Epilessia ieri e oggi. Nuovi orizzonti terapeutici

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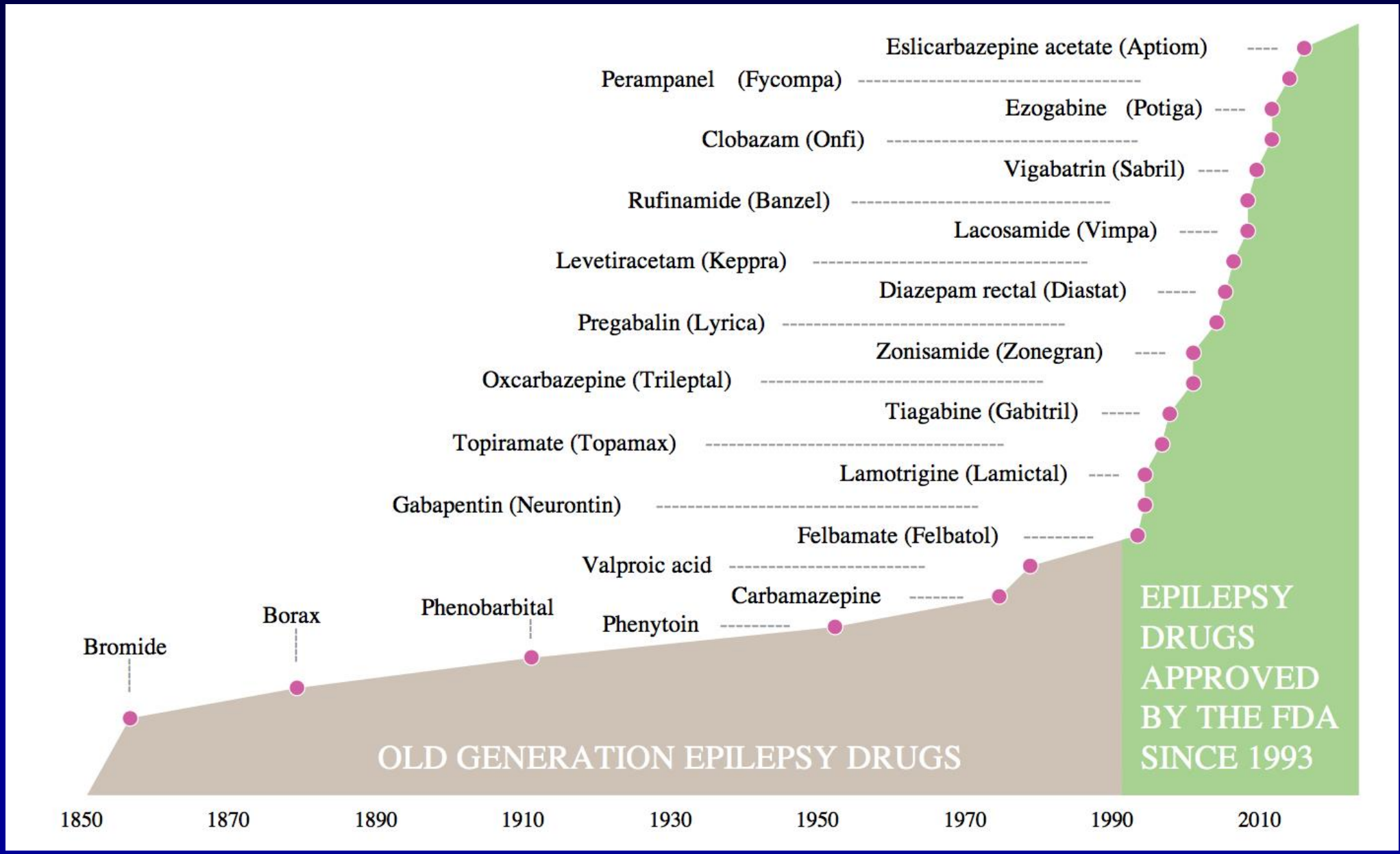
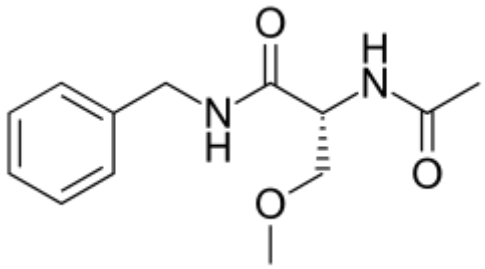
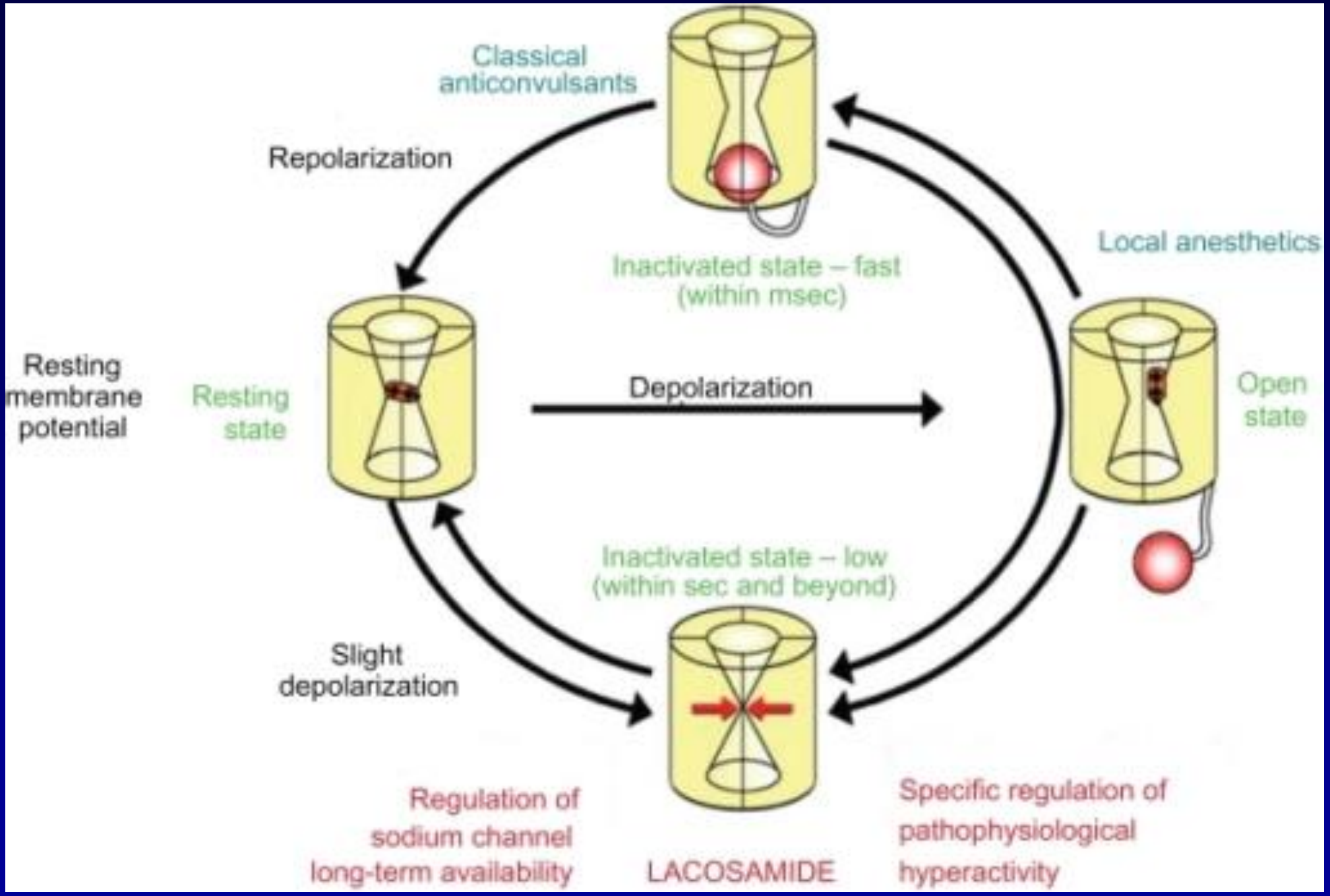

Eslicarbazepine acetate (Aptiom)
Perampanel (Fycompa)
Ezogabine (Potiga)
Clobazam (Onfi)
Vigabatrin (Sabril)
Rufinamide (Banzel)
Lacosamide (Vimpa)
Levetiracetam (Keppra)
Diazepam rectal (Diastat)
Pregabalin (Lyrica)
Zonisamide (Zonegran)
Oxcarbazepine (Trileptal)
Tiagabine (Gabitril)
Topiramate (Topamax)
Lamotrigine (Lamictal)
Gabapentin (Neurontin)
Felbamate (Felbatol)
Valproic acid
Carbamazepine
Phenytoin
Phenobarbital
Borax
Bromide
EPILEPSY DRUGS APPROVED BY THE FDA SINCE 1993
OLD GENERATION EPILEPSY DRUGS
1850
1870
1890
1910
1930
1950
1970
1990
2010

2008



LACOSAMIDE

- Oral Bioavailability – ~ 100%.
- Time to Peak Levels – 0.5-4 hours following oral dose.
- Half life – 12-16 hours
- Elimination – Partly by Renal excretion in unchanged form in urine (40%) and partly by metabolism (primarily demethylation) follwed by excretion.


Classical anticonvulsants
Repolarization
Inactivated state – fast (within msec)
Local anesthetics
Resting membrane potential
Resting state
Depolarization
Open state
Inactivated state – low (within sec and beyond)
Slight depolarization
Regulation of sodium channel long-term availability
LACOSAMIDE
Specific regulation of pathophysiological hyperactivity

Cochrane Library

Cochrane Database of Systematic Reviews

Lacosamide add-on therapy for partial epilepsy (Review)

Weston J, Shukralla A, McKay AJ, Marson AG

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Lacosamide compared with placebo for partial epilepsy

Patient or population: people with partial epilepsy
Settings: outpatients
Intervention: lacosamide
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Lacosamide				
50% reduction in seizure frequency - lacosamide any dose	**226 per 1000**	**384 per 1000** (311 to 474)	**RR 1.7** (1.38 to 2.1)	1294 (3 studies)	⊕⊕⊕⊕ **High**	
Seizure freedom - lacosamide any dose	**8 per 1000**	**21 per 1000** (7 to 61)	**RR 2.5** (0.85 to 7.34)	1294 (3 studies)	⊕⊕⊕⊖ [1] Moderate	
Treatment withdrawals - lacosamide any dose	**129 per 1000**	**243 per 1000** (181 to 325)	**RR 1.88** (1.4 to 2.52)	1308 (3 studies)	⊕⊕⊕⊕ **High**	

Epilepsy & Behavior 52 (2015) 119–127

Contents lists available at ScienceDirect

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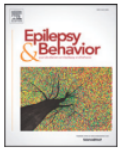
journal homepage: www.elsevier.com/locate/yebeh



Safety and tolerability of lacosamide as adjunctive therapy for adults with partial-onset seizures: Analysis of data pooled from three randomized, double-blind, placebo-controlled clinical trials

Victor Biton [a], Antonio Gil-Nagel [b], Jouko Isojarvi [c,1], Pamela Doty [c], David Hebert [c], Nathan B. Fountain [d,*]

- Inclusion criteria

✓ Patients aged 16–70 years (18–65 years in SP667) with a diagnosis of focal epilepsy

✓ POS (with or without secondary generalization) for 2 years or longer despite therapy with two or more AEDs (concurrently or sequentially)

✓ An average of at least four POS (simple partial with motor signs, complex partial, or secondarily generalized seizures) per 28 days, with seizure-free periods lasting no longer than 21 days, in the 8 weeks prior to baseline and during the 8-week baseline period

✓ A stable dosing regimen of 1–3 concomitant AEDs (no more than two in SP667) with or without vagus nerve stimulation for at least 4 weeks prior tobaseline and throughout the trial

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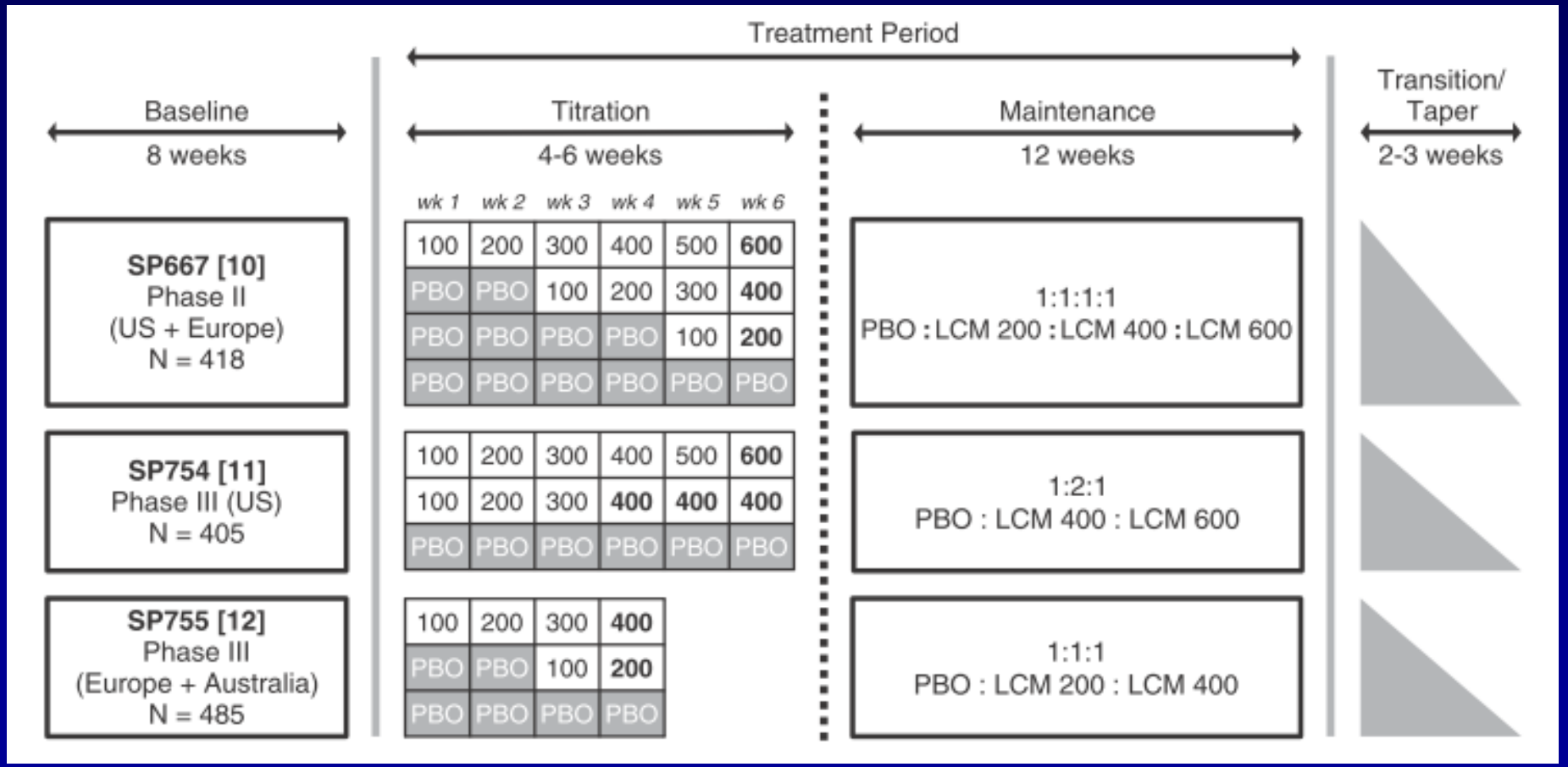
Safety and tolerability of lacosamide as adjunctive therapy for adults with partial-onset seizures: Analysis of data pooled from three randomized, double-blind, placebo-controlled clinical trials

