- Treatment of neurodegenerative diseases
- Antiepileptic Drugs

Lecture 7

College of Pharmacy

By:

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Drugs Used in Alzheimer Disease

Dementia of the Alzheimer type has three distinguishing features:

1) Accumulation of senile plaques (β-amyloid accumulations)
2) Formation of numerous neurofibrillary tangles
3) Loss of cortical neurons, particularly cholinergic neurons.

Current therapies aim to either:

- Improve cholinergic transmission within the CNS
- Or prevent excitotoxic actions resulting from overstimulation of NMDA-glutamate receptors in selected areas of the brain.

Do they alter the underlying neurodegenerative process?

A. Acetylcholinesterase inhibitors

- It is postulated that i**nhibition of acetylcholinesterase (AChE) within the CNS improves cholinergic transmission,** at least at those neurons that are still functioning.

- The **reversible AChE inhibitors** approved for the treatment of Alzheimer disease include **donepezil, galantamine, and rivastigmine**.
- These agents have some selectivity for AChE in the CNS, as compared to the periphery.
- **Galantamine** may also augment the action of acetylcholine at nicotinic receptors in the CNS.
- **Rivastigmine** is the only agent approved for the management of dementia associated with Parkinson disease and also the only AChE inhibitor available as a transdermal formulation.
- **Rivastigmine** is hydrolyzed by AChE to a carbamylated metabolite and has no interactions with drugs that alter the activity of CYP450 enzymes.
- The other agents are substrates for CYP450 and have a potential for such interactions.
- Common adverse effects include nausea, diarrhea, vomiting, anorexia, tremors, bradycardia, and muscle cramps.

B. NMDA receptor antagonist

- Binding of glutamate to the NMDA receptor assists in the opening of an ion channel that allows Ca^{2+} to enter the neuron. Excess intracellular Ca^{2+} can activate a number of processes that ultimately damage neurons and lead to apoptosis.
- **Memantine** is an **NMDA receptor antagonist indicated for moderate to severe Alzheimer disease.**
- It acts by **blocking the NMDA receptor** and **limiting Ca^{2+} influx into the neuron**, **such that toxic intracellular levels are not achieved.**
- It is well tolerated, with few dose-dependent adverse events.
- Expected adverse effects, such as confusion, agitation, and restlessness, are often indistinguishable from the symptoms of Alzheimer disease.
- Memantine is often given in combination with an AChE inhibitor.

Drugs Used in Multiple Sclerosis

- **MS is an autoimmune inflammatory demyelinating disease of the CNS.**
- **Corticosteroids** (for example, dexamethasone and prednisone) have been used to treat acute exacerbations of the disease.
- **Chemotherapeutic agents**, such as cyclophosphamide and azathioprine, have also been used.

A. Disease-modifying therapies

- Indicated to decrease relapse rates or, in some cases, to prevent accumulation of disability.
- The major target of these medications is to modify the immune response through inhibition of white blood cell–mediated inflammatory processes that eventually lead to myelin sheath damage and decreased or inappropriate axonal communication between cells.

1. Interferon b1a and interferon b1b

- The immunomodulatory effects of interferon help to **diminish the inflammatory responses that lead to demyelination of the axon sheaths.**
- Adverse effects of these medications may include depression, local injection site reactions, increases in hepatic enzymes, and flu-like symptoms.

2. Glatiramer

Glatiramer is a synthetic polypeptide that resembles myelin protein and may act as a decoy to T-cell attack. Postinjection reaction that includes flushing, chest pain, anxiety, and itching.

3. Fingolimod

Fingolimod is an oral drug that alters lymphocyte migration, resulting in fewer lymphocytes in the CNS. It may cause first-dose bradycardia and is associated with an increased risk of infection and macular edema.

4. Teriflunomide

Teriflunomide is an oral pyrimidine synthesis inhibitor that leads to a lower concentration of active lymphocytes in the CNS. It may cause elevated liver enzymes. It should be avoided in pregnancy.

5. Dimethyl fumarate

Dimethyl fumarate is an oral agent that may alter the cellular response to oxidative stress to reduce disease progression. Flushing and abdominal pain are the most common adverse events.

6. Monoclonal antibodies

- Alemtuzumab, daclizumab, natalizumab, and ocrelizumab are monoclonal antibodies indicated for the treatment of MS.
- These agents can be associated with significant toxicities, such as progressive multifocal leukoencephalopathy with natalizumab, serious infections with daclizumab and alemtuzumab, and autoimmune disorders with alemtuzumab. As such, these agents may be reserved for patients who have failed other therapies.

