UNIT-IV
HYPNOTICS AND SEDATIVES

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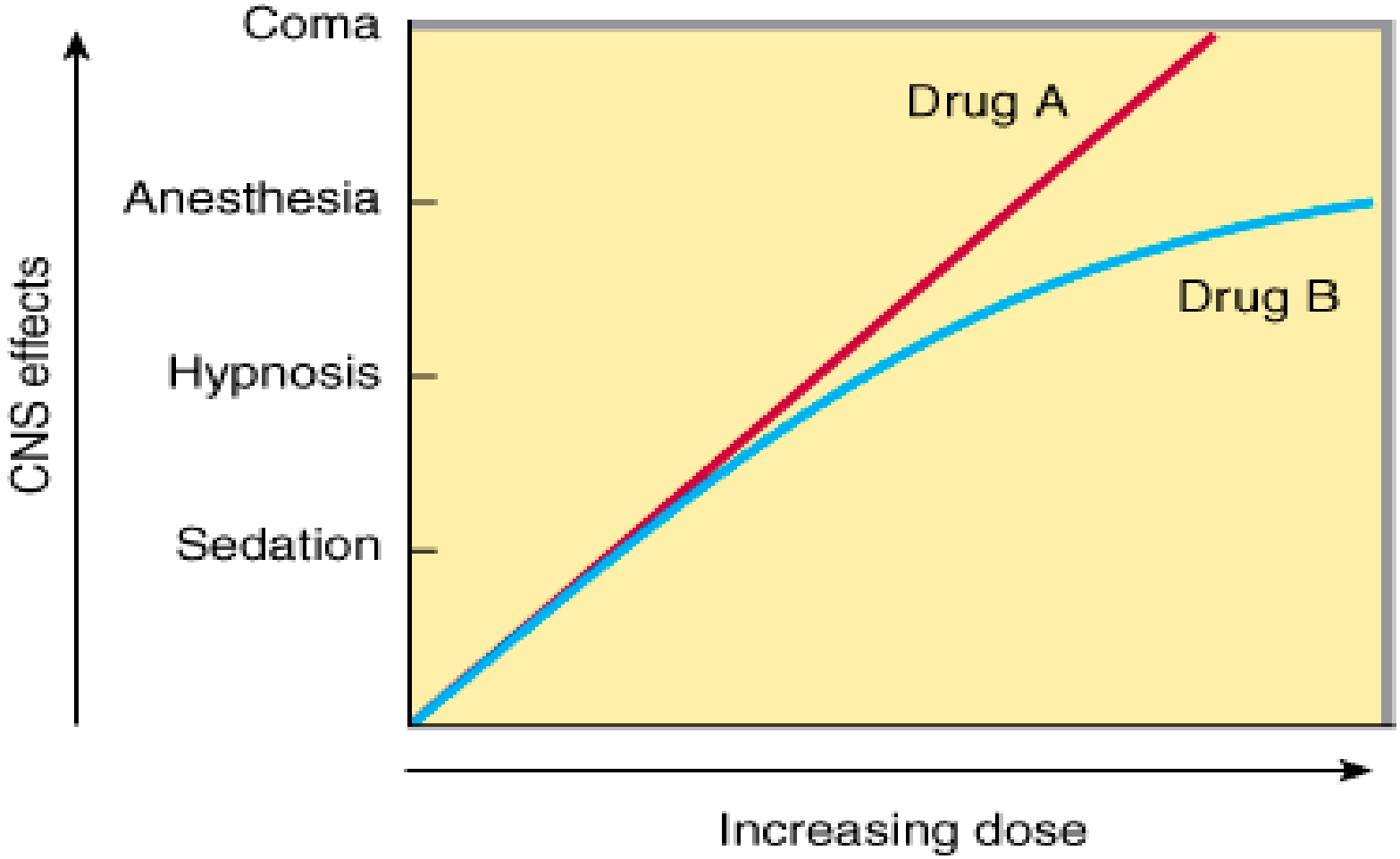
- **SEDATIVES –** reduce anxiety and exert a calming effect

- **HYPNOTICS -** produces drowsiness and facilitates the onset and maintenance of a state of sleep.

Figure 22–1



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Dose-response curves for two hypothetical sedative-hypnotics.

CLASSIFICATION

1. *Barbiturates*

Long acting	*Short acting*	*Ultra-short acting*
Phenobarbitone	Butobarbitone	Thiopentone
	Pentobarbitone	Methohexitone

2. *Benzodiazepines*

Hypnotic	*Antianxiety*	*Anticonvulsant*
Diazepam	Diazepam	Diazepam
Flurazepam	Chlordiazepoxide	Lorazepam
Nitrazepam	Oxazepam	Clonazepam
Alprazolam	Lorazepam	Clobazam
Temazepam	Alprazolam	
Triazolam		

