สมาคมโรคลมชักแห่งประเทศไทย
Epilepsy Society of Thailand
ขอเชิญแพทย์และผู้สนใจเข้าร่วมการประชุมวิชาการออนไลน์

ครั้งที่ 11

Epilepsy Course for Neurology and Pediatrics Neurology Residents

PHARMACOLOGY OF ANTIEPILEPTIC DRUGS

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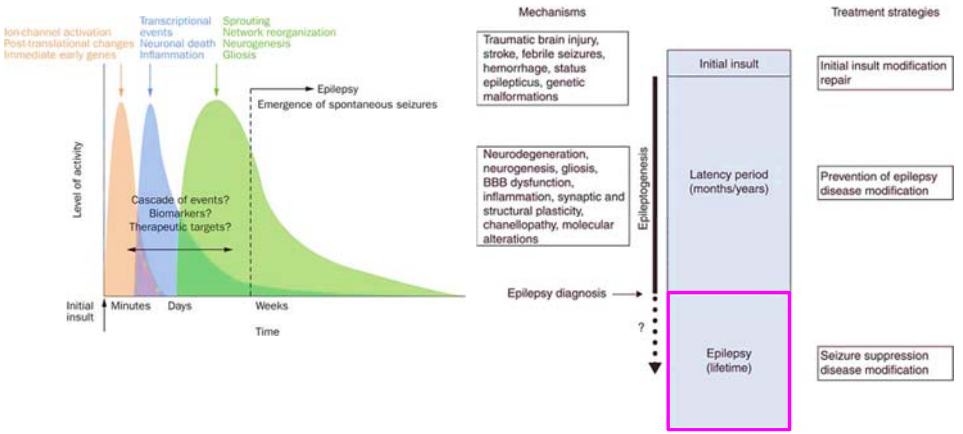
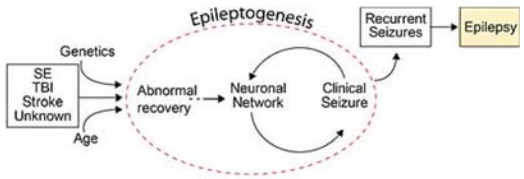
Epileptogenesis, modulating factors, and treatment approaches

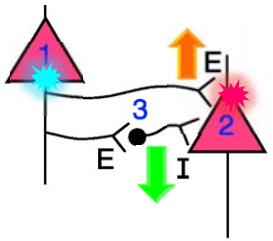


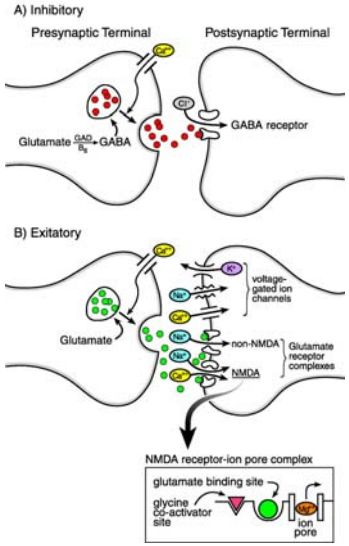
Rakhade SN, Jensen FE. Nat Rev Neurol. 2009 Jul;5(7):380-91. doi: 10.1038/nrneurol.2009.80.

Lukasiuk K. Epileptogenesis. Encyclopedia of the Neurological Sciences, 2014. Pages 196-9. https://doi.org/10.1016/B978-0-12-385157-4.00297-9.



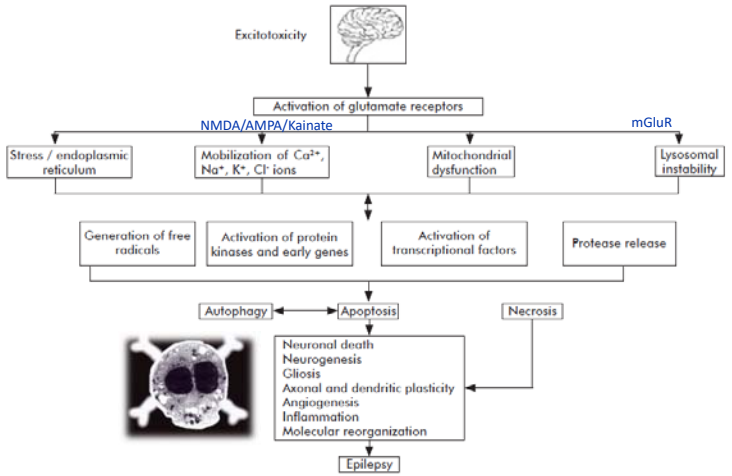
Neuronal network synaptic transmission





Stafstrom CE. Pediatr Rev 1998;19:342-51.

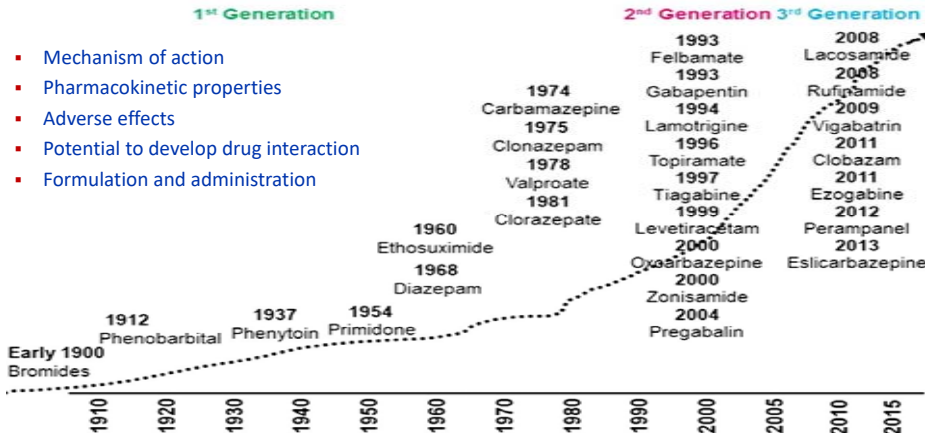
Excitotoxicity and neurodegeneration in epilepsy



Lorigados L, et al. Biotecnologia Aplicada 2013;30:9-16.

Chronological development timeline of antiepileptic drug

- Mechanism of action
- Pharmacokinetic properties
- Adverse effects
- Potential to develop drug interaction
- Formulation and administration



Rudzinski LA, et al. J Investig Med. 2016 Aug;64(6):1087-101. doi: 10.1136/jim-2016-000151.

Mechanisms of neuronal excitability and target of actions for AED

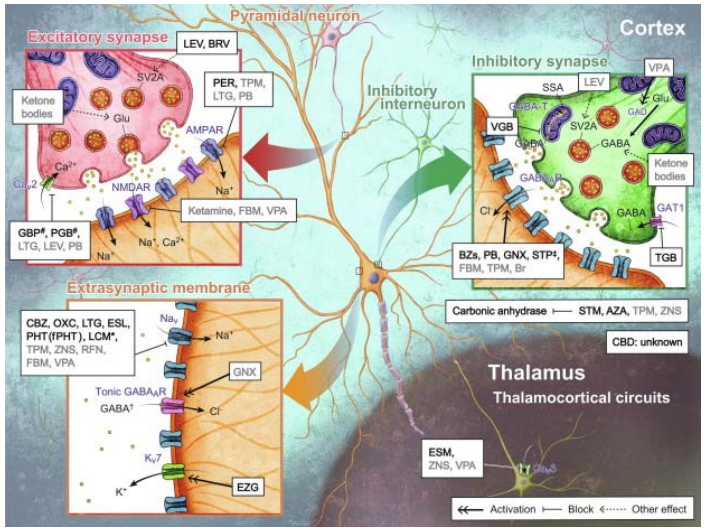
- ↑ Voltage sensitive Na^+ channels
- ↑ Voltage sensitive Ca^{2+} channels
- ↓ Voltage sensitive K^+ channel

- Receptor-ion channel complex
  - ↑ Excitatory amino acid receptor-cation channel complexes
    - Glutamate
    - Aspartate
  - ↓ GABA-Cl^- channel complex

Action of antiepileptic drugs on neurons

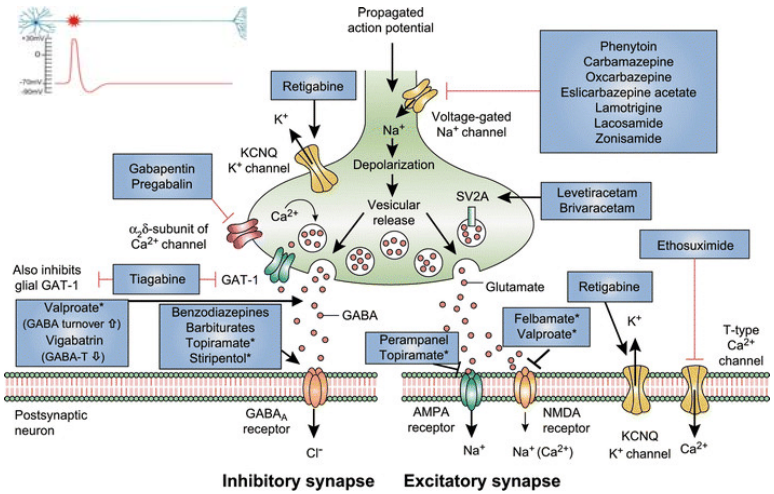
CBZ, carbamazepine; OXC, oxcarbazepine; LTG, lamotrigine; LCM, lacosamide; ESL, eslicarbazepine acetate; PHT, phenytoin; fPHT, fosphenytoin; TPM, topiramate; ZNS, zonisamide; RFN, rufinamide; LEV, levetiracetam; BRV, brivaracetam; PER, perampanel; PB, phenobarbital; GBP, gabapentin; PGB, pregabalin; FBM, felbamate; EZG, ezogabine (retigabine); VPA, sodium valproate; VGB, vigabatrin; TGB, tiagabine; BZ, benzodiazepine; STP, stiripentol; GNX, ganaxolone; Br, bromide; ESM, ethosuximide; STM, sulthiame; AZA, acetazolamide; CBD, cannabidiol

† extrasynaptic GABA
*enhancement of slow inactivation of sodium channel
‡ acting on α2δ protein of the presynaptic P/Q-type HVA and N-type calcium channel
‡ additional effect to elevate the clobazam level by inhibition of cytochrome P450 (CYP)
Drug names in gray indicate secondary, fractional, or uncertain action



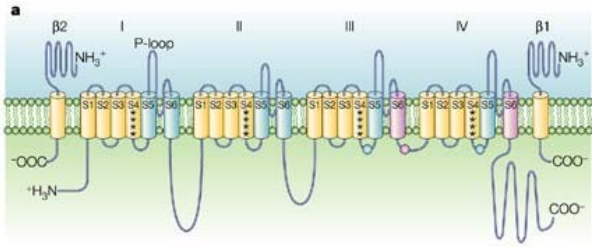
Kobayashi K, et al. Brain Dev. 2020 Jan;42(1):2-5. doi: 10.1016/j.braindev.2019.07.006.

