DRUGS FOR EPILEPSY

From Lippincott

By Fatima Haider

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.
The site of origin of the abnormal neuronal firing determines the symptoms that are produced. 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.
The neuronal discharge in epilepsy results from the firing of a small population of neurons in a specific area of the brain referred to as the “primary focus.”

CLASSIFICATION OF SEIZURES

1. Focal
2. Generalized
3. Unknown

FOCAL	
SIMPLE PARTIAL	**COMPLETE PARTIAL**
-abnormal electrical activity 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. - may occur at any age	-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. - may occur at any age.

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)					
TONIC CLONIC	**ABSENCE**	**MYO CLONIC**	**CLONIC**	**TONIC**	**ATONIC**
-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	-These seizures involve a brief, abrupt, and selflimiting 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 sec. - An absence seizure has a very distinct three-per-second spike and wave discharge seen on EEG	-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.	-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.	-These seizures involve increased tone in the extension muscles and are generally less than 60 seconds long	-These seizures are also known as drop attacks and are characterized by a sudden loss of muscle tone.

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

MOA OF ANTI EPILEPSY DRUGS: blocking voltage-gated channels (Na+ or Ca2+), enhancing inhibitory γ-aminobutyric acid (GABA)-ergic impulses and interfering with excitatory glutamate transmission.

ANTI EPILEPSY DRUGS

DRUG	**MOA**	**THEEAPEUTIC USES**	**ADVERSE EFFECTS**
BENZODIAZEPENES	bind to GABA inhibitory receptors to reduce firing rate.	-Diazepam is available for rectal administration to avoid or interrupt prolonged generalized tonic–clonic seizures or clusters when oral administration is not	-Most benzodiazepines are reserved for emergency or acute seizure treatment due to tolerance.

		possible	
BRIVARACETAM	Demonstrated high and selective affinity for a synaptic vesicle protein (SV2A)	Approved for treatment of focal onset seizures in adults	
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.	-Hyponatremia, esp in the elderly -Carbamazepine should not be prescribed for patients with absence seizures because it may cause an increase in seizures
ESLICARBAZEPINE	It is a voltage-gated sodium channel blocker	-approved for partial-onset seizures in adults	-dizziness, somnolence, diplopia, and headache. -rash, psychiatric side effects, and hyponatremia
ETHOSUXIMIDE	reduces propagation of abnormal electrical activity in the brain, most likely by inhibiting T-type calcium channels.	-only effective in treating absence seizures	
FELBAMATE	multiple proposed mechanisms including the blocking of voltage-dependent sodium channels, competing with the glycine coagonist binding site on the N-methyl-d-aspartate (NMDA) glutamate receptor, blocking of calcium channels, and potentiating GABA action.	It is reserved for use in refractory epilepsies (particularly Lennox-Gastaut syndrome) because of the risk of aplastic anemia (about 1:4000) and hepatic failure	risk of aplastic anemia (about 1:4000) and hepatic failure
GABAPENTIN	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.	-approved as adjunct therapy for focal seizures and treatment of postherpetic neuralgia - Gabapentin is well tolerated by the elderly population with partial seizures due to its relatively mild adverse effects. - It may also be a good choice for the older patient because there are few drug interactions.	-Reduced dosing is required in renal disease.
LOCOSAMIDE	-affects voltage-gated	-Lacosamide is approved for	-dizziness, headache, and

	sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing. -Lacosamide binds to collapsin response mediator protein-2 (CRMP-2), a phosphoprotein involved in neuronal differentiation and control of axonal outgrowth. The role of CRMP-2 binding in seizure control is unknown.	adjunctive treatment of focal seizures. -It is available in an injectable formulation.	fatigue.
LAMOTRIGINE	blocks sodium channels, as well as high voltage-dependent calcium channels.	-effective in a wide variety of seizure types, including focal, generalized, absence seizures, and Lennox-Gastaut syndrome. - treat bipolar disorder	-Lamotrigine dosages should be reduced when adding valproate to therapy. - Slow titration is necessary with lamotrigine (particularly when adding lamotrigine to a regimen that includes valproate) due to risk of rash, which may progress to a serious, life-threatening reaction
LEVITIRACETAM	The exact mechanism of anticonvulsant action is unknown. It demonstrates high affinity for a synaptic vesicle protein (SV2A).	-approved for adjunct therapy of focal onset, myoclonic, and primary generalized tonic–clonic seizures in adults and children.	-mood alterations
OXCARBAZEPINE	-blocks sodium channels, preventing the spread of the abnormal discharge. - It is also thought to modulate calcium channels.	-approved for use in adults and children with partial-onset seizures.	-hyponatremia in elderly
PERAMPANEL	selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid antagonist resulting in reduced excitatory activity.	- It is approved for adjunctive treatment of partial-onset seizures in patients 12 years or older.	
PHENOBARBITAL and PRIMIDONE	enhancement of the inhibitory effects of GABA-mediated neurons	-Phenobarbital is used primarily in the treatment of status epilepticus when other agents fail	