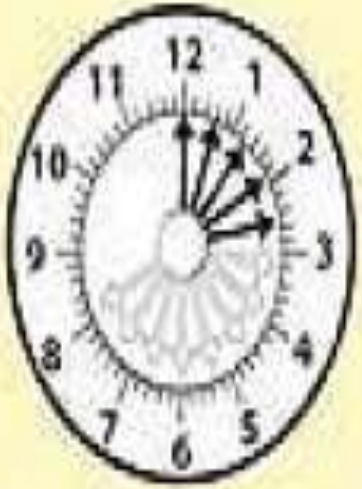
Non Benzodiazepine hypnotics

- **ZOLPIDEM**
- **ZALEPLON**
- **ZOPICLONE (ESZOPICLONE)**

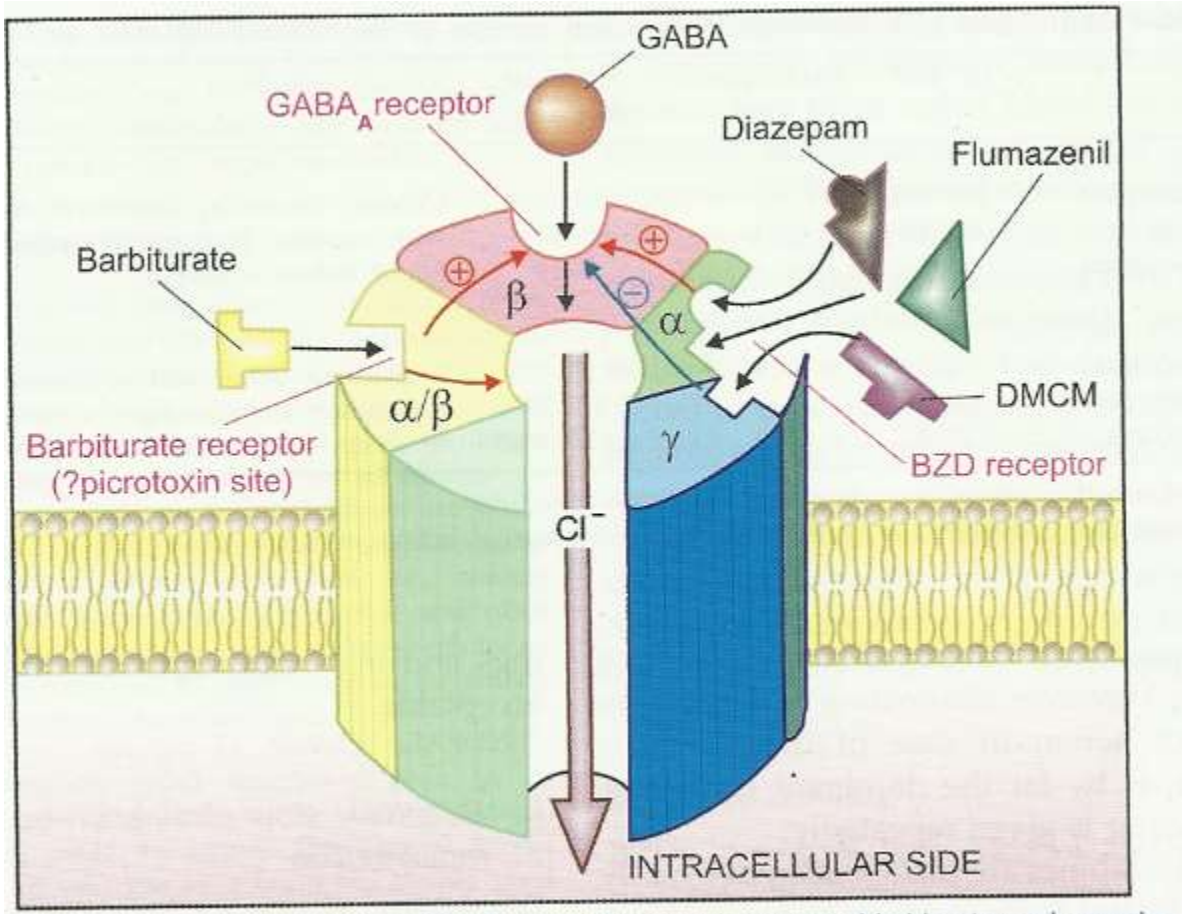
Miscellaneous

- **MELATONIN**
- **RAMELTEON**

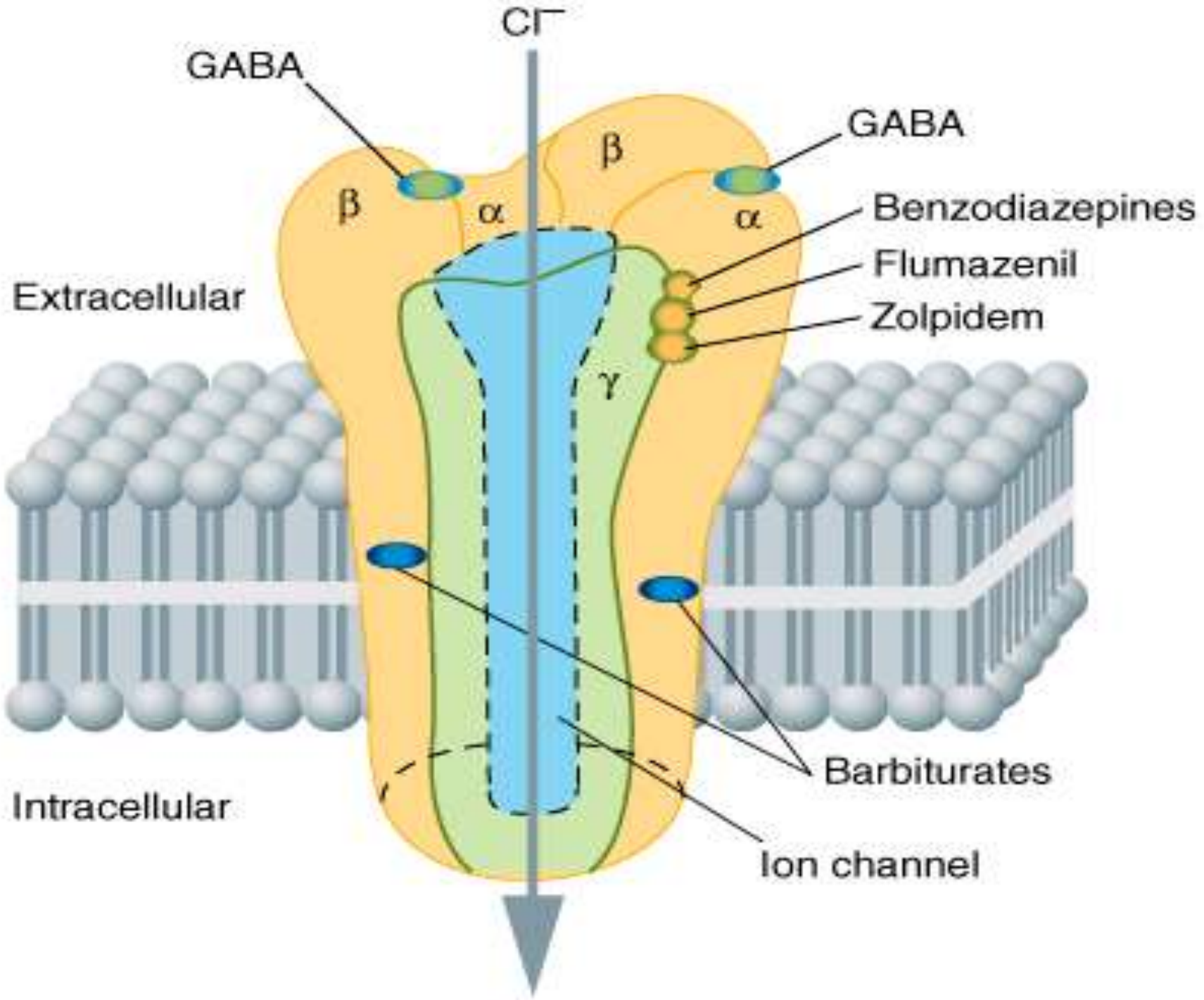
BARBITURATES CLASSIFIED ACCORDING TO THEIR DURATIONS OF ACTION

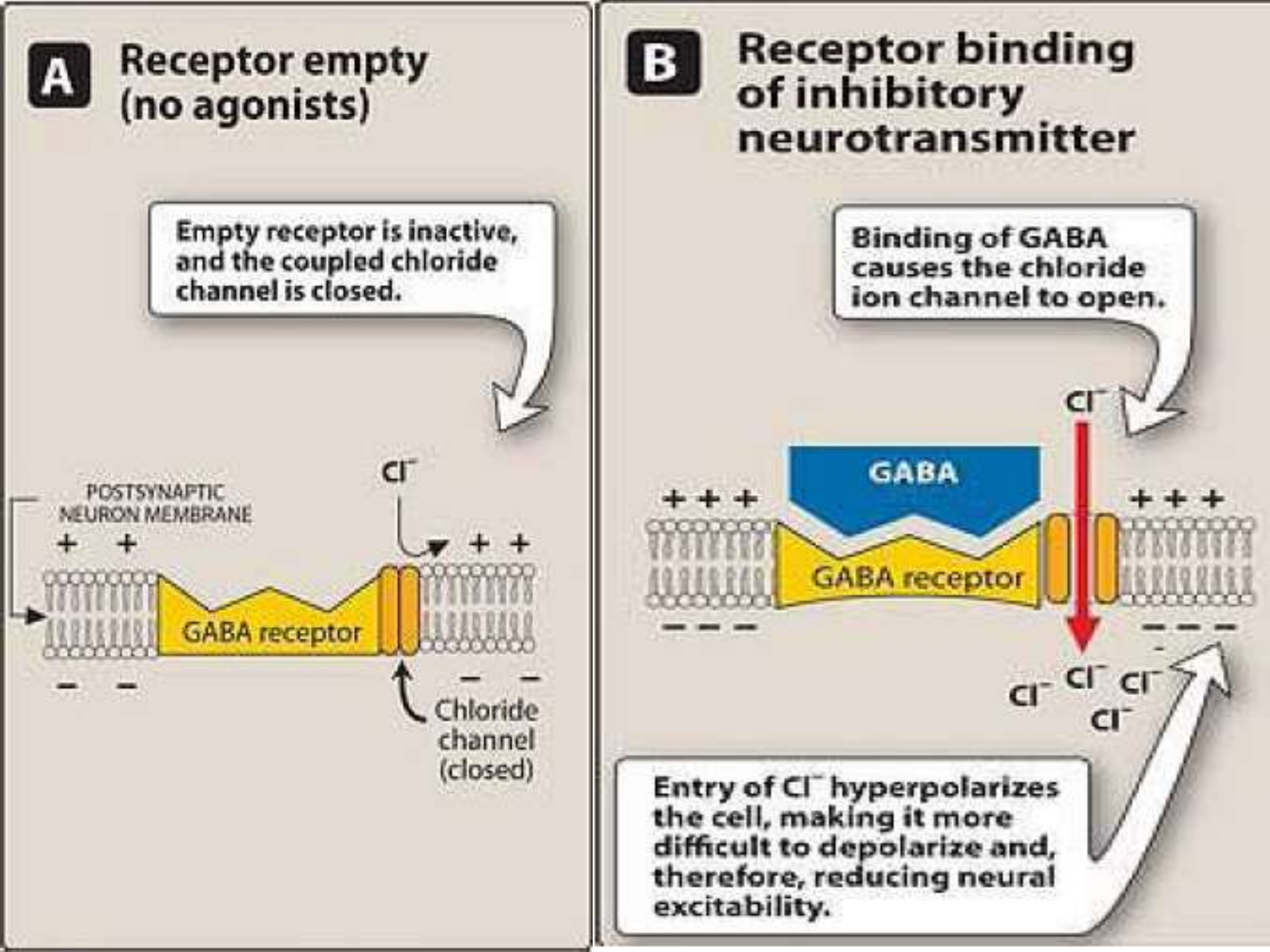
Long-acting	Short-acting	Ultra-short-acting
	 3–8 Hours	 20 Minutes
Phenobarbital	*Pentobarbital* *Secobarbital* *Amobarbital*	*Thiopental*

