
Epilepsy



Patient Encounter 1: New-Onset Seizures

A 22-year-old man is seen by his physician 4 days after having a generalized tonic-clonic seizure in his college dorm room. The seizure lasted for 5 minutes, according to his roommate. He was confused for several minutes and went to sleep for a few hours after the seizure.

His physical examination is completely normal, and no focal neurologic deficits were observed. An MRI was ordered and reported as right mesial temporal sclerosis. An EEG shows right fronto-temporal sharp waves.

What additional information is needed to make a decision about pharmacotherapy?

How should this information be used to make choices concerning AED therapy?

During the visit, he mentions several previous brief episodes of loss of consciousness, and friends tell him his left hand fumbles with his shirt. These started a couple of years ago and now occur 2 to 3 days each week.

LEARNING OBJECTIVES

- **Upon completion of the chapter, the reader will be able to:**
 1. Describe the epidemiology and social impact of epilepsy.
 2. Define terminology related to epilepsy, including seizure, convulsion, and epilepsy.
 3. Describe the basic pathophysiology of seizures and epilepsy.
 4. Differentiate and classify seizure types given a description of the clinical presentation of the seizure and electroencephalogram.
 5. Identify key therapeutic decision points and therapeutic goals in the treatment of epilepsy.
 6. Discuss nonpharmacologic treatments for epilepsy.
 7. Recommend an appropriate pharmacotherapeutic regimen with monitoring parameters for the treatment of epilepsy.
 8. Devise a plan for switching a patient from one antiepileptic regimen to a different regimen.
 9. Manage potential drug interactions with antiepileptic drugs.
 10. Determine when and how to discontinue antiepileptic drug therapy.

Social Impact:

- *individuals who have recently had a seizure face major obstacles to engaging in simple activities.*
- *Restrictions on driving and employment.*
- *50% of patients with epilepsy report cognitive and learning difficulties.*
- *the social stigma of embarrassment or injury due to seizures in public results in isolation of the patient.*
- *Patients with epilepsy often depend on caregivers to assist with medications, transportation, and ensuring the patient's safety.*

EPIDEMIOLOGY and ETIOLOGY

Epidemiology:

- *Epilepsy: is a disorder that afflicts approximately 2 million individuals in the United States.*
- *The incidence of epilepsy in the United States is estimated at 35 to 75 cases per 100,000 persons per year.*
- *In developing countries, the incidence is higher at 100 to 190 cases per 100,000 persons per year.*

Etiology:

- *In approximately 80% of patients with epilepsy, the underlying etiology is unknown.*
 - *The most common causes of epilepsy are head trauma and stroke.*
 - *Genetic defects cause about 5% of cases.*
 - *Brain tumors, CNS infections, and neurodegenerative diseases are other common causes.*

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- *Isolated seizures can be caused by stroke, CNS trauma, CNS infections, metabolic disturbances (eg, hyponatremia, hypoglycemia).*
 - *If these causes of seizures are **not corrected**, they may lead to the development of epilepsy.*
 - *Drugs commonly associated with causing seizures are: tramadol, bupropion, theophylline, some antidepressants, some antipsychotics, amphetamines, cocaine, imipenem, lithium, excessive doses of penicillins or cephalosporins, and sympathomimetics or stimulants.*

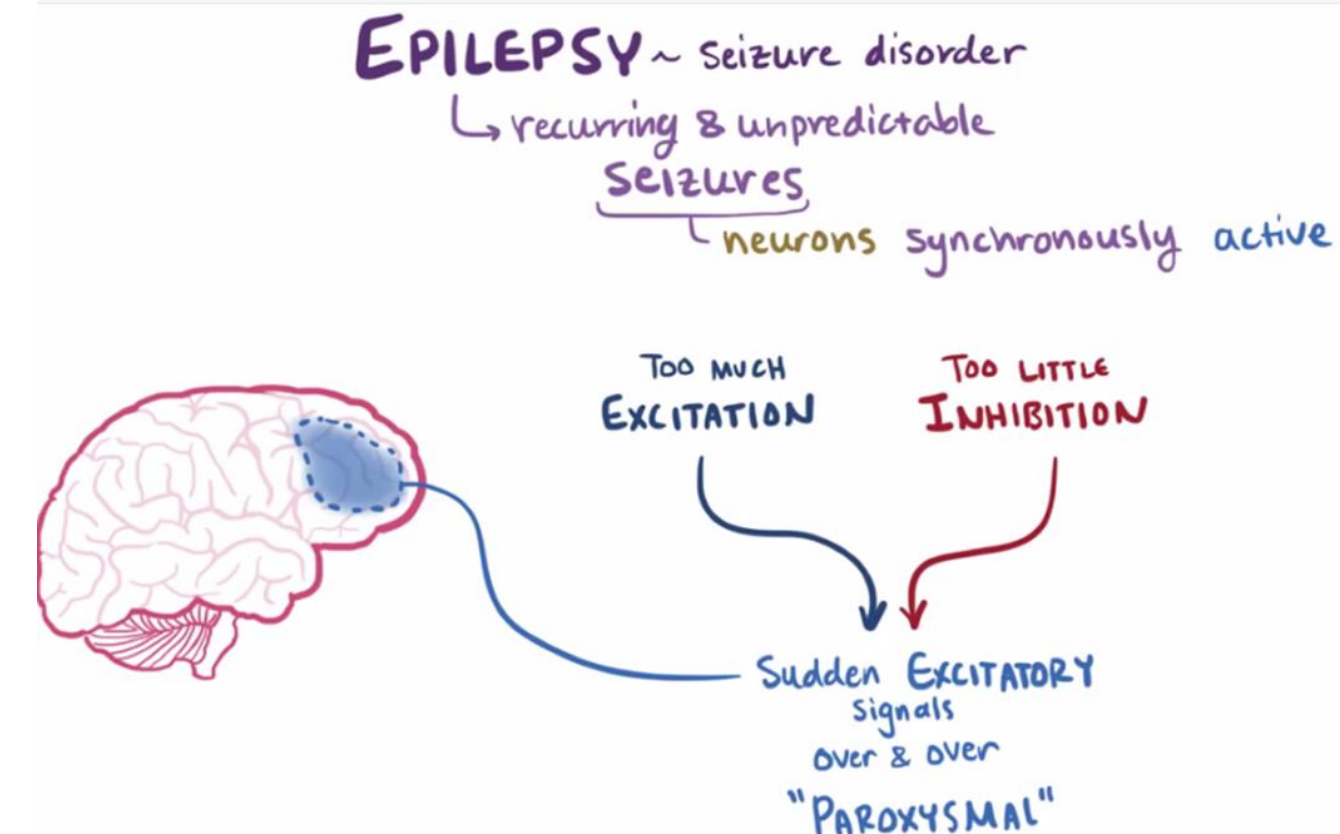
PATHOPHYSIOLOGY

Seizures:

- *Regardless of the underlying etiology, all seizures involve a sudden electrical disturbance of the cerebral cortex.*
- *A population of neurons **fires rapidly** and **repetitively** for **seconds to minutes**.*
- *This phenomenon is probably related to:*
 - *an **excess of excitatory** neurotransmitter action,*
 - *a **failure of inhibitory** neurotransmitter action, or*
 - *a **combination of the two**.*

