Epilepsy Course for Neurology and Pediatric Neurology Residents

PHARMACOLOGY OF ANTISEIZURE MEDICATIONS

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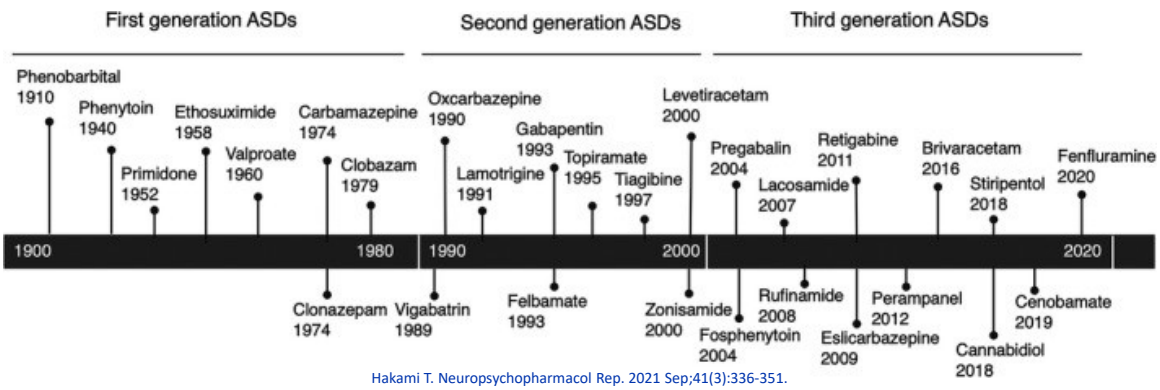
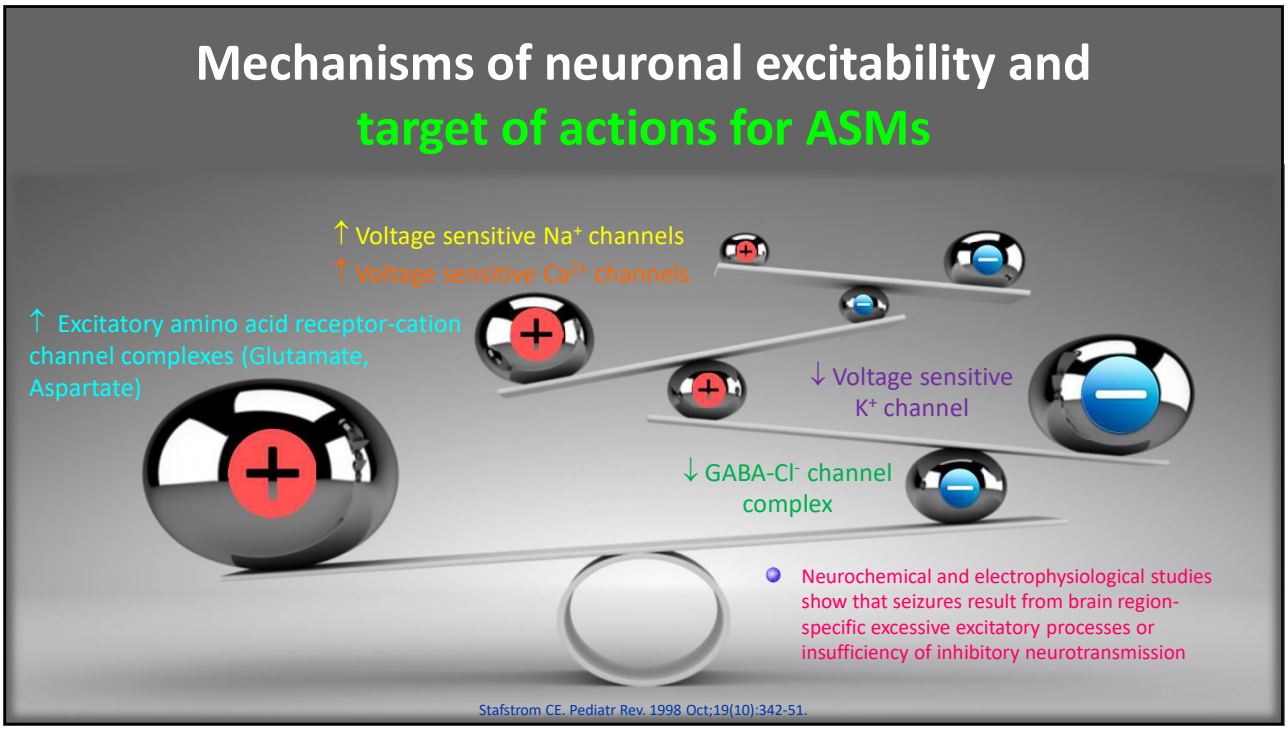
Classification and year of introduction of ASMs

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



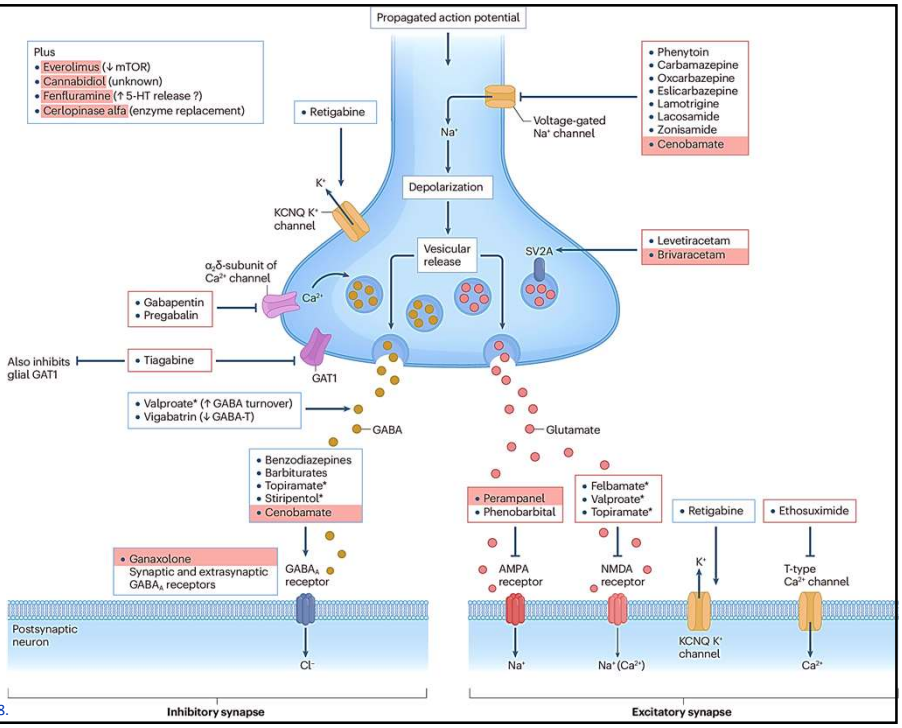
Hakami T. Neuropsychopharmacol Rep. 2021 Sep;41(3):336-351.

Mechanisms of neuronal excitability and target of actions for ASMs



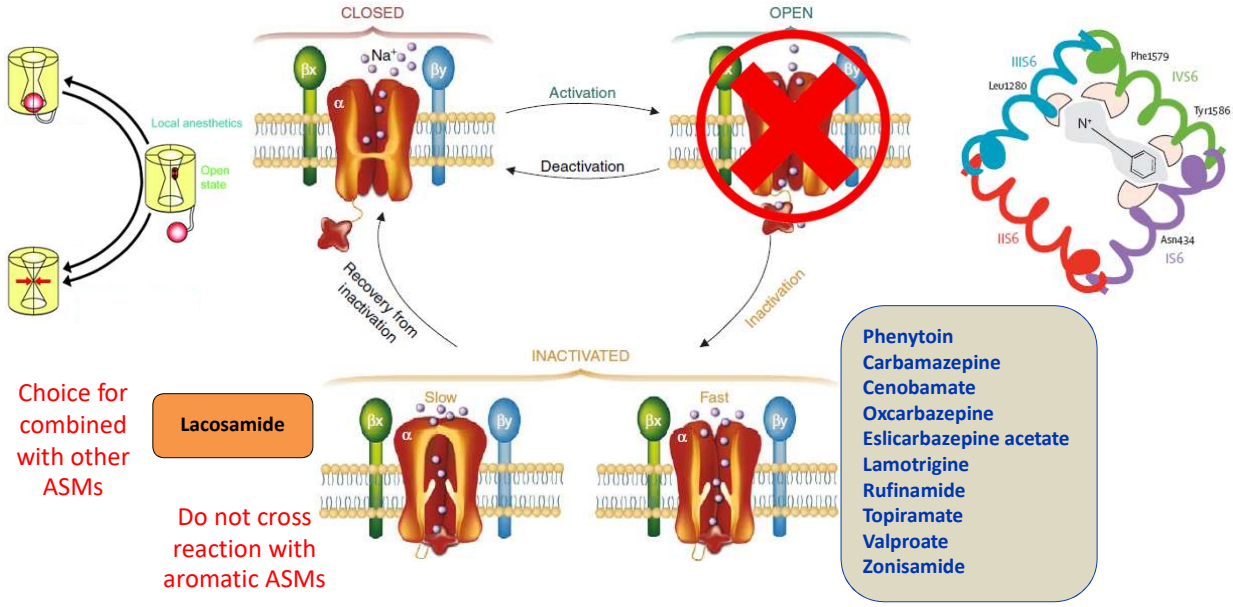
Stafstrom CE. Pediatr Rev. 1998 Oct;19(10):342-51.

