Seizing an Opportunity to Control Refractory Focal Epilepsy in Children: Will Lacosamide Cause Bursts of Excitement or Will it Fall Flat?

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Epilepsy

- Chronic disorder characterized by recurrent unprovoked seizures
- Affects 0.5 – 1% of all children
- Broad classification:
  - Focal
  - Generalized

Pediatrics in Review. 1998 Oct; 19(10): 342-51
Semin Pediatr Neurol. 2010; 17: 214 – 223
Pediatric Epilepsy 3rd Ed. 2007

Electroclinical Syndromes

Neonatal period
- Benign neonatal seizures^
- Benign familial neonatal epilepsy (BFNE)
- Ohtahara syndrome
- Early Myoclonic encephalopathy (EME)

Infancy
- Febrile seizures^, Febrile seizures plus (FS+)
- Benign infantile epilepsy
- Benign familial infantile epilepsy (BFIE)
- West syndrome
- Dravet syndrome
- Myoclonic epilepsy in infancy (MEI)
- Myoclonic encephalopathy in nonprogressive disorders
- Epilepsy of infancy with migrating focal seizures

Childhood
- Febrile seizures^, Febrile seizures plus (FS+)
- Early onset childhood occipital epilepsy (Panayiotopoulos syndrome)
- Epilepsy with myoclonic atonic (previously astatic) seizures
- Childhood absence epilepsy (CAE)
- Benign epilepsy with centrotemporal spikes (BECTS)
- Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)
- Late onset childhood occipital epilepsy (Gastaut type)
- Epilepsy with myoclonic absences
- Lennox-Gastaut syndrome (LGS)
- Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)+
- Landau-Kleffner syndrome (LKS)

Epilepsia, 51(4):676–685, 2010

Treatment

- Initiate monotherapy
  - Usually after second seizure
  - Based on syndrome/type

- Focal Seizures:
  - First line:
    - Carbamazepine
    - Lamotrigine

Epilepsy. NICE Guidelines. 2012

Treatment

- Alternatives:
  - Levetiracetam
  - Oxcarbazepine
  - Valproic acid
- Adjunct treatment options:
  - Clobazam
  - Gabapentin
  - Topiramate
- Combination therapy only if monotherapy failed twice

Epilepsy. NICE Guidelines. 2012

Refractory Epilepsy

- 30% of children with epilepsy develop seizures refractory to medical management
- Concern for cognitive development
- Factors associated with poor response to therapy:
  - Multiple seizures prior to initiation of therapy
  - Unresponsive to initial treatment

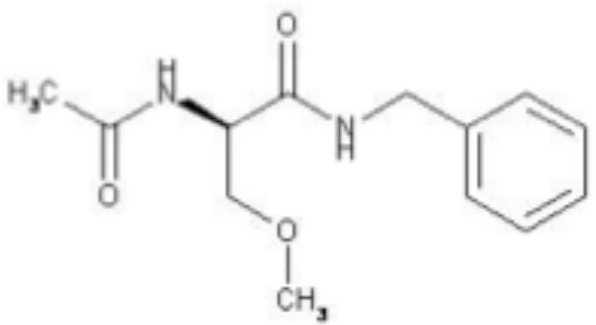
Epilepsy Behav 2011; 20: 691-93
N Engl J Med 2000; 342:314-319

Additional Treatment

- If adjunctive treatment is ineffective, a specialist may prescribe:
  - Lacosamide
  - Phenobarbital
  - Phenytoin
  - Pregabalin
  - Vigabatrin
  - Zonisamide