B. Symptomatic treatment

Many different classes of drugs are used to manage symptoms of MS such as spasticity, constipation, bladder dysfunction, and depression. Dalfampridine, an oral potassium channel blocker, improves walking speeds in patients with MS.

Drugs Used in Amyotrophic Lateral Sclerosis

- ALS is characterized by **progressive degeneration of motor neurons, resulting in the inability to initiate or control muscle movement.**
- **Riluzole and edaravone** are indicated for the management of ALS.
- Riluzole, an oral NMDA receptor antagonist, is believed to act by inhibiting glutamate release and blocking sodium channels. It may improve survival time in patients suffering from ALS.

- **Edaravone** is an intravenous free radical scavenger and antioxidant that may slow the progression of ALS.

Antiepileptic Drugs

- Epilepsy is not a **single entity** but 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.

- This **abnormal electrical activity may result** in a variety of events, including:

✓ loss of consciousness
✓ abnormal movements
✓ atypical or odd behavior
✓ distorted perceptions

- The **site of origin of abnormal neuronal firing determines the symptoms that occur**. For example, 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.

Etiology of Seizures

- Epilepsy can be due to an **underlying genetic, structural, or metabolic cause or an unknown etiology.**
- The neuronal discharge in epilepsy results from firing of a small population of neurons in a specific area of the brain referred to as the “primary focus.”
- Focal areas that are functionally abnormal may be triggered into activity by :

✓ changes in physiologic factors, such as an alteration in blood gases, pH, electrolytes, and blood glucose

✓ changes in environmental factors, such as sleep deprivation, alcohol intake, and stress.

Classification of Seizures

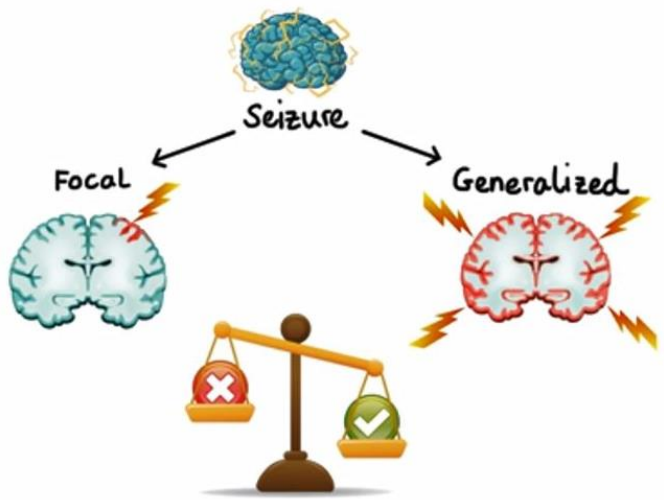
- Seizures have been categorized by:

site of origin, etiology, electrophysiologic correlation, and clinical presentation.

- The symptoms of each seizure type depend on:

✓ the site of neuronal discharge

✓ the extent to which the electrical activity spreads to other neurons in the brain.



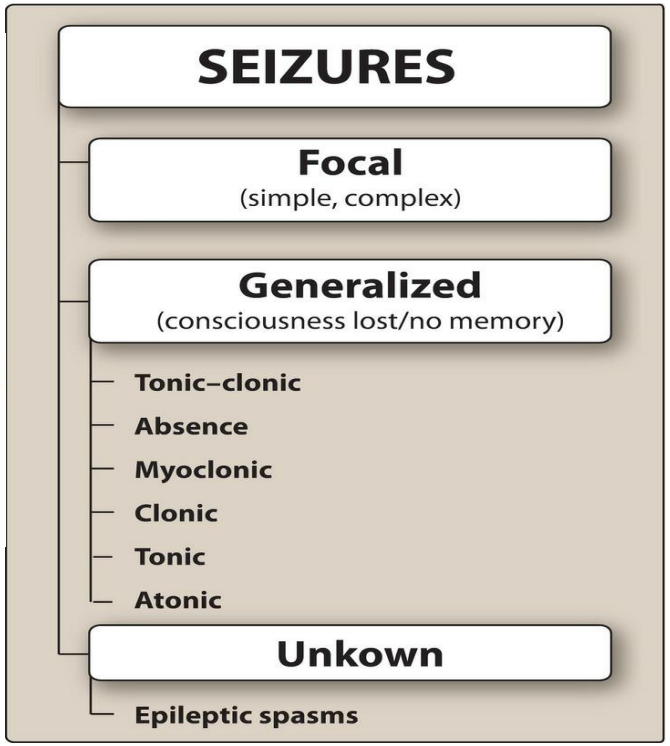


Figure 1: Classification of epilepsy.

