ASMs Selection, Initiation and Discontinuation

Kamornwan Katanyuwong M.D.
Pediatrics Department, Chiangmai University Hospital
Chiangmai Thailand

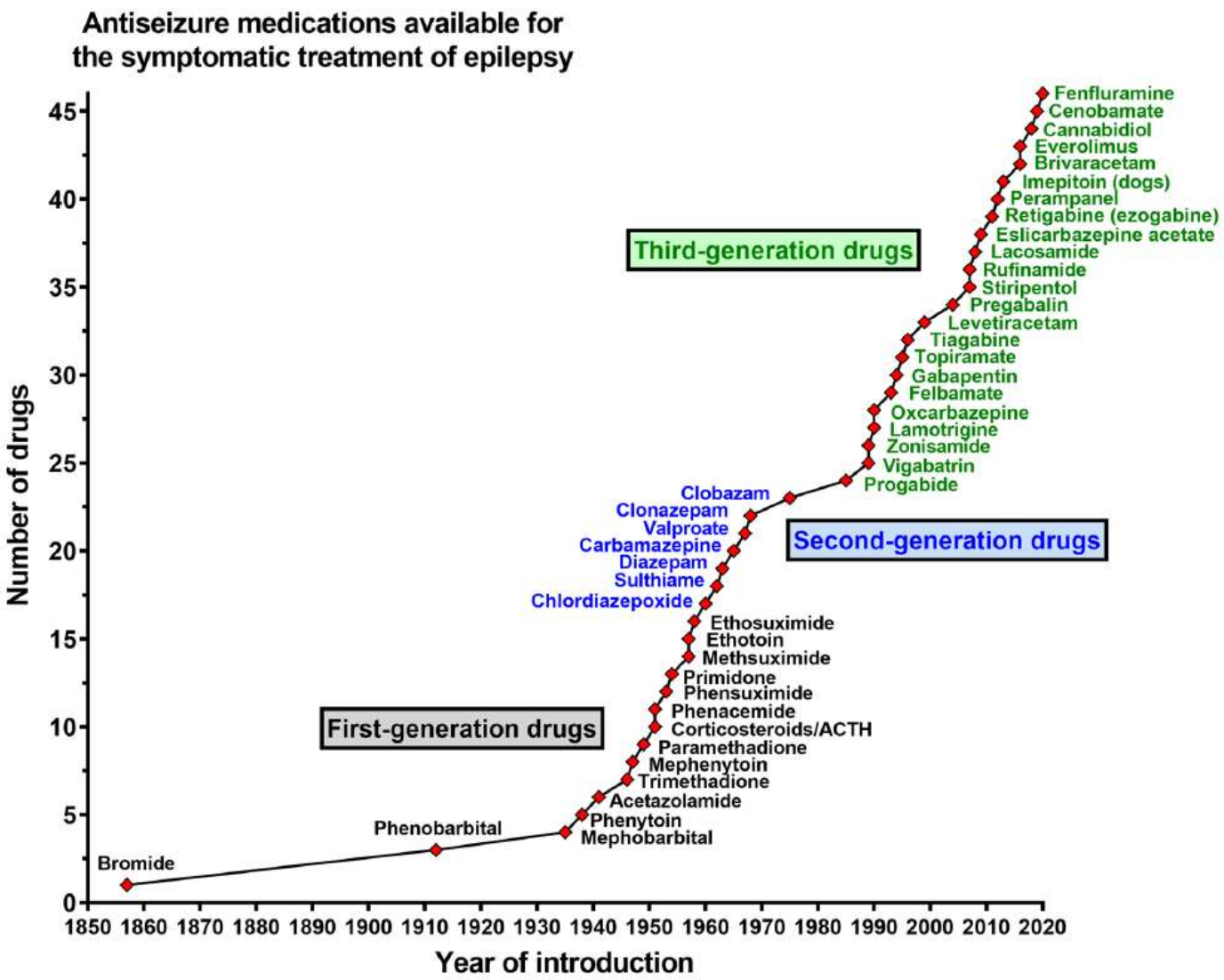
13th Epilepsy Course for Neurology Residents and Pediatric Fellow: Nov 2022


