Pragmatic Algorithm to Select Appropriate Antiseizure Medications (ASMs) (in Pediatrics)

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Outline

- Facts about ASMs and epilepsy in Thailand
- Evidence based for ASMs selection across ages
- Pragmatic algorithm to select ASMs in Thailand

Pragmatic Meaning

- Solving problem in a practical and sensible way rather than having fixed ideas or theories
- Synonym: “realistic”

Oxford Dictionary

Facts About ASMs and Epilepsy

- 2/3 of people with epilepsy attain complete seizure free with appropriately chosen ASMs
- Number of ASMs has been increased over the years (20 ASMs now in common use)
- Suboptimal ASM selection is common and may cause harm

Clinical Variables to Select ASMs

ASM-specific variables	Patient-specific variables	Nation-specific variables
•Seizure type or epilepsy syndrome specific efficacy or effectiveness •Dose-dependent adverse effects •Idiosyncratic reactions •Chronic toxicities •Teratogenicity •Carcinogenicity •Pharmacokinetics •Interaction potential •Formulations	•Genetic background •Age •Gender •Comedications •Comorbidities •Insurance coverage •Ability to swallow pills/tablets	•ASMs availability •ASMs cost •Insurance coverage

Available ASMs in Thailand

- **Classical ASM:**
  - Phenobarbital (PB)
  - Phenytoin (PHT)
  - Carbamazepine (CBZ)
  - Sodium valproate (VPA)
  - Clonazepam (CNZ)
  - Nitrazepam (NZP)

- **New ASM:**
  - Vigabatrin (VGB)
  - Zonisamide (ZNS)
  - Lamotrigine (LTG)
  - Topiramate (TPM)
  - Gabapentin (GBP)
  - Oxcarbazepine (OXC)
  - Levetiracetam (LEV)
  - Pregabalin (PGB)
  - Lacosamide (LCM)
  - Perampanel (PER)
  - Clobazam (CLB)
  - Rufinamide (RUF)
  - Enriched Canabidiol (CBD)

Reality

สปสช.

สำนักงานหลักประกันสุขภาพแห่งชาติ

NLEM บัญชียาหลักแห่งชาติ
National List of Essential Medicines

กรมบัญชีกลาง

สำนักงานประกันสังคม

National List of Essential Medicines
(บัญชียาหลักแห่งชาติ)

