


คณะแพทยศาสตร์ศิริราชพยาบาล ม
มหาวิทยาลัยมหิดล

**Choosing AEDs :
What are the common pitfalls?▶**

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Talk

- Misdiagnosis of non-epileptic attacks as epilepsy
- Misdiagnosis of seizure type
- Failure to diagnose the epilepsy syndrome
- Failure to recognize antiepileptic drug-induced seizure
- Failure to recognize cross drug reaction

Talk

- Failure to ensure the maximum tolerated dose in uncontrolled epilepsy
- Failure to recognize maximum tolerated dose
- Failure to recognize drug titration
- Suboptimal use of new AEDs
- Failure to recognize rational polytherapy

Talk

- Failure to recognize specific issues of woman with epilepsy
- Failure to recognize bone issue
- Failure to balance between evidence base and expert opinion

**MISDIAGNOSIS OF
NON-EPILEPTIC ATTACKS AS
EPILEPSY**

Disorders that mimic epilepsy

A. Systemic disturbances

- Syncope
- Metabolic and endocrine disorders
- Systemic nonepileptic paroxysmal disorders from neonatal to childhood periods

Disorders that mimic epilepsy

B. Neurological disturbances

- Migraine
- Cerebrovascular disorders
- Sleep disorders
- Myoclonus and Myoclonic syndromes
- Movement disorders
- Sensory disorders
- Nonepileptic neurologic paroxysmal disorders and episodic symptoms in infants

Disorders that mimic epilepsy

C. Psychiatric disturbances

- Psychogenic non-epileptic disorders
- Episodic dyscontrol
- Dissociative disorders
- Panic disorders and hyperventilation
- Obsessive-compulsive behavior
- Non-affective psychoses, schizophrenia and schizophrenia-like psychoses

MISDIAGNOSIS OF SEIZURE TYPE

Seizures misdiagnosed with absence

- Complex partial seizure
- Generalized atonic seizure

Absence NICE 2012


Seizure type	First-line AEDs	Adjunctive AEDs	Other AEDs that may be considered on referral to tertiary care	Do not offer AEDs (may worsen seizures)
Absence	Ethosuximide Lamotrigine ^a Sodium valproate	Ethosuximide Lamotrigine ^a Sodium valproate	Clobazam ^a Clonazepam Levetiracetam ^a Topiramate ^a Zonisamide ^a	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin

Partial (focal) seizure NICE 2012

Seizure type	First-line AEDs	Adjunctive AEDs	Other AEDs that may be considered on referral to tertiary care	Do not offer AEDs (may worsen seizures)
Focal	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate	Carbamazepine Clobazam ^a Gabapentin ^a Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate Topiramate	Eslicarbazepine acetate ^a Lacosamide Phenobarbital Phenytoin Pregabalin ^a Tiagabine Vigabatrin Zonisamide ^a	

NICE 2012

Generalized tonic & atonic seizure

Seizure type	First-line AEDs	Adjunctive AEDs	Other AEDs that may be considered on referral to tertiary care	Do not offer AEDs (may worsen seizures)
Tonic or atonic 	Sodium valproate	Lamotrigine ^a	Rufinamide ^a Topiramate ^a	Carbamazepine Gabapentin Oxcarbazepine Pregabalin Tiagabine Vigabatrin

The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. NICE clinical guideline 2012

- ### Seizures misdiagnosed with myoclonic seizure
- Tonic-clonic seizure
 - Clonic seizure


NICE 2012

Myoclonic seizure

Seizure type	First-line AEDs	Adjunctive AEDs	Other AEDs that may be considered on referral to tertiary care	Do not offer AEDs (may worsen seizures)
Myoclonic	Levetiracetam ^a Sodium valproate Topiramate ^a	Levetiracetam Sodium valproate Topiramate ^a	Clobazam ^a Clonazepam Piracetam Zonisamide ^a	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin

NICE 2012

Generalized tonic-clonic seizure

Seizure type	First-line AEDs	Adjunctive AEDs	Other AEDs that may be considered on referral to tertiary care	Do not offer AEDs (may worsen seizures)
Generalised tonic-clonic 	Carbamazepine Lamotrigine Oxcarbazepine ^a Sodium valproate	Clobazam ^a Lamotrigine Levetiracetam Sodium valproate Topiramate		(If there are absence or myoclonic seizures, or if JME suspected) Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin

FAILURE TO DIAGNOSE THE EPILEPSY SYNDROME


- ### Over AED treatment
- AED may not be necessary in
 - Benign childhood epilepsy with centrotemporal spikes
 - Juvenile myoclonic epilepsy with mild and infrequent myoclonic seizures alone

Choosing wrong AED

- Misdiagnosis of JME or idiopathic generalized epilepsy
 - Presenting with generalized tonic-clonic seizure but failure to diagnose absence and/or myoclonic seizure may lead to wrong choice of AED.

