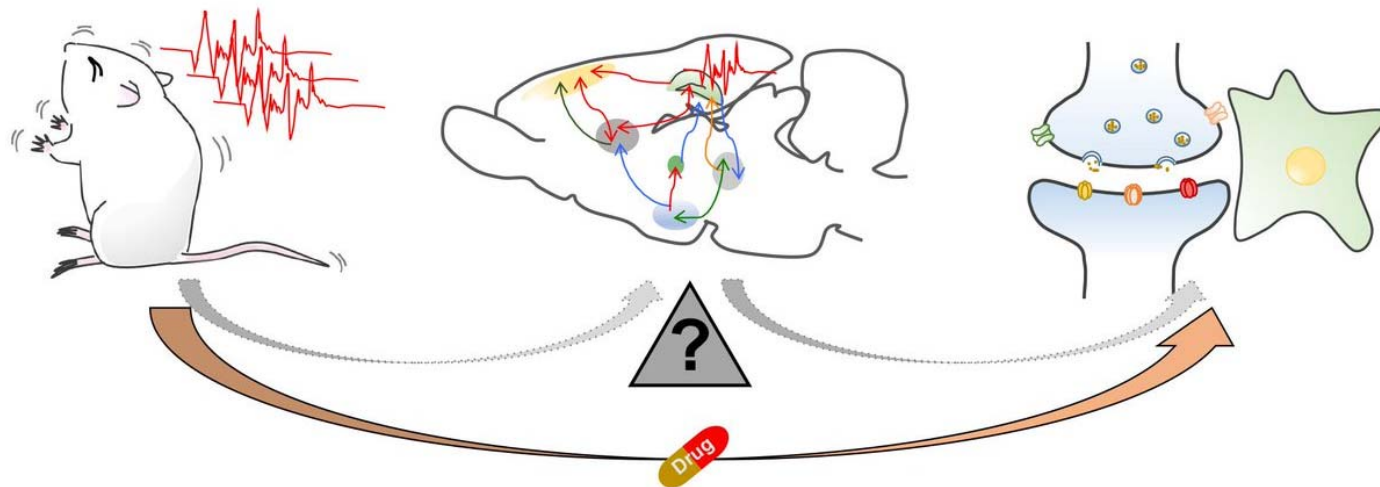


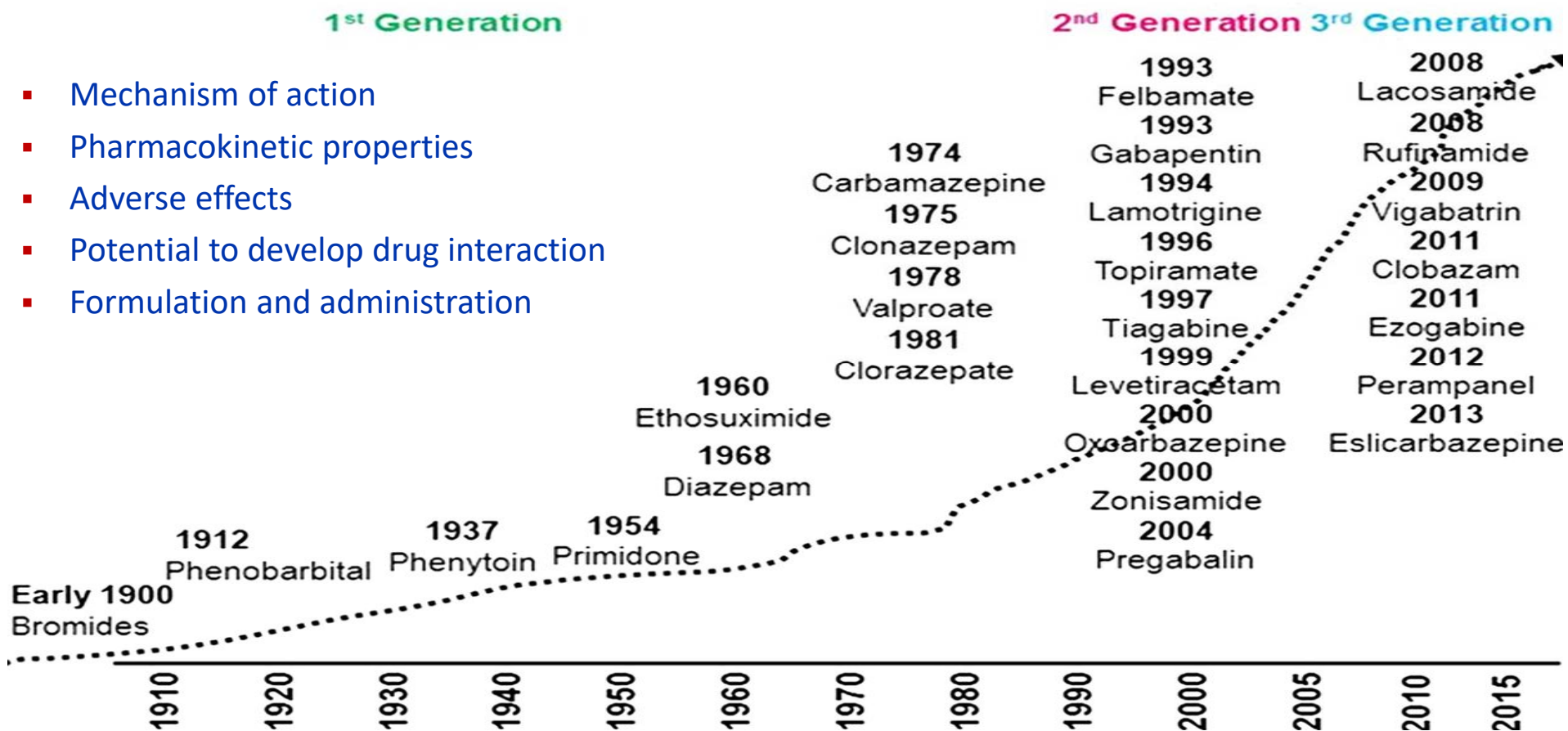


# PHARMACOLOGY OF ANTIEPILEPTIC DRUGS



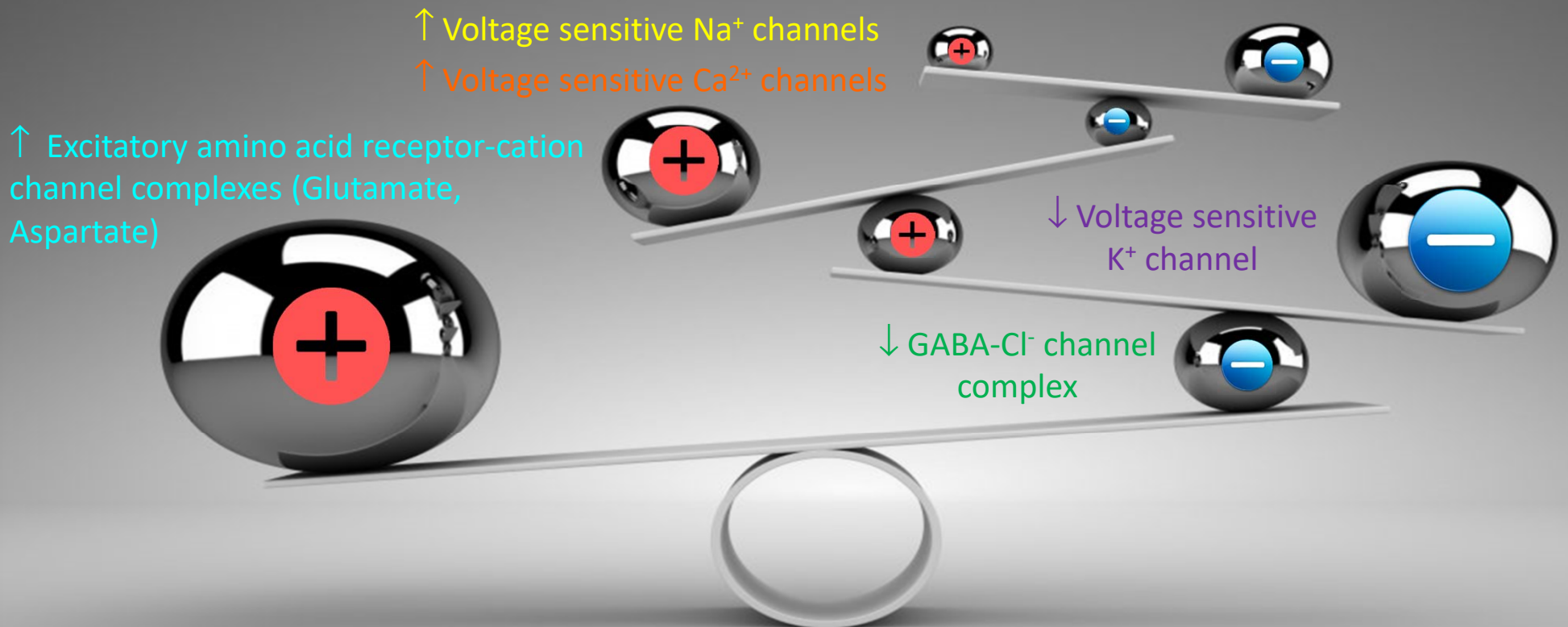
**THANARAT SUANSANAE** *B.S.(Pharm), BCPP, BCGP*  
Division of Clinical Pharmacy, Department of Pharmacy  
Faculty of Pharmacy, Mahidol University

