
بسم الله الرحمن الرحيم

ANXIOLYTIC/ SEDATIVE AND HYPNOTICS

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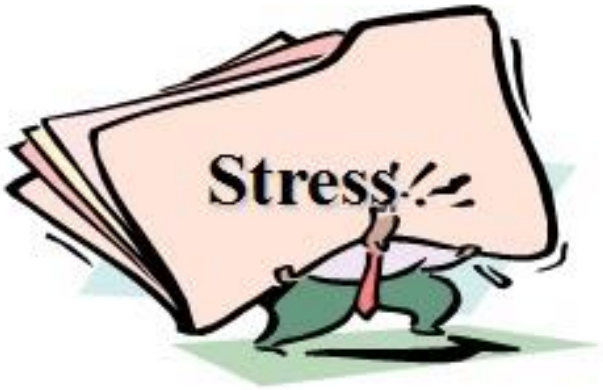


Restless

Worry

Frighten

servingnature

Learning objectives

- Introduction: What is Anxiolytic/ Sedative/ hypnotic
- Neurologic basis of anxiety and insomnia

  GABA RECEPTOR

- Classification of the drugs used as Anxiolytic/ Sedative/ hypnotic.
- Regarding **Prototype Drugs,** details of the following:
    - Chemistry,Pharmacokinetics
    - Mechanism of action
    - Pharmacologic effects
    - Therapeutic uses
    - Adverse effects / Drug interactions
    - Contraindications / Cautions
- Brief discussion of the other drugs

Introduction :

Disorders involving anxiety and sleep are the most common mental disturbances.

- Anxiety
- an unpleasant state of tension , apprehension, or uneasiness. It is a fear which arises from an unknown cause.
- Symptoms of anxiety –
- tachycardia, sweating, trembling, palpitations , apprehension, uneasiness, involve sympathetic activation.
- Anxiolytic or minor tranquillizers
- Anti-anxiety drugs also cause sedation –anxiolytic in low dose and hypnotic in high dose.

.

- The chronic debilitating anxiety(not minor anxiety) is treated with

Anxiolytics / some form of behavioral /psychological therapy

SEDATIVE / ANXIOLYTIC:

Sedative/Anxiolytic drug has a calming effect with minimal depression of motor mental functions. It reduces anxiety.

HYPNOTIC:

Hypnotic drug produces drowsiness and drug-induced sleep-like state.

So, Sedative-Hypnotics are the drugs that Reduce the Anxiety and cause induction of sleep

Neurological basis of anxiety

- Neuronal pathways related to amygdala
- Sensory systems, cortical processing, and memory are involved in interpreting a stimulus to be dangerous and creating a state of heightened arousal.

- Motor systems and autonomic processing participate in the exaggerated responses to an anxiety state.

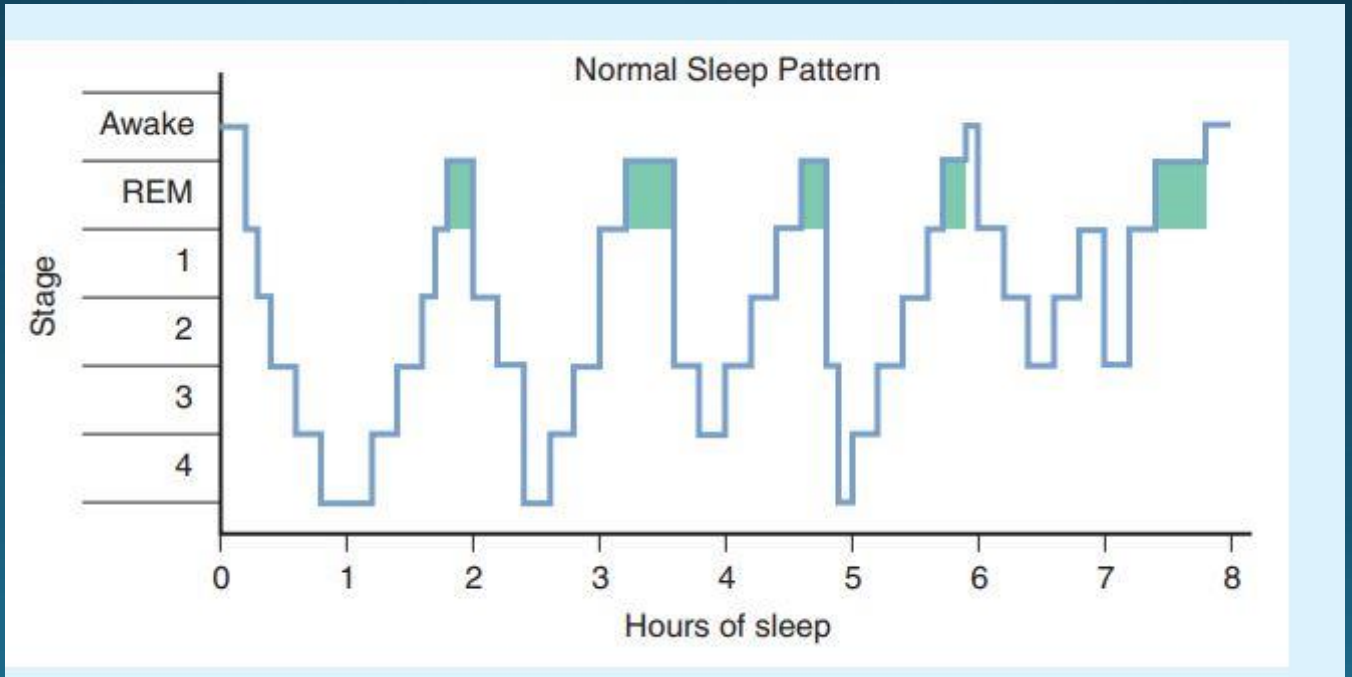
- Role of long term potentiation

Classification of anxiety disorders

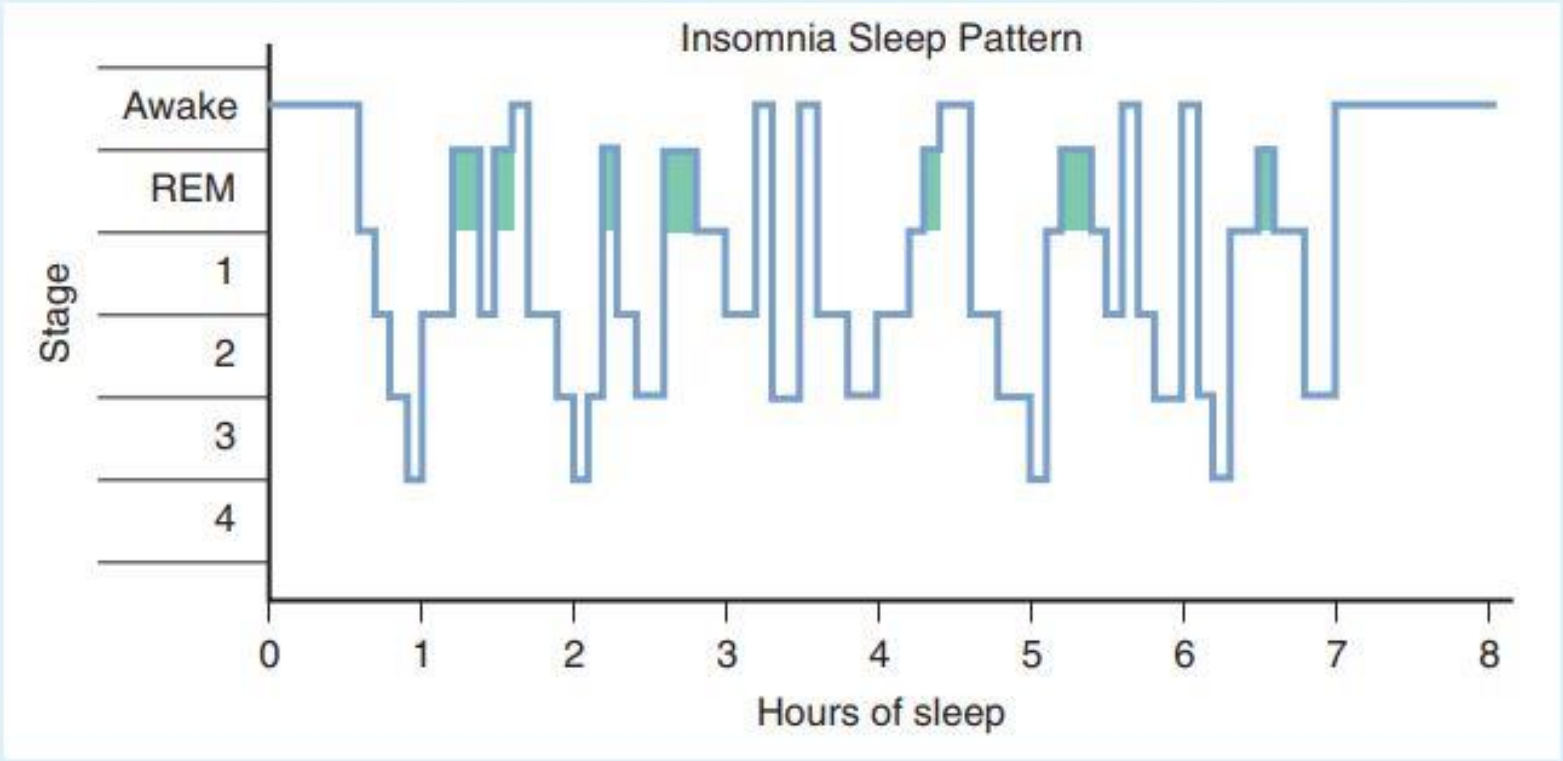
- Acute anxiety. (BZD)
- Panic disorder . (BZD /Antidepressants)
- Phobic disorders. (BZD/ Antidepressants/Propranolol)
- OCD (Antidepressants)
- GAD. (Antidepressants)
- Post traumatic stress disorder

