Optimal use of old and new AEDs

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Content

- Goal of epilepsy treatment
- Old AEDs versus new AEDs
- How to select AED
- Optimal use of old and new AEDs
  - Interactive session

Goal of epilepsy treatment

- Seizure-free
- No or acceptable side effects
- Reasonable cost
- Complying with (local) guideline

Ideal properties of AEDs

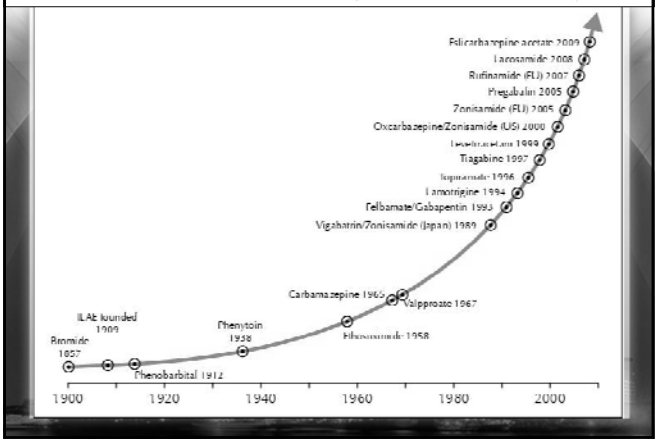
- Broad spectrum
- No risk of serious side effects
- Pharmacokinetic advantage
  - Linear kinetics
  - Fast and easy dose escalation rate
  - Half-life compatible with OD or BID dosing
  - Low drug interaction potential

Ideal properties of AEDs

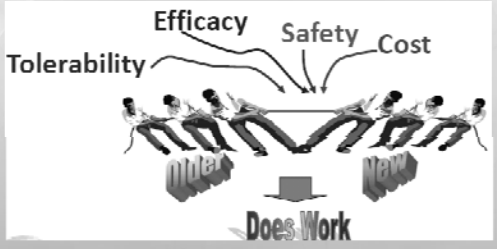
- No teratogenicity
- Low cost
- No need of intensive laboratory monitoring
- Availability of convenient formulations
  - including convenient paediatric dosage forms and parenteral formulation

Return Quality of Life

Timeline of AEDs development over 100 years



Older versus New AEDs



Quality of Life

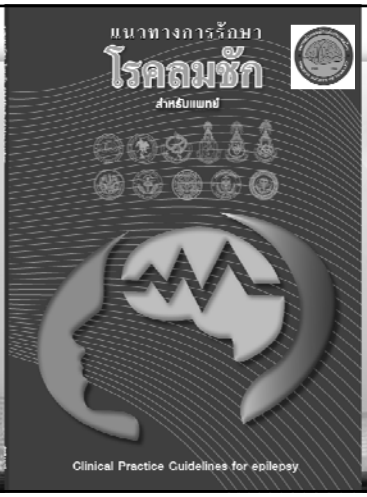
Principle of AED selection

- In era of new AEDs, selection of optimum therapy is more complex.
- However, **patient characteristics** can narrow the AED choices.

Key factors on optimal use of AEDs

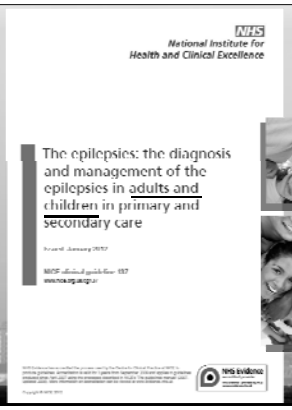
- Efficacy
- Side effect / Safety / tolerability
- Pharmacology
  - Initiation/dosage
  - Hepatic enzyme induction
  - Drug-drug interaction
- Co-morbidities
- Special groups

THAI Clinical Practice Guidelines for Epilepsy **2010**



NHS (UK) Epilepsy Guideline 2012 (NICE guideline)

NICE 2012



ครูหญิง อายุ 56 ปี

- 1 ปีก่อน หมดสติไม่ทราบสาเหตุ ไม่มีอาการเตือน 3 ครั้ง
- ตรวจร่างกายปกติ
- EEG :
  - Normal background activity
  - Localized sharp wave at left temporal lobe
- Normal CT scan of brain
- Dx: Localization-related epilepsy of unknown etiology

What is the optimal AED?