สมาคมโรคลมชักแห่งประเทศไทย
Epilepsy Society of Thailand
ครั้งที่ 13
Epilepsy Course for Neurology and Pediatric Neurology Residents
วันที่ 26 - 27 พฤศจิกายน 2565
ณ โรงแรม ฮอลิเดย์อิน แอนด์สวีท ศรีราชา จังหวัดชลบุรี
Saturday 26 November 2022
Time | Session | Speaker
08:30-08:45 | Opening remark | พลตรี นพ.ชาครินทร์ ณ บางช้าง
Moderator : พลตรี นพ.ชาครินทร์ ณ บางช้าง
08:45-09:15 | Seizure semiology | ผศ.พ.อ.พญ.ภิรดี สุวรรณภักดี
09:15-09:45 | Epileptic seizure vs seizure mimickers | อ.นพ. พีรสิทธิ์ ตรีสุทธาธีพ
09:45-10:00 | Q & A
10:00-10:15 | Break
Moderator : ผศ.ดร.นพ.ชูศักดิ์ ลิ้มทัย
10:15-11:00 | Psychiatric comorbidities in epilepsy | ศ.พญ.ณหทัย วงศ์ปการันย์
11:00-11:30 | Epilepsy syndromes of adolescence/adulthood | อ.พญ.สุดา จิรสกุลเดช
11:30-12:00 | Natural history of epilepsy | อ.พญ.ปาณิสรา สุดาจันทร์
12:00-12:15 | Q & A
12:15-13:00 | Lunch
Moderator : อ.พญ.สุธิดา เย็นจันทร์
13:00-13:30 | SUDEP | ผศ.นพ.อธิวัฒน์ สุนทรพันธ์
13:30-14:00 | Genetic testing in epilepsy | ผศ. (พิเศษ) นพ. กุลเสฏฐ ศักดิ์พิชัยสกุล
14:00-14:30 | Neuroimaging in epilepsy | อ.พญ.ปัญจมา เลิศบุษยานุกูล
14.30-15.15 | Epilepsy syndromes in neonates/infants/children | รศ.นพ.ชัยยศ คงคติธรรม
15:15-15:30 | Q & A
15.30-16.15 | Research consultation: meets the mentors (Pre-meeting research topic registration is available for residents/fellows) | คณาจารย์สมาคมโรคลมชักแห่งประเทศไทย Moderator: - รศ.นพ.ชัยยศ คงคติธรรม (Pediatrics) - ผศ.ดร.นพ.ชูศักดิ์ ลิ้มทัย (Adults)
Sunday 27 November 2022
Time | Session | Speaker
Moderator : อ.นพ.อาคม อารยาวิชานนท์
08:00-08:45 | Pharmacology in epilepsy | รศ.ดร.ภก.ธนรัตน์ สรวลเสน่ห์
08:45-09:15 | ASMs selection, initiation, and discontinuation | ผศ.พญ.กมรวรรณ กตัญญูวงศ์
09:15-09:45 | Selection of ASMs in special population | รศ.พญ.กนกวรรณ บุญญพิสิฐฐ์
09:45-10:00 | Q & A
10:00-10:15 | Break
Moderator : พ.อ.พญ.พาสิรี สิทธินามสุวรรณ
10.15-10.45 | Management of drug resistant epilepsy | อ.นพ.ศรัทธาวุธ วงษ์เวียงจันทร์
10:45-11:15 | Presurgical evaluation and epilepsy surgery | อ.นพ.กินนกร ยาดี
11:15-11:45 | Status epilepticus | พ.อ.พญ.พาสิรี สิทธินามสุวรรณ
11:45-12:00 | Q & A
12:00-13:00 | Lunch
ขอเชิญเฉพาะแพทย์ประจำบ้านสาขาประสาทวิทยา ปีที่ 3 แพทย์อนุสาขาประสาทวิทยาโรคลมชัก ปีที่1 ปีที่2 และแพทย์กุมารเวชศาสตร์ ประสาทวิทยา ปีที่ 2 เข้าร่วมการอบรมครั้งนี้ (โดยไม่มีค่าใช้จ่าย)
ติดต่อสอบถามเพิ่มเติมที่ คุณ พิมพชญา ปักศรีสิงห์ 02-716-5114
สนับสนุนการประชุมโดย
sanofi
human health care
Eisai
gsk
Abbott
VIATRIS
Mylan
Upjohn

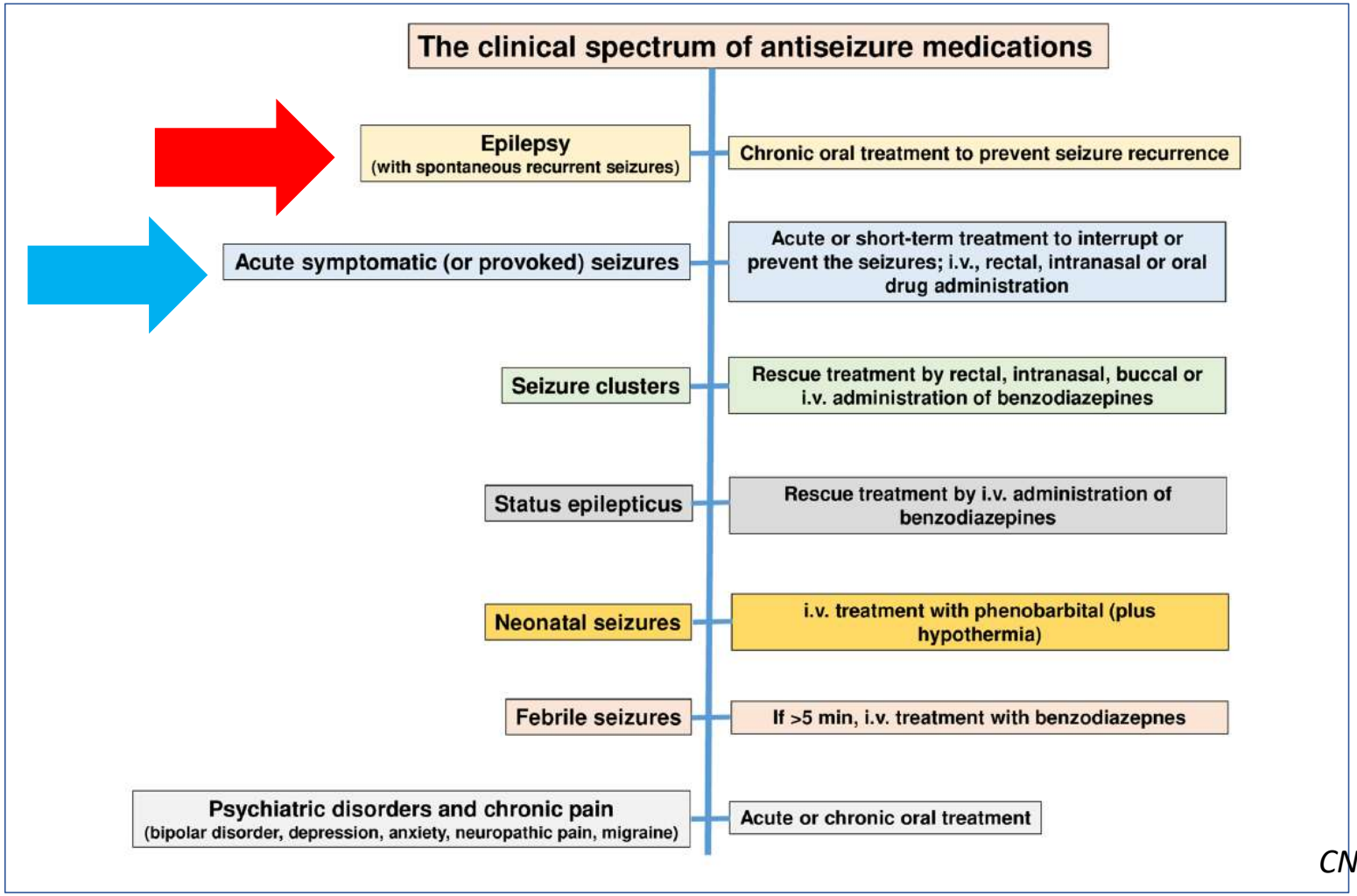
Outline

- *General practice of ASMs selection*
- Initiation of ASMs in different etiologies
- Discontinuation of AEDs

