EUROPEAN PAEDIATRIC NEUROLOGY SOCIETY

Antiepileptic drug treatment in infancy and childhood

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EPNS Education and Training Course, Budapest, 9 March, 2016

Outline

EUROPEAN PAEDIATRIC NEUROLOGY SOCIETY

When?

Initiating antiepileptic drug treatment. Treat or not to treat?

What?

1st,2nd, 3rd line choices of AED treatment

Adverse effects of antiepileptic treatment

From the very-common – to the very rare adverse events

„Medics are from Mars and Patients are from Pluto”

How to communicate with the children and their parents?

How much?

„As much as necessary, as little as possible.”

Recommendation for management of infantile and childhood seizures

Rational polytherapy

How long?

AED withdrawal

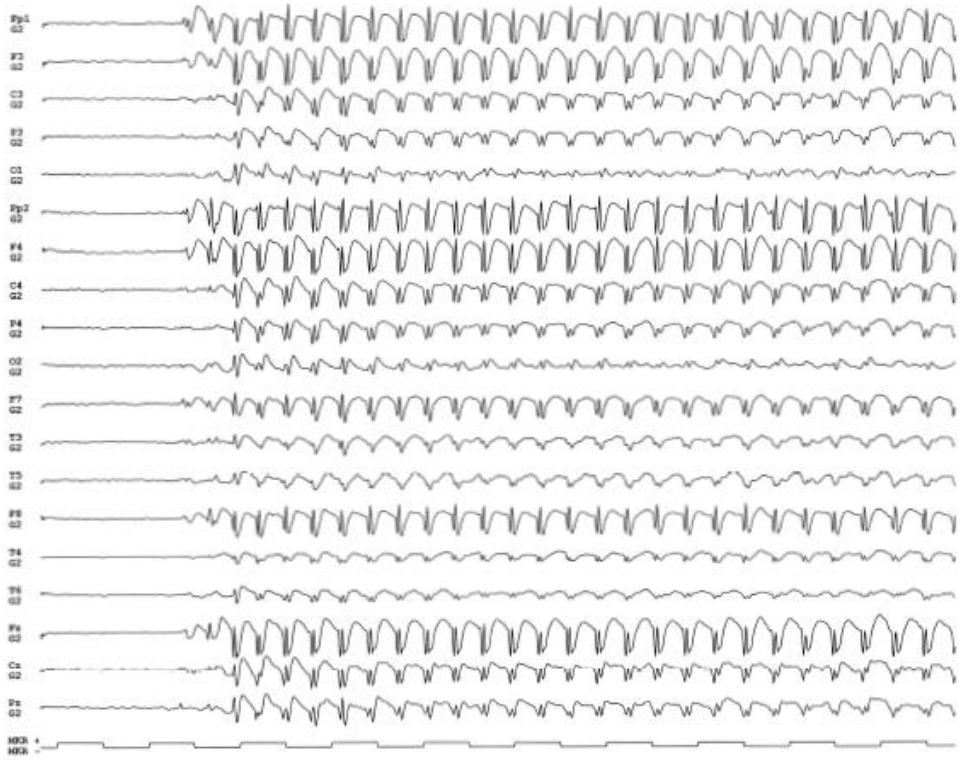
Initiating antiepileptic drug treatment

The decision of whether to initiate treatment in a child with one or more seizures or not must balance the **risks and benefits of treatment** in each case

Has the child epileptic seizures?

Probability of bad diagnosis is low:

- Frequent seizures
- Seizure semiology is typical
- Good correlation with the EEG



Risk of wrong diagnosis is high:

- Rare seizures
- Seizure semiology is atypical
- Missing or not characteristic EEG signs

Treat or not to treat?

- Probability of seizure recurrence
- Potential risks (physical /psychological) associated with seizure recurrence
- Potential risk associated with chronic antiepileptic therapy

Treat or not to treat?

First unprovoked seizure – routine initiating of AED – not indicated
Has to be tailored to each patient

Risk of seizure recurrence after a first unprovoked seizure:

Overall	**40 %**
No identifiable etiology EEG without epileptiform abnormalities	25 %
Remote symptomatic seizure EEG with epileptiform abnormalities	65 %

AED treatment is recommended if the risk is higher than 50 %.

Berg & Shinnar 1991

AED selection criteria

- Seizure type ?
- Epilepsy syndrome ?
- Age ?
- Gender ?
- Pharmacokinetics ?
- Interactions ?
- Form of AEDs (syrups, tablets, capsules) ?
- Community (kindergarten, school) ?
- Associated diseases, conditions ?
- Side effects ?
- Cognition ?
- Patient’s and/or parents’ preference and acceptance
- Expectations ?

Initial monotherapy

Evidence-based guidelines – great limitations

- few randomized controlled trials in the paediatric age
- missing data on adverse effects

Suggested choices of AEDs by seizure types or epilepsy sndromes in children

	1st	2nd	3rd
Partial seizures (with or without sec. gen.)	CBZ/OXCBZ, LEV	LTG, VPA, GBP	TPM,ZNS,PHT, PB, primidone
BECT	sulthiame,GBP	VPA, LEV, OXCBZ	
GTCS	VPA, LEV, LTG	CBZ/OXCBZ, TPM, PHT	ZNS, PB, primidone
Childhood absence	ESX,VPA	LTG	
Juvenile absence	VPA (males), LTG (females)	ESX, LEV, TPM, ZNS, BZP	
Juvenile myoclonic	VPA (males)	LEV, LTG, TPM, clonazepam (add-on only)	ZNS, PB, primidone
Epileptic (infantile) spasm	ACTH, VGB	VPA, TPM, ZNS, BZP, ketogenic diet	
Lennox-Gastaut sy.	TPM, LTG	VPA, RUF	ketogenic diet, FBM, ZNS, BZP, PB

Abbreviations: CBZ: carbamazepine; ESX: ethosuximide; FBM: felbamate; GBP: gabapentin; LEV: levetiracetam; LTG: lamotrigine; OXC: oxcarbazepine; PB: Phenobarbital; PHT: phenytoin; RUF: rufinamide; TGB: tiagabine; TPM: topiramate; VIG: vigabatrin; VPA: valproic acid.

Hadjiloizou&Bourgeois 2007

TABLE 31-4

Comparison of Evidence Based and Consensus Guidelines Recommendations for the Treatment for different pediatric seizure types and epilepsy syndromes. (ref. 84)

Seizure Type or Epilepsy Syndrome	Pediatric Expert Consensus Survey	ILAE	SIGN	NICE	French Study	FDA Approved
Partial-onset	OXC, CBZ	A: OXC; B: *none* C: CBZ, PB, PHT TPM, VPA	PHT, VPA, CBZ LTG, TPM, OXC, VGB, CLB	CBZ, VPA, LTG OXC, TPM,	OXC, CBZ, LTG (adult males)	PB, PHT, CBZ OXC, TPM
BECT	OXC, CBZ	A, B: *none* C: CBZ, VPA	*not specifically mentioned*	CBZ, OXC, LTG, VPA	*not surveyed*	*none*
Childhood absence epilepsy	ESM	A, B: *none*	VPA, ESM, LTG	VPA, ESM, LTG	VPA, LTG	ESM, VPA
Juvenile myoclonic epilepsy	VPA, LTG	A, B, C: *none*	VPA, LTG, TPM	VPA, LTG	VPA, LTG	TPM
Lennox-Gastaut syndrome	VPA, TPM, LTG	*not reviewed*	*not specifically mentioned*	LTG, VPA, TPM	*not surveyed*	FLB, TPM, LTG
Infantile spasms	VGB, ACTH	*not reviewed*	*not specifically mentioned*	VGB, corticosteroids	*not surveyed*	*none*

ACTH, adrenocorticotropin; CBZ, carbamazepine; CLB, clobazam; ESM, ethosuximide; FLB, felbamate; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid.

