


UNDERSTANDING PHARMACOLOGY OF ANTIEPILEPTIC DRUGS:

PK/PD, SIDE EFFECTS, DRUG INTERACTION

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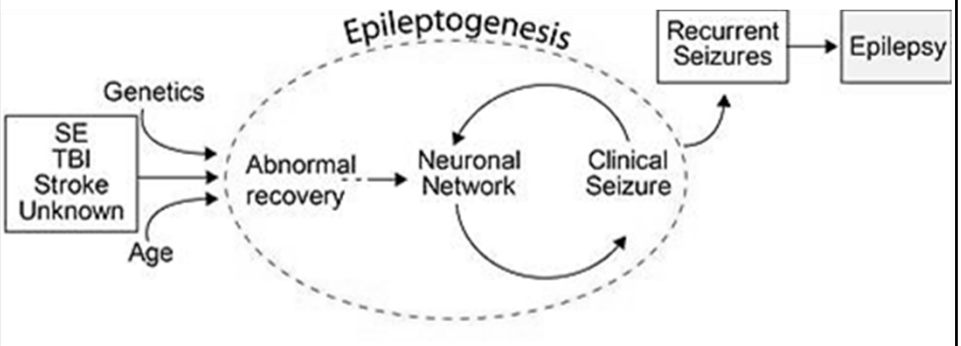
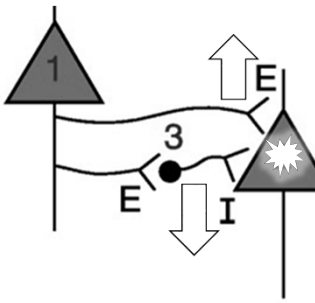
Content

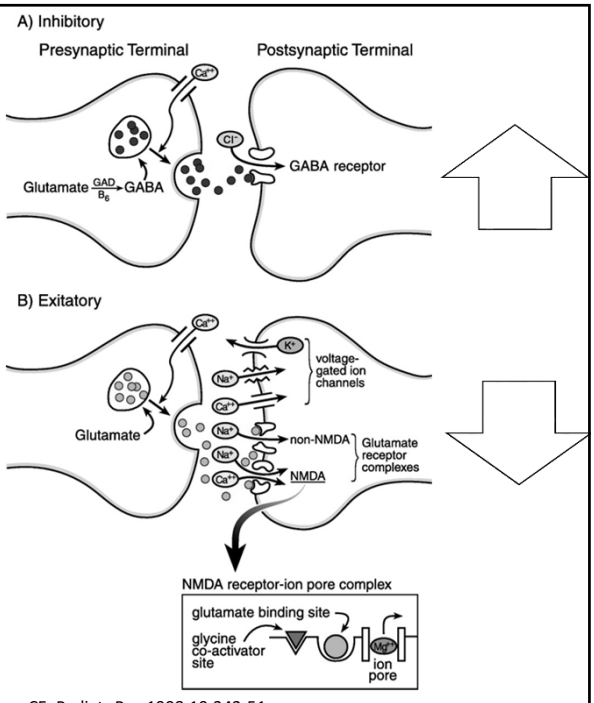
- Mechanism of action
- Pharmacokinetic
- Adverse effects
- Drug interaction

Epileptogenesis



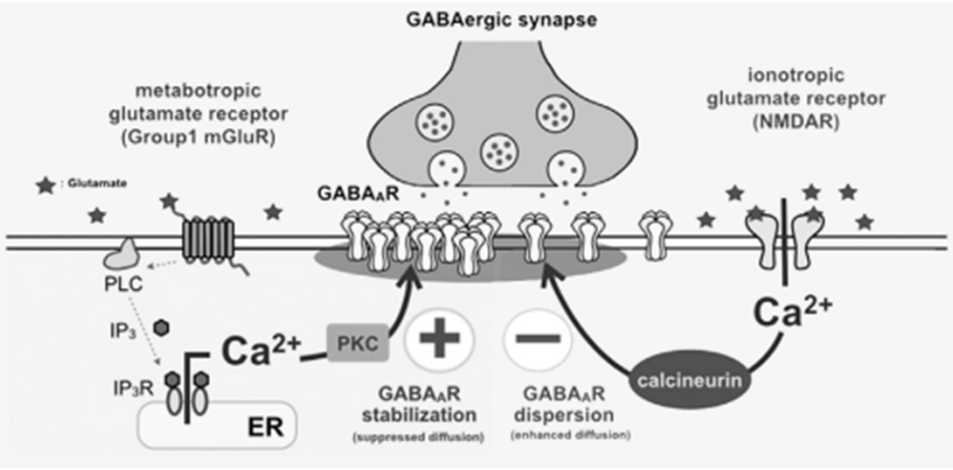
Neuronal Network Synaptic Transmission





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

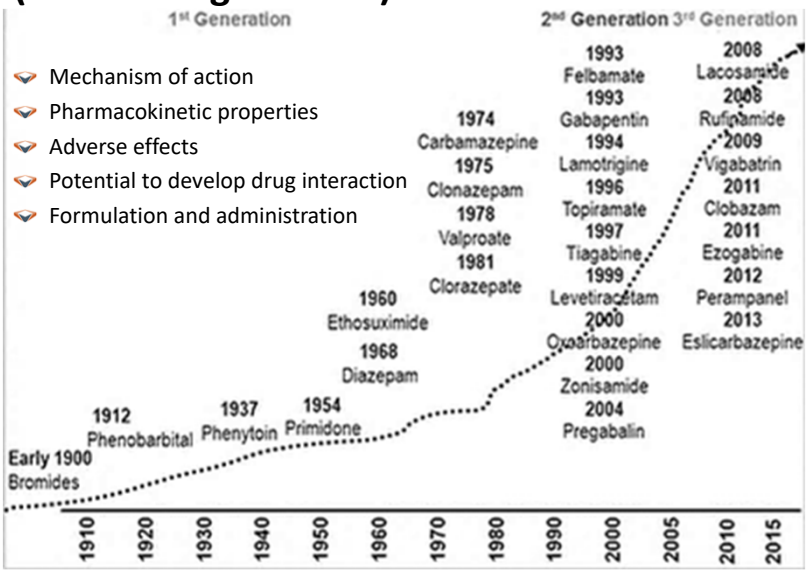
Two opposing signaling pathways for modulating $GABA_A$ receptor positioning and thus the excitatory/inhibitory balance within the brain



Bannai H, et al. Cell Rep 2015. doi: 10.1016/j.celrep.2015.12.002

Introduction of AEDs in the World (US FDA Registration)

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



Rudzinski LA, et al. J Investig Med 2016;64:1087-101.

Importance of PK/PD of AEDs in Clinical Practice

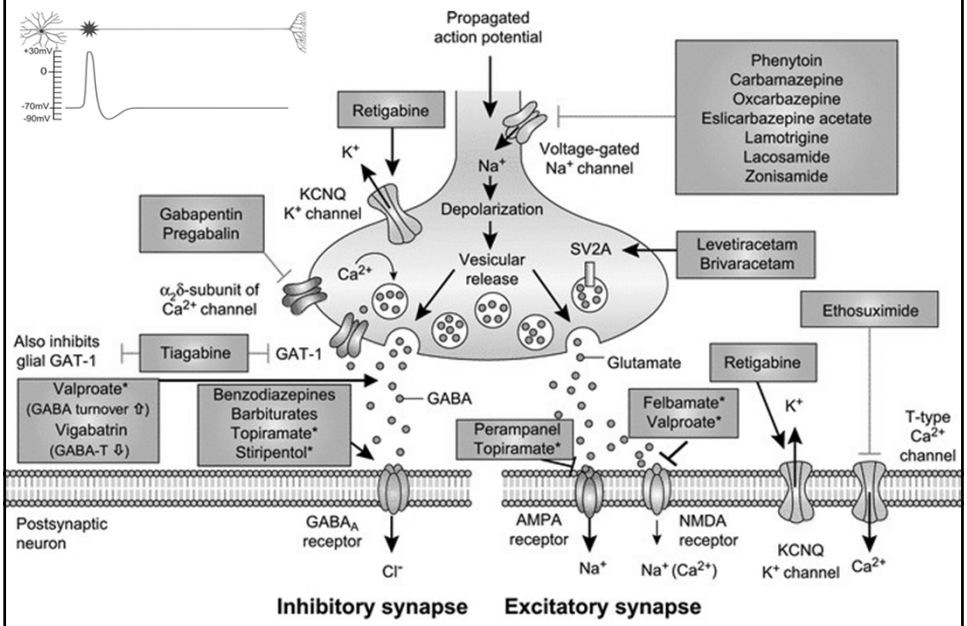
- Spectrum of actions
  - Match with seizure type
  - Combination regimen
- Dosage regimen
  - Absorption
  - Distribution
  - Metabolism
  - Elimination
- Drug interactions
- ADR (contraindications, cautions)

