VNS
in drug resistant childhood epilepsy

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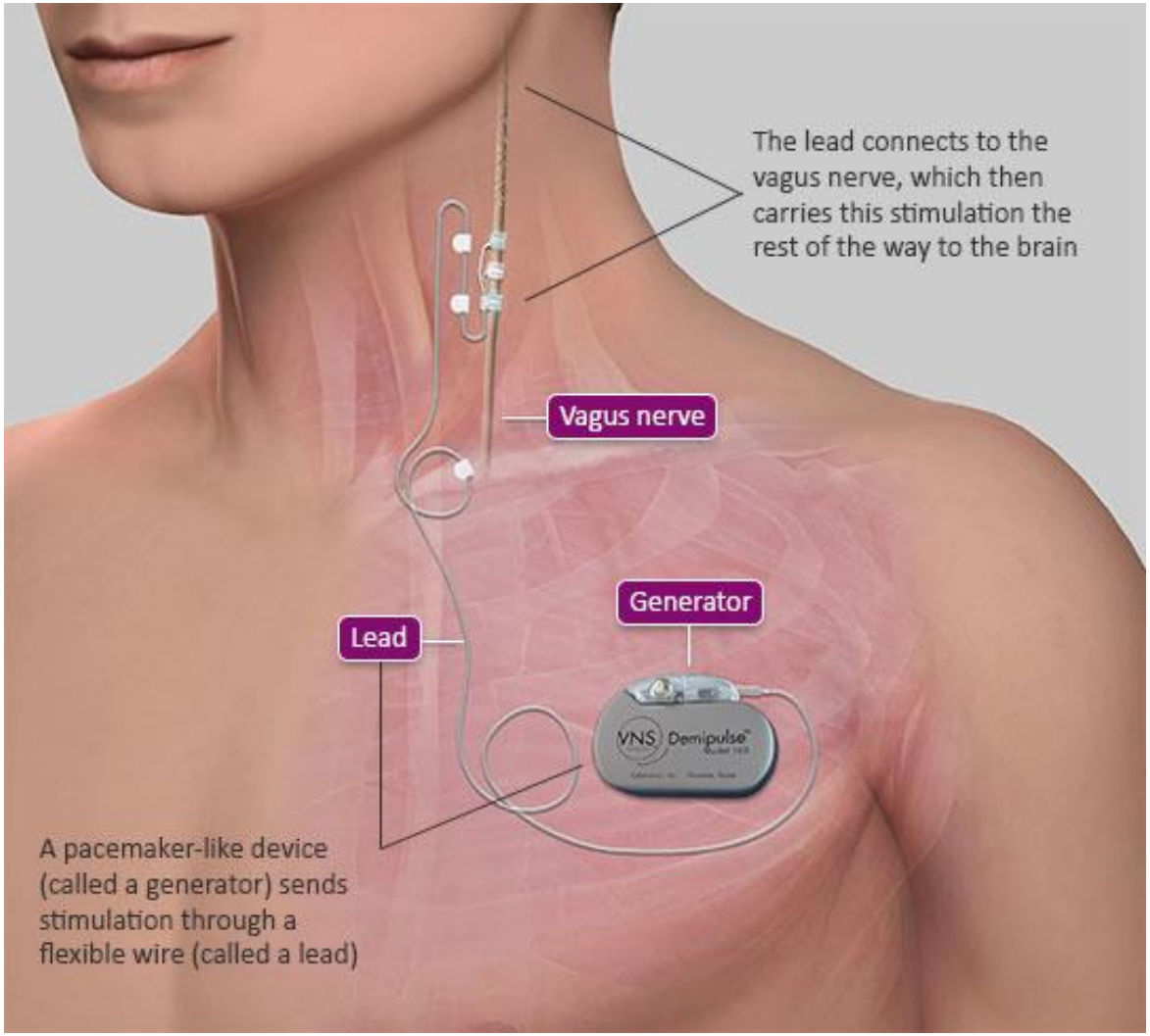
Drug – resistant epilepsy and not a good candidate for resective surgery

VNS approved

ILAE Consensus Statement

The failure of two appropriately chosen and tolerated AEDs (whether as monotherapies or in combination) to control seizures when used for an adequate period of time[1]

Vagus Nerve Stimulation



Duty Cycles (% On Time)

$$\text{Duty cycle (\%)} = \frac{\text{On Time (sec)} + 4 \text{ seconds}}{\text{On Time (sec)} + \text{Off Time (sec)}} \times 100$$

	OFF TIME Minutes								
ON TIME Seconds	**0.2**	**0.3**	**0.5**	**0.8**	**1.1**	**1.8**	**3**	**5**	**10**
7	58	44	30	20	15	10	6	4	2
14	69	56	41	29	23	15	9	6	3
21	76	64	49	36	29	19	12	8	4
30	81	71	57	44	35	25	16	**10**	5
60	89	82	71	59	51	38	27	18	10

Note: On Time should not exceed Off Time

issues

- Indication : which epilepsies ?
- Timing of VNS in disease course ?
- Optimal parameters ?
- Only focal (non surgery) or also generalized?
- Predictors of outcome ?
- Long term studies : no control for AEDs changes
- Younger children ?
- Control groups ?