AEDs = ASMs


Antiseizure medications available for the symptomatic treatment of epilepsy
Number of drugs
Year of introduction
0
5
10
15
20
25
30
35
40
45
1850 1860 1870 1880 1890 1900 1910 1920 1930 1940 1950 1960 1970 1980 1990 2000 2010 2020
Bromide
Phenobarbital
Phenytoin
Mephobarbital
Acetazolamide
Trimethadione
Mephenytoin
Paramethadione
Corticosteroids/ACTH
Phenacemide
Phensuximide
Primidone
Methsuximide
Ethotoin
Ethosuximide
Chlordiazepoxide
Sulthiame
Diazepam
Carbamazepine
Valproate
Clonazepam
Clobazam
Progabide
Vigabatrin
Zonisamide
Lamotrigine
Oxcarbazepine
Felbamate
Gabapentin
Topiramate
Tiagabine
Levetiracetam
Pregabalin
Stiripentol
Rufinamide
Lacosamide
Eslicarbazepine acetate
Retigabine (ezogabine)
Perampanel
Imepitoin (dogs)
Brivaracetam
Everolimus
Cannabidiol
Cenobamate
Fenfluramine
First-generation drugs
Second-generation drugs
Third-generation drugs

The clinical spectrum of ASMs



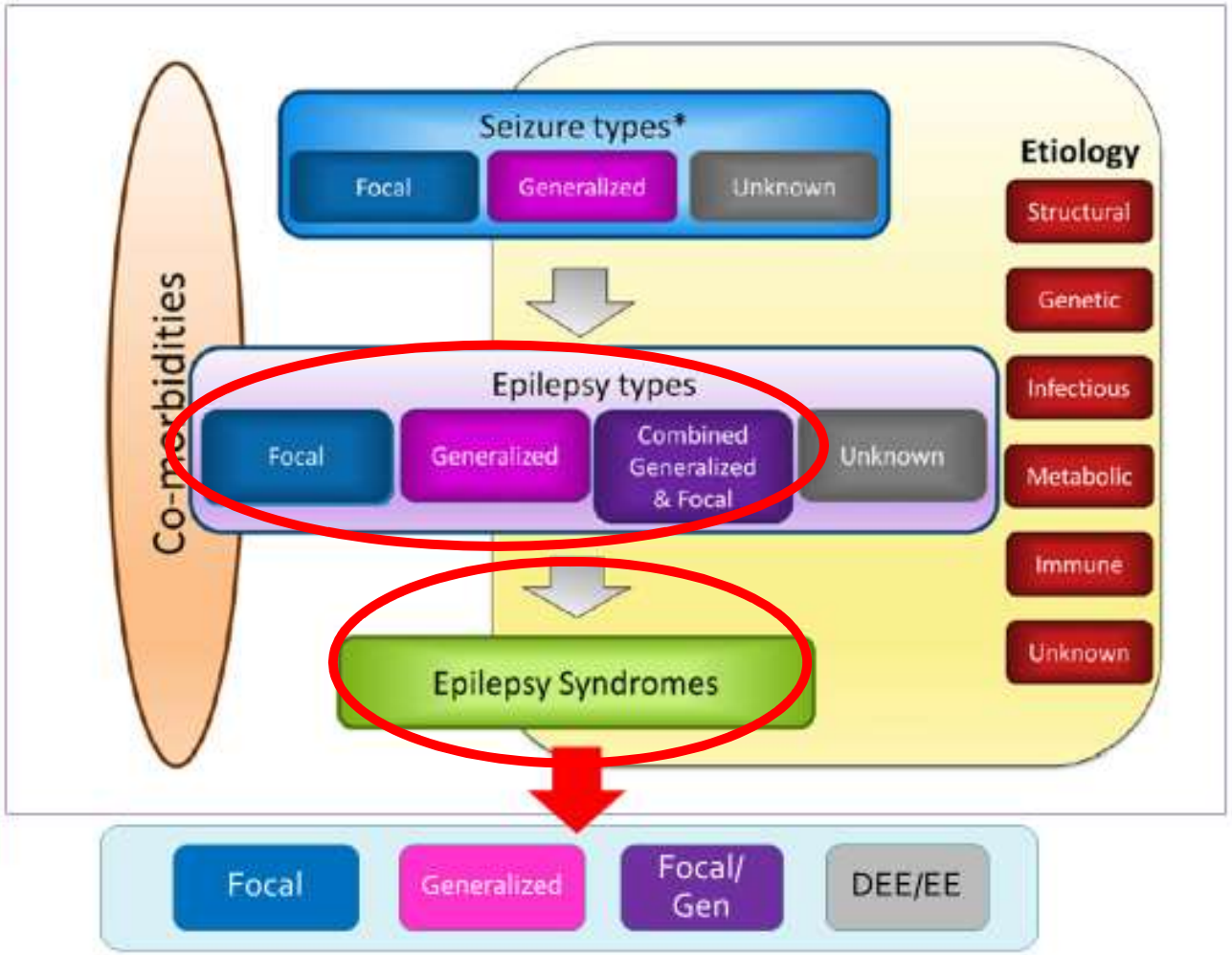
CNS Drugs (2021)

Variables that affect a specific ASMs

ASM specific variables	Patient-specific variables	Nation-specific variables
• Sz type or syndrome efficacy/effectiveness • Pharmacokinetics • Idiosyncratic reaction • Dose-dependent AE • Interaction potential • Formulation • Chronic toxicity • Teratogenicity • *MOA* • *Rational Rx*	• 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

