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MEDICINAL CHEMISTRY – I

UNIT 4

TOPIC :

- **C. Anticonvulsants : SAR of Anticonvulsants, mechanism of anticonvulsant action**

Barbiturates : Phenobarbitone, Methobarbital.

Hydantoins : Phenytoin, Mephenytoin, Ethotoin

Oxazolindione diones : Trimethadione, Paramethadione

Succinimides : Phensuximide, Methsuximide, Ethosuximide

Urea and monoacylureas : Phenacemide, Carbamazepine*

Benzodiazepines : Clonazepam

Miscellaneous : Primidone, Valproic acid , Gabapentin, Felbamate

Anticonvulsants

- Anticonvulsants (antiepileptics) are drugs used to prevent or control seizures in epilepsy.
- They act mainly by stabilizing neuronal excitability and reducing abnormal, excessive neuronal firing.
- Different classes act by blocking sodium/calcium channels, enhancing GABA action, or inhibiting excitatory neurotransmitters (e.g., glutamate).

Mechanism of Action of Anticonvulsants

Anticonvulsants work by four major mechanisms:

- 1. Enhancement of GABA-mediated inhibition**
 - Increase GABA levels (e.g., valproic acid, vigabatrin).
 - Enhance GABA-A receptor activity (benzodiazepines, barbiturates).
→ Increases neuronal inhibition, reducing excitability.
- 2. Inhibition of voltage-gated sodium channels**
 - Phenytoin, Carbamazepine, Lamotrigine.
 - Stabilize inactive state of Na⁺ channels → prevent repetitive firing of neurons.
- 3. Inhibition of calcium channels (T-type Ca²⁺ channels)**
 - Ethosuximide, Valproic acid.
 - Suppresses thalamic neuron activity → useful in absence seizures.
- 4. Inhibition of excitatory neurotransmission (glutamate)**
 - Felbamate, Topiramate.
 - Block NMDA or AMPA/kainate glutamate receptors → reduce excitatory signals.

SAR (Structure–Activity Relationship) of Anticonvulsants

Although anticonvulsants belong to diverse chemical classes, some general SAR features are common:

1. Hydantoin derivatives (e.g., Phenytoin)

- Imide (–NH–CO–) group is essential for activity.
- Substitution at C-5 position with aromatic/alkyl groups enhances anticonvulsant potency.
- Larger substitutions at C-5 increase lipid solubility and CNS penetration.

2. Barbiturates (e.g., Phenobarbital)

- The barbituric acid nucleus is essential.
- Substitution at C-5 with aryl/alkyl groups increases anticonvulsant activity.
- Substitution at N-1/N-3 alters potency and pharmacokinetics.

3. Succinimides (e.g., Ethosuximide)

- Succinimide ring is essential.
- Substituents at α -position (next to imide group) influence activity and toxicity.
- Ethyl substitution → best anticonvulsant effect in absence seizures.

4. Benzodiazepines (e.g., Diazepam, Clonazepam)

- A benzodiazepine nucleus with electron-withdrawing substituents enhances binding to GABA-A receptors.
- Substitution at position 7 (Cl, NO₂) → increases potency.

5. Valproic acid

- Simple branched chain fatty acid.
- The carboxylic group is essential.
- The length and branching of carbon chain influence potency.

6. Newer anticonvulsants

- Gabapentin, Pregabalin → GABA analogues with alkyl substitutions that enhance lipophilicity and brain penetration.
- Topiramate → sulfamate-substituted monosaccharide; hydroxyl groups improve water solubility and activity.

Barbiturates

- Barbiturates are a class of drugs derived from barbituric acid.
- They act as central nervous system (CNS) depressants.
- Depending on the dose, they can produce sedation, hypnosis, anxiolysis, anticonvulsant effects, and anesthesia.
- Although their use has declined due to the availability of benzodiazepines and safer alternatives, some are still used in the treatment of epilepsy, anxiety, and anesthesia.

Examples

- Phenobarbitone,
- Methobarbital.

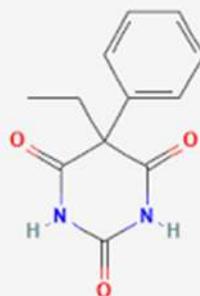
Mechanism of Action

- ❖ Barbiturates act mainly by enhancing the activity of GABA (gamma-aminobutyric acid), the major inhibitory neurotransmitter in the CNS.
- ❖ They bind to a distinct site on the GABA-A receptor-chloride channel complex.
- ❖ This increases the duration of chloride channel opening, leading to hyperpolarization of the neuronal membrane.
- ❖ Hyperpolarization → reduced excitability → CNS depression.
- ❖ At higher doses, they can also directly activate GABA-A receptors (unlike benzodiazepines).