VNS Therapy evaluated in five clinical trials

- E01-E05 evaluated the safety, tolerability, and efficacy of VNS Therapy
  - 454 patients received VNS Therapy, with 440 available for assessment of long-term (3-year) treatment
  - AED changes were allowed in the extension phase

Study	Design	Seizure type	N	Time frame
E01/E02	Pilot, single blind	Partial	14	1988-1990
E03	Randomized, double blind, active control	Partial	114	1990-1992
E04	Compassionate use	All	124	1991-1995
E05	Randomized, double blind, active control	Partial	199	1995-1996

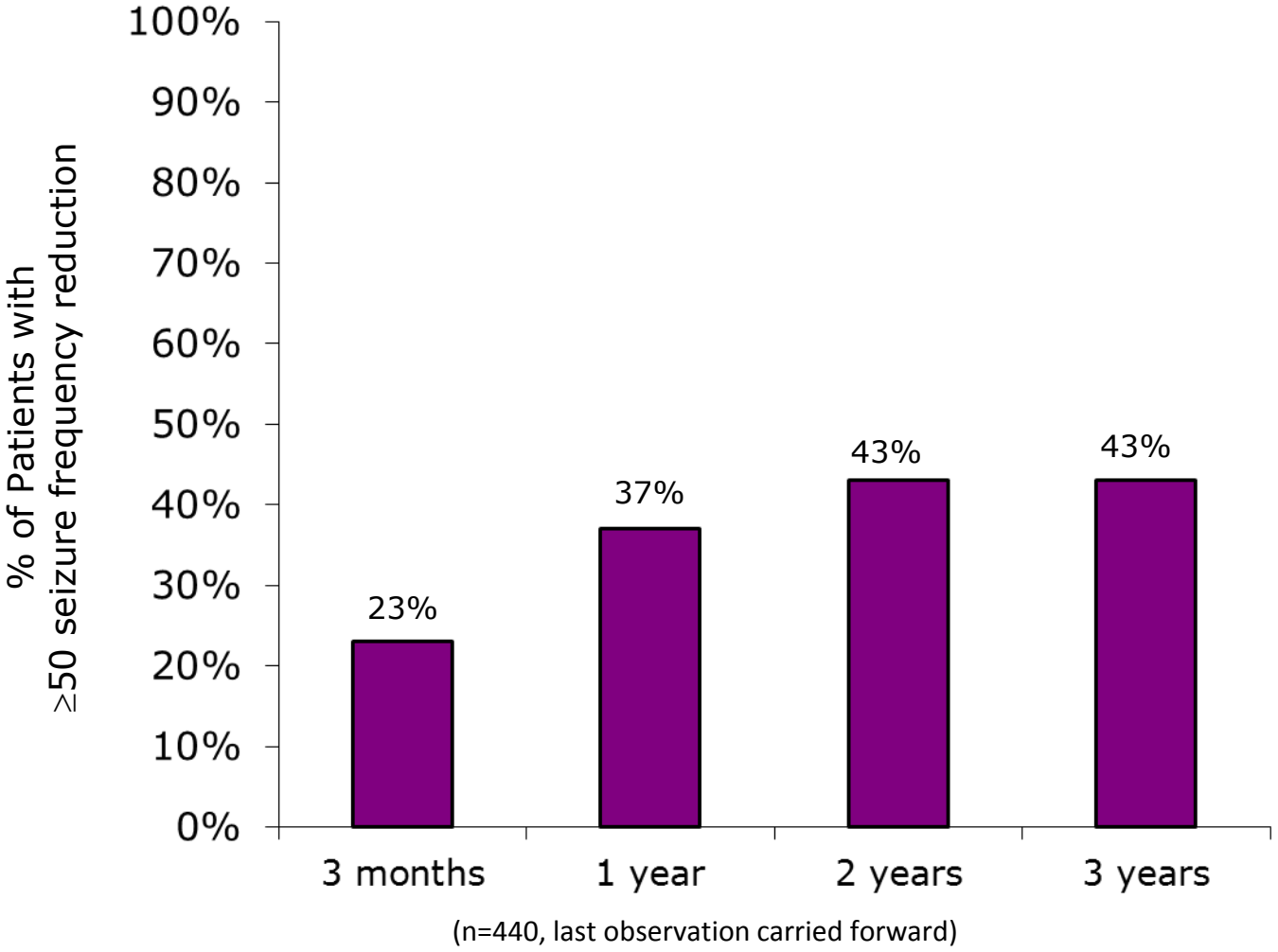
Morris GL, et al. Neurology 1999;53:1731-5.

Patients in the VNS Therapy trials had severe, refractory epilepsy

Patient characteristics	n=452
Mean age (years)	30.8
Mean duration of epilepsy (years)	20.7
Mean # of seizures per day (baseline)	1.73
Mean # of AEDs (at time of enrollment)	2.09

Morris GL, et al. Neurology 1999;53:1731-5.

Reductions in seizure frequency with VNS improve over time, are sustained long-term



(n=440, last observation carried forward)

Morris GL, et al. Neurology 1999;53:1731-5.

Vagus nerve stimulation for children with treatment-resistant epilepsy: a consecutive series of 141 cases

Clinical article

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Variable	Value*
sex	
F	75 (53.2)
M	66 (46.8)
age at seizure onset (yrs)	
mean	2.8 ± 3.6
range	birth–16 yrs
duration of epilepsy prior to VNS	
mean (yrs)	8.4 ± 4.4
range	7 days–17.9 yrs
age at VNS insertion (yrs)	
mean	11.1 ± 4.7
range	1.3–18
pt age	
<12 yrs†	86 (61.0)
≥12 yrs	55 (39.0)
seizure frequency (no. per wk)	
median	10
range	0.1–2000
no. of AEDs	
mean	2.6 ± 0.9
range	1–7
no. of AEDs failed	
mean	5.5 ± 2.9
range	2–15
prior failed intracranial epilepsy surgery	30 (21.3)
no. of seizure types	
mean	2.2 ± 1.1
range	1–6
developmental delay	112 (79.4)

J Neurosurg Pediatrics, 2011

Variable	No. of Pts	Median Sz Reduction (%)	p Value†
epilepsy classification			
focal	5	86.2	0.042
MFPE	55	50.0	<0.001
MFPE/SGE	18	72.0	<0.001
SGE	41	62.5	<0.001
IGE	19	66.7	0.003
epilepsy etiology			
neuronal migration disorder	14	50.0	0.001
CP/static encephalopathy	15	68.9	0.016
LGS	11	51.0	0.008
infection	13	45.0	0.012
TSC	8	75.0	0.018
genetic/metabolic syndrome	14	66.7	0.003
unknown	54	65.0	<0.001
EEG findings			
focal	5	86.2	0.042
multifocal	62	54.6	<0.001
diffuse	61	64.8	<0.001
multifocal & diffuse	13	68	0.002

* CP = cerebral palsy; Sz = seizure.