Adapted from Epilepsia 47,2006

Epilepsy Classification 2017 + Epilepsy syndromes 2022



Definition of terms

Epilepsy *ILAE 2014*	• At least two unprovoked 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) • Diagnosis of epilepsy syndrome
Acute symptomatic seizure	Caused by acute illness (stroke, CNS infection, TBI): seizure within 7 days of an insult
Remote symptomatic seizure (unprovoked seizure)	Pre-existing brain injury: seizure greater than 7 days after insult
Provoked seizure	Caused by transient reversible alterations without structural change (toxin, metabolic factors, medication); occurs at time of insult or within 7 days

ASM Selections @ seizure type/syndrome

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

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

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

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

Cumulative risk in 2 important issues

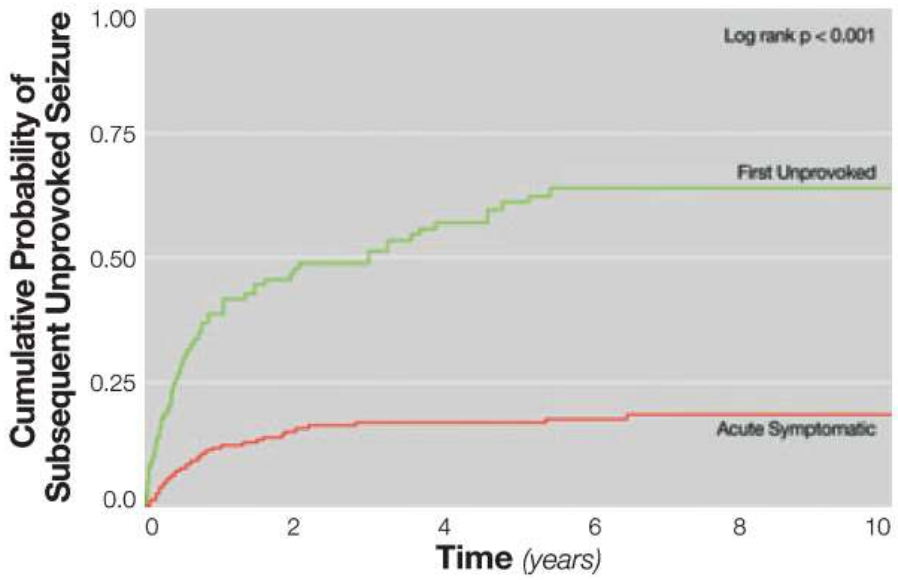


Figure 3.
Cumulative risk of subsequent unprovoked seizure after first acute symptomatic seizure and first unprovoked seizure.
Epilepsia © ILAE

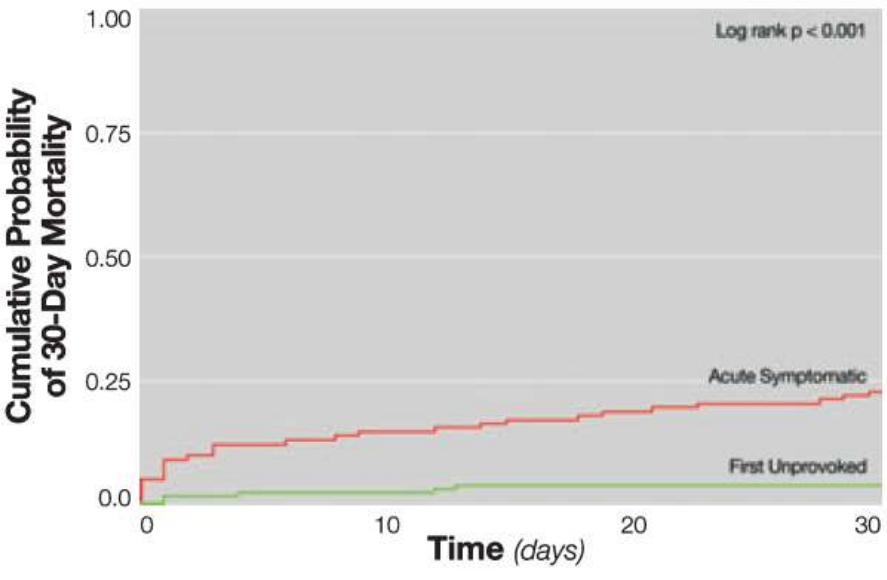


Figure 1.
Cumulative risk of death in the first 30 days after first acute symptomatic seizure and first unprovoked seizure.
Epilepsia © ILAE

