Newest Antiepileptic Drug Evidence-Based and Practice

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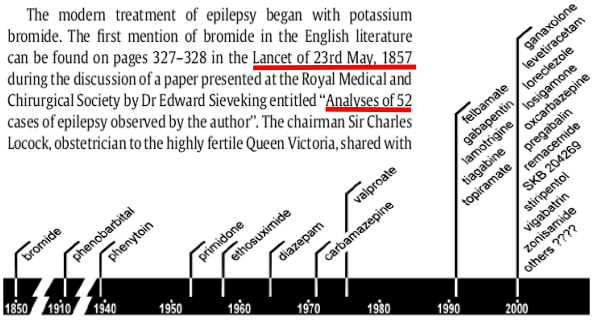
ทำไมต้องมียาใหม่ๆ

- ความต้องการของมนุษย์ที่มีความต้องการไม่หยุดยั้ง
- ความจำเป็นที่ต้องมียาใหม่
- ข้อจำกัดของรุ่นเก่า
- ความเก่งและสามารถของมนุษย์
- ธุรกิจ
- การพัฒนาอย่างต่อเนื่อง

Bromide is a first AEDs : 157 years

The modern treatment of epilepsy began with potassium bromide. The first mention of bromide in the English literature can be found on pages 327–328 in the Lancet of 23rd May, 1857 during the discussion of a paper presented at the Royal Medical and Chirurgical Society by Dr Edward Sieveking entitled "Analyses of 52 cases of epilepsy observed by the author". The chairman Sir Charles Locock, obstetrician to the highly fertile Queen Victoria, shared with



Old vs New vs Newest AEDs

Old AEDs	New-AEDs	
	1993-2005	2009-2011
Phenobarbital	Felbamate	Vigabatrin
Phenytoin	Gabapentin	Clobazam
Clonazepam	Lamotrigine	Rufinamide
Diazepam	Levetiracetam	Lacosamide
Lorazepam	Tiagabine	Ezogabine
Ethosuximide	Pregabalin	Oxcarbazepine
Primidone	Topiramate	Eslicarbazepine acetate
Carbamazepine	Zonisamide	10-hydroxy-carbazepine
Valproate	Fosphenytoin	

Latest approved AED

The older generation		New AEDs	
Name	Time of USA approval	Name	Time of USA approval
Bromides	1857*	FBM, GBP	1993
PHB	1920s-1940*	LTG	1994
PHT	1953 (FDA approved) -1938*	TGB, TPM	1997
ESM	1960	LEV	1999
CBZ	1974	OXC, ZNS	2000
		PGB	2005
		LCM	2009
VPA	1978	VGB**	2009
		RFN	2010
		CBM	2011
		EZG	2013

*: Indicates time of development **: First was approved in Europe in 1989

CBM: clobazam, CBZ: carbamazepine, ESM: ethosuximide, EZG: ezogabine, FBM: felbamate, LCM: Lacosamide, LEV: levetiracetam, OXC: oxcarbazepine, PGB: pregabaline, PHB: phenobarbital, PHT: phenytoin, RFN: Rufinamide, TGB: tiagabine, TPM: topiramate, VGB: vigabatrin, VPA: valproic acid, ZNC: zonisamide

การพัฒนาการของยากันชัก 160 ปี

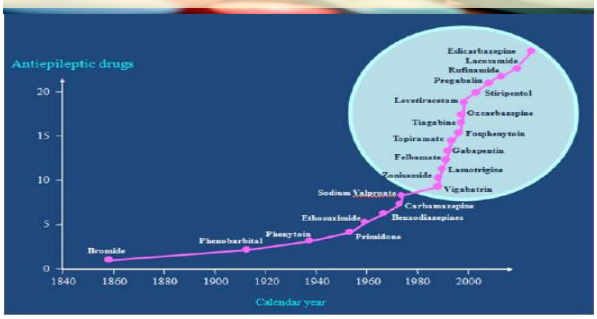


Fig. 1. Chronology of antiepileptic drug introduction over the past 150 years.

วัตถุประสงค์

- ❑นำเสนอผลการศึกษายากันชักรุ่นใหม่ล่าสุด
- ❑นำเสนอวิธีการนำผลการศึกษามาใช้ในทางปฏิบัติ