Victor Biton [a], Antonio Gil-Nagel [b], Jouko Isojarvi [c,1], Pamela Doty [c], David Hebert [c], Nathan B. Fountain [d,*]



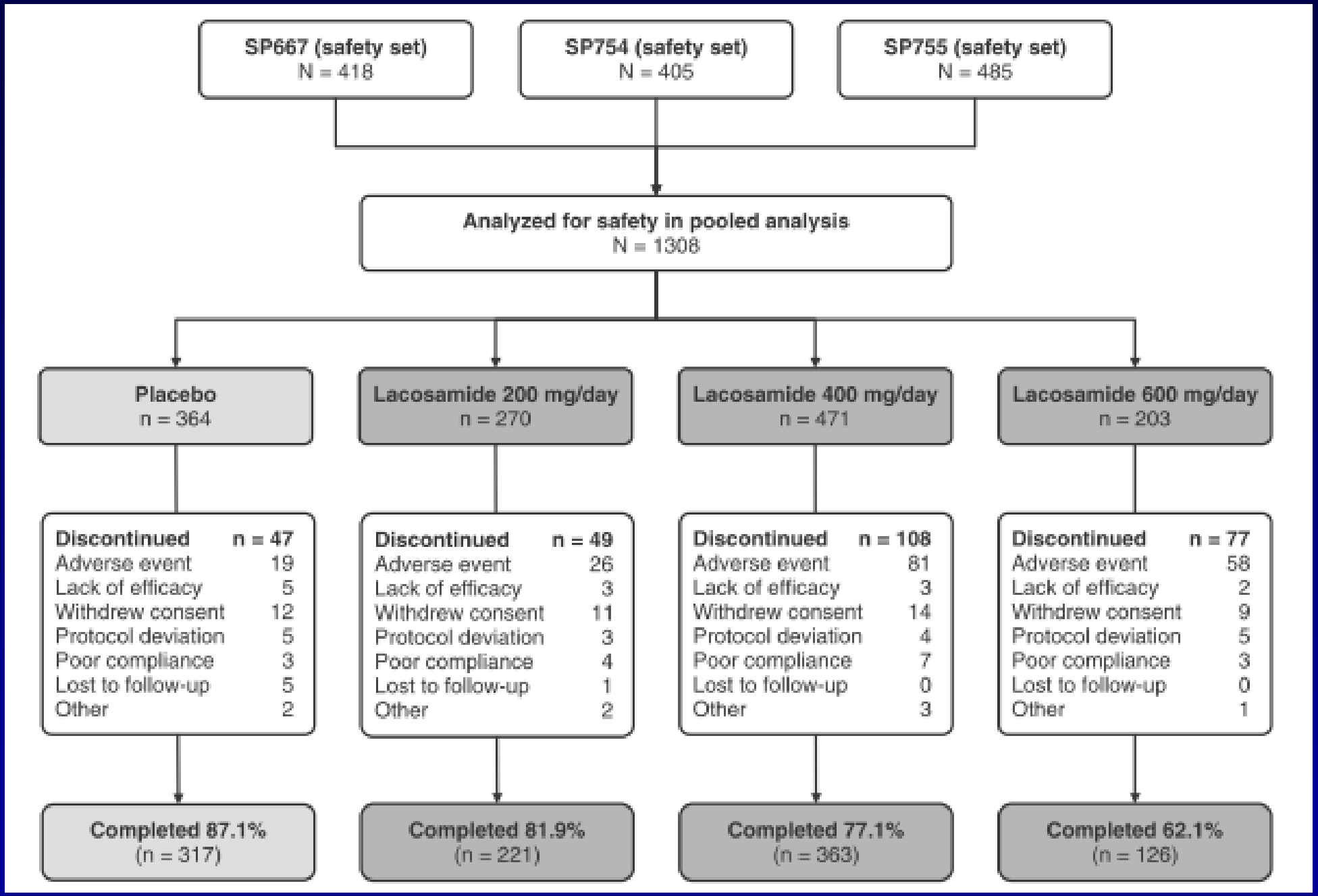

SP667 (safety set)
N = 418
SP754 (safety set)
N = 405
SP755 (safety set)
N = 485
Analyzed for safety in pooled analysis
N = 1308
Placebo
n = 364
Lacosamide 200 mg/day
n = 270
Lacosamide 400 mg/day
n = 471
Lacosamide 600 mg/day
n = 203
Discontinued n = 47
Adverse event 19
Lack of efficacy 5
Withdrew consent 12
Protocol deviation 5
Poor compliance 3
Lost to follow-up 5
Other 2
Discontinued n = 49
Adverse event 26
Lack of efficacy 3
Withdrew consent 11
Protocol deviation 3
Poor compliance 4
Lost to follow-up 1
Other 2
Discontinued n = 108
Adverse event 81
Lack of efficacy 3
Withdrew consent 14
Protocol deviation 4
Poor compliance 7
Lost to follow-up 0
Other 3
Discontinued n = 77
Adverse event 58
Lack of efficacy 2
Withdrew consent 9
Protocol deviation 5
Poor compliance 3
Lost to follow-up 0
Other 1
Completed 87.1%
(n = 317)
Completed 81.9%
(n = 221)
Completed 77.1%
(n = 363)
Completed 62.1%
(n = 126)

Table 1
Demographic and baseline characteristics of patients participating in double-blind, placebo-controlled clinical trials of lacosamide for the adjunctive treatment of adults with partial-onset seizures (safety set).

	Placebo (n = 364)	Adjunctive lacosamide			Total population (N = 1308)
		200 mg/day (n = 270)	400 mg/day (n = 471)	600 mg/day (n = 203)	
Age (mean ± SD, years)	38.5 ± 11.25	38.1 ± 11.78	39.2 ± 12.44	38.1 ± 11.18	38.6 ± 11.79
Female, n (%)	177 (48.6)	134 (49.6)	245 (52.0)	111 (54.7)	667 (51.0)
Time since diagnosis, (mean ± SD, years)[a]	23.3 ± 12.56	23.7 ± 12.56	24.0 ± 13.14	23.5 ± 12.97	23.7 ± 12.82
Lifetime AEDs, n (%)					
1–3	80 (22.0)	62 (23.0)	112 (23.8)	32 (15.8)	286 (21.9)
4–6	121 (33.2)	84 (31.1)	151 (32.1)	68 (33.5)	424 (32.4)
≥7	160 (44.0)	120 (44.4)	205 (43.5)	102 (50.2)	587 (44.9)
Missing	3 (0.8)	4 (1.5)	3 (0.6)	1 (0.5)	11 (0.8)
Number of concomitant AEDs, n (%)					
1	62 (17.0)	34 (12.6)	78 (16.6)	30 (14.8)	204 (15.6)
2	214 (58.8)	168 (62.2)	281 (59.7)	151 (74.4)	814 (62.2)
3[b]	88 (24.2)	68 (25.2)	112 (23.8)	22 (10.8)	290 (22.2)
Most common[c] concomitant AEDs, n (%)					
Carbamazepine	129 (35.4)	115 (42.6)	150 (31.8)	69 (34.0)	463 (35.4)
Lamotrigine	117 (32.1)	70 (25.9)	159 (33.8)	62 (30.5)	408 (31.2)
Levetiracetam	103 (28.3)	70 (25.9)	147 (31.2)	61 (30.0)	381 (29.1)
Valproate	95 (26.1)	74 (27.4)	99 (21.0)	40 (19.7)	308 (23.5)
Topiramate	83 (22.8)	70 (25.9)	106 (22.5)	32 (15.8)	291 (22.2)
Median baseline seizure frequency per 28 days[d]	11.0	12.2	11.0	13.5	11.5

AEDs, antiepileptic drugs.
[a] n = 470 for 400 mg/day, 202 for 600 mg/day, and 1306 for total population.
[b] Trial SP667 did not allow patients taking three concomitant AEDs.
[c] Represents the five most commonly used concomitant AEDs.
[d] n = 359 for placebo, 267 for 200 mg/day, 469 for 400 mg/day, 202 for 600 mg/day, and 1297 for total population.

Table 2
Incidence of common drug-associated TEAEs[a] during the treatment phase (titration and maintenance) in double-blind, placebo-controlled clinical trials of lacosamide for the adjunctive treatment of adults with partial-onset seizures (safety set).

MedDRA preferred term	Placebo (n = 364)	Adjunctive lacosamide			
		200 mg/day (n = 270)	400 mg/day (n = 471)	600 mg/day (n = 203)	All doses of lacosamide (n = 944)
Dizziness	30 (8.2)	43 (15.9)	139 (29.5)	107 (52.7)	289 (30.6)
Nausea	16 (4.4)	20 (7.4)	53 (11.3)	35 (17.2)	108 (11.4)
Diplopia	7 (1.9)	17 (6.3)	49 (10.4)	33 (16.3)	99 (10.5)
Vomiting	9 (2.5)	16 (5.9)	40 (8.5)	32 (15.8)	88 (9.3)
Fatigue	21 (5.8)	19 (7.0)	34 (7.2)	30 (14.8)	83 (8.8)
Vision blurred	9 (2.5)	6 (2.2)	40 (8.5)	33 (16.3)	79 (8.4)
Ataxia[b]	6 (1.6)	11 (4.1)	34 (7.2)	31 (15.3)	76 (8.1)
Tremor	15 (4.1)	10 (3.7)	29 (6.2)	24 (11.8)	63 (6.7)
Nystagmus	14 (3.8)	6 (2.2)	21 (4.5)	21 (10.3)	48 (5.1)
Balance disorder	0 (0)	3 (1.1)	24 (5.1)	13 (6.4)	40 (4.2)
Memory impairment	6 (1.6)	3 (1.1)	7 (1.5)	12 (5.9)	22 (2.3)

MedDRA, Medical Dictionary for Regulatory Activities.
For each TEAE, data are presented as n (%) of patients experiencing the TEAE at least once.
[a] Common drug-associated TEAEs defined as those TEAEs occurring in ≥5% of patients in any lacosamide treatment group and at least twice as often as in the placebo group.
[b] Reported as coordination abnormal.

Epilepsy & Behavior 19 (2010) 650–651

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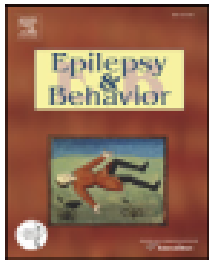


Case Report

Does lacosamide aggravate Lennox–Gastaut syndrome? Report on three consecutive cases

Antonella Cuzzola [a,b], Edoardo Ferlazzo [c,*], Domenico Italiano [c], Rocco Salvatore Calabrò [c], Placido Bramanti [c], Pierre Genton [a]

Acta Neurologica Scandinavica

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

ACTA NEUROLOGICA SCANDINAVICA

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

Grosso S, Coppola G, Cusmai R, Parisi P, Spalice A, Foligno S, Verrotti A, Balestri P. Efficacy and tolerability of add-on lacosamide in children with Lennox-Gastaut syndrome. Acta Neurol Scand 2014: 129: 420–424.