Pellock, Bourgeois, Dodson : Pediatric Epilepsy: Diagnosis and Therapy, 3rd ed. 2008

Has to be tailored to each patient…

Adverse effects of AED treatment

No seizures, no side effects.

Paracelsus

"All things are poison and nothing is without poison; only the dose makes a thing not a poison."

Adverse effect

undesired harmful effect resulting from a medication

Toxic adverse effects	**Usually dose dependent**
Teratogenic and és mutagenic effects	**Impair genetical substance of cells**
Idiosyncrasy and intolerance	**Increased sensitvity against some medicines**
Allergic reactions	**Immune reactions after earlier sensibility**
Drug tolerance	**Decreasing of drug sensitivity**
Drug dependency	**Dependency against drug**

The main and common and potentially severe side-effects of the AED must be explained to the child and her/his parents!

Cross-sensitivity of skin rashes with antiepileptic drug use

1875 patients (>12 ys)
14.3% - rash attributed to at least one AED;
2.8% had a rash to 2 or more AEDs

e 1 Rash cross-sensitivity rates in six commonly used antiepileptic drugs (AEDs) most associated with rash

			…Rate of rash with this AED is:				
	Rash	% (n)	CBZ	LTG	OXC	PB	PHT
CBZ	Yes	8.3% (62/745)		20% (10/50)	33% (5/15)	26.7% (8/30)	57.6% (34/59)
	No	91.7% (683/745)		7.7% (28/366)	2.6% (2/76)	3.3% (4/120)	17.5% (47/268)
LTG	Yes	8.9% (77/864)	26.3% (10/38)		20% (3/15)	7.7% (1/13)	38.9% (14/36)
	No	91.1% (787/864)	10.8% (40/378)		4.9% (5/103)	6.5% (8/124)	16.4% (60/365)
OXC	Yes	5.0% (10/201)	71.4% (5/7)	37.5% (3/8)		0% (0/4)	33.3% (3/9)
	No	95.0% (191/201)	11.9% (10/84)	10.9% (12/110)		8.6% (3/35)	14.9% (11/74)
PB	Yes	6.2% (17/276)	66.7% (8/12)	11.1% (1/9)	0% (0/3)		53.3% (8/15)
	No	93.8% (259/276)	15.9% (22/138)	9.4% (12/128)	11.1% (4/36)		21.1% (33/156)
PHT	Yes	11.9% (85/716)	42% (34/81)	18.9% (14/74)	21.4% (3/14)	19.5% (8/41)	
	No	88.1% (631/716)	10.2% (25/246)	6.7% (22/327)	8.7% (6/69)	5.4% (7/130)	

Conclusion:
Cross-sensitivity rates between certain AEDs are high, especially when involving carbamazepine and phenytoin.

Hirsch LJ Neurology 2008

p<0.001, significant | 0.001<p<0.05, trend

Valproate - induced enuresis

Prospective study
72 children (43M/29F)
5-12 ys
24 % sec. enuresis
Δ 3 weeks after exposure to VPA
Enuresis ceased in all after discontinuation of VPA

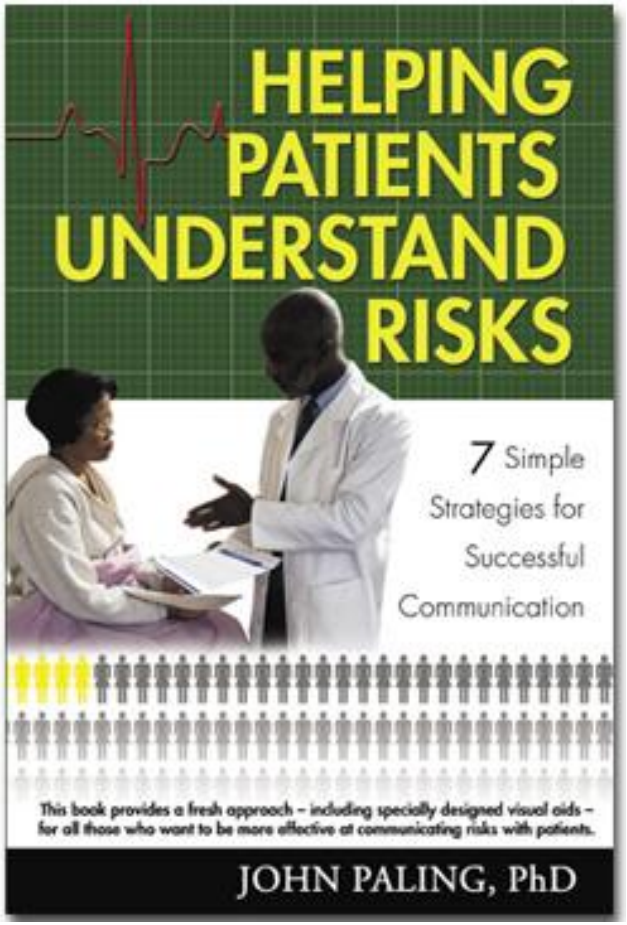
Lancet. 1985 Apr 27;1(8435):980-1.
Nocturnal enuresis associated with sodium valproate.
Panayiotopoulos CP.

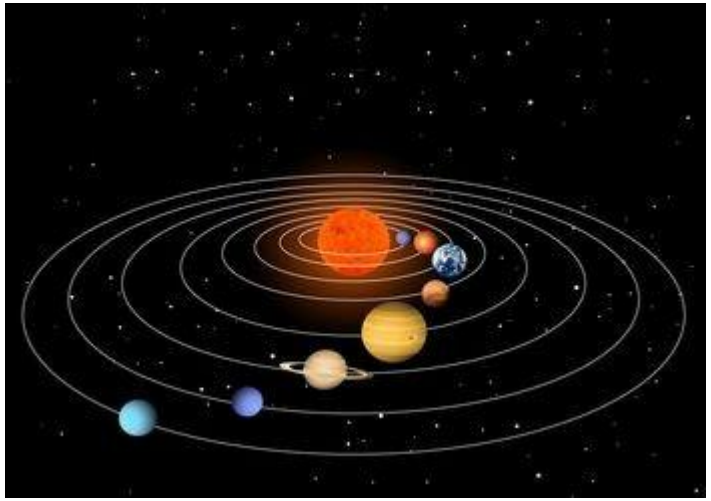
Common side effects of VPA
drowsiness
dizziness
headache
changes in appetite
weight changes
agitation
mood swings
abnormal thinking
loss of coordination
blurred or double vision
ringing in the ears
hair loss

How to share our professional knowledge in a patient-focused way?

"Each capsule contains your medication,
plus a treatment for each of its side effects."

„Medics are from Mars and Patients are from Pluto”





Monotherapy or polytherapy?

Bourgeois BFD Combination Drug Therapy: Monotherapy Versus Polytherapy)
Pediatric Epilepsy: Diagnosis and Therapy, 3rd ed. 2008

Mechanism of action of major AEDs

Na channel	**CBZ**	**FBM**	**LAC**	**LTG**	**OXCBZ**	**PHT**	**RUF**	**TPM**	**VPA**	**ZNS**
Ca channel	**ESX**	**GBP**	**LTG**	**OXCBZ**	**PGB**	**PB**	**PHT**	**TPM**	**VPA**	**ZNS**
GABA enhancers	**BZD**	**PB**	**CBZ**	**GBP**	**PGB**	**TGB** (GABA uptake inhibitor)	**TPM**	**VGB** (GABA trans-aminase inhibitor)	**VPA**	
Glutamate antagonists	**CBZ**	**FBM**	**OXCBZ**	**PB**	**TPM**					
Carboanhydrase inhibitors	**TPM**	**ZNS**								
Other	**CBZ** (adenosine receptor binding)	**LAC** (collapsin responsive mediator protein-2)	**LEV** (synaptic protein SV2A binding)	**PHT** (inhibit neuro-transmitter release)						

Abbreviations: CBZ: carbamazepine; ESX: ethosuximide; FBM: felbamate; GBP: gabapentin; LEV: levetiracetam; LTG: lamotrigine; OXC: oxcarbazepine; PB: Phenobarbital; PHT: phenytoin; RUF: rufinamide; TGB: tiagabine; TPM: topiramate; VIG: vigabatrin; VPA: valproic acid.