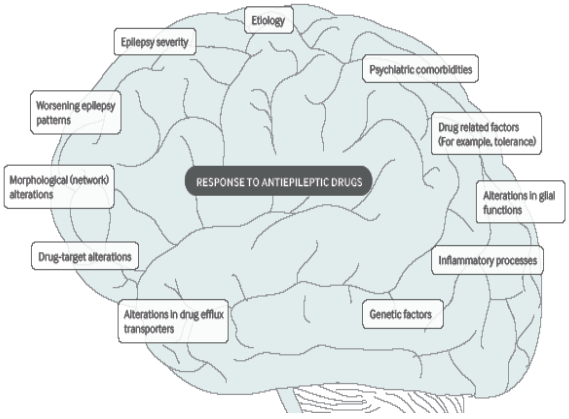
ทำไมต้องมียากันชักรุ่นใหม่ๆ

- ❑ยากันชักรุ่นมาตรฐานมีข้อจำกัด
- ❑ยากันชักรุ่นใหม่ก็ยังดีไม่พอ
- ❑ผู้ป่วยไม่ตอบสนองต่อยากันชักที่มีอยู่ในปัจจุบัน
- ❑ผลเสียของยากันชักที่มีในปัจจุบัน
- ❑ทิศทางการรักษาด้วย polytherapy ในกรณีรักษายาก
- ❑ผลการรักษายังไม่ดีพอ จำเป็นต้องมียาชนิดใหม่ๆ
- ❑การพัฒนาการของมนุษย์ที่มีอย่างต่อเนื่อง
- ❑ธุรกิจที่ต้องมีการแข่งขันการอย่างรุนแรงและต่อเนื่อง

Pharmacoresistance is a moving target

William Gowers :

"What is the prospect, in any given case, that an arrest of the fits can be obtained by treatment? The indications of the prognosis have been materially changed by the introduction of the bromides as remedies for epilepsy. Not only do they arrest fits far more frequently than any other remedy, but they are effective in many cases which, according to experience previous to the introduction of these remedies, would have been regarded as most unpromising. Hence, by their use, the conditions of the prognosis have been essentially changed".[52]



Mechanism of antiepileptic drugs

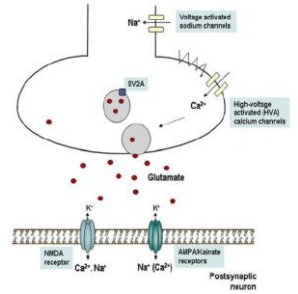


Fig. 1. The figure illustrates different targets directly or indirectly influencing excitatory signaling. Please note that voltage-gated ion channels are not only expressed

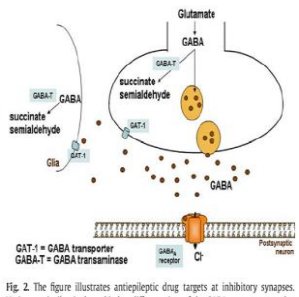


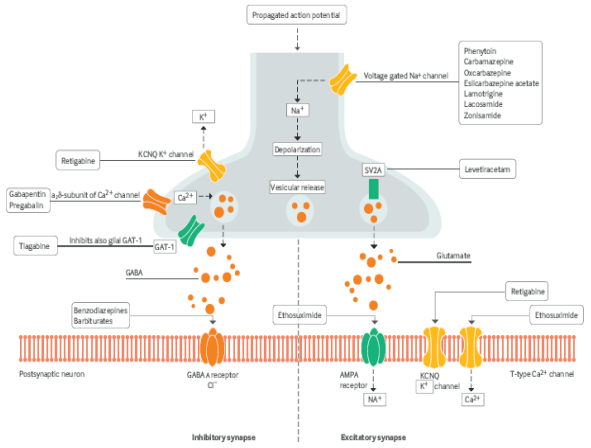
Fig. 2. The figure illustrates antiepileptic drug targets at inhibitory synapses. Various antiepileptic drugs bind to different sites of the $GABA_A$ receptor complex and act as agonists at $GABA_A$ receptors allosterically enhancing GABAergic

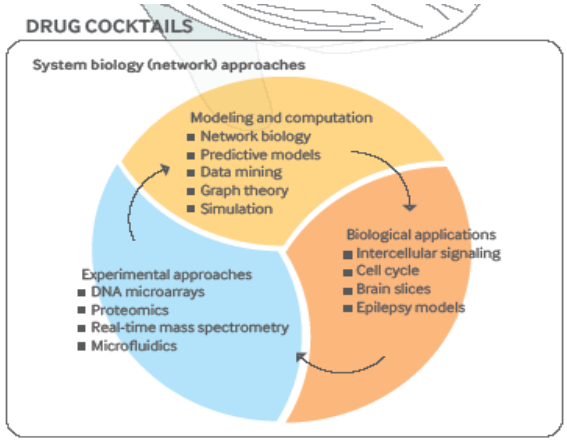
Mechanism of antiepileptic drugs

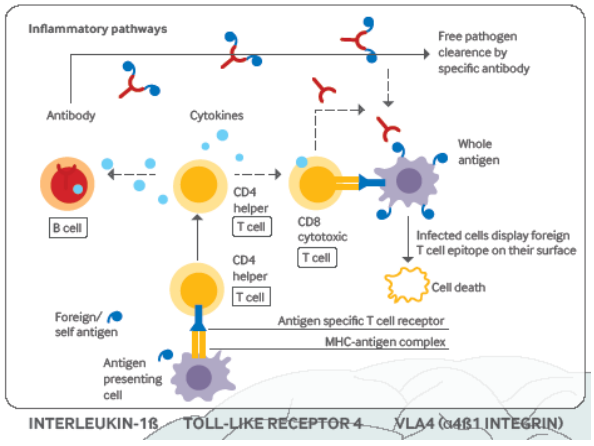
- ❑ Targeting of voltage-gated sodium and calcium channels
- ❑ Targeting of GABAergic neurotransmission
- ❑ Targeting of glutamatergic neurotransmission
- ❑ SV2A
- ❑ KCNQ/Kv7 potassium channels
- ❑ HCN channels