# Chronological development timeline of antiepileptic drug

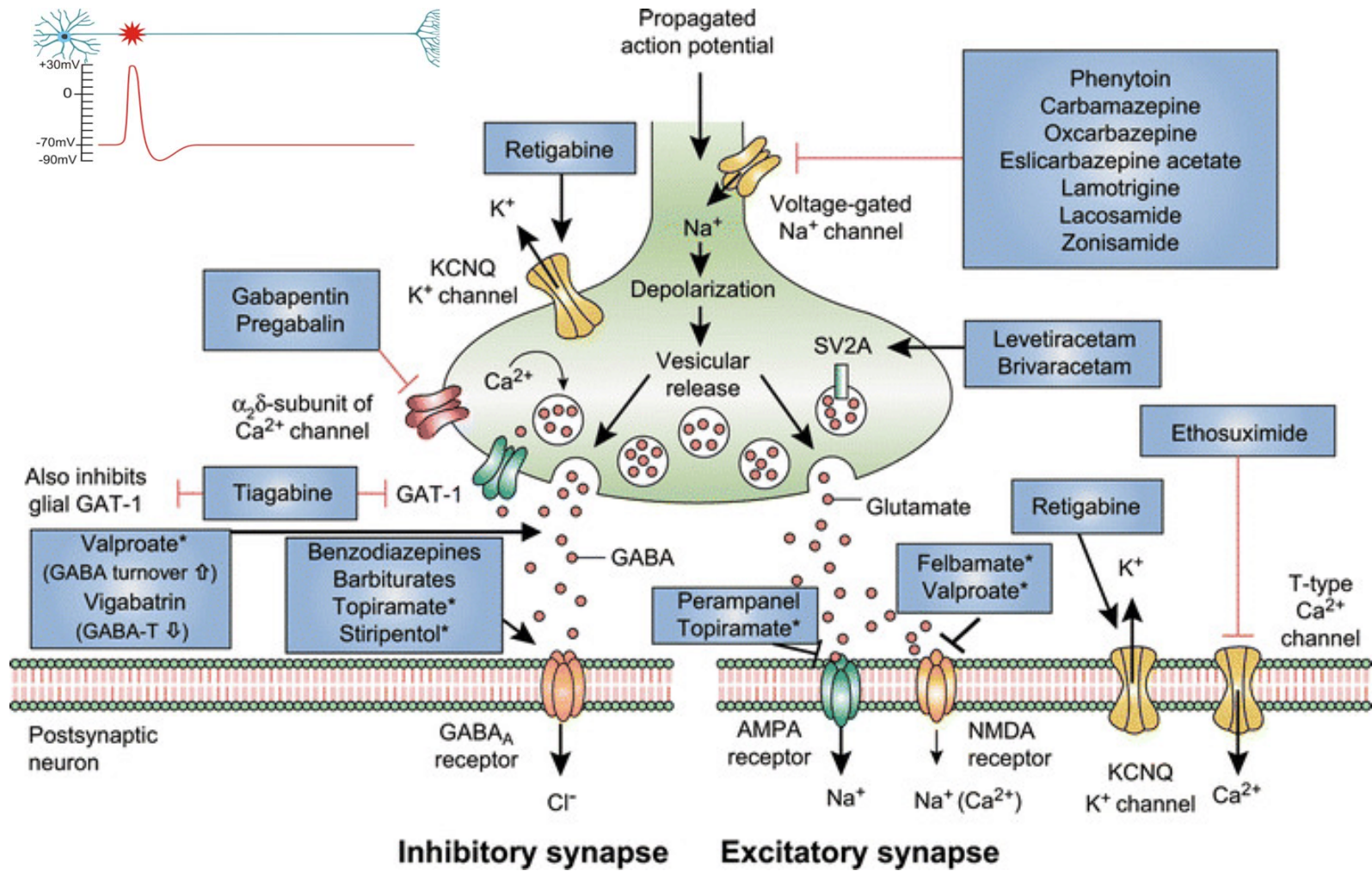


- Mechanism of action
- Pharmacokinetic properties
- Adverse effects
- Potential to develop drug interaction
- Formulation and administration