Rational combinations

Different mechanisms of action? Different side effects?

Good combinations:

lamotrigine + valproic acid
valproic acid + ethosuximide

Combinations to be avoided:

barbiturates + benzodiazepines
barbiturates + topiramate (sedation, cognitive effects)
topiramate + zonisamide or acetazolamide (nephrolithiasis, acidosis, weight loss)
carbamazepine with oxcarbazepine (hyponatremia)
valproate and gabapentin (weight gain)

Bourgeois BFD Combination Drug Therapy: Monotherapy Versus Polytherapy)
Pediatric Epilepsy: Diagnosis and Therapy, 3rd ed. 2008

Combination drug therapy

ADVANTAGES

Better seizure control

Similar seizure control with fewer dose-related side-effects

DISADVANTAGES

Pharmacokinetic interactions

more frequent drug level determinations and dosage readjustments necessary

Interpretation of drug effect

difficult to determine which drug has caused a reduction in seizure frequency and which drug is responsible for side effects

Idiosyncratic adverse side effects

are not dose related. Certain idiosyncratic reactions are more likely to occur when two drugs are taken in combination

Cumulative toxicity

increase the frequency of adverse effects

Effect of reduction of AEDs in patients with drug-refractory epilepsy

Prospective study
Aim: modifications in the number and dosage of AED
962 patients, 28 % < 10 years
Mean duration of epilepsy Δ 7 ys (1-28 ys)

Mean number of AEDs - Δ 4,24 (3-6)
58 % were receiving 4 AEDs

Drug tapering according to a standardized protocol
Target max. 3 AED
Follow up 6 months

After tapering – 82 % of patients – no change or decreasing of seizure frequency
2 SE in the 1st month
Adverse event profile improved also

718/942 subsequently underwent epilepsy surgery

Tripathi M Seizure 2015

Effect of reduction of AEDs in patients with drug-refractory epilepsy

Adverse effect profile:
Drowsiness
Ataxia
Double vision

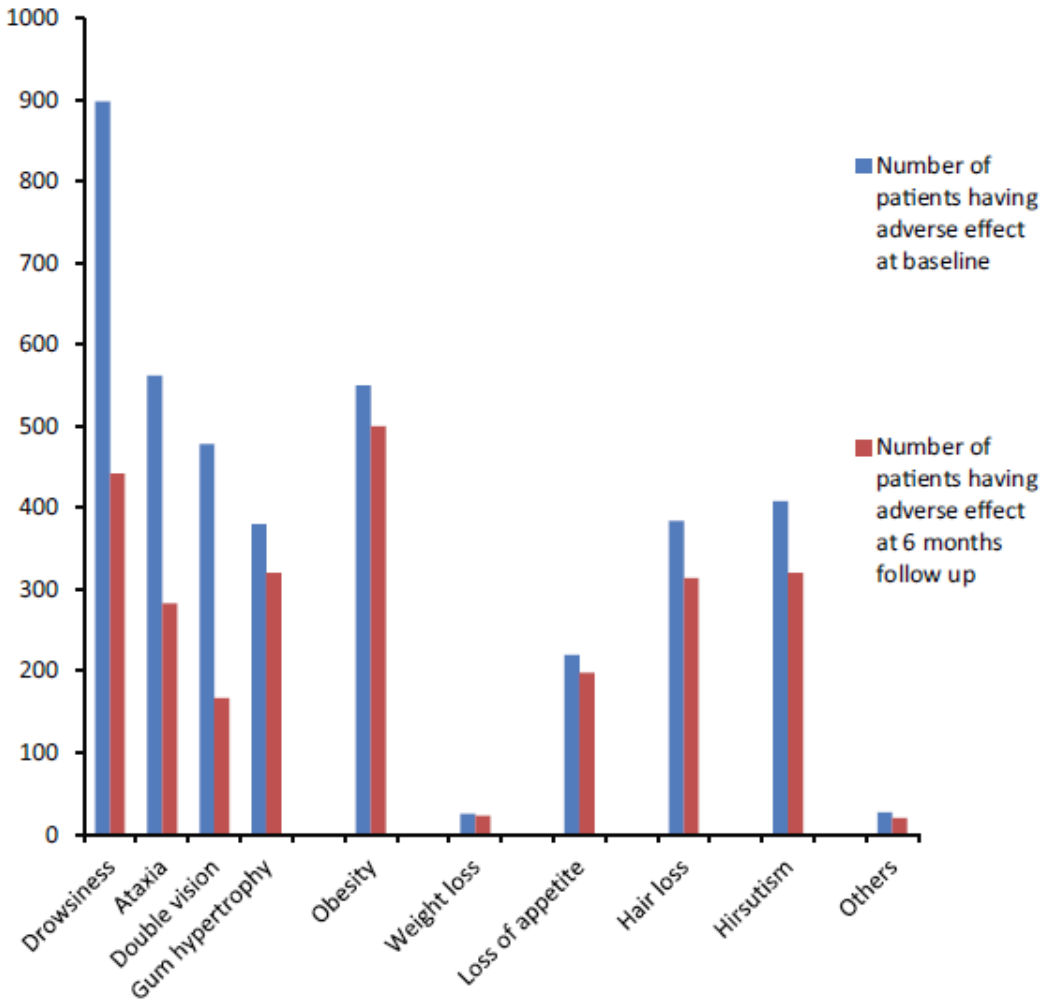


Fig. 1. Different adverse effects at initial assessment and after 6 months of follow up.

Tripathi M Seizure 2015

May antiepileptic drugs worsen epilepsy?

CBZ – BCTE - negative myoclonus

LTG, CBZ, PHT - can provoke myoclonus (Dravet sy)

VGB – can provoke absence, complex partial seizures

VPA, CBZ – rapid introduction– encephalopathia

BZP – LGS – can provoke tonic seizures

Bad choices:

absence – CBZ, PH

Focal or GTCS – ESX

Idiopathic generalized epilepsy - CBZ, PH, VGB

„As much as necessary, as little as possible.”

Infants, children have higher drug clearances – require higher doses of AEDs

If the seizures will be not controlled initially, the dose should be increased beyond the initial target dose, as tolerated.

It should not be concluded that the 1st AED has failed, unless the maximal tolerated dose has been reached.

Further dosage adjustments – by seizure control and side-effects. Clinical observation and judgment!

Lab tests

Baseline laboratory tests for certain AEDs must be obtained before initiating the treatment.

Steady state (1 to 3 weeks)

AED level blood tests should be taken at a consistent time (in the morning before taken AED)