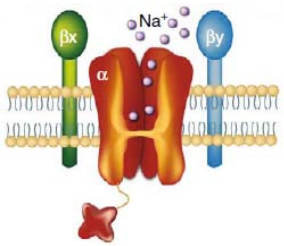
Mechanism of action of clinically approved anti-seizure drugs



Loscher W, et al. CNS Drugs 2016;30:1055-77.

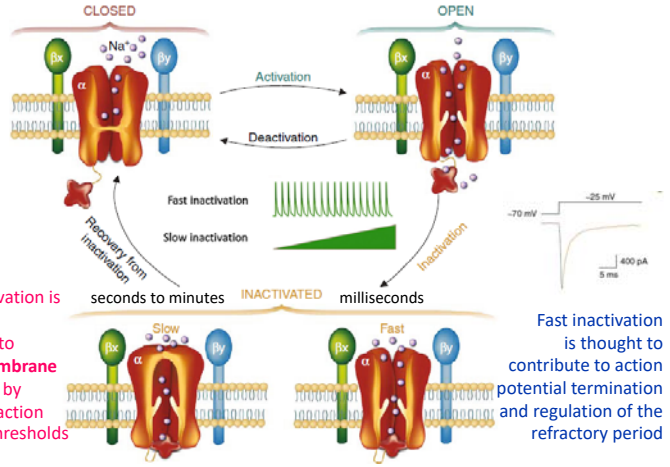
Primary structures of voltage-gated sodium channel





Rogawski MA, et al. Nat Rev Neurosci 2004;5:553-64.

Working cycle of voltage-gated sodium channels (VGSCs)

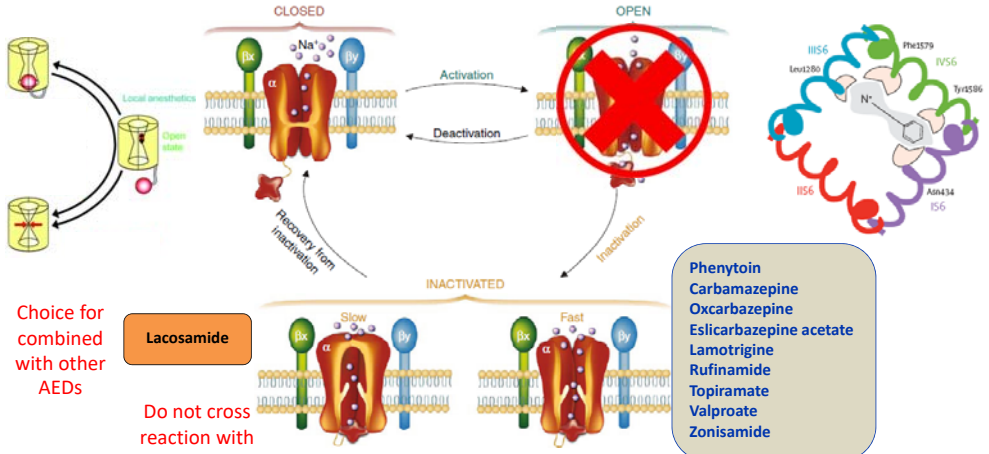


Slow inactivation is thought to contribute to **overall membrane excitability** by increasing action potential thresholds

Fast inactivation is thought to contribute to action potential termination and regulation of the refractory period

Curia G, et al. CNS Drugs 2009;23:555-68.

Mechanism of actions of VGSC (sodium channel) blockers



Choice for combined with other AEDs

Lacosamide

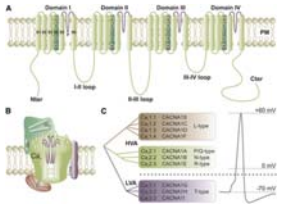
Do not cross reaction with aromatic AEDs

Phenytoin
Carbamazepine
Oxcarbazepine
Eslicarbazepine acetate
Lamotrigine
Rufinamide
Topiramate
Valproate
Zonisamide

Tissue distribution of NaV subtypes

Channel nomenclature	*Gene*	*Chromosomal location (human)*	*Tetrodotoxin sensitivity*	*Major tissue expression*	*Effect of mutation*
Nav1.1	*SCN1A*	2q24	✓	CNS, PNS	Epilepsy
Nav1.2	*SCN2A*	2q23–24	✓	CNS, PNS	Epilepsy
Nav1.3	*SCN3A*	2q24	✓	CNS, PNS	None reported
Nav1.4	*SCN4A*	17q23–25	✓	Skeletal muscle	Myotonia, periodic paralysis
Nav1.5	*SCN5A*	3p21	X	Heart	Long QT, Brugada syndrome, progressive familial heart block
Nav1.6	*SCN8A*	12q13	✓	CNS, PNS	Cerebellar atrophy
Nav1.7 Nav1.8 Nav1.9	*SCN9A* *SCN10A* *SCN11A*	2q24 3 3	✓ X X	PNS (SNS and PAs)	Increased and decreased pain sensitivity

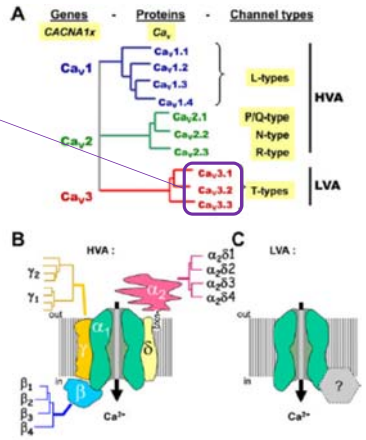
Voltage-gated calcium channels (VGCCs)



A number of single base changes have been identified in the genes encoding for the $Ca_V3.1$ and $Ca_V3.2$ T-type calcium channels in some patients with generalized epilepsies

Channel type	Gene name	Chromosome loc.	SNPs/mutations in human diseases
$Ca_V3.1$	CACNA1G	17q22	Juvenile myoclonic epilepsy (JME)
$Ca_V3.2$	CACNA1H	16p13.3	Childhood absence epilepsy (CAE) and other idiopathic generalized epilepsies (IGE) Autism spectrum disorder (ASD)
$Ca_V3.3$	CACNA1I	22q13	–

Huc S, et al. Biochim Biophys Acta. 2009;1793:947-52.



Proft J, et al. Mol Pharmacol. 2015'87(6):890-906.

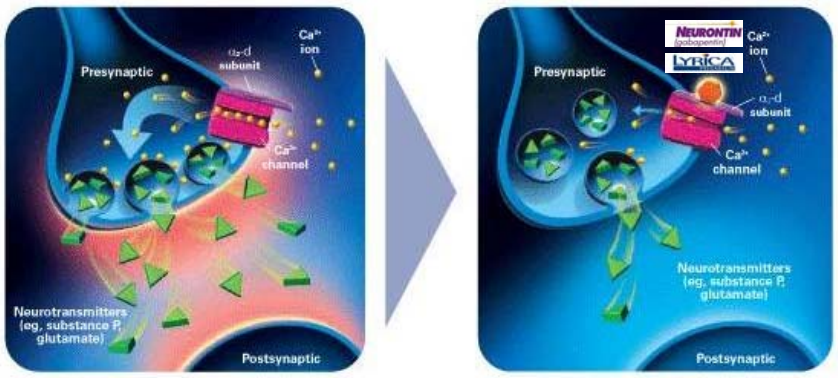
Zamponi GW, et al. Pflugers Arch – Eur J Physiol 2010;460:395-403.

Subunit composition and function of Ca^{2+} channel types

Ca^{2+} channel	Ca^{2+} current type	Primary localizations	Previous name of α_1 subunits	Specific blocker	Functions
$Ca_V1.1$	L	Skeletal muscle	α_{1S}	DHPs	Excitation-contraction coupling Calcium homeostasis Gene regulation
$Ca_V1.2$	L	Cardiac muscle Endocrine cells Neurons	α_{1C}	DHPs	Excitation-contraction coupling Hormone secretion Gene regulation
$Ca_V1.3$	L	Endocrine cells Neurons	α_{1D}	DHPs	Hormone secretion Gene regulation
$Ca_V1.4$	L	Retina	α_{1F}		Tonic neurotransmitter release
$Ca_V2.1$	P/Q	Nerve terminals Dendrites	α_{1A}	ω-Agatoxin	Neurotransmitter release Dendritic Ca^{2+} transients
$Ca_V2.2$	N	Nerve terminals Dendrites	α_{1B}	ω-CTx-GVIA	Neurotransmitter release Dendritic Ca^{2+} transients
$Ca_V2.3$	R	Cell bodies Dendrites Nerve Terminals	α_{1E}	None	Ca^{2+}-dependent action potentials Neurotransmitter release
$Ca_V3.1$	T	Cardiac muscle Skeletal muscle Neurons	α_{1G}	None	Repetitive ring
$Ca_V3.2$	T	Cardiac muscle Neurons	α_{1H}	None	Repetitive ring
$Ca_V3.3$	T	Neurons	α_{1I}	None	Repetitive ring

Catterall WA. Annu Rev Cell Dev Biol 2000;16:521-55.

