MAHIDOL UNIVERSITY
Wisdom of the Land

UNDERSTANDING THE PHARMACOLOGY OF ANTIEPILEPTIC DRUGS

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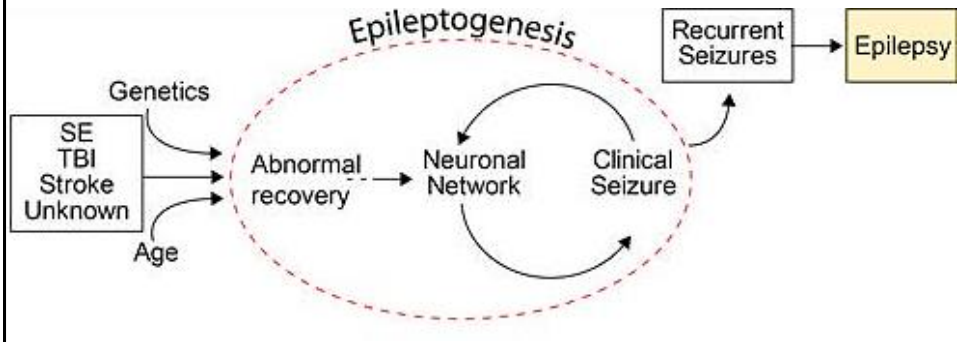
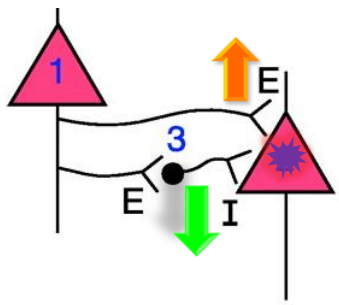
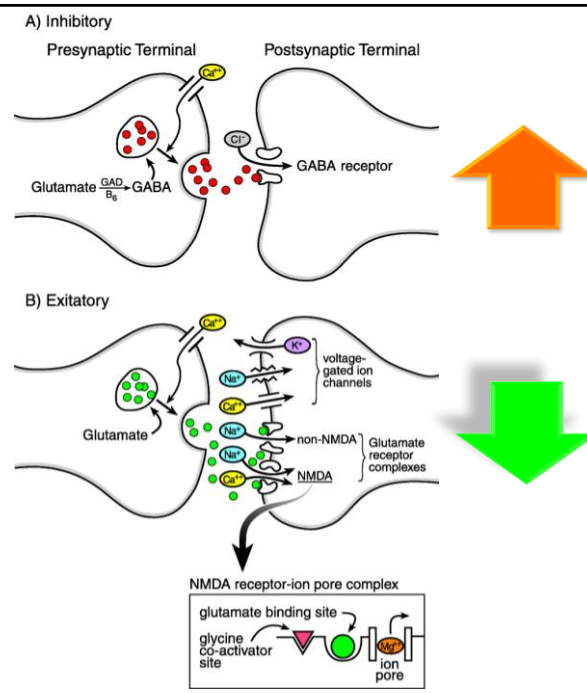
Epileptogenesis



Neuronal Network Synaptic Transmission





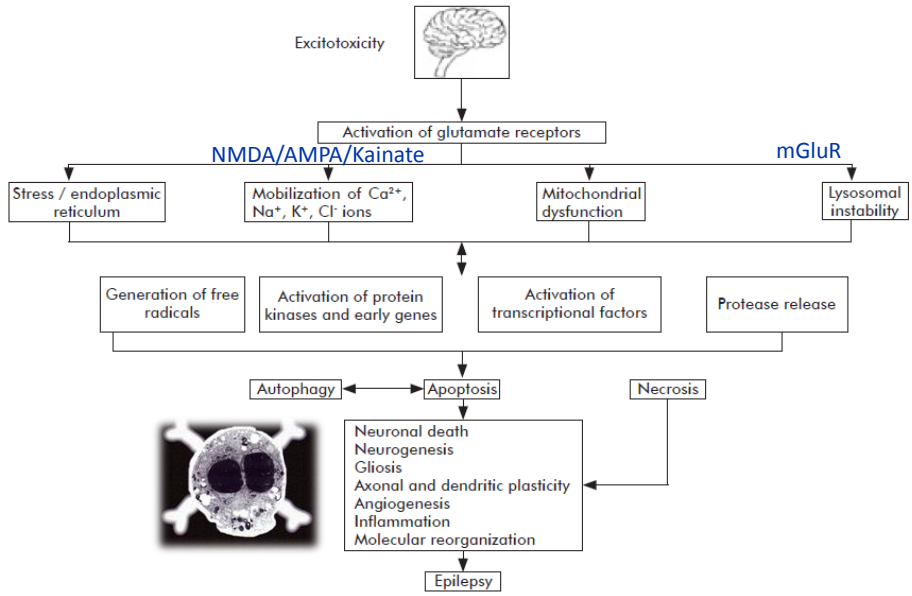
Stafstrom CE. Pediatr Rev 1998;19:342-51.