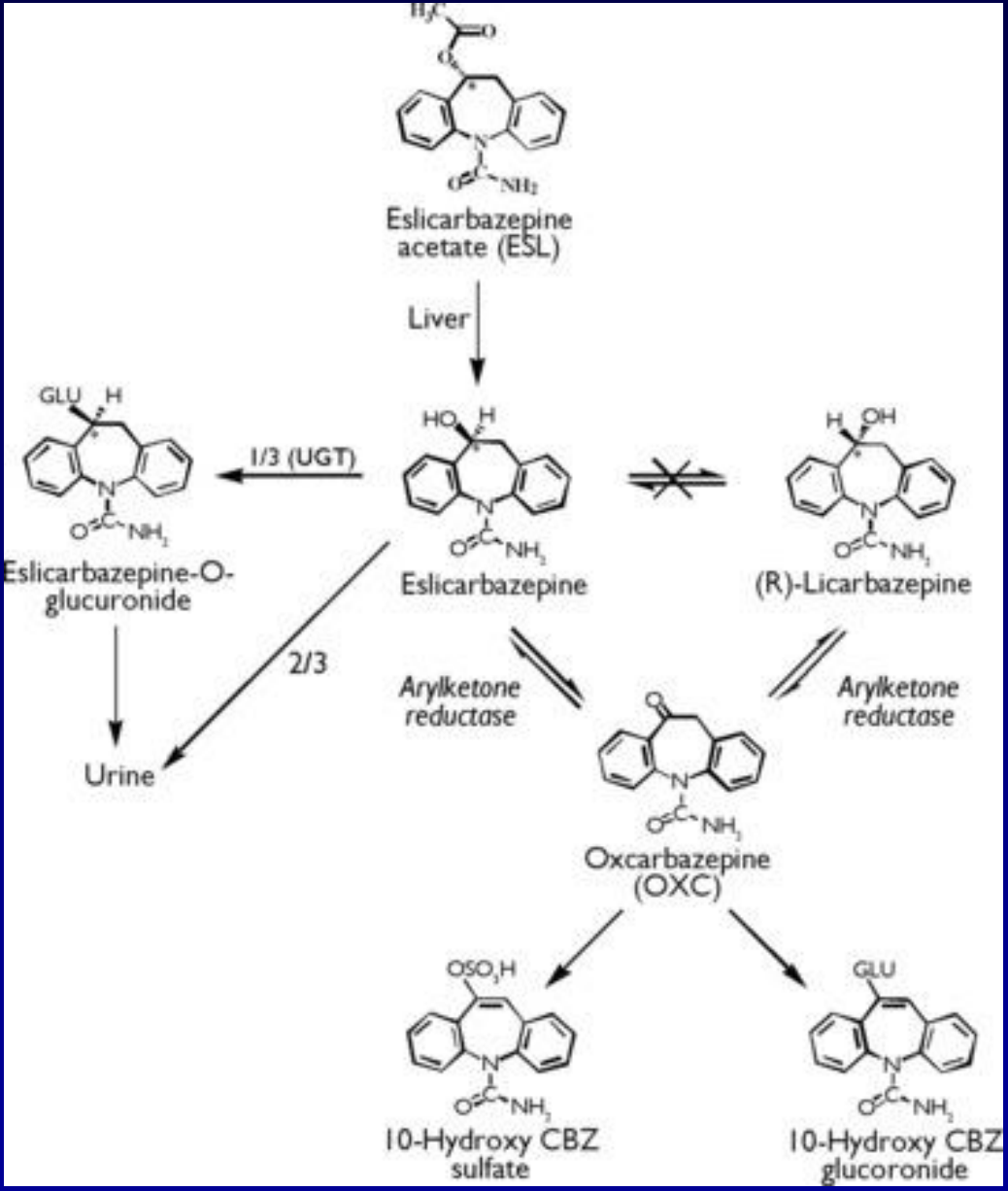
S. Grosso[1,2], G. Coppola[3], R. Cusmai[4], P. Parisi[5], A. Spalice[6], S. Foligno[5], A. Verrotti[7], P. Balestri[2]

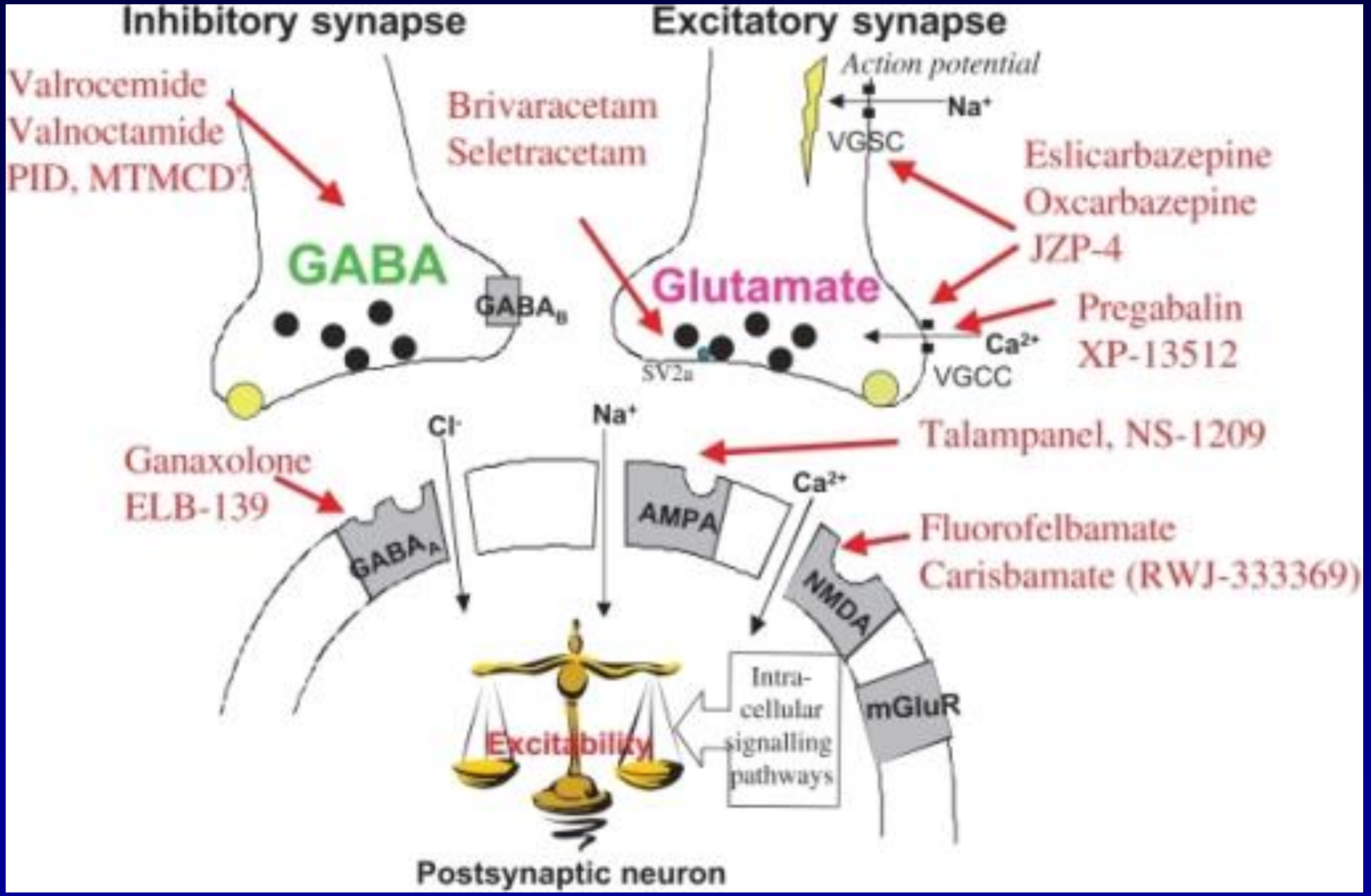
Objective – Available data on the efficacy of lacosamide in children with Lennox-Gastaut syndrome (LGS) are scarce and controversial. We present our experience with lacosamide therapy in children affected by LGS. *Material and Methods* – Medical charts of all children affected by LGS receiving oral lacosamide adjunctive therapy in six paediatric neurology centres were retrospectively evaluated. Efficacy was determined according to the frequency of countable seizures during the 4 weeks prior to treatment and the frequency in the last 4 weeks of observation. Patients whose seizure frequency was reduced by at least 50% were defined as responders. *Results* – Eighteen children (mean age 12.3 years) were identified. After a mean follow-up period of 9 months, 33% of patients were responders. None of them was seizure-free during the study period. The overall seizure reduction rate was 29%. The percentage reductions from baseline in tonic seizures and drop-attacks rates were 31% and 20%, respectively. Adverse reactions occurred in 44% of patients. The drug was discontinued in four (22%) patients because of increased seizure frequency (three cases) and walking instability (another patient). *Conclusions* – A third of children with LGS were responders after lacosamide adjunctive therapy. Although caution is still necessary when the drug is used in children with LGS, our preliminary observations suggest that lacosamide might be effective and represent a possible therapeutic option in children affected by LGS.

2009

ESLICARBAZEPINE ACETATE

- Oral Bioavailability – ~ 100%.
- Time to Peak Levels – 2-3 hours following oral dose.
- Half life – 13-20 hours
- Elimination – Hydrolyzed rapidly to Eslicarbazepine, which is excreted in urine in free and conjugated form. Minor metabolites include (R)-licarbazepine, oxcarbazepine and their conjugates.




Inhibitory synapse
Excitatory synapse
Valrocemide
Valnoctamide
PID, MTMCD?
Brivaracetam
Seletracetam
Action potential
Na+
VGSC
Eslicarbazepine
Oxcarbazepine
JZP-4
GABA
GABAB
Glutamate
Pregabalin
XP-13512
Ca2+
SV2a
VGCC
Cl-
Na+
Talampanel, NS-1209
Ganaxolone
ELB-139
Ca2+
AMPA
Fluorofelbamate
Carisbamate (RWJ-333369)
GABAA
NMDA
mGluR
Intra-
cellular
signalling
pathways
Excitability
Postsynaptic neuron

Epilepsia, 54(1):98–107, 2013
doi: 10.1111/j.1528-1167.2012.03605.x

FULL-LENGTH ORIGINAL RESEARCH

Efficacy and safety of eslicarbazepine acetate as add-on treatment in patients with focal-onset seizures: Integrated analysis of pooled data from double-blind phase III clinical studies

*António Gil-Nagel, †Christian Elger, ‡Elinor Ben-Menachem, §Peter Halász, ¶José Lopes-Lima, #Alberto A. Gabbai, **Teresa Nunes, †††‡Amílcar Falcão, §§Luis Almeida, and **¶¶Patrício Soares-da-Silva

- Inclusion & exclusion criteria

✓ Men and women age ≥18 years
✓ With simple or complex partial seizures with or without secondary generalization for at least 12 months before screening, who were receiving one or two (1–3 in study BIA 2093-302) concomitant AEDs in a stable dosage regimen for at least 2 months before screening
✓ At least four partial-onset seizures in the two 4-week periods of the 8-week baseline phase with no seizure-free interval exceeding 21 consecutive days
✓ Patients taking felbamate were excluded for safety reasons
✓ Oxcarbazepine was not allowed as concomitant AED as it shares common metabolites with ESL
✓ Patients with known hypersensitivity to carbamazepine or oxcarbazepine were excluded

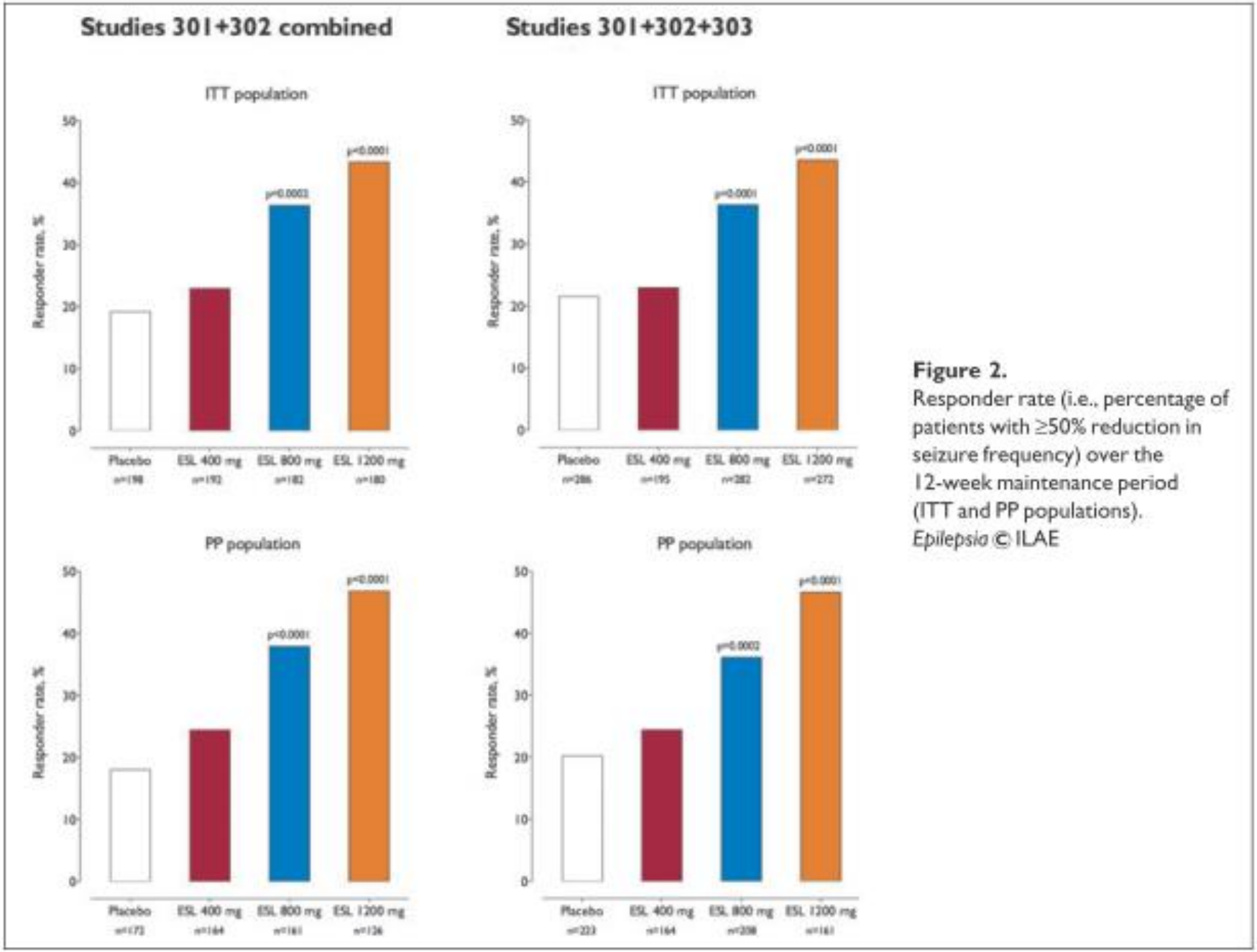
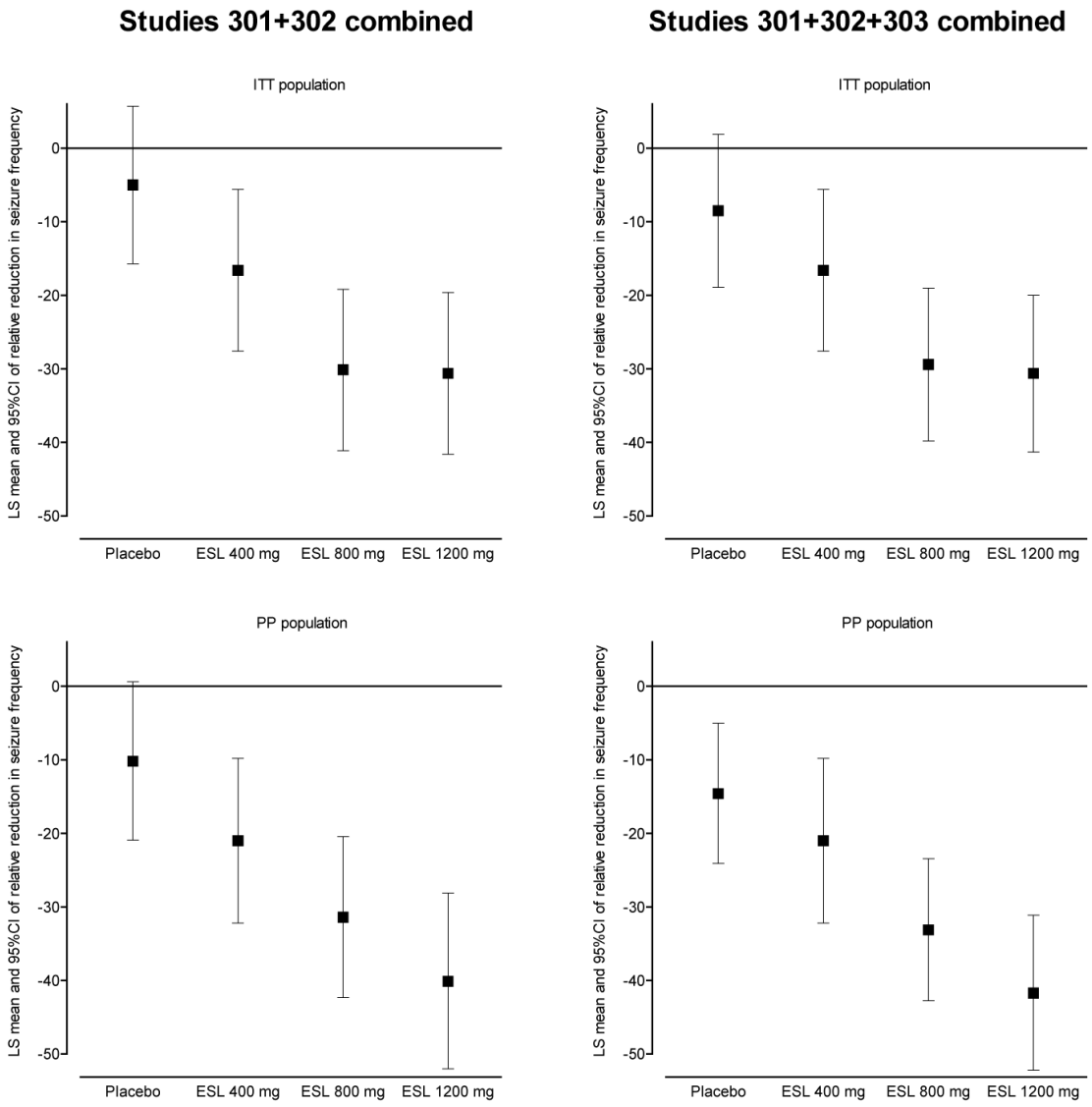


