Early Recognition and Management of Refractory Epilepsy

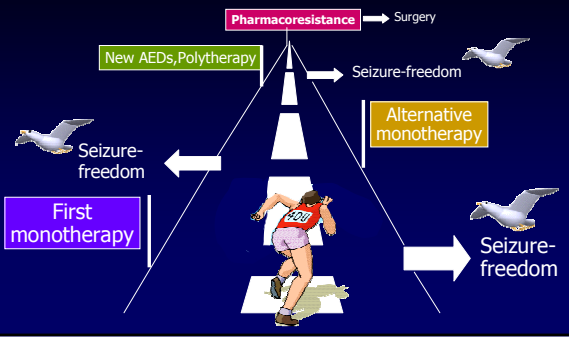
Associate Professor Somsak Tiamkao
Division of Neurology, Department of Medicine
Faculty of Medicine, Khon Kaen University
Khon Kaen, e-mail:somtia@kku.ac.th
http://epilepsy.kku.ac.th

17 April ,2008

Topics

- How to predict who developed refractory epilepsy
- How to manage patient with refractory epilepsy
- Thailand's guideline of management
- Clinical trial of Lamictal

Common Epilepsy Treatment Path



Natural History of Treated Epilepsy
Unanswered Questions

- Outcome with respect to treatment course
- Response to the first drug, second drug … etc
- When to use polytherapy ?
- What are useful combinations ?
- When is drug resistant epilepsy recognised ?
- Can refractory epilepsy be identified early ?

What are Prediction Factors?

- Seizure type
- Etiologies
- Frequency of seizures
- Response to first AED
- Genetic?

Early Identification of Refractory Epilepsy
Glasgow Study

- Prospective follow up at AED initiation
- 525 consecutive patients untreated at referral
- 470 never treated previously
- Median age 29 years (range 9-93)
- Median follow up 5 years (2-15.6)
- 1 year terminal seizure-free: 63%

Kwan P and Brodie MJ. N Engl J Med 2000;342:314-319

Newly Diagnosed Epilepsy
One year terminal remission

First drug monotherapy	47%
Second drug monotherapy	13%
Third drug monotherapy	1%
Duotherapy	3%
Total seizure free	64%

Kwan P and Brodie MJ. N Engl J Med 2000;342:314-9

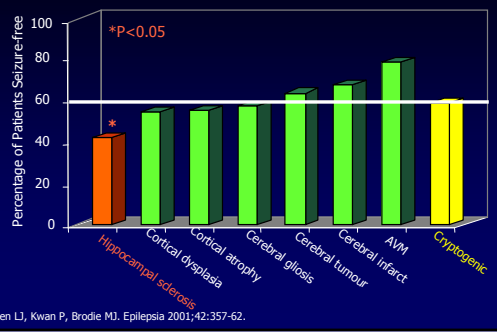
Outcome and Classification
Glasgow Study

	n	Seizure free
Idiopathic	140	74% *
Symptomatic	150	57%
Cryptogenic	235	62%

*p=0.004; idiopathic vs. symptomatic + cryptogenic

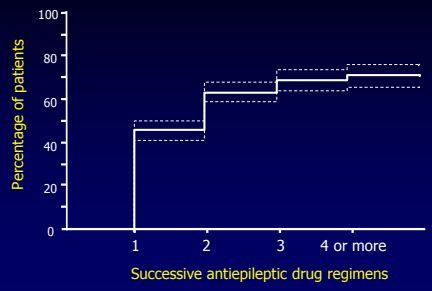
Kwan P and Brodie MJ. N Engl J Med 2000;342:314-9

Outcome and Etiology
Glasgow Study



Stephen LJ, Kwan P, Brodie MJ. Epilepsia 2001;42:357-62.

Newly Diagnosed Epilepsy
Probability of seizure-freedom



Kwan P and Brodie MJ, Neurology 2002;58(Suppl 5):S2-S8

Response to first drug trial predicts outcome in childhood temporal lobe epilepsy

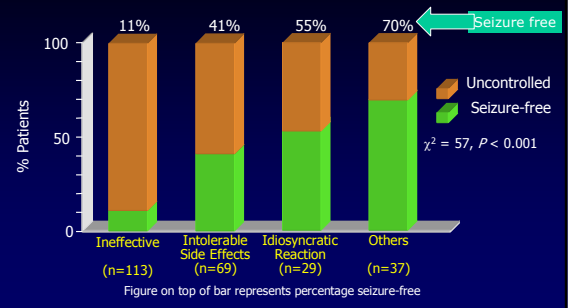
Dlugos DJ, Sammel MD, Strom BL, Farrar JT
Neurology 2001;57:2259-64

First Drug Failure and Outcome

- Retrospective study
- 120 patients aged 1 to 18 years
- Outcome at 2 years after onset of TLE
- Only "failure of first AED trial" predicted poor outcome
  - Positive predictive value 0.89
  - Negative predictive value 0.95

