Anti-seizure Medications in Children: Optimizing Efficacy and Minimizing Side Effects

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EPILEPSY ACROSS THE LIFESPAN: TAILORING TREATMENT FROM CHILDHOOD TO ELDERLY

31 Thursday July 2025 – 1 Friday August 2025 | ห้องประชุม Amoma Grand Ballroom ชั้น 3 โรงแรมอโนมา แกรนด์ กรุงเทพฯ

THURSDAY 31 July 2025

08.30-08.40 **Opening Remark**
รศ.พญ.กนกวรรณ บุญญพิสิฐ์

08.40-09.50 **Episode 1: How do the Experts Think and Do?** (Round-Table Discussion)
- *Case Vignette 1:*
  - รศ.พญ.กนกวรรณ บุญญพิสิฐ์
  - อ.พญ.ฐาปนี สนธุรถ์
  - อ.พญ.ศศิพร ภาศิลีย
- *Case Vignette 2:*
  - ผศ.พญ.กมรวรรณ กลิญกูวงศ์
  - รศ.นพ.เอียยศ ศองศิธรรม
  - อ.พญ.กษมา พุกธิสวัสดิ์

09.50-10.20 **Epilepsy Syndromes in Children: Understanding Developmental and Genetic Factors**
ผศ.นพ.มงคล ชาญวณิชตระกูล

10.20-10.35 Break

10.35-11.05 **Epilepsy in Adults: Risk Factors and Disease Progression**
รศ.นพ.อธิวัฒน์ สุนทรเมินธ์

11.05-11.35 **Epilepsy and Neurodevelopmental Disorders: Identifying and Managing Comorbidities**
อ.พญ.สาธิตา พูนภากสกิตย์

11.35-11.50 Break

11.50-12.50 **Symposium: Embracing a New Chapter of Refractory Epilepsy Management for Emergency Case (Abbott®)**
Speaker: รศ.ศร.ภญ.จุฑามณี สุทธิสิลิงย์
Moderator: พ.อ.หญิง รศ.ภิรดี สุวรรณภักดี

12.50-13.30 Break (Lunchtime)
Epilepsy Society of Thailand Meeting

13.30-14.30 **Symposium: Time-tested and Trusted: A Legacy of Efficacy in Epilepsy Management (Viatris®)**
Speaker: พ.อ.พญ.แกสิร สิกธิบานสุวรรณ
พศ.พญ.กมรวรรณ กลิญกูวงศ์

14.30-15.00 **Epilepsy in the Elderly: Clinical Features and Special Considerations**
อ.นพ.ศรัทธาวุธ วงษ์เวียงจันทร์

15.00-15.30 **Anti-seizure Medication in Children: Optimizing Efficacy and Minimizing Side Effects**
ผศ.พญ.กมรวรรณ กลิญกูวงศ์

15.30-16.00 **Treatment of Epilepsy in Older Adults: Balancing Efficacy and Polypharmacy**
พ.อ.พญ.แกสิร สิกธิบานสุวรรณ

FRIDAY 1 August 2025

08.30-09.00 **Epilepsy Highlights**
ศ.นพ.ศาติพงษ์ ปราบพาล

09.00-10.00 **Episode 2: How do the Experts Think and Do?** (Round-Table Discussion)
- *Case Vignette 1:*
  - รศ.พญ.สิลสิยา ธรรมประภาพกุล
  - อ.พญ.สุดา จิรสกุลเดช
  - พญ.วิธญาภรณ์ เอมราช
- *Case Vignette 2:*
  - อ.นพ.พีรสิทธิ์ ศรีสุทธาทิพ
  - อ.พญ.กฤติมา อัศวชีระเดช
  - อ.นพ.ศรัทธ์ธร ปิ่นจริญกุล

10.00-10.30 **Emerging Technologies in Epilepsy Care Across the Lifespan**
รศ.ศร.นพ.ภูษิทศ์ ลิ้มเกียง

10.30-10.45 Break

10.45-11.15 **Epilepsy Surgery in Pediatric Populations: When, Why, and How**
พ.อ.หญิง รศ.ภิรดี สุวรรณภักดี

11.15-12.15 **Symposium: Early Maximizing to Use of ASM in Across the Ages Patients Group (GSK®)**
Speaker: รศ.ศร.นพ.ภูษิทศ์ ลิ้มเกียง
พ.อ.หญิง รศ.ภิรดี สุวรรณภักดี
Moderator: ผศ.พญ.กมรวรรณ กลิญกูวงศ์