Molecular targets of antiseizure medications



Klein P, et al. Nat Rev Drug Discov. 2024 Sep;23(9):682-708.

Mechanism of actions of VGSC (sodium channel) blockers



Choice for combined with other ASMs

Lacosamide

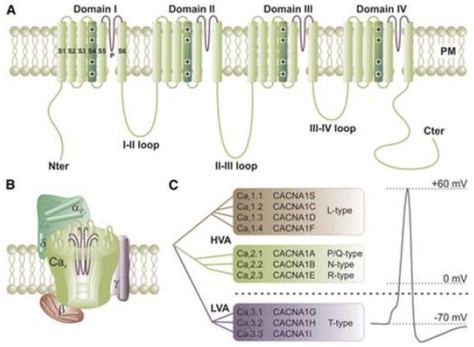
Do not cross reaction with aromatic ASMs

Phenytoin
Carbamazepine
Cenobamate
Oxcarbazepine
Eslicarbazepine acetate
Lamotrigine
Rufinamide
Topiramate
Valproate
Zonisamide

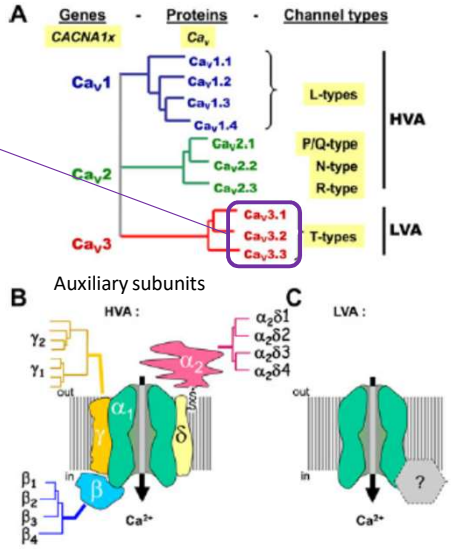
Tissue distribution of NaV subtypes

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	–

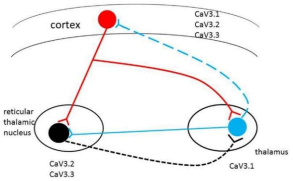
Huc S, et al. Biochim Biophys Acta. 2009;1793:947-52.

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

T-Type calcium channel in absence seizures



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.; Chen Y, et al. Front Neurol. 2014 May 9;5:45.

T-type calcium channel mutations in epilepsy

- T-type calcium channels are critically involved in normal burst firing in the thalamocortical circuitry recruited in the spike-wave discharges that underlie absence seizures and in the intrinsic burst firing of hippocampal pyramidal neurons in temporal lobe epilepsy (TLE)
  - Variants in the T-type calcium channel gene *CACNA1H* which encodes a low-threshold T-type Ca2+ channel were associated with childhood absence epilepsy
  - T-type calcium currents were significantly larger in CA1 pyramidal cells of animals in the kindling model of TLE
- An inhibitor of T-type Ca2+ currents show anticonvulsive effects in the treatment of absence seizures

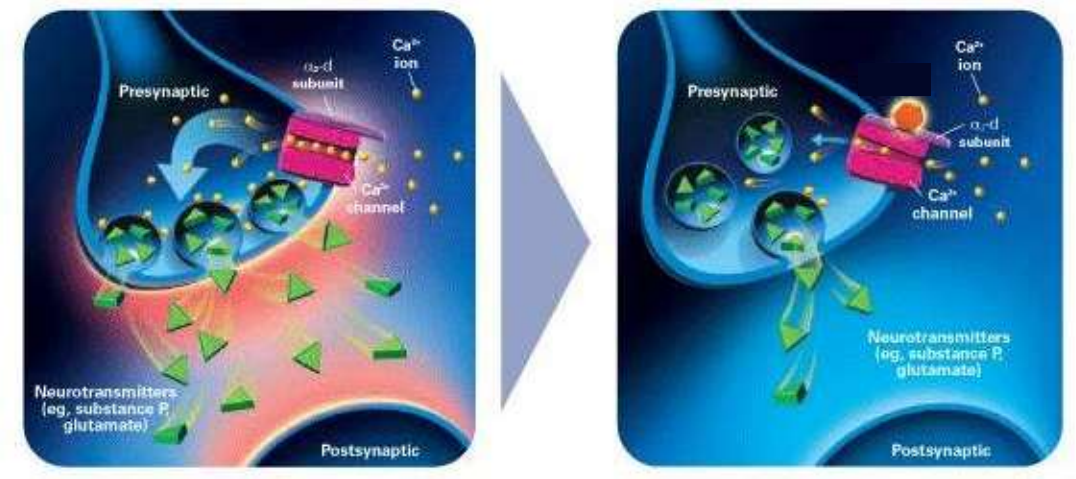
Gambardella A, Labate A. Prog Brain Res. 2014;213:87-96.

Ancillary subunits of voltage-gated calcium channels in seizure disorders

- Ancillary calcium channel subunits are important regulators of HVA calcium channel function
- Mutations in either γ- or $\alpha 2$-δ-subunits have so far not been linked to epilepsy in humans (absence epilepsy, ataxia, TLE, juvenile myoclonic epilepsy)

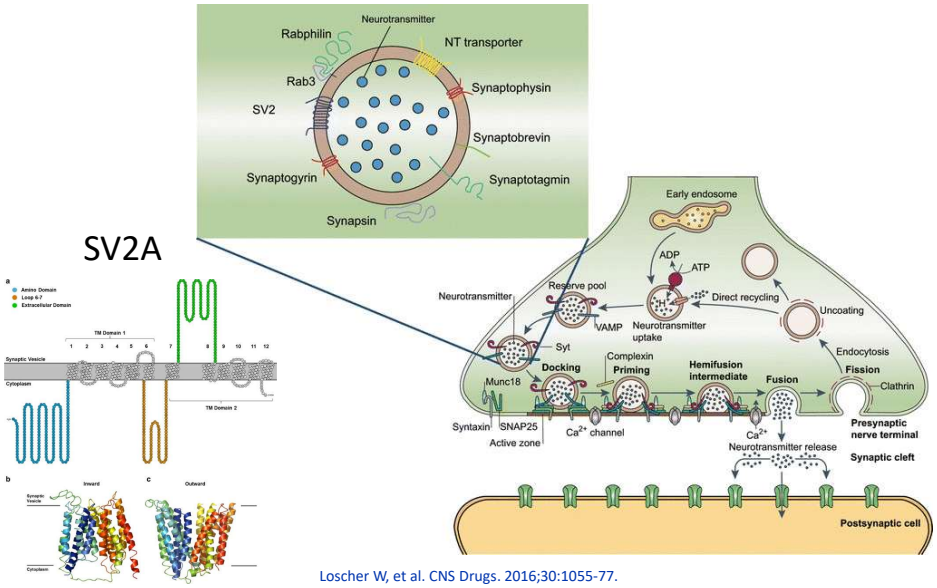
Gambardella A, Labate A. Prog Brain Res. 2014;213:87-96.

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.

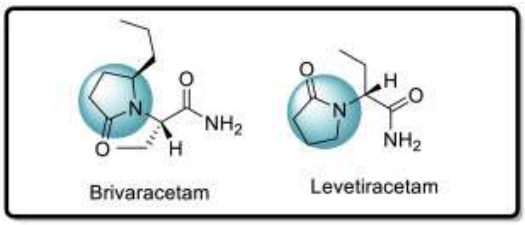
The dynamics of SVs at the presynaptic terminal, illustrating detailed mechanism of NT release and synaptic vesicle recycling

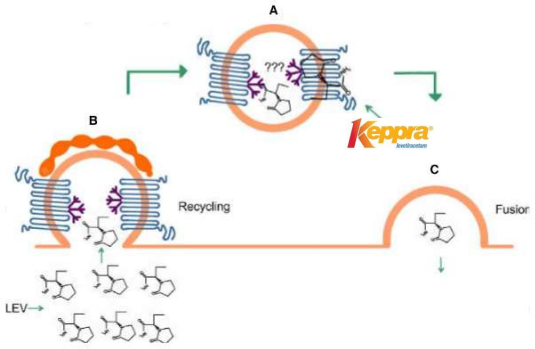


Loscher W, et al. CNS Drugs. 2016;30:1055-77.

