Epilepsy Medications: The Basics

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Objectives

1. Discuss general principles of using medications to treat epilepsy
2. Discuss general principles of starting and stopping seizure medications
3. Describe how medication metabolism can effect their impact on seizures and the body
4. Discuss some aspects of commonly used seizure medications

What is a seizure

- A seizure is the result of an abnormal firing of neurons in the brain leading to excessive excitatory currents
  - This usually affect how a person appears or acts
- Abnormal excitatory firing is either the result of excessive excitatory currents, or a lack of appropriate inhibitory currents

Epilepsy vs. Seizures

. Definition of Epilepsy (ILAE New Definition: 2014)

- **A person is considered to have epilepsy if they meet any of the following conditions.**
- **At least two unprovoked (or reflex) seizures occurring greater than 24 hours apart.**
- **One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.**
- **Diagnosis of an epilepsy syndrome**
  - **Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years**

Seizure Medications

- Seizure medications exist that can either stop or control seizures for most children with epilepsy
- The first goal for children with epilepsy is to find the right medication for each individual patient
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Seizure Medications

- Most children with epilepsy are treated with medication
- Doctors will not usually prescribe medications until a child has had more than one seizure and has been diagnosed with epilepsy
- When a child is taking medication for epilepsy, the goals are for a child to:
  - Have no seizures, or few as possible
  - Have little or no problems with side effects
  - Take one medication (monotherapy), or as few as possible
  - Take the lowest dosage possible

Seizure Medications

- Many medications are available for children with epilepsy
- Most are taken by mouth, and come in tablets, capsules, sprinkles or syrup
- In choosing which medication is best for a child, your doctor will consider
  - What types of seizures is your child having
  - What other medications your child is taking
  - What are the side effects of each drug, and how those side effects might impact your child's quality of life

Seizure Medications

- As children grow up, the right dosage for their weight can change
- Every child reacts differently to various medications

Seizure Medications

- For some children, generic seizure medications can be less expensive than brand name medications
- Although brand name and generic medications may be nearly the same, some minor differences may impact a child's response to medication, and you should always ask your doctor before switching from a brand name to generic medication

Seizure Medications

- Most children are able to control their seizures with medication
- Medications often work so well that parents may be tempted to take their child off medication or reduce the dosage
  - Doing so without a doctor's recommendation can cause a serious increase in seizures, or for seizures to become prolonged
- In most cases, children need to stay on their medication for a few years before trying to stop
- Taking medication consistently is important for children with epilepsy
- Missed or incorrect medication dosages can greatly increase a child's chances of having seizures.
- As children grow, they should begin to take some responsibility for remembering to take their medication

Stopping Medication

- While it's very important that children with epilepsy stay on their medications for as long as their doctors recommend, after a few years of seizure freedom, some children are able to stop taking them.
- Studies show that 65-70% of children who have been on medication for a few years without seizures can stop taking it gradually without seizures starting again
- Medicine should always be stopped slowly, under careful supervision from a doctor.
- Stopping medication all at once can lead to seizures and even prolonged seizures or status epilepticus

Why is it hard for children to take medications

- For some children, taking seizure medications may feel embarrassing or disrupt other, more pleasant activities
- Medication schedules may be too complicated
- Young children may require adaptations in giving their medicine to ensure they take it all
  - Crushing pills and putting the powder in favorite foods, or giving a small reward
- Some children may refuse to take pills. Some children see medication as a visible reminder that they have seizures, or that something is 'different'

How can we make it easier for a child to take their seizure medication?

- Talk to your child about why the medications are important
- Teach children how to take the medicine
  - Children love imitation
  - Warning: Keep all medications out of the reach of young children
- Find a form of seizure medication that the child can swallow
  - As if it comes in chewable, sprinkle or liquid form
  - Have the child practice swallowing tablets or capsules by learning to swallow a whole M&M, Reece Piece, chewed up cookie
  - Try placing a pill on the back of the tongue and take with water or juice from a glass
  - Medication can also be mixed with a food or taken just when a mouthful of food has been chewed and swallowed