บัญชียา ก

- PB
- PHT
- CBZ
- VPA

บัญชียา ข

- CNZ

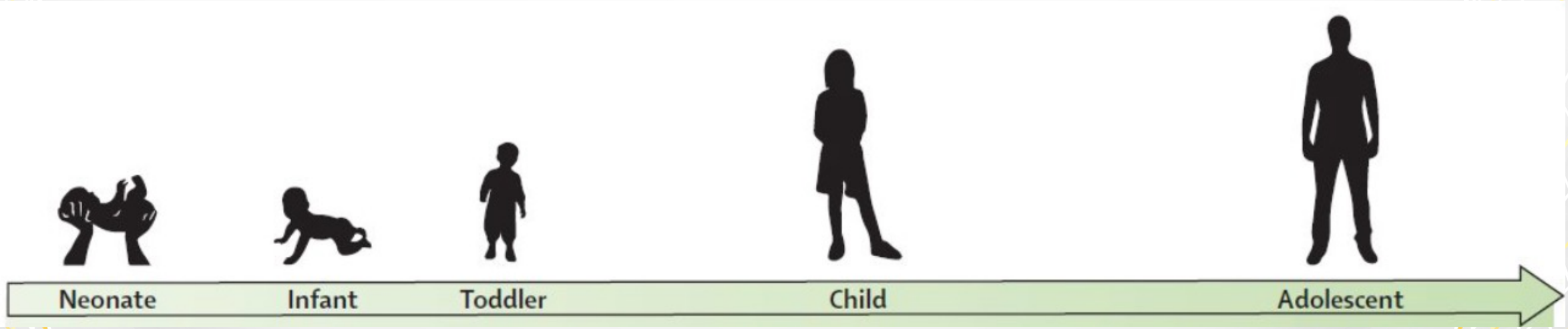
บัญชียา ง

- LTG
- LEV
- NZP
- TPM
- VGB

นอกบัญชี

- CLB
- GBP
- LCM
- OXC
- PER
- PGB
- RUF
- ZNS

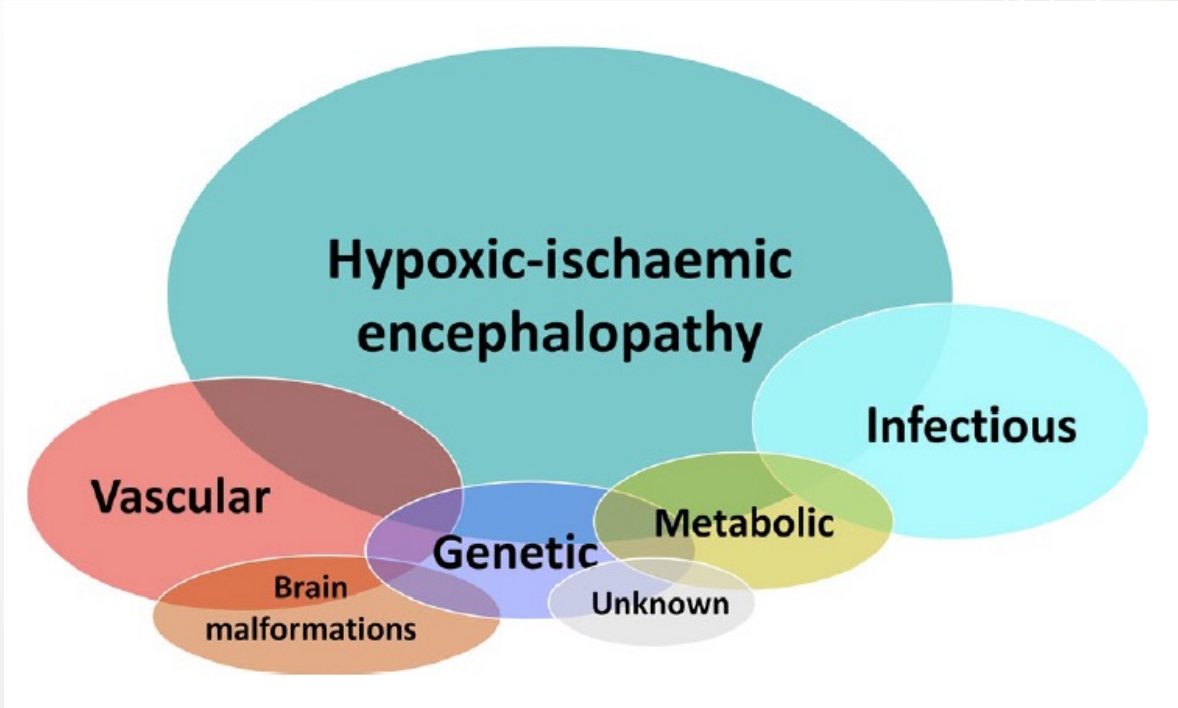
Evidence Based for ASMs Selection Across Ages



Neonatal Seizures

- Majority of seizures are provoked by an acute illness or brain insult (acute provoked seizures)
- Clinical diagnosis is difficult (50% correct)
- Uncoupling is common
- Few randomized, double blind trial of drugs
- Several open label trials and retrospective studies

- Etiologies of neonatal seizures



Pressler RM, et al., ILAE classification 2021

Randomized Trial for ASMs as First Drug in Neonatal Seizures

- PB vs PHT as first line
  - PB — 43% efffective
  - PHT — 45% effective
  - PB + PHT combined — 57% effective
- PB (20 mg/kg/dose) vs LEV (40 mg/kg/dose)
  - PB — 80% effective (higher rates of adverse effects)
  - LEV — 28% effective (7.5% increased efficacy with dose increment to 60 mg/kg/dose)

