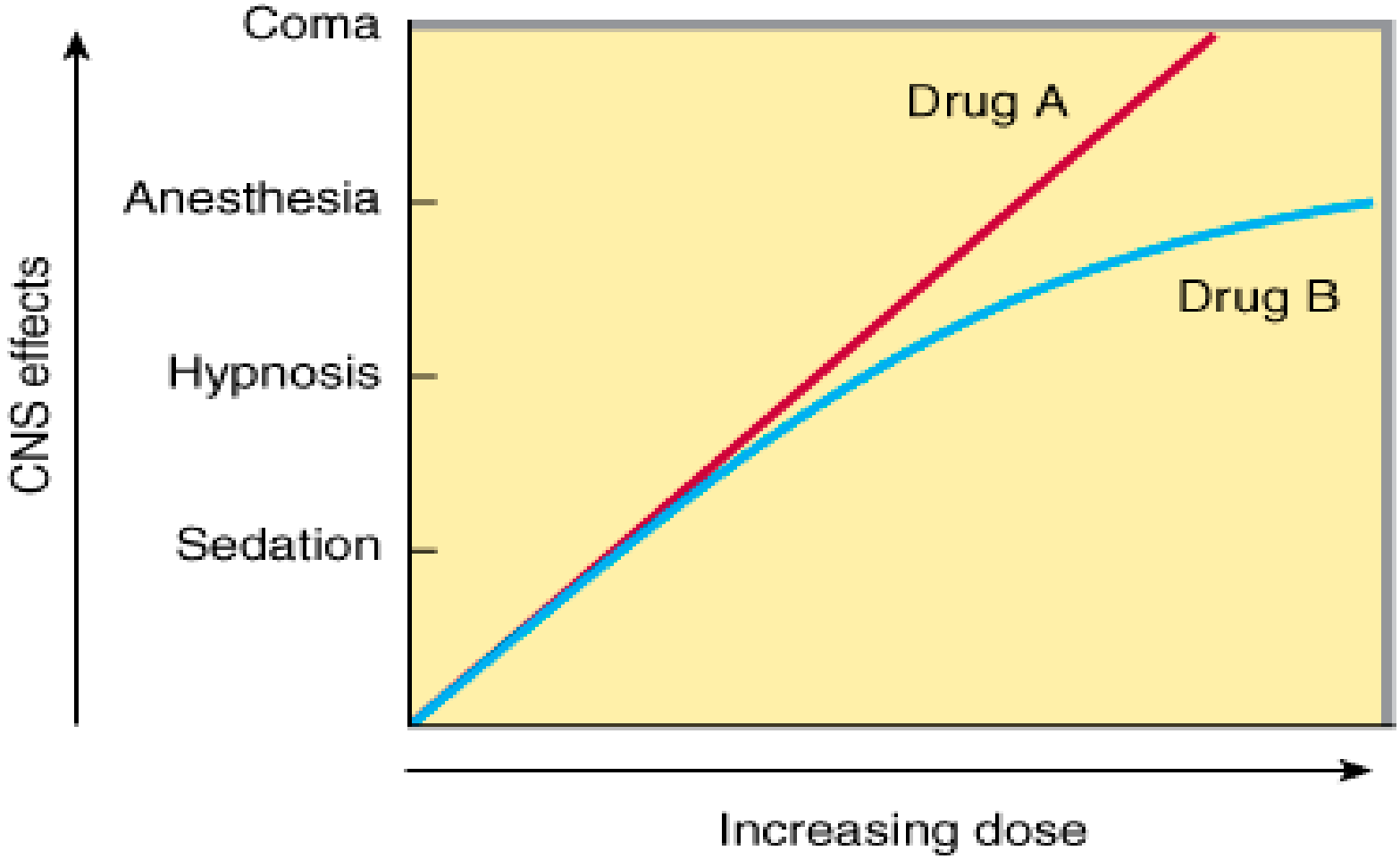
HYPNOTICS AND SEDATIVES

- **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		

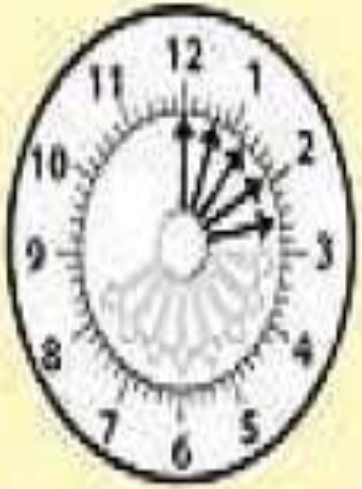
