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ศิริราชพยาบาล

When to start and how to select AED(s)?

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When to start AED?

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When to start AED?

Diagnosis of epilepsy

First unprovoked seizure

A practical clinical definition of epilepsy

*Robert S. Fisher, †Carlos Acevedo, ‡Alexis Arzimanoglou, §Alicia Bogacz, ¶J. Helen Cross, #Christian E. Elger, **Jerome Engel Jr, ††Lars Forsgren, ‡‡Jacqueline A. French, §§Mike Glynn, ¶¶Dale C. Hesdorffer, ##B.I. Lee, ***Gary W. Mathern, †††Solomon L. Moshé, ‡‡‡Emilio Perucca, §§§Ingrid E. Scheffer, ¶¶¶Torbjörn Tomson, ###Masako Watanabe, and ****Samuel Wiebe

Epilepsia, 55(4):475–482, 2014
doi: 10.1111/epi.12550

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When to start AED?

Diagnosis of epilepsy

1. ≥ 2 unprovoked (or reflex) SZs occurring >24 hours apart
2. 1 unprovoked (or reflex) SZ with probability of further SZs (>60%) over the next 10 yr
3. Diagnosis of epileptic syndrome

Similar to general recurrent risk after 2 unprovoked SZs

Fisher et al. Epilepsia 2014

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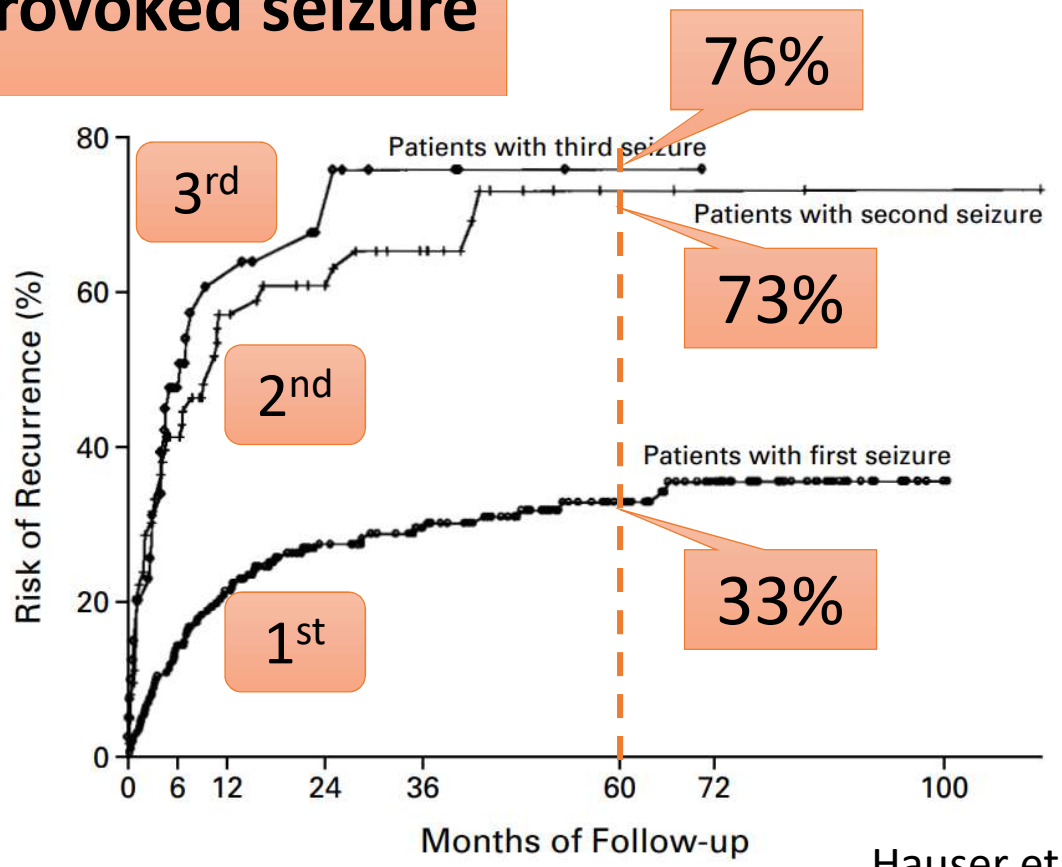
When to start AED?

First unprovoked seizure

Follow 1st unprovoked SZ for 204 pts



Hauser et al. NEJM 1998

When to start AED?