12.15-12.45 Break (Lunchtime)

12.45-13.45 **Symposium: Everyday Clinical Challenges: ASM Selection in Epilepsy Patients with Common Comorbidities (Eisai®)**
Speaker: อ.นพ.พีรสิทธิ์ ศรีสุทธาทิพ
Moderator: อ.นพ.ศรัทธาวุธ วงษ์เวียงจันทร์

13.45-14.15 **Stroke-Related Epilepsy in Adults and Elderly: Prevention and Treatment**
อ.พญ.วิมนิษา วงษ์พิพิธน์พงษ์

14.15-14.45 **Reproductive Health and Epilepsy in Women and Adolescents**
รศ.พญ.กนกวรรณ บุญญพิสิฐ์

14.45-15.00 Break

15.00-15.30 **Surgical Treatment for Drug-Resistant Epilepsy: Resection or Neuromodulation**
ผศ.อ.นพ.สิรรุจน์ สกุลณะบรรหาร

15.30-16.00 **Autoimmune Epilepsy and Immune-mediated Epilepsy: An Update**
อ.นพ.นธา อภิวัฒนกุล

Outline

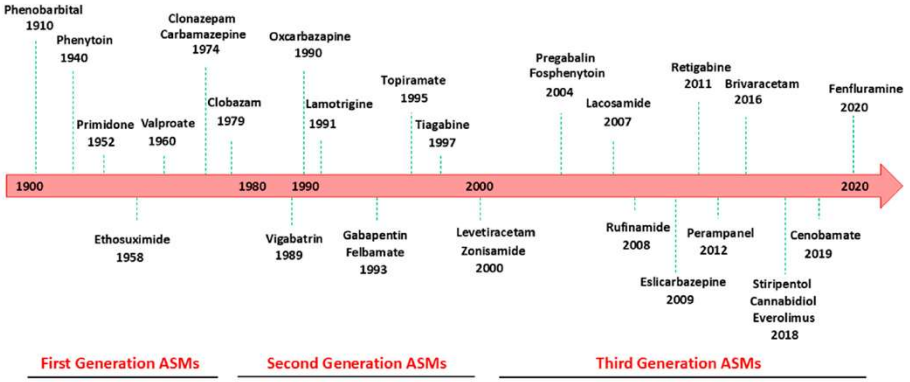
- ASMs preparation for children
- Factors affecting efficacy
- Enhanced efficacy ASMs
- Side effect of ASMs