# Mechanisms of neuronal excitability and target of actions for AEDs



# Mechanism of action of clinically approved anti-seizure drugs



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

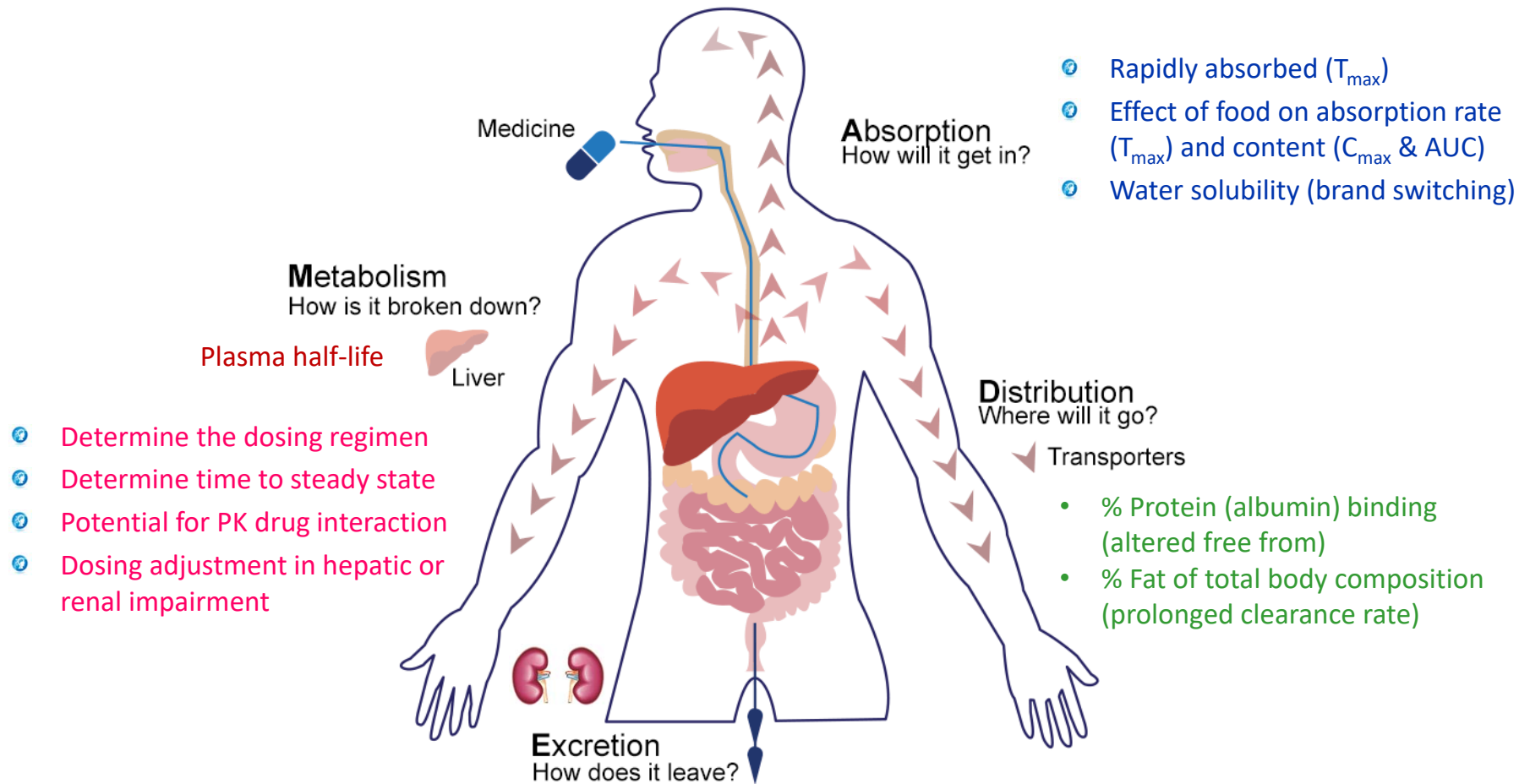
AED	Inhibition of glutamate excitation		Increase of GABA inhibition			Ionic channel			Other MOA	
	↓ Glu release	Receptor blockade	↑ GABA release/brain level	Bind GABA <sub>A</sub> receptor	Inhibit GABA transporter	Inhibit GABA transaminase	Blockade of VGSC	Blockade of VGCC		Activation of KCNQ/Kv7
Benzodiazepines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

## Summarize mechanisms of action of AED

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

PAM: positive allosteric modulator

# Pharmacokinetic properties (ADME) of AED





# Pharmacokinetic profiles of conventional AED

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

# Pharmacokinetic profiles of second generation AED

AED (serum conc)	F (%)	Vd (L/Kg)	Protein binding (%)	T <sub>1/2</sub> (h)	Metabolism & Elimination	Active metabolite
