New Antiepileptic Drugs in Children

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Antiepileptic drugs: FDA approval

Before 1993	1993-2005	2009-2014
Carbamazepine	Felbamate	Vigabatrin
Clonazepam	Gabapentin	**Rufinamide** (≥ 4 yrs with LGS)
Diazepam	Lamotrigine	**Lacosamide** (≥ 17 yrs)
Ethosuccimide	Levetiracetam	Clobazam (≥ 2 yrs with LGS)
Lorazepam	Oxcarbazepine	Ezogabine (≥ 18 yrs)
Phenobarbital	Pregabalin	**Perampanel** (≥ 12 yrs)
Phenytoin	Tiagabine	Eslicarbazepine (≥ 18 yrs)
Primidone	Topiramate	
Valproic acid	VNS	**Stiripental (only in Europe)**
	Zonisamide	

Lacosamide

- Available now in Thailand
- FDA approve in adjunctive therapy in patients ≥ 17 years with partial onset seizure
- Available in
  - Oral solution
  - Tablet
  - Injection

Pediatric use of Lasosamide

- Not yet FDA approve
- However, data of the use of lacosamide in pediatric population is promising
  - Use in pediatric patients
  - Use in very young patients
  - Use in Lennox-Gastaut syndrome
  - Use in Status epilepticus

Table 2. Pediatric Lacosamide Case Series and Retrospective Studies[8-11]

Study	No. of Patients Age (range)	Seizure Type	Patients experiencing ≥50% reduction in seizure frequency	Patients who discontinued therapy (%)	Mean Effective Dosage (mg/kg/day) (range)	Adverse effects reported during treatment (%)
Gavatha et al[9]	14 (3-18 yr)	Focal onset	5 (36%)	12 (67%) due to lack of efficacy at initial assessment 1 (6%) due to ADE	6.34 (1.7-10)	Somnolence (17%), irritability (11%), sleep disturbances (6%), pancytopenia (6%)
Guilhoto et al[10]	16 (8-21 yr)	Focal onset	6 (37.5%)	2 (12.5%) due to lack of efficacy 4 (25%) due to ADE	4.7 (0.5-8.8)	Nausea and vomiting (12.5%), headache (6%), blurred vision (6%), tics (6%), behavioral outbursts (6%), ataxia(6%), and depression (6%)
Heyman et al[11]	17 (1.5-16 yr)	Focal onset, tonic, generalized tonic-clonic*	6 (35%)	6 (35%) due to lack of efficacy	12.39 (6.7-20)	Nausea (18%), dizziness (18%), restlessness (12%), fatigue (12%), headache (12%), increased appetite (6%), prolonged crying (6%)
Rastogi et al[12]	16 (1-16 yr)	Focal, atonic, tonic, tonic, clonic, myolonic, atypical absence*	8 (50%)	NR	9.4 (2.4-19.4)	nausea, vomiting, gastrointestinal intolerance, dizziness, headache, somnolence, facial edema (frequency not specified)

ADE, adverse drug event; NR, not reported
** Included patients with Lennox-Gastaut syndrome (LGS)*