Binding of gabapentin & pregabalin to the α_2-δ subunit resulting in decreased release of glutamate, substance P, calcitonin-gene-related peptide, and norepinephrine



Durkin B, et al. Expert Opin Pharmacother 2010;11:2751-8.

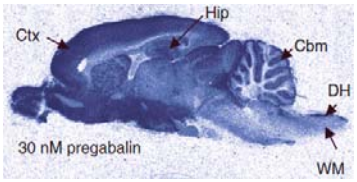
Subtypes of α_2-δ auxiliary subunit of N-type calcium channel

Channel protein name	Gene locus name	Location of expression	Distinguishing properties
$\alpha_2\delta$—(Type 1)	*CACNA2D1*	Neocortex, amygdala, hippocampus, striatum, dorsal horn of spinal cord	Binds pregabalin, gabapentin
$\alpha_2\delta$—(Type 2)	*CACNA2D2*	Cerebellum (molecular layer), hypothalamus	Binds pregabalin, gabapentin
$\alpha_2\delta$—(Type 3)	*CACNA2D3*	Striatum, neocortex, thalamus (by mRNA)	No drug binding
$\alpha_2\delta$—(Type 4)	*CACNA2D4*	Pituitary, adrenal gland, intestine	No drug binding

Taylor CP, et al. Epilepsy Res 2007;73:137-150.

Affinities of Gabapentin and Pregabalin on auxilary subunit of α_2-δ N-type calcium channel

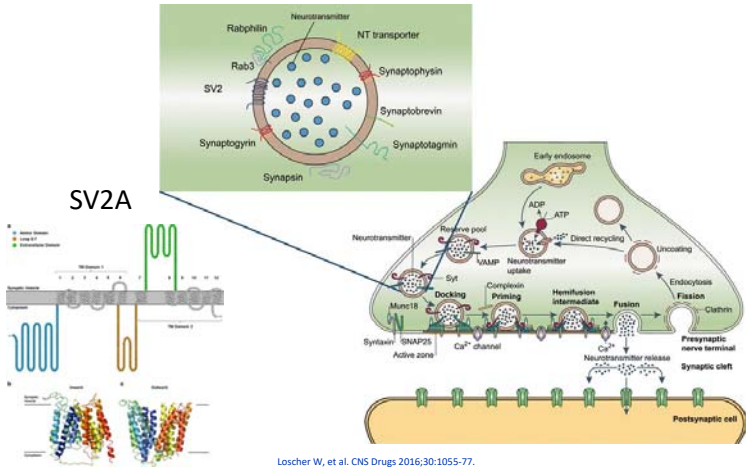
	α_2-δ-1 IC_{50} (μm)	α_2-δ-2 IC_{50} (μm)
Gabapentin	0.052 + 0.013	0.055 + 0.006
Pregabalin	0.075 + 0.015	0.118 + 0.018



Pregabalin has high specific binding in brain than gabapentin (neocortex, amygdala, dorsal horn, cerebellum)

Zheng L, et al. Eur J Pharmacol 2011;667:80-90.

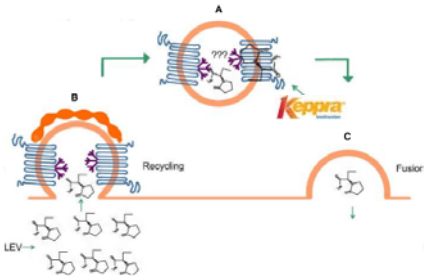
The dynamics of SVs at the presynaptic terminal, illustrating detailed mechanism of NT release and synaptic vesicle recycling



Loscher W, et al. CNS Drugs 2016;30:1055-77.

Mechanism of levetiracetam

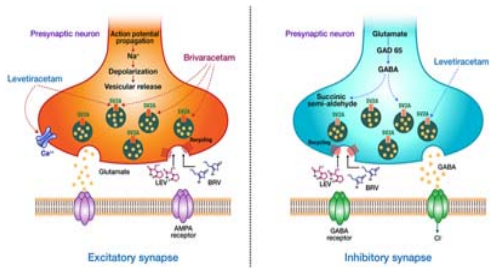
- LEV binds reversibly, saturably, and sterospecifically to SV2A
  - LEV does not bind to its two isoforms, SV2B and SV2C
- LEV binds to SV2A leading to decreased transmitter release



- LEV can inhibit HVA-Ca^2 channels (N-type), negate the inhibition of negative allosteric modulators such as zinc and β-carbolines of GABA- and glycine-gated currents, and diminish the calcium release from intraneuronal stores

Mendoza-Torreblanca JG, et al. Eur J Neurosci 2013;38:3529-39.

Brivaracetam: an analog of levetiracetam

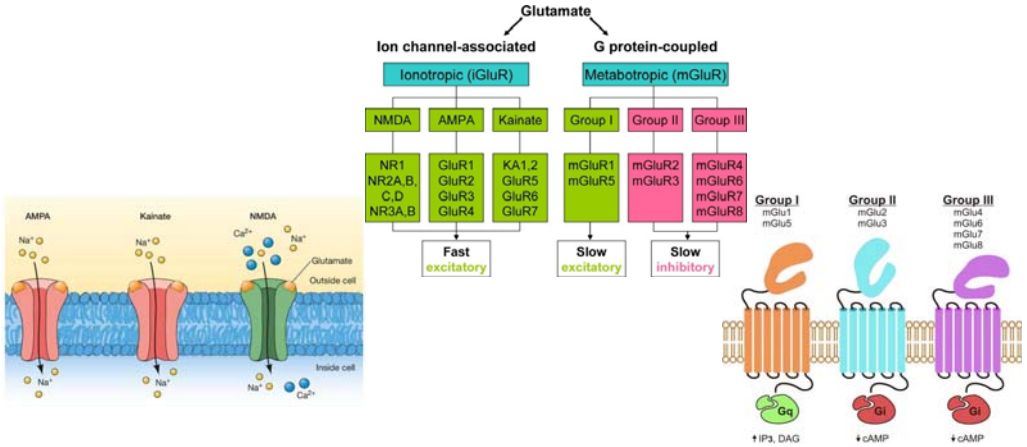


	Brivaracetam	Levetiracetam
Dosage formulations Oral Intravenous	25 mg, 50 mg, 75 mg, 100 mg 50 mg/5 mL	250 mg, 500 mg, 750 mg, 1000 mg 500 mg/5 mL; 500 mg/100 mL; 1500 mg/5 mL
Bioavailability	100%* (may be delayed with high-fat meal)	>95%
Time to peak, median (range)	2 hr (1–4 hrs)	1 hr (1–2 hrs)
Protein binding	15–20%	<10%
Metabolism	Hydrolysis-primary metabolism Hydroxylation (CYP2C19)-16% Unchanged-9%	34% metabolized (hydrolysis) 66%-unchanged
Involvement of CYP450 enzymes	Yes (CYP2C19)	No
Elimination half-life (t1/2)	7–8 hrs	6–8 hrs
Time for steady state	2 days of repeated dosing	24–48 hrs of repeated dosing
Clearance	95% via kidney (8–10% unchanged)	100% via kidney (66% unchanged)
Dose adjustment in renal failure/dialysis	Not required	Required (50% supplemental dose following HD)
Dosing adjustment in liver failure	Reduce dose by 1/3 may be needed	Not required
Relevant drug-drug interaction	Reduced by co-administration of rifampin Reduce combined OCPs by 20–30% at 400 mg/day	None

- BRV was found to have 15–30 times greater affinity for SV2A and faster brain permeability than LEV
  - Correlated well with its higher potency and efficacy in various animal models of focal, generalized, and drug-resistant seizures
- BRV does not Inhibit high-voltage-gated calcium currents or modulate inhibitory or excitatory postsynaptic ligand-gated receptors at therapeutic brain concentrations

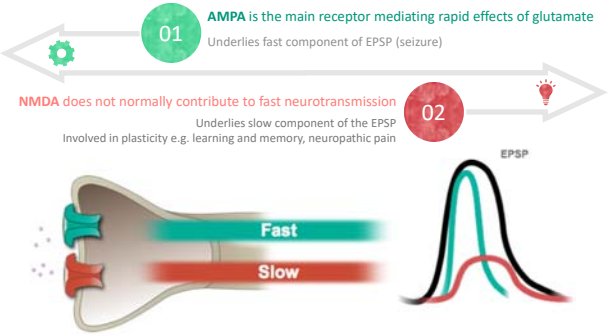
Feyissa AM. Neuropsychiatr Dis Treat. 2019 Sep 9;15:2587-2600. doi: 10.2147/NDT.S143548.