† Analyzed via paired-samples Wilson signed-rank test.

Vagus nerve stimulation in children with intractable epilepsy: a randomized controlled trial

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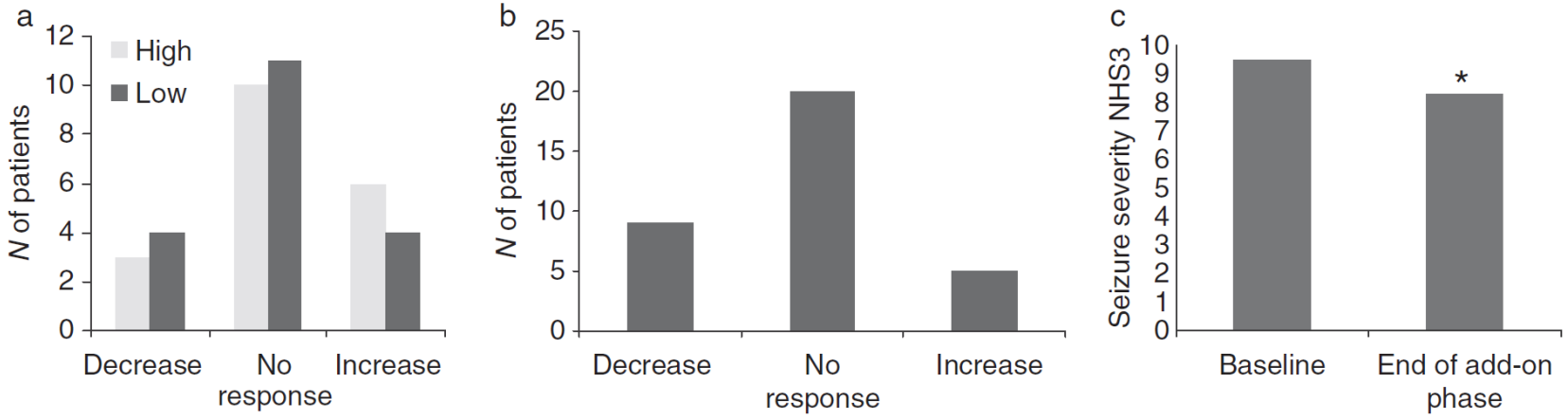
	High-output stimulation	Low-output stimulation
Number of participants (male/female)	21 (11/10)	20 (12/8)
Mean age at implantation, y:mo (range)	10:11 (3:10–17:8)	11:6 (4:2–17:2)
Mean age at onset, y:mo (range)	2:10 (0–12y)	1:8 (0–5y)
Median age at onset, y:mo (range)	1:2 (0–12y)	1:2 (0–5y)
Mean interval onset-implantation, y:mo (range)	7:8 (2–16y)	9:5 (3–15y)
Median seizure frequency at baseline (seizures/day)	2.1 (0.1–53.7)	0.9 (0.1–31.7)
ILAE classification		
Localization related	19 (90%)	16 (80%)
Symptomatic	15 (71%)	10 (50%)
Cryptogenic	4 (19%)	6 (30%)
Generalized	2 (10%)	4 (20%)
Idiopathic	0	2 (10%)
Symptomatic	2 (10%)	2 (10%)
Mean total exposure of AEDs	7.0 (5–10)	7.3 (4–14)

ILAE, International League Against Epilepsy; AEDs, antiepileptic drugs.



5 months study period

No significant differences seizure frequency

Seizure severity

VNS Therapy : The E-102 study

Vagus nerve stimulation for drug-resistant epilepsy: A European long-term study up to 24 months in 347 children

*Iren Orosz, †David McCormick, ‡Nelia Zamponi, §Sophia Varadkar, ¶Martha Feucht, #Dominique Parain, **Roger Griens, ††Louis Vallée, ‡‡Paul Boon, §§Christopher Rittey, ¶¶Amara K. Jayewardene, ¶¶Mark Bunker, ##Alexis Arzimanoglou, and ***Lieven Lagae

Epilepsia. 2014 Oct;55(10):1576-84

E- 102 Study : European VNS Multicentre Study

STUDY CRITERIA

- **Primary**
  - Seizure frequency change from baseline to one year

- **Secondary**
  - Seizure frequency change of all seizure types
  - Evaluate seizure severity
  - Evaluate Quality of Life
  - Determine device settings
  - Determine other anti-epileptic treatments and the change during follow up
  - Determine adverse events

INCLUSION & EXCLUSION CRITERIA

INCLUSION CRITERIA

- Documented diagnosis of refractory epilepsy
- Age at implantation : < 18 years old
- 3 month pre-implantation data available
- Minimum documented follow up : 1 year
- Ethical committee approval and informed consent

EXCLUSION CRITERIA

- No other investigative medication or treatment after implantation
- Brain surgery within the first year after implantation