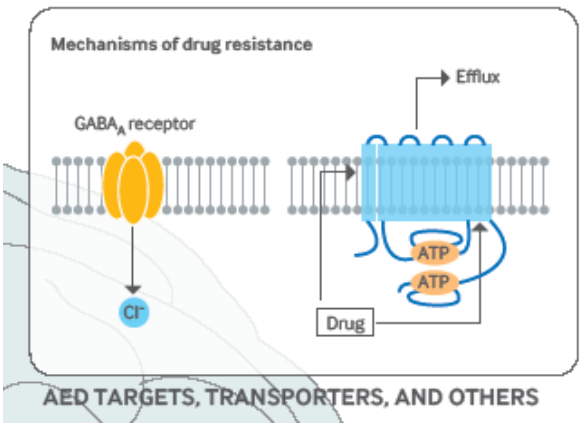
Pharmacological treatment strategies: Mechanisms of antiepileptic drugs Epileptology 1 (2013) 31–37

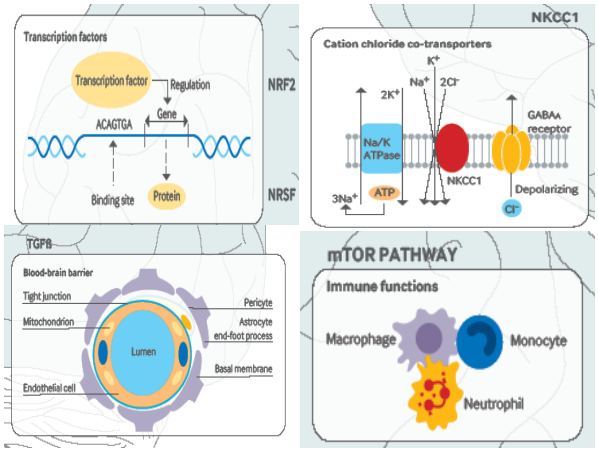
Heidrun Potschka*


Propagated action potential
Voltage gated Na+ channel
Phenytoin
Carbamazepine
Oxcarbazepine
Eslicarbazepine acetate
Lamotrigine
Lacosamide
Zonisamide
Na+
K+
Depolarization
Retigabine
KCNQ K+ channel
Vesicular release
SV2A
Levetiracetam
Gabapentin
Pregabalin
α2δ-subunit of Ca2+ channel
Ca2+
Tiagabine
Inhibits also glial GAT-1
GAT-1
GABA
Glutamate
Retigabine
Benzodiazepines
Barbiturates
Ethosuximide
Ethosuximide
Postsynaptic neuron
GABA A receptor
Cl−
AMPA receptor
NA+
KCNQ K+ channel
T-type Ca2+ channel
Ca2+
Inhibitory synapse
Excitatory synapse


DRUG COCKTAILS
System biology (network) approaches
Modeling and computation
Network biology
Predictive models
Data mining
Graph theory
Simulation
Biological applications
Intercellular signaling
Cell cycle
Brain slices
Epilepsy models
Experimental approaches
DNA microarrays
Proteomics
Real-time mass spectrometry
Microfluidics


Inflammatory pathways
Free pathogen clearence by specific antibody
Antibody
Cytokines
Whole antigen
B cell
CD4 helper T cell
CD8 cytotoxic T cell
Infected cells display foreign T cell epitope on their surface
CD4 helper T cell
Cell death
Foreign/ self antigen
Antigen specific T cell receptor
MHC-antigen complex
Antigen presenting cell
INTERLEUKIN-1ß
TOLL-LIKE RECEPTOR 4
VLA4 (α4ß1 INTEGRIN)


Mechanisms of drug resistance
Efflux
GABA$_A$ receptor
ATP
ATP
Cl−
Drug
AED TARGETS, TRANSPORTERS, AND OTHERS