Gabapentin 4-16 µg/mL	35-60	0.85	0	5-7	R (>90%): unchanged	No
Lamotrigine 4-18 µg/mL	≥95	0.9-1.3	55	15-35	H (76%): UGT1A4	No
Levetiracetam 5-40 µg/mL	≥95	0.5-0.7	<10	6-8	R (66%): unchanged Non-hepatic (30%): hydrolysis by type B esterase in WBC	No
Oxcarbazepine 10-35 µg/mL (MHD)	>90 prodrug	0.75 (MHD)	60 (OXC) 40 (MHD)	8-15 (MHD)	H (80%): cytosolic arylketone reductase (OXC), YGT (MHD) R (20%): unchanged	S-licarbazepine R-licarbazepine
Pregabalin N/E	≥90	0.57	0	5-7	R (>95%): unchanged	No
Topiramate 5-20 µg/mL	≥80	0.6-0.8	15	20-30	R (70%): unchanged H (30%): CYP2C19 and glucuronidation	No
Vigabatrin 0.8-36 µg/mL	60-80	0.8	0	5-8	R (95%): unchanged	No
Zonisamide 10-40 µg/mL	≥90	1.0-1.9	40	27-70	H (70%): CYP3A4 (major), NATs (15%), CYP2C19 R (30%): unchanged	No
Felbamate 30-140 µg/mL	<90	0.7-1.0	25	22-25	R (50%): unchanged H (50%): CYP2E1 (major), CYP3A4 (20%), UGT (20%)	No
Tiagabine N/E	≥90	1.0	96	5-9	H (98%): CYP3A4	No