Nearly all seizures stop spontaneously,

*because **brain inhibitory** mechanisms overcome the **abnormal excitation**.*



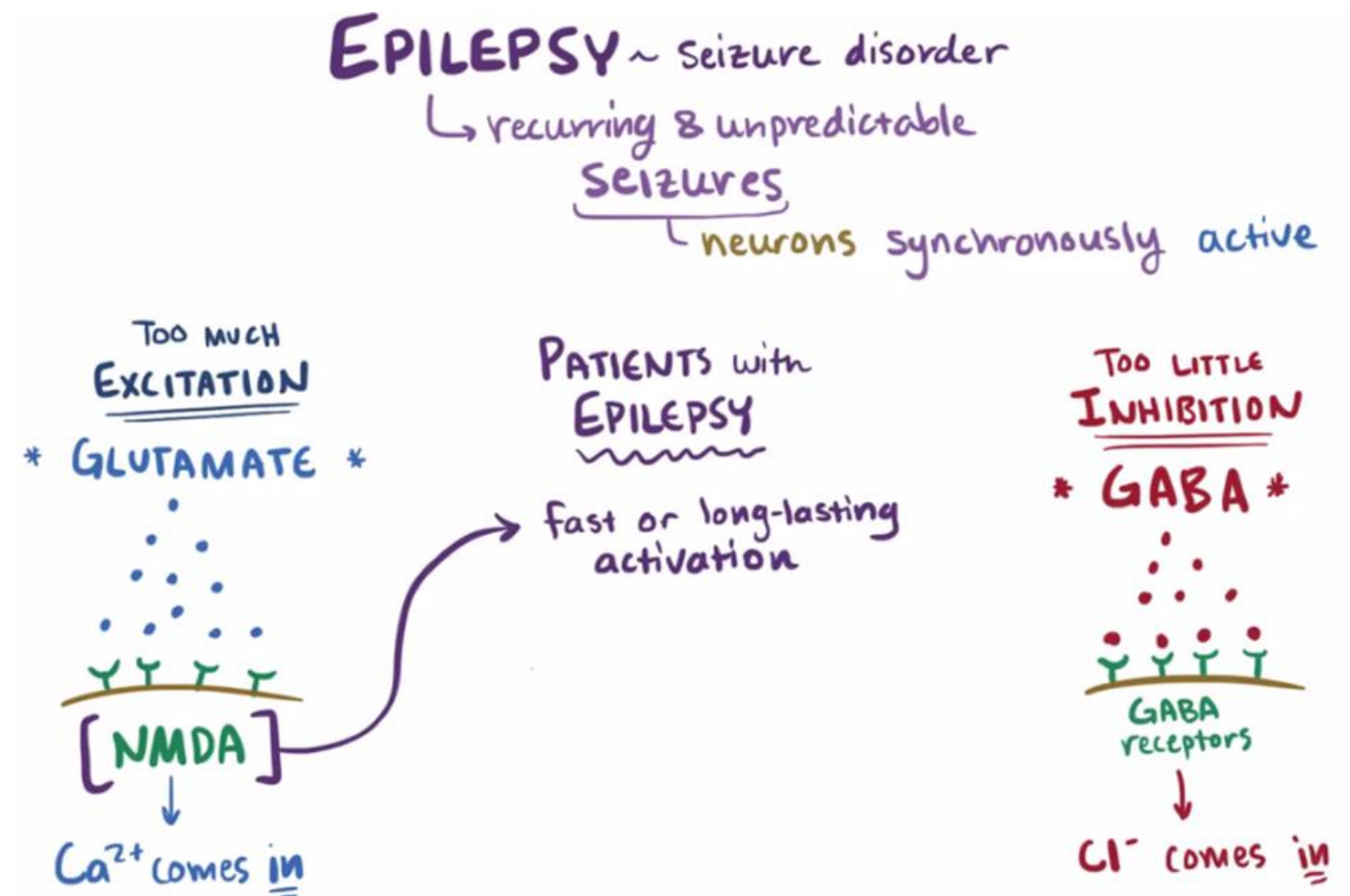
Neurotransmitters:

The major excitatory neurotransmitter is glutamate.

- Many antiepileptic drugs (AED) (eg, phenytoin, carbamazepine, lamotrigine) work by interfering with this mechanism, blocking the release of glutamate or by blocking sodium or calcium channels.

The major inhibitory neurotransmitter is γ -aminobutyric acid (GABA).

- Barbiturates and benzodiazepines
- Primarily act to enhance the action of GABA.



Epilepsy:

Epilepsy is the tendency to have recurrent, unprovoked seizures(≥ 2 seizures)

- *after a brain insult, epilepsy may develop **days, months, or years.***
- *Epilepsy may remain stable, decrease in severity, or worsen over time.*
- *Repeated seizures may **cause further damage** to the **cortex** and loss of neurons, **especially inhibitory neurons.***
- *Early control of epileptic seizures may reduce the possibility of **permanent changes in brain function.***

Seizure classification and presentation

General Principles:

- *Classification of epileptic seizures is based on electroencephalographic (EEG) findings combined with the clinical symptoms.*
- *Clinical presentation of seizures varies widely depending on the region and amount of brain involved in the seizure.*

Type of seizure :

Primary Generalized Seizures (either motor or non-motor) : the entire cerebral cortex is involved in the seizure.

Partial Seizures (focal seizure): the seizure begins in a localized area of the brain.