Non Benzodiazepine hypnotics

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

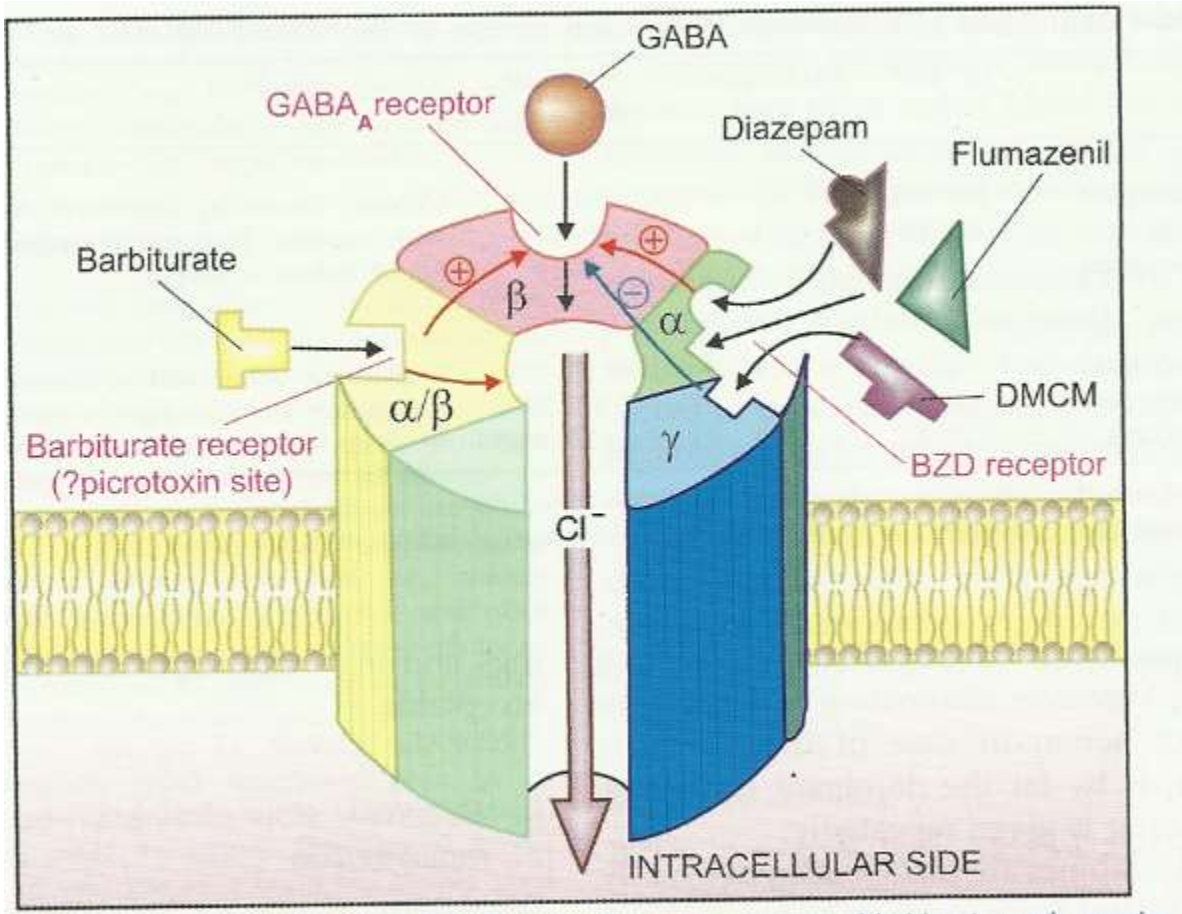
Miscellaneous