E- 102 Study : European VNS Multicentre Study

Study population demographics

Gender			
	- Male	199	(57,3 %)
	- Female	146	(42,1 %)
		345	
Age at implantation			
	- Median	**10,7 y**	(0,4 – 23,2 y)
	- < 6 y	47	(13,5 %)
	6 – 10	91	(26,2 %)
	10-12	57	(16,4 %)
	12-18	152	(43,8 %)
Age at epilepsy onset			
	- Median	1,5 y	(0,1 – 14 y)

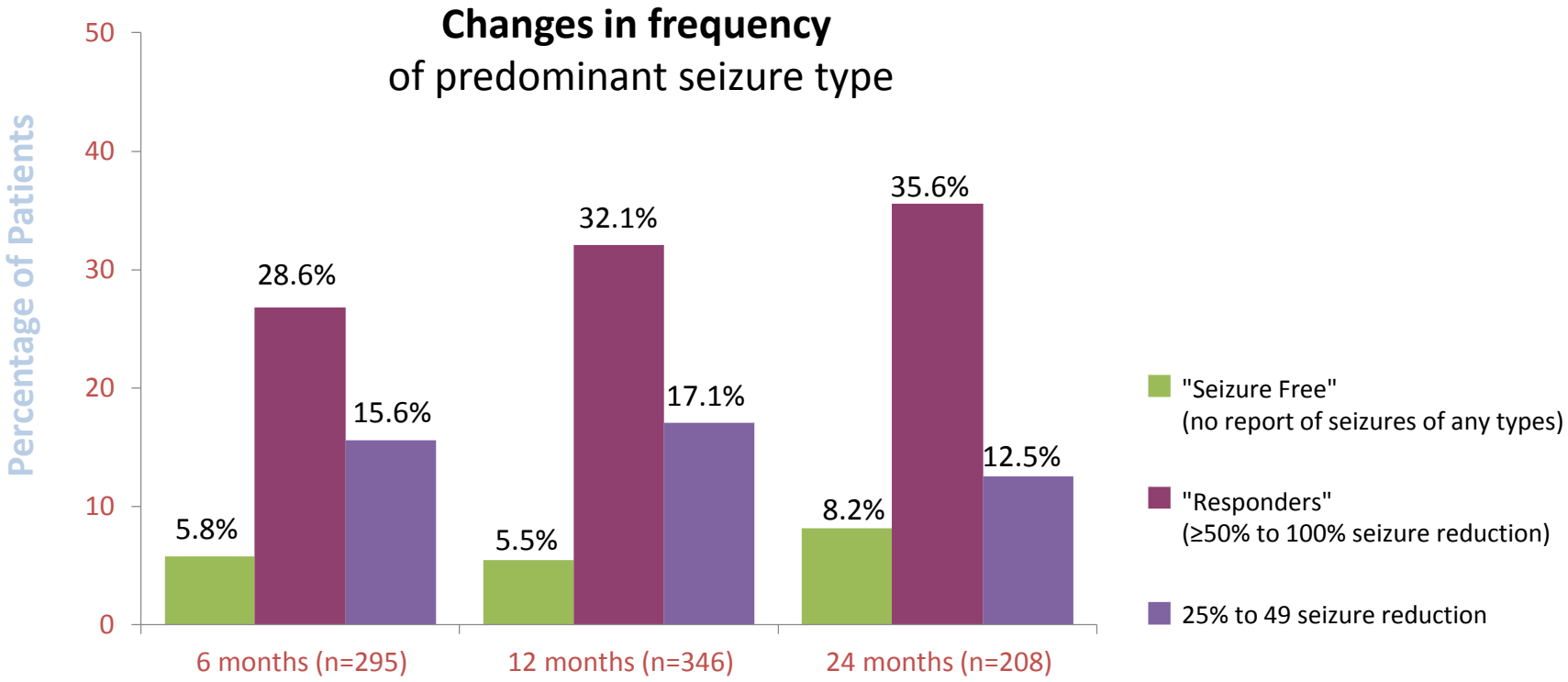
Baseline Disease Characteristics

PREDOMINANT SEIZURE TYPE

partial onset +/- secondary generalization	41,2%
myoclonic seizures	4,6%
atonic seizures	4,6%
tonic-clonic seizures	26,5%
typical absence seizures	1,7%
atypical absence seizures	3,2%
myoclonic absence seizures	1,7%
myoclonic astatic seizures	0,6%
epileptic / infantile spasms	1,4%
other seizure types	12,7%

