Matching antiepileptic medications with epilepsy patients

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Which medications?

- ลักษณะการชักและประเภทของโรคลมชักของผู้ป่วย
- การบริหารยา
- ผลข้างเคียงของยากันชัก
- Drug interaction กรณีที่ผู้ป่วยได้ยาหลายชนิดพร้อมกัน
- Special situations
  - Reproductive age
  - Elderly
  - Hepatic impairment
  - Renal impairment

Traditional antiepileptic drugs

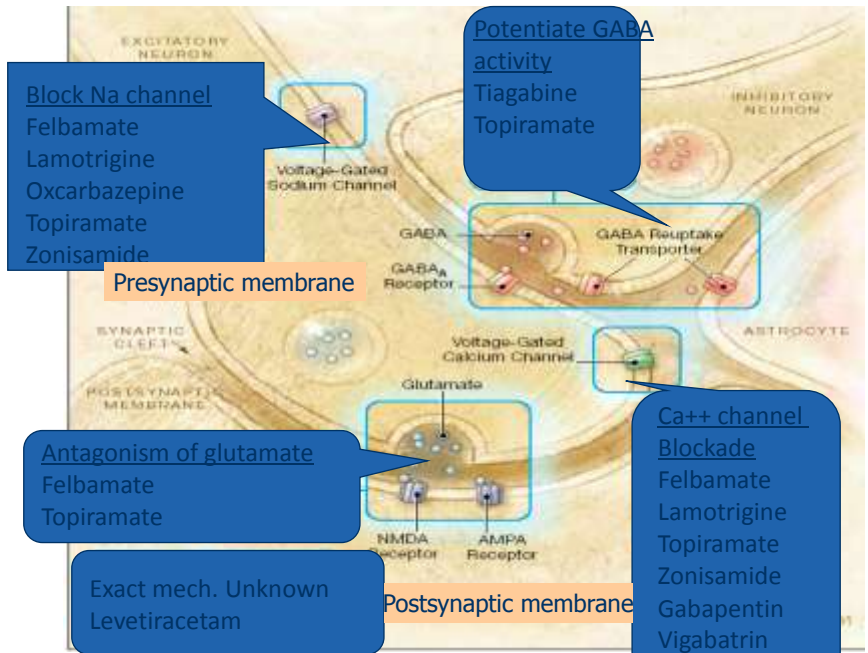
- Phenobarbital
- Phenytoin
- Carbamazepine
- Sodium valproate
- Benzodiazepine

New antiepileptic drugs

- Felbamate (1993)
- Gabapentin (1993)
- Lamotrigine (1994)
- Topiramate (1996)
- Tiagabine (1997)
- Levetiracetam (1999)
- Oxcarbazepine (2000)
- Zonisamide (2000)
- Pregabalin (2005)
- Vigabatrin

