Epilepsy

Epilepsy

- Epilepsy is an assortment of different seizure types and syndromes originating from several mechanisms that have in common the sudden, excessive, and synchronous discharge of cerebral neurons
- Can cause
  - Loss of consciousness
  - Abnormal movements
  - Atypical or odd behavior
  - Distorted perceptions

Epilepsy

- The site of origin of the abnormal neuronal firing determines the symptoms that are produced
- If the motor cortex is involved, the patient may experience abnormal movements or a generalized convulsion
- Seizures originating in the parietal or occipital lobe may include visual, auditory, and olfactory hallucinations

Convulsion

- Involuntary violent spasm of large muscles of face, neck, arms, and legs
- Not synonymous with seizure

- In most cases epilepsy has no identifiable cause (Idiopathic epilepsy)
- Symptomatic epilepsy (secondary to another cause)
- Activity in focal areas that are functionally abnormal may be triggered by:
  - Changes in physiologic factors such as blood gases, pH, electrolytes, and blood glucose
  - Changes in environmental factors such as sleep deprivation alcohol intake and stress

Idiopathic epilepsy (primary)

- When no specific anatomic cause for the seizure, such as trauma or neoplasm, is present
- Can result from inherited abnormality in the CNS
- Patients are treated chronically with anti-seizure drugs or vagal nerve stimulation

Symptomatic epilepsy

- Can be caused by illicit drug use, tumor, head injury, hypoglycemia, meningeal infection, and the rapid withdrawal of alcohol in alcoholics
- When two or more seizures occur, the patient may be diagnosed with symptomatic (secondary) epilepsy
- The primary cause of the seizure should be corrected if possible

Classification of seizures

- Seizure classification determines treatment

- Seizures have been classified by:
  - Site of origin
  - Etiology
  - Electrophysiologic correlation
  - Clinical presentation

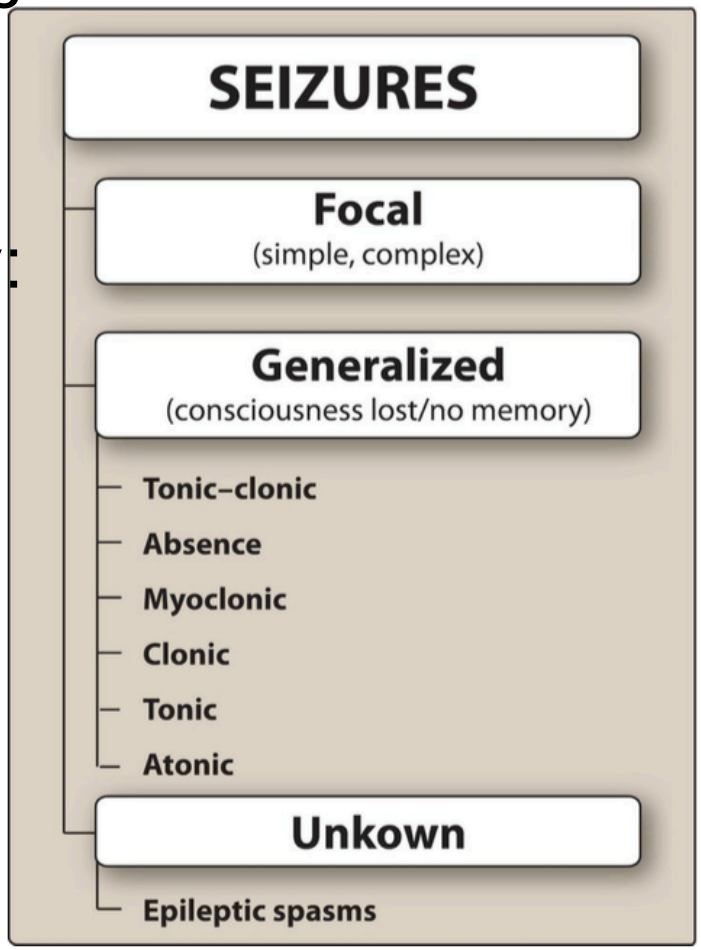


Figure 12.2 Classification of epilepsy.

