ASMs: Selection, Initiation and Discontinuation

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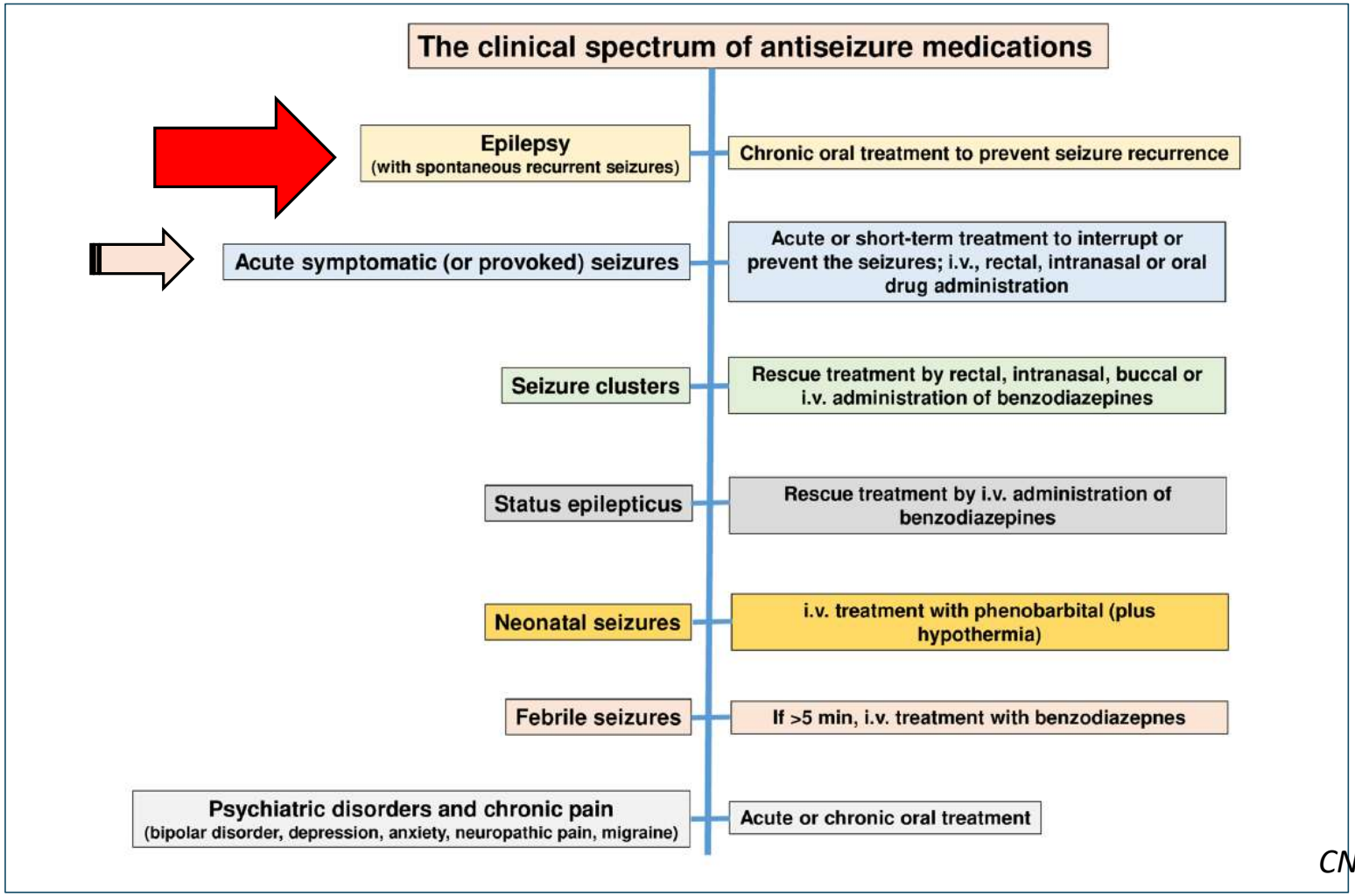
Epilepsy Course for Neurology Residents and Pediatric Neurology Fellows

Outline

- *ASM Selection*
- ASM Initiation
- ASM Discontinuation

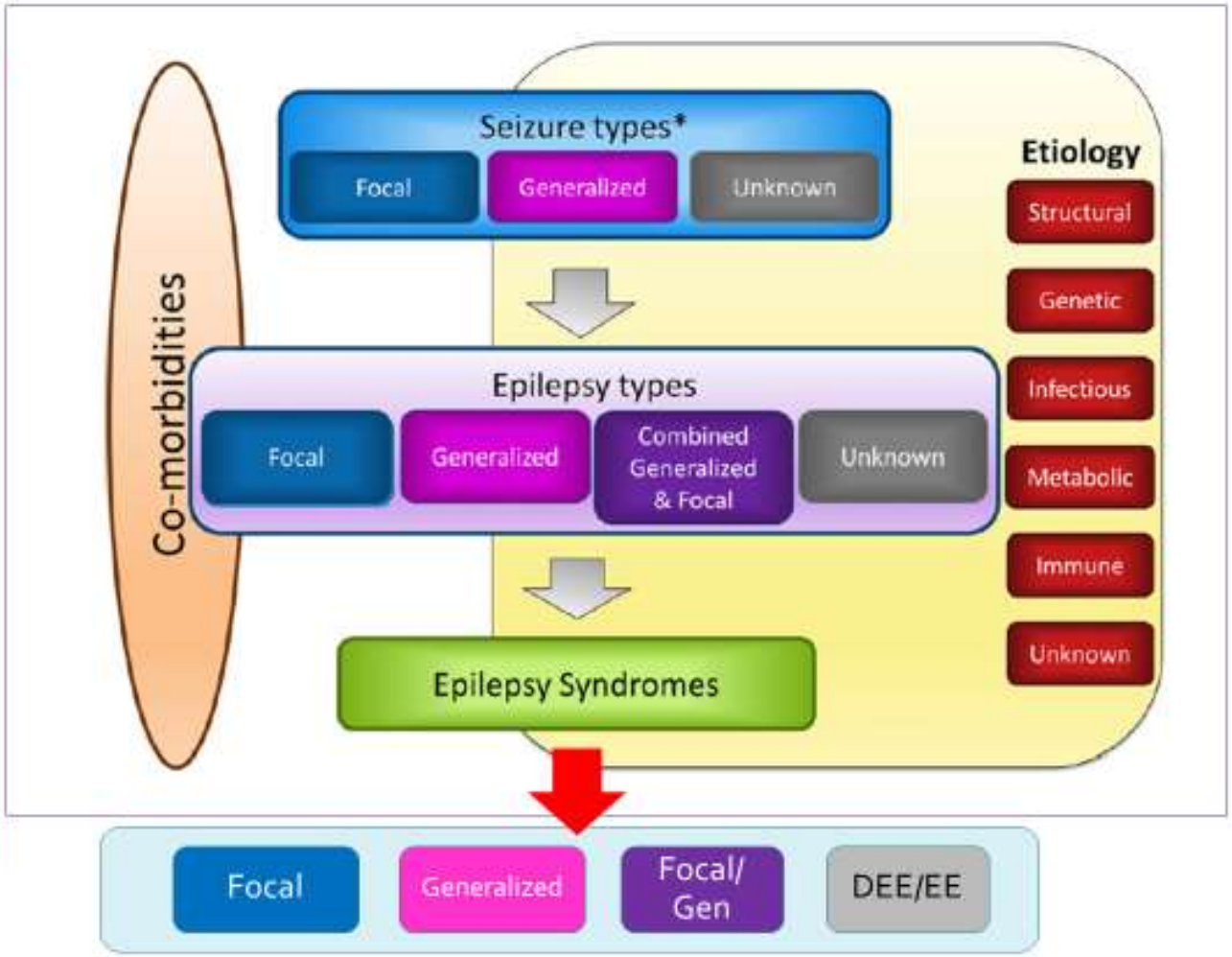
ASMs Selection

The Clinical Spectrum of ASMs



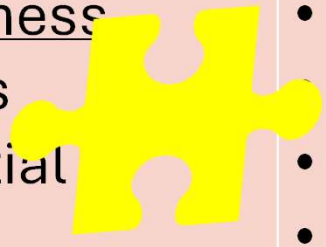
CNS Drugs (2021)