Brivaracetam	A levetiracetam analogue and SV2A ligand with additional sodium channel-blocking properties, in phase III development in refractory epilepsy
Carisbamate	A carbamate derivative completing phase III development for refractory partial epilepsy
E-2007	An AMPA receptor antagonist in phase II development for refractory partial epilepsy
Eslicarbazepine acetate	An oxcarbazepine derivative completing phase III development for refractory partial epilepsy
Fluorofelbamate	A felbamate derivative completing phase I studies
Ganaxolone	A neurosteroid that acts as modulator of $GABA_A$-mediated transmission, in phase II development for refractory epilepsy
Huperzine A	An alkaloid approved in China for Alzheimer's disease, undergoing initial assessment in epilepsy
JZP-4	A structural analogue of lamotrigine in phase I assessment
Lacosamide	A methoxypropionamide derivative completing phase III development for refractory partial epilepsy and neuropathic pain
Licarbazepine	The monohydroxy derivative of oxcarbazepine being developed as a racemate for bipolar disorder
Losigamone	A β methoxy-butenolide with phase III clinical trial data for refractory partial epilepsy
NS 1209	A competitive AMPA antagonist in phase II assessment for refractory status epilepticus
Retigabine	A selective opener of KCNQ2/3 and KCNQ3/5 channels in phase III development for refractory partial epilepsy
Rufinamide	A sodium channel-blocker approved as adjunctive treatment for Lennox-Gastaut syndrome by EMEA, under assessment by the FDA as adjunctive treatment for the syndrome and for refractory partial seizures
Seletracetam	A levetiracetam analogue with increased potency, currently in phase II
Safinamide	A sodium channel-blocker and MAO-B inhibitor, currently in phase III development, which is focused mainly on Parkinson's disease
Stiripentol	A metabolic inhibitor that has received conditional approval by EMEA as adjunctive therapy to clobazam and valproic acid in severe myoclonic epilepsy in infancy
T2000	A non-sedating barbiturate with antiepileptic activity currently in phase IIa assessment for essential tremor
Talampanel	A non-competitive AMPA receptor antagonist that completed phase II studies for refractory partial seizures
Tonabersat	A carabersat analogue, currently undergoing phase IIa assessment for migraine prophylaxis
Valnoctamide	A metabolically stable constitutional isomer of valpromide (the primary amide of valproic acid) with broad-spectrum anticonvulsant activity in animal models, currently undergoing phase II assessment in bipolar disorder as a racemate
Valrocemide (SPD-493)	A derivative of valproic acid in phase II development in refractory epilepsy with potential additional CNS indications
XP-13512	A gabapentin prodrug, with better oral bioavailability than gabapentin, currently undergoing clinical trails for restless-legs syndrome
YKP3089	A compound with activity in animal models of epilepsy, anxiety, and neuropathic pain, in phase I development

AMPA=α-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropionic acid; EMEA=European Medicines Agency; FDA=US Food and Drug Administration; MAO-B=monoamine



JAMA. 2004;291:605-614

Spectrum of traditional AEDs

ชนิดของอาการชัก	Traditional AEDs
Absence	Sodium valproate
Myoclonic, atonic	Sodium valproate
Generalized tonic clonic	Phenobarbital Phenytoin Carbamazepine Sodium valproate

Spectrum of traditional AEDs

ชนิดของอาการชัก	Traditional AEDs
Partial	Phenobarbital Phenytoin Carbamazepine Sodium valproate
Infantile spasm	Vigabatrin

Spectrum of new AEDs

Type of seizure	FBM	VGB	TGB	GBP	OXC	LTG	TPM	LEV	PGB	ZNS
Partial	+	+	+	+	+	+	+	+	+	+
Second generalize	+	+	+	+	+	+	+	+	+	+
Tonic clonic	?+	?+	?	?+	+	+	+	+	?	+
Absence	?+	-	-	-	-	+	?	?+	?	?+
Myoclonic	?	-	?	-	-	+*	+	+	?	+
Lennox Gastaut	+	?	?	?	-	+	+	?	?	?
Infantile spasm	?	+	?+	?	-	?+	?+	?	?	?+

Hitiris N, Brodie MJ. Curr Opin Neurol 2006;19:175-80

Aggravation of seizures by AEDs

	CBZ	OXC	PHT	LTG	VPA	GBP	VGB	BDZ
Absence	+++	+	+++			+	++	
Myoclonic	+++	+	+++	+		+	+	
JME	++	+	++	+				
LGS/MAE	++	+	++	+		+	++	++
BECTS	+			+	+			
LKS/ESES	+		+					
ULD			+					

ชนิดของอาการชัก	Traditional AEDs	New AEDs
Absence	Sodium valproate	Lamotrigine Clonazepam
Myoclonic, atonic	Sodium valproate	Lamotrigine Topiramate Clonazepam
Generalized tonic clonic	Phenobarbital Phenytoin Carbamazepine Sodium valproate	Lamotrigine Topiramate Oxcarbazepine Levitiracetam Gabapentin Clonazepam