Dlugos DJ et al, Neurology 2001;57:2259-64

Outcome after Failure on First AED

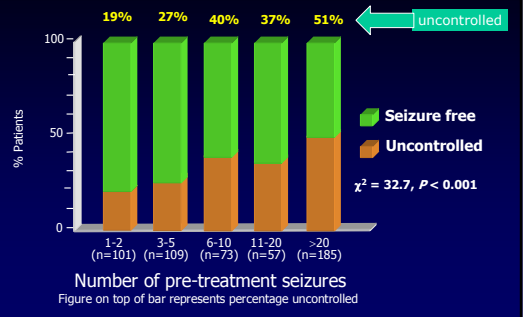


Kwan P and Brodie MJ. N Engl J Med 2000;342:314-9

Initial AED Response and Outcome

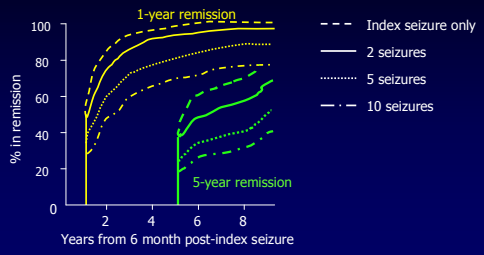
- Poor response to AED at 6 –12 months predicts poor long-term outcome:
  - Sillanpää M et al, 1998
  - Arts WFM et al, 1999
  - Hans L et al, 2001

Outcome and Pre-treatment Seizure Number
Glasgow Study



Kwan P and Brodie MJ. N Engl J Med 2000;342:314-9

Outcome and Initial Seizure Density
National GP Epilepsy Study



MacDonald BK et al, Ann Neurol 2000;48:833-41

Pre-treatment seizure number

- High number predicts poor outcome:
  - Reynolds et al, 1989
  - Camfield et al, 1993
  - Arts et al, 1999
  - Kwan and Brodie, 2000

Association of multidrug resistance in epilepsy with a polymorphism in the drug-transporter gene *ABCB1*

Siddiqui A, Kerb R, Weale ME et al.
N Engl J Med 2003;348:1442-8

MDR1 and Epilepsy

- P-glycoprotein encoded by *MDR1* (or *ABCB1*)
- Pumps drugs out of cells
- Expressed in cerebral capillary endothelium (BBB)
- Over-expressed in patients with refractory epilepsy
- Induced by experimental seizures
- Certain AEDs are substrates of P-gp

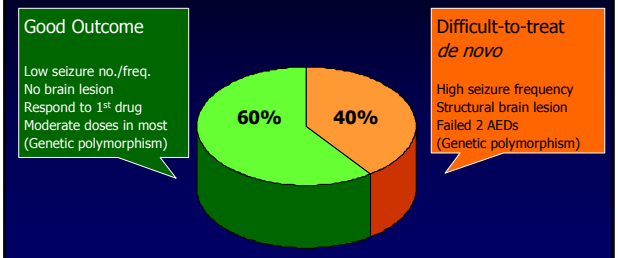
Hypothesis: Over-expression of *MDR1* causes drug resistance by reducing AED access to the epileptogenic lesion

Cordon-Cardo et al, 1989; Tishler DM et al, 1995; Kwan P et al, 2002; Sills GJ, Kwan P et al, 2003

Conclusion: Poor Prognostic Factors

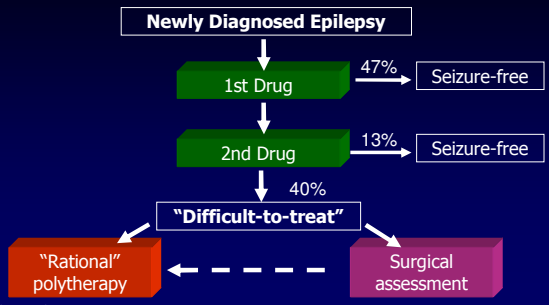
- Symptomatic/lesional epilepsy (MTS)
- Poor response to the first antiepileptic drug
- High pre-treatment seizure number/frequency
- Others:
  - Poor response to AED at 6 – 12 months
  - Generalised epileptiform activity on EEG
  - Generalised tonic-clonic seizures
- Genetic predisposition?

Newly Diagnosed Epilepsy
"Two-population Theory"



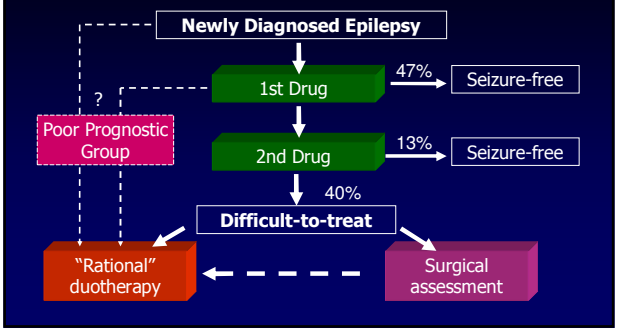
Brodie MJ and Kwan P, Neurology 2002;58(8 Suppl 5):S2-8.