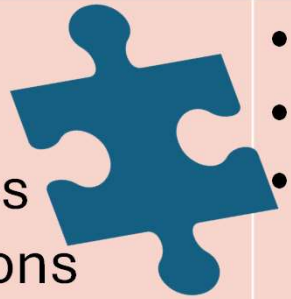
Epilepsy Classification 2017 + Epilepsy syndromes 2022

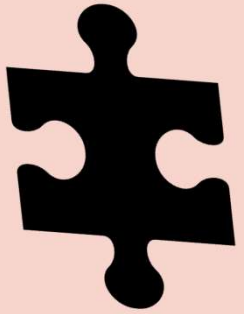


Variables that affect a specific ASMs

ASM specific variables	Patient-specific variables	Nation-specific variables
• Sz type or syndrome efficacy/effectiveness • Pharmacokinetics • Interaction potential • Formulation • Dose-dependent AE • Idiosyncratic reacti • Chronic toxicity • Teratogenicity • MOA • Rational Rx (mono vs polyRx)	• Age, Gender • Genetic BG • Comorbidities • Co-medications • Ability to swallow tablets • Insurance coverage • Relative wealth • Sz type and syndrome • Stage of the epileptic condition	• AED availability • AED cost • บัญชียาและการเบิกจ่าย







Adapted from Epilepsia 47,2006

ASM Selections @ Seizure Type/Syndrome

1. 1.1 First seizure (acute symptomatic sz **or** unprovoked sz) [Hx, PE, Ix]
   1.2 Epileptic syndrome [Hx, EEG]

2. Whether it is a first one or the patient does not remember?

3. Does the patient need to start Rx after first seizure?

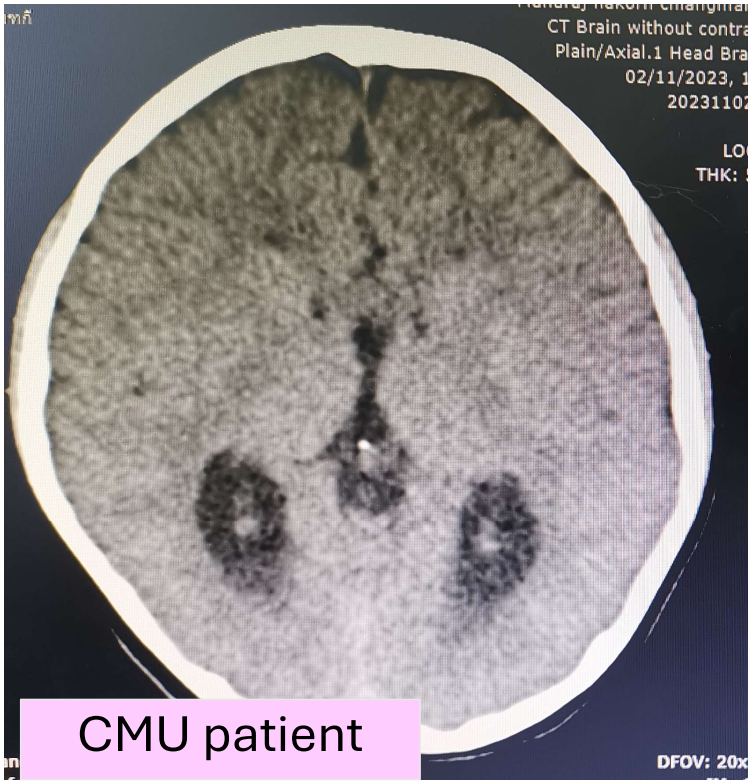
4. Epilepsy (2 unprovoked sz/ 2 reflex sz)

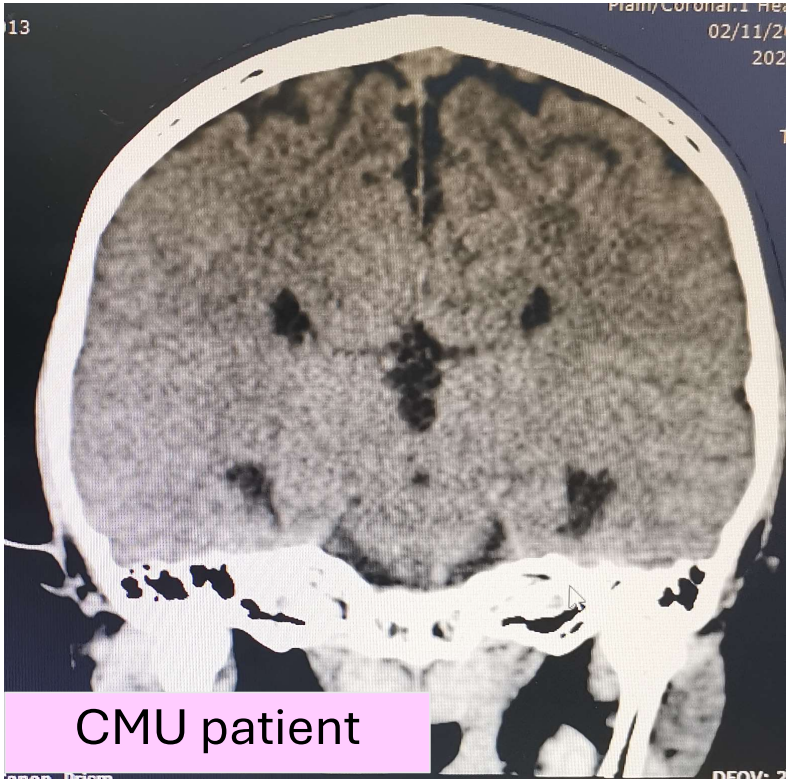
Case Scenario-1

- ดญ ไทย อายุ 10 ปี ระหว่างยืนเข้าแถวที่โรงเรียน ครูสังเกตเห็น วูบล้มหงายหลัง มีอาการเกร็งแขนขา มีตาลอย ปากเขียว หน้าซีด 45-60 วินาที
- ไม่มีปัสสาวะ อุจาระราด
- สะลึมสะลือนาน 10 นาที หลังจากนั้นถามตอบรู้เรื่อง แต่จำเหตุการณ์ไม่ได้ ร.ร. แจ้งญาติ จากนั้น นำส่ง รพ
- ที่ ER มีอาเจียน 2 ครั้ง แต่ภายหลังรู้ตัวดี และตรวจร่างกายไม่มี focal deficit
- Basic lab = normal
- CT brain:
- Diagnosis = ?
- Rx issue?

