

Treatment of epilepsy 2

Dr.Samaher Jaber Younis

BCPS

ANTISEIZURE MEDICATIONS

Benzodiazepines

- i. Mechanism of action: Augment γ -aminobutyric acid (GABA)-mediated chloride influx
- ii. Tolerance may develop: Usually used as adjunctive, short-term therapy
- iii. Most commonly used drugs: **Chlorazepate, clobazam, clonazepam, diazepam (Valium), and lorazepam.**
- iv. All benzodiazepines are controlled substances, scheduled as C-IV.
- v. Nonepileptic indications: **Chlorazepate** (anxiety disorders, anxiety), **clonazepam** (panic disorder with or without agoraphobia), **lorazepam** (anxiety disorders, anxiety, alcohol withdrawal)

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.

Brivaracetam

- i. Mechanism of action: Unknown mechanism, but has high affinity for synaptic vesicle protein 2A
- ii. Adverse effects: Somnolence, sedation, dizziness, fatigue
- iii. Drug interactions: Carbamazepine, phenobarbital, phenytoin

Cannabidiol

- i. The only U.S. Food and Drug Administration (FDA)-approved cannabis product for epilepsy
- ii. Approved for Dravet syndrome and Lennox-Gastaut syndrome
- iii. Adverse effects: Sedation, drowsiness, diarrhea, intestinal cramping, increased liver transaminase (11% of patients); 3% of patients discontinued because of increased liver function tests
- iv. Metabolized by cytochrome P450 (CYP) 2C19 and 3A4
- v. Interaction with clobazam and other antiepileptic drugs (AEDs)
- vi. Dose 10–20 mg/kg/day

Ethosuximide

- i. Mechanism of action: T-type calcium current blocker
- ii. Useful only for absence seizures

Felbamate

- i. Mechanism of action: Blocks glycine site on *N*-methyl-d-aspartate receptor
- ii. Serious adverse effects: Hepatotoxicity, aplastic anemia. Patient or guardian must sign consent form. Used only when seizures are severe and refractory to other medications and when the benefit clearly outweighs the potential adverse effects.

Carbamazepine

- i. Mechanism of action: Fast sodium channel blocker
- ii. Pharmacokinetics: Enzyme inducer, autoinduction
- iii. Adverse effects: Rash (occurs after a delay of 2–8 weeks), syndrome of inappropriate antidiuretic hormone release, aplastic anemia, thrombocytopenia, anemia, leukopenia
- iv. Extended-release tablets (Tegretol XR) 100, 200, and 400 mg; extended-release capsules 100, 200, and 300 mg available. Dosing is still twice daily. Do not crush or chew. Extended-release capsules (Carbatrol) can be opened and sprinkled on food. Ghost tablets can occur in the stool with the extended-release tablets (Tegretol XR).
- v. Patients with the *HLA-B*1502* allele are at a 10-fold elevated risk of Stevens-Johnson syndrome.
 - (a) Testing is recommended for Asians (including Indians).
 - (b) More than 15% of populations in Hong Kong, Malaysia, the Philippines, and Thailand have this allele.
- vi. Patients with the *HLA-A*3101* allele are also at a 12-fold elevated risk of hypersensitivity syndrome and a 3-fold elevated risk of maculopapular exanthema.
 - (a) Prevalence of this allele is 2%–5% in northern European populations and 9.1% in Japanese populations.
 - (b) No recommendations have been issued for testing for this allele.
- vii. Nonepileptic indication: Trigeminal neuralgia

Oxcarbazepine

- i. Mechanism of action: Fast sodium channel blocker
- ii. Pharmacokinetics: Active metabolite 10-monohydroxy oxcarbazepine; enzyme inducer, no autoinduction
- iii. Adverse effects: Hyponatremia more common than with carbamazepine (increased dose and increased age increase risk of hyponatremia); blood dyscrasias less common than with carbamazepine; 25%–30% of patients with hypersensitivity to carbamazepine will have hypersensitivity to oxcarbazepine; rash

Eslicarbazepine acetate

- i. Mechanism of action: Fast sodium channel blocker
- ii. Prodrug for eslicarbazepine, with active metabolites; *R*-licarbazepine 5%, oxcarbazepine 1%
- iii. Adjust dose if creatinine clearance (CrCl) is less than 50 mL/minute/1.73 m².