Old AED	New AED
a) Phenytoin	e) Topiramate
b) Carbamazepine	f) Lamotrigine
c) Phenobarbital	g) Levetiracetam
d) Sodium valproate	

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Take Home Message

- Overall new AEDs were proven not to be more efficacious than old AEDs in newly-diagnosed epilepsy.
- However, some epileptic patients fail to many old AEDs.

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Take home message

- Controlling seizures is one of the most important influences on quality of life (QOL).
- Some seizures have little impact on QOL.
- Some drug' adverse effects lower quality of life much more than seizures.
- **Therefore, therapy should aim at QOL, not only seizure control.**

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พนักงานไปรษณีย์ชาย อายุ **58** ปี

- มีอาการชัก complex partial seizure ตั้งแต่หลังเกิดอุบัติเหตุ right frontal lobe contusion and subdural hematoma
- ได้ยา phenytoin (100mg) 3 cap PO hs และ valproate (chrono 500 mg) 2 tab PO bid
- ยังมีอาการชักเดือนละ 2-3 ครั้ง
- 2 วันนี้ เป็นไข้หวัด เกิดอาการชักถี่มาก วันละ 5-6 ครั้ง ซึมๆ งงๆ โต้ตอบช้า

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พนักงานไปรษณีย์ชาย อายุ **58** ปี

- กินยากันชักสม่ำเสมอ
- รับประทาน paracetamol prn
- Dx :
  1. Common cold
  2. Symptomatic localization-related epilepsy
  3. Serial repetitive seizures

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What should be done? (ตอบได้มากกว่า **1** ข้อ)

a) Load IV phenytoin 15 mg/kg then 100 mg IV every 8 hr
b) Load IV valproate 20 mg/kg then 500 mg IV every 6 hr
c) Load IV phenobarbital 20 mg/kg then 60 mg IV every 12 hr
d) Load IV levetiracetam 1,500 mg then 500 mg IV every 6 hr
e) Taking oral levetiracetam with rapid titration

Take Home Message

- Patients remain at risk for another seizures until reaching therapeutic level
- Favorable AED
  - Initiation at therapeutic dose
  - Rapid titration
  - Linear relationships pharmacokinetics

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AEDs initiated at therapeutic dose (minimum effective dose)

- **Old AEDs**
  - Sodium valproate 500-750 mg/d
- **New AEDs**
  - Levetiracetam 250 mg, bid
    - If necessary, 500 mg, bid

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AEDs initiated at therapeutic dose (minimum effective dose)

- **Old AEDs**
  - Phenytoin : 3-5 mg/kg/d (300 mg/d)
  - Phenobarbital : grain 1 /d
- Despite of starting at therapeutic dose, steady state of serum drug level of phenytoin and phenobarbital need one week (5-half-life period).

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Rapid titration

Old AEDs	New AEDs
• Sodium valproate –If necessary, –250-500 mg/d –every few days	• Levetiracetam –If necessary, –500 mg/d –every day

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Hepatic enzyme induction

- Most of old generation AEDs strongly induce cytochrome P450 enzyme system.
- Most of new generation AED have no or minimal enzyme inducing effect.
- Many intrinsic substances such as vitamins and hormones are subjected to induced cytochrome P450 enzyme system.
- Several drugs including some AEDs are metabolized via cytochrome P450 enzyme system.

Perucca E. Br J Clin Pharmacol. 2006 March; 61(3): 246–255.