[Hx, PE, Ix]

CT brain

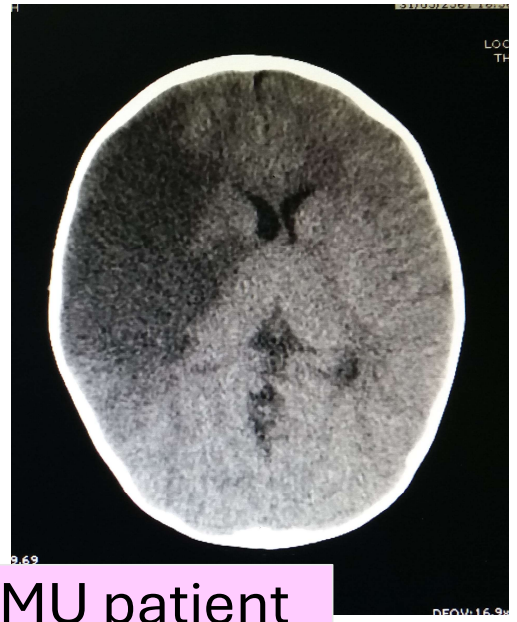




First episode unprovoked seizure

Case Scenario-2

- เด็กชาย อายุ 10 ปี มีอาการปวดศีรษะตอนกลางคืน ตอนเช้าแม่ไปเรียก ดูสะลึมสะลือมาก และมีแขนข้างซ้ายอ่อนแรง ช่วงสายมีอาการเกร็ง กระตุก 1 นาทีบนเตียง
- นำส่ง ER ไม่มีอาการชัก แต่ clinical obtundation
- Imaging as picture
- Diagnosis = ?
- What would you do in this case?



CMU patient

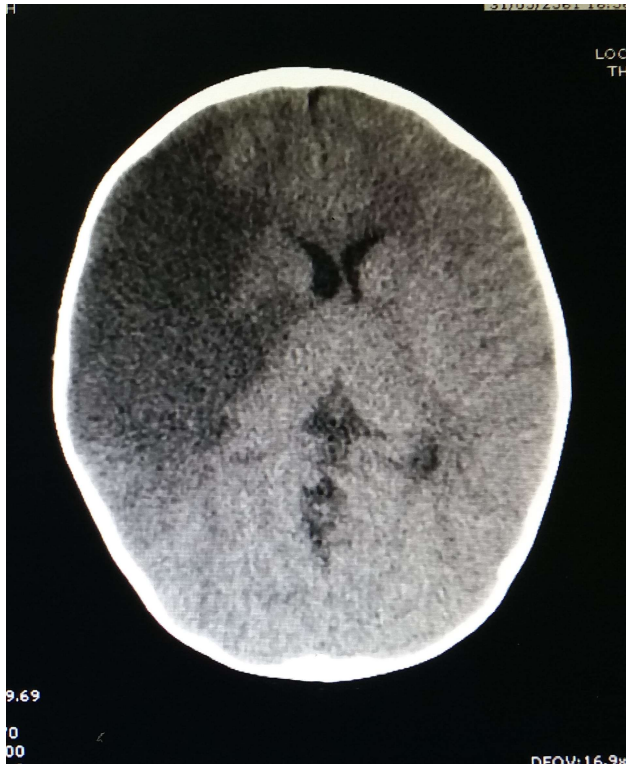
[Hx, PE, Ix]

Acute symptomatic seizure (from stroke)

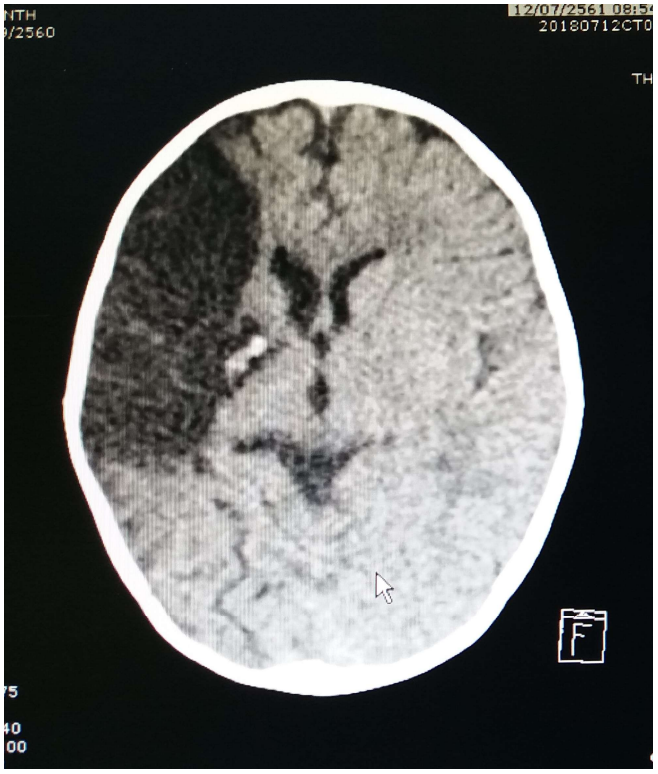
	Acute symptomatic sz	Unprovoked seizure
Stroke	33%	71%

CMU patient

CT brain



CT during acute symptomatic seizure



CT 4 weeks later

Definition and Terminology

Epilepsy *ILAE 2014*	• At least two unprovoked (2 reflexes) seizures more than 24 h apart or • one unprovoked seizure with a probability of a subsequent seizure recurrence risk of approximately 60% (similar to 10-year recurrence risk after two unprovoked seizures) or • Diagnosis of epilepsy syndrome
Acute symptomatic seizure	Caused by acute illness (stroke, CNS infection, TBI): seizure within 7 days of an insult
Provoked seizure Situation-related seizure	Caused by transient reversible alterations without structural change (toxin, metabolic factors, medication); occurs at time of insult or within 7 days
Unprovoked seizure	Seizure occurring in the absence of a potentially responsible clinical condition or beyond the interval estimated for the occurrence of acute symptomatic seizures
Remote symp' seizure (*unprovoked seizure*)	Pre-existing brain injury: seizure greater than 7 days after insult

Definition and Terminology

Acute symptomatic seizure	Caused by acute illness (stroke, CNS infection, TBI): seizure within 7 days of an insult
	Etiology may be the same The difference is time window
Unprovoked seizure	Seizure occurring [illegible] not [illegible] clinical condition or beyond the interval estimated for the occurrence of acute symptomatic seizures
Remote symp' seizure (*unprovoked seizure*)	Pre-existing brain injury: seizure greater than 7 days after insult

Patient: children or adults

First seizure:

[Hx, PE, Ix]

1st Acute Symptomatic Seizure

(structural or non-structural)

VS.

