

## Anticonvulsants (Antiseizure Drugs) — Classification and Side Effects

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**A seizure is a brief episode of signs/symptoms resulting due to uncontrolled, abnormal electrical activity in the brain. In this article, we will study in detail the classification, mechanism of action, and adverse effects and interactions of antiseizure drugs. First and second-line drugs for various types of seizures will also be studied.**



### Definitions and Classification of Seizures

**Epilepsy** is a group of neurological disorders characterized by the recurrence of seizures. A seizure is a brief surge of uncontrolled, abnormal electrical activity in the brain which may produce a physical convulsion in some individuals or minor physical signs in others. Yet other people may suffer thought disturbances or a combination of symptoms. Many structures and processes are involved in the development of a seizure, including neurons, ion channels, receptors, glia, and inhibitory and excitatory synapses.

**Epilepsy is defined by any of the following:**

1. At least two unprovoked (or reflex) seizures occurring greater than 24 hours apart
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60 %) after two unprovoked seizures,

occurring over the next 10 years

### 3. Diagnosis of an epilepsy syndrome

**Anti-seizure or antiepileptic drugs**, therefore, are targeted to inhibit neurotransmission. This can be achieved via blocking sodium or calcium excitatory channels/currents, enhancing the inhibitory activity of **gamma-aminobutyric acid (GABA)**, or by blocking **glutamate receptors**.

Seizures can be primary (idiopathic) or secondary to a specific cause such as trauma or a [tumor](#). Most antiseizure drugs require dose adjustment in patients with liver and/or [kidney failure](#), and some have considerable drug-drug interactions.

Seizures are clinically classified as partial or generalized:

## Partial seizures

- Simple partial seizures, in which consciousness **is not impaired**.
- Complex partial seizures, in which consciousness **is impaired**.
- Both types of partial seizures can spread, resulting in **secondarily generalized tonic-clonic seizures**.

## Generalized seizures

Generalized seizures are those in which the first clinical changes indicate that both hemispheres are initially involved. Consciousness usually is impaired during generalized seizures, although some seizures, such as the myoclonic type, may be so brief that impairment of consciousness cannot be assessed.

- Generalized tonic-clonic seizures, aka *grand mal* or GTC
- Absence seizures, aka *petit mal* seizures
- Tonic seizures
- Atonic seizures
- Clonic seizures
- Myoclonic seizures
- Infantile spasms

The meanings of some of the terms involved are as follows:

- **Simple:** no loss of consciousness
- **Complex:** accompanied by loss of consciousness
- **Partial:** a part of the body is involved
- **Complete:** the whole body is involved, e.g., status epilepticus
- **Absence:** no epileptic movements, but there is impaired consciousness

## Relevant Pathophysiology of Seizure Types

### Focal

- **Decreased inhibition**—defective activation of GABA neurons, defective GABA-A/ -B inhibition, a defect in intracellular calcium regulation
- **Increased excitation**—increased activation of glutamate N-methyl-D-aspartate (NDMA) receptors, increased synchrony or activation of neurons

### Generalized

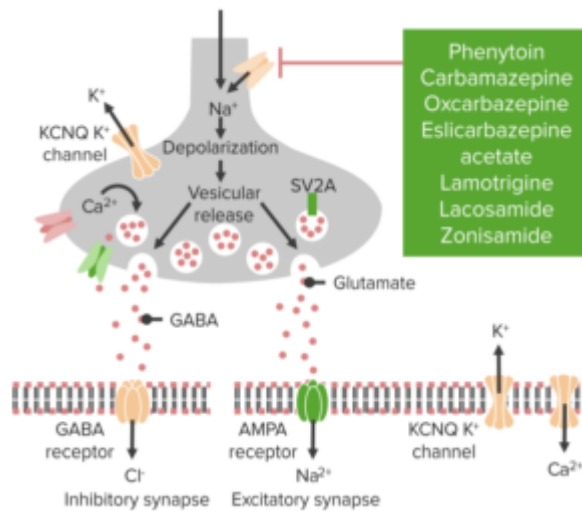
- **Altered thalamocortical rhythms** (regulated by the T-type calcium channels/currents)

## Antiseizure Drugs (Anticonvulsants)

As already mentioned, the main effect of antiseizure drugs is to suppress the abnormal **electrical activity** at the **epileptic foci** in the brain. This is achieved by many different mechanisms.