Phenobarbitone (Phenobarbital)

Structure

- Chemical class: Barbiturate, long-acting.
- Core structure:
 - Derivative of barbituric acid.
 - Substitutions at C5 position with alkyl or aryl groups increase lipid solubility and anticonvulsant activity.
 - Keto groups at C2, C4, and C6 are essential for activity.



Mechanism of Action (MOA)

- GABA-A receptor positive allosteric modulator → enhances the effect of GABA, the major inhibitory neurotransmitter.
- Prolongs opening of chloride channels → hyperpolarization of neurons.
- CNS depressant effect: anticonvulsant, sedative, and hypnotic.
- At high concentrations, can directly activate GABA-A channels independent of GABA.

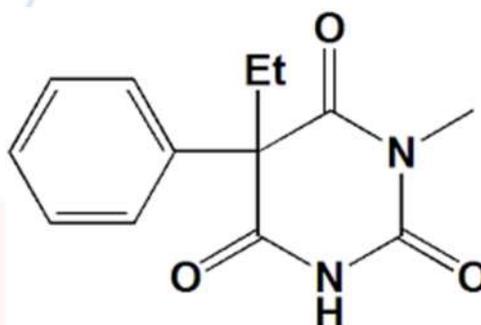
Therapeutic Uses

- Epilepsy: generalized tonic-clonic and partial seizures.
- Sedative/Hypnotic: short-term management of anxiety or insomnia (less commonly used now).
- Pre-anesthetic medication (rarely, in some protocols).
- Status epilepticus (as alternative to benzodiazepines in some cases).

Mephobarbital (Methabarbital)

Structure

- Chemical class: Barbiturate, long-acting anticonvulsant.
- Core structure:
 - Derivative of barbituric acid.
 - Substitutions at C5 position with methyl and phenyl groups enhance anticonvulsant activity.
 - Contains keto groups at C2, C4, and C6 essential for binding and activity.



Mephobarbital

Mechanism of Action (MOA)

- GABA-A receptor positive allosteric modulator → potentiates the inhibitory effect of GABA in CNS.
- Prolongs chloride channel opening → hyperpolarizes neurons and reduces excitability.
- Slower onset and longer duration → suitable for long-term seizure prophylaxis.
- At high concentrations, can directly open GABA-A channels.

Therapeutic Uses

- Epilepsy: generalized tonic-clonic and partial seizures.
- Sedative/hypnotic: rarely used due to long half-life.
- Prophylaxis of febrile seizures (in children, rarely).

Hydantoins

- Hydantoins are a class of heterocyclic compounds derived from imidazolidine-2,4-dione.
- They are mainly used as anticonvulsants (antiepileptic drugs).
- Their main therapeutic role is in the treatment of generalized tonic-clonic seizures and partial seizures.
- They are effective in controlling excessive neuronal firing without producing general CNS depression.

Examples

- Phenytoin (Dilantin).
- Mephenytoin
- Ethotoin

Mechanism of Action (MOA)

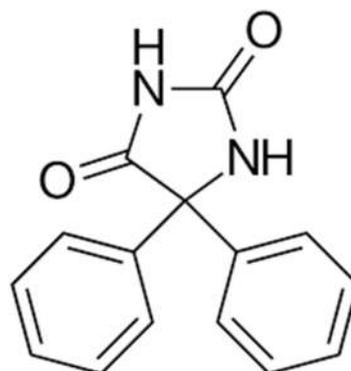
- Hydantoins mainly act by blocking voltage-gated sodium (Na^+) channels in neurons.
- This prevents rapid and repetitive firing of action potentials.
- Stabilizes the neuronal membrane and limits seizure spread.
- Unlike barbiturates and benzodiazepines, they do not enhance GABA activity, so they cause less sedation.

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Phenytoin

Structure

- Chemical class: Hydantoin derivative.
- Core structure:
 - Imidazolidine-2,4-dione (hydantoin ring).
 - Substitutions at C5 position with phenyl groups enhance anticonvulsant activity.
 - Poorly soluble in water; usually administered as sodium salt (phenytoin sodium).



Mechanism of Action (MOA)

- Voltage-gated sodium channel blocker in neuronal membranes.
- Stabilizes inactive state of Na^+ channels → prevents repetitive firing of action potentials.
- Reduces hyperexcitability in neurons → prevents spread of seizure activity.
- Minimal effect on GABA or glutamate directly.