- Focal seizures involve only a portion of one hemisphere of the brain. The symptoms of each seizure type depend on the site of neuronal discharge and on the extent to which the electrical activity spreads to other neurons in the brain. Focal seizures may progress to become bilateral tonic–clonic seizures. Patients may lose consciousness or awareness. This seizure type may begin with a motor or nonmotor activity.

- Generalized seizures may begin locally and then progress to include abnormal electrical discharges throughout both hemispheres of the brain. Primary generalized seizures may be convulsive or nonconvulsive, and the patient usually has an immediate loss of consciousness.

1. Tonic–clonic

These seizures result in loss of consciousness, followed by tonic (continuous contraction) and clonic (rapid contraction and relaxation) phases. The seizure may be followed by a period of confusion and exhaustion due to depletion of glucose and energy stores.

2. Absence

These seizures involve a brief, abrupt, and self-limiting loss of consciousness. The onset generally occurs in patients at 3 to 5 years of age and lasts until puberty or beyond. The patient stares and exhibits rapid eye blinking, which lasts for 3 to 5 seconds. An absence seizure has a very distinct three-per-second spike and wave discharge seen on electroencephalogram.

3. Myoclonic

These seizures consist of short episodes of muscle contractions that may recur for several minutes. They generally occur after wakening and exhibit as brief jerks of the limbs. Myoclonic seizures 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 as compared to myoclonic.

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.

Mechanism of action of antiseizure medications

Drugs reduce seizures through mechanisms such as:

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

Antiseizure medications suppress seizures but do not “cure” or “prevent” epilepsy.

Drug Selection

Choice of drug treatment is based on the:

- ✓ classification of the seizures
- ✓ patient-specific variables
- ✓ characteristics of the drug

