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# MEDICINAL CHEMISTRY – I

# UNIT 4

TOPIC :

- **C. Anticonvulsants :** SAR of Anticonvulsants, mechanism of anticonvulsant action
  **Barbiturates :** Phenobarbitone, Methabarbital.
  **Hydantoins :** Phenytoin, Mephenytoin, Ethotoin
  **Oxazolidine 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 $Ca^{2+}$ 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, $NO_2$)** → 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,
- Methabarbital.

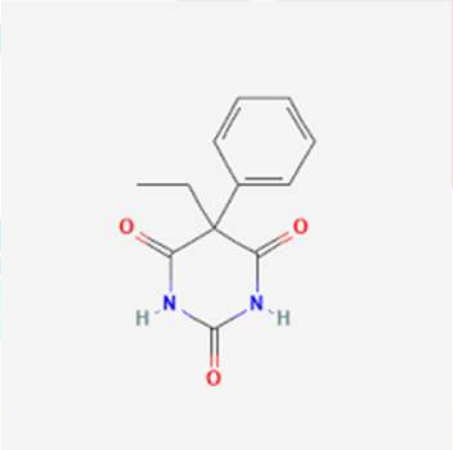
Mechanism of Action

❖ 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.

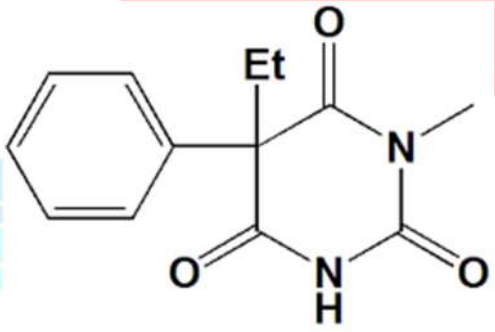
Therapeutic Uses

- **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**

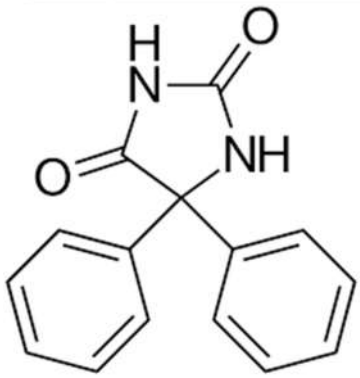
Mechanism of Action (MOA)

- 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.

# 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.

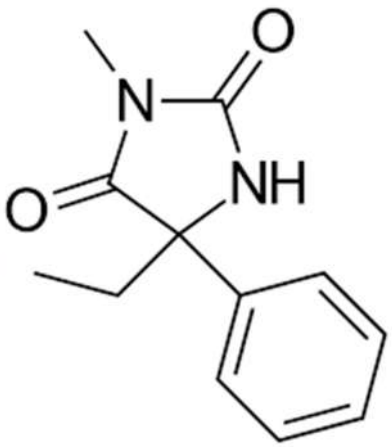
## Therapeutic Uses

- 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.

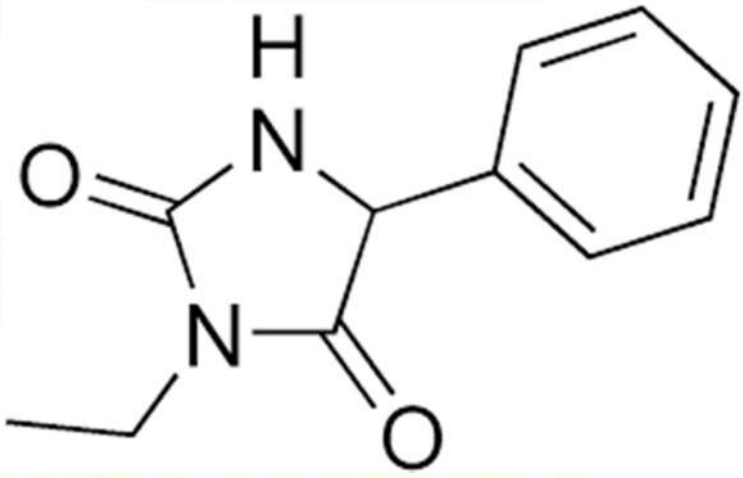
## Therapeutic Uses

- 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**.

