# Sedatives-Anxiolytics-Hypnotics-Drugs

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**Sedative drug:**

A drug which produces a calming effect and reduces anxiety, excitement without inducing sleep or affecting the motor or mental functions. Sedation is a minimum degree of CNS depression.

**Hypnotic drug:**

A drug which produces drowsiness and facilitates onset and maintenance of sleep which resembles the natural sleep (patient can easily aroused). Hypnosis is a higher degree of CNS depression than sedation.

Sedative-hypnotics produce dose-dependent CNS depression, i.e. increasing the dose leads to a higher degree of CNS depression.

# Neurobiology of Anxiety Disorders

**-CNS equilibrium is determined by a balance between excitatory and inhibitory neurotransmission**

**Excitation - Glutamate**

**Inhibition - GABA**

**-Inhibition via GABA is primarily mediated by the ionotropic GABA-A receptor.**

**GABA binding to GABA-A results in an increase in neuronal $Cl^-$ conductance and subsequent neuronal hyperpolarization.**

# SEDATIVE-HYPNOTIC DRUGS

| 1Benzodiazepins | 2-Barbiturates | 3-Miscellaneous agents |
|---|---|---|
| Short acting | Ultra action | Zolpidem Zaleplon Chloralhydrate Buspirone |
| Intermediate acting | Short acting | |
| Long acting | Intermediate acting | |
| | Long acting | |

# 1-Benzodiazepines:

## Classification of benzodiazepines:

### short acting benzodiazepines:

Triazolam and midazolam. They have short $t_{½}$ (2-4 hours) and metabolized to active metabolites which have shorter $t_{½}$ (1-1.5 hours).

### Intermediate-acting benzodiazepines:

Oxazepam, temazepam, lorazepam and alprazolam. They have longer $t_{½}$ (5-20 hours) and can be used once daily. They have no active metabolites except alprazolam.

## Long-acting benzodiazepines:

**Diazepam, clonazepam, flurazepam and nitrazepam. They have long $t_{½}$ (about 60 hours). They have active metabolites except nitrazepam.**