Mechanisms of Neuronal Excitability

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

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

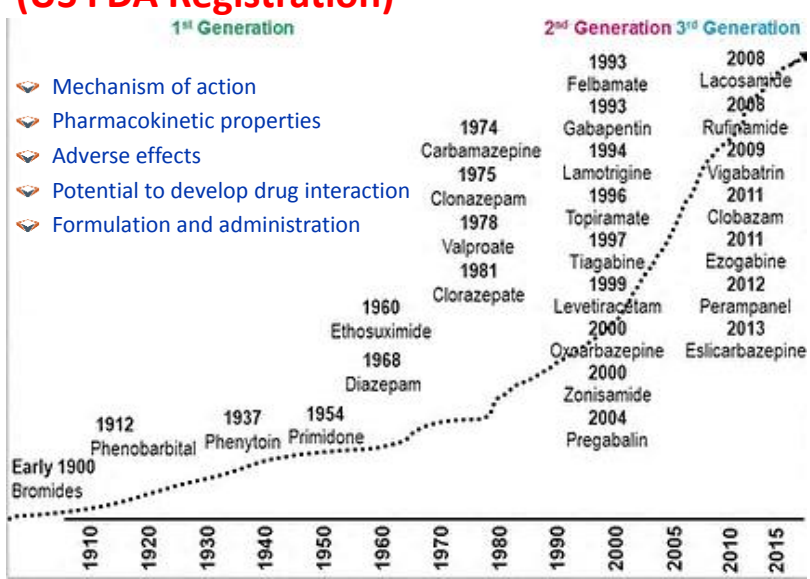
Excitotoxicity and Neuronal Death in Epilepsy



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

Introduction of AEDs in the World (US FDA Registration)

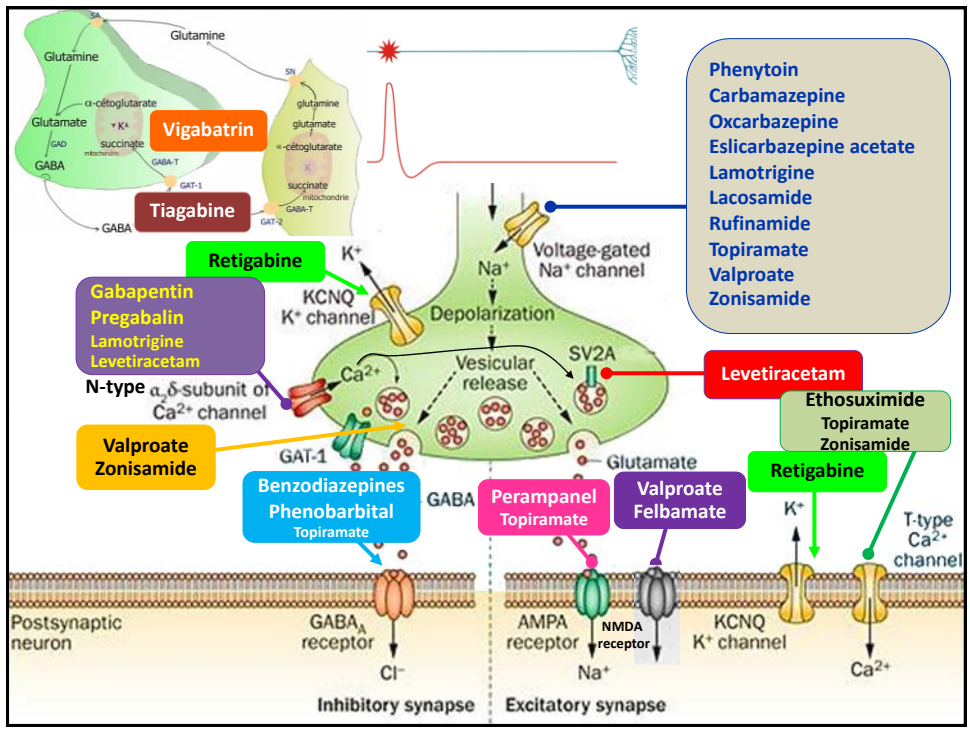
- Mechanism of action
- Pharmacokinetic properties
- Adverse effects
- Potential to develop drug interaction
- Formulation and administration