First unprovoked seizure

TABLE 2. RECURRENCE OF SEIZURES AT VARIOUS TIMES AFTER THE INDEX SEIZURE AND ACCORDING TO THE SEIZURE-FREE INTERVAL.*

VARIABLE	FIRST SEIZURE	SECOND SEIZURE	THIRD SEIZURE
No. of patients	204	63	41
	percent with recurrence (95% confidence interval)		
Within 12 mo	21 (16–27)	57 (45–70)	61 (44–77)
Within 24 mo	27 (21–34)	61 (48–73)	67 (51–84)
Within 36 mo	29 (23–36)	65 (53–78)	76 (60–91)
Within 48 mo	32 (25–38)	73 (59–87)	76 (60–91)
Within 60 mo	33 (26–40)	73 (59–87)	76 (60–91)

Hauser et al. NEJM 1998

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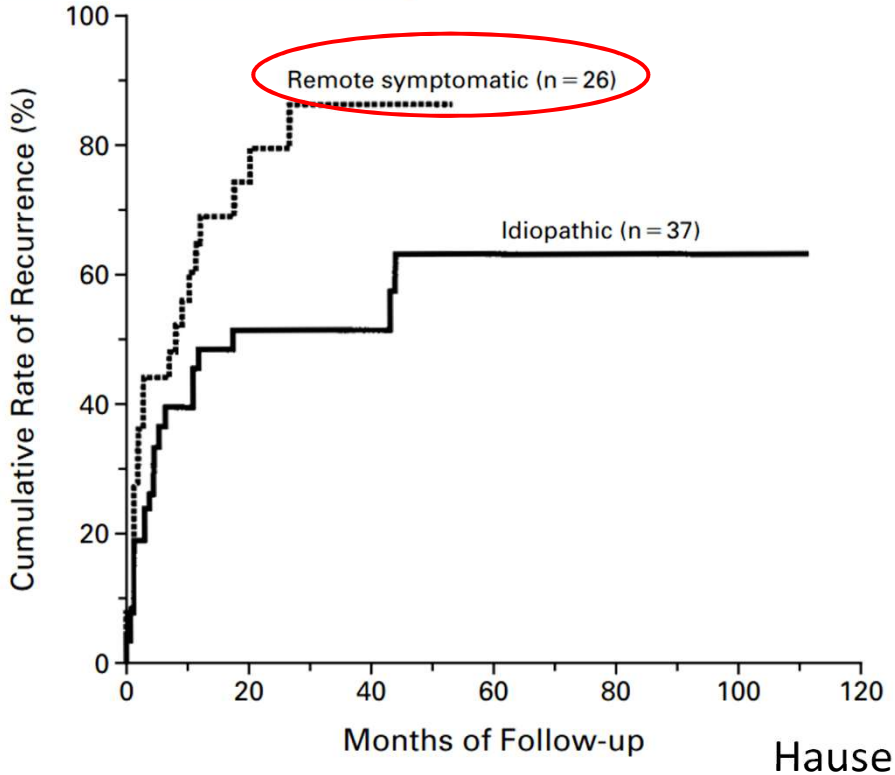
When to start AED?

First unprovoked seizure



Hauser et al. NEJM 1998

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21-45% (36%)

				Seizure recurrences at various times, n (%)								
Ref.	Class	Age, y	No.	Treated	1 mo	3 mo	6 mo	1 y	2 y	3 y	5 y	>5 y
10, 11	I	70% >19	238	164 (69)	—	—	—	38 (16)	50 (21)	60 (29)	70 (34)	81 (39)
12, 13	I	72% >16	397	204 (51)	24 (6)	58 (15)	75 (19)	98 (25)	111 (28)	—	—	—
17	II	≥16	147	62 (42)	—	—	39 (27)	50 (34)	60 (41)	61 (41)	—	—
18	II	Mean >20	76	36 (47)	2 (3)	18 (24)	20 (26)	22 (29)	—	—	—	—
16	II	≥16	306	41 (13)		55 (18)	79 (26)	111 (36)	136 (44)	144 (47)	—	—
19	II	75% >15	424	?	38 (9)	89 (21)	127 (30)	153 (36)	191 (45)	204 (48)	237 (56)	244 (58)
20	II	14-91	497	127 (26)	—		—	191 (38)	—	—	—	—
15	II	60% >20	812	404 (50)	—		179 (22)	—	288 (35)	—	378 (46)	398 (49)
21	II	≥16	228	113 (50)	—	—	—	68 (30)	—	—	—	—
22	II	18-50	87	45 (52)	—		—	30 (34)	37 (43)	39 (45)	—	—
Total			3,212	1,196 (43)	64 (7)	220 (18)	519 (24)	761 (32)	873 (36)	508 (42)	685 (46)	723 (49)