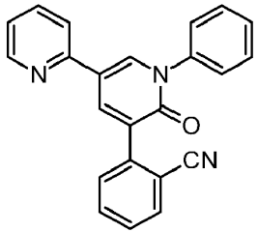
Figure 2.
Responder rate (i.e., percentage of patients with ≥50% reduction in seizure frequency) over the 12-week maintenance period (ITT and PP populations).
Epilepsia © ILAE

Supplementary Figure 2. Mean and 95%CI of relative (%) reduction in seizure frequency over the 12-week maintenance period (ITT and PP populations).



Adverse events (≥ 10%)

Studies 301 + 302 + 303 combined			
	Placebo (n = 289)	ESL 800 mg (n = 284)	ESL 1,200 mg (n = 280)
Total patients with TEAEs, n (%)	134 (46.4)	178 (62.7)	189 (67.5)
Mild	56 (19.4)	72 (25.4)	56 (20.0)
Moderate	65 (22.5)	82 (28.9)	101 (36.1)
Severe	13 (4.5)	24 (8.5)	32 (11.4)
Dizziness, n (%)	21 (7.3)	60 (21.1)	81 (28.9)
Mild	13 (4.5)	33 (11.6)	33 (11.8)
Moderate	6 (2.1)	21 (7.4)	36 (12.9)
Severe	2 (0.7)	6 (2.1)	12 (4.3)
Somnolence, n (%)	27 (9.3)	37 (13.0)	42 (15.0)
Mild	18 (6.2)	22 (7.7)	19 (6.8)
Moderate	7 (2.4)	12 (4.2)	19 (6.8)
Severe	2 (0.7)	3 (1.1)	4 (1.4)
Headache, n (%)	25 (8.7)	29 (10.2)	38 (13.6)
Mild	12 (4.2)	13 (4.6)	19 (6.8)
Moderate	12 (4.2)	13 (4.6)	17 (6.1)
Severe	1 (0.3)	3 (1.1)	2 (0.7)
Nausea, n (%)	6 (2.1)	21 (7.4)	28 (10.0)
Mild	3 (1.0)	8 (2.8)	9 (3.2)
Moderate	3 (1.0)	11 (3.9)	16 (5.7)
Severe	0	2 (0.7)	3 (1.1)



Fycompa® / perampanel

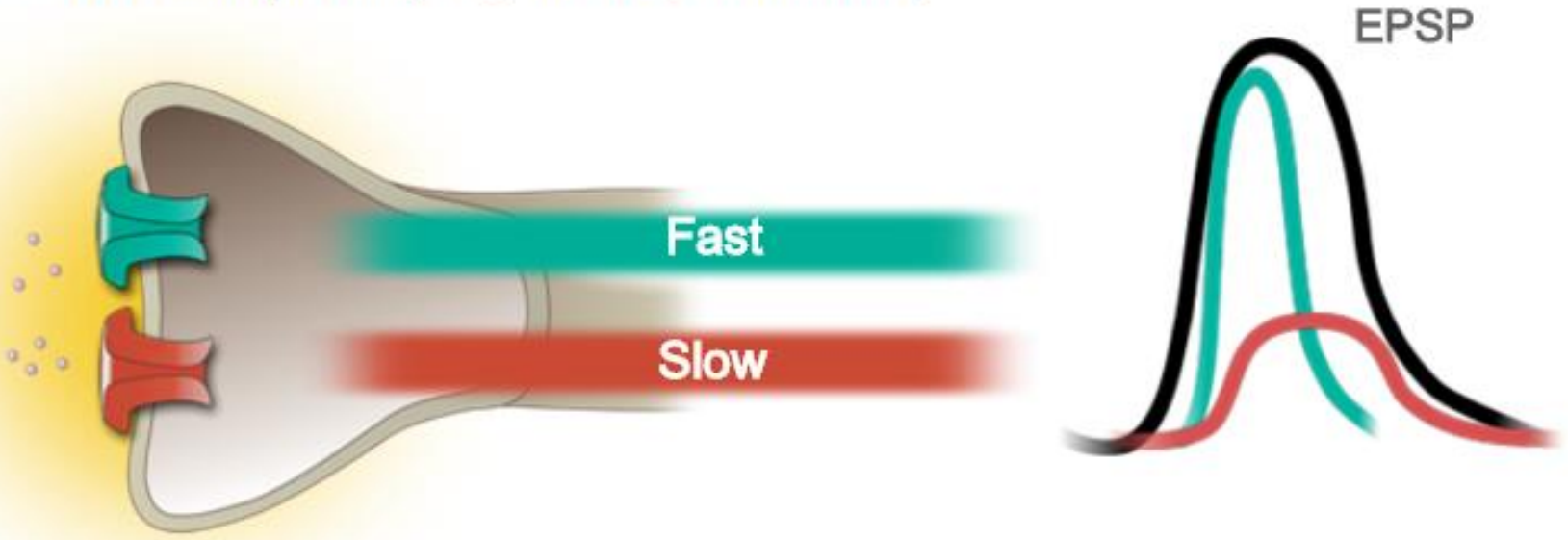
Drug Facts

2012

- Pharmacokinetics
  - **A** – T_{peak}: 0.5-2.5 hours, rapid and complete
  - **D** – Protein binding: ~95%
  - **M** – Hepatic, extensive CYP3A4/5 primary oxidation, then glucuronidation
  - **E** – T ½: 105 hours; Feces (48%); urine (22%)

Glutamate mediates most fast excitatory neurotransmission in the CNS

- **AMPA** is the main receptor mediating rapid effects of glutamate[1]
  - Underlies fast component of EPSP[1,2]
- **NMDA** receptor does not normally contribute to fast neurotransmission[1,2]
  - Underlies slow component of the EPSP[1,2]
  - Involved in plasticity e.g. learning and memory[1,3]



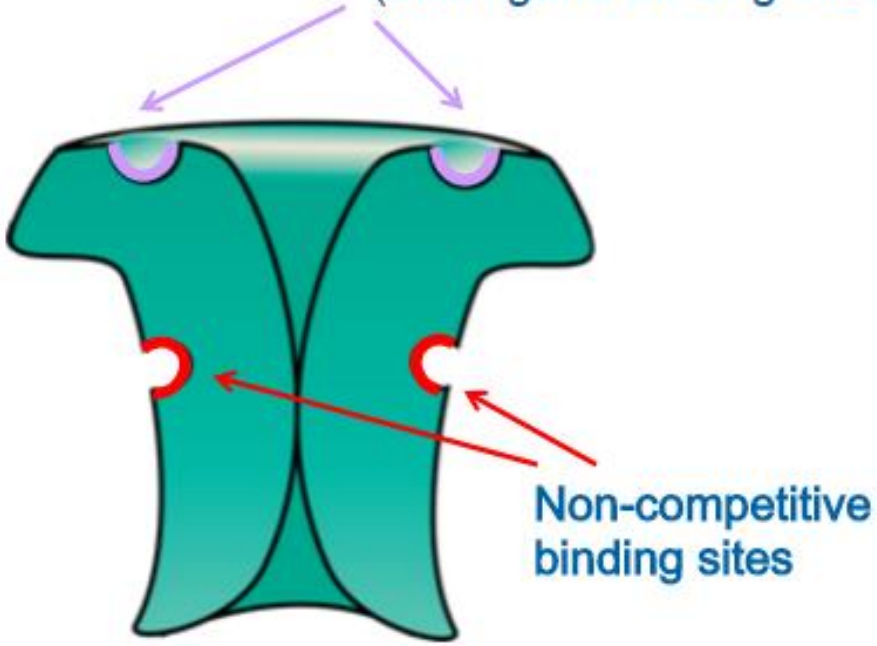
[1]Rogawski MA. *Epilepsy Currents* 2011;11:56–63;[2]Meldrum BS. *J Nutr* 2000;130:1007S–1015S;[3]Meldrum BS, Rogawski MA. *Neurotherapeutics* 2007;4:18–61.

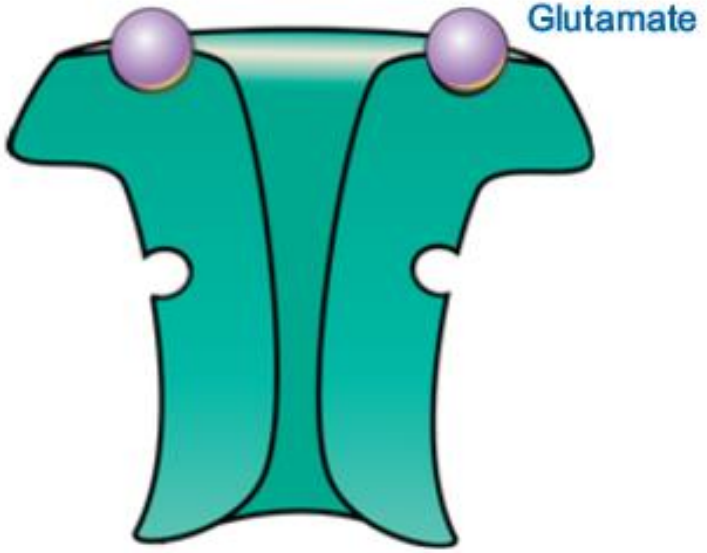
AMPA receptor structure

AMPA receptor
(closed, inactive state)

AMPA receptor
(open, active state)

Glutamate-binding sites
(also ligand-binding sites or domains)



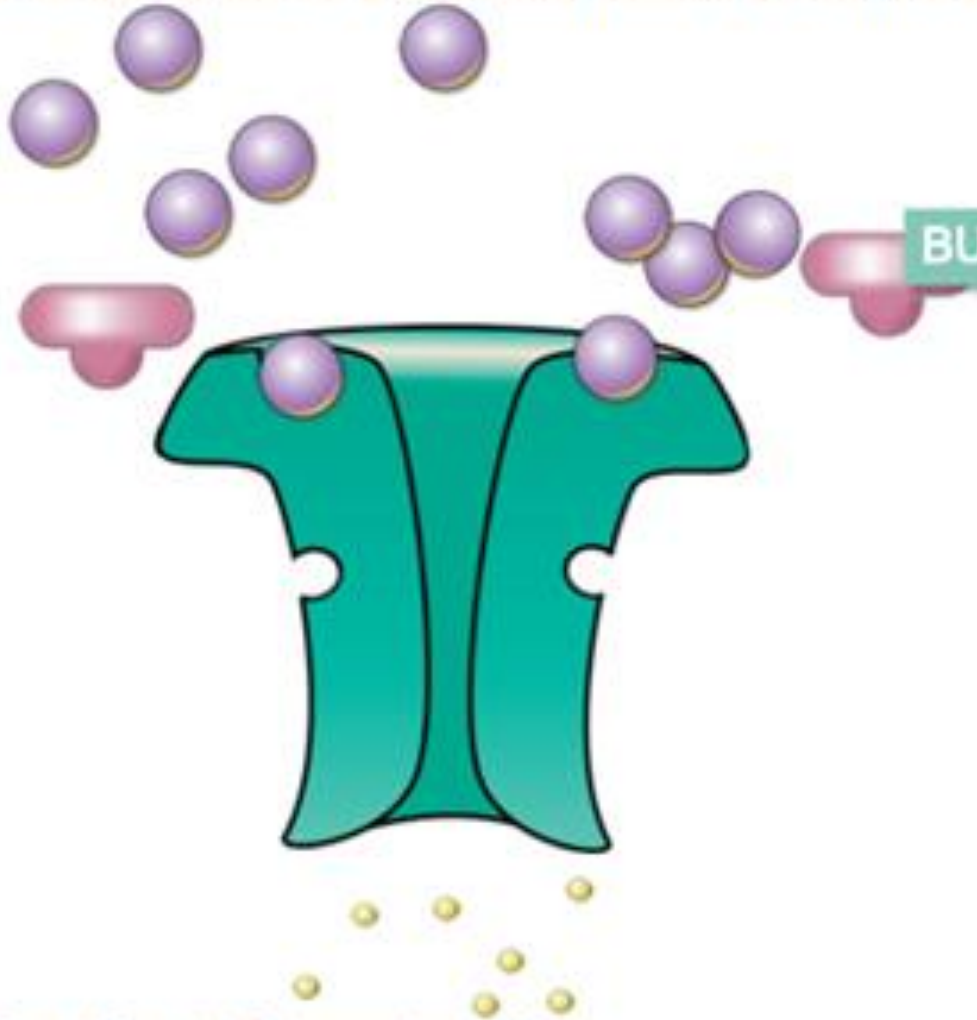


The receptor's ion channel allows influx of Na^+ ions (and sometimes Ca^{2+} ions) into the neuron

[1]Wilcox KS *et al. In: Epilepsy: a comprehensive textbook* 2008;
[2]Clements JD *et al. J Neurosci* 1998;18:119–121.