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. -Fosphenytoin is a prodrug that is rapidly converted to phenytoin in the blood within minutes.	-effective for treatment of focal and generalized tonic– clonic seizures and in the treatment of status epilepticus.	-Depression of the CNS occurs particularly in the cerebellum and vestibular system, causing nystagmus and ataxia. The elderly are highly susceptible to this effect. -Gingival hyperplasia may cause the gums to grow over the teeth - Long-term use may lead to development of peripheral neuropathies and osteoporosis -Whereas fosphenytoin may be administered intramuscularly (IM), phenytoin sodium should never be given IM, as it causes tissue damage and necrosis. Fosphenytoin is the drug of choice and standard of care for IV and IM administration of phenytoin.
PREGABALIN	binds to the α2 -δ site, an auxiliary subunit of voltage-gated calcium channels in the CNS, inhibiting excitatory neurotransmitter release. T	-the drug has proven effects on focal-onset seizures, diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia.	-Dosage adjustments are needed in renal dysfunction. -Weight gain and peripheral edema have been reported.
RUFINAMIDE	acts at sodium channels.	-pproved for the adjunctive treatment of seizures associated with LennoxGastaut syndrome in children over age 4 years and in adults.	-potential for shortened QT intervals
TIAGABINE	blocks GABA uptake into presynaptic neurons permitting more GABA to be available for receptor binding, and therefore, it enhances inhibitory activity.	-effective as adjunctive treatment in partial-onset seizures.	- seizures have occurred in patients using tiagabine who did not have epilepsy. Tiagabine should not be used for indications other than epilepsy
TOPIRAMATE	It blocks voltage-dependent sodium channels, reduces high-voltage calcium currents (L type), is a	-effective for use in partial and primary generalized epilepsy. -approved for prevention of migraine.	-somnolence -weight loss -paresthesias -Renal stones

	carbonic anhydrase inhibitor, and may act at glutamate (NMDA) sites.		-glaucoma -oligohidrosis (decreased sweating) -hyperthermia
VALPROIC ACID and DIVALPROEX	Possible mechanisms of action include sodium channel blockade, blockade of GABA transaminase, and action at the T-type calcium channels.	-effective for the treatment of focal and primary generalized epilepsies.	-Rare hepatotoxicity may cause a rise in liver enzymes, which should be monitored frequently -Teratogenic
VIGABATRIN	an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T). GABA-T is the enzyme responsible for metabolism of GABA.		associated with visual field loss ranging from mild to severe in 30% or more of patients.
ZONISAMIDE	-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	-approved for use in patients with focal epilepsy	- CNS adverse effects - kidney stones -Oligohidrosis has been reported, and patients should be monitored for increased body temperature and decreased sweating. -Zonisamide is contraindicated in patients with sulfonamide or carbonic anhydrase inhibitor hypersensitivity

ANTI EPILEPSY MEDICATIONS AND CONTRACEPTIVES: Several antiepilepsy medications increase the metabolism of hormonal contraceptives, potentially rendering them ineffective. These include phenytoin, phenobarbital, carbamazepine, topiramate, oxcarbazepine, rufinamide, and clobazam. These medications increase the metabolism of contraceptives regardless of the delivery system used (for example, patch, ring, implants, and oral tablets).

ANTI EPILEPSY DRUGS AND PREGNANCY: Pregnancy planning is vital, as many antiepilepsy 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. If possible, women already taking divalproex should be placed on other therapies prior to pregnancy and counseled about the potential for birth defects, including cognitive (Figure 12.11) and behavioral abnormalities and neural tube defects. The pharmacokinetics of antiepilepsy medications and the frequency and severity of seizures may change during pregnancy. Regular monitoring by both an obstetrician and a neurologist is important.