Epilepsy. NICE Guidelines. 2012

Lacosamide
Vimpat®



- NOC September 2010

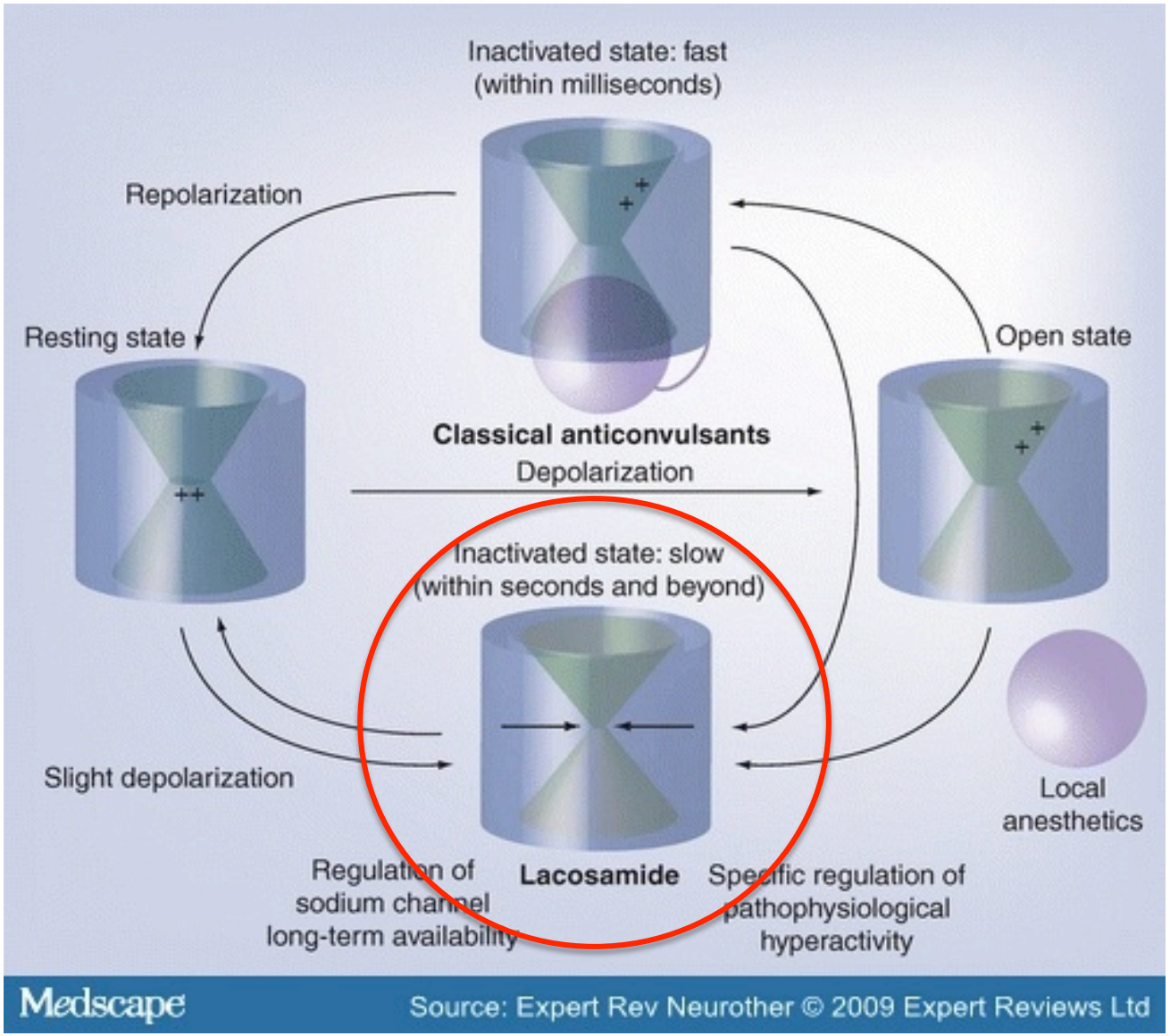
- Adjunctive therapy for:
  - Focal seizures not controlled with conventional therapy
  - Adult population

- Oral and IV formulations available

- Dose: 50 mg BID to 200 mg BID

NOC database. Health Canada 2013
Lacosamide product monograph. UCB Canada 2012

Mechanism of Action



Lacosamide

Pharmacokinetics

- Bioavailability 100%
- Metabolized by CYP2C19, CYP2C9, CYP3A4
- Excreted mainly in urine
- Half life ~ 13 hours