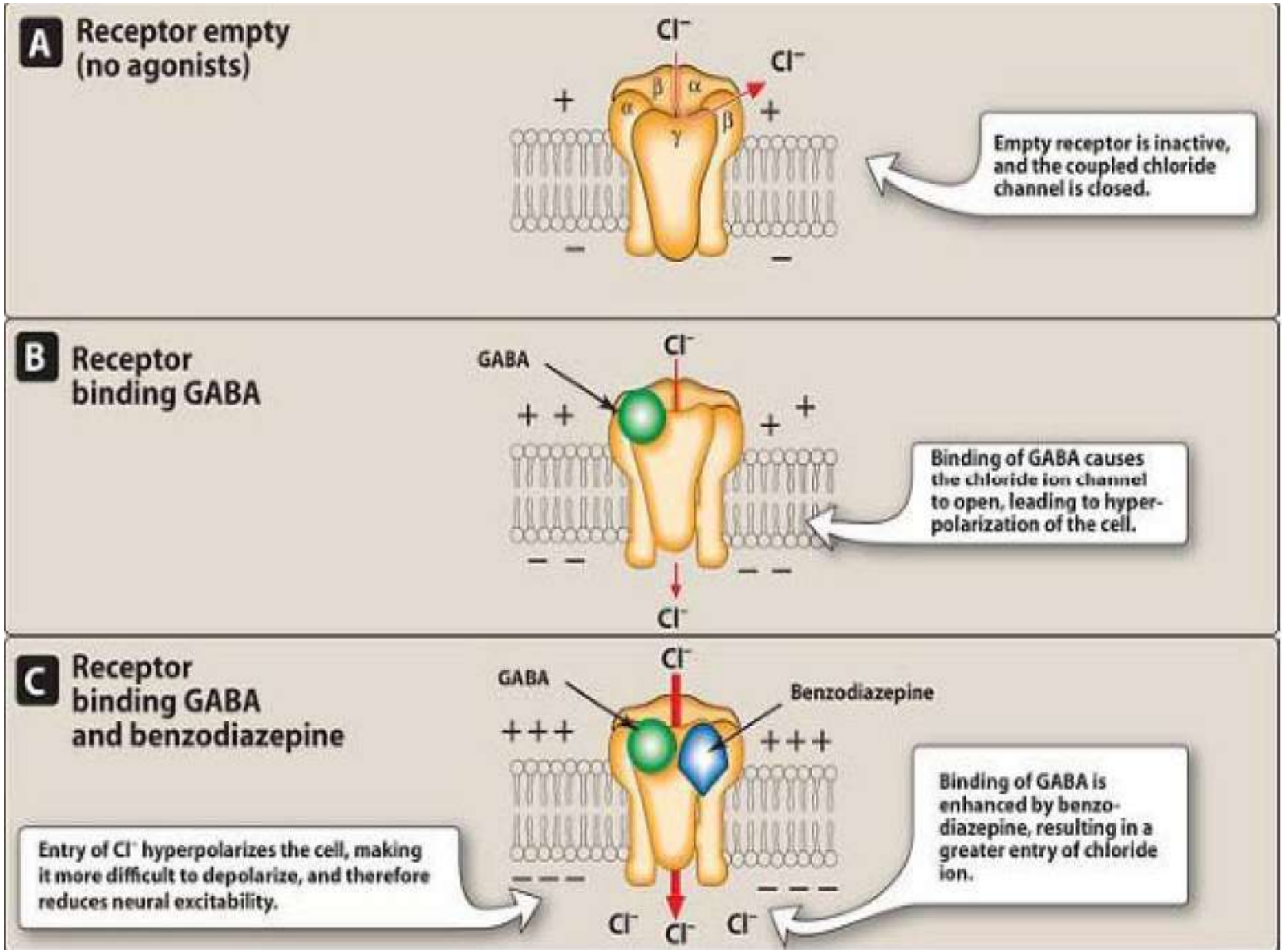
The chloride channel is gated by the primary ligand GABA acting on $GABA_A$ receptor located on the β subunit. The benzodiazepine (BZD) receptor located on the interface of α and γ subunits modulates $GABA_A$ receptor in either direction: agonists like diazepam facilitate, while inverse agonists like DMCM hinder GABA mediated Cl^- channel opening, and BZD antagonist flumazenil blocks the action of both. The barbiturate receptor, located either on α or β subunit also facilitates GABA and is capable of opening Cl^- channel directly as well. Bicuculline blocks $GABA_A$ receptor, while picrotoxine blocks the Cl^- channel directly



g. 29.3: Schematic depiction of $GABA_A$-benzodiazepine receptor-chloride channel complex


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


A
Receptor empty (no agonists)
Empty receptor is inactive, and the coupled chloride channel is closed.
POSTSYNAPTIC NEURON MEMBRANE
Cl⁻
GABA receptor
Chloride channel (closed)
B
Receptor binding of inhibitory neurotransmitter
Binding of GABA causes the chloride ion channel to open.
GABA
GABA receptor
Cl⁻
Entry of Cl⁻ hyperpolarizes the cell, making it more difficult to depolarize and, therefore, reducing neural excitability.


A
Receptor empty (no agonists)
Cl⁻
Cl⁻
β
α
α
γ
β
+
+
−
−
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.

Barbiturates

- enhance the binding of GABA to $GABA_A$ receptors
- Prolonging duration
- Only α and β (not ϒ) subunits are required for barbiturate action
- Narrow therapeutic index
- in small doses, barbiturates increase reactions to painful stimuli.
- Hence, they cannot be relied on to produce sedation or sleep in the presence of even moderate pain.

Bezodiazepines

- enhance the binding of GABA to $GABA_A$ receptors
- increasing the frequency
- Unlike barbiturates, benzodiazepines do not activate $GABA_A$ receptors directly

BARBITURATES

Mechanism of Action- Bind to specific **$GABA_A$** receptor subunits at CNS neuronal synapses facilitating GABA-mediated chloride ion channel opening, enhance membrane hyperpolarization.

Effects- Dose-dependent depressant effects on the CNS including

- Sedation
- Relief of anxiety
- Amnesia
- Hypnosis
- Anaesthesia
- Coma
- Respiratory depression steeper dose-response relationship than benzodiazepines

BARBITURATES

ACTIONS

1. **Depression of CNS: At low doses, the barbiturates produce sedation (calming effect, reducing excitement).**

2. **Respiratory depression: Barbiturates suppress the hypoxic and chemoreceptor response to CO2, and overdosage is** followed by respiratory depression and death.

3. **Enzyme induction: Barbiturates induce P450 microsomal enzymes in the liver.**

BARBITURATES

PHARMACOKINETICS

- All barbiturates redistribute in the body.
- Barbiturates are metabolized in the liver, and inactive metabolites are excreted in the urine.
- They readily cross the placenta and can depress the fetus.
- **Toxicity:** Extensions of CNS depressant effects
  dependence liability > benzodiazepines.
- **Interactions:** Additive CNS depression with ethanol and many other drugs induction of hepatic drug-metabolizing enzymes.

THERAPEUTIC USES

ANESTHESIA (THIOPENTAL, METHOHEXITAL)

- Selection of a barbiturate is strongly influenced by the desired duration of action.

- The ultrashort-acting barbiturates, such as thiopental, are used intravenously to induce anesthesia.

ANXIETY

- **Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension, and insomnia.**

  When used as hypnotics, they suppress REM sleep more than other stages. However, most have been replaced by the benzodiazepines.

THERAPEUTIC USES

ANTICONVULSANT: (PHENOBARBITAL, MEPHOBARBITAL)

- **Phenobarbital is used in long-term management of tonic-clonic seizures, status epilepticus, and eclampsia.**

- Phenobarbital has been regarded as the drug of choice for treatment of young children with recurrent febrile seizures.

- However, phenobarbital can depress cognitive performance in children, and the drug should be used cautiously.

- Phenobarbital has specific anticonvulsant activity that is distinguished from the nonspecific CNS depression.

ADVERSE EFFECTS

1. **CNS:** Barbiturates cause **drowsiness**, **impaired concentration.**

2. **Drug hangover: Hypnotic doses of barbiturates produce a feeling of tiredness well after the patient wakes.**

3. **Barbiturates induce the P450 system.**

4. By inducing aminolevulinic acid (ALA) synthetase, barbiturates increase **porphyrin synthesis**, and are contraindicated in patients with acute intermittent porphyria.

