Antidepressants

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Depression and Mania

- Depression is characterized by feelings of sadness and hopelessness, as well as the inability to experience pleasure in usual activities, changes in sleep patterns and appetite, loss of energy, and suicidal thoughts.

- Mania is characterized by the opposite behavior: enthusiasm, anger, rapid thought and speech patterns, extreme self-confidence, and impaired judgment.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Fluoxetine, Citalopram, Escitalopram, Fluvoxamine, Paroxetine, Sertraline

- SSRIs are a group of antidepressant drugs that specifically inhibit serotonin reuptake, having 300- to 3000-fold greater selectivity for the serotonin transporter, as compared to the norepinephrine transporter.

- This contrasts with the tricyclic antidepressants (TCAs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) that nonselectively inhibit the reuptake of norepinephrine and serotonin.

- Because they have different adverse effects and are relatively safe even in overdose, the SSRIs have largely replaced TCAs and monoamine oxidase inhibitors (MAOIs) as the drugs of choice in treating depression.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Fluoxetine, Citalopram, Escitalopram, Fluvoxamine, Paroxetine, Sertraline

- **Actions:** The SSRIs block the reuptake of serotonin, leading to increased concentrations of the neurotransmitter in the synaptic cleft.

- Antidepressants, including SSRIs, typically take at least 2 weeks to produce significant improvement in mood, and maximum benefit may require up to 12 weeks or more.

- **Therapeutic uses:** The primary indication for SSRIs is depression, although they can be used in obsessive–compulsive disorder, panic disorder, social anxiety disorder, (only fluoxetine is approved for bulimia).

Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)

Venlafaxine, Desvenlafaxine, Levomilnacipran, Duloxetine

- SNRIs inhibit the reuptake of both serotonin and norepinephrine.
- SNRIs, may be effective in treating depression in patients in whom SSRIs are ineffective.
- Venlafaxine is a potent inhibitor of serotonin reuptake and, at medium to higher doses, is an inhibitor of norepinephrine reuptake.
- Duloxetine inhibits serotonin and norepinephrine reuptake at all doses.

Atypical Antidepressants

Bupropion, Mirtazapine, Nefazodone, Trazodone, Vilazodone, Vortioxetine

- Bupropion is a weak dopamine and norepinephrine reuptake inhibitor that is used to alleviate the symptoms of depression.

- Mirtazapine enhances serotonin and norepinephrine neurotransmission by serving as an antagonist at presynaptic α2 receptors.

- Vilazodone is a serotonin reuptake inhibitor and a 5-HT1a partial agonist.

Tricyclic Antidepressants

Imipramine, Amitriptyline, Clomipramine, Doxepin, Trimipramine, Desipramine, Nortriptyline, Protriptyline, Maprotiline, Amoxapine

- The TCAs block norepinephrine and serotonin reuptake into the presynaptic neuron.

- **Actions:** The TCAs elevate mood, improve mental alertness, increase physical activity, and reduce morbid preoccupation in 50% to 70% of individuals with major depression.

- The onset of the mood elevation is slow, requiring 2 weeks or longer.

- **Therapeutic uses:** The TCAs are effective in treating moderate to severe depression.

Monoamine Oxidase (MAO) Inhibitors

Phenelzine, Tranylcypromine, Isocarboxazid, Selegiline

- **Mechanism of action:** cause irreversible inactivation of MAO. This results in increased stores of norepinephrine, serotonin, and dopamine within the neuron and subsequent diffusion of excess neurotransmitter into the synaptic space.

- **Therapeutic uses:** The MAOIs are indicated for depressed patients who are unresponsive or allergic to TCAs and SSRIs or who experience strong anxiety.

Treatment of Mania and Bipolar Disorder

A. Lithium: Lithium salts are used acutely and prophylactically for managing bipolar patients. Lithium is effective in treating 60% to 80% of patients exhibiting mania and hypomania.

B. Other drugs

- Several anti-epileptic drugs, including **carbamazepine, valproic acid, and lamotrigine**, have been approved as mood stabilizers for bipolar disorder.