Classification of glutamate receptors



Distinct roles of NMDA and AMPA receptor
Same glutamate receptor … Different action

Glutamate mediates most fast excitatory neurotransmission in the CNS

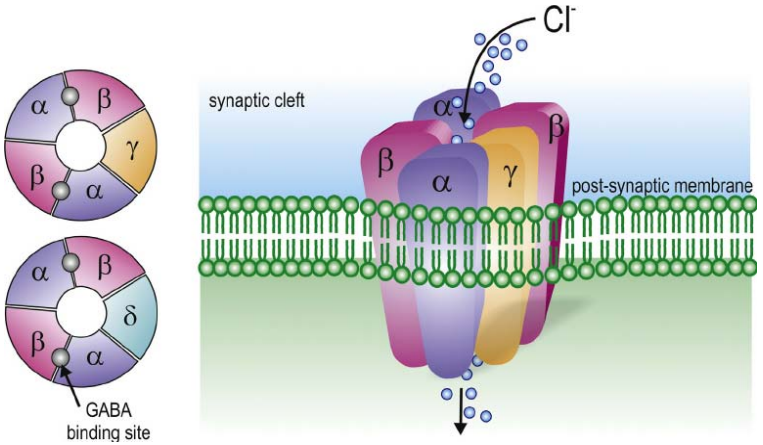


Mechanism of AED at AMPA receptor

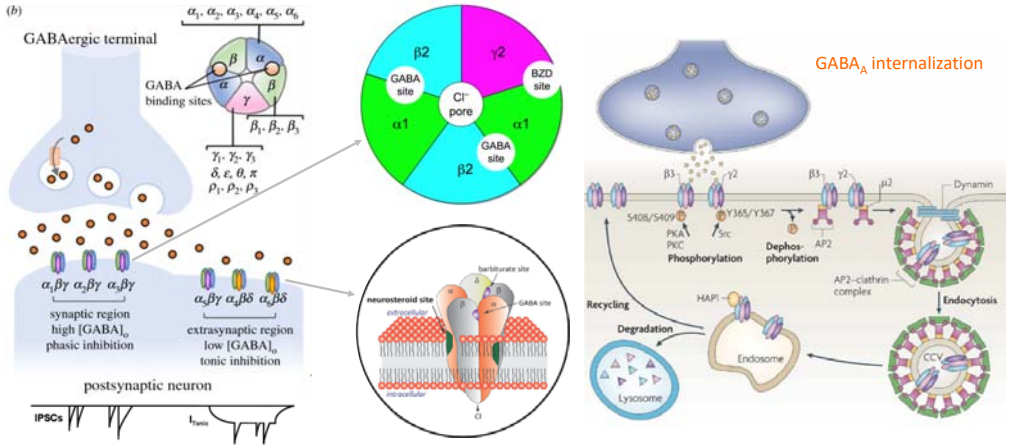
Reduce postsynaptic neuronal excitability

Possible neuroprotective effect

Structure of $GABA_A$ receptor



Synaptic and extrasynaptic $GABA_A$ receptor



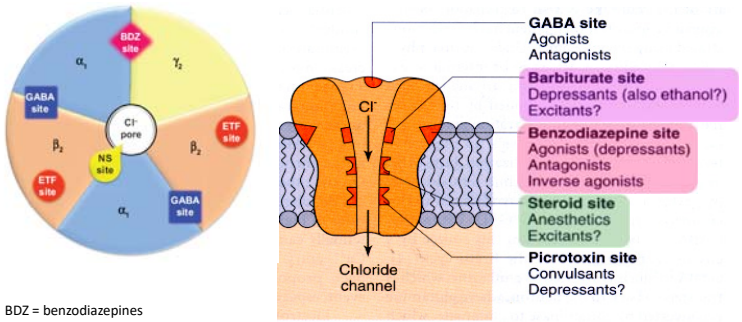
Jacob TC, et al. Nat rev Neurosci 2008;9:331-43.

Pharmacology of $GABA_A$ receptors classified by α-subunit

	α1	α2	α3	α5
Sedation / Dependence	+	-	-	-
Anterograde amnesia	+	ND	ND	ND
Anticonvulsant activity	+	-	-	-
Anxiolysis	-	+	-	-
Myorelaxation	-	+	+	+

Rudolph U. Benzodiazepines. In Encyclopedia of Molecular Pharmacology 2008.

AED acting on $GABA_A$ receptor



BDZ = benzodiazepines
ETF = etifoxine
NS = neurosteroids

Increases intracellular chloride levels

Increases transmembrane polarity

Makes the occurrence of action potential more difficult

Basic Neurochemistry: Molecular, Cellular, and Medical Aspects. 6th editions. Philadelphia: Lippincott,Williams & Wilkins ; 1999.

Differential pharmacology of AED

Properties	1st generation	2nd generation	3rd generation
Mechanism of action (MOA)	Simple MOAs (VGSC, GABA receptor)	Multiple MOAs or Specific target of action (SV2A, T-type VGCC, N-type VGCC, GAT, GABA-T, AMPA/kainite receptor)	Novel target of action (PAM at AMPA, slow-inactivated VGSC)

AED	Inhibition of glutamate excitation		Increase of GABA inhibition				Ionic channel			Other MOA
	↓Glu release	Receptor blockade	↑GABA release/brain level	Bind $GABA_A$ receptor	Inhibit GABA transporter	Inhibit GABA transminase	Blockade of VGSC	Blockade of VGCC	Activation of KCNQ/Kv7	
Benzodiazepines				(PAM at BZD)						
Brivaracetam	(bind SV2A)									
Carbamazepine							(fast)			
Eslicarbazepine							(fast)			
Ethosuximide								(T)		
Felbamate		(NMDA)		(↑ inh. effect)			(fast)			
Gabapentin								(N, P/Q)		
Ganaxolone				(neurosteroid)						
Lacosamide							(slow)			
Lamotrigine							(fast)	(N, P)		5-HT_{1A} PA
Levetiracetam	(bind SV2A)							(N)		
Oxcarbazepine							(fast)	(N, P)		
Perampanel		(PAM at AMPA)								
Phenobarbital		(AMPA)		(barbiturate)						
Phenytoin							(fast)			
Pregabalin								(N, P/Q)		
Retigabine/Ezogabine									(PAM at Kv2-5)	
Stiripentol				(PAM at α3, δ)						
Tiagabine										
Topiramate		(AMPA/kainite)		(↑ inh. effect)			(fast)	(L)		Inh. CAI II,IV
Valproic acid			(↑ synthesis, ↓ metabolism/reuptake)				(fast)	(T)		Inh. histone deacetylase
Vigabatrin										
Rufinamide							(fast)			
Zonisamide			(↑ release, ↓ uptake)				(fast)	(T)		Free radical scavenger, inh. CAI

PAM: positive allosteric modulator

Summarize mechanisms of action of AED

Miziak B, et al. Expert Opin Drug Discov 2013;8:1415-27.

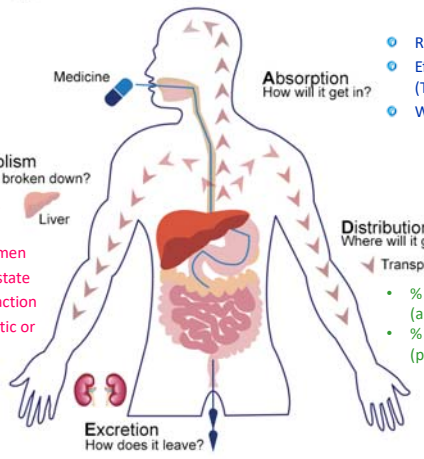
AED	Focal Seizures	Generalized Tonic-Clonic Seizures	Generalized Absence Seizures	Generalized Myoclonic Seizures	Lennox-Gastaut Syndrome	Infantile Spasms
Carbamazepine	I	Suggested	X	X		
Phenobarbital	I	Suggested	X	IV		
Phenytoin	I	Suggested	X	X		
Valproic acid	I	Suggested	I	Suggested	Suggested	Suggested
Ethosuximide	X	X	I	X		
Felbamate	I	Suggested	?	?	I	
Oxcarbazepine	I	?	X	X		
Gabapentin	I	X	X	X		
Pregabalin	I	X	X	X		
Lamotrigine	I	I	Suggested	Variable	I	
Levetiracetam	I	I	Suggested	I		
Topiramate	I	I	X	?	I	
Tiagabine	I	X	X	X		
Vigabatrin	I	X	X	X		I
Zonisamide	I	Suggested	Suggested	Suggested		
Lacosamide	I	?	X	X		
Perampanel	I	I	?			
Rufinamide	I	Suggested	?	?	I	
Ezogabine	I	?	?	?		
Eslicarbazepine acetate	I	?	X	X		
Clobazam	Suggested	Suggested	Suggested	Suggested	I	

Approved Indications by US FDA. Abou-Khalil BW. Continuum (Minneap Minn) 2016;2:132-56.

AED	Psychiatric Disorders	Pain	Neurological Disorders	Others
Carbamazepine	Mania, BD I, Agitation	TGN, PHN, DPN, Phantom limb pain		
Phenobarbital				Sedation induction
Phenytoin		NeP		Paroxysmal atrial tachycardia, Ventricular tachycardia
Valproic acid	Mania, BD, Agitation		Migraine prophylaxis	
Ethosuximide				
Felbamate				
Oxcarbazepine	Mania, BD I	TGN		
Gabapentin	Anxiety	PHN, DPN, Phantom limb pain, Fibromyalgia	RLS, Migraine prophylaxis	
Pregabalin	GAD, Social phobia	NeP, Fibromyalgia, PHN, Spinal cord injury		
Lamotrigine	BD II (depression)			
Levetiracetam				
Topiramate	Bulimia nervosa, Binge-eating disorder, Alcohol dependence		Migraine prophylaxis	
Tiagabine				
Vigabatrin				
Zonisamide	Binge-eating disorder			
Lacosamide				
Perampanel				
Rufinamide				
Ezogabine				
Eslicarbazepine acetate				
Clobazam				

Approved Indications by US FDA. Marvanova M, et al. Ment Health Clin 2016;6:8-20.

Pharmacokinetic properties (ADME) of AED



- Rapidly absorbed (T_{max})
- Effect of food on absorption rate (T_{max}) and content (C_{max} & AUC)
- Water solubility (brand switching)

- Determine the dosing regimen
- Determine time to steady state
- Potential for PK drug interaction
- Dosing adjustment in hepatic or renal impairment

- % Protein (albumin) binding (altered free from)
- % Fat of total body composition (prolonged clearance rate)

Pharmacokinetic profiles of conventional AED

AED (serum conc)	F (%)	Vd (L/Kg)	Protein binding (%)	T1/2 (h)	Metabolism & Elimination	Active metabolite
Carbamazepine 4-12 µg/mL (CBZ), <0.2-2.0 µg/mL (epoxide)	85	0.8-2.0	76	12-17	H (100%): CYP3A4 (major), CYP1A2, CYP2B8	CBZ-10,11-epoxide
Phenobarbital 15-40 µg/mL	70-90	0.5-1.0	55	36-118	H: glucosidase, CYP2C9, CYP2C19, CYP2E1 R (20%): unchanged	No
Phenytoin 10-20 µg/mL (total), 1-2 µg/mL (free)	90-100	0.5-1.0	90	7-42	H (98%): CYP2C9 (major), CYP2C19	No
Valproic acid 50-100 µg/mL (total), 5-12.5 µg/mL (free)	100	0.1-0.2	90 (conc-dependent)	6-17	H (95%): beta-oxidation, UGT1A6, UGT1A9, UGT2B7, CYP2C9, CYP2C19	No
Ethosuximide 40-100 µg/mL	100	0.6-0.7	0	25-60	H: CYP3A4 (major), CYP2E1 R (20%): unchanged	No
Primidone 5-12 µg/mL (PRM), 15-40 µg/mL (PHB)	60-80	0.6-0.7	20-45 (PHB), <10 (PRM, PEMA)	10-12 (PEMA), 29-36 (PHB)	R (40-60%): unchanged and smaller amount of PEMA and PGB inactive H: CYP2C9/19, alcohol dehydrogenase PHB (15-25%) and amide hydrolysis PEMA (75%)	Phenobarbital (PHB) Phenylethylmalonamide (PEMA)

Marvanova M, et al. Ment Health Clin 2016;6:8-20.