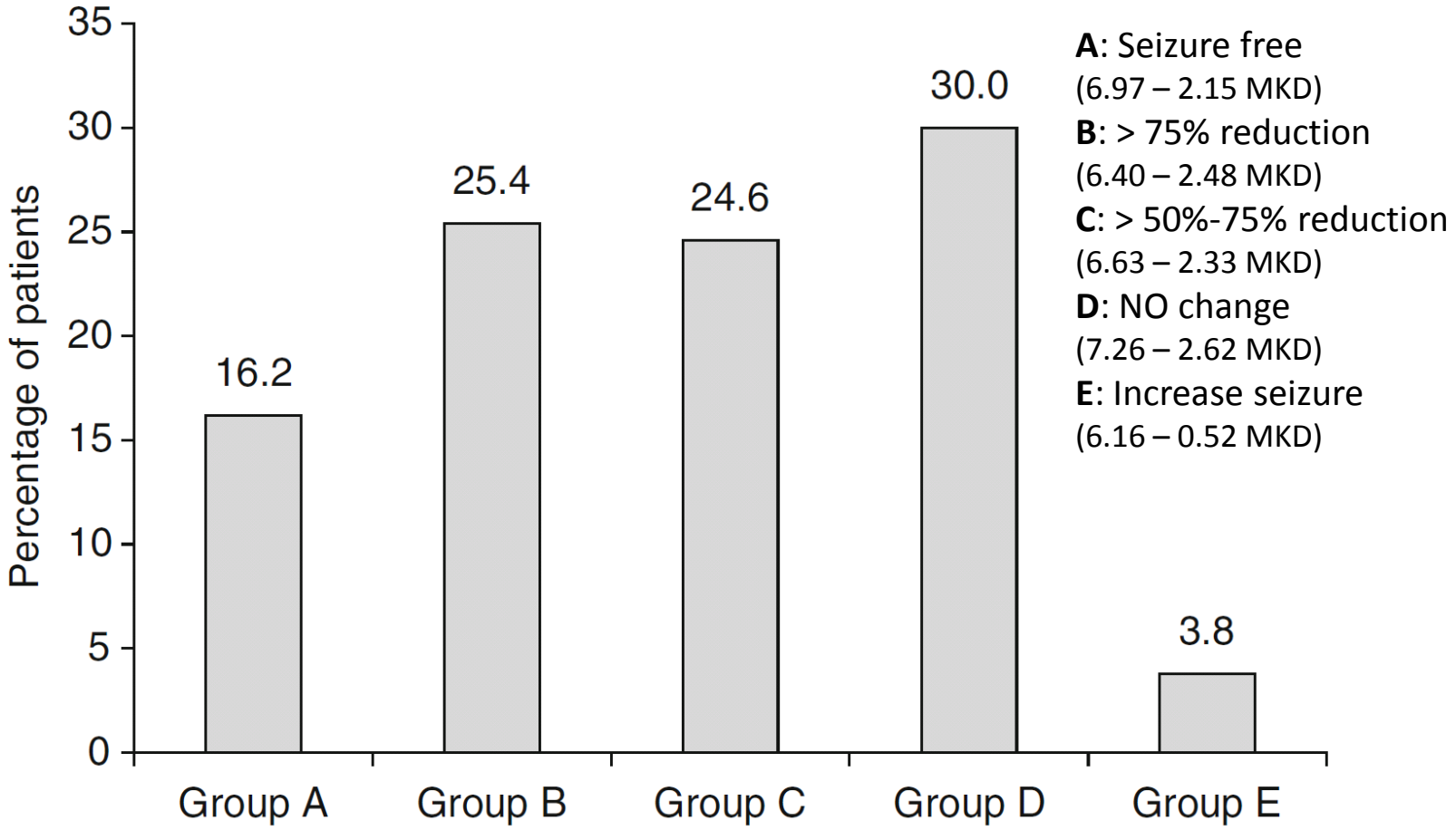
Efficacy and Tolerability of Lacosamide in the Concomitant Treatment of 130 Patients Under 16 Years of Age with Refractory Epilepsy

A Prospective, Open-Label, Observational, Multicenter Study in Spain

- Prospective, open-label, observational
- Multicenter study
- 130 patients (6 mo. – 16 years)
- 1-2 MKD initial dose to 6.80 ± 2.39 MKD
- Accessed at 3 mo.

Casas-Fernandez, 2012

Result


Percentage of patients
35
30
25
20
15
10
5
0
16.2
25.4
24.6
30.0
3.8
Group A
Group B
Group C
Group D
Group E
A: Seizure free
(6.97 – 2.15 MKD)
B: > 75% reduction
(6.40 – 2.48 MKD)
C: > 50%-75% reduction
(6.63 – 2.33 MKD)
D: NO change
(7.26 – 2.62 MKD)
E: Increase seizure
(6.16 – 0.52 MKD)