E- 102 Study : European VNS Multicentre Study

Seizure Reduction



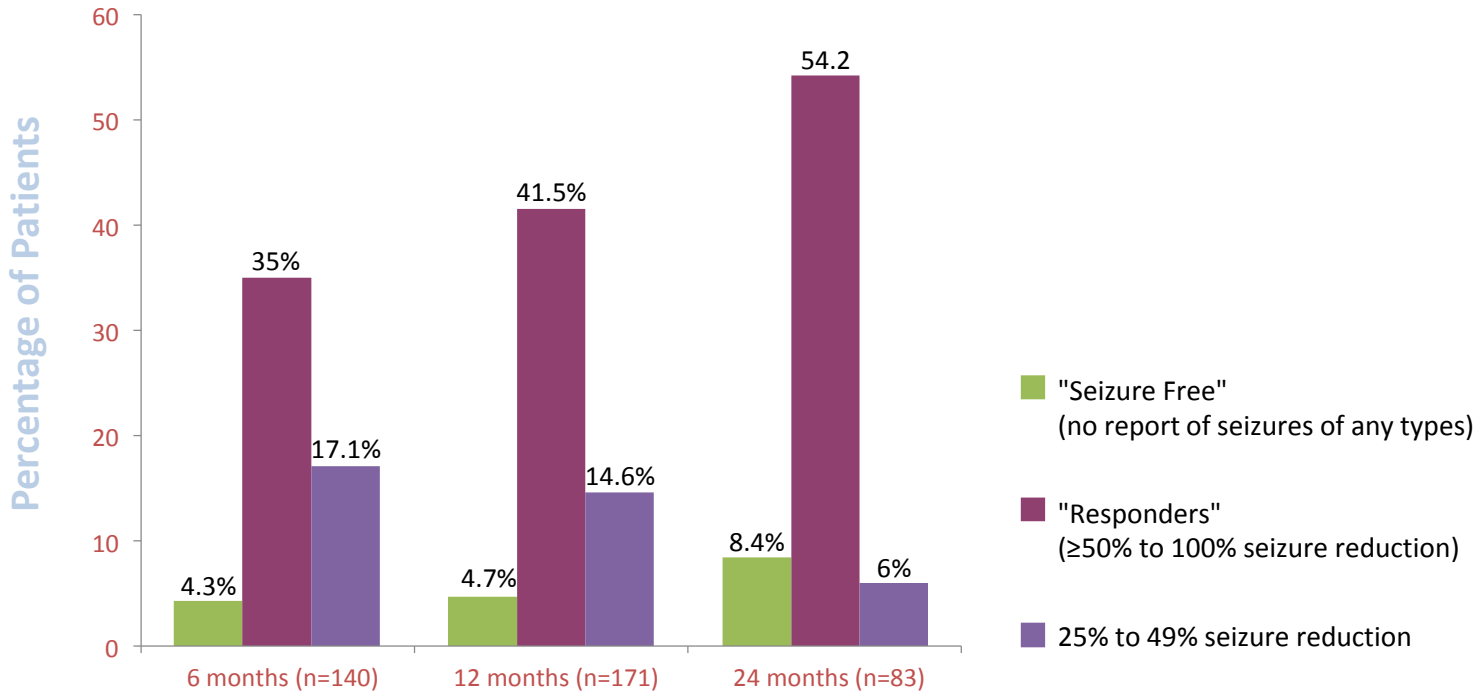
How poor are they that have not patience! William Shakespeare

Orosz, I et al. Epilepsia 2014 doi: 10.1111/epi.12762

E- 102 Study : European VNS Multicentre Study

Seizure Reduction

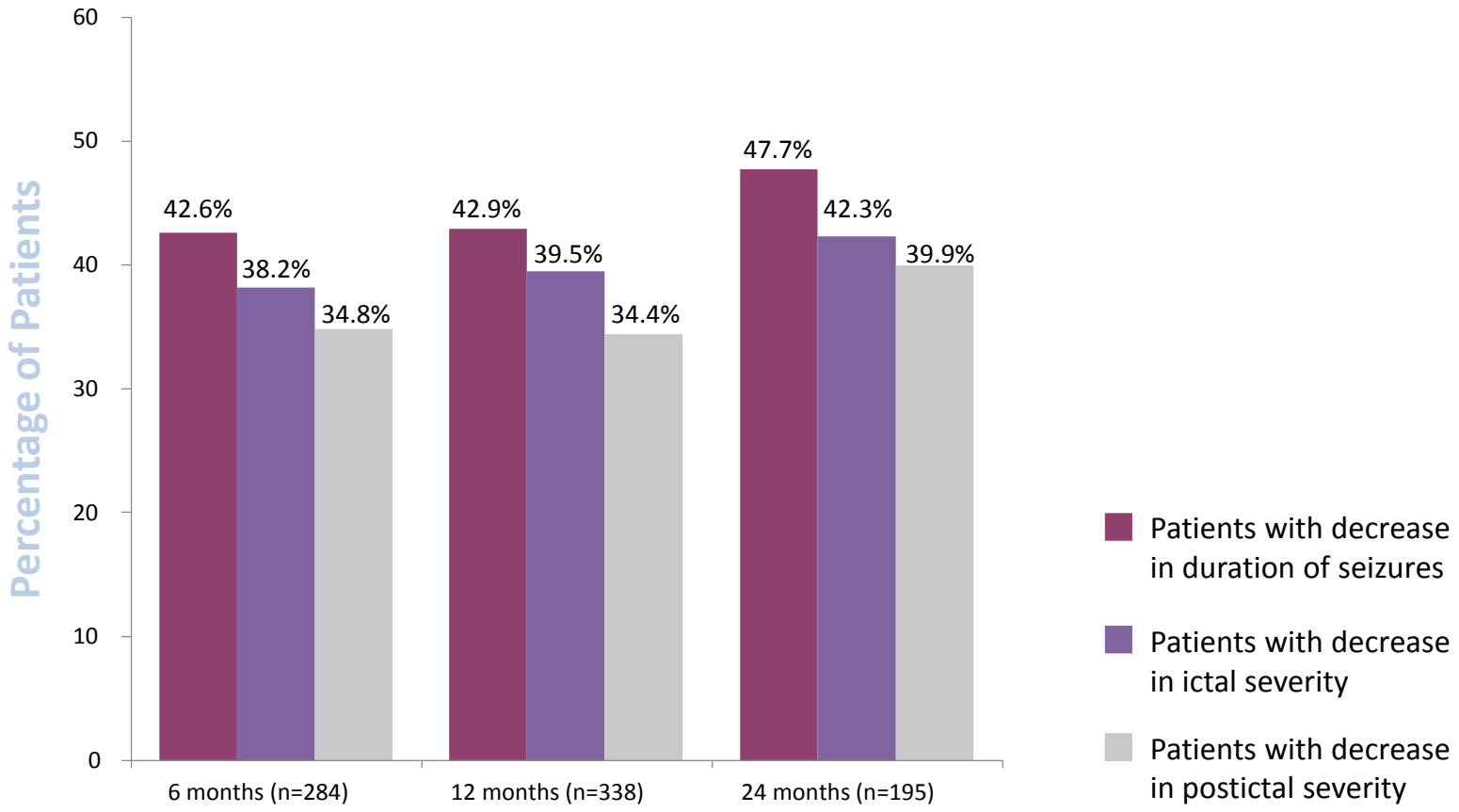
Changes in frequency of predominant seizure type;
Patients with **no changes in AEDs** from baseline
N= 172 (49.6%)