Phenytoin

- i. Mechanism of action: Fast sodium channel blocker
- ii. Pharmacokinetics: Enzyme inducer, nonlinear kinetics
- iii. Administration considerations
 - (a) Intravenous formulation: Very basic product. Phlebitis and extravasation are concerns; hypotension; maximal infusion rate of 50 mg/minute. Can prepare only in normal saline Solution
 - (b) Oral suspension: Must be shaken well; adheres to feeding tubes and is bound by enteral nutrition products
- iv. Dose-related adverse effects: Nystagmus, ataxia, drowsiness, cognitive impairment
- v. Non-dose-related adverse effects: Gingival hyperplasia, hirsutism, acne, rash, hepatotoxicity, coarsening of facial features

Fosphenytoin

- i. Mechanism of action: Prodrug for phenytoin; fast sodium channel blocker
- ii. Uses: Parenteral formulation for loading or maintenance dosing in place of phenytoin; status epilepticus
- iii. Pharmacokinetics: Enzyme inducer, nonlinear kinetics
- iv. Dosing: Phenytoin equivalents (PE) are used. Loading dose: 10–20 mg of phenytoin sodium equivalents (PE)/kg intravenous or intramuscular dosing is appropriate. Maintenance dosage: Begin with 4–6 mg PE/kg/day in divided doses after administration of the loading dose.
- v. Adverse effects: Hypotension, perianal itching, other adverse effects of phenytoin
- vi. Advantages over phenytoin
 - (a) Intramuscular or intravenous dosing
 - (b) Phlebitis is minimized.
 - (c) Infusion can be up to 150 mg PE per minute. In status epilepticus, infusion should be at 100–150 mg PE per minute. Maximum infusion rate is not to exceed 150 mg PE per minute.
 - (d) Can deliver in normal saline solution or D5W (5% dextrose [in water] injection)

Gabapentin

- i. Mechanism of action: Inhibition of $\alpha_2\delta$ subunit of voltage-dependent calcium channels
- ii. Pharmacokinetics: Not metabolized, eliminated renally; adjustments may be necessary for renal dysfunction and hemodialysis
- iii. Nonepileptic indication: Postherpetic neuralgia pain
- iv. Doses often exceed product information maximum of 3600 mg/day.
- v. Extended-release tablets 300 and 600 mg are available. Their indication is for postherpetic neuralgia, not epilepsy.
- vi. Gabapentin enacarbil extended-release tablets 300 and 600 mg are available. This agent is a prodrug for gabapentin and is indicated for postherpetic neuralgia and restless legs syndrome, not epilepsy.

Lacosamide

- i. Mechanism of action: Slow sodium channel blocker
- ii. Maximal dose is 300 mg/day with a CrCl of 30 mL/minute/1.73 m² or less or with mild to moderate hepatic impairment.
- iii. Adverse effects: PR interval prolongation or first-degree atrioventricular block; baseline and steady-state electrocardiogram (ECG) recommended in patients with known cardiac conduction problems, taking medications known to induce PR interval prolongation, or with severe cardiac disease
- iv. Controlled substance schedule V because of euphoric effects
- v. Parenteral formulation: Has an FDA indication only for replacement of oral formulation

Lamotrigine

- i. Mechanism of action: Decreases glutamate and aspartate release, delays repetitive firing of neurons, blocks fast sodium channels
- ii. Rash is a primary concern; lamotrigine must be titrated slowly to avoid a rash.
- iii. Valproic acid decreases lamotrigine metabolism (increases the serum concentration of lamotrigine); this interaction requires even slower titration and lower final doses.
- iv. Estrogen-containing oral contraceptives increase lamotrigine clearance, so twice the amount of lamotrigine may be necessary.
- v. Extended-release tablets (Lamictal XR) are available (25 mg, 50 mg, 100 mg, 200 mg, 250 mg, 300 mg).
- vi. Nonepileptic indications: Maintenance treatment of type I bipolar disorder

Levetiracetam (Keppra)

- i. Mechanism of action: May prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity
- ii. Pharmacokinetics: Not metabolized extensively; adjust dose in renal dysfunction; no drug interactions with other seizure medications
- iii. Parenteral use: Currently FDA indicated only for replacement of oral dosing; however, sometimes used for status epilepticus
- iv. Extended-release tablets (500 mg, 750 mg) are available for once-daily dosing.

Perampanel

- i. Mechanism of action: Noncompetitive antagonist of the inotropic α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptor
- ii. Pharmacokinetics: 95%–96% protein bound to albumin and α 1-acid glycoprotein; metabolized by CYP 3A4 and 3A5; 105-hour half-life
- iii. Adverse effects: Neuropsychiatric effects (irritability, aggression, anger, anxiety), dizziness, gait disturbance, weight gain
- iv. Perampanel is a schedule III controlled substance.