Mechanisms of Neuronal Excitability

- ↑ 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

Mechanism of action of clinically approved anti-seizure drugs



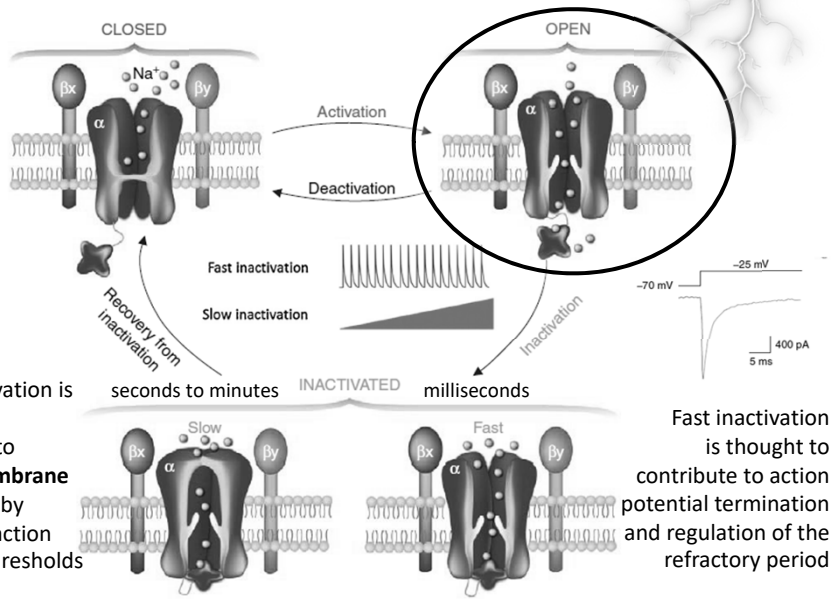
Loscher W, et al. CNS Drugs 2016;30:1055-77.

Summarize Mechanisms of Action of AEDs

AED	Inhibition of glutamate excitation	Increase in GABA level	Affinity to $GABA_A$ receptor	Blockade of sodium channels	Blockade of calcium channels	Activation of potassium channels	Other
Benzodiazepines			+				
Brivaracetam				+			+
Carbamazepine				+	+ (L)		
Eslicarbazepine				+			
Ethosuximide					+ (T)		
Felbamate	+ (NMDA)	+	+	+	+ (L)		+
Gabapentin					+ (N, P/Q)		
Ganaxolone		+					
Lacosamide				+			
Lamotrigine	+	+		+	+ (N, P/Q, R, T)	+	inh. GSK3β
Levetiracetam			+		+ (N)		SV2A, inh. Ca^{2+} store
Oxcarbazepine	+ (NMDA)			+	+ (N, P)		+
Phenobarbital	+	+	+	+			
Phenytoin				+			+
Pregabalin					+ (N, P/Q)		
Retigabine		+	+			+ (Kv7.2-7.5)	
Stiripentol		+	+				
Talampanel	+ (AMPA)						
Tiagabine		+					
Topiramate	+ (AMPA)	+	+	+	+ (L)		inh. CAI II, IV
Valproate		+			+ (T)		+
Vigabatrin		+					
Rufinamide				+			
Zonisamide				+	+ (T)		Free radical scavenger, inh. CAI

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

Inactivation Processes of VGSCs

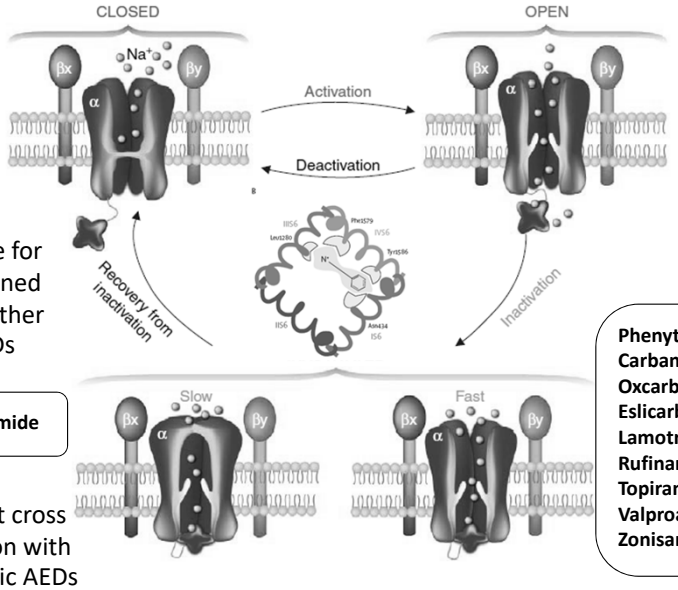


Slow inactivation is thought to contribute to **overall membrane excitability** by increasing action potential thresholds

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 Sodium Channel Blockers



Choice for combined with other AEDs

Lacosamide

Do not cross reaction with aromatic AEDs

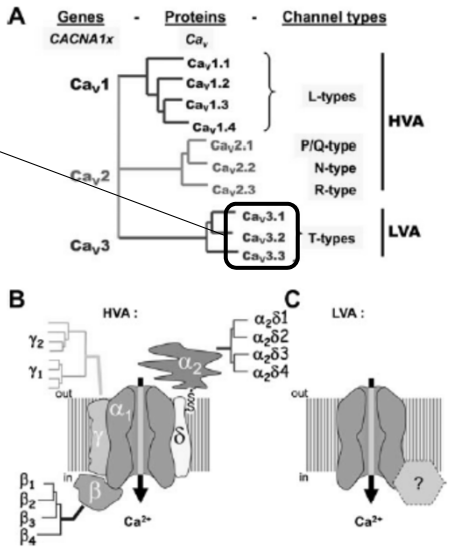
Phenytoin
Carbamazepine
Oxcarbazepine
Eslicarbazepine acetate
Lamotrigine
Rufinamide
Topiramate
Valproate
Zonisamide

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	✗	Heart	Long QT, Brugada syndrome, progressive familial heart block
Nav1.6	*SCN8A*	12q13	✓	CNS, PNS	Cerebellar atrophy
Nav1.7	*SCN9A*	2q24	✓	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



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

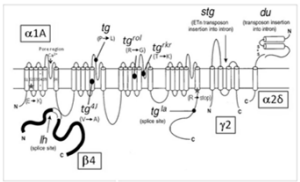
Subunit composition and function of Ca^{2+} channel types

Ca^{2+} channel	Ca^{2+} current type	Primary localizations	Previous name of $\alpha\gamma$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.

T-type calcium channel genes and related diseases

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	–

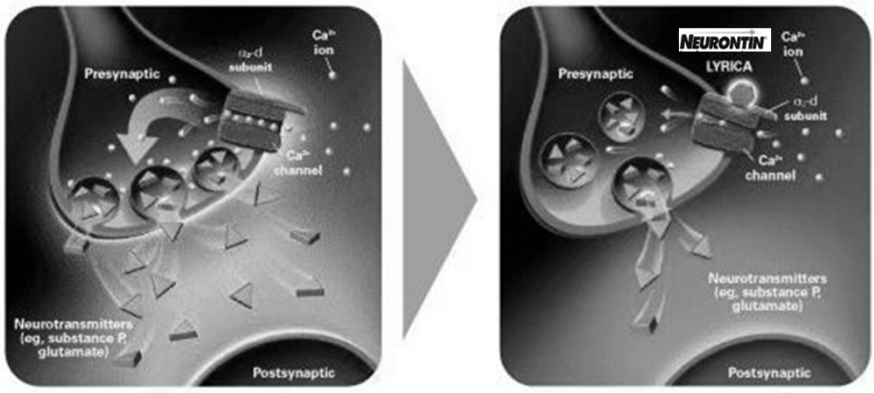


Huc S, et al. Biochim Biophys Acta 2009;1793:947-52.