ชนิดของอาการชัก	Traditional AEDs	New AEDs
Partial	Phenobarbital Phenytoin Carbamazepine Sodium valproate	Lamotrigine Topiramate Oxcarbazepine Levitiracetam Gabapentin Clonazepam Clobazam
Infantile spasm	Vigabatrin	Sodium valproate Topiramate Clonazepam Clobazam

AEDs	Dosage in children	Dosage in adults	Half life (hrs)
Phenytoin	4-8 mg/kg/d	300 mg/d	20-30
Carbamazepine	10-20 mg/kg/d	400-600 mg bid	10-20
Sodium valproate	30-60 mg/kg/d	1000-1500 mg/d	8-12
Phenobarbital	2-5 mg/kg/d	120-250 mg/d	96
Clonazepam		0.5 mg bid	18-50

Absorbtion

- Most of the new AEDs are rapidly absorbed with high bioavailability
- Gabapentin absorbtion is dose dependent

AED	Protein binding %	T/2	Site of elimination	Remarks
Gabapentin	0	4-6	Renal, 100% Not metabolize	Dose dependent absorption
Lamotrigine	55	15-30	Hepatic, 90% Glucoronidation	Clearance increased by enzyme inducing AEDs, reduced by VPA
Topiramate	9-17	15-23	Renal, 40-70%	Fraction hepatically metabolized, increased by enzyme inducing AEDs
Levetiracetam	0	6-8	Renal, 66%; hydrolysis of acetamide gr, 34%	Metabolism is nonhepatic hydrolysis
Oxcarbazepine	40	4-9	Hepatic, 70% Hepatic conversion to active metabolite	Based upon 10 Hydroxy carbazepine (MHD), the major active metabolite
Zonisamide	40-60	24-60	Hepatic, 70%	Clearance increased by enzyme inducing AEDs
Pregabaline	0	6	Renal Not metabolize	

Dosing table in adults

Drugs	Starting dose (mg/d) Rate of ↑	Common dose (mg/d)	Maintenance range (mg/d)	Dosing interval
Gabapentin	**300-400 (300mg/d)**	**2400**	**1800-3600**	**tid**
Lamotrigine	**12.5-25***	**200-400**	**100-400**	**OD-bid**
Levetiracetam	**500 (500mg/wk)**	**2000-3000**	**1000-4000**	**bid**
Oxcarbazepine	**150-300 (300 mg/wk)**	**900-1800**	**900-2400**	**Bid-tid**
Topiramate	**25-50**	**200-400**	**100-1000**	**bid**
Zonisamide	**100**	**400**	**400-600**	**OD-bid**
Pregabalin	**150**	**300**	**150-600**	**Bid-tid**