Adverse Effects

- Dizziness (30%)
- Nausea/vomiting (10%)
- Blurred vision (10%)
- Ataxia (7%)
- Tremor (6%)
- Nystagmus (5%)
- Dose - dependent prolongations in PR interval

Lacosamide product monograph. UCB Canada 2012

Clinical Question

P	Children with refractory focal seizures
I	Lacosamide (as adjunct)
C	Other antiepileptic drugs, placebo, or not using lacosamide
O	Mortality Neurological deficits Seizure frequency Adverse effects Quality of life

Search Strategy

Databases	Medline, PubMed, Embase, IPA, Google, Google Scholar, Clinicaltrials.gov
Search Terms	Lacosamide, Vimpat, harkoseride, erlosamide, refractory, focal, partial, epilepsy, seizures, children, pediatrics
Limits	Human, English
Results	3 Prospective observational studies 3 Retrospective studies 1 Case report

Efficacy and tolerability of oral lacosamide as adjunctive therapy in pediatric patients with pharmacoresistant focal epilepsy

M. Gavatha *, I. Ioannou, A.S. Papavasiliou

Department of Neurology, Pendeli Children's Hospital, Athens, Greece

Epilepsy & Behavior 20 (2011) 691–693

Gavatha et al

Design	Prospective, observational
Patient Population	N = 18 Mean age: 10 years (3 y – 18 y) Inclusion criteria: - Focal epilepsy - Pharmacoresistance - Current treatment with stable doses of other AEDs
Intervention	Lacosamide (po) initial 1 mg/kg/day divided q12h Mean dose: 6.34 mg/kg/day (1.7 – 10 mg/kg/day) Mean duration: 8 months (3 weeks – 17 months)
Comparator	-
Outcomes	Seizure frequency reduction $\geq$ 50% Adverse effects Reasons for discontinuation

Gavatha et al – Patient Characteristics

Table 1
Patients' demographic and clinical characteristics.

Patient	Sex	MRI findings	Number of failed AEDs	Concurrent AEDs[a]
1	F	Cortical dysplasia	10	LVT, CBZ
2	M	Cortical dysplasia	8	TPM
3	F	CNS malformation	7	VPA, LVT, TPM
4	M	Perinatal/ischemic	11	PHT, PHB, PRG
5	M	Perinatal/ischemic	8	VPA, LTG, TPM
6	M	Perinatal/ischemic	9	VPA
7	M	Perinatal/ischemic	3	OXC, TPM
8	F	Normal	10	LTG, RUF
9	F	CNS malformation	5	LVT, RUF
10	F	Neurocutaneous syndrome	4	LVT
11	F	Normal	6	LVT
12	M	Hippocampal sclerosis	8	OXC
13	F	Perinatal/ischemic	3	VPA, ZNS
14	M	Normal	16	TPM, VPA, RUF
15	M	Perinatal/ischemic	7	VPA, LTG
16	M	Normal	5	LVT, VPA
17	M	Normal	4	OXC, LVT
18	M	Neurocutaneous syndrome	3	VPA, LTG

Gavatha et al - Results

Initial Assessment (N = 18)	
Seizure reduction ≥ 50%	5* Efficacy of 4 patients not reported
Treatment discontinuation	8 (Ineffective)
	1 (Adverse effects)

1 Year Assessment (N = 18) (4 patients still taking lacosamide)	
Seizure reduction ≥ 50%	3**
Treatment discontinuation	4 (Ineffective)
	1 (Changed doctor)

* 2 patients achieved complete seizure freedom
** 1 patient still had complete seizure freedom

Gavatha et al - Results

Initial Assessment	
Reported Side Effects	**Number of Patients**
Somnolence	3
Irritability	2
Sleep disturbance	1
Pancytopenia	1

No adverse events reported at the 1 year assessment

Gavatha et al

- Authors' Conclusions:

"In conclusion, open-label lacosamide was associated with relative efficacy and good tolerability in a small group of children with refractory epilepsy. Further studies are needed to validate and extend these findings."