1st Unprovoked Seizure

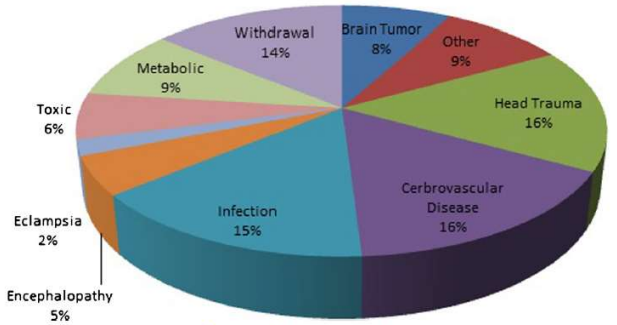


Fig. 1. Etiologies of acute symptomatic seizures [2] (copyright 2005 by ILAE. Adapted with permission).

Acute Symptomatic

First Unprovoked

Cumulative Risk in 2 Important Issues

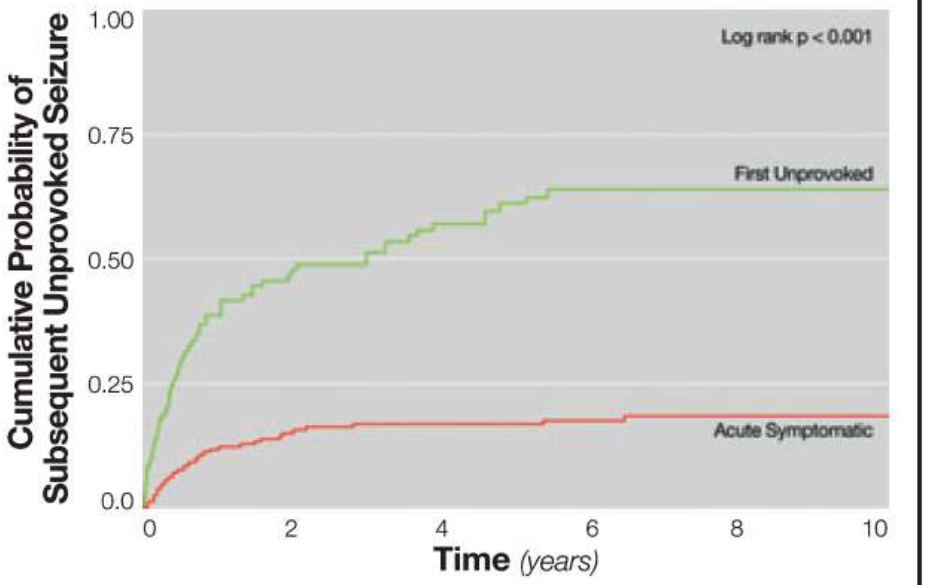


Figure 3.
Cumulative risk of subsequent unprovoked seizure after first acute symptomatic seizure and first unprovoked seizure.
Epilepsia © ILAE

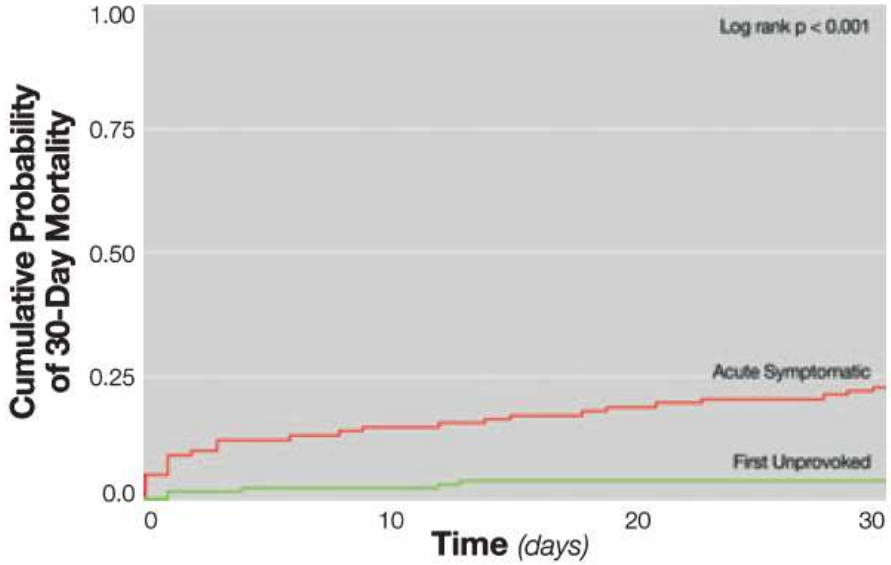


Figure 1.
Cumulative risk of death in the first 30 days after first acute symptomatic seizure and first unprovoked seizure.
Epilepsia © ILAE