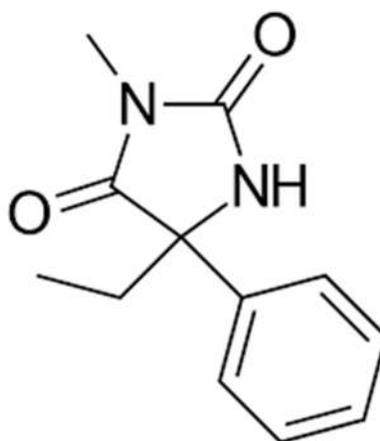
Therapeutic Uses

- Epilepsy:
 - Generalized tonic-clonic seizures.
 - Partial (focal) seizures with or without secondary generalization.
- Status epilepticus (after benzodiazepines).
- Occasionally used for trigeminal neuralgia.

Mephenytoin

Structure

- Chemical class: Hydantoin derivative (similar to Phenytoin).
- Core structure:
 - Hydantoin ring (imidazolidine-2,4-dione).
 - Substitutions at C5 position with aryl and alkyl groups influence anticonvulsant activity.
- Less commonly used than phenytoin due to variable metabolism.



Mechanism of Action (MOA)

- Voltage-gated sodium channel blocker → stabilizes inactive Na⁺ channels in neurons.
- Prevents repetitive firing and propagation of seizure activity.
- Reduces neuronal excitability in the CNS.

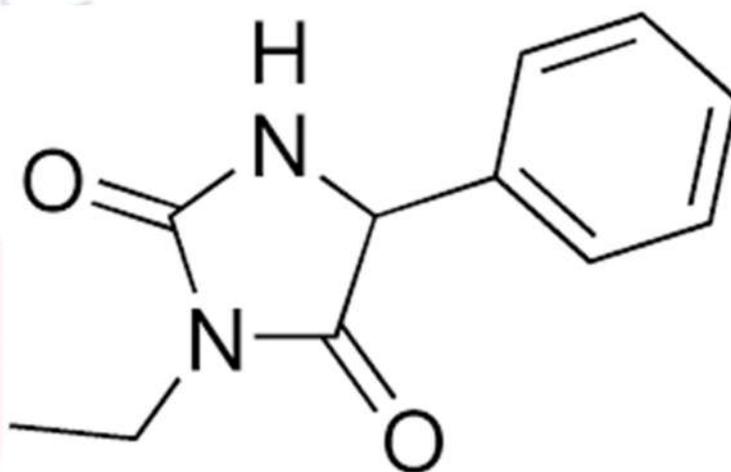
Therapeutic Uses

- Epilepsy:
 - Partial (focal) seizures.
 - Generalized tonic-clonic seizures (less preferred).
- Rarely used today due to hepatic metabolism variability and availability of safer alternatives.

Ethotoin

Structure

- Chemical class: Hydantoin derivative (similar to Phenytoin).
- Core structure:
 - Imidazolidine-2,4-dione (hydantoin ring).
 - Substituted at C5 with ethyl and phenyl groups → influences anticonvulsant activity.
- Water solubility: Low; administered orally.



Mechanism of Action (MOA)

- Voltage-gated sodium channel blocker → stabilizes inactive Na⁺ channels.
- Reduces repetitive neuronal firing → prevents seizure propagation.
- Minimal effect on GABA or glutamate directly.
- Slower onset and longer duration than phenytoin → suitable for long-term seizure prophylaxis.

Therapeutic Uses

- Epilepsy:
 - Partial (focal) seizures.
 - Generalized tonic-clonic seizures.
- Rarely used now due to less potency and availability of safer drugs.

Oxazolidine Diones

- Oxazolidine diones are a class of heterocyclic compounds containing an oxazolidine ring with two keto groups.
- They are among the older anticonvulsant drugs, but their use is limited today due to toxicity and side effects.
- They mainly act by reducing neuronal excitability and thus prevent seizures.

Examples

- Trimethadione
- Paramethadione.

Mechanism of Action (MOA)

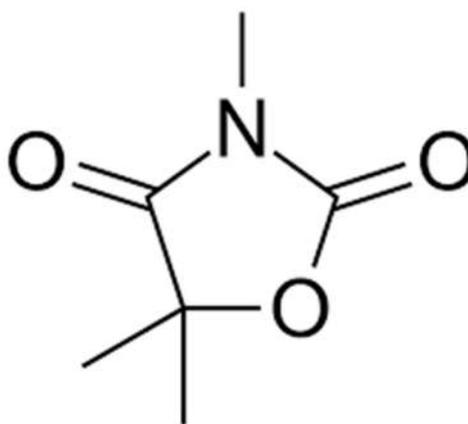
- They act by blocking T-type calcium (Ca^{2+}) channels in thalamic neurons.
- This inhibits the repetitive neuronal firing associated with absence (petit mal) seizures.
- Result: stabilization of nerve activity and prevention of seizure spread.

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Trimethadione

Structure

- Chemical class: Oxazolidinedione derivative.
- Core structure:
 - Five-membered ring containing nitrogen and two carbonyl groups (oxazolidinedione ring).
 - Substituted at N3 or C5 positions to modify anticonvulsant activity.
- Physical properties: White crystalline powder, slightly soluble in water.