Krumholz et al. Neurology 2015

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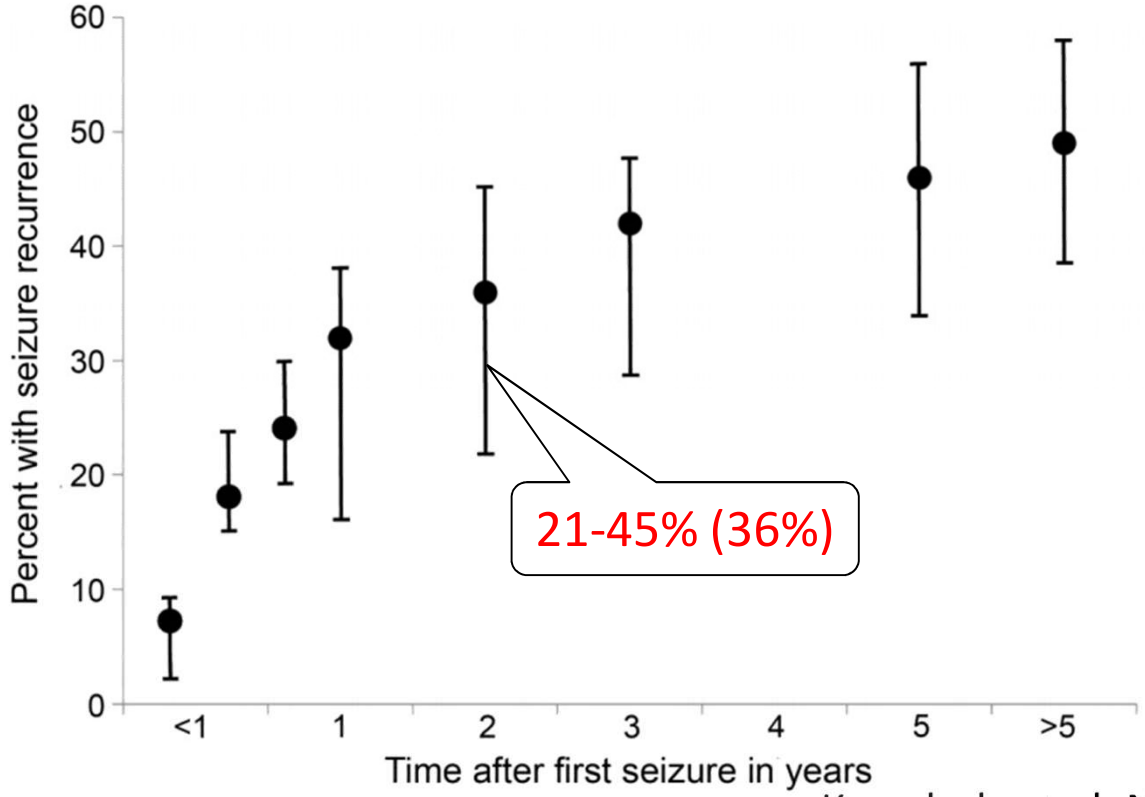

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- Factors asso w/ increased risk for SZ recurrence:
  1. Prior brain insult (level A)
  2. EEG shows epileptiform discharge (level A)
  3. Significant brain-imaging abnormality (level B)
  4. Nocturnal seizure (level B)

Krumholz et al. Neurology 2015

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Table 2 Rates for short-term (1 and 2 years) seizure recurrence after an unprovoked first seizure in adults as related to immediate antiepileptic drug treatment (Class I and II studies)

Ref.	Class	No.	Treated, n (%)	Recur. rate treated, n (%)	Recur. rate untreated, n (%)	Length of follow-up, y
12-14	I	397	204 (51)	36 (18)[a]	75 (39)	2
18	II	76	36 (47)	4 (11)[a]	18 (45)	1
15	II	812	404 (50)	129 (32)	159 (39)	2
21	II	228	113 (50)	5 (4)[a]	63 (55)	1
22	II	87	45 (52)	9 (20)[a]	28 (66)	2
Total		1,600	804 (50)	183 (23)	343 (43)	1 or 2

Krumholz et al. Neurology 2015

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Table 3 Rates of 2-year seizure remission over the longer term (>3 years), comparing immediate with deferred antiepileptic drug treatment of an unprovoked first seizure in adults (Class I and II studies)

Ref.	Class	No.	Immediate treatment, n (%)	Remission, immediate treatment, n (%)	Remission, deferred treatment, n (%)	Length of follow-up
12-14	I	419	215 (51)	174 (81), NS	159 (78)	More than 3 y[a]
15	II	812	404 (50)	372 (92), NS	375 (92)	5 y[b]
Total		1,231	619 (50)	546 (88)	534 (87)	

Krumholz et al. Neurology 2015

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Conclusion

Risk of SZ recurrence

- Chance for a recurrent SZ is greatest within the first 2 years at 21-45%
- Factors asso w/ increased risk for SZ recurrence:
  - Prior brain insult (level A)
  - EEG shows epileptiform discharge (level A)
  - Significant brain-imaging abnormality (level B)
  - Nocturnal seizure (level B)

Krumholz et al. Neurology 2015

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Management

- Does immediate AED treatment change short-term prognosis?
  - Reduce the risk for a recurrent SZ in the first 2 years.
  - But over the long term (>3yrs) is unlikely to improve the prognosis for sustained SZ remission.

- Risk of AED treatment
  - AEs range from 7-31% and usually mild and reversible

Krumholz et al. Neurology 2015

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Acute symptomatic SZs

- SZs asso w/ acute insults to the brain need to be treated
- BUT AED treatment should not be given to prevent the development of epilepsy because this is ineffective
- AEDs should be discontinued w/in or at most six months after the insult.

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Provoked SZs

- SZs exclusively provoked by external factors, e.g. alcohol withdrawal, should be treated by avoiding the provocation.

How to select AEDs?