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

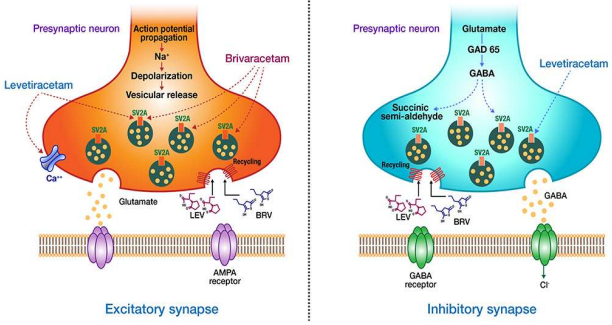




- LEV can inhibit HVA-Ca^2 channels (N-type), negate the inhibition of negative allosteric modulators such as zinc and β-carbolines of GABA- and glycine-gated currents, and diminish the calcium release from intraneuronal stores

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

Brivaracetam: an analog of levetiracetam



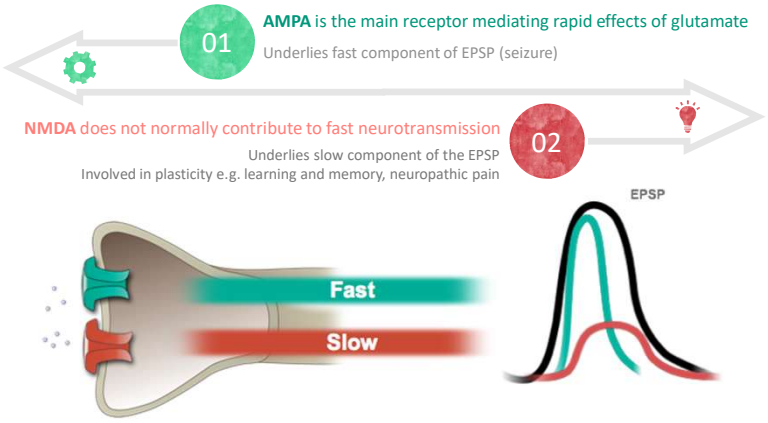
	Brivaracetam	Levetiracteam
Dosage formulations Oral Intravenous	 25 mg, 50 mg, 75 mg, 100 mg 50 mg/5 mL	 250 mg, 500 mg, 750 mg, 1000 mg 500 mg/5 mL; 500 mg/100 mL; 1500 mg/5 mL
Bioavailability	100%* (may be delayed with high-fat meal)	>95%
Time to peak, median (range)	2 hr (1–4 hrs)	1 hr (1–2 hrs)
Protein 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.

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

Glutamate mediates most fast excitatory neurotransmission in the CNS

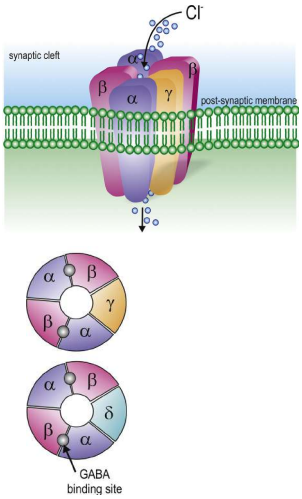


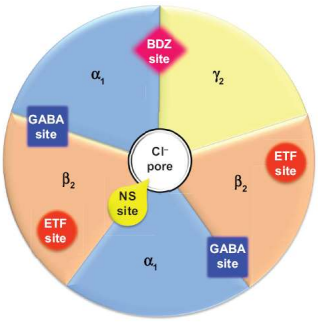
Mechanism of ASMs at AMPA receptor

Reduce postsynaptic neuronal excitability

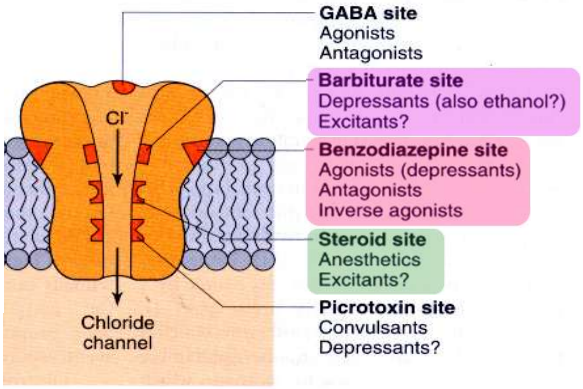
Perampanel is not displaced by higher concentrations of glutamate

ASMs acting on $GABA_A$ receptor





BDZ = benzodiazepines
ETF = etifoxine
NS = neurosteroids



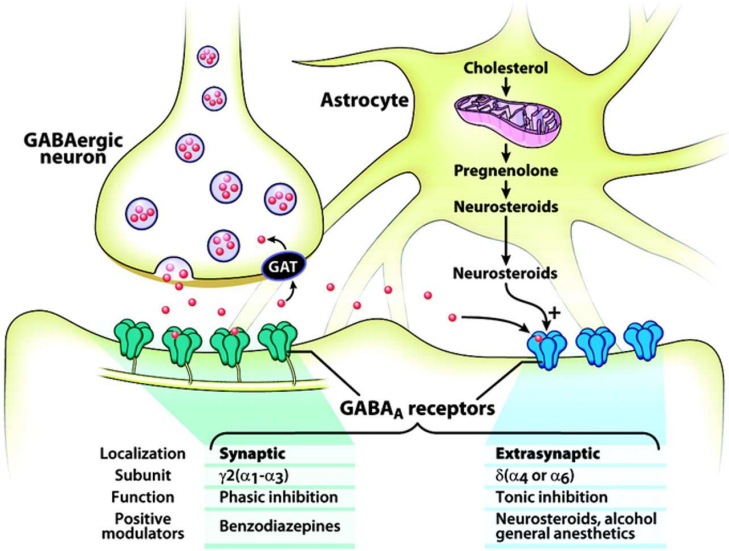
Increases intracellular chloride levels

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.

Synaptic and extrasynaptic $GABA_A$ receptors



Benarroch EE. Neurology. 2007 Feb 20;68(8):612-4.

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	Inhibition of glutamate excitation		Increase of GABA inhibition				Ionic channel			Other MOA
	↓ Glu release	Receptor blockade	↑ GABA release/brain level	Allosteric modulators of $GABA_A$ receptor	Inhibit GABA transporter-1	Inhibit GABA transaminase	Modulators of VGSC	Blockade of VGCC	Activation of KCNQ/Kv7	
Benzodiazepines				● (PAM at BZD)						
Brivaracetam	● (bind SV2A)						● (fast)			
Cannabidiol										Block I_{NaP}
Cenobamate				●			● (fast)			Block persistent Na current (I_{NaP})
Carbamazepine							● (fast)			Block I_{NaP}
Eslicarbazepine							● (fast)	● (LV-T, 3.2)		Block I_{NaP}
Ethosuximide								● (LV-T, 3.2)		
Felbamate		● (NMDA)	●	● (↑ inh. effect)			● (fast)			
Gabapentin								● (N, P/Q)		Block I_{NaP}
Ganaxolone				● (neurosteroid)						
Lacosamide							● (slow)			Block I_{NaP}, Inh. CA
Lamotrigine							● (fast)	● (N, P)		Block I_{NaP}, 5-HT_{1A} PA
Levetiracetam	● (bind SV2A)	● (AMPA)						● (HV-T)		
Oxcarbazepine							● (fast)	● (N, P)		Block I_{NaP}
Perampanel		● (PAM at AMPA)								
Phenobarbital		● (AMPA)		● (barbiturate)				● (HV-T)		
Phenytoin							● (fast)	● (HV-T)		Block I_{NaP}
Pregabalin								● (N, P/Q)		
Retigabine/Ezogabine				●					● (PAM at K_v7)	
Stiripentol			●	● (PAM at α3, δ)						
Tiagabine					●					
Topiramate		● (AMPA/kainite), ●	●	● (↑ inh. effect)			● (fast)	● (L)		Block I_{NaP}, Inh. CA II,IV
Valproic acid		● (NMDA)	● (↑ synthesis, ↓ metabolism/reuptake)					● (LV-T, 3.2)		Block I_{NaP}, Inh. histone deacetylase, activate GAD
Vigabatrin						●				
Rufinamide							● (fast)			
Zonisamide			● (↑ release, ↓ uptake)				● (fast)	● (T)		Free radical scavenger, inh. CA

From pharmacodynamic properties of ASMs to clinical application

- Classification based on MOAs --> epileptic syndrome
  - Single target of action
  - Multiple target of actions
- Therapeutic uses --> comorbidities
  - Narrow spectrum
  - Broad spectrum
- Combination ASMs
  - Additive effects
  - Synergistic effects

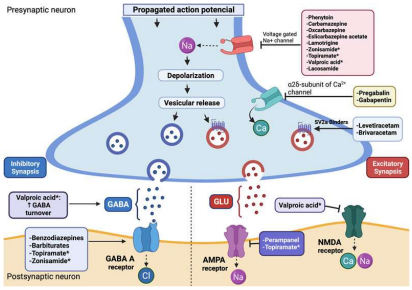
Spectrum of antiseizure effects of approved antiseizure medications in preclinical seizure models and patients with epilepsy