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)



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.

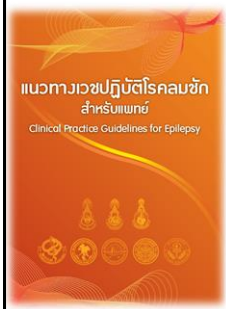
How AEDs Are They Differ?

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.

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.

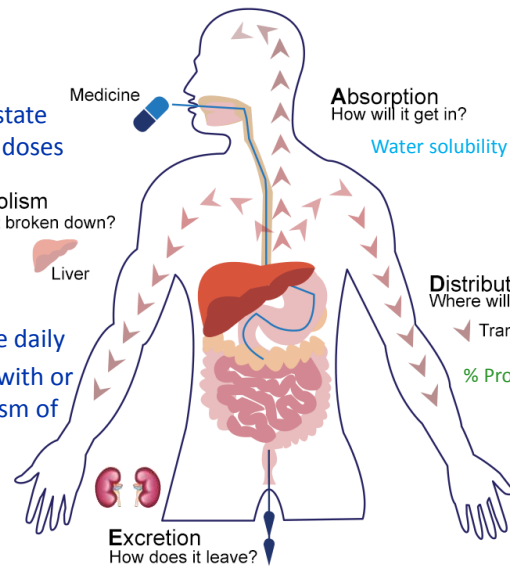
Combination AEDs Determined by Isobolographic Studies in Animals

	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

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



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

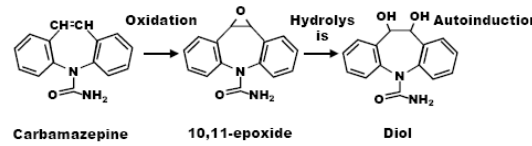
Patsalos PN, et al. Epilepsia 2008;49:1239-76.

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)

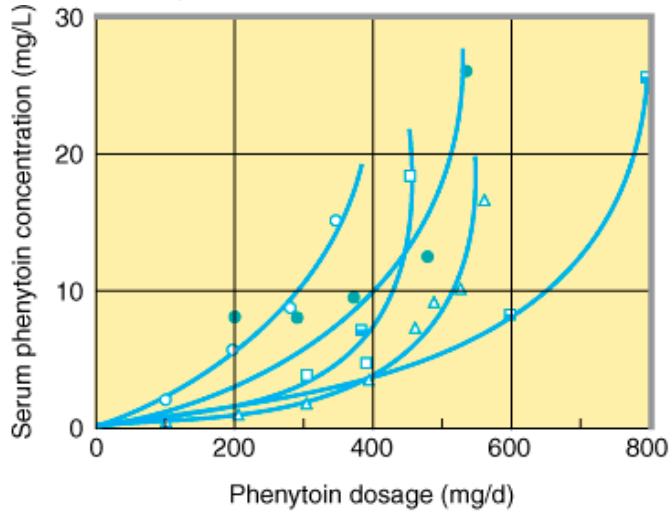
Marvanova M, et al. Ment Health Clin 2016;6:8-20.