↑ Efficacy and
↓Side Effect

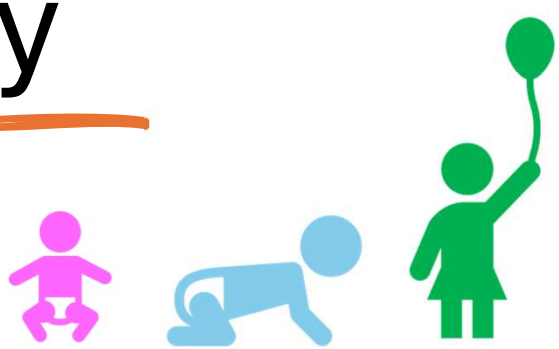
Variables that affect a specific ASMs

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

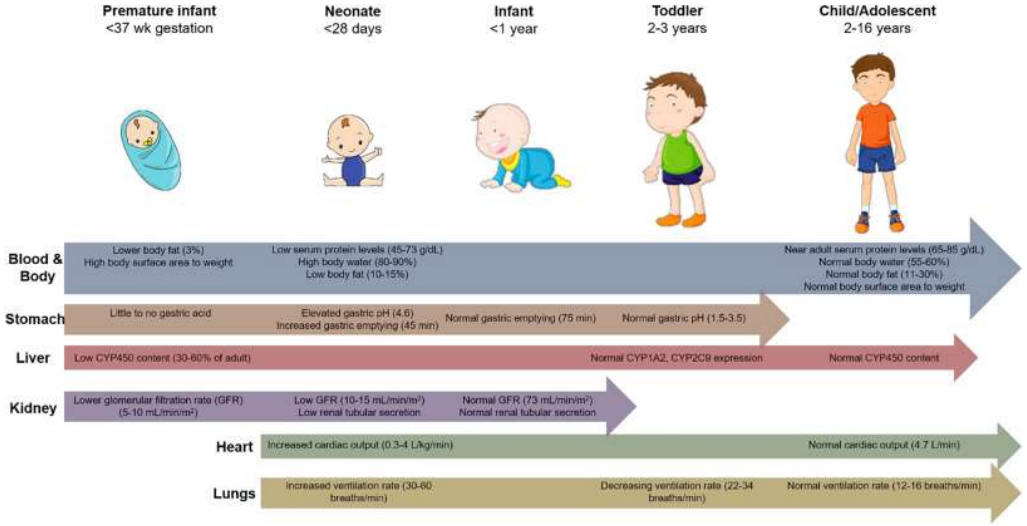

Phenobarbital 1910
Phenytoin 1940
Primidone 1952
Ethosuximide 1958
Valproate 1960
Clonazepam Carbamazepine 1974
Clobazam 1979
Oxcarbazapine 1990
Lamotrigine 1991
Vigabatrin 1989
Gabapentin Felbamate 1993
Topiramate 1995
Tiagabine 1997
Levetiracetam Zonisamide 2000
Pregabalin Fosphenytoin 2004
Lacosamide 2007
Rufinamide 2008
Eslicarbazepine 2009
Retigabine 2011
Perampanel 2012
Brivaracetam 2016
Stiripentol Cannabidiol Everolimus 2018
Cenobamate 2019
Fenfluramine 2020
1900
1980
1990
2000
2020
First Generation ASMs
Second Generation ASMs
Third Generation ASMs

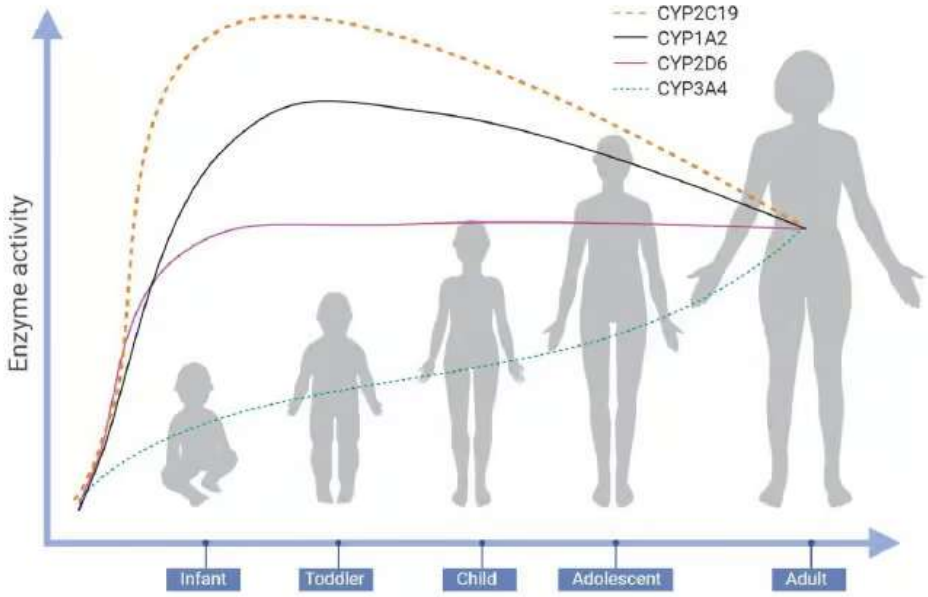
↑Efficacy



Factor Affecting Efficacy of ASMs in Children

- pharmacokinetics and *pharmacodynamics*:





Pharmaceutical Preparation

Route of administration

1. **Oral route**: tablet, capsule, granule, syrup, elixir, suspension, solution, emulsion, powder, lozenge
2. **Parenteral route**: injection (IV, IM, SC), infusion

3. Topical/transdermal route: cream, ointment, lotion, gel, patch
4. Inhalation route: inhaler, nebulizer solution
5. Rectal/vaginal route: suppository, enema, vaginal tablet
6. Ophthalmic/otic/nasal route: eye drops, ear drops, nasal spray/drops

Pharmaceutical Preparation

Physical form

1. **Solid dosage** forms: tablet, capsule, powder, granule
2. **Liquid dosage** forms: syrups, elixir, suspension, emulsion, solution
3. Semisolid dosage forms: cream, ointment, gel
4. Gaseous dosage forms: inhalers, aerosol