Drug	Efficacy in preclinical rodent models				Clinical efficacy						
	Primary generalized tonic-clonic seizures (MES test)	Focal seizures (6-Hz test; 32 or 44 mA)	Focal seizures (kindling)	Absence seizures (GAERS or WAG/Rij rat strains)	Focal-onset seizures	Primary generalized seizures			Lennox–Gastaut syndrome	Infantile spasms (West syndrome)	Dravet syndrome
						Tonic-clonic	Absence	Myoclonic			
Acetazolamide[a]	+	?	?+	?	?+	?+	?+	?+	?	?	?
Brivaracetam	+	+	+	+	+	?+	?+	?+	?	?	?
Cannabidiol	+	+	?+	?	+	?	?	?	+	?	+
Carbamazepine	+	?+	+	0	+	+	0	0	0	0	0
Cenobamate	+	+	+	+	+	?	?	?	?	?	?
Clobazam	+	+	+	?	+	+	?	+	+	?+	+
Clonazepam[a]	+	+	+	+	+	+	?	+	?+	?+	?+
Eslicarbazepine acetate	+	+	+	?	+	?	?	?	?	?	?
Ethosuximide	0	0	0	+	0	0	+	0	0	0	?+
Felbamate	+	+	+	?	+	+	?+	?	+	+	?
Fenfluramine	?+	?+	0	?	?	?	?	?	?	?	+
Gabapentin	+	+	+	0	+	?+	0	0	?	?	0
Lacosamide	+	+	+	?	+	+	?	?	?	?	?
Lamotrigine	+	0	+	+	+	+	+	+	+	?+	0
Levetiracetam	0	+	+	+	+	+	?+	+	?+	?	+
Oxcarbazepine	+	?	+	0	+	+	0	0	0	0	0
Perampanel	+	+	+	0	+	+	?+	?+	?+	?	?+
Phenobarbital	+	+	+	+	+	+	+	0	?	?	?+
Phenytoin	+	?+	+	0	+	+	0	0	0	0	0
Pregabalin	+	+	+	0	+	?	?	?	?	?	0
Primidone	+	?	0	0	+	+	0	?	?	?	?
Retigabine (ezogabine)[b]	+	+	+	0	+	?	?	?	?	?	?
Rufinamide	+	+	0	?	+	+	?+	?+	+	?	0
Stiripentol	+	?	?	?	+	+	?+	+	?+	?+	+
Sulthiame[c]	+	?	?	?+	?	?	?	?	?	?+	?
Tiagabine	0	+	+	0	+	?	0	?	?	?+	0
Topiramate	+	0	+	+	+	+	?	+	+	?	+
Valproate	+	+	+	+	+	+	+	+	+	+	+
Vigabatrin	0	?	+	0	+	?+	0	0	?	+	0
Zonisamide	+	+	+	?	+	?+	?+	?+	?+	?+	+

GAERS genetic absence epilepsy rat from Strasbourg, *Hz* Herz, *MES* maximal electroshock seizures, *WAG/Rij* Wistar Albino Glaxo from Rijswijk, + indicates efficacy, 0 indicates inefficacy or worsening of seizures, ?+ indicates inconsistent or preliminary findings, ? indicates insufficient data

Löscher W, et al. CNS Drugs. 2021 Sep;35(9):935-963.

Pharmacodynamic interactions of antiseizure medications

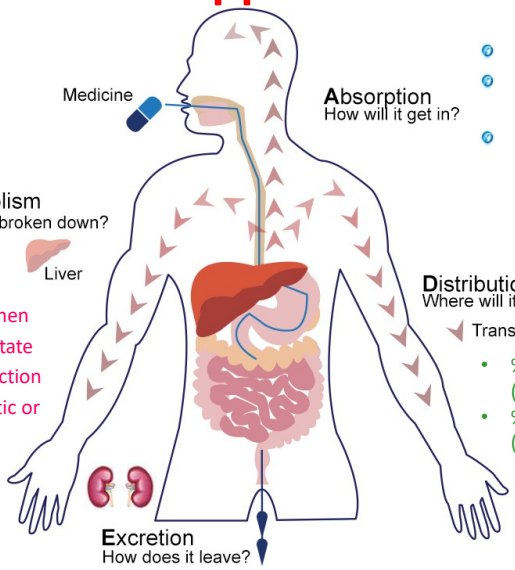


Antiseizure medications combination	Antiseizure activity	Toxicity
GBP + OXC	Synergy	No toxicity
LCM + TPM	Synergy	No toxicity
LCM + LTG	Synergy	No toxicity
LEV + LCM	Synergy	No toxicity
LTG + VPA	Synergy	Antagonism
TPM + LTG	Synergy	Antagonism
GBP + CBZ	Synergy	Additivity
GBP + VPA	Synergy	Additivity
GBP + PHT	Synergy	Additivity
LTG + PB	Synergy	Synergy
TPM + OXC	Synergy	Additivity
VPA + PHT	Synergy	Additivity
CBZ + VPA	Additivity	Antagonism
PHT + PB	Additivity	Antagonism
PB + VPA	Additivity	Additivity
CBZ + PB	Additivity	Additivity
PGB + LTG	Additivity	Additivity
PGB + OXC	Additivity	Additivity
PGB + TPM	Additivity	Additivity
LTG + CBZ	Antagonism	Additivity
OXC + PHT	Antagonism	Additivity
LTG + OXC	Antagonism	Synergy

CBZ = carbamazepine; GBP = gabapentin; LCM = lacosamide; LEV = levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; PB = phenobarbital; PHT = phenytoin; PGB = pregabalin; TPM = topiramate; VPA = valproic acid

Verrotti A, et al. Epilepsy Behav. 2020 Mar;104(Pt A):106939.

Pharmacokinetic properties (ADME) of ASMs and clinical application



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

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

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

Pharmacokinetic profiles of ASMs

Highly protein bound (≥88%)
Moderate protein binding (range 27.7-74.8%)
Minimally bound (<22%)
Non-protein-bound

(Patsalos PN, et al. Epilepsia. 2017 Jul;58(7):1234-1243.)

NE, not established
++++ Extensive hepatic metabolism and active metabolite(s)
+++ Extensive hepatic metabolism but no active metabolite(s)
++ Hepatic metabolism (with or without active metabolites) and renal excretion
+ Variable (or moderate) hepatic metabolism (with or without active metabolites)
- Renal excretion (unchanged). No hepatic metabolism
[a] ng/mL
[b] Saturable

Hakami T. Neuropsychopharmacol Rep. 2021 Sep;41(3):336-351.

Antiseizure drug	Bioavailability %	Peak concentration (hr)	Plasma protein binding (%)	Elimination half-life (hr)	Route of elimination	Therapeutic serum concentration (mcg/mL)
Brivaracetam	~ 95	1	≤ 20	7-10	++	0.2-2
Carbamazepine	75-85	4-5	70-80	10-17	++++	4-11
Cannabidiol	10-20	2.5-5	>94	56-61	++++	NE
Cenobamate	88	1-4	60	50-60	+++	NE
Clobazam	90-100	1-3	80-90	36-42	++++	0.03-3
Clonazepam	>80	1-4	80-90	24-48	+++	10-70[a]
Eslicarbazepine	>90	1-4	<40	13-20	++++	5-35
Ethosuximide	95-100	3-7	0	30-60	++	40-100
Felbamate	>90	3-5	22-36	16-22	++	30-60
Gabapentin	50	2-3	0	5-9	-	3-21
Lacosamide	100	1-2	<30	12-14	+	3-10
Lamotrigine	~ 90	1-3	55	8-35	+++	3-13
Levetiracetam	~ 95	1-2	<10	6-8	-	5-41
Oxcarbazepine	100	4-5	75	10-17	++++	3-36
Perampanel	100	0.5-3	95-96	70-110	+++	0.1-1
Phenobarbital	>90	0.5-4	55	90	++	12-30
Phenytoin	85-90	5-7	90	24	+++[b]	10-20
Pregabalin	~90	1-2	0	4.5-7	-	2-6
Primidone	>90	2-6	10	8-15	++	8-12
Rufinamide	>90	4-6	35	6-10	++	4.5-31
Stiripentol	Variable	2-3	99	4.5-13	+	4-22
Tiagabine	~90	0.5-2	96	2-9	+++	0.02-0.2
Topiramate	~80	2-4	15	20-30	+	2-10
Valproate	>90	2-4	90	15	++++	50-100
Vigabatrin	100	1	0	5-8	-	20–160[a]
Zonisamide	>90	2-6	40-60	50-68	++	10-38

AEDs	BCS class	Bioavailability (%)	Protein binding (%)	Hepatic Metabolism		Renally Excretion (%)
				Phase I (CYP)	Phase II (UGT)	
Carbamazepine	II	85	75	3A4		
Clonazepam	II	90	85	3A4		
Diazepam	II	>90	98	2C19, 3A4		
Ethosuximide	I	100	0	2E1, 3A4		20
Lorazepam	I	90	93		2B15	
Midazolam	I	35-44	95	3A4		
Phenobarbital	I	95-100	55	2C9, 2C19		22
Phenytoin	II	90-100	90	2C9, 2C1		
Valproic acid	I	100	90	B-oxidation, 2C9, 2C19	1A6, 1A9, 2B7	
Brivaracetam	I	100	<20	2C19, hydrolysis		9
Clobazam	II	100	85	2C19, 3A4		
Eslicarbazepine	I	>90	<40		UGT1A4, 1A9, 2B4, 2B7, 2B17	90
Felbamate	II	<90	25	2E1, 3A4	UGT	50
Gabapentin	III	35-60	0			>90
Lacosamide	I	100	<15	2C19		40
Lamotrigine	I	≥98	55		1A4	
Levetiracetam	I	100	0	Amidase		66
Oxcarbazepine MHD	II	>90	40	Cytosolic reductase	UGT	20
Perampanel	N/D	100	95	3A4		
Pregabalin	I	≥90	0			>90
Retigabine	I	60	80		UGT, NAT	20-30
Rufinamide	III	≥85	35	Carboxylesterase		
Topiramate	I	≥80	15	CYP		30
Vigabatrin	I	60-80	0			95
Zonisamide	I	≥90	50	3A4, 2C19		35

Anderson GD, et al. Clin Pharmacokinet. 2014;53(1):29-49.