Sleep Architecture

- Reversible state of reduced consciousness
- Changes in EEG
- REM &NREM sleep
- Involvement of forebrain nuclei &reticular formation



Insomnia


Insomnia Sleep Pattern
Awake
REM
1
2
3
4
Stage
0
1
2
3
4
5
6
7
8
Hours of sleep

CLASSIFICATION

CLASSIFICATION OF SEDATIVE-HYPNOTIC AND ANXIOLYTIC DRUGS

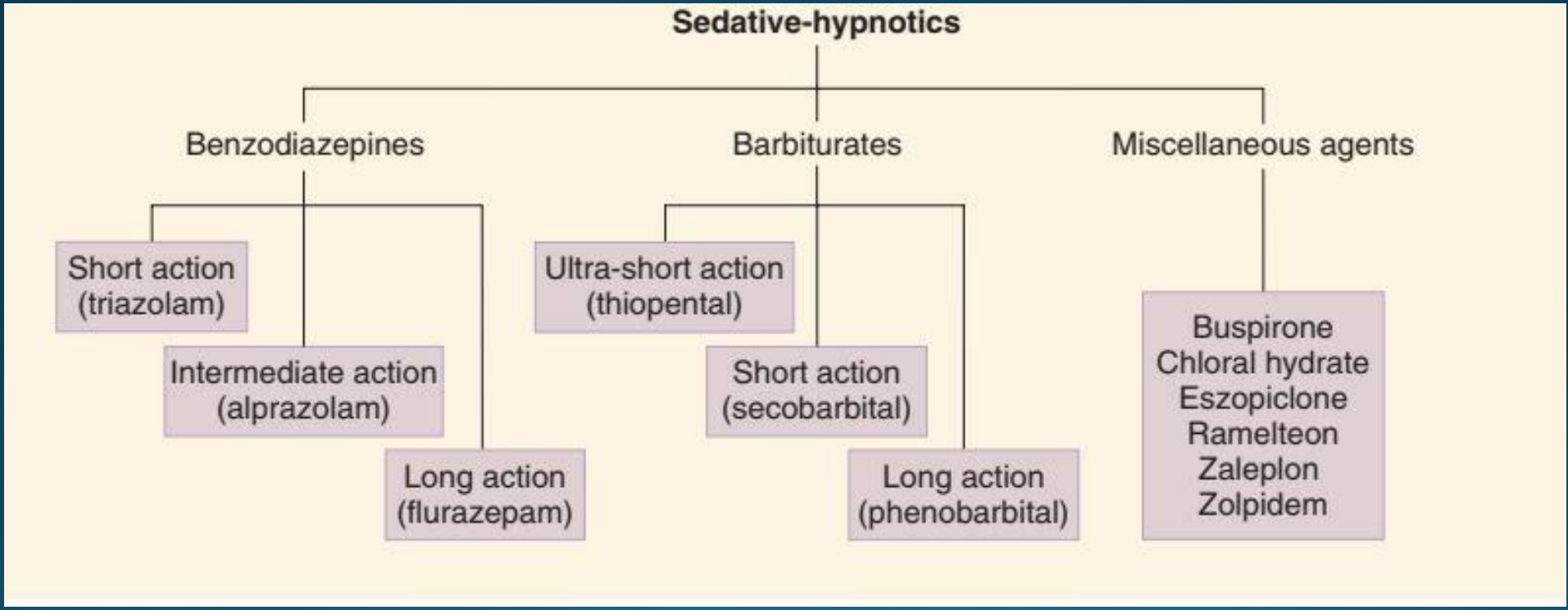
Benzodiazepines
- Alprazolam (XANAX)
- Chlordiazepoxide (LIBRIUM)
- Clonazepam (KLONOPIN)
- Diazepam (VALIUM)
- Lorazepam (ATIVAN)
- Midazolam (VERSED)
- Triazolam (HALCION)[a]
- Flumazenil (ROMAZICON)[b]

Barbiturates
- Amobarbital (AMYTAL)
- Pentobarbital (NEMBUTAL)
- Phenobarbital (LUMINAL)
- Thiopental (PENTOTHAL)

Antihistamines
- Diphenhydramine (BENADRYL)
- Doxepin (SILENOR)
- Hydroxyzine (ATARAX)

Other Sedative-Hypnotic Drugs
- Zolpidem (AMBIEN)
- Zaleplon (SONATA)
- Eszopiclone (LUNESTA)
- Ramelteon (ROZEREM)

Nonsedating Anxiolytic Drugs
- Buspirone (BUSPAR)
- Propranolol (INDERAL)


Sedative-hypnotics
Benzodiazepines
Barbiturates
Miscellaneous agents
Short action (triazolam)
Intermediate action (alprazolam)
Long action (flurazepam)
Ultra-short action (thiopental)
Short action (secobarbital)
Long action (phenobarbital)
Buspirone
Chloral hydrate
Eszopiclone
Ramelteon
Zaleplon
Zolpidem

Classification of Anxiolytics / Sedative Hypnotics

I. Benzodiazepines.According to DOA-- $t_{1/2}$

a. ***Long-Acting (20 to 100 hrs):*** Flurazepam, , Diazepam, Nitrazepam, Clonazepam, Chlorazepate

b. ***b .Intermediate-Acting(10 to 40 hrs):*** Oxazepam, Lorazepam, , Alprazolam, Chlordiazepoxide, Temazepam, Quazepam

c. ***Short-Acting (2 to 6 hrs):*** Midazolam, Triazolam

II. Barbiturates:According to DOA

a. ***Long-Acting*** ***(onset > 1 Hr; Duration < 12 Hr):*** Phenobarbital, Methyl-phenobarbital, Barbital, Metharbital

b. ***Intermediate-Acting*** ***(onset 1 Hr; Duration < 8 Hr):*** Amobarbital, Butabarbital, Secobarbital

c. ***Short-Acting*** ***onset 15 min; Duration < 6 Hr):*** Pentobarbital, Quinalbarbital, Cyclobarbital.

d. ***Ultra-Short Acting*** ***(onset 30 sec.; Duration 30 min):*** Thiopental, Thiamylal, Methohexital

III. Newer sedative- hypnotics/ anxiolytic Drugs:

- ***BZ_1-selective New Drugs :*** Zolpidem, Eszopiclone, Zaleplon
- **5 HT_{1A} Agonist: Buspiron,** Gepirone, Ipsapiron, Tandospirone
- **Melatonin Receptor (MT_1 & $MT_{2)}$ agonist:** Ramelteon
- **Orexin antagonist.** **Suvorexant**

IV. Miscellaneous sedative/ hypnotics:

- Chloral hydrate, Meprobamate, Paraldehyde, Ethanol
- Some antihistaminics: Promethazine, Hydroxyzine, Diphenhydramine,
- Some neuroleptics: Chlorpromazine, Triflupromazine,
- Opioids: Morphine, Pethidine.
- anti cholinergics,: Hyoscine
- Beta blocker: Propranolol

BZD and Barbiturates

Mechanism of action (Enhance GABA action)

- Typical sedative hypnotics depress CNS by neuronal membrane inhibition through their action on GABA Cl ion channel complex

- Drugs which bind to GABA receptor

(agonist)