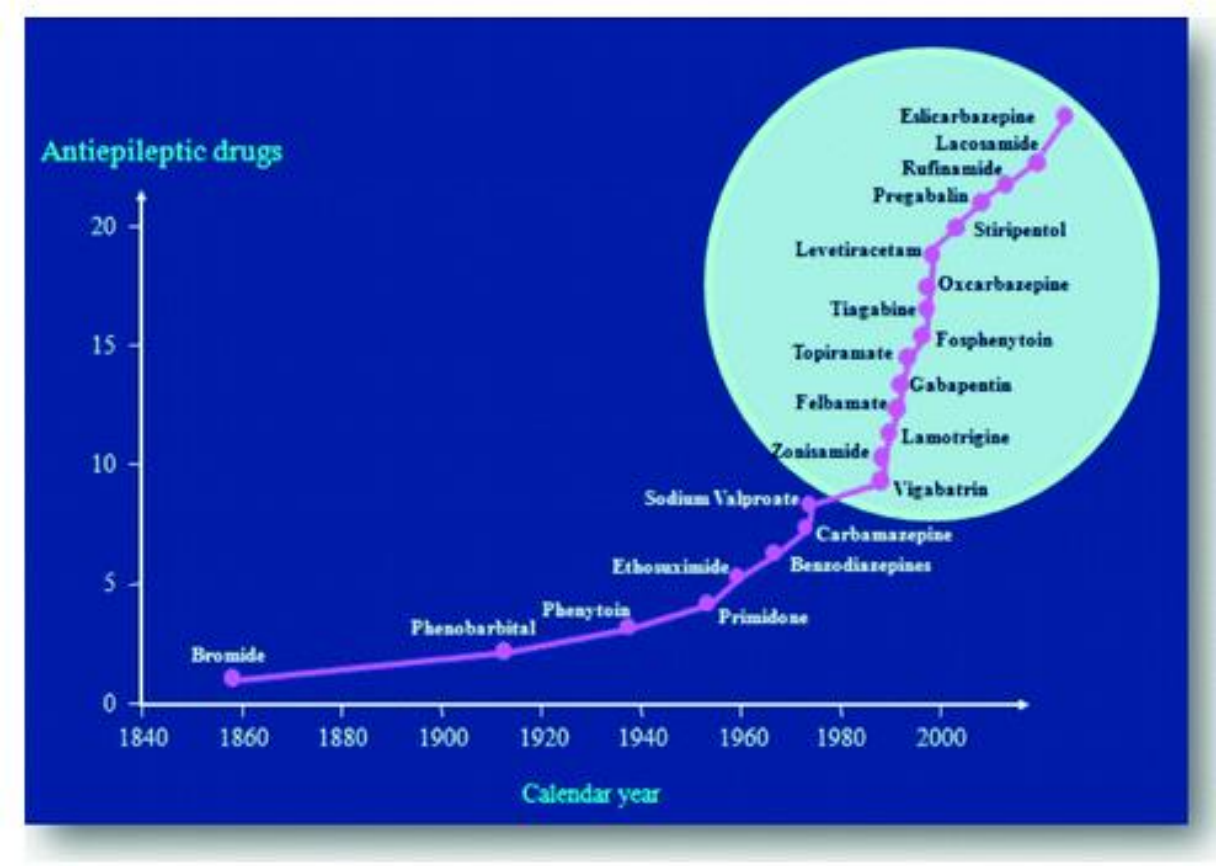
How can we make it easier for a child to take their seizure medication?

- Ask your doctor or nurse what to do if your child
  - Misses a dose of medicine
  - Throws up just after taking a medicine
  - Is sick and can't swallow or hold down foods, fluids, or pills
  - Needs to take another medication, to make sure it can be taken with the epilepsy medication

How can I make it easier for my child to take medicine when not at home

- Work with your child to organize a pillbox and teach him or her how to use it.
  - Always make sure there is an adult overseeing the child's use of the pillbox
- Make sure extra doses are sent with the child if they're going to be away for more than one day
- Ask your pharmacy to give pills in a blisterpak or bubblepack

