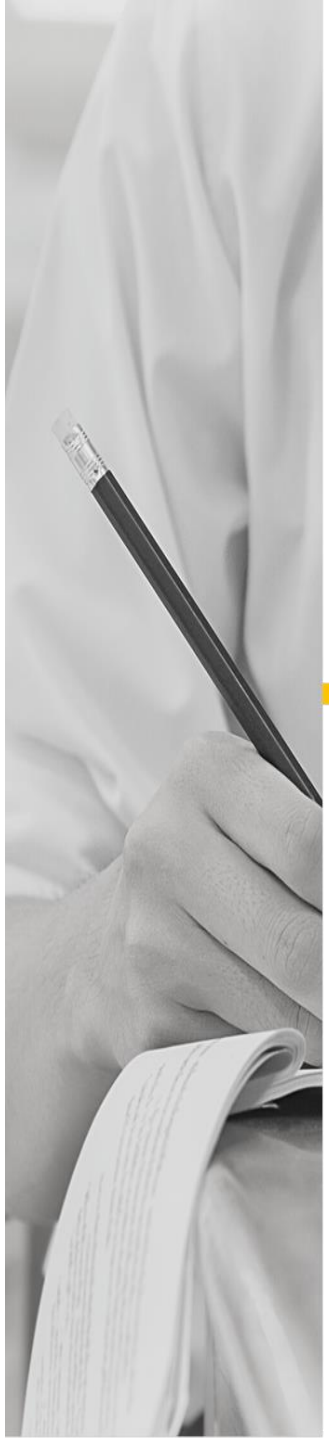

Tikrit University
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Subject name:DRUG EVALUATION

Subject year: MSc - PHARMA

Lecturer name: MICRO. ASSAY

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Subject name:Advanced Pharma

Subject year: MSc - PHARMA

LECTURER : Prof Dr Husamuldeen Alnajar

Lecture name: Drugs Act On CNS.

Academic Email:Sbc.s4@tu.edu.iq

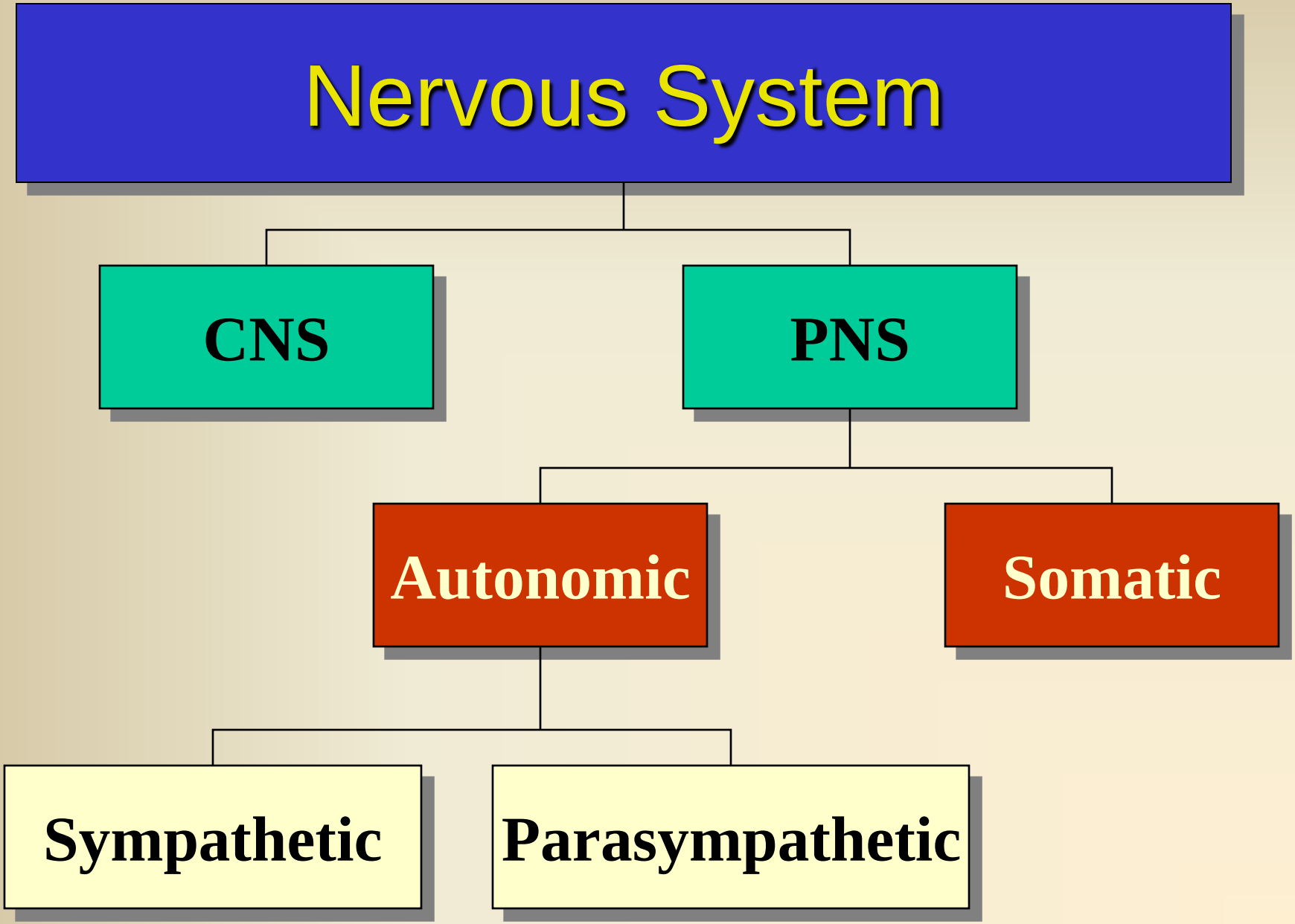
Tikrit University
College of Vet. Medicine

First Term - M.Sc Pharmacology
Advanced Pharmacology

Prof Dr Husamuldeen Alnajar

2023-2024

Drugs acting on the CNS (1)


Nervous System
CNS
PNS
Autonomic
Somatic
Sympathetic
Parasympathetic

Ranking of CNS drugs

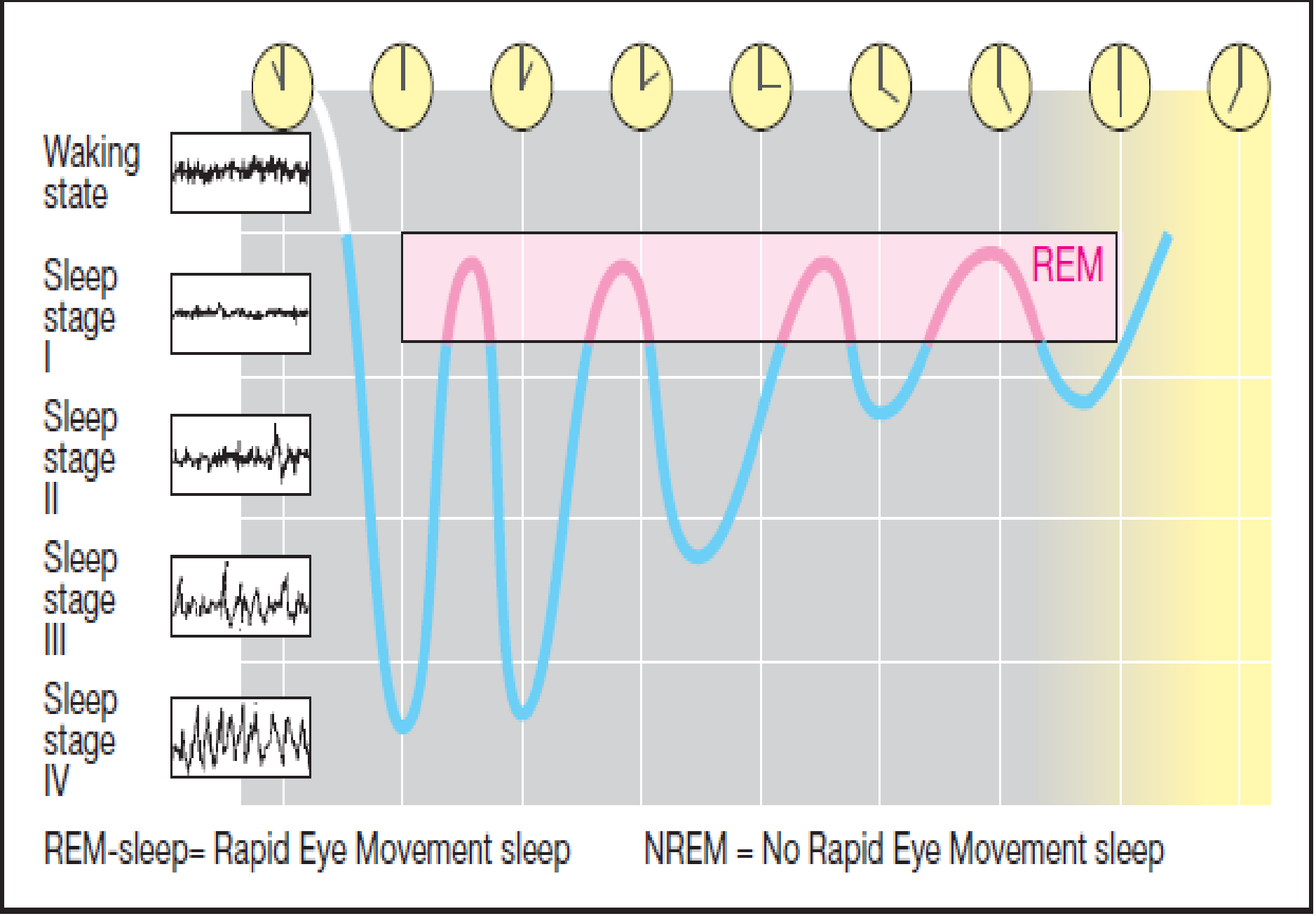
- **SSRIs**
  - Celexa[35] (citalopram)
  - **Lexapro[24] (escitalopram)**
  - Prozac[30] (fluoxetine)
  - Zoloft[20] (sertraline)
  - Paxil[48] (paroxetine)
- **Other AntiDepressants**
  - **Wellbutrin/Zyban[36] (bupropion)**
  - **Cymbalta[59] (duloxetine)**
  - Desyrel[47] (trazodone)
  - **Effexor[44] (venlafaxine)**
- **"Atypical" Anti-Pyschotics**
  - **Abilify[149] (aripiprazole)**
  - **Zyprexa[185] (olanzapine)**
  - Seroquel[81] (quetiapine)
  - Risperdal[112] (risperidone)

- **Anxiolytics/Hypnotics**
  - Xanax[10] (alprazolam)
  - BuSpar[155] (buspirone)
  - Valium[60] (diazepam)
  - Ativan[33] (lorazepam)
  - Restoril[106] (temazepam)
  - **Ambien[16] (zolpidem)**
- **Anticonvulsants**
  - Klonopin[34] (clonazepam)
  - Neurontin[37] (gabapentin)
  - Lamictal[103] (lamotrigine)
  - **Keppra[213] (levetiracetam)**
  - Dilantin[147] (phenytoin)
  - **Lyrica[93] (Pregabalin)**
  - Topamax[107] (topiramate)
  - Depakote[122] (Valproic Acid)
- **Stimulants**
  - **Strattera[216] (atomoxetine)**
  - Concerta/Ritalin[110] (methylphenidate)
  - Adderall[57] (dextro/amphetamine salts)

