Anticonvulsant agents

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- **Epilepsy is a chronic disorder characterized by recurrent seizures, which are finite episodes of brain dysfunction resulting from abnormal discharge of cerebral neurons**
- Epilepsy is the most prevalent neurological disorder affecting more than 0.5% of the world's population

Epilepsy

- The etiology of epilepsy is largely unknown even though recent evidence suggests that it may have a genetic component associated with its disease development.
- Seizures: are symptoms of disturbed electrical activity in the brain characterized by episodes of abnormal, excessive, and synchronous discharge of a group of neurons within the brain that cause involuntary movement, sensation, or thought.
- seizures may result from primary or acquired neurological disturbances of brain function as a result of an imbalance between excitatory and inhibitory processes in the brain.
- There are many possible causes of seizures including brain tumors or infections, head trauma, neurological diseases, systemic or metabolic disorders, alcohol abuse, drug overdose, or toxicities.

Classification of epileptic seizures

I. Partial (local, focal) seizures
   A. Simple (consciousness not impaired)
   B. Complex partial seizures (psychomotor seizures)
      1. Beginning as simple partial seizures, progressing to complex seizures
      2. With impairment of consciousness at onset
   C. Partial seizures evolving to secondarily generalized tonic-clonic convulsions
II. Generalized seizures (convulsive or nonconvulsive)
   A. Absence seizures
      Typical (petit mal)
      Atypical
   B. Myoclonic
   C. Clonic
   D. Tonic
   E. Tonic-clonic (grand mal)
   F. Atonic
III. Unclassified epileptic seizures (includes some neonatal seizures)

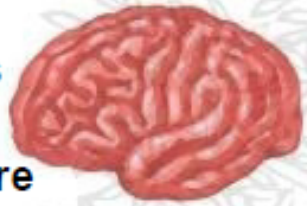
Types and features of seizures

Table 11.1 ▶ **Types of Seizures**

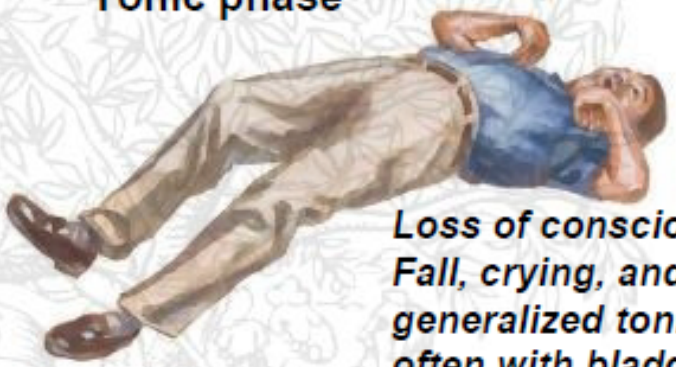
	Seizure Type	Features
Partial seizures (focal, local)	Simple	Motor, somatosensory, autonomic, or psychic symptoms, with loss of consciousness
	Complex	Impaired consciousness at the outset Simple partial seizure followed by impaired consciousness
Generalized seizures (convulsive or nonconvulsive)	Absence	
	Typical	Sudden brief lapses of consciousness with loss of posture
	Atypical	Typical form + brief motor activity or loss of muscle tone
	Myoclonic	Isolated jerking movements
	Clonic	Repetitive jerking movements without muscle rigidity
	Tonic	Muscle rigidity without jerking movements
	Tonic-clonic	Muscle rigidity followed by rhythmic jerking movements
	Atonic	Loss of muscle tone

* Partial seizures can evolve to generalized tonic-clonic

Simultaneous bilateral cortical seizure attack



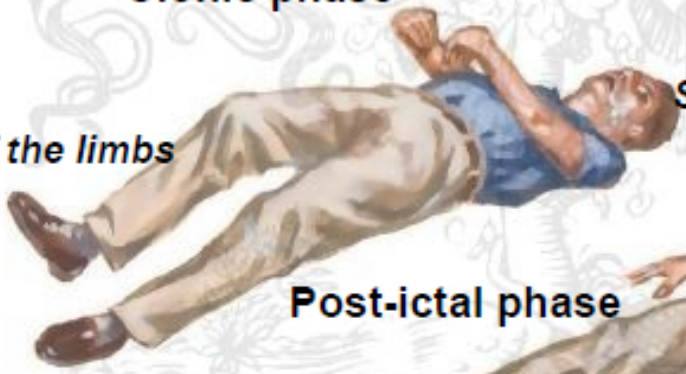
Tonic phase



Cyanosis
Cry

Loss of consciousness,
Fall, crying, and
generalized tonic stiffening
often with bladder incontinence