Antipsychotic Drugs

Schizophrenia

- Schizophrenia is a type of chronic psychosis characterized by delusions, hallucinations (often in the form of voices), and thinking or speech disturbances.

- The onset of illness is often during late adolescence or early adulthood. It occurs in about 1% of the population and is a chronic and disabling disorder.

- Schizophrenia has a strong genetic component and probably reflects some fundamental biochemical abnormality, possibly a dysfunction of the mesolimbic or mesocortical dopaminergic neuronal pathways.

A. First-generation antipsychotics

(also called conventional, typical, or traditional antipsychotics)

Low potency (chorpromazine, thioridazine) and high potency (fluphenazine, haloperidol, loxapine, perphenazine, pimozide, prochlorperazine, thiothixene, trifluoperzine)

- They are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blocking of dopamine D2 receptors.

- They are more likely to be associated with movement disorders known as extrapyramidal symptoms (EPS), particularly drugs that bind tightly to dopaminergic neuroreceptors, such as haloperidol.

- No one drug is clinically more effective than another.

B. Second-generation antipsychotic drugs

(also called “atypical” antipsychotics)

Aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone

- They have a lower incidence of EPS than the first-generation agents but are associated with a higher risk of metabolic side effects, such as diabetes, hypercholesterolemia, and weight gain.

- The second-generation drugs appear to owe their unique activity to blockade of both serotonin and dopamine and, perhaps, other receptors.

Drug selection

- Second-generation agents are generally used as first-line therapy for schizophrenia to minimize the risk of debilitating EPS associated with the first-generation drugs.

- The second-generation antipsychotics exhibit an efficacy that is equivalent to, and occasionally exceeds, that of the first-generation antipsychotic agents.

- **Refractory patients:** Approximately 10% to 20% of patients with schizophrenia have an insufficient response to all first- and second-generation antipsychotics.
- Clozapine has shown to be an effective in refractory patients with a minimal risk of EPS. However, its clinical use is limited to refractory patients because of serious adverse effects.

Mechanism of Action

1. **Dopamine antagonism:** All of the first-generation and most of the second-generation antipsychotic drugs block D2 dopamine receptors in the brain and the periphery.
2. **Serotonin receptor–blocking activity:** Most of the second-generation agents appear to exert part of their unique action through inhibition of serotonin receptors (5-HT), particularly 5-HT2A receptors.

- Clozapine has high affinity for D1, D4, 5-HT2, muscarinic, and α-adrenergic receptors, but it is also a weak dopamine D2 receptor antagonist.
- Risperidone & Olanzapine block 5-HT2A receptors to a greater extent than it does D2 receptors.
- Aripiprazole is a partial agonist at D2 and 5-HT1A receptors, as well as an antagonist of 5-HT2A receptors.
- Quetiapine blocks D2 receptors more potently than 5-HT2A receptors but is relatively weak at blocking either receptor. Its low risk for EPS may also be related to the relatively short period of time it binds to the D2 receptor.

Drugs for Epilepsy

Epilepsy

- Globally, epilepsy is the third most common neurologic disorder after cerebrovascular and Alzheimer's disease.

- 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, and distorted perceptions that are of limited duration but recur if untreated.

- Medications are the most widely used mode of treatment for patients with epilepsy. In general, seizures can be controlled with one medication in approximately 75% of patients.

- Patients may require more than one medication in order to optimize seizure control, and some patients may never obtain total seizure control.

Etiology of Epilepsy

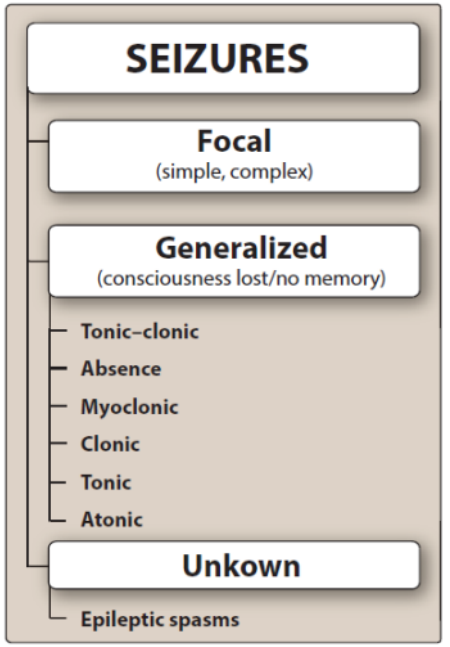
A. **Genetic epilepsy:** These seizures result from an inherited abnormality in the central nervous system (CNS).