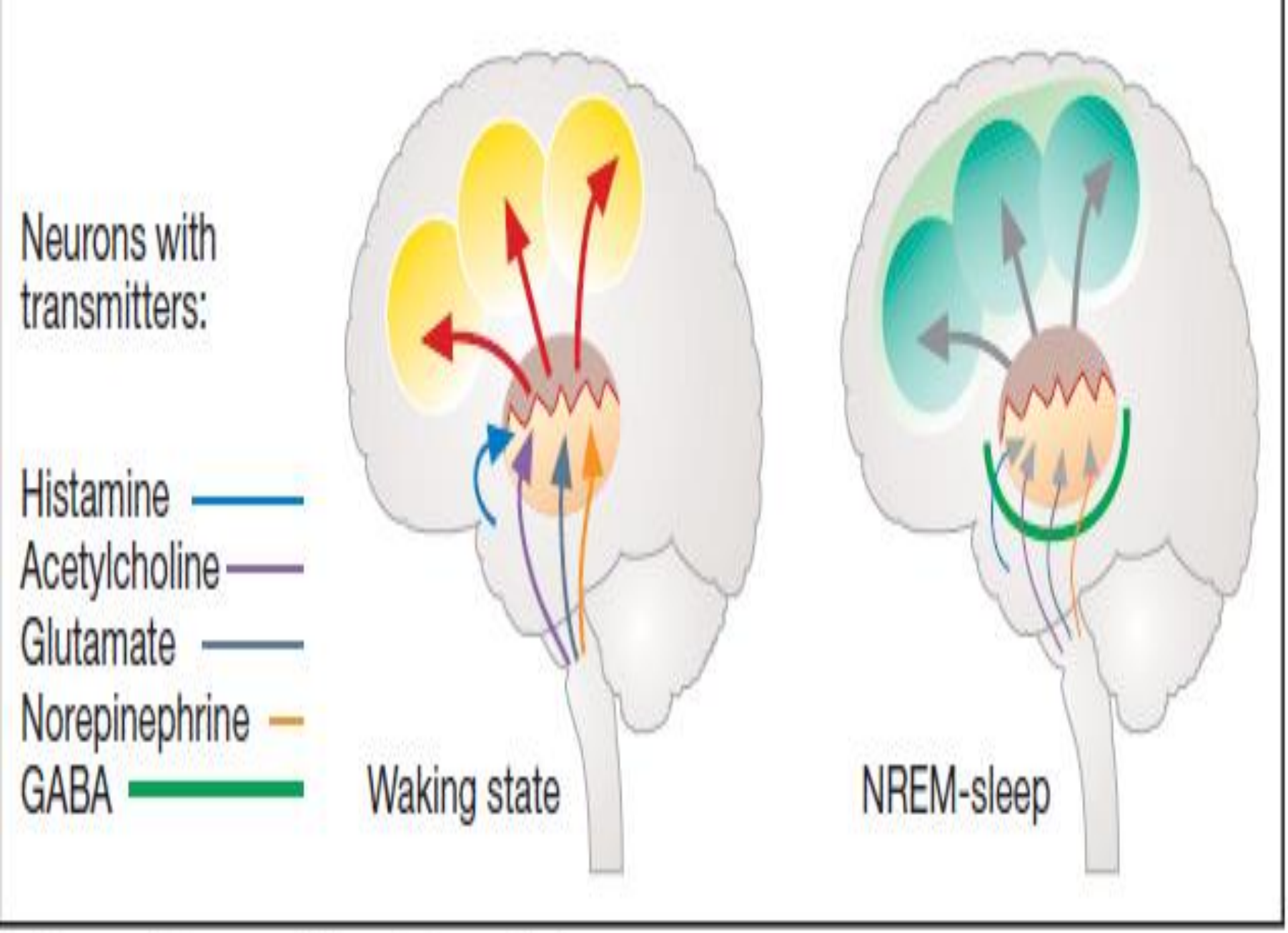
- **Skeletal Muscle Relaxants**
- Soma[73] (carisoprodol)
- Flexeril[42] (cyclobenzaprine)
- Robaxin[190] (methocarbamol)

- **TCAs**
- Elavil[63] (amitriptyline)
- Remeron[143] (mirtazapine)
- Pamelor[219] (nortriptyline)

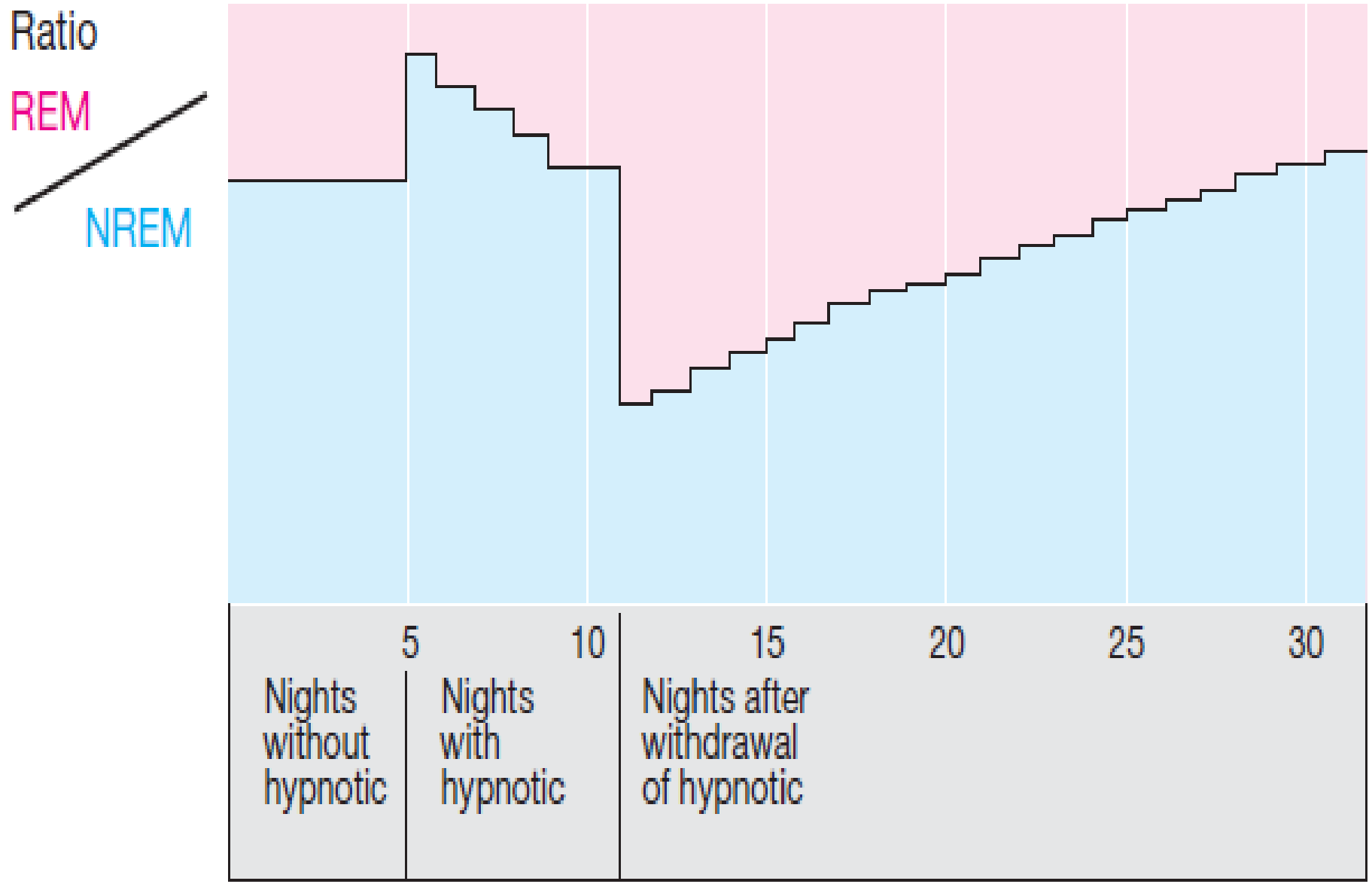
Anxiolytic and Hypnotic Drugs



A. Succession of different sleep phases during night rest



A. Transmitters: waking state and sleep



3. Effect of hypnotics on proportion of REM/NREM

Definitions Sedative & Hypnotics

- **Anxiety is** an unpleasant state of **tension,** apprehension, or a **fear** that seems to arise from an unknown source.

- **Anxiolytics** : Drugs that **clam** the patient and reduce anxiety **without inducing normal sleep.**

- **Hypnotics** : Drugs that initiate and maintain the normal sleep.

- Anxiolytic (anti anxiety drugs)
- hypnotic (sleep-inducing agent)

Types of anxiety disorders

1. **Generalized anxiety disorder— persistent state of heightened anxiety with increased levels of motor tension and autonomic hyperactivity.**

2. **Panic disorder— recurrent, discrete periods of sudden and intense fear or discomfort accompanied by autonomic arousal.**

Classification of hypnotic drugs

1. **Benzodiazepines (BDZ)**
2. **Barbiturates**
3. **Miscellaneous (non BDZ non barbiturate drugs).**
   - **Zolpidem**
   - **Zaleplon**
4. H1-antihistamines with sedative activity

Benzodiazepines :

End with suffix azolam or azepam

- Triazolam
- Alprazolam
- Estazolam
- Lorazepam
- Diazepam
- Oxazepam
- Temazepam
- Nitrazepam

Classification of benzodiazepines

According to duration of action :

- **Short acting: (3-5 hours) : Triazolam**
- **Intermediate: (6-24 hours):**

  Lorazepam

  Estazolam

  Oxazepam

  Temazepam

  Alprazolam

  Nitrazepam

- **Long acting: (24-72 hours)**

- **Chlorazepate**
- **Diazepam**
- **Quazepam**
- **Chlordiazepoxide**
- **Flurazepam**
- **Prazepam**

According to uses

- **Anxiolytics:**

Lorazepam Oxazepam Alprazolam Chlordiazepoxide Diazepam Prazepam Clonazepam

- **Hypnotics :**

short: Triazolam

Intermediate:

Lorazepam , Estazolam

Temazepam Nitrazepam

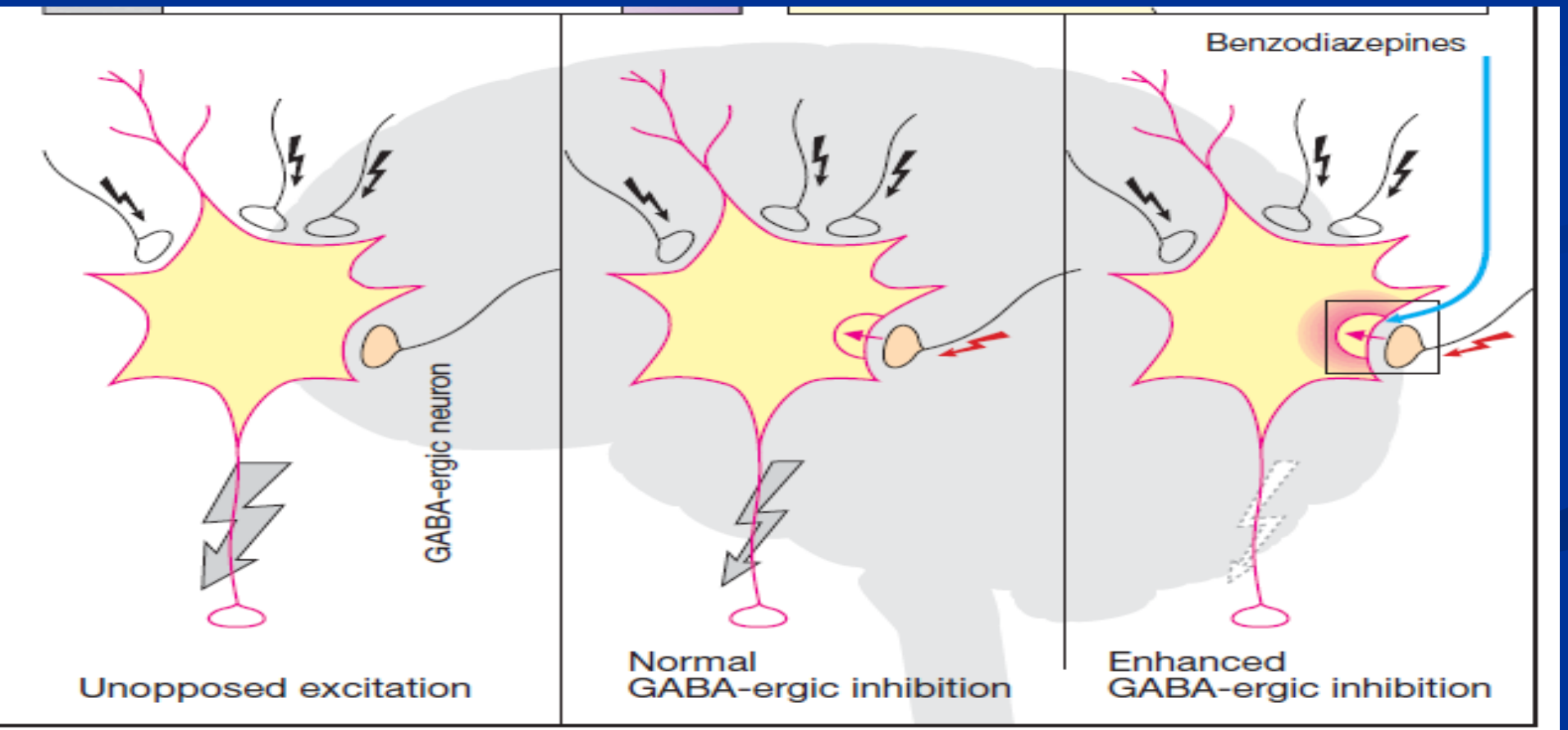
Long: Flurazepam, Quazepam

- **Preanesthetics : Diazepam - Midazolam**

1-Benzodiazepines

Benzodiazepines are the most widely used **anxiolytic drugs.**

Benzodiazepines are more **effective and safer**



A. Action of benzodiazepines

Benzodiazepines receptors

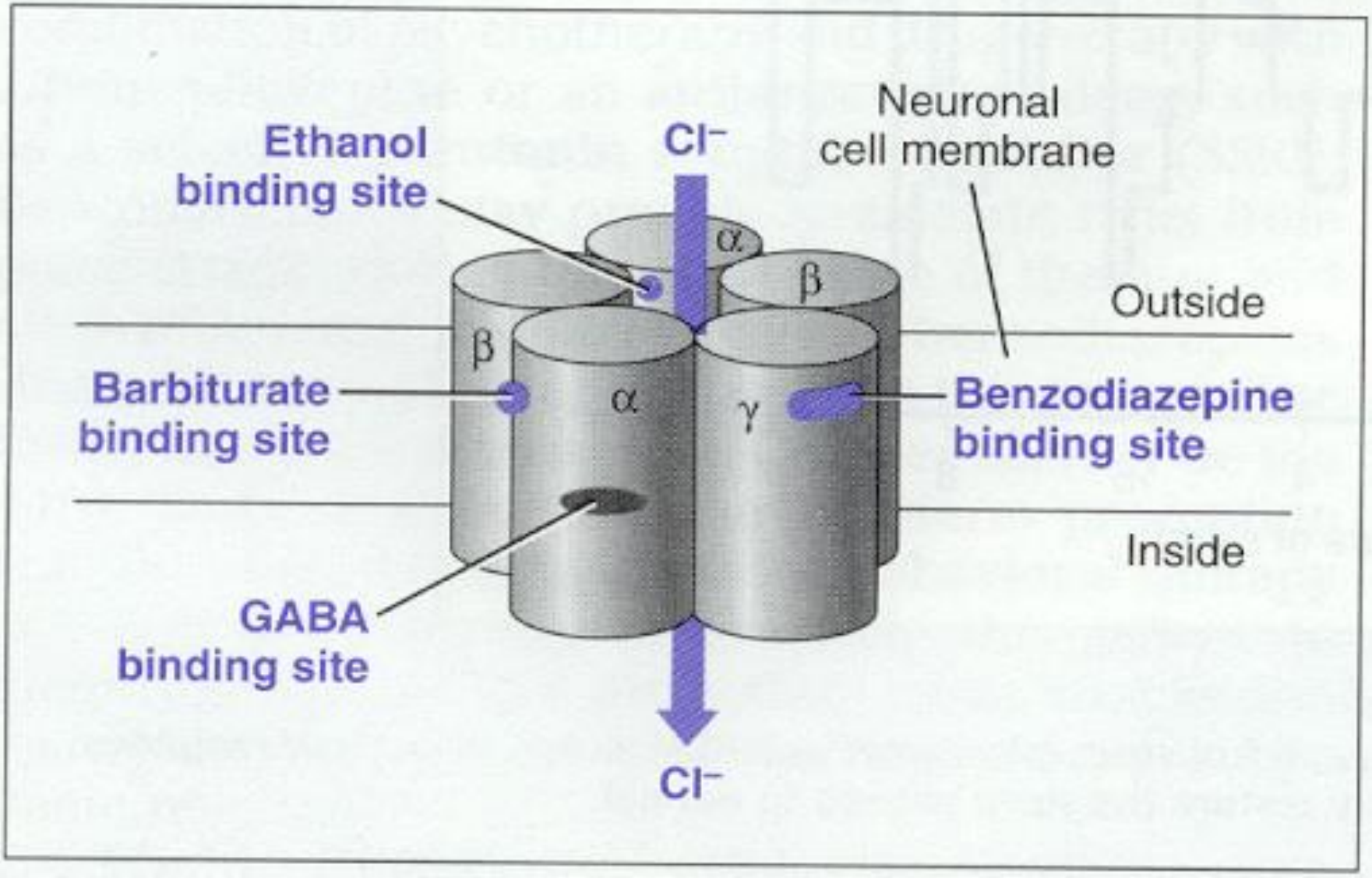
There are 3 types of BZ receptors :

1-BZ1 ⇒ central receptor linked to sleep

2-BZ2 ⇒ central receptor linked to cognition & motor function

3-periphral BZ receptors (?)

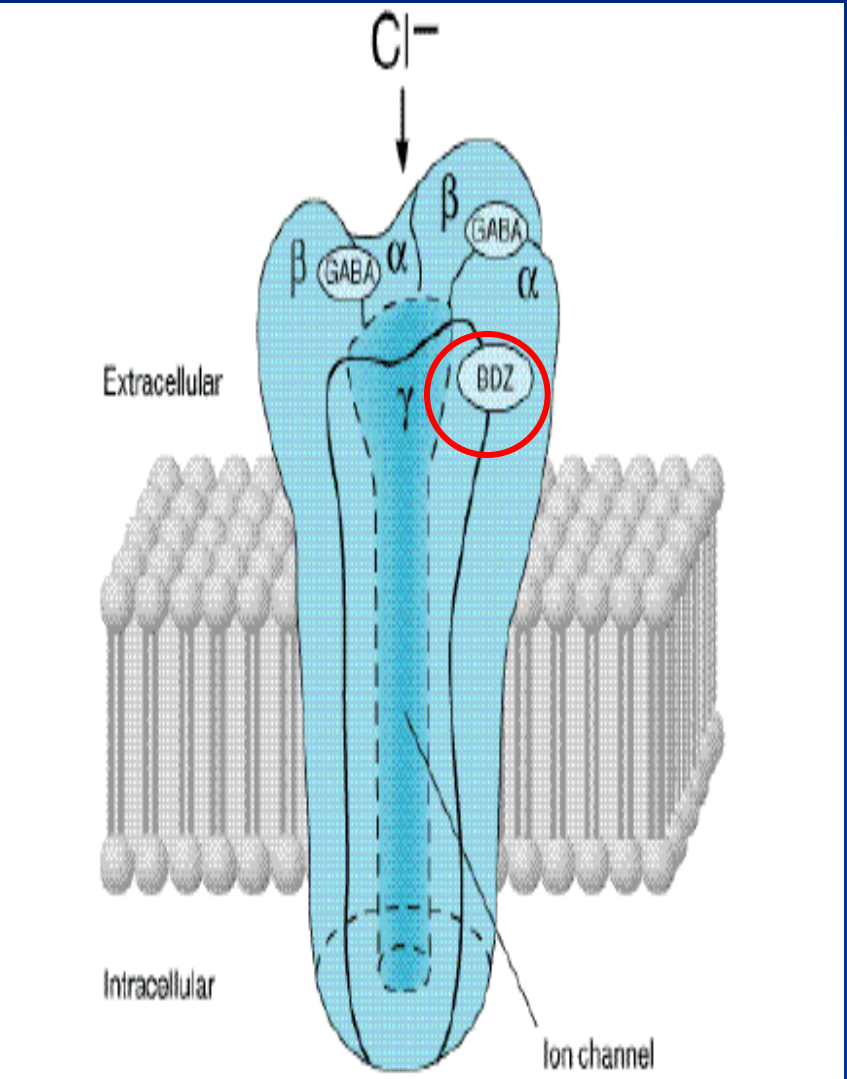
Gamma-aminobutyric acid *receptor (GABA)*



Benzodiazepines Mechanism of action

- The **benzodiazepines bind** with high affinity to **specific** ***benzodiazepine-binding sites (*** **BZ1 and BZ2** receptors subtypes***) for*** Gamma-aminobutyric acid ***(GABA),***
- ***(GABA): which is the major inhibitory neurotransmitter***

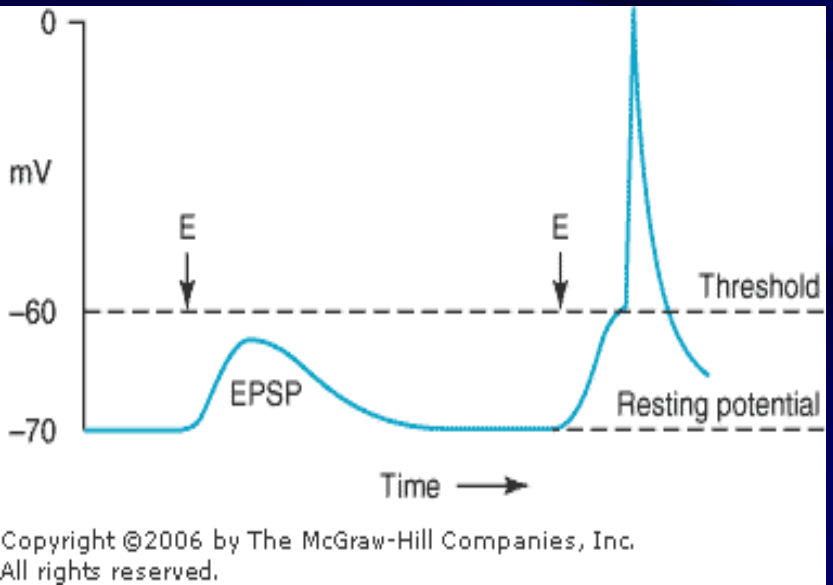
in the brain.