Management Paradigm

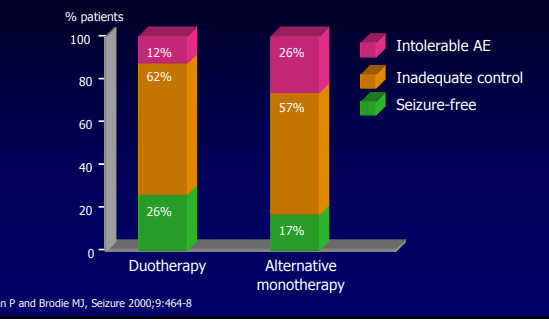


Brodie MJ and Kwan P, CNS Drugs 2001;15:1-12

Management Paradigm



Monotherapy vs. Duotherapy
Failed 1st AED due to lack of efficacy



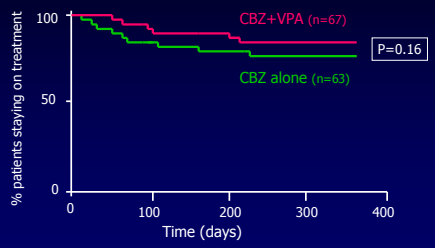
Kwan P and Brodie MJ, Seizure 2000;9:464-8

Monotherapy vs. Duotherapy
Double-blind RCT

- 130 newly diagnosed untreated epilepsy patients
- Equal drug loads of CBZ or CBZ+VPA
- 12-month follow-up
- No difference in neurotoxicity score
- No difference in seizure frequency during follow up
- Withdrawal due to adverse events
  - Duotherapy 14%
  - Monotherapy 22%

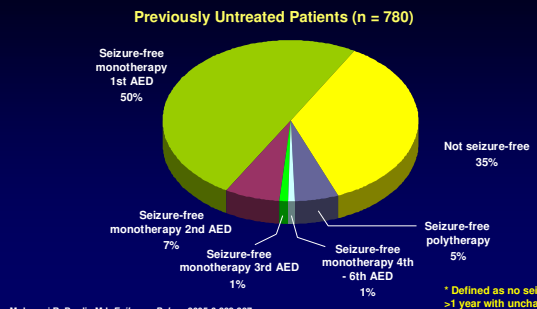
Deckers CLP et al, Epilepsia 2001;42:1387-94.

Monotherapy vs. Duotherapy
Retention Rate



Deckers CLP et al, Epilepsia 2001;42:1387-94

Seizure-Free* Rates with Monotherapy and Polytherapy



Mohanraj R, Brodie MJ. *Epilepsy Behav.* 2005;6:382-387.

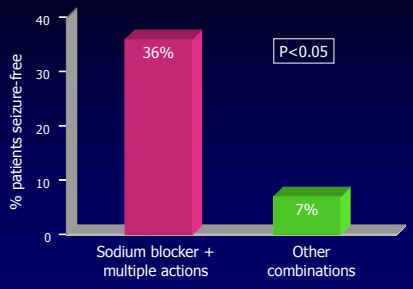
* Defined as no seizures for >1 year with unchanged AED dosage

Expert Opinion for the Treatment of Epilepsy (2005): *Overall Treatment Strategies*

- STEP 1: Monotherapy
- STEP 2: Second monotherapy
- STEP 3: Additional trials of monotherapy or combination of 2 AEDs
- STEP 4: Second combination of 2 AEDs or evaluation for surgery
- STEP 5: Multiple options including additional combinations of 2 AEDs, combination of 3 AEDs, VNS, ketogenic diet

Karceski S, et al. *Epilepsy Behav.* 2005;7:S1–S64.

"Rational" Duotherapy
Mechanistic Approach



Kwan P and Brodie MJ, Seizure 2000;9:464-8

"Rational" Duotherapy
Mechanistic Approach

Combinations	Mechanisms	Seizure type
PHT/PB	Na^+ blocker/GABA	GTCS, Partial-onset
PHT/VPA	Na^+ blocker/multiple	GTCS
PHT/CLZ	Na^+ blocker/GABA	GTCS
CBZ/VPA	Na^+ blocker/multiple	GTCS, Partial-onset
CBZ/VGB	Na^+ blocker/GABA	Partial-onset
CBZ/TPM	Na^+ blocker/multiple	GTCS
LTG/VPA	Na^+ blocker/multiple	GTCS, Partial-onset
LTG/TPM	Na^+ blocker/multiple	GTCS, Partial-onset
PB/TPM	GABA/multiple	GTCS
VPA/ESM	Multiple/T-Ca^{2+}	Absence

Deckers CLP et al, Epilepsia 2000;41:1364-74

Management of Epilepsy

- Goals of therapy[1]
  - Control seizures
  - Minimize adverse events
  - Improve quality of life
- Important considerations
  - Comorbidities[2,3]
  - Psychosocial needs[4]

1. Dam M. In: Engel J Jr, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook.* Vol 2. Philadelphia, Pa: Lippincott-Raven; 1997:1103-1105.
2. Boro A, Haut S. *Epilepsy Behav.* 2003;4:S2-S12.
3. Karceski S, et al. *Epilepsy Behav.* 2005;7:S1-S64.
4. Schachter SC. *Epilepsy Behav.* 2000;1:120-127.

Neuropsychological Effects
Established AEDs

Drug	Cognitive	Behavioural
Phenobarbital	++	++
Phenytoin	+	0
Carbamazepine	+	0
Valproate	+	0
Clobazam	+	+
Clonazepam	++	+

Kwan P and Brodie MJ, Lancet 2001;357:216-22

Neuropsychological Effects
Newer AEDs

	Cognitive	Behavioural
Lamotrigine	0	0
Vigabatrin	0	+
Gabapentin	0	0
Topiramate	(+)	?
Tiagabine	0	0
Oxcarbazepine	?	0
Zonisamide	0	?
Levetiracetam	0	?