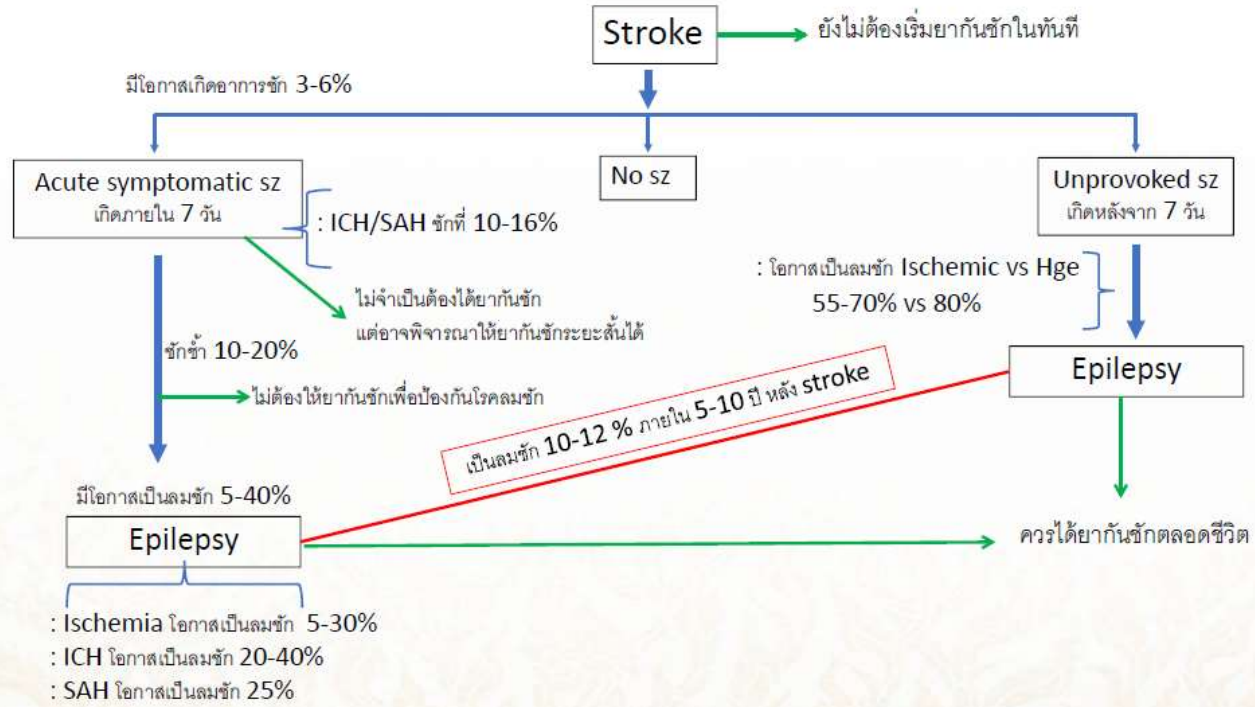
Epilepsia, 50(5):1102–1108, 2009

Management guideline

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 and Hx of acute symp seizures	if pt develops remote symp sz in setting of underlying lesion

Curr Treat Options Neurol (2018) 20: 41

รูปที่ 1 แสดงโอกาสการเกิดอาการชัก การเป็นโรคลมชัก ของผู้ป่วยหลอดเลือดสมอง และการพิจารณาการให้ยากันชักในผู้ป่วยกลุ่มนี้



Management guideline

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 pt 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

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 the 2 years = 21-45%

Child risk at 2 yrs = 37%

Initial Rx after 1st sz ↓ 35%

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%

Initial Rx of 1st unprovoked sz

- 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 seizure relapses if ASMs are not started (JME)
2. A good prognosis under ASM Rx (JME)
3. Limited chance of adopting lifestyle
4. A first seizure with loss of consciousness
5. Abnormal EEG findings with epileptiform discharges
6. Abnormal MRI finding
7. Adult age
8. A high personal risk in case of seizure relapses due to casual habits or professional circumstance

Seizure 49 (2017) 92-94

ASM Initiation

ASM decision making

- **Initiation**: primary monoRx

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

: Narrow spectrum ASM → focal sz

- **Uncontrolled sz**: secondary/third monoRx or polyRx

Broad spectrum vs Narrow spectrum ASMs

VPA

TPM, ZNS

LTG

LEV

PER

RFN

CLB (CLN), CZP

PB

~~***PRM*****, FBM**~~

PHT

CBZ, ~~***ESL***~~

OXC

VGB

PGB, GBP

LCM

~~***TGB***~~

~~***EZG***~~

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

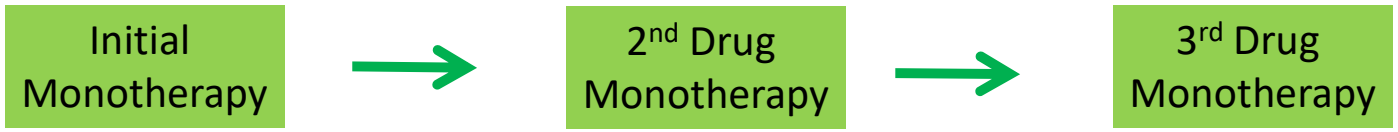
Desirable Pk Properties of an AED

- 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

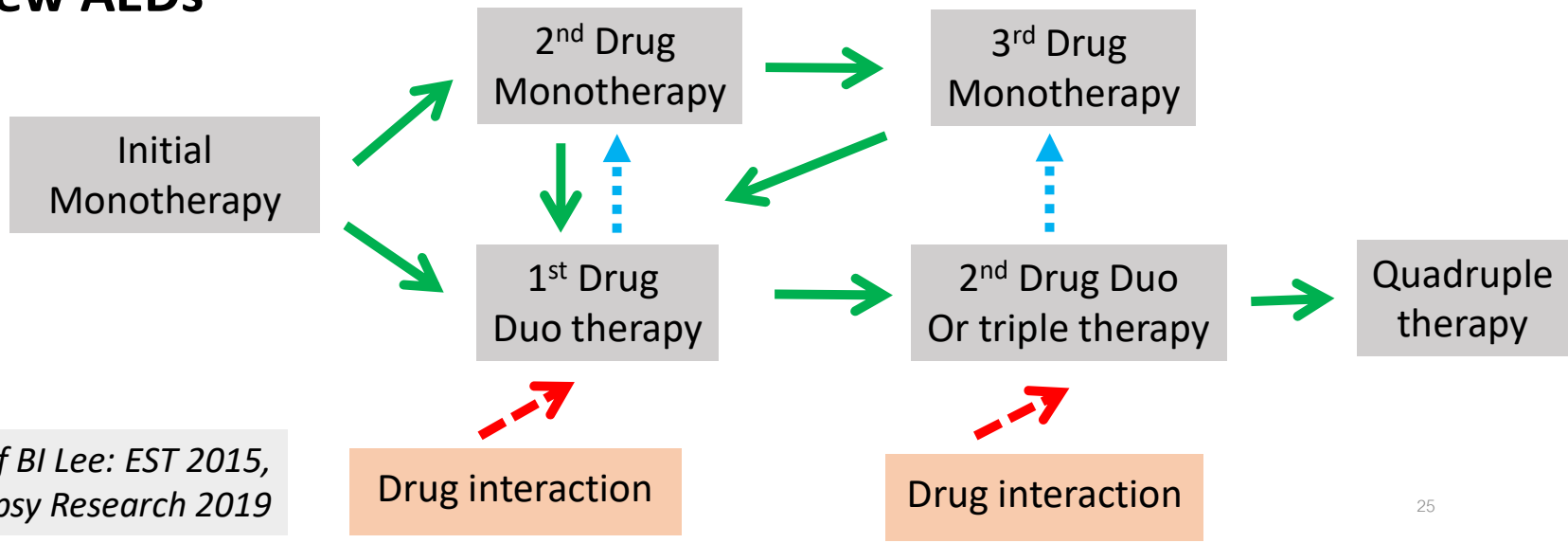
Epileptic Disord 2003; 5 (Suppl 1): S17–S26