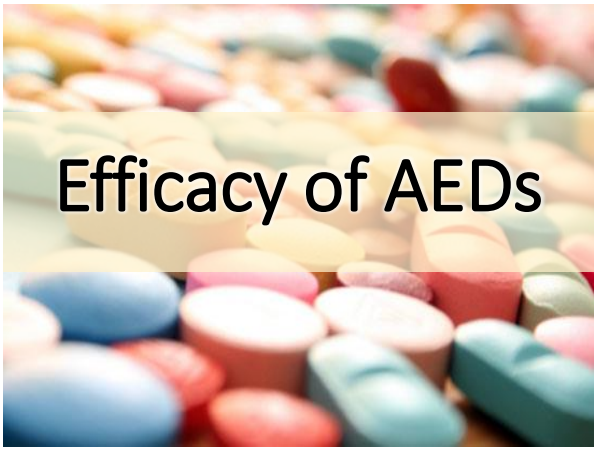
Compound	Sodium channel[a]	Calcium channel	GABA system	Other (incl. glutam. system)
Benzodiazepines			$GABA_A$ R	
Carbamazepine	Na_v fast inactivation			
Eslicarbazepine acetate	Na_v fast inactivation			
Ethosuximide		Ca_v T-type		
Felbamate	Na_v fast inactivation	Ca_v HVA	$GABA_A$ R	NMDA R
Gabapentin		Ca_v HVA ($\alpha_2\delta$)	↑ GABA turnover	
Lacosamide	Na_v slow inactivation			
Lamotrigine	Na_v fast inactivation	Ca_v HVA		HCN channel
Levetiracetam		Ca_v HVA	Affects modulation of $GABA_A$ R	SV2A
Oxcarbazepine	Na_v fast inactivation			
Perampanel				AMPA R
Phenobarbital		Ca_v HVA	$GABA_A$ R	AMPA R
(Fos)Phenytoin	Na_v fast inactivation			
Pregabalin		Ca_v HVA ($\alpha_2\delta$)		
Retigabine			$GABA_A$ R	K_v7 (KCNQ)
Tiagabine			GABA transporter GAT-1	
Topiramate	Na_v fast inactivation	Ca_v HVA	$GABA_A$ R	KA/AMPA R
Valproate	Na_v?	Ca_v T-type?	↑ GABA turnover GABA transaminase	
Vigabatrin			GABA release ↑	
Zonisamide	Na_v fast inactivation	Ca_v T-type		

Na_v voltage-gated sodium channel; Ca_v voltage-gated calcium; HVA high voltage activated calcium channel; GABA γ-aminobutyric acid; NMDA R N-methyl-D-aspartate; KA R kainate receptor; AMPA R α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; K_v7 (KCNQ) potassium channel subtype.

Mechanisms of action of antiepileptic drugs.

	Decreased Na^+ channels	Decreased Ca^{2+} channels[a]	Increased GABA transmission	Decreased glutamate transmission
Established antiepileptic drugs				
Benzodiazepines			++	
Carbamazepine	++			
Ethosuximide		++ (T-type)		
Phenobarbital		?	++	?
Phenytoin	++			
Valproate	?	? (T-type)	+	?
Modern antiepileptic drugs				
Eslicarbazepine	++			
Felbamate	+	?	+	+
Gabapentin	?	++ (alpha2-delta)	+	
Lacosamide	+			
Lamotrigine	++	?		
Levetiracetam[*]		?	?	?
Oxcarbazepine	++			
Pregabalin		++ (alpha2-delta)		
Rufinamide	++			
Tiagabine			++	
Topiramate	+	+	+	+
Vigabatrin			++	
Zonisamide	+	+ (T-type)		?

(++) primary action; (+) probable action; (?) possible action.
[a] Unless otherwise stated, action on high voltage activated calcium channels.
[*] Levetiracetam acts by binding to synaptic vesicle protein 2A (SV2A).



Network meta-analyses of antiepileptic drug efficacy and tolerability in drug-resistant focal epilepsies: a clinical perspective

Published online: 28 March 2014
Eur J Clin Pharmacol
DOI 10.1007/s00228-014-1669-y

Gaetano Zaccara · Fabio Giovannelli · Gail S. Bell · Josemir W. Sander

Responder rate	Percentage of individuals with a ≥ 50 % seizure improvement compared with a baseline preceding randomization. This measure usually refers to all seizures. The responder rate has also been separately calculated in some studies for each different kind of seizure (either simple or complex), and most importantly, for secondarily generalized seizures in individuals with these seizures. These measures may refer to the maintenance phase or to the total duration of a double-blind study (titration plus maintenance)
Percentage of patients who achieved seizure freedom	Percentage of individuals who acquire seizure freedom. This outcome measure may refer to the maintenance phase or to the total duration of a double-blind study (titration plus maintenance)
Withdrawal rate	Percentage of individuals who discontinued from the study (all causes)
Rate of withdrawal due to adverse effects	Percentage of individuals who discontinued because of adverse effects
Adverse effects rates	Percentages of individuals with at least one treatment emergent adverse effect

- Studies do not measure relevant outcomes in children
- Newer generation drugs offer better kinetics and tolerability
- Vigabatrin for infantile spasms due to tuberous sclerosis
- Topiramate, clobazam, and stiripentol for Dravet syndrome
- Lamotrigine for children with a range of epilepsies
- Felbamate use in the severe epilepsies of childhood

- Greater variety of drugs allowing better patient tailoring
- New agents not involved in hypersensitivity or interactions
- Avoidance of valproate and polytherapy in pregnancy
- Introduction of buccal midazolam as a rescue medication
- Lamotrigine with valproate for difficult-to-treat epilepsies
- Levetiracetam /topiramate for idiopathic generalised epilepsies

Table 2 Newer AED vs placebo: responder rates (Mean and 95%CI).