Emergence of Seizure Medications



Mechanisms of Action

Molecular target	AEDs that act on target
Voltage-gated ion channels	
Voltage-gated sodium channels	Phenytoin, fosphenytoin,[a] carbamazepine, oxcarbazepine,[b] eslicarbazepine acetate,[c] lamotrigine, and lacosamide; possibly, topiramate, zonisamide, and rufinamide
Voltage-gated calcium channels	Ethosuximide
Voltage-gated potassium channels	Ezogabine
GABA inhibition	
$GABA_A$ receptors	Phenobarbital, primidone, and benzodiazepines including diazepam, lorazepam, and clonazepam; possibly, topiramate and felbamate
GAT-1 GABA transporter	Tiagabine
GABA transaminase	Vigabatrin
Synaptic release machinery	
SV2A	Levetiracetam
α2δ	Gabapentin, gabapentin enacarbil,[d] and pregabalin
Ionotropic glutamate receptors	
AMPA receptor	Perampanel
Mixed/unknown	Valproate, felbamate, topiramate, zonisamide, rufinamide, and adrenocorticotropin

[a]Fosphenytoin is a prodrug for phenytoin.

[b]Oxcarbazepine serves largely as a prodrug for licarbazepine, mainly S-licarbazepine.

[c]Eslicarbazepine acetate is a prodrug for S-licarbazepine.

[d]Gabapentin enacarbil is a prodrug for gabapentin.

Spectrum of Anti-Epileptic Medication Activity

Table 15.4 Grouping of AEDs according to their spectrum of activity

Broad spectrum AEDs	Narrow spectrum AEDs
Valproate	Phenytoin*
Felbamate	Ezogabine*
Phenobarbital#	Perampanel*
Lamotrigine	Lacosamide*
Topiramate	Carbamazepine~
Zonisamide	Gabapentin~
Levetiracetam	Pregabalin~
Benzodiazepines	Tiagabine~
Primidone	Oxcarbazepine~
	Vigabatrin@
	Rufinamide
	Ethosuximide

Epilepsy Syndromes and Seizure Medications

Children with partial-onset seizures	1	0	19	**Level A: OXC** Level B: None Level C: CBZ, PHB, PHT, TPM, VPA, VGB Level D: CLB, CZP, LTG, ZNS
Children with generalized-onset tonic–clonic seizures	0	0	14	**Level A: None** Level B: None Level C: CBZ, PB, PHT, TPM, VPA Level D: OXC
Children with absence seizures	1	0	7	**Level A: ESM, VPA** Level B: None Level C: LTG Level D: None
Benign epilepsy with centrotemporal spikes (BECTS)	0	0	3	**Level A: None** Level B: None Level C: CBZ, VPA Level D: GBP, LEV, OXC, STM
Juvenile myoclonic epilepsy (JME)	0	0	1	**Level A: None** Level B: None Level C: None Level D: TPM, VPA

Indications for Seizure Types

Table 15.8 Indication

Indication	Try	Avoid
Seizure type		
Focal or secondary generalized	LTG, LEV, OXC, LCM, TPM > CBZ, > VPA, ESL, PHT	
Primary Generalized (GTC)	VPA, LEV, LTG, TPM, ZNS	
Primary Generalized (Absence)	ESX, VPA > LTG	PHT, CBZ, GBP, TGB, VGB
Primary Generalized (Myoclonic)	LEV, VPA, CLZ	PHT, CBZ, GBP, TGB, VGB, PGB
Rolandic (centrotemporal)	LEV, OXC	
Other factors		
Young women	LTG, LEV, LCM	VPA > > CBZ, PHT
Depression	LTG	PHT, PHB, PRM,
Labile, impulsive	VPA, CBZ, LTG, OXC, TPM	LEV
Liver disease	LEV, LTG, PGB	VPA, PHT, CBZ
Obesity	TPM, ZNS	VPA, GPN, PGB
Pain	GBP, PGB, CBZ, OXC	
Headache	TPM, VPA, GBP, PGB	
Type A personality (baseline irritability)		LEV
Polytherapy (non AEDs)	LEV, PGB, GBP	Enzyme Inducers
Asian (Han Chinese or Taiwanese)		CBZ, OXC (if have to use **check HLA-b 1502**)