Pharmacokinetic profiles of second generation AED

AED (serum conc)	F (%)	Vd (L/Kg)	Protein binding (%)	T1/2 (h)	Metabolism & Elimination	Active metabolite
Gabapentin 4-16 µg/mL	35-60	0.85	0	5-7	R (>90%): unchanged	No
Lamotrigine 4-18 µg/mL	≥95	0.9-1.3	55	15-35	H (76%): UGT1A4	No
Levetiracetam 5-40 µg/mL	≥95	0.5-0.7	<10	6-8	R (66%): unchanged Non-hepatic (30%): hydrolysis by type B esterase in WBC	No
Oxcarbazepine 10-35 µg/mL (MHD)	>90 prodrug	0.75 (MHD)	60 (OXC) 40 (MHD)	8-15 (MHD)	H (80%): cytosolic arylketone reductase (OXC), YGT (MHD) R (20%): unchanged	S-licarbazepine R-licarbazepine
Pregabalin N/E	≥90	0.57	0	5-7	R (>95%): unchanged	No
Topiramate 5-20 µg/mL	≥80	0.6-0.8	15	20-30	R (70%): unchanged H (30%): CYP2C19 and glucuronidation	No
Vigabatrin 0.8-36 µg/mL	60-80	0.8	0	5-8	R (95%): unchanged	No
Zonisamide 10-40 µg/mL	≥90	1.0-1.9	40	27-70	H (70%): CYP3A4 (major), NATs (15%), CYP2C19 R (30%): unchanged	No
Felbamate 30-140 µg/mL	<90	0.7-1.0	25	22-25	R (50%): unchanged H (50%): CYP2E1 (major), CYP3A4 (20%), UGT (20%)	No
Tiagabine N/E	≥90	1.0	96	5-9	H (98%): CYP3A4	No

Marvanova M, et al. Ment Health Clin 2016;6:8-20.

Pharmacokinetic profiles of third generation AED

AED (serum conc)	F (%)	Vd (L/Kg)	Protein binding (%)	T1/2 (h)	Metabolism & Elimination	Active metabolite
Brivaracetam	100	15-20	<20	7-8	R (9%): unchanged H: hydrolysis, CYP2C19	No
Clobazam 100-300 µg/mL	100	0.9-1.4	85 (CBZ), 70 (N-DMC)	18 (CBZ), 42 (N-DMC)	H (98%): CYP3A4 (major), CYP2C19, CYP2C6	N-desmethylclobazam (N-DMC, norclobazam)
Eslicarbazepine acetate N/E	>90 prodrug	2.7	<40	20-24	R (66%): unchanged Non-hepatic: hydrolysis by esterase to ELC (91%) H (33%): UGT	Eslicarbazepine Oxcarbazepine
Ezogabine N/E	60	2-3	80	8-10	H (50-65%): UGT1A4, NAT R (20-30%): unchanged	No
Gabapentin enacarbil N/E	75	0.85	0	5-7	R (>90%): gabapentin Non-hepatic: first-pass hydrolysis to GBP by carboxylesterase in enterocytes	Gabapentin
Lacosamide 10-20 µg/mL	100	0.5-0.8	<30	13	R (40%): unchanged H: demethylation, CYP2C19 (30%)	No
Perampanel 0.05-0.4 µg/mL	100	1.1	95	52-129	H (98%): CYP3A4 (major), CYP3A5	No
Rufinamide 10-40 µg/mL	≥85	0.7-1.1	35	6-10	H: non-CYP hydrolysis by carboxylesterase	No

Marvanova M, et al. Ment Health Clin 2016;6:8-20.

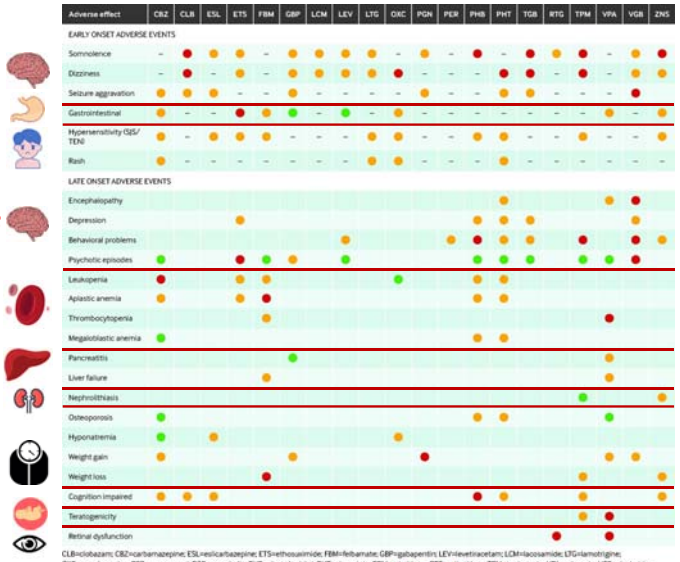
AEDs	Protein binding (%)	Hepatic Metabolism		Renally Excretion (%)
		Phase I (CYP)	Phase II (UGT)	
Carbamazepine	75	3A4		
Clonazepam	85	3A4		
Diazepam	98	2C19, 3A4		
Ethosuximide	0	2E1, 3A4		20
Lorazepam	93		2B15	
Midazolam	95	3A4		
Phenobarbital	55	2C9, 2C19		22
Phenytoin	90	2C9, 2C1		
Valproic acid	90	B-oxidation, 2C9, 2C19	1A6, 1A9, 2B7	
Brivaracetam	<20	2C19, hydrolysis		9
Clobazam	85	2C19, 3A4		
Felbamate	25	2E1, 3A4	UGT	50
Gabapentin	0			>90
Lacosamide	<15	2C19		40
Lamotrigine	55		1A4	
Levetiracetam	0	Amidase		66
Oxcarbazepine MHD	40	Cytosolic reductase	UGT	20
Perampanel	95	3A4		
Pregabalin	0			>90
Retigabine	80		UGT, NAT	20-30
Rufinamide	35	Carboxylesterase		
Topiramate	15	CYP		30
Vigabatrin	0			95
Zonisamide	50	3A4, 2C19		35

Anderson GD, et al. Clin Pharmacokinet. 2014 Jan;53(1):29-49. doi: 10.1007/s40262-013-0107-0.

Differential pharmacology of AED

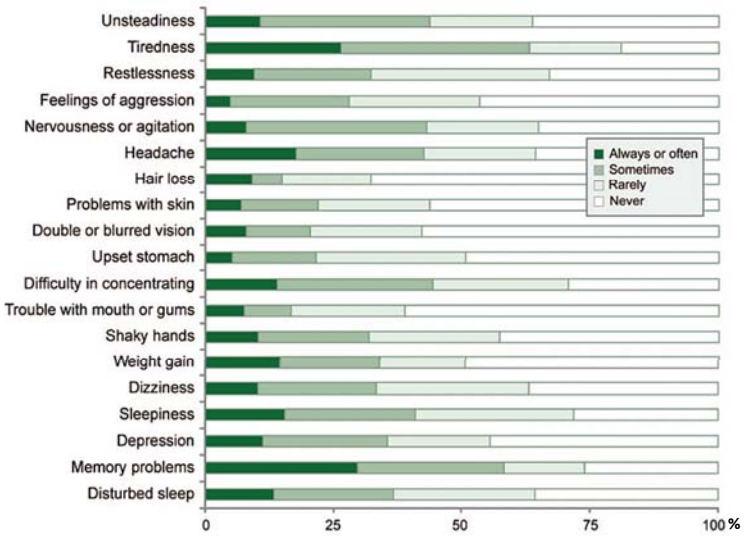
Properties	1st generation	2nd generation	3rd generation
Mechanism of action (MOA)	Simple MOAs (VGSC, GABA receptor)	Multiple MOAs or Specific target of action (SV2A, T-type VGCC, N-type VGCC, GAT, GABA-T, AMPA/kainite receptor)	Novel target of action (PAM at AMPA, slow-inactivated VGSC)
Pharmacokinetic properties			
- Absorption	Limited	Good	Good/prodrug
- Distribution	High % PB	Low %PB	+/-
- Metabolism	Mainly by CYP	Minor route	Mainly by CYP
- Elimination	Inactive metabolite	Unchanged form	Unchanged (some)

Overview of adverse effects of individual antiepileptic drugs



Schmidt D, Schachter SC. BMJ. 2014 Feb 28;348:g254. doi: 10.1136/bmj.g254.

Type A adverse antiepileptic drug effects



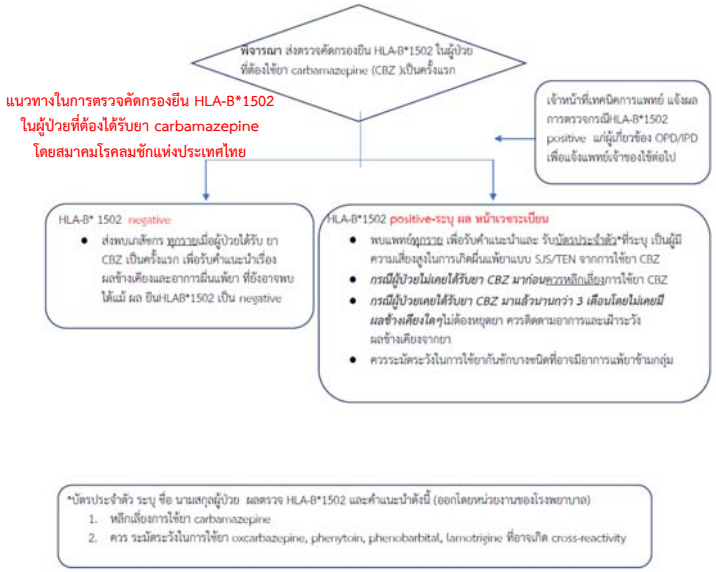
Perucca P, et al. Neurology 2009;72:1223–9.