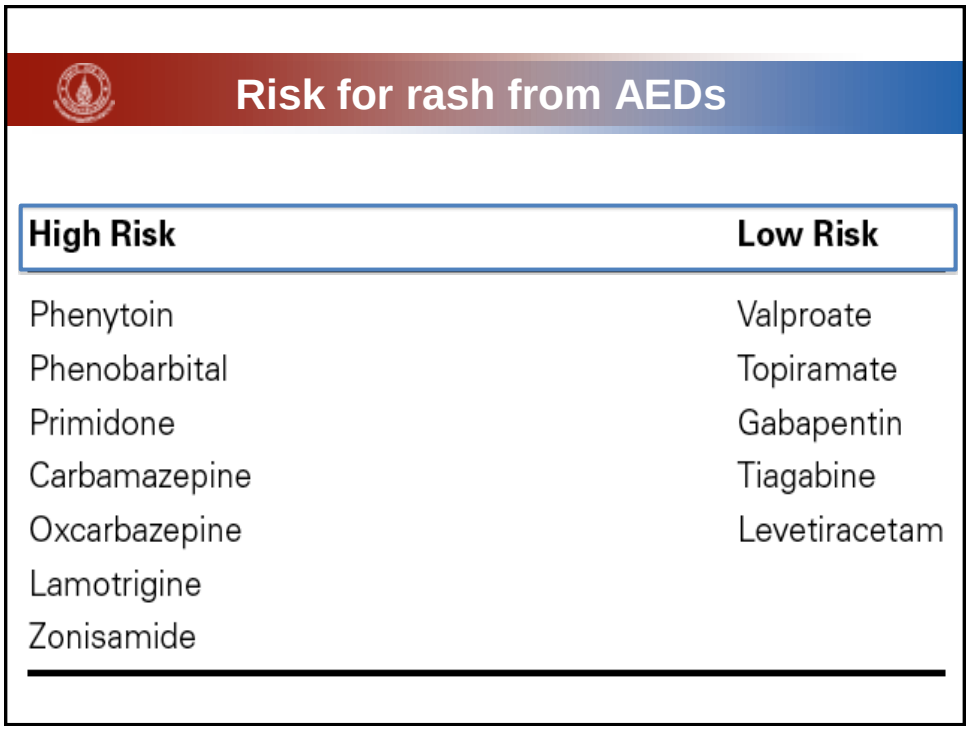
	MonoRx	Titrate	With Valproate	Titrate	With other AEDs	Titrate
Adult						
Wk 1-2	25 mg OD		12.5 mg OD/AD	Slow	50 mg OD	
Wk 3-4	25 mg bid	25mg/ wk	25 mg OD	Slow	50 mg bid	50mg/ wk
Mainte nance	50-100 mg bid		50-100 mg bid		100-200 mg bid	
Children						
Wk 1-2	0.5 mg/kg		0.15 mg/kg		0.6 mg/kg	
Wk 3-4	1 mg/kg	0.5 mg/kg /2wk	0.3 mg/kg	0.1-0.3 mg/kg/ 2wk	1.2 mg/kg	1-2 mg/kg /2wk
Mainte nance	2-8 mg/kg		1-5 mg/kg		5-15 mg/kg	

Side effects of AEDs

Side effects of old AEDs

AEDs	Common side effects	Serious side effects
Phenytoin	Nystagmus, ataxia, drowsiness, gum hypertrophy	Rash, Steven Johnson syndrome, elevated LFT
Carbamazepine	Nystagmus, ataxia, drowsiness	Rash, Steven Johnson syndrome, elevated LFT, leukopenia, hyponatremia
Sodium valproate	Drowsiness, tremor, alopecia, weight gain	Thrombocytopenia, elevated LFT, fulminant hepatic failure (rare)
Phenobarbital	Drowsiness, mental slowness, behavioral disorder	Rash, Steven Johnson syndrome, elevated LFT
Clonazepam	Drowsiness, mental slowness	

Drugs	Potentially serious adverse events	Nonserious adverse events
Gabapentin	None	Weight gain, peripheral edema, behavioral changes
Lamotrigine	Rash, including Stevens Johnson and TENS, hypersensitivity reactions	Tics, insomnia
Levetiracetam	None	Irritability/ behavior changes
Oxcarbazepine	Hyponatremia (elderly), rash	None
Tiagabine	Stupor or spike wave stupor	Weakness
Topiramate	Renal calculi, open angle glaucoma, anhidrosis	Weight loss, language dysfunction,paresthesia
Zonisamide	Rash, renal calculi, anhidrosis	Irritability, weight loss
Pregabalin	None	Dizziness and somnolence, myoclonus