Principles of AED treatment

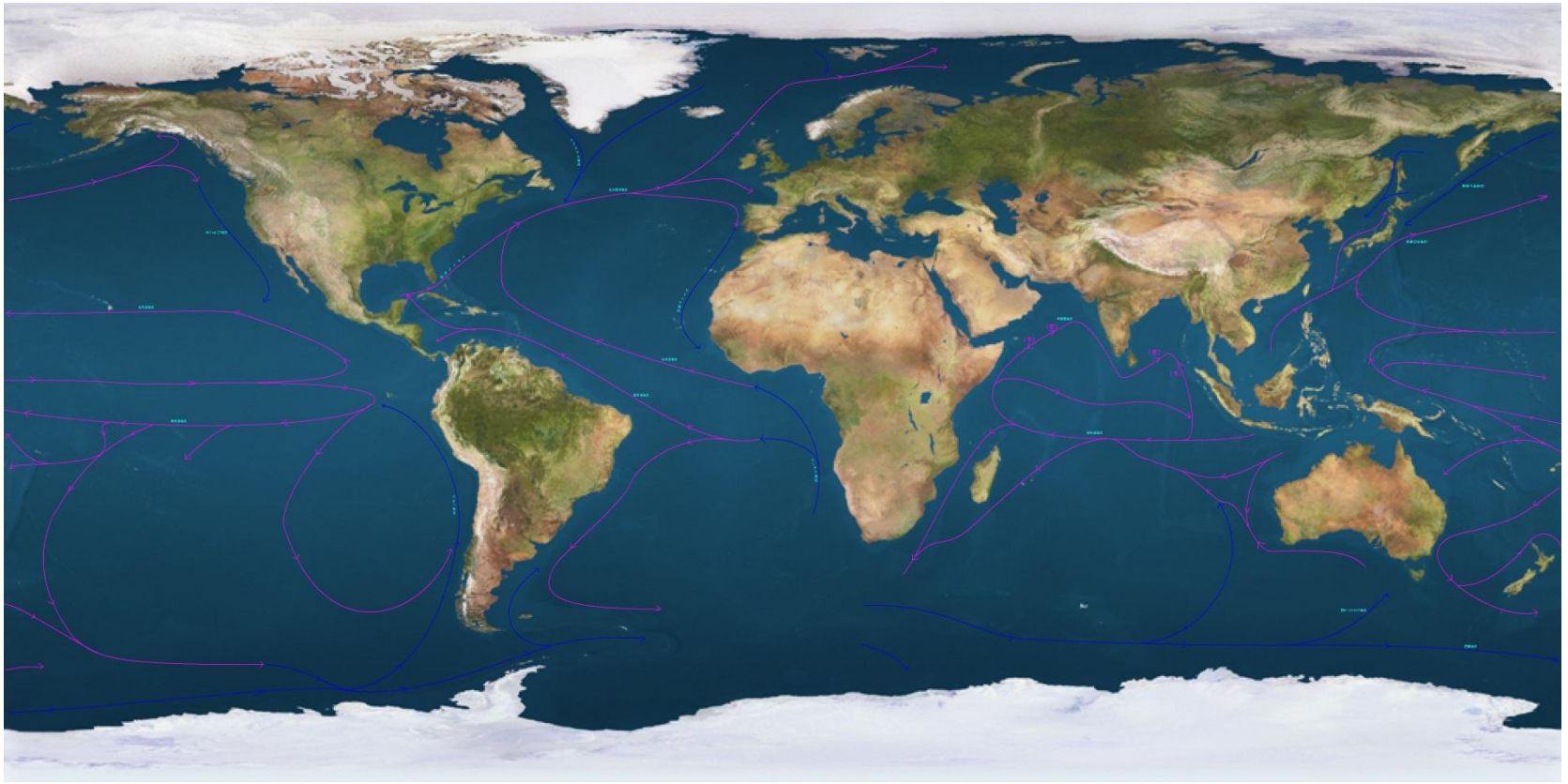
- Monotherapy, if possible
- Rational bi-polytherapy, if necessary
- „Start low, going slow” (usually)
- Dose increasing gradually until seizures stop or side effects do not occur
- Prolonged-release preparations
- Serum AED level control (introduction of AED, politherapy, toxicity, compliance)