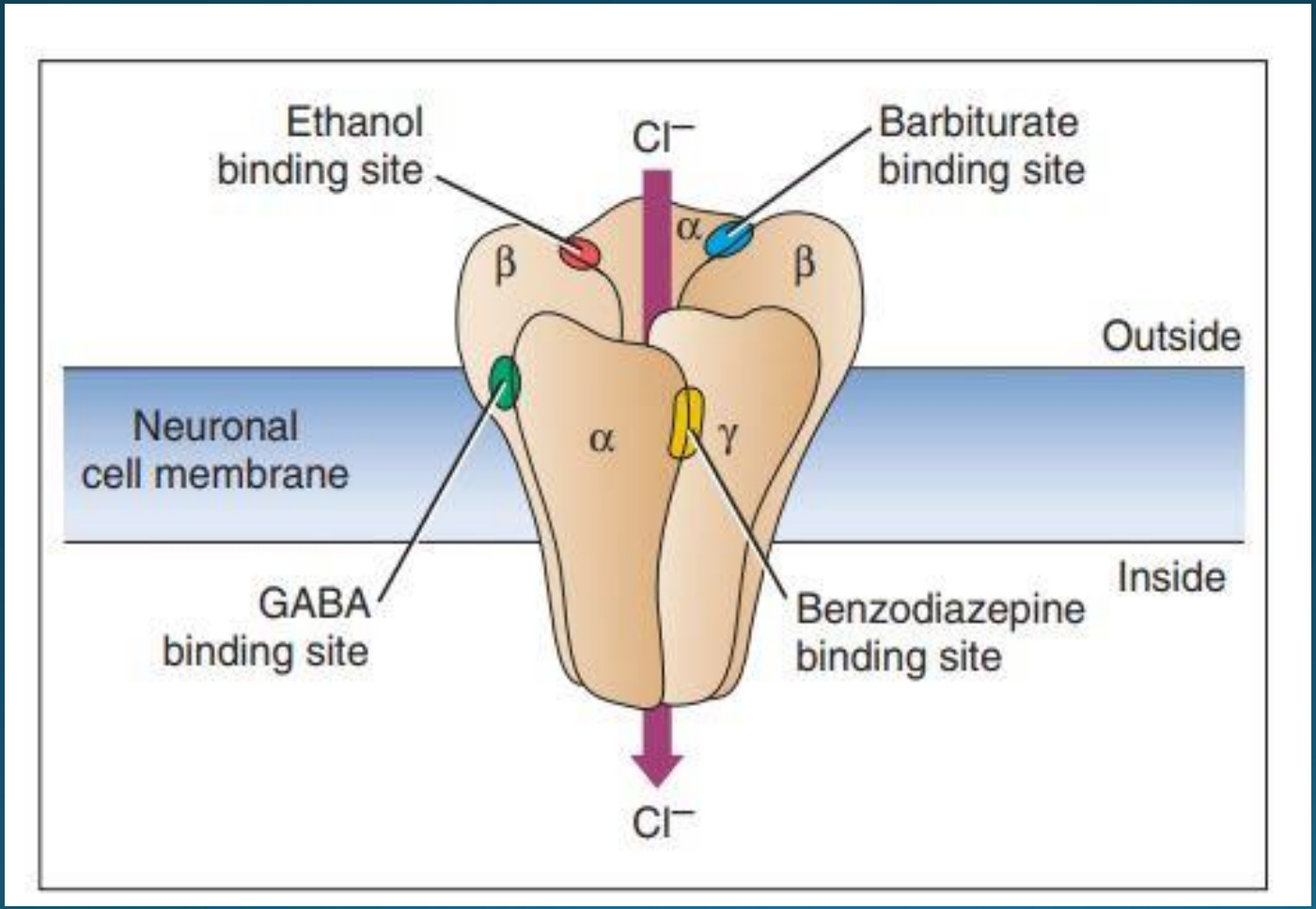
- BZD,Barbiturates, Z drugs
- Alcohol, anesthetics, steroids

Antagonist. *Flumazenil*

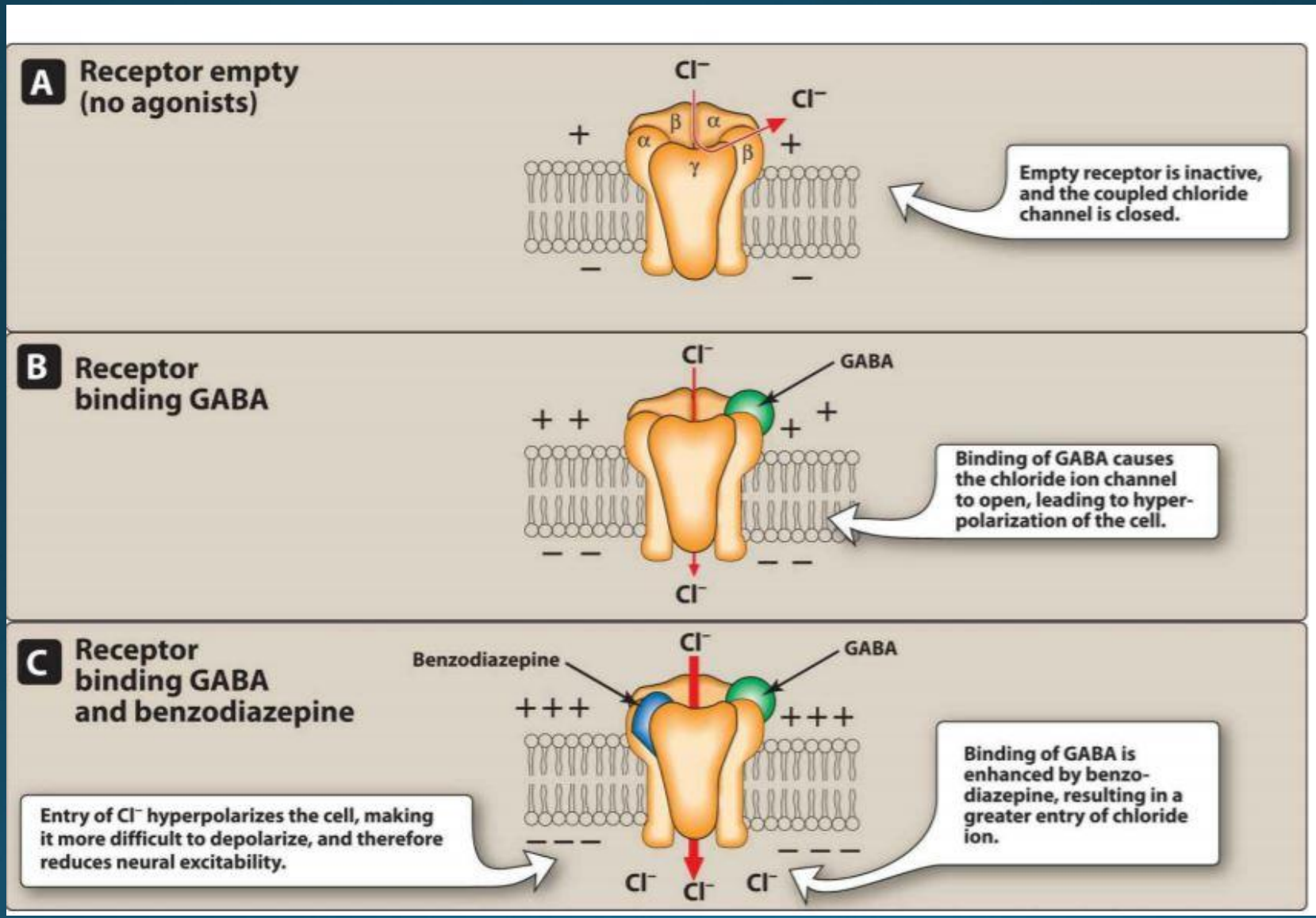
Inverse agonist. *B carbolines*

STRUCTURE OF GABA RECEPTOR

GABA-A, GABA B



GABA-A Cl ion channel complex


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

Drug binds to specific site at Receptors

Facilitate the GABA action

Opening of the chloride Channel

Influx of chloride ions

Hyper polarization

Decrease neuronal Excitability

Site of action

- Midbrain
- Ascending reticular formation
- Limbic System
- Cerebellum
- Medulla

MOA

BENZODIAZEPINES

- BZD increase the frequency of opening of GABA channel
- *GABAergic*
- BZD increase adenosine by inhibiting neuronal uptake
- Safe,Less toxic,less CNS depression
- *Antagonist..flumazenil*
- *No enzyme induction*