Effect of AEDs on each subtype of calcium channel activity

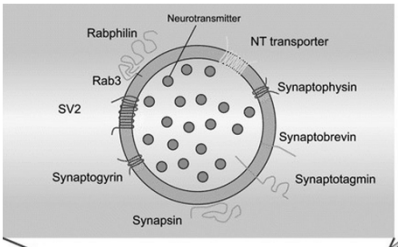
Anticonvulsant	Calcium ion channel			
	L-type	N-type	P/Q-type	T-type
Carbamazepine	*			
Ethosuximide				*
Fosphenytoin	*			*
Gabapentin	?		*	
Lamotrigine		*	?	
Levetiracetam		*	?	
Oxcarbazepine (MHD)			*	*
Phenobarbital	*	*		*
Phenytoin	*			*
Topiramate	*	*		
Zonisamide				*

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

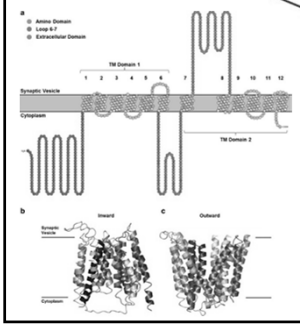


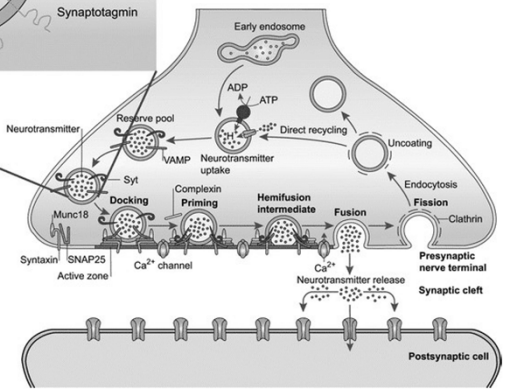
Durkin B, et al. Expert Opin Pharmacother 2010;11:2751-8.

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



SV2A

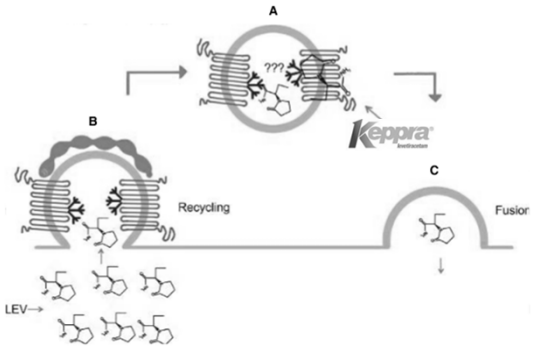




Loscher W, et al. CNS Drugs 2016;30:1055-77.

Mechanism of Levetiracetam

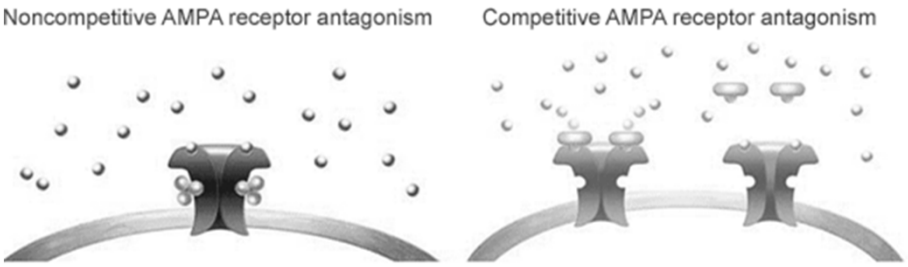
- LEV binds reversibly, saturably, and sterospecifically to SV2A
  - LEV does not bind to its two isoforms, SV2B and SV2C
- LEV binds to SV2A leading to decreased transmitter release



- 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

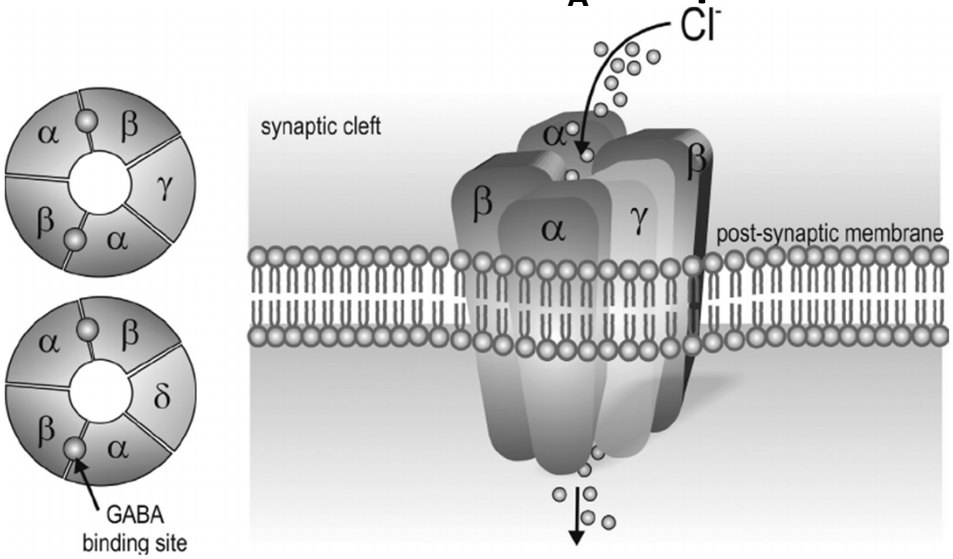
Mendoza-Torreblanca JG, et al. Eur J Neurosci 2013;38:3529-39.

Mechanism of Perampanel

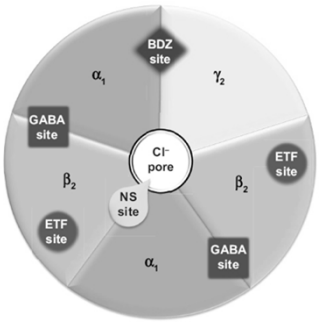


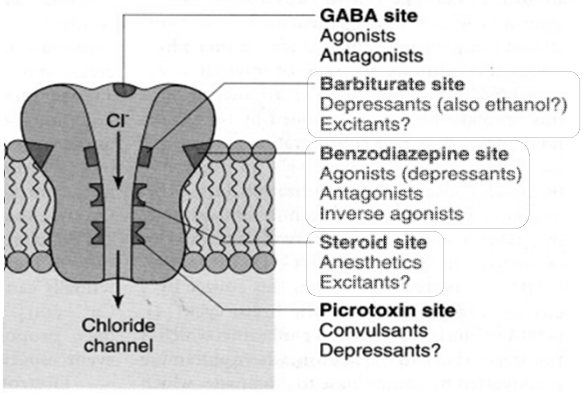
Selective non-competitive antagonist of AMPA receptor

Structure of $GABA_A$ receptor



$GABA_A$ receptor agonists





ETF = etifoxine

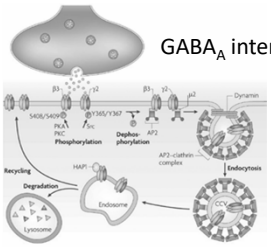
Increases intracellular chloride levels

Increases transmembrane polarity

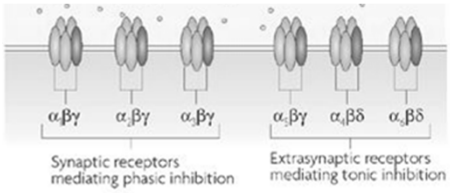
Makes the occurrence of action potential more difficult