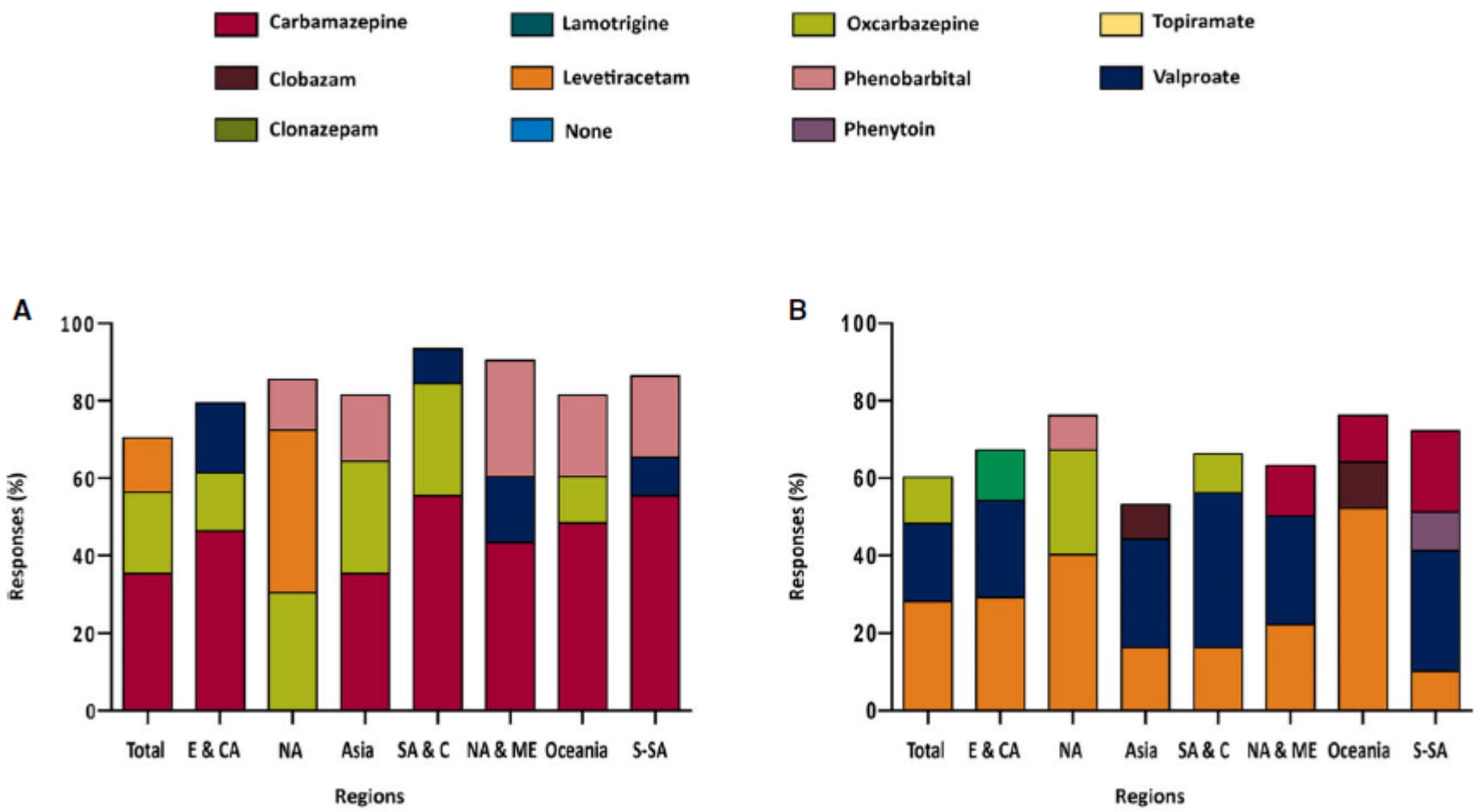
FULL-LENGTH ORIGINAL RESEARCH

Treatment of infants with epilepsy: Common practices around the world

*Jo M. Wilmshurst, *Richard Burman, †William D. Gaillard, and ‡J. Helen Cross

Epilepsia, 56(7):1033–1046, 2015



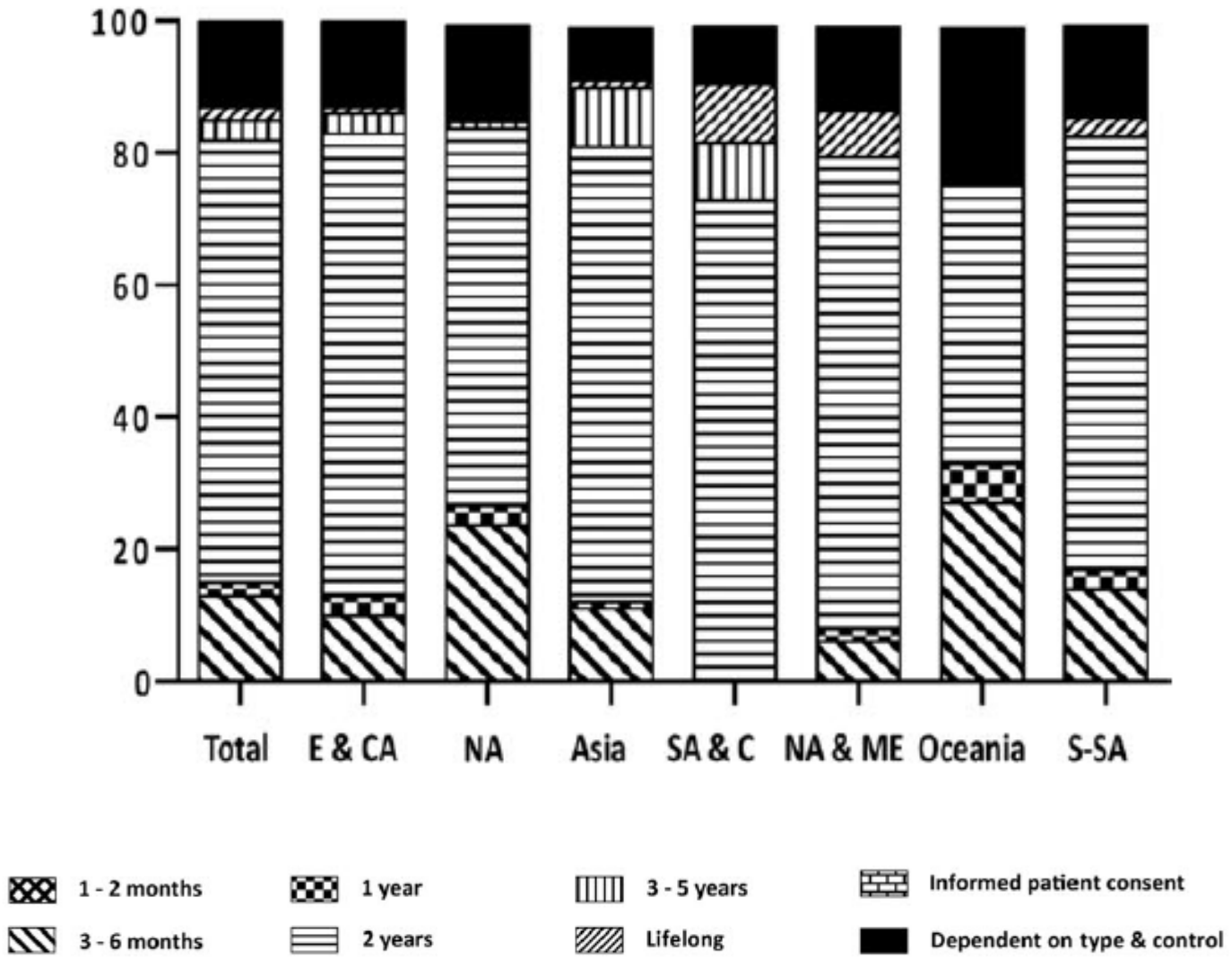


Focal seizures

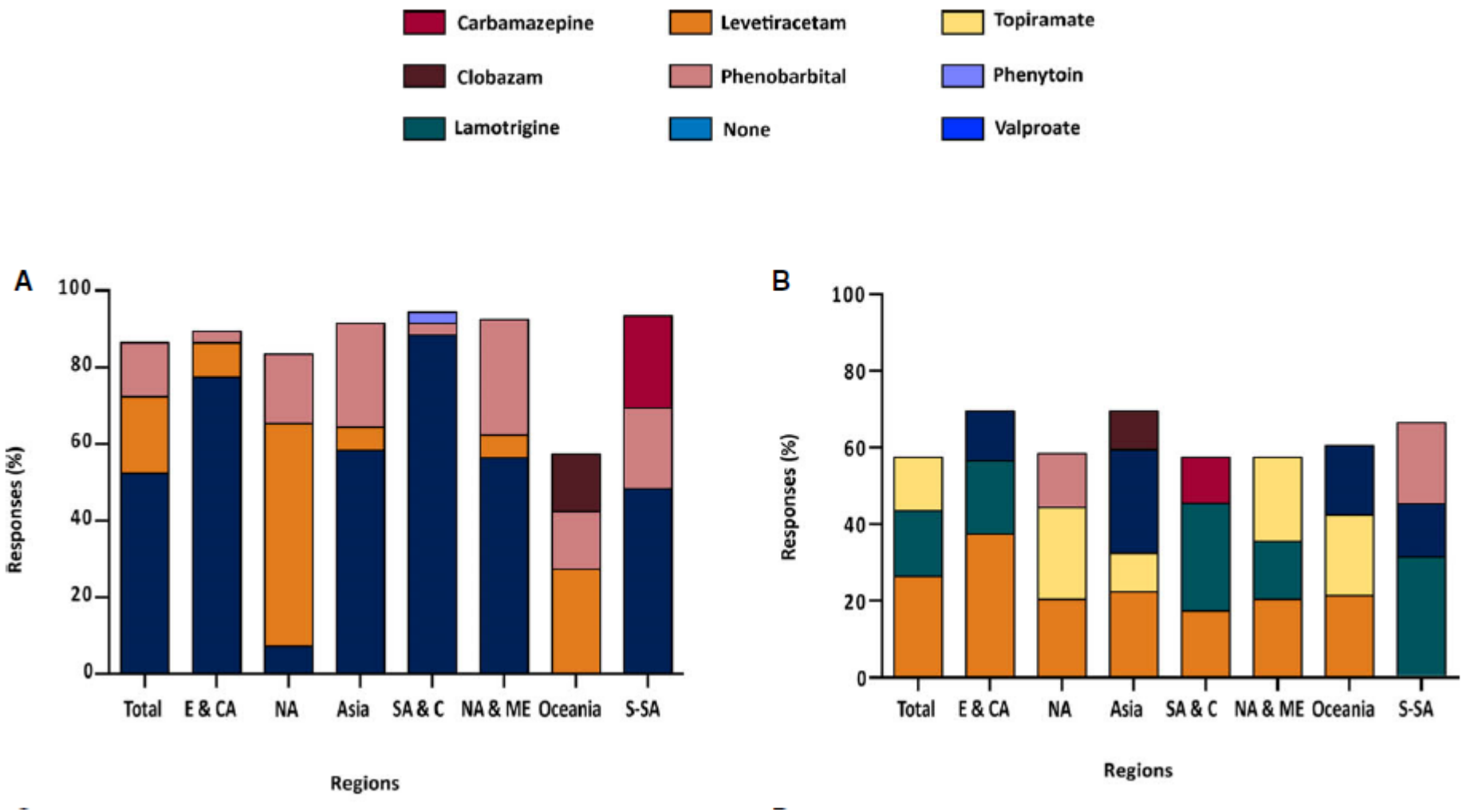
graphs illustrate regional top three AED preferences for first- (A) and second- (B) line intervention