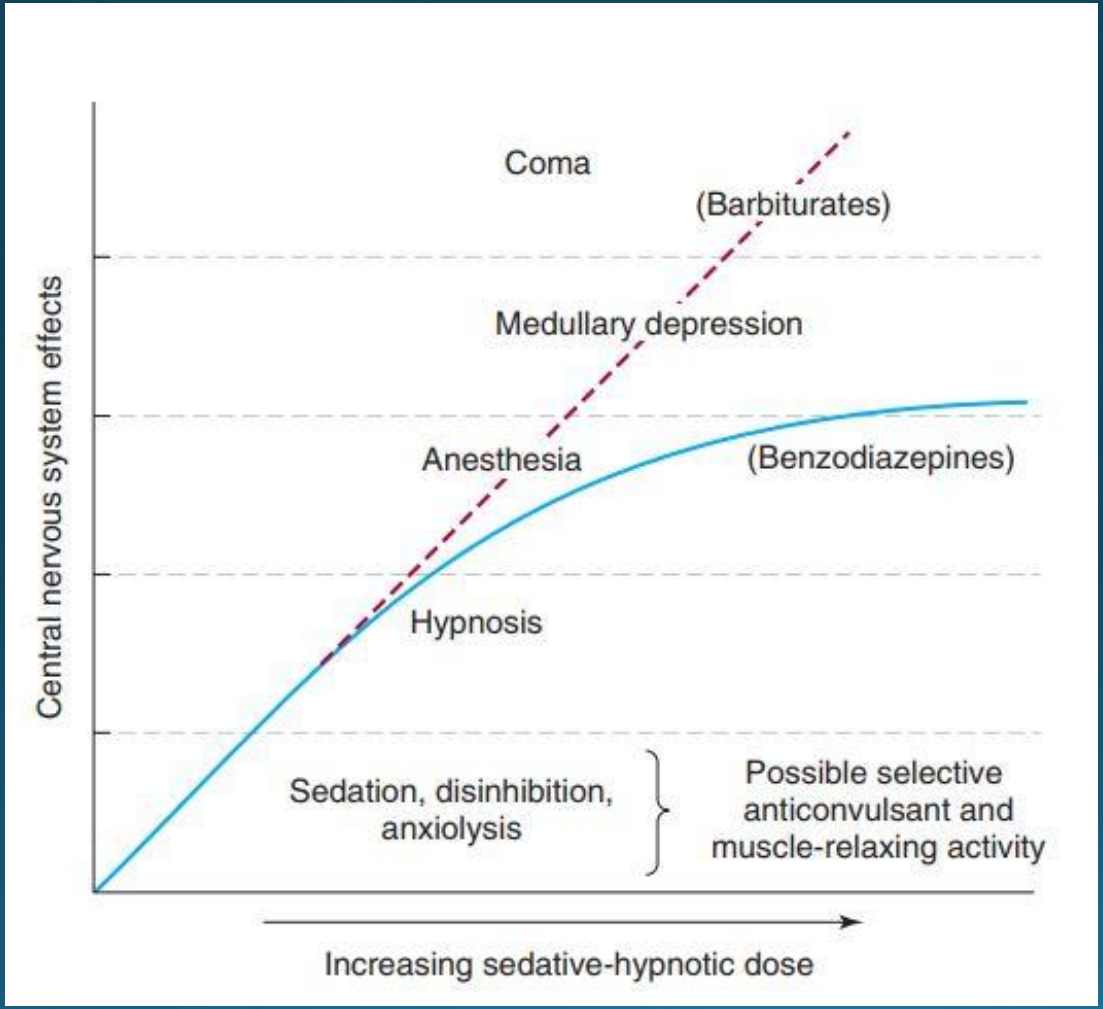
BARBITURATES

- Increase the duration of opening of GABA channel (independent of presence of GABA) *GABAmimetic*
- Inhibits glutamate and sodium channels at high dose
- *No antagonist*
- *Enzyme inducer*

Pharmacological Actions

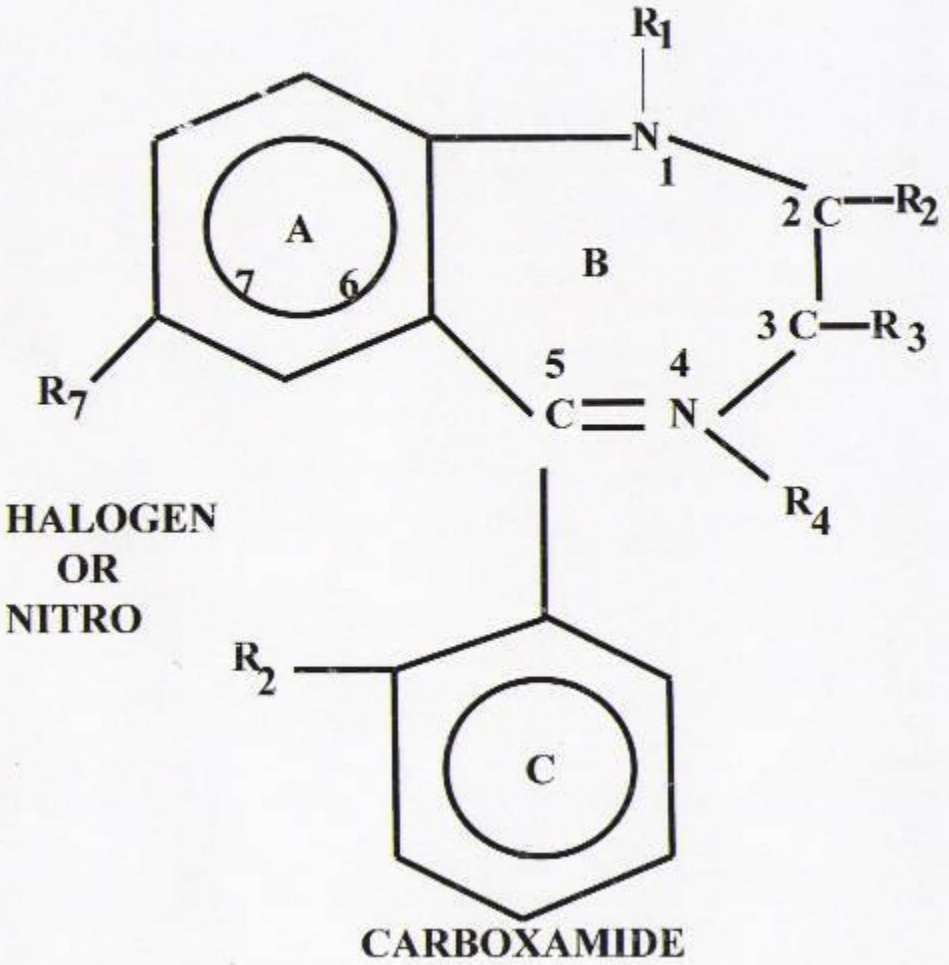
- *Sedation*
- *Hypnosis*
- *Anterograde amnesia (BZDs)*
- *Anticonvulsants*
- *Muscle relaxation*
- *Anaesthesia*

Dose-Response Curves for Sedative Hypnotics
A: Barbiturates----- B: Benzodiazepines



BENZODIAZEPINES (BZDs)