### Sodium channel

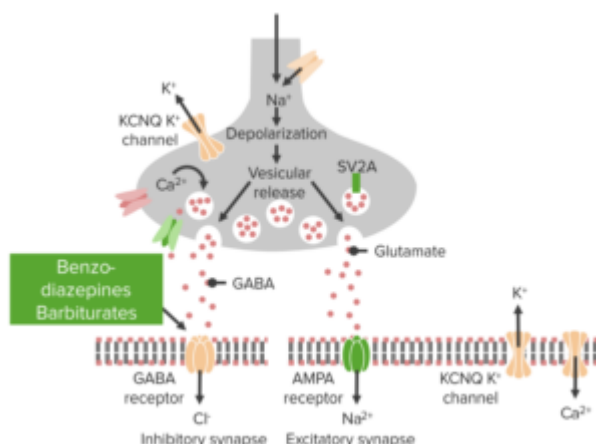
**blockade: phenytoin and phenobarbital and valproic acid at high doses**



The block of **voltage-gated sodium channels** in neuronal membranes prevents **Na<sup>+</sup> influx**, which results in decreased **axonal conductance** by increasing the **refractory period** of the neuron.

### Promotion of GABA-related inhibition:

- Increase the **frequency of chloride ion channel opening**—**benzodiazepines**
- Increase the **duration** of chloride ion channel opening—**barbiturates**, such as phenobarbital

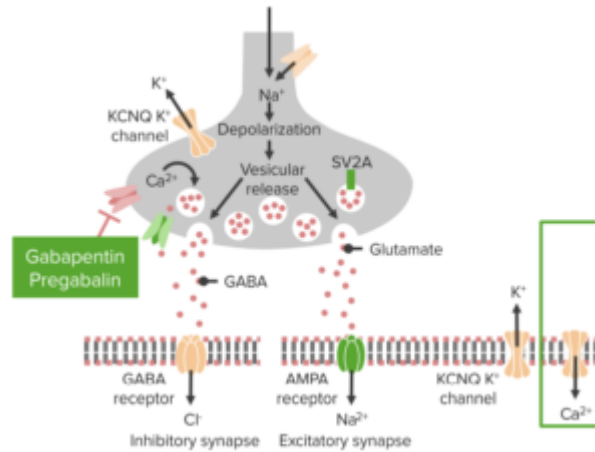


- **Irreversible inactivation of GABA amino transaminase** (which terminates the activity of GABA)—**vigabatrin** and **at high doses valproic acid**
- Inhibition of a **GABA transporter (GAT-1)**, thereby prolonging GABA action—**tiagabine**
- Structural analog of GABA—**gabapentin**

**Glutamate NMDA receptor blockade: decreased glutamic acid**

excitability—**felbamate**

**Calcium channel blockade:**  
inhibition of the T-type  $\text{Ca}^+$  currents,  
**especially in thalamic neurons,**  
and decreased  $\text{Ca}^+$  influx in  
presynaptic vesicles. E.g.,  
**ethosuximide and valproic acid.**

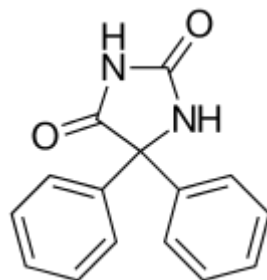


## General pharmacokinetics

- Good absorption from the gut, with a bioavailability of 80–100%
- They usually do not have high plasma protein binding (exceptions: valproic acid, phenytoin, and tiagabine).
- Mainly metabolized by the [liver](#)
- Some are excreted unchanged in the urine, and these have minimal drug-drug interaction.
- Usually, medium-to-long acting because of relatively low plasma clearance; longer half-lives
- Phenytoin and gabapentin can exhibit nonlinear pharmacokinetics.

## Important Antiseizure Drugs

### Phenytoin



[Image:](#) "2D structure of anticonvulsive drug phenytoin" by Harbin - Own work. License: Public Domain

- Most widely used antiepileptic drug
- **Fosphenytoin** is a water-soluble prodrug; it can be used parenterally (intravenous and intramuscular).
- Highly bound to plasma proteins

**Mechanism of action:** sodium channel blockade

**Use:**

- Status epilepticus
- GTC seizures (primary or secondary)
- Focal seizures

**Notable adverse effects:**

- **Nystagmus and ataxia** (because of cerebellar depression), **gingival hyperplasia**, **hirsutism**, diplopia, **folic acid deficiency** (manifested as depression, apathy, psychomotor retardation, and cognitive decline)
- Long-term use mild peripheral neuropathy, **osteomalacia** (due to vitamin D metabolism abnormalities)
- **Fosphenytoin**'s adverse effects (not found with phenytoin) include perineal paresthesias and rash/itching, and these are concentration-dependent.
- **Stevens-Johnson syndrome** and **toxic epidermal necrolysis** may occur.