💧 Liquid Suspensions

- Biphasic liquids with dispersed drug particles
- Easy dosing for children or dysphagia
- Shake before use to ensure consistency
- Example: PER *suspension,* CBZ *suspension*

💊 Film-coated

- Protect drug from humidity and oxidation
- Improves patient compliance by masking taste
- May allow for modified-release properties
- Example: LEV, LTG, VPA, LCM

✨ Sprinkles / Sachets

- Granules/powders added to soft food
- Flexible for swallowing challenges
- Example: TPM *Sprinkles*

🧂 Powder in Capsule

- Drug powder in gelatin/HPMC capsules
- Capsules can be opened and sprinkled
- Allows modified dosing and release

🍸 Elixir (uniform throughout)

- Contains **alcohol** (often 10–20%), No shaking needed
- More palatable due to sweeteners and flavoring

🍸 Solution (uniform throughout)

- No alcohol
- Example: LEV, VPA

🍓 Chewable Tablets

- Designed to be chewed, then swallowed
- Flavored to enhance palatability
- Suitable for pediatric use
- Example: PHT infatab

💊 Orally Dissolving Tablets (ODTs)

- Dissolve rapidly in the mouth without water
- Convenient in emergencies or for dysphagia
- Examples: *Clonazepam ODT*, *Lamotrigine ODT*

Dosage Form	Appearance	Drug Solubility	Alcohol	Sweetness	Viscosity	Use Cases	Notes
Syrup	Thick, clear/opaque	Dissolved	None	High	Thick	Pediatric use, taste masking	May contain sugar, sorbitol, flavors
Elixir	Clear liquid	Dissolved	**Yes** (~10–20%)	Moderate	Low–moderate	Adult meds, sedatives	Not suitable for children
Solution	Clear, watery liquid	Fully dissolved	None	Varies	Low	Fast-acting meds (e.g. Depakine TH)	No particles; true solution
Suspension	Cloudy/opaque liquid	Not dissolved (dispersed)	None	Often sweetened	Moderate–thick	Poorly soluble drugs, pediatric dosing	Shake well before use

LEV, VPA

CBZ, PER

Tablet Medication

Formulation	Key Benefits	Challenges in Pediatrics
IR (Immediate) **LEV, LTG, TPM**	Flexible dosing, titration, *available in liquids*	Requires frequent dosing, peaks/troughs may cause side effects
SR/ER (Sustained/Extended) **PHT (100)**	Reduced dosing frequency, improved adherence	Hard to swallow, not suitable for splitting/crushing
CR (Controlled) **VPA (500), CBZ CR (200)**	Precise plasma control, fewer side effects	Limited availability, rarely used in children

Feature	Sustained Release (SR)	Controlled Release (CR)
Goal	Prolong drug action over time	Maintain consistent drug levels over time
Release Rate	Slower than immediate release, but may vary	Designed for a constant, predictable release rate
Kinetics	Often follows first-order kinetics	Typically follows zero-order kinetics
Plasma Concentration	May show fluctuations (peaks and troughs)	Aims for steady-state concentration
Formulation Complexity	Generally simpler (e.g. matrix tablets)	More complex (e.g. osmotic pumps, reservoir systems)
Examples	SR tablets that dissolve slowly	CR systems like transdermal patches or osmotic-release tablets

e.g. PHT kapseal (SR)
PHT capsule (ER)

e.g Depakine CR (500)
Tegretal CR

Best Practices for Taking Tablets

- If scored line present: designed to be split
- Release type: Immediate-release may be split if scored

- Tablet integrity: splitting may damage the coating, affecting taste, absorption and drug stability

- Drug with a narrow therapeutic window (PHT, CBZ): uneven splitting can be dangerous

- Film-coated, immediate release: can be split if needed e.g. LEV, LTG
- Film-coated, controlled release: should not be split e.g. VPA CR (500)

Food & Drink and ASMs

- Most ASMs can be take with or without food, no significant food effect, can be taken anytime

- Taking with food may reduce GI upset
- CBZ CR: preferably with food: improve absorption and reduce GI irritation
- OXC: with or without food: food may help reduce dizziness/nausea

- Presence of food may slow absorption
- PHT: avoid high fat meals: fat delays absorption and ↓bioavailability