BENZODIAZEPINES: STRUCTURE



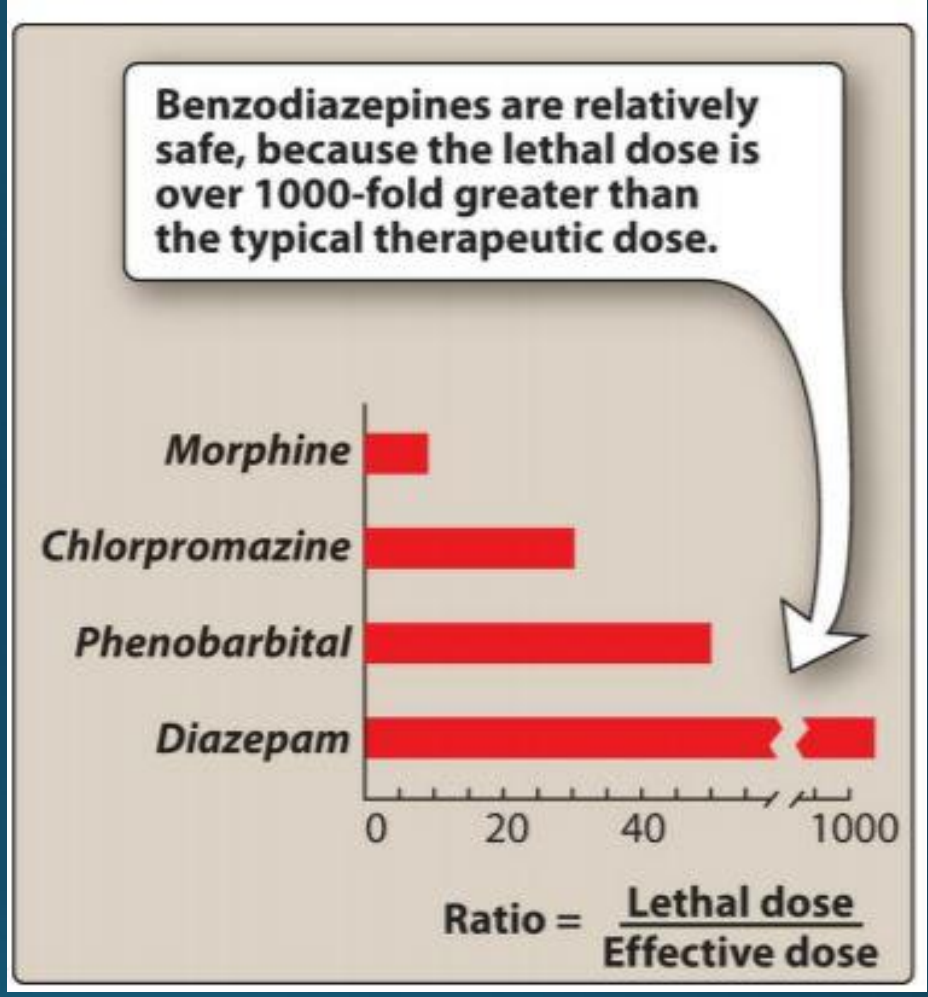
BENZODIAZEPINE'S (BZDs)

most commonly used sedative, anxiolytic & hypnotic drugs after Barbiturates.

Advantages / **Preference over Barbiturates**

- Higher Margin of Safety
- Selectivity of Action
- Lack of Drug Interactions
- Do not cause Hyperalgesia
- Less incidence of Dependence / Addiction
- Less Severe Withdrawal Syndrome

BZ have good safety margin compared to other sedative drugs.



PHARMACOKINETICS Of BZDs

- Rate of absorption from the gut differs according to many factors ,including lipid solubility.

So OOA related to lipid solubility.

- Most BZs easily cross the BBB and placental barrier.
- Also secreted in breast milk.
- $t_{1/2}$ of BZs are very important as duration of action determines the use.

Biotransformation:-

Clorazepate is a pro-drug , converted to active form -- Desmethyldiazepam by acid hydrolysis in the stomach

(non-enzymatically---Holfmann elimination)

- Most BZ are extensively metabolized by the hepatic microsomal enzymes
- Undergo phase-1 reactions specially by CYP 3A4 ---oxidation reactions--- Triazolam & **Lorazepam** conjugated to glucuronides--phase-2 reactions.

Metabolism of many drugs is affected by enzyme inducers & inhibitors. Also by age & liver disease.

PHARMACOKINETICS Of BZs ---

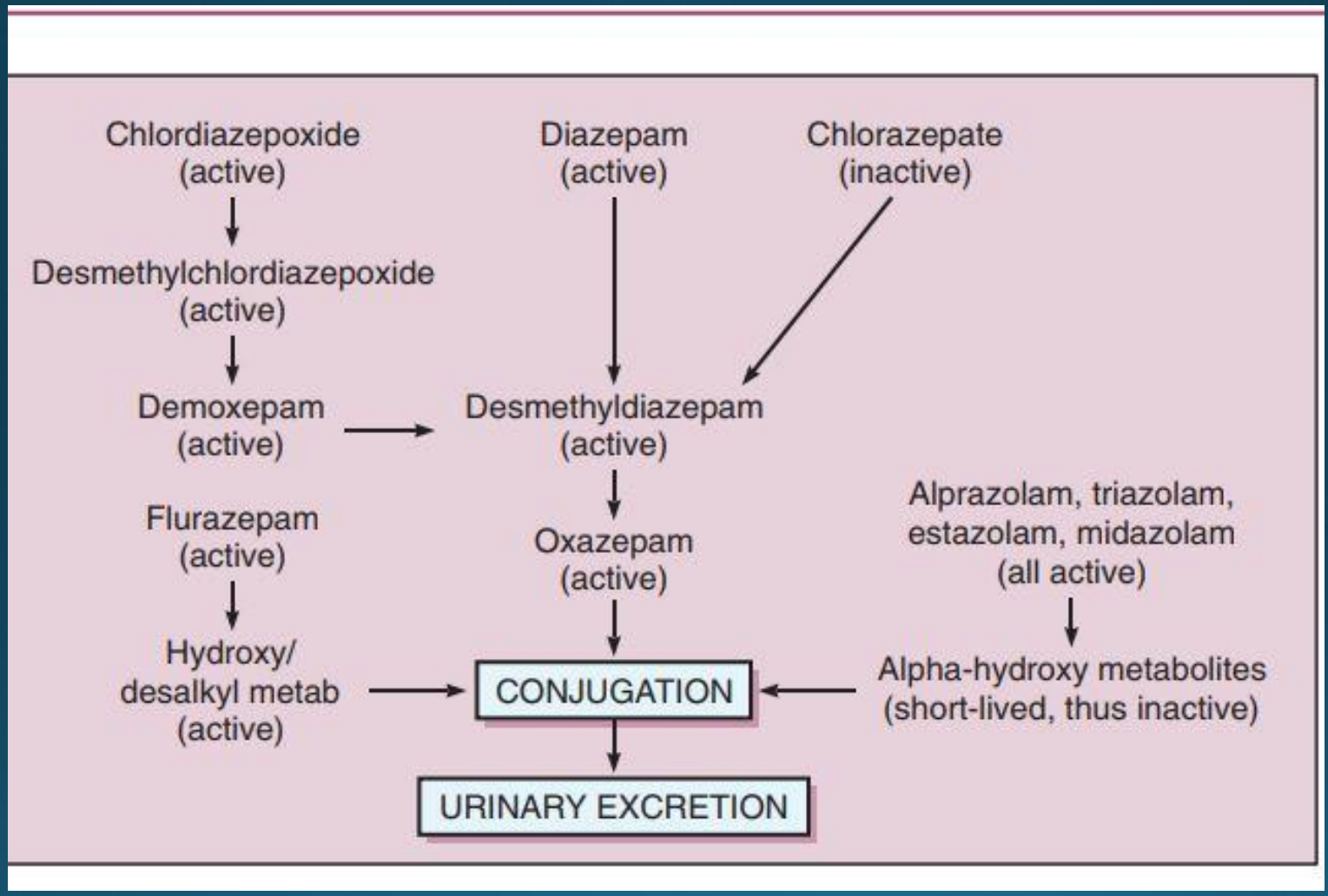
- The longer acting agents form active metabolites with long half-lives---

Chlordiazepoxide ,Diazepam ,Prazepam ,Clorazepate (prodrug) are converted to Desmethyldiazepam—half life is greater than 40 hours

- The apparent half-life therefore represents the combined actions of the parent drugs and its metabolites.

Excretion: BZs are excreted in the urine as glucuronide conjugates.