B. **Structural/metabolic epilepsy:** A number of causes, such as illicit drug use, tumor, head injury, hypoglycemia, meningeal infection, and the rapid withdrawal of alcohol from an alcoholic, can precipitate seizures.

C. **Unknown cause:** When no specific anatomic cause for the seizure, such as trauma or neoplasm, is evident, a patient may be diagnosed with seizures where the underlying cause is unknown. Most cases of epilepsy are due to an unknown cause.

Classification of seizures

- Seizures have been categorized by **site of origin, etiology, electrophysiologic correlation, and clinical presentation**.
- Seizures have been classified into two broad groups: **focal and generalized**.



A. Focal: Focal seizures involve only a portion of the brain, typically part of one lobe of one hemisphere. Focal seizures may progress to become generalized tonic–clonic seizures and could occur at any age.

1. **Simple partial:** These seizures are caused by a group of hyperactive neurons exhibiting abnormal electrical activity and are confined to a single locus in the brain. The electrical discharge does not spread, and the patient does not lose consciousness or awareness. The patient often exhibits abnormal activity of a single limb or muscle group that is controlled by the region of the brain experiencing the disturbance. The patient may also show sensory distortions. This activity may spread.

2. **Complex partial:** These seizures exhibit complex sensory hallucinations and mental distortion. Motor dysfunction may involve chewing movements, diarrhea, and/or urination. Consciousness is altered. Simple partial seizure activity may spread to become complex and then spread to a secondarily generalized convulsion.

Classification of seizures

B. Generalized: 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.

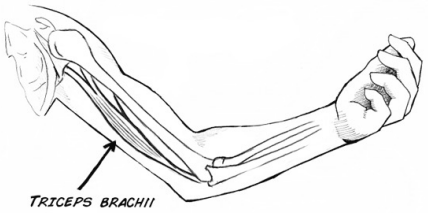
1. Tonic–clonic: These seizures result in loss of consciousness, followed by tonic (continuous contraction) and clonic (rapid contraction and relaxation) phases. The seizure may be followed by a period of confusion and exhaustion due to the depletion of glucose and energy stores.

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 long.