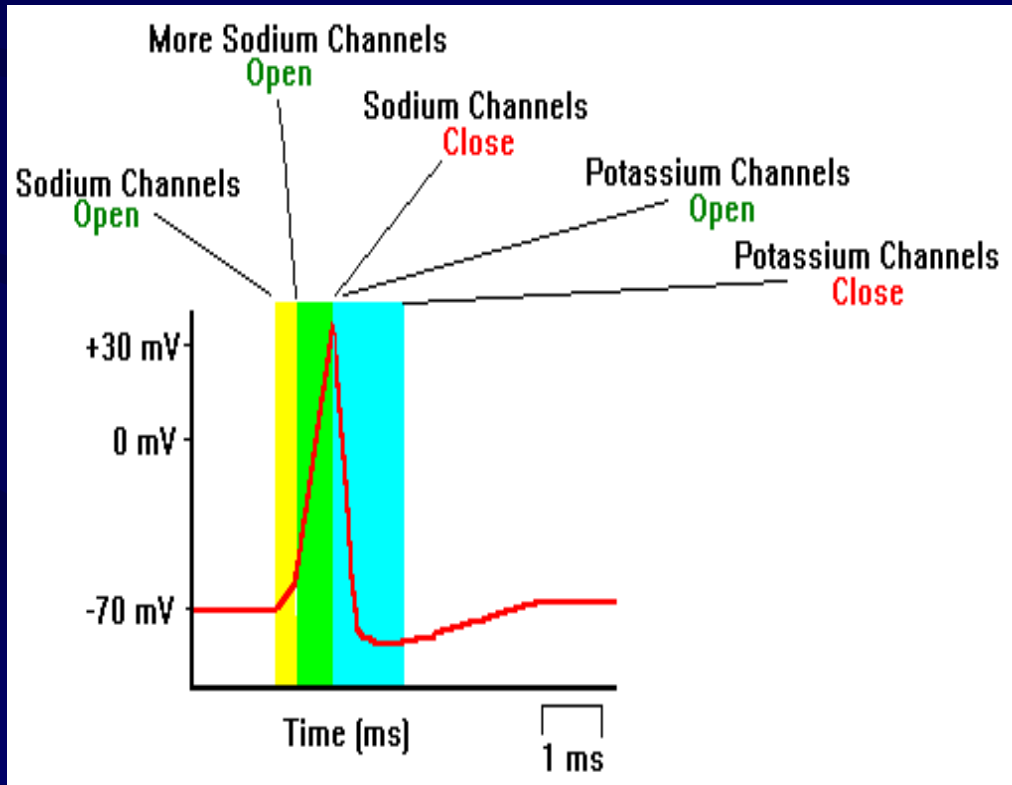


Mechanism of Action

By binding to BZ receptors (BZ1 or BZ2).

Bzs facilitate GABA-induced chloride channels hyperpolarization = GABA-mediated inhibitory neurotansmission





Mechanism of Action

Benzodiazepines combine with BZ receptors → increase GABA action on GABA receptors → chloride channels opening →

↑ chloride influx to the cell → cell membrane hyperpolarization → inhibition of propagation of action potential → inhibitory effect on different sites of the brain especially motor cortex & limbic system.(so it will increase inhibitory effect of GABA**)**

Benzodiazepines therapeutic uses

1. Anxiety disorders :
   - Both acute and chronic anxiety
   - Diazepam is used for long period
2. Muscular disorders: Diazepam in muscle spasms
3. Amnesia:
   - short acting agents used.
   - in endoscopy, bronchoscopy & angioplasty.
4. Seizures: Clonazepam in chronic epilepsy
   - Diazepam is the drug of choice in status eplipticus
5. Diazepam & Oxzepam in treatment of alcohol withdrawal.

Benzodiazepines therapeutic uses

6. Sleep disorders:

- Effective drugs

1. Triazolam.
2. Temazepam.
3. Flurazepam

Benzodiazepines

4. Zolpidem.
5. Zaleplon.

Nonbenzodiazepens

Benzodiazepines Adverse Eeffects

1. 1- Drowsiness; Confusion.
2. Ataxia (high doses).
3. Impaired Motor Performance.
4. Cognitive impairment.
5. **Interaction with alcohol.**
6. Dependency **and Physical Addiction**: related to the production of "***withdrawl effects***"

- **Psychological addiction : in** High dose. And Prolong treatment

Benzodiazepine Antagonists: Flumazenil

- **Flumazenil** which is used to manage over dose & coma of BZ , given I.V & produce effects within 1-2min
- High affinity for the benzodiazepine receptor
- **Act as selective competitive antagonists on GABA receptor.**
- It is the only benzodiazepine receptor antagonist available for clinical use at present. Should be used IV because drug is Undergoe extensive first pass metabolism.
- intravenously, flumazenil acts rapidly but has a short half-life (0.7–1.3 hours) due to rapid hepatic clearance.
- **Uses**
- Reversing the central nervous system depressant effects of benzodiazepine overdose
- Hasten recovery following use of these drugs in anesthetic and diagnostic procedure

2-Non benzodiazepines : Zolpidem(Ambien)

- Act on BZ_1 receptors. & facilitate GABA .
- Its action is antagonized **by flumazenil.**
- No anticonvulsant, or muscle relaxant effects.
- Minimal rebound insomnia, little tolerance.
- Rapid onset, short duration(3 hours).

  Adverse effects: Nightmares. .Headache. GIT upset.
- Dizziness. Daytime drowsiness. Respiratory depression occur at high doses in combination with other CNS depressant as ethanol.

Uses : a hypnotic drug for short term treatment of insomnia.

3- Buspirone

- Useful in the treatment of generalized anxiety disorders.
- Not effective in treating panic disorder.
  - Minimal sedation, less drowsiness, fatigue than most benzodiazepines
  - Long latency to obtain anxiolytic effect
  - **mode of** Action:
  - The action is mediated by serotonin receptors.(**activates 5-HTreceptor) (Serotonin agonist)**
- Adverse effects:
  - Dizziness
  - Nervousness
  - ligthheadness
  - **No anticonvulsant, or muscle relaxant effects.**

4- Barbiturate

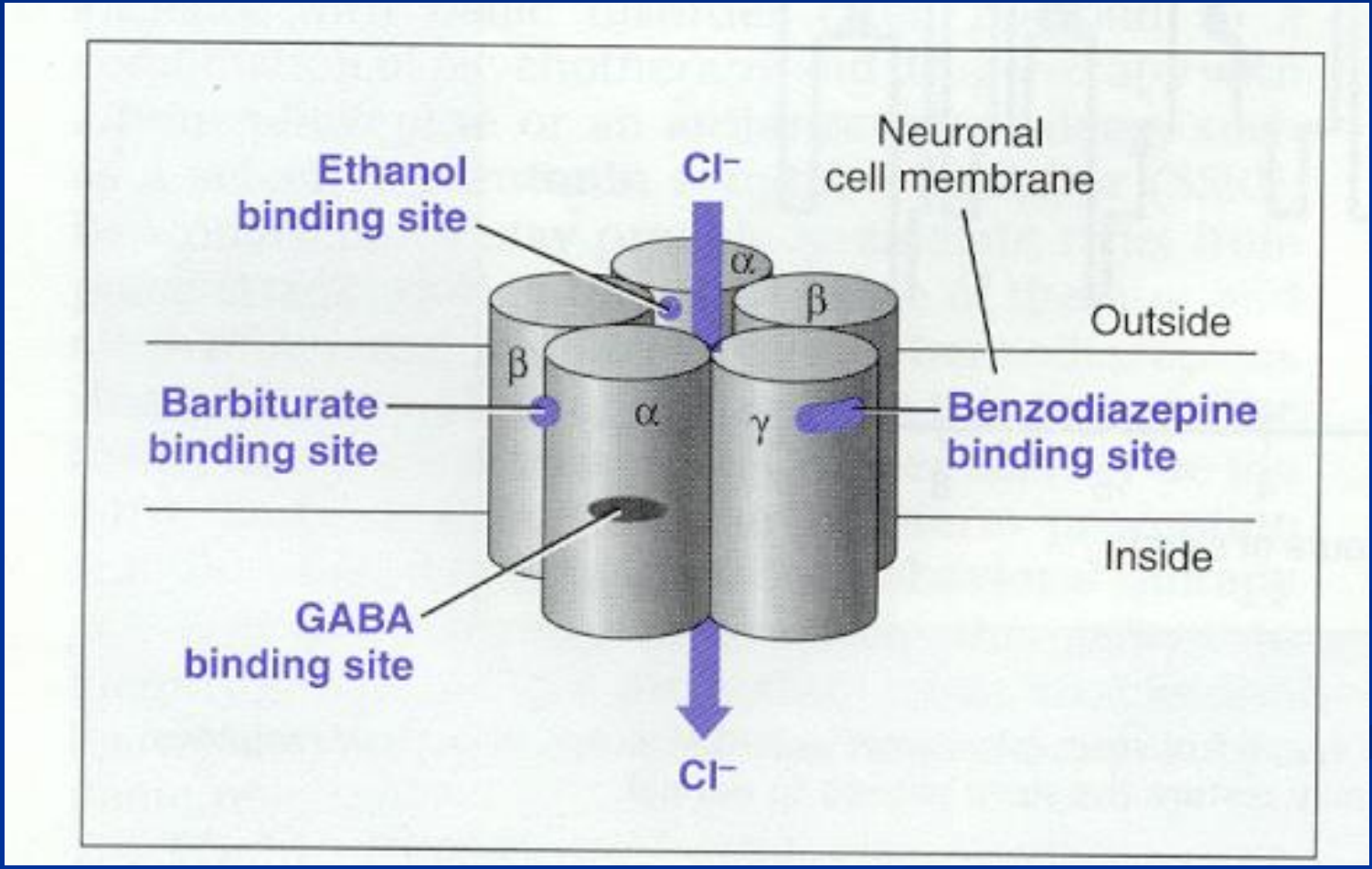
- **Barbiturates** potentiate GABA action **on chloride entry into the neuron**, although they do **not bind at the benzodiazepine** receptor.

BB enhance GABA binding & **increase the duration of GABA- activated chloride ion channel opening** by acting at specific BB binding sites on the GABA receptor complex **leading to hyper polarization & decrease neuronal firing .**

At high dose BB act directly on chloride ion channel & not require presence of GABA, **also BB have action of glutamate receptor inhibition.**

4-barbiturates

Barbiturate Mechanism of action



Classification of barbiturates

- **Long acting:**

Onset of action 1-3hr

Duration 10 hr

Uses convulsive disorders

e.g. Phenobarbital

- **Short to intermediate acting** :

onset of action 30-60 min

Duration 3-8 hr

Uses sedative , hypnotic

e. g Amobarbital , pentobarbital , secobarbital

- **Ultra short acting:**

Onset of action immediate

Duration 15-30min

Uses sedative , anesthetics (I.V) e.g. thiopental

Therapeutic uses

1. **Anesthesia:** The ultra-short-acting barbiturates, such as thiopental used intravenously to induce anesthesia.
2. **Anticonvulsant: Phenobarbital** is used in

a. long-term management of tonic-clonic seizures.

b. status epilepticus

c. eclampsia.

d. drug of choice for treatment of young children with recurrent **febrile seizures.**

3. **Anxiety:** Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension, and insomnia. Most have been replaced by the benzodiazepines.

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 awakes**. This drug hangover leads to impaired ability to function normally for many hours after waking. Occasionally, nausea and dizziness occur.

Precautions: barbiturates **induce the cytochrome P-450 system** and therefore may **decrease the effect** of drugs that are metabolized by these hepatic enzymes.

5- Chloral hydrate (*Noctec, Somnos*)

- was developed in the late 1800s and is still used as a **sedative–hypnotic agent.**
- The drug is an effective sedative and hypnotic that induces sleep **in about 30 minutes and lasts about 6 hours.**
- It produces a high incidence of **gastric irritation and allergic responses.**
- occasionally causes **cardiac arrhythmias.**
- unreliable in patients with liver damage.