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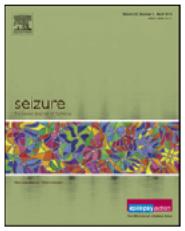
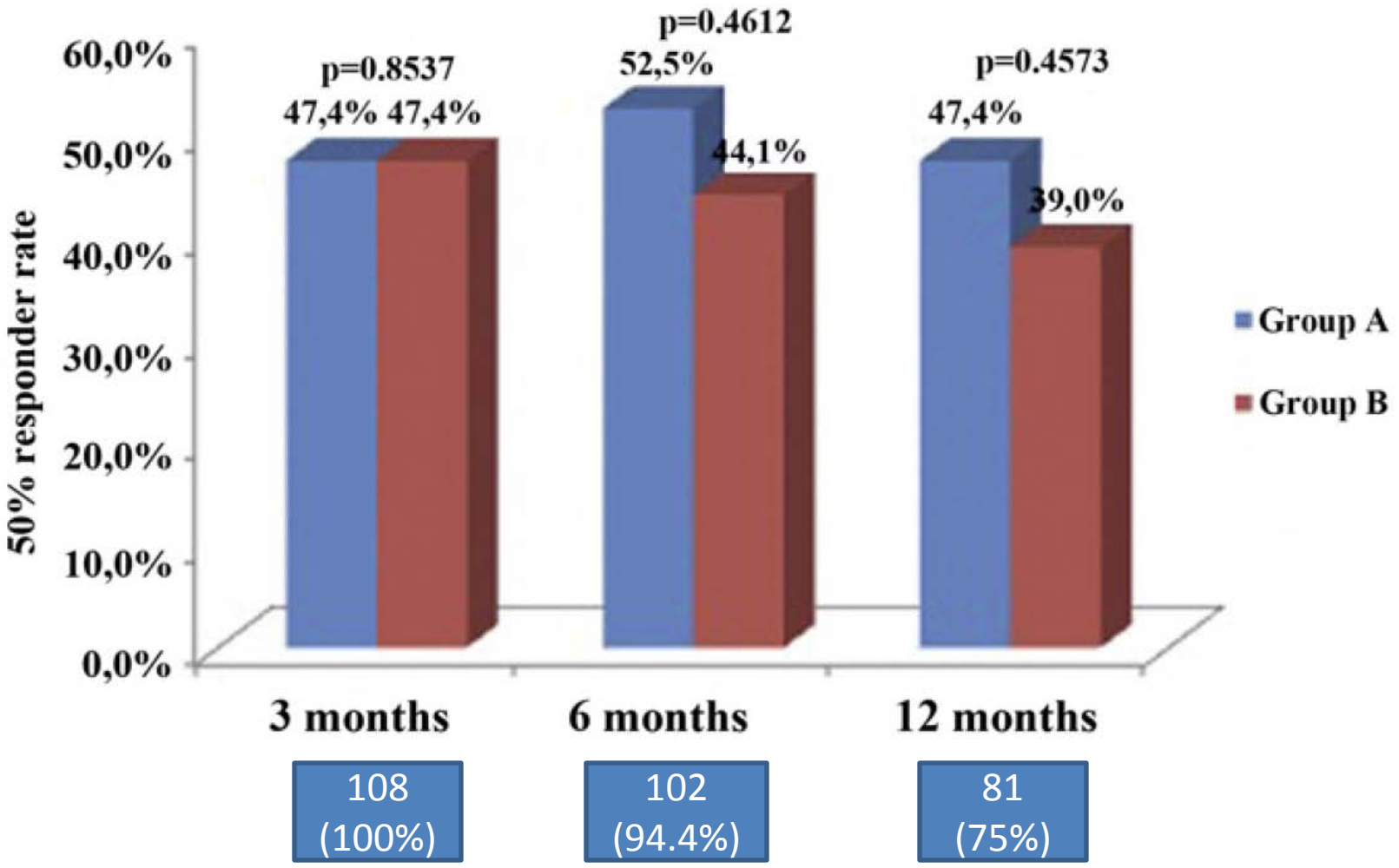


Lacosamide in pediatric and adult patients: Comparison of efficacy and safety

Alberto Verrotti [a,*], Giulia Loiacono [a], Antonella Pizzolorusso [a], Pasquale Parisi [b], Oliviero Bruni [b], Anna Luchetti [b], Nelia Zamponi [c], Silvia Cappanera [c], Salvatore Grosso [d], Gerhard Kluger [e], Christine Janello [e], Emilio Franzoni [f], Maurizio Elia [g], Alberto Spalice [h], Giangennaro Coppola [i], Pasquale Striano [j], Piero Pavone [k], Salvatore Savasta [l], Maurizio Viri [m], Antonino Romeo [m], Paolo Aloisi [n], Giuseppe Gobbi [o], Alessandro Ferretti [b], Raffaella Cusmai [p], Paolo Curatolo [q]

- Prospective study
- **Group A** (4 - ≤ 16 yr) 1 MKD to 3-12 MKD
- **Group B** (≥ 16 yr) 100 mg/day to 100-600 mg/day
- Uncontrolled generalized and focal epilepsy

General efficacy



Responses by seizure types

Table 2
Efficacy by seizure type.

