic and sedative doses, it has little effects on cardiac and skeletal muscle.

1. **On CNS**

Barbiturates produce all degrees of depression from mild sedation to general anesthesia. Certain barbiturates such as Phenobarbitone have anti-convulsant activity. Oxybarbiturates are used to produce sleep. Thiopentone and Ultra-short acting barbiturates are used intravenously to produce surgical anesthesia.

2. **On respiration**

Barbiturates produce respiratory depression when taken in large or excessive doses. They depress both respiratory drive and mechanism responsible for the rhythmic character of respiratory movement. The neurogenic drive is much more sensitive to these drugs.

3. **On liver**

Barbiturates combine with cytochrome P_{450} and interfere with the biotransformation of a no. of substrate of this enzyme.

4. **On CVS**

In oral sedative and hypnotic doses, barbiturates do not produce any significant effects except slight decrease in BP and HR (Heart rate).

5. **On GIT**

Barbiturates decrease the gastrointestinal motility.

Untoward reaction

After effects

Drowsiness may last for few hours after a hypnotic dose.

Paradoxical excitement

In some geriatric and debilitated patient, Barbiturates may produce excitement rather than depression.

Hypersensitivity

Allergic reactions occur in persons who tend to have asthma, urticaria etc.

Drug interaction

Barbiturates combine with other CNS depressants to cause severe depression. Ethanol and antihistamine increase the CNS depressant effect with barbiturates.

Therapeutic uses

Barbiturates are used for-

- Sedation
- Hypnosis
- Anticonvulsant effect (e.g. Phenobarbitone)
- Anesthesia (e.g. Ultra-short acting barbiturates)

Benzodiazepines

Benzodiazepines (BDZs) are the most widely used hypnotic and anxiolytic drug.

Hypnotics

- Flurazepam
- Nitrazepam
- Flunitrazepam
- Temazepam
- Midazolam
- Triazolam

Antianxiety

- Diazepam
- Clonazepam
- Oxazepam

- Alprazolam
- Chlordiazepoxide.

Classification of Benzodiazepines

1. Long acting benzodiazepine → Duration of action is 1-3 days

E.g.: Diazepam

Nitrazepam

Flurazepam

Flunitrazepam

2. Intermediate acting → Duration of action is 10-20 hr

E.g.: Alprazolam

Lorazepam

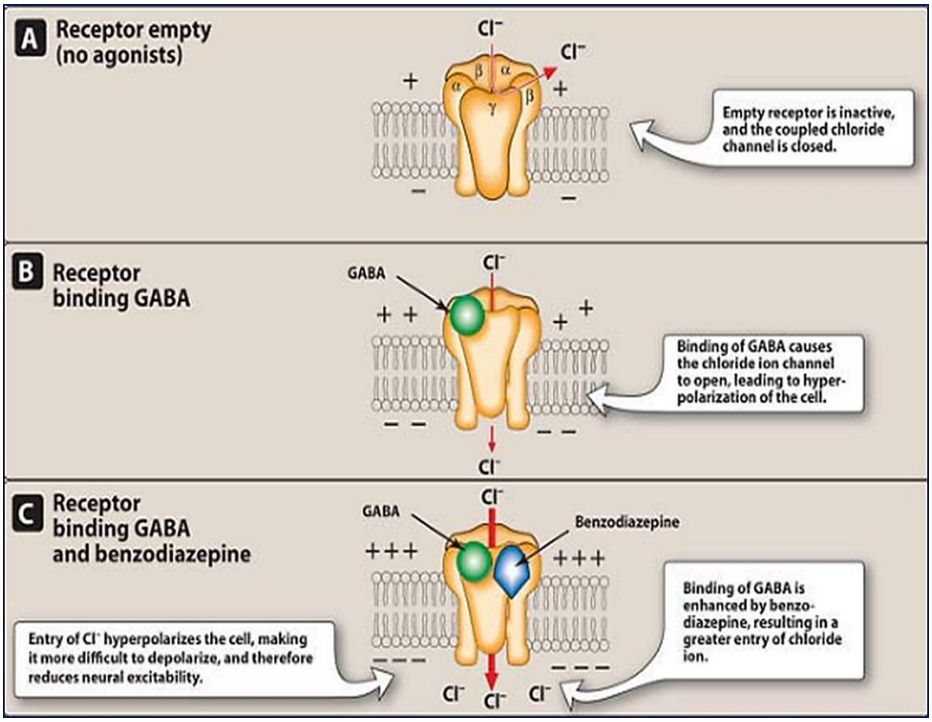
Temazepam

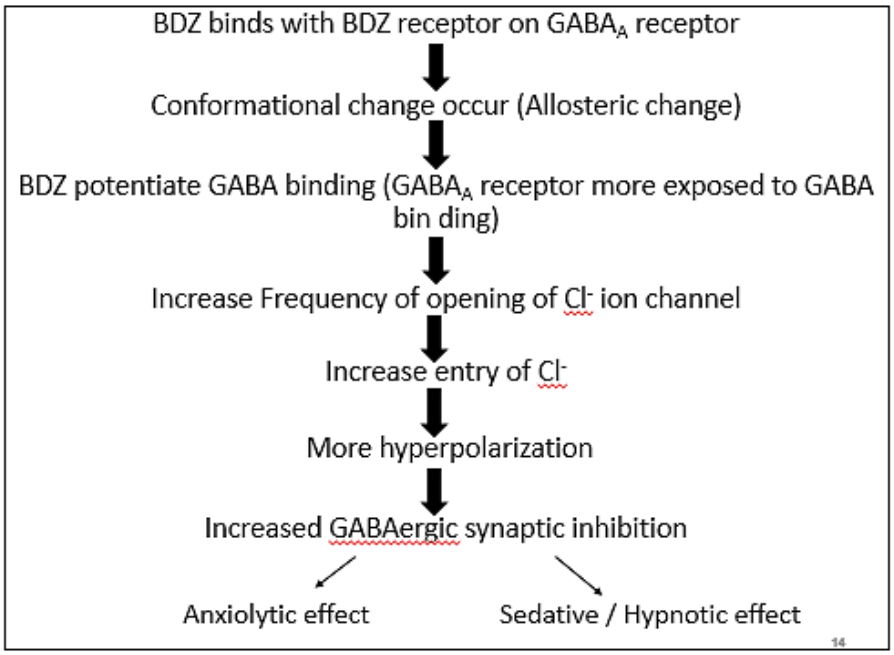
3. Short acting → Duration of action is 3-8 hr

E.g.: Oxazepam

Triazolam

Mechanism of action





Pharmacological action

1. **Sedative and hypnotic effect**: At low doses, BDZs act as sedative and anxiolytic. At high doses, BDZs produce hypnosis.
2. **Anticonvulsant effects**: BDZs have anticonvulsant effects and they may be used against epilepsy and other seizure disorders.
3. **Muscle relaxants**: As muscle relaxant, Clonazepam is popular.
4. **On CVS**: the CVS effects of BDZs are minor.
5. **On GIT**: BDZs can produce relief of GI disorders. They also inhibit nocturnal HCl secretion in peptic ulcer patient.
6. **On respiration**: The effects of BDZs on respiration are mild and insignificant. However, BDZ and alcohol taken together causes serious respiratory depression.

Therapeutic uses

BDZs are used in-

- Insomnia,
- Muscle rigidity,
- Seizure,
- Preanesthesia.

Dependence

Psychological and physical dependence on BDZs can develop if high doses of drug are given over a prolonged period.

Precautions

BDZs can be used carefully in patients with liver disease. They potentiate alcohol and other CNS depressants**.**