Rational of ASM treatment

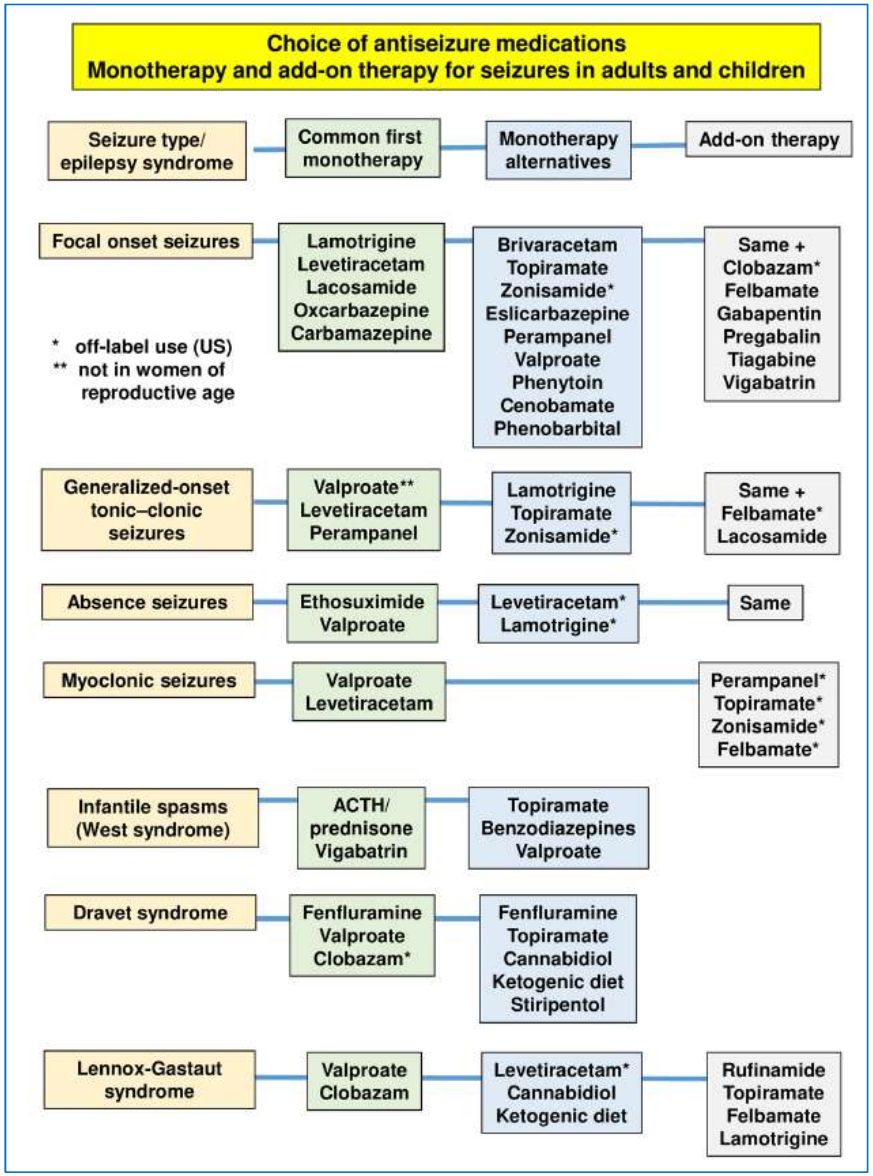
- **Era of conventional AED**



- **Era of New AEDs**



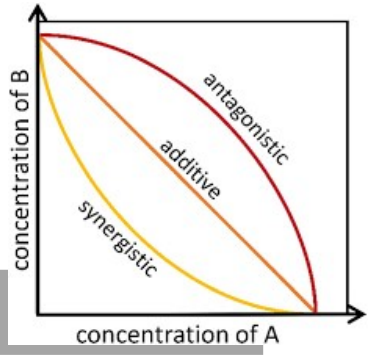
Modified from Prof BI Lee: EST 2015, Journal of Epilepsy Research 2019