Seizure type	3-Month follow-up				6-Month follow-up				12-Month follow-up			
	100% responders *n* (%)	50% responders *n* (%)	Non-responders *n* (%)	Worsening patients *n* (%)	100% responders *n* (%)	50% responders *n* (%)	Non-responders n (%)	Worsening patients *n* (%)	100% responders *n* (%)	50% responders *n* (%)	Non-responders *n* (%)	Worsening patients *n* (%)
Generalized												
Group A (*n* = 12)	1 (8.3%)	4 (33.3%)	3 (25%)	4 (33.3%)	–	4 (33.3%)	2 (16.7%)	–	–	4 (33.3%)	1 (8.3%)	–
Group B (*n* = 4)	1 (25%)	–	2 (50%)	1 (25%)	1 (25%)	–	2 (50%)	–	1 (25%)	–	1 (25%)	–
Total (*n* = 16)	2 (12.5%)[c]	4 (25%)	5 (31.2%)	5 (31.2%)[a,b]	1 (6.3%)	4 (25%)[a]	4 (25%)	–	1 (6.3%)	4 (25%)[a]	2 (12.5%)	–
Focal												
Group A (*n* = 19)	3 (15.8%)	7 (36.8%)	8 (42.1%)	1 (5.3%)	–	12 (63.2%)	6 (31.6%)	–	–	11 (57.9%)	4 (21.1%)	–
Group B (*n* = 10)	1 (10%)	6 (60%)	3 (30%)	–	–	7 (70%)	3 (30%)	–	–	7 (70%)	1 (10%)	–
Total (*n* = 29)	4 (13.8%)[d]	13 (44.8%)	11 (37.9%)	1 (3.5%)[a]	–	19 (65.5%)[a]	9 (31%)	–	–	18 (62.1%)[a]	5 (17.2%)	–
Focal evolving to bilateral seizure												
Group A (*n* = 7)	–	5 (71.4%)	2 (28.6%)	–	–	3 (42.9%)	4 (57.1%)	–	–	2 (28.6%)	5 (71.4%)	–
Group B (*n* = 8)	–	4 (50%)	4 (50%)	–	–	3 (37.5%)	4 (50%)	–	–	2 (25%)	2 (25%)	–
Total (*n* = 15)	–	9 (60%)	6 (40%)	–	–	6 (40%)	8 (53.3%)	–	–	4 (26.7%)	7 (46.7%)[b]	–
Mixed												
Group A (*n* = 21)	–	12 (57.1%)	7 (33.3%)	2 (9.5%)	–	12 (57.1%)	7 (33.3%)	–	–	11 (52.4%)	8 (38.1%)	–
Group B (*n* = 37)	–	18 (48.7%)	17 (45.9%)	2 (5.4%)	–	16 (43.2%)	14 (37.8%)	2 (5.4%)	1 (2.7%)	14 (37.8%)	6 (16.2%)	–
Total (*n* = 58)	–	30 (51.7%)	24 (41.4%)	4 (6.9%)	–	28 (48.3%)	21 (36.2%)	2 (3.4%)	1 (1.7%)	25 (43.1%)	14 (24.1%)	–
Entire study population (*n* = 118)	6 (5.1%)	56 (47.4%)	46 (39%)	10 (8.5%)	1 (0.8%)	57 (48.3%)	42 (35.6%)	2 (1.7%)	2 (1.7%)	51 (43.2%)	28 (23.7%)	–

[a] $p < 0.05$, for comparison between generalized and focal groups.
[b] $p < 0.05$, for comparison between generalized and focal evolving to bilateral seizure groups.
[c] $p < 0.05$, for comparison between generalized and mixed groups.
[d] $p < 0.05$, for comparison between focal and focal evolving to bilateral seizure groups.

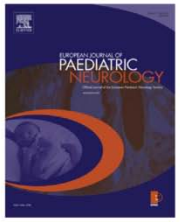
Poorer response in generalized group and best response in focal group

Side effects

- Generally mild
  - Dyspepsia
  - Headache
  - Dizziness, vomiting , irritability
- overall side effect 29.7%
  - Off the study due to SE 3.4%

EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 18 (2014) 55–59

Official Journal of the European Paediatric Neurology Society



Original article

Efficacy and safety of lacosamide in infants and young children with refractory focal epilepsy

- < 4 years old
- Focal seizure
- Start at 1-2 MKD increase weekly to maximum dose of 15.5 MKD
- 24 patients

Result

- At 3 month
  - 10/24 (42%) have > 50% seizure reduction
    - 4 (17%) seizure free
    - 6 (25%) with 50 % reduction
  - 9/24 (37.5%)Unchanged
  - 1/24 (4%) Increased
- More responder in cryptogenic > symptomatic
- 33% have adverse SE (drowsiness, nervousness, vomiting,)
  - Resolve with decreasing dose
  - 17% discontinue due to SE

Acta Neurologica Scandinavica

Acta Neurol Scand 2014: 129: 420–424 DOI: 10.1111/ane.12221

ACTA NEUROLOGICA
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Efficacy and tolerability of add-on lacosamide in children with Lennox-Gastaut syndrome

- Retrospective
- Multicenter
- Age < 16 yrs
- 18 patients (5.6-15 yrs)
- Atonic/Tonic/Atypical absence/Myoclonic/GTC and Focal seizure