Focal seizures

- Involve only a portion of the brain, typically part of one lobe of one hemisphere
- Symptoms depend on the site of neuronal discharge and on the extent to which the electrical activity spreads to other neurons
- May occur at any age
- Consciousness is usually preserved
- Partial seizures may progress to become generalized tonic-clonic seizures
- Include

1. Simple partial seizures
2. Complex partial seizures

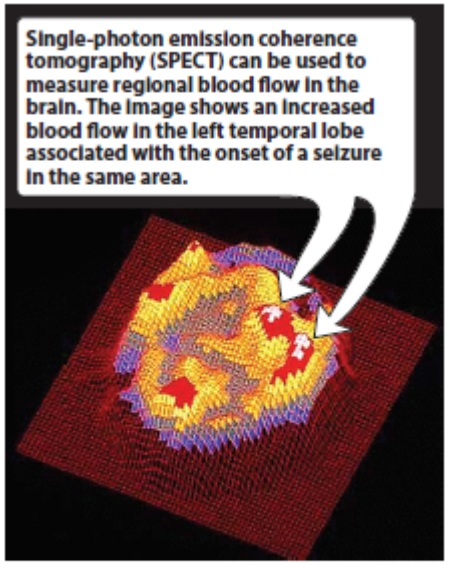


Figure 12.2
Region of the brain in a person with epilepsy showing increased blood flow during a seizure.

Focal seizures

1. Simple focal siezures:

- Caused by a group of hyperactive neurons confined to a single locus in the brain
- The patient does not lose consciousness
- Abnormal activity of a single limb or muscle group controlled by the region of the brain experiencing the disturbance
- The patient may also show sensory distortions
- May occur at any age

Partial seizures

2. Complex focal seizures:

- Complex sensory hallucinations and mental distortion
- Motor dysfunction may involve chewing movements, diarrhea, and/or urination
- Consciousness is altered

Generalized seizures

- Include abnormal electrical discharges throughout both brain hemispheres
- May be convulsive or nonconvulsive
- Patient usually has an immediate loss of consciousness

1. Tonic-clonic seizures
2. Absence seizures
3. Myoclonic seizures
4. Clonic seizures
5. Tonic seizures
6. Atonic seizures
7. Febrile seizures
8. Status epilepticus

Generalized seizures

1. Tonic-clonic seizures:

- Result in loss of consciousness, followed by tonic and clonic phases
- May be followed by a period of confusion and exhaustion due to the depletion of glucose and energy

2. Absence seizures:

- Involve a brief, abrupt, and self-limiting loss of consciousness
- Onset: 3-5 years of age and lasts until puberty or beyond
- The patient stares and exhibits rapid eye-blinking for 3-5 seconds

Generalized seizures

3. Myoclonic seizures:

- Short episodes of muscle contractions that may recur for several minutes
- Occur at any age but usually begin around puberty or early adulthood

4. Clonic

- These seizures consist of short episodes of muscle contractions that may closely resemble myoclonic seizures.
- Consciousness is more impaired with clonic seizures

5. Tonic

These seizures involve increased tone in the extension muscles and are generally less than 60 seconds.

6. Atonic

These seizures are also known as drop attacks and are characterized by a sudden loss of muscle tone.

Generalized seizures

7. Febrile seizures:

- Young children may develop seizures with illness accompanied by high fever
- Consist of generalized tonic-clonic convulsions and do not necessarily lead to a diagnosis of epilepsy

8. Status epilepticus:

- Life-threatening and requires emergency treatment
- Two or more seizures occur without recovery of full consciousness between them

Mechanism of action of antiepileptic drugs

- Blocking voltage gated channels (Na^+ or Ca^{2+})
- Enhancing inhibitory GABA impulses
- Interfering with excitatory glutamate transmission