- Incidence of adverse

Country/Region	Incidence of severe ACDR, per million persons year	Incidence of HLA B*1502 in normal population, percent	Incidence of HLA B*1502 in CBZ-SJS/TEN, percent
• Thailand		8.5-27.5[10,39-40]	83.3[41]

population and carbamazepine-induced Steven-Johnson syndrome and toxic epidermal necrolysis

Lim KS, et al. Neurology Asia 2008;13:15-21.



Dosage and administration of lamotrigine

Initiating lamotrigine in adult
Not taking drugs known to increase the clearance of lamotrigine or valproate

Weeks 1 & 2	Weeks 3 & 4	Week 5	Week 6
25 mg/day	50 mg/day	100 mg/day	Target dose 200 mg/day

Taking valproate

Weeks 1 & 2	Weeks 3 & 4	Week 5	Week 6
25 mg/every other day	25 mg/day	50 mg/day	Target dose 100 mg/day

Taking drugs known to increase the clearance of lamotrigine and not taking valproate

Weeks 1 & 2	Weeks 3 & 4	Week 5	Week 6	Week 7
50 mg/day	100 mg/day in divided doses	200 mg/day in divided doses	300 mg/day in divided doses	Target dose up to 400 mg/day in divided doses

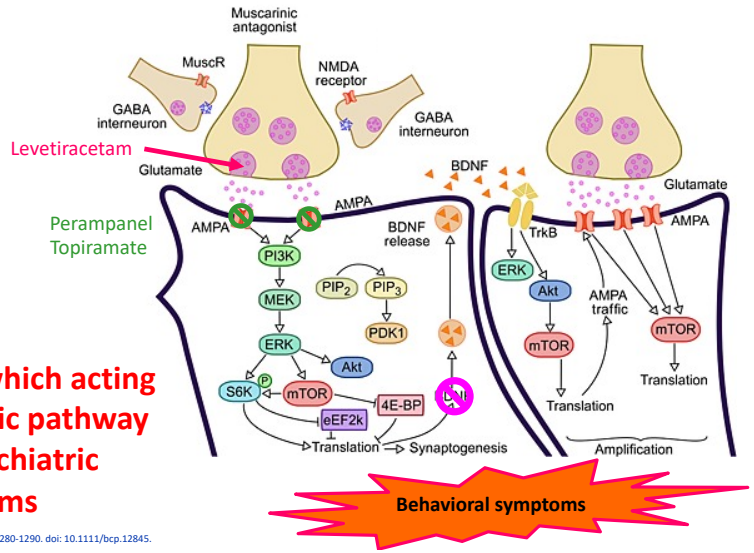
- Doses above target dose are not recommended
- To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations should not be exceeded

Disturbances of cognitive abilities of AED

- Major cognitive effects of AEDs
  - Impair attention/vigilance
  - Impair psychomotor speed (significant cognitive slowing and verbal fluency, word-finding difficulties)
  - Secondary effects on other cognitive functions
- Factors associated side effects
  - Increase dose with rapid initiation
  - Higher dosages and concentrations
  - Use of polytherapy

Meador KJ. Neurology. 2002;58(Suppl 5):S21–S26.

Effects of AED which acting on glutamatergic pathway in neuropsychiatric symptoms



Ignácio ZM, et al. Br J Clin Pharmacol. 2016 Nov;82(5):1280-1290. doi: 10.1111/bcp.12845.

AED and neuropsychiatric symptoms

- Based on available data, levetiracetam, perampanel, and topiramate were associated with increase rate of irritable, hostility or aggression, particularly in patients with history of psychiatric symptoms
- Should closely monitor patients for these symptoms, especially within the first 6 months of starting or titrating AEDs
  - However, this can be occurred within 1-3 years after treatment

Brodie MJ, et al. Pharmacol Rev. 2016 Jul;68(3):563-602. doi: 10.1124/pr.115.012021.

Relative teratogenic risk profiles of antiepileptic drugs

Antiepileptic Drug	Use (Seizure Types)	Major Malformations	FDA Pregnancy Category	Panel Opinion*
Carbamazepine	Partial, tonic–clonic	Facial, spina bifida, cardiac	D	Caution
Ethosuximide	Absence	No specific	C	Safe
Felbamate	Partial, tonic–clonic, absence, myoclonic	Unknown	C	Unknown
Gabapentin	Partial, tonic–clonic	Unknown	C	Unknown†
Lamotrigine	Partial, tonic–clonic, absence, myoclonic, atonic	Unknown	C	Safe?‡
Levetiracetam	Partial, tonic–clonic, ?absence, myoclonic	Unknown	C	Unknown
Oxcarbazepine	Partial, tonic–clonic	Unknown	C	Unknown†
Phenobarbital	Partial, tonic–clonic, ?myoclonic	Cleft palate, heart	D	Caution
Phenytoin	Partial, tonic–clonic	Cleft palate, heart	D	Caution
Tiagabine	Partial, tonic–clonic	Unknown	C	Unknown
Topiramate	Partial, tonic–clonic, myoclonic, atonic	Unknown	C	Unknown†
Valproate	Partial, tonic–clonic, absence, myoclonic, atonic	Spina bifida	D	Caution
Zonisamide	Partial, tonic–clonic, myoclonic, ?absence, atonic	Unknown	C	Unknown†

* At an experts' roundtable meeting, "Epilepsy in Women: The Biological Basis for the Female Experience," February 28, 2003, New York, NY. Panel opinion is based on clinical experience and does not imply results from a scientific controlled study, which is unavailable at this time.
† Sufficient data not yet available.
‡ Based on 360 fetal outcomes with first-trimester exposure to monotherapy; major malformation rate 2.8%.[33] Manufacturer cites insufficient data to conclude confidently that drug is safe during pregnancy.

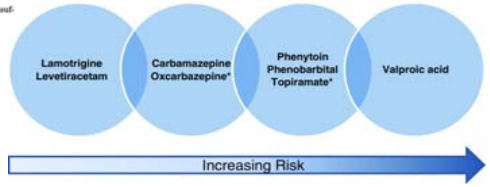
การเลือกใช้ยากันชักในผู้หญิงที่ตั้งครรภ์ ❸

- โดยทั่วไปโอกาสการเกิดความผิดปกติของทารกในครรภ์มีเพิ่มขึ้น 2-3 เท่า ของผู้หญิงที่ไม่ได้รับประทานยากันชัก **(ตารางที่ 23)** โดยโอกาสการเกิดจะขึ้นกับชนิดของยากันชักขนาด และจำนวนของยากันชักเป็นสำคัญ
- ยากันชักที่มีรายงานการก่อให้เกิดความผิดปกติของทารกในครรภ์ชัดเจน ได้แก่ carbamazepine, phenobarbital, phenytoin และ valproate
- ถ้ามีความจำเป็นจะต้องให้ยา valproate ควรใช้ในขนาดที่ต่ำกว่า 800 มิลลิกรัมต่อวัน เพื่อลดโอกาสการเกิดความผิดปกติของทารกในครรภ์

ตารางที่ 23 อัตราการเกิด congenital malformation จากยากันชักชนิดต่างๆ

ยากันชัก	อัตราการเกิด congenital malformation (ร้อยละ)
carbamazepine	2.1-6.3
phenytoin	2.6-7.4
phenobarbital	2.9-6.5
sodium valproate	6.1-16.3*
lamotrigine	1.4-5.2
gabapentin	0.8-5.9**
topiramate	2-4.8**
levetiracetam	2**

* หากใช้ sodium valproate ในขนาดไม่เกิน 700-1000 mg ต่อวัน อัตราการเกิด malformation จะอยู่ในช่วงร้อยละ 6-9
** จำนวนผู้ป่วยที่รายงานใน registry ยังมีจำนวนไม่มาก



Pennell PB. Neurotherapeutics. 2016 Oct;13(4):811-820. doi: 10.1007/s13311-016-0464-0.

QTc prolongation by AED and risk of torsade de pointes

- Both experimental and clinical evidence suggest that treatment with AEDs appears to add relatively little risk of QT prolongation (and potential malignant arrhythmia) in most patients
  - Carbamazepine has high reported
- Special populations requiring greater caution
  - patients with underlying cardiac dysfunction, older individuals (>65 years), female patients, or those with electrolyte imbalances (such as hypokalemia or hypomagnesemia), patients requiring combination therapy with any medication proven to cause QT interval prolongation
  - Monitoring of electrolytes and ECG evaluation in these patients would seem prudent

Feldman AE, et al. Epilepsy Behav 2013;26:421-6.