Mechanism of Action (MOA)

- Reduces neuronal excitability by blocking T-type calcium channels in thalamic neurons.
- Specifically effective in absence seizures (petit mal).
- Minimal effect on sodium channels or GABAergic transmission.

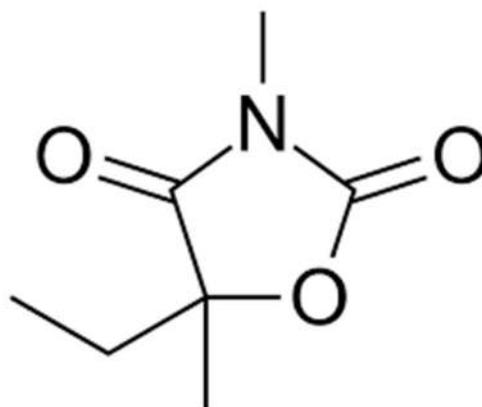
Therapeutic Uses

- Epilepsy:
 - Absence seizures (petit mal) — drug of choice historically.
 - Not effective for tonic-clonic or partial seizures.
- Largely replaced by ethosuximide due to better safety and tolerability.

Paramethadione

Structure

- Chemical class: Oxazolidinedione derivative (similar to Trimethadione).
- Core structure:
 - Five-membered oxazolidinedione ring containing nitrogen and two carbonyl groups.
 - Substituted with a methyl group to modify anticonvulsant activity.
- Physical properties: White crystalline powder, slightly soluble in water.



Mechanism of Action (MOA)

- Blocks T-type calcium channels in thalamic neurons.
- Reduces abnormal rhythmic firing → effective in absence (petit mal) seizures.
- Minimal effect on sodium channels.

Therapeutic Uses

- Epilepsy:
 - Mainly used for absence seizures.
 - Historically preferred before ethosuximide became standard.
- Rarely used today due to toxicity and adverse effects.

Succinimides

- Succinimides are a class of cyclic imides with a five-membered heterocyclic ring containing:
 - Two carbonyl (C=O) groups.
 - One nitrogen atom.
- They are considered as anticonvulsant drugs, specifically effective in absence (petit mal) seizures.
- Compared to oxazolidine diones, succinimides are safer and more widely used.

Examples

- Ethosuximide
- Phensuximide.
- Methsuximide

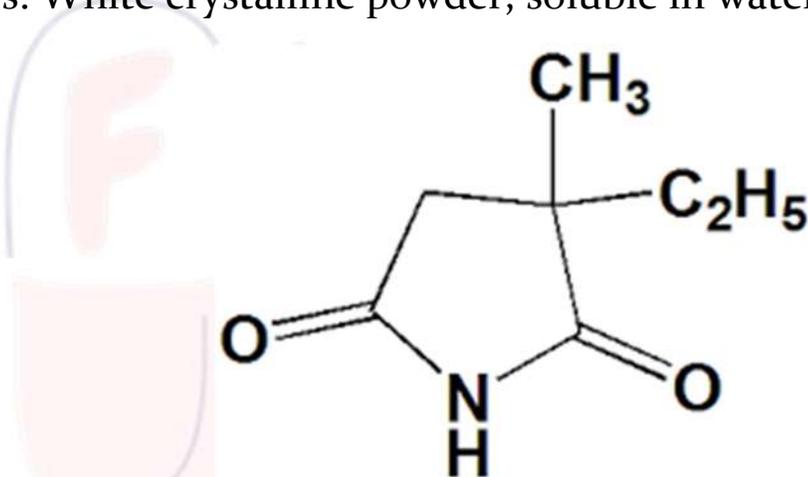
Mechanism of Action (MOA)

- Succinimides act by inhibiting T-type calcium channels in thalamic neurons.
- These channels are responsible for the rhythmic cortical discharges seen in absence seizures.
- Blocking them prevents abnormal synchronization of neurons → reduces frequency of seizures.

Ethosuximide

Structure

- Chemical class: Succinimide derivative.
- Core structure:
 - Five-membered cyclic imide (succinimide) ring.
 - Substituted at nitrogen with an ethyl group → increases anticonvulsant activity.
- Physical properties: White crystalline powder, soluble in water and alcohol.



Ethosuximide

Mechanism of Action (MOA)

- Blocks T-type calcium channels in thalamic neurons.
- Reduces low-threshold calcium currents responsible for rhythmic firing in absence seizures.
- Does not significantly affect sodium channels or GABAergic transmission.
- Leads to suppression of 3 Hz spike-and-wave discharges on EEG.