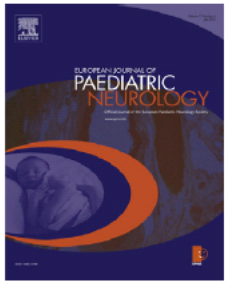
Result

- 33% show more than 50% reduction in seizure frequency after 9 mo. period
  - Highest in Tonic (31%)
  - Medium in GTC (29%)
  - Lowest in Drop attack (22%)
  - With focal seizure more than 75% reduction in 4/5 patients
- No seizure free
- Increase seizure frequency 17%

Status epilepticus

ELSEVIER

Official Journal of the European Paediatric Neurology Society



Original article

Lacosamide in children with refractory status epilepticus. A multicenter Italian experience

Salvatore Grosso [a,d,*], *Nelia Zamponi* [b], *Arnaldo Bartocci* [c], *Elisabetta Cesaroni* [b], *Silvia Cappanera* [b], *Rosanna Di Bartolo* [d], *Paolo Balestri* [d]

[a] *Pediatric Neurology-Immunology and Endocrinology Unit, University of Siena, Italy*
[b] *Child Neuropsychiatric Unit, University of Ancona, Italy*
[c] *Clinical Neurophysiology, University of Perugia, Italy*
[d] *Department of Pediatrics, University of Siena, Italy*

- Use of lacosamide as 4th or later AED
- 11 children (7-symptomatic)
- 6 with convulsive and 5 non-convulsive
- Mean bolus dose 8.6 mg/kg
- Effective in 45%
- Seizure terminate within 12 hrs in 3/11

Rufinamide

- Triazole derivative
- Modulation of sodium channel, in particular, prolongation of the time spent in the inactive state of the channel
- FDA approve of using as adjunctive treatment for patients with Lennox-Gastaut syndrome

Rufinamide

- Well absorb by oral administration with bioavailability of > 85%
- Absorption decrease progressively with chronic use
- Time to peak 4-6 hrs.
- Increase absorption with food
- Extensively metabolized (mainly with carboxyl-amidic group)
- Low plasma protein binding (< 35%)

Drug interaction

- Increase level with the use of VPA
- Decrease level with PB, PHT, CBZ
- Decrease CBZ, LTG,
- Increase level of PB, PHT

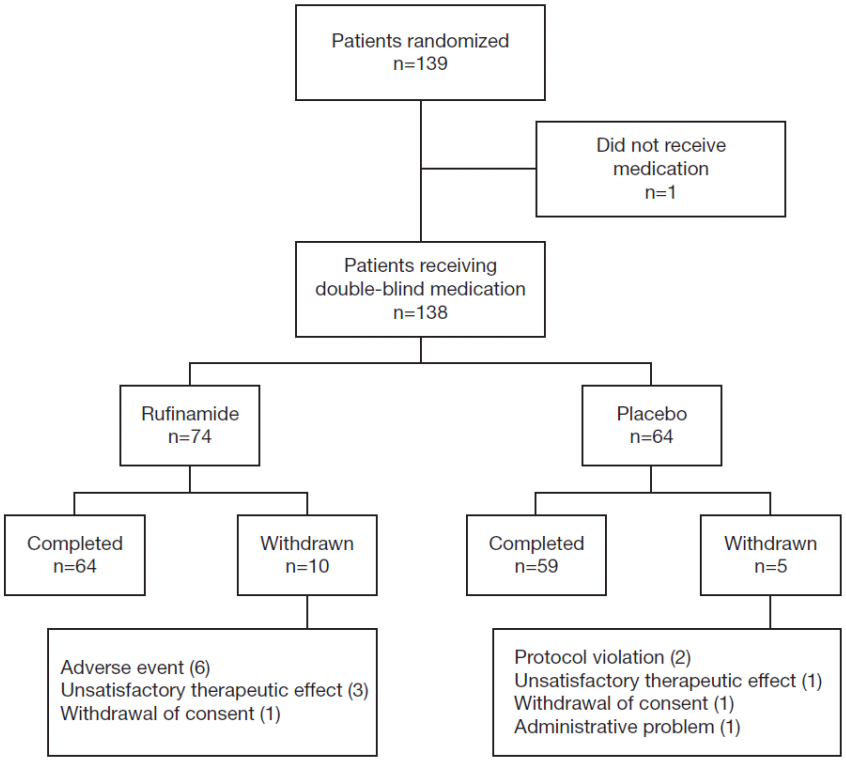
AED	AED	Rufinamide
PB	↑	↓
PHT	↑	↓
CBZ	↓	↓
VPA	↔	↑
LTG	↓	↔
TPM	↔	↔