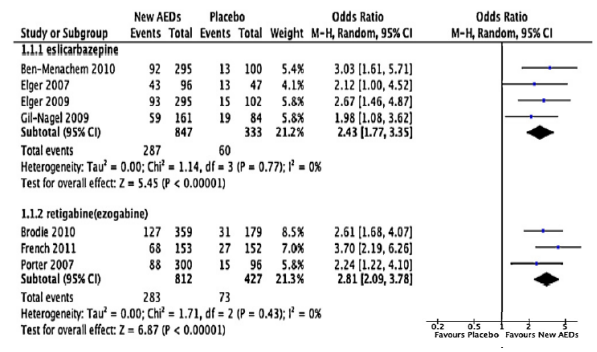
New AED	Risk Ratio (RR)	Risk Difference (RD)	NNT (all doses)	NNT (dose with maximum responder rate)
ESL	1.89 (1.47, 2.42)	0.17 (0.12, 0.22)	5.88 (4.55, 8.33)	4.55 (3.45, 6.67)[a]
RTG	2.16 (1.71, 2.71)	0.19 (0.12, 0.26)	5.26 (3.85, 8.33)	4.34 (3.23, 6.67)[b]
CAR	1.35 (1.12, 1.61)	0.07 (0.04, 0.11)	14.29 (9.09, 25.00)	NA
LAC	1.68 (1.35, 2.08)	0.16 (0.11, 0.21)	6.25 (4.76, 9.09)	5.00 (3.58, 9.09)[c]
BRI	2.58 (1.39, 4.81)	0.26 (0.14, 0.39)	3.85 (2.56, 7.14)	NA
PER	1.53 (0.89, 2.61)	0.11 (−0.02, 0.24)	9.09 (4.17, 50.00)	NA

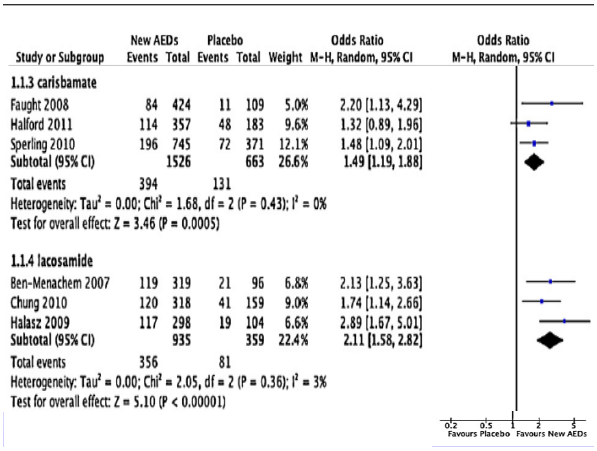
NA: not available.
[a] Eslicabazepine 1200 mg/day.
[b] Retigabine 1200 mg/day.
[c] Lacosamide 600 mg/day.

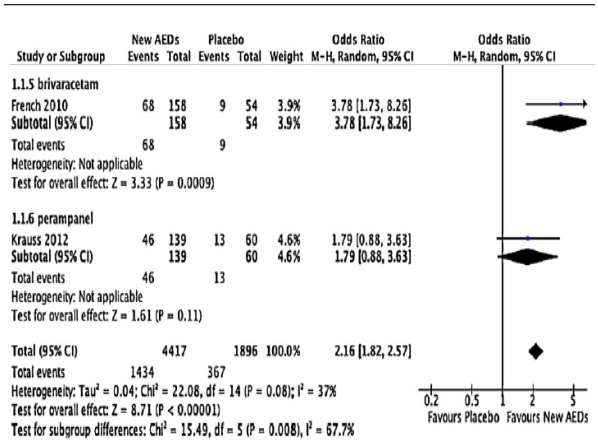
Clinical efficacy and safety of the newer antiepileptic drugs as adjunctive treatment in adults with refractory partial-onset epilepsy: A meta-analysis of randomized placebo-controlled trials

Epilepsy Research (2013) 103, 31—44

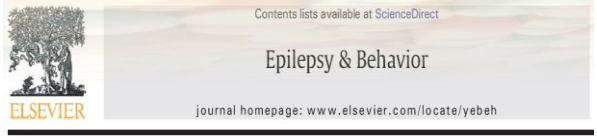
Efficacy of AEDs







Efficacy of AEDs add on therapy in clinical practice



Prospective audits with newer antiepileptic drugs in focal epilepsy: Insights into population responses?

Martin J. Brodie, Kevin Kelly, Linda J. Stephen *

Epilepsy Unit, Western Infirmary, Glasgow, Scotland, UK

Efficacy of AEDs add on therapy

Outcomes in prospective audits with adjunctive new antiepileptic drugs (AEDs) in localization-related epilepsies.