Choosing wrong AED

NICE 2012

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FAILURE TO RECOGNIZE ANTIEPILEPTIC DRUG-INDUCED SEIZURE

AED-induced seizure

- Some AEDs may induce some seizure types such as
 - Absence
 - Myoclonic seizure
 - Tonic seizure

Absence


NICE 2012

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Absence	Ethosuximide Lamotrigine ^a Sodium valproate	Ethosuximide Lamotrigine ^a Sodium valproate	Clobazam ^a Clonazepam Levetiracetam ^a Topiramate ^a Zonisamide ^a	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin

Myoclonic seizure

NICE 2012

Seizure type	First-line AEDs	Adjunctive AEDs	Other AEDs that may be considered on referral to tertiary care	Do not offer AEDs (may worsen seizures)
Myoclonic	Levetiracetam ^a Sodium valproate Topiramate ^a	Levetiracetam Sodium valproate Topiramate ^a	Clobazam ^a Clonazepam Piracetam Zonisamide ^a	Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin

Generalized tonic & atonic seizure NICE 2012				
Seizure type	First-line AEDs	Adjunctive AEDs	Other AEDs that may be considered on referral to tertiary care	Do not offer AEDs (may worsen seizures)
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FAILURE TO RECOGNIZE CROSS DRUG REACTION

Aromatic AEDs and cross reactivity

- In patients with a history of another AED-related rash
 - Phenytoin, carbamazepine and oxcarbazepine caused rash 27-35%
 - Lamotrigine caused another rash 17%
- Clinicians should be aware of the cross-reactivity of the aromatic AEDs regarding cutaneous adverse events

Alvestad S, et al. Epilepsy Res.2008;80:194-200

FAILURE TO ENSURE THE MAXIMUM TOLERATED DOSE IN UNCONTROLLED EPILEPSY

Ensure maximum tolerated dose

- Most AEDs have dose-response relationship in treating epilepsy.
- Failure to use the maximum tolerated dose in patients still having seizures is still one of the most common pitfall.
- Do not rely on serum concentrations for the determination of maximum tolerated dose particularly short half-life AEDs.

Ensure maximum tolerated dose

- Titrate stepwise until initial clinical adverse effects appear.
- Then reduce the dose to prevent chronic toxicity and add on another AED or switch to other AED.

AED dose in adult (mg/day)		
Drug	Usual dose	Maximum tolerated dose
Phenytoin	300-500	500
Carbamazepine	600-1200	2000
Phenobarbital	60-120	180
Sodium valproate	1000-3000	3000

AED dose in adult (mg/day)		
Drug	Usual dose	Maximum tolerated dose
Gabapentin	900-3600	≤ 3600
Lamotrigine	100-400	≤ 400
Levetiracetam	1000-3000	≤ 3000
Oxcarbazepine	600-2400	≤ 2400
Pregabalin	150-600	≤ 600
Topiramate	200-400	≤ 400
Vigabatrin	2000-4000	≤ 4000

**FAILURE TO RECOGNIZE
MAXIMUM TOLERATED DOSE**

Recognize maximum tolerated dose

- Pay attention not only on seizure control but drug's side effect also.
- Some patients have maximum tolerated dose lower than maximum effective dose in some AEDs,
 - Particularly; drowsiness, dizziness
- Treat the patient, do not treat the drug level.

**FAILURE TO RECOGNIZE DRUG
TITRATION**

AED titration

- Common pitfall for AED titration
 - Failure to choose drug started with minimum effective dose
 - Failure to choose drug with capacity of rapid titration
 - Too rapid drug titration

AEDs initiated at therapeutic dose (minimum effective dose)

- 1st generation AEDs
 - Sodium valproate 500-750 mg/d
- 2nd generation AEDs
 - Levetiracetam 250 mg, bid
 - If necessary, 500 mg, bid

AEDs initiated at therapeutic dose (minimum effective dose)

- 1st generation 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).

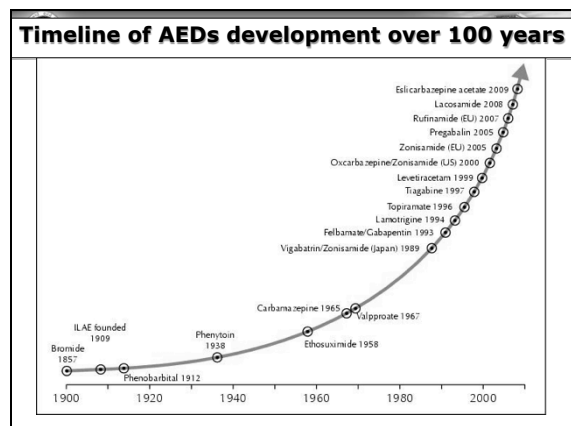
Rapid titration

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

Too rapid drug titration

- AEDs with intolerant adverse effect if too rapid titration
 - Dizziness-vertigo:
 - Carbamazepine, oxcarbazepine
 - Nausea-vomiting:
 - Topiramate
 - Drowsiness:
 - Phenobarbital, gabapentin, pregabalin

SUBOPTIMAL USE OF NEW AEDS



Suboptimal use of new AEDs

- There are too many new AEDs to choose for patients who fail or are intolerant to old AED.
- Some doctors may choose only new AEDs with broad spectrum.
- However, in some situation broad spectrum AEDs may not work or carry adverse effect.