Carbamazepine



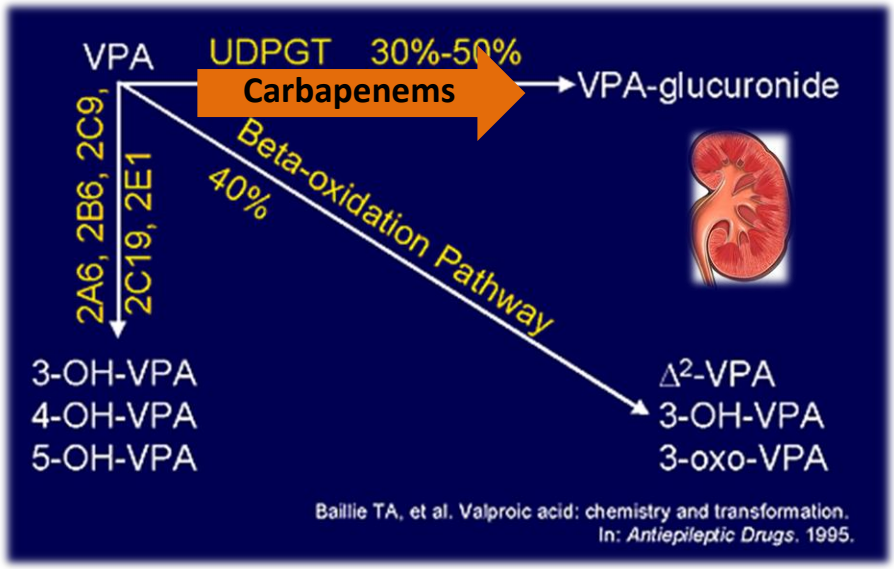
- Dosage forms
  - Available in 100 mg; 200 mg tablets; suspension – BID/TID
  - Available in a slow release preparations (CR formulation) - BID
- Carbamazepine half life — time dependent/auto-induction
  - First 2-6 weeks: 30-35 hrs
  - After 2-6 weeks: 12-20 hrs

Dose-Plasma Concentration Profile of Oral Phenytoin



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Valproic Acid



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 MHD	40	Cytosolic reductase	UGT	20
Perampanel	95	3A4		
Pregabalin	0			>90
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)

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.

Summary of the Effect of Hepatic and Renal Disease on Antiepileptic Drugs

AED	Hepatic disease	Renal disease		Comments
	Dose adjustment	Dose adjustment in dysfunction	Dialysis changes after 4 h of dialysis for routine use (not overdose)	
Renal elimination				
Gabapentin	Not necessary	Decrease dose based on reduced clearance	~35 % dialyzed (need supplementation)	
Pregabalin	Not necessary	Decrease dose based on reduced clearance	50–60 % dialyzed (need supplementation)	
Vigabatrin	Not necessary	Decrease dose based on reduced	Unknown	

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

AED	Hepatic disease	Renal disease		Comments
	Dose adjustment	Dose adjustment in dysfunction	Dialysis changes after 4 h of dialysis for routine use (not overdose)	
Metabolic elimination				
Carbamazepine	Lower dose in cirrhosis recommended	No significant effect expected	Minor	Some LFT elevation and risk Total serum levels underestimate unbound serum levels Carbamazepine epoxide is pharmacologically active
Clobazam	Lower initial dose and slower titration with dysfunction	No significant effect expected	Unknown	
Clonazepam	$t_{½}$ prolonged Lower initial dose and slower titration	No significant effect expected	Unknown	
Diazepam	$t_{½}$ prolonged Lower initial dose and slower titration	No significant effect expected	Unknown	
Lamotrigine	Reduced with severe dysfunction	No significant effect found	Minor	TDM is recommended