International League Against Epilepsy seizure classification

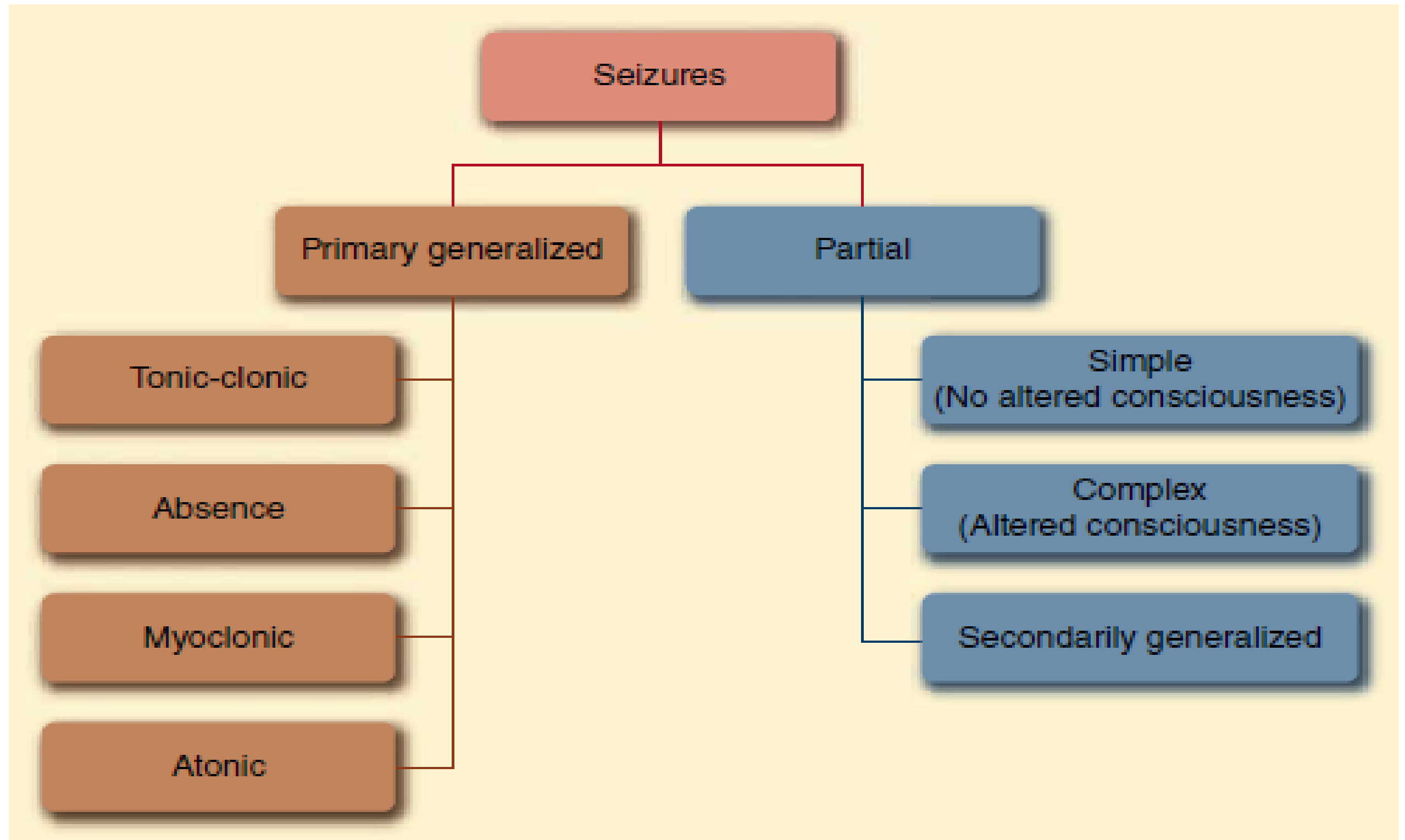


Table 32–1

ILAE 2017 Classification of Seizure Types¹⁷Focal Onset^{a,b}Aware^c or Impaired Awareness^d**Motor**

Automatisms

Atonic

Clonic

Epileptic spasms

Hyperkinetic

Myoclonic

Tonic

Nonmotor

Autonomic

Behavior arrest

Cognitive

Emotional

Sensory

Focal to bilateral tonic-clonic^eGeneralized Onset^{a,f}**Motor**

Tonic-clonic

Clonic

Tonic

Myoclonic

Myoclonic-tonic-clonic

Myoclonic-atonic

Atonic

Epileptic spasms

Nonmotor (absence)^g

Typical

Atypical

Myoclonic

Eyelid myoclonia

Unknown Onset

Motor

Tonic-clonic

Epileptic spasms

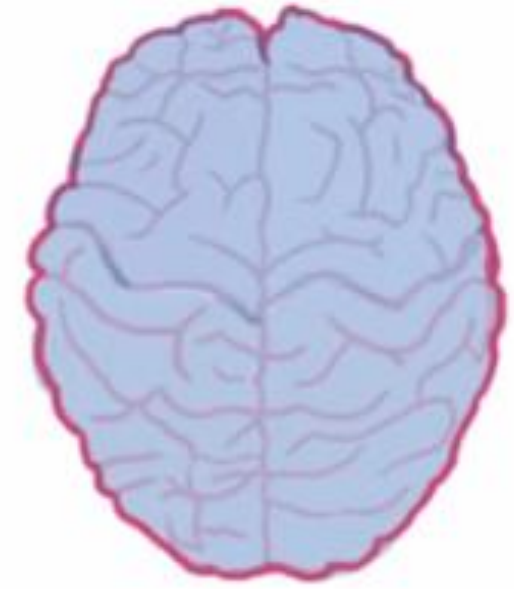
Nonmotor

Behavior arrest

Unclassified

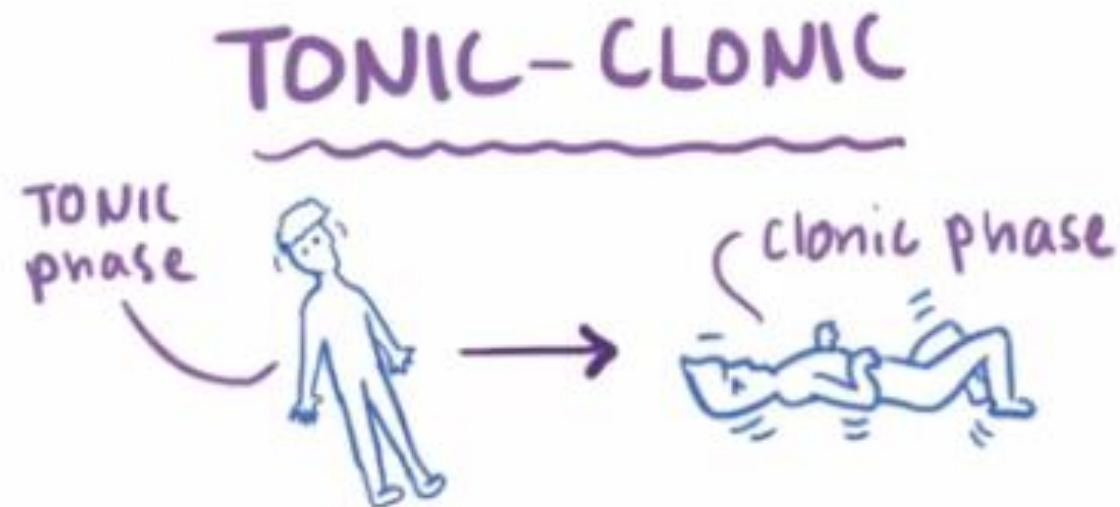
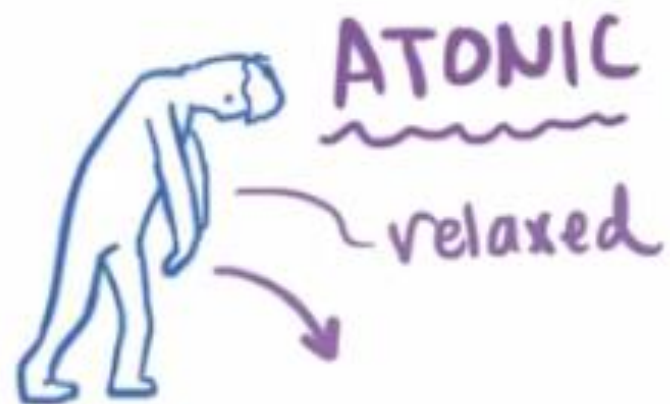
EPILEPSY ~ seizure disorder

↳ recurring & unpredictable
Seizures



GENERALIZED SEIZURES

BOTH HEMISPHERES + LOSS OF CONSCIOUSNESS



shock-like contractions of a group of muscles,



DIAGNOSIS

A *proper diagnostic workup* of a patient presenting with seizures includes the following elements:

- Complete *neurologic examination*
- *EEG* (normal between seizures, need 24h-EEG Monitoring)
- *Laboratory tests* (CBC, [LFTs], serum chemistry).. r/o electrolyte Imbalance, and infection.
- *Neuroimaging* (preferably magnetic resonance imaging [*MRI*]).

Seizures are typically brief disease, *lasting less than 5 minutes*. However, *prolonged seizures lasting greater than or equal to 5 minutes or occurring one after another without recovery in between* are *status epilepticus*.