AED	Number of patients	Seizure-free (%)	Responders[a] (%)	Marginal response[b] (%)	Withdrawn (%)
Topiramate	135	28 (20.7)	65 (48.2)		42 (31.1)
Levetiracetam	136	32 (23.5)	28 (20.6)	32 (23.5)	44 (32.4)
Zonisamide	141	18 (12.8)	21 (14.9)	43 (30.5)	59 (41.8)
Pregabalin	135	14 (10.4)	33 (24.4)	20 (14.8)	68 (50.4)
Lacosamide	160	35 (21.9)	35 (21.9)	54 (33.7)	36 (22.5)

[a] ≥50% reduction in seizure frequency compared with baseline seizure frequency.
[b] <50% reduction in seizure frequency compared with baseline seizure frequency.

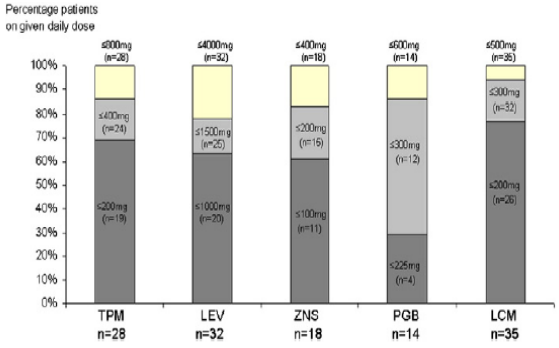


Fig. 2. Daily dosing in patients seizure-free on adjunctive topiramate (TPM), levetiracetam (LEV), zonisamide (ZNS), pregabalin (PGB), or lacosamide (LCM).

Tolerability of new AEDs

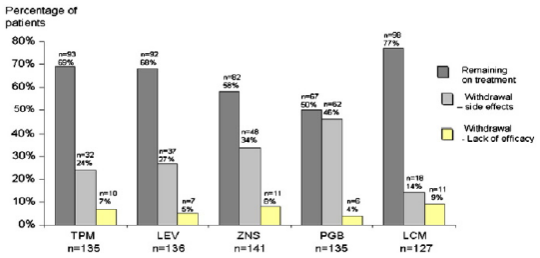


Fig. 3. Percentage of patients who continued or discontinued topiramate (TPM), levetiracetam (LEV), zonisamide (ZNS), pregabalin (PGB), or lacosamide (LCM).

Commonest side effect

Topiramate n = 42, 31.1%		Levetiracetam n = 44, 32.4%	
Side effect	n	Side effect	n
Fatigue	17	Sedation	20
Weight loss	12	Fatigue	4
Irritability	9	Headache	4
Paraesthesia	8	Worsening seizures	4
Depression	7	Aggression	3
Headache	6		
Word finding problems	4		
Tremor	3		
Diplopia	3		

Commonest side effect

Zonisamide n = 59, 41.8%		Pregabalin n = 68, 50.4%		Lacosamide n = 36, 22.5%	
Side effect	n	Side effect	n	Side effect	n
Sedation	14	Sedation	18	Nausea/vomiting	6
Nausea/vomiting	13	Weight gain	14	Dizziness	5
Depression	7	Ataxia	9	Sedation	5
Rash	6	Worsening seizures	7	Headache	4
Weight loss	6	Vertigo	6	Tremor	4
Poor memory	6	Fatigue	5	Ataxia	4
Headache	5	Diplopia	5	Rash	4
Abdominal pain	4	Depression	4	Diplopia	3
Aggression	3	Nausea	3		
Anorexia	3				
Ataxia	3				

Medical management of refractory epilepsy—Practical treatment with novel antiepileptic drugs

Elinor Ben-Menachem

- ❑Rufinamide
- ❑Lacosamide
- ❑Vigabatrin
- ❑Perampanel
- ❑Eslicarbazepine acetate
- ❑Retigabine

Rufinamide

- ❑Adjunctive treatment of Lennox-Gastaut syndrome (LGS) in the United States in 2004 and in 2007 in the EU, age >4 yr
- ❑Adjunctive treatment of partial seizures in adults and adolescents
- ❑Added to any other AED with minimal interactions occurring
- ❑No special black box warnings
- ❑Start at a low dose such as 400 mg and increase every few days

Lacosamide

- ❑Adjunctive therapy for patients with partial epilepsy
- ❑Dual mode of action—enhancement of sodium channel slow inactivation and modulation of collapsing response mediator protein-2 (CRMP-2) are novel mechanisms
- ❑Randomized phase II/III clinical trials and long-term follow-up
- ❑Dizziness, headache, nausea, and diplopia
- ❑Starting dose of 50 mg with a titration rate of 50 mg/week
- ❑Refractory status epilepticus