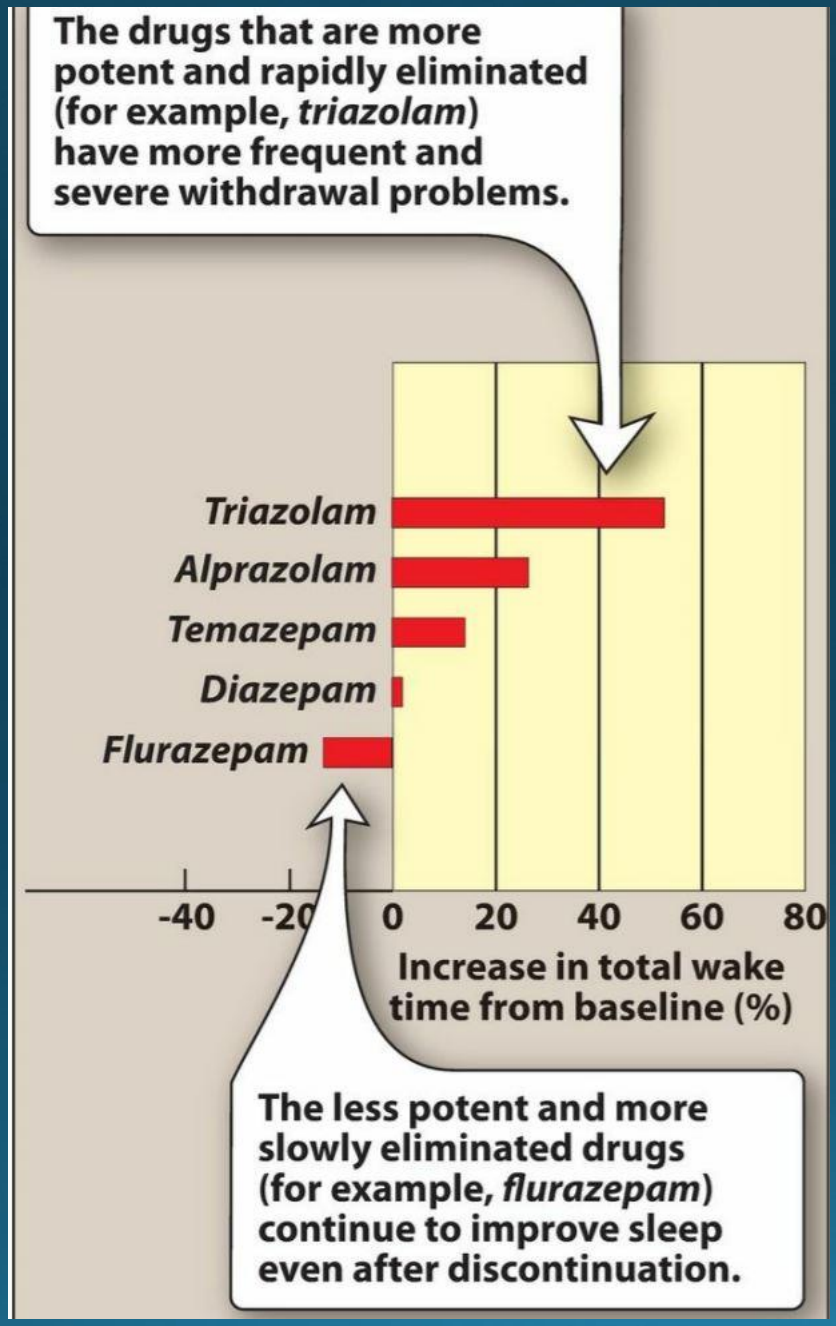
Biotransformation of Benzodiazepines



➢Phase 1 metabolism (oxidation, reduction, hydrolysis etc.) is reduced in the elderly and in patients taking drugs that inhibit hepatic metabolism or have liver disease.

TABLE 19-1 Pharmacokinetic Properties and Clinical Uses of Sed

DRUG	ONSET OF ACTION*	DURATION OF ACTION*	ACTIVE METABOLITES
Benzodiazepines			
Alprazolam	Fast	Medium	Yes
Chlordiazepoxide	Fast; very fast (IV)	Long	Yes
Clonazepam	Fast	Medium	No
Diazepam	Fast; very fast (IV)	Long	Yes
Estazolam	Fast	Medium	Yes
Flurazepam	Fast	Long	Yes
Lorazepam	Fast; very fast (IV)	Medium	No
Midazolam	Very fast (IV)	Short (IV)	Yes
Oxazepam	Fast	Short	No
Temazepam	Fast	Medium	No
Triazolam	Fast	Short	Yes
Barbiturates			
Amobarbital	Fast	Medium	No
Pentobarbital	Fast	Short	No
Phenobarbital	Slow	Long	No
Thiopental	Very fast (IV)	Short (IV)	No
Antihistamines			
Diphenhydramine	Fast	Medium	No
Hydroxyzine	Fast	Long	No
Other Sedative-Hypnotic Drugs			
Zolpidem	Fast	Short	No
Zaleplon	Fast	Very short	No
Eszopiclone	Fast	Short	No
Ramelteon	Slow	Short	Yes
Nonsedating Anxiolytic Drugs			
Buspirone	Very slow	Long	No
Propranolol	Fast	Medium	Yes


The drugs that are more potent and rapidly eliminated (for example, *triazolam*) have more frequent and severe withdrawal problems.
Triazolam
Alprazolam
Temazepam
Diazepam
Flurazepam
-40
-20
0
20
40
60
80
Increase in total wake time from baseline (%)
The less potent and more slowly eliminated drugs (for example, *flurazepam*) continue to improve sleep even after discontinuation.

GROUP ACTIONS OF BDZs-----

1.Decrease anxiety

pre-anesthetic medication & as adjuncts along with other drugs in GA.

- Relieve agoraphobia – fear of open spaces
- Relieve Neophobia – fear of new places, also other fears like fear of flying.
- Antidepressant– only Alprazolom relieves depression.

2.Anticonvulsant action: Inhibition of development & spread of epileptiform convulsions.

Clonazepam , Diazepam, Clobazam

3.Central muscle relaxation: At high doses decrease muscle spatisity by increasing pre-synaptic inhibition in the spinal cord. This effect is mediated by α_2 $GABA_A$

4.Effect on CVS:

- Normal doses –minimal effect

In higher doses/ CV disease--- decrease blood pressure , due to decreased Myocardial contractility & VMC depression & ganglion blockade. Circulatory collapse in toxic doses.

5. Effect on respiration: Dose related depression of respiration.

6. Tolerance & Dependence after prolonged use.

Both psychological & physical dependence, occurs.

Abrupt withdrawal may produce anxiety, insomnia, CNS exitability –may lead to convulsions.

THERAPEUTIC USES

- **Anxiety states:** To relieve symptoms of anxiety secondary to:

  panic attacks, generalized anxiety disorder (GAD), social anxiety disorder, performance anxiety, post traumatic stress disorder.

- Insomnia (Short/Long Acting)
- **Conscious sedation ,** Induction of General anesthesia
- Convulsions,Epilepsy (grand Mal,Status epilepticus, withdrawal, Local anes)
- Anti-emetic
- **For muscle relaxation in specific neuromuscular disorders**
- **Depression**
- Withdrawal states

STATE	RAPID EYE MOVEMENTS	PATTERN ON EEG	EFFECT OF BENZODIAZEPINES	EFFECT OF NEW AGENT
Awake	No	High-frequency, low-amplitude pattern	Induce sleep	Induces sleep
Stages 1 and 2 sleep	No	Lower-frequency, higher-amplitude pattern than awake state	Increase length of stages	Little change
Stages 3 and 4 sleep	No	Lower-frequency, higher-amplitude pattern than stages 1 and 2	Decrease length of stages	Little change
REM sleep	Yes	High-frequency, low-amplitude pattern	Decrease length of stage	Little change

ADVERSE EFFECTS

- Sedation– decreased alertness.
- Hang-over –persistent sedation next morning.
- Confusional states, specially in elderly.
- Ataxia at higher doses—avoid driving an automobile.
- Cognitive impairment (decreased long term recall & retention of new knowledge) can occur due to loss of memory – (Antero-grade amnesia).
- Tolerance & Dependence – after prolonged use.

  Both psychological & physical dependence, occurs.
- Abrupt withdrawal may produce anxiety, insomnia, CNs exitability – may lead to convulsions.
- Cross-tolerance exists between BZ and other CNS depressants. GIT upsets / epigastric distress
- Floppy Baby Syndrome

Drug Interactions

- BZ act in an additive manner with alcohol, barbiturates and anticonvulsants
- Smoking induces P450 enzyme which metabolizes BZ, therefore smokers need larger doses of the drug
- Selective Serotonin Reuptake Inhibitors(SSRIs) increase diazepam levels by altering clearance.