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

Mechanism of action of antiepilepsy medications

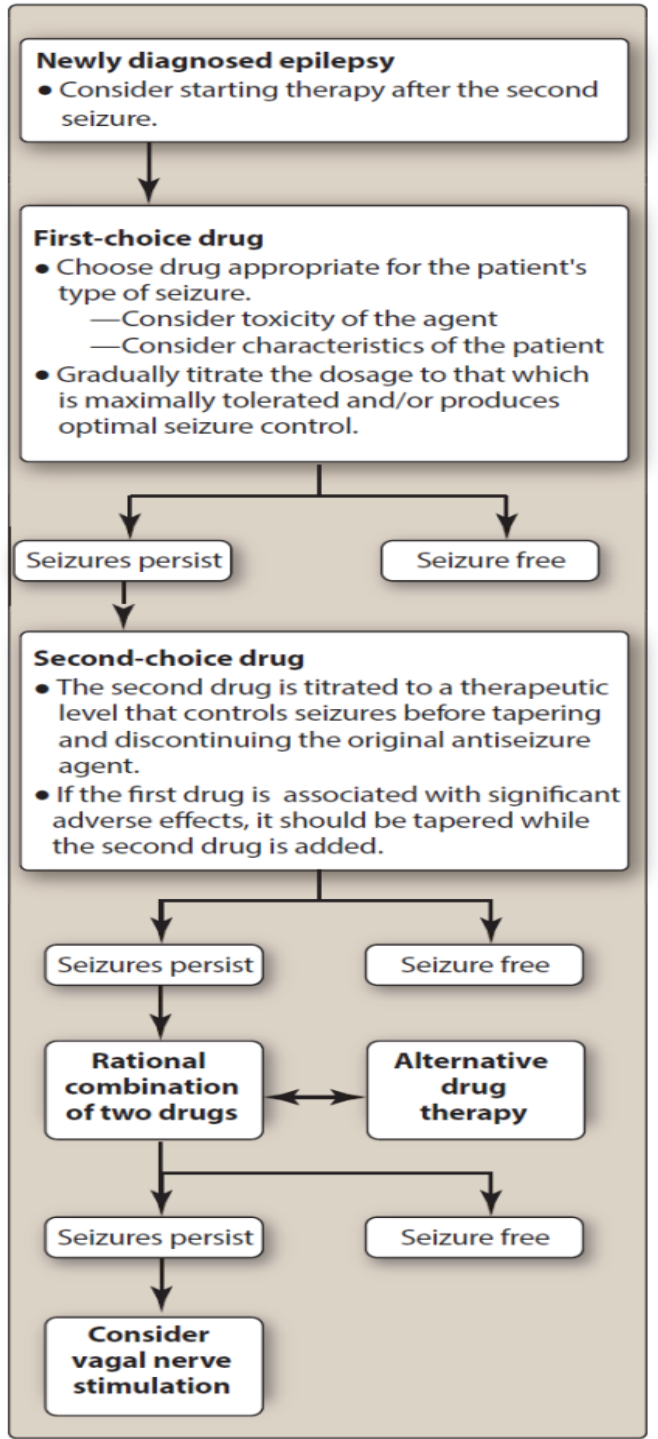
- Drugs reduce seizures through such mechanisms as blocking voltage-gated channels (Na^+ or Ca^{2+}), enhancing inhibitory γ-aminobutyric acid (GABA)-ergic impulses and interfering with excitatory glutamate (NMDA) transmission.

- Some anti-epilepsy medications appear to have multiple targets within the CNS, whereas the mechanism of action for some agents is poorly defined.

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

Drug Selection

- In newly diagnosed patients, monotherapy is instituted with a single agent until seizures are controlled or toxicity occurs.
- Compared to those receiving combination therapy, patients receiving monotherapy exhibit better medication adherence and fewer side effects.
- If seizures are not controlled with the first medication, monotherapy with an alternate medication or the addition of medications should be considered.
- Failing that, other medical management (vagal nerve stimulation, surgery, etc.) should be considered.



A. Benzodiazepines

- Benzodiazepines bind to GABA inhibitory receptors to reduce 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.

B. Carbamazepine

- Carbamazepine blocks sodium channels, thereby inhibiting the generation of repetitive action potentials in the epileptic focus and preventing their spread.

- Carbamazepine is effective for treatment of focal seizures and, additionally generalized tonic–clonic seizures, trigeminal neuralgia, and bipolar disorder.

C. Eslicarbazepine (S-licarbazepine)

- S-licarbazepine is the active metabolite of oxcarbazepine. It is a voltage-gated sodium channel blocker and is approved for partial-onset seizures in adults.

D. Ethosuximide

- Ethosuximide reduces propagation of abnormal electrical activity in the brain, most likely by inhibiting T-type calcium channels. It is only effective in treating absence seizures.

E. Ezogabine

- Ezogabine is thought to open voltage-gated M-type potassium channels leading to stabilization of the resting membrane potential.

F. Felbamate

- Multiple proposed mechanisms including the blocking of voltage-dependent sodium channels, competing with the glycine co-agonist binding site on NMDA glutamate receptor, blocking of calcium channels, and potentiating GABA action.
- It is reserved for use in refractory epilepsies.

G. Gabapentin

- Gabapentin is an analog of GABA. However, it does not act at GABA receptors, enhance GABA actions or convert to GABA. Its precise mechanism of action is not known. It is approved as adjunct therapy for focal seizures and treatment of postherpetic neuralgia.