Clonic phase



Salivary frothing

Jerking of the limbs

Post-ictal phase

Patient feels lethargic and confused after seizures
Often sleeps

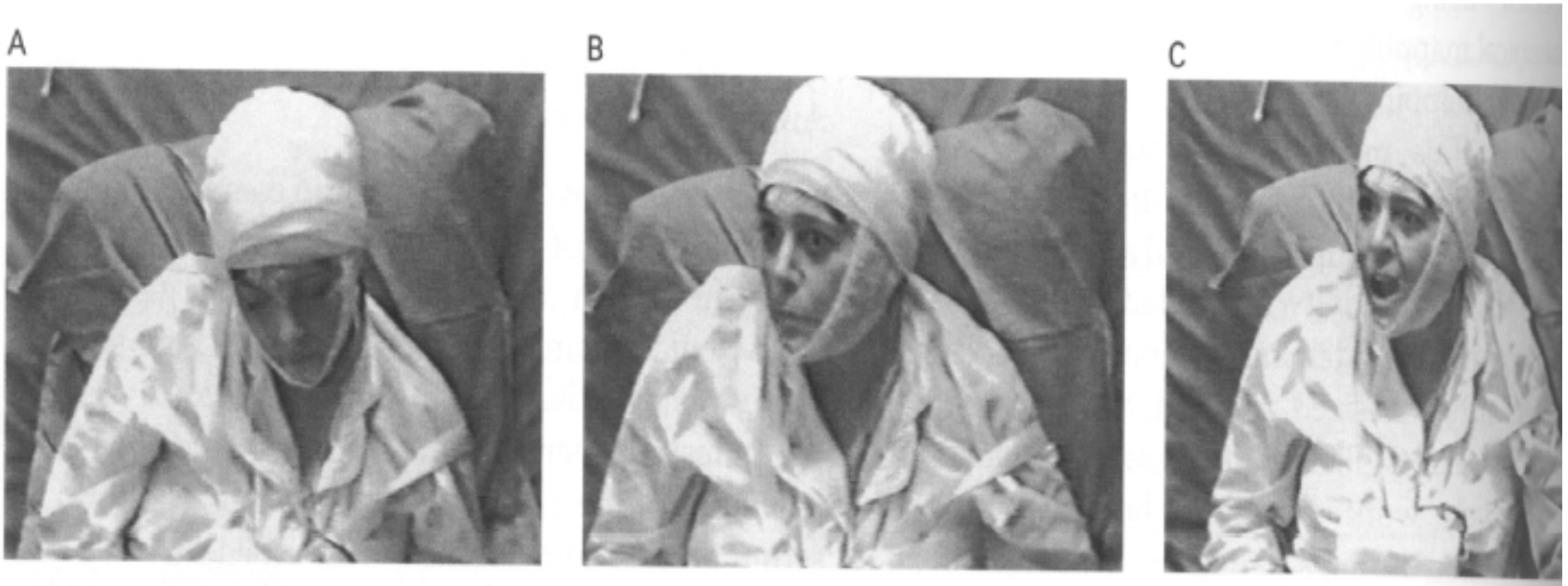


Figure 46-15 The patient was monitored with closed-circuit television simultaneous EEG and telemetry. The monitoring revealed stereotypical complex partial seizures. The patient is shown reading quietly in the period preceding the seizure (**A**), during the period when she reported a feeling of fear (**B**), and during the period when there was alteration of consciousness and an audible scream (**C**). (Courtesy of Dr. M Salinsky, Oregon Health Sciences University Epilepsy Cen

Stereotypical complex partial seizures

Status epilepticus

- *Status epilepticus* is the term used to describe prolonged seizures (usually lasting 30 minutes or more) or multiple seizures that occur without recovery of consciousness.
- Status epilepticus constitutes a medical emergency, as the risk of death or brain damage increases the longer the seizures continue.
- Treatment involves maintaining the patient's airway and giving oxygen, a bolus of glucose (as the brain is a huge consumer of glucose), and intravenous (IV) or rectal diazepam to terminate the seizure.
- IV diazepam is given in the form of an emulsion to prevent thrombophlebitis (inflammation of a vein due to a blood clot).