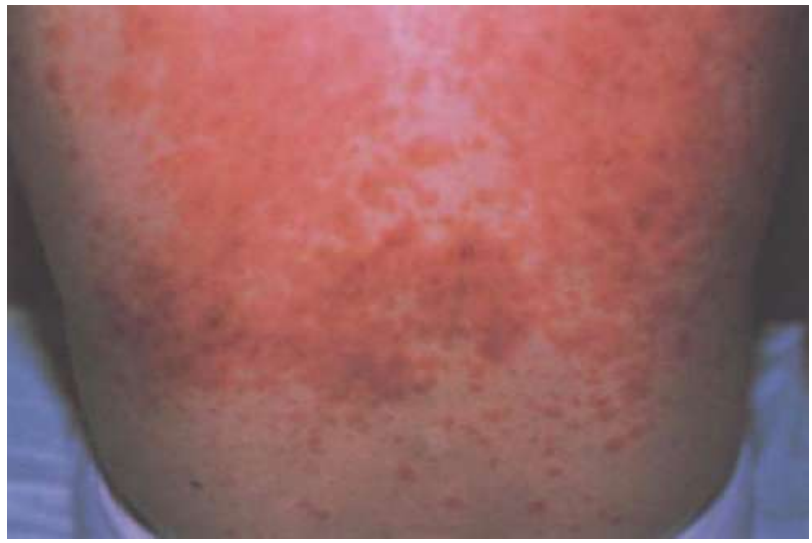


AEDs hypersensitivity syndrome

Manifestation	Incidence (%)
Fever	100
Skin rash	87
Hepatitis	51
Eosinophilia	30
Blood dyscrasia	23
Nephritis	11
Lung involvement	9
Atypical lymphocytosis	6

AEDs hypersensitivity syndrome

- **Incidence:**
  - Phenytoin 2.3-4.5/10,000
  - Carbamazepine 1-4.1/10,000
  - Lamotrigine ?
- **Delayed type hypersensitivity**
- **Occurs 2-8 weeks after starting AEDs**
- **Occurs with older aromatic AEDs**
- **Cross reactivity between PHT, PB and CBZ is quite high (up to 70-80% on testing)**



Epilepsia. 2010 May;51(5):926-30. Epub 2010 Mar 19.

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

Tassaneeyakul W, Tiamkao S, Jantararoungtong T, Chen P, Lin SY, Chen WH, Konyoung P, Khunarkornsiri U, Auvichayapat N, Pavakul K, Kulkantrakorn K, Choonhakarn C, Phonhiamhan S, Piyatrakul N, Aungaree T, Pongpakdee S, Yodnopaglaw P.

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Abstract

Carbamazepine (CBZ) has been reported as the most common culprit drug for Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in several Asian countries including Thailand. A strong association between HLA-B*1502 and CBZ-induced SJS/TEN has been reported in Han Chinese but not in Caucasian and Japanese populations. A case-control study was conducted to determine whether HLA-B*1502 is a valid pharmacogenetic test for SJS/TEN caused by CBZ in a Thai population. Among 42 CBZ-induced patients with SJS/TEN, 37 (88.10%) patients carried the HLA-B*1502 while only 5 (11.90%) of the CBZ-tolerant controls had this allele. The risk of CBZ-induced SJS/TEN was significantly higher in the patients with HLA-B*1502, with an odds ratio (OR) of 54.76 [95% confidence interval (CI) 14.62-205.13, p = 2.89 x 10(-12)]. The sensitivity and specificity of HLA-B*1502 for prediction of CBZ-induced SJS/TEN were 88.10%. By assuming a 0.27% as a prevalence rate of CBZ-induced SJS/TEN in a Thai population, the positive predictive value (PPV) and negative predictive value (NPV) of the HLA-B*1502 were 1.92% and 99.96%. Results from this study suggest that HLA-B*1502 may be a useful pharmacogenetic test for screening Thai individuals who may be at risk for CBZ-induced SJS and TEN.

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Weight issues from AEDs

Weight Gain	Weight Neutral	Weight Loss
Valproate	Lamotrigine	Topiramate
Gabapentin	Levetiracetam (?)	Zonisamide
Carbamazepine	Phenytoin	Felbamate
Tiagabine (?)		
Vigabatrin		

Cognitive and behavioral side effects

	Cognitive	Behavioral
Conventional AEDs		
Carbamazepine	+	0
Phenobarbital	++	++
Phenytoin	+	0
Na Valproate	+	0
New AEDs		
Gabapentin	0	0
Lamotrigine	0	0
Levetiracetam	0	+
Oxcarbazepine	+?	0
Topiramate	+ **(reduced by slow titration)**	+?
Zonisamide	0	+?
Pregabalin	0	0

AEDs and osteoporosis

- Enzyme inducing AEDs may interfere with metabolism of vitamin D, therefore can cause increased incidence of osteoporosis with long term use.