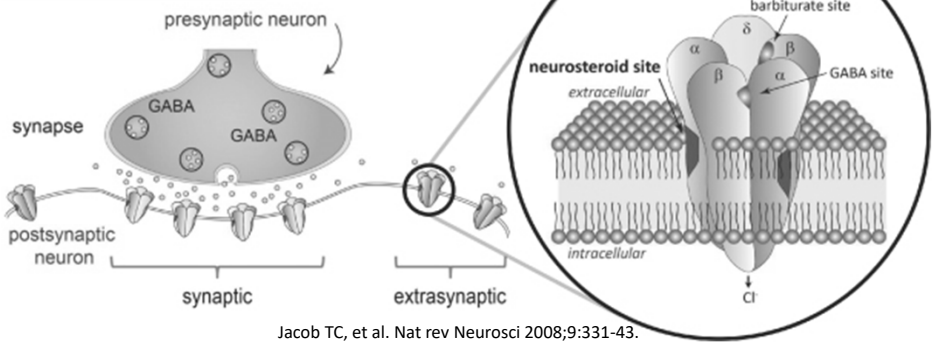
Basic Neurochemistry: Molecular, Cellular, and Medical Aspects. 6th editions. Philadelphia: Lippincott,Williams & Wilkins ; 1999.

Synaptic and extrasynaptic GABA receptor



$GABA_A$ internalization





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	+	–	–	–
Anterograde amnesia	+	ND	ND	ND
Anticonvulsant activity	+	–	–	–
Anxiolysis	–	+	–	–
Myorelaxation	–	+	+	+
Dependence	+	-	+	+

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

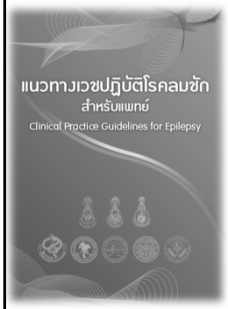
How AEDs Are They Differ?

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 (AMPA, slow-inactivated VGSC)

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.

Recommended AEDs for Epilepsy Management



ชนิดของการชัก	บัญชียา ก	บัญชียา ข	บัญชียา ง	ไม่อยู่ในบัญชียาหลักแห่งชาติ
Adults with partial onset seizure	carbamazepine phenytoin sodium valproate phenobarbital	clonazepam	lamotrigine (elderly) topiramate levetiracetam gabapentin (elderly)	oxcarbazepine zonisamide clobazam pregabalin
Children with partial onset seizure	carbamazepine phenytoin phenobarbital sodium valproate	clonazepam	topiramate lamotrigine	oxcarbazepine zonisamide clobazam
Generalized tonic clonic seizure	phenobarbital sodium valproate phenytoin carbamazepine	clonazepam	lamotrigine topiramate levetiracetam gabapentin	oxcarbazepine clobazam
Absence epilepsy	sodium valproate	clonazepam	lamotrigine	
Juvenile myoclonic epilepsy	sodium valproate		topiramate	
Atonic/tonic seizure	sodium valproate	clonazepam	topiramate lamotrigine nitrazepam levetiracetam	

Thai CPG of Epilepsy 2559.

Combination AEDs Determined by Isobolographic Studies in Animals

	CBZ	OXC	GBP	LEV	VPA	LTG	PHT	TPM	FBM	PB	ETX	VGB	PGB
CBZ		✓	✓	✓	✓	X		✓	X			✓	
OXC						X	X		X				
GBP		✓		✓	✓	✓	✓	✓		✓			X
LEV	✓	✓						✓		✓			
VPA	✓		✓			✓	✓	✓			✓		
LTG	X	X						✓					
PHT		X	✓		✓					✓			
TPM	✓	✓	✓	✓	✓	✓			✓				

✓ Favorable effects (in animal studies)
X Unfavorable effects in animal studies
Effective antiepileptic combinations in focal seizure, absence seizure, or any seizure

Broad vs. Narrow Spectrum AEDs

Broad Spectrum	Narrow Spectrum	Seizure Specific
Clonazepam	Carbamazepine	Absence
Felbamate	Ezogabine	Ethosuximide
Lacosamide[a]	Gabapentin	Valproic acid
Lamotrigine	Oxcarbazepine	Lamotrigine
Levetiracetam[a]	Perampenel	Infantile spasms
Rufinamide	Phenytoin[a]	Adrenocorticotropic hormone
Topiramate	Pregabalin	Vigabatrin
Valproate[a]	Tiagabine	
Zonisamide	Vigabatrin	

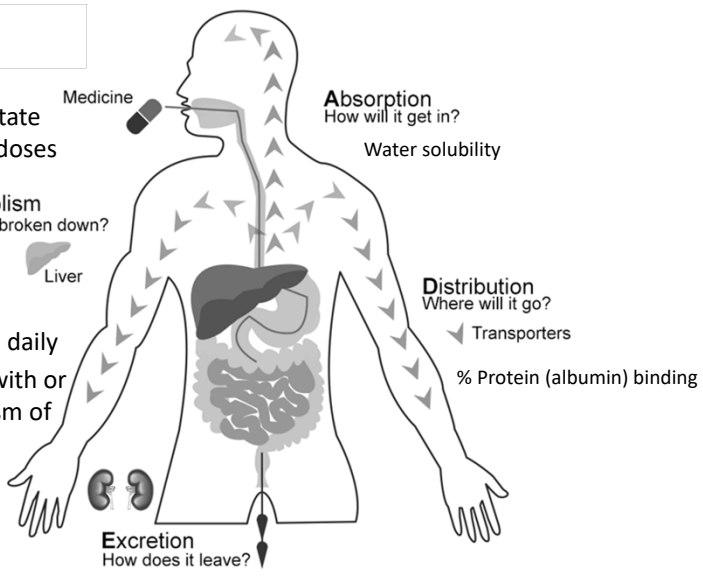
[a]Available as intravenous formulation.

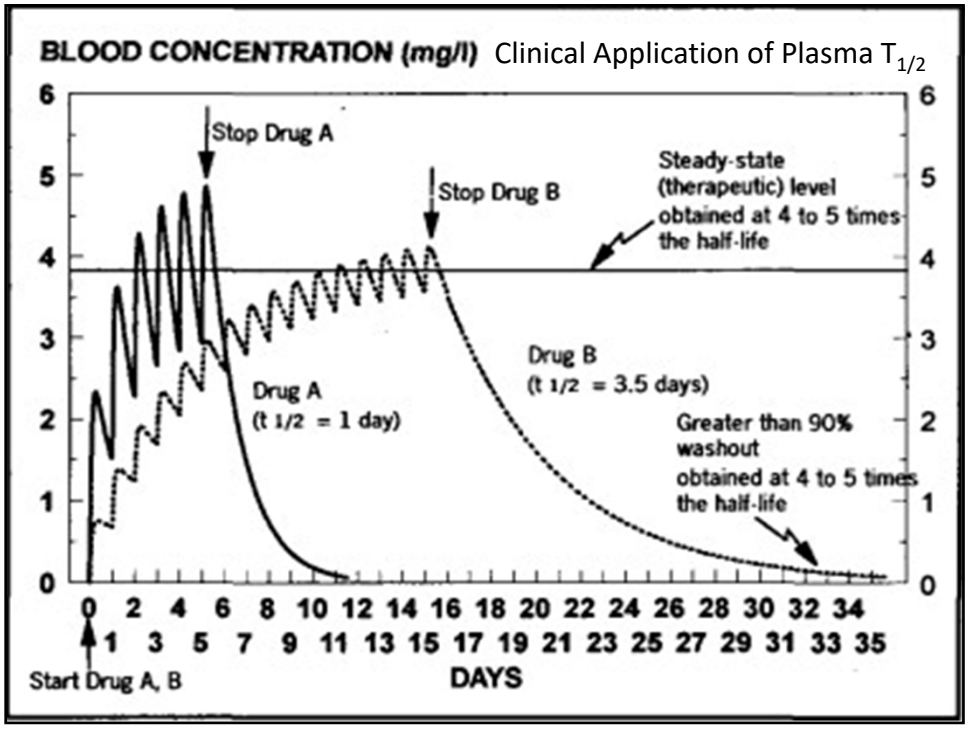
AED	Psychiatric Disorders	Pain	Neurological Disorders	Others
Carbamazepine	Mania, BD I, Agitation	TGN, PHN, DPN, Phantom limb pain		
Phenobarbital				Sedation induction
Phenytoin		NeP		Paroxysmal atrial tachycardia, Ventricular tachycardia
Valproic acid	Mania, BD, Agitation		Migraine prophylaxis	
Ethosuximide				
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