6- Antihistamines

- Several H1 histamine antagonists (e.g.diphenhydramine, promethazine and hydroxyzine)
- Effective in treating milder types of insomnia.
- **Hydroxyzine**

is an antihistamine with anti emetic activity

- Used in patient with anxiety who have a history of drug abuse
- Used for sedation prior to dental procedure or surgery

7-Ethanol (ethyl alcohol)

- It's a CNS depressant.
- Producing sedation and hypnosis with increasing dosage.
- Has antianxiety and sedative effects.
- It's toxic potential .
- Alcohol synergizes with many other sedative agents and can produce severe CNS depression with antihistamines or barbiturates.

Tikrit University
College of Vet. Medicine

First Term - M.Sc Pharmacology
Advanced Pharmacology

Prof Dr Husamuldeen Alnajar

2023-2024

Drugs acting on the CNS (2)

Antidepressant drugs

Mood Disorder

- **The most common mood disorders are:**

1. **Major depression (unipolar depression).**
2. **Manic-depressive illness (bipolar disorder).**

Major depression and bipolar disorder are pervasive mood altering illnesses affecting energy,

sleep,

appetite,

libido

and the ability to function.

Introduction

- The symptoms of **depression are:**

1. Intense feelings of sadness.
2. Hopelessness.
3. Despair.
4. The inability to experience pleasure in **usual activities.**

Mania is characterized by **the opposite behavior**, that is:

- enthusiasm
- rapid thought and speech patterns
- extreme self-confidence
- impaired judgment the brain.

Biogenic amine Theory

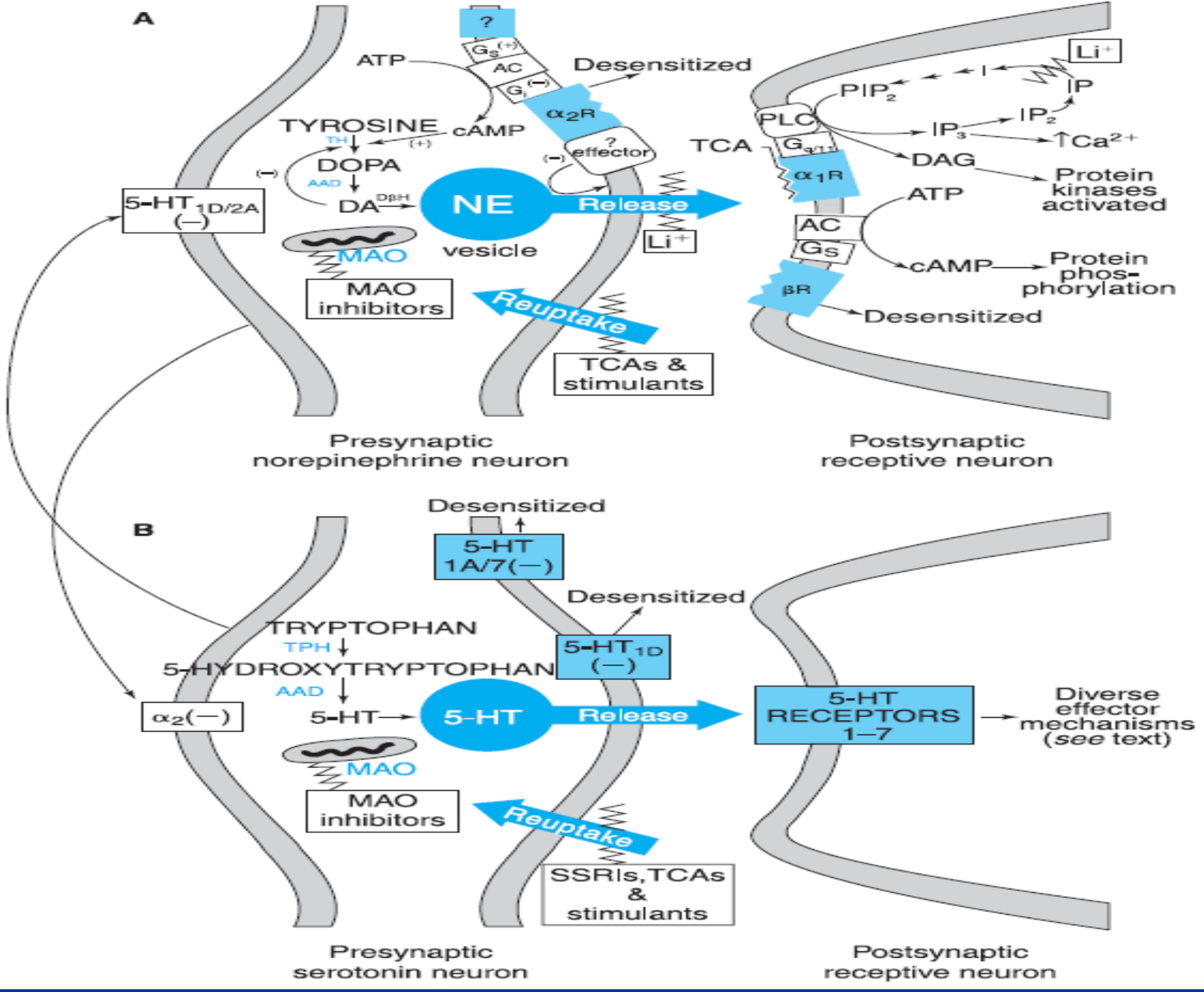
- **Depression** is due to a **deficiency of monoamines** such as **norepinephrine and serotonin** at certain key sites in the brain.
- **Mania** is caused **by an over production of these neurotransmitters.**
- It is **not known** which of these neurochemical systems is most responsible for the **antidepressant activity**
- **All clinically useful antidepressant drugs potentiate, either directly or indirectly, the actions of norepinephrine, dopamine, and/or serotonin in the brain.**

Antidepressant Drugs

1. **Tricyclic / polycyclic antidepressants (TCA).**
2. **Selective serotonin-reuptake inhibitors (SSRI).**
3. **Monoamine oxidase inhibitors (MAOI).**

Drugs used to treat mania:

- Lithium salts.


A
?
G_s (+)
AC
G_i (−)
ATP
cAMP
Desensitized
α_2R
TYROSINE
TH
(+)
DOPA
AAD
DA
DβH
NE
Release
vesicle
(−)
? effector
(−)
5-HT 1D/2A (−)
MAO
MAO inhibitors
Reuptake
TCAs & stimulants
Li+
Presynaptic norepinephrine neuron
Li+
PIP2
I
IP
PLC
IP3
IP2
↑Ca2+
TCA
$G_{q/11}$
DAG
α_1R
Protein kinases activated
ATP
AC
G_S
cAMP
Protein phos-phorylation
βR
Desensitized
Postsynaptic receptive neuron
B
Desensitized
5-HT 1A/7(−)
Desensitized
TRYPTOPHAN
TPH
5-HYDROXYTRYPTOPHAN
AAD
5-HT
5-HT
Release
5-HT 1D (−)
α_2(−)
MAO
MAO inhibitors
Reuptake
SSRIs, TCAs & stimulants
5-HT RECEPTORS 1–7
Diverse effector mechanisms (see text)
Presynaptic serotonin neuron
Postsynaptic receptive neuron

1- Tricyclic/polycyclic antidepressants

older tricyclic antidepressants

1. Imipramine .
2. Amitriptyline .
3. desipramine .
4. Nortriptyline (a demethylated derivative of imipramine).
5. Protriptyline .
6. Doxepin.

7. Amoxapine.
8. Maprotiline

} second generation

Tricyclic/polycyclic antidepressants

Amitriptyline, imipramine

Mechanism of action

1. **Inhibition of neurotransmitter uptake:**

   TCAs inhibit the neuronal re-uptake of norepinephrine, and serotonin into presynaptic nerve terminals.

2. **Blocking of receptors:**

   TCAs block serotonergic, α1-adrenergic, histamine, and muscarinic receptors.(This is manifested in terms of side effects)

Actions

- TCAs elevate mood, improve mental alertness, increase physical activity, and reduce morbid in 50 to 70% of individuals with major depression.
- The onset of the mood-elevation is slow, requiring 2 weeks or longer.
- These drugs do not produce CNS stimulation or mood elevation in normal individuals.
- Tolerance to the anticholinergic properties of the TCAs develops within a short time. Some tolerance to the autonomic effects of TCAs develops.
- Physical and psychological dependence have been reported.
- The drugs can be used for prolonged treatment of depression without loss of effectiveness.

Therapeutic uses

- severe major depression. And Some panic disorders.
- Imipramine has been used to control bed-wetting in children (older than 6 years) by causing contraction of the internal sphincter of the bladder.

Note: At present it is used cautiously, because of the inducement of cardiac arrhythmias and other serious cardiovascular problems.

Adverse effects

- Antimuscarinic effects . Cardiovascular , Sedation

The tricyclic antidepressants have a narrow therapeutic index; for example, 5 to 6 times the maximal daily dose of imipramine can be lethal. Depressed patients who are suicidal should be given only limited quantities of these drugs and should be monitored closely.

2- Selective Serotonin–Reuptake Inhibitors (SSRI Inhibitors)

The SSRI are **a new group** of chemically antidepressant drugs that **specifically inhibit serotonin reuptake.**

- Fewer side effects than TCA's.
- Compared with tricyclic antidepressants, the SSRIs cause fewer anticholinergic effects and lower cardiotoxicity.
- **Clinical Effects:**
  1. Effective in treating depression,
  2. Obsessive –Compulsive Disorder

Fluoxetine

Fluoxetine is effective SSRI in the treatment of major depression as tricyclic antidepressants.

- The drug is free of most of the troubling side effects of tricyclic antidepressants. Therefore is preferred over tricyclic antidepressants
- **Therapeutic uses:**
  - antidepressants.
  - effective in treating obsessive-compulsive disorder.
  - The drug has been used for a variety of other indications, including : - anorexia nervosa, - panic disorder,

- pain associated with diabetic neuropathy,

Adverse affects:

- Gastrointestinal symptoms.
- Sleep disturbance .
- sexual dysfunction,
- anxiety (acutely), insomnia, tremor.
- Overdoses of fluoxetine do **not** cause **cardiac arrhythmias but can cause seizures.**
- **For example, in a report of patients who took an** overdose of fluoxetine (up to **1200 mg** compared with 20 mg/day as a therapeutic dose) about half of the patients had no symptoms.

3-MAO Inhibitors

- (MAO) is a mitochondrial enzyme found in neural and other tissues, such as the gut and liver.
- **Mode of Action of MAO enzyme :**

  MAO enzyme **inactivates excess** NE, DO, 5-HT ⟶ lead to increase the amounts of these neurotransmitters that is produce **physiological** depression.