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Ideal Properties for AEDs

- High efficacy & Good tolerability
- No or rapid titration
- No risk of allergic or idiosyncratic reaction
- Low interaction potential
- Favorable pharmacokinetics
  - Linear kinetics
  - No dose adjustment in renal impairment
  - No hepatic enzyme induction or inhibition
  - Once daily dosage

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How to choose AEDs

- Identify epilepsy syndrome and SZ types
  - Focal vs Generalized
- Other factors:
  - Age
  - Gender
  - Comorbidity & drug interaction
  - Cost & availability

Antiepileptic Drugs

Old	Newer (2nd gen)	Newest (3rd gen)
Phenobarbital 1919	Felbamate 1993	**Pregabalin 2005**
Phenytoin 1938	**Gabapentin 1993**	Rufinamide 2009
Primidone 1954	**Lamotrigine 1994**	**Lacosamide 2009**
Ethosuximide 1960	**Topiramate 1996**	Vigabatrin 2009
Carbamazepine 1974	Tiagabine 1997	**Clobazam 2011**
Valproic acid 1978	**Levetiracetam 1999**	Ezogabine 2011
	Oxcarbazepine 2000	**Perampanel 2012**
	Zonisamide 2000	Eslicarbazepine 2014

No difference between newer and older AEDs
in efficacy to control seizures

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Advantage Newer vs Older AEDs

- Not affecting hepatic enzyme function (GBP, PGB, LTG, LEV, LCM)
- Rapid onset of action (GBP, OXC, LEV, LCM)
- Intravenous loading (LEV, LCM)
- Broad spectrum efficacy (LTG, TPM, ZNS, LEV)

Unterberger I. Epileptologie 2015

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AE & tolerability: New vs Old AEDs

- Adverse effects
  - Approximately 50% of pts reported ≥ 1 AE from CBZ or VPA as well as from newer AEDs (LTG, GBP, OXC, TPM)

- Tolerability
  - Newer AEDs: better
  - Fewer or no dermatologic hypersensitivity reaction in newer AEDs (except LTG)
  - Less or no drug interaction

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Narrow & Broad spectrum AEDs

Table 2
Spectrum of action of the commonly used antiepileptic drugs

Narrow-Spectrum Drugs	Broad-Spectrum Drugs
Partial or Secondarily Generalized Tonic-Clonic Seizures	**Partial and Generalized Seizures**
Carbamazepine	Lamotrigine
Gabapentin	Levetiracetam
Lacosamide	Rufinamide[a]
Oxcarbazepine	Topiramate
Phenobarbital	Valproate
Phenytoin	Zonisamide[b]
Pregabalin	
Primidone	
Tiagabine	

Neurol Clin 28 (2010) 843–852

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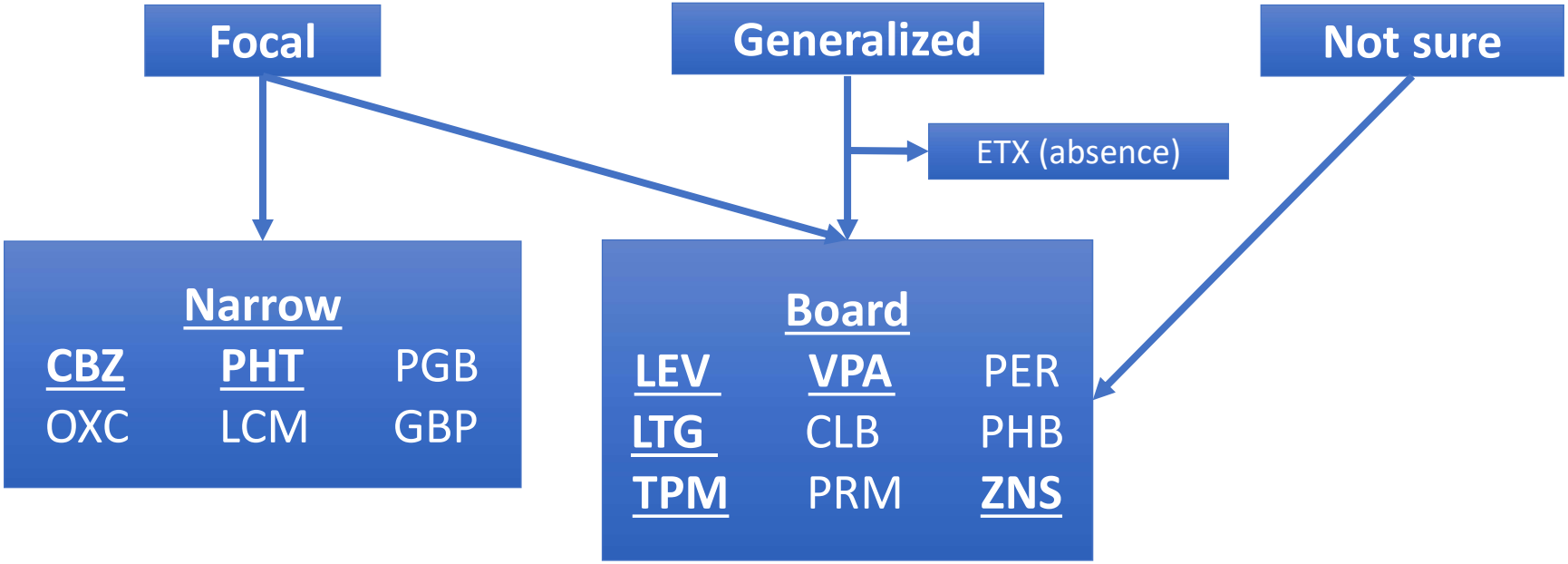
How to choose AEDs