- Rapidly absorbed
- Reaches a steady state within one or two doses
- Can be dosed once daily
- Does not interact with or alter the metabolism of other medications





Time to Reach Steady State of AEDs

	F (%)	Tmax (h)	Vd (L/kg)	Protein binding (%)	$T_{\frac{1}{2}}$ (h)	Tse (d)	Therapeutic range (serum)		Maintenance dose (mg/kg/d)	
							ug/L	umol/L	Infant	Children
Newer AEDs										
CLB	> 90	1~4	3.0	85	20~40	6	20~75	60~250	0.5~1	0.25~0.75
FBM	> 90	2~6	0.75	25	14~23	4	-	-	-	15
GBP	30~60	2~3	0.85	0	5~9	2	-	-	-	30~90
LEV	> 90	1~2		-	6~8	2				20~8 -
LTG	> 90	1~3	1.0	55	15~60	3~10	-	-	-	2~8
OXC	> 90	-	-	45	10~15	2	8~20	30~80	15~60	20~50
TGB	> 90	1~2	1.4	96	2~9	1~2	-	-		0.1~1 (adult)
TPM	> 90	1~4	0.65	15	12~30	3~5	-	-	2~2-	2~10
VGB	80	0.5~2	0.8	-	5~7	2	-	-	80~150	40~80
ZNS	-	2~5	1.5	55	50~70	10~15	-	-	-	5~20
Established AEDs										
CBZ	75~85	4~12	0.8~2	75	20~50	20~30	3~12	12~50	10~40	10~40
CNZ	> 90	1~4	4	85	20~40	6	20~75	60~250	0.1~0.2	0.05~0.5
DZP	> 90	1	1~2	95	36	7	100~700	350~2500		0~0.5
ESM	> 90	1~4	0.65	< 10	30~60	7	40~100	300~700	20~40	15~45
PB	> 90	0.5~4	0.55	45	65~110	15	10~30	4~130	3~5	3~5
PHT			0.7~1.2	74~90	40~60		10~20		5~15	4~7
VPA	> 90	1~8	0.16	70~93	5~15	2	50~100	350~700	20~40	15~60

Chung S. J Korean Med Assoc 2009;52:611-26.

Comparative Pharmacokinetics of Conventional AEDs

Drug	Oral bioavailability (%)	Serum protein binding (%)	Time to peak concentration (h)	Time to steady-state[j] (days)	Half-life in the absence of interacting comedication (h)	Half-life in patients comedicated with enzyme inducers (h)	Comment	Reference range (mg/L)
Carbamazepine	≤85	75	2–9[a]	2–4[b]	8–20[b]	5–12[b]	Active 10,11 epoxide metabolite contributes to clinical effects	4–12
Clobazam	≥95	85	1–3	7–10[c]	10–30	?	Active N-desmethyl-metabolite contributes to clinical effects	0.03–0.3 (clobazam) 0.3–3 (desmethyl metabolite)
Clonazepam	≥95	85	1–4	3–10	17–56	11–35	7-amino metabolite retains some pharmacological activity	0.02–0.07
Ethosuximide	≥90	0	1–4	7–10	40–60	20–40		40–100
Phenobarbital	≥95	55	0.5–4	12–24	70–140	70–140		10–40
Phenytoin	≥80[f]	90	1–12[f]	5–17	30–100[g]	30–100[g]		10–20
Valproic acid	≥90	90[i]	3–6[k]	2–4	11–20	6–12		50–100

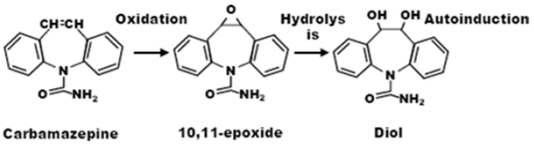
Patsalos PN, et al. Epilepsia 2008;49:1239-76.

Pharmacokinetic Profiles of Conventional AEDs

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.

Carbamazepine

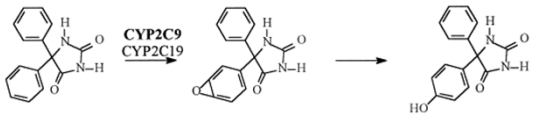


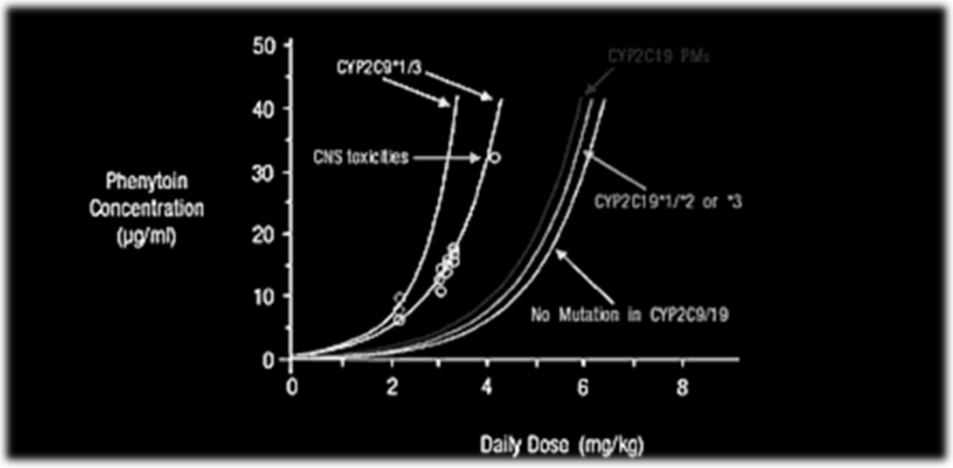
- Dosage forms
  - Available in 100 mg; 200 mg tablets; suspension – BID/TID
  - Available in a slow release preparations (CR formulation) - BID
- Carbamazepine half life — time dependent/auto-induction
  - First 2-6 weeks: 30-35 hrs -----> OD dosing
  - After 2-6 weeks: 12-20 hrs -----> BID/TID dosing

Dosing of Carbamazepine : Titration is Importance

- Initiation of therapy, All Patients
  - week 1 : ¼-⅓ the maintenance dose rate
  - week 2 : ½-⅔ the maintenance dose rate
  - week 3 : ¾- all of the maintenance dose rate
- Maintenance Therapy
  - Adult and child (> 15y) 7- 15 mg/kg/d
    - usual maintenance dose: 400-1,600 mg/d
  - Children (< 15y) 11-40 mg/kg/d

Genotype of CYP2C9 and CYP2C19 of Phenytoin Metabolism





Phenytoin Product Formulations

- Oral
  - PHT 50 mg tab: q8h

  - PHT sodium 100 mg ER capsule (Dilantin®): OD/TID

  - PHT suspension (125 mg/5 mL): q8h

- Injection
  - PHT sodium solution: q8h

- Generics
  - PHT sodium IR capsule: q8h

PK Disadvantages of Conventional AEDs

- Low to intermediate bioavailability
- High percentage of plasma protein binding
- Mainly be metabolized by CYP450
  - PHT has a non-linear metabolism property
- Induce or inhibit CYP450 activity
  - CBZ, PHT, PB are inducer of CYP450 and UGT
  - VPA is an inhibitor of CYP2C9 and UGT
- Narrow therapeutic index

Pharmacokinetic Profiles of Second-Generation AEDs

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 2-25 μg/mL	≥80	0.6-0.8	15	20-30	R (70%): unchanged H (30%): CYP2C19 and glucuronidation	No
Vigabatrin N/E	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.