Clinical Presentation

Clinical presentation of epilepsy include :

- ❖ •• *Episodes of sudden and brief loss of consciousness*
- ❖ •• *Episodes of uncontrolled jerking of groups of muscles*
- ❖ •• *Sudden unexplained falls*
- ❖ •• *Sudden and brief episodes of confusion*

Associated Symptoms:

- ❖ •• Incontinence, usually of urine
- ❖ •• Tongue or cheek biting
- ❖ •• Traumatic injuries, usually associated with falling during a seizure

TREATMENT

Desired Outcomes:

- *The goal for any patient with epilepsy is **elimination of all seizures** without **adverse effects of the treatment**.*
- *The treatment should **enable the patient to** drive, perform well in school, hold a reasonable job, and function effectively in the family and community.*

General Approach to Treatment

- *Selection of appropriate pharmacotherapy depends on distinguishing, identifying, and understanding different seizure types.*
- *Without an accurate classification of the seizure type, it is possible to select a medication that is ineffective or even harmful to the patient.*
- *Prior to starting pharmacologic therapy, it is essential to determine the risk of having a subsequent seizure.*
- *in hyponatremia and CNS infection, the risks of another seizure and the development epilepsy are very small; in theses cases correct the underlying problem and possibly use an AED short-term.*

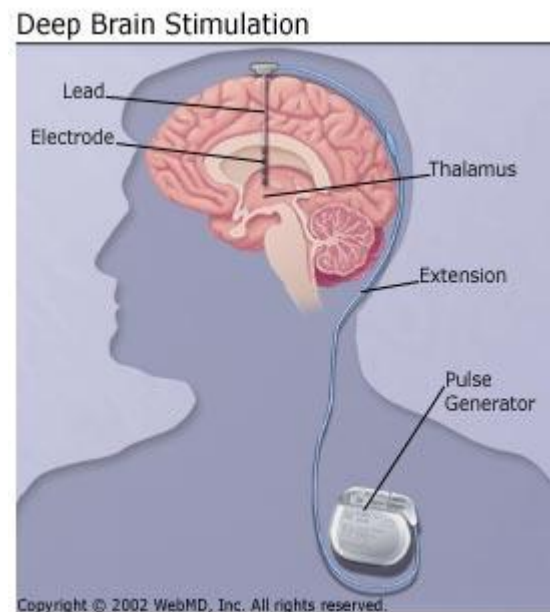
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- *Risk factors for repeated seizures in patients without an underlying disorder include.*
 - •• *Structural CNS lesion*
 - •• *Abnormal EEG*
 - •• *Partial seizure type*
 - •• *Positive family history*
 - *If no risk factors are present, the **risk of another seizure is 10% to 15%.** However, if two or more risk factors are present, the risk of another seizure is 100%.*

Nonpharmacologic Therapy

- **Surgery**: e.g :temporal lobectomy. surgical removal of the seizure focus can result in 80% to 90% of patients becoming seizure free.



- **Vagal nerve stimulation** is another nonpharmacologic approach to treating all types of seizures. (*reserved for patient who is not candidate to surgery or not respond to medication*)



- **ketogenic diet** :The diet consists of **dietary fats** (eg, butter, heavy cream, fatty meats) and **protein** with no added sugar. Used in children with difficult to control seizures.
- deep brain stimulation

Treatment algorithm for seizures.

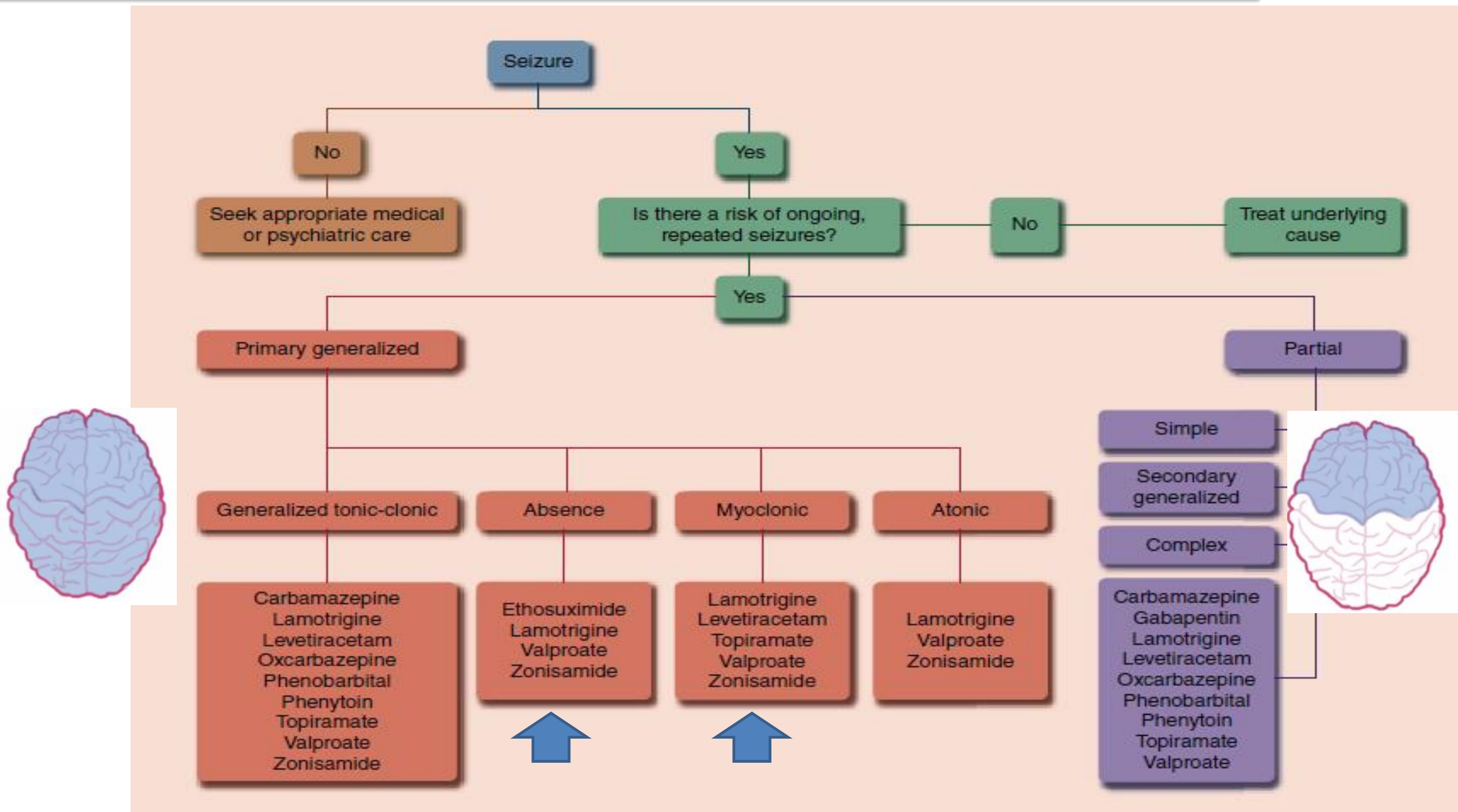


Table 32-2

Evidence-Based Selection of Antiepileptic Drugs for Initial Monotherapy Treatment of Epilepsy²⁴⁻²⁷

Seizure Type	Drugs
Generalized onset: Motor	Carbamazepine (except myoclonic) Lamotrigine Levetiracetam Oxcarbazepine (except myoclonic) Perampanel Phenobarbital Phenytoin Topiramate Valproate
Generalized onset: Nonmotor (Absence)	Clobazam Clonazepam Ethosuximide (preferred) Lamotrigine Topiramate Valproate Zonisamide
Focal onset: Motor and nonmotor	Carbamazepine Cenobamate Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Phenobarbital Phenytoin Topiramate Valproate

Pharmacologic Therapy

Special Considerations:

Use of ASMs presents some unique challenges:

Zero-order Pharmacokinetics (formerly MMM): *Phenytoin metabolism is capacity limited. Under a normal dose, maximum capacity of hepatic enzymes to metabolize the drug is reached. small changes in doses result in large changes in serum concentrations, causing concentration-related toxicity or breakthrough seizures*