ADVERSE EFFECTS

5. **Physical dependence:** Abrupt withdrawal from barbiturates may cause **tremors**, **anxiety**, **weakness**, **restlessness**, **nausea** and **vomiting**, **seizures**, **delirium**, and **cardiac arrest**.
6. **Poisoning: Barbiturate poisoning has been a leading cause of death resulting from drug overdoses for many decades.**

   It may be due to automatism.

- Severe depression of respiration is coupled with central cardiovascular depression, and results in a shock-like condition with shallow, infrequent breathing.

ADVERSE EFFECTS

Potential for Addiction

Drowsiness

Nausea

Vertigo

Tremors

Enzyme Induction

THE TREATMENT OF ACUTE BARBITURATE INTOXICATION

Treatment includes artificial respiration and purging the stomach of its contents if the drug has been recently taken.

- **No specific barbiturate antagonist is available**.
- General supportive measures.
- Hemodialysis or hemoperfusion is necessary only rarely.
- Use of CNS stimulants is contraindicated because they increase the mortality rate.

THE TREATMENT OF ACUTE BARBITURATE INTOXICATION

- If renal and cardiac functions are satisfactory, and the patient is hydrated, **forced diuresis and alkalinization** of the urine will hasten the excretion of phenobarbital.

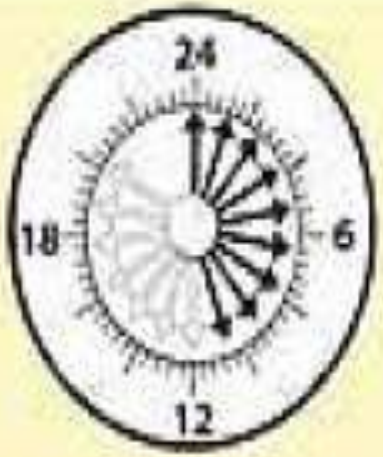
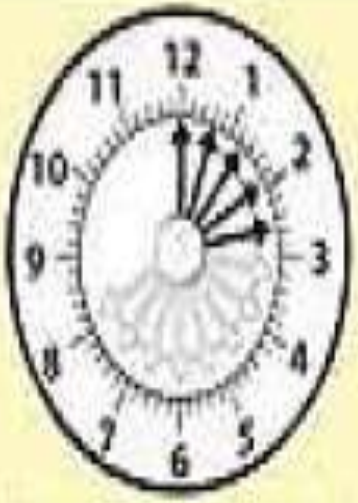
- In the event of renal failure - hemodialysis

- circulatory collapse is a major threat. So hypovolemia must be corrected & blood pressure can be supported with dopamine.

- Acute renal failure consequent to shock and hypoxia accounts for perhaps one-sixth of the deaths.

BENZODIAZEPINES

COMPARISON OF THE DURATIONS OF ACTION OF THE BENZODIAZEPINES

Long-acting	Intermediate-acting	Short-acting
	 **10–20 Hours**	 **3–8 Hours**
Clorazepate *Chlordiazepoxide* *Diazepam* *Flurazepam* *Quazepam*	*Alprazolam* *Estazolam* *Lorazepam* *Temazepam*	*Oxazepam* *Triazolam*

Effects of benzodiazepine

- On increasing the dose sedation progresses to hypnosis and then to stupor.

- But the drugs do not cause a true general anesthesia because

  -awareness usually persists

  -immobility sufficient to allow surgery cannot be achieved.

- However at "preanesthetic" doses, there is amnesia.

Effects on the (EEG) and Sleep Stages

- ↓ sleep latency
- ↓ number of awakenings
- ↓ time spent in stage 0, 1, 3, 4
- ↓ time spent in REM sleep (↑number of cycles of REM sleep)
- ↑ total sleep time (largely by increasing the time spent in stage 2)

- Respiration-Hypnotic doses of benzodiazepines are without effect on respiration in normal subjects

- CVS-In preanesthetic doses, all benzodiazepines decrease blood pressure and increase heart rate

PHARMACOKINETICS

- A short elimination $t_{1/2}$ is desirable for hypnotics, although this carries the drawback of increased abuse liability and severity of withdrawal after drug discontinuation.

- Most of the BZDs are metabolized in the liver to produce active products (thus long duration of action).

- After metabolism these are conjugated and are excreted via kidney.

ADVERSE EFFECTS

- Light-headedness
- Fatigue
- **Increased reaction time**
- **Motor incoordination**
- Impairment of mental and motor functions
- **Confusion**
- Antero-grade **amnesia**
- Cognition appears to be affected less than motor performance.
- All of these effects can greatly impair driving and other psychomotor skills, especially if combined with ethanol.

FLUMAZENIL: A BENZODIAZEPINE RECEPTOR ANTAGONIST

- competitively antagonism
- Flumazenil antagonizes both the electrophysiological and behavioral effects of agonist and inverse-agonist benzodiazepines and **β -**carbolines.
- Flumazenil is available only for intravenous administration.
- On intravenous administration, flumazenil is eliminated almost entirely by hepatic metabolism to inactive products with a **$t_{1/2}$ of ~1 hour**; the duration of clinical effects usually is only **30-60 minutes**.

FLUMAZENIL: A BENZODIAZEPINE RECEPTOR ANTAGONIST

PRIMARY INDICATIONS FOR THE USE OF FLUMAZENIL ARE:-

- Management of suspected benzodiazepine overdose.
- Reversal of sedative effects produced by benzodiazepines administered during either general anesthesia.

The administration of a series of small injections is preferred to a single bolus injection.

- A total of **1 mg** flumazenil given over 1-3 minutes usually is sufficient to abolish the effects of therapeutic doses of benzodiazepines.
- Patients with suspected benzodiazepine overdose should respond adequately to a cumulative dose of 1-5 mg given over 2-10 minutes;
- A lack of response to 5 mg flumazenil strongly suggests that a benzodiazepine is not the major cause of sedation.

Novel Benzodiazepine Receptor Agonists

- **Z compounds**

  zolpidem , zaleplon , zopiclone and **eszopiclone**

- structurally unrelated to each other and to benzodiazepines

- therapeutic efficacy as hypnotics is due to agonist effects on the benzodiazepine site of the $GABA_A$ receptor

- Compared to benzodiazepines, **Z compounds** are

  -less effective as anticonvulsants or muscle relaxants

  -which may be related to their relative selectivity for $GABA_A$ receptors containing the **α1** subunit.

Novel Benzodiazepine Receptor Agonists

- The clinical presentation of overdose with **Z compounds** is similar to that of benzodiazepine overdose and can be treated with the benzodiazepine antagonist flumazenil.

- Zaleplon and zolpidem are **effective in relieving sleep-onset insomnia**. Both drugs have been approved by the FDA for use for up to **7-10 days** at a time.

- Zaleplon and zolpidem **have sustained hypnotic efficacy** without occurrence of rebound insomnia on abrupt discontinuation.

ZALEPLON

- Its plasma **$t_{1/2}$ is ~1 hours**

- **approved for use immediately at bedtime or when the patient has difficulty falling asleep after bedtime.**

ZOLPIDEM

- Its plasma **$t_{1/2}$ is ~2 hours**

- **Cover most of a typical 8-hour sleep period, and is presently approved for bedtime use only.**

Eszopiclone

- **Used for the long-term treatment of insomnia and for sleep maintenance.**

- **$t_{1/2}$ of ~6 hours.**

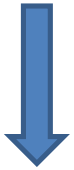
MELATONIN CONGENERS

RAMELTEON

- Synthetic tricyclic analog of **MELATONIN**.
- It was approved for the treatment of insomnia, specifically sleep onset difficulties.

MECHANISM OF ACTION

- Melatonin levels in the suprachiastmatic nucleus rise and fall in a circadian fashion



concentrations increasing in the evening as an individual prepares for sleep, and then reaching a plateau and ultimately decreasing as the night progresses.

MELATONIN CONGENERS

Mechanism of Action

- Two **GPCRs** for melatonin, **MT_1** and **MT_2,** are found in the suprachiasmatic nucleus, each playing a different role in sleep.
- **RAMELTEON** binds to both **MT_1** and **MT_2** receptors with high affinity.
- Binding of **Melatonin** to **MT_1** receptors **promotes the onset of sleep**.
- Binding of **Melatonin** to **MT_2** receptors shifts the timing of the circadian system.
- **RAMELTEON** is efficacious in combating both transient and chronic insomnia

Prescribing Guidelines for the Management of Insomnia

Hypnotics that act at **$GABA_A$** receptors, including the benzodiazepine hypnotics and the newer agents zolpidem, zopiclone, and zaleplon, are preferred to barbiturates because they have a

- **Greater therapeutic index**
- **Less toxic in overdose**
- **Have smaller effects on sleep architecture**
- **Less abuse potential**.