Pharmacokinetics

Drug	Time to peak concentration (hours)	Time to steady state (days)	Half-life monotherapy, adults (hours)	Half-life AED + enzyme inducers (hours)	Half-life monotherapy, children (hours)	Half-life monotherapy, elderly (hours)	Serum protein binding (%)	Reference range (mg/L)	Reference range (μmol/L)	Active metabolite
Carbamazepine	4–8[a]	2–4	8–20[b]	5–12[b]	10–13[b]	30–50[b]	75	4–12	17–51	Carbamazepine-epoxide
Clobazam	1–3	2–7	10–30	<30	~16	30–48	85	0.03–0.3	0.1–1.0	
N-Desmethyl clobazam	——	7–10	36–46	——	——	——	——	0.02–0.07	1.0–10.5	*N*-Desmethyl clobazam
Clonazepam	1–4	2–10	17–56	12–46	22–33	——	86	0.02–0.07	0.60–0.22	
Eslicarbazepine acetate[c]	2–3	4–5	20–24	13–20	——	——	30	3–35	12–139	Eslicarbazepine also known as 10-hydroxycarbazepine
Ethosuximide	1–4	8–12	40–60	20–40	30–40	——	0	40–100	283–708	
Felbamate	2–6	3–5	16–22	10–18	——	——	25	30–60	126–252	
Gabapentin	2–3	1–2	5–9[b]	5–9[b]	——	——	0	2–20	12–117	
Lacosamide	1–2	2–3	12–16	——	——	——	<30	10–20	40–80	
Lamotrigine	1–3	3–7	15–35 (+valproic acid = 30–90)	8–20 (+valproic acid = 15–35)	——	——	55	3–15	10–59	
Levetiracetam	1–2	1–2	6–8	5–8	5–6	10–11	0	12–46	70–270	
Oxcarbazepine[c]	4–6	2–3	8–15	7–12	——	——	40	3–35	12–139	10-Hydroxycarbazepine
Perampanel	0.25–2	14	52–129	25	——	——	95	0.05–0.4	0.14–1.14	
Phenobarbital	2–4	15–29	70–140	50–160	63–69	——	55	10–40	43–172	
Phenytoin	1–12	6–21	30–100[b]	30–100[b]	30–100[b]	——	90	10–20	40–79	
Pregabalin	1–2	1–2	5–7	5–7	——	——	0	2–8	13–50	
Primidone	2–6	2–4	7–22	3–12	5–11	——	10	5–10	23–46	Phenobarbital
Retigabine	0.5–2	1–2	7–11	——	——	9–14	80	NE	NE	
Rufinamide	3–6	1–2	6–10	4–7	——	——	35	30–40	126–168	
Stiripentol	1–2	7	4–13[b]	——	——	——	99	4–22	17–94	
Tiagabine	0.5–2	1–2	5–9	2–4	——	——	96	0.02–0.2	0.05–0.53[e]	
Topiramate	2–4	4–5	20–30	10–15	13–20	——	15	5–20	15–59	
Valproic acid	3–7[d]	2–4	12–16[b]	5–9[b]	8–13[b]	——	90[d]	50–100	346–693	
Vigabatrin	1–2	1–2	5–8	5–8	——	——	0	2–36	6–279	
Zonisamide	2–5	10–15	50–70	25–35	——	——	40	10–40	47–188	

[a]Conventional tablets.

[b]Concentration dependent.

[c]Values refer to pharmacologically active metabolite eslicarbazepine/10-hydroxycarbazepine.

[d]Enteric-coated tablets.

Pharmacokinetics

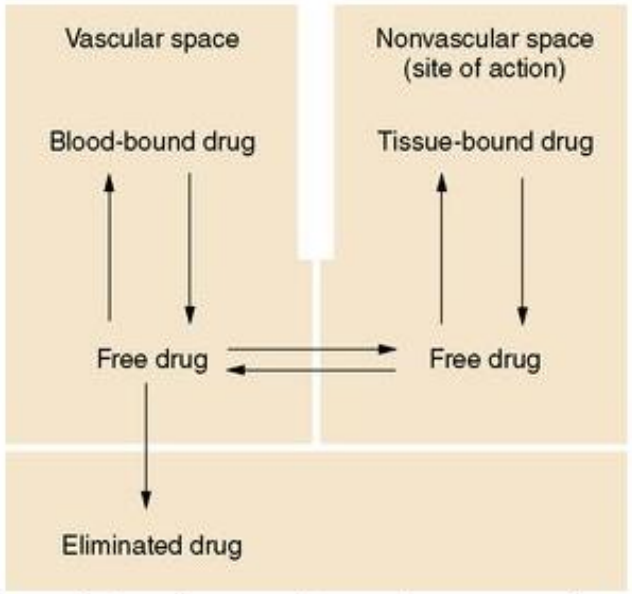


Fig. 59-1 Relationship of unbound drug in vascular and nonvascular compartments.