Dose adjustments for ASM in patients with renal impairment

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[a]; 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

Títoff V, et al. Am J Kidney Dis. 2019 Jan;73(1):90-101.

ASM pharmacokinetics, likelihood of removal by CRRT modality and empiric dosing strategies

Agent	PPB (%)	MW (Da)	V_D (L/kg)	Main route of elimination	Therapeutic range	Likelihood of removal			Empiric dosing for CRRT
						CVVHD	CVVH	CVVHDF	
Carbamazepine	76	236	0.8-1.4	Hepatic[a]	4-12 μg/mL	−	±	+	100 mg every 6 h[b,c,d]
Clobazam	80-90	300.7	100 L	Hepatic[a]	Not established	−	±	±	5 mg every 12 h
Eslicarbazepine	<40	296	0.9	Renal	Not established	+	+	+	400-1600 mg daily
Ethosuximide	0	141.2	0.62-0.72	Hepatic/20% unchanged renally	40-100 μg/mL	+	+	+	500-1500 mg daily
Ezogabine	80	303.3	2-3	Renal	Not established	±	±	±	50 mg every 8 h
Felbamate	22-25	238	0.7-0.8	50% unchanged renally	30-60 μg/mL	±	+	+	200 mg every 8 h
Gabapentin	<3	171.2	58 L	Renal	2-20 μg/mL	++	++	++	300 mg every 8 h
Lacosamide	<15	250.3	0.6	Renal	5-10 μg/mL	++	++	++	200-600 mg/d[e]
Lamotrigine	55	256	0.9-1.3	Hepatic	3-14 μg/mL	±	±	+	25 mg daily[e,f]
Levetiracetam	<10	170.2	0.5-0.7	Renal	6-20 μg/ml	++	++	++	1000 mg every 12 h
Oxcarbazepine	40	252	0.7	Hepatic[a]	3-35 μg/mL	−	±	±	300 mg every 12 h[b]
Perampanel	95	362.9	1.1	Hepatic	Not established	−	−	−	2 mg daily[e]
Phenobarbital	20-45	254	0.9	25-50% unchanged renally	10-40 μg/mL	+	+	++	2-3 mg/kg per day[d,e]
Phenytoin	90	252	0.6-0.8	Hepatic	10-20 μg/mL; free 1-2 μg/mL	±	±	±	5-7 mg/kg per day[d,e,g]
Pregabalin	0	159.2	0.5	Renal	2.8-8.3 μg/mL	++	++	++	150-600 mg/d[e]
Primidone	40-49	218	0.59	40% unchanged renally	5-10 μg/mL	±	+	++	250 mg every 8-12 h
Rufinamide	34	238.2	0.7	Hepatic	Not established				200-400 mg every 12 h
Tiagabine	96	412	52L[h]	Hepatic	0.02-0.2 μg/mL	−	−	−	4 mg daily[i]
Topiramate	15	339.4	0.6-0.8	Renal	5-20 μg/mL	+	±	+	200 mg every 12 h
Valproic acid	90-95	144	92 L/1.73 m^2	Hepatic	50-100 μg/mL free 5-15 μg/mL	±	++	++	5 mg/kg every 8 h[d,j]
Vigabatrin	0	129.2	1.1	Renal	0.8-36 μg/mL	+	±	+	500 mg every 12 h
Zonisamide	40	212.2	1.45	Renal	10-40 μg/mL	+	+	+	100 mg daily

− removal unlikely, ± removal possible, + removal likely, ++ removal highly likely (may consider dose adjustment, TDM recommended if available).

[a] active metabolite;
[b] test for HLA-B*1502 prior to initiation;
[c] suspension formulation;
[d] TDM recommended;
[e] divided in 2 to 3 doses;
[f] based on regimens not containing enzyme-inducing drugs or VPA;
[g] use ideal body weight for obese patients (Body Mass Index >30 kg/m^2);
[h] may vary from 15.6-188 L based on body height and concomitant AED use;
[i] in patients currently taking enzyme inducing AED (CBZ, PHT, PM, PB), use lower doses in patients not taking these medications;
[j] CVVH/CVVHDF only.

Smetana KS, et al. J Crit Care. 2016 Dec;36:116-124.

Recommendations for usual dosing and monitoring of specific ASMs in liver disease

Drug	Amount of Dosing Reduction	Useful Metabolic Labs to Monitor	Frequency of Labs Examination
Barbiturates	50%-75%	AST, ALT, Coag,	1-2 mo
Phenytoin	50%-75%	AST, ALT, Coag,Albumin	1-2 mo
Carbamazepine	50%-75%	AST, ALT, Coag,Albumin, Na+,CBC	1-2 mo
Oxcarbazepine	25%-50%	AST, ALT,Na+,Cr	1-3 mo
Valproic acid	25%-50%	AST, ALT,Coag,Albumin, platelets	1-2 mo
Ethosuximide	25%-50%	AST, ALT,Coags,CBC, platelets	1-2 mo
Benzodiazepines	50%-75%	AST, ALT,Coag	1-2 mo
Lamotrigine	50%-75%	AST, ALT,Coags,levels	1-2 mo
Gabapentin	Minimal	-	3-6mo
Pregabalin	Minimal	-	3-6mo
Topiramate	25%-50%	AST, ALT,Coags	3-6mo
Zonisamide	25%-50%	AST, ALT,Coags	2-6mo
Levetiracetam	25%-50%	-	3-6mo
Tiagabine	50%-75%	AST, ALT,Coags	3-6mo
Vigabatrin	None	AST, ALT	1-3mo
Rufinamide	25%-50%	-	3-6mo
Lacosamide	25%-50%	AST, ALT,Coags	3-6mo
Felbamate[b]	NA	AST, ALT,CBC,differential	2-4wk

[a]Dosing and monitoring for all patients should be individualized. Monitoring of levels may be helpful in some cases

[b]Agent of last option in liver disease ALT alanine transaminase, AST aspartate transaminase, CBC complete blood count, coags coagulation values

Dosage of perampanel in hepatic insufficiency

- **A)** Mild impairment: Initial, 2 mg orally once daily at bedtime and may increase dose by 2 mg/day no more frequently than every 2 weeks to MAX, 6 mg/day
- **B)** Moderate impairment: Initial, 2 mg orally once daily at bedtime and may increase by 2 mg/day no more frequently than every 2 weeks to MAX, 4 mg/day
- **C)** Severe impairment: Use not recommended

Shehata GA. Arch Neurol Neurosci 6(3):2020. DOI: 10.33552/ANN.2020.06.000638

Selected CYP3A4 inducers and inhibitors

TABLE 3: CYP3A4 INHIBITORS[a]

Almorexant
Amiodarone
Amprenavir
Aprepitant
Atazanavir
Boceprevir
Casopitant
Ceritinib
Chloramphenicol
Clarithromycin
Cobicistat
Conivaptan
Crizotinib
Cyclosporine
Dalfopristin
Danazol
Darunavir
Dasatinib
Deferasirox
Delavirdine
Diltiazem
Dronedarone
Erythromycin
Fluconazole
Fluoxetine
Fluvoxamine
Fosamprenavir
Fosaprepitan
Fusidic Acid
Grapefruit Juice
Idelalisib
Imatinib
Indinavir
Interferon alpha
Isoniazid
Itraconazole
Ketoconazole
Lapatinib
Lomitapide
Miconazole
Nefazodone
Nelfinavir
Posaconazole
Propoxyphene
Quinupristin
Ritonavir
Saquinavir
Simeprevir
Telaprevir
Telithromycin
Tipranavir
Troleandomycin
Verapamil
Voriconazole

[a]Not a complete listing.