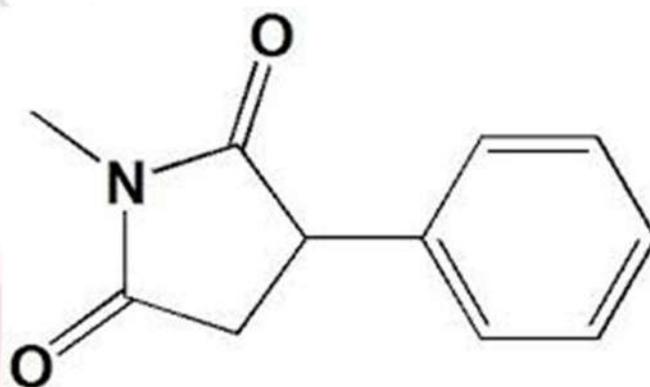
Therapeutic Uses

- Epilepsy:
 - Drug of choice for absence (petit mal) seizures.
 - Can be used in children and adults with typical absence seizures.
- Not effective for tonic-clonic or partial seizures.

Phensuximide

Structure

- Chemical class: Succinimide derivative.
- Core structure:
 - Five-membered cyclic imide (succinimide) ring.
 - Substituted at nitrogen with a phenyl group → enhances anticonvulsant activity.
- Physical properties: White crystalline powder, slightly soluble in water, soluble in alcohol.



Mechanism of Action (MOA)

- Blocks T-type calcium channels in thalamic neurons.
- Reduces low-threshold calcium currents, preventing abnormal rhythmic firing associated with absence seizures.
- Minimal effect on sodium channels or GABAergic neurotransmission.
- Suppresses 3 Hz spike-and-wave discharges on EEG.

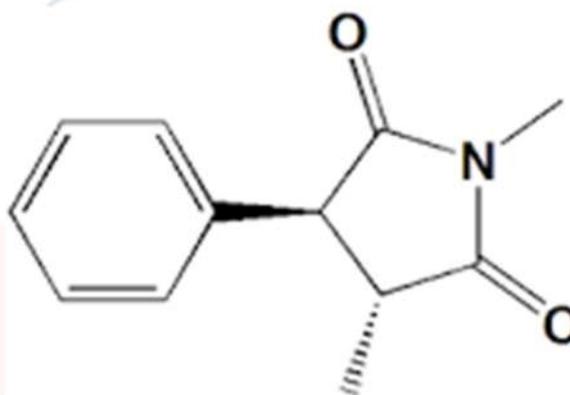
Therapeutic Uses

- Epilepsy:
 - Used primarily for absence (petit mal) seizures.
 - Alternative to ethosuximide when contraindicated or not tolerated.
- Not effective for tonic-clonic or partial seizures.

Methsuximide

Structure

- Chemical class: Succinimide derivative.
- Core structure:
 - Five-membered cyclic imide (succinimide) ring.
 - Substituted at nitrogen with a methyl group → increases lipid solubility and CNS penetration.
- Physical properties: White crystalline powder, slightly soluble in water, soluble in organic solvents.



Methsuximide

Mechanism of Action (MOA)

- Blocks T-type calcium channels in thalamic neurons.
- Reduces low-threshold calcium currents, preventing the abnormal rhythmic firing responsible for absence seizures.
- Minimal effect on sodium channels or GABA-mediated inhibition.
- Suppresses 3 Hz spike-and-wave discharges on EEG.

Therapeutic Uses

- Epilepsy:
 - Used for refractory absence seizures (when ethosuximide or phensuximide are ineffective).
 - May be considered in pediatric and adult patients with atypical absence seizures.
- Not effective for tonic-clonic or partial seizures.