Gavatha et al - Analysis

- Observational
- Small sample size
- 4 patients not included in efficacy analysis
- No information on seizure frequency prior to lacosamide
- Wide age range
- Parent/patient reporting

Lacosamide in Refractory Mixed Pediatric Epilepsy: A Prospective Add-on Study

Reena Gogia Rastogi, MD[1], and Yu-Tze Ng, MD, FRACP[2]

Journal of Child Neurology
27(4) 492-495

DOI: 10.1177/0883073812436741
http://jcn.sagepub.com
SAGE

Rastogi et al

Design	Prospective, observational
Patients	N = 21 Mean age 8.6 years (12 months – 16 years) Refractory epilepsy (multiple seizure types) Lacosamide for minimum of 3 months
Intervention	Lacosamide po Mean initial dose: 5.8 mg/kg/day Mean final dose: 9.4 mg/kg/day (2.4 – 19.4 mg/kg/day) Mean follow up: 9.8 months (3 – 18 m)
Comparator	-
Outcomes	Response to addition of lacosamide (classified into 3 groups): - > 90% reduction in seizure frequency - > 50% reduction in seizure frequency - No change in seizure frequency Adverse effects

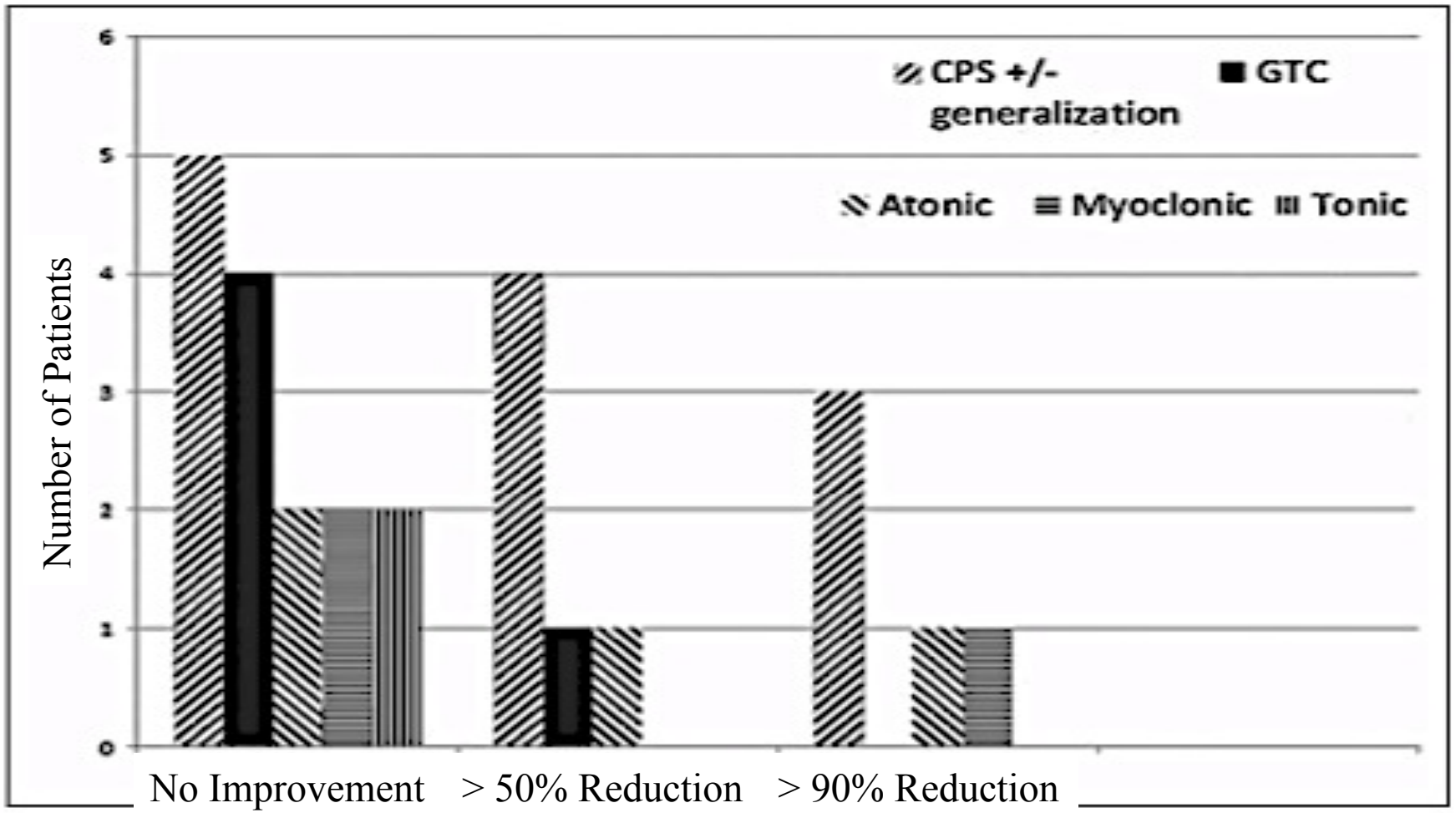
Rastogi et al – Patient Characteristics

Table 1. Patients' Clinical Information and Response to Lacosamide

Age	Sex	Diagnosis	Seizure Types	No. of Current AEDs	No. of Failed AEDs
8	M	LGS	Atonic, tonic, GTC	2	9
13	M	LRE	CPS +/– 2° GTC	2	11
7	M	CGE	Atonic, GTC	2	9
5	F	LGS	Myoclonic, atonic, CPS +/– 2° GTC	1	7
13	F	LGS	CPS, atypical absence, GTC	2	9
5	F	SGE	Tonic, GTC	1	3
16	M	LRE	CPS +/– 2° GTC	2	9
9	F	LRE	CPS +/– 2° GTC	0	2
6	F	LRE	CPS	2	7
13	M	LGS	CPS, myoclonic, atonic	2	5
9	M	LRE	CPS	1	6