FLUMAZENIL

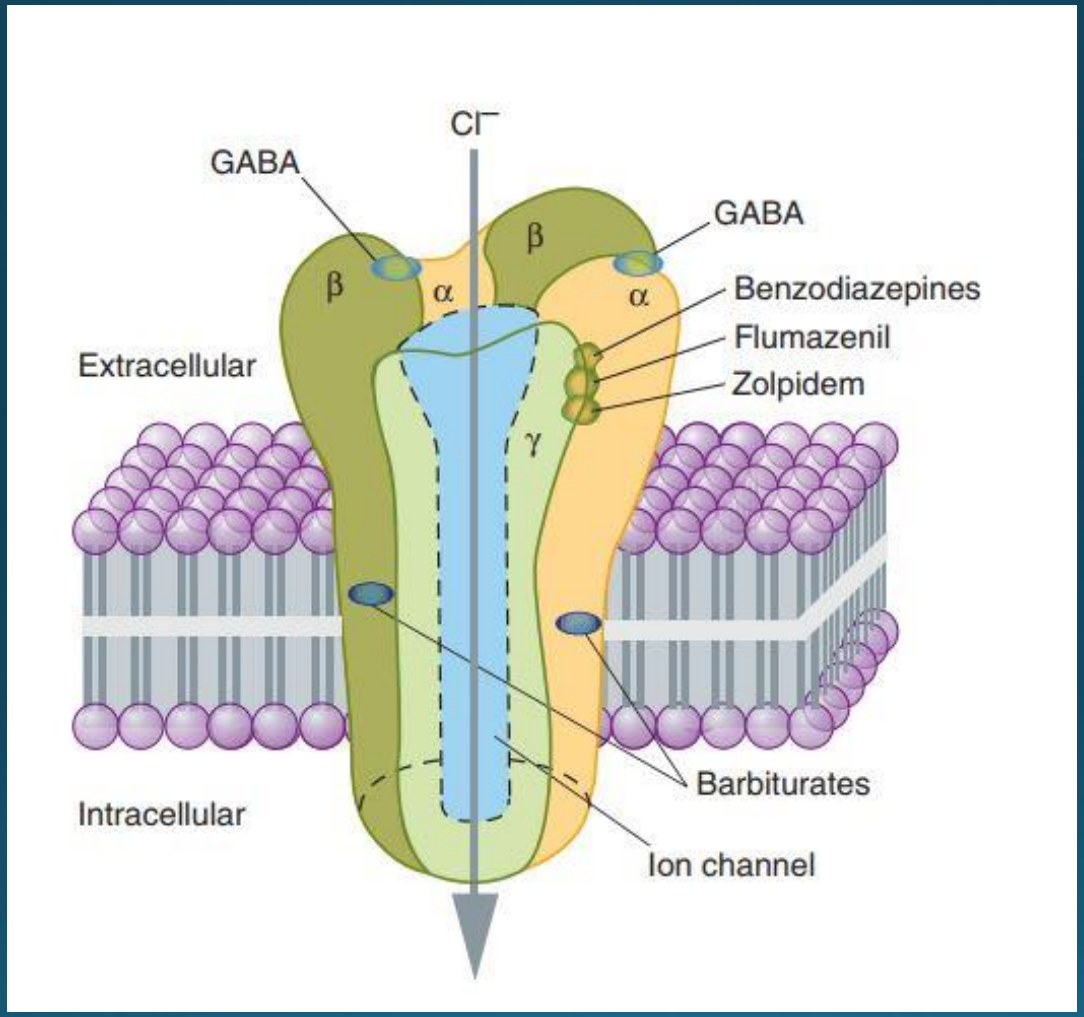
BZs antagonist

Flumazenil: It is 1,4- Benzodiazepine derivative.

- It has high affinity for the Benzodiazepine binding site on $GABA_A$ receptor complex, but no intrinsic activity.
- Acts as competitive antagonist

to Benzodiazepines, Zolpidem, Zaleplon & Eszopiclone.

It does not antagonize the effects of Buspirone or other Sedative/hypnotics.


Cl⁻
GABA
GABA
β
α
β
α
Benzodiazepines
Flumazenil
Zolpidem
Extracellular
γ
Barbiturates
Intracellular
Ion channel

Th. Uses of Flumazenil :

- Benzodiazepine overdose, reverses the effects,
- To hasten recovery when BZs are used in GA.
- Given I/V. Rapid OOA,
- Half life short--0.7-1.3 hrs– repeated administration may be required as BZs have long half lives
- Rapidly metabolized by liver.

A/E of Flumazenil :

Agitation, confusion, dizziness & nausea.

Can precipitate abstinence syndrome in pts who have developed physiologic dependence on BZs.

In pts who have ingested TCAs with BZs, it can produce seizures & cardiac arrhythmias.

BZ antagonists: other than Flumazenil

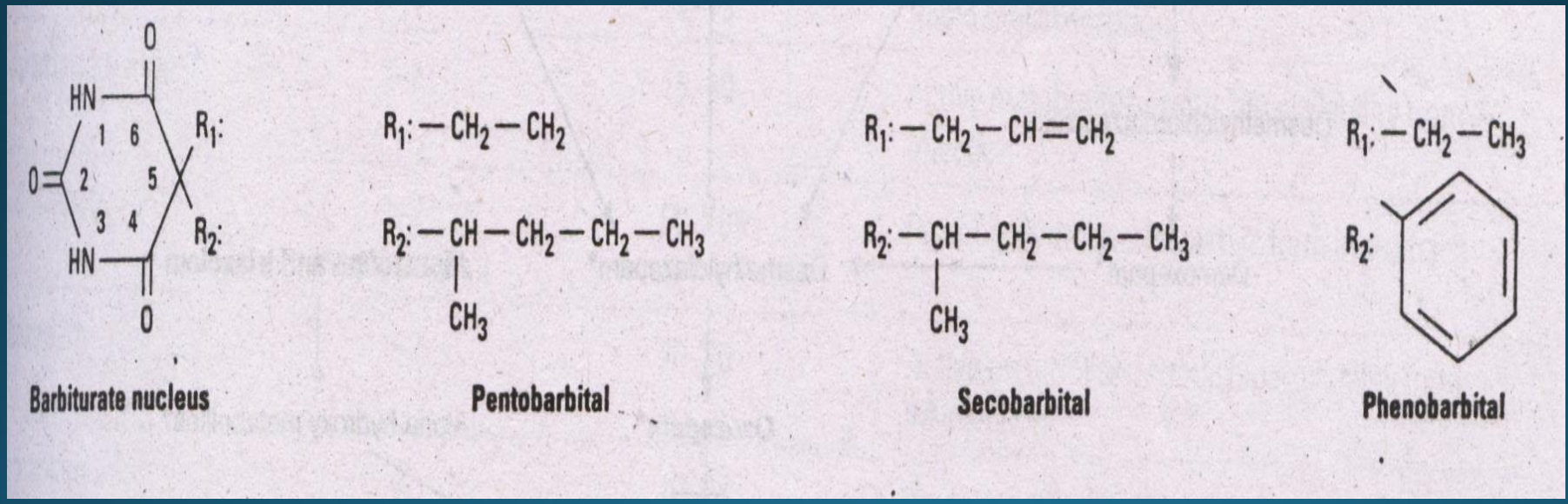
- An endogenous BZ like mediator--Diazepam Binding Inhibitor (DBI)
- $GABA_A$ receptor antagonist: Bicuculline
- GABA Synthesis inhibitor :Thiosemicarbazide
- BZ Inverse Agonist: β- carbolines

BARBITURATES

CHEMISTRY

Barbiturates are derivatives of *Barbituric acid.*

Barbiturates were the main drugs used as sedative & hypnotics , but have been replaced by Benzodiazepine, ,due to certain disadvantages.



Disadvantages of Barbiturates as compared to Benzodiazepines

- Low Therapeutic Index
- Potent Enzyme Inducers , which produces drug interactions.
- Drug of Abuse
- Risk of Physical Dependence
- Severe Withdrawal Syndrome
- Can precipitate attack of acute porphyria.

***PHARMACOKINETICS*:**

Orally given drugs are absorbed from GIT.

Distribution: throughout the body – lipid soluble so rapidly distributed to the brain, then redistribute from the brain to splanchnic areas/ skeletal muscles & finally to adipose tissues.

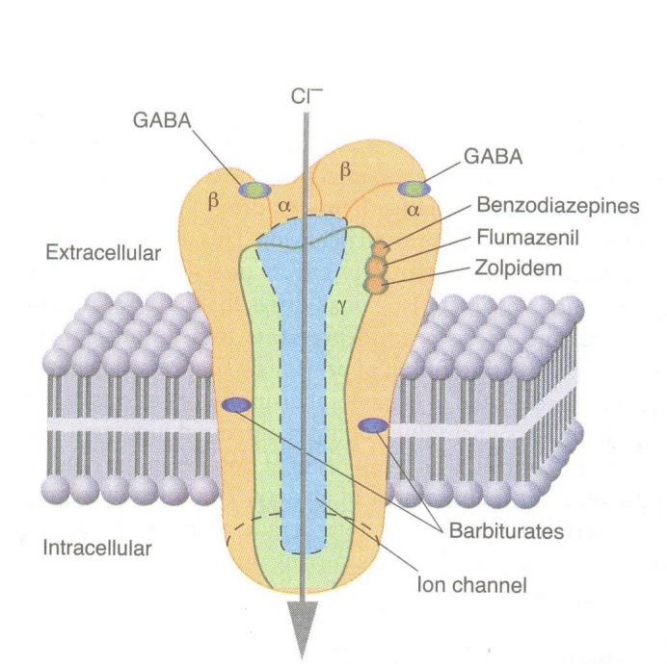
The DOA depends upon REDISTRIBUTION.