PK Advantages of Second-Generation AEDs

- Rapid absorption, high oral bioavailability
- Less protein binding (<10%)
- Primarily renal elimination or mix metabolic pathway
- Lack of cytochrome P450 (CYP) enzyme-inducing potential and interactions with other drugs

Pharmacokinetic Profiles of Third-Generation AEDs

AED (serum conc)	F (%)	Vd (L/Kg)	Protein binding (%)	T1/2 (h)	Metabolism & Elimination	Active metabolite
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 <15 μg/mL	100	0.5-0.8	<30	13	R (40%): unchanged H: demethylation, CYP2C19 (30%)	No
Perampanel N/E	100	1.1	95	52-129	H (98%): CYP3A4 (major), CYP3A5	No
Rufinamide N/E	≥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.

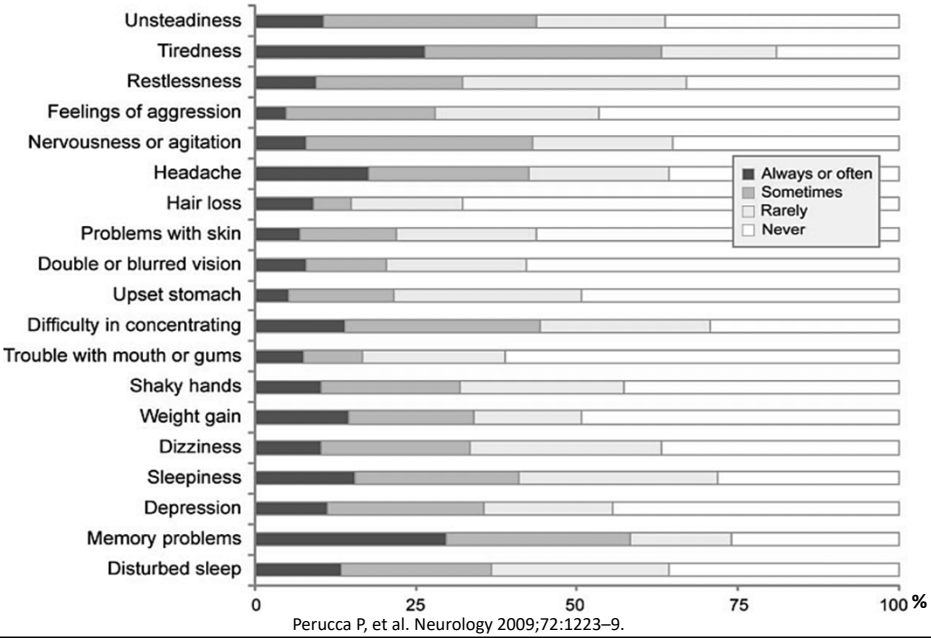
AEDs	Protein binding (%)	Hepatic Metabolism		Renally Excretion (%)
		Phase I (CYP)	Phase II (UGT)	
Carbamazepine	75	3A4		
Clobazam	85	2C19, 3A4		
Clonazepam	85	3A4		
Diazepam	98	2C19, 3A4		
Lorazepam	93		2B15	
Midazolam	95	3A4		
Phenobarbital	55	2C9, 2C19		22
Phenytoin	90	2C9, 2C1		
Valproate	90	B-oxidation,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

Anderson GD, et al. Clin Pharmacokinet 13 Oct 2013. DOI 10.1007/s40262-013-0107-0

How AEDs Are They Differ?

Properties	1st generation	2nd generation	3rd generation
Mechanism of action (MOA)	Simple MOAs	Multiple MOAs or Specific target of action	Novel target of action
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)

Type A Adverse Antiepileptic Drug Effects



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

Adverse Effects of AEDs

Adverse effect	CBZ	CLB	ESL	ETS	FBM	GBP	LCM	LEV	LTG	OXC	PGN	PER	PHB	PHT	TGB	RTG	TPM	VPA	VGB	ZNS
EARLY ONSET ADVERSE EVENTS																				
Somnolence	–	●	●	●	–	●	●	●	●	–	●	–	●	–	●	●	●	–	●	●
Dizziness	–	●	–	●	–	●	●	●	●	●	–	–	–	●	●	–	●	–	●	●
Seizure aggravation	●	●	●	–	–	●	–	–	–	–	●	–	–	●	●	–	–	–	●	
Gastrointestinal	●	–	–	●	●	●	–	●	–	●	–	–	–	–	–	–	–	●	–	●
Hypersensitivity (SJS/TEN)	●	–	●	●	●	–	–	–	●	●	–	–	●	●	–	–	●	–	–	●
Rash	●	–	–	–	–	–	–	–	●	●	–	–	–	●	–	–	–	–	–	–

CLB=clobazam; CBZ=carbamazepine; ESL=eslicarbazepine; ETS=ethosuximide; FBM=felbamate; GBP=gabapentin; LEV=levetiracetam; LCM=lacosamide; LTG=lamotrigine; OXC=oxcarbazepine; PER=perampanel; PGB=pregabalin; PHB=phenobarbital; PHT=phenytoin; PRM=primidone; RTG=retigabine; ; TPM=topiramate; VPA=valproate; VGB=vigabatrin; ZNS=zonisamide; SJS/TEN=Stevens-Johnson syndrome or toxic epidermal necrolysis. Key: – no increase, ● low risk, ● medium risk, ● high risk

Schmidt D, et al. BMJ 2014;348:g254.

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
USA	In general 2.6-7.1[19], Boston 4.2[18] (2 per 100,000 patient year exposure)[24]	0% in Caucasian and native American[30-32], Asian 4.9[33]	
Europe	In general, 2-3[3]; Sweden 0.4, French 1.2 Germany 2.03 (2-9 per 100,000 patient year exposure)[24]	Rare (1-2)[7,28,34] Ireland 0[10]	
South America		Argentina 0[35]	
• Thailand		8.5-27.5[10,39-40]	83.3[41]
• Malaysia[38]	(41 per 100,000 patient year exposure)[24]	Malay 15.7, Chinese 5.7, Indian 0, Myanmese 100 (1 patient)	Malay 75, Indian 100
• Thailand		8.5-27.5[10,39-40]	83.3[41]
• Vietnam		>10[42]	
• Indonesia		16	
• Philippines	(55 per 100,000 patient year exposure)	Ivatan (minority) 36#	
• India		Mumbai 1.9[43], Kandesh 6[44], Tamil Nadu 0[45], Bhil 4[46], Parsi 0[47] Punjab 1[48]	
• Sri Lanka		Rare[49]	
• Japan	(17 per 100,000 patient year exposure)[24]	0.2#	
• Korea		0.4#	

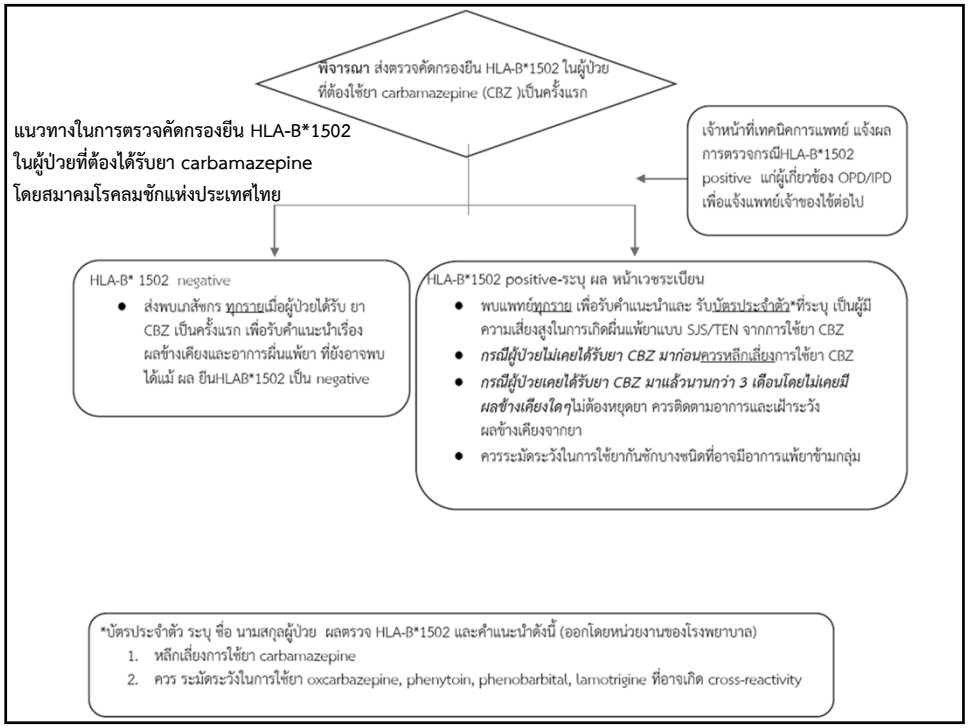
CBZ: carbamazepine, SJS: Steven-Johnson syndrome, TEN: toxic epidermal necrolysis
Data in bracket was quoted from Novartis CBZ SJS/TEN Reports 2000-2006, per 100,000 patient exposure year.[24]
Allele frequency based on volunteers in the U.S. National Marrow Donor Program.[24]