**Important points:**

- Zero order (non-linear)
- Requires dose adjustment in patients with **renal failure**.
- Slow-/extended-release formulation available, which can be administered once daily.
- **Calcium and vitamin D supplements** required in long-term use to prevent **osteomalacia**.

**Drug-drug interactions of phenytoin:**

Drug	Effect	Management
Lamotrigine	Increased metabolism of lamotrigine (glucuronidation induction)	Adjust lamotrigine dose
Oxcarbazepine	Possible phenytoin toxicity with higher doses of oxcarbazepine	Reduce phenytoin dose
Tiagabine	Increased tiagabine metabolism (CYP3A4)	Monitor clinical status
Topiramate	Possible phenytoin toxicity with higher doses of topiramate	Monitor clinical status and phenytoin concentration
Valproic acid	Increased valproic acid metabolism → increased the formation of a toxic metabolite. Thus, decreased efficiency and increased toxicity	Monitor valproic acid concentration and adjust the dose
Zonisamide	Decreased zonisamide metabolism (CYP3A4)	Monitor zonisamide concentration and adjust the dose

## Carbamazepine

**Mechanism of action:** sodium channel blockade

**Use:**

- Focal seizures
- GTC seizures
- Trigeminal neuralgia
- Bipolar disorder
- Not in absence seizures (may increase them)

**Notable adverse effects:** **hyponatremia** (partly due to increased responsiveness of collecting tubules in the **kidney** to ADH), dizziness, drowsiness, and nausea.

**Important points:**

- It induces its own metabolism.
- Inducer of CYP1A2, CYP2C, CYP3A, and UDP glucuronosyltransferase
- Severe, even fatal, dermatological reactions may rarely occur—**toxic**

**epidermal necrolysis** and **Stevens-Johnson syndrome**.

- Contraindicated in pregnancy due to the risk of **fetal carbamazepine syndrome**
- Contraindicated in patients with a history of **bone marrow suppression** and administration of monoamine oxidase (MAO) inhibitors in the past 14 days.

## Oxcarbazepine

This is a prodrug and converted to active **monohydroxy derivative (MHD) metabolite**. It shows fewer drug interactions than carbamazepine because it is a less potent inducer of CYP3A and UDP glucuronosyltransferase.

**Hyponatremia** is a significant adverse effect (probably higher than that in carbamazepine).

## Valproic acid

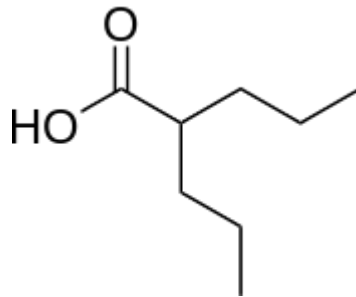


Image: "2D structure of anticonvulsant valproic acid (Depakote)" by Harbin - Own work.  
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- Highly bound to plasma proteins

**Mechanism of action:** sodium channel and calcium T-type current blockade

Inhibits GABA transaminase

**Use:**

- **Complex partial seizures** as monotherapy and/or adjuvant
- Simple and complex absence seizures
- **Myoclonic seizures**
- Migraine prophylaxis
- Bipolar mania.

**Notable adverse effects:** weight gain, **pancreatitis**, tremor, **thrombocytopenia**, headache, **azoospermia**, **hirsutism**, hair color change

**Important points:**

- Being a teratogenic drug it can cause **spina bifida** if given during pregnancy.
- **P450 inhibitor**
- High drug-drug interactions:
  - Competes with phenytoin for protein binding.
  - Inhibits metabolism of carbamazepine, ethosuximide, phenytoin, phenobarbital, and lamotrigine.