Epilepsia 56(7):1033-46, 2015

Focal seizures - How long respondents would treat



Epilepsia 56(7):1033-46, 2015

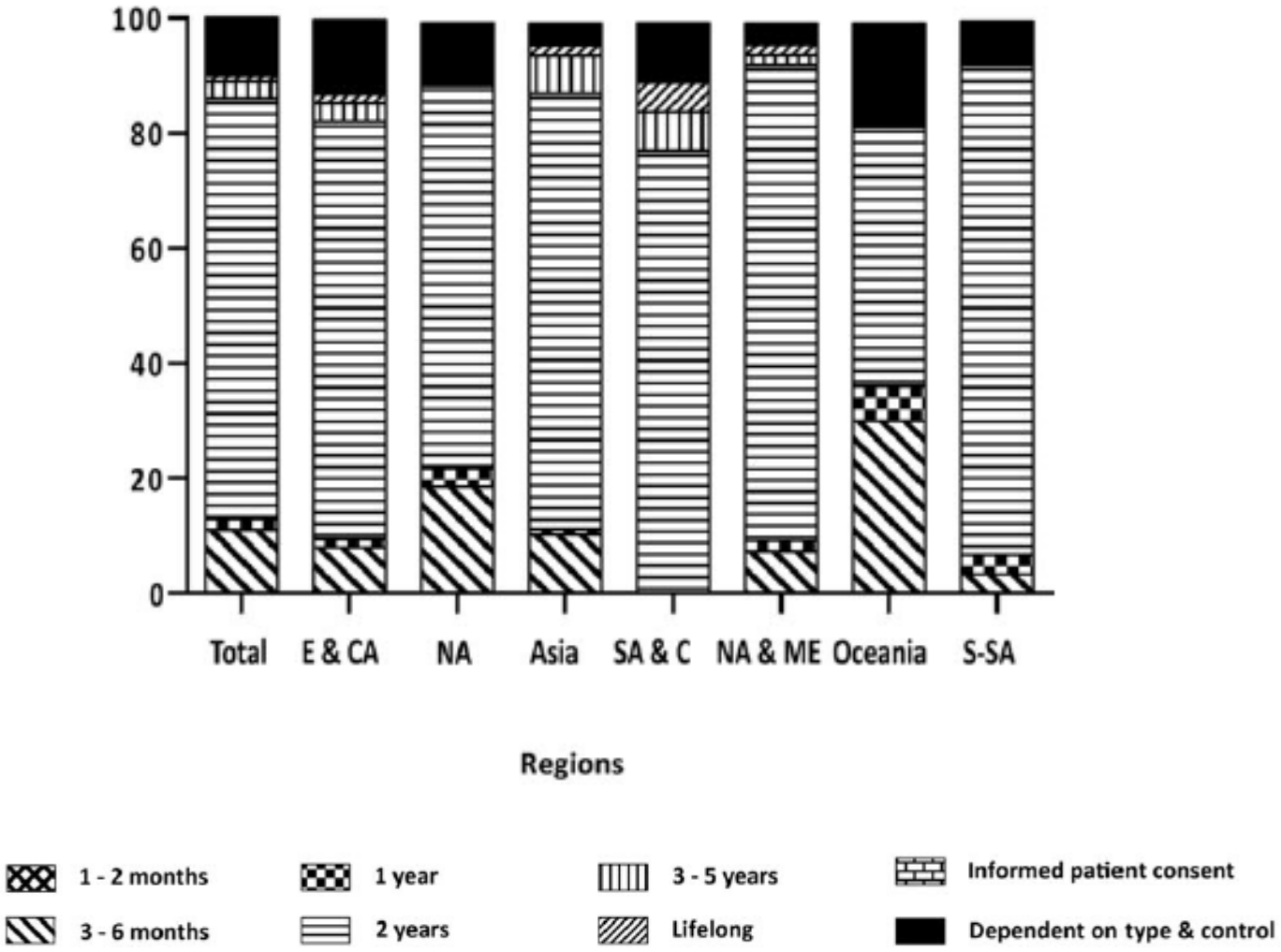


Generalized seizure

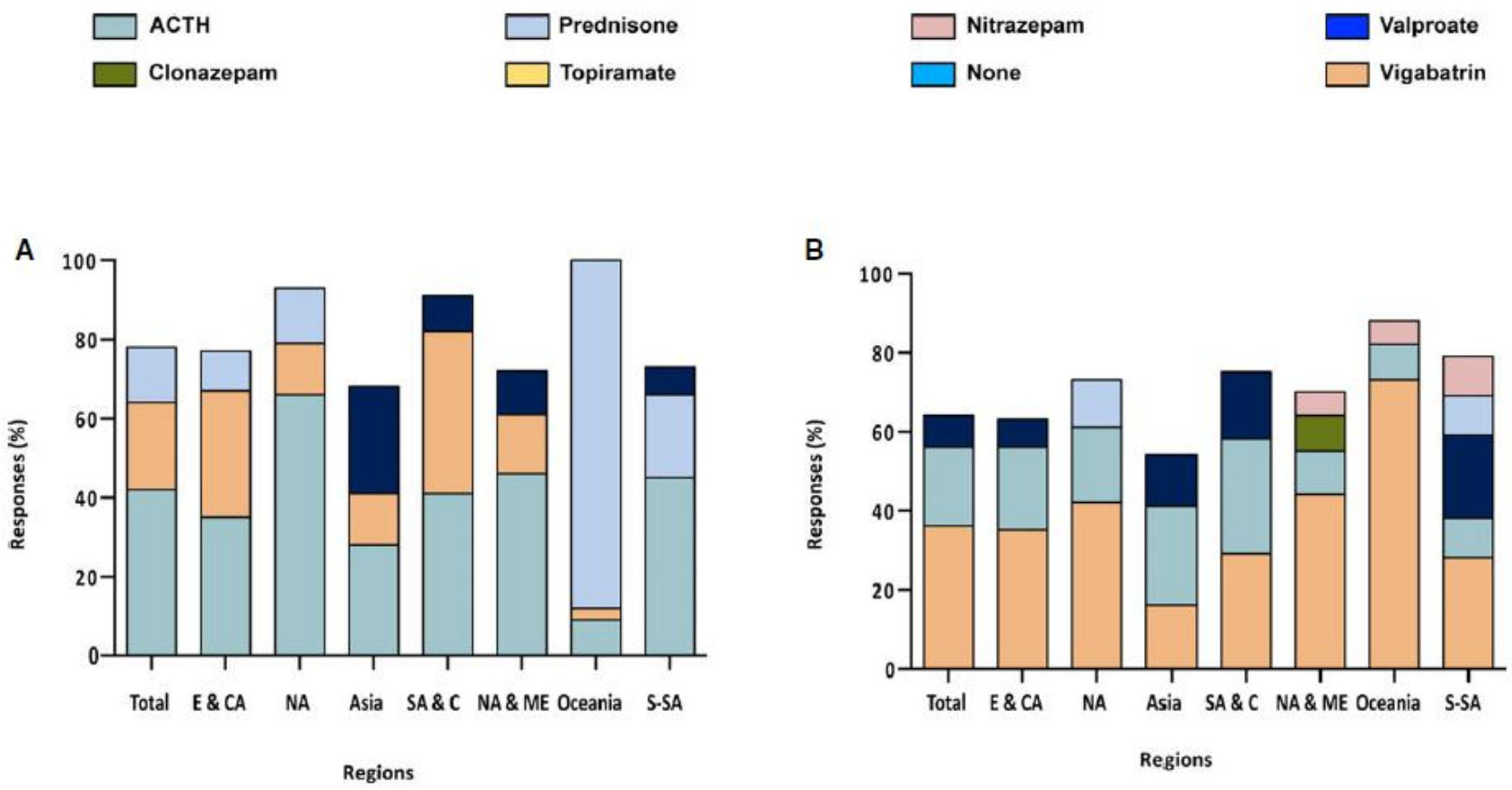
graphs illustrate regional top three AED preferences for first- (A), second- line (B)intervention