- 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 in Adult Patients

NOT TAKING carbamazepine, phenytoin, primidone, phenobarbital, rifampin, 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

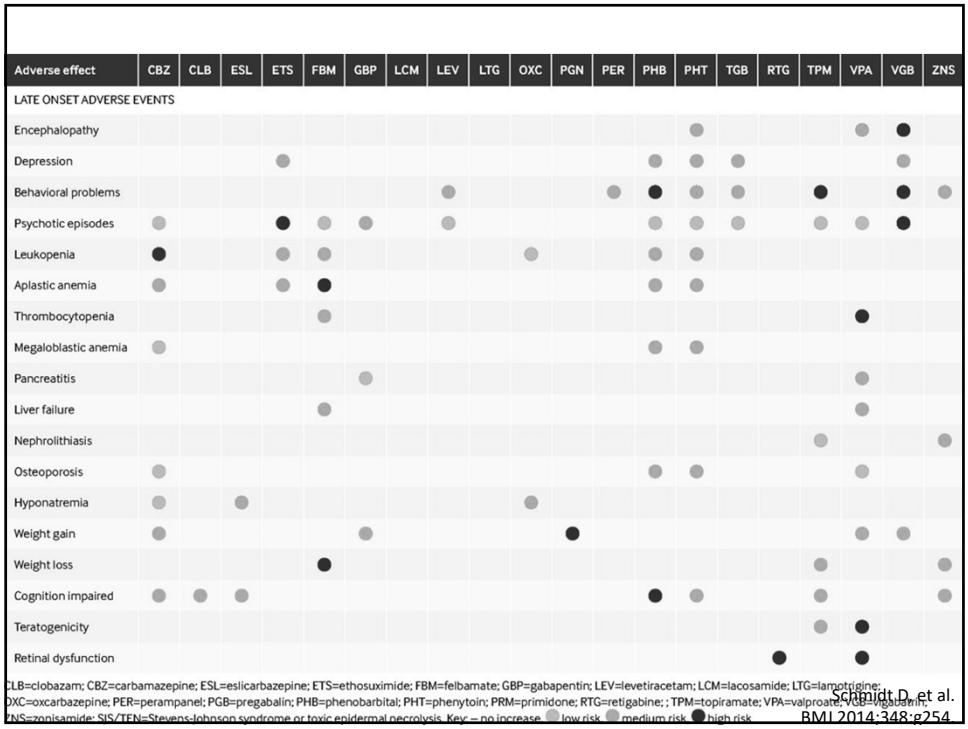
TAKING valproate

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

TAKING carbamazepine, phenytoin, primidone, phenobarbital, or rifampin and NOT TAKING val

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**



Schmidt D, et al. BMJ 2014;348:g254

ชื่อยา	ผลข้างเคียงที่พบบ่อย	ผลข้างเคียงสำคัญที่ต้องเฝ้าระวัง	การแพ้ยา
carbamazepine	คลื่นไส้ ซึม เดินเซ เห็นภาพซ้อน	Hyponatremia (SIADH), aplastic anemia, ตับอักเสบ เม็ดเลือดขาวต่ำ	skin rash, Steven Johnson syndrome*
clonazepam	อ่อนเพลีย ง่วง hypotonia พฤติกรรมเปลี่ยนแปลง น้ำลายและเสมหะมาก	กดการหายใจ (ถ้าใช้ยาฉีด)	
gabapentin	ง่วงนอน ซึม เวียนศีรษะ บวม		
lamotrigine	มึนงง เห็นภาพซ้อน เดินเซ		skin rash, Steven Johnson syndrome
levetiracetam	ซึม มึนงง	อารมณ์หงุดหงิด ก้าวร้าว อาการทางจิต	
nitrazepam	ง่วงซึม เสมหะ น้ำลายมาก อ่อนเพลีย hypotonia		
oxcarbazepine	มึนงง ง่วงซึม เดินเซ	hyponatremia	
phenobarbital	เด็ก: ชูกชนไม่อยู่สุข พฤติกรรม เปลี่ยนแปลงก้าวร้าว ผู้ใหญ่: ง่วงซึม อ่อนเพลีย บุคลิกภาพเปลี่ยนแปลง เครียด	serum sickness	skin rash, Steven Johnson syndrome
phenytoin	เวียนศีรษะ เห็นภาพซ้อน ซึม เดินเซ คลื่นไส้ อาเจียน เหงือกบวม หน้าหยาบ hirsutism สิวเพิ่มขึ้น	ตับอักเสบ แคลเซียมต่ำ choreo-athetosis ไข้ และต่อมน้ำเหลืองโตทั่วไป เส้นประสาทอักเสบ megaloblastic anemia (folate deficiency) cerebellar degeneration	skin rash, Steven Johnson syndrome
pregabalin	ง่วงนอน ซึม เวียนศีรษะ		
sodium valproate	มือสั่น คลื่นไส้ อาเจียน ปวดท้อง ผมร่วง น้ำหนักเพิ่ม	ตับอักเสบ ตับอ่อนอักเสบ ภาวะเกล็ดเลือดต่ำ ภาวะ hyperammonemia	
topiramate	มึนงง เดินเซ การพูดผิดปกติ น้ำหนักลด	นิ่วในไต ต้อหิน เหงื่อออกน้อย (oligohidrosis) ความคิดเชื่องช้า ภาวะ hyperammonemia	
vigabatrin	มึนงง ง่วงซึม	ความผิดปกติของลานสายตา	
zonisamide	มึนงง ง่วงซึม เดินเซ เบื่ออาหาร คลื่นไส้	นิ่วในไต ภาวะ agranulocytosis, aplastic anemia	skin rash โดยเฉพาะมีประวัติแพ้ยากลุ่ม Sulfonamide
lacosamide	มึนงง ง่วงซึม ภาพซ้อน เดินเซ	atrioventricular block, palpitation	
perampanel	มึนศีรษะ ง่วงซึม เดินเซ	หงุดหงิด ก้าวร้าว อาการทางจิต มี suicidal ideation	

Clinical Practice Guideline in Epilepsy 2559.