( ) Avoided by slow titration

Kwan P and Brodie MJ, Lancet 2001;357:216-22

Selected Epilepsy Comorbidities

- Behavioral or mood disturbances
- Cognitive impairment
- Reproductive endocrine dysfunction

Boro A, Haut S. Medical comorbidities in the treatment of epilepsy. *Epilepsy Behav.* 2003;4(suppl 2):S2-S12.

Epilepsy Comorbidities: Psychiatric

Psychiatric Disorder	Rate, %
Anxiety disorders[1]	19% to 66%
Major depression[1]	20% to 57%
Bipolar symptoms[2]	12%
Psychosis[1]	
Interictal psychosis	9%
Postictal psychosis	6%

1. Boro A, Haut S. *Epilepsy Behav.* 2003;4(suppl 2):S2-S12.
2. Ettinger AB, et al. *Neurology* 2005;65:535-540.

Epilepsy Comorbidities: Cognitive Impairment

- Causes[1-3]
  - Underlying disease
  - Seizures
  - *Treatment*
- Types
  - Memory loss
    - Memory loss is common in epilepsy[2]
    - Especially in temporal lobe epilepsy[2,4]
  - Speech or behavior effects[3]

1. Meador KJ. *Neurology.* 2002;58(suppl 5):S21-S26.
2. Glowinski H. *J Nerv Ment Dis.* 1973;157:129-137.
3. Aldenkamp AP, et al. *Epilepsia.* 2003;44(suppl 4):21-29.
4. Jokeit H, et al. *Neurology.* 2001;57:125-126.

Reproductive Endocrine Dysfunction

Polycystic Ovary Syndrome (PCOS)

- Ovulatory dysfunction and hyperandrogenism in absence of adrenal or thyroid disease
- More common in female patients with epilepsy than in the general population
- Associated with health risks, including insulin resistance, type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease

Duncan S. *Epilepsia*, 2001, 42:311-315.
Genton P, et al. *Epilepsia*. 2001;42:295-304.
Herzog AG, Schachter SC. *Epilepsia*. 2001;42:311-315.

AEDs and risk of fractures

	Odd ratio
Carbamazepine	1.88
Valproate	1.57
Phenobarbital	1.84
Phenytoin	1.67
Lamotrigine	0.58
Polytherapy	2.82

Pathogenesis of bone disorder

1. Accelerated vit D metabolism
2. Hyperparathyroidism
3. Altered vit K metabolism
4. Low calcitonin, calcium absorption
5. Low exercise
6. Fall
7. Hormonal changes

Seizure (2006) xxx, xxx–xxx

ELSEVIER

SEIZURE

www.elsevier.com/locate/yseiz

Effect of lamotrigine on sexual function in patients with epilepsy

A. Gil-Nagel [a,*], F. López-Muñoz [b], J.M. Serratosa [c], I. Moncada [d], P. García-García [b], C. Álamo [b]

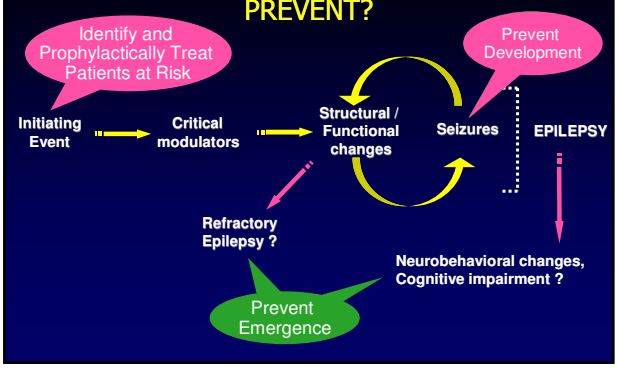
[a] Epilepsy Program, Neurology Department, Ruber International Hospital, La Masó 38, 28034 Madrid, Spain
[b] Department of Pharmacology, Faculty of Medicine, University of Alcalá, Ctra. Madrid-Barcelona, Km. 33,600, 28871 Alcalá de Henares, Madrid, Spain
[c] Epilepsy Unit, Jiménez-Díaz Foundation Hospital, Avenida Reyes Católicos 2, 28040 Madrid, Spain
[d] Andrology Unit, Ruber International Hospital, La Masó 38, 28034 Madrid, Spain

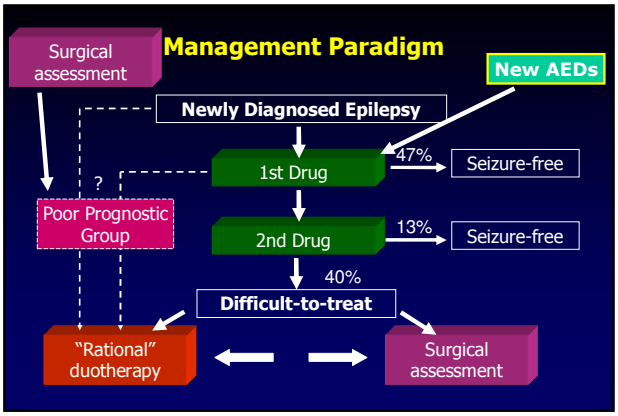
Received 18 May 2005; received in revised form 4 December 2005; accepted 12 December 2005

Table 1. Effects of antiepileptic drugs on weight

Weight neutral	Weight gain	Weight loss
Levetiracetam	Gabapentin	Topiramate
Lamotrigine	Carbamazepine	Zonisamide
Phenytoin	Valproate	Felbamate
	Tiagabine	

What do we want to MODEL and then PREVENT?