  - **Examples** MAO Inhibitors:

  Phenylzine, isocarboxazide

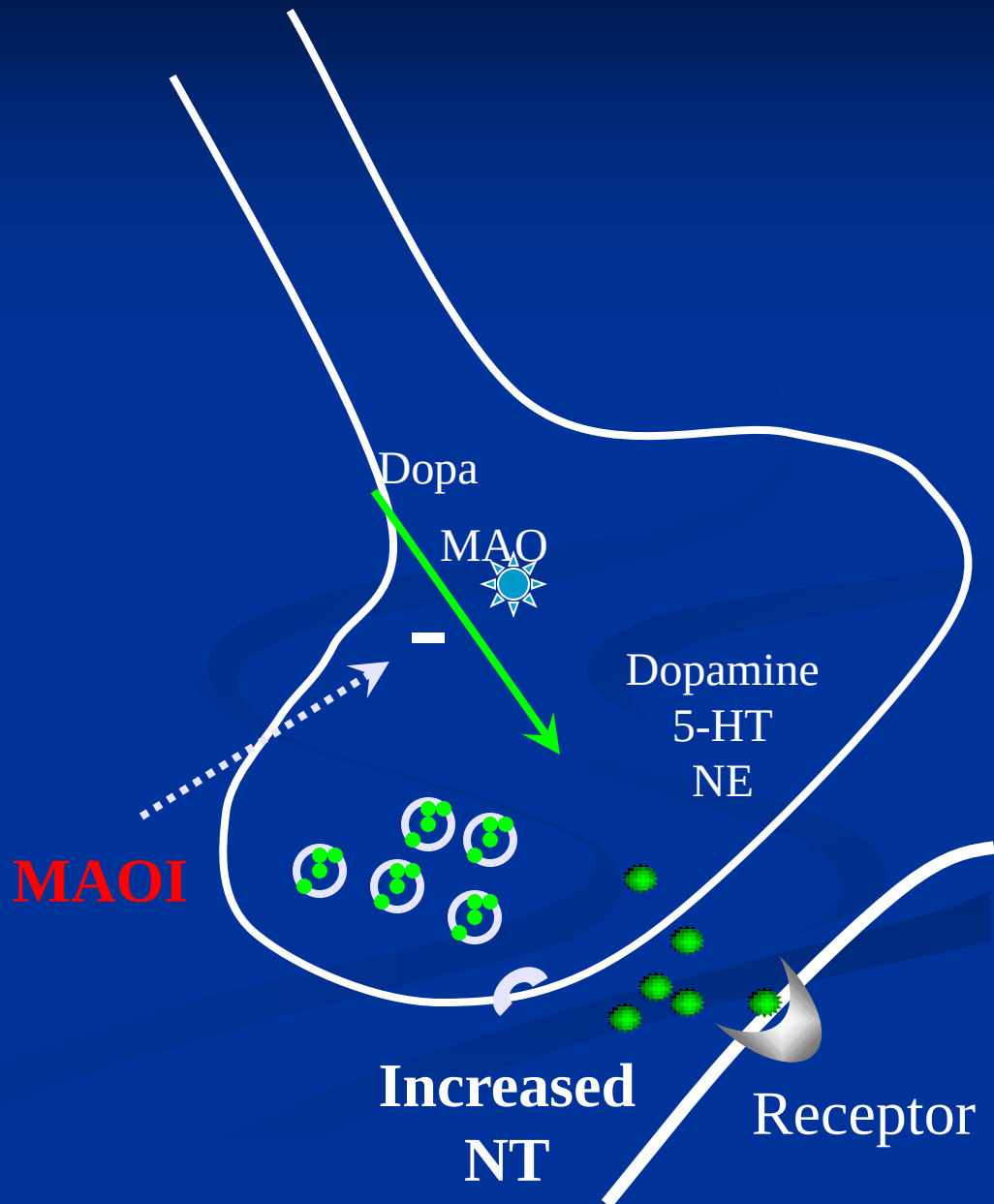
MONOAMINE OXIDASE INHIBITORS

- **The MAO inhibitors** may **irreversibly or reversibly inactivate the enzyme(MAO),** permitting neurotransmitter molecules to escape degradation and therefore to both accumulate within the presynaptic neuron and to leak into the **synaptic space.**
- This causes **activation of norepinephrine and serotonin receptors,** and may be responsible for the antidepressant action of these drugs.

Mechanisms of Action of MAOI

- MAOI **causing irreversible inactivation** enzyme(MAO).
- This results in increased stores of norepinephrine, serotonin and dopamine within the neuron, and subsequent diffusion of excess neurotransmitter into the synaptic space.

- These drugs inhibit not only MAO in brain, but oxidases that catalyze oxidative deamination of drugs and potentially toxic substances, such as tyramine, which is found in certain foods.
- The MAO inhibitors therefore show a high incidence of drug-drug and drug- food interactions.



Therapeutic uses

1. Depressed patients who are unresponsive or allergic to tricyclic antidepressants or who experience strong anxiety.
2. Patients with **low psychomotor activity** may benefit from the stimulant properties of MAO inhibitors.
3. Treatment of **phobic states.**
4. **Atypical depression**, may respond to MAOIs.

- Atypical depression is characterized by labile mood, rejection sensitivity and appetite disorders.

Adverse effects

- **Tyramine,** contained in certain foods, such as aged cheeses, chicken liver, beer, and red wines, is **normally inactivated by MAO in the gut.**
- Individuals receiving a **MAO inhibitor** are unable to **degrade tyramine obtained** from the diet.
- Tyramine causes the release of **large amounts of stored catecholamines from nerve terminals,** resulting in headache, tachycardia, nausea, hypertension, cardiac arrhythmias, and stroke.
- Use of MAO inhibitors is now limited because of the complicated dietary restrictions required of patients taking MAO inhibitors.

Lithium Salts

- **Mode of Action:**
  - Affects **inositol triphosphate** (IP3), blocks Na^+ channels
- Clinical Effects:
  - Treatment of manic/depressive patients
  - VERY TOXIC

Clinical uses

1. **Used prophylactically in treating manic-depressive patients .**
2. **Treatment of manic episodes.**
3. **Effective in treating 60 to 80% of patients exhibiting mania and hypomania.**

Lithium salts

Mechanism of action

- Although many cellular processes are **altered by treatment with lithium salts,** the mode of action is unknown.
- It is currently proposed that Lithium acts by **altering the cellular concentration of the second messenger, inositol triphosphate (IP3)**

Lithium salts

Adverse effects:

1. Ataxia.
2. Tremors.
3. Confusion.
4. Convulsions.

Lithium causes no noticeable effect on normal individuals.

It is not a sedative, euphoriant or depressant.

Anticonvulsants

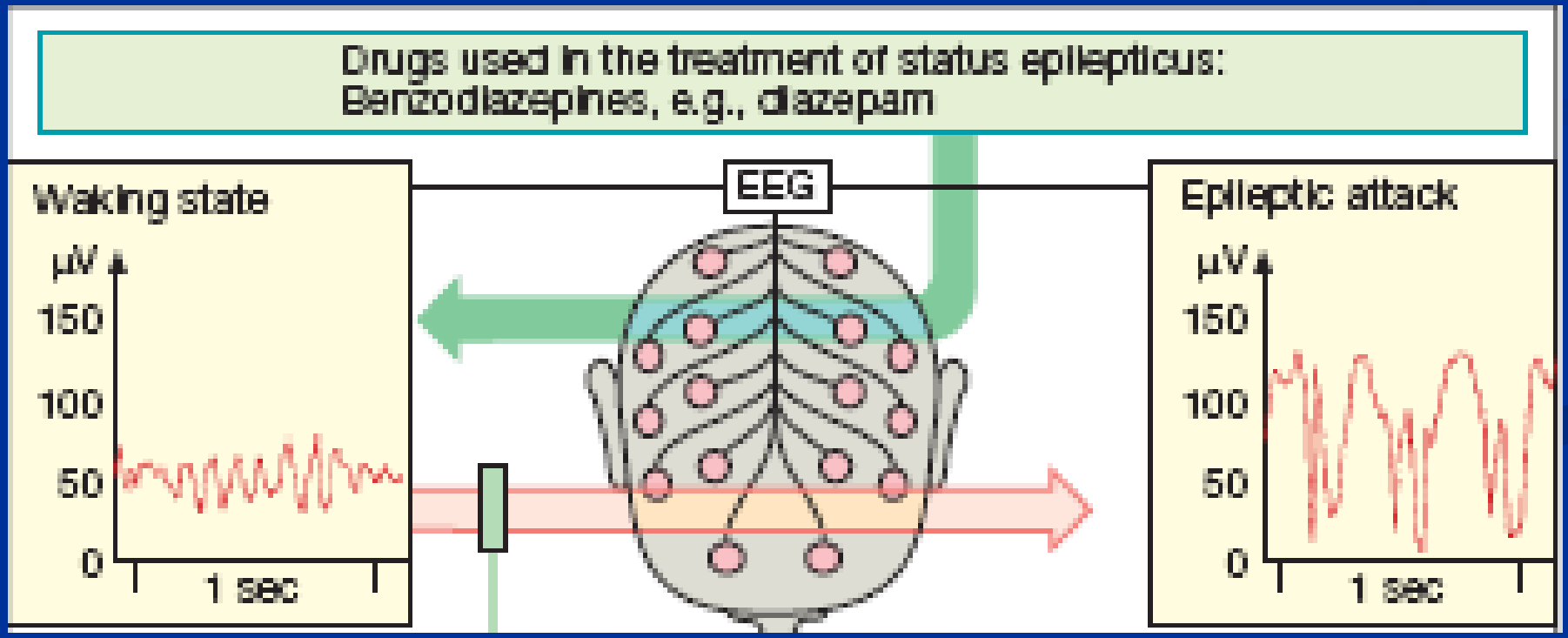
ANTIEPLEPTICS

Epilepsy

- is a common neurological abnormality
- affecting about 1% of the human population.
- Epilepsy is **a chronic**, usually life-long disorder characterized by recurrent **seizures or convulsions** and usually, episodes of unconsciousness and/or amnesia

What is seizure

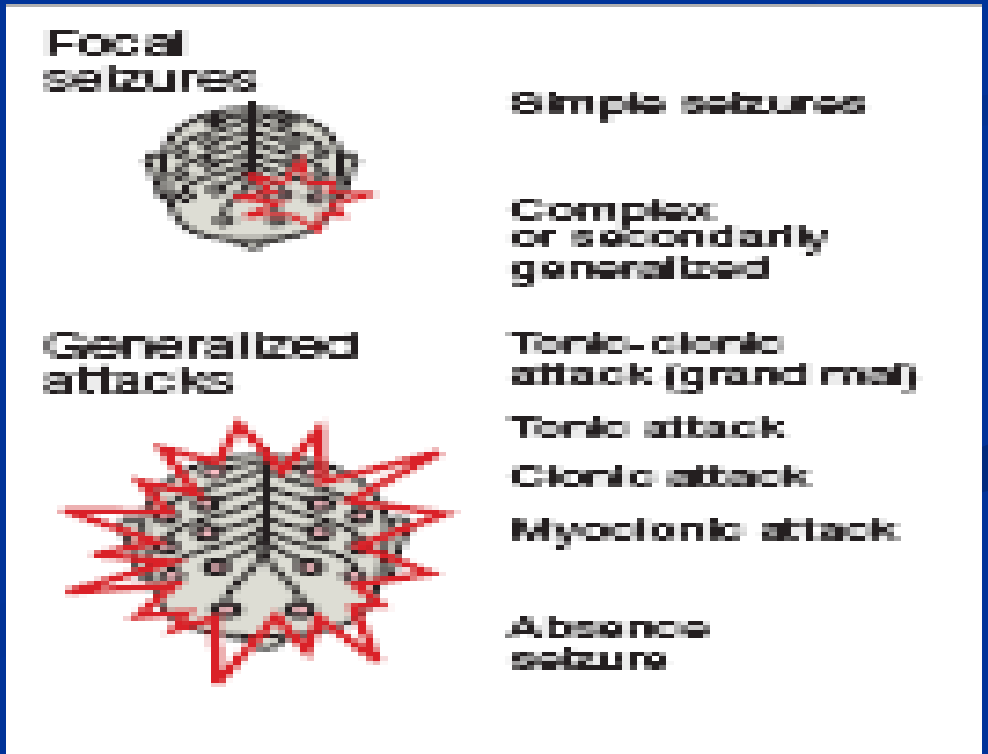
- Seizures are finite episodes of brain dysfunction resulting from abnormal discharge of cerebral neurons .