Non-cardiac medication and QT interval prolongation

Drugs that cause QT interval prolongation seem to share a common property in that they can all block IKr channels

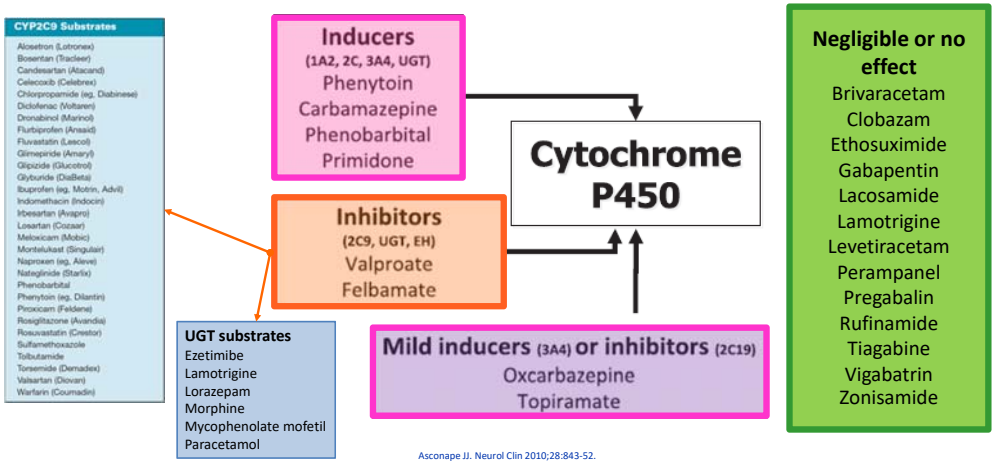
Class of medications	Examples
Antihistamines	Terfenadine, astemizole
Antipsychotics	Haloperidol, droperidole, thioridazine, chlorpromazine
Fluoroquinolone antibiotics	Levofloxacin, moxifloxacin, gemifloxacin, gatifloxacin
Macrolide antibiotics	Erythromycin, clarithromycin, telithromycin
Tricyclic antidepressants	Desipramine, imipramine, doxepin
Selective serotonin reuptake inhibitors	Paroxetine, sertraline, doxepin, venlafaxine, fluoxetine, norfluoxetine, fluvoxamine, citalopram
Opioids	Methadone
5HT3-receptor antagonists	Ondansetron, dolasetron, granisetron
5HT1D agonists	Sumatriptan, naratriptan, zolmitriptan
Prokinetic agents	Cisapride, domperidone

Feldman AE, et al. Epilepsy Behav 2013;26:421-6.

Differential pharmacology of AED

Properties	1st generation	2nd generation	3rd generation
Mechanism of action (MOA)	Simple MOAs (VGSC, GABA receptor)	Multiple MOAs or Specific target of action (SV2A, T-type VGCC, N-type VGCC, GAT, GABA-T, AMPA/kainite receptor)	Novel target of action (PAM at AMPA, slow-inactivated VGSC)
Pharmacokinetic properties			
- Absorption	Limited	Good	Good/prodrug
- Distribution	High % PB	Low %PB	+/-
- Metabolism	Mainly by CYP	Minor route	Mainly by CYP
- Elimination	Inactive metabolite	Unchanged form	Unchanged (some)
Adverse effects		---------- Individualized ----------	

Potential to develop drug-drug interactions of AED



Asconape JJ. Neurol Clin 2010;28:843-52.

Expected changes in plasma concentrations when an AED is added to a pre-existing regimen

	Pre-existing AED														
AED added	PB	PHT	PRM	ETS	CBZ	VPA	OXC	LTG	GBP	TPM	TGB	LEV	ZNS	VGB	FBM
PB	··	PHT↑↓	NCCP	ETS⇓	CBZ⇓	VPA⇓	H-OXC↓	LTG⇓	↔	TPM⇓	TGB⇓	↔	ZNS⇓	↔	FBM⇓
PHT	PB↑	··	PRM↓ PB↑	ETS⇓	CBZ⇓	VPA⇓	H-OXC↓	LTG⇓	↔	TPM⇓	TGB⇓	↔	ZNS⇓	↔	FBM⇓
PRM	NCCP	PHT↑↓	··	ETS⇓	CBZ⇓	VPA⇓	?	LTG⇓	↔	TPM⇓	TGB⇓	↔	ZNS⇓	↔	FBM⇓
ETS	↔	↔	NE	··	↔	VPA↓	NE	NE	NE	NE	NE	NE	NE	NE	NE
CBZ	↔	PHT↑↓	PRM↓ PB↑	ETS⇓	··	VPA⇓	H-OXC↓	LTG⇓	↔	TPM⇓	TGB⇓	↔	ZNS⇓	NE	FBM⇓
VPA	PB⇑	PHT↓*	PB⇑	ETS↑↓	CBZ-E↑	··	↔	LTG⇑	↔	TPM↓	↔	↔	↔	NE	↔
OXC	PB↑	PHT↑	?	?	CBZ↓	↔	··	LTG↓	NE	?	?	NE	?	NE	?
LTG	↔	↔	NE	NE	↔	↔	NE	··	NE	NE	NE	↔	↔	NE	NE
GBP	↔	↔	NE	NE	↔	↔	NE	NE	··	NE	NE	↔	NE	NE	NE
TPM	↔	PHT↑	↔	NE	↔	VPA↓	?	?	NE	··	?	NE	?	NE	?
TGB	↔	↔	↔	NE	↔	↔	NE	NE	NE	NE	··	NE	NE	NE	NE
LEV	↔	↔	↔	NE	↔	↔	NE	↔	↔	NE	NE	··	NE	NE	NE
ZNS	↔	↔	NE	NE	CBZ↑↓	↔	?	↔	NE	NE	NE	NE	··	NE	?
VGB	PB↓	PHT↓	PRM↓ PB↓	NE	CBZ↑	↔	NE	NE	NE	NE	NE	NE	NE	··	NE
FBM	PB⇑	PHT⇑	?	?	CBZ↓ CBZ-E↑	VPA⇑	↔	↔	NE	?	?	NE	?	↔	··

PB=phenobarbital; PHT=phenytoin; PRM=primidone; ETS=ethosuximide; CBZ=carbamazepine; VPA=valproic acid; OXC=oxcarbazepine; LTG=lamotrigine; GBP=gabapentin; TPM=topiramate; TGB=tiagabine; LEV=levetiracetum; ZNS=zonisamide; VGB=vigabatrin; FBM=felbamate; H-OXC=10-hydroxy-oxcarbazepine (active metabolite of OXC); CBZ-E=carbamazepine-10,11-epoxide. NE=none expected; *free (pharmacologically active) concentration may increase; NCCP=not commonly coprescribed; ↔=No change; ↓=a minor (or inconsistent) decrease in plasma concentration; ⇓=a clinically significant decrease in plasma concentration; ↑=a minor (or inconsistent) increase in plasma concentration; ⇑=a clinically significant increase in plasma concentration

Patsalos PN, et al. Lancet Neurol 2003;2:347-56.

Concerning issues on DDI of AED

- Carbapenems
- Folate
- Vitamin D & Calcium
- Oral contraceptives
- Immunosuppressants

Valproate

AEDs with CYP inducers

Differential pharmacology of AED

Properties	1st generation	2nd generation	3rd generation
Mechanism of action (MOA)	Simple MOAs (VGSC, GABA receptor)	Multiple MOAs or Specific target of action (SV2A, T-type VGCC, N-type VGCC, GAT, GABA-T, AMPA/kainite receptor)	Novel target of action (PAM at AMPA, slow-inactivated VGSC)
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- Absorption	Limited	Good	Good/prodrug
- Distribution	High % PB	Low %PB	+/-
- Metabolism	Mainly by CYP	Minor route	Mainly by CYP
- Elimination	Inactive metabolite	Unchanged form	Unchanged (some)
Adverse effects		---------- Individualized ----------	
Potential to develop drug interaction	High risk - CYP substrate - CYP inducers / inhibitors	Low to moderate	Low to moderate

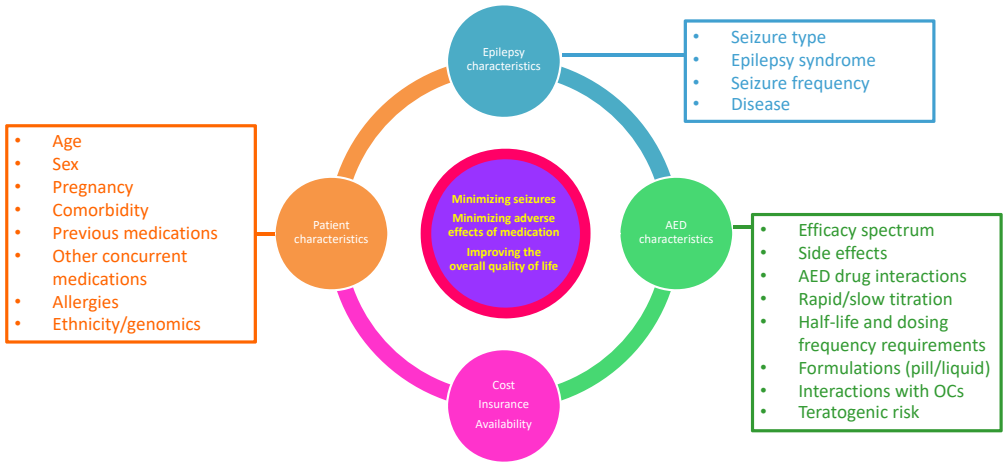
Advantages and disadvantages of selected AED

AEDs	Advantages	Disadvantages
Carbamazepine	High efficacy	Relatively low therapeutic index, enzyme inducer, rash
Valproate	Broad spectrum, IV, rapid titration	Weight gain, encephalopathy, tremor
Gabapentin	Rapid titration, few AEs, no drug interaction	Limited efficacy, multiple-daily dosing, renal clearance
Pregabalin	No drug interaction	Somnolence, weight gain
Lamotrigine	Broad spectrum, no cognitive AEs, psychotropic effect	Rash, slow and complex titration
Levetiracetam	High efficacy, broad spectrum, rapid titration, IV, no interaction, no cognitive AEs	Psychiatric dysfunction, dose adjustment according to the GFR
Oxcarbazepine	High efficacy, better PK/AE profile than carbamazepine	Rash, hyponatremia
Topiramate	High efficacy, broad spectrum, low PK interaction	Cognitive AEs, weight loss, glaucoma, renal stone
Zonisamide	High efficacy, broad spectrum, low PK interaction, once-daily dosing	Cognitive AEs, weight loss, renal stone
Lacosamide	High efficacy, rapid titration, IV, no PK interaction, low cognitive SE	Dizziness, arrhythmia
Perampanel	Broad spectrum, long half-life	Somnolence, dizziness

AEDs, antiepileptic drugs; IV, intravenous administration; AEs, adverse effects; GFR, glomerular filtration rate; PK, pharmacokinetic; SE, status epilepticus.