4	F	LRE	CPS +/– 2° GTC	3	6
16	M	CGE	GTC	2	6
11	M	LRE	CPS	2	9
1	M	LRE	CPS	2	2
2	F	SGE	CPS, myoclonic, GTC	2	5

Rastogi et al - Results

- 8 (50%) patients had a seizure reduction of at least 50%
- 3 (19%) patients had a seizure reduction of > 90%



Rastogi et al

Adverse Effects
Nausea
Vomiting
Dizziness
Headache
Somnolence
Facial edema
Increased Seizures

Rastogi et al

- Authors' Conclusions:

"Lacosamide may be an excellent second-line treatment for localization-related epilepsy. We suggest that it could be used as an early alternative in older children with localization-related epilepsy because of its efficacy and safety profile and may be tried later in younger children with generalized epilepsies who have failed several other treatments."

Rastogi et al - Analysis

- Observational
- Mixed seizure types
- 5 patients excluded from analysis
- Inappropriate reporting of results
- No information on seizure frequency prior to lacosamide
- No information on other AEDs
- Wide age range
- Poor reporting of adverse effects
- Parent/patient reporting of seizures
- Authors' conclusion not based on information found in their study

ORIGINAL RESEARCH ARTICLE

Drugs R D 2012; 12 (4): 187-197
1179-6901/12/0004-0187

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

Carlos Casas-Fernández,[1] *Antonio Martínez-Bermejo,*[2] *Miguel Rufo-Campos,*[3] *Patricia Smeyers-Durá,*[4] *José L. Herranz-Fernández,*[5] *Salvador Ibáñez-Micó,*[1] *Jaume Campistol-Plana,*[6] *Helena Alarcón-Martínez*[1] and *Jaime Campos-Castelló*[7]