Orosz, I et al. Epilepsia 2014 doi: 10.1111/epi.12762

E- 102 Study : European VNS Multicentre Study

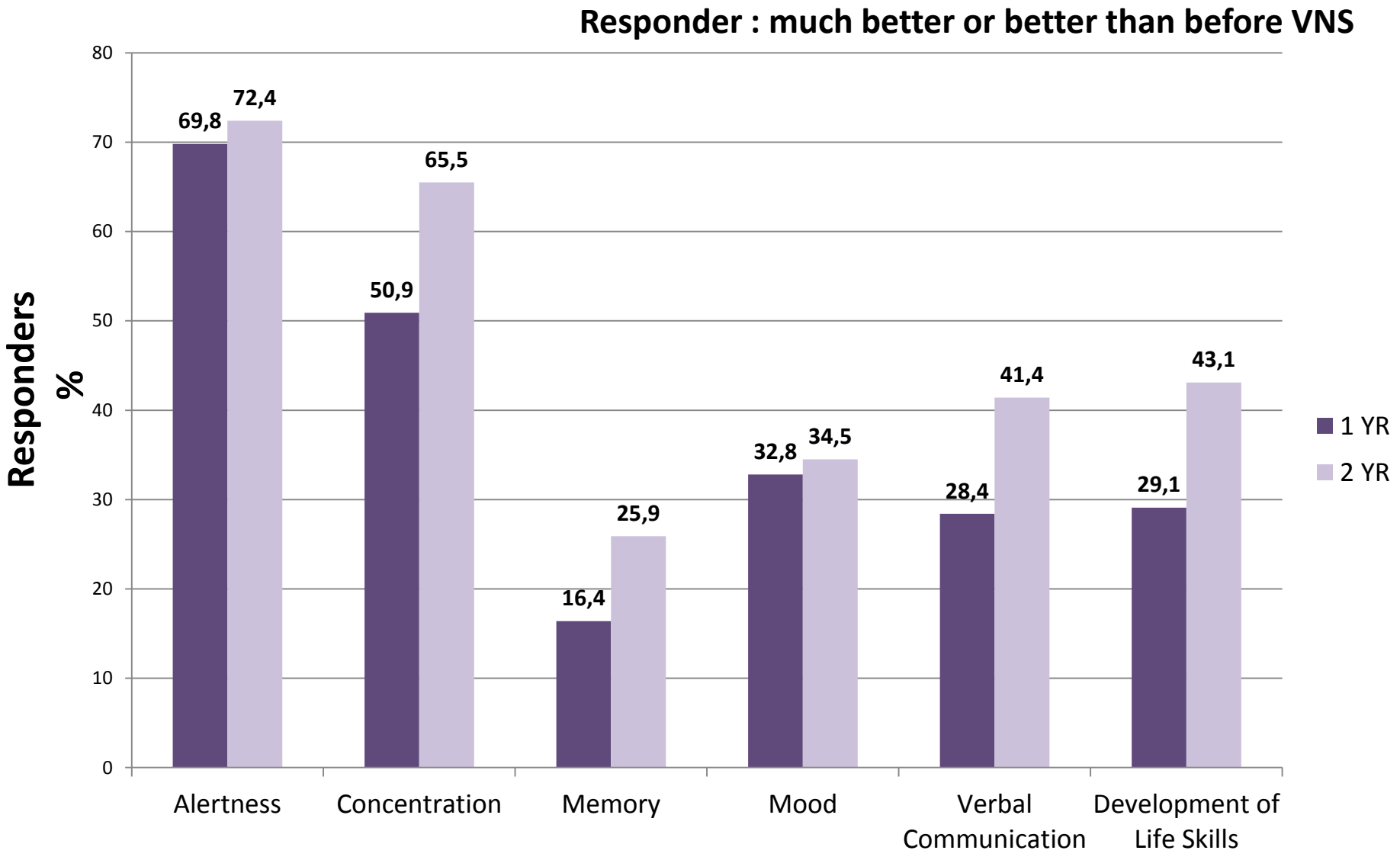
ITT population: Reduction in severity



Orosz, I et al. Epilepsia 2014 doi: 10.1111/epi.12762

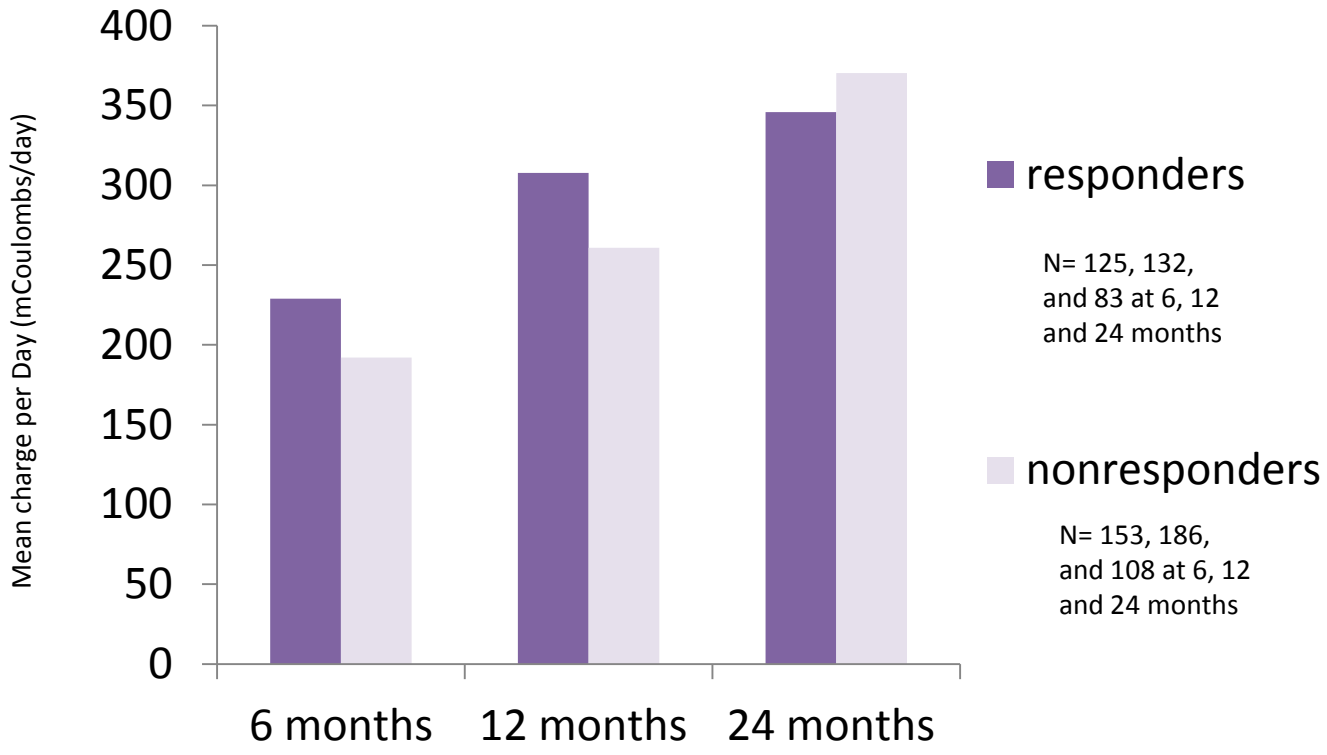
E- 102 Study : European VNS Multicentre Study

Quality of Life



E- 102 Study : European VNS Multicentre Study

ITT population: Total charge delivered per day to responders versus non-responders



$$Q_{Total} = \left(\frac{T_{period}(I/1000)(P_W/10^6) f (t_{ON} + 4)}{t_{ON} + (t_{OFF} * 60)} \right)$$

Orosz, I et al. Epilepsia 2014 doi: 10.1111/epi.12762

Age at implantation

- Under 12 years: n = 193
  - < 6years : n= 46
  - 6-12 years : n= 147
- 12-18 years: n= 154
- Mean age at onset epilepsy :
  - <12 years : 1.9 years (median 1.1)
  - 12-18 years : 3.7 years (median 2.0)

E- 102 Study : European VNS Multicentre Study

Age at implantation

No differences between 2 groups in :

- Frequency intellectual disability