- Identify epilepsy syndrome and SZ types
  - Focal vs Generalized



1st line & refractory epilepsy AED choices

Table 2
Preferred first-line antiepileptic drugs for new-onset and refractory epilepsy in adults

New-Onset Partial Epilepsies	Refractory Partial Epilepsies
Carbamazepine	Lacosamide
Gabapentin	Pregabalin
Lamotrigine	Zonisamide
Levetiracetam	Perampanel
Oxcarbazepine	Clobazam
Topiramate	
Valproate	
New-Onset Idiopathic Generalized Epilepsies	**Refractory Idiopathic Generalized Epilepsies**
Lamotrigine	Clobazam
Topiramate	Levetiracetam
Valproate	

Schmidt D. Neurol Clin 2015

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Updated ILAE evidence review

Seizure type or epileptic syndrome	Level of efficacy and effectiveness evidence (in alphabetical order)
Adult w/ partial-onset SZs	Level A: CBZ, LEV, PHT, ZNS Level B: VPA Level C: GBP, LTG, OXC, PB, TPM Level D: CZP
Elderly adults w/ partial-onset SZs	Level A: GBP, LTG Level B: None Level C: CBZ Level D: TPM, VPA
Adults w/ generalized onset tonic-clonic SZs	Level A, B: None Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA Level D: GBP, LEV

Epilepsia, 54(3):551–563, 2013

Updated ILAE evidence review

Seizure type or epileptic syndrome	Level of efficacy and effectiveness evidence (in alphabetical order)
Children w/ absence SZs	Level A: VPA Level B: None Level C: LTG
Benign epilepsy w/ centrotemporal spikes (BECTS)	Level A, B: None Level C: CBZ, VPA Level D: GBP, LEV, OXC
Juvenile myoclonic epilepsy (JME)	Level A, B, C: None Level D: TPM, VPA

Epilepsia, 54(3):551–563, 2013

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AEDs	Focal	GTC	Absence	Myoclonic	LGS
PB	++	+	xx	+	
PHT	++	+	xx	xx	
CBZ	++	+	xx	xx	
VPA	++	+	++	+	+
ETX	-	-	++	-	
Clobazam	+	+	+	+	++
GBP/PGB	++	-	-	-	
LTG	++	++	+	+/-	++
TPM	++	++	-		++
LEV	++	++	+	++	
ZNS	++	+	+	+	
LCS	++		-	-	
PER	++	++			

How to choose AEDs

- Identify epilepsy syndrome and SZ types
  - Focal vs Generalized
- Other factors:
  - Age
  - Gender
  - Comorbidity & drug interaction
  - Cost & availability

Keyword for old gen AEDs

	CYP450	Spectrum	Keywords
Phenobarbital	Inducer	Narrow	Long half-life (3-6 days) SE: Dupuytren's contracture
Phenytoin	Inducer 2C9, 2C19	Narrow	High protein binding Non linear kinetic, Paradoxical response SE: ataxia, rash, gum hypertrophy
Carbamazepine (gold standard for focal epi)	Inducer 3A4	Narrow	Auto-induction Inh by macrolide (except Azithro) SE: rash (HLA B*1502), leukopenia, hypoNa
Valproate (gold standard for gen epi)	Inhibitor	Board	High protein binding Use in migraine, mood d/o SE: wt gain, hair loss, tremor, PCOS Hepatitis, pancreatitis Teratogenic SE (Dose dependent) both structural & cognitive