Metabolism and Clearance

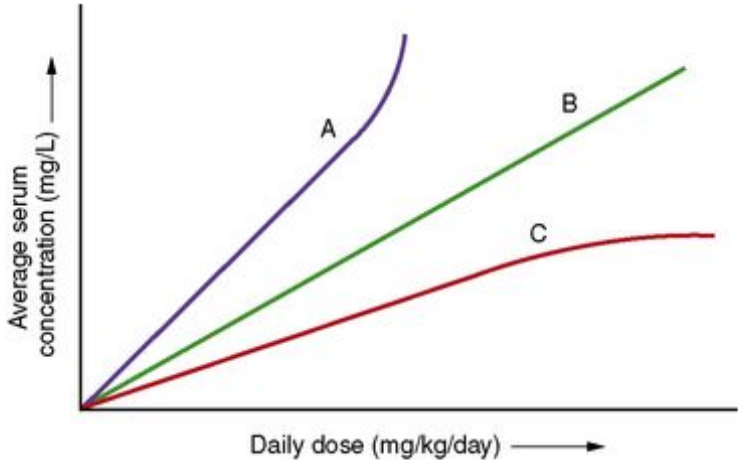


Fig. 59-2 Effect of dose on elimination kinetics.
Curve A plots nonlinear pharmacokinetics (of the Michaelis–Menten type) in which clearance decreases with increasing dose, as with phenytoin. Curve B plots linear pharmacokinetics, in which clearance remains the same with increasing dose, as with phenobarbital, felbamate, vigabatrin, tiagabine, topiramate, and valproic acid (unbound drug). Curve C plots nonlinear pharmacokinetics in which clearance increases with dose, as with valproic acid (total), carbamazepine, and lamotrigine.