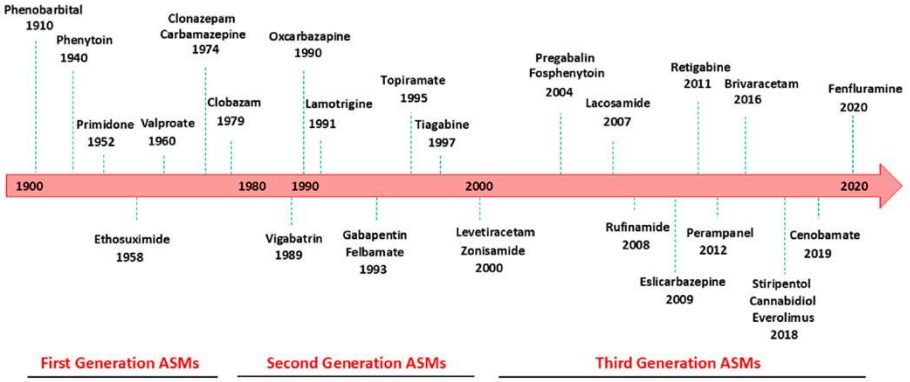
Milk & Juice and ASMs

- Most ASMs can be take with milk e.g. VPA, LEV, TPM, PER
- Caution with PHT and CBZ: high calcium in milk may bind the drug and reduce absorption

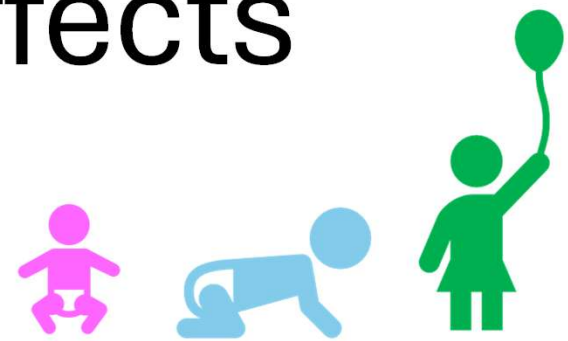
- Grapefruit juice (pomegranate juice): high risk, enz inhibitor CYP 3A4, ↑ level of CBZ, PER
- Orange juice: mild risk, may affect absorption
- Apple juice: safe, no significant interaction with ASMs

Crushing Multiple ASMs Together

- Unpredictable pK: erratic plasma level
- DDI: CYP inhibitor/inducer: amplify adverse effects or reduce efficacy
- Formulation damage
- Stability concerns: some ASMs degrade quickly in water and may change therapeutic effect
- Taste and adherence: bitter and reduce compliance
- **Safer choice:** administer separately