Competitive antagonists may be displaced by high levels of glutamate

In the presence of a competitive antagonist



1. Glutamate cannot bind so cannot activate the receptor

BUT when glutamate levels are high...

2. Glutamate displaces the antagonist...

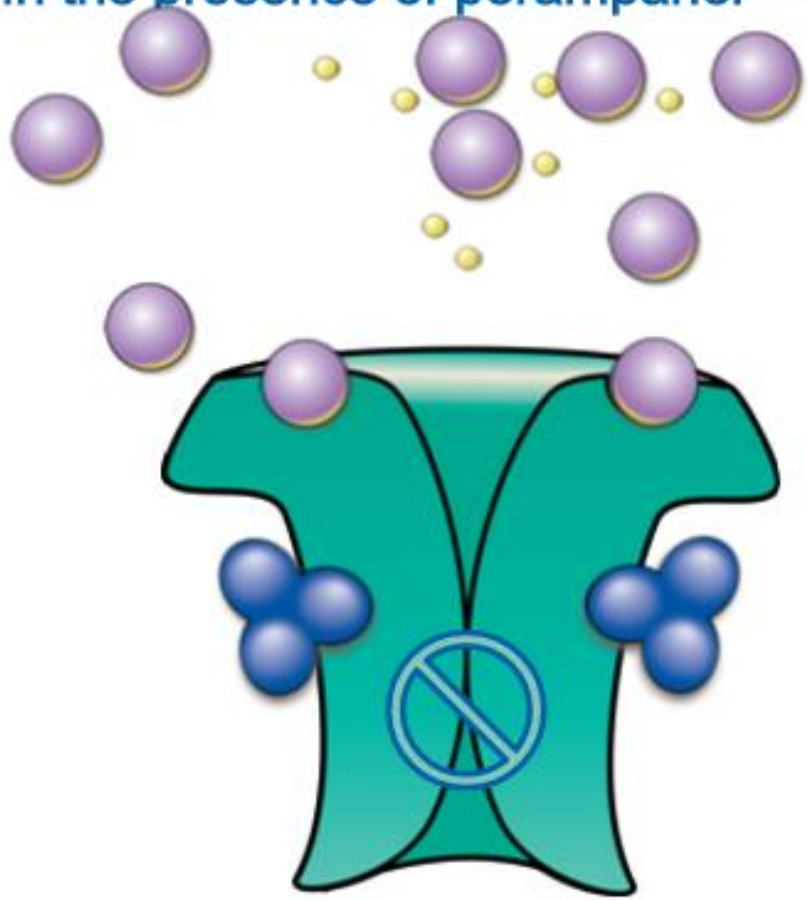
3. ...binds to the receptor and activates it, opening the channel and allowing Na^+ influx

Na^+ ions
Glutamate
Competitive antagonist

Rang HP *et al. In: Pharmacology.* 1995.

Non-competitive antagonists should maintain activity even when glutamate levels are high

In the presence of perampanel [1]



1. **Glutamate binds** but cannot activate the receptor[1]

AND when glutamate levels are high...

2. **...non-competitive antagonist is not displaced by glutamate** [2]

3. **Receptor antagonism is maintained and the channel remains closed**

Na^+ ions
Glutamate
Perampanel

[1]Hanada T *et al. Epilepsia* 2011;52:1331–1340;[2]Kenakin T. *Molecular Interventions* 2004;4:222–229.

Disegno degli studi di fase III, partecipanti e trattamento

Disegno degli studi[1]

- Studi randomizzati, in doppio-cieco, controllati con placebo, a gruppi paralleli, multicentrici per valutare perampanel come terapia aggiuntiva in pazienti con crisi parziali
- 6 settimane al basale, seguite da una fase di trattamento in doppio-cieco di 19 settimane (titolazione di 6 settimane, mantenimento di 13 settimane)

Partecipanti[1,2]

- Pazienti di età ≥12 anni con crisi parziali non controllate
  - Crisi non controllate nonostante trattamento con ≥2 FAE nei due anni precedenti
  - Pazienti con almeno 5 crisi parziali e senza periodi liberi da crisi di 25 giorni durante le 6 settimane di osservazione al basale, nonostante trattamento con 1-3 FAE a dosi stabili per almeno 3 settimane prima della randomizzazione (consentito un solo FAE induttore enzimatico)
  - Esclusi I pazienti che presentavano esclusivamente crisi parziali semplici non motorie, crisi primariamente generalizzate, sindrome di Lennox-Gastaut, status epilepticus (nei 12 mesi precedenti la visita 1), crisi in cluster, patologie ematologiche, patologie neurologiche progressive o tumori.
- Centri Sperimentali in >40 Paesi in 5 Continenti[2]

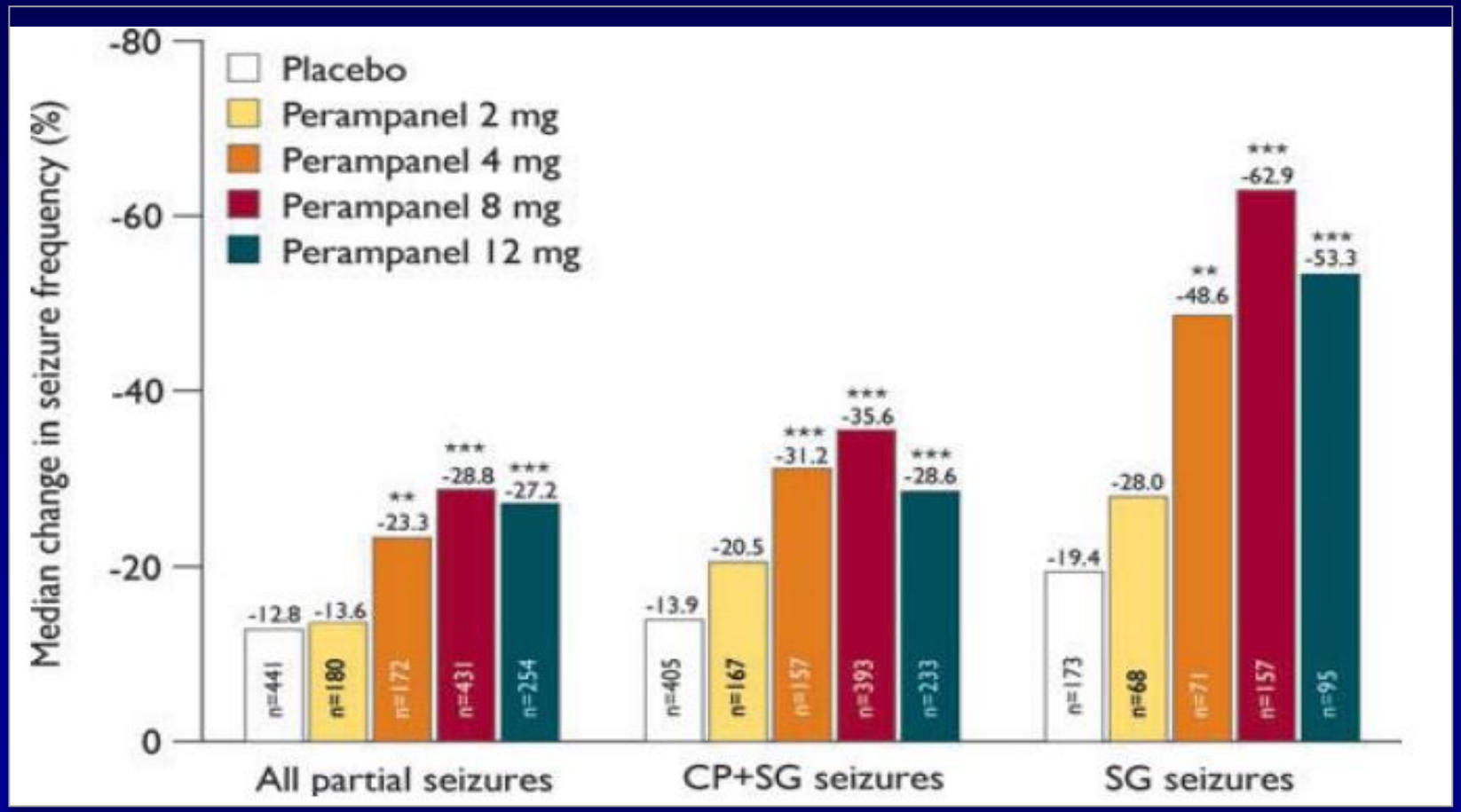
Trattamento[1,2]

- 304 e 305: Perampanel 8 e 12 mg/die o placebo
- 306: Perampanel 2, 4 e 8 mg/die o placebo

[1]Krauss GL *et al*. *Neurology* 2012;78:1408–1415; [2]Steinhoff BJ *et al*. *Epilepsia* 2013;54:1481–1489.

Analisi aggregata degli studi di fase III

Mediana della variazione percentuale della frequenza delle crisi per tipo di crisi

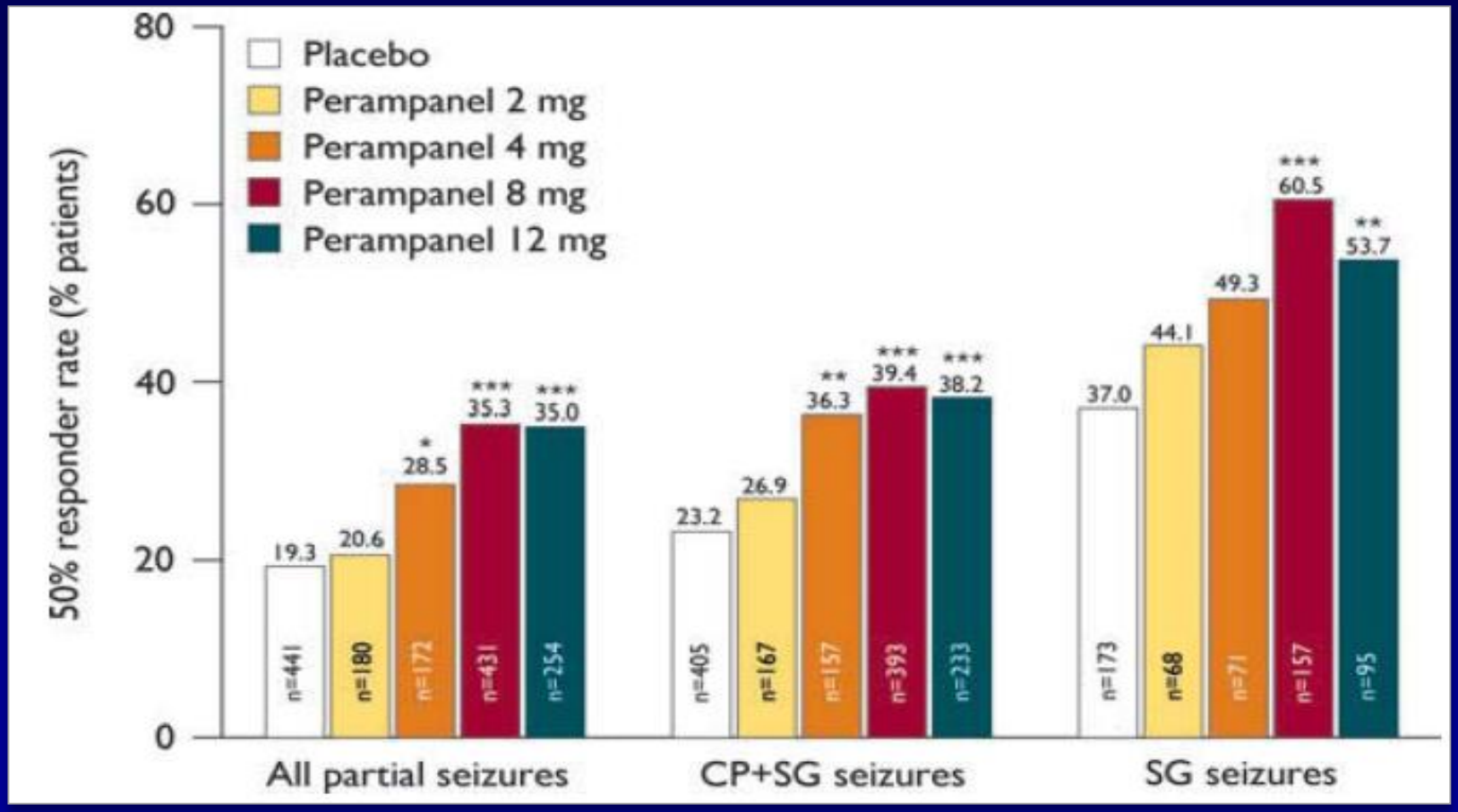


Steinhoff, et al. *Epilepsia 2013; 54(8): 481-89.*

Pooled Phase III

Analisi aggregata degli studi di fase III

50% responder rate per tipo di crisi



Steinhoff, et al. *Epilepsia 2013; 54(8): 481-89.*

Pooled Phase III

Analisi aggregata degli studi di fase III

TEAEs* che si sono verificati in >5% dei pazienti

*TEAEs: treatment-emergent adverse events

Table 4. TEAEs occurring in > 5% of patients in any treatment group

		Perampanel			
Adverse event, n (%)	Placebo (n = 442)	2 mg (n = 180)	4 mg (n = 172)	8 mg (n = 431)	12 mg (n = 255)
Any TEAE	294 (66.5)	111 (61.7)	111 (64.5)	350 (81.2)	227 (89.0)
Dizziness	40 (9.0)	18 (10.0)	28 (16.3)	137 (31.8)	109 (42.7)
Somnolence	32 (7.2)	22 (12.2)	16 (9.3)	67 (15.5)	45 (17.6)
Headache	50 (11.3)	16 (8.9)	19 (11.0)	49 (11.4)	34 (13.3)
Fatigue	21 (4.8)	8 (4.4)	13 (7.6)	36 (8.4)	31 (12.2)
Irritability	13 (2.9)	7 (3.9)	7 (4.1)	29 (6.7)	30 (11.8)
Nausea	20 (4.5)	4 (2.2)	5 (2.9)	25 (5.8)	20 (7.8)
Fall	15 (3.4)	2 (1.1)	3 (1.7)	22 (5.1)	26 (10.2)
Nasopharyngitis	18 (4.1)	7 (3.9)	9 (5.2)	23 (5.3)	11 (4.3)
Upper respiratory tract infection	12 (2.7)	11 (6.1)	6 (3.5)	14 (3.2)	10 (3.9)
Ataxia	0 (0.0)	0 (0.0)	1 (0.6)	14 (3.2)	21 (8.2)
Balance disorder	2 (0.5)	0 (0.0)	0 (0.0)	22 (5.1)	8 (3.1)