Old gen AED and CYP 450 enzyme system

Drug	Main route(s) of elimination	Main enzyme system involved
Carbamazepine	Oxidation	**CYP3A4** (active 10, 11-epoxide metabolite cleared by epoxide hydrolase)
Ethosuximide	Oxidation	**CYP3A4**
Phenobarbital	Oxidation + N-glucosidation (75% of the dose) and renal excretion (25%)	**CYP2C9** and **CYP2C19**
Phenytoin	Oxidation	**CYP2C9** and **CYP2C19**
Valproic acid	Oxidation (>50%) and glucuronide conjugation (30–40%)	Mitochondrial oxidases, **CYPs** and glucuronyl transferases

Perucca E. Br J Clin Pharmacol. 2006 March; 61(3): 246–255.

New gen AED and CYP 450 enzyme system

Drug	Main route(s) of elimination	Main enzyme system involved
Gabapentin	Renal excretion	None
Lamotrigine	Glucuronide conjugation	Glucuronyl transferase type 1A4
Levetiracetam	Renal excretion (75%) and hydrolysis (25%)	Hydrolase
Oxcarbazepine	Glucuronide conjugation (>50%) and renal excretion (<30%)	Glucuronyl transferases
Pregabalin	Renal excretion	None

Perucca E. Br J Clin Pharmacol. 2006 March; 61(3): 246–255.

New gen AED and CYP 450 enzyme system

Drug	Main route(s) of elimination	Main enzyme system involved
Zonisamide	Oxidation + reduction + N-acetylation (>50%) and renal excretion (30%)	**CYP3A4** and N-acetyl-transferases
Topiramate	Oxidation (20–60%) and renal excretion (40–80%)	Inducible **CYP** isoforms
S-Vigabatrin	Renal excretion	None
Tiagabine	Oxidation	**CYP3A4**
Felbamate	Oxidation (>50%) and renal excretion (>30%)	Inducible **CYP** isoforms

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Drug-drug interaction

- Better knowledge on pharmacology help to select proper AEDs particularly in patients who need polytherapy AEDs or polypharmacy.
- New generation AEDs have better pharmacokinetics such as lower or non protein binding property, no liver metabolism etc.

From: Br J Clin Pharmacol. 2006 March; 61(3): 246–255.
Published online 2006 October 27. doi: 10.1111/j.1365-2125.2005.02529.x

Perucca E. Br J Clin Pharmacol. 2006; 61(3): 246–255.

Table 2

Drugs which have been found to increase the serum concentration of antiepileptic drugs, presumably by inhibiting their metabolism

Affected drug		Interfering drug
Carbamazepine	*Antiepileptic drugs:*	Felbamate[1], valproic acid[1], valpromide[1]
	Antidepressants:	Fluoxetine, fluvoxamine, nefazodone, trazodone, viloxazine
	Antimicrobials:	Clarithromycin, erythromycin, fluconazole, isoniazid, ketoconazole, metronidazole, ritonavir, troleandomycin
	Miscellaneous:	Cimetidine, danazol, dextropropoxyphene, diltiazem, risperidone, quetiapine[2], ticlopidine, verapamil
Ethosuximide	*Antimicrobials:*	Isoniazid
Lamotrigine	*Antiepileptic drugs:*	Valproic acid
	Antidepressants:	Sertraline
Phenobarbital	*Antiepileptic drugs:*	Felbamate, phenytoin, sulthiame, valproic acid
	Antimicrobials:	Chloramphenicol
	Miscellaneous:	Dextropropoxyphene
Phenytoin	*Antiepileptic drugs:*	Felbamate, oxcarbazepine, sulthiame, valproic acid[2]
	Antidepressants:	Fluoxetine, fluvoxamine, imipramine, sertraline, trazodone, viloxazine
	Antimicrobials:	Chloramphenicol, fluconazole, isoniazid, miconazole, sulfaphenazole
	Antineoplastic drugs:	Doxifluridine, fluorouracil, tamoxifen, tegafur, UFT
	Miscellaneous:	Allopurinol, amiodarone, azapropazone, cimetidine, chlorpheniramine, dextropropoxyphene, diltiazem, disulfiram omeprazole, phenylbutazone, sulfinpyrazone tacrolimus, ticlopidine, tolbutamide
Valproic acid	*Antiepileptic drugs:*	Felbamate

Perucca E. Br J Clin Pharmacol. 2006 March; 61(3): 246–255.