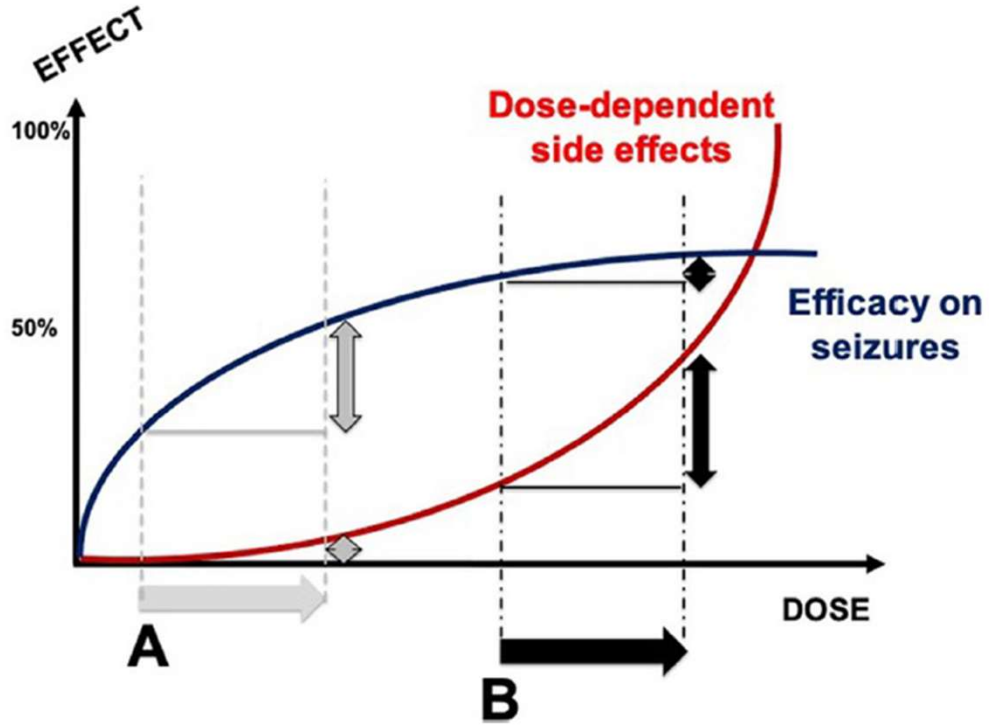
↓Side Effects



Minimize ASM side effects in children

1. Start low, go slow
2. Choose right ASM for seizure type
3. **Monitor for early warning signs**
4. Optimize formulation and dosing schedule
5. Avoid poly ASMs to reduce DDI. If combine **choose different MOA**
6. Regular lab monitoring
7. Adjust dose based on weight changes
8. **Educate** caregivers: safe administration, consistent dosing times
9. Behavioral and cognitive support
10. Switching or discontinuing ASMs

Efficacy and Side Effect Risk



Dev Med Child Neurol. 2022;64:1444–1452

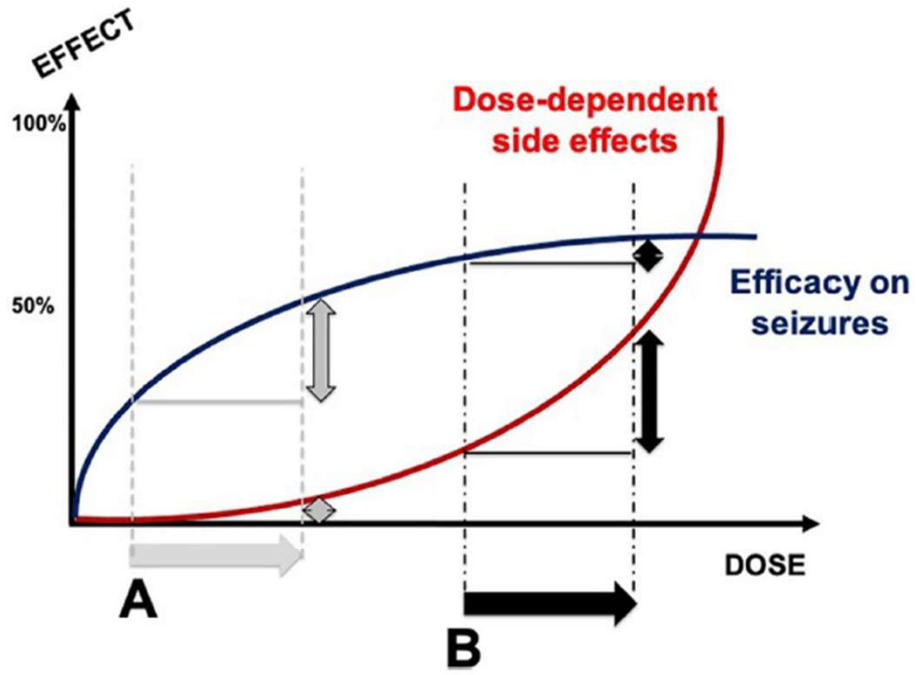


FIGURE 1 Efficacy and side effect risk of antiseizure medication (ASM). The relationship between the amount of prescribed drug and the effect of the expected efficacy (blue curve) and the expected side effect risk (red curve) are shown. An increase in the prescribed amount resulted in a change in the frequency of seizures, which then reached a plateau (blue curve). 'A' indicates an increase in the amount of ASM (grey arrow), which results in a significant increase in efficacy with a small increase in side effects (grey double arrows). 'B' indicates an increase in the amount of ASM (black arrow) that does not change efficacy but results in an important increase in side effects (black double arrows).