Vigabatrin

- A synthetic GABA derivative
- Vigabatrin may worsen myoclonic seizures
- Irreversible VF defects 30–40%, depression, weight gain
- No drug interactions between VGB and AEDs
- Monotherapy in the treatment of infantile spasms
- Adjunctive therapy for very resistant partial seizures
- Black box warnings for VGB : check VF

Perampanel: approved 2012

- Noncompetitive a-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid (AMPA)–type glutamate receptor antagonist
- Add-on therapy for refractory partial onset seizures with or without generalization
- Phase III good efficacy with tolerable side effects, dizziness, somnolence, diplopia, and ataxia
- CBZ will decrease the half-life of PER

Eslicarbazepine acetate

- Eslicarbazepine acetate (ESL) is the third member in a family of dibenz/b,f/asepine AEDs represented by CBZ (first-generation) and oxcarbazepine (OXC, second generation)
- Cytochrome P450 (CYP) liver enzyme system.
- Less risk for drug–drug interaction when compared to CBZ and OXC
- The phase III refractory partial onset seizures as an add-on
- Monotherapy studies for new-onset epilepsy are ongoing

Retigabine: available since 2011

- Add-on therapy for patients with refractory partial onset
- First neuronal KCNQ agonist to be approved as an AED
- Opening of the voltage-gated potassium channel, enhancing the M-type potassium current
- Phase III positive in patients with refractory focal onset
- Most common side effects are dizziness, somnolence, fatigue, confusion, dysarthria, ataxia, diplopia, and urinary tract infection
- Risk for urinary retention
- The unexpected side effect is the development of a blue hue to the skin and retina after long-term use

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SHORT COMMUNICATION

Adjunctive use of ezogabine/retigabine with either traditional sodium channel blocking antiepileptic drugs (AEDs) or AEDs with other mechanisms of action: Evaluation of efficacy and tolerability

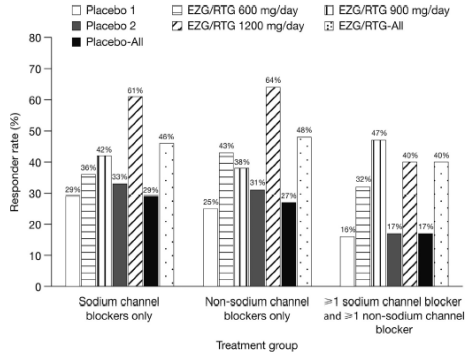


Figure 1 Responder rates during the maintenance phase for patients receiving EZG/RTG or placebo adjunctive to traditional sodium channel blocking AEDs, non-sodium channel blocking AEDs, or ≥1 sodium and ≥1 non-sodium channel blocking AED. AEDs, antiepileptic drugs; EZG/RTG, ezogabine/retigabine.

Stiripentol: Dravet syndrome, no hepatologic

Analysis 1.1. Comparison 1 Add-on stiripentol versus placebo, Outcome 1 ≥ 50% seizure reduction.

Review: Stiripentol for focal refractory epilepsy

Comparison: 1 Add-on stiripentol versus placebo

Outcome: 1 ≥ 50% seizure reduction

Study or subgroup	Add-on stiripentol n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Chiron 2006	12/17	7/15		100.0 %	1.51 [0.81, 2.82]
Total (95% CI)	**17**	**15**		**100.0 %**	**1.51 [0.81, 2.82]**

Total events: 12 (Add-on stiripentol), 7 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 1.30 (P = 0.19)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
More in placebo group More in stiripentol group

Seizure Exacerbation

- CBZ (carbamazepine), OXC (oxcarbazepine), PHT (phenytoin), VGB (vigabatrin), and TGB (tiagabine) may worsen myoclonus and absences
- GBP (gabapentin),myoclonus
- LTG (lamotrigine), myoclonus
- Benzodiazepines, tonic seizures

Box 2 | Preferred first line antiepileptic drugs for new onset and refractory epilepsy in adults[26 43]

New onset partial epilepsies
Carbamazepine
Gabapentin
Lamotrigine
Levetiracetam
Oxcarbazepine
Topiramate
Valproate

New onset idiopathic generalized epilepsies
Lamotrigine
Topiramate
Valproate

Refractory partial epilepsy
Lacosamide
Pregabalin
Zonisamide
Perampanel
Clobazam

Refractory idiopathic generalized epilepsies
Clobazam
Levetiracetam

Drug treatment of epilepsy in adults

Dieter Schmidt,[1] Steven C Schachter[2]

BMJ 2014;348:g2546

Short communication

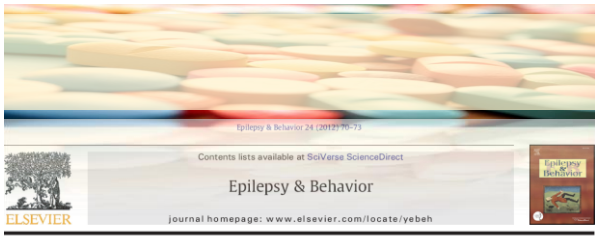
Efficacy of intravenous lacosamide as an add-on treatment in refractory status epilepticus: A multicentric prospective study

Efficacy of IV Lacosamide

Treatment parameters and outcomes.