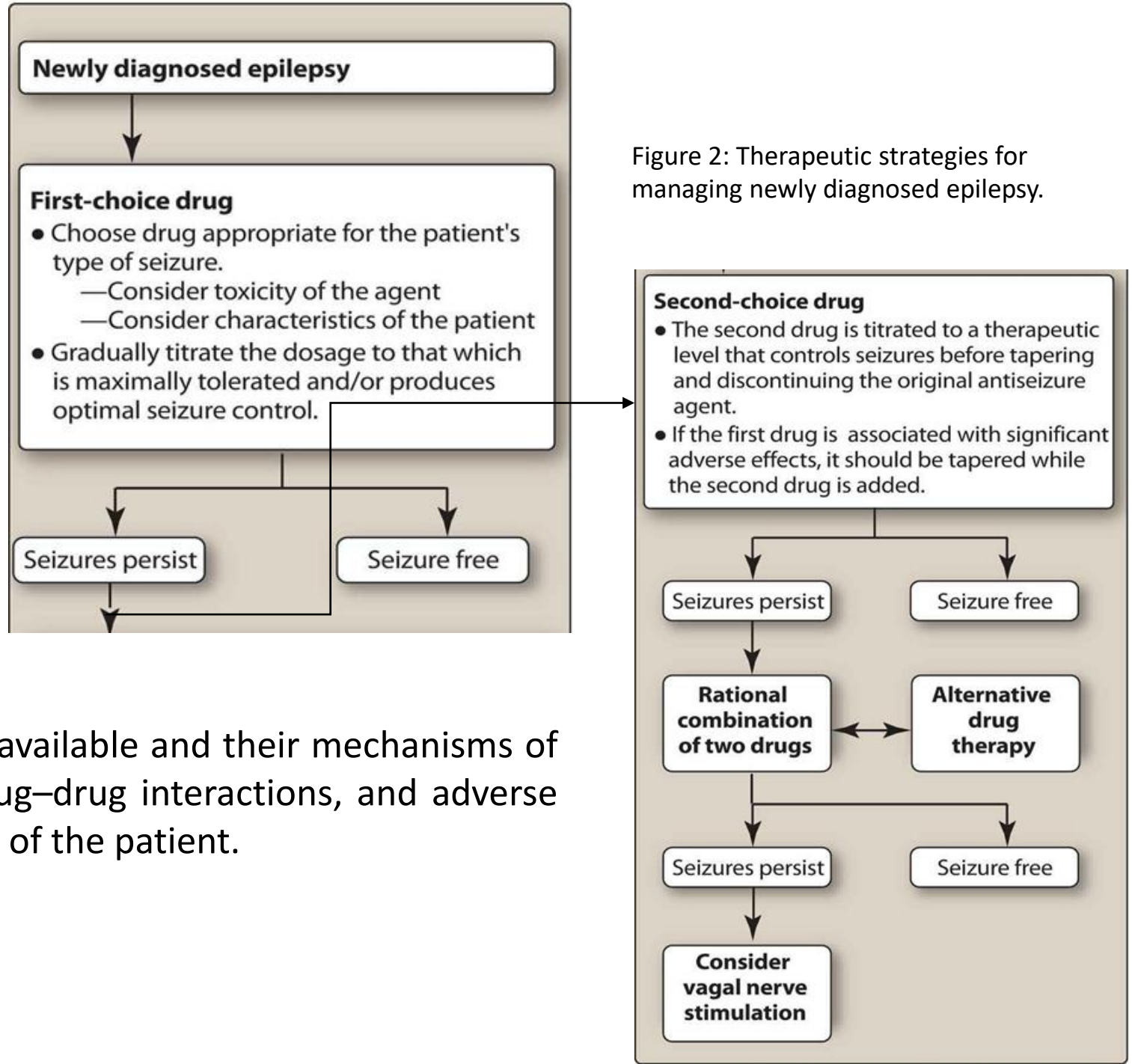
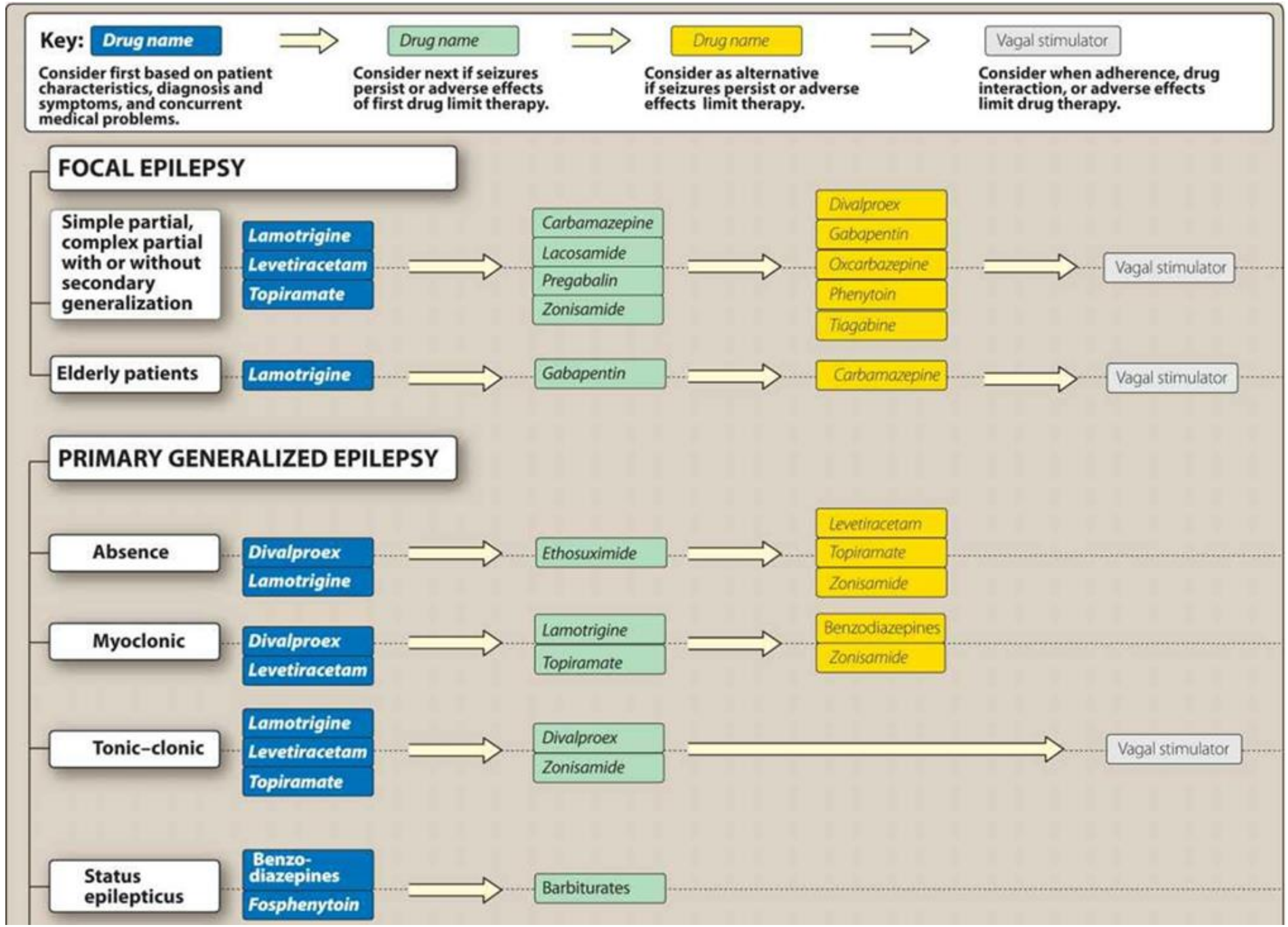