- Some antiepileptic drugs appear to have multiple targets in CNS

- Antiepilepsy drugs suppress seizures but do not "cure" or "prevent" epilepsy

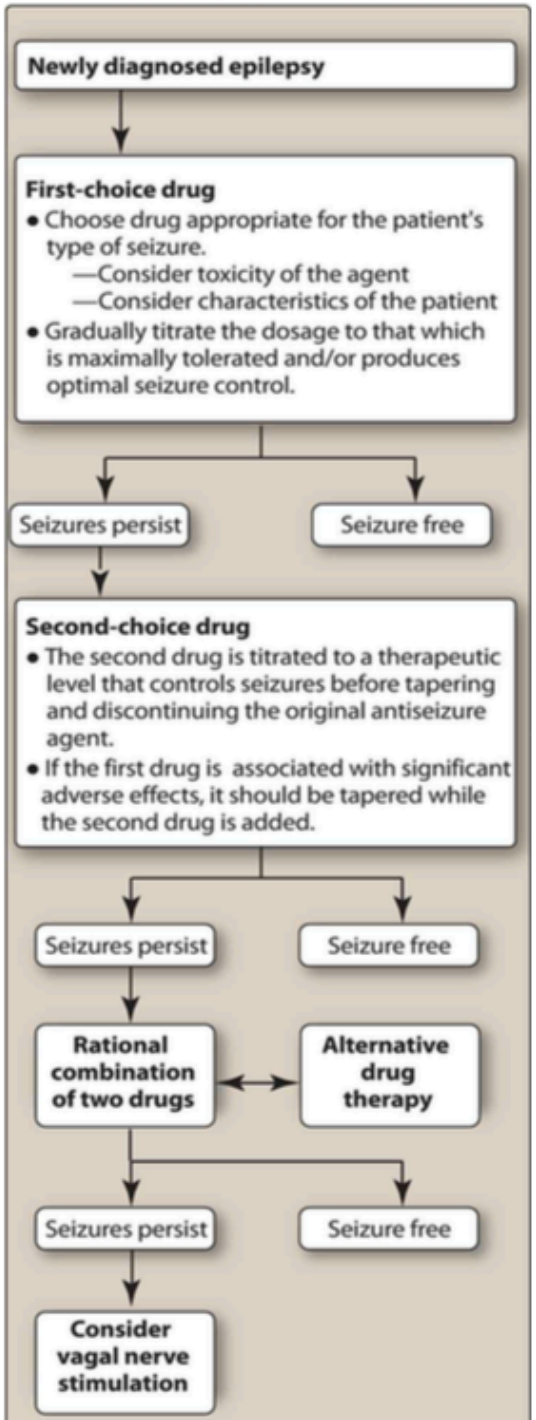
Drug choice for epilepsy

Choice of drug treatment is based on:

- Classification of the seizures
- Patient-specific variables (age, comorbid medical conditions)
- Characteristics of the drug (cost, toxicity and drug interactions)

Drugs used for epilepsy

- Diazepam
- Lorazepam
- Phenobarbital
- Primidone
- Tiagabine
- Carbamazepine
- Vigabatrin
- Phenytoin
- Fosphenytoin
- Oxcarbazepine
- Ethosuximide
- Pregabalin
- Felbamate
- Gabapentin
- Lamotrigine
- Levetiracetam
- Topiramate
- Valproic acid
- Divalproex
- Zonisamide


Newly diagnosed epilepsy
First-choice drug
• Choose drug appropriate for the patient's type of seizure.
—Consider toxicity of the agent
—Consider characteristics of the patient
• Gradually titrate the dosage to that which is maximally tolerated and/or produces optimal seizure control.
Seizures persist
Seizure free
Second-choice drug
• The second drug is titrated to a therapeutic level that controls seizures before tapering and discontinuing the original antiseizure agent.
• If the first drug is associated with significant adverse effects, it should be tapered while the second drug is added.
Seizures persist
Seizure free
Rational combination of two drugs
Alternative drug therapy
Seizures persist
Seizure free
Consider vagal nerve stimulation