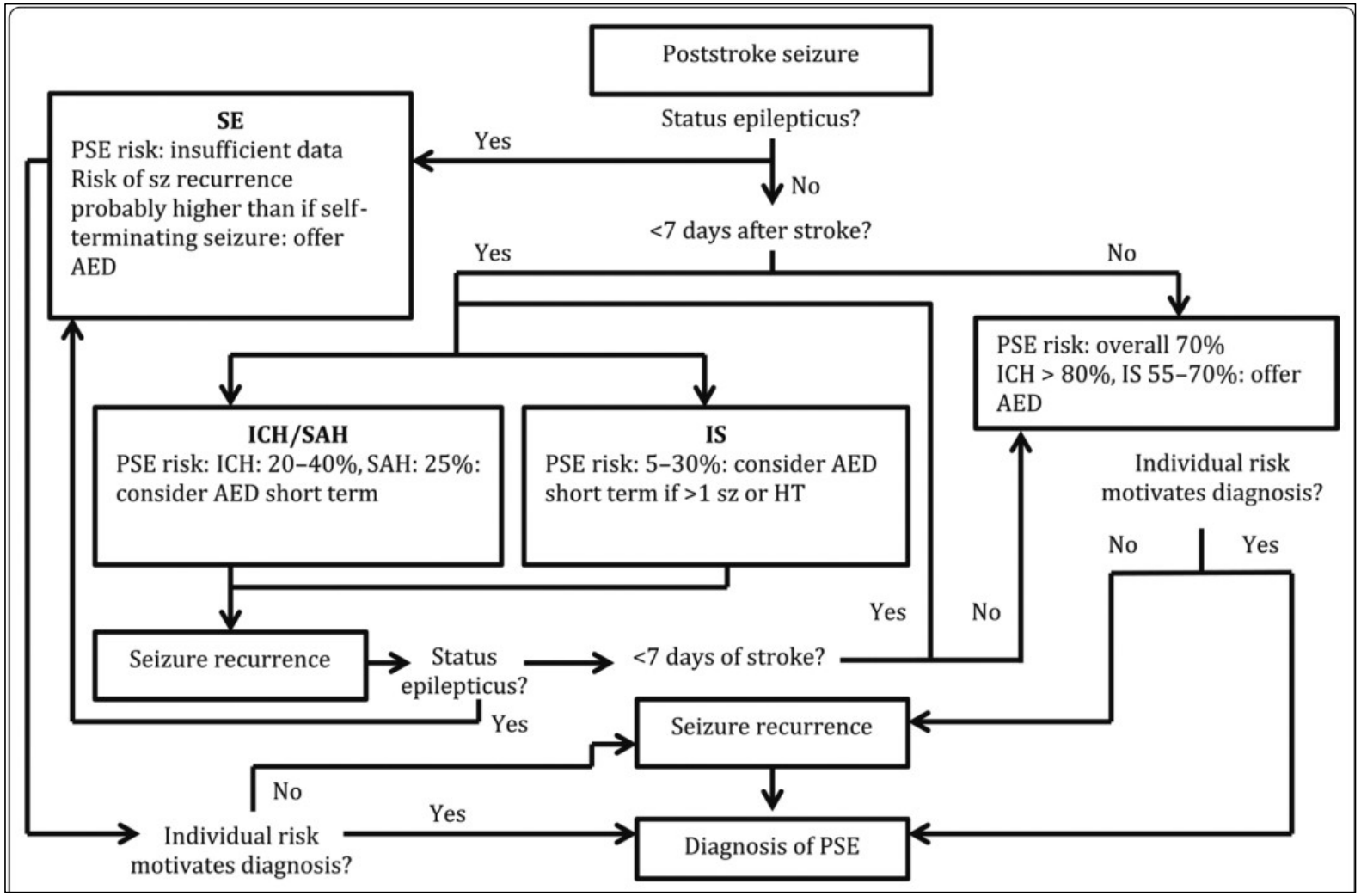
Epilepsia, 50(5):1102–1108, 2009

ASM Initiation

Management Guideline in Acute Symptomatic Seizure

Etiology of sz	Type of sz	Short-term ASM	Long-term ASM
Ischemic, Hge, subdural, SAH	Acute symptomatic	• a short course may be necessary due to higher mortality rates in the short term	• if pt develops remote symp sz in setting of underlying lesion
CVST	Acute symptomatic	• up to 6 mo–1 yr of ASM Rx may be necessary due to higher mortality rate in the short term and • ↑risk of unprovoked sz with : hemorrhagic infarcts, : sup^{r} sagittal thrombosis, : Hx of acute symp seizures	• if pt develops remote symp sz in setting of underlying lesion

Curr Treat Options Neurol (2018) 20: 41



Zöllner et al. Neurol. Res. Pract. (2021) 3:63

Management Guideline in Acute Symptomatic Seizure

Etiology of sz	Type of sz	Short-term ASM	Long-term ASM
Trauma	Acute symptomatic	• 1 week of ASM • Longer (1–3 mo of Rx) in mod-severe depressed skull fx, penetrating injury, subdural requiring evacuation, multiple contusions, epileptiform EEG, prolonged period of LOC or amnesia	• if pt develops remote symp sz in setting of underlying lesion

Curr Treat Options Neurol (2018) 20: 41

Management Guideline in Acute Symptomatic Seizure

Etiology of sz	Type of sz	Short-term ASM	Long-term ASM
CNS infection	Acute symptomatic	• A short course is necessary due to high mortality in short term • Consider 1–3 mo of Rx in pts with viral encephalitis	• if pt has remote symp sz or unprovoked sz with structural lesion

Curr Treat Options Neurol (2018) 20: 41

First Unprovoked Seizure

Disease stage

1st unprovoked sz

2nd unprovoked sz

Year.....1.....2

Recurrence risk in adult in the first 2 years = 21-45%

Child risk at 2 yrs = 37%

Initial Rx after 1st sz ↓ risk
35% to have recurrent sz
in 2 yrs

Neurology 2015;84:1705–1713

Seizure Recurrence in Children

- After an unprovoked sz: 42% had subsequent seizures
- Cumulative risk at 1 yr = 29% , at 2 yr = 37%, at 3 yr = 42%

- **Risk factors for sz recurrence**: remote symptomatology, abnormal EEG, seizures in sleep, Hx of prior febrile seizures and Todd paralysis
- Risk of seizure recurrence with normal EEG = 30% over 5 yrs

  with non-specific abn EEG = 45%

  with epileptiform EEG = 60%

Adult

Initial Rx of 1st Unprovoked Seizure

- **Reduce** recurrent risk of 2nd unprovoked seizure
- **No** difference in likelihood of long-term epilepsy remission

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

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)	

Neurology 2015;84:1705–1713

Factors that are indicative for the initiation of ASMs therapy after a first seizure

1. High syndrome-dependent risk of sz relapses (JME)
2. A first seizure with loss of consciousness
3. Adult age
4. Abnormal EEG findings with epileptiform discharges
5. Abnormal MRI finding
6. A high personal risk in case of seizure relapses due to casual habits or professional circumstance

Good time EEG prediction = 16 hrs

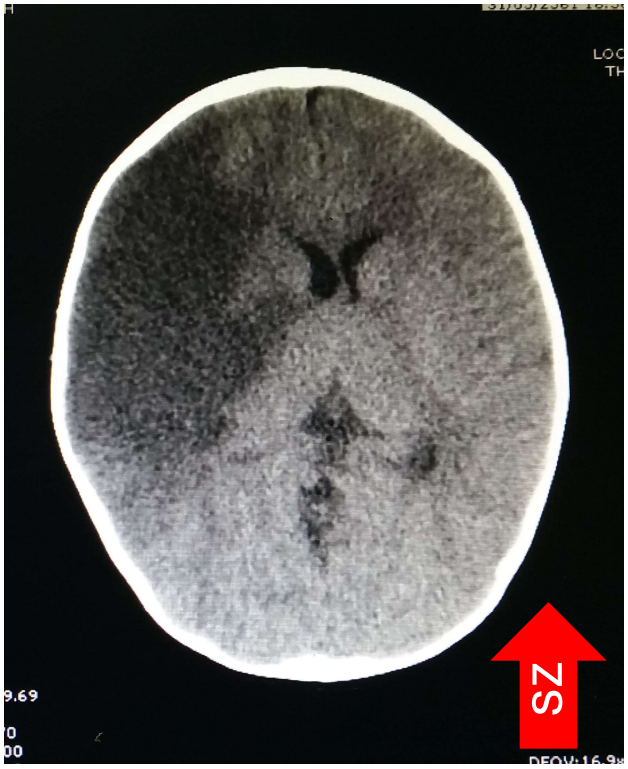
Seizure 49 (2017) 92-94

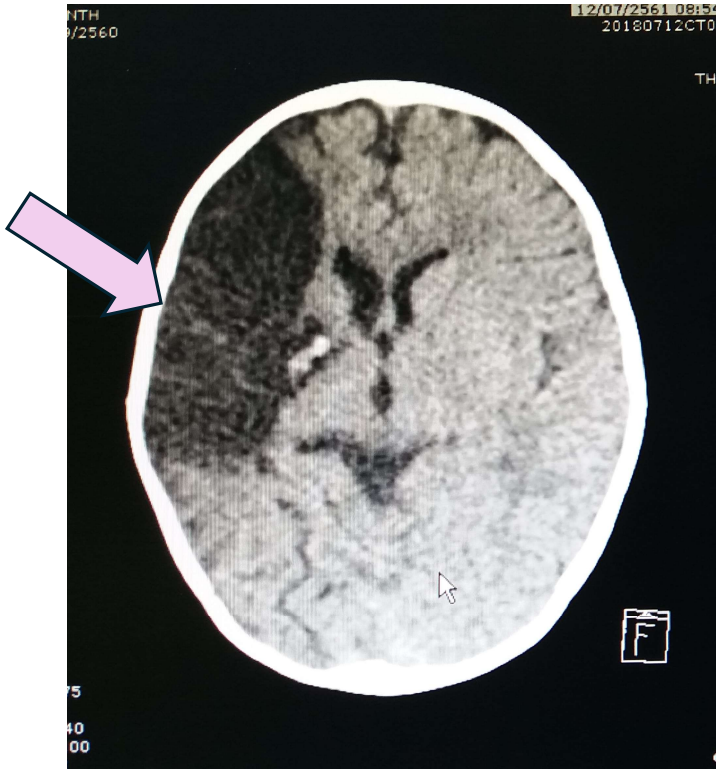
Stroke	Acute symptomatic sz	Unprovoked seizure
Seizure	3%%	71%