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

AED	Hepatic disease	Renal disease		Comments
	Dose adjustment	Dose adjustment in dysfunction	Dialysis changes after 4 h of dialysis for routine use (not overdose)	
Lorazepam	May need larger initial dose due to increased V_d. However, $t_{½}$ is also increased	No significant effect expected	Minor	
Midazolam	$t_{½}$ prolonged	No significant effect	Unknown	
Phenytoin	May need lower doses with severe dysfunction	No significant effect expected	Minor	Some LFT elevation and risk Total serum levels underestimate unbound serum levels. Measure unbound phenytoin
Rufinamide	Unknown: use not recommended	No significant effect expected	Unknown (may be significant)	
Stiripentol	Unknown. May need lower doses	No significant effect expected	Unknown (likely insignificant)	
Tiagabine	Unknown. May need lower doses	No significant effect expected	Unknown (likely insignificant)	
Valproate	Caution advised Reduce dose if severe	No significant effect expected	Minor	Some LFT elevation and risk Total serum levels underestimate unbound serum levels Theoretical risk of renal injury Risk of hepatic encephalopathy due to increased ammonia

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

AED	Hepatic disease	Renal disease		Comments
	Dose adjustment	Dose adjustment in dysfunction	Dialysis changes after 4 h of dialysis for routine use (not overdose)	
Metabolic and renal elimination				
Eslicarbazepine acetate	May need lower doses if severe	Reduce dose if CL_{CR} <60 mL/min	Dialyzable—extent unclear (supplementation needed)	
Ethosuximide	May need lower doses if severe	No significant effect expected	60–100 % dialyzable (need supplementation)	
Felbamate	Use not recommended	May be necessary	Unknown	Not recommended in renal disease, risk of fulminant hepatic failure
Lacosamide	May need lower doses if severe	Reduce dose if CL_{CR} <30 mL/min	~50 % dialyzed (need supplementation)	
Levetiracetam	May need lower doses if severe	May be necessary	~50 % dialyzed (need supplementation)	
Oxcarbazepine—MHD	Unclear	Reduce dose if CL_{CR} <30 mL/min	Unknown (may be significant)	
Perampanel	Not recommended for severe disease Reduce dose in mild or moderate dysfunction	No significant effect expected	Unknown	

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

AED	Hepatic disease	Renal disease		Comments
	Dose adjustment	Dose adjustment in dysfunction	Dialysis changes after 4 h of dialysis for routine use (not overdose)	
Phenobarbital	May need lower doses if severe	No significant effect expected	Unknown	Some LFT elevation and risk TDM recommended with hepatic or renal disease
Retigabine	May need lower doses if moderate or severe	No significant effect expected	Unknown	
Topiramate	May need lower doses if moderate or severe	Reduce dose if CL_{CR} <60 mL/min	~50 % dialyzed (need supplementation)	Risk of renal injury from nephrolithiasis Risk of hepatic encephalopathy due to increased ammonia
Zonisamide	May need lower doses if moderate or severe	No significant effect	Unknown	Risk of renal injury from nephrolithiasis Risk of hepatic encephalopathy due to increased ammonia

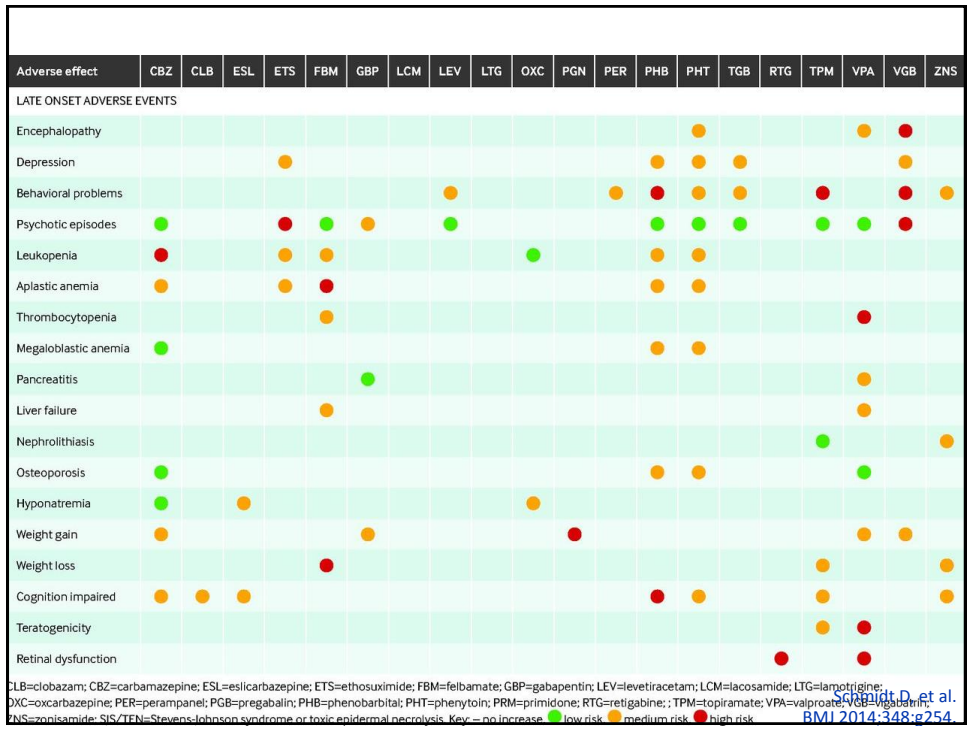
Anderson GD, et al. Clin Pharmacokinet 2014;53:29-49.

