OPTIMAL USE OF OLD AND NEW AEDS

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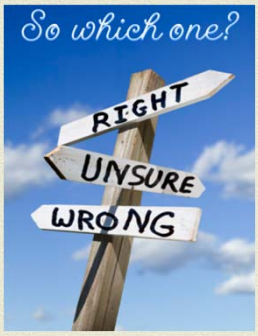
Old vs New AEDs



Ideal characteristics for AEDs

Efficacy เหมาะสม ,ชอบ	• broad **spectrum of indication** • rapid clinical improvement • sustained efficacy • lack of paradoxical effect
Tolerability ใช่ สบายใจ	• high therapeutic index • not teratogenic • few acute SE • rare idiosyncratic SE • rare serious or annoying chronic SE
Ease of use ง่าย เข้ากัน	• once/twice daily dosing • linear pharmacokinetic • no drug-drug interaction • no relevant metabolism • major route of excretion renal • no titration to lowest effective dos • no relevant protein binding

ลด Freq, severity

SE

Cost !!

Special issue in children

- **Absorption**: erratic absorption of PHT and PB in neonates
- **Distribution**: Vd of PB, PHT is larger in neonates than in older infants and children, need larger loading dose but similar loading doses of LZP, DZP
- **Elimination**: Birth; renal function ~25-30%
  6 mo; renal function ~50-75%
  2-3 yrs; full maturation

Doses of drugs …excreted predominantly unchanges by kidney…need to be reduced for neonates and infants

Special issue in children

- CYP: Birth; ~50-70% of adult level
  : 2-3 yrs; exceed than adult level
  : puberty; similar to adult level
- CYP3A4 : CBZ
- UGT: low level in neonate an reach adult level at age 3-4 years

TABLE 1. *Age effects on pharmacokinetic parameters (compared with adult values)*

	Neonates/Infant	Children	Adults
Renal	⇓	⇔	⇔
Metabolism			
CYP	⇓	⇑	⇔
UGT	⇓	⇔	⇔
Albumin	⇓	⇔	⇔

CYP, cytochrome P450; UGT, uridine diphosphate, glucuronosyl transferase.

Epilepsia 2002;43:53-59

Special issue in children

4. ในเด็กอาจจำเป็นต้องใช้ยากันชักในขนาดที่สูงกว่าเมื่อเทียบเป็น mg/kg/day และต้องให้ยาถี่กว่าในผู้ใหญ่เพราะ
   - บทบาทของ cytochrome P450 ซึ่งจะเกี่ยวกับ drug metabolism เช่น CYP 2C9, CYP 2C19 นั้น จะสมบูรณ์เหมือนผู้ใหญ่เพียงไม่กี่สัปดาห์หลังคลอดและการทำงานของ enzyme นี้จะยิ่งมากขึ้นเมื่อเป็นวัยทารกและเด็กเล็ก ก่อนที่จะลดลงเท่ากับระดับผู้ใหญ่เมื่อเข้าวัยรุ่น ดังนั้นการให้ขนาดของยากันชักในเด็กเล็กจึงต้องมากกว่าผู้ใหญ่
   - ในเด็กจะมี ค่าครึ่งชีวิต (T 1/2) ที่สั้นกว่าในผู้ใหญ่ในยาบางตัวเช่น carbamazepine และ phenytoin ดังนั้นควรให้ยาหลายครั้งต่อวันมากกว่าที่จะให้ยาเพียงครั้งเดียว
   - วัยเด็กเล็กจนถึงวัยรุ่น CYP 3A4 จะมี activity ที่สูงกว่าผู้ใหญ่ ทำให้ carbamazepine ถูกขจัด ออกได้ไวกว่า จึงสามารถให้ carbamazepine ได้มากถึง 3 ครั้งต่อวันในผู้ป่วยเด็ก

Half-life

- Preterm, full-term neonates tend to have 3-9 times longer half-life than adult.
- Difference disappears by 2-6 months.
- Beyond 6 mo, half-life can be shorter than adult in specific drugs and pathway