Febrile convulsions

- Febrile seizures (seizures associated with elevated body temperature) are the most
- common type in children, affecting 2 to 5% between the ages of 6 months and 5 years, with the peak incidence at 18 months.
- These seizures are not associated with trauma, infection, metabolic disturbances, or a history of seizures, and most last less than 10 minutes.
- More serious illnesses must be ruled out, but treatment of simple febrile seizures with anticonvulsants is generally not recommended, as the potential drug toxicities associated with these medications outweigh the relatively minor risks associated with the convulsion.
- There is also no need to specifically cool the child in a cooling bath or to administer an antipyretic drug, e.g., acetaminophen, to reduce the fever. Most febrile convulsions will stop on their own after a few minutes.

Lennox-Gastaut syndrome

- Lennox-Gastaut syndrome is a disorder of childhood characterized by multiple difficult-to-treat seizure types.
- It is usually accompanied by some form of cognitive impairment.
- Antiepileptic drugs may control seizures for a time, but tolerance frequently develops.

Important Note

- Misdiagnosis or improper drug selection generally makes epilepsy worse, so it is critical that the correct seizure disorder is identified and that it is treated with the most efficacious drug.
- If the drug of choice fails to control the seizures, then a follow-up agent is used.

Neuronal sites of action of antiepileptics.

- Antiepileptic drugs act at many neuronal sites to inhibit excitation of the neuron. Gamma-aminobutyric acid (GABA) mimetics enhance the inhibitory effects of GABA at the GABAA receptor/Cl– channel.
- Other antiepileptics block voltage-dependent Na+ channels, which can inhibit the release of the excitatory neurotransmitter glutamate, or they can act on the neurons themselves to inhibit action potentials.
- Other drugs block the *N*-methyl-d-aspartate (NMDA) glutamate receptor or T-type Ca2+ channels

Mechanisms of action of anticonvulsants

(a) modulation of voltage-gated ion channels (Na, Ca2, and K),

(b) Enhancement of -aminobutyric acid (GABA)-mediated inhibitory neurotransmission

(c) attenuation of excitatory (particularly glutamate-mediated) neurotransmission in the brain.

VOLTAGE-GATED SODIUM CHANNELS

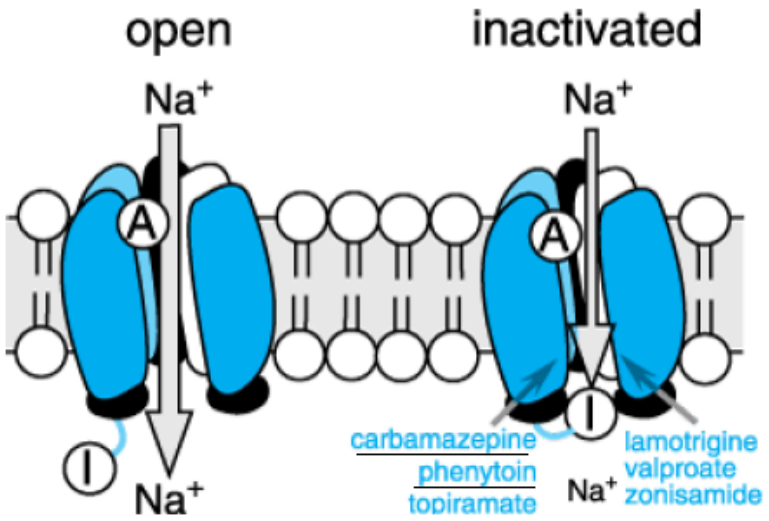
in the presynaptic nerve terminal of the excitatory glutamate receptors