Casas – Fernandez et al

Design	P, Open label, Observational, MC
Patients	N = 130 Mean age 8 yo (6 months – 16 yo) Refractory Epilepsy (focal and generalized) Inclusion criteria: - Initiated lacosamide - Lack of response to prior antiepileptic treatment (minimum two AEDs)
Intervention	Lacosamide (PO or IV) 1 -2 mg/kg/day divided q12h Titrated mean dose 6.8 mg/kg/day Duration: 3 months
Comparator	-
Outcome	- Proportion of responders to 3 months lacosamide therapy (responder defined as reduction in seizure frequency of > 50%) - Divided into 5 categories: - Group A: complete responder - Group B: reduction in frequency of > 75% - Group C: reduction in frequency > 50% < 75% - Group D: no change - Group E: increase in frequency - Adverse effects (patient/family report, lab tests, EEG)

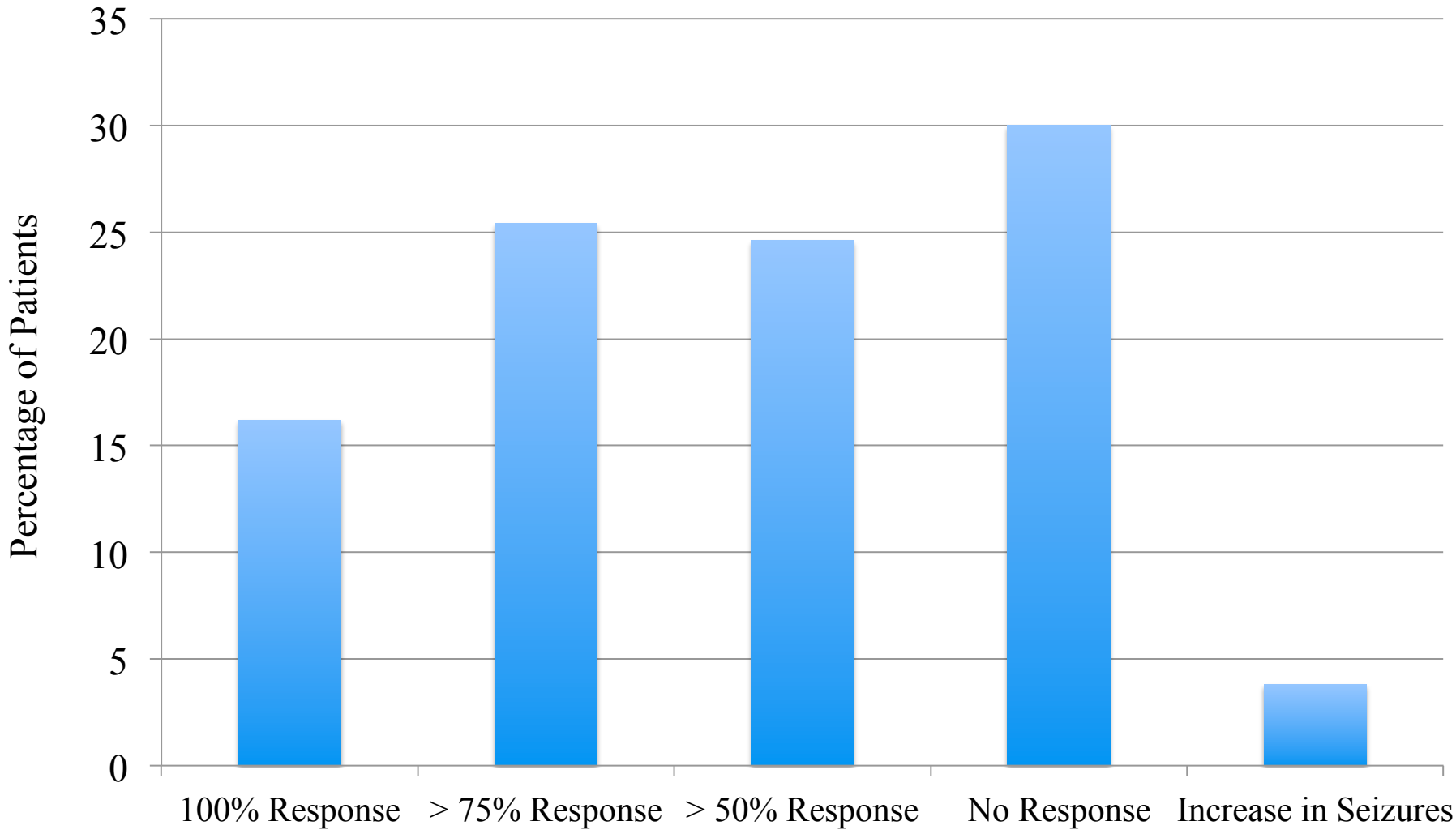
Casas – Fernandez et al – Patient Characteristics