Lee SK. J Epilepsy Res. 2019;9(1):27-35.

Selection the AED for individualized patients



Moosa ANV. Continuum (Minneap Minn). 2019 Apr;25(2):381-407. doi: 10.1212/CON.0000000000000712.

Concerning factors for choosing AED in elderly

Factor	CBZ	PHT	PB	VPA	GBP	LMT	LEV	OXC	PGB	TOP	ZNS	BVR	CLO	LAC	PER	RUF
High protein bound		X		X											X	
Metabolism by CYP	X	X	X	X		X				X	X	X	X	X	X	
Eliminated by renal					X		X	X	X	X				X		
Removed by HD					X		X		X	X				X		
Additional dose after HD			X		X	X	X		X	X				X		X
Cognitive impairment	X	X	X	X						X	X		X			
Osteoporosis	X	X	X													
Hematologic toxicity	X	X	X	X												
Rash	X	X	X			X		X								
Cardiac side effects	X	X						X						X		X
Hyponatremia	X							X								
Psychiatric effects							X			X					X	
↑/↓ bodyweight	↑			↑	↑				↑	↓	↓					
↑/↓ comedications	↓	↓	↓	↑				↑/↓		↑/↓						
Once daily	X	X	X									X			X	

Dose adjustments for AED in kidney disease

AED	GFR > 60	GFR 30-59	GFR 15-29	GFR < 15	Hemodialysis
Brivaracetam	50-100 mg 2×/d	No adjustment needed	No adjustment needed	No adjustment needed	No adjustment needed
Carbamazepine	200-800 mg 2×/d	No adjustment needed	No adjustment needed	No adjustment needed	Supplemental dose not needed
Clobazam	20-40 mg daily	No adjustment needed	No adjustment needed	No adjustment needed	Supplemental dose not needed
Eslicarbazepine	800-1,600 mg daily	No adjustment needed	600 mg daily max	600 mg daily max	Not established; may need supplemental dose
Felbamate	1,200-3,600 mg	50% dose reduction	Insufficient data, reduce dose by 50%; use w/ caution	Insufficient data, reduce dose by 50%; use w/ caution	Insufficient data, avoid
Gabapentin	300-1,200 mg 3×/d	200-700 mg 2×/d	200-700 mg daily	100-300 mg daily; use w/ caution	100%-200% daily dose post-HD
Lacosamide	50-200 mg 2×/d	No adjustment needed	Slow titration; max 300 mg daily	Slow titration; max 300 mg daily	50% daily dose as post-HD supplement
Lamotrigine	50-250 mg 2×/d	Dose reduction may be needed; use w/ caution	Dose reduction may be needed; use w/ caution	Dose reduction may be needed; use w/ caution	Consider post-HD supplemental dose
Levetiracetam	500-1,500 mg 2×/d	50% dose reduction	50% dose reduction	50% dose reduction	500-1,000 mg daily & 50% daily dose as post-HD supplement
Oxcarbazepine	300-1,200 mg 2×/d	No adjustment needed	Initiate at 1/2 of usual daily dose	Initiate at 1/2 of usual daily dose	Insufficient data; may monitor levels*; proceed w/ caution
Perampanel	4-12 mg daily	Not established; likely no adjustment needed	Not established; likely no adjustment needed	Not established; likely no adjustment needed	Not established; supplementation likely not needed
Phenobarbital	60-100 mg 2×/d or 3×/d	Use w/ caution; dose reduction may be needed	Use w/ caution; dose reduction may be needed	Use w/ caution; dose reduction may be needed	Consider 50% of daily dose in PD & as post-HD supplement
Phenytoin	150-200 mg 2×/d or 3×/d	Oral loading dose not needed; otherwise no change	Oral loading dose not needed; otherwise no change	Oral loading dose not needed; otherwise no change	Oral loading dose not needed; otherwise no change
Pregabalin	600 mg max daily	50% dose reduction	25-150 mg daily	25-75 mg daily	Replacement dose 25-150 mg post-HD
Rufinamide	200-1,600 mg 2×/d based on weight	No adjustment needed	No adjustment needed	No adjustment needed	30% supplemental dose post-HD
Tiagabine	32-56 mg	No adjustment needed	No adjustment needed	No adjustment needed	Supplemental dose not needed
Topiramate	100-200 mg 2×/d	50% dose reduction	50% dose reduction	50% dose reduction	50% daily dose as post-HD supplement
Valproic acid	30-60 mg/kg/d 2×/d to 3×/d	No adjustment needed	No adjustment needed	No adjustment needed	Supplementation usually not given; high-flux dialysis may remove the drug
Vigabatrin	1,000-3,000 mg daily	25% dose reduction	50% dose reduction	75% dose reduction	50% supplemental dose post-HD
Zonisamide	100-600 mg daily	No adjustment needed	Unclear, use w/ caution	Unclear, use w/ caution	Give daily after HD; 50% supplemental dose may be needed for post-HD seizures

Titoff V, et al. Am J Kidney Dis. 2019 Jan;73(1):90-101. doi: 10.1053/j.ajkd.2018.03.021.

Product formulations of AED

- Oral route
  - Immediate formulation
  - Controlled-release formulation
    - Carbamazepine CR tablet
    - Phenytoin SR capsule
    - Sodium valproate SR tablet
- Injection route
  - Intramuscular: midazolam, fosPHT, PB
  - Intravenous

Antiepileptic drugs, recommended dosage, and laboratory monitoring

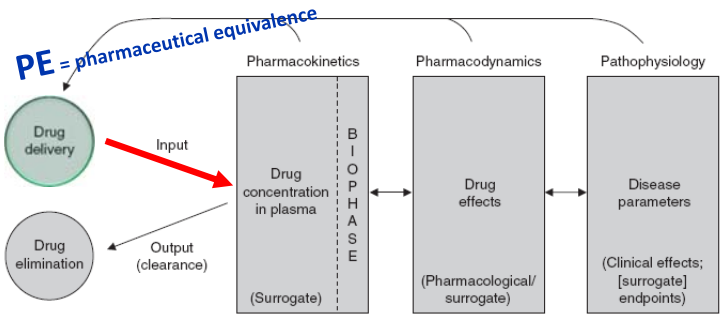
Drug	Half life (hours)	Formulations	Starting dose (mg/kg per day)	Maintenance dose (mg/kg per day)	Dosing schedule	Clinical/ laboratory monitoring
Carbamazepine	25-65	tab, SR tab, susp	10	10-35	TID	CBC, LFT, hyponatremia, serum levels
Phenobarbital	24-140	tab, susp, IV	3	3-6	QD – BID	Sedation, CBC, LFT, serum levels
Phenytoin	7-42	cap, SR cap, susp, IV	4	4-8	QD – TID	CBC, LFT, serum levels
Valproate	5-15	sugar-coated tab, ER tab, susp, IV	15	15-45	TID – QID	CBC, LFT, serum levels
Gabapentin	4-7	cap, tab	10	25-50	TID	Weight
Lamotrigine	6-11	tab	0.15-0.5	5-15	BID	Rash, CBC, LFT
Levetiracetam	6-8	tab, ER tab, liquid, IV	10	40-100	BID	Behavior
Oxcarbazepine	7-9	Tab	8-10	30-46	BID	CBC, LFT, hyponatreamia
Pregabalin	6-8	cap, tab	3.5	Up to 14	BID – TID	Weight
Topiramate	8-12	tab, sprinkle cap	1-3	5-9	BID	Weight, renal stones, cognition, ocular pressure
Vigabatrin	6-10	tab	350-500 mg	1,000-3,000 mg	BID	Vision, behavior
Zonisamide	63	tab	2-4	4-12	BID	CBC, weight, renal stones, rash
Brivaracetam	9	tab, IV	1	2-4	BID	Behavior
Clobazam	36-42	tab	5 mg	20-40 mg	BID	Sedation
Lacosamide	13	tab, IV	1	2-8	BID	EKG (PR interval)
Perampanel	105	tab	2 mg	8-12 mg	QHS	Behavior
Rufinamide	6-10	tab	10	45	BID	EKG (QT interval)

Sankaraneni R, et al. Pediatr Ann. 2015 Feb;44(2):e36-42. doi: 10.3928/00904481-20150203-10.

Differential pharmacology of AED

Properties	1st generation	2nd generation	3rd generation
Mechanism of action (MOA)	Simple MOAs (VGSC, GABA receptor)	Multiple MOAs or Specific target of action (SV2A, T-type VGCC, N-type VGCC, GAT, GABA-T, AMPA/kainite receptor)	Novel target of action (PAM at AMPA, slow-inactivated VGSC)
Pharmacokinetic properties			
- Absorption	Limited	Good	Good/prodrug
- Distribution	High % PB	Low %PB	+/-
- Metabolism	Mainly by CYP	Minor route	Mainly by CYP
- Elimination	Inactive metabolite	Unchanged form	Unchanged (some)
Adverse effects		---------- Individualized ----------	
Potential to develop drug interaction	High risk - CYP substrate - CYP inducers / inhibitors	Low to moderate	Low to moderate
Formulation and administration	IR, CR, Inj 2-3 times/day	IR, Inj 1-2 times/day	IR, Inj 2 times/day

Relationship of PK-PD-diseases: Concept of generics and bioequivalence



Bioavailability
(amount of drug that, once ingested, reaches the bloodstream)

Dingemanse J, Appel-Dingemanse S. Clin Pharmacokinet 2007;46:713-37.

Recommendations and considerations on the use of generic AEDs for treatment of epilepsy

- Generic AEDs that are bioequivalent to brand AEDs represent a valuable choice in the management of epilepsy, particularly for patients initiating monotherapy or as adjunctive treatment in patients with persistent seizures
- Generic substitutions are **not recommended** in patients who achieved seizure remission
- Switches between one generic AED to another should preferably be **avoided**
- ER or modified release (MR) formulations of AEDs should **not be used interchangeably** with IR brand or generic products

Bialer M. Epilepsia 2007;48:1825-32.