Disturbances of Cognitive Abilities of AEDs

- 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

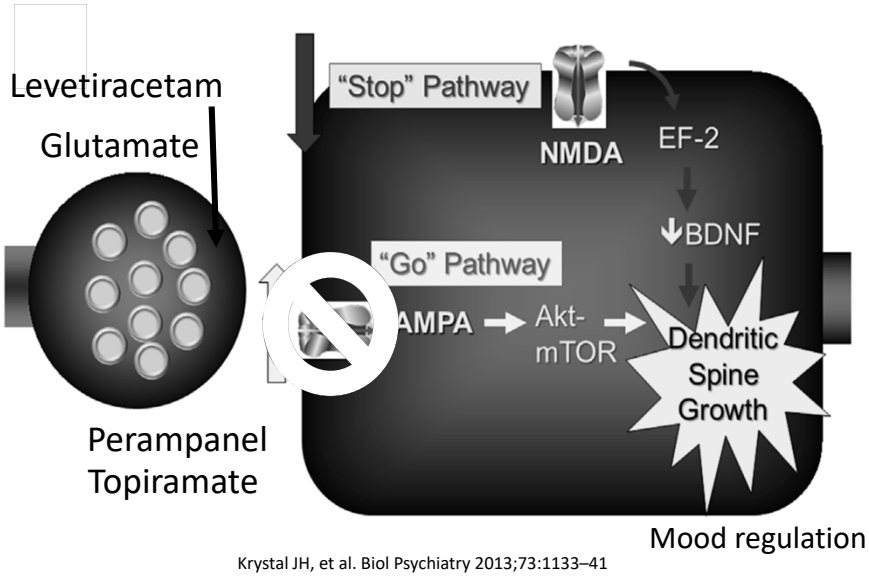
Meador KJ.NEUROLOGY.2002;58(Suppl 5):S21–S26.

AEDS 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

Pharmacol Rev 2016;68:563-602.

Effects of AEDs which Acting on Glutamatergic Pathway in Neuropsychiatric Symptoms



Krystal JH, et al. Biol Psychiatry 2013;73:1133–41

QTc Prolongation by AEDs 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.

Noncardiac QT Interval-Prolonging Medications

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.

Teratogenic Profile 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," New York, N.Y.; February 28, 2003. 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. See discussion by Yerby and colleagues on page S33 of this supplement.

Penovich PE, et al. Clev Clin J Med 2004;71(Suppl 2):S49-57.

Conditions Potentially Exacerbated by AEDs

Myasthenia gravis	PHT, GBP
Mitocondrial disorders	VPA**
Porphyria	CBZ, PB, PHT, PRM, TPM, VPA, ESM, MDZ, ZNS, LTG, *FBM, TGB*
	Preferably use LEV, GBP, PGB, CLB, LZP, OXC
	No data for LCM, RUF
HIV	VPA ??
OSA	VPA, GBP, PGB, VGB
Respiratory depression	PB, PRM, BZD

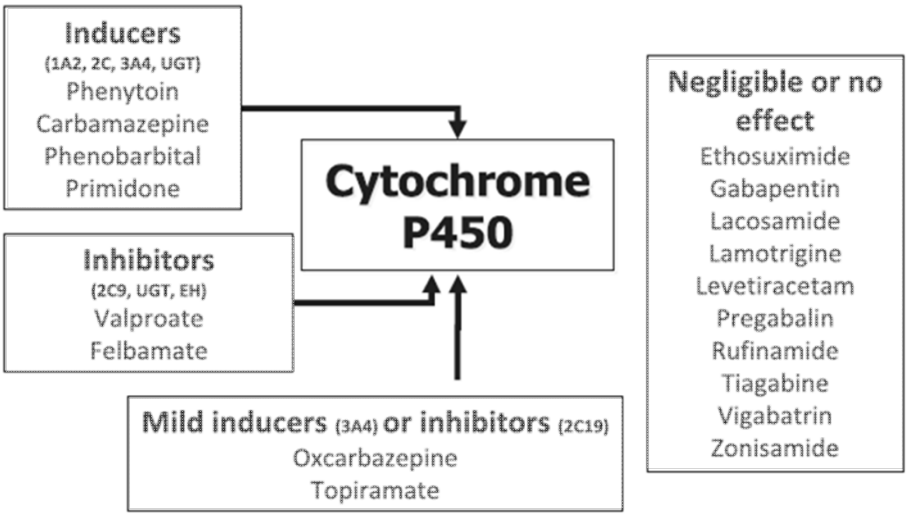
** Liver failure in Alpers-Huttenlocher syndrome; hyperammonemic encephalopathy in ornithine transcarbamylase deficiency

Gaitatzis A, et al. CNS Drugs 2013;27:435-55.

How AEDs Are They Differ?

Properties	1st generation	2nd generation	3rd generation
Mechanism of action (MOA)	Simple MOAs	Multiple MOAs or Specific target of action	Novel target of action
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 AEDs



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 AEDs

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

Valproate

AEDs with CYP inducers

How AEDs Are They Differ?

Properties	1st generation	2nd generation	3rd generation
Mechanism of action (MOA)	Simple MOAs	Multiple MOAs or Specific target of action	Novel target of action
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

Product Formulations of AEDs

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

How AEDs Are They Differ?

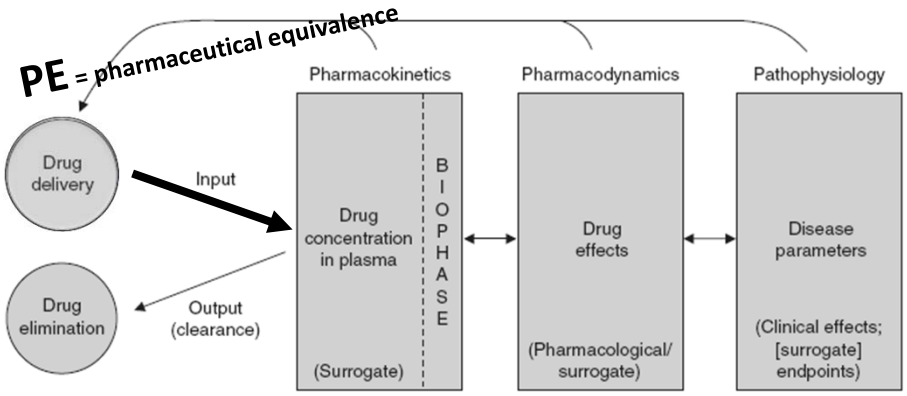
Properties	1st generation	2nd generation	3rd generation
Mechanism of action (MOA)	Simple MOAs	Multiple MOAs or Specific target of action	Novel target of action
Pharmacokinetic properties			
- Absorption	Limited	Good	Good/prodrug
- Distribution	High % PB	Low %PB	+/-
- Metabolism	Mainly by CYP	Minor route	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

Initiation, Escalation and Dosage Regimen of AEDs

Drug	Dosing regimen	Ped initial dose (mg/kg/day)	Ped escalation	Ped usual dose (mg/kg/day)	Adult initial dose (mg/day)	Adult escalation	Adult usual maintenance dose (mg/day)	Time to steady state (day)
carbamazepine	bid-tid	10-15	5 mg/kg/wk	10-30	200	200 mg/wk	600-1200	3-4
gabapentin	tid-qid	10	300 mg/day	30-100	300	300 mg/day	900-3600	1-2
lamotrigine	bid	ดูตารางที่ 15						3-10
levetiracetam	bid	10	10 mg/kg/wk	20-80	500	500 mg/wk	1000-3000	2
oxcarbazepine	bid	10	10 mg/kg/wk	20-50	150-300	300 mg/wk	600-2400	2
phenobarbital	od-bid	4-6	1-2 mg/kg /2wks	3-5	60-90	30 mg/4wks	90-120	15-20
phenytoin	od-bid	5	1-2 mg/kg /2 wks	5-8	200-300	50-100 mg/wk	300-500	15-20
pregabalin	bid	NA	NA	NA	75-150	75 mg/wk	150-600	< 2
sodium valproate	bid-tid	10-15	5-10 mg/kg/wk	20-60	500-1000	200-250 mg/wk	1000-3000	2
topiramate	bid	1	1 mg/kg/wk	5-9	25-50	25 mg/wk	200-400	3-5
vigabatrin	bid	40-50	10-20 mg/kg/ wk	100-150	500-1000	500 mg/wk	2000-4000	2
lacosamide	bid	NA	NA	NA	200	100 mg/wk	300-400	3
zonisamide	od-bid	NA	NA	NA	100	50 mg/wk (200mg/day at least in 2 wks)	100-600	14
perampanel	od (hs)	NA	NA	NA	2	2 mg/wk	4-8	15-20

Clinical Practice Guideline in Epilepsy 2559.

Relationship of PK-PD-diseases: Concept of 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.