Painter MJ, NEJM 1999, Sharpe C, et al. Pediatrics 2020

Infantile/Early-Life Epilepsy

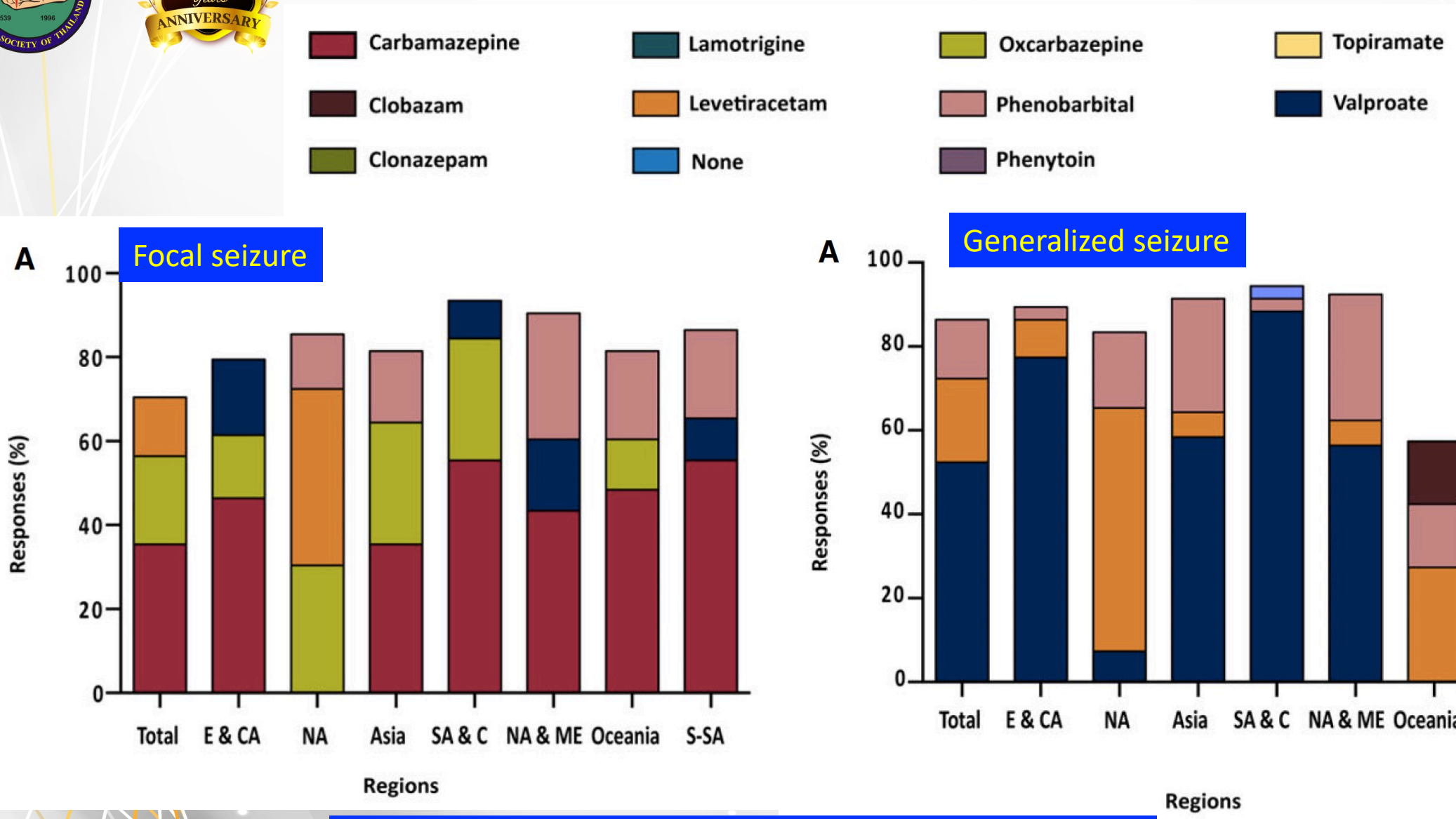
- Highest incidence of all age groups (2/1,000 children)
- Various epilepsy syndromes particularly West syndrome
- Concerns about effect of ASMs on the developmental trajectory of brain
- Failure to control seizures may be associated with adverse neurodevelopmental outcomes
- No evidence-based treatment except epileptic spasms