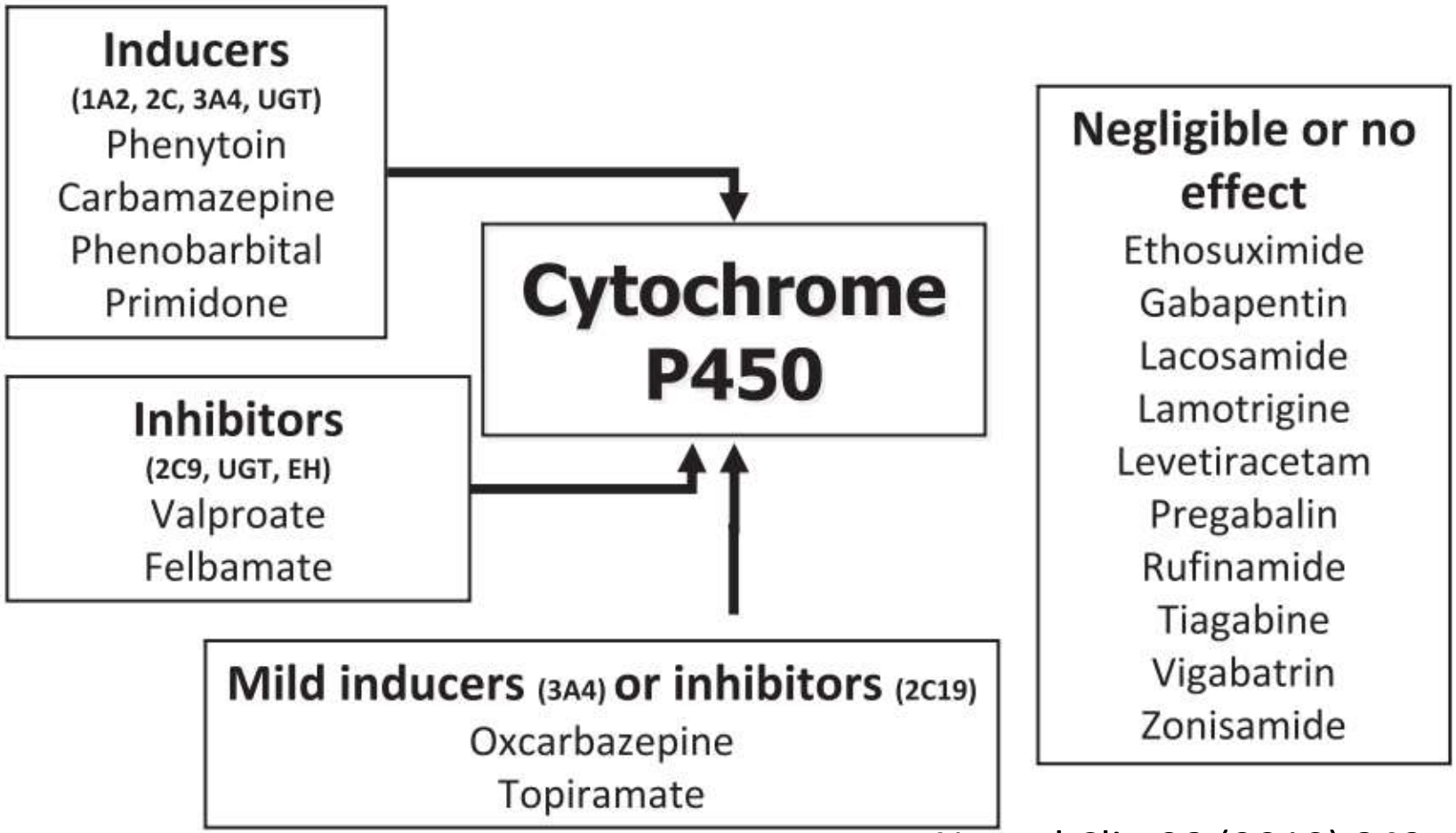
Keyword for new gen AEDs

	Spectrum	Keywords
LTG	Board	May exarcerbate myoclonus, Auto-induction ↓clearance by VPA (use with cautious) ↑clearance by EIAEDs, estrogen & pregnancy Safe for teratogenicity Use in mood d/o SE: rash
TPM	Board	CYP 3A4 inducer (dose >200) CYP 2C19 inhibitor (may ↑PHT level) Use in migraine, CDH SE: stone, glaucoma, hypohydrosis, paresthesia, cognitive impair Wt loss, Teratogenicity
ZNS	Board	Do not use in sulfa allergy Once daily dose
LEV	Board	Renal excretion: need supplement after dialysis No drug interaction SE: psychiatric

AED dosing administration

Slow titration	Rapid titration
• Carbamazepine (2-5 wk)	• Phenytoin
• Lamotrigine (8-12 wk)	• Valproate
• Topiramate	• Levetiracetam
• Zonisamide	• Oxcarbazepine (1-2 wk)
	• Gabapentin

Effects of AEDs to CYP450



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Increased clearance drugs by EIAEDs

Table 5
Increased clearance of commonly used drugs in the presence of enzyme-inducing antiepileptic drugs (carbamazepine, phenobarbital, phenytoin, and primidone)

Drug Type	Increased Clearance (Higher Doses Needed)
Antiepileptic	Lacosamide, lamotrigine, oxcarbazepine, rufinamide, tiagabine, topiramate, valproate, zonisamide, diazepam
Psychiatric	Amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, citalopram, paroxetine, buproprion, haloperidol, chlorpromazine, clozapine, olanzapine, risperidone, quetiapine
Cardiac	Mexiletine, quinidine, amiodarone, propranolol, metoprolol, nifedipine, felodipine, nimodipine, digoxin, lovastatin, simvastatin, dicumarol, warfarin
Antineoplastic	Cyclophosphamide, busulfan, etoposide, methotrexate, teniposide, some vinca alkaloids
Anti-infective	Praziquantel, albendazole, doxycycline, nevirapine, efavirenz, delavirdine, indinavir, ritonavir, saquinavir
Immunosuppressants	Cyclosporine, tacrolimus
Other	Oral contraceptive pills, prednisone, theophylline, methadone