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

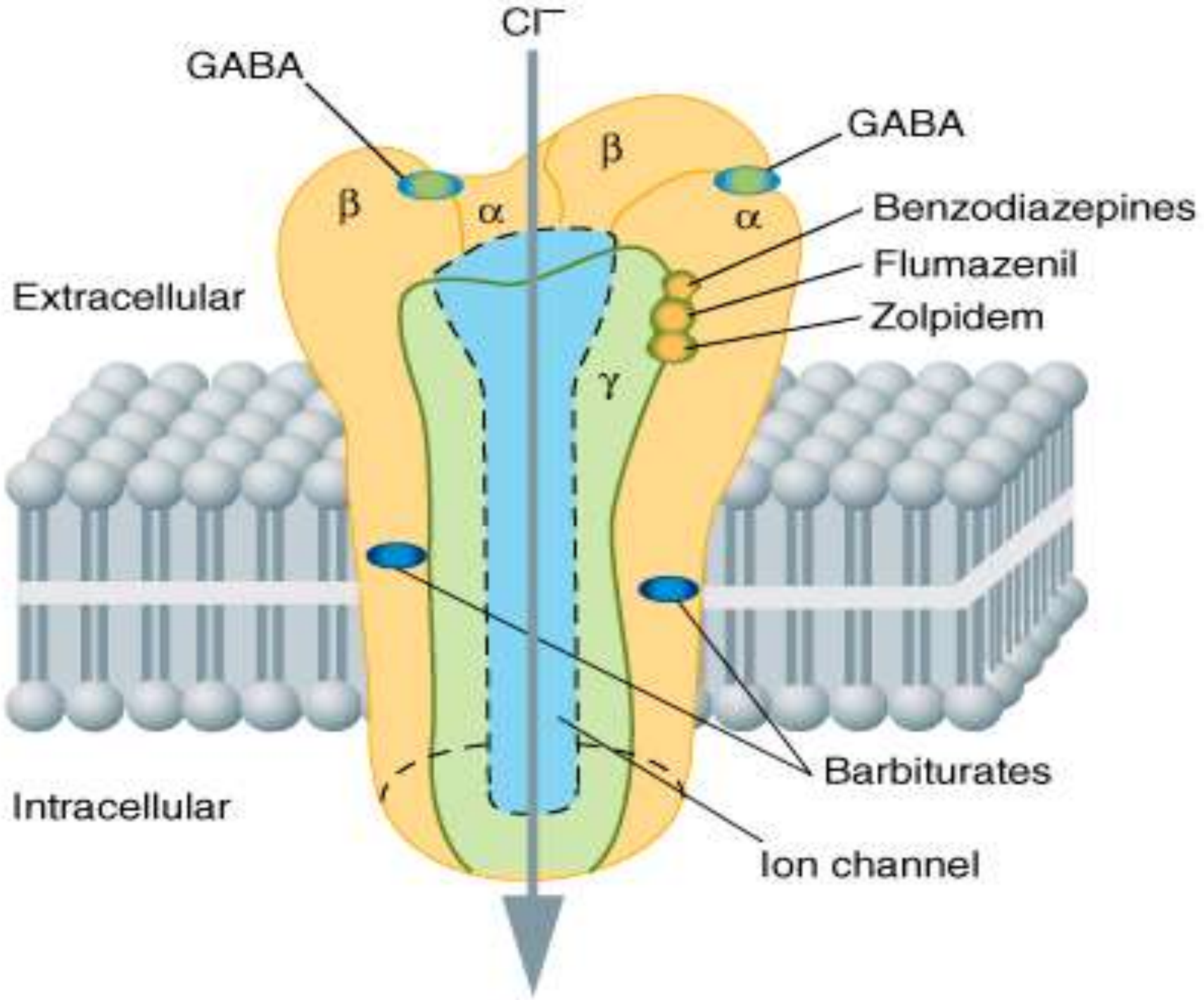
BARBITURATES CLASSIFIED ACCORDING TO THEIR DURATIONS OF ACTION