ARTICLES

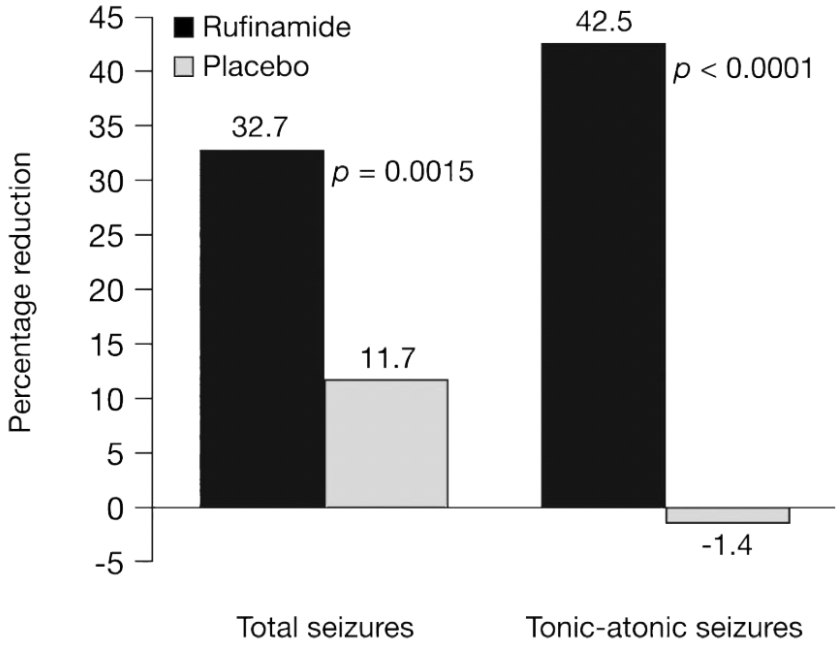
Rufinamide for generalized seizures associated with Lennox–Gastaut syndrome

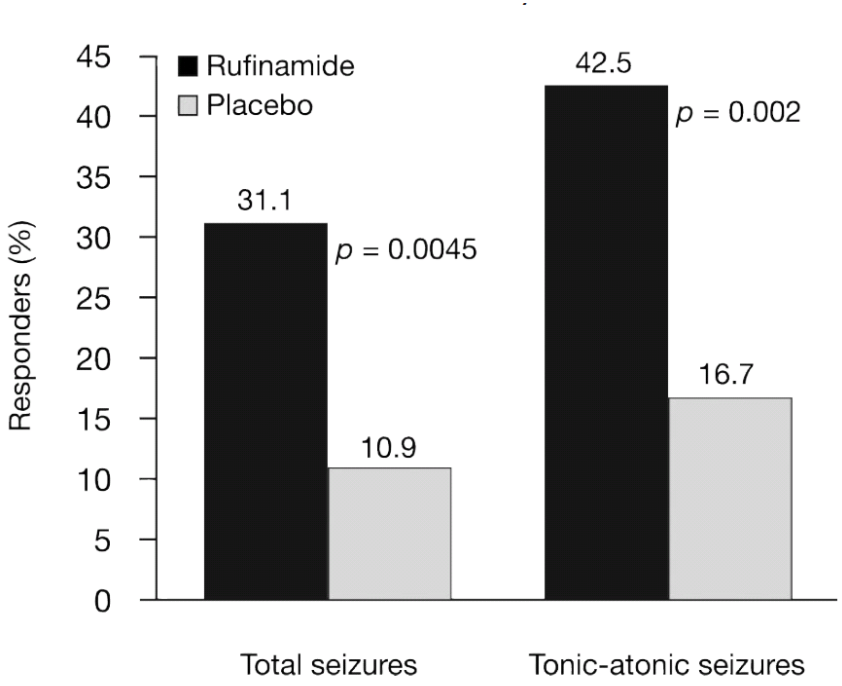
- Double-blind, placebo-controlled, randomized
- 138 patients with LGS (4 yrs to 30 yrs)
- Endpoint:
  - total seizure
  - atonic seizure
  - severity of the seizure
- 28 days

Figure 1 Patient disposition



Result


Percentage reduction
45
40
35
30
25
20
15
10
5
0
-5
Rufinamide
Placebo
32.7
p = 0.0015
11.7
42.5
p < 0.0001
-1.4
Total seizures
Tonic-atonic seizures


Responders (%)
45
40
35
30
25
20
15
10
5
0
Rufinamide
Placebo
31.1
p = 0.0045
10.9
42.5
p = 0.002
16.7
Total seizures
Tonic-atonic seizures

Common side effect

- Somnolence
- Vomiting
- Cautions in Short QT syndrome

Acta Neurol Scand 2010: 122: 202–208 DOI: 10.1111/j.1600-0404.2010.01334.x

ACTA NEUROLOGICA
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Adjunctive rufinamide in Lennox-Gastaut syndrome: a long-term, open-label extension study