แนวทางการดูแลผู้ป่วยโรคลมชัก :Thai CPG ไม่ตอบสนองต่อการรักษา

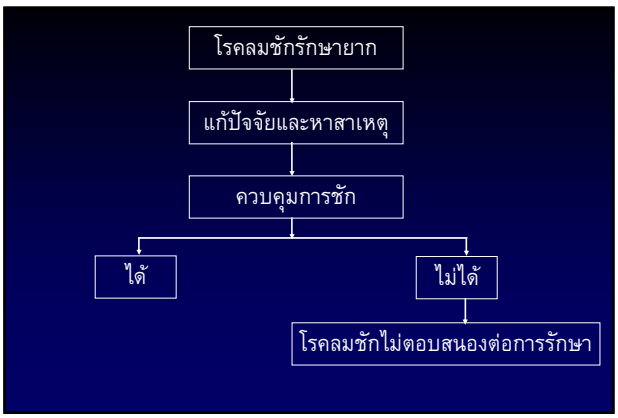
1. โรคลมชักที่รักษายาก (difficult-to-treat)
2. โรคลมชักที่ไม่ตอบสนองต่อการรักษา (refractory)

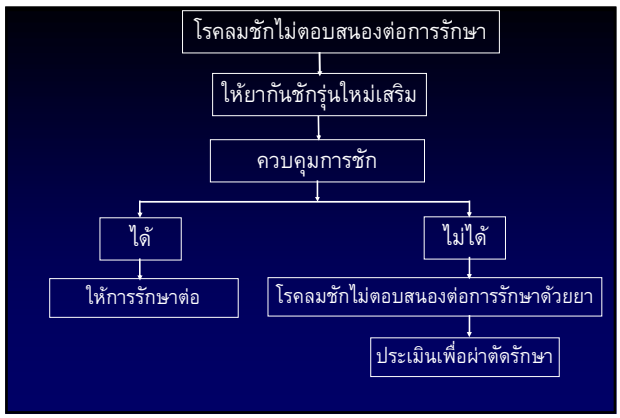
โรคลมชักที่รักษายาก

1. วินิจฉัยผิดว่าเป็นอาการชัก
2. มีสาเหตุที่ไม่ได้รักษา
3. มีปัจจัยกระตุ้นที่ไม่ได้แก้ไข
4. ผู้ป่วยทานยาไม่สม่ำเสมอ
5. ได้รับยาที่ไม่เหมาะสม
6. ไม่ได้รับการปรับยาอย่างเหมาะสม

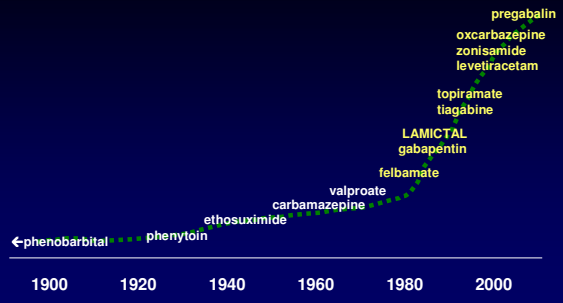
Medical refractory epilepsy

- ผู้ป่วยที่ได้รับยากันชักพื้นฐาน
- CBZ, PHT, VPA, PB
- แบบ monotherapy 2 ชนิด หรือ
- ใช้ร่วมกัน 2 ตัว อย่างน้อย 1 คู่
- ในขนาดและเวลาที่เหมาะสมยังควบคุมอาการไม่ได้





Antiepileptic Drugs in the United States



Selecting an Antiepileptic Drug

- Choose the antiepileptic drug most suited to the individual patient[1]
  - Seizure/epilepsy type
  - Side effects
  - Patient profile (eg, sex, age)
  - Ease of use
  - Cost
- Balance efficacy, tolerability, and safety[1,2]
- Epilepsy may be a lifelong diagnosis[1]

1. Dam M. In: Engel J Jr, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook.* Vol 2. Philadelphia, Pa: Lippincott-Raven; 1997:1103-1105.
2. French JA, et al. *Neurology.* 2004;62:1252-1260.