Compounds with a **shorter $t_{1/2}$** are favored in patients with sleep-onset insomnia but without significant daytime anxiety who need to function at full effectiveness during the day.

- These compounds also appropriate for the elderly because of a decreased risk of falls and respiratory depression.
- One should be aware that early-morning awakening, rebound daytime anxiety, and amnestic episodes also may occur.
- These undesirable side effects are more common at higher doses of the benzodiazepines.

Prescribing Guidelines for the Management of Insomnia

- **Benzodiazepines with longer $t_{1/2}$**

  are favored for patients

  - --- who have significant daytime anxiety and

  ----- who may be able to tolerate next-day sedation.

- However can be associated with

  -next-day cognitive impairment

  -delayed daytime cognitive impairment (after 2-4 weeks of treatment) as a result of drug accumulation with repeated administration.

- Older agents such as barbiturates, chloral hydrate, and meprobamate have high abuse potential and are dangerous in overdose.

CATEGORIES OF INSOMNIA

Transient insomnia	Short-term insomnia	Long-term insomnia
•Lasts <3 days •---Caused by a brief environmental or situational stressor. •---Respond to attention to sleep hygiene rules. •--- Hypnotics should be used at the lowest dose and for only 2-3 nights.	**•3 days to 3 weeks** •--- Caused by a personal stressor such as illness, grief, or job problems. •---Sleep hygiene education is the first step. •---Hypnotics may be used adjunctively for 7-10 nights. •---- Hypnotics are best used intermittently during this time, with the patient skipping a dose after 1-2 nights of good sleep.	**•lasted for >3 weeks** •**---N**o specific stressor may be identifiable. •---A more complete medical evaluation is necessary in these patients, but most do not need an all-night sleep study.

LONG-TERM INSOMNIA

Nonpharmacological treatments are important for all patients with long-term insomnia.These include

- Reduced caffeine intake
- Avoidance of alcohol
- Adequate exercise
- Relaxation training
- Behavioral-modification approaches, such as sleep-restriction and stimulus-control therapies.
- Nonpharmacological treatments for insomnia have been found to be particularly effective in reducing sleep-onset latency and time awake after sleep onset.

Management of Patients after Long-Term Treatment with Hypnotic Agents

- If a benzodiazepine has been used regularly for **>2 weeks**, it should be tapered rather than discontinued abruptly.
- In some patients on hypnotics with a short $t_{1/2}$, it is easier to switch first to a hypnotic with a long $t_{1/2}$ and then to taper.
- The onset of withdrawal symptoms from medications with a long $t_{1/2}$ may be delayed.
- Consequently, the patient should be warned about the symptoms associated with withdrawal effects.

Atypical Anxiolytics

- Buspiron
- Ipsapirone
- Gepirone

- Buspirone relieves anxiety

  -without causing marked sedative, hypnotic, or euphoric effects.

  - no anticonvulsant or muscle relaxant properties.
- Buspirone does not interact directly with GABAergic systems.
- Anxiolytic effects of **buspirone** is by acting as a partial **agonist at brain 5-HT_{1A} receptors**.

- the anxiolytic effects of buspirone may take more than a week
- unsuitable for management of acute anxiety states
- no rebound anxiety or withdrawal signs on abrupt discontinuance
- The drug is not effective in blocking the acute withdrawal syndrome resulting from abrupt cessation of use of benzodiazepines or other sedative-hypnotics
- Buspirone has minimal abuse liability
- The drug is **used in generalized anxiety** states
- but is **less effective in panic disorders**

MCQs

Q1. Sleep promoting effect of ramelteon is mediated by receptor:

- A. $GABA_A$ receptor
- B. Opiate receptors
- C. $GABA_B$ receptor
- D. Melatonin receptors MT_1 and MT_2

- Ans- D

Q2. Which one of the following effects is NOT seen with barbiturates?

- A. Analgesic
- B. Anticonvulsant
- C. Induction and maintenance of anaesthesia
- D. Sedation

- Ans- A

Q3. An ideal hypnotic drug should NOT have:

- A. rapid onset of action
- B. sustained effect throughout the night
- C. without any residual effect in the following morning
- D. increase in sleep latency

- Ans- D

Q4. True statement about effect of bezodiazepines on sleep is:

- A. Time spent in stage 2 is decreased
- B. Time spent in stages 1, 3 and 4 is increased
- C. Shortening of REM sleep
- D. Increase sleep latency

- Ans- C

Q5. Beta carboline at benzodiazepine receptor act as:

- A. Agonist
- B. Inverse agonist
- C. Antagonist
- D. Partial agonist

- Ans- B

Q6. Benzodiazepine antagonist is:

- A. Naloxone
- B. Zolpidem
- C. Nalorphine
- D. Flumazenil

- Ans- D

Q7. Benzodiazepines act by:

- A. Activating $GABA_A$ receptors directly
- B. Modulating the effects of GABA on $GABA_A$ receptors
- C. Antagonistic effect on $GABA_A$ receptors
- D. GABA mimetic effect

- Ans- B

Q8. Administration of barbiturate is contraindicated in:

- A. Kernicterus
- B. Anxiety
- C. Epilepsy
- D. Acute Intermittant porphyria

- Ans-D

Q9. Which is NOT true about Flumazenil?

- A. Acts on $GABA_A$ receptor
- B. Specific antagonist of benzodiazepine
- C. Given intravenously
- D. May be used in barbiturate poisoning

- Ans- D

Q10. True statement about zolpidem:

- A. Relieve sleep onset insomnia
- B. Cause profound rebound insomnia
- C. Cause profound REM suppression
- D. Has strong anticonvulsant effect

- Ans- A

Bibliography

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THANKS

UNIT-IV
ANTIPSYCOTICS

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Psychosis

- The psychoses affect approximately 1% of the population in all cultures.
- They are psychogenic mental disorders involving a loss of contact with reality.
- The psychotic disorders include **schizophrenia and the manic phase of bipolar** (manic–depressive) illness.
- The psychoses (eg: schizophrenia) are among the most severe mental illnesses.

Schizophrenia (Split-Mind)

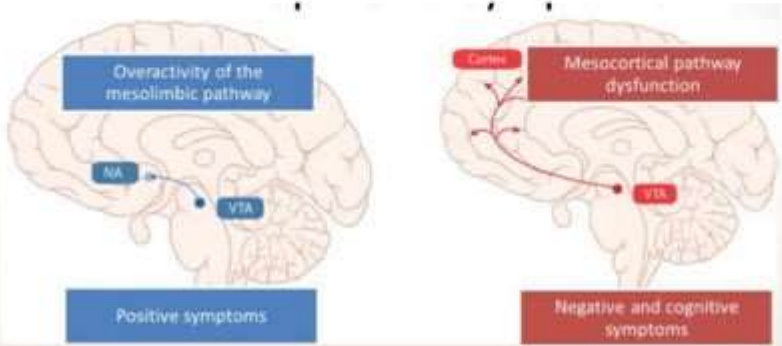
- The most common is schizophrenia, in which perception, thinking, communication, social functioning, and attention are altered.
- Schizophrenia is defective dopamine neurotransmission relative excess of central dopaminergic activity.

Symptoms

Positive (HDBS)(e.g. hallucination (false perception) and delusions (false belief),behavior(disorganization), speech (disturbances)

Negative (e.g., lack of motivation, social withdrawal, lack of interest in fun activity, doesn't respond to questions);

Cognitive dysfunction (disorganization) may occur.



- Some researchers have suggested that dopamine systems in the mesolimbic pathway may contribute to the 'positive symptoms' of schizophrenia (whereas problems with dopamine function in the mesocortical pathway may be responsible for the 'negative symptoms'.