Drugs that increase concentration of AEDs, presumably by inhibiting their metabolism

Ethosuximide	***Antimicrobials:***	**Isoniazid**
Lamotrigine	*Antiepileptic drugs:*	Valproic acid
	Antidepressants:	Sertraline

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Special groups

- (Children)
- Women
- Bone health
- The elderly

AED in women

Old AEDs need consideration on

- Women with childbearing potential
  - Hormonal contraception
  - Pregnancy
  - Breast feeding

Hormonal contraception and AEDs

- Estrogen is metabolized by CYP 450 enzyme system.
- Most of old gen AEDs except valproate induced CYP 450 enzyme system; therefore, hormonal contraception may fail.
- In contrast, many new gen AED do not induce CYP 450 enzyme system and are safely used with hormonal contraception.

Risk of AED teratogenesis

North American pregnancy registry
(Total registries 5,525 pts, complete study 3,916 pts)

AED (monotherapy)	MM/n	% MM	95%CI	RR; 95%CI
Phenobarbital	5/77	6.5%	2.1-14.5%	4.2; 1.5-9.4%
Valproate	16/149	10.7%	6.3-16.9%	7.3; 4.4-12.2%
Carbamazepine	22/873	2.5%	1.6-3.7%	1.6; 0.9-2.8%
Lamotrigine	15/564	2.7%	1.5-4.3%	1.7; 1.0-2.7%

Pregnancy registry: a 6-year experience. Arch Neurol 2004;61:673-678

AED and unplanned pregnancy

- หญิง อายุ 19 ปี
- Unclassified epilepsy of unknown etiology
- Taking phenytoin 325 mg hs
  topiramate 50 mg bid
- 1 เดือนก่อน ทะเลาะกับมารดาเรื่อง unplanned pregnancy แล้วเกิด GTCs 4 ครั้ง
- อายุครรภ์ 10 สัปดาห์

What should be done?

a) Maintain the current dose of both phenytoin and topiramate
b) Maintain current dose of phenytoin and titrate up topiramate
c) Maintain current dose of phenytoin and switch topiramate to lamotrigine
d) Maintain current dose of topiramate and switch phenytoin to carbamazepine
e) Switch both phenytoin and topiramate to levetiracetam

Bone health

- A 78-year old woman who has post stroke epilepsy and has been seizure-free with sodium valproate 1,250 mg/d for 5 years has recent osteoporotic lumbar spine compression fracture. What should be done regarding antiepileptic drug?

What should be done regarding antiepileptic drug?

a) Switch to levetiracetam
b) Antiepileptic drug discontinuation
c) Maintain sodium valproate 1,250 mg/d
d) Decreased dose of sodium valproate to 1,000 mg/d
e) No data for recommendation

Bone health

- All of old AEDs has negative effect on bone density!
- There are evidence that levetiracetam does not have negative effect on bone density.

Levetiracetam has no negative effect on bone density

Epilepsy Research (2013) 104, 134–139

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journal homepage: www.elsevier.com/locate/epilepsyres

Effects of levetiracetam as a monotherapy on bone mineral density and biochemical markers of bone metabolism in patients with epilepsy

Dae Lim Koo, Eun Yeon Joo, Daeyoung Kim, Seung Bong Hong*

Levetiracetam has no negative effect on bone density

Epilepsia, **(*):1–5, 2013
doi: 10.1111/epi.12162

BRIEF COMMUNICATION

***Effect of switching hepatic enzyme-inducer antiepileptic* drug to levetiracetam on bone mineral density, 25 hydroxyvitamin D, and parathyroid hormone in young adult patients with epilepsy**

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AED in the elderly

- The elderly tend to have
  - Lower threshold of side effects such as sedation, cognitive dysfunction, unsteady gait.
  - Liver and renal impairment
  - Polypharmacy
- New generation AEDs with superior pharmocokinetics may be necessary in some old patients such as levetiracetam.