## Other Anticonvulsants

Drug	Mechanism of Action	Use	Significant Adverse Effects	Other remarks
<b>Ethosuximide</b>	T-type calcium channel blockade	Only in absence seizures (drug of choice with valproic acid)	Commonly, gastric effects: pain, nausea, and vomiting	More effective than lamotrigine for absence seizures; long half-life (~40 hours)
<b>Felbamate</b>	Glutamate NMDA receptor blockade and calcium and sodium channel blockade	Third-line drug for refractory partial seizures and for Lennox-Gastaut syndrome	Aplastic anemia (1:4000) and hepatic failure.	Increases plasma phenytoin and valproic acid levels but decreases levels of carbamazepine
<b>Gabapentin</b>	GABA analog	Adjunct for focal seizures and postherpetic neuralgia	Sedation	Excreted unchanged in kidneys; minimal drug interaction; preferable in the elderly because of milder side effects;
<b>Lamotrigine</b>	Sodium channel blockade, high voltage-dependent calcium channel blockade	Many seizures, Lennox-Gastaut syndrome, bipolar disorder	Skin rashes, life-threatening Stevens-Johnson syndrome	Dose reduction required with valproic acid
<b>Levetiracetam</b>	Facilitate GABA-mediated inhibition—although the exact mechanism is unclear (binds to binds selectively to the synaptic vesicular protein SV <sub>2</sub> A)	Adjunct for focal, myoclonic, and primary GTC seizures	Behavior changes—may require dose reduction or change of drug altogether	Excreted unchanged in kidneys with minimal drug interaction
<b>Phenobarbital</b>	Promotion of GABA-related inhibition, glutamate blockade, Na and Ca current blockade at high concentrations	Status epilepticus, partial seizures, GTC, febrile seizures	Skin rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, learning difficulties, ataxia	May worsen seizures in absence, atonic, and infantile spasms; <b>Primidone</b> (a prodrug) is metabolized to phenobarbital and phenylethylmalonamide (both have antiseizure activity)
<b>Tiagabine</b>	Block reuptake of GABA	Adjunct for partial-onset seizures	Dizziness, difficulty concentrating, abdominal pain, nausea	Both hepatic metabolism and renal elimination; should not be used in patients who do not have epilepsy (as it may precipitate seizures).
<b>Topiramate</b>	Sodium channel blockade, carbonic anhydrase inhibitor, glutamate NDMA receptor blockade, etc.	Partial and primary generalized epilepsy	Somnolence, weight loss, paresthesias	Both hepatic metabolism and renal elimination
<b>Vigabatrin</b>	Increases GABA levels by inhibiting GABA transaminase	Focal epilepsy (adjunct > monotherapy)	Visual field loss (mild to severe) in about 1/3 of the patients	Excreted unchanged in kidneys with minimal drug interaction
<b>Zonisamide</b>	Sodium channel and T type calcium current blockade.	Focal epilepsy	Kidney stones, decreased sweating (oligohidrosis), severe skin reactions	Both hepatic metabolism and renal elimination; contraindicated when hypersensitivity to sulfonamides or carbonic anhydrase inhibitors present.

### Notes:

Drug excreted unchanged through the kidneys requires **dose reduction in renal disease**.

Newer antiseizure drugs have somewhat fewer neurotoxic and systemic side effects than the older/standard ones.

### Other points on toxicity:

- Most antiseizure drugs are **CNS depressants**. Therefore, overdose can depress the respiration center.
- Respiratory depression is managed using conservative treatment.
- Many of these drugs can cause drowsiness, sedation, mood/ behavior changes (particularly depression).
- Withdrawal of antiseizure drugs should be gradual; sudden cessation can cause increased frequency and/or severity of seizures.

## Selection of antiseizure drugs

	GTC Seizures	Focal (Partial) Seizures	Typical Absence Seizures	Atypical Absence Seizures, Myoclonic Seizures
<b>First line</b>	Valproic acid Topiramate Carbamazepine Phenytoin Phenobarbital (infants)	Lamotrigine Carbamazepine (or oxcarbazepine) Phenytoin	Ethosuximide <sup>a</sup> Valproic acid <sup>b</sup>	Valproic Acid Lamotrigine <sup>c</sup>
<b>Second Line</b>	Phenytoin Phenobarbital (adults)	Phenobarbital Topiramate Valproic Acid	Lamotrigine Clonazepam <sup>d</sup> Levetiracetam Zonisamide	Clonazepam Levetiracetam Zonisamide
<b>Adjuncts (in refractory cases)</b>	Perampanel Levetiracetam Zonisamide	Gabapentin Pregabalin Perampanel Zonisamide		Felbamate

<sup>a</sup>primarily in uncomplicated cases of absence seizures

<sup>b</sup>useful in cases accompanied by GTC or myoclonic seizures

<sup>c</sup>alone or as an adjunct

<sup>d</sup>main side effects include drowsiness and sedation; tolerance may develop with longer use

## Other Epileptic Conditions

### Status epilepticus

Status epilepticus is a series of epileptic episodes (usually **tonic-clonic**) without recovery of consciousness between attacks. It is a **life-threatening emergency**.

#### Management of status epilepticus:

- Securing airway, breathing, and [circulation](#)
- Start IV benzodiazepine (diazepam or lorazepam) for immediate control
- Maintenance by phenytoin (fosphenytoin)
- If seizures continue, a loading dose of phenobarbital
- If seizures still continue, intubate and administer [general anesthesia](#).