Suboptimal use of new AEDs

- It is helpful to remember or have reference at hand about AEDs' mode of action and AED guideline.

THAI Clinical Practice Guidelines for Epilepsy 2010

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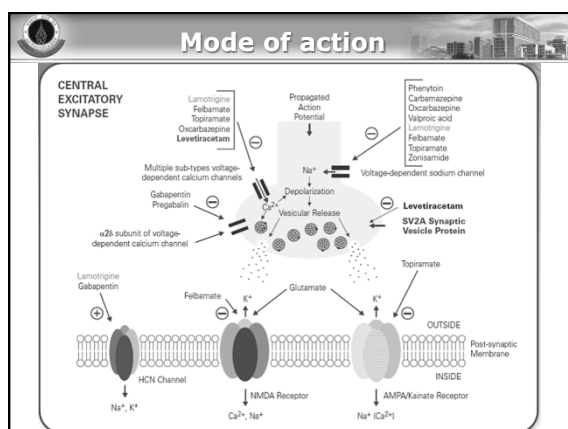
Clinical Practice Guidelines for epilepsy

NICE (UK) Clinical Guideline on Epilepsy 2012

NHS
National Institute for Health and Clinical Excellence

The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care

Issued: January 2012
NICE clinical guideline 137
www.nice.org.uk



AEDs mode of action

AED	Voltage-dependent channels		Neuromodulation		Carbonic Anhydrase	Novel Target
	Na ⁺	Ca ²⁺	GABA ergic	Glutamatergic		
ETX		↓				
CBZ	↓					
PHB			↑			
PHT	↓					
VPA	↓	↓	↑			

AEDs mode of action						
AED	Voltage-dependent channels		Neuromodulation		Carbonic Anhydrase	Novel Target
	Na ⁺	Ca ²⁺	GABA ergic	Glutamat ergic		
FBM	↓	↓	↑	↓ NMDA		
GBP		↓				α _{2δ} subunit
LCS	↓					
LTG	↓					h-current
LEV						SV2A
OXC	↓					
PGB		↓				α _{2δ} subunit

AEDs mode of action						
AED	Voltage-dependent channels		Neuromodulation		Carbonic Anhydrase	Novel Target
	Na ⁺	Ca ²⁺	GABA ergic	Glutamat ergic		
RTG						Kv7 potassium channels
RFN	↓					
TGB			↑ decrease reuptake			
TPX	↓	↓	↑		↓ AMPA/kainate	
VGB			↑ decrease metabolism			
ZNS	↓	↓	↑ ?			

FAILURE TO RECOGNIZE RATIONAL POLYOTHERAPY

- ### Rational polytherapy
- Keys
 - Mode of action
 - Supra additive drugs' adverse effect
 - Drug-drug interaction

FAILURE TO RECOGNIZE SPECIFIC ISSUES OF WOMAN WITH EPILEPSY

- ### Woman with epilepsy
- Concerns
 - Figure
 - Menstruation
 - Contraception
 - Pregnancy

Figure

- Over weight
 - Do not choose AEDs-induced appetite
 - Valproate, Gabapentin, Pregabalin
- Under weight
 - Do not choose AED-induced anorexia
 - Topiramate, Zonisamide

Figure

- Hirsutism
 - Phenytoin
- Hair loss
 - Sodium valproate
- Gum hypertrophy
 - Phenytoin

Menstruation

- Sodium valproate may induce
 - Spotting / menometrorrhagia
 - Amenorrhea

Hormonal contraception and AEDs

- Estrogen is metabolized by CYP 450 enzyme system.
- Almost all of old AEDs except valproate induced CYP 450 enzyme system; therefore, hormonal contraception may fail.
- In contrast, most new AEDs, except topiramate over 200 mg/d, 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;61:673-8


FAILURE TO RECOGNIZE BONE ISSUE

AEDs and bone health

- There is established evidence that all old AEDs (PHT, PB, CBZ, VPA) may reduce bone mass.
- There is not enough evidence of new AEDs on bone health.
- However, there are few evidence that levetiracetam has no negative effect on bone density.

Levetiracetam has no negative effect on bone density

Epilepsy Research (2013) 104, 134–139



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, 54(7):1–5, 2013
doi:10.1111/epi.12102

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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FAILURE TO BALANCE BETWEEN EVIDENCE BASE AND EXPERT OPINION