CME

Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new onset epilepsy

Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society

J.A. French, MD*; A.M. Kanner, MD†; J. Bautista, MD; B. Abou-Khalil, MD; T. Browne, MD; C.L. Harden, MD; W.H. Theodore, MD; C. Bazil, MD, PhD; J. Stern, MD; S.C. Schachter, MD; D. Bergen, MD; D. Hirtz, MD; G.D. Montouris, MD; M. Nespeca, MD; B. Gidal, PharmD; W.J. Marks, Jr., MD; W.R. Turk, MD; J.H. Fischer, MD; B. Bourgeois, MD; A. Wilner, MD; R.E. Faught, Jr., MD; R.C. Sachdeo, MD; A. Beydoun, MD; and T.A. Glauser, MD

NEUROLOGY 2004;62:1252–1260

Treatment of new onset epilepsy

Drugs	Newly diagnosed MonoRx Partial/Mixed	Newly diagnosed Absence
Gabapentin	Yes	No
Lamotrigine	Yes	Yes
Topiramate	Yes	No
Tiagabine	No	No
Oxcarbazepine	Yes	No
Levetiracetam	No	No
Zonisamide	No	No

NEUROLOGY 2004;62:1252–1260

Type of seizure	FBM	VGB	TGB	GBP	OXC	LTG	TPM	LEV	PGB	ZNS
Partial	+	+	+	+	+	+	+	+	+	+
Second generalize	+	+	+	+	+	+	+	+	+	+
Tonic clonic	?+	?+	?	?+	+	+	+	+	?	+
Absence	?+	-	-	-	-	+	?	?+	?	?+
Myoclonic	?	-	?	-	-	+*	+	+	?	+
Lennox Gastaut	+	?	?	?	-	+	+	?	?	?
Infantile spasm	?	+	?+	?	-	?+	?+	?	?	?+

Hitiris N, Brodie MJ. Curr Opin Neurol 2006;19:175-80

Milestones for LAMICTAL

1981: Epilepsy studies initiated

1990: First marketing approval for epilepsy granted (Ireland)

1994: FDA approval in US as adjunctive therapy for partial seizures in adults with epilepsy

1998: FDA approval for generalized seizures of Lennox-Gastaut syndrome (adjunctive therapy in pediatric and adult patients) and conversion to monotherapy for adults with partial seizures taking carbamazepine, phenytoin, phenobarbital, or primidone as the single antiepileptic drug

Milestones for LAMICTAL

2002: First global approval for use in bipolar disorder

2003: FDA approval for adjunctive therapy for partial seizures in pediatric patients ≥2 years of age

FDA approval for maintenance treatment of adults with bipolar I disorder to delay the time to occurrence of mood episodes in adult patients treated for acute mood episodes with standard therapy

2004: FDA approval for conversion to monotherapy for adults with partial seizures taking valproate

2006: FDA approval for adjunctive therapy for primary generalized tonic-clonic seizures in adults and pediatric patients ≥2 years of age

LAMICTAL: Adjunctive Therapy for PGTC Seizures in Patients ≥2 Years of Age

LAMICTAL as Adjunctive Therapy for PGTC Seizures: Primary Objective

- To assess the efficacy and tolerability of LAMICTAL as adjunctive therapy in pediatric and adult patients with PGTC seizures

Biton V, et al. *Neurology*. 2005;65:1737-1743.

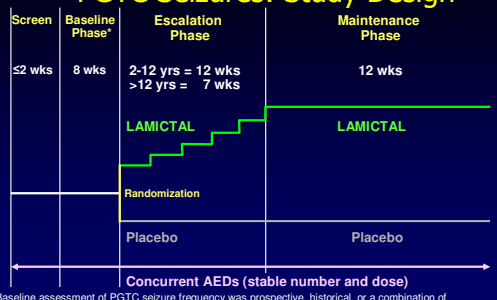
LAMICTAL as Adjunctive Therapy for PGTC Seizures: Key Inclusion Criteria

- Patients ≥2 years of age and ≥13 kg
- Diagnosis of epilepsy with PGTC seizures (with or without other idiopathic generalized seizure types)
- ≥1 PGTC seizure in the 8 consecutive weeks prior to baseline
- ≥3 PGTC seizures during 8-week baseline phase*
- Receiving 1 or 2 AEDs at a stable dose for ≥4 weeks
- Patients with partial seizures were excluded on the basis of seizure history and screening EEG

* Baseline assessment of PGTC seizure frequency was prospective, historical, or a combination of prospective and historical.

Biton V, et al. *Neurology*. 2005;65:1737-1743.

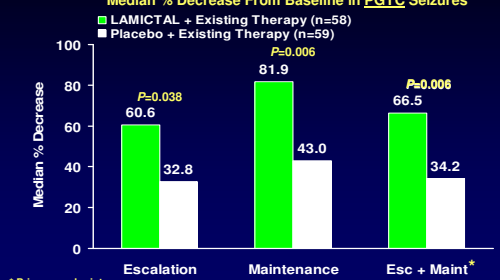
LAMICTAL as Adjunctive Therapy for PGTC Seizures: Study Design



* Baseline assessment of PGTC seizure frequency was prospective, historical, or a combination of prospective and historical.

Biton V, et al. *Neurology*. 2005;65:1737-1743.

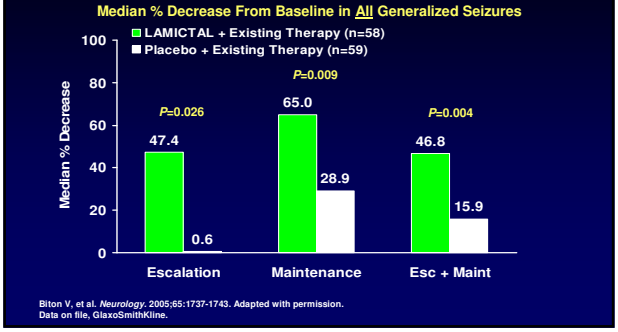
LAMICTAL as Adjunctive Therapy for PGTC Seizures: Primary Endpoint Results



* Primary endpoint.