- *for routine clinical practice, dosage adjustments for adult can be made using the following plan:*
 - *For serum conc. < than 7 mcg/mL, TDD is increased by 100 mg.*
 - *For serum conc. of 7 to 12 mcg/mL, TDD is increased by 50 mg.*
 - *For serum conc. more than 12 mcg/mL, TDD is increased by no more than 30 mg.*

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- **Protein Binding:** *phenytoin and valproate, (88% to 92% of phenytoin is bound to plasma protein, leaving 8% to 12% as unbound). The unbound component produces the clinical effect in the CNS*
 - *Certain conditions and disorders (CKD, neonate, pregnant woman, taking multiple highly protein-bound drugs, critical care patient Increased unbound percentage of drug.*

Autoinduction: *Carbamazepine is a potent inducer of hepatic microsomal enzymes.*

- *Most dosage regimens for carbamazepine use a starting dose that is 25% to 30% of the typical maintenance dose (15 mg/ kg/day). The dosage is increased weekly until the target maintenance dose is achieved within 3 to 4 weeks.*

Drug Selection and Seizure Type

*The key to selecting effective pharmacotherapy is **based on the seizure type**.*

- For initial treatment of **absence seizures**, **ethosuximide** is preferred.
- In **absence** (generalized non-motor seizure) and **myoclonic** (generalized motor) **seizures**, carbamazepine, oxcarbazepine, gabapentin, tiagabine, and pregabalin **should be avoided** due to association with **worsening of these seizure types**.

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- Antiepileptic drug therapy should usually be *initiated carefully using a titration schedule* to minimize adverse events.
 - *If seizures continue*, the dose is increased gradually *until the patient becomes seizure free or adverse effects appear*.
 - Treatment of refractory seizures (ie, unresponsive to at least two first-line AEDs) is somewhat different. Combinations of drugs may be useful in patients with difficult to control seizures.
 - All AEDs, *except ethosuximide*, are effective in *combination therapy* for partial seizures.

Complications of Pharmacotherapy

Two types of adverse effects occur with AEDs:



❑ *serum concentration-related(dose related): sedation, ataxia, and diplopia*

❑ *idiosyncratic (not related to dose or conc.): e.g: **Rash** (common) and **Severe skin, hepatic, or hematological reactions** (rarely), but life threatening. The AED should be discontinued immediately.*

- genetic testing for human leukocyte antigen (HLA) is needed prior initiation of Carbamazepine, phenytoin to avoid the possibility of severe skin reactions.
- *A/E are considered one of the selection criteria for AEDs.*
- *if a patient has a job that requires **mental alertness**, it is best to choose an AED that is less likely to cause sedation (eg, lamotrigine).*

Chronic Adverse Effects:

- Some chronic adverse effects associated with AEDs include **peripheral neuropathy**, **cerebellar atrophy** and **weight gain**.
- **Osteoporosis** is a major chronic adverse effect of several AEDs.
- Patients taking **carbamazepine**, **oxcarbazepine**, **phenytoin**, **phenobarbital**, or **valproate** more than 6 months should take supplemental **calcium** and **vitamin D**.

Patient Encounter 2: Managing Chronic Adverse Reactions

PL is a 45-year-old man with a long history of seizures. He has taken carbamazepine for 20 years with good control of his seizures. Other than some occasional dizziness, he reports no adverse effects from the carbamazepine.

What chronic adverse effects are important to monitor in this patient?

How should monitoring for these adverse effects be done?

What measures can be taken to prevent these adverse effects?

Practical Issues

Comorbid Disease States:

- *Patients with headaches and Seizure need special attention in the selection of an AED.*
- *Agents known to prevent headache (eg, **valproate** and **topiramate**) may be preferred, and agents associated with increased headaches (eg, **lamotrigine** and **felbamate**) may be secondary or tertiary alternatives.*
- ***Depression is common in patients with epilepsy(30%).** Most AEDs can exacerbate depression, Some AEDs (eg, **lamotrigine**, **carbamazepine**, **oxcarbazepine**) may be useful in treating depression.*

Switching Drugs:

- *Changing from one AED to another can be a **complex process**. breakthrough seizures may occur if the first drug **is stopped too abruptly**.*
- *Changes in AED regimens should be done in a **stepwise fashion**. Typically, the new drug is started at a **low initial dose** and **gradually increased over several weeks**. Once the new drug is at a minimally effective dose, the drug to be discontinued is gradually tapered while the dose of the new drug continues to be increased to the target dose.*

Stopping Therapy:

Discontinuation of AEDs should be done gradually, only after the patient has been seizure free

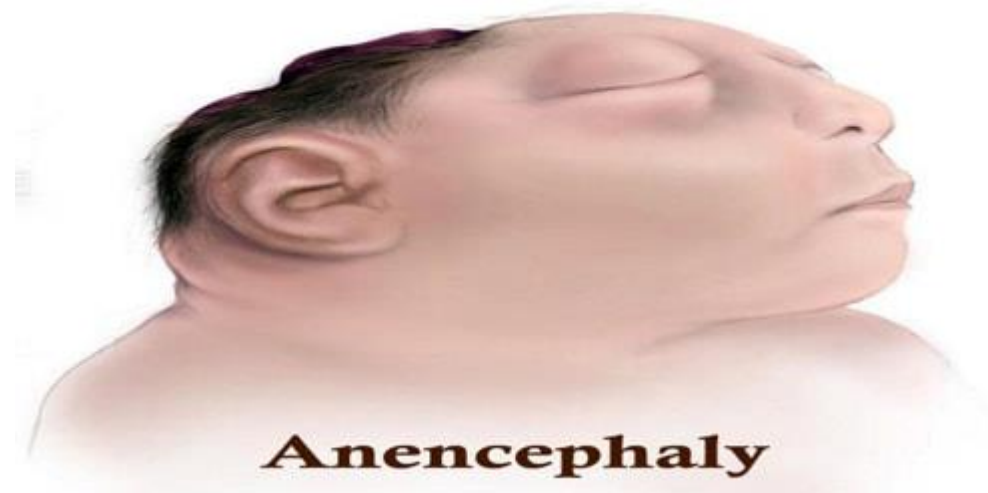
According to these criteria:

- *No seizures for 2 to 5 years;*
- *Normal neurologic examination*
- *Normal intelligence percentage;*
- *Single type of partial or generalized seizure;*
- *Normal EEG with treatment.*

Individuals who fulfill all of these criteria have a 60% chance of remaining seizure free after AEDs are discontinued.

Special Populations

- *When treating a child*, it is imperative to control seizures as quickly as possible to *avoid interference with development of the brain and cognition*.
- doses of AEDs are typically higher on a milligram per kilogram basis compared with adults, *why?*.
- *Neural tube defects* (eg, *spina bifida*, *microcephaly*, *anencephaly*) are associated most commonly with valproate and possibly carbamazepine.
- valproate is associated with impaired cognitive development in children born to women taking valproate during pregnancy.