13 yrs old girl

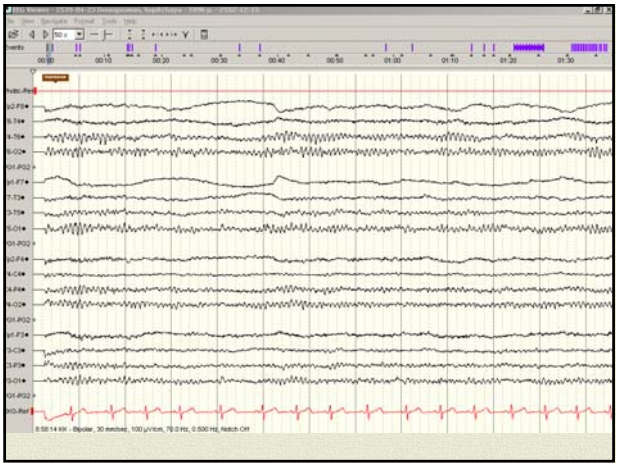
Case

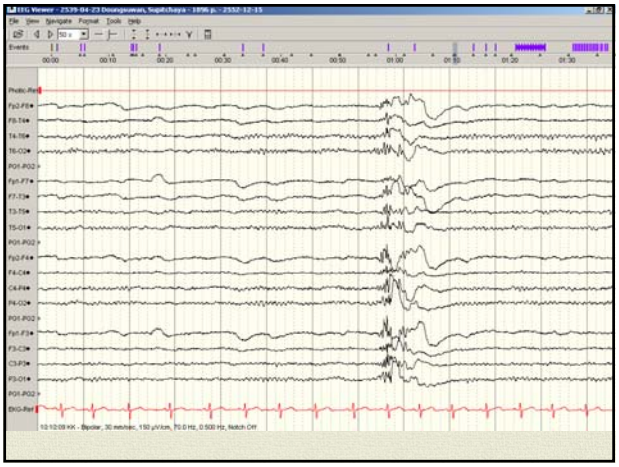
- Intermittent limbs shaking in the past 2 months
- Often occurs in the morning but also seen at other times

13 yrs old girl

Case

- Intermittent limbs shaking in the past 2 months
- Often occurs in the morning but also seen at other times
- Recently, had one episode of GTC





What would be your AED selection ?

A. Depakine
B. Phenytoin
C. Topiramate
D. Lamotrigine
E. Levetiracetam

old

New

What is your diagnosis ?

A. Non-epileptic seizures
B. Simple partial seizure
C. Juvenile myoclonic epilepsy
D. Partial with secondarily generalized seizure
E. Epilepsy with grand mal seizure upon awakening

Efficacy

- Seizure type and epileptic syndrome

Sz/AED	VPA	LTG	TPM	LEV
Myoclonic	✓	✓?	✓	✓
GTC	✓	✓	✓	✓
Absence	✓	✓	✓	✓

Table 4. Comparison of recommendations for the treatment of pediatric epilepsy.

Seizure type or epilepsy syndrome	U.S. pediatric expert consensus survey[a,b]	European pediatric expert consensus survey[b]	ILAE[c]	SIGN[d]	NICE[e]	French study[f]	FDA approved[g]
Partial-onset	OXC, CBZ	OXC, CBZ	A: OXC; B: none C: CBZ, PB, PHT TPM, VPA	PHT, VPA, CBZ, LTG, TPM, OXC, VGB, CLB	CBZ,VPA, LTG, OXC, TPM	OXC, CBZ, LTG (adult males)	PB, PHT, CBZ, OXC, TPM
BECT	OXC, CBZ	VPA	A, B: none C: CBZ, VPA	Not specifically mentioned	CBZ, OXC, LTG, VPA	Not surveyed	None
Childhood absence epilepsy	ESM	VPA	A, B: none C: ESM, LTG, VPA	VPA, ESM, LTG	VPA, ESM, LTG	VPA, LTG	ESM, VPA
Juvenile myoclonic epilepsy (JME)	VPA, LTG	VPA	A, B, C: none	VPA, LTG, TPM	VPA, LTG	VPA, LTG	TPM, LTG, LEV
Lennox-Gastaut syndrome	VPA, TPM	VPA	Not reviewed	Not specifically mentioned	LTG, VPA, TPM	Not surveyed	FLB, TPM, LTG
Infantile spasms	VGB, ACTH	VGB	Not reviewed	Not specifically mentioned	VGB, corticosteroids	Not surveyed	None

Epileptic disorder 2001

Table 4. Comparison of recommendations for the treatment of pediatric epilepsy.

ILAE2006: Class IV : CZP,LTG,LEV,TPM,VPA,ZNS

ILAE 2013: Level D : TPM, VPA

Epileptic disorder 2001

What's the chance to have good seizure control in this patient?

A. 60%
B. 70%
C. 80%
D. 90%
E. 100%

The main reason for Rx JME with other AEDS than VPA

- The occurrence of side effects
  - Tremor
  - Weight gain
  - Loss of hair
- Pregnancy

14 yrs old

Continued Case

- Patient was given with VPA
- Titrate to 1,000 mg/day
- Good seizure control
- One year later…the patient is pregnant

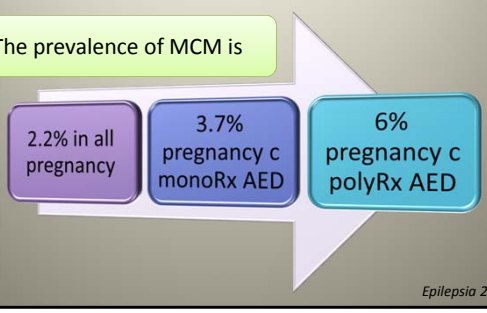
Intrauterine exposure to AED increases risk of congenital malformations

- MCMs = structural abnormalities with surgical, medical or cosmetic importance.
- Minor malformation, facial dysmorphism, were not considered in statistic analysis