CNS Drugs (2021) 35:935–963

Combination regimens

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



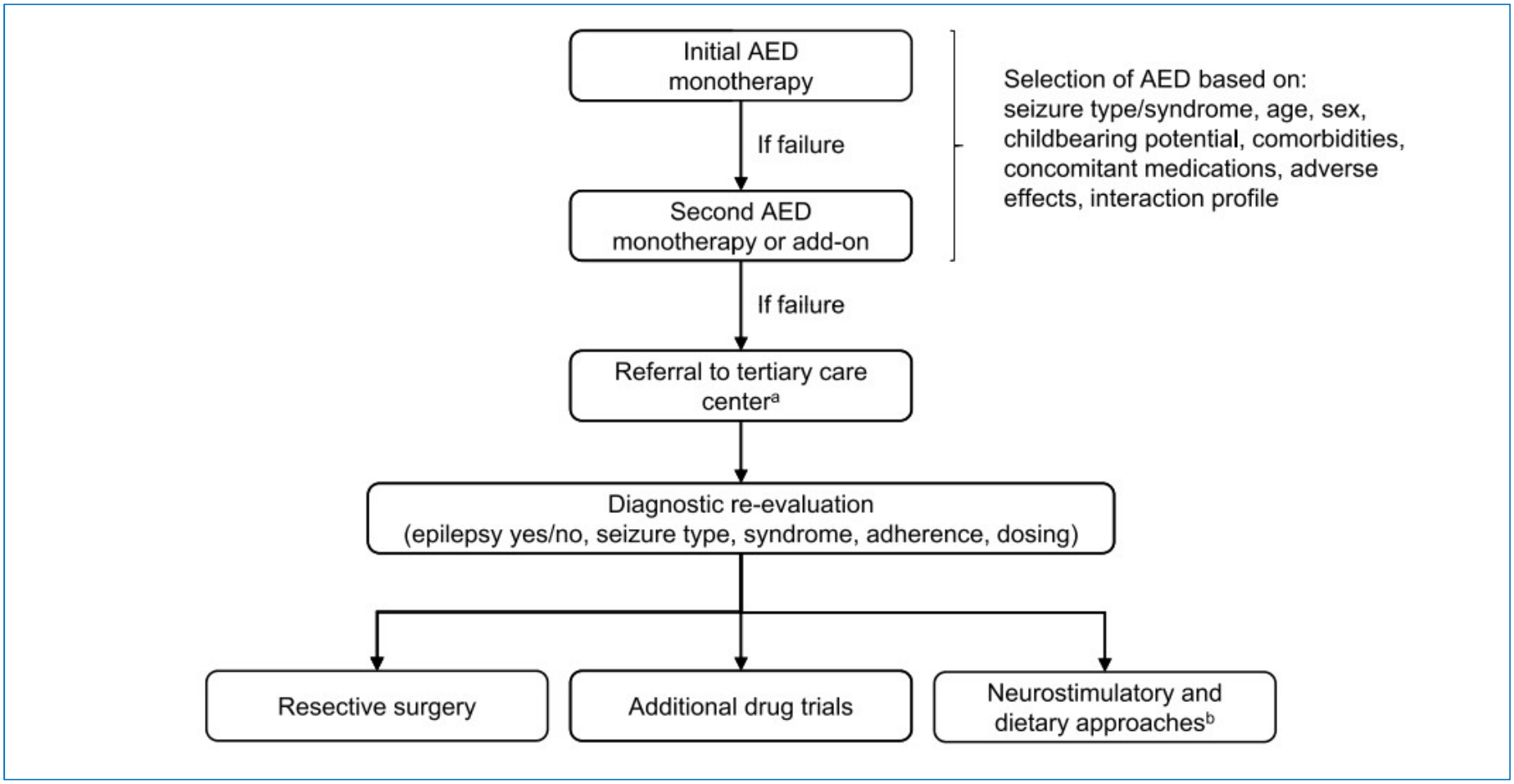
Drug combination	comment
SCB(+) + SCB(+)	**Additive efficacy or antagonism**
SCB(+) + *SCB(+)*	**Synergistic efficacy**
SCB(+) + Multiple actions	**Variable and unpredictable**
SCB(+) [*or SCB(+)*] **+ Enhanced GABAergic**	**Synergistic efficacy**
Multiple actions + Multiple actions	**Synergistic efficacy**
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,
Tonic seizure (in LGS)	
CSWS/ESES	CBZ, OXC
Dravet syndrome	Sodium channel blockers
LGS	CBZ, OXC, PHT, TGB

?

?