Urea and Monoacylureas

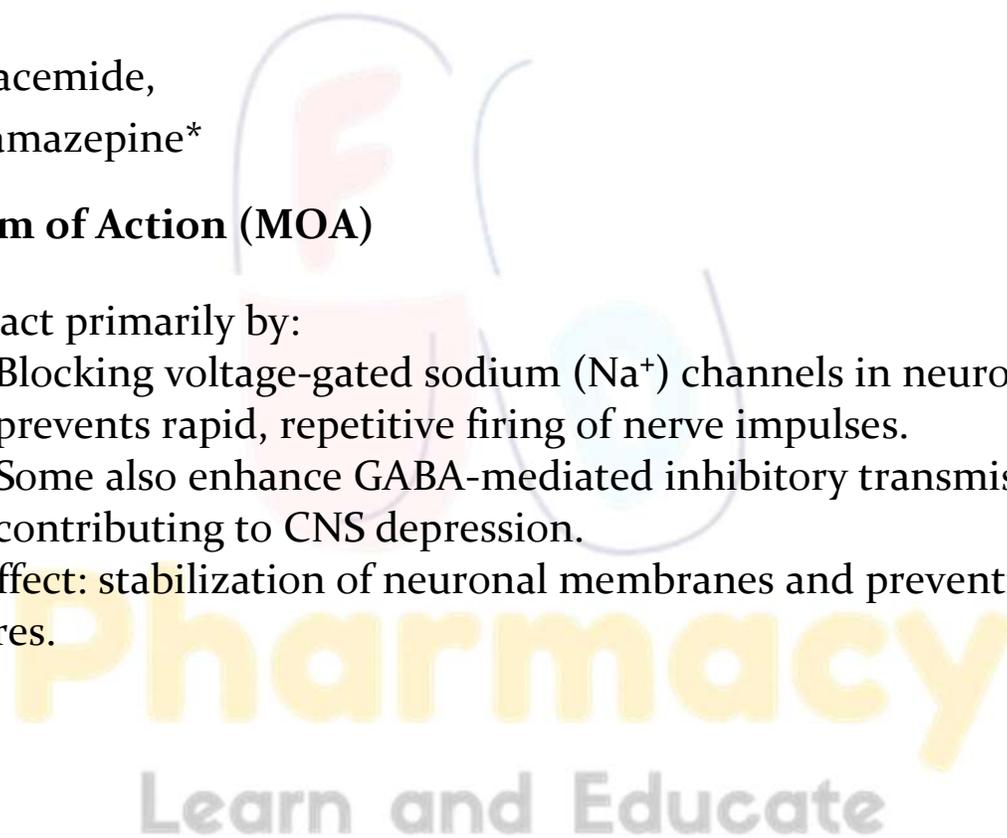
- Ureas are compounds containing the functional group:
–NH–CO–NH–
- Monoacylureas are derivatives of urea where one of the hydrogens of urea is substituted by an acyl group (–CO–R).
- These groups of drugs were investigated as anticonvulsants, but only a few are in clinical use due to side effects.

Examples

- Phenacemide,
- Carbamazepine*

Mechanism of Action (MOA)

- They act primarily by:
 1. Blocking voltage-gated sodium (Na^+) channels in neurons → prevents rapid, repetitive firing of nerve impulses.
 2. Some also enhance GABA-mediated inhibitory transmission, contributing to CNS depression.
- Net effect: stabilization of neuronal membranes and prevention of seizures.



Phenacemide

Structure

- Chemical class: Urea derivative anticonvulsant.
- Core structure:
 - Contains a urea functional group ($-NH-CO-NH-$) substituted with a phenyl group.
 - Structurally related to hydantoins but less potent.
- Physical properties: White crystalline powder, soluble in water and ethanol.

Mechanism of Action (MOA)

- Stabilizes neuronal membranes by inhibiting repetitive firing of neurons.
- Blocks voltage-gated sodium channels → reduces abnormal depolarization.
- Minimal effect on calcium channels.
- Helps prevent propagation of seizure activity in the CNS.

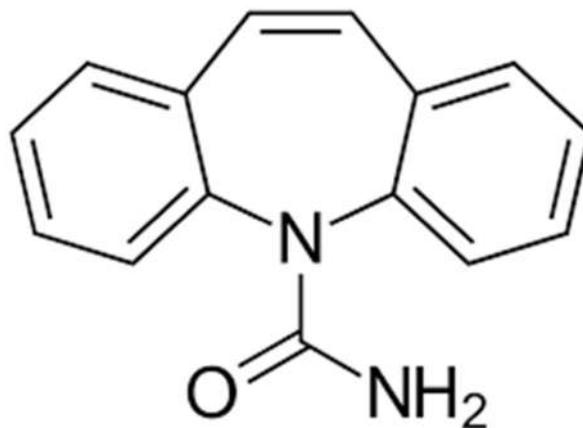
Therapeutic Uses

- Epilepsy:
 - Used for tonic-clonic (grand mal) and partial seizures.
 - Rarely used today due to toxicity and availability of safer alternatives.
- Not effective for absence (petit mal) seizures.

Carbamazepine

Structure

- Chemical class: Dibenzazepine derivative, anticonvulsant.
- Core structure:
 - Tricyclic compound containing a carboxamide group.
 - Structurally related to tricyclic antidepressants.
- Physical properties: White crystalline powder, slightly soluble in water, soluble in organic solvents.



Mechanism of Action (MOA)

- Blocks voltage-gated sodium channels in hyperactive neurons.
- Stabilizes the inactivated state of sodium channels → prevents repetitive neuronal firing.
- Reduces synaptic propagation of abnormal electrical discharges in the CNS.
- Weak anticholinergic and antimuscarinic effects.

Therapeutic Uses

- Epilepsy:
 - First-line for partial seizures (simple and complex) and secondary generalized tonic-clonic seizures.
 - Occasionally used for generalized tonic-clonic seizures.
- Trigeminal neuralgia: Effective in controlling neuropathic pain.
- Bipolar disorder: Used as a mood stabilizer in mania.