H. Lacosamide

- Lacosamide affects voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing.
- Lacosamide is approved for adjunctive treatment of focal seizures. It is available in an injectable formulation.

I. Lamotrigine

- Lamotrigine blocks sodium channels, as well as high voltage-dependent calcium channels.
- Lamotrigine is effective in a wide variety of seizure types, including focal, generalized, absence seizures.

J. Levetiracetam

- Levetiracetam is approved for adjunct therapy of primary generalized tonic–clonic seizures in adults and children.
- The exact mechanism of anticonvulsant action is unknown.

K. Oxcarbazepine

- It blocks sodium channels, preventing the spread of the abnormal discharge.
- It is also thought to modulate calcium channels. It is approved for use in adults and children with partial-onset seizures.

L. Perampanel

- Perampanel is a selective α-amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid (AMPA) antagonist resulting in reduced excitatory activity.
- It is approved for adjunctive treatment of partial-onset seizures in patients 12 years or older.

M. Phenobarbital and primidone

- Phenobarbital enhances the inhibitory effects of GABA-mediated neurons. Primidone is metabolized to phenobarbital (major) and phenylethylmalonamide, both with anticonvulsant activity.
- Phenobarbital is used primarily in the treatment of status epilepticus when other agents fail.

N. Phenytoin and fosphenytoin

- Phenytoin blocks voltage-gated sodium channels by selectively binding to the channel in the inactive state and slowing its rate of recovery.
- It is effective for treatment of focal and generalized tonic–clonic seizures and in the treatment of status epilepticus.
- Gingival hyperplasia may cause the gums to grow over the teeth.
- Fosphenytoin is a prodrug that is rapidly converted to phenytoin in the blood within minutes.

O. Pregabalin

- Pregabalin binds to the α2-δ site, an auxiliary subunit of voltage-gated calcium channels in the CNS, inhibiting excitatory neurotransmitter release.
- The drug has proven effects on focal-onset seizures, diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia.

P. Rufinamide

- Rufinamide acts at sodium channels.
- It is approved for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children over age 4 years and in adults.

Q. Tiagabine

- Tiagabine blocks GABA uptake into presynaptic neurons.
- Tiagabine is effective as adjunctive treatment in partial-onset seizures.

R. Topiramate

- Topiramate blocks voltage-dependent sodium channels, reduces high-voltage calcium currents (L type), is a carbonic anhydrase inhibitor, and may act at glutamate (NMDA) sites.
- Topiramate is effective for use in partial and primary generalized epilepsy. It is also approved for prevention of migraine.