Neurol Clin 28 (2010) 843–852

PHT & Non-AEDs interaction

Table 4.—**Non-Antiepileptic Drugs That Interact With Phenytoin***

Non-AEDs affected by PHT		Non-AEDs affecting PHT levels	
PHT decreases	*PHT increases*	*Decrease PHT levels*	*Increase total PHT levels*
Chloramphenicol	Warfarin (usually)	Alcohol—long-term use	Alcohol—shortly after intake
Cyclosporine		Antacids	Amiodarone
Dexamethasone		Folic acid	Chloramphenicol
Doxycycline		Rifampin	Chlordiazepoxide
Folic acid			Chlorpheniramine
Furosemide		*Increase free PHT levels*	Cimetidine
Haloperidol		Aspirin	Disulfiram
Meperidine		Diazoxide	Fluconazole
Methadone		Tolbutamide	Fluoxetine
Oral contraceptives			Imipramine
Quinidine			Isoniazid
Theophylline			Metronidazole
Vitamin D			Omeprazole
			Propoxyphene
			Sulfonamides
			Trazodone

Mayo Clin Proc, 1996 (71)

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CBZ & Non-AEDs interaction

Table 5.—**Non-Antiepileptic Drugs That Interact With Carbamazepine***

Non-AEDs affected by CBZ	Non-AEDs affecting CBZ levels	
CBZ decreases	*Increase CBZ levels*	*Decrease CBZ levels*
Doxycycline	Cimetidine	Alcohol—
Folic acid	Danazol	long-term use
Haloperidol	Diltiazem	Folic acid
Oral contraceptives	Erythromycin	
Theophylline	Fluoxetine	
Warfarin	Imipramine	
	Isoniazid	
	Nicotinamide	
	Propoxyphene	
	Verapamil	

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Drug-drug interaction

Table 6
Relative drug-drug interaction potential of the antiepileptic drugs

None	Low[a]	High
Ethosuximide	Lacosamide	Carbamazepine
Gabapentin	Lamotrigine	Felbamate
Levetiracetam	Oxcarbazepine[b]	Phenytoin
Pregabalin	Rufinamide	Phenobarbital
Vigabatrin	Topiramate[b]	Primidone
	Tiagabine	Valproate
	Zonisamide	

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AEDs & effects on weight

Table 3. AEDs and effects on weight

Weight promoters Weight gain	Nonpromoters of weight gain Weight neutral	Weight loss
(Carbamazepine)		Felbamate
Gabapentin	Lamotrigine	Topiramate
Pregabalin	Levetiracetam	Zonisamide
Valproate	Phenytoin	
Vigabatrin		

Epilepsia, 48(Suppl. 9):42–45, 2007

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Unique patient and AED choices

TABLE 6-3 **Antiepileptic Drug Preferences in Special Circumstances**

Patient Characteristics	Antiepileptic Drug Preferences
Depression	Lamotrigine, oxcarbazepine
Migraine	Topiramate, valproate
Chronic pain	Pregabalin, gabapentin, oxcarbazepine, carbamazepine, lacosamide
Obesity	Topiramate, zonisamide
	Avoid pregabalin, gabapentin, valproate
Woman of childbearing potential	Avoid valproate
Older adult	Lamotrigine, gabapentin, topiramate
Asian	Avoid carbamazepine
Nephrolithiasis	Avoid topiramate and zonisamide
Atopic (rash prone)	Avoid lamotrigine, carbamazepine

Continuum Lifelong Learning Neurol 2010;16(3)

AEDs to Use Cautiously or Avoid	
Liver dz	VPA, PHT, PB, CBZ, LTG
Renal fail	LEV, GBP, PB, PGB, TOP, ZNS
h/o renal stone	ZNS, TOP
Arrhythmia	CBZ, PHT
Pancreatic dz	VPA, CBZ
Hypothyroidism	CBZ, OXC, PHT
Hyponatremia	CBZ, OXC
Osteopenia	PHT > CBZ, PB
Obesity	VPA, PGB, GBP
Anorexia	FBM, TOP, ZNS
PCOS	VPA

AEDs to Use Cautiously or Avoid (cont.)	
Taking OCPs	CBZ, OXC, PHT, PB, TOP (>200)
Bleeding diathesis	VPA (dose-related thrombocytopenia)
Blood dyscrasia	CBZ (idiosyncratic leukopenia)
Peripheral edema	PGB
h/o hypersense	AED w/ risk of rash (PHT, CBZ, LTG)
Psychiatric d/o	LEV, PB
Taking warfarin	↓ warfarin: PHT, PB, CBZ
	↑ warfarin: VPA
Absence szs	PHT, CBZ, PB
Myoclonic szs	PHT, CBZ


Rational polytherapy

- 1st AED fails due to lack of tolerability → 2nd mono
- 1st AED fails due to inefficiency
  - →Add-on (partially effective from 1st AED)
  - →2nd mono (totally ineffective from 1st AED)
- 2nd mono should be considered in
  - Elder, women w/ child bearing age
  - Compliance challenging
  - Cost
- Add-on: consider different MOA and co-morbidity