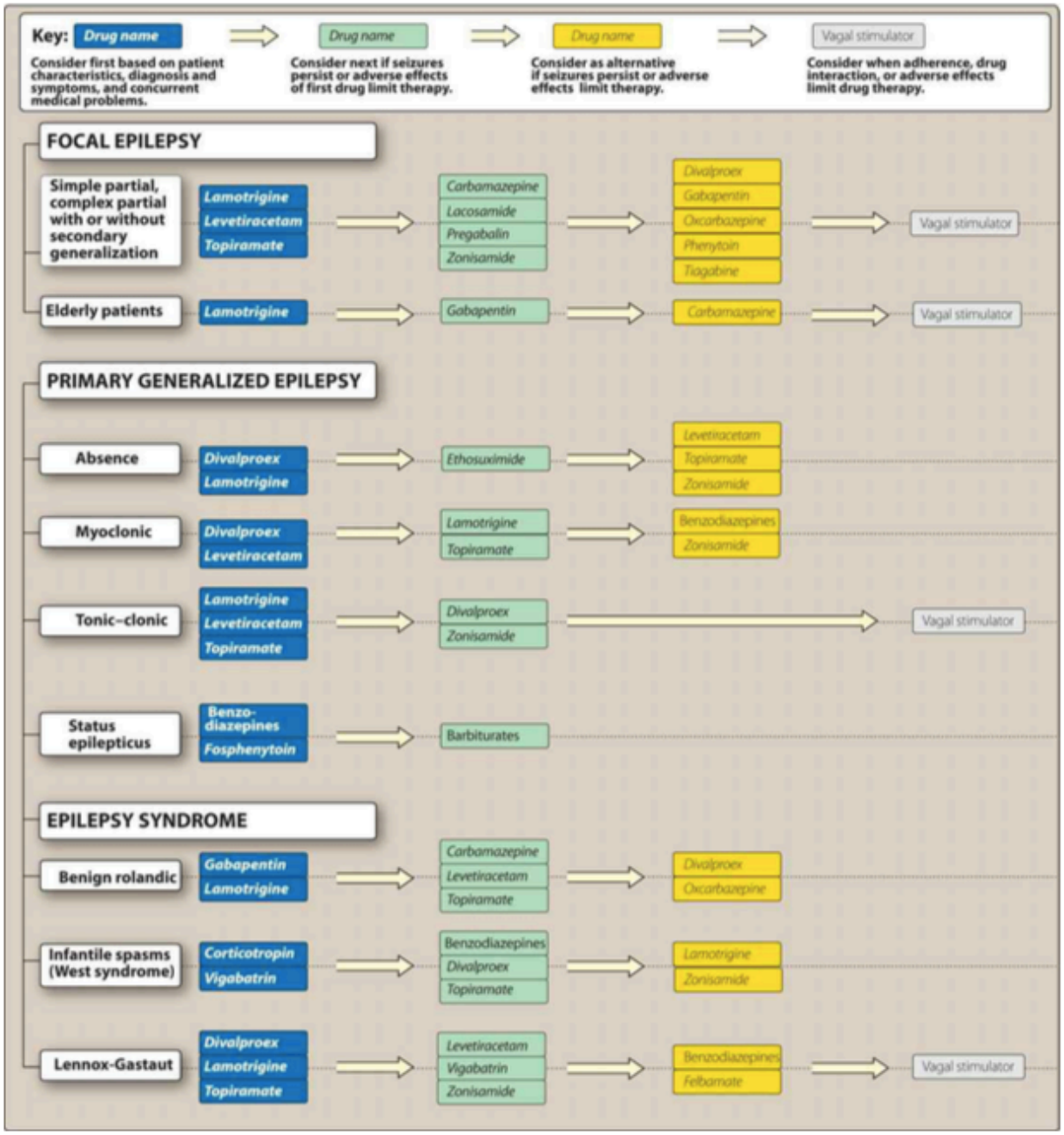


Figure 12.4 Therapeutic indications for the antiseizure agents. Benzodiazepines = *diazepam* and *lorazepam*.

Benzodiazepines

- Most are reserved for emergency or acute seizures
- Bind to GABA inhibitory receptors to reduce firing rate
- Clonazepam, clobazam, diazepam and lorazepam are used as adjunctive therapy for myoclonic, partial and generalized tonic-clonic seizures
- Diazepam is available for rectal administration

Phenobarbital

- Enhances the inhibitory effects of GABA-mediated neurons
- Phenobarbital in epilepsy should be used primarily in the treatment of status epilepticus

Primidone

- Metabolized to phenobarbital
- Adverse effects: Agranulocytosis

Tiagabine

- Blocks GABA uptake into presynaptic neurons, permitting more GABA to be available for receptor binding, and enhancing inhibitory activity
- Used as adjunctive treatment I focal seizures
- > 95% protein bound
- Adverse effects: fatigue, dizziness, GI upset

Vigabatrin

- Irreversible inhibitor of GABA transaminase
- Adverse effects:
  - Visual field loss

Carbamazepine

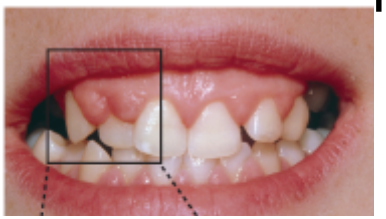
- Blocks sodium channels inhibiting generation of repetitive action potentials in the epileptic focus and preventing their spread
- Effective for partial seizures and generalized tonic-clonic seizures
- Also used for trigeminal neuralgia and bipolar disorder
- Absorbed slowly and erratically following oral administration and may vary from generic to generic
- Metabolized by CYP3A4
- Inducer of CYP1A2, CYP2C, CYP3A enzymes
- Not well tolerated by the elderly
- Adverse effects:
  - Hyponatremia may be noted in some patients, especially elderly
  - Rash
- Should not be prescribed for patients with absence seizures because it may increase seizures

Phenytoin and fosphenytoin

- Phenytoin blocks voltage-gated sodium channels
- Phenytoin is effective for treatment of partial seizures and generalized tonic-clonic seizures and status epilepticus
- Phenytoin is 90% bound to plasma albumin
- Phenytoin exhibits saturable enzyme metabolism at low concentration