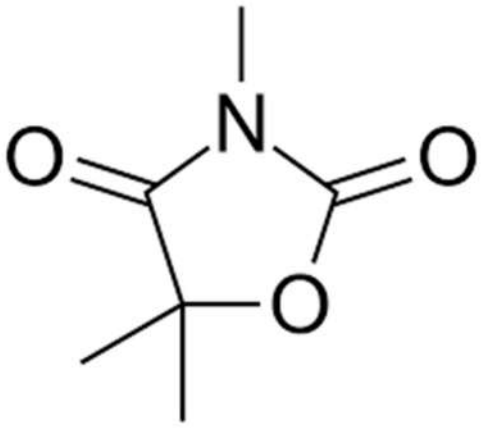
Mechanism of Action (MOA)

- 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.

# 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.

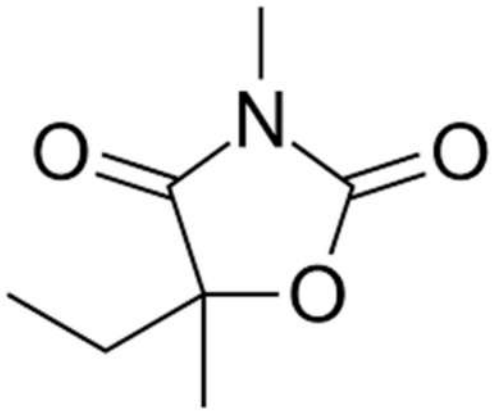
## Therapeutic Uses

- 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**

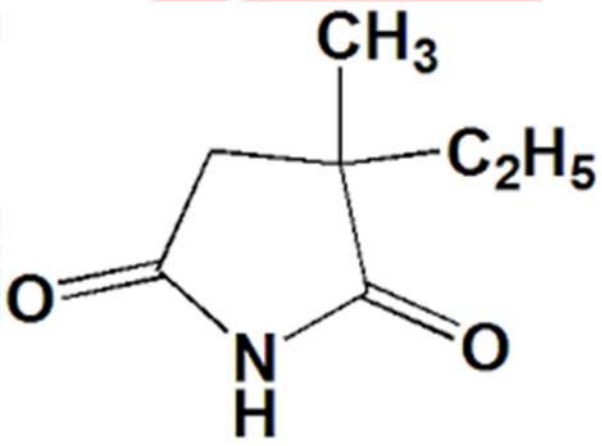
Mechanism of Action (MOA)

- 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.

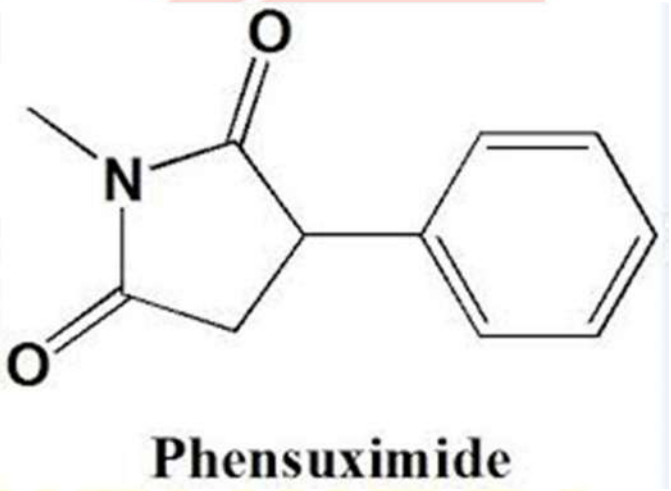
Therapeutic Uses

- **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.



**Phensuximide**

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.

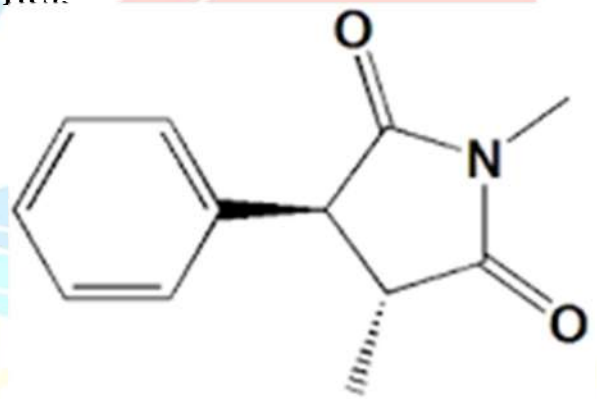
Therapeutic Uses

- **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.