- Aggressività 1%, 2%, 3% con 4, 8, e 12 mg (placebo 1%)

Steinhoff, et al. *Epilepsia 2013; 54(8): 481-89.*

Pooled Phase III

Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy

A randomized trial

OPEN

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Gregory L. Krauss, MD
Robert T. Wechsler, MD, PhD
Xue-Feng Wang, MD
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Eugen Trinka, MD, MSc
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ABSTRACT

Objective: To assess efficacy and safety of adjunctive perampanel in patients with drug-resistant, primary generalized tonic-clonic (PGTC) seizures in idiopathic generalized epilepsy (IGE).

Methods: In this multicenter, double-blind study (ClinicalTrials.gov identifier: NCT01393743; funded by Eisai Inc.), patients 12 years or older with PGTC seizures and IGE were randomized to placebo or perampanel during a 4-week titration period (perampanel uptitrated from 2 to 8 mg/d, or highest tolerated dose) and 13-week maintenance period. The primary endpoint was percent change in PGTC seizure frequency per 28 days (titration plus maintenance vs baseline). The key secondary endpoint (primary endpoint for European Union registration) was 50% PGTC seizure responder rate (patients achieving ≥50% reduction in PGTC seizure frequency; maintenance vs baseline). Treatment-emergent adverse events were monitored.

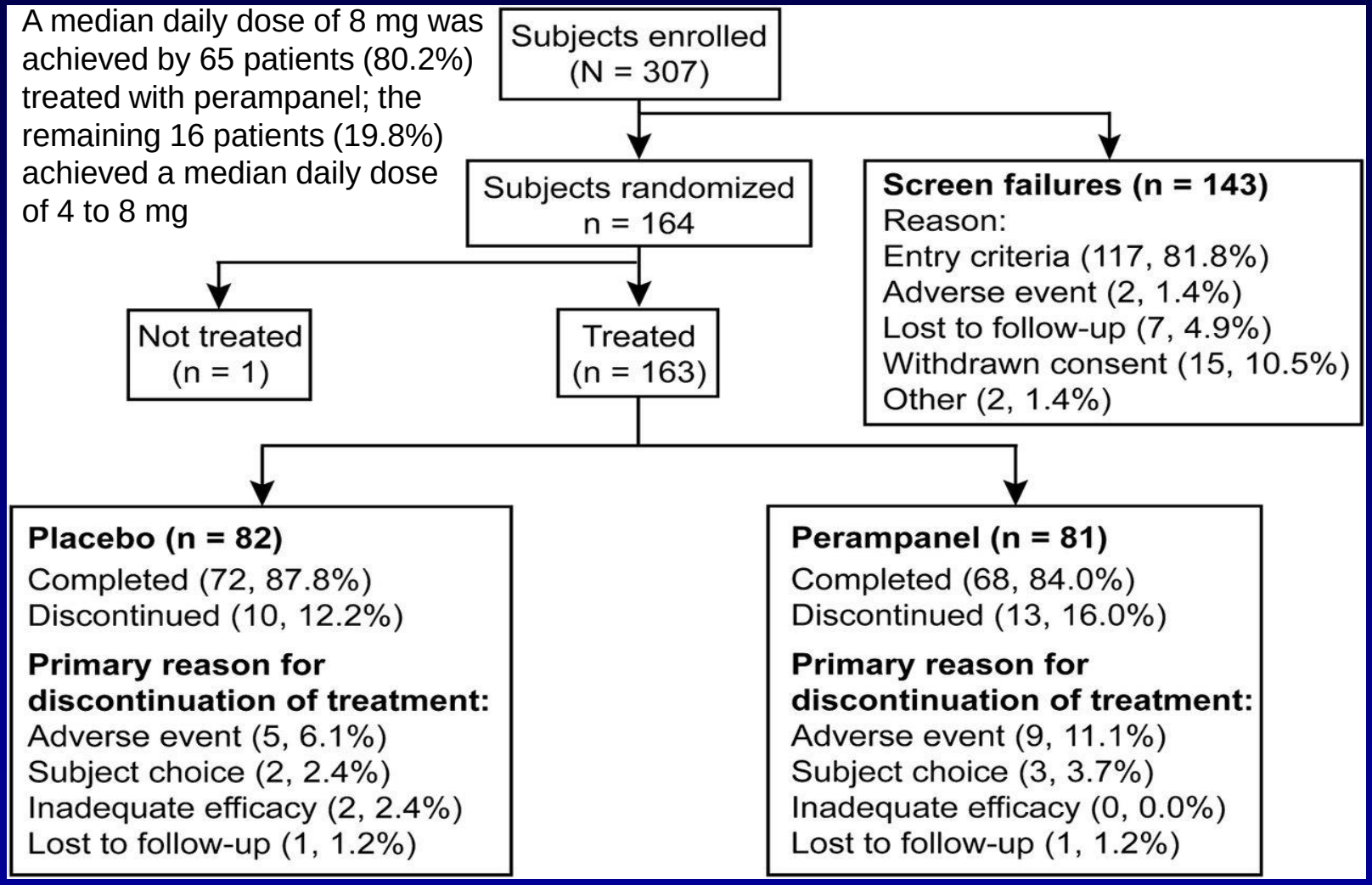
Results: Of 164 randomized patients, 162 comprised the full analysis set (placebo, 81; perampanel, 81). Compared with placebo, perampanel conferred a greater median percent change in PGTC seizure frequency per 28 days (−38.4% vs −76.5%; $p < 0.0001$) and greater 50% PGTC seizure responder rate (39.5% vs 64.2%; $p = 0.0019$). During maintenance, 12.3% of placebo-treated patients and 30.9% of perampanel-treated patients achieved PGTC seizure freedom. For the safety analysis (placebo, 82; perampanel, 81), the most frequent treatment-emergent adverse events with perampanel were dizziness (32.1%) and fatigue (14.8%).

Conclusions: Adjunctive perampanel was well tolerated and improved control of drug-resistant PGTC seizures in patients with IGE.

Classification of evidence: This study provides Class I evidence that adjunctive perampanel reduces PGTC seizure frequency, compared with placebo, in patients with drug-resistant PGTC seizures in IGE. *Neurology*® 2015;85:950–957

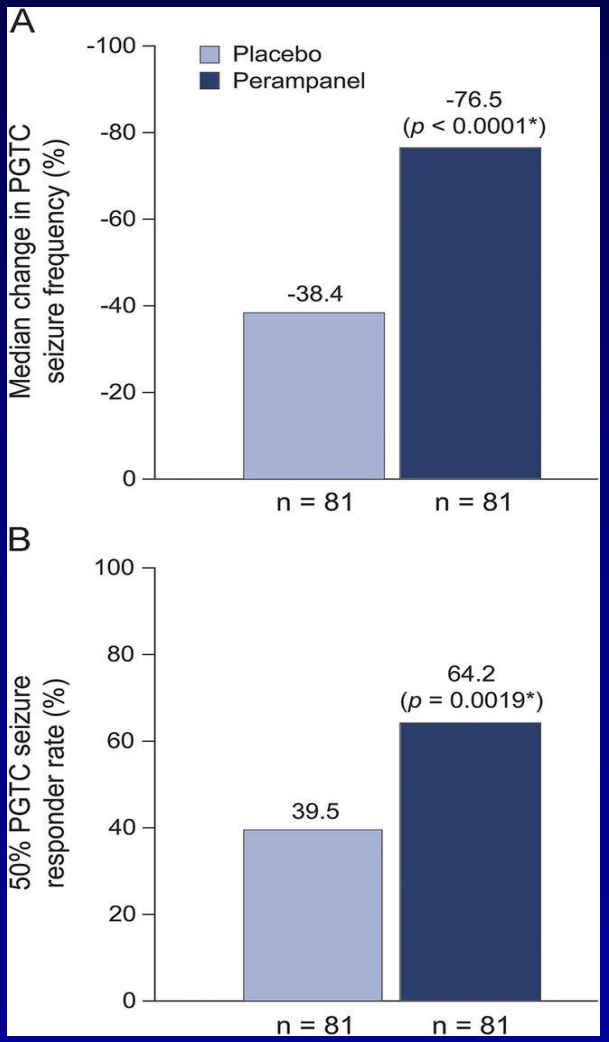
Figure 1 - Patient disposition

A median daily dose of 8 mg was achieved by 65 patients (80.2%) treated with perampanel; the remaining 16 patients (19.8%) achieved a median daily dose of 4 to 8 mg



Jacqueline A. French et al. Neurology 2015;85:950-957

Figure 2 - Median percent change in PGTC seizure frequency and 50% PGTC seizure responder rates



Compared with placebo, there was also a greater median percent change in the frequency of all seizures per 28 days in the perampanel group (-22.9 vs -43.4; p = 0.0018)

During the maintenance period, 12.3% of placebo-treated patients and 30.9% of perampanel-treated patients achieved freedom from PGTC seizures; 4.9% of placebo-treated patients and 23.5% of perampanel-treated patients achieved freedom from all seizures

Jacqueline A. French et al. Neurology 2015;85:950-957

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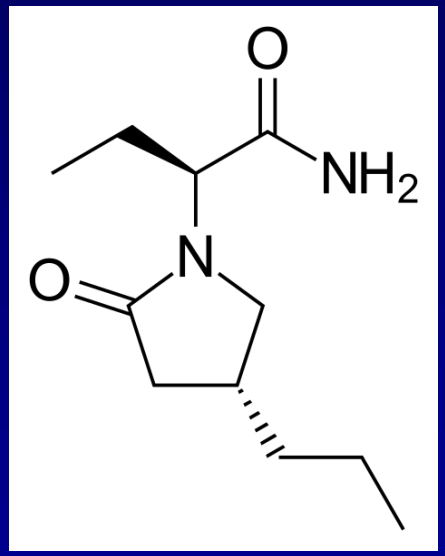
Table 2 TEAEs reported in ≥5% of patients treated with either placebo or perampanel

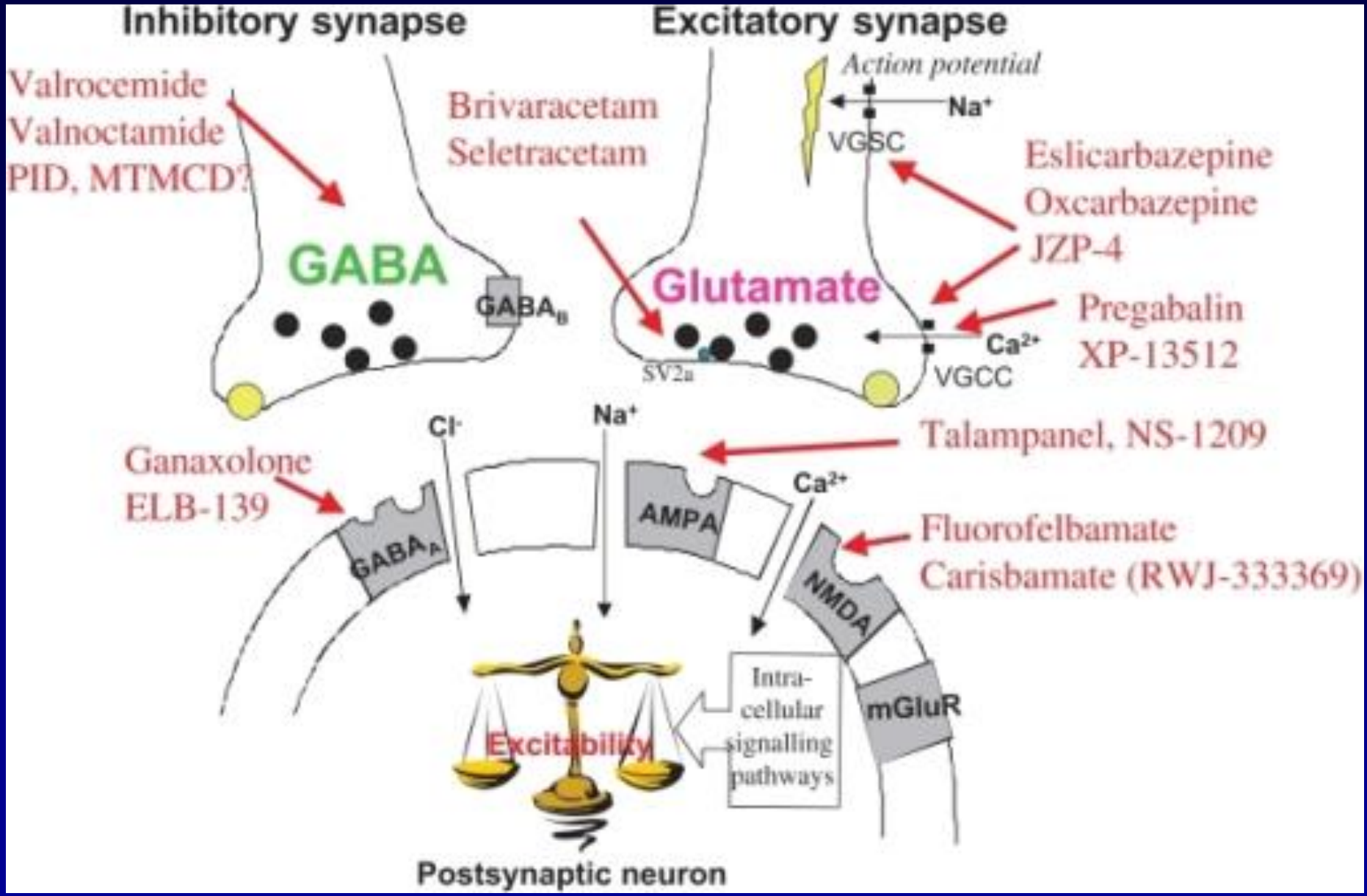
TEAE	Placebo (n = 82)	Perampanel (n = 81)
Any TEAE	59 (72.0)	67 (82.7)
Dizziness	5 (6.1)	26 (32.1)
Fatigue	5 (6.1)	12 (14.8)
Headache	8 (9.8)	10 (12.3)
Somnolence	3 (3.7)	9 (11.1)
Irritability	2 (2.4)	9 (11.1)
Nasopharyngitis	7 (8.5)	7 (8.6)
Vertigo	2 (2.4)	7 (8.6)
Vomiting	2 (2.4)	7 (8.6)
Weight increased	3 (3.7)	6 (7.4)
Contusion	3 (3.7)	5 (6.2)
Nausea	4 (4.9)	5 (6.2)

Abbreviation: TEAE = treatment-emergent adverse event.
Data are n (%).