(zero-order pharmacokinetics)

- Small increases in a daily dose can produce large increases in the plasma concentration resulting in drug induced t
- Side effects:
  - Gingival hyperplasia (the gums growing over the teeth
  - Nystagmus
  - Ataxia
  - Peripheral neuropathies



- Fosphenytoin may also be administered intramuscularly (IM)
- Phenytoin sodium should never be given IM because it can cause tissue damage and necrosis
- Fosphenytoin is the drug of choice for IV and IM administration

Rufinamide

- Acts at sodium channels
- Approved for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children one year of age and older and in adults.
- Weak inhibitor of CYP2E1 and a weak inducer of CYP3A4 enzymes.
- Food increases absorption and peak serum concentrations
- Carbamazepine and phenytoin can reduce and valproate can increase the serum concentrations of rufinamide.

Oxcarbazepine

- A prodrug that is rapidly reduced to the 10-monohydroxy (MHD) metabolite responsible for its anticonvulsant activity
- MHD blocks sodium channels, preventing the spread of the abnormal discharge
- Approved for use in adults and children with partial onset seizures

Levetiracetam

- Approved for adjunct therapy of partial seizures, myoclonic seizures, and primary generalized tonic-clonic seizures in adults and children
- The exact mechanism of anticonvulsant action is unknown
- Side effects: dizziness, sleep disturbances, headache, and weakness

Ethosuximide

- Reduces propagation of abnormal electrical activity in the brain by inhibiting calcium channels
- Effective in treating only primary generalized absence seizures

Pregabalin

- Binds to voltage-gated calcium channels in the CNS, inhibiting excitatory neurotransmitter release
- Effective for focal onset seizures, neuropathic pain associated with diabetic peripheral neuropathy, postherpatic neuralgia, and fibromyalgia
- Side effects: Drowsiness, blurred vision, weight gain, and peripheral edema

Felbamate

- Broad spectrum anticonvulsant
- Proposed mechanisms

1) Blocking voltage-dependent sodium channels
2) Competing with the glycine-coagonist binding site on the N-methyl-D-aspartate (NMDA) glutamate receptor
3) Blocking calcium channels
4) Potentiating the action of GABA

- Reserved for use in refractory epilepsies because of the risk of aplastic anemia and hepatic failure

Gabapentin

- GABA analog
- Does not act at GABA receptors
- Mechanism of action is not known
- Approved as adjunct therapy for partial seizures

Lamotrigine

- Blocks sodium channels and calcium channels
- Effective in a wide variety of seizures including partial seizures and generalized seizures
- Approved for use in bipolar disorder
- Half life is decreased by enzyme inducing drugs like carbamazepine and phenytoin and increased by greater than 50% with the addition of valproate
- Rapid titration to high serum concentrations of lamotrigine can cause a rash, which may progress to a serious life-threatening reaction

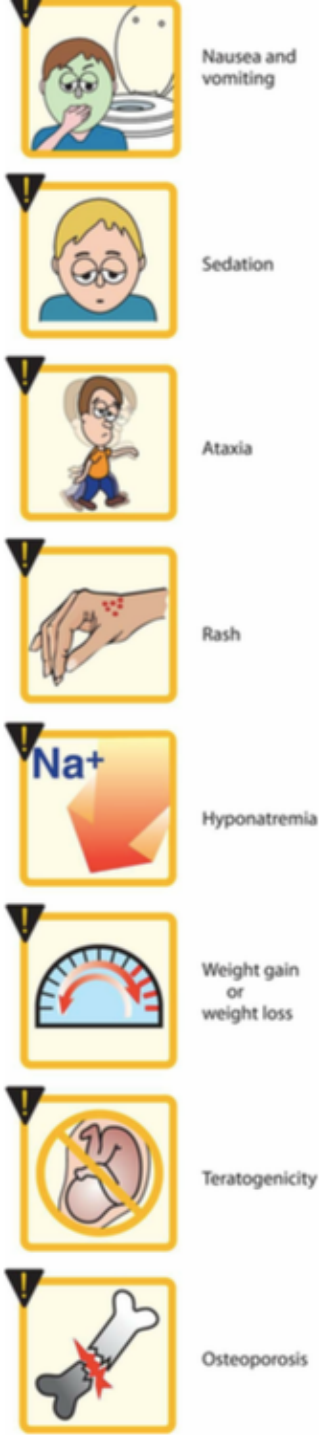
Topiramate

- Broad spectrum anti-seizure activity
- MOA
  - Blocks voltage-dependent Na channels
  - Increases the frequency of chloride channel opening by binding to the GABA receptor
  - Reduces high-voltage Ca currents
  - May act at glutamate (NMDA) sites
- Effective and approved for partial and primary generalized epilepsy
- Also approved for treatment of migraine
- It inhibits CYP2C19 and is induced by phenytoin and carbamazepine
- Coadministration of topiramate reduces ethinyl estradiol
  - Women taking the drug should be counseled to use additional methods of birth control
- Adverse effects: somnolence, weight loss and paresthesias