Figure 2: Therapeutic strategies for managing newly diagnosed epilepsy.

Awareness of the antiseizure medications available and their mechanisms of action, pharmacokinetics, potential for drug–drug interactions, and adverse effects is essential for successful treatment of the patient.


Key:
Drug name
Consider first based on patient characteristics, diagnosis and symptoms, and concurrent medical problems.
Drug name
Consider next if seizures persist or adverse effects of first drug limit therapy.
Drug name
Consider as alternative if seizures persist or adverse effects limit therapy.
Vagal stimulator
Consider when adherence, drug interaction, or adverse effects limit drug therapy.
FOCAL EPILEPSY
Simple partial, complex partial with or without secondary generalization
Lamotrigine
Levetiracetam
Topiramate
Carbamazepine
Lacosamide
Pregabalin
Zonisamide
Divalproex
Gabapentin
Oxcarbazepine
Phenytoin
Tiagabine
Vagal stimulator
Elderly patients
Lamotrigine
Gabapentin
Carbamazepine
Vagal stimulator
PRIMARY GENERALIZED EPILEPSY
Absence
Divalproex
Lamotrigine
Ethosuximide
Levetiracetam
Topiramate
Zonisamide
Myoclonic
Divalproex
Levetiracetam
Lamotrigine
Topiramate
Benzodiazepines
Zonisamide
Tonic–clonic
Lamotrigine
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Vagal stimulator
Status epilepticus
Benzo-diazepines
Fosphenytoin
Barbiturates