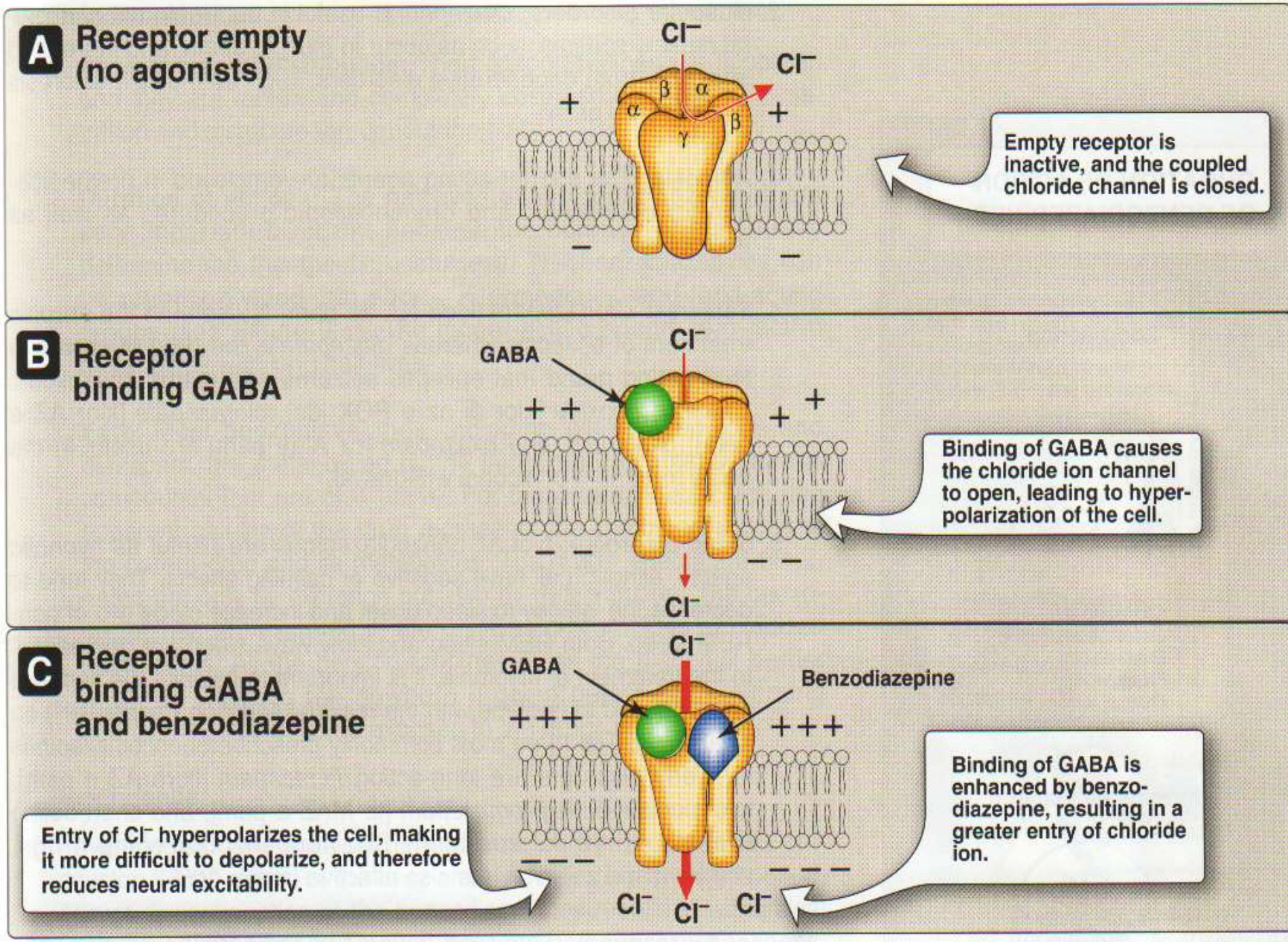
# Benzodiazepines –Mechanism of action

**-Benzodiazepines act very selectively on $GABA_A$-receptors, which mediate the fast inhibitory synaptic response produced by activity in GABA-ergic neurons.**

**-The effect of benzodiazepines is to enhance the response to GABA, by facilitating the opening of GABA-activated chloride channels**

-Entry of Cl ion hyperpolarize the cell, making it more difficult to depolarize, so neuronal excitability is reduced.

-Benzodiazepines bind specifically to a regulatory site on the receptor, distinct from the GABA binding site, and enhanced receptor affinity for GABA.


A
Receptor empty (no agonists)
Cl⁻
Cl⁻
β
α
α
β
γ
+
+
−
−
Empty receptor is inactive, and the coupled chloride channel is closed.
B
Receptor binding GABA
GABA
Cl⁻
+ +
+ +
− −
− −
Cl⁻
Binding of GABA causes the chloride ion channel to open, leading to hyper-polarization of the cell.
C
Receptor binding GABA and benzodiazepine
Cl⁻
GABA
Benzodiazepine
+++
+++
− − −
− − −
Cl⁻
Cl⁻
Cl⁻
Entry of Cl⁻ hyperpolarizes the cell, making it more difficult to depolarize, and therefore reduces neural excitability.
Binding of GABA is enhanced by benzo-diazepine, resulting in a greater entry of chloride ion.

# Pharmacological actions:

Antianxiety (anxiolytic) action. All benzodiazepines are equally effective in reducing anxiety. This action is due to inhibition of the limibic system .It occurs with smaller dose than the sedative dose.

Sedative action. All benzodiazepines reduce aggression and excitement (taming effect).

Hypnotic action. Triazolam, temazepam and flurazepam are more specific.

Anticonvulsant (Antiepileptic) action by acting on the motor cortex.

Central skeletal muscle relaxant effect by inhibiting polysynaptic spinal reflexes

# Therapeutic uses:

-To relief anxiety. Any benzodiazepine can be used. **Alprazolam** has higher efficacy in anxiety associated with panic (phobic) disorders.

-As sedatives for excitement, aggression, violence. Any benzodiazepine can be used.

-As hypnotics in insomnia (triazolam for sleep induction, temazepam for sleep maintenance and flurazepam for awakening early in the morning).

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-**Anticonvulsants (Antiepileptics).** IV diazepam is used in status epilepticus, while clonazepam is used in other types of epilepsy.

-**Skeletal muscle spasm** and in alcohol withdrawal.

-**In anaesthesia** → IV diazepam for minor surgical procedures, and in preanaesthetic medication (midazolam is preferred because it has more rapid onset and can be used IV or IM).

## Advantages of benzodiazepines:

Wide safety margin (minor effect of respiratory and vasomotor centers).

Lower liability for drug abuse (less addictive).

No effect on hepatic microsomal enzymes and so fewer drug interactions than barbiturates.

No change in the normal sleep pattern (no depression of REM sleep).

No hangover effect which means that sedation and drowsiness persists in the next morning after taking the hypnotic dose at night.

Flumazenil is a specific antagonist at benzodiazepine receptor can be used in benzodiazepine overdose.

# PHARMACOKINETIC ASPECTS

-Well absorbed when given orally;

-They bind strongly to plasma protein, and their high lipid solubility cause many of them to accumulate gradually in body fat.

- Distribution volumes is big.

-Metabolic transformation in the microsomal drug-metabolizing enzyme systems of the liver, eventually excreted as glucuronide conjugates in the urine.

## Adverse effects:

**Sedation, drowsiness, confusion which reduce driving ability.**

**Anterograde amnesia which reduce learning ability.**

**Acquired tolerance after repeated use. This is due to down-regulation of benzodiazepine receptors.**

**Drug dependence (addiction) after prolonged use → sudden stopping can produce withdrawal symptoms (anxiety, insomnia, convulsions), so gradual withdrawal is recommended after chronic use with large doses.**

# Acute toxicity:

**Benzodiazepines in acute overdose are considerably less dangerous than other sedative-hypnotic drugs. Cause prolonged sleep,without serious depression of respiration or cardiovascular center.**

**effective antagonist, flumazenil reverses the CNS effects of benzodiazepines**

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# 2-Barbiturates:

**Long-acting:** Phenobarbital (phenobarbitone) has the least lipid-solubility, slow GI absorption, slow onset and long duration of action (6-8 hours).