Glaucoma

- Acute myopia and secondary angle closure glaucoma
- Reported in association with more than 25 medications mostly sulfonamide gr. And carbonic anhydrase
- Occurs from acute bilateral swelling of the choroid and ciliary body, causing structures to displace forward and closure of the angle of the anterior chamber

Glaucoma

- 55 cases of acute bilateral glaucoma were reported in association with topiramate (up to Dec 2001)
- 86% were female
- Occurred between approx. 5-21 days after initiation of topiramate (All cases occurred before 26 days)
- Dosage 25-150 mg/d
- Condition was reversible in 24 hrs, if detected early

Common drug-drug interaction

Metabolic pathways of AEDs

CYP 1A2	CYP 2C9	CYP 2C19	CYP 3A4
Carbamazepine*	Phenytoin	Phenytoin*	Carbamazepine
	Phenobarbital	Diazepam	Tiagabine
	Valproate*		Zonisamide
			Ethosuximide
			Felbamate

*Minor metabolic pathway.

Between AEDs

- Enzyme inducing AEDs (PHT, PB, CBZ) VS other AEDs
  - Reduce all AEDs level esp. sodium valproate and lamotrigine

Effects of enzyme inducing drugs on the concentration and clearance of concurrent AEDs

Effect on Concurrent AED Serum Concentration	Approximate Change in AED Clearance
↓ Ethosuximide	↑ 20–50%
↓ Valproate	↑ Two- to fourfold
↓ Lamotrigine	↑ Two- to fourfold
↓ Topiramate	↑ 40–50%
↓ Tiagabine	↑ Two- to fourfold
↓ Felbamate	↑ 50%
↓ Zonisamide	↑ 30–50%
↓ Oxcarbazepine	↑ 25–40%
Levetiracetam	No change

Between AEDs

- Enzyme inhibitors
- Sodium valproate→ ↑↑↑ lamotrigine
- Topiramate, oxcarbazepine→ ↑ phenytoin

Main inhibitory interaction of AEDs

Newly Introduced Drug	Effect on Serum Concentration of Concurrent AEDs	Metabolic Pathway/ Enzymes Inhibited
Valproate	↑ Phenobarbital (15–40%)	N-glucosidation, p-hydroxylation
	↑ Lamotrigine (40–60%)	Glucuronidation
	↑ Carbamazepine epoxide*	Epoxide hydrolase
	↑ Felbamate (15–20%)	
Felbamate	↑ Phenytoin** (30–100%)	2C19
	↑ Carbamazepine epoxide* (40–50%)	
	↑ Valproate (30–50%)	Beta-oxidation
	↑ Phenobarbital (40–50%)	2C19
Topiramate	↑ Phenytoin** (25%)	2C19
Oxcarbazepine	↑ Phenytoin** (20–30%)	2C19

*Carbamazepine levels will not reflect this increase as the epoxide is not measured routinely.
**Effect may be enhanced by the nonlinear (saturable) elimination kinetics of phenytoin.