Gaily E, et al. Epilepsia 2016, Berg AT, et al. JAMA Pediatr 2017

Evidence Based Treatment for Epileptic Spasms

Study	Outcome Measure	Steroids	VGB
UKISS (only non TSC patients)	Spasm cessation on days 14	72% (40/55)	54% (28/52)
	Sustained spasms control with no relapse until 12-14 months of age	40% (22/55)	37% (19/52)
PERC	Cessation of spasms within 2 wks of therapy, with resolution of hypsarrhythmia sustained at 3 months	49% (74/151)	36% (17/47)
Study	**Outcome Measure**	**Steroids**	**Steroids plus VGB**
ICISS	No witnessed spasms between days 14-42	57% (108/191)	72% (133/186)
	Electroclinical response (no spasms + EEG resolution)	55% (104/189)	66% (123/186)

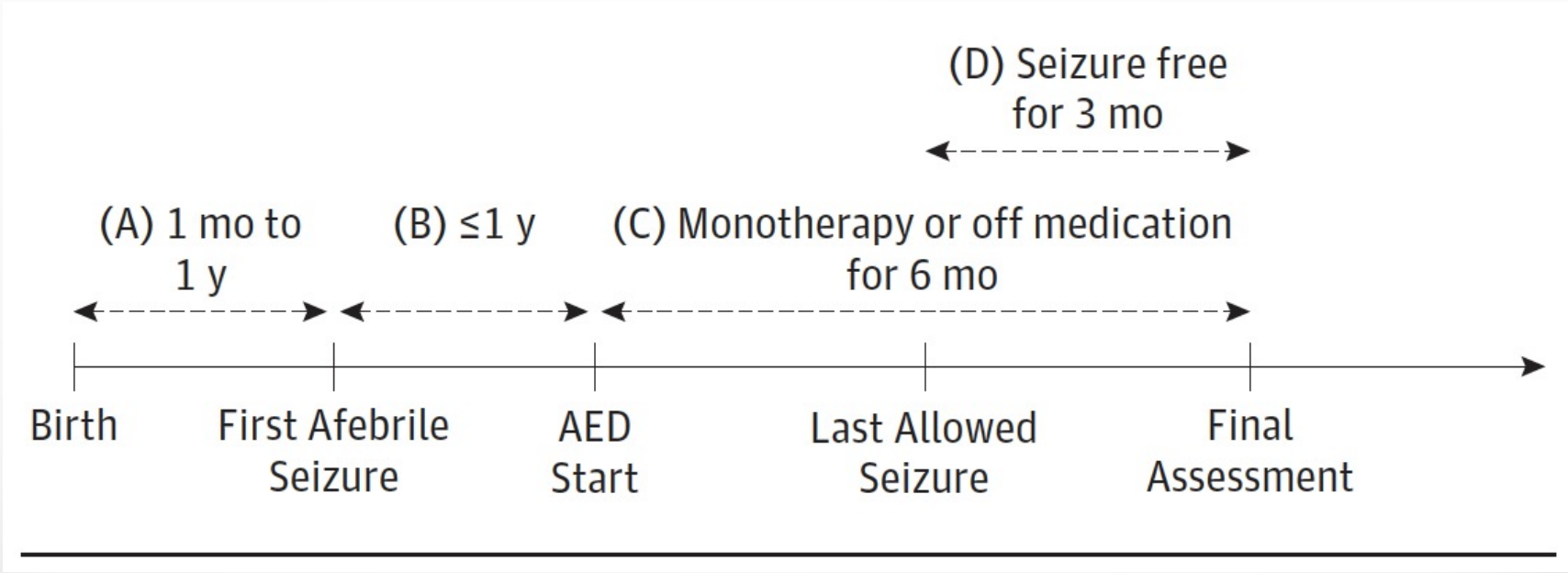
Infantile/Early-Life Epilepsy



Different treatment practice among regions

Wilmshurst JM, et al. Epilepsia 2015

Nonsyndromic Infantile Epilepsy



	LEV (n = 117)	vs PB (n = 38)
Age at Sz onset (mo)	5.2 (3.5-8.2)	vs 3.0 (2.0-4.4)
Free from monotherapy failure	47 (40.2%)	vs 6 (15.8%)
ORs of a better outcome for LEV vs PB	4.2 (1.1-16), NNT = 3.5 (1.7-60)	

Grinspan ZM, et al. JAMA Pediatr 2018

Oral PHT in Infancy

- IV PHT is useful in the treatment of seizures and SE in neonates and infants
- Oral dosing is difficult to obtain adequate plasma concentration
- Very short half life, age-dependent absorption pattern
- Very high doses of 10-20 mg/kg/day are required

Albani M, Pediatr Pharmacol 1983, Bourgeois BF, Neurology 1983, Sicca F, Brain Dev 2000, Cheng A, J Popul Ther Clin Pharmacol 2010

Childhood Epilepsy

- Think about generalized absence seizures at this age
- Broad spectrum ASMs (VPA, LEV, LTG) may be appropriate as first line in patients with generalized absence seizures or unknown onset seizures
- Narrow spectrum ASMs can be used in documented focal seizures
- HLAB*1502 screening is warranted in Thai patients when thinking about CBZ use

Tassaneeyakul W, et al. Epillepsia 2010

Adolescent Epilepsy