Valproic acid and divalproex

- Valproic acid is available as a free acid
- Divalproex sodium is a combination of sodium valproate and valproic acid that is converted to valproate when it reaches the GIT
  - Improved GI tolerance of valproic acid
- All forms are equivalent in efficacy
- Mechanisms of action:
  - Sodium channel blockade
  - Blockade of GABA transaminase
  - Calcium channel blockade
- Broad spectrum of activity against seizures
- Effective for partial and primary generalized epilepsies
- >90% bound to albumin
- Adverse effects:
  - Rare hepatic toxicity
  - Teratogenic; cognitive and behavioral abnormalities and neural tube defects

Adverse effects of anti-seizure drugs



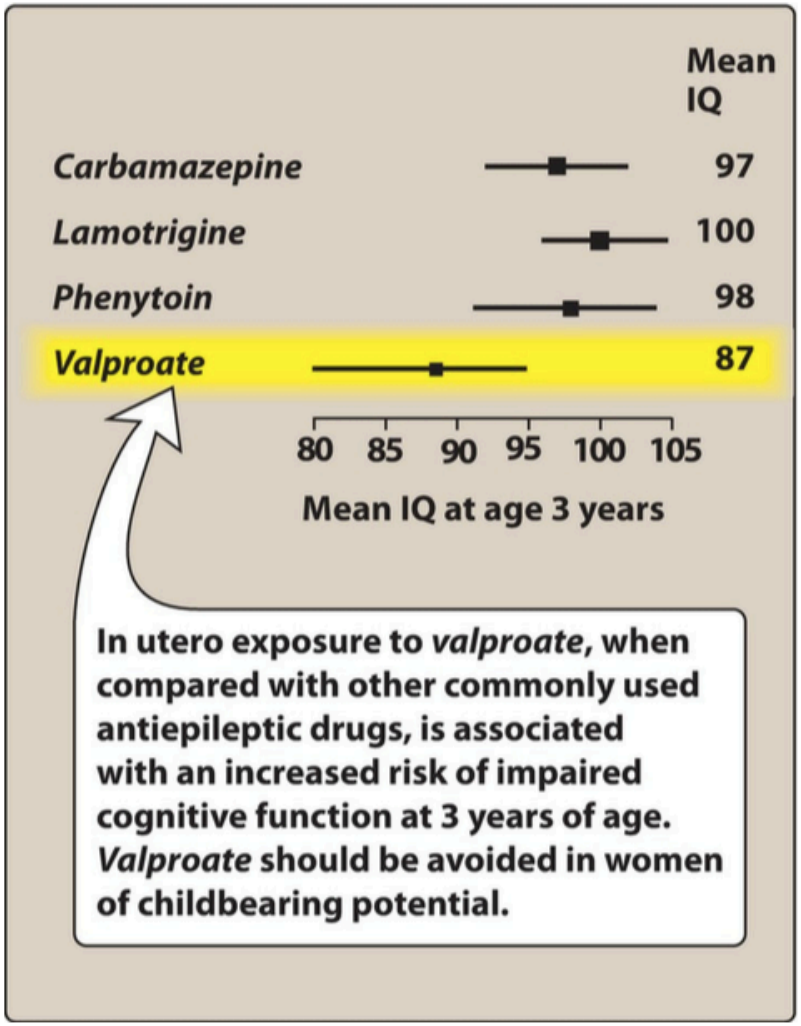


Figure 12.10 Cognitive function at 3 years of age after fetal exposure to doses of antiepileptic drugs. The means (*black squares*) and 95% confidence intervals (*horizontal lines*) are given for the children's IQ as a function of the antiepileptic drugs.