**Intermediate-acting:** Amobarbital has moderate lipid-solubility, moderate GI absorption, moderate onset and moderate duration of action (4-6 hours).

**Short-acting:** Pentobarbital have high lipid-solubility, rapid GI absorption, rapid onset and short duration of action (2-4 hours).

**Ultrashort-acting:** Thiopental has very high lipid-solubility, very rapid onset (within 30 seconds) and very short duration of action (20-30 minutes).

## Mechanism of action:

**Barbiturates act on the reticular activating system (RAS) and the cortex.**

**Barbiturates share with benzodiazepines the ability to enhance the action of GABA, but they bind a different site on the GABA-receptor/chloride channel, and their action seems to prolong the duration of the opening of GABA-activated chloride channels.**

**At high concentrations, barbiturates can directly produce GABA effect on $Cl^-$ channels (GABA-mimetic action) leading to marked CNS depression.**

# Pharmacokinetics:

They are well absorbed from GIT and distributed, mainly concentrated in the brain.

Ultrashort-acting barbiturates (thiopental) are highly lipophilic and penetrate rapidly BBB and have rapid onset of action, while long-acting barbiturates (phenobarbital) are less lipophilic and have slower penetration through BBB and slow onset of action.

Barbiturates are redistributed from the brain to the peripheral tissues as skeletal muscles and adipose tissue.

They are metabolized by hepatic microsomal enzymes. They are hepatic microsomal enzyme inducers and increase rate of their own metabolism and metabolism of other drugs.

Metabolites are excreted in urine. Barbiturates are acidic and rate of excretion is increased in alkaline urine.

## Therapeutic uses:

**Ultrashort-acting barbiturates (thiopental) are used for IV anesthesia. They are used alone in minor surgical procedures and used for rapid induction of general anesthesia.**

**Barbiturates are not used now as sedative-hypnotics and are replaced by benodiazepines.**

Phenobarbital was used as an antiepileptic drug but not used now because other safer and more effective drugs are available.

Phenobarbital was used in neonatal hyperbilirubinemia (kernicterus). It is a hepatic microsomal enzyme inducer → increase bilirubin conjugation. It is not used now and replaced by light therapy.

## Disadvantages of barbiturates:

Narrow safety margin (overdoses lead to marked depression of respiratory and vasomotor centers).

High liability for drug abuse (more addictive) with marked withdrawal symptoms.

Powerful microsomal enzyme inducers leading to many drug interactions.

They alter normal sleeping pattern (depression of REM sleep and increase duration of NREM sleep). After discontinuation, there is rebound increase in REM sleep and nightmares.

Hangover effect occurs.

No specific antagonist in available. •

# Adverse effects

**After effect: hangover---dizzy, drowsiness, amnesia, impaired judgment, disorientation.**

**Tolerance: decreased responsiveness to a drug following repeated exposure because of down-regulation of receptors and induction of hepatic drug-metabolising enzymes.**

# Adverse effects

**-Dependence: including psychologic and physiologic dependence. Withdrawal symptoms: excitation, insomnia, tremor, anxiety, hallucinations and sometimes convulsions.**

**-Depressant effect on respiration: can cross the placental barrier during pregnancy and secrete in breast milk.**

**-Others: Skin eruptions and porphyria**

# Treatment of acute overdosage

**An overdose can result in coma, diminished reflexes, severe respiratory depression, hypotension leading to cardiovascular collapse, and renal failure.**

**Treatment :**

**(1) supporting respiration and circulation.**

**(2) alkalinizing the urine and promoting diuresis.**

**(3) Hemodialysis or peritoneal dialysis.**

# 3-Miscellaneous agents

## Zolpidem , Zaleplone , Zopiclone

They are short-acting non-benzodiazepine hypnotics that potentiate GABA by binding to $GABA_A$-receptors at the same location as benzodiazepines.

They have rapid onset (within 15 minutes) and short half-lives (2-3 hours).

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-They are used for **sleep induction** (to decrease sleep latency).

-They do not cause hangover effect and are **less addictive** than benzodiazepines.

- **Flumazenil** can also be used to treat overdose with these agents

## Buspirone

Selective anxiolytic drug (no sedative- hypnotic, no anticonvulsant, no muscle relaxant effects).

Acts as an agonist at central 5-$HT_{1A}$ receptors.

No drug dependence and no withdrawal symptoms after prolonged use.

No decrease in driving ability (no sedation, drowsiness).

It has slow onset of action (1-2 weeks), so it is not used in acute anxiety (with panic disorders). It is used for chronic anxiety.

## Chloral hydrate

(1) relatively safe hypnotic, inducing sleep in a half hour and lasting about 6h.

(2) used mainly in children and the elderly, and the patients when failed to other drug.

# Thank You