- Distinguish seizure type(s) first: Generalized vs Focal
  - Generalized: Absence/myoclonic/GTC alone without focal features or undetermined onset
- JME is the most common epilepsy syndrome in this age
- Adolescence is a turbulent period of development
- ASM selection should take future needs into consideration

Evidence Based of ASMs Selection in Children

	Focal seizures	GTCs	Generalized Absence	Generalized Myoclonic	Other Epilepsy syndromes
บัญชียา ก					
CBZ	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**	ไม่ได้ผล	ไม่ได้ผล	น่าจะได้ผลแต่ไม่เคยมี **Class I trials (BECTS)**
PB	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**	ไม่ได้ผล	ไม่มีข้อมูล	ไม่มีข้อมูล
PHT	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**	ไม่ได้ผล	ไม่ได้ผล	น่าจะได้ผลแต่ไม่เคยมี **Class I trials (BECTS)**
VPA	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**	**Class I trials**	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**
บัญชียา ข					
CNZ	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**	ไม่มีข้อมูล

Modified from Draft Clinical Practice Guidelines for Epilepsy Thailand 2021
Abou-Khalil BW, Continuum 2019

Evidence Based of ASMs Selection in Children

	Focal seizures	GTCs	Generalized Absence	Generalized Myoclonic	Other Epilepsy syndromes
บัญชียา ง					
LTG	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**	ผลการรักษาไม่แน่นอน	**Class I trials (LGS)**
LEV	**Class I trials**	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**	**Class I trials**	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**	**Class I trials (BECTS)**
TPM	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**	น่าจะได้ผลแต่ไม่เคยมี **Class I trials**	**Not effective in Class I trials**	ไม่มีข้อมูล	**Class I trials (LGS)**
VGB	**Class I trials**	ไม่ได้ผล	ไม่ได้ผล	ไม่ได้ผล	**Class I trials (Epileptic spasms)**

Modified from Draft Clinical Practice Guidelines for Epilepsy Thailand 2021
Abou-Khalil BW, Continuum 2019