Brivaracetam pharmacokinetics



- Brivaracetam is highly permeable and is rapidly and almost completely absorbed after oral administration
- Pharmacokinetics is dose-proportional from 10 to 600 mg
- Brivaracetam is weakly bound to plasma proteins (20%)
- Brivaracetam is metabolized by CYP2C19 and CYP2C9
- Brivaracetam is eliminated primarily in the urine
- The terminal plasma half-life (t½) is approximately 9 hours



Brivaracetam has a >30-fold affinity for SV2A than levetiracetam; the binding enhances an SV2A function that inhibits abnormal neuronal activity

Epilepsy Research 127 (2016) 179–185

Contents lists available at www.sciencedirect.com

Epilepsy Research

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Efficacy, safety, and tolerability of adjunctive brivaracetam for secondarily generalized tonic-clonic seizures: Pooled results from three Phase III studies

Brian D. Moseley (MD)[a,*], Michael R. Sperling (MD)[b,1], Ali A. Asadi-Pooya (MD)[b,c,2], Anyzeila Diaz (PharmD)[d,3], Sami Elmouft (MSc)[e,4], Jimmy Schiemann (MD)[e,5], John Whitesides (PhD)[e,6]

NCT00490035; NCT00464269; NCT01261325

- Inclusion criteria

- ✓ Patients aged ≥16–70 years or aged ≥16–80 years were eligible for study enrollment
- ✓ Well-characterized focal seizures or a focal epilepsy syndrome
- ✓ Focal seizures had to be uncontrolled despite 1–2 concomitant AEDs at stable and optimal doses for ≥1 month prior to the first study visit
- ✓ At least 2 focal seizures/month for the 3 months prior to screening and ≥8 focal seizures during the 8-week prospective baseline period
- ✓ In addition, ≥2 focal seizures in each 4-week interval of the baseline period in study NCT01261325.

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Efficacy, safety, and tolerability of adjunctive brivaracetam for secondarily generalized tonic-clonic seizures: Pooled results from three Phase III studies

Brian D. Moseley (MD)[a,*], Michael R. Sperling (MD)[b,1], Ali A. Asadi-Pooya (MD)[b,c,2], Anyzeila Diaz (PharmD)[d,3], Sami Elmouft (MSc)[e,4], Jimmy Schiemann (MD)[e,5], John Whitesides (PhD)[e,6]

NCT00490035; NCT00464269; NCT01261325

each study consisted of an 8-week prospective baseline period and 12-week treatment period

409 patients

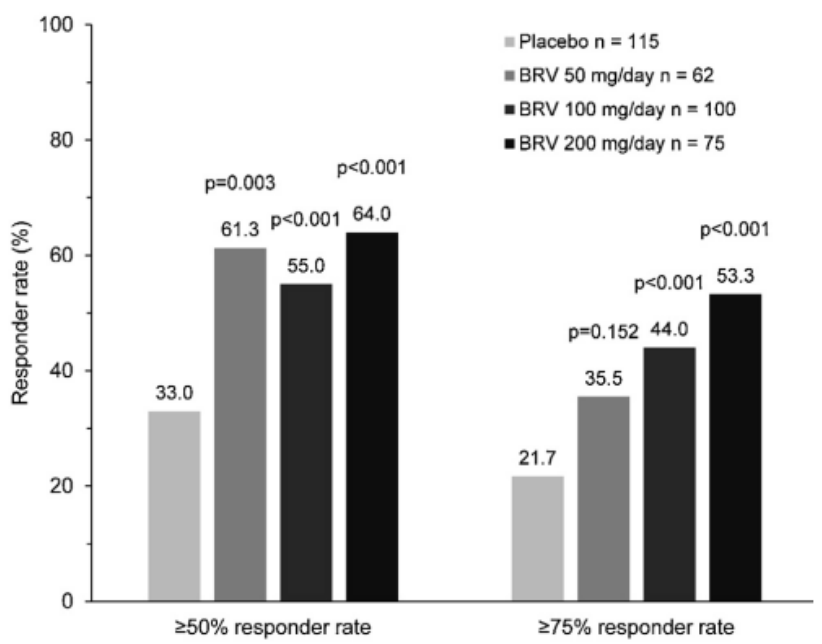


Fig. 1. ≥50% and ≥75% responder rates for secondary generalized tonic-clonic seizures during the 12-week treatment period (efficacy population). *P*-values are versus placebo.

Table 2
Median percent reduction from baseline in secondary generalized tonic-clonic seizures/28 days during the 12-week treatment period (efficacy population).

	Placebo (n = 115)	BRV 50 mg/day (n = 62)	BRV 100 mg/day (n = 100)	BRV 200 mg/day (n = 75)	BRV ≥50 mg/day (n = 237)
Median percent reduction from baseline in SGTCS/28 days	33.3	66.6	61.2	82.1	67.5
Median difference vs placebo		28.4	25.1	38.9	29.4
95% CI (LL, UL)		(11.0, 45.0)	(6.0, 43.6)	(16.1, 53.1)	(14.6, 43.8)
P-value		<0.001	0.002	<0.001	<0.001

BRV = brivaracetam; CI = confidence interval; LL = lower limit; SGTCS = secondary generalized tonic-clonic seizure; UL = upper limit.

The most commonly reported side effects included somnolence (12.6%), headache (11.0%), dizziness (8.3%), fatigue (7.9%), and nausea (5.9%)

Efficacy and safety of brivaracetam for partial-onset seizures in 3 pooled clinical studies

by Elinor Ben-Menachem, Rūta Mameniškienė, Pier Paolo Quarato, Pavel Klein, Jessica Gamage, Jimmy Schiemann, Martin E. Johnson, John Whitesides, Belinda McDonough, and Klaus Eckhardt

Neurology
Volume 87(3):314-323
July 19, 2016

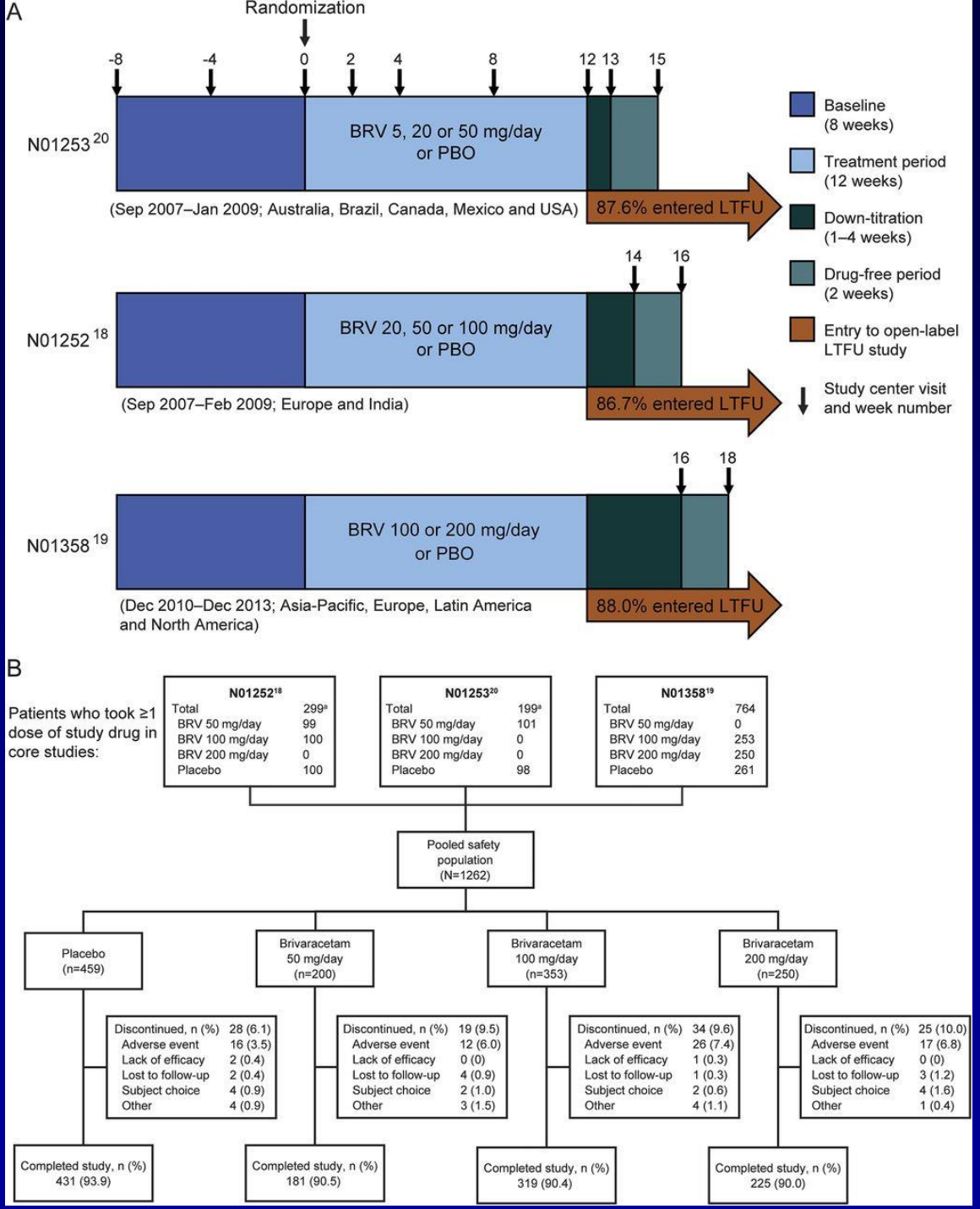

A
Randomization
-8
-4
0
2
4
8
12
13
15
N01253 20
BRV 5, 20 or 50 mg/day or PBO
(Sep 2007–Jan 2009; Australia, Brazil, Canada, Mexico and USA)
87.6% entered LTFU
14
16
N01252 18
BRV 20, 50 or 100 mg/day or PBO
(Sep 2007–Feb 2009; Europe and India)
86.7% entered LTFU
16
18
N01358 19
BRV 100 or 200 mg/day or PBO
(Dec 2010–Dec 2013; Asia-Pacific, Europe, Latin America and North America)
88.0% entered LTFU
Baseline (8 weeks)
Treatment period (12 weeks)
Down-titration (1–4 weeks)
Drug-free period (2 weeks)
Entry to open-label LTFU study
Study center visit and week number
B
Patients who took ≥1 dose of study drug in core studies:
N01252[18]
Total 299[a]
BRV 50 mg/day 99
BRV 100 mg/day 100
BRV 200 mg/day 0
Placebo 100
N01253[20]
Total 199[a]
BRV 50 mg/day 101
BRV 100 mg/day 0
BRV 200 mg/day 0
Placebo 98
N01358[19]
Total 764
BRV 50 mg/day 0
BRV 100 mg/day 253
BRV 200 mg/day 250
Placebo 261
Pooled safety population (N=1262)
Placebo (n=459)
Brivaracetam 50 mg/day (n=200)
Brivaracetam 100 mg/day (n=353)
Brivaracetam 200 mg/day (n=250)
Discontinued, n (%) 28 (6.1)
Adverse event 16 (3.5)
Lack of efficacy 2 (0.4)
Lost to follow-up 2 (0.4)
Subject choice 4 (0.9)
Other 4 (0.9)
Discontinued, n (%) 19 (9.5)
Adverse event 12 (6.0)
Lack of efficacy 0 (0)
Lost to follow-up 4 (0.9)
Subject choice 2 (1.0)
Other 3 (1.5)
Discontinued, n (%) 34 (9.6)
Adverse event 26 (7.4)
Lack of efficacy 1 (0.3)
Lost to follow-up 1 (0.3)
Subject choice 2 (0.6)
Other 4 (1.1)
Discontinued, n (%) 25 (10.0)
Adverse event 17 (6.8)
Lack of efficacy 0 (0)
Lost to follow-up 3 (1.2)
Subject choice 4 (1.6)
Other 1 (0.4)
Completed study, n (%) 431 (93.9)
Completed study, n (%) 181 (90.5)
Completed study, n (%) 319 (90.4)
Completed study, n (%) 225 (90.0)