1-Phenyl-substituted succinimide cause some Na^+-channel block

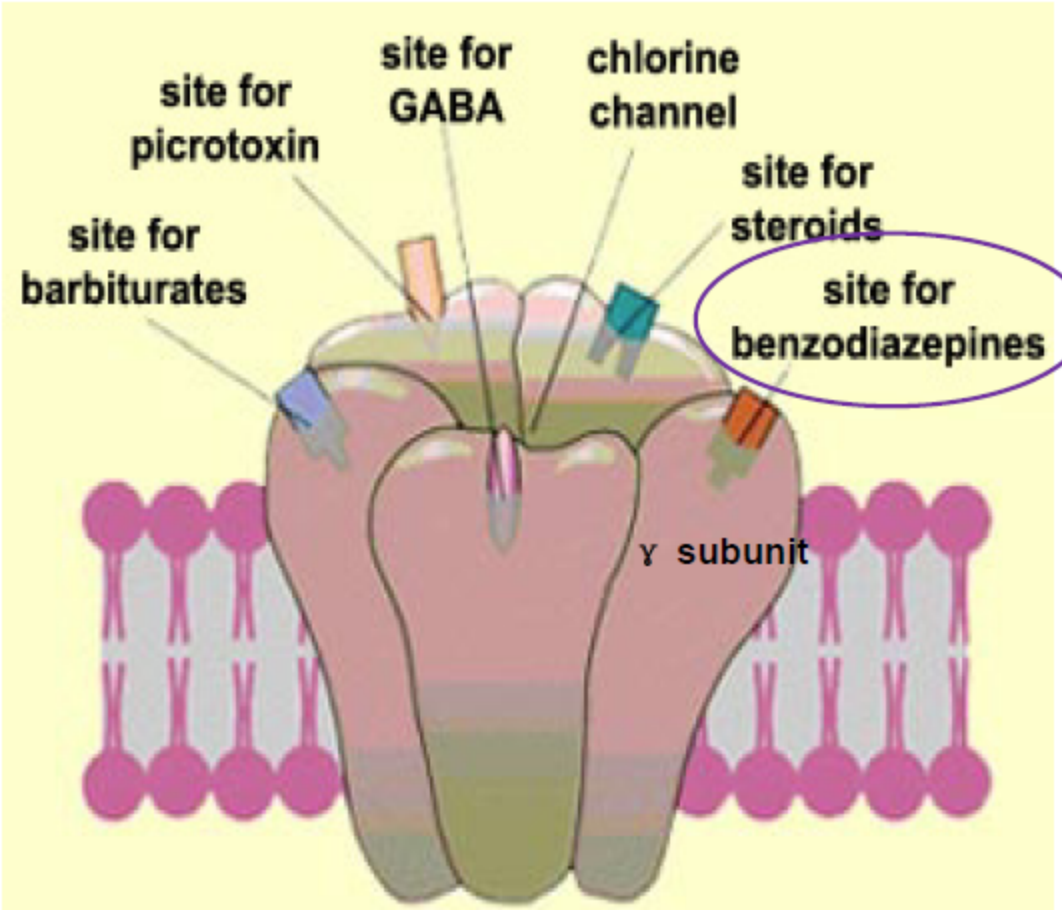
2-phenytoin, carbamazepine, oxacarbazepine, valproic acid, and felbamate is Phenobarbital, may also block voltage gated Na^+-channel

Drugs which act on Na+ channel

- Phenytoin
- Carbamazepine
- Oxcarbazepine
- Lamotrigine



(2) Interaction with $GABA_A$ receptor



Phenytoin

- **Mechanism of action**: Phenytoin limits the repetitive firing of action potentials in brain
- neurons by slowing the rate of recovery of voltage-activated Na+ channels from inactivation
- **Pharmacokinetics**
- — Slow, unpredictable absorption
- — Ninety percent bound to plasma proteins
- — Metabolized in liver to inactive metabolites
- **Uses**
- — Effective in all types of epilepsy except absence and atonic seizures
- — Trigeminal neuralgia

Phenytoin

- **Side effects**. Phenytoin is relatively safe, but the following may occur:
- — Gingival hyperplasia is the most common side effect in children (20% of patients). Infections are minimized by good oral hygiene.
- — CNS: nystagmus, ataxia, vertigo, and diplopia
- — Hyperglycemia, osteomalacia, lymphadenopathy, rashes (Stevens-Johnson syndrome [erythema multiforme bullosum]), and hematological reactions (leukopenia, megaloblastic anemia, thrombocytopenia, agranulocytosis, and aplastic anemia). These are allergic reactions that require cessation of therapy.
- — Hirsutism
- — Fetal abnormalities
- — Cardiovascular collapse can occur after IV phenytoin.

Phenytoin

- **Drug interactions**
- — Metabolism of phenytoin can be increased or decreased by agents that can induce or inhibit cytochrome P-450 enzymes.
- — Phenytoin induces hepatic microsomal enzymes; it thus reduces the plasma concentration of drugs that are metabolized by these enzymes, including warfarin, oral contraceptives, carbamazepine, and some antibiotics.
- — Drugs that bind to plasma proteins will displace phenytoin, which could result in toxicity

Carbamazepine

- **Mechanism of action**. Carbamazepine limits the repetitive firing of action potentials by slowing the rate of recovery of voltage-activated Na+ channels from inactivation
- **Pharmacokinetics**
- — Absorption slow and erratic
- — Metabolized in liver; may induce hepatic enzymes
- **Uses**
- — Generalized tonic-clonic seizures
- — Complex partial seizures
- — Trigeminal neuralgia
- *Note:* Carbamazepine is ineffective for absence seizures.