Dopamine and EPS

- Studied in Parkinson indicated that Dopamine is a Neurotransmitter (NT) involved in movement (in balance with acetylcholine)
- When dopamine levels decreases, due to action of antipsychotic drugs in all Dopamine pathways, movement related disorders called Extra Pyramidal symptoms (EPS) arise which includes
  - akinesia (inability to initiate movement)
  - akathisia (inability to remain motionless)
  - acute dystonia (twisting of muscles)

Mechanism of action

- The antipsychotic mechanism of action of neuroleptics involves modulation of dopamine neurotransmission in the mesolimbic- mesocortical pathway.
- This may achieve via direct D2 receptor interaction and include functional spectrum antagonism, inverse agonism and/or partial agonism.
- These drugs clinical efficacy however not only depends on D2 receptor interaction , other CNS system receptors are also involved (ach, histamine, norepinephrine and serotonin) appears to be involved , specially for the atypical drugs.

Classification of Antipsychotic Drugs

A) Typical Antipsychotics (more EPS, D2 blokage)	B) Atypical Antipsychotics (less EPS, D2 and 5HT2a blokage)	C) Both (Typical and Atypical)
1) Phenothiazine: **a) aliphatic:** Chlorpromazine Triflupromazine Promazine Levomepromazine **b) Piperidine:** Thioridazine Mesoridazine Pericyazine pipotiazine **c) Piperizine:** Fluphenazine Perphenazine Trifluoperazine	**1) Diphenylbutylpiperidine:** Pimozide	**1) Dihydroindolones:** Molindone
2) Thioxanthenes: Chlorprothixene Flupenthixol	**2) Benzioxazole:** Resperidone	**2) Benzamide:** Remoxipride
3) Fluorobutyrophenones: Haloperidol Droperidol	**3) Dibenzodiazepine:** Loxapine Clozapine	

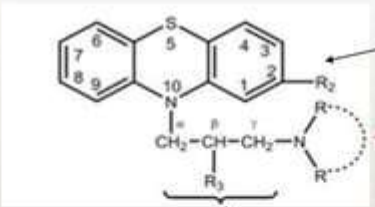
- **Typical antipsychotics** (e.g., chlorpromazine, haloperidol) are better for treating positive signs than negative signs. For treating negative signs, the newer **(atypical) antipsychotic** drugs (e.g., clozapine, risperidone) target D_2 receptor and other receptors.
- The bases of the atypical group's activity against negative symptoms may be serotonin-2A receptor (5-HT_2A) block, block at receptors yet to be determined, and possibly decreased striatal D_2 block.
- The conventional typical antipsychotics (neuroleptics) are characterized by the production of EPS(Extrapyramidal Symptoms), roughly approximating the symptoms of Parkinson disease. Atypical antipsychotics date from the discovery of clozapine, its antipsychotic properties, and its much lower production of EPS. It has reduced EPS, has increased activity against negative symptoms, and, in addition to its DA-blocking ability, is a 5-HT_2A antagonist

Phenothiazines

Chemical Class	Side Chain	Drug
Phenothiazines	Aliphatic (low/medium-potency agents)	Chlorpromazine
		Levomepromazine
		Promazine
		Triflupromazine
	Piperidine (low/medium potency agents)	Mesoridazine
		Pericyazine
		Pipotiazine
		Thioridazine
	Piperazine (medium/high-potency agents)	Perphenazine
		Fluphenazine
		Trifluoperazine

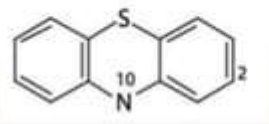
SARs of phenothiazines

- Phenothiazines have a tricyclic structure (6-6-6 system) in which two benzene rings are linked by sulfur and a nitrogen atom



1) Unsubstituted Phenothiazines has no activity but has enough lipophilicity for good brain penetration.

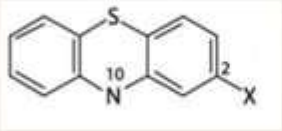
Substitution at C2 and N10 is required for activity.



Position 2

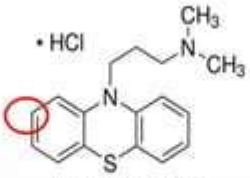
2) The best position for substitution is the 2-position. C2 must have an electrowithdrawing group.

- Activity increases as electron-withdrawing ability of the 2-substituent increases.
- The activity for these various group is as X = - SO2NR2 > -CF3 > -CO-CH3 > -Cl.

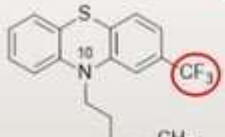


Position 2

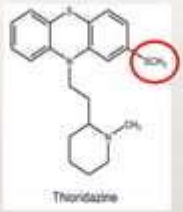
low antipsychotic activity



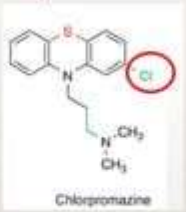
Promazine HCl



Triflupromazine



Thioridazine



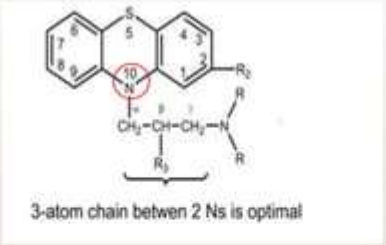
Chlorpromazine

Levomepromazine

Position 10

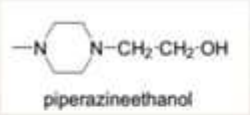
3) The three-carbon chain between position 10 and the aliphatic amino nitrogen is critical for neuroleptic activity.

- Shortening or lengthening the chain at this position drastically decreases the activity.
- The three-atom chain length may be necessary to bring the protonated amino nitrogen in proximity with the 2-substituent.
- Shortening the chain to two carbons has the effect of amplifying the antihistaminic and anticholinergic activities

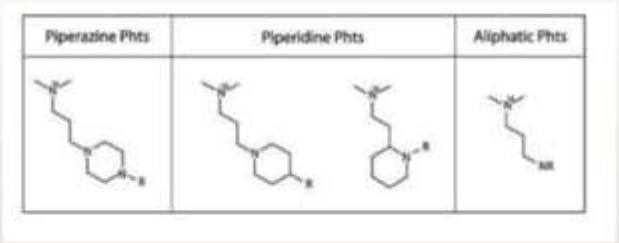


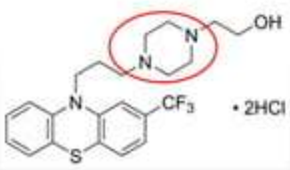
4) A terminal amino substituent must be present at N10. It can be piperazine, piperidine or aliphatic and their intensity could be ranked as follows:

Piperazine ethanol > piperazine group >piperidine group > aliphatic chain

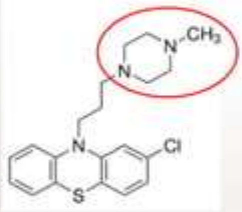


piperazineethanol

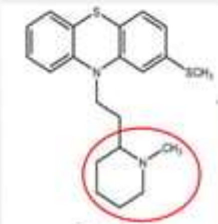




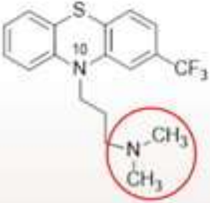
Fluphenazine HCl



Prochlorperazine



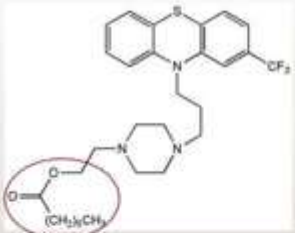
Thioridazine



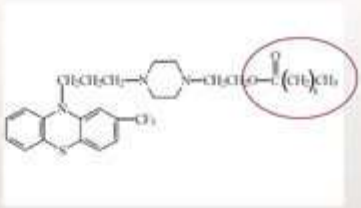
Triflupromazine

5) Esterification of the OH containing piperazine derivatives extensively increases the duration of action.

Long –acting neuroleptics for IM Depot injection

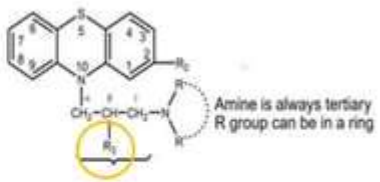


Fluphenazine enanthate

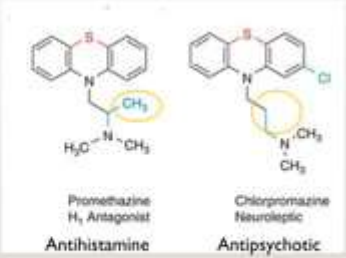


Fluphenazine decanoate

6)Methyl branching on the β-position has a variable effect on activity.



- There must be an linear (unbranched) alkyl linker between the core ring and the terminal amino ring those length is optimum at three methylene units CH2-CH2-CH2
- Reduction of these carbon number changes receptor affinity



7) The sulfur atom at position 5 is in a position analogous to the p-hydroxyl group of DA, and it was also assigned a receptor-binding function.