S. Valproic acid and divalproex

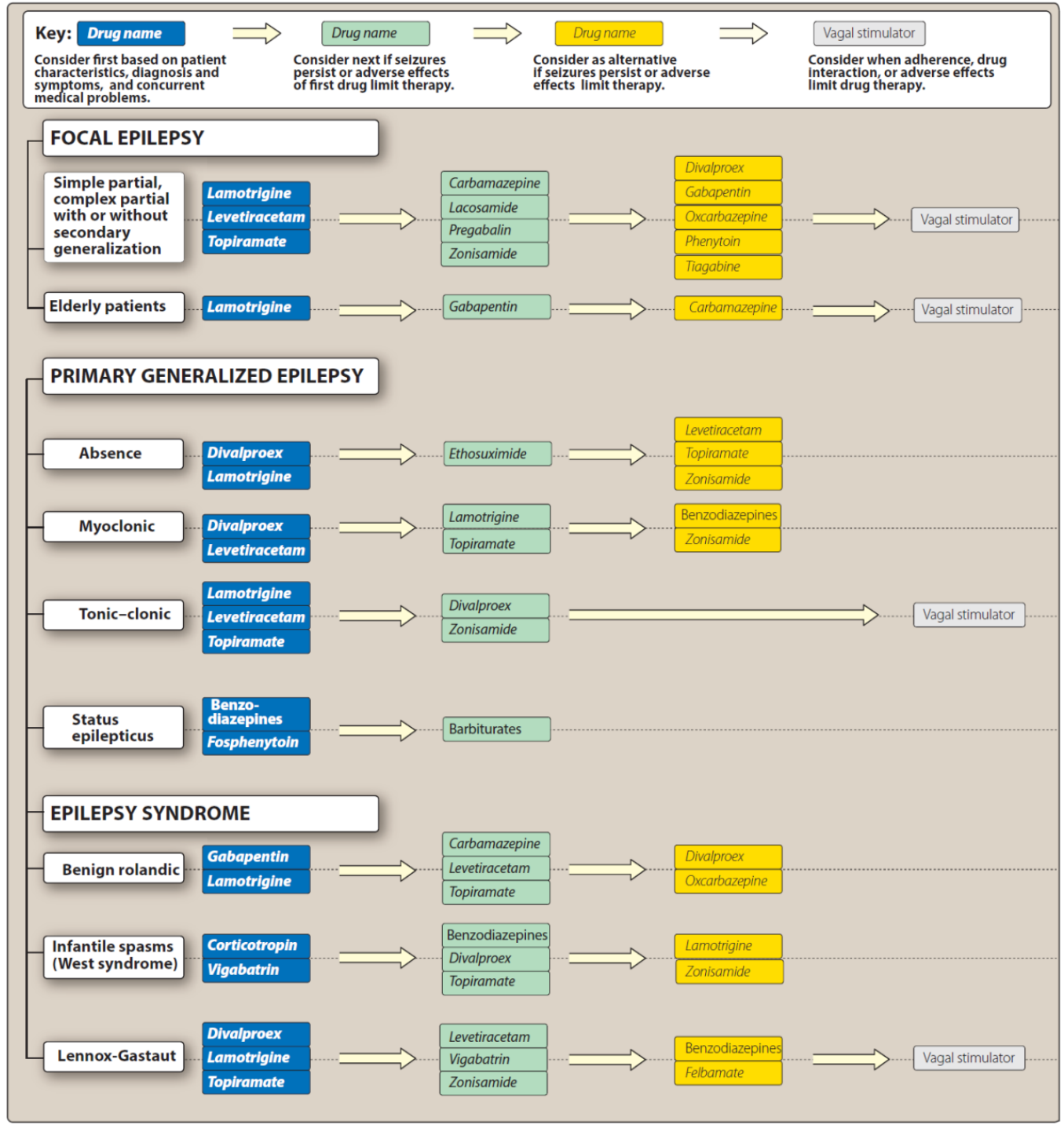
- Divalproex sodium is a combination of sodium valproate and valproic acid that is converted to valproate when it reaches the gastrointestinal tract.
- Possible mechanisms of action include sodium channel blockade, blockade of GABA transaminase, and action at the T-type calcium channels.
- These varied mechanisms provide a broad spectrum of activity against seizures. It is effective for the treatment of focal and primary generalized epilepsies.

T. Vigabatrin

- Vigabatrin acts as an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T). GABA-T is the enzyme responsible for metabolism of GABA.

U. Zonisamide

- Zonisamide is a sulfonamide derivative that has a broad spectrum of action.
- The compound has multiple effects, including blockade of both voltage-gated sodium channels and T-type calcium currents. It has a limited amount of carbonic anhydrase activity.
- Zonisamide is approved for use in patients with focal epilepsy.


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
Levetiracetam
Topiramate
Divalproex
Zonisamide
Vagal stimulator
Status epilepticus
Benzo-diazepines
Fosphenytoin
Barbiturates
EPILEPSY SYNDROME
Benign rolandic
Gabapentin
Lamotrigine
Carbamazepine
Levetiracetam
Topiramate
Divalproex
Oxcarbazepine
Infantile spasms (West syndrome)
Corticotropin
Vigabatrin
Benzodiazepines
Divalproex
Topiramate
Lamotrigine
Zonisamide
Lennox-Gastaut
Divalproex
Lamotrigine
Topiramate
Levetiracetam
Vigabatrin
Zonisamide
Benzodiazepines
Felbamate
Vagal stimulator


Thank
you