Metabolism and Clearance

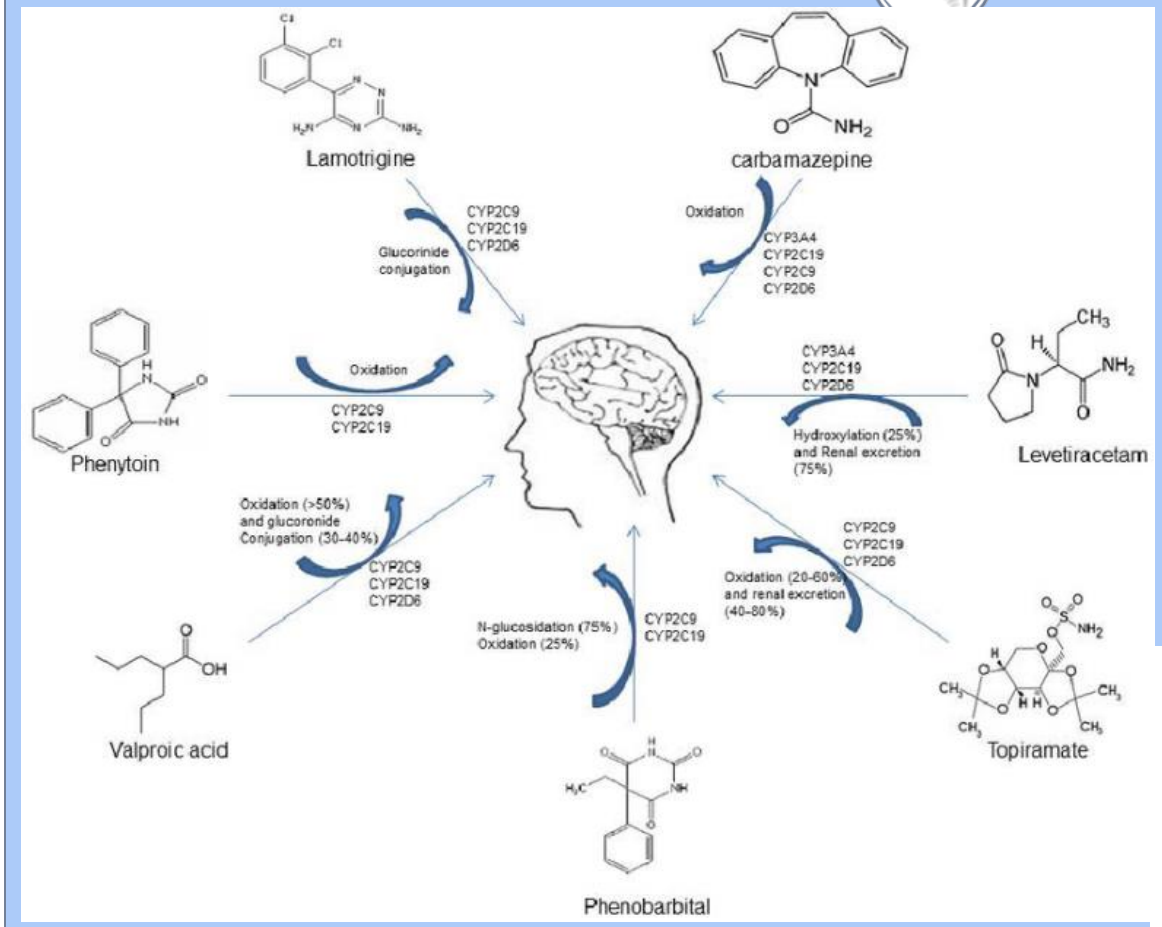


Table 15.10 P450 enzyme modulation of several AEDs

Enzyme inducing AEDs (strong)	Enzyme inhibiting AEDs (strong)
Phenobarbital	Valproic acid
Primidone	Topiramate (weak)
Phenytoin	
Carbamazepine	
Oxcarbazepine (doses > 900 mg)	
Lamotrigine (weak)	

Idiosyncratic Reactions

- Unpredictable, dose-independent, host-dependent reactions that are not associated with the known pharmacological effects of the drug
- May manifest as allergic dermatitis, rash, erythema multiforme, Stevens-Johnson syndrome, lupus-like rash, aplastic anemia, dyskinesia

Common Seizure Medications

Carbamazepine

- Sodium channel inhibitor
- Relative bioavailability similar four all formulations (i.e., suspension, chewable tablet, ER, regular Tablet)
- Rate of absorption faster for tablets than suspension
  - Occasionally, concentration-dependent side effects
- Active metabolite: carbamazepine-10,11-epoxide
- Autoinduction: dosage increases produce a less than proportional increase in steady-state toal concentration
  - Some children require 3-4 doses a day to maintain targeted plasma concentration
  - Sustained release preparations overcome this
- Side effects: Dizziness, nausea, low sodium

Oxcarbazepine

- Sodium channel inhibitor
- Prodrug converted to active compound: 10,11-dihydro-10-hydroxy-carbamazepine
- Co-administration with food leads to an increase in bioavailability and max plasma concentrations
- Not metabolized to the active epoxide metabolite, which causes side effects with carbamazepine

Eslicarbazepine

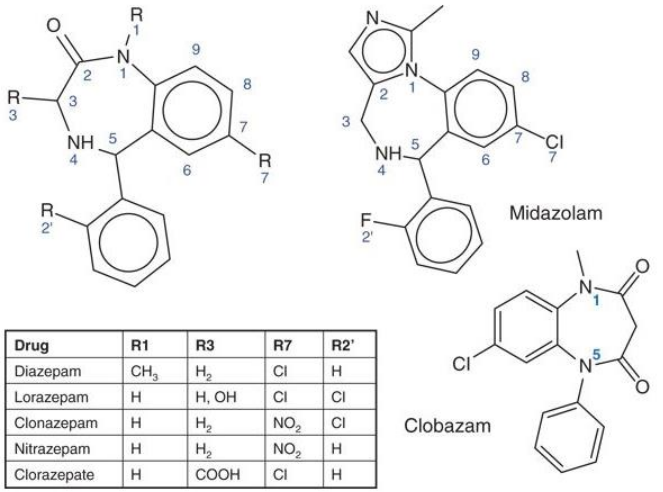
- Voltage-gated calcium channel blocker, recently FDA approved
- Chemical structure similar to oxcarbazepine/carbamazepine
- Does not produce an epoxide metabolite or exhibit autoinduction
- Suspension and scored tablets – 200 mg, 400 mg, 600 mg, 800 mg
- Clears faster in young children compared to adults