Benzodiazepines

- Benzodiazepines (BZDs) are a class of psychoactive drugs widely used as anxiolytics, sedatives, hypnotics, anticonvulsants, and muscle relaxants.
- First discovered in 1961 (Chlordiazepoxide).
- They act as CNS depressants but are safer and less toxic than older drugs like barbiturates.
- They are commonly prescribed in psychiatry, neurology, and anesthesia.

Examples

- Clonazepam

Mechanism of Action (MOA)

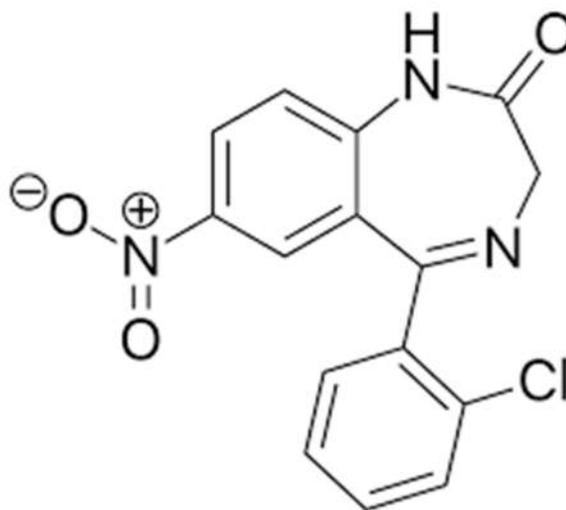
- ❖ Benzodiazepines enhance the effect of GABA (gamma-aminobutyric acid), the chief inhibitory neurotransmitter in the CNS.
- ❖ They bind to a specific site on the GABA-A receptor (benzodiazepine binding site).
- ❖ This increases the frequency of Cl^- channel opening → hyperpolarization of neuronal membrane → reduced excitability.
- ❖ Result: sedation, anxiolysis, anticonvulsant, muscle relaxation, and hypnosis

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Clonazepam

Structure

- Chemical class: Benzodiazepine derivative.
- Core structure:
 - 1,4-benzodiazepine ring with nitro group at position 7.
 - Contains chloro substituent at position 2 on the aromatic ring.
- Physical properties: White crystalline powder, slightly soluble in water, soluble in alcohol and organic solvents.



Mechanism of Action (MOA)

- Enhances GABAergic neurotransmission by binding to benzodiazepine site on GABA-A receptors.
- Increases the frequency of chloride channel opening → hyperpolarizes neurons → decreases excitability.
- Produces anticonvulsant, anxiolytic, sedative, and muscle relaxant effects.

Therapeutic Uses

- Epilepsy:
 - Effective for absence seizures, myoclonic seizures, and Lennox-Gastaut syndrome.
- Panic disorder and anxiety (off-label in some cases).
- Muscle relaxation: Occasionally used for spasticity.

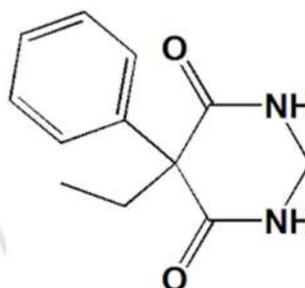
Miscellaneous

- Primidone, Valproic acid , Gabapentin, Felbamate

Primidone

Structure

- Chemical class: Barbiturate derivative.
- Core structure: Phenyl-substituted barbituric acid derivative.
- Physical properties: White crystalline powder, slightly soluble in water, soluble in alcohol and organic solvents.
- Prodrug: Metabolized in the liver to phenobarbital and phenylethylmalonamide (PEMA), which contribute to its anticonvulsant activity.



Primidone

Mechanism of Action (MOA)

- Enhances GABAergic activity: Acts on GABA-A receptors → increases chloride ion influx → hyperpolarizes neurons → reduces excitability.
- Sodium channel modulation: Stabilizes neuronal membranes, reducing repetitive firing of action potentials.
- Metabolites (phenobarbital, PEMA): Contribute to overall anticonvulsant effect.

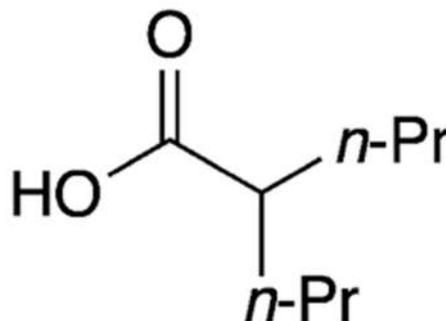
Therapeutic Uses

- Epilepsy:
 - Partial (focal) seizures
 - Generalized tonic-clonic seizures
 - Sometimes used for myoclonic seizures (less common).
- Adjunct therapy: In patients not responding to other anticonvulsants.