Evidence Based of ASMs Selection in Children

	Focal seizures	GTCs	Generalized Absence	Generalized Myoclonic	Other Epilepsy syndromes
นอกบัญชี					
CLB	น่าจะได้ผลแต่ไม่เคยมี Class I trials	น่าจะได้ผลแต่ไม่เคยมี Class I trials	น่าจะได้ผลแต่ไม่เคยมี Class I trials	น่าจะได้ผลแต่ไม่เคยมี Class I trials	Class I trials (LGS)
GBP	ไม่มีข้อมูล	ไม่ได้ผล	ไม่ได้ผล	ไม่ได้ผล	ไม่มีข้อมูล
LCM	Class I trials	ไม่มีข้อมูล	ไม่ได้ผล	ไม่ได้ผล	ไม่มีข้อมูล
OXC	Class I trials	ไม่มีข้อมูล	ไม่ได้ผล	ไม่ได้ผล	ไม่มีข้อมูล
PER	Class I trials	Class I trials	ไม่มีข้อมูล	ไม่มีข้อมูล	ไม่มีข้อมูล
PGB	Class I trials	ไม่มีข้อมูล	ไม่ได้ผล	ไม่ได้ผล	ไม่มีข้อมูล
RUF	น่าจะได้ผลแต่ไม่เคยมี Class I trials	น่าจะได้ผลแต่ไม่เคยมี Class I trials	ไม่มีข้อมูล	ไม่มีข้อมูล	Class I trials (LGS)
ZNS	น่าจะได้ผลแต่ไม่เคยมี Class I trials	น่าจะได้ผลแต่ไม่เคยมี Class I trials	น่าจะได้ผลแต่ไม่เคยมี Class I trials	น่าจะได้ผลแต่ไม่เคยมี Class I trials	ไม่มีข้อมูล

Modified from Draft Clinical Practice Guidelines for Epilepsy Thailand 2021
Abou-Khalil BW, Continuum 2019

Pragmatic Algorithm for ASM Selection

Pragmatic Algorithm Tool

- Facilitate ASM selection for individuals whose epilepsy begins at ≥ 10 years
- Web based application at: https://epipick.org/#/

A pragmatic algorithm to select appropriate antiseizure medications in patients with epilepsy

Ali A. Asadi-Pooya[1,2] | Sándor Beniczky[3,4] | Guido Rubboli[5,6] |
Michael R. Sperling[2] | Stefan Rampp[7,8] | Emilio Perucca[9,10]

Asadi-Pooya Ali, et al. Epillepsia 2020

A 13-Year-Old Boy

- Had first GTC occurred during sleep lasting 2 minutes
- 1 year ago, he had frequent jerking during awakening, frequency 1-2/week
- The jerkings wake him up, sometimes make him fall
- PMHx: febrile seizure at 7-month-old
- FMHx: no epilepsy or seizures
- Normal development
- Examination: normal

Epipick: 13-Year-Old Male

Recommended antiseizure medication based on the following:

- Age 13
- Male
- Seizure type: Primary generalized tonic-clonic seizures

The drug choices below are based on scientific evidence and expert opinion. The recommendations are not influenced by medication cost, which may affect your selection. Patients who fail to respond to more than two appropriate antiseizure medications should undergo further evaluation at a specialized epilepsy center.

Group 1 (Best options)

Right click on drug names to download info material and see the explanation of the choice.

- Valproate

Group 2 (Second best options)

- Lacosamide
- Lamotrigine
- Levetiracetam
- Perampanel

Group 3 (Least desirable options though still acceptable)

- Brivaracetam
- Carbamazepine
- Clobazam
- Oxcarbazepine
- Topiramate
- Zonisamide
- Phenobarbital
- Phenytoin

Epipick: 13-Year-Old Female

Recommended antiseizure medication based on the following:

- Age 13
- Female, premenopausal
- Seizure type: Primary generalized tonic-clonic seizures

The drug choices below are based on scientific evidence and expert opinion. The recommendations are not influenced by medication cost, which may affect your selection. Patients who fail to respond to more than two appropriate antiseizure medications should undergo further evaluation at a specialized epilepsy center.