Lacosamide

- Sodium channel inhibitor
- Completely and rapidly absorbed with bioavailability of 100 percent
- Follows linear pharmacokinetics and Cmax is between 1-4 hours after oral dose

Clobazam

- Benzodiazepine – GABA agonist
- Widely used benzodiazepine for the long term treatment of epilepsy b/c of low tendency t produce sedation
- Effective for all seizure types
  - Significant drops in atonic seizures in patients with Lennox Gastaut syndrome
  - Suppresses spike-wave activity in electrical status epilepticus in sleep
- Side effects
  - Drowsiness, sedation



Drug	R1	R3	R7	R2'
Diazepam	CH_3	H_2	Cl	H
Lorazepam	H	H, OH	Cl	Cl
Clonazepam	H	H_2	NO_2	Cl
Nitrazepam	H	H_2	NO_2	H
Clorazepate	H	COOH	Cl	H

Ethosuximide

- Used for the treatment of absence seizures
- 250-mg capsules or 250 mg / 5 mL syrup
- Mechanism: reduces low-threshold T-Type calcium currents in thalamic neurons
- Largely metabolized by the liver
- Maintenance dosage: 15-40 mg/kg/day
- Side effects: nausea, abdominal comfort, vomiting, diarrhea

Felbamate

- Mechanism: NMDA antagonist; also acts on sodium and calcium channels
- FDA approved for patients with partial seizures, with or without generalization, and adjunctive therapy for patients with Lennox Gastaut Syndrome
- Dosages: 30 to 45 mg/kg/day
- Side Effects
  - Common: nausea, vomiting, headache, anoresxia, insomnia
  - Serious: aplastic anemia, hepatotoxicity

Lamotrigine

- Primary mechanism: sodium channel inhibitor
  - Also affects high voltage activated calcium channels and N- and P/Q-type calcium channels
- Good for multiple seizures types
  - Generalized seizures, focal seizures, absence seizures
- Metabolized primarily by the liver
- Drugs that inhibit UGT, such as valproic acid, decrease lamotrigine levels and increase serum concentrations
- Known mood stabilizer
- Most significant side effect: Rash, Steven-Johnson Syndrome

Levetiracetam

- Inhibitor to synaptic vesicle protein 2A (SV2A)
  - Component to secretory vesicle membranes; shown to mediate calcium-dependent vesicular neurotransmitter release
- Primarily renally excreted as unchanged drug, representing 2/3 of administered dose
- Effective for multiple seizure types
- Side effects: Agitation

Perampanel

- Mechanism: selective non-competitive AMPA receptor antagonist
- Effective for partial-onset seizures and primary generalized tonic-clonic seizures
- Metabolized by the lier: CYP3A4
- Dosages: 4-12 mg daily

Table 59.1 Incidence of Common Side Effects (>5% of Patients) During Adjunctive Perampanel Treatment: Pooled Analysis