Special Populations

- *All women of childbearing potential who take AEDs should take 1 to 4 mg daily of supplemental folic acid to reduce the risk of birth defects.*
- *Many AEDs induce hepatic microsomal enzyme systems and reduce the effectiveness of hormonal contraceptives. So, other forms of birth control should be used .*
- *Valproate has been associated with a drug-induced PCOS.*
- *Carbamazepine, lamotrigine, and gabapentin have been studied in older adults, and all are effective in controlling seizures.*

Table 32–6

Management of ASMs During Pregnancy⁴⁰

- Give supplemental folic acid 1–4 mg daily to all women of childbearing potential
- Use monotherapy whenever possible
- Use lowest doses that control seizures
- Continue pharmacotherapy that best controls seizures prior to pregnancy
- Monitor ASM serum concentrations at start of pregnancy and monthly thereafter
- Adjust ASM doses to maintain baseline serum concentrations
- Administer supplemental vitamin K during eighth month of pregnancy to women receiving enzyme-inducing ASMs
- Monitor postpartum ASM serum concentrations to guide adjustments of drug doses
- Avoid valproate, if possible

Characteristics of Common ASMs

Drug	Mechanism of Action	Dose	Pharmacokinetic Parameters	Usual Serum Concentration Range	Dose-Related Adverse Effects	Idiosyncratic Adverse Effects
Brivaracetam (Briviact)	Modulate synaptic vesicle protein 2A	Maintenance Dose: 50–100 mg twice daily	Half-life: 9 hours Apparent Vd: 0.5 L/kg Protein binding: 17.5% Primary elimination route: Hepatic	Not established	Ataxia, dizziness, fatigue, somnolence	Angioedema, bronchospasm, suicidal behavior and ideation
Cannabidiol (Epidiolex)	Unknown mechanism, does not work through cannabinoid receptors	Maintenance Dose: 10–20 mg/kg/day in two divided doses. Titrate by starting at 5 mg/kg/day in two divided doses and increase to target maintenance dose.	Half-life: 56–61 hours Apparent Vd: 300–600 L/kg Protein Binding: > 94% Primary elimination route: hepatic	Not established	Somnolence, fatigue, malaise	Hepatotoxicity, anorexia, pyrexia, vomiting, diarrhea
Carbamazepine (Tegretol and generic, Tegretol XR, generic), Carbatrol, Epitol, Equetro	Fast sodium channel inactivation	Maintenance dose: Titrate dosage to target over 3–4 weeks Adults: 800–1200 mg/day in divided doses Children: 20–30 mg/kg/day as a divided dose Intravenous: Indicated for oral replacement therapy at 70% of the total oral maintenance dose divided into four equal doses given every 6 hours	Half-life: 10–25 hours with chronic dosing Apparent Vd: 0.8–1.9 L/kg Protein binding: 67%–81% Primary elimination route: Hepatic	4–12 mcg/mL (mg/L; 17–51 µmol/L)	Diplopia, drowsiness, nausea, sedation	Aplastic anemia, hyponatremia, leukopenia, osteoporosis, rash
Cenobamate (Xcopri)	Modulate voltage-gated sodium channels, modulate GABA _A ion channel	Maintenance dose: Target dose 200 mg/day; 12.5 mg/day for 2 weeks, 25 mg/day for 2 weeks, 50 mg/day for 2 weeks, 100 mg for 2 weeks, 150 mg for 2 weeks, then 200 mg/day. Titration schedule should not be exceeded	Half-life: 50–60 hours Apparent Vd: 0.6–0.7 L/kg Protein binding: 60% Primary elimination route: Hepatic	Not established	Somnolence, fatigue, diplopia	Drug reaction with eosinophilia and systemic symptoms, QT interval shortening
Clobazam (Onfi)	Enhance GABA activity	Weight< 30 kg, start 5 mg/day, titrate to 20 mg/day in divided doses Weight> 30 kg start 10 mg/day in divided doses, titrate to 40 mg/day in divided doses CYP 2C19 poor metabolizers: start 5 mg/day, titrate to 10–20 mg/day, maximum dose 40 mg/day	Half-life: 10–50 hours Apparent Vd: ~0.9 L/kg Protein binding: ~90% Primary elimination route: Hepatic; metabolized to active metabolite that is further metabolized by CYP 2C19	Not established	Sedation, somnolence, lethargy, pyrexia, irritability, drooling, aggression	
Clonazepam (Klonopin, generic)	Enhance GABA activity	Maintenance dose: Initiate at 0.5 mg one to three times daily, titrate dose to effectiveness, usually 3–5 mg daily in two or three divided doses Pediatric dosing in children < 10 years or < 30 kg: Initiate at 0.01–0.03 mg/kg/day in two to three divided doses, titrate dose to effectiveness	Half-life: 30–40 hours Apparent Vd: 3.2 L/kg Protein binding: 47%–80% Primary elimination route: Hepatic	Not established	Ataxia, memory impairment, sedation, slowed thinking	

Characteristics of Common ASMs (Continued)						
Drug	Mechanism of Action	Dose	Pharmacokinetic Parameters	Usual Serum Concentration Range	Dose-Related Adverse Effects	Idiosyncratic Adverse Effects
Eslicarbazepine (Aptiom)	Fast sodium channel inactivation	<i>Maintenance dose:</i> Adults: Initiate at 400 mg daily and titrate in increments of 400–600 mg daily to a maintenance dose of 800–1600 mg daily Pediatrics: Initial, incremental increases, and maintenance dose based on body weight	<i>Half-life:</i> 13–20 hours in adults <i>Apparent Vd:</i> 0.85–0.9 L/kg <i>Protein binding:</i> < 40% <i>Primary route of elimination:</i> Renal	Not established	Ataxia, dizziness, diplopia, drowsiness, sedation, nausea, vomiting, hyponatremia	
Ethosuximide (Zarontin, generic)	Modulate calcium channels	<i>Maintenance dose:</i> Initiate at 250 mg twice daily and titrate to 500–1000 mg twice daily	<i>Half-life:</i> 60 hours <i>Apparent Vd:</i> 0.6–0.7 L/kg <i>Protein binding:</i> None <i>Primary elimination route:</i> Hepatic	40–100 mcg/mL (mg/L; 283–708 µmol/L)	Ataxia, sedation, GI upset	Hepatotoxicity, neutropenia, rash
Everolimus (Afinitor)	Inhibits mammalian target of rapamycin (mTOR) downstream of the PI3K/AKT pathway.	<i>Maintenance dose:</i> 5 mg/m ² adjusted to maintain concentrations in target range	<i>Half-life:</i> 30 hours <i>Apparent Vd:</i> highly variable depending on age <i>Protein binding:</i> 74% <i>Primary elimination route:</i> Hepatic	5–15 mg/mL (mcg/L; 5.2–15.7 nmol/L)		Stomatitis, noninfectious pneumonitis, angioedema, myelosuppression, increase infections
Felbamate (Felbatol)	Inhibit glutamate activity	<i>Maintenance dose:</i> 1200–3600 mg/day in three or four divided doses	<i>Half-life:</i> Monotherapy: 20 hours Concurrent enzyme inducers: 11–16 hours <i>Apparent Vd:</i> 0.7–0.8 L/kg <i>Protein binding:</i> 25%–35% <i>Primary elimination route:</i> Hepatic	Not established	Anxiety, insomnia, nausea	Anorexia, aplastic anemia, headache, hepatotoxicity, weight loss
Fenfluramine (Fintepla)	Mechanism unknown	<i>Maintenance dose:</i> 0.1 mg/kg twice daily with maximum daily dose of 26 mg without stiripentol; 0.1 mg/kg twice daily with maximum daily dose of 17 mg with stiripentol	<i>Half-life:</i> 20 hours <i>Apparent Vd:</i> 11.9 L/kg <i>Protein Binding:</i> 50% <i>Primary elimination route:</i> Hepatic	Not established	Somnolence, fatigue, lethargy, ataxia, gait disturbance	Pulmonary arterial hypertension, valvular heart disease
Gabapentin (Neurontin, generic)	Modulate calcium channels and enhance GABA activity	<i>Maintenance dose:</i> Adults: 900–3600 mg/day in three or four divided doses Pediatrics: Age 3–4 Initial dose 10–15 mg/kg/day, titrate to a maximum of 50 mg/kg/day divided in divided three doses; age 5–11 initial dose 10–15 mg/kg/day, titrate to maximum of 50 mg/kg/day in three divided doses; age > 12 Initial dose 300 mg thrice daily, titrate to a maximum of 360 mg/day divided in three doses	<i>Half-life:</i> 5–7 hours (proportional to creatinine clearance) <i>Apparent Vd:</i> 0.6–0.8 L/kg <i>Protein binding:</i> < 10% <i>Primary elimination route:</i> Renal	Not established	Drowsiness, sedation	Peripheral edema, weight gain