- In this conformation the aromatic ring and sulfur of phenothiazine correlates with the structure of dopamine (S with pOH of dopamine)

Pharmacokinetic of Phenothiazine:

- Most phenothiazines undergo significant first-pass metabolism. Chlorpromazine and other phenothiazines are metabolized extensively by CYP2D6.
- A major route is 7-hydroxylation of the tricyclic system. Because electron-withdrawing 2-Cl substituent blocks the hydroxylation on chlorophenyl ring, the hydroxylation occurs at 7-position rather than 2-position.
- Thus, the major initial metabolite is frequently the 7-hydroxy compound (active metabolite). This compound is further metabolized by conjugation with glucuronic acid.

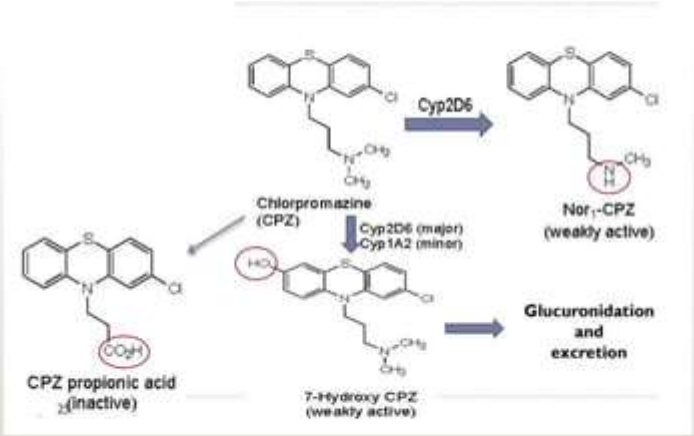
Chlorpromazine Hydrochloride:

- Chlorpromazine was the first phenothiazine compound used in treatment of schizophrenia.
- It is still useful as an antipsychotic
- Other uses as antiemetic agent and against hiccups
- Has high incidence of Extra Pyramidal side effects .
- Oral doses of chlorpromazine and thioridazine have systemic availability of 25% to 35% because of significant first-pass metabolism.
- Chlorpromazine and other phenothiazines are metabolized extensively by CYP2D6.
- In contrast, bioavailability of chlorpromazine may be increased up to 10-fold with injections, but the clinical dose usually is decreased by only threefold to fourfold.
- It's metabolite has strong antiadrenergic, weak anticholinergic and slight antihistaminergic and antiserotonergic properties (not parent molecule).

MOA:

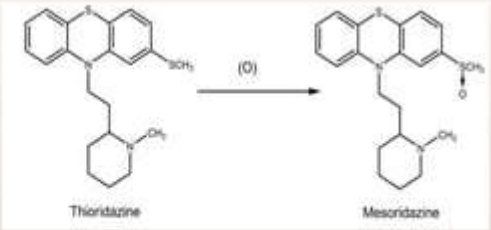
- It antagonizes Dopamine D2 in the Mesocortical and Mesolimbic pathway

Metabolic Pathways for Chlorpromazine



Thioridazine Hydrochloride:

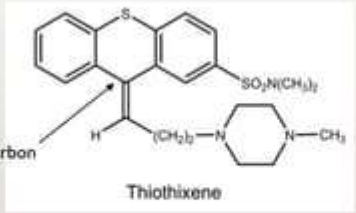
- The drug has high anticholinergic activity, and this activity in the striatum, counterbalancing a striatal DA block, may be responsible for the low EPS.
- The drug has sedative and hypotensive activity in common with chlorpromazine and less antiemetic activity.
- At high doses, pigmentary retinopathy has been observed.
- Its major metabolites include N-demethylated, ring hydroxylated, and S-oxidized products.
- Thioridazine is prominently converted to the active metabolite mesoridazine which probably contributes to the antipsychotic activity of thioridazine.



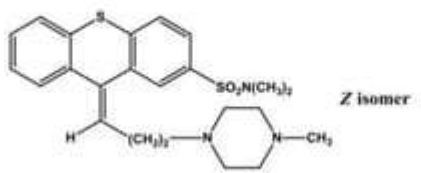
Thiothixene:

- The thioxanthene system differs from the phenothiazine system by replacement of the N-H moiety with a carbon atom doubly bonded to the propylidene side chain. With the substituent in the 2-position, Z-and E-isomers are produced.
- In accordance with the concept that the presently useful antipsychotics can be superimposed on DA, the Z-isomers are the more active antipsychotic isomers.
- The compounds of the group are very similar in pharmacological properties to the corresponding phenothiazines. Thus, thiothixene displays properties similar to those of the piperazine subgroup of the phenothiazines.

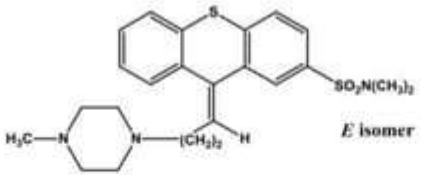
Replacement of the N-H moiety with a carbon atom doubly bonded



Thiothixene



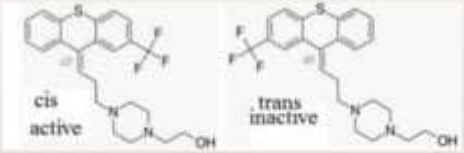
Z isomer



E isomer

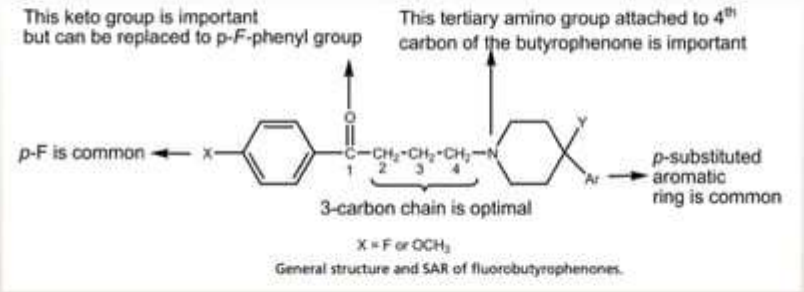
Flupenthixol ;

- It is a Thioxanthine derivative used for treatment of schizophrenia
- It can exist in cis and trans form and only cis is active because it mimics the conformation of Dopamine
- It's duration of action is long (2-3 weeks) and hence useful in patients who have a poor compliance with medication MOA- It is nonselective and antagonizes both Dopamine D1 and D2 in the Mesocortical and Mesolimbic pathway



Fluorobutyrophenones

SAR of Butyrophenones

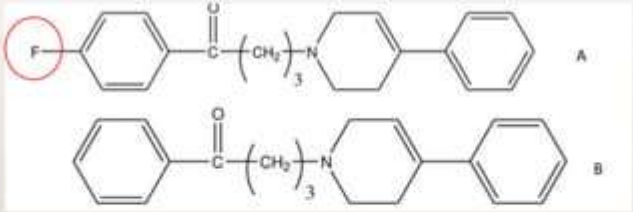


General structure and SAR of fluorobutyrophenones.

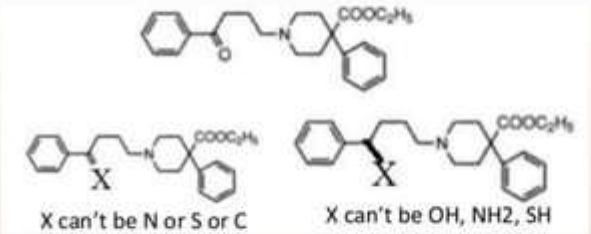
SAR of Butyrophenones

1) Modification of benzoyl group:

- Anything other than fluorine in the para position lowers activity
- A is 4 times more potent than B due to F

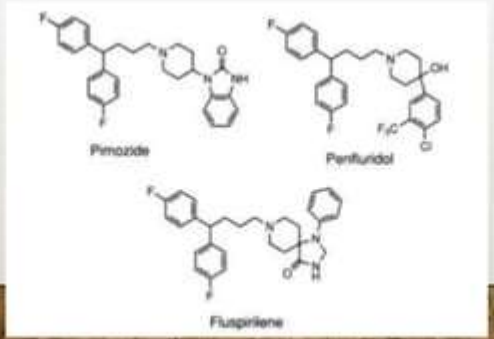


2) Replacing the carbonyl group with isoteric group or any other functional group lowers activity X can't be N or S or C X can't be OH, NH2, SH.