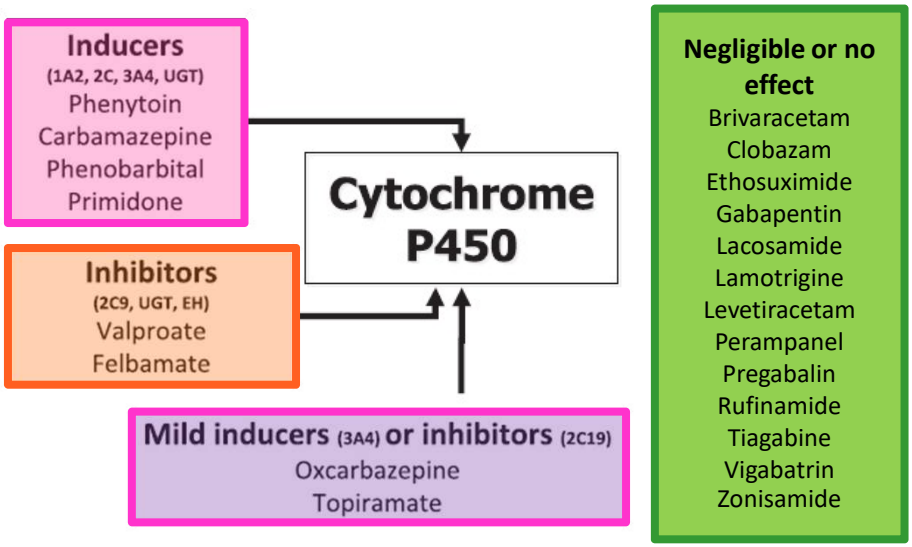
TABLE 4: CYP3A4 INDUCERS[a]

Aminoglutethimide
Armodafinil
Barbiturates
Bexarotene
Bosentan
Carbamazepine
Dabrafenib
Dexamethasone
Efavirenz
Enzalutamide
Eslicarbazepine
Etravirine
Fosamprenavir
Fosphenytoin
Griseofulvin
Lumacaftor
Modafinil
Nafcillin
Nevirapine
Oxcarbazepine
Phenytoin
Primidone
Rifabutin
Rifampin
Rifapentine
St. John's wort

[a]Not a complete listing.

https://www.pharmacytimes.com/view/drug-interactions-with-cyp3a4-an-update

Potential to develop drug-drug interactions of ASMs



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

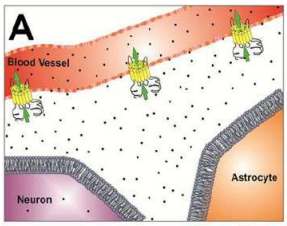
Expected changes in plasma concentrations when an AED is added to a pre-existing regimen

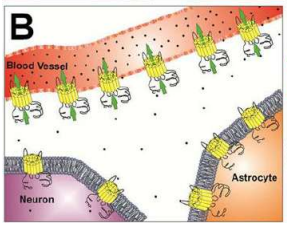
	Pre-existing AED														
AED added	**PB**	**PHT**	**PRM**	**ETS**	**CBZ**	**VPA**	**OXC**	**LTG**	**GBP**	**TPM**	**TGB**	**LEV**	**ZNS**	**VGB**	**FBM**
PB	··	PHT↑↓	NCCP	ETS⇓	CBZ⇓	VPA⇓	H-OXC↓	LTG⇓	↔	TPM⇓	TGB⇓	↔	ZNS⇓	↔	FBM⇓
PHT	PB↑	··	PRM↓ PB↑	ETS⇓	CBZ⇓	VPA⇓	H-OXC↓	LTG⇓	↔	TPM⇓	TGB⇓	↔	ZNS⇓	↔	FBM⇓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

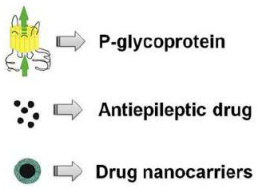
PB=phenobarbital; PHT=phenytoin; PRM=primidone; ETS=ethosuximide; CBZ=carbamazepine; VPA=valproic acid; OXC=oxcarbazepine; LTG=lamotrigine; GBP=gabapentin; TPM=topiramate; TGB=tiagabine; LEV=levetiracetum; ZNS=zonisamide; VGB=vigabatrin; FBM=felbamate; H-OXC=10-hydroxy-oxcarbazepine (active metabolite 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.

Some ASMs are P-glycoprotein substrate and inducer







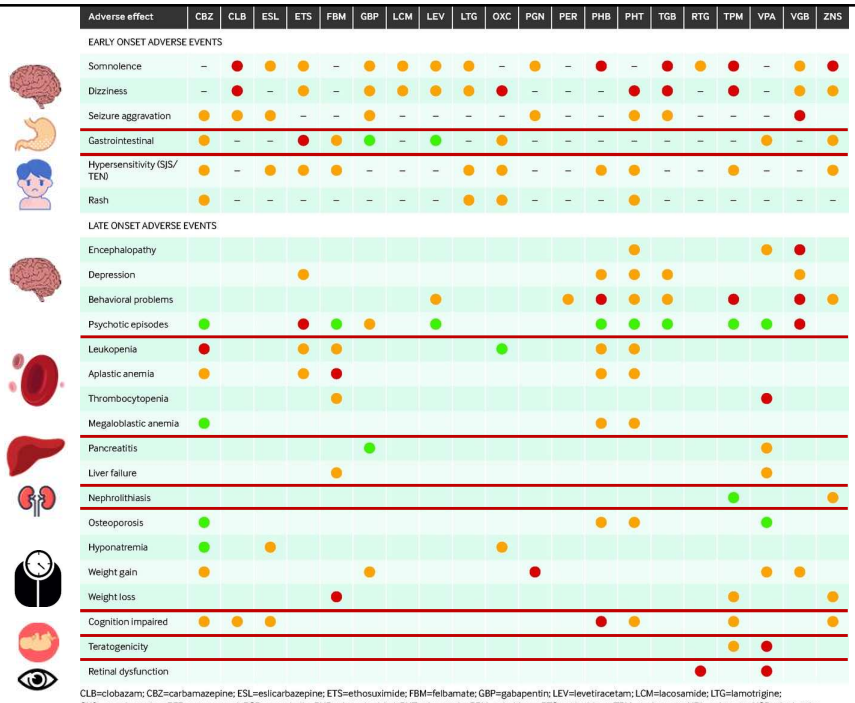
P-gp substrate
phenytoin, felbamate, topiramate, carbamazepine, lamotrigine, phenobarbital, gabapentin, topiramate

Inhibitors	Inducers
Quinidine	Dexamethasone
Amiodarone	Phenobarbital
Azoles	Rifampin
Statins	Rifabutin
Ritonavir	St.Johns Wort
Saquinavir	Phenytoin
Nelfinavir	Carbamazepine
Macrolides	
Cyclosporin-A	
Verapamil	

Adapted from FDA draft guidance from industry, Drug interaction studies - study design, Data analysis and implications for dosing and labeling, September 2006

Veiga-Matos J, et al. Molecules. 2023 Nov 10;28(22):7532.; Rosillo-de la Torre A, et al. Front Biosci (Elite Ed). 2014 Jun 1;6(2):329-40.

Overview of adverse effects of individual antiseizure drugs



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	●	–	–	–	–	–	–	–	●	●	–	–	–	●	–	–	–	–	–	–
LATE ONSET ADVERSE EVENTS																				
Encephalopathy														●				●	●	
Depression				●									●	●	●				●	
Behavioral problems								●				●	●	●	●		●		●	●
Psychotic episodes	●			●	●	●		●					●	●	●		●	●	●	
Leukopenia	●			●	●					●			●	●						
Aplastic anemia	●			●	●								●	●						
Thrombocytopenia					●													●		
Megaloblastic anemia	●												●	●						
Pancreatitis						●												●		
Liver failure					●													●		
Nephrolithiasis																	●			●
Osteoporosis	●												●	●				●		
Hyponatremia	●		●							●										
Weight gain	●					●					●							●	●	
Weight loss					●												●			●
Cognition impaired	●	●	●										●	●			●			●
Teratogenicity																	●	●		
Retinal dysfunction																●		●		

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, Schachter SC. BMJ. 2014 Feb 28;348:g254.

Common and serious adverse effects of ASMs

Antiseizure drug	Systemic adverse effects	Neurologic adverse effects	Rare idiosyncratic reactions
Brivaracetam	Nausea, vomiting, constipation, fatigue	Headache, somnolence, dizziness, abnormal coordination, nystagmus, mood changes	
Carbamazepine	Nausea, vomiting, diarrhea, aplastic anemia, leukopenia, hyponatremia (common reason for discontinuation), hepatotoxicity, rash, pruritus	Ataxia, dizziness, blurred vision, diplopia, headache	Erythematous maculopapular rash (Steven-Johnson syndrome and toxic epidermal necrolysis), teratogenicity
Cenobamate	Nausea, vomiting, fatigue, hyperkalemia, QT shortening	Somnolence, dizziness, headache, balance disorder, diplopia	Drug reaction with eosinophilia and systemic symptoms (DRESS)/ multiorgan hypersensitivity (at high doses)
Eslicarbazepine	Nausea, vomiting, diarrhea, hyponatremia, rash	Dizziness, drowsiness, headache, somnolence, diplopia, ataxia, blurred vision, tremor	
Ethosuximide	Nausea, vomiting	Sleep disturbance, drowsiness, hyperactivity	
Felbamate	Nausea, vomiting, anorexia, weight loss	Insomnia, dizziness, headache, ataxia	Aplastic anemia, severe hepatitis/ hepatic failure
Gabapentin	Infrequent	Somnolence, dizziness, ataxia, headache, tremor, and fatigue	
Lacosamide	Nausea, vomiting, increased cardiac conduction (PR interval)	Dizziness, ataxia, diplopia, headache	
Lamotrigine	Nausea, rash, cardiac arrhythmias	Dizziness, tremor, diplopia	Steven-Johnson syndrome

Hakami T. Neuropsychopharmacol Rep. 2021 Sep;41(3):336-351.

HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions

Association between *HLA-B*1502* and carbamazepine-induced severe cutaneous adverse drug reactions in a Thai population

*Wichittra Tassaneeyakul, †Somsak Tiamkao, *Thawinee Jantararoungtong, ‡Pei Chen, ‡Shu-Yi Lin, ‡Wei-Hsuan Chen, §Parinya Konyoung, §Usanee Khunarkornsiri, ¶Narong Auvichayapat, **Kasemsin Pavakul, ††Kongkiat Kulkantrakorn, †Charoen Choonhakarn, ‡‡Siranun Phonhiamhan, §§Namfon Piyatrakul, ¶¶Thiti Aungaree, ***Sunsanee Pongpakdee, and †††Praphan Yodnopaglaw

Table 2. Frequencies of certain *HLA-B* alleles in CBZ-induced SJS/TEN and CBZ-tolerant patients

	Number of patients (%)				
HLA-B allele*	CBZ-induced SJS/TEN (n = 42)	CBZ-tolerant control (n = 42)	OR	95% CI	p-value
1502	37 (88.10)	5 (11.90)	54.76	14.62–205.13	2.89×10^{-12b}
1521	2 (4.76)	0 (0)	5.25	0.24–112.66	0.2398
1535	3 (7.14)	0 (0)	7.53	0.38–150.47	0.1245
1301	3 (7.14)	5 (11.90)	0.57	0.13–2.55	0.4572
1801	2 (4.76)	5 (11.90)	0.37	0.07–2.02	0.2363

- The risk of CBZ-induced SJS/TEN was higher in the patients with 1502 allele with OR of 54.76 [95% CI 14.62–205.13]
- Sensitivity and Specificity = 88.10 %

ประกาศคณะกรรมการหลักประกันสุขภาพแห่งชาติ
เรื่อง ประเภทและขอบเขตของบริการสาธารณสุข (ฉบับที่ ๑๓)
พ.ศ. ๒๕๖๑

โดยที่เป็นการสมควรแก้ไขเพิ่มเติมประเภทและขอบเขตของบริการสาธารณสุข ที่ผู้มีสิทธิจะได้รับตามพระราชบัญญัติหลักประกันสุขภาพแห่งชาติ พ.ศ. ๒๕๔๕

อาศัยอำนาจตามความในมาตรา ๕ วรรคสาม และมาตรา ๑๘ (๓) แห่งพระราชบัญญัติหลักประกันสุขภาพแห่งชาติ พ.ศ. ๒๕๔๕ ประกอบกับมติของคณะกรรมการหลักประกันสุขภาพแห่งชาติ ในการประชุมครั้งที่ ๑/๒๕๖๑ เมื่อวันที่ ๕ มิถุนายน ๒๕๖๑ คณะกรรมการหลักประกันสุขภาพแห่งชาติ จึงออกประกาศไว้ ดังต่อไปนี้

ข้อ ๑ ประกาศนี้เรียกว่า "ประกาศคณะกรรมการหลักประกันสุขภาพแห่งชาติ เรื่อง ประเภทและขอบเขตของบริการสาธารณสุข (ฉบับที่ ๑๓) พ.ศ. ๒๕๖๑"

ข้อ ๒ ประกาศนี้ให้ใช้บังคับตั้งแต่วันที่ ๔ มิถุนายน ๒๕๖๑ เป็นต้นไป

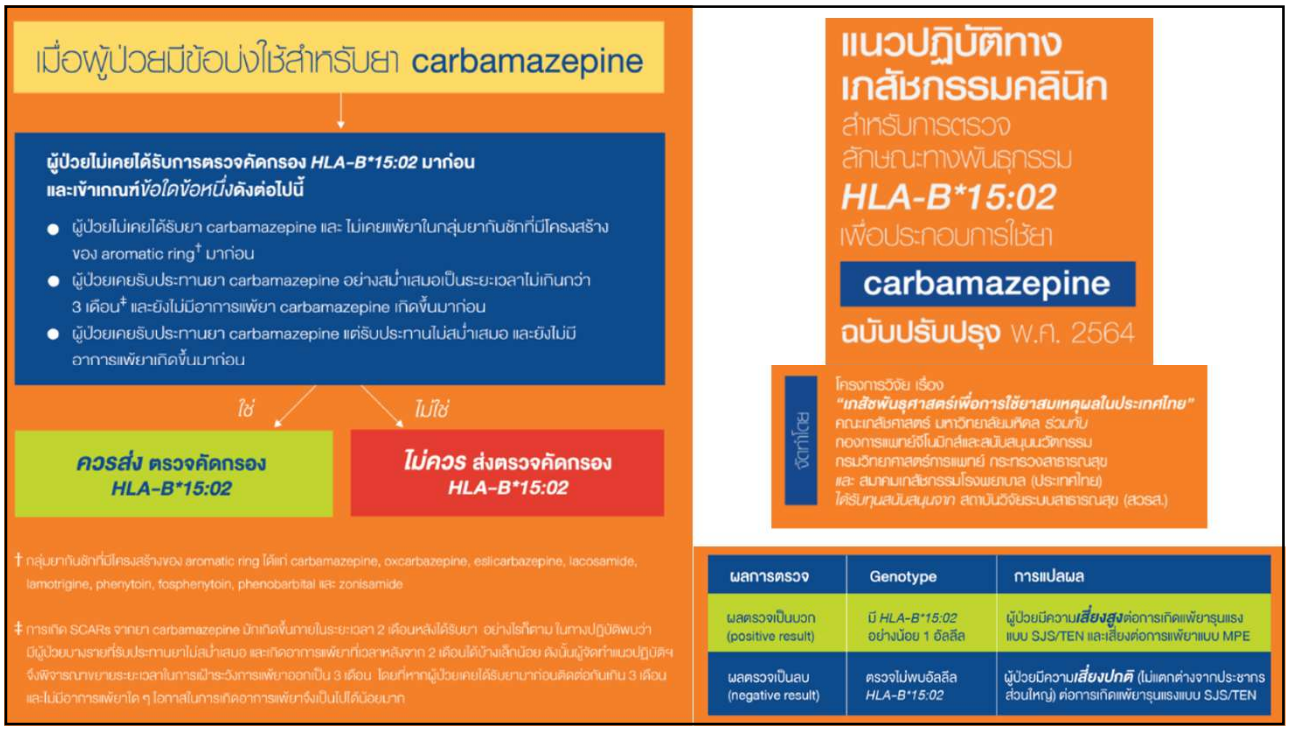
ข้อ ๓ ให้การตรวจคัดกรองยีน Human Leukocyte Antigen (HLA) allele-B*๑๕๐๒ (HLA-B*๑๕๐๒) ในผู้ป่วยโรคลมชักก่อนเริ่มยา Carbamazepine เพื่อป้องกันผื่นแพ้ยาชนิดรุนแรง (Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)) อยู่ในประเภทและขอบเขตของบริการสาธารณสุขที่ผู้มีสิทธิจะได้รับตามพระราชบัญญัติหลักประกันสุขภาพแห่งชาติ พ.ศ. ๒๕๔๕

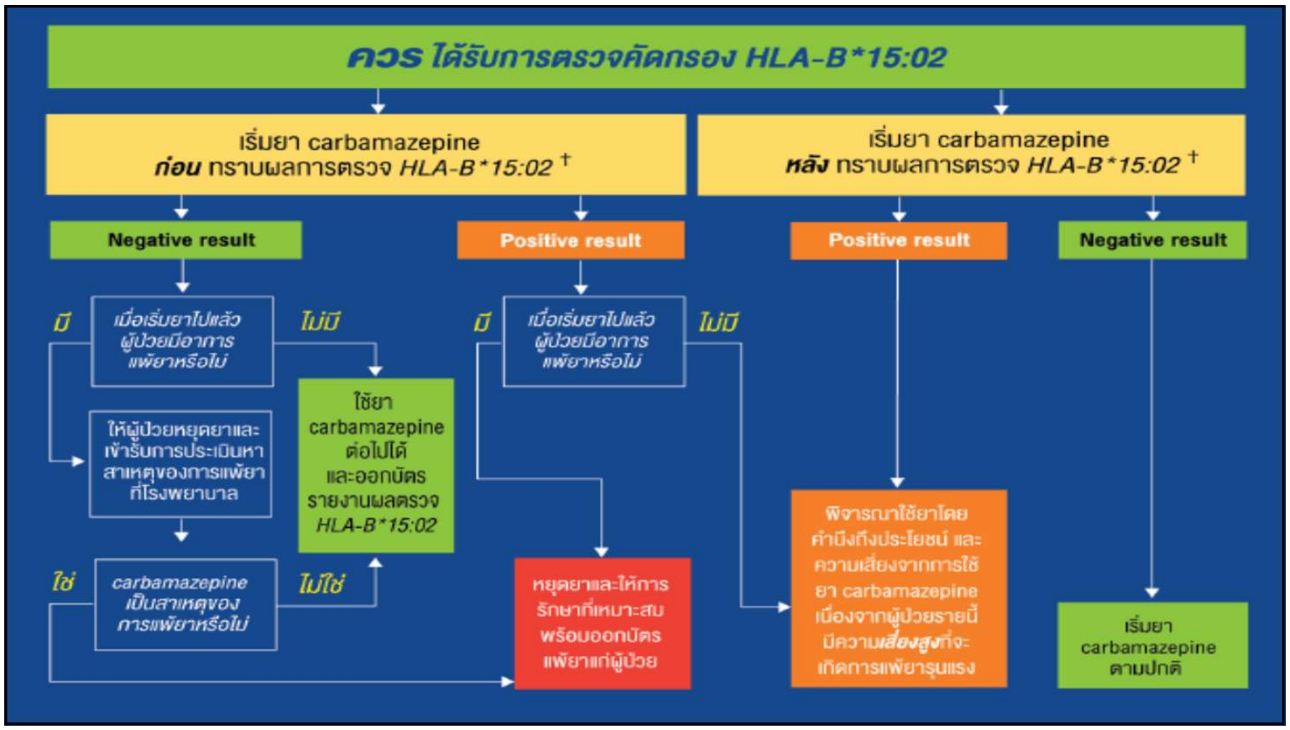
ข้อ ๔ ให้ประธานกรรมการหลักประกันสุขภาพแห่งชาติ รักษาการตามประกาศนี้