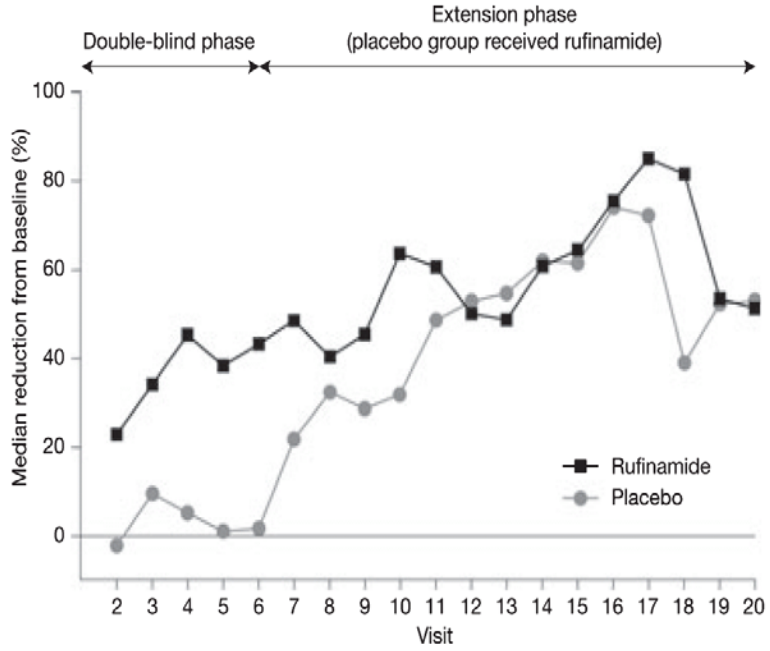


Figure 3. Comparison of median percentage reduction in total seizure frequency in patients receiving open-label rufinamide who had previously received either rufinamide or placebo for 12 weeks.

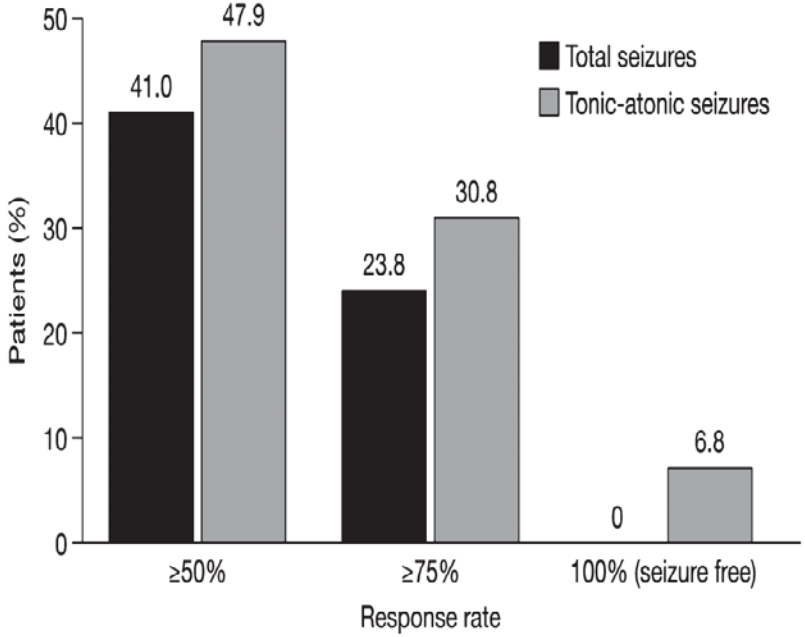


Figure 4. Response rates and seizure freedom for total and tonic–atonic seizures during the last 12 months of treatment.

Advantages-Disadvantages

- Efficacy in LGS
- Favorable cognitive profile
- Rare seizure worsening
  No intravenous formulation
- Mild side effect profile
- Low potential for drug-to-drug interactions
- Option for a quick titration when indicated in the clinical setting

- Not enough data on long-term efficacy and safety
- Ineffective in myoclonic seizures
- Only licensed as orphan drug for LGS; expensive
- Few controlled studies in epileptic syndromes other than LGS
- Few pharmacokinetic data, especially in young children