Biton V, et al. *Neurology*. 2005;65:1737-1743. Adapted with permission.

LAMICTAL as Adjunctive Therapy for PGTC Seizures: Secondary Endpoint Results



Biton V, et al. *Neurology*. 2005;65:1737-1743. Adapted with permission.
Data on file, GlaxoSmithKline.

LAMICTAL as Adjunctive Therapy for PGTC Seizures: Overall Conclusions

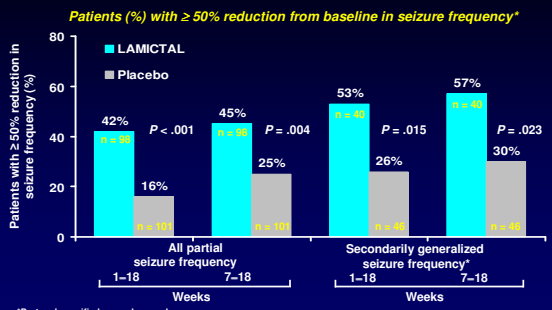
- Significant benefits of adjunctive LAMICTAL versus placebo:
  - Median percent reductions in PGTC seizures: 67% for LAMICTAL vs 34% for placebo*
  - Median percent reductions in all generalized seizures: 47% for LAMICTAL vs 16% for placebo*
  - Percent of patients with ≥50% reduction in PGTC seizure frequency: 64% for LAMICTAL vs 39% for placebo*
- Efficacy was similar across age groups
- Favorable tolerability profile in adults, adolescents, and children

* In Escalation and Maintenance phases combined.

Biton V, et al. *Neurology*. 2005;65:1737-1743.

LAMICTAL: Adjunctive Therapy for Partial Seizures in Pediatric Patients ≥2 Years of Age

LAMICTAL as Adjunctive Therapy for Partial Seizures in Pediatric Patients: *Efficacy*

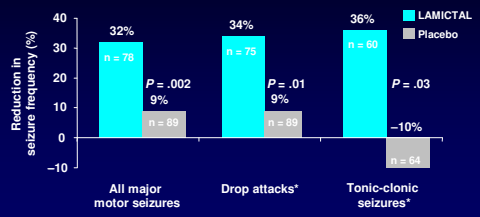


*Protocol-specified secondary analyses.
Duchowny M, et al. *Neurology*. 1999;53:1724–1731.

LAMICTAL: Adjunctive Therapy for Generalized Seizures of Lennox-Gastaut Syndrome in Patients ≥2 Years of Age

LAMICTAL as Adjunctive Therapy for Generalized Seizures of LGS: *Efficacy*

Patients Treated with LAMICTAL Experienced a Significantly Greater Reduction in Seizure Frequency Than Those Treated with Placebo



Median Reduction from Baseline in Weekly Seizures During Treatment Weeks 1–16

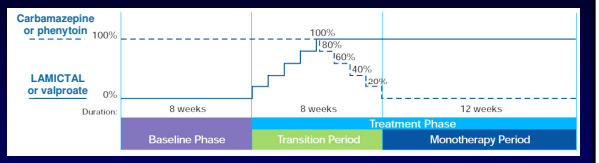
*A protocol-specified secondary analysis

Motte J, et al. *N Engl J Med*. 1997;337:1807–1812.

LAMICTAL: Conversion to Monotherapy with LAMICTAL from Carbamazepine or Phenytoin as the Single AED in Patients ≥16 Years of Age with Partial Seizures

LAMICTAL: *Conversion from a Single EIAED* in Adults*

Randomized, double-blind, double-dummy study to evaluate efficacy and safety of* LAMICTAL 500 mg as *monotherapy

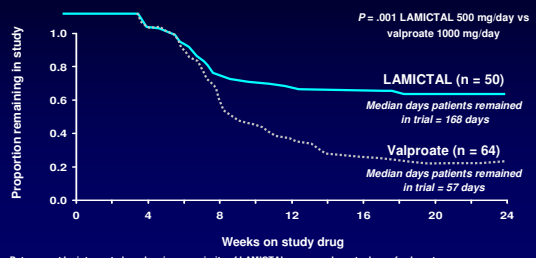


- 156 outpatients (13–73 years of age) with partial seizures uncontrolled with carbamazepine or phenytoin as monotherapy
- Valproate 1000 mg/day was given as an active control to provide some degree of seizure protection

*Enzyme-inducing antiepileptic drug
Data cannot be interpreted as showing superiority of LAMICTAL over an adequate dose of valproate.
Gilliam F, et al. *Neurology*. 1998;51:1018–1025. Adapted with permission.

LAMICTAL: *Conversion from a Single EIAED in Adults*

Kaplan-Meier curve of proportion of patients remaining in trial after addition of LAMICTAL or valproate



Data cannot be interpreted as showing superiority of LAMICTAL over an adequate dose of valproate.
Gilliam F, et al. *Neurology*. 1998;51:1018–1025. Adapted with permission.