Phenobarbital (Luminal)

- i. Mechanism of action: Increases GABA-mediated chloride influx
- ii. Pharmacokinetics: Enzyme inducer
- iii. Adverse effects: Hyperactivity, cognitive impairment
- iv. Phenobarbital is a schedule IV controlled substance.
- v. Nonepileptic use: Anxiety

Primidone

- i. Mechanism of action: Increases GABA-mediated chloride influx
- ii. Metabolized to phenobarbital and phenylethylmalonamide
- iii. Primidone, phenobarbital, and phenylethylmalonamide all have antiepileptic action.
- iv. Pharmacokinetics: Enzyme inducer

Pregabalin (Lyrica)

- i. Mechanism of action: Inhibition of $\alpha 2\delta$ subunit of voltage-dependent calcium channels
- ii. Pharmacokinetics: Not metabolized, renally excreted; reduce dose in renal dysfunction
- iii. Adverse effects: Drowsiness, blurred vision, weight gain, edema, angioedema, creatine kinase elevations (three reports of rhabdomyolysis), rash
- iv. Schedule V controlled substance: Insomnia, nausea, headache, diarrhea reported after abrupt discontinuation
- v. Nonepileptic indications: Neuropathic pain associated with diabetic neuropathy, postherpetic neuralgia, and fibromyalgia

Rufinamide

- i. Mechanism of action: Fast sodium channel blocker
- ii. Pharmacokinetics: Absorption increased by food (should be administered with food); metabolized by hydrolysis rather than through CYP enzymes
- iii. Decreases concentrations of ethinyl estradiol and norethindrone
- iv. Has an FDA indication only for Lennox-Gastaut syndrome
- v. Slightly shortens the QT interval and therefore should not be used in patients with familial short QT syndrome

Tiagabine

- i. Mechanism of action: Blocks GABA reuptake in the presynaptic neuron
- ii. Associated with new-onset seizures and status epilepticus in patients without epilepsy

Topiramate (Topamax)

- i. Mechanism of action: Fast sodium channel blocker, enhances GABA activity and antagonizes AMPA/kainate activity, weak carbonic anhydrase inhibitor
- ii. Pharmacokinetics: Not extensively metabolized, eliminated in urine
- iii. Adverse effects: Drowsiness, paresthesias, psychomotor slowing (titrate slowly), weight loss, renal stones, acute-angle closure glaucoma, metabolic acidosis, and hyperthermia (associated with decreased perspiration, or oligohidrosis)
- iv. Nonepileptic indication: Prophylaxis of migraine headaches

Vigabatrin

- i. Mechanism of action: Irreversible inhibition of GABA transaminase
- ii. Pharmacokinetics: Induces CYP2C9; renal elimination
- iii. Adverse effects: Fatigue, somnolence, nystagmus, tremor, blurred vision, vision impairment, weight gain, arthralgia, abnormal coordination, and confusional state
- iv. Serious adverse effect: Vision loss; increased risk with higher total dose and duration; periodic vision testing necessary; restricted distribution program; only used for refractory complex partial seizures and infantile spasms

ANTI-EPILEPSY MEDICATION	PROTEIN BINDING ¹	HALF-LIFE ²	ACTIVE METABOLITE	MAJOR ORGAN OF ELIMINATION
<i>Brivaracetam</i>	Low	0		Liver
<i>Carbamazepine</i>	Moderate	6–15	CBZ-10,11-epoxide	Liver
<i>Eslicarbazepine acetate</i> ²	Low	8–24	<i>Eslicarbazepine</i> (S-licarbazepine)	Kidney
<i>Ethosuximide</i>	Low	25–26		Liver
<i>Felbamate</i>	Low	20–23		Kidney/Liver
<i>Fosphenytoin</i> ³	High	12–60	<i>Phenytoin</i>	Liver
<i>Gabapentin</i>	Low	5–9		Kidney
<i>Lacosamide</i>	Low	13		Various
<i>Lamotrigine</i>	Low	25–32		Liver
<i>Levetiracetam</i>	Low	6–8		Hydrolysis
<i>Oxcarbazepine</i> ³	Low	5–13	Monohydroxy metabolite (MHD)	Liver
<i>Perampanel</i>	High	105		Liver
<i>Phenobarbital</i>	Low	72–124		Liver
<i>Phenytoin</i>	High	12–60		Liver
<i>Primidone</i>	High	72–124	<i>Phenobarbital</i> , PEMA	Liver
<i>Pregabalin</i>	Low	5–6.5		Kidney
<i>Rufinamide</i>	Low	6–10		Liver
<i>Tiagabine</i>	High	7–9		Liver
<i>Topiramate</i>	Low	21		Various
<i>Valproic acid</i> (<i>Divalproex</i>)	Moderate/High	6–18	Various	Liver
<i>Vigabatrin</i>	Low	7.5		Kidney
<i>Zonisamide</i>	Low	63		Liver