Table I. Characteristics of patients enrolled in the study (N = 130)

Characteristic	Value
Male sex (n [%])	72 [55.4]
Age (years)	
Mean ± standard deviation	8.01 ± 4.25
Range	0.5–16
Etiology (n [%])	
Symptomatic origin	82 [63.1]
Presumed symptomatic origin	36 [27.7]
> 20 seizures per month:	70 (54%)
Type of seizure:	
Focal	129
Generalized	1
Use of co- AEDs:	
≥ 2 co AEDs	88 (68%)
Type of co AED:	
Valproic Acid	59 (45%)
Levetiracetam	51 (39%)
Clobazam	18 [13.8]
Topiramate	17 [13.1]

Casas - Fernandez et al - Results

- 86 (66%) responded to lacosamide therapy



Casas – Fernandez et al - Results

- 39 (30%) patients reported adverse effects
- 10 (8%) patients required cessation of lacosamide

Adverse Effects			
Nausea and Vomiting	13	Asthenia	1
Instability	10	Headache	1
Dizziness	5	Insomnia	1
Nystagmus	3	Irritability	1
Somnolence	3	Attention deficit	1
Weakness	2	Agitation	1
Adynamia “lack of vigor”	2	Vision impairment	1
Anorexia	1	Stiff neck	1
Disorientation	1	Psychotic Reaction	1

Casas – Fernandez et al

- Authors' Conclusions:

"Lacosamide appears to be an effective and generally well tolerated AED in children and adolescents with pharmacoresistant focal epileptic seizures."

Casas– Fernandez et al - Analysis

- Observational
- Wide age range
- Parent/patient reporting
- Short duration
- Small sample size
- Lacosamide PO and IV formulations used

Summary

	Mortality	Neurological Deficits	Reduction in Seizure Frequency ≥ 50%	Adverse Events	QOL
Gavatha et al	✖	✖	Initial: 28% 1 year: 17%	1 discontinuation due to somnolence	✖
Rastogi et al	✖	✖	50%	N/A	✖
Casas – Fernandez et al	✖	✖	3 months: 66%	Discontinuation due to adverse events: 8% Increase in seizures: 3.8%	✖

Conclusion

- Adjunctive agent
- Refractory focal epilepsy
- Initiate 1mg/kg/day divided BID
- Optimal dose?
- Optimal duration?
- Other seizure types?
- Best combination?