Early onset AEs

Adverse effect	CBZ	CLB	ESL	ETS	FBM	GBP	LCM	LEV	LTG	OXC	PGN	PER	PHB	PHT	TGB	RTG	TPM	VPA	VGB	ZNS
EARLY ONSET ADVERSE EVENTS																				
Somnolence	–	🔴	🟡	🟡	–	🟡	🟡	🟡	🟡	–	🟡	–	🔴	–	🔴	🟡	🔴	–	🟡	🔴
Dizziness	–	🔴	–	🟡	–	🟡	🟡	🟡	🟡	🔴	–	–	–	🔴	🔴	–	🔴	–	🟡	🟡
Seizure aggravation	🟡	🟡	🟡	–	–	🟡	–	–	–	–	🟡	–	–	🟡	🟡	–	–	–	🔴	
Gastrointestinal	🟡	–	–	🔴	🟡	🟢	–	🟢	–	🟡	–	–	–	–	–	–	–	🟡	–	🟡
Hypersensitivity (SJS/TEN)	🟡	–	🟡	🟡	🟡	–	–	–	🟡	🟡	–	–	🟡	🟡	–	–	🟡	–	–	🟡
Rash	🟡	–	–	–	–	–	–	–	🟡	🟡	–	–	–	🟡	–	–	–	–	–	–

🟢 Low risk
🟡 Medium risk
🔴 High risk

BMJ 2014;348:g2546

Skin Rash and ASMs

Rash onset
Fever
Histological finding
CBC, LFT
Organ involvement

- Rash
  - Drug eruption
    - SJS/TEN
    - DRESS
    - AGEP
    - Fixed drug eruption
  - Infectious diseases
  - Autoimmune disease
  - Others

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

- A spectrum of epidermal necrolysis, mucocutaneous blistering and sloughing
- Usually occur 1–3 weeks after drug exposure and are.
- **SJS**: <10% BSA detachment
- **SJS/TEN** overlap: 10–30% BSA detachment
- **TEN**: >30% BSA detachment
- Mortality ranges from 5% in SJS to >30% in TEN

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

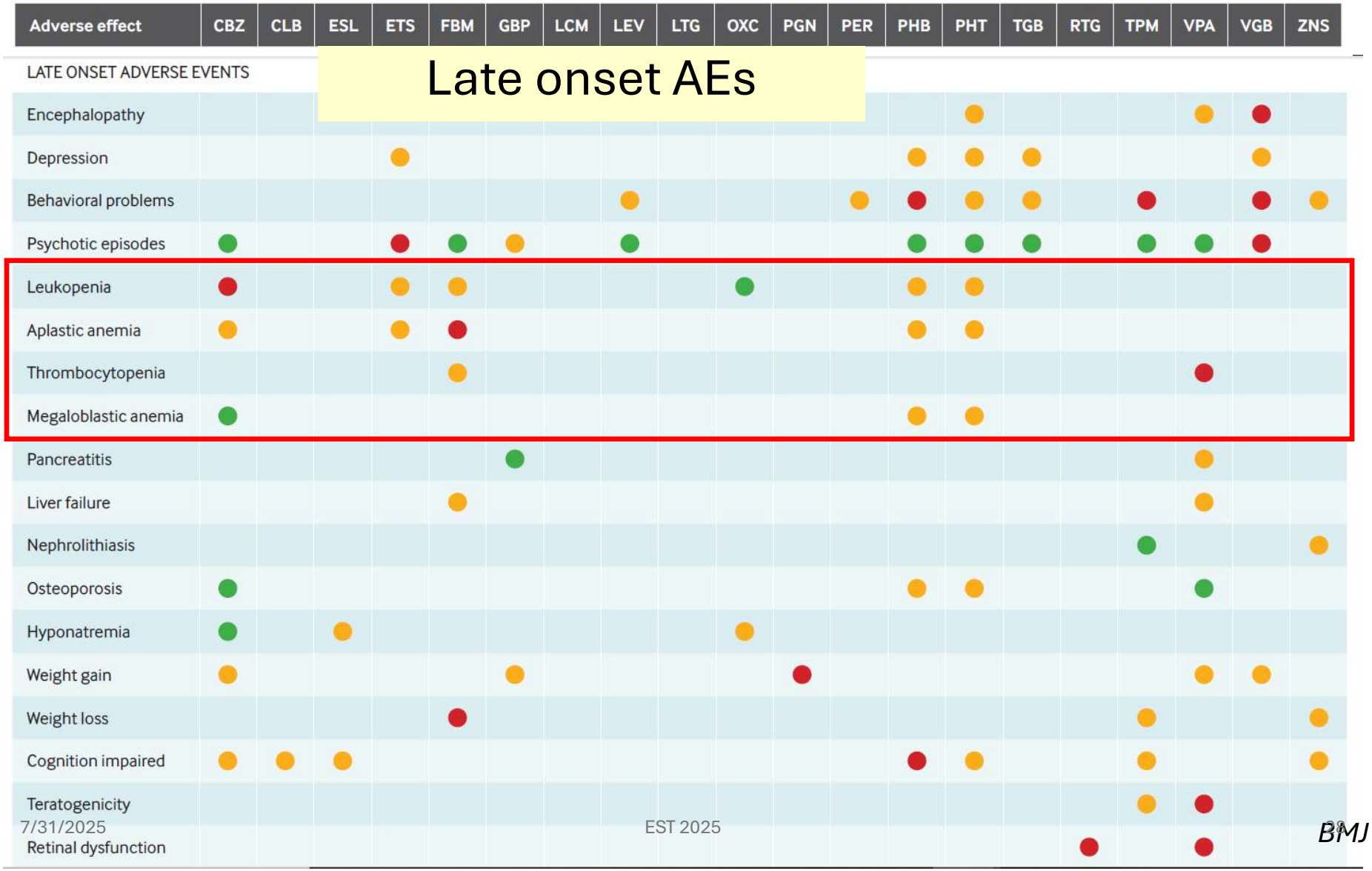
- delayed hypersensitivity reaction, typically appearing in 2–8 weeks