Seizure Medication	Other Drug	Effect on the Seizure Medication	Mechanism
Carbamazepine	Cimetidine	Increased serum concentration	Inhibition of carbamazepine metabolism
	Diltiazem	Increased serum concentration	Inhibition of carbamazepine metabolism
	Erythromycin	Increased serum concentration	Inhibition of carbamazepine metabolism
	Isoniazid	Increased serum concentration	Inhibition of carbamazepine metabolism
	Nefazodone	Increased serum concentration	Inhibition of carbamazepine metabolism
	Theophylline	Decreased serum concentration	Increased carbamazepine metabolism
	Troleandomycin	Increased serum concentration	Inhibition of carbamazepine metabolism
	Verapamil	Increased serum concentration	Inhibition of carbamazepine metabolism
Clobazam	Fluconazole	Increased serum concentration	Inhibitor of CYP2C19
	Fluvoxamine	Increased serum concentration	Inhibitor of CYP2C19
	Omeprazole	Increased serum concentration	Inhibitor of CYP2C19
	Ticlopidine	Increased serum concentration	Inhibitor of CYP2C19
Gabapentin	Antacids	Decreased serum concentration	Decreased bioavailability
Lamotrigine	Estrogen-containing contraceptives	Decreased serum concentration	Possibly induction of glucuronidation of lamotrigine
	Rifampin	Decreased serum concentration	Possibly induction of glucuronidation of lamotrigine
Perampanel	Ethanol and other CNS depressants	CNS additive or supra-additive effects	Additive CNS depression
	Rifampin	Decreased serum concentration	Increased metabolism
	St. John's wort	Decreased serum concentration	Increased metabolism
Phenobarbital; primidone	Ethanol	Acute ethanol ingestion may cause CNS additive effects and respiratory depression; chronic ethanol ingestion may result in variable effects	Additive CNS depression and decreased barbiturate metabolism with acute ethanol ingestion

Seizure Medication	Other Drug	Effect on the Seizure Medication	Mechanism
Phenytoin	Anticoagulants, oral	May increase phenytoin serum concentration; decreased or increased anticoagulant effects	Complex mechanism
	Antineoplastics (bleomycin, cisplatin, vinblastine, methotrexate, carmustine)	Decreased pharmacologic effect	Unknown, possible decreased absorption caused by antineoplastic mucosal damage
	Chloramphenicol	Increased phenytoin serum concentration; decreased or increased chloramphenicol serum concentration	Inhibition of phenytoin metabolism; effect on chloramphenicol unknown
	Cimetidine	Increased serum concentration	Inhibition of phenytoin metabolism
	Diazoxide	Decreased pharmacologic effect; decreased serum concentration	Increased phenytoin metabolism
	Diltiazem	Increased serum concentration	Inhibition of phenytoin metabolism
	Disulfiram	Increased serum concentration	Inhibition of phenytoin metabolism
	Folic acid	Decreased serum concentration	Complex mechanism
	Isoniazid	Increased serum concentration	Inhibition of phenytoin metabolism
	Phenylbutazone	Increased serum concentration	Inhibition of phenytoin metabolism; plasma protein displacement
	Rifampin	Decreased serum concentration	Increased phenytoin metabolism
	Sulfonamides	Increased serum concentration	Inhibition of phenytoin metabolism
Topiramate	Trimethoprim	Increased serum concentration	Inhibition of phenytoin metabolism
Valproic acid	Hydrochlorothiazide	Increased serum concentration	Unknown
	Estrogen-containing oral contraceptives	Decreased serum concentration	Possibly induction of glucuronidation of lamotrigine
	Meropenem	Decreased serum concentration	Increased valproic acid metabolism
	Rifampin	Decreased serum concentration	Increased valproic acid metabolism
	Salicylates	Increased pharmacologic effect	Plasma protein displacement; increased free valproic concentration