Valproic Acid (VPA)

Structure

- Chemical class: Short-chain fatty acid derivative.
- Core structure: $\text{CH}_3\text{-CH}_2\text{-CH}(\text{COOH})\text{-CH}_3$
- Physical properties: Colorless or slightly yellow liquid (or sodium valproate: white crystalline powder), soluble in water and alcohol.



Mechanism of Action (MOA)

- Enhances GABAergic neurotransmission:
 - Increases brain levels of GABA by inhibiting GABA transaminase (enzyme responsible for GABA breakdown) and increasing glutamic acid decarboxylase activity.
- Modulates ion channels:
 - Blocks voltage-gated sodium channels → stabilizes neuronal membranes.
 - Inhibits low-threshold T-type calcium channels, reducing neuronal excitability.
- Overall effect → suppression of seizure activity.

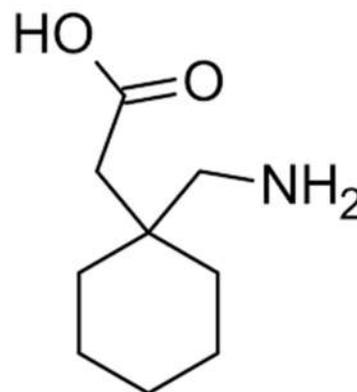
Therapeutic Uses

- Epilepsy:
 - Generalized tonic-clonic seizures
 - Absence seizures
 - Myoclonic seizures
 - Partial (focal) seizures (adjunct therapy)
- Bipolar disorder: Mood stabilizer.
- Migraine prophylaxis: Prevents migraine attacks.

Gabapentin

Structure

- Chemical class: GABA analogue (γ -aminobutyric acid derivative).
- Core structure: 1-(aminomethyl)cyclohexaneacetic acid.
- Physical properties: White crystalline powder, freely soluble in water, not metabolized significantly in humans.



Mechanism of Action (MOA)

- Binds to $\alpha 2\delta$ subunit of voltage-gated calcium channels in the CNS.
- Reduces calcium influx into neurons \rightarrow decreases release of excitatory neurotransmitters (glutamate, substance P, norepinephrine).
- Does not directly bind GABA receptors, despite being a GABA analogue.
- Net effect \rightarrow reduces neuronal hyperexcitability and seizure activity, also reduces neuropathic pain signaling.

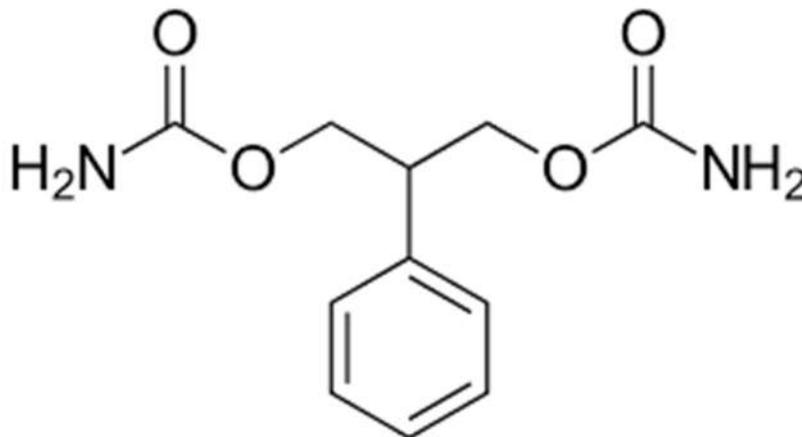
Therapeutic Uses

- Epilepsy:
 - Adjunct therapy for partial (focal) seizures with or without secondary generalization.
- Neuropathic pain:
 - Postherpetic neuralgia
 - Diabetic neuropathy
- Other off-label uses:
 - Restless leg syndrome
 - Anxiety disorders

Felbamate

Structure

- Chemical class: Carbamate derivative.
- Core structure: 2-phenyl-1-propyl-1-carbamate.
- Physical properties: White crystalline powder, freely soluble in water, stable under normal conditions.



Mechanism of Action (MOA)

- Inhibits excitatory neurotransmission:
 - Blocks NMDA (N-methyl-D-aspartate) glutamate receptors, reducing excitatory synaptic activity.
- Enhances inhibitory neurotransmission:
 - Potentiates GABA-A receptor activity, increasing chloride influx → neuronal hyperpolarization.
- Stabilizes neuronal membranes → prevents repetitive firing of neurons.
- Net effect → anticonvulsant activity in various seizure types.

Therapeutic Uses

- Epilepsy:
 - Refractory partial (focal) seizures
 - Lennox-Gastaut syndrome (especially in children)
- Adjunct therapy when other antiepileptics fail.