# Pharmacokinetic profiles of third generation AED

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

AEDs	Protein binding (%)	Hepatic Metabolism		Renally Excretion (%)	Elimination T <sub>1/2</sub> (h)
		Phase I (CYP)	Phase II (UGT)		
Brivaracetam	<20	2C19, amidase		9	9
Carbamazepine	75	3A4		<1	12-17
Clobazam	85	2C19, 3A4		2	10-30
Clonazepam	85	3A4		<1	22-40
Diazepam	98	2C19, 3A4		<3	24-48
Ethosuximide	0	3A4, 2E1		20	25-60
Felbamate	25	3A4, 2E1	UGT	50	22-25
Gabapentin	0	-	-	>90	5-9
Lacosamide	<15	2C19		40	13
Lamotrigine	55		1A4	<1	12-60
Levetiracetam	<10	Amidase		66	6-8
Lorazepam	93		2B15	<1	17-56
Midazolam	95	3A4		<1	2-7
Oxcarbazepine MHD	40 40	Cytosolic reductase	UGT	<1 20	1-2.5 8-11
Perampanel	95	3A4, 3A5		30	60-130
Phenobarbital	55	Glucosidase, 2C9, 2C19, 2E1		22	36-118
Pregabalin	0	-	-	>90	5-7
Phenytoin	90	2C9, 2C19		2	7-42
Retigabine	80		UGT, NAT	20-30	6-10
Rufinamide	35	Carboxylesterase		<2	6-10
Stiripentol	99	CYP	UGT	<1	3-8
Tiagabine	96	3A4		<2	3-8
Topiramate	15	CYP		30	21
Vigabatrin	0	-	-	95	5-8
Valproic acid	90	β-oxidation, 2C9, 2C19	1A6, 1A9, 2B7	<5	6-17
Zonisamide	50	3A4, 2C19	NAT2	35	27-70

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

# Overview of adverse effects of individual antiepileptic 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

# Potential to develop drug-drug interactions of AED

- CYP2C9 Substrates**
- Alosetron (Lotronex)
  - Bosentan (Tracleer)
  - Candesartan (Atacand)
  - Celecoxib (Celebrex)
  - Chlorpropamide (eg, Diabinese)
  - Diclofenac (Voltaren)
  - Dronabinol (Marinol)
  - Flurbiprofen (Ansaid)
  - Fluvastatin (Lescol)
  - Glimepiride (Amaryl)
  - Glipizide (Glucotrol)
  - Glyburide (DiaBeta)
  - Ibuprofen (eg, Motrin, Advil)
  - Indomethacin (Indocin)
  - Irbesartan (Avapro)
  - Losartan (Cozaar)
  - Meloxicam (Mobic)
  - Montelukast (Singulair)
  - Naproxen (eg, Aleve)
  - Nateglinide (Starlix)
  - Phenobarbital
  - Phenytoin (eg, Dilantin)
  - Piroxicam (Feldene)
  - Rosiglitazone (Avandia)
  - Rosuvastatin (Crestor)
  - Sulfamethoxazole
  - Tolbutamide
  - Torsemide (Demadex)
  - Valsartan (Diovan)
  - Warfarin (Coumadin)

- Inducers**  
(1A2, 2C, 3A4, UGT)  
Phenytoin  
Carbamazepine  
Phenobarbital  
Primidone

- Inhibitors**  
(2C9, UGT, EH)  
Valproate  
Felbamate

- UGT substrates**  
Ezetimibe  
Lamotrigine  
Lorazepam  
Morphine  
Mycophenolate mofetil  
Paracetamol