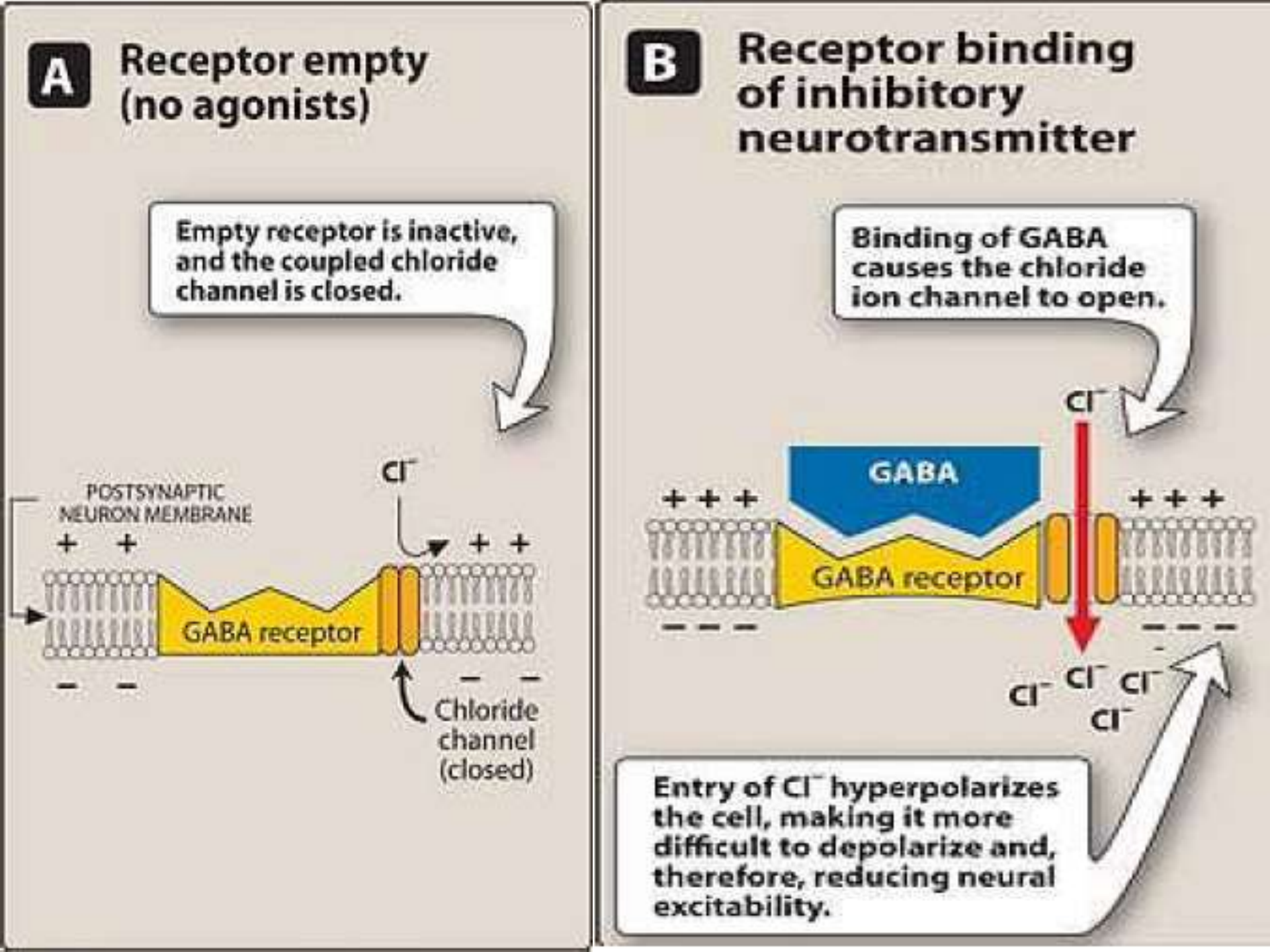
Long-acting	Short-acting	Ultra-short-acting
	 3–8 Hours	 20 Minutes
Phenobarbital	*Pentobarbital* *Secobarbital* *Amobarbital*	*Thiopental*