Epilepsia 2009

Intrauterine exposure to AED increases risk of major congenital malformations

The prevalence of MCM is



Epilepsia 2009

1

AED regimens with relatively high teratogenicity

- **VPA**> 1,000 mg/day (some > 1,500)
- PB > 200 mg/day
- CBZ + VPA
- CBZ+ VPA+ PB+/- PHT
- PB+ PHT + primidone
- Benzodiazepines + other AEDs
- Caffeine + PB+/- other AEDs

Samren et al, Battino et al, Lindout et al, Dansky

2

AED regimens with relatively high teratogenicity

- Greater malformation in VPA> 1,500 mg/day
- No association between epilepsy type or GTC in the 1st trimester and a greater risk of major congenital malformation
- LTG> 200 mg/day in UK study but not others

Lancet Neurol 2011

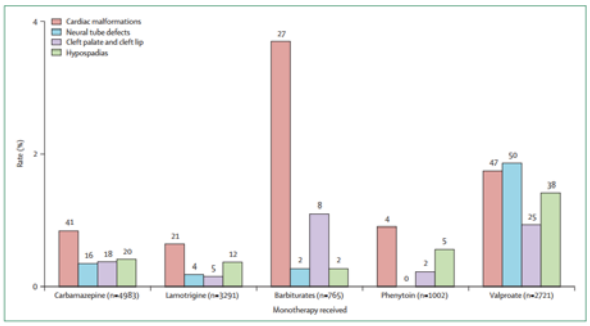


Figure 2: Rates of some specific major congenital malformations associated with exposure to monotherapy with antiepileptic drugs
The number of fetuses with specific malformations are shown on top of the bars. The figure is based on combined data from 21 prospective studies.

Lancet Neurol 2012;11:803-13

Neural tube defects: risk factors

Medical	Non medical
• Prior NTD • Partner with NTD • Close relative with NTD • DM type 1 • AED: VPA, CBZ • Pre-pregnancy obesity> 110 kg	• Chemicals and pesticides • Cleansing solvents and disinfectants • Radiation • Anesthetic agents • Hot tubs, Saunas, Fever • Lead • Tobacco smoke

Intrauterine exposure to AED reduces cognitive outcome

Recommendation to reduce risk of poor cognitive outcomes
Cognitive risk related to AED exposure may be present throughout pregnancy
Level B: MonoRx should be considered in place of polyRx
Level B: Avoiding VPA should be considered
Level C: Avoiding PHT, PB may be considered

Epilepsia 2009

11 yrs old boy

case

- F/U epilepsy case in OPD
- Underlying PDD, VSD
- Good seizure control in the past 6 months
- The mother asks about gum hypertrophy

11 yrs old

case

- Underlying PDD, hyperactive child, VSD
- Epilepsy starts at age 5 years old
- Sz: body stiffening and left sided jerking, often seen in sleep, 2-4 times/day
- EEG: Rt T sharp/slow wave
  : B-TP/CP spike/slow wave
- 1st MRI : negative

2009

Which AEDs would be your choice?

A. Phenytoin
B. Carbamazepine
C. Depakine
D. Topiramate
E. Levetiracetam

Sz: body stiffening and left sided jerking, often seen in sleep, 2-4 times/day

Treatment of new onset epilepsy

Before 2004 | Current

Drugs	Newly diagnosed MonoRx Partial sz	Newly diagnosed MonoRx Partial sz
Gabapentin	No	No
Lamotrigine	Yes	Yes
Topiramate	Yes	Yes
Tiagabine	No	No
Oxcarbazepine	Yes	Yes
Levetiracetam	No	Yes
Zonisamide	No	No

Yes: Add on
Yes: Add on
Mono 16 yrs
Add 1 mo
Yes: Add on

2009

Which AEDs would be your 1st AED?

A. Phenytoin
B. Carbamazepine
C. Depakine
D. Topiramate
E. Levetiracetam

Sz: body stiffening and left sided jerking, often seen in sleep, 2-4 times/day

2009

After commenced on 1st AED

- No seizure improvement
- What should we do next ?

A. Switch to 2nd monotherapy
B. Add on 2nd AED

Add on 2nd AED

A. Phenytoin
B. Carbamazepine
C. Depakine
D. Phenobarbital
E. Levetiracetam

Add on 2nd AED

A. Phenytoin
B. Carbamazepine
C. Depakine
D. Phenobarbital
E. Levetiracetam

1

Gum hypertrophy, Gingival enlargement/overgrowth

Drug induced enlargement

: AEDs : PHT, 50%

: PB, LTG,VPA, VGB,ETX,TPX, primidone

: Cyclosporin 30%

: Ca channel blockers: amlodipine, nifedipine, verapamil 10-20%

2

Gum hypertrophy, Gingival enlargement/overgrowth

- Drug induced enlargement
- Inflammatory enlargement
- Enlargement associated with systemic factors/condition *(pregnancy, Vt C def, leukemia, neoplasm)*

Take home message: AED selection

1. Seizure type	• Clinical history, EEG, VEM • +/- imaging
2. Efficacy & Tolerability	• Mechanism • Indication/side effect
3. Mono or polyRx	• Indication • Basic science
4. Drug interaction	• With AEDs • With other medications