Carbamazepine

- **Side effects**
- — Gastrointestinal (GI) upset
- — Vertigo, diplopia, and blurred vision
- — Hematological disorders: aplastic anemia, thrombocytopenia (low platelet count), agranulocytosis (failure of bone marrow to produce white blood cells), and leucopenia (low white blood cell count)
- — Hypersensitivity

Carbamazepine

- **Drug interactions**
- — Metabolism of carbamazepine can be increased or decreased by agents that can induce or inhibit cytochrome P-450 enzymes.
- — Carbamazepine induces hepatic microsomal enzymes; it thus reduces the plasma concentration of drugs that are metabolized by these enzymes, including warfarin, oral contraceptives, and some antibiotics.

Phenobarbital

- **Mechanism of action.** Phenobarbital is a long-acting barbiturate that potentiates and mimics gamma-aminobutyric acid (GABA). It increases the threshold for action potential firing and inhibits the spread of activity from focus.
- **Pharmacokinetics**
- — Effective orally
- — Induces hepatic enzymes
- **Uses**
- — Generalized tonic-clonic epilepsy
- — Partial seizures
- — Prophylaxis or treatment of febrile convulsions

Phenobarbital

- **Side effects**
- — Sedation (tolerance develops)
- — Rashes are seen in 1 to 2% of patients. These may be scarlatiniform or morbilliform and are symptomatic of allergic reaction.
- — Nystagmus (a rapid, involuntary, oscillatory motion of the eyeball) and ataxia (the inability to coordinate voluntary muscular movement) at excessive doses
- *Note:* Respiratory depression is not seen with this long-acting barbiturate given orally, but it may be observed after IV injection.

Phenobarbital

- **Drug interactions**
- — Phenobarbital induces hepatic microsomal enzymes; it thus reduces the plasma concentration
- of drugs that are metabolized by these enzymes including warfarin, oral contraceptives, carbamazepine, and some antibiotics
- **— Additive effects** are seen when phenobarbital is taken with other CNS depressants.
- — Valproic acid increases phenobarbital blood levels by inhibiting cytochrome P-450 enzymes.

Primidone

- **Mechanism of action**. Mechanism is similar to that of phenobarbital.
- Pharmacokinetics. Primidone is metabolized in the liver to phenobarbital and phenylethylmalonamide (PEMA).
- **Uses**
- — Complex partial seizures (primidone is more effective than phenobarbital)
- — Generalized tonic-clonic seizures and simple partial seizures
- — Frequently combined with phenytoin in refractory cases
- **Side effects**
- — Rashes, leukopenia, thrombocytopenia, and systemic lupus erythematosus
- — CNS depression
- Drug interactions. Drug interactions are the same as for phenobarbital.

Valproic Acid

- **Mechanism of action**. Valproic acid increases Na+ channel inactivation, increases GABA mediated synaptic inhibition, and inhibits T-type Ca2+ channel activation.
- Its anticonvulsant action continues after the drug has been withdrawn.
- **Pharmacokinetics**
- — Ninety percent bound to plasma proteins
- — Metabolized by the cytochrome P-450 enzymes, but it does not induce these enzymes.
- **Uses**
- — Absence seizures, especially of the myoclonic types that are difficult to treat with other drugs.
- It appears to have an equivalent effect as ethosuximide for absence seizures.
- — Combination therapy in the treatment of generalized tonic-clonic seizures and for complex partial seizures

Valproic Acid

- **Side effects**
- — Alopecia (reversible) in 5% of patients
- — Transient GI effects in 16% of patients
- — CNS: mild behavioral effects, ataxia, and tremor; not a CNS depressant
- — Hepatic failure has been reported but is rare.
- *Note:* Valproic acid should not be used in pregnancy, as it has been shown to be teratogenic in animals.
- **Drug interactions**
- — Valproic acid increases blood levels of phenobarbital and primidone by inhibiting their metabolism
- — Valproic acid lowers phenytoin levels