Epilepsia 56(7):1033-46, 2015

Generalized seizures - and how long respondents would treat



Epilepsia 56(7):1033-46, 2015

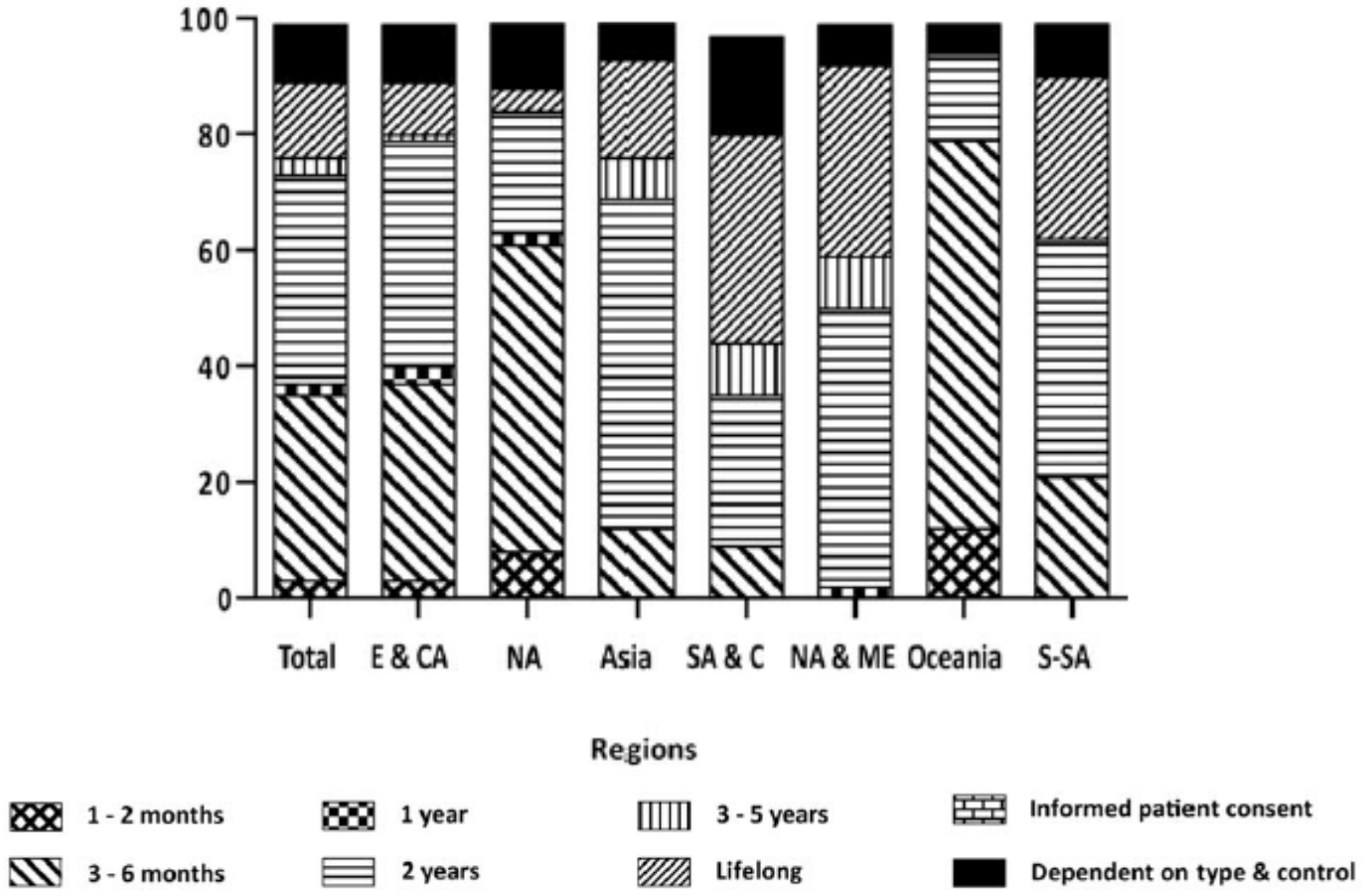


Epileptic spasms

graphs illustrate regional AED preferences for first- (A), second- line(B), intervention

Epilepsia 56(7):1033-46, 2015

Epileptic spasms – how long respondents would treat



Epilepsia 56(7):1033-46, 2015

Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics

Working Group: *Jo M. Wilmshurst, †William D. Gaillard, ‡Kollencheri Puthenveettil Vinayan, §Tammy N. Tsuchida, ¶Perrine Plouin, #Patrick Van Bogaert, **Jaime Carrizosa, ††Maurizio Elia, ‡‡§§Dana Craiu, ¶¶Nebojsa J. Jovic, ##Doug Nordli, ***Deborah Hirtz, †††‡‡‡Virginia Wong, §§§Tracy Glauser, ¶¶¶###Eli M. Mizrahi, and ****J. Helen Cross

Epilepsia, 56(8):1185–1197, 2015

- Evidence-based guidelines for the management of seizures in infants are lacking
- Incidence of epilepsy in the infantile period is the highest of all age groups
- Epileptic spasms are the largest subgroup and, in the first 2 years of life, febrile seizures are the most commonly occurring seizures
- Infants with recurrent seizures warrant urgent assessment for initiation of AED drugs
- No high-level evidence to support any particular current agents for use in infants with seizures.

Summary of published studies addressing AED treatment for infants with seizures

Epilepsy type	AED effective	AED possibly effective	AED probably effective	AED poorly effective	AED ineffective	exacerbate	strength of efficacy
focal seizures	**LEV**				**TPM,LAM, GBP,OXCBZ**		**strong**
generalized seizures		**LEV,VPA, LAM, TPM,CLO**					weak
epileptic spasm			**ACTH** (low or high dose)				**strong**
			prednisone				weak
			VGB				weak except TS
Dravet sy	**Stiripentol**						**strong**
		TOP, ZNS, VPA, Br					weak
						LTG,CBZ, PHT	**strong**
BMEI		**VPA, TPM, LTG, CLO**					weak
Ohtahara sy				**TPM,ACTH, prednisone, pyridoxin**			weak

Epilepsia 56(8):1185-97,2015

Epileptic spasms – West syndrome

1st choice

TS – vigabatrin (90% response rate in TS, in others 54 %)
Vigabatrin – possibly effective (Level C evidence)
Especially in the case of TS complex (Level C evidence)
100 mg/kg/day
Retinal toxicity – visual field restriction
It takes > 15 months to appear

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE 2015, 57: 60–67

Does vigabatrin treatment for infantile spasms cause visual field defects? An international multicentre study

RAILI RIIKONEN[1] | ZVONKA RENER-PRIMEC[2] | LIONEL CARMANT[3] | MARIA DOROFEEVA[4] | KATALIN HOLLODY[5] | ILONA SZABO[6] | BRANKA S KRAJNC[7] | GABRIELE WOHLRAB[8] | IIRIS SORRI[9]

- Largest study to report the results of visual field testing in children who received vigabatrin treatment for infantile spasms
- VDFs were found in 34 % of the children
- The risk of VFDs increased from 9 % to 63 % depending on the duration of VB administration

Antiepileptic treatment before the onset of seizures reduces epilepsy severity and risk of mental retardation in infants with tuberous sclerosis complex

TS – epilepsy 70-80 %
45 infants
2 groups:

		Mental retardation (%)	Seizure-free patients (%)
standard	AED after sz starting	48	35
preventive	AED before sz starting, but EEG positive	14	93

Preventative antiepileptic treatment markedly improves the neurodevelopmental outcome and reduces the incidence of drug-resistant seizures in infants with TS.

Jóźwiak S et al, EJPN 2011

Epileptic spasms – West syndrome

1st choice other than TS

ACTH – (Level B evidence)
Low-dose or high dose? (Level B evidence)
20-40 IU
Oral steroids – probably effective (Level C evidence)
prednisone 2 mg/kg/day
adverse events: gastritis, infections, hypertonia, hyperexcitability

Better long-term neurodevelopmental outcome than treatment with vigabatrin in children with epileptic spasms due to unknown etiologies (Level C evidence)

Epileptic spasms – West syndrome

2nd choice

topiramate (high dose)
zonisamide
felbamate
valproic acid
nitrazepam
lamotrigine
sulthiame
lacosamide
pyridoxin
thyrotropin releasing hormone
IVIG
ketogenic diet

Safety of levetiracetam among infants younger than 12 months - Results from a European multicenter observational study.

oral solution
1-11 months
101 infants / 75 completed the study
80 % took 1 ≥ concomitant AED
focal (38.6%), generalized (20.8%), particularly frontal lobe epilepsy (20.0%), West sy.(20.0%).

71.8% showed improvement in epilepsy severity,
18.8% remained stable
9.4% showed worsening.

CONCLUSION:
In this prospective study, which included the largest number of patients in this age range so far, levetiracetam was found to be well tolerated and efficacious for the treatment of infants with epilepsy.