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.



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

Long-Term Adverse Effects of AEDs

Body system	Condition	AEDs
Metabolic		
Reproductive health	Amenorrhea, oligomenorrhea	PHT, PB, PRM, CBZ
	Impotence in men	PHT, PB, PRM, CBZ, GBP
	Infertility in women	VPA, *PHT, PB, PRM, CBZ*
	Polycystic ovarian syndrome	VPA
Bone health	Vitamin D deficiency	PHT, PB, PRM, *CBZ*
	Osteopenia, osteoporosis	PHT, PB, *TPM, CBZ, VPA*
Body weight	Weight gain, obesity	VPA, GBP, PGB, VBG, *CBZ*
	Weight loss	TPM, ZNS, *FBM*
lipids	Hyperlipidemia	PHT, CBZ, *PB, PRM, VPA, OXC, TPM*
	Metabolic syndrome	VPA
Vitamins	Folate deficiency	PHT, CBZ, PB, PRM, *OXC, VPA, GBP*
Renal and electrolytes	Renal stones, metabolic acidosis	TPM, *ZNS, ACZ*
	Hyponatremia	CBZ, OXC
	Urinary retention/hesitancy	RTG
Gastrointestinal	Pancreatitis	VPA
	Hepatic failure	FBM, VPA

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

Long-Term Adverse Effects of AEDs

Body system	Condition	AEDs
Skin and cosmetic	Alopecia, hair loss	VPA, *CBZ, OXC, LTG*
	Gum hypertrophy	PHT
	Hirsutism, hypertrichosis	VPA, *PB, PHT, PRM*
	Acne	VPA, *PHT*
	Blue skin discoloration	RTG
	Oligohydrosis (decreased sweating)	TPM, ZNS
Connective tissue	Plantar fibromatus, Dupuytren's contracture, shoulder-hand syndrome	PB
Hematological	Leukopenia	CBZ, *VPA*
	Thrombocytopenia, coagulopathy	VPA
	Aplastic anemia	FBM, *CBZ, PHT*
	Pseudolymphoma	PHT, *CBZ, PB, VPA*
Cardiac	AV block	CBZ, *LCM, PGB, ESL*
	Arrhythmia	CBZ, *LCM*
Visual	Peripheral visual field loss	VGB
	Pigmentary changes in retina	RTG
	Glaucoma (narrow-angle)	TPM, CBZ
Immunological	IgA deficiency	PHT
	SLE-like syndrome	CBZ, *PHT, PRM, ESM*

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

Long-Term Adverse Effects of AEDs

Body system	Condition	AEDs
Neurological	Neuropathy	PHT
	Essential tremor	VPA
	Parkinsonism	VPA
	Drowsiness, excessive sleep	PB, PRM, CBZ, GBP, PGB, VGB, *ZNS*
	Insomnia	LTG, FBM
	Cognitive impairment	PB, PRM, TGB, BZD, *PHT, ZNS*
Psychiatric	Depression	PB, VGB, TGB, ZNS, TPM, LEV
	Anxiety	LTG, LEV
	Irritability, agitation	PB, LEV, ZNS, TGB
	Psychosis	VGB, TGB, ZNS, LEV, *FBM, EM, TPM*
	Suicide	No definite increased risk from use of AEDs for treatment of epilepsy

GABA-ergic AEDs: VGB, TGB, PB, BZD, VPA

Antiglutaminergic AEDs: LTG, FBM, TPM

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

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: ซุกซนไม่อยู่สุข พฤติกรรมเปลี่ยนแปลงก้าวร้าว 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.