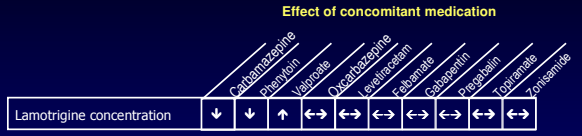
Cognitive Effects of Adjunctive LAMICTAL for Pediatric* and Adult Patients With Epilepsy: Results

- No significant clinical impairment on tested cognitive domains[1,2]
  - Tested cognitive domains included
    - Memory
    - Attention and concentration
    - Cognitive and motor speed
    - Language

* ≥7 years of age.

1. Blum D, et al. *Neurology*. 2006;67:400-406.
2. Pressler RM, et al. *Neurology*. 2006;66:1495-1499.

Effects of Other AEDs on Serum Concentration of Lamotrigine



Effects of LAMICTAL on Serum Concentration of Other AEDs

	Effect of concomitant LAMICTAL
Carbamazepine concentration	↔
Phenytoin concentration	↔
Valproate concentration	↓*
Oxcarbazepine concentration	↔
Levetiracetam concentration	↔
Felbamate concentration	Not assessed
Gabapentin concentration	Not assessed
Pregabalin concentration	↔
Topiramate concentration	↔†
Zonisamide concentration	Not assessed

*Approximately 25% decrease in healthy volunteers; however, no change in plasma concentration in adult or pediatric patients has been observed in controlled trials.
†Slight increase not expected to be clinically relevant.

Dosing of LAMICTAL in Patients >12 Years of Age With Epilepsy

taking Valproate*

Weeks 1 & 2	Weeks 3 & 4	Weeks 5 onwards to maintenance	Usual maintenance dose
25 mg every *other* day	25 mg every day	Increase by 25 to 50 mg/day every 1 to 2 weeks	100 to 400 mg/day (1 or 2 divided doses)

not taking CBZ, PHT, PB, Primidone, or Rifampin† and not taking Valproate*

Weeks 1 & 2	Weeks 3 & 4	Weeks 5 onwards to maintenance	Usual maintenance dose
25 mg every day	50 mg/day	Increase by 50 mg/day every 1 to 2 weeks	225 to 375 mg/day (in 2 divided doses)

taking CBZ, PHT, PB, Primidone, or Rifampin† and not taking Valproate*

Weeks 1 & 2	Weeks 3 & 4	Weeks 5 onwards to maintenance	Usual maintenance dose
50 mg/day	100 mg/day in 2 divided doses	Increase by 100 mg/day every 1 to 2 weeks	300 to 500 mg/day (in 2 divided doses)

- Doses above target dose are not recommended
- To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations should not be exceeded

*Valproate has been shown to decrease the apparent clearance of LAMICTAL.
†CBZ, PHT, PB, primidone, and rifampin have been shown to increase the apparent clearance of LAMICTAL.

Use of LAMICTAL in Special Populations

Pregnancy

- June 2006
  - GlaxoSmithKline voluntarily issued a Dear HCP Letter to inform healthcare professionals about emerging data from the North American AED Pregnancy Registry, which suggests an association between LAMICTAL and an increased risk of nonsyndromic oral clefts
- September 2006
  - Information Sheets for patients and healthcare professionals regarding this information were posted on the FDA's Web site
  - The Information Sheets provide no new information regarding the oral cleft pregnancy registry findings
- To view the Information Sheets go to: www.fda.gov/cder
- LAMICTAL is Pregnancy Category C
- Odd ratio is more less than other AEDs

Epilepsy in Older Adults: *Special Treatment Considerations*

- Seizure type and etiology
- Pharmacokinetic changes
  - Slower drug metabolism
  - Decreased protein binding
  - Decreased renal clearance
- Reduced compliance
  - Memory loss
  - Visual impairment
- Comorbid illnesses
- Concomitant medications
  - Drug interactions

Sabers A, Gram L. *Drugs.* 2000;60:23–33.

Guideline of Epilepsy: Thailand

New AEDs

1. Partial, GTC seizure
   - LTG,GBP, TPM, VGB, TGB, LEV, OXC
2. Infantile spasms
   - VGB

Guideline of Epilepsy: Thailand

New AEDs

3. Lennox-Gastaut syndrome
   - LTG, TPM, FBM, ZNS
4. Monotherapy
   - LTG, TPM, GBP, OXC

Type of seizure	FBM	VGB	TGB	GBP	OXC	LTG	TPM	LEV	PGB	ZNS
Partial	+	+	+	+	+	+	+	+	+	+
Second generalize	+	+	+	+	+	+	+	+	+	+
Tonic clonic	?+	?+	?	?+	+	+	+	+	?	+
Absence	?+	-	-	-	-	+	?	?+	?	?+
Myoclonic	?	-	?	-	-	+*	+	+	?	+
Lennox Gastaut	+	?	?	?	-	+	+	?	?	?
Infantile spasm	?	+	?+	?	-	?+	?+	?	?	?+

Hitiris N, Brodie MJ. Curr Opin Neurol 2006;19:175-80

AMERICAN ACADEMY OF NEUROLOGY

Summary of AAN evidence-based guidelines level A or B recommendation

AED	Partial adjunctive adult	Partial Monotherapy	Primary generalized	Symptomatic generalized	Pediatric partial
Gabapentin	Yes	No	No	No	Yes
Lamotrigine	Yes	Yes	Yes	Yes	Yes
Levetiracetam	Yes	No	No	No	No