### Infantile spasms

Infantile spasms are an epileptic syndrome characterized by **myoclonic jerks**; however, the manifestation varies.

- Reported association with infection, **kernicterus**, **tuberous sclerosis**, and **hypoglycemia**
- Patients usually have **cognitive deficiency**, and therapy may not alleviate this.

#### Management of infantile spasms:

- Intramuscular corticotropin or oral prednisolone; if seizures recur, repeat the course.
- Benzodiazepines—clonazepam or nitrazepam (as effective as corticosteroids)
- Vigabatrin (sometimes considered the drug of choice)



# Nonepileptic Uses of Antiseizure Drugs



Image: "Trigeminal Neuralgia." by BruceBlaus - Own work. License: [CC BY-SA 4.0](https://creativecommons.org/licenses/by-sa/4.0/)

- **Phenytoin** is a group 1B antiarrhythmic agent.
- Several drugs, especially carbamazepine and lamotrigine, are useful for **bipolar disorder**.
- Gabapentin is useful in **postherpetic neuralgia**.
- Carbamazepine is the drug of choice of **trigeminal neuralgia**.
- Many drugs are useful in **migraine**, e.g., phenytoin, gabapentin, topiramate.

## High-yield points to remember regarding antiseizure drugs

High drug-drug interactions	Phenytoin, carbamazepine, valproic acid
Dose adjustment/cessation required in renal insufficiency/failure	Gabapentin, levetiracetam, topiramate, vigabatrin
Preferred in the elderly	Gabapentin
Increase weight Decrease weight Weight neutral	Carbamazepine, valproic acid felbamate, topiramate Lamotrigine, levetiracetam, phenytoin
Can exacerbate seizures	Carbamazepine—absence, atonic, or myoclonic seizures Phenytoin, vigabatrin—generalized seizures Gabapentin—myoclonic jerks

## Review Questions

The correct answers can be found below the references.

**1. A 37-year-old female with a BMI of 29.6 is diagnosed with absence seizures. Which of the following is the most suitable drug?**

- A. Carbamazepine
- B. Valproic acid
- C. Lamotrigine
- D. Felbamate
- E. Phenytoin

**2. A 17-year-old male presented to the emergency department with fever,**

**vomiting, facial edema, and an erythematous rash over his face, neck, chest, and back. He had been diagnosed with juvenile myoclonic epilepsy two weeks ago and had been started on an antiepileptic drug. Which of the following drugs could be responsible?**

- A. Phenytoin
- B. Lamotrigine
- C. Clonazepam
- D. Carbamazepine
- E. Ethosuximide

**3. A 68-year-old woman was newly diagnosed with epilepsy. Considering the adverse effect profile, especially in an elderly person, which of the following drugs should be prescribed?**

- A. Carbamazepine
- B. Phenytoin
- C. Phenobarbital
- D. Valproic acid
- E. Lamotrigine

## References

Biton, V. (2003). Effect of antiepileptic drugs on bodyweight. *CNS drugs*, 17(11), 781-791.

Eldon, M. A., Loewen, G. R., & Voightman, R. E. (1993). Pharmacokinetics and tolerance of fosphenytoin and phenytoin administration intravenously to healthy subjects. *Can J Neurol Sci*, 20(5), 180.

Harvey, R. A., Clark, M. A., Finkel, R., Rey, J. A., & Whalen, K. (2012). *Lippincott's illustrated reviews: Pharmacology*. Philadelphia: Wolters Kluwer.

Katzung, B. G. (Ed.). (2012). *Basic & clinical pharmacology* (Vol. 12). New York, NY, USA: Lange Medical Books/McGraw-Hill.

Reynolds, E. (2006). Vitamin B12, folic acid, and the nervous system. *The lancet neurology*, 5(11), 949-960.

Rzany, B., Correia, O., Kelly, J. P., Naldi, L., Auquier, A., & Stern, R. (1999). Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. *The lancet*, 353(9171), 2190-2194.

Trevor, A. J., Katzung, B. G., Masters, S. B., & Kruidering-Hall, M. (2010). *Pharmacology Examination & Board Review*. New York: McGraw-Hill Medical.

Tripathi, K. D. (2013). *Essentials of medical pharmacology*. JP Medical Ltd.

[Antiseizure drugs: Mechanism of action, pharmacology, and adverse effects](#) via uptodate.com

[Epilepsy and Seizures](#) via medscape.com

Correct answers: 1C, 2B, 3E

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