- Mild inducers (3A4) or inhibitors (2C19)**  
Oxcarbazepine  
Topiramate

**Cytochrome P450**

- Negligible or no effect**
- Brivaracetam
  - Clobazam
  - Ethosuximide
  - Gabapentin
  - Lacosamide
  - Lamotrigine
  - Levetiracetam
  - Perampanel
  - Pregabalin
  - Rufinamide
  - Tiagabine
  - Vigabatrin
  - Zonisamide

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

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

AED added	Pre-existing AED														
	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=levetiracetam; 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

## 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, hyponatremia
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)



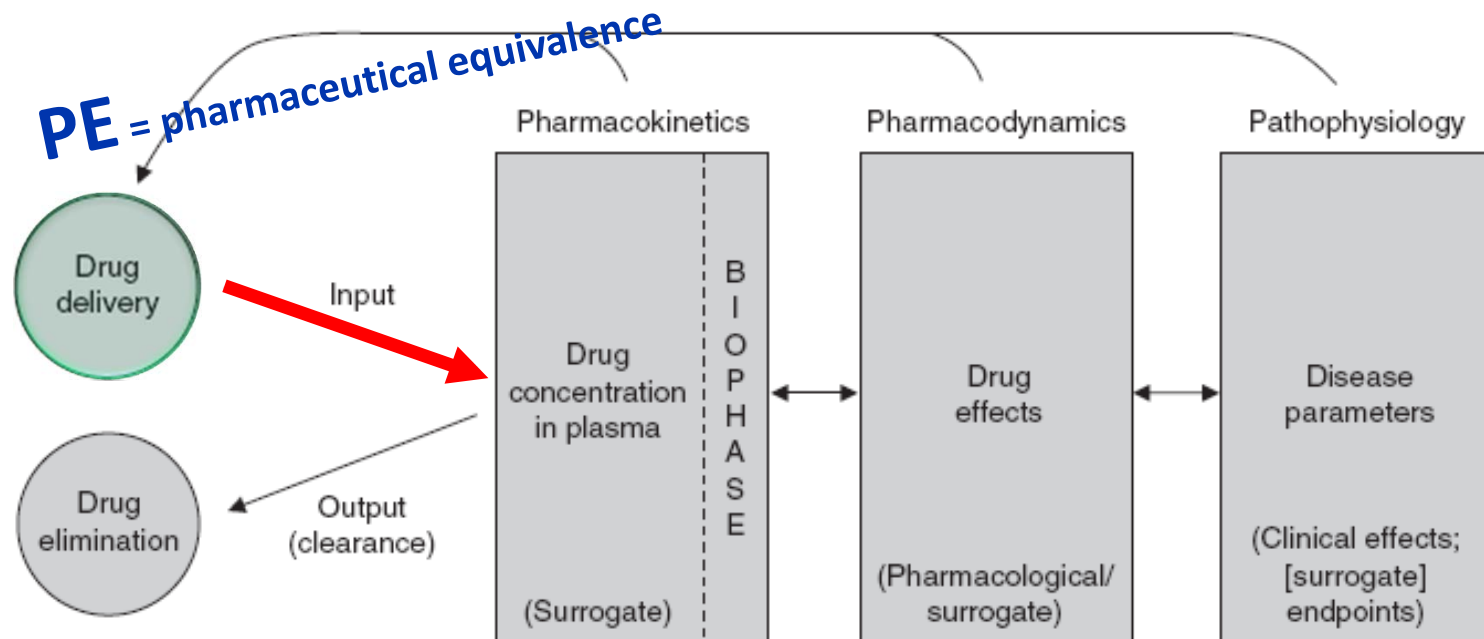
# Dose adjustments for AED in kidney disease

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

# Differential pharmacology of AED

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

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



## Bioavailability

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

## 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

# Selection the AED for individualized patients