Case scenario 2

CMU patient

CT brain





CT during acute symptomatic seizure

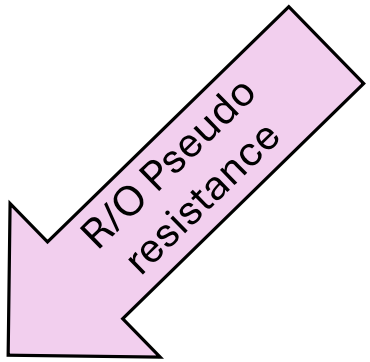
CT 4 weeks later

ASM Decision Making

- **Initiation**: primary monoRx

: Broad spectrum ASM → generalized sz, genetic generalized sz, unknown etiology

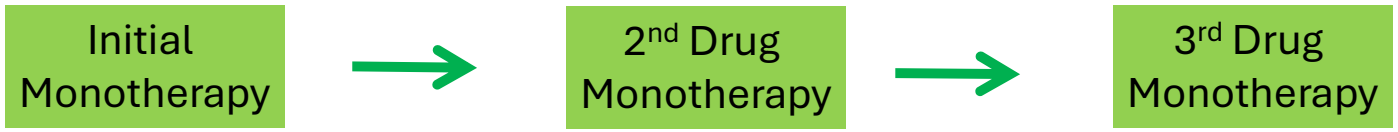
: Narrow spectrum ASM → focal sz



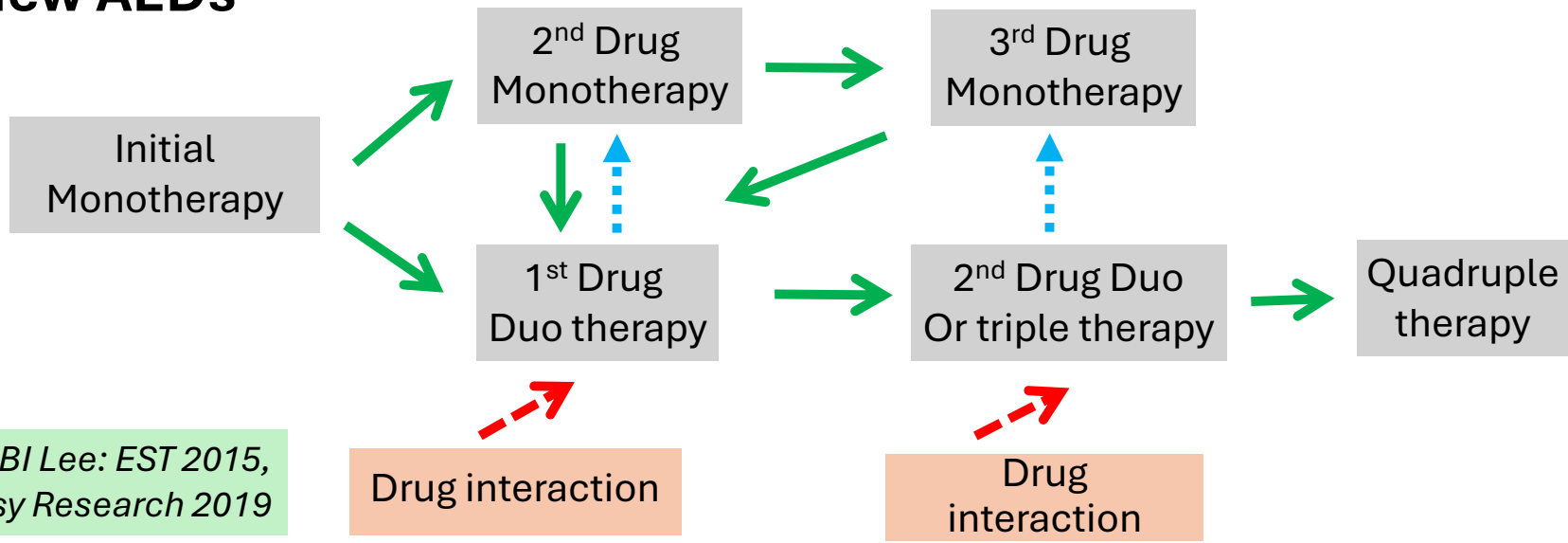
- **Uncontrolled sz**: $2^{nd}/3^{rd}$ monoRx **or** polyRx

Rational of ASM Treatment

- **Era of conventional AED**



- **Era of New AEDs**



Modified from Prof BI Lee: EST 2015, Journal of Epilepsy Research 2019

Desirable Pk Properties of an ASM

- High oral bioavailability
- Low plasma protein binding
- Linear kinetics
- Ready penetration across the BBB
- Long half-life
- No active metabolites
- Significant renal elimination
- Elimination, not involving oxidation or conjugation
- Low vulnerability to drug interactions

Epileptic Disord 2003; 5 (Suppl 1): S17–S26

Broad spectrum vs Narrow spectrum ASMs

Broad spectrum	Narrow spectrum
VPA	PHT
TPM, ZNS	CBZ, ~~*ESL*~~
LTG	OXC
LEV	VGB
PER	PGB, GBP
RFN	LCM
CLB (CLN), CZP	~~*TGB*~~
PB	~~*EZG*~~
~~*PRM*~~, ~~*FBM*~~	

Table 1 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	+	+	+	?	+	?+	?+	?+	?+	?+	+

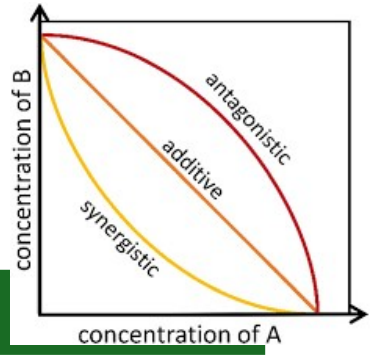
Data sourced from various publications [5, 11, 29, 62, 63, 168, 169] and a PubMed search of recent literature

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

CNS Drugs (2021) 35:935–963

Combination Regimens

SCB(+) = fast activated
SCB(+) = slow activated



Drug combination	Comment
SCB(+) + SCB(+)	**Additive efficacy or antagonism**
SCB(+) + *SCB(+)*	**Synergistic efficacy**
SCB(+) + Multiple actions	**Variable and unpredictable**
SCB(+) [*or SCB(+)*] **+ Enhanced GABAergic**	**Synergistic efficacy**
Multiple actions + Multiple actions	**Synergistic efficacy**
LEV*(SV2)* + Other AEDS *(SCB/multiple)*	**Additive or synergistic efficacy**
GBP + Other AEDS	**Synergistic efficacy**