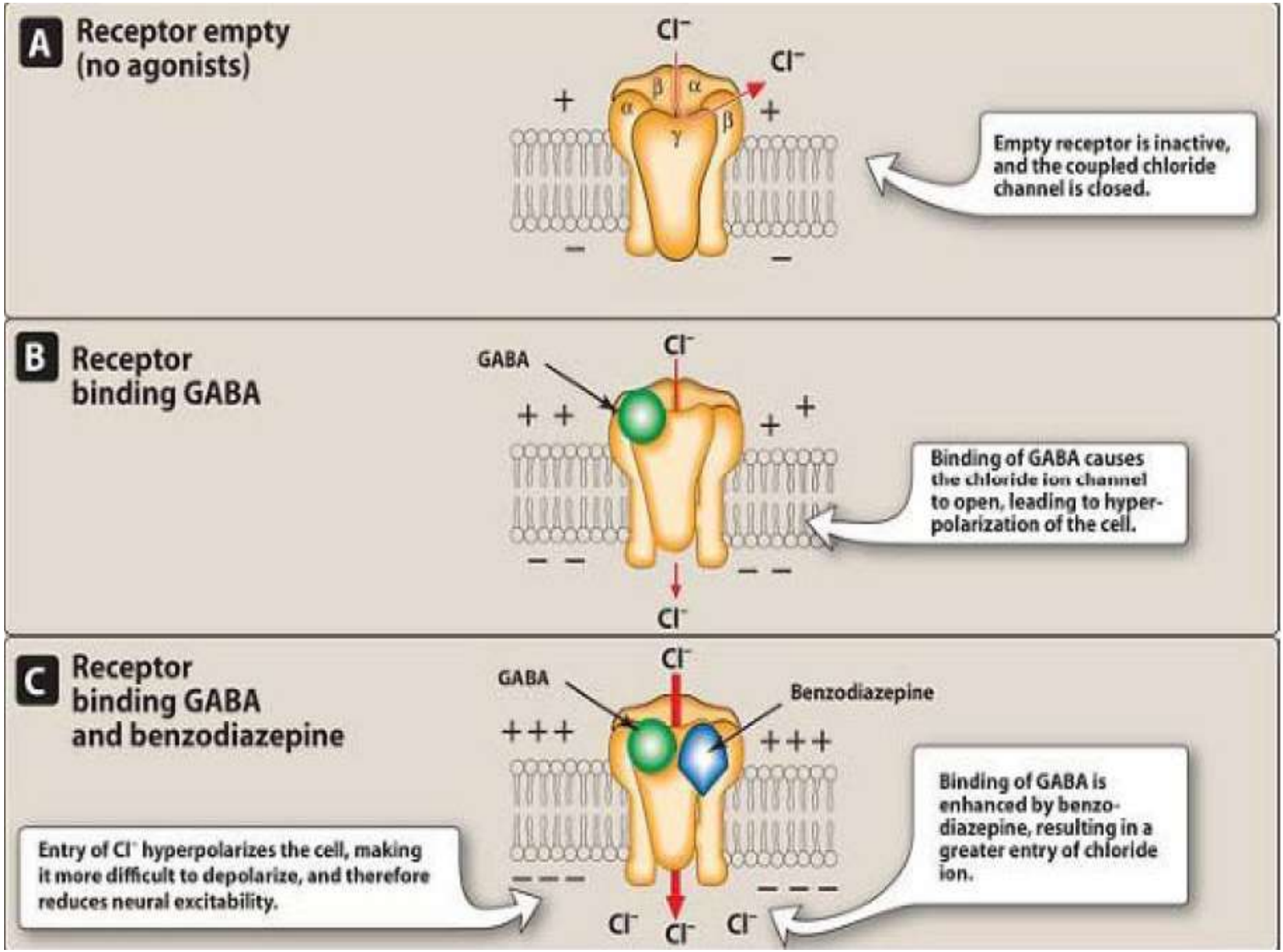
The chloride channel is gated by the primary ligand GABA acting on $GABA_A$ receptor located on the β subunit. The benzodiazepine (BZD) receptor located on the interface of α and γ subunits modulates $GABA_A$ receptor in either direction: agonists like diazepam facilitate, while inverse agonists like 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.

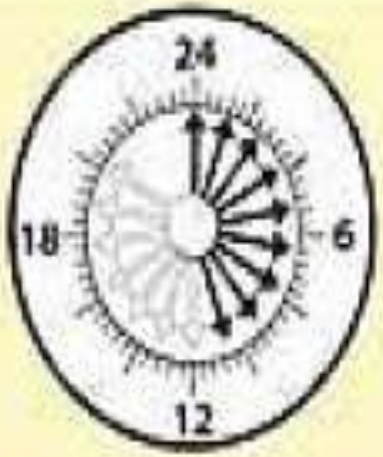
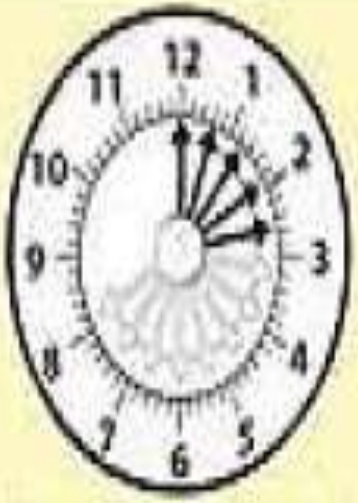
- In the event of renal failure - hemodialysis

- 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.**

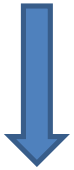
MELATONIN CONGENERS

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

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THANKS