Figure 2 Primary efficacy outcomes

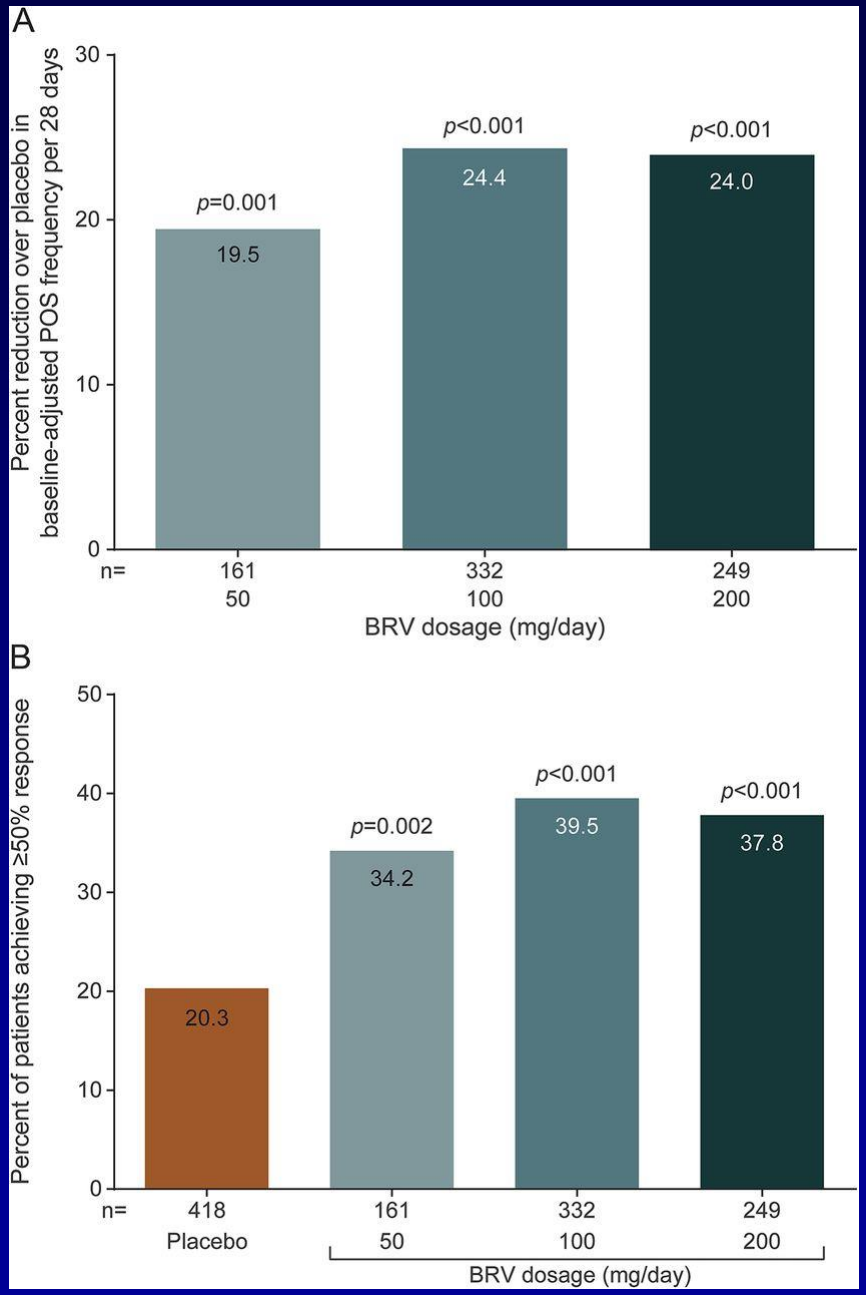


Figure 3 Secondary efficacy outcomes

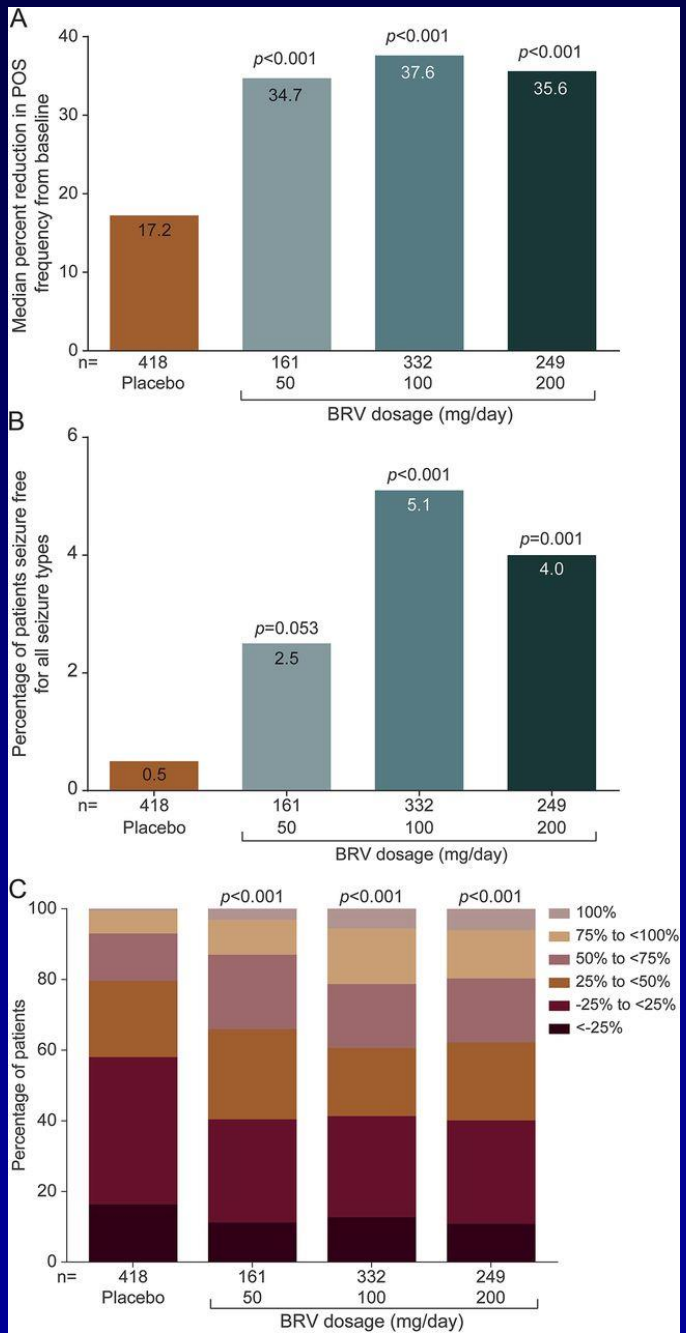
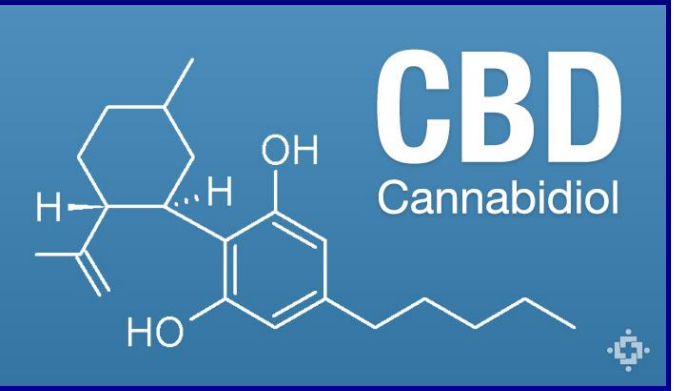


Table 2 Summary and incidence of TEAEs (reported in ≥3% of patients taking BRV), n (%) (safety population)

	Placebo (n = 459)	BRV dosage, mg/d			BRV overall (n = 803)
		50 (n = 200)	100 (n = 353)	200 (n = 250)	
Any TEAE	285 (62.1)	142 (71.0)	236 (66.9)	168 (67.2)	546 (68.0)
Discontinuation because of TEAE	18 (3.9)	10 (5.0)	27 (7.6)	17 (6.8)	54 (6.7)
Drug-related TEAEs	139 (30.3)	94 (47.0)	141 (39.9)	109 (43.6)	344 (42.8)
Severe TEAEs	19 (4.1)	12 (6.0)	17 (4.8)	16 (6.4)	45 (5.6)
Treatment-emergent SAE	13 (2.8)	6 (3.0)	9 (2.5)	9 (3.6)	24 (3.0)
Drug-related treatment-emergent SAE	2 (0.4)	1 (0.5)	3 (0.8)	2 (0.8)	6 (0.7)
Deaths	1 (0.2)	1 (0.5)	0	2 (0.8)	3 (0.4)
TEAEs reported in ≥3% of BRV-treated patients overall					
Somnolence	39 (8.5)	23 (11.5)	57 (16.1)	42 (16.8)	122 (15.2)
Dizziness	33 (7.2)	23 (11.5)	31 (8.8)	36 (14.4)	90 (11.2)
Headache	47 (10.2)	32 (16.0)	26 (7.4)	19 (7.6)	77 (9.6)
Fatigue	17 (3.7)	14 (7.0)	27 (7.6)	29 (11.6)	70 (8.7)
Nausea	11 (2.4)	8 (4.0)	15 (4.2)	9 (3.6)	32 (4.0)
Nasopharyngitis	14 (3.1)	6 (3.0)	12 (3.4)	9 (3.6)	27 (3.4)
Irritability	5 (1.1)	10 (5.0)	9 (2.5)	7 (2.8)	26 (3.2)

Abbreviations: BRV = brivaracetam; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Data represent the number of patients reporting a TEAE at any point during the entire study.



Pharmacological Research 107 (2016) 85–92

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Review

Cannabidiol and epilepsy: Rationale and therapeutic potential

Antonio Leo[a], Emilio Russo[a], Maurizio Elia[b,*]

As widely reported in literature, the exact molecular target(s) by which CBD exerts its pharmacological properties are still undetermined [23]. However, it has already been demonstrated how CBD, in comparison to THC, does not activate the cannabinoid type 1 (CB1) and type 2 (CB2) receptors. Despite this low affinity for the cannabinoid receptors, CBD is able to antagonize CB1 and CB2 receptor agonists *in vitro* with unexpectedly high potency [24]. These properties of CBD could explain its lack of psychotropic effects [25,26]. Accordingly, it has been possible to affirm that the CBD's therapeutic properties in neurological disorders, such as epilepsy, are independent of the endocannabinoid-signalling pathway, whereas, according to Devinsky et al. [15], these properties could be linked to a "multi-target drug" profile.

Among the molecular targets of CBD, currently identified, there are several enzymes, receptors, ion channels, and transporters.

Cannabidiol pharmacokinetics

- The oral bioavailability has been estimated in about 10%
- Half-life has been assessed in about 24 h
- CBD in the plasma is highly bound to proteins (>99%)
- CBD results mainly metabolized by cytochrome P450 (CYP450) pathway, whereas its metabolites are widely excreted in the faeces
- CBD inhibits CYP450 and increases plasma concentrations of clobazam

6 YR OLD CHARLOTTE FIGI STOPS 300 SEIZURES PER WEEK WITH MARIJUANA

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Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial

Orrin Devinsky, Eric Marsh*, Daniel Friedman*, Elizabeth Thiele, Linda Laux, Joseph Sullivan, Ian Miller, Robert Flamini, Angus Wilfong, Francis Filloux, Matthew Wong, Nicole Tilton, Patricia Bruno, Judith Bluvstein, Julie Hedlund, Rebecca Kamens, Jane Maclean, Srishti Nangia, Nilika Shah Singhal, Carey A Wilson, Anup Patel, Maria Roberta Cilio*

Lancet Neurol 2016; 15: 270–78

Summary

Background Almost a third of patients with epilepsy have a treatment-resistant form, which is associated with severe morbidity and increased mortality. Cannabis-based treatments for epilepsy have generated much interest, but scientific data are scarce. We aimed to establish whether addition of cannabidiol to existing anti-epileptic regimens would be safe, tolerated, and efficacious in children and young adults with treatment-resistant epilepsy.

Methods In this open-label trial, patients (aged 1–30 years) with severe, intractable, childhood-onset, treatment-resistant epilepsy, who were receiving stable doses of antiepileptic drugs before study entry, were enrolled in an expanded-access programme at 11 epilepsy centres across the USA. Patients were given oral cannabidiol at 2–5 mg/kg per day, up-titrated until intolerance or to a maximum dose of 25 mg/kg or 50 mg/kg per day (dependent on study site). The primary objective was to establish the safety and tolerability of cannabidiol and the primary efficacy endpoint was median percentage change in the mean monthly frequency of motor seizures at 12 weeks. The efficacy analysis was by modified intention to treat. Comparisons of the percentage change in frequency of motor seizures were done with a Mann-Whitney *U* test.

Results Between Jan 15, 2014, and Jan 15, 2015, 214 patients were enrolled; 162 (76%) patients who had at least 12 weeks of follow-up after the first dose of cannabidiol were included in the safety and tolerability analysis, and 137 (64%) patients were included in the efficacy analysis. In the safety group, 33 (20%) patients had Dravet syndrome and 31 (19%) patients had Lennox-Gastaut syndrome. The remaining patients had intractable epilepsies of different causes and type. Adverse events were reported in 128 (79%) of the 162 patients within the safety group. Adverse events reported in more than 10% of patients were somnolence (n=41 [25%]), decreased appetite (n=31 [19%]), diarrhoea (n=31 [19%]), fatigue (n=21 [13%]), and convulsion (n=18 [11%]). Five (3%) patients discontinued treatment because of an adverse event. Serious adverse events were reported in 48 (30%) patients, including one death—a sudden unexpected death in epilepsy regarded as unrelated to study drug. 20 (12%) patients had severe adverse events possibly related to cannabidiol use, the most common of which was status epilepticus (n=9 [6%]). The median monthly frequency of motor seizures was 30·0 (IQR 11·0–96·0) at baseline and 15·8 (5·6–57·6) over the 12 week treatment period. The median reduction in monthly motor seizures was 36·5% (IQR 0–64·7).

Treatment-emergent serious adverse events*	
Status epilepticus	9 (6%)
Diarrhoea	3 (2%)
Weight decreased	2 (1%)
Convulsion	1 (<1%)
Decreased appetite	1 (<1%)
Drug concentration increased	1 (<1%)
Hepatotoxicity	1 (<1%)
Hyperammonaemia	1 (<1%)
Lethargy	1 (<1%)
Unspecified pneumonia	1 (<1%)
Aspiration pneumonia	1 (<1%)
Bacterial pneumonia	1 (<1%)
Thrombocytopenia	1 (<1%)

"I'm referring you to a specialist to treat the side effects from this drug I'm prescribing."