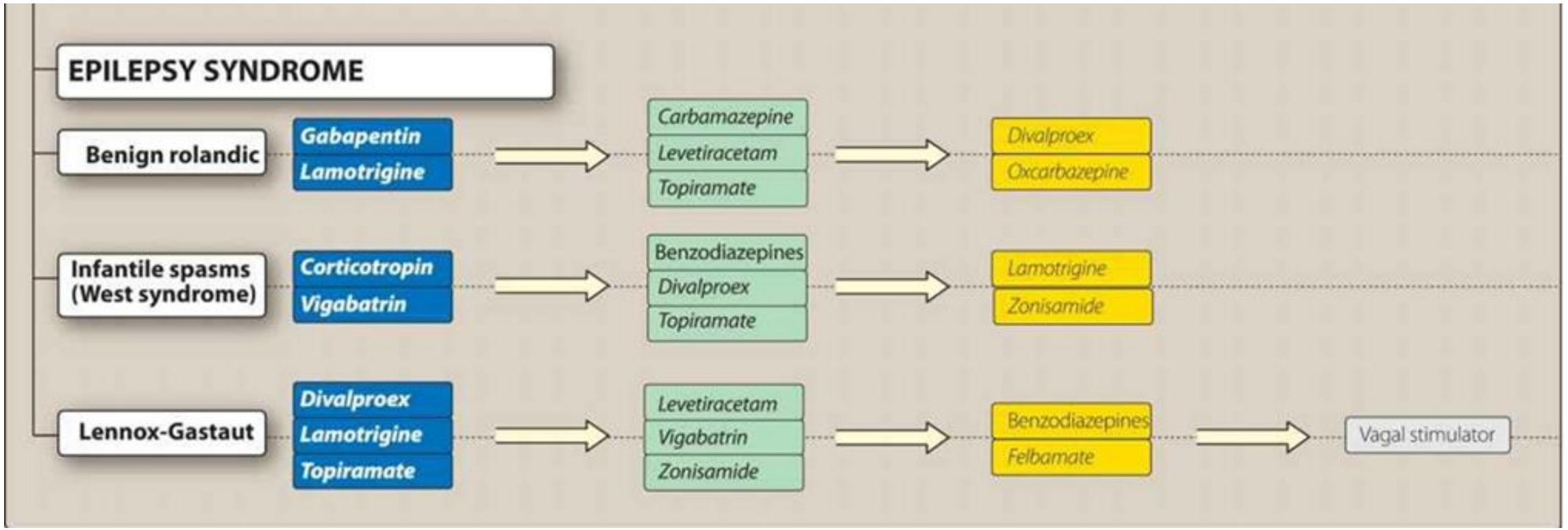


Figure 3: Therapeutic indications for the antiseizure agents. Benzodiazepines = diazepam and lorazepam.

Antiseizure Medications

- The Food and Drug Administration has approved many new antiseizure medications in the last few decades.
- Some of these agents are thought to have potential advantages over older drugs in terms of pharmacokinetics, tolerability, and reduced risk for drug–drug interactions.
- Suicidal behavior and suicidal ideation have been identified as a risk with antiseizure medications.
- In addition, virtually, all antiseizure medications have been associated with multiorgan hypersensitivity reactions, a rare idiosyncratic reaction characterized by rash, fever, and systemic organ involvement.

Benzodiazepines

Benzodiazepines bind to GABA inhibitory receptors to reduce the firing rate. Most benzodiazepines are reserved for emergency or acute seizure treatment due to tolerance. However, clonazepam and clobazam may be prescribed as adjunctive therapy for particular types of seizures. Diazepam is also available for rectal administration to avoid or interrupt prolonged generalized tonic–clonic seizures or clusters when oral administration is not possible.

DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS AND COMMENTS
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.

Figure 4: Summary of antiseizure drugs. AMPA = α-amino-3-hydroxy-5-methyl-4isoxazolepropionic acid; CBC = complete blood count; GABA = γ-aminobutyric acid; GABA-T = γ aminobutyric acid transaminase; GI = gastrointestinal; SLE = systemic lupus erythematosus.

ANTISEIZURE MEDICATION	PROTEIN BINDING*	HALF-LIFE**	ACTIVE METABOLITE	MAJOR ORGAN OF ELIMINATION	DRUG INTERACTIONS
Brivaracetam	Low	9		Liver	✔
Carbamazepine	Moderate	6–15	CBZ-10,11-epoxide	Liver	✔
*Eslicarbazepine acetate^*	Low	8–24	Eslicarbazepine (S-licarbazepine)	Kidney	✔
Ethosuximide	Low	25–26		Liver	✔
Felbamate	Low	20–23		Kidney/Liver	✔
*Fosphenytoin^*	High	12–60	phenytoin	Liver	✔
Gabapentin	Low	5–9		Kidney	
Lacosamide	Low	13		Various	
Lamotrigine	Low	25–32		Liver	✔
Levetiracetam	Low	6–8		Hydrolysis	

*Oxcarbazepine^*	Low	5–13	Monohydroxy metabolite (MHD)	Liver	✔
Perampanel	High	105		Liver	✔
Phenobarbital	Low	72–124		Liver	✔
Phenytoin	High	12–60		Liver	✔
Pregabalin	Low	5–6.5		Kidney	
Primidone	High	72–124	Phenobarbital, PEMA	Liver	✔
Rufinamide	Low	6–10		Liver	✔
Tiagabine	High	7–9		Liver	✔
Topiramate	Low	21		Various	✔
Valproic acid (Divalproex)	Moderate/ High	6–18	Various	Liver	✔
Vigabatrin	Low	7.5		Kidney	✔
Zonisamide	Low	63		Liver	✔

*Low = 60% or less, Moderate = 61%-85%, High = >85%. **Half-life in hours. ^Prodrug. PEMA = phenylethylmalonamide.