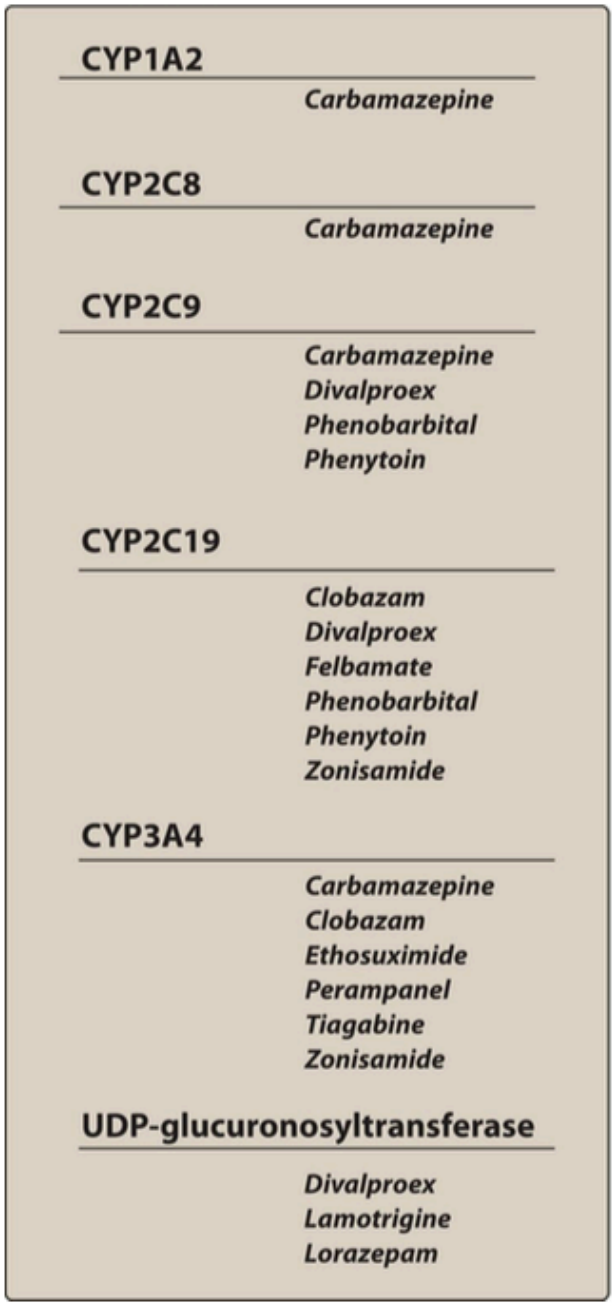


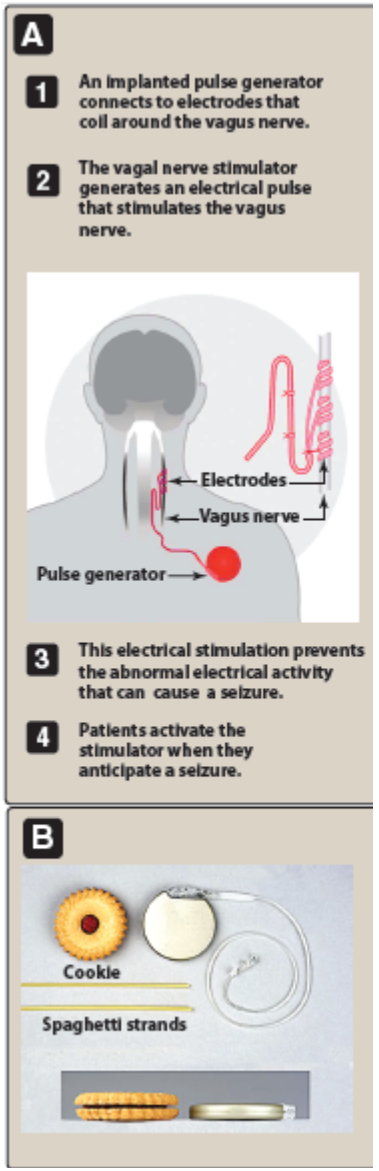
Figure 12.7 CYP metabolism of the antiseizure medications.

Vagal nerve stimulation (VNS)

- Requires surgical implant of a small pulse generator with a battery and a lead wire for stimulus
- The device is implanted and its lead wires wrapped around the patient's vagal nerve
- The device is also approved for treatment of depression
- The mechanism of action is unknown
- Effective in treatment of partial onset seizures and has enabled reduction of drug therapy in some cases
- Used as an alternative when drug therapy is not successful
- VNS is a costly and invasive procedure.