		Perampanel treatment groups			
Adverse event, *n* (%)	Placebo (*n* = 442)	2 mg (*n* = 180)	4 mg (*n* = 172)	8 mg (*n* = 431)	12 mg (*n* = 255)
Any treatment-emergent adverse event	294 (66.5)	111 (61.7)	111 (64.5)	350 (81.2)	227 (89.0)
Dizziness	40 (9.0)	18 (10.0)	28 (16.3)	137 (31.8)	109 (42.7)
Somnolence	32 (7.2)	22 (12.2)	16 (9.3)	67 (15.5)	45 (17.6)
Headache	50 (11.3)	16 (8.9)	19 (11.0)	49 (11.4)	34 (13.3)
Fatigue	21 (4.8)	8 (4.4)	13 (7.6)	36 (8.4)	31 (12.2)
Irritability	13 (2.9)	7 (3.9)	7 (4.1)	29 (6.7)	30 (11.8)
Nausea	20 (4.5)	4 (2.2)	5 (2.9)	25 (5.8)	20 (7.8)
Fall	15 (3.4)	2 (1.1)	3 (1.7)	22 (5.1)	26 (10.2)
Nasopharyngitis	18 (4.1)	7 (3.9)	9 (5.2)	23 (5.3)	11 (4.3)
Upper respiratory tract infection	12 (2.7)	11 (6.1)	6 (3.5)	14 (3.2)	10 (3.9)
Ataxia	0 (0.0)	0 (0.0)	1 (0.6)	14 (3.2)	21 (8.2)
Balance disorder	2 (0.5)	0 (0.0)	0 (0.0)	22 (5.1)	8 (3.1)

Data derived from Steinhoff BJ, Ben-Menachem E, Ryvlin P, et al. Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: a pooled analysis of three phase III studies [published online ahead of print May 10, 2013]. *Epilepsia*. 2013;54(8):1481–1489.

Phenobaarbital

- Favorable enhancement of GABA inhibition
- Historically a favored drug in neonatal seizures
- Effective for every seizure type, except absence seizures
- Eliminated by liver and kidneys
- Dosage: 3-5 mg/kg/day
- Side effects: Sedation, ataxia, rarely dyskinesias

Rufinamide

- Prolongs inactivation of voltage-dependent sodium channels
- FDA Approved as an adjunctive treatment for Lennox Gastaut Syndrome
  - Tonic and tonic-atonic seizures
- Dosage: up to 3200 mg daily
- Side effects: headache, dizziness, fatigue, somnolence, nausea

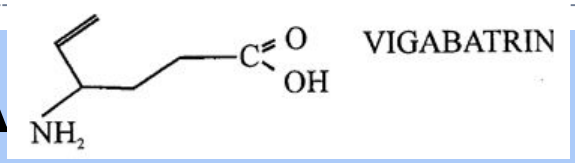
Topiramate

- Approved for partial onset or generalized tonic-clonic seizures
- Acts at various receptor sites
  - AMPA antagonist, GABA-A agonist
  - Carbonic anhydrase inhibition
- Eliminated primarily by renal excretion
- Known side effects: Psychomotor slowing, kidney stones, impaired sweating, appetite suppression

Valproic Acid

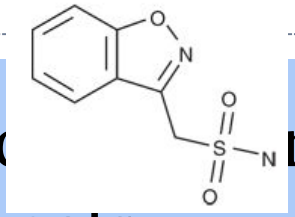
- Effective against many seizure types
- Multiple mechanisms
  - GABA agonist, Sodium channel inhibitor
- Side effects: Weight gain, Hair loss, thrombocytopenia, menstrual irregularities,

Vigabatrin



- Mechanism: Specific inhibitor of GA
- 500 mg tablets or 500 mg powder packets
- Largely used for the treatment of infantile spasms, especially in children with Tuberous Sclerosis Complex Disorder
- Dosage: Frequently titrated up to 100 to 150 mg/day
- Common Side effects: fatigue, somnolence, dizziness, nystagmus
- Serious adverse effects: peripheral visual field deficits

Zonisamide



- Mechanism Blockage of T-Type cal nnels and inhibition of slow sodium channels
  - Some activity as a carbonic anhydrase inhibitor
- Metabolism: Liver, primarily CYP3A4
- Broad spectrum – good for multiple seizure types

Table 66.4 Most Frequently Reported Adverse Effects in Clinical Trials

Adverse event	Percent reporting range
Fatigue	3.3%–22.5%
Ataxia	3.3%–11.3%
Nausea/vomiting	4.2%–15%
Headache	5%–15.9%
Somnolence	5.2%–18.3%
Rhinitis	5.2%–14.4%
Confusion	5.6%–10.6%
Anorexia	6.7%–15%
Dizziness	6.9%–16.9%
Nervousness	8.8%–9.9%
Thinking abnormal	9.7%–11.3%

Questions/Discussion