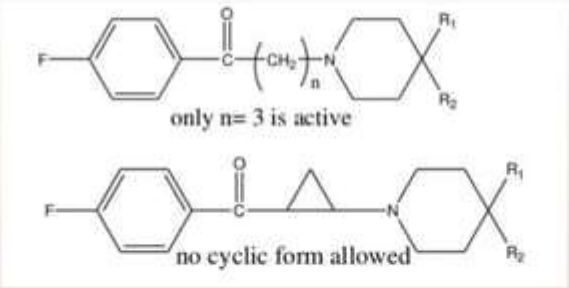
- **An important exception - Diphenylbutylpiperidines**
  - Replacement of the carbonyl of haloperidol with para fluro phenyl group creates a new class of compounds called **diphenylbutylpiperidines** that has following advantage:
- ✓ Long acting
- ✓ NO sedative, autonomic, extrapyrimidal side effects
- ✓ Useful in autism (Autism is a mental disorder in children characterized by impaired social interaction and verbal and non-verbal communication, and by repetitive behavior)

Diphenylbutylpiperidines
The keto group has been replaced with para Fluro group



3) Modification of the -CH2- linker group

- The linker has to be a propylene.
- Any alteration to the -CH2- linker region such as shortening, lengthening, branching, or incorporation into a ring system, results in a marked decrease or even complete loss of neuroleptic activity.

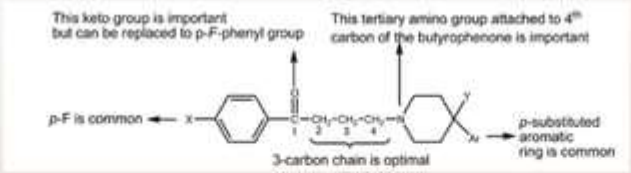


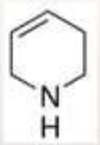
4) Modification of the amino group

a) A tertiary amino group should be present

b) A tertiary amine in some cyclic form (piperidine, tetrahydropyridine or piperazine ring) increases potency

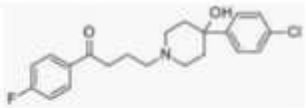
c) Further modification of the ring at para position can de done for better potency and reducing toxicity





tetrahydropyridine

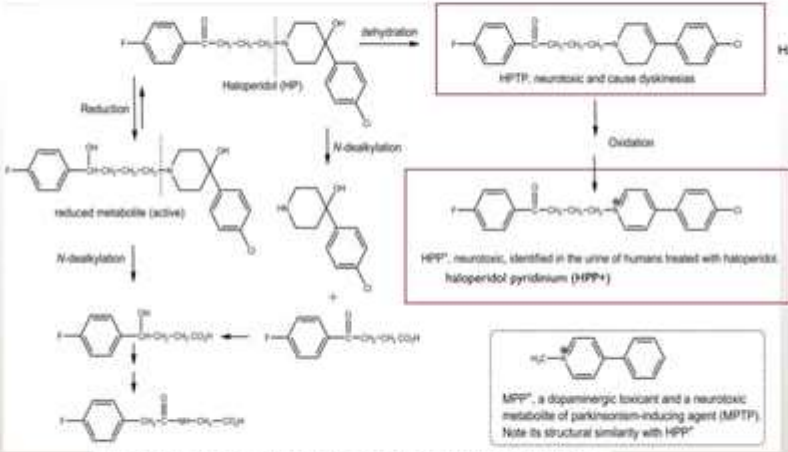
Haloperidol, (Haldol):



- It is a Butyrophenone derivative used in the treatment of schizophrenia , delirium and in psychoses associated with brain damage.
- It can also help prevent suicide in people who are likely to harm themselves. It also reduces aggression and the desire to hurt others. It can decrease negative thoughts and hallucinations.
- It has High incidences of Extra Pyrimidal Side effects (EPS – tremor and motor dysfunction) but Low hypotension and low autonomic side effects and sedative effects lower than Chlorpromazine.

Metabolism

- Haloperidol-induced dyskinesias may involve neurotoxicological metabolite similar to dopaminergic toxicant MPP+.

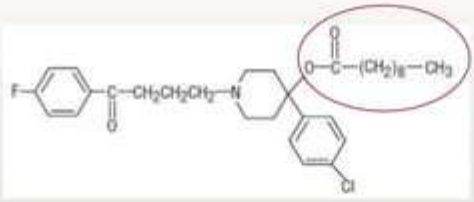


Metabolism of haloperidol and its possible neurotoxic metabolites.

MPP+ (1-methyl-4-phenylpyridinium) i

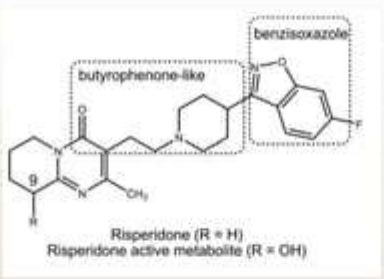
Haloperidol decanoate

- Decanoate Esterifation at the OH group forms a long acting derivative .
- Haloperidol decanoate is used for long-term treatment of a certain mental/mood disorder (schizophrenia).
- It may be used in people who have trouble remembering to take medication every day.
- This medicine helps you to think more clearly, feel less nervous, and take part in everyday life



Risperidone (Risperdal, a benzisoxazole):

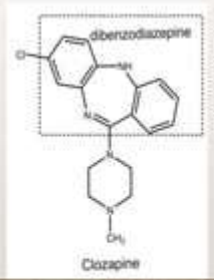
- Risperidone has the structural features of a hybrid molecule between a butyrophenone antipsychotic and a trazodone-like antidepressant. It is an important atypical antipsychotic.



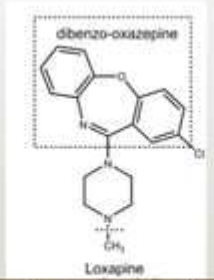
Ring Analogs of Phenothiazines:

Benzazepines, Dibenzoxazepines, and Dibenzodiazepines:

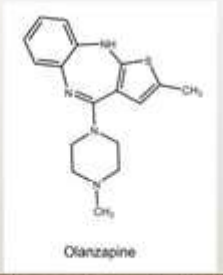
- Additional tricyclic antipsychotic agents are the benzazepines, containing a seven-membered central ring (6-7-6 system).
- These newer atypical antipsychotics include dibenzodiazepines (clozapine with 2-Cl), dibenzoxazepines (loxapine with 2-Cl), thienobenzodiazepines (olanzapine without 2-substituent), and dibenzothiazepines (quetiapine without 2-substituent)



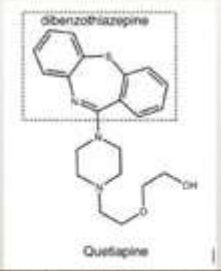
Clozapine



Loxapine



Olanzapine



Quetiapine

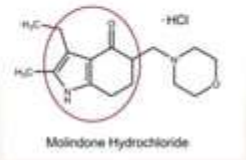
5-THA2A - D2 block

Both (Typical and Atypical):

Dihydroindolones:

- **Molindone Hydrochloride.**

- Molindone hydrochloride (Moban) is about as potent an antipsychotic as trifluoperazine. Overall, side effects resemble those of the phenothiazines.

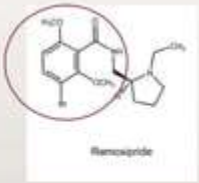


Molindone Hydrochloride

Benzamides:

- **Remoxipride (Roxiam).**

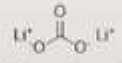
- Remoxipride is a D_2 receptor blocker. It is as effective as haloperidol with fewer EPS
- . Negative symptoms of schizophrenia are diminished.
- The drug is classed as an atypical antipsychotic. Life-threatening aplastic anemia was reported with its use, which prompted its withdrawal from the market.


Remoxipride

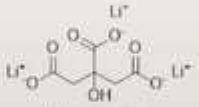
Antimanic Agents:

- **Lithium Salts:**

- The lithium salts used in the United States are the carbonate (tetrahydrate) and the citrate.
- Lithium chloride is not used because of its hygroscopic nature and because it is more irritating than the carbonate or citrate to the GI tract.
- The active species in these salts is the lithium ion.
- Accordingly, it might prevent excessive release of NTs (e.g., DA) that characterize the manic state.
- It works to stabilize the mood and reduce extremes in behavior by restoring the balance of certain natural substances (neurotransmitters) in the brain.



Lithium carbonate



Lithium citrate


Thank
You