Benzodiazepines

- **Mechanism of action**. Benzodiazepines augment the action of GABA at GABAA receptors, which are ligand-gated chloride ion channels
- **Uses**
- — Chronic treatment of epilepsy (clonazepam and clorazepate)
- — Status epilepticus (lorazepam or diazepam IV)
- — Atonic and akinetic seizures, especially as adjuncts
- — Absence seizures, but not preferred because of CNS depression
- *Note:* Benzodiazepines do not prevent generalized tonic-clonic seizures
- **Side effects**
- — Sedation is the most common side effect.
- — Ataxia
- — Behavioral problems, such as aggression, anxiety, and restlessness
- — Amnesia

Ethosuximide

- **Mechanism of action**. The mechanism of action for ethosuximide is unknown, but it does enhance CNS inhibition.
- **Uses**.
- Ethosuximide is effective only in absence seizures. It is the drug of choice for this condition.
- **Side effects**
- — GI irritation: nausea, vomiting, and anorexia (a lack or loss of appetite for food)
- — CNS depression: drowsiness, lethargy, euphoria, dizziness, headache, and hiccups
- — Rashes: urticaria (hives) and Stevens-Johnson syndrome (rare)
- — Blood dyscrasias (an abnormal condition of the blood) (rare)

Gabapentin

- **Mechanism of action.** The mechanism of action for gabapentin is unknown. Gabapentin is chemically related to GABA but is not an agonist at GABA receptors. It may enhance GABA release .
- **Uses**
- — Treatment of partial seizures as an adjunctive to other drugs
- **Side effects**
- — Sedation, dizziness, ataxia, nystagmus, and tremor
- *Note*: Gabapentin should be used with caution in children because it may produce adverse
- psychiatric symptoms, including thought disorders and hostility.
- **Drug interactions**. This agent does not alter serum concentration of other anticonvulsants.

Felbamate

- **Uses**
- — Partial seizures
- — Lennox-Gastaut syndrome in children
- **Side effects**
- — CNS: insomnia and headache
- — GI: anorexia, vomiting, and nausea
- — Allergic reactions: hematological and dermatological reactions
- — Acute liver failure
- **Drug interactions.** Felbamate may alter concentrations of other anticonvulsants.

Lamotrigine

- **Mechanism of action.** Lamotrigine inhibits voltage-dependent Na+ channels of presynaptic membrane, which decreases the release of excitatory amino acid neurotransmitters.
- **Uses**
- — Monotherapy and adjunctive therapy for partial and secondarily generalized tonic-clonic seizures in adults
- — Lennox-Gastaut syndrome in both children and adults
- **Side effects.** Approximately 1 in 1000 people experience severe and potentially life-threatening skin rashes. These are rarely fatal, but children are at higher risk. This can be reduced by slowly increasing the dose.

Topiramate

- **Mechanisms of action**
- — Inhibits voltage-dependent Na+ channels of presynaptic membrane
- — Potentiates the action of GABA by a unique mechanism, different from that of the benzodiazepines
- or barbiturates
- — Blocks excitatory amino acid receptors
- **Uses**
- — Monotherapy in patients 10 years of age and older with partial onset or primary generalized
- tonic-clonic seizures
- — Adjunctive therapy in partial seizures
- **Side effects**
- — Mainly involve CNS depression: fatigue, dizziness, ataxia, and decreased cognition
- — Hypersensitivity

Tiagabine

- **Mechanism of action.** Tiagabine is a GABA reuptake inhibitor
- **Uses**
- — Adjunctive therapy in partial seizures
- **Side effects**
- — Mainly involve CNS depression: fatigue, dizziness, ataxia, and decreased cognition

Levetiracetam

- Mechanism of action. The mechanism of action for levetiracetam is unknown.
- Uses
- — Adjunctive therapy in partial seizures
- Side effects
- — Mainly involve CNS depression: fatigue, dizziness, ataxia, and decreased cognition

Summery of antiepileptic drugs

Seizure Disorder	Drug(s) of Choice	Alternative Drugs
Partial, including secondarily generalized	Carbamazepine or phenytoin	Lamotrigine or levetiracetam or topiramate or valproic acid
Typical absence	Ethosuximide	Valproic Acid
Atypical absence	Valproic Acid	Combination of valproic acid and ethosuximide or lamotrigine
Myoclonic	Valproic Acid	Lamotrigine or topiramate
Clonic or tonic	Valproic Acid	Phenytoin
Tonic-clonic	Carbamazepine or phenytoin or valproic acid	Lamotrigine or topiramate
Atonic/akinetic	Valproic Acid	Clonazepam or phenytoin
Recurrent febrile	Diazepam	Phenobarbital
Status epilepticus	Lorazepam or diazepam, followed by phenytoin	Phenytoin or phenobarbital

The End