Lamotrigine

- Pregnancy, hormonal contraception can significantly lower lamotrigine level
- Therapeutic drug monitoring may be necessary during pregnancy
- **Valproate is a potent inhibitor of UGT dependent metabolism of lamotrigine and can significantly prolong lamotrigine half-life
- UGTs enzyme inducer AEDs (CBZ, PHT, PB) can increased metabolism of lamotrigine

Interaction with other drugs

- **Interaction between CYP3A4 inhibitors and carbamazepine**
- **Warfarin**
- **OCPs**
- **Psychiatric drugs**
- **Cardiac drugs**
- **Chemotherapy and immunosuppressive agents**

Commonly used medications that inhibit the CYP3A4 isoenzymes

Erythromycin	Fluvoxamine
Clarithromycin	Nefazodone
Troleandomycin	Sertraline
Cimetidine	Ritonavir
Diltiazem	Indinavir
Verapamil	Nelfinavir
Fluconazole	Omeprazole
Itraconazole	Propoxyphene
Ketoconazole	

Drug interaction with warfarin

- **Metabolites through CYP3A4, 2C9**
- **Phenytoin, phenobarbital and carbamazepine reduce the concentration of warfarin by up to 50-65%**
- **Phenobarbital and carbamazepine also reduce the anticoagulation effects of warfarin metabolites**
- **Newer AEDs do not have signinificant interaction with anticoagulant**

Drug interaction with OCPs

- **AEDs that cause induction of CYP 3A4 increase metabolism of oral contraceptives resulting in failure of contraceptives.**
- **Potent enzyme inducing AEDs:**
  - phenytoin, carbamazepine, primidone, phenobarbital.
- **Less-potent enzyme inducing AEDs:**
  - oxcarbazepine, lamotrigine
  - topiramate >200 mg.

Drug interaction with OCPs

- **Oral contraceptives should contain >50 micrograms of estrogen in the combination and external methods to prevent insufficient protection.**

Drug Class	Interactions with AEDs
Antiarrhythmics	Inductor AEDs enhances antiarrhythmics metabolism; phenytoin decreases amiodarone metabolism.
Hypotensive agents	Inductor AEDs enhances beta-blockers and calcium-antagonist metabolism; verapamil and diltiazem inhibit carbamazepine metabolism.
Digoxin	Phenytoin increases digoxin metabolism.
Lipid-lowering drugs	Inductor AEDs enhance lipid-lowering agents metabolism.
Immunosuppressants	Phenytoin, carbamazepine, and barbiturates enhance tacrolimus, sirolimus, and methylprednisolone metabolism.
Antivirals	Inductor AEDs enhance anti-HIV agents metabolism; anti-HIV agents increase carbamazepine, gabapentin, levetiracetam, and lamotrigine levels.
Antibiotics	Carbapenems decrease valproate levels; macrolides increase carbamazepine levels.
Antifungal	Antifungals enhance carbamazepine and phenytoin levels.
Tuberculostatics	Rifampicin enhances phenytoin, carbamazepine, valproate, ethosuximide, and lamotrigine metabolism; isoniazide inhibits it.