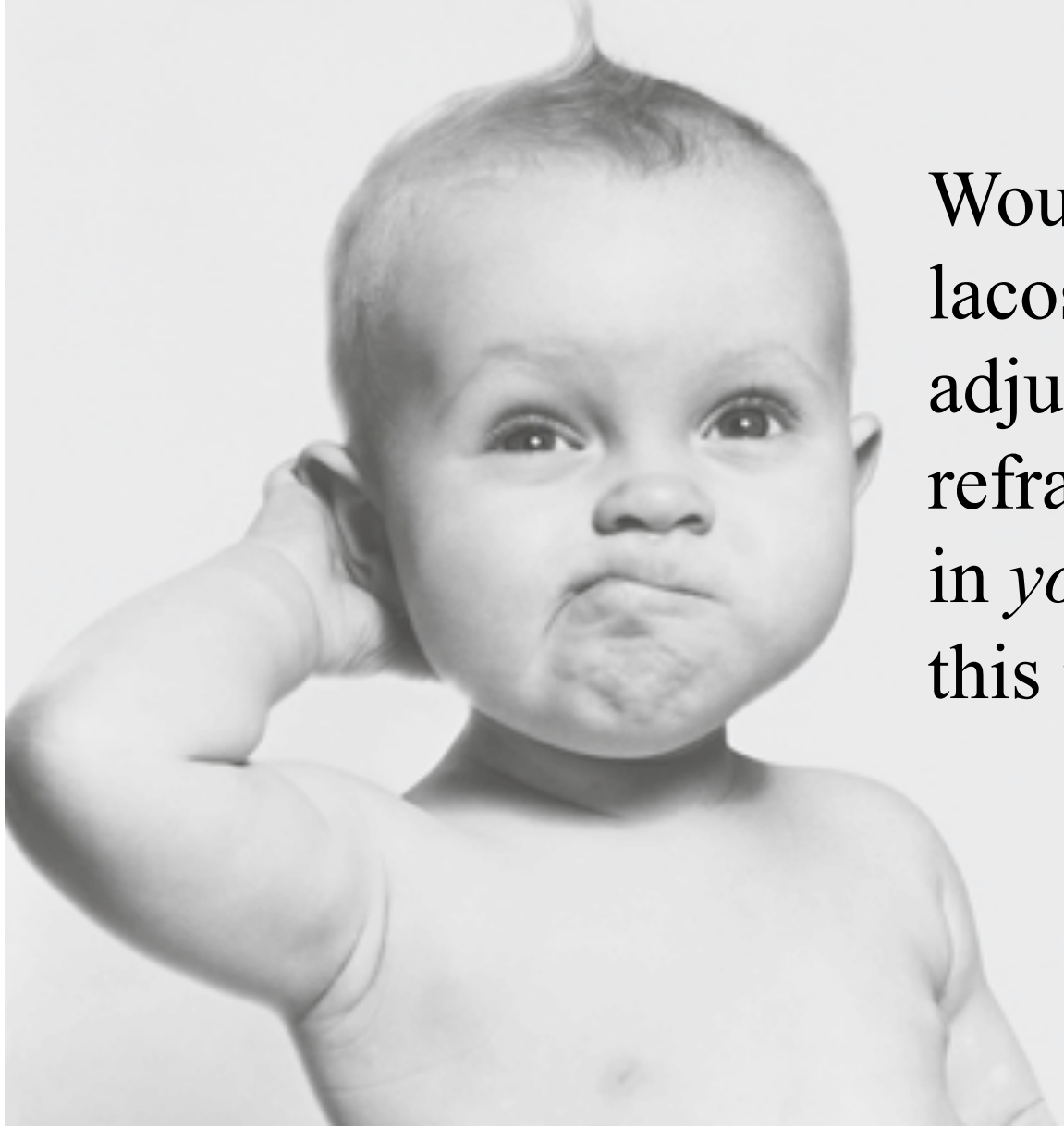
FYI…

- Lacosamide achieved BC Children's Hospital formulary approval September 2012

FYI…

- **ClinicalTrials.gov:**
  - The Safety of Intravenous Lacosamide. NCT00832884. – Recruiting participants
  - An Open-Label Study to Determine Safety, Tolerability, and Efficacy of Oral Lacosamide in Children With Epilepsy. NCT00938912 – Enrolling participants
  - A Multicenter, Open-Label Study To Investigate The Safety And Pharmacokinetics Of Lacosamide In Children With Partial Seizures. NCT00938431 – Recruiting participants

Conclusion



Would you use lacosamide as an adjunctive agent in refractory focal epilepsy in *your* child based on this information?

Questions?