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Rational polytherapy

- Combining 2 Na-channel blockers:
  - Associate with higher rates of toxicity
- **"LTG + VPA"** is the only single regimen that shows "synergistic" in humans

Lamotrigine (LTG)

- Starts 25mg/d then increase 25mg q 1wk.
- Very slow titration to avoid the rash
- Dose
  - 100-200 mg/d (monotherapy or with VPA)
  - 200-400 mg/d (with enz. Inducing AEDs)

<u>When combine with valproate</u>

•12.5-25 mg/d x 1-2 wks

•then titrate 12.5-25 mg/wk, until 100 mg

•AEs: Rash (SJS, TEN) avoid by gradual titration

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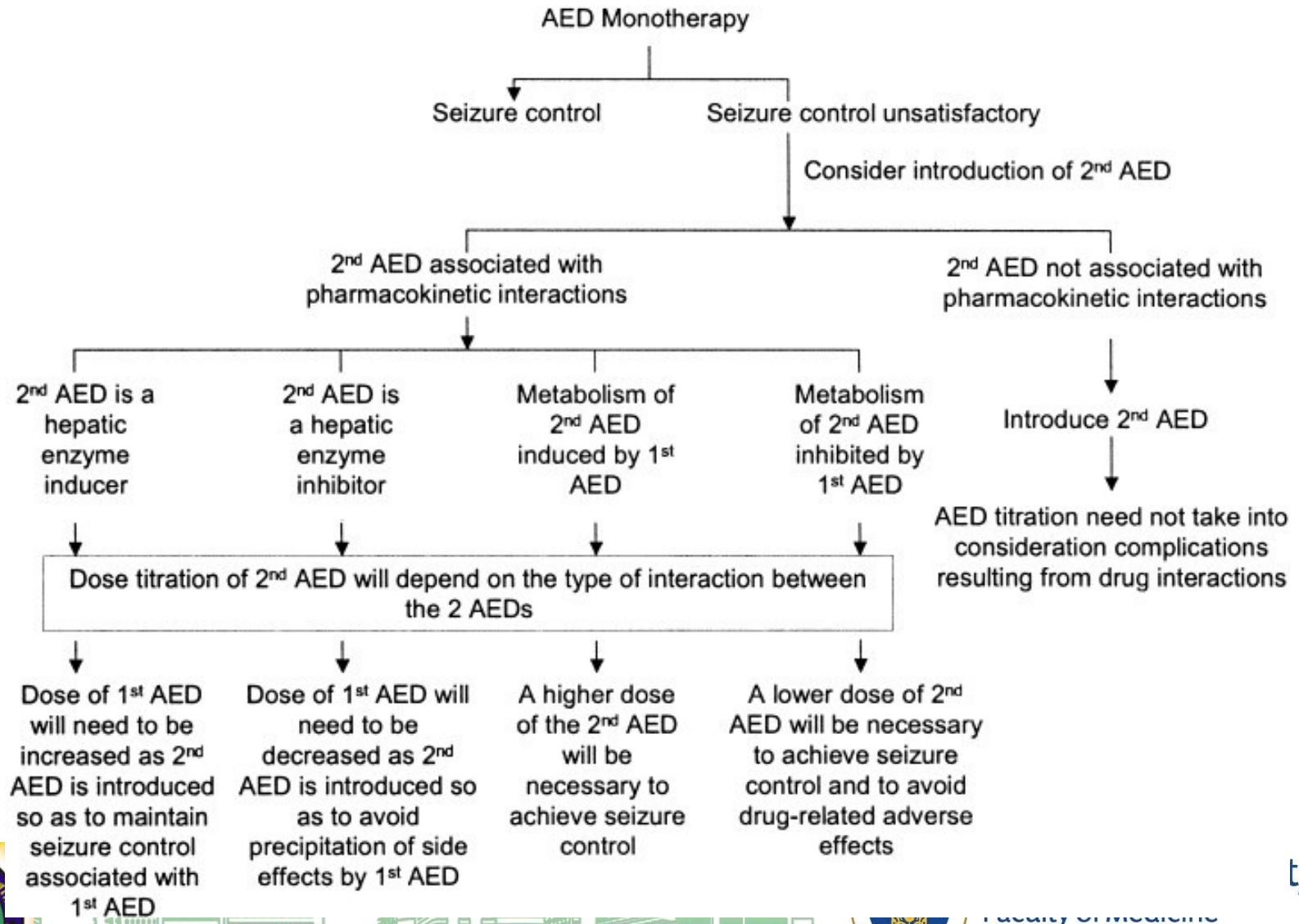
Interaction between 1st & 2nd AEDs



Summary

- When to start AED
  - Diagnosis of epilepsy
  - 1st unprovoked seizure with high risk of recurrence
  - Acute symptomatic/ provoked seizure (for < 6months)

- How to select AED(s)
  - Epilepsy syndrome and SZ types: Focal vs Generalized
  - Other factors:
    - Age & Gender
    - Comorbidity & drug interaction
    - Cost & availability

Thank you for your attention

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