Figure 5: Summary of the pharmacokinetics of antiseizure medications used as chronic therapy

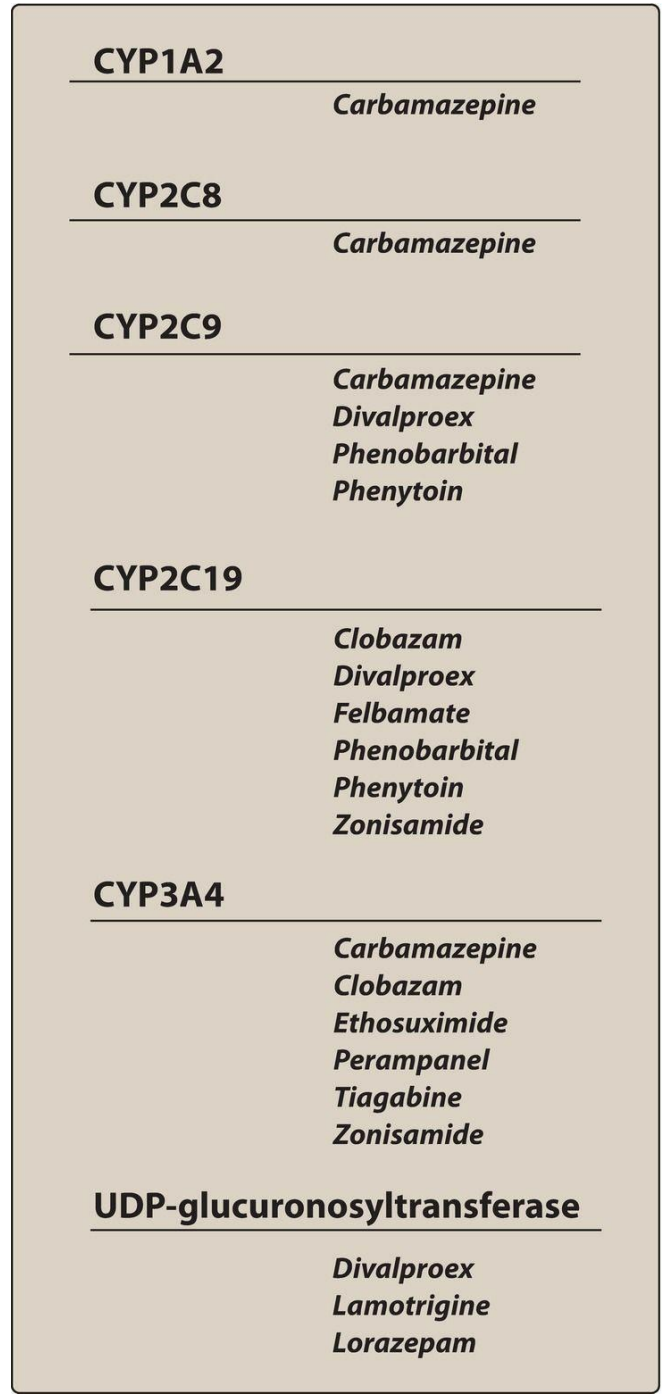


Figure 6: CYP metabolism of the antiseizure medications.