Childhood absence epilepsy

1st choice: Ethosuximide, valproate,

2nd choice: lamotrigine (less efficient than ESX or high doses of VPA – Glauser 2010)

In very refractory cases: combination of all three drugs

Aggravate: CBZ, OXCBZ, PB, PHT, VGB

Refractory absence seizures: An Italian multicenter retsrospective study (17 centers)

Franzoni et al EJPN 2015

92 children

Inclusion criteria:

- <14 ys
- normal neurological status
- brief absence
- EEG 3 Hz spike-wave
- 1st line AED
  - VPA 100 %
  - ESM 87 %
  - LEV 65 %
  - LTG 57 %
  - CLB, TPM, CZP, acetazolamid
- 47 % - 3 AEDs
- 53 % - ≥ 4 AEDs

51 % seizure free

CAE is not so benign as we believed it before

Benign epilepsy of childhood with centrotemporal spikes (BECTS)

1st question : Should be treated?

1st choice : sulthiame, gabapentin
(randomized controlled trials- both failed Glauser 2006)

2nd choice : LEV, OXCBZ – promising
VPA

Duration of treatment: 1 yr following the last seizure (whatever the EEG finding)

How long to treat ?
AED withdrawal

The majority of children who are seizure free on medications for **at least 2 years**
will remain seizure free
when medications are withdrawn.

Early versus late AED withdrawal for people with epilepsy in remission

THE COCHRANE COLLABORATION®

The optimal timing of AED discontinuation is still not clear.

- Approx. 2 years
- Partial epilepsies have a higher seizure recurrence, than generalized types
- When to withdraw AEDs in children with generalized seizures?
- Decisions have to be based on the underlying epilepsy syndrome
- Abnormal EEG findings (paroxysmal activity) – higher seizure recurrence
- Children < 2 or > 10 ys of age at epilepsy onset – higher risk of recurrence
- IQ < 70
- History of SE
- Higher seizure frequency prior or during treatment

Risks of discontinuing AEDs

The majority of seizure recurrences occur shortly after withdrawal.

50 % of the relapses occuring within 6 months
60-80 % within on year

Antiepileptic withdrawal in medically and surgically treated patients: a meta-analysis of seizure recurrence and systematic review of its predictors

61 articles

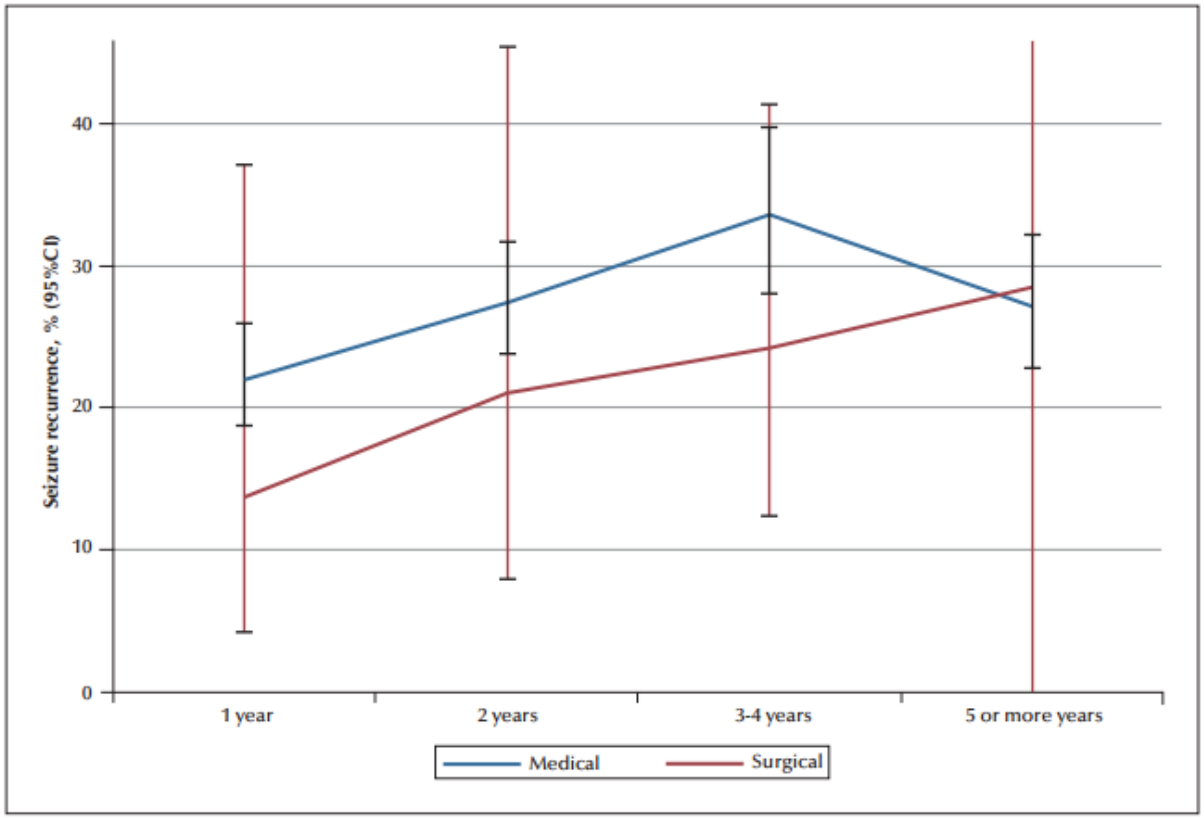


Figure 2. Cumulative recurrence risk after AED withdrawal in medical and surgical cohorts. Error bars indicate 95% confidence interval. See *table 1* for exact recurrence rates with 95% CI.

No significant difference of long-term cumulative recurrence risk between surgically (29 %) and medically treated populations (34 %)

Braun KPJ et al, Epileptic Disorders 2015

IQ improves after AED withdrawal following pediatric epilepsy surgery

TimeToStop cognitive outcome study group

Timing of AED withdrawal does not majorly influence long-term seizure outcome.

What about IQ?
301 children
Mean age 9,6 ±4,5 ys
Mean interval to complete cessation of AEDs 2,5 ys

Mean IQ change 4,1-5,6

IQ improves after AED withdrawal following pediatric epilepsy surgery

TimeToStop cognitive outcome study group Ann Neurol 2015

TABLE 3. Type of AED Reduced in Relation to Delta IQ

AED Reduced	All Patients Who Had Started AED Reduction before Latest Postoperative NPA, n = 155	
	Patients Who Reduced That AED, No. (%)	Mean IQ Change per Type of AED Reduced
Carbamazepine	18 (27)	4.2 ± 10.7
Clobazam	17 (41)	5.0 ± 10.7
Clonazepam	3 (38)	3.0 ± 3.5
Gabapentin	2 (40)	5.0 ± 12.7
Levetiracetam	15 (24)	3.3 ± 11.2
Lamotrigine	21 (26)	6.4 ± 10.6
Oxcarbazepine	30 (25)	5.3 ± 14.3
Phenobarbital	2 (22)	26.7 ± 23.6
Phenytoin	7 (44)	−2.1 ± 9.3
Sultiame	3 (43)	10.0 ± 1.4
Topiramate	9 (27)	1.4 ± 11.5
Vigabatrin	11 (73)	−0.1 ± 10.6
Valproic Acid	8 (42)	6.5 ± 7.6
Primidone	2 (33)	10.0 ± 9.9

Mozart's music in children with drug-refractory epileptic encephalopathies

11 CP children 1,5-21 ys
2 hour/day for 15 days (total 30 hours)
Home treatment
AED therapy remained unchanged
5/11 had seizure reduction > 50%
2/11 had a 50-75 % seizure reduction

EEG
Interictal SW discharges were unchanged,
but significantly lower incidence of occipital foci in responders

All responders had improvement in nighttime sleep and daytime behavior.

Coppola et al: Epilepsy and Behavior 50:18-22, 2015

Mozart's music in children with drug-refractory epileptic encephalopathies

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