Advantage of new AEDs

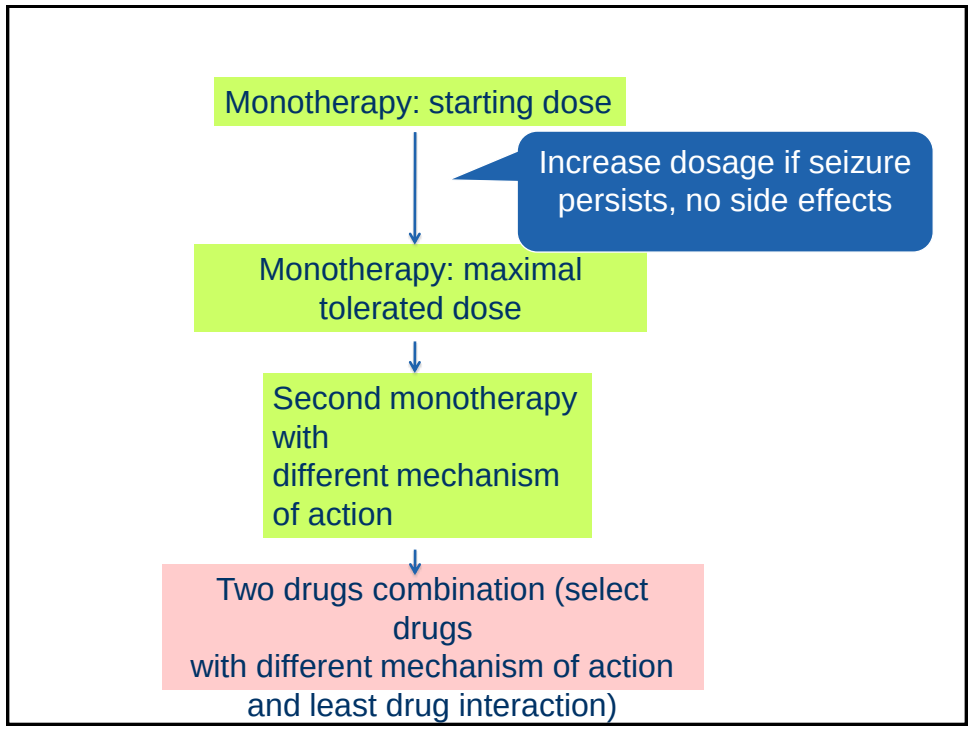
- Give clinician more choices of antiepileptic medications especially more choices of broad spectrum AEDs
- Better tolerability?
- Better pharmacokinetic properties
- Low protein binding
- Most of the new AEDs are not strong hepatic enzyme inducers→ fewer drug interaction
- Fewer serious adverse events?

Disadvantage of new AEDs

- **Cost effectiveness**
- **Availability**

	Tab	Cost/day	Cost/month
Conventional AEDs			
Carbamazepine Tegretol tab (200) Tegretol CR (200) Tegretol CR (400)	 6.28 6.66 14.76	30-60	900-1800
Phenobarbital Phenobarbital (30) Phenobarbital (60)	 0.30 0.41	1-2	30-60
Phenytoin Phenytoin (50) Dilantin cap (100)	 0.97 2.87	9	270
Na Valproate Depakine (200) Depakine chrono (500)	 6.45 15.99	32-64	960-1920

	Tab	Cost/day	Cost/month
New AEDs			
Gabapentin Neurontin (100) Neurontin (300) Neurontin (400)	 17.42 32.00 38.00	128-384	3840-11520
Lamotrigine Lamictal (25) Lamictal (100)	 15.37 41.00	82-164	2460-4920
Topiramate Topamax (25) Topamax (50) Topamax (100)	 17.42 27.67 47.15	94-189	2829-5658
Oxcarbazepine		60-120	1800-3600
Levetiracetam		90-270	2700-8100

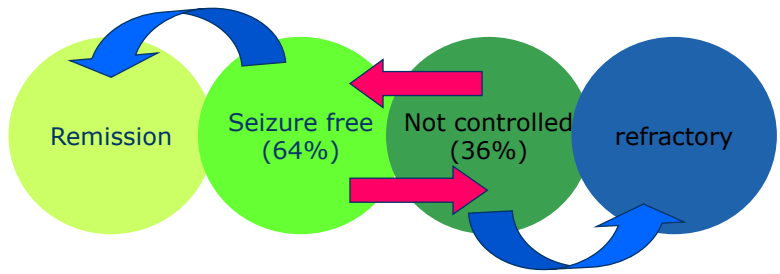


How to adjust the medications?

- **ก่อนจะพิจารณาเปลี่ยนหรือปรับยาในแต่ละขั้นตอนต้องคำนึงถึงสิ่งต่อไปนี้เสมอ**
  - Is the diagnosis correct?
  - ยากันชักที่เลือกใช้เหมาะสมกับชนิดของการชักของผู้ป่วยหรือไม่?
  - Compliance
  - Avoid precipitating factors
  - Drug interaction

Prognosis in epilepsy patients

Natural history of treated epilepsy



1. There seem to be two class of patient :easy versus difficult to control de novo
2. Patient with difficult to control epilepsy commonly have underlying cerebral pathology and higher number (>20) of seizure prior to treatment