Deep brain stimulation (DBS)

- Uses a pacemaker-like device to deliver targeted electrical stimulation to the anterior nucleus of the thalamus
- Approved with conditions for adjunctive treatment for partial-onset seizures in adults with medically refractory epilepsy
- DBS is also approved for advanced Parkinson disease



Status epilepticus

- Two or more seizures occur without recovery of full consciousness in between episodes
- May be focal or primary generalized, convulsive or nonconvulsive
- Requires emergency treatment
  - Fast-acting medication such as a benzodiazepine
  - Slower-acting medication such as phenytoin, fosphenytoin, divalproex or levetiracetam

Epilepsy in pregnancy

- Planning is the most important component
- Some antiepilepsy medications increase the metabolism of hormonal contraceptives (**phenytoin, phenobarbital, carbamazepine, topiramate, oxcarbazepine, rufinamide, clobazam**)
- All women considering pregnancy should be on high doses of folic acid prior to conception
- Divalproex and barbiturates should be avoided
- When seizures are controlled maintenance medication may be reduced if possible to the lowest dose that provides control
- If seizures are not controlled, medications and dosages will need to be adjusted prior to pregnancy if possible
- The frequency and severity of seizures may change during pregnancy
- Regular monitoring by both an obstetrician and a neurologist is important

Brivaracetam	**Binds SV2A**	Sedation, dizziness, fatigue, and irritability.
Carbamazepine	**Blocks Na^+ channels**	Hyponatremia, drowsiness, fatigue, dizziness, and blurred vision. Drug use has also been associated with Stevens-Johnson syndrome. Blood dyscrasias: neutropenia, leukopenia, thrombocytopenia, pancytopenia, and anemias.
Divalproex	**Multiple mechanisms of action**	Weight gain, easy bruising, nausea, tremor, hair loss, GI upset, liver damage, alopecia, and sedation. Hepatic failure, pancreatitis, and teratogenic effects have been observed. Broad spectrum of antiseizure activity.
Eslicarbazepine acetate	**Blocks Na^+ channels**	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.
Ethosuximide	**Blocks Ca^{2+} channels**	Drowsiness, hyperactivity, nausea, sedation, GI upset, weight gain, lethargy, SLE, and rash. Blood dyscrasias can occur; periodic CBCs should be done. Abrupt discontinuance of drug may cause seizures.
Felbamate	**Multiple mechanisms of action**	Insomnia, dizziness, headache, ataxia, weight gain, and irritability. Aplastic anemia and hepatic failure. Broad spectrum of antiseizure activity. Requires patient to sign informed consent at dispensing.
Gabapentin	**Unknown**	Mild drowsiness, dizziness, ataxia, weight gain, and diarrhea. Few drug interactions. One hundred percent renal elimination.
Lacosamide	**Multiple mechanisms of action**	Dizziness, fatigue, and headache. Few drug interactions; Schedule V.
Lamotrigine	**Multiple mechanisms of action**	Nausea, drowsiness, dizziness, headache, and diplopia. Rash (Stevens-Johnson syndrome—potentially life threatening). Broad spectrum of antiseizure activity.
Levetiracetam	**Binds SV2A**	Sedation, dizziness, headache, anorexia, fatigue, infections, and behavioral symptoms. Few drug interactions. Broad spectrum of antiseizure activity.
Oxcarbazepine	**Blocks Na^+ channels**	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.
Perampanel	**Blocks AMPA glutamate receptors**	Serious psychiatric and behavioral reactions, dizziness, somnolence, fatigue, gait disturbance, and falls, long half-life.
Phenytoin	**Blocks Na^+ channels**	Gingival hyperplasia, confusion, slurred speech, double vision, ataxia, sedation, dizziness, and hirsutism. Stevens-Johnson syndrome—potentially life threatening. Not recommended for chronic use. Primary treatment for status epilepticus (*fosphenytoin*).
Pregabalin	**Multiple mechanisms of action**	Weight gain, somnolence, dizziness, headache, diplopia, and ataxia. One hundred percent renal elimination; Schedule V.
Rufinamide	**Unknown**	Shortened QT interval. Multiple drug interactions.
Tiagabine	**Blocks GABA uptake**	Sedation, weight gain, fatigue, headache, tremor, dizziness, and anorexia. Multiple drug interactions.
Topiramate	**Multiple mechanisms of action**	Paresthesia, weight loss, nervousness, depression, anorexia, anxiety, tremor, cognitive complaints, headache, and oligohidrosis. Few drug interactions. Broad spectrum of antiseizure activity.
Vigabatrin	**Irreversible binding of GABA-T**	Vision loss, anemia, somnolence, fatigue, peripheral neuropathy, weight gain. Available only through SHARE pharmacies.
Zonisamide	**Multiple mechanisms of action**	Nausea, anorexia, ataxia, confusion, difficulty concentrating, sedation, paresthesia, and oligohidrosis. Broad spectrum of antiseizure activity.