- Behavioral problems
- Verbal communication
- Predominant seizure type
- Epilepsy syndrome
- Etiology

E- 102 Study : European VNS Multicentre Study

Age at implantation

	< 12 years	12-18 years	
	N=193	n=153	
Responders 1 year	**43 %**	**30,7 %**	p=0.019
Seizure free	7.8 %	2.6 %	
	N= 124	N=84	
Responders 2 year	**50%**	**34,5 %**	p=0.024
Seizure free	11,3 %	3,6 %	

E- 102 Study : European VNS Multicentre Study

Lennox Gastaut

	Lennox Gastaut	Non Lennox Gastaut
n =	146	200
1 YEAR		
Responders	32,9 % (25-40)	41 % (34,2 – 47,8)
Seizure free	4,7 %	6 %
	n=121	n=87
2 YEARS		
Responders	39,1% (28,8 – 49,3)	47,1 % (38,6 – 56,4)
Seizure free	6,9 %	9,1 %

No age differences at implantation
Only 13 % in LGS group : “idiopathic”

E- 102 Study : European VNS Multicentre Study

Tuberous Sclerosis

	Non –TSC	TSC
n =	324	22
1 YEAR		
Responders	36,4 % (31,2-41,7)	54,5 % (33-75)
Seizure free	5,6 %	4,5 %
n =	190	18
2 YEARS		
Responders	41,6 % (34-48)	66,7 % (44,9-88,4)
Seizure free	8,4 %	5,6 %