Status epilepticus

a. Treatment principles

- i. Ascertain ABCs (airway, breathing, and circulation).
- ii. Laboratory values (fingerstick blood glucose, CBC, basic metabolic panel, calcium, magnesium and seizure medication serum concentrations, if applicable) are sent to determine any reversible causes of status epilepticus.
- iii. Give an emergency medication to stop the seizure immediately.
- iv. Follow with an urgent medication to prevent the recurrence of seizures.
- v. In general, all drugs for status epilepticus should be given parenterally.
- vi. Neuromuscular-blocking drugs do not stop seizures; they stop only the muscular response to the brain's electrical activity.

b. Emergency medications

i. Lorazepam: Drug of choice

- (a) Rapid onset (2–3 minutes)
- (b) Dosage 0.1 mg/kg (up to 4 mg/dose) at rate of up to 2 mg/minute; may repeat every 5–10 minutes

ii. Diazepam

- (a) Rapid onset, short duration
- (b) Dosage 0.15 mg/kg (up to 10 mg/dose) at rate of up to 5 mg/minute. May repeat every 5 minutes
- (c) Rectal gel formulation can be given in the absence of intravenous access.

iii. Midazolam: Preferred for intramuscular administration

- (a) Rapid onset, short duration
- (b) Dosage 0.2 mg/kg (up to 10 mg/dose). Can be given intramuscularly, intranasally, or buccally

Urgent medications

- i. Phenytoin: Dosage 20 mg/kg; administration rate less than 50 mg/minute
 - ii. Fosphenytoin: Administration rate less than 150 mg of phenytoin equivalent per minute
 - iii. Phenobarbital: Dosage 20 mg/kg at 50–100 mg/minute
 - iv. Valproic acid: Dosage 20–40 mg/kg at up to 6 mg/kg/minute; does not have FDA-labeled approval for status epilepticus
 - v. Levetiracetam: 20–30 mg/kg over 15 minutes; does not have FDA-labeled approval for status epilepticus
 - vi. Lacosamide: 200- to 400-mg bolus over 15 minutes; does not have FDA-labeled approval for status epilepticus
- d. Refractory status epilepticus medications
- i. Pentobarbital: Load 5–15 mg/kg up to 50 mg/minute; follow with a 0.5- to 5-mg/kg/hour infusion.
 - (a) May have severe hypotension, necessitating treatment with vasopressors; should have continuous blood pressure measurement
 - (b) Must be on ventilator
 - ii. Thiopental: Load 2–7 mg/kg up to 50 mg/minute; follow with a 0.5- to 5-mg/kg/hour infusion.
 - (a) May have severe hypotension, respiratory depression, cardiac depression
 - (b) Must be on ventilator
 - iii. Midazolam: Load 0.2-mg/kg infused up to 2 mg/minute; follow with a 0.05- to 2-mg/kg/hour infusion.
 - (a) May have hypotension, respiratory depression
 - (b) May have tachyphylaxis
 - iv. Propofol: Load a 1- to 2-mg/kg intravenous bolus for 30–60 seconds; follow with a 20- to 200-mcg/kg/minute infusion.
 - (a) Significant source of lipids
 - (b) Some reports of seizure exacerbation with propofol
 - (c) Must be on ventilator

**Stage 1:
First 30
minutes**



**Stage 2:
30-120
minutes**



**Stage 3:
>120
minutes**



**After 24
hours**

Stage 1 - Early Status Epilepticus

Treat with benzodiazepines - for instance IV lorazepam, buccal midazolam, IV or rectal diazepam



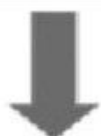
Stage 2 - Established Status Epilepticus

Treat with IV antiepileptic drugs – for instance, phenytoin, phenobarbital or valproate



Stage 3 - Refractory Status Epilepticus

Treat with general anaesthesia – for instance, propofol, midazolam, or thiopental/pentobarbital



Super-refractory Status Epilepticus: Status epilepticus which has continued or recurred despite therapy with general anaesthesia for 24 hours or more

Women's health

i. During their reproductive years, women with epilepsy should:

(a) Take the best drug for their seizure type. Women of childbearing age should not be given valproic acid unless other therapies have failed.

(b) Be treated with monotherapy, if possible

(c) Discuss the possible decrease in hormonal contraceptive effectiveness if taking enzyme inducing medications

(d) Use folic acid supplementation with no less than 0.4 mg/day

ii. Three practice guidelines exist regarding epilepsy during pregnancy (relevant material excerpted in the text that follows).

(a) Avoiding valproic acid monotherapy or polytherapy during the first trimester of pregnancy should be considered to decrease the risk of major congenital malformations, particularly neural tube defects, facial clefts, hypospadias, and poor cognitive outcomes. Valproic acid use has now been associated with lower IQ scores at ages 3 and 4½