Lacosamide (Vimpat)	Slow sodium channel inactivation; modulate collapsin response; mediator protein-2	<i>Maintenance dose:</i> 200–400 mg/day; start at 100 mg/day in two divided doses and titrate upward according to response	<i>Half-life:</i> Approximately 13 hours <i>Volume of distribution:</i> 0.6 L/kg <i>Protein binding:</i> < 15% <i>Primary elimination route:</i> 40% renal 60% hepatic	Not established	Ataxia, dizziness, diplopia, headache, nausea, vomiting	PR interval prolongation. first- degree AV block
Lamotrigine (Lamictal, Lamictal XR, generic)	Fast sodium channel inactivation	<i>Initial dose:</i> With valproate 25 mg every other day for 2 weeks, then 25 mg daily for 2 weeks, then 25 mg twice daily for a week, increase by 25 mg/day every week until maintenance dose of 150 mg/day is achieved; without enzyme inhibitor or inducer 25 mg daily for 2 weeks, then 25 mg twice daily for 2 weeks, then increase by 25 mg daily every week maintenance dose of at least 200 mg/day is achieved; with enzyme inducer 25 mg twice daily for 2 weeks, then 50 mg twice daily for 2 weeks, then increase by 100 mg/day every week until maintenance dose of 300–500 mg/ day is achieved <i>Maintenance dose:</i> 150–800 mg/day in two or three divided doses Pediatric: age 2–12 with valproate 0.15 mg/kg/ day for 2 weeks, then 0.3 mg/kg/day for 2 weeks, then increase by 0.3 mg/kg/day every week until maintenance dose of 1–5 mg/kg/ day achieved; without inhibitor or inducer 0.3 mg/kg/day for 2 weeks, then 0.6 mg/kg/day for 2 weeks, then increase by 0.6 mg/kg/day weekly until maintenance dose of 4.5–7.5 mg/kg/day achieved; with inducer 0.6 mg/kg/day in two divided doses for 2 weeks, then 1.2 mg/kg/day in two divided doses for 2 weeks, then increase by 1.2 mg/kg/ day weekly until maintenance dose of 5–15 mg/kg/day is achieved	<i>Half-life:</i> Monotherapy: 24 hours Concurrent enzyme inducers: 12–15 hours Concurrent enzyme inhibitors: 55–60 hours <i>Apparent Vd:</i> 1.1 L/kg <i>Protein binding:</i> 55% <i>Primary elimination route:</i> Hepatic	Not established	Ataxia, drowsiness, headache, insomnia, sedation	Rash, cardiac arrhythmia

Characteristics of Common ASMs (Continued)

Drug	Mechanism of Action	Dose	Pharmacokinetic Parameters	Usual Serum Concentration Range	Dose-Related Adverse Effects	Idiosyncratic Adverse Effects
Levetiracetam (Keppra, Keppra XR, generic)	Modulate synaptic vesicle protein 2A	<p><i>Adult Maintenance dose:</i> 1000–3000 mg/day. Start at 1000 mg/day and titrated upward as indicated by response</p> <p><i>Pediatric:</i> 1–6 months 7 mg/kg twice daily titrate by 7 mg/kg twice daily every 2 weeks to maintenance dose of 21 mg/kg twice daily; 6 months to 4 years 10 mg/kg twice daily then increase by 10 mg/kg twice daily every 2 weeks to maintenance dose of 25 mg/kg twice daily; 4–16 years 10 mg/kg twice daily then increase by 30 mg/kg twice daily</p> <p>Renal failure: CrCl 50–80 mL/min (0.84–1.33 mL/s) 500–1000 mg twice daily, CrCl 30–50 mL/min (0.50–0.84 mL/s) 250–750 mg twice daily, CrCl < 30 mL/min (0.50 mL/s) 250–500 mg twice daily, end stage on dialysis 500–1000 mg daily</p>	<p><i>Half-life:</i> 6–8 hours <i>Apparent Vd:</i> 0.5–0.7 L/kg <i>Protein binding:</i> < 10% <i>Primary elimination route:</i> 70% renal 30% hepatic</p>	Not established	Somnolence, dizziness	Depression, agitation, aggressive behavior
Perampanel (Fycompa)	Antagonist of glutamate receptors on postsynaptic neurons	<p><i>Maintenance dose:</i> without CYP3A4 inducers 8–12 mg once daily. Start at 2 mg once daily, increase by 2 mg/day increments to desired response</p> <p>With CYP3A4 inducers Start at 4 mg once daily, increase by 2 mg/day increments to desired response with maximum dose of 12 mg daily</p>	<p><i>Half-life:</i> 105 hours <i>Apparent Vd:</i> 0.7–1.5 L/kg <i>Protein binding:</i> 95%–96% <i>Primary elimination route:</i> Hepatic</p>	Not established	Ataxia, dizziness, drowsiness, somnolence	Suicidal behavior and ideation, agitation, hostility, aggression, hypersensitivity reactions
Oxcarbazepine (Trileptal, generic)	Fast sodium channel inactivation	<p><i>Maintenance dose:</i> 600–1200 mg/day. Start at 300 mg twice daily and titrated upward as indicated by response</p> <p><i>Pediatric dosing</i> <i>Maintenance dose:</i> 20 kg 300–450 mg twice daily; 25–30 kg 450–600 mg twice daily; 35–40 kg 450–750 mg twice daily; 40–50 kg 600–750 mg twice daily; 50–55 kg 600–900 mg twice daily; 60–65 kg 600–1050 mg twice daily</p> <p>Renal failure dosing CrCl < 30 mL/min (0.50 mL/s) starting dose of 150 mg twice daily and titrate at a slower rate</p>	<p><i>Half-life:</i> Parent drug: Approximately 2 hours 10-monohydroxy metabolite: Approximately 9 hours <i>Apparent Vd:</i> 0.5–0.7 L/kg <i>Protein binding:</i> 40% <i>Primary elimination route:</i> Hepatic</p>	Not established	Diplopia, dizziness, somnolence	Hyponatremia, 25%–30% cross-sensitivity in patients with hypersensitivity to carbamazepine