Group 1 (Best options)

Right click on drug names to download info material and see the explanation of the choice.

- Lamotrigine
- Levetiracetam

Group 2 (Second best options)

- Lacosamide
- Perampanel

Group 3 (Least desirable options though still acceptable)

- Brivaracetam
- Carbamazepine
- Clobazam
- Oxcarbazepine
- Topiramate (For premenopausal women who may become pregnant, Topiramate is a suboptimal choice.)
- Valproate (Valproate is associated with a high teratogenic risk and risk of impaired postnatal cognitive development in prenatally exposed offspring. If use in premenopausal females is considered, appropriate measures should be taken to prevent the risk of conception. If pregnancy is desired and this drug is necessary, careful planning is important with appropriate advice from a specialist.)
- Zonisamide
- Phenobarbital (For premenopausal women who may become pregnant, Phenobarbital is a suboptimal choice.)
- Phenytoin

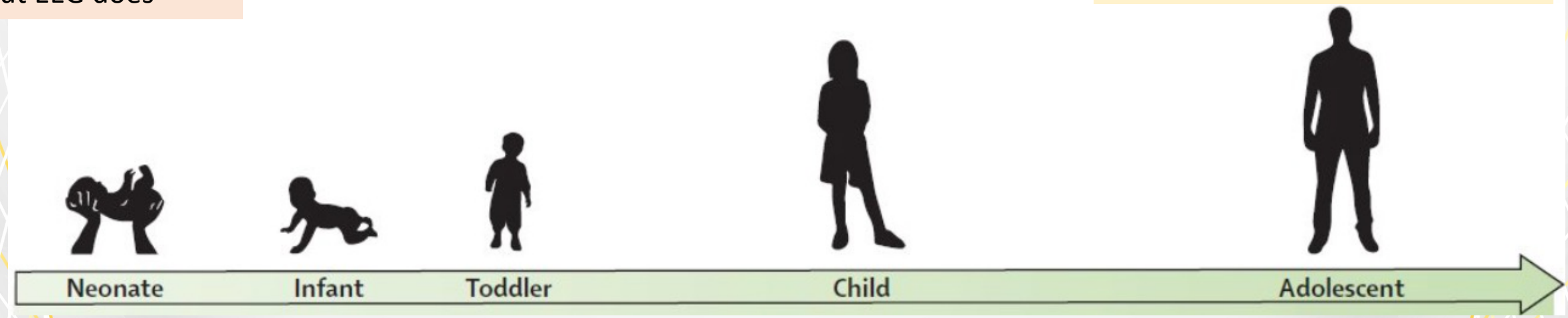
Pragmatic Selection of ASMs Across Ages
(Personal Opinion)

Sz type(s) do not matter
But EEG does

Epileptic spams or not
Difficult to use PHT

Absence Sz or not
HLAB*1502 for focal Sz

Gen Sz (absence/myoclonic/GTC) vs Focal Sz (HLAB*1502)
Gender



Option 1: PB
Option 2: PHT, LEV

Epileptic spasms (ES)
Option 1: VGB, Pred
Non-ES
Option 1: PB, VPA, LEV

Absence Sz
Option 1: VPA
Gen/undetermined onset Sz
Option 1: VPA
Focal Sz
Option 1: PHT, CBZ, VPA

Gen/undetermined onset Sz
Male option 1: VPA
Female option 1: LEV, LTG, BDZ, VPA
Focal Sz
Option 1: PHT, CBZ, VPA

Take Home Messages

- Evidence is available about comparative efficacy and safety of ASMs
- Inappropriate drug choice can adversely affect comorbidities and diminish the efficacy of other drugs
- Pragmatic ASM selection depends not only on seizure type(s), but also on other patient-specific factors
- No fixed rules when selecting a medication (patient-tailored drug selection)