Types of seizures

classified as:

- general vs. focal seizures;
- seizures with or without loss of consciousness;

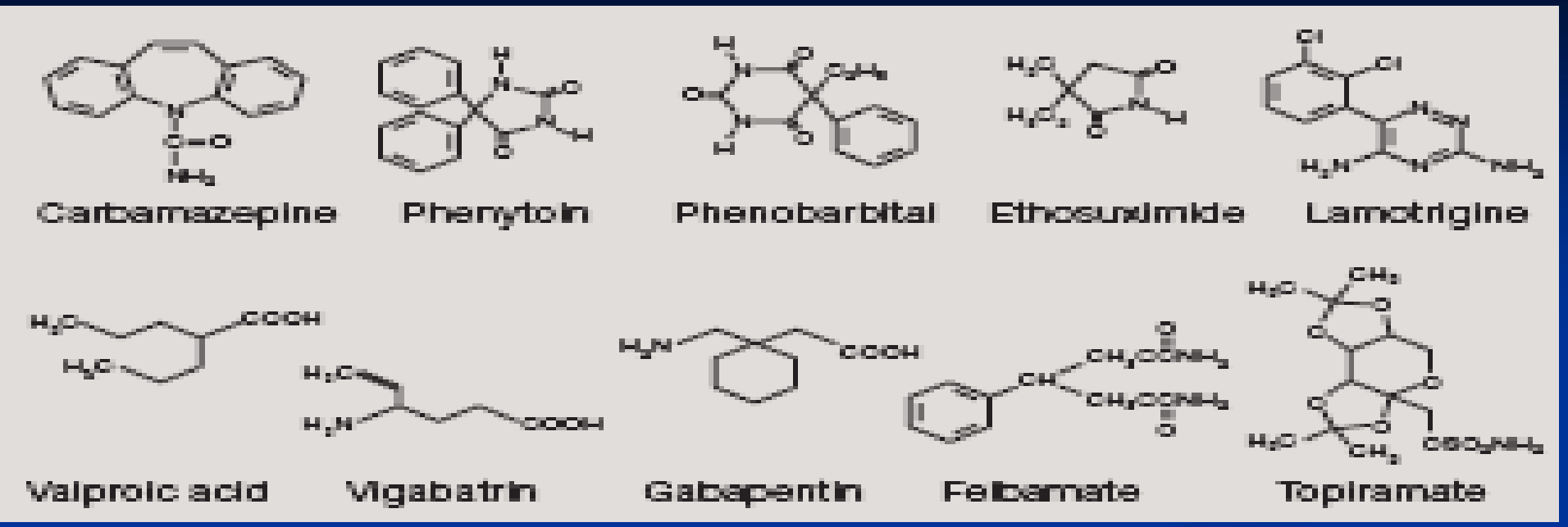


The causes of seizures

1. Head trauma.
2. Meningitis.
3. Childhood fevers, Seizures often occur in hyperthermia (febrile seizures are very common in infants).
4. Brain tumors.
5. Degenerative diseases of the cerebral circulation.
6. Toxic manifestation of the action of central nervous system (CNS) stimulants and certain other drugs.

7- Eclampsia, uremia, hypoglycemia, or pyridoxine deficiency.

Antiepileptics



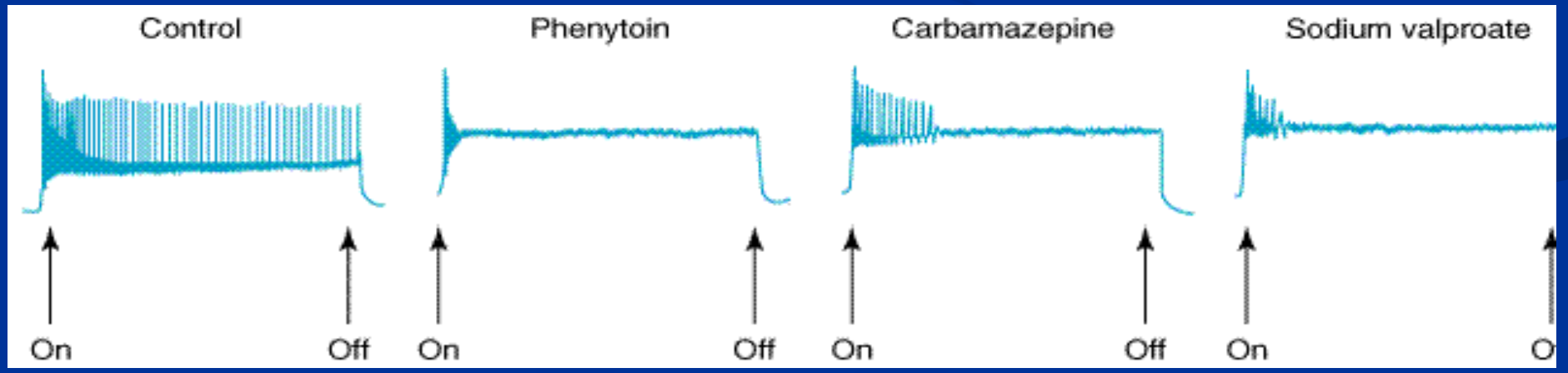
1- **Phenytoin :** Discovered in 1938

Therapeutic uses :

1. Generalized tonic–clonic seizures.
2. partial seizures with complex symptoms.

Mechanism of Action

- enhance **inactivation** of voltage- gated **sodium and calcium channel** and limit the spread of electrical excitation by **inhibiting sustained high-frequency firing of neurons.**



Mechanism of action

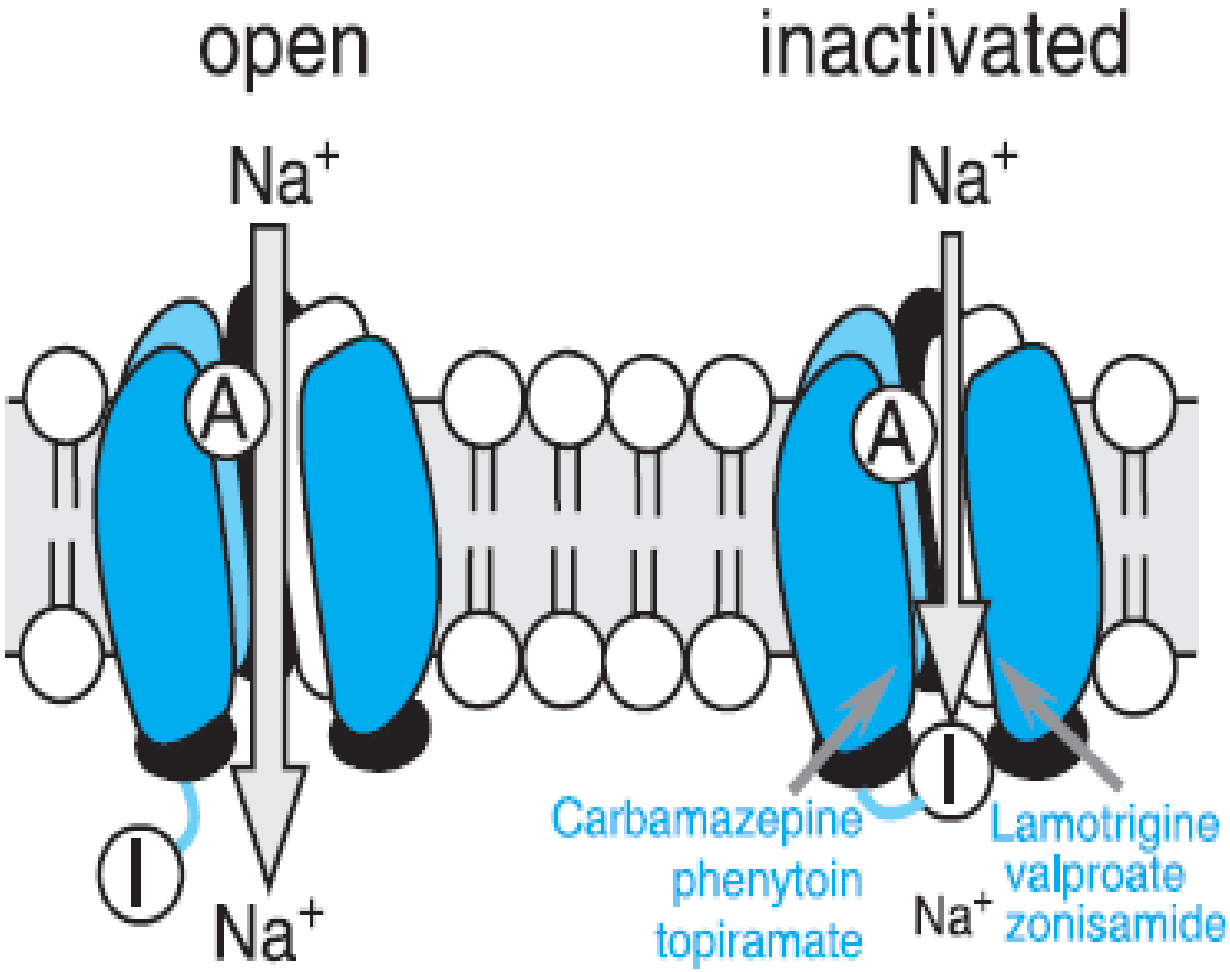


FIGURE 19–1 ***Antiseizure drug–enhanced Na⁺*** **channel inactivation.** Some antiseizure drugs (shown in blue text) prolong the inactivation of the Na^+ channels, thereby reducing the ability of neurons to fire at high frequencies. Note that the inactivated channel itself appears to remain open, but is blocked by the inactivation gate (I). A, activation gate.

Adverse effects of phenytoin

- usually result from overdosage.

1- Nystagmus , ataxia, vertigo, and diplopia

2- Higher doses lead to altered levels of consciousness and cognitive changes.

3- Idiosyncratic reactions may be seen shortly after therapy has begun.

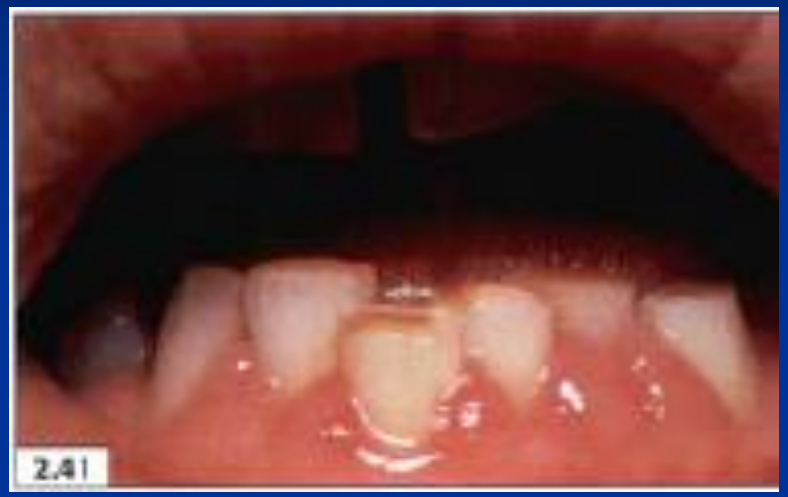
1. Skin rashes are most common.
2. Exfoliative dermatitis or toxic epidermal necrolysis

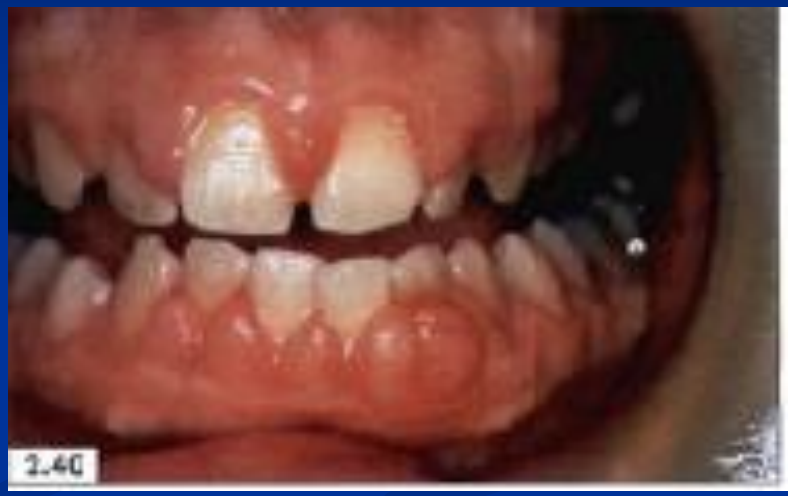
4- Megaloplastic anemia occur because drug interferes with Vit B12 metabolism and hepatic necrosis.