Key features:

- Fever, rash, and facial edema
- Lymphadenopathy
- Eosinophilia and atypical lymphocytosis
- Internal organ involvement (liver, kidneys, lungs, heart, pancreas)
- Mortality up to 10% if unrecognized

Feature	SJS/TEN	DRESS	Morbilliform Exanthem	AGEP	Fixed Drug Eruption
Onset Timing	1–3 weeks	2–6 weeks	4–14 days	1–4 days	Hours to days (faster on re-exposure)
Lesion Location	Mucosa, face, trunk, limbs	Widespread	Widespread trunk and limbs	Face, folds → trunk, limbs	Same site(s) each time (hands, lips, genitals)
Morphology	Targetoid lesions, bullae, epidermal detachment	Morbilliform ± facial edema, lymphadenopathy	Maculopapular rash	Pinhead pustules on erythematous base	Round/oval erythematous patches ± blisters
Systemic Symptoms	Severe mucosal involvement, systemic toxicity	Fever, eosinophilia, organ involvement	Mild fever occasionally	Fever, neutrophilia	None or mild
Recurrence Pattern	Rare recurrence	Possible recurrence	No fixed location	Rare recurrence unless re-exposed	Same site with each exposure
Resolution	Weeks to months, high morbidity	Prolonged course	Resolves in days after drug withdrawal	Resolves in 1–2 weeks	Days to weeks, leaves hyperpigmentation

Late onset AEs



Adverse effect	CBZ	CLB	ESL	ETS	FBM	GBP	LCM	LEV	LTG	OXC	PGN	PER	PHB	PHT	TGB	RTG	TPM	VPA	VGB	ZNS
LATE ONSET ADVERSE EVENTS																				
Encephalopathy														●				●	●	
Depression				●									●	●	●				●	
Behavioral problems								●				●	●	●	●		●		●	●
Psychotic episodes	●			●	●	●		●					●	●	●		●	●	●	
Leukopenia	●			●	●					●			●	●						
Aplastic anemia	●			●	●								●	●						
Thrombocytopenia					●													●		
Megaloblastic anemia	●												●	●						
Pancreatitis						●												●		
Liver failure					●													●		
Nephrolithiasis																	●			●
Osteoporosis	●												●	●				●		
Hyponatremia	●		●							●										
Weight gain	●					●					●							●	●	
Weight loss					●												●			●
Cognition impaired	●	●	●										●	●			●			●
Teratogenicity																	●	●		
Retinal dysfunction																●		●		

BMJ 2014

Recommended Lab Monitoring for ASMs in Children

- Initial monitoring: Baseline CBC, LFT, *Electrolytes, renal function, ammonia*
- Ongoing monitoring: depend on ASM
- Drug level: trough level (just before the next dose)
- Special populations may need frequent monitoring: infant, poly Rx, hepatic/renal failure
- New symptoms always check lab: fatigue, bleeding, rash, vomiting, behaviour change

- *VPA: q 3-6 months*
- *CBZ: q 6 months*
- *PHT, PB, TPM, ZNS: q 6-12 months*
- *LEV, LTG: clinical monitoring*

Thank You for Your Attention