Adverse effects

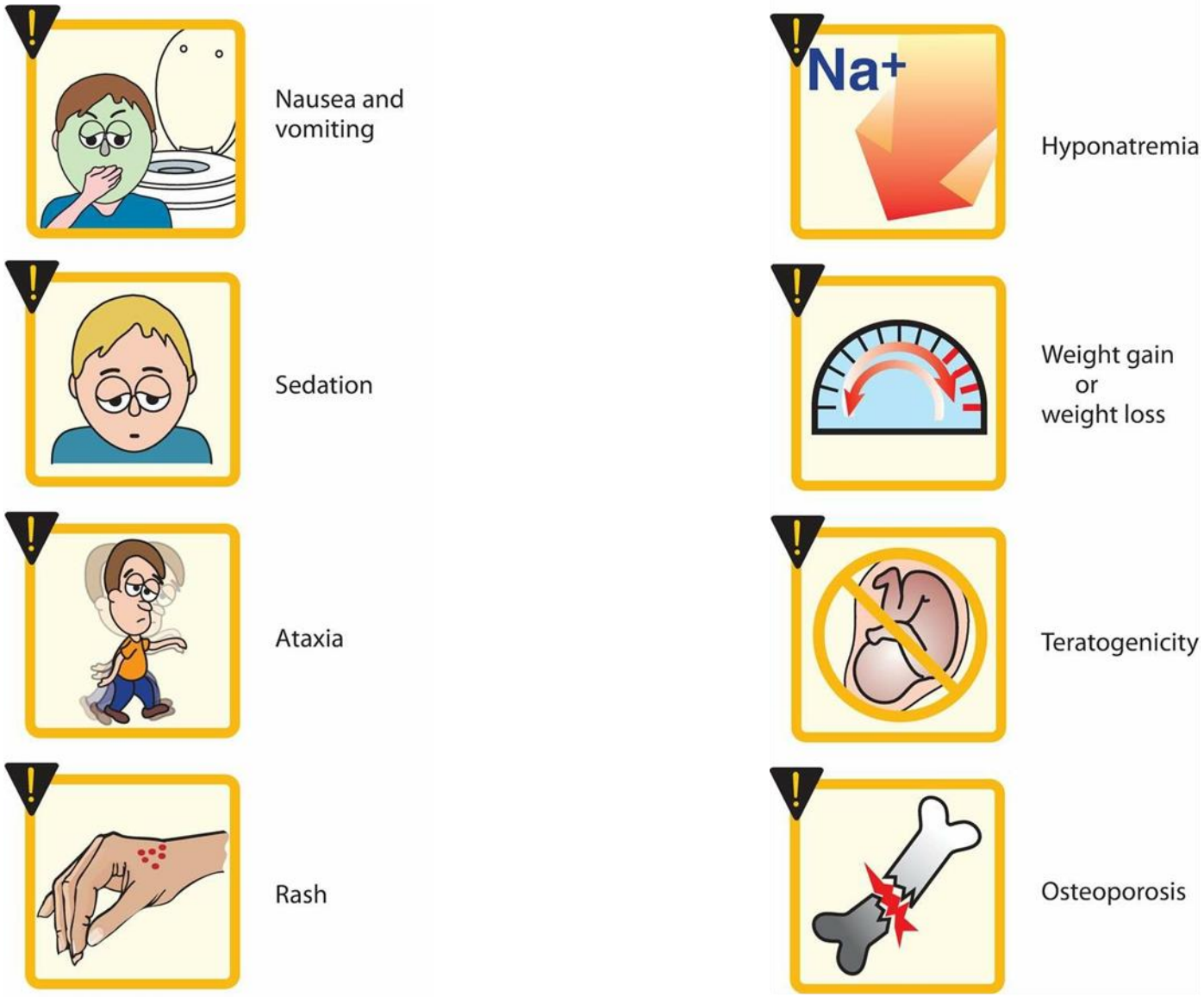
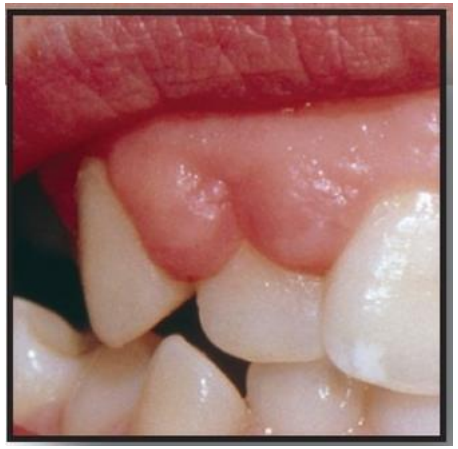


Figure 7: Notable adverse effects of antiseizure medications



Gingival hyperplasia in patient treated with phenytoin.

Status Epilepticus

- In status epilepticus, **two or more seizures occur without recovery of full consciousness in between episodes.**
- These may be **focal or generalized**, **convulsive or nonconvulsive**.
- Status epilepticus is **life threatening and requires emergency treatment** usually consisting of parenteral administration of a **fast-acting medication** such as a benzodiazepine, followed by **a slower- acting medication** such as phenytoin**,** fosphenytoin, divalproex, or levetiracetam.

Women's Health and Epilepsy

- Women of childbearing potential with epilepsy require assessment of their antiseizure medications in regard to contraception and pregnancy planning.
- Several antiseizure medications increase the metabolism of hormonal contraceptives, potentially rendering them ineffective.
- Pregnancy planning is vital, as many antiseizure medications have the potential to affect fetal development and cause birth defects.

- All women considering pregnancy should be on high doses (1 to 5 mg) of folic acid prior to conception. Divalproex and barbiturates should be avoided.
- The pharmacokinetics of antiseizure medications and the frequency and severity of seizures may change during pregnancy.
- Regular monitoring by both an obstetrician and a neurologist is important.
- All women with epilepsy should be encouraged to register with the Antiepileptic Drug Pregnancy Registry


Thank You!