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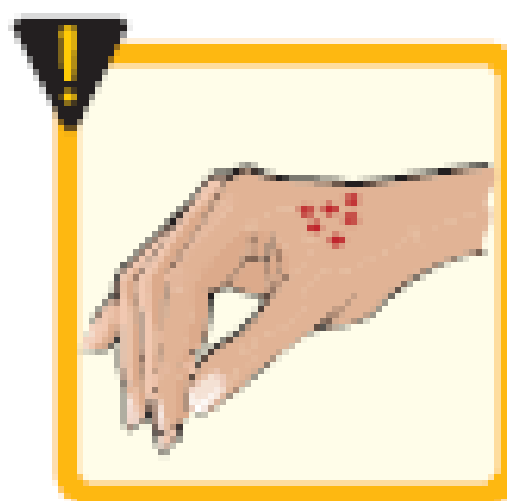
Phenobarbital (Luminal, generic) Primidone (Mysoline, generic) gets metabolized to phenobarbital	Fast sodium channel inactivation	<i>Loading dose:</i> 10–20 mg/kg as single or divided IV infusion or orally in divided doses over 24–48 hours <i>Maintenance dose:</i> Adults: 1–4 mg/kg/day as a single or divided dose Children: 3–6 mg/kg/day as divided dose Neonates: 1–3 mg/kg/day as divided dose	<i>Half-life:</i> Adults: 49–120 hours Children: 37–73 hours Neonates: approximately 115 hours <i>Volume of distribution:</i> 0.7–1 L/kg <i>Protein binding:</i> Approximately 50% <i>Primary elimination route:</i> Hepatic	15–40 mcg/mL (mg/L; 65–172 µmol/L)	Ataxia, drowsiness, sedation	Attention deficit, cognitive impairment, hyperactivity, osteoporosis, passive–aggressive behavior
Phenytoin (Dilantin, Phenytek, generic)	Fast sodium channel inactivation	<i>Loading dose:</i> Adults: 15–20 mg/kg single IV dose or divided oral dose Infants younger than 3 months: 10–15 mg/kg single IV dose Neonates: 15–20 mg/kg single IV dose <i>Maintenance dose:</i> Adults: 5–7 mg/kg/day, as single or divided dose Children: 6–15 mg/kg/day, as divided dose Neonates: 3–8 mg/kg/day, as divided dose	<i>Half-life:</i> Follows capacity- limited or Michaelis–Menten pharmacokinetics. Half-life increases as the dose and serum concentration increases. <i>Volume of distribution:</i> Adults: 0.7 L/kg Children: 0.8 L/kg Neonates: 1.2 L/kg <i>Protein binding:</i> Adults, children: 88%–92% Neonates: 65% <i>Primary elimination route:</i> Hepatic	10–20 mcg/mL (mg/L; 40–79 µmol/L) total concentration 1–2 mcg/ mL (mg/L; 4–8 µmol/L) unbound concentration	Ataxia, diplopia, drowsiness, sedation, nystagmus	Anemia, gingival hyperplasia, hirsutism, lymphadenopathy, osteoporosis, rash IV ADE: phlebitis, hypotension
Rufinamide (Banzel)	Unknown, may enhance inactivation of sodium channels	<i>Maintenance dose:</i> Adults: 3200 mg/day; start at 400–800 mg/ day in two divided doses and titrate upward according to response Children: 45 mg/kg/day or 3200 mg/day; start at 10 mg/kg/day in two divided doses and titrate upward according to response	<i>Half-life:</i> 6–10 hours <i>Apparent Vd:</i> Approximately 0.7 L/kg, varies with dose <i>Protein binding:</i> 34% (27% to albumin) <i>Primary elimination route:</i> Hepatic	Not established	Dizziness, fatigue, headache, nausea, somnolence, vomiting	
Stiripentol (Diacomit)	Mechanism unknown	<i>Maintenance dose:</i> 50 mg/kg/day in two to three divided doses	<i>Half-life:</i> 4.5–13 hours <i>Apparent Vd:</i> 1 L/kg <i>Protein binding:</i> 99% <i>Primary elimination route:</i> hepatic	Not established	Somnolence, anorexia, agitation, ataxia, nausea tremor, dysarthria	
Tiagabine (Gabitril, generic)	Enhance GABA activity	<i>Maintenance dose:</i> With concomitant hepatic enzyme inducers Initiate with 4 mg/day for 1 week, increase weekly by 4–8 mg/day in two to three divided doses with maximum dose of 56 mg/day Without concomitant hepatic enzyme inducers Initiate with 2–4 mg/day for 1 week, increase weekly by 2–4 mg/day to maintenance dose of 12–22 mg/day in two to three divided doses Pediatric dosing Age > 12 Initiate with 4 mg/day for 1 week, then	<i>Half-life:</i> Monotherapy: 7–9 hours Concurrent enzyme inducers: 2.5–4.5 hours <i>Apparent Vd:</i> 0.6–0.8 L/kg <i>Protein binding:</i> 96% <i>Primary elimination route:</i> Hepatic	Not established	Dizziness, somnolence, irritability, slowed thinking	Suicidal ideation

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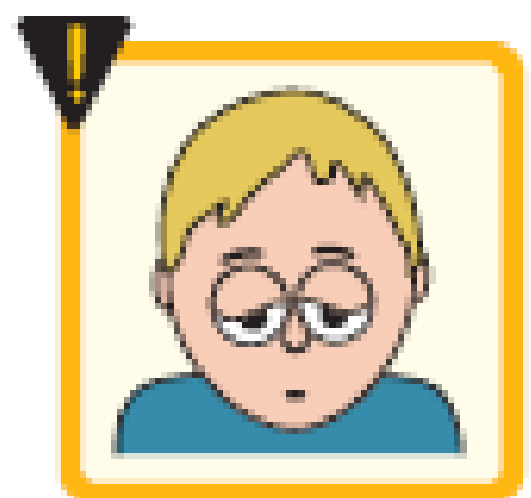
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Nausea and
vomiting



Rash



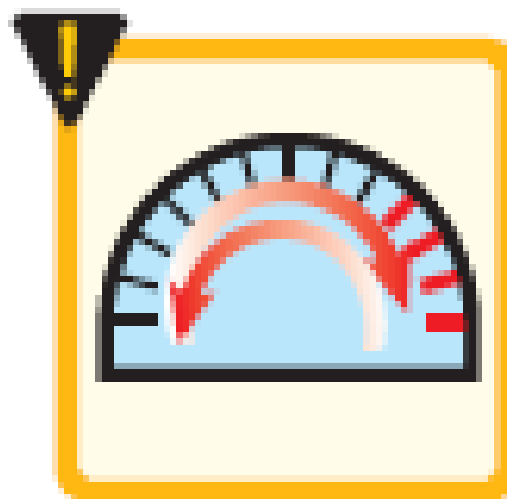
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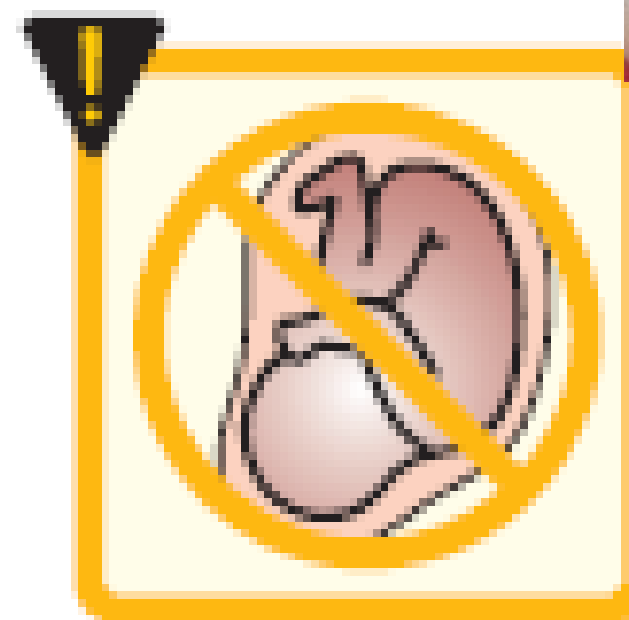
Hyponatremia



Ataxia



Weight gain
or
weight loss



Teratogenicity



Osteoporosis