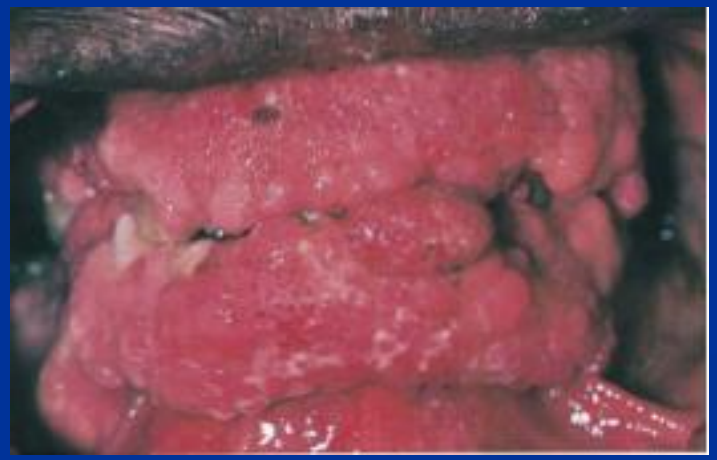
5 - phenytoin is Teratogenic .

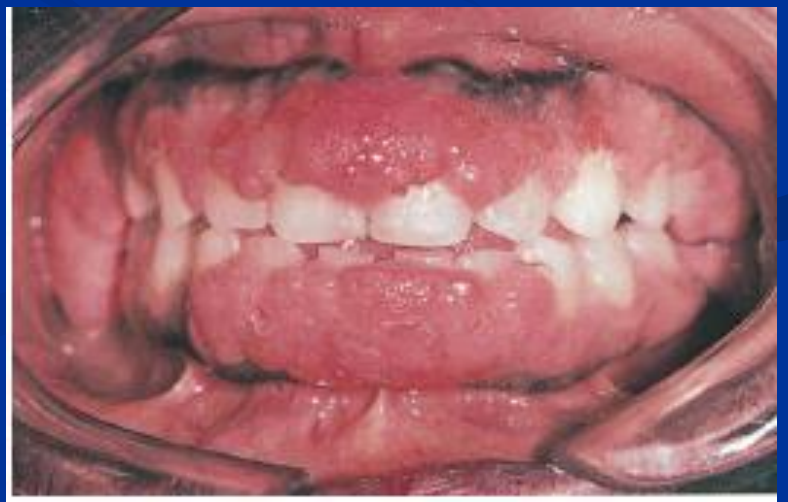
6- Gingival hyperplasia:

occurs in up to 50% of patients.







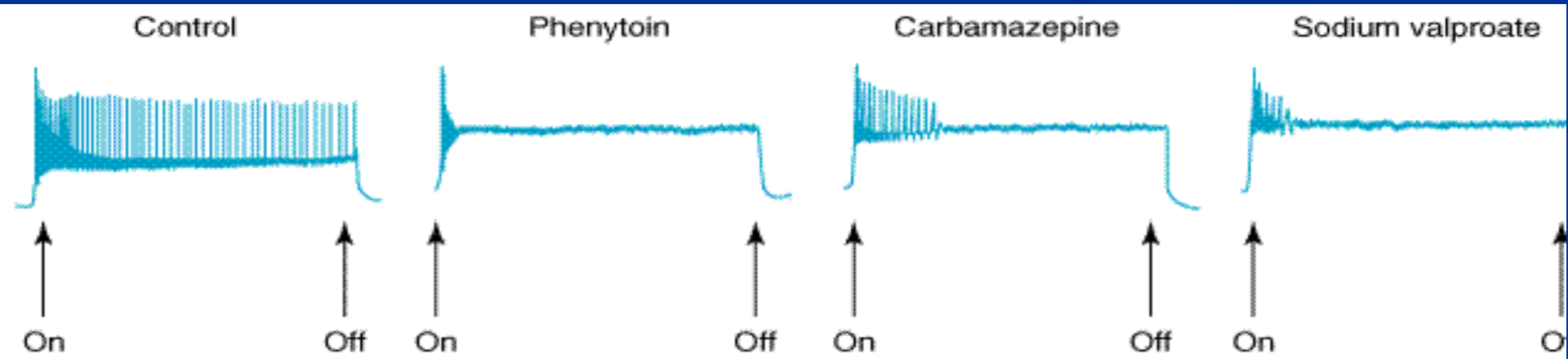


Drug Interaction

- Coadministration of the following drugs can result in elevations of plasma phenytoin levels in most patients:
- cimetidine, chloramphenicol, disulfiram and isoniazid (inhibition of microsomal responsible for phenytoin metabolism).
- Phenytoin often causes a decline in plasma carbamazepine levels if these two drugs are given concomitantly.(phenytoin induce the P-450)

2- Carbamazepine

- Is a tricyclic compound . Closely related to **Imipramine** and other antidepressants.
- Carbamazepine Mechanism of Action:
- **Carbamazepine, like phenytoin, blocks sodium** channels at therapeutic concentrations and inhibits high-frequency repetitive firing in neurons .
- **It also acts presynaptically to decrease synaptic transmission.**



Carbamazepine Clinical Uses:

1. Drug of choice for both partial seizures and generalized tonic-clonic seizures(not sedative).
2. It can be used with phenytoin in many patients who are difficult to control.
3. Very effective in Trigeminal neuralgia and other neuropathic pain.
4. useful in mania (bipolar disorder).

Carbamazepine Adverse Effects

1. dose-related diplopia and ataxia.
2. mild gastrointestinal upsets.
3. idiosyncratic blood dyscrasias including fatal cases of a plastic anemia and agranulocytosis

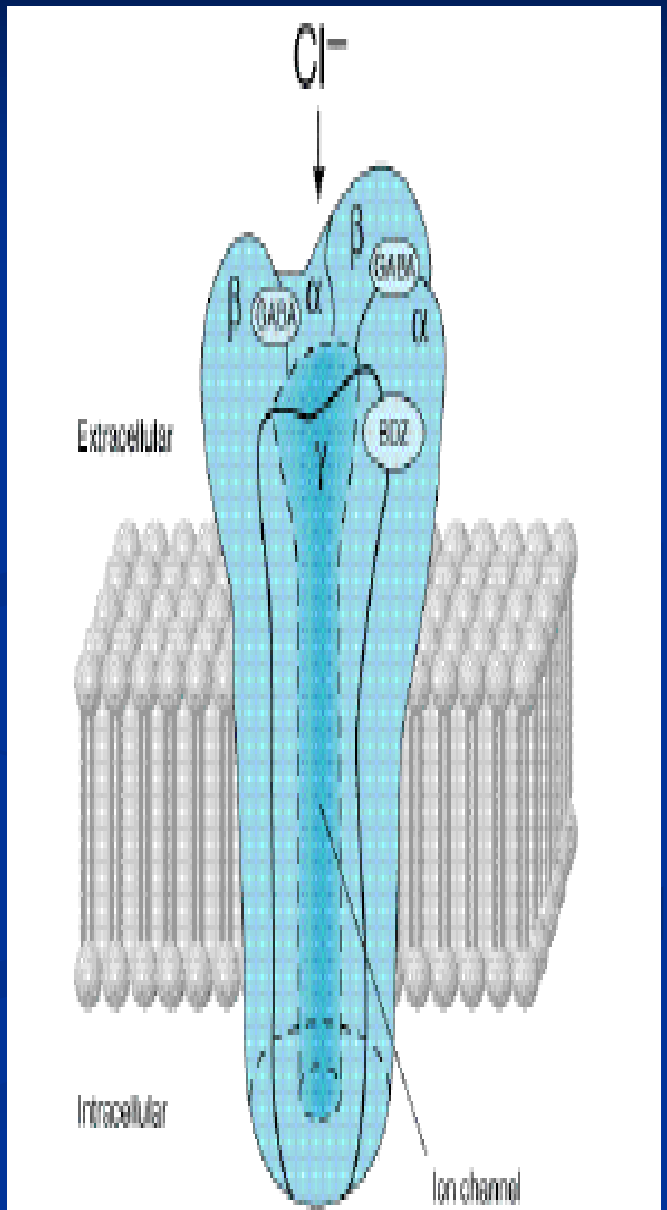
-The mild and persistent leukopenia.

-The most common idiosyncratic reaction is an erythematous skin rash.

3- Phenobarbital

- Is the oldest of the currently available anti seizure drugs (sedative effects).

- **Mechanism of Action**
  Phenobarbital binds to an allosteric regulatory site on the GABA $_A$ receptor.
- Phenobarbital also blocks excitatory responses induced by glutamate.



- **Clinical Use:**

1. Treatment of **partial seizures and generalized tonic-clonic** seizures, although the drug is often tried for every seizure type, especially when attacks are difficult to control.
2. The drugs of choice for seizures only in infants

- **Toxicity:**
- Sedation , Ataxia , Nystagmus , Vertigo , Acute psychotic , reaction Nausea and vomiting , rashes , Agitation and confusion
- Rebound seizures on discontinuance

4- Valproic Acid

Mechanism of Action

reduces the propagation of abnormal electrical discharge in the brain. It may enhance GABA action at inhibitory synapses.

Clinical Use

1. Treatment of myoclonic seizures.
2. The drug diminishes absence seizures but is a second choice because of its hepatotoxic potential.
3. Reduces the incidence and severity of tonic-clonic seizures

Toxicity

- It does not induce P-450 enzyme synthesis.
- Nausea and vomiting.
- Sedation, ataxia, and tremor.
- Hepatic toxicity may cause a rise in hepatic enzymes in plasma, which should be monitored frequently.
- Rash and alopecia may occur
- Bleeding times may increase because of both thrombocytopenia and an inhibition of platelet aggregation.
- Valproic acid inhibits phenobarbital metabolism, thereby increasing circulating levels of that barbiturate.

5- Benzodiazepines

- **Clonazepam suppresses seizure.**
- **Diazepam and Lorazepam, is the drug of choice in the acute treatment of status epilepticus.**
- **Diazepam** given intravenously or rectally is highly effective for stopping continuous seizure activity, especially generalized tonic-clonic status epileptics.
- **Toxicity**
- Sedative properties, drowsiness, somnolence, and fatigue.
- Higher dosage ataxia, dizziness and behavior changes.
- Respiratory depression and cardiac depression may occur when given intravenously in acute

6- Gabapentin

- Gabapentin is an amino acid, an analog of GABA, that is effective against partial seizures.
- **Its mechanism is not known:** The drug also binds to the 2 subunit of voltage-sensitive Ca2+ channels.
- **Clinical Use:**
- Gabapentin is effective as an adjunct against partial seizures and generalized tonic-clonic seizures. treatment of neuropathic pain
- **Adverse effects :** somnolence, dizziness, ataxia, headache, and tremor.


BAĞHER