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

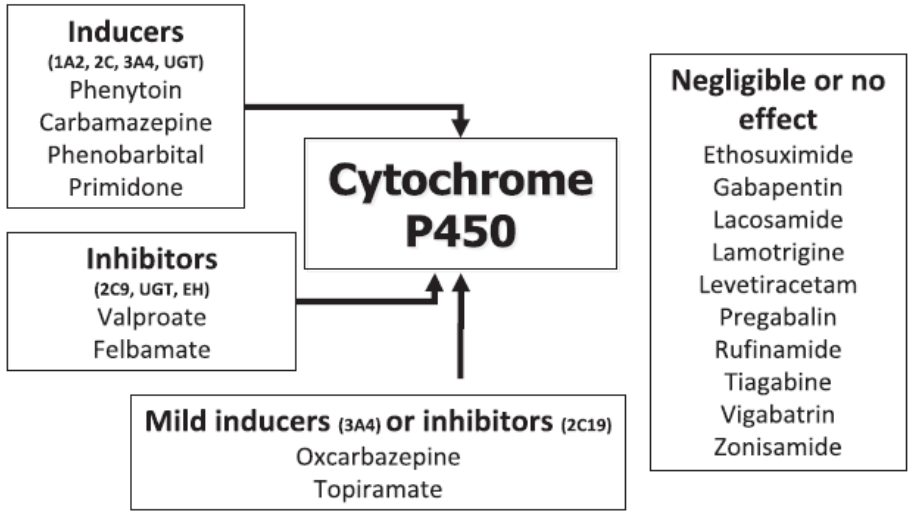
** Liver failure in Alpers-Huttenlocher syndrome; hyperammonemic encephalopathy in ornithine transcarbamylase deficiency

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.

Concerning Issues on DDI of AEDs

- Carbapenems

Valproate

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

AEDs with CYP inducers

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.

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

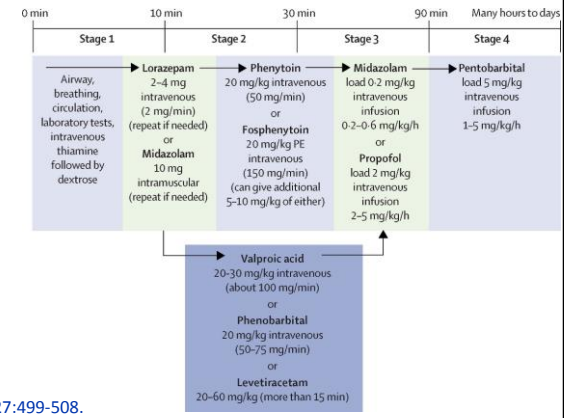
Parenteral AEDs

Characteristic	LZP	DZP	PHT	FosPHT	PB	VPA	LEV	LAC
Rapid onset of action	X	X	X	X		X	X	X
Intermediate to long duration	X		X	X	X	X	X	X
Broad spectrum	X	X			X	X	X	
Ease of administration	X	X		X	X	X	X	X
IV solution compatibility				X		X	X	X
Minimally morbidity				X		X	X	X
Useful as maintenance AEDs			X	X	X	X	X (1:1)	X (1:1)

Modified from Wheless JW, and Treiman DM. Epilepsia 2008;49(Suppl 9):74-8.

AEDs of Choices for Treatment Acute Seizure

- Prophylaxis of seizure following TBI
  - Phenytoin
  - Levetiracetam
    - *Valproate, carbamazepine, phenobarbital, magnesium*
- Treatment of acute seizure/status epilepticus



Zimmermann LL, et al. Neurosurg Clin N Am 2016;27:499-508.

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