Readily cross placenta & depress fetus.

Metabolized by CYP450 in liver, potent enzyme inducers(exception secobarbital—Enz inhibitor)---D/I.

Inactive metabolites excreted in urine.

Receptor of Barbiturates



Group Actions of Barbiturates

- Sedation: At low doses calming effect.
- Hypnosis: At increasing doses induce sleep
- Antiepileptic: At higher doses control the seizures.
- Hyperalgesia: Lack analgesic effect & if given in pain –increase the perception of pain
- Amnesia & Automatism: Patient may forget that she has taken the drug & may take more drug--- overdose toxicity
- Respiratory depression: Depress respiration in therapeutic doses in pulmonary diseases . They also depress the response of RC to CO_2
- Action on Liver: Enzyme induction --- D/I – Therapeutic failure of co-administered drug– to be discussed with A/E
- Dependence: – to be discussed with A/E

Therapeutic uses of Barbiturates

- **Sedation**: At low doses calming effect ,decreased excitability. Used previously
- **For Insomnia:** Used previously– Secobarbital
- **General Anesthetic:** Ultra short acting barbiturates—
  -Induction of GA .
  - As main GA in operation of short duration.
- **Antiepileptic:** Phenobarbital is used in treatment of Partial & Generalized tonic –clonic epileptic seizures, status epilepticus
- **Anticonvulsant:** Used in eclampsia, also in febrile convulsions in children
- ***Neonatal jaundice & Kernictrus*:** Phenobarbital

is useful, it induces enzyme glucuronyl transferase & increases metabolism of bilirubin

ADVERSE EFFECTS

- **CNS effects:** Drowsiness, impaired concentration , mental & physical sluggishness.
- **Hangover–** Hypnotic doses, produce:

  feeling of tiredness. Impaired ability to work normally for many hours after patient wakes up.

  Nausea & dizziness occasionally.
- **Drug Automatism:** Elderly patient may forget that she has taken the drug & may take more drug--- overdose toxicity.
- **Additive CNS depression** with alcohol & other CNS depressant drugs.
- **Depression of fetal respiration,** if mother is given Barbiturates.

- **Attacks of Acute Porphyria:** Due to increased synthesis of porphyrins by the enzyme Delta-amino levolunic acid synthetase – induced by barbiturates. So they are C/I in patients of Porphyria
- **Enzyme Induction producing D/I–** They are potent inducers of hepatic CYP450 enzymes, the metabolism of co-administered coumarins, phenytoin & Digitalis is accelerated--- decreased plasma levels--- therapeutic failure.
- **Autoinduction ---- Pharmacokinetic tolerance may occur**

Drug Dependence of Barbiturates: :

- Severe physical dependence.
- Withdrawal symptoms –
  - Tremors
  - Anxiety
  - weakness
  - restlessness
  - Nausea & vomiting
  - delirium & cardiac defects.

Withdrawal syndrome is even more severe than opioids & can result in death.

Contraindications to Barbiturates:

- Liver diseases &Hepatic failure
- Renal diseases
- Severe pulmonary insufficiency--- emphysema
- Obstructive sleep apnea
- Intermittent Porphyria

Acute Barbiturate Poisoning

Acute Barbiturate Poisoning has been a leading cause of death for many decades.

Symptoms:

- Severe CNS depression, Coma
- Severe respiratory depression with shallow infrequent breathing.
- Central CVS depression, resulting in a shock like state.
- Renal shut down

Acute Barbiturate Poisoning----

Treatment: Symptomatic; No specific antidote available.

- Gastric lavage
- Take care of the airway, breathing & circulation..
- Alkalinization of urine to enhance urinary excretion– forced alkaline diuresis with sodium bicarbonate.
- Artificial respiration--- if required
- Hemodialysis in severe cases.

Barbiturates	BZDs
They are general depressants for all excitable cell.	They are selective CNS depressant
They bind to picrotoxin site between α and β units on GABA-Cl channel complex	They bind between α & GAMA sub units
They prolong duration of Cl channel opening	They increase the frequency of Cl channel opening
They have GABA mimetic action	They have GABA ergic action
They block excitatory glutamate receptor	No effects
They can cause hyperalgesia but no analgesic property	They have analgesic property

Barbiturates	BZDs
They induce P450 microsomal enzyme in liver	They do not
Toxic doses can cause coma and death	Death usually not occur
Chronic use leads to tolerance and dependence	Minimal tolerance occur
Severe withdrawl symptoms occur on abrupt discontinuation	Not so severe
Flumezanil does not antagonize its effects	Flumezanil is its competitive antagonist at its receptor
They can impair learning short term memory	No such effect

Other Anti anxiety drugs

Buspirone

: Newer selective anti-anxiety drug.

MOA:

- Partial agonist at brain $5HT_{1A}$ Receptors
- Agonist at brain Dopamine D_2 Receptors.

Actions are NOT antagonized by Flumazenil

Important Ph.K : Rapidly absorbed from GIT. Short half life , forms active metabolite. OOA 1-2 weeks.

- **Metabolized by CYP 3A4 ,inhibited by Erythromycin & induced** by Rifampin

USES: Used for generalized anxiety disorder

Not effective in panic disorders as OOA 1-2 weeks.

Differences of **Buspirone** from BDZ:

- OOA 1-2 weeks. Unsuitable for acute anxiety states
- Does not bind to BZ receptor
- Actions are NOT antagonized by Flumazenil
- No marked Sedative, Euphoric & Hypnotic effect
- Less psychomotor impairment.
- Minimal abuse liability
- No withdrawal signs on abrupt discontinuation.
- No additive CNS depression with other sedative hypnotic drugs.
- Elderly patients are not more sensitive to its effects.

Adverse Effects of Buspirone

- Dizziness, headache, fatigue, drowsiness, decreased concentration--less marked than BZs.
- Tachycardia, paresthesias, GIT distress,
- D/I: Metabolized by CYP 3A4.

Metabolism inhibited by Erythromycin.

Metabolism induced by Rifampin.

Analogs: Ipsapirone, Gepirone, Tandospirone.

Z drugs


2 x 10 Tablets
ZOLP®
(Zolpidem Tartrate)
Each film coated tablet contains:
Zolpidem Tartrate B.P. 10mg
adamjee
Pharmaceuticals
Manufactured by:
Adamjee Pharmaceuticals (Pvt.) Ltd.
Plot 39, Sector 15, Korangi Industrial Area, Karachi,Pakistan.

ZOLPIDEM , ZALEPLON & ESZOPICLONE:

Newer oral non- Benzodiazepines hypnotics.

MOA:- Structurally unrelated but as effective as Benzodiazepines

- Bind selectively to a sub group $GABA_A$ receptors like Benzodiazepines
- Facilitate GABA-mediated neuronal inhibition.
- Actions are antagonized by Flumazenil.

Characteristics of Zolpidem :

- Minimal muscle relaxing and anticonvulsant effects.
- Larger doses produce amnesia.
- Minor effects on sleep pattern.
- Rebound insomnia may occur on abrupt discontinuance.
- Resp. depression with larger doses.
- Actions are antagonized by Flumazenil
- Less risk of dependence and tolerance than BZs.

Ramelteon:

given orally ,metabolized by hepatic cyp450

- a selective agonist at mt1 & mt2 -- melatonin receptors in the suprachiasmatic nucleus of hypothalamus.
- stimulation of mt1 & mt2 of melatonin receptors is able to induce sleep & is thought to maintain the circadian rhythm, responsible for normal sleep –wake cycle.
- minimal abuse liability. no evidence of dependence or withdrawal signs on abrupt discontinuation.
- used for sleep disorders in which there is difficulty in falling asleep, can be given for long periods.
- A/E: dizziness , fatigue & somnolence, increased prolactin levels

B: Antihistamines:

Diphenhydramine, Hydroxyzine & Doxylamine:

May be used for mild situational insomnia

- Useful for patients of anxiety with drug abuse.
- Also used for sedation prior to dental procedures or surgery.

C: Antidepressants:

- All groups may be used for chronic anxiety , specially in patients with concerns of dependence

Chloral hydrate: Previously used

- Trichlorinated derivative of Acetaldehyde.
- A pro-drug converted to active metabolite—Trichloroethanol.
- Effective sedative & hypnotic

Paraldehyde: Cyclic Ether

CLINICAL USES: Previously used :

- Orally ___ hypnotic
- I/M as Anticonvulsant __ in
  - Status epilepticus
  - Tetanus
  - Eclampsia