ประกาศ ณ วันที่ ๔ มิถุนายน พ.ศ.๒๕๖๑

(นายปิยะสกล สกลสัตยาทร)
รัฐมนตรีว่าการกระทรวงสาธารณสุข
ประธานกรรมการหลักประกันสุขภาพแห่งชาติ

Tassaneeyakul W, et al. Epilepsia. 2010 May;51(5):926-30.


เมื่อผู้ป่วยมีข้อบ่งใช้สำหรับยา carbamazepine
ผู้ป่วยไม่เคยได้รับการตรวจคัดกรอง HLA-B*15:02 มาก่อน และเข้าเกณฑ์ข้อใดข้อหนึ่งดังต่อไปนี้
ผู้ป่วยไม่เคยได้รับยา carbamazepine และ ไม่เคยแพ้ยาในกลุ่มยากันชักที่มีโครงสร้างของ aromatic ring† มาก่อน
ผู้ป่วยเคยรับประทานยา carbamazepine อย่างสม่ำเสมอเป็นระยะเวลาไม่เกินกว่า 3 เดือน‡ และยังไม่มีอาการแพ้ยา carbamazepine เกิดขึ้นมาก่อน
ผู้ป่วยเคยรับประทานยา carbamazepine แต่รับประทานไม่สม่ำเสมอ และยังไม่มีอาการแพ้ยาเกิดขึ้นมาก่อน
ใช่
ไม่ใช่
ควรส่ง ตรวจคัดกรอง HLA-B*15:02
ไม่ควร ส่งตรวจคัดกรอง HLA-B*15:02
† กลุ่มยากันชักที่มีโครงสร้างของ aromatic ring ได้แก่ carbamazepine, oxcarbazepine, eslicarbazepine, lacosamide, lamotrigine, phenytoin, fosphenytoin, phenobarbital และ zonisamide
‡ การเกิด SCARs จากยา carbamazepine มักเกิดขึ้นภายในระยะเวลา 2 เดือนหลังได้รับยา อย่างไรก็ตาม ในทางปฏิบัติพบว่า มีผู้ป่วยบางรายที่รับประทานยาไม่สม่ำเสมอ และเกิดอาการแพ้ยาที่เวลาหลังจาก 2 เดือนได้บ้างเล็กน้อย ดังนั้นผู้จัดทำแนวปฏิบัติฯ จึงพิจารณาขยายระยะเวลาในการเฝ้าระวังการแพ้ยาออกเป็น 3 เดือน โดยที่หากผู้ป่วยเคยได้รับยามาก่อนติดต่อกันเกิน 3 เดือน และไม่มีอาการแพ้ยาใด ๆ โอกาสในการเกิดอาการแพ้ยาจึงเป็นไปได้น้อยมาก
แนวปฏิบัติทางเภสัชกรรมคลินิก
สำหรับการตรวจลักษณะทางพันธุกรรม
HLA-B*15:02
เพื่อประกอบการใช้ยา
carbamazepine
ฉบับปรับปรุง พ.ศ. 2564
จัดทำโดย
โครงการวิจัย เรื่อง
"เภสัชพันธุศาสตร์เพื่อการใช้ยาสมเหตุผลในประเทศไทย"
คณะเภสัชศาสตร์ มหาวิทยาลัยมหิดล ร่วมกับ
กองการแพทย์จีโนมิกส์และสนับสนุนนวัตกรรม
กรมวิทยาศาสตร์การแพทย์ กระทรวงสาธารณสุข
และ สมาคมเภสัชกรรมโรงพยาบาล (ประเทศไทย)
ได้รับทุนสนับสนุนจาก สถาบันวิจัยระบบสาธารณสุข (สวรส.)
ผลการตรวจ | Genotype | การแปลผล
ผลตรวจเป็นบวก (positive result) | มี HLA-B*15:02 อย่างน้อย 1 อัลลีล | ผู้ป่วยมีความเสี่ยงสูงต่อการเกิดแพ้ยารุนแรงแบบ SJS/TEN และเสี่ยงต่อการแพ้ยาแบบ MPE
ผลตรวจเป็นลบ (negative result) | ตรวจไม่พบอัลลีล HLA-B*15:02 | ผู้ป่วยมีความเสี่ยงปกติ (ไม่แตกต่างจากประชากรส่วนใหญ่) ต่อการเกิดแพ้ยารุนแรงแบบ SJS/TEN


ควร ได้รับการตรวจคัดกรอง HLA-B*15:02
เริ่มยา carbamazepine ก่อน ทราบผลการตรวจ HLA-B*15:02 †
เริ่มยา carbamazepine หลัง ทราบผลการตรวจ HLA-B*15:02 †
Negative result
Positive result
Positive result
Negative result
มี
เมื่อเริ่มยาไปแล้ว ผู้ป่วยมีอาการแพ้ยาหรือไม่
ไม่มี
ใช้ยา carbamazepine ต่อไปได้ และออกบัตรรายงานผลตรวจ HLA-B*15:02
ให้ผู้ป่วยหยุดยาและเข้ารับการประเมินหาสาเหตุของการแพ้ยาที่โรงพยาบาล
ใช่
carbamazepine เป็นสาเหตุของการแพ้ยาหรือไม่
ไม่ใช่
มี
เมื่อเริ่มยาไปแล้ว ผู้ป่วยมีอาการแพ้ยาหรือไม่
ไม่มี
หยุดยาและให้การรักษาที่เหมาะสม พร้อมออกบัตรแพ้ยาแก่ผู้ป่วย
พิจารณาใช้ยาโดยคำนึงถึงประโยชน์ และความเสี่ยงจากการใช้ยา carbamazepine เนื่องจากผู้ป่วยรายนี้มีความเสี่ยงสูงที่จะเกิดการแพ้ยารุนแรง
เริ่มยา carbamazepine ตามปกติ

Antiseizure drug	Systemic adverse effects	Neurologic adverse effects	Rare idiosyncratic reactions
Levetiracetam	Fatigue, infection, anemia, leukopenia	Somnolence, dizziness, agitation, anxiety, irritability, depression, psychosis	
Oxcarbazepine	Nausea, rash, hyponatremia (more common)	Somnolence, headache, dizziness, vertigo, ataxia, diplopia	
Perampanel	Weight gain, fatigue, nausea	Dizziness, somnolence, irritability, gait disturbance, falls (with high dose), aggression, mood alteration	
Phenobarbital	Nausea, rash	Somnolence, ataxia, dizziness, confusion, cognitive dysfunction, tolerance, dependence	
Phenytoin	Gingival hyperplasia, hirsutism, megaloblastic anemia, peripheral neuropathy, osteoporosis, rash	Nystagmus (early sign of phenytoin administration), diplopia, ataxia, somnolence	
Pregabalin	Weight gain, peripheral edema, dry mouth	Somnolence, dizziness, ataxia, headache, and tremor	
Rufinamide	Nausea, vomiting, leukopenia, cardiac conduction (QT interval shortening)	Somnolence, fatigue, dizziness, ataxia, headache, diplopia	
Tiagabine	Abdominal pain, nausea, lack of energy	Dizziness, difficulty concentrating, somnolence, nervousness, tremor, language problems	
Topiramate	Anorexia, weight loss, paresthesia, fatigue	Nervousness, psychomotor slowing, language problems, depression, anxiety, mood problems, tremor	Acute glaucoma (may require prompt drug withdrawal).
Valproate	Gastrointestinal irritation, weight gain, hair loss, easy bruising	Ataxia, somnolence, tremor	Hepatotoxicity, teratogenicity, and thrombocytopenia
Vigabatrin	Fatigue	Somnolence, headache, dizziness, agitation, confusion, psychosis.	Irreversible bilateral concentric visual field defect
Zonisamide	Weight loss, nausea, anorexia	Somnolence, dizziness, confusion, headache, psychosis	Potentially serious skin rashes

Hakami T. Neuropsychopharmacol Rep. 2021 Sep;41(3):336-351.

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.

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

Selection the AED for individualized patients

Moosa ANV. Continuum (Minneap Minn). 2019 Apr;25(2):381-407.