Coppola, 2014

Childhood indication

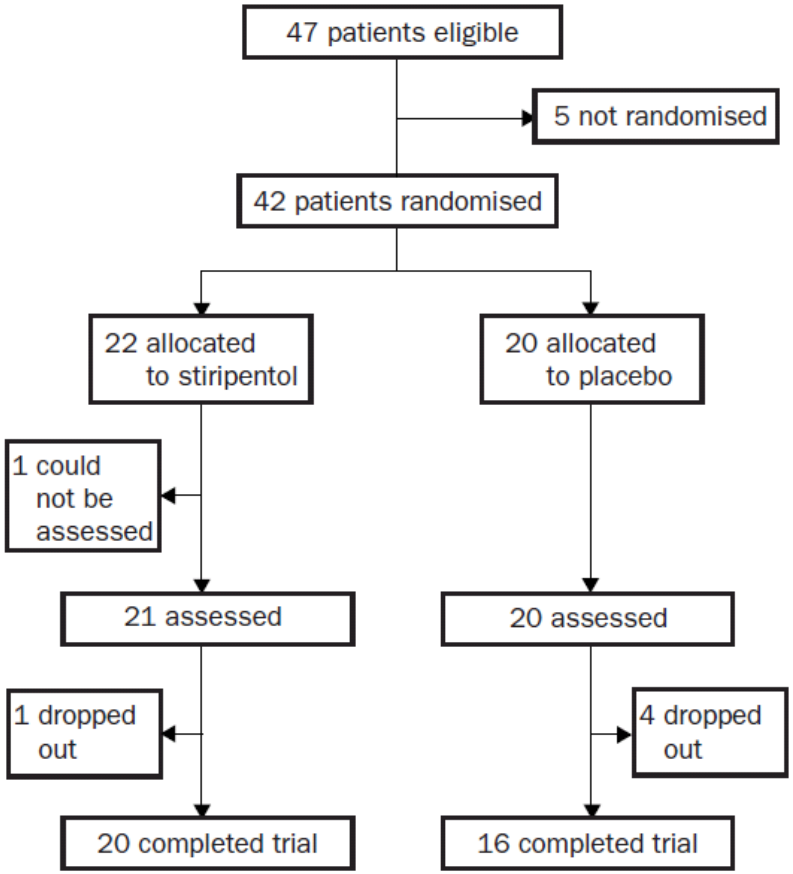
- FDA approve in adjunctive treatment in LGS > 4 yrs of age especially in “Drop attack” (atonic and tonic seizure)
- Other use
  - Infantile spasm (Olsen, Epilepsy & Behavior, 2012)
    - 107 patients (17 mo.-23 yrs)
    - Median follow-up 171 day (10-408)
    - Responder rate 53% (median reduction 50%)
    - Side effect 38% (discontinue 18%)
- Focal seizures
- NOT for Dravet syndrome

Stiripentol

- First “orphan medicine” for severe myoclonic epilepsy in infancy (Dravet syndrome)
- FDA approve in 2008
- Other use
  - Partial seizure
  - Atypical absence

Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial

*C Chiron, M C Marchand, A Tran, E Rey, P d'Athis, J Vincent, O Dulac, G Pons, and the STICLO study group**



Trial profile

	Stiripentol (n=21)	Placebo (n=20)	p*
Responders (95% CI)	15 (71%) (52·1–90·7)	1 (5%) (0–14·6)	<0·0001
Seizure-free patients (95% CI)	9 (43%) (21·9–65·9)	0 (0·0–13·9)	0·0013
Median (range) monthly seizures in double-blind period	5 (0–27)	14 (2–23)	0·0063
Mean change from baseline (%) of seizure frequency (95% CIs)	−69 (−50 to −88)	7 (25 to −11)	<0·0001

There was one drop-out in stiripentol group, due to status, and four drop-outs in placebo group (one for status, two inefficiency, one adverse event). *Difference between groups.

Table 2: **Comparison of groups**

Chiron, 2000

Pharmacokinetics

- Nonlinear pharmacokinetics
- Enzyme inhibitor
- Well absorbed after oral administration
- Take with food not with diary products, fruit juice, carbonated drinks
- Peak 1.5 hr with half-life 4.3-13 hrs
- 99% protein bound
- Metabolite in liver and excrete in urine

Doses and Interaction

- Starting dose: 50 MKD
- Target dose: 100 MKD
- Bid or tid schedule

AED	AED	STP
CBZ	↑	ND
Clonazepam	↔	↔
Phenobarb	↑	↓
Valproic	↓	↑

Key message

- Orphan drug for Dravet syndrome
- Disadvantage
  - Nonlinear pharmacokinetics
  - Potent inhibition of liver cytochrome P450 enzymes
  - High protein binding and drug interaction

Summary

- Newer antiepileptic drugs are now available
- More diverse and new mechanism of AEDs
- Studies are mostly from adult patients
- Two new hopes for devastating epileptic syndrome , LGS and Dravet syndrome
- More works and data are needed in pediatric population