Aggravation of seizure by ASMs

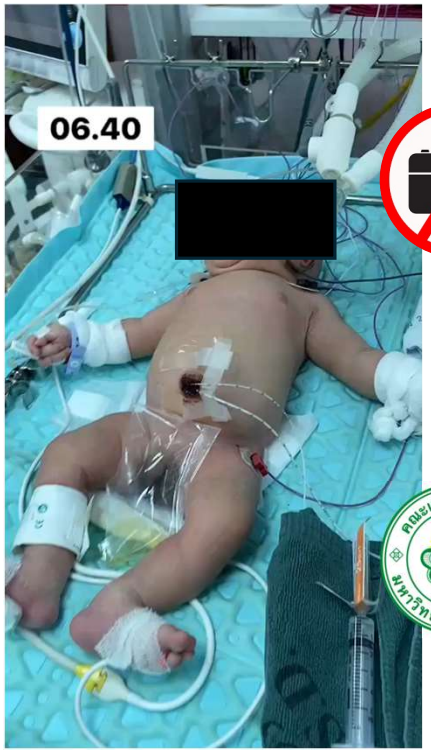
Seizure type/syndrome	Avoid
Myoclonic seizure	PHT, CBZ, OXC, VGB, GBP, PGB, TGB
	Use with precaution: LTG
Absence seizure	PHT, CBZ, OXC, VGB, GBP, PB (high dose), TGB, CLB, CLZ
Tonic seizure (in LGS)	?
CSWS/ESES	?
Dravet syndrome	Sodium channel blockers
LGS	CBZ, OXC, PHT, TGB