	Total	LCM third/fourth	LCM fifth or later
	34	18 (52.9%)	16 (47.1%)
LCM efficacy	22 (64.7%)	13 (72.2%)	9 (56.3%)
Latency (h) onset SE–SE therapy			
Median (range)	4.5 (0.3–240)	12.0 (1.0–144)	1.0 (0.3–240)
Latency (h) onset SE–LCM			
Median (range)	48.0 (1.0–250)	60.0 (6.0–168)	48.0 (1.0–250)
Treatment before LCM			
Benzodiazepines	29	13	16
Phenytoin	24	8	16
Valproic acid	28	13	15
Levetiracetam	30	14	16
Anesthesia	1	0	1
LCM dose (mean, range)	323.53 (100–400)	322.22 (100–400)	325.00 (200–400)
Mean initial bolus (mg)	323.53 (100–600)	355.56 (100–600)	287.50 (100–400)
Mean daily dose (mg)			
Termination of SE by LCM iv			
<12 h after LCM iv	17 (50%)	9 (50%)	8 (50%)
>12 to <48 h after LCM iv	5 (14.7%)	4 (22.2%)	1 (6.3%)
Further AED therapy needed	12 (35.3%)	5 (27.8%)	7 (43.7%)
Outcome	31 (91.2%)	18 (100%)	13 (81.3%)
Termination of SE	3 (8.8%)	0	3 (18.7%)
No termination of SE			

LCM, lacosamide; SE, status epilepticus; iv, intravenous; AED, anti-epileptic drugs.



Newer antiepileptic drugs in the treatment of status epilepticus: Impact on prognosis

Léonore Jaques, Andrea O. Rossetti *
Department of Clinical Neurosciences, University Hospital (CHUV) and Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland

- SE severity score, and number of compounds needed to terminate SE, newer AEDs were independently related to a reduced likelihood of return to baseline (pb0.001) but not to increased mortality

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Newer antiepileptic drugs in the treatment of status epilepticus: Impact on prognosis

	Lack of return to baseline	Mortality
Use of newer AED	2.14 (1.11–4.12), p = 0.022	1.00 (0.40–2.51), p = 1.000
STESS 3–6	3.94 (2.33–6.67), p < 0.001	3.80 (1.65–8.62), p = 0.002
Potentially fatal etiology	5.38 (3.12–9.13), p < 0.001	4.32 (1.99–9.39), p < 0.001
Use of > 2 AED	2.16 (1.06–4.42), p = 0.034	1.37 (0.85–2.13), p = 0.106

AED = antiepileptic drugs; STESS = status epilepticus severity score.

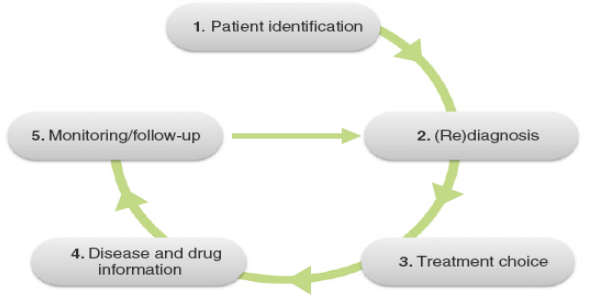
Multivariable logistic regression models using risk of lack to return to baseline clinical conditions at hospital discharge, or mortality, as outcome. Results are given as OR (95% CI).

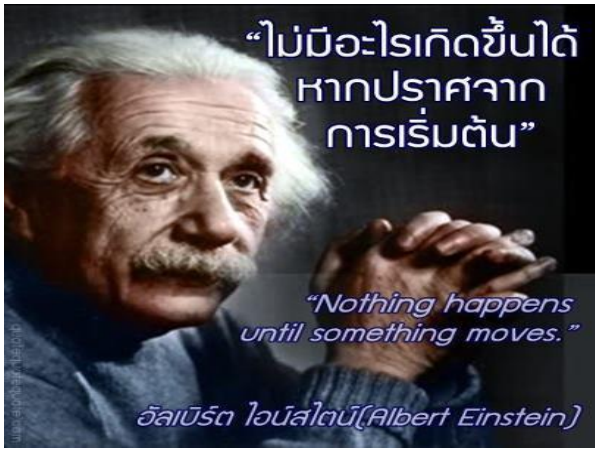
Side effect of AEDs

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	●	-	-	-	-	-	-	-	●	●	-	-	-	●	-	-	-	-	-	-

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																●		●		

วงจรการรักษาผู้ป่วยโรคลมชัก




“ไม่มีอะไรเกิดขึ้นได้
หากปราศจาก
การเริ่มต้น”
“Nothing happens
until something moves.”
อัลเบิร์ต ไอน์สไตน์(Albert Einstein)