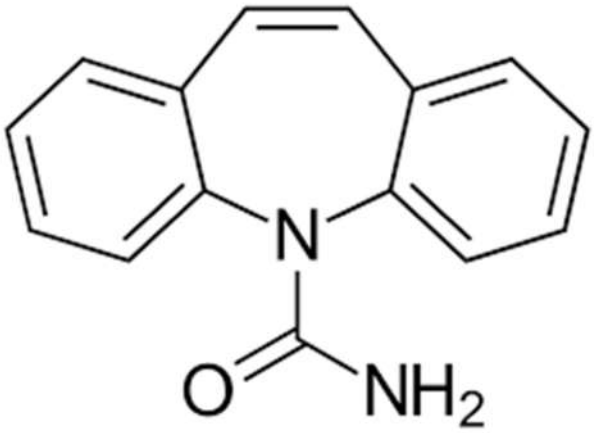
Therapeutic Uses

- **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

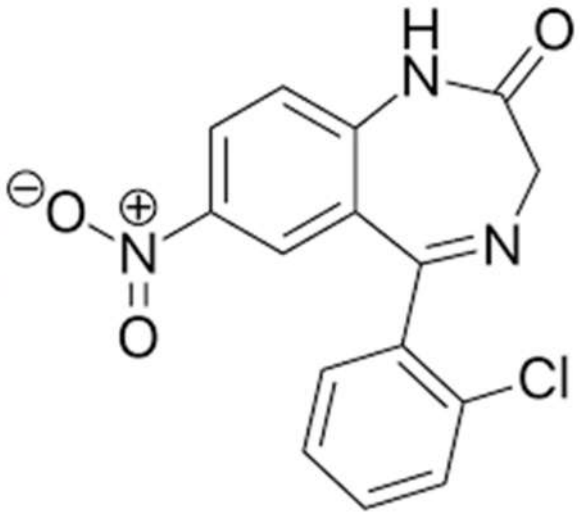
Mechanism of Action (MOA)

- ❖ 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

# 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.

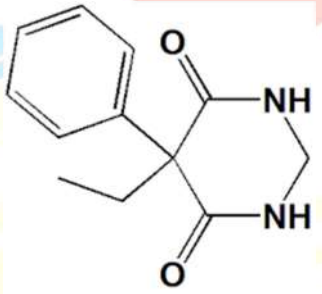
# Miscellaneous

- 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.

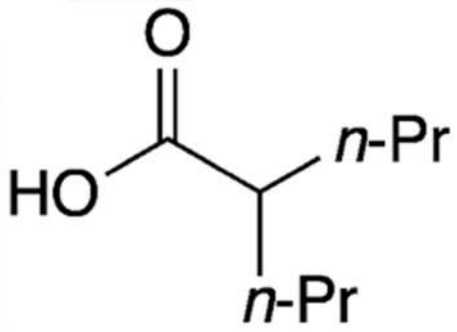
## Therapeutic Uses

- 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: $CH_3–CH_2–CH(COOH)–CH_3$
- 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.

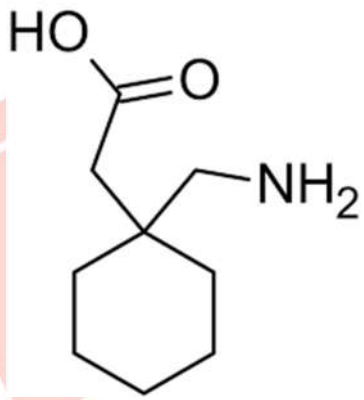
## Therapeutic Uses

- 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 α2δ subunit of voltage-gated calcium channels in the CNS.
- Reduces calcium influx into neurons → decreases release of excitatory neurotransmitters (glutamate, substance P, norepinephrine).
- Does not directly bind GABA receptors, despite being a GABA analogue.
- Net effect → reduces neuronal hyperexcitability and seizure activity, also reduces neuropathic pain signaling.

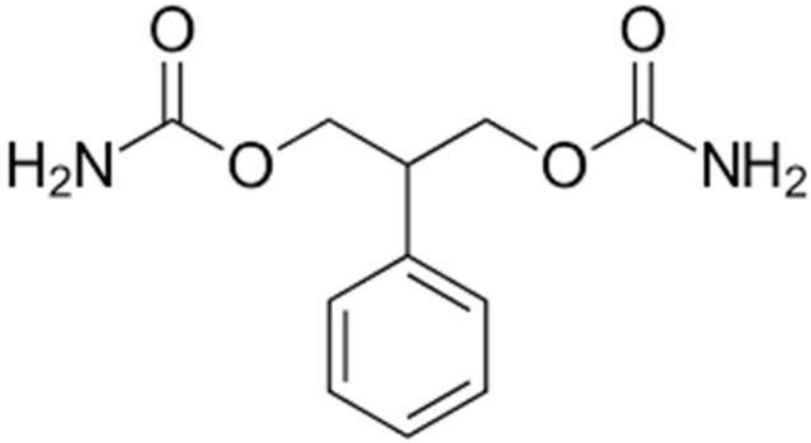
## Therapeutic Uses

- 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.