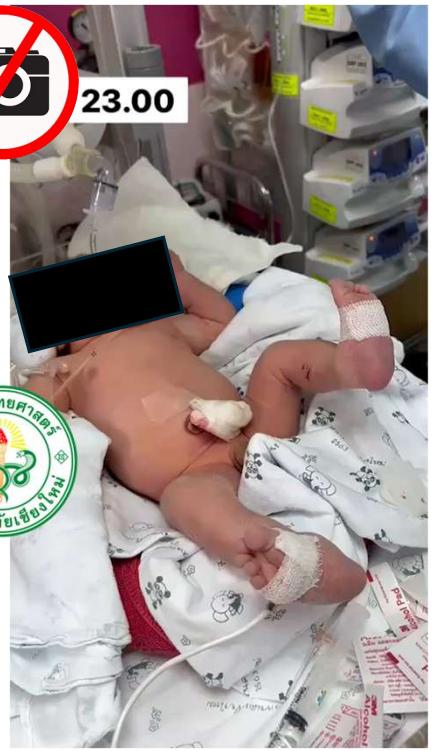
ASM Selections @ seizure type/syndrome

0 Not seizure

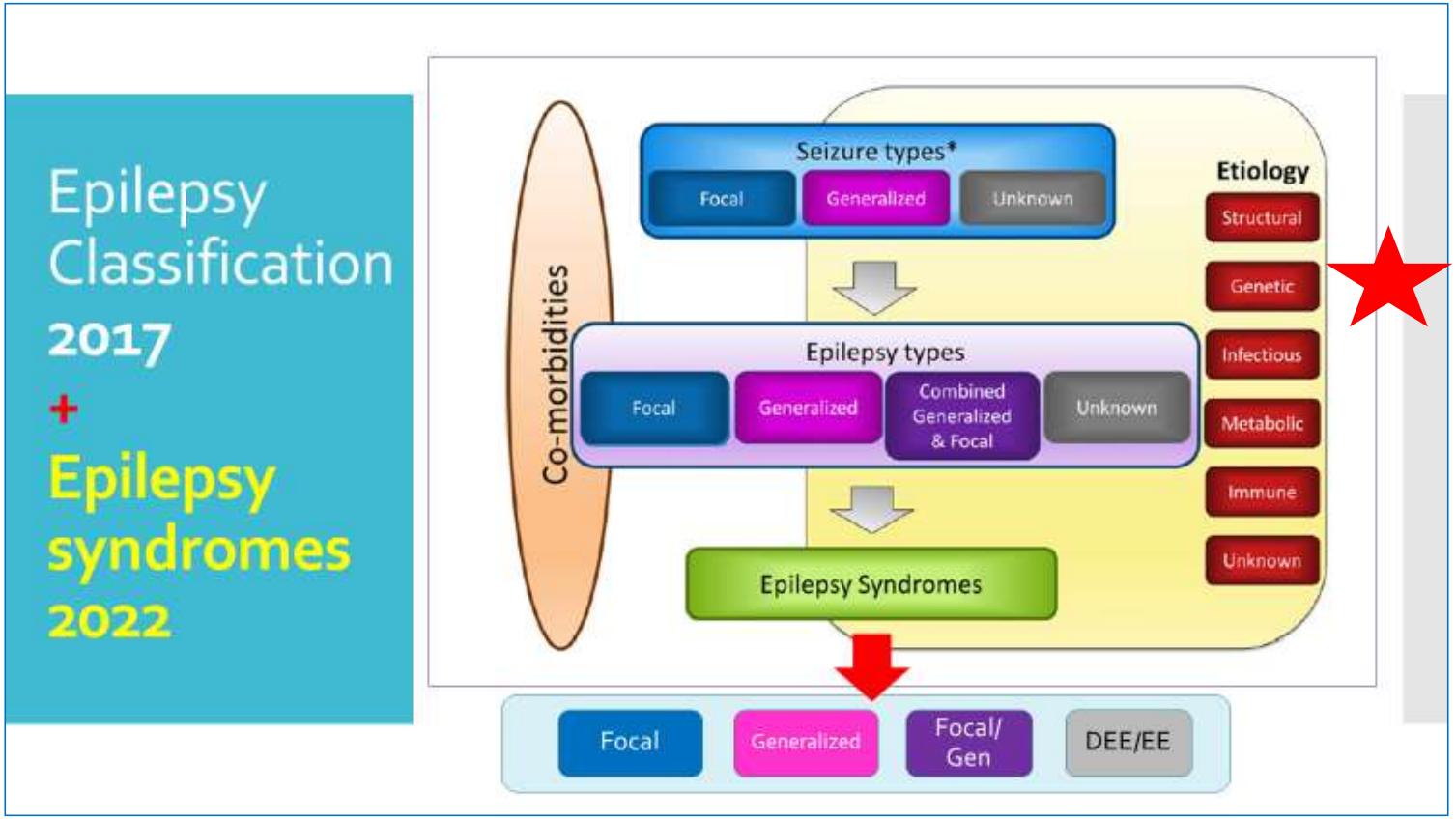
1.1 First seizure

1.2 Epileptic syndrome

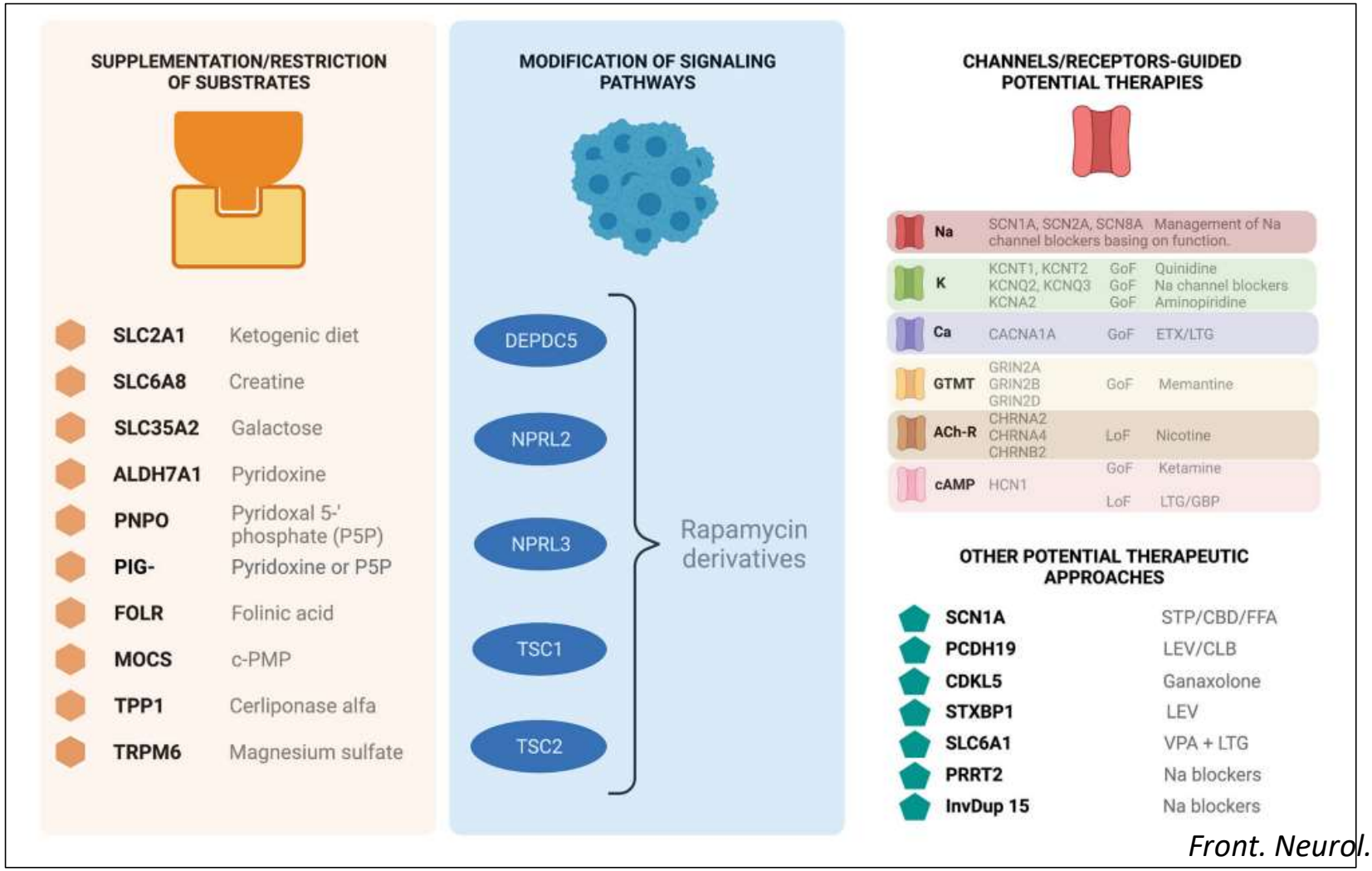




ASM Initiation



Genetic background



Front. Neurol. 13:777115

Treatment in Genetic Epilepsy

	Condition	Gene(s)	Treatment
a. Established treatments	Pyridoxine-dependent epilepsy	*ALDH7A1*, *PROSC*	Pyridoxine (vitamin B6)
	Unverricht-Lundborg disease	*CSTB*	Avoid sodium channel blockers, GABAergic drugs
	POLG-related epilepsy	*POLG*	Avoid valproate
	Pyridoxal 5′-phosphate dependent epilepsy	*PNPO*	Pyridoxal 5′-phosphate
	Dravet syndrome, *SCN1A*-related epilepsy	*SCN1A*	Avoid sodium channel blockers
	SCN2A-related epilepsy	*SCN2A*	Phenytoin
	SCN8A-related epilepsy	*SCN8A*	Phenytoin
	GLUT1 deficiency syndrome	*SLC2A1*	Ketogenic diet
	Tuberous sclerosis complex	*TSC1*, *TSC2*	Vigabatrin for infantile spasms
b. Treatment considerations	*GRIN2A*-related epilepsy (GOF)	*GRIN2A*	Memantine
	KCNQ2-related epilepsy (LOF)	*KCNQ2*	Retigabine (ezogabine)
	KCNT1-related epilepsy (GOF)	*KCNT1*	Quinidine

GOF gain of function, *LOF* loss of function

Curr Genet Med Rep 2018; 6: 73-82

ASMs Discontinuation

ASMs Discontinuation Issues

Children	Adult
No difference in sz recurrence between tapering ASMs after 2 or 4 years of seizure freedom	In long-term (24-60 mo) risk of sz recurrence is possibly higher in adults who tapering ASMs after 2 years
Interictal epileptiform activity possibly increases risk of seizure recurrence (low confidence)	
Withdrawal ASMs at a rate of 25% every 10 days-2 weeks or 25% every 2 months has no difference	

Neurology 2021;97:1072-1081

Seizure recurrence vs Seizure freedom after ASMs discontinuation

Factors associated w an increased risk of seizure recurrence

- Long duration of epilepsy before remission
- More than 10 seizures before remission
- Short seizure-free interval before ASM withdrawal
- Older age at onset of epilepsy (in pts >25 yrs)
- History of febrile seizures
- Not a self-limiting epilepsy syndrome
- Developmental delay
- Epileptiform abnormality on EEG before withdrawal

Factors associated w long-term seizure freedom (at 10 years after ASM withdrawal)

- Short duration of epilepsy before remission
- Low number of seizures before remission
- One or low number of ASM before withdrawal
- Long seizure-free interval (years) before ASM withdrawal
- No history of focal seizures
- No epileptiform abnormality on EEG before withdrawal

Aust Prescr 2021;44:53–6

Risk Factors for Recurrence of Epileptic Seizures after ASM Withdrawal in Pediatric patients

- Generalized non-motor absence seizures: 20-30% relapse
- Focal seizures: 44% relapse. Focal seizures with diminished awareness have greater risk of relapse
- Juvenile myoclonic epilepsy: recurs in 33-78%, only 25-26% can undergo treatment withdrawal
- West, Lennox-Gastaut, and Dravet syndromes have a high risk of recurrence

Rev Mex Neuroci. 2019;20(2):123-128

Other Risk Factors of Seizure Recurrence:

- Symptomatic epilepsies: 41-42% risk
- Neurological anomalies at birth
- Impaired neurodevelopment, intellectual quotient < 70
- ≥ 10 seizures / Prolonged epilepsy before remission
- Average of five seizures per year: 68% relapse
- Prolonged seizures
- Hx of febrile seizures has 2 times the risk of relapse
- Age of onset of epilepsy younger than 2 or older than 12 years old
- EEG with epileptiform activity before withdrawal.

Rev Mex Neuroci. 2019;20(2):123-128

ASMs Selection,

ASM Initiation,

ASM Discontinuation

Precision medicine

Thank you for your attention