Acta Neurologica Belgica (2021) 121:241–257

ASM 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

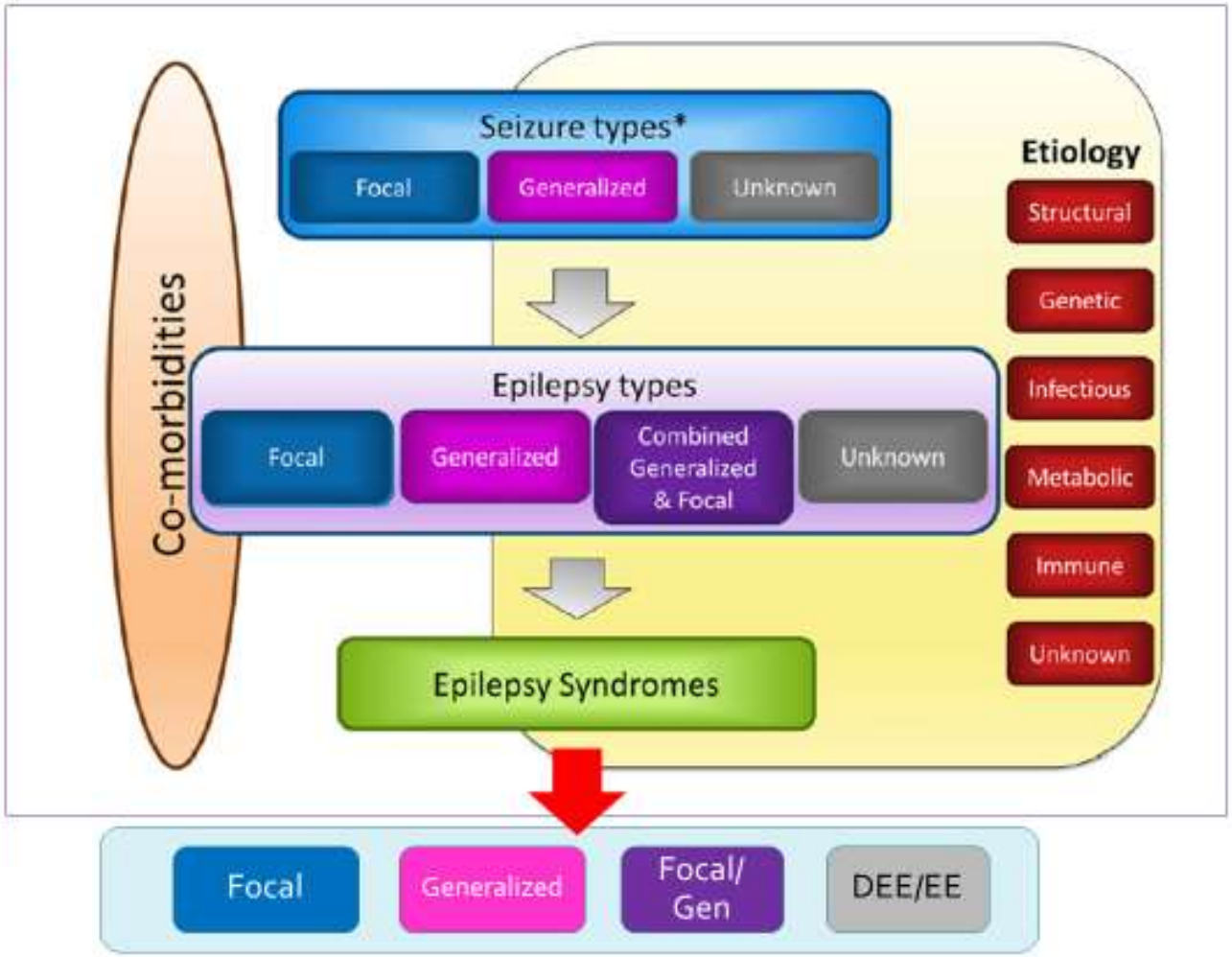
Aust Prescr 2021;44:53–6

Other risk factors of seizure recurrence:

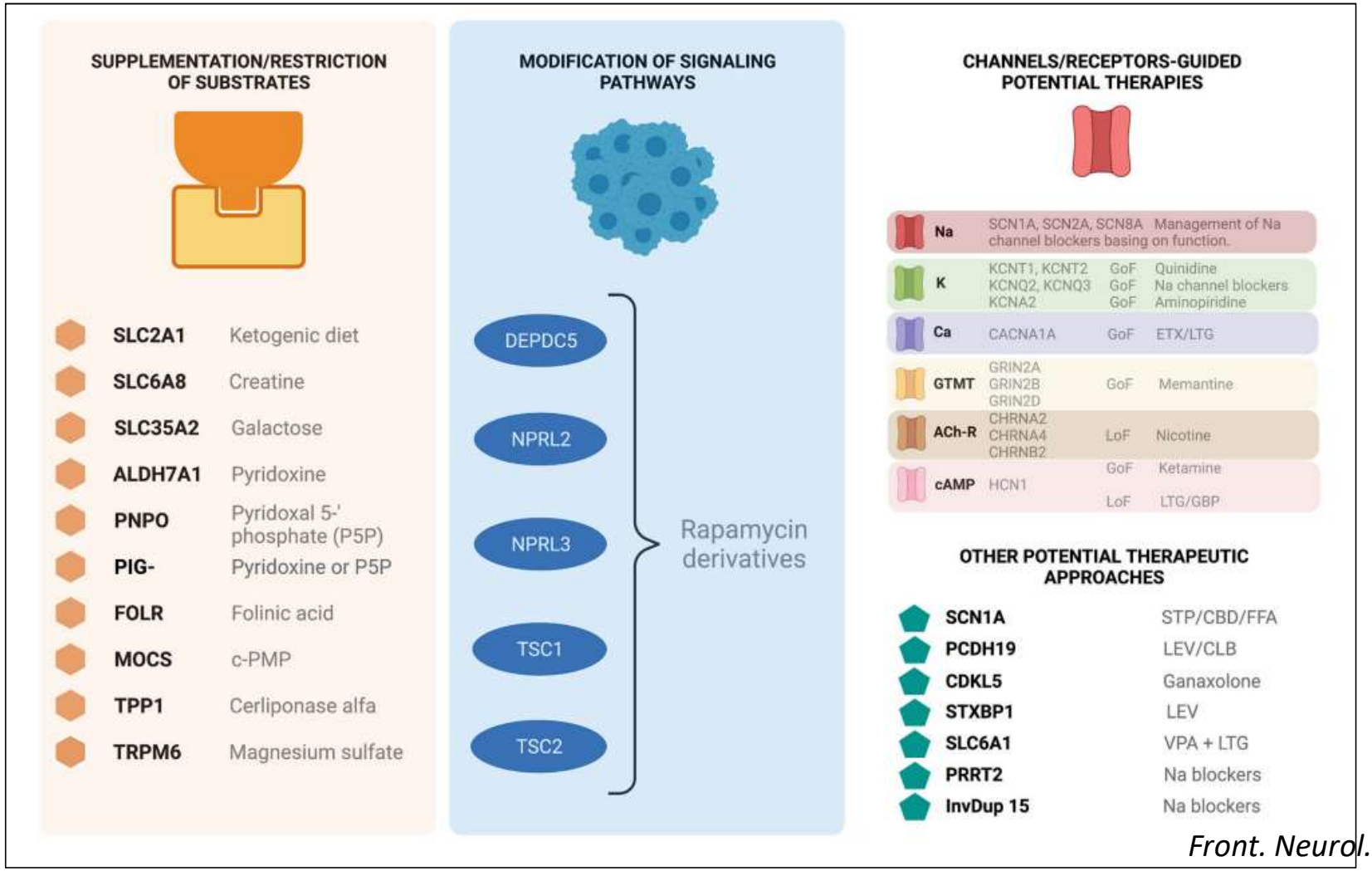
- Symptomatic epilepsies: 41-42% risk
- Neurological anomalies at birth
- Impaired neurodevelopment, intellectual quotient < 70
- ≥ 10 seizures / Prolonged epilepsy before remission
- Average of five seizures per year: 68% relapse
- Prolonged seizures
- Hx of febrile seizures has 2 times the risk of 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

Epilepsy Classification 2017 + Epilepsy syndromes 2022



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

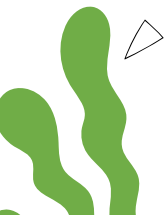
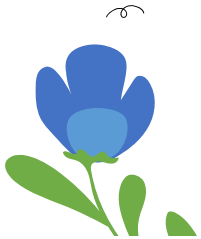
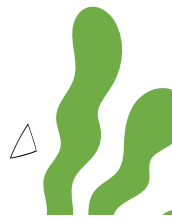
Curr Genet Med Rep 2018; 6: 73-82

ASMs Selection,

Precision medicine

ASM Initiation,

ASM Discontinuation

Thank you for your attention