E- 102 Study : European VNS Multicentre Study

Dravet Syndrome

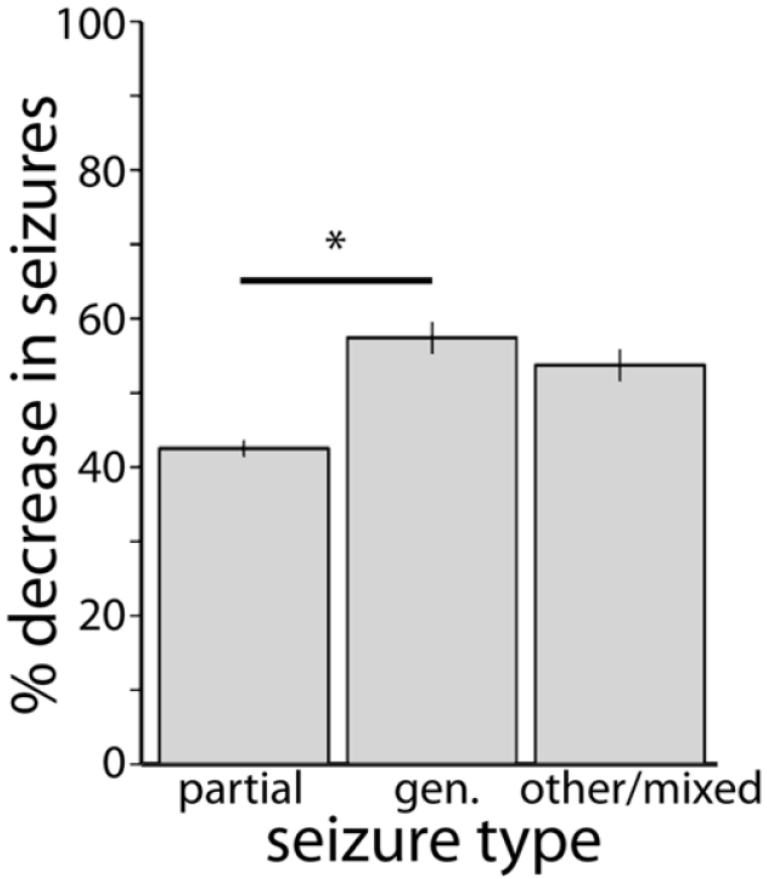
		Dravet syndrome
n=		20
1 YEAR		
Responders %		25 % (6,0-44,0)
Seizure free		0 %
n=		13
2 YEARS		
Responders %		38,5 % (12-64)
Seizure free		0 %

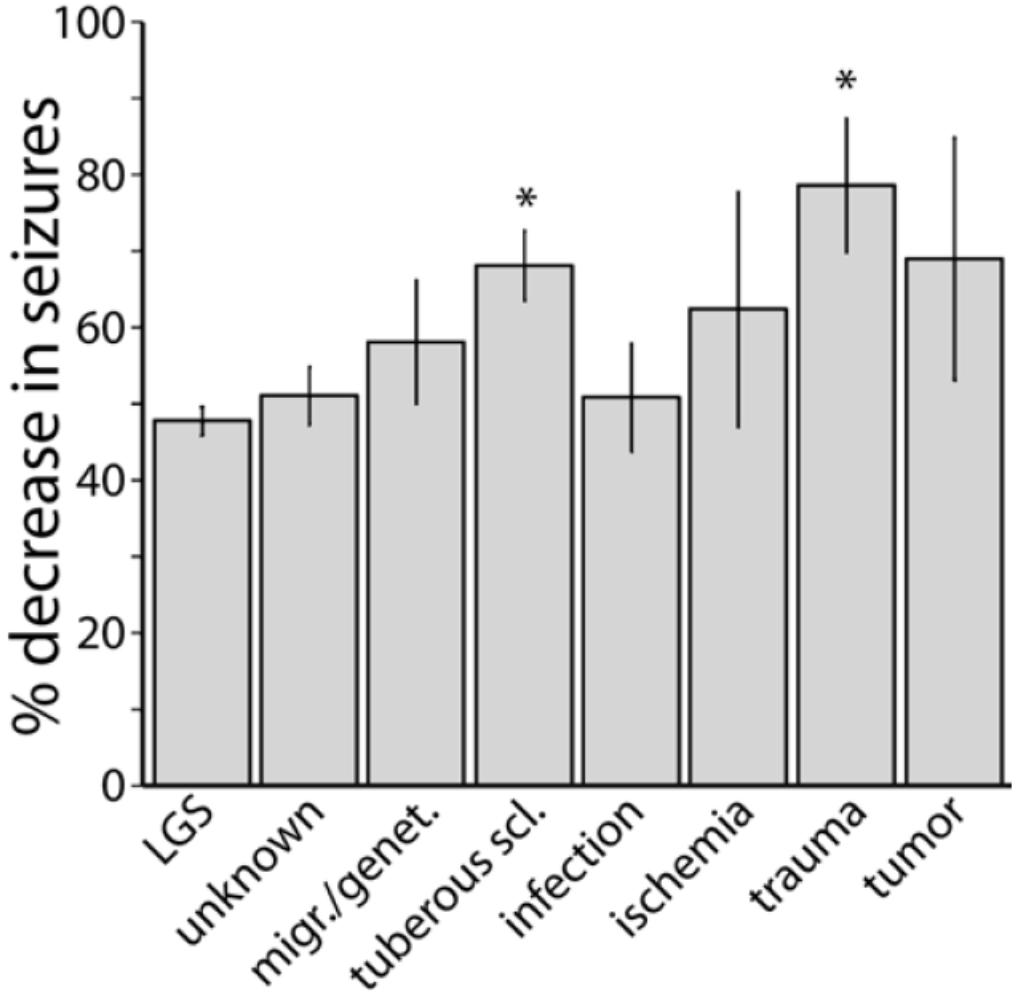
GTC and other seizure types

	Generalised Tonic Clonic	Other seizure types
n =	92	254
1 YEAR		
Responders	21,7% (13,3-30,2)	43,3 % (37,2-49,4)
Seizure free	2,2 %	6,7 %
2 YEARS	N=58	N=150
Responders	29,3 % (17,6 – 41,0)	49,3 % (41,6 – 57,7)
Seizure free	5,2 %	9,2 %

TABLE 2: Seizure outcomes reported by Engel class

	Engel Class, % Seizure Decrease				
Parameter	I, 100%	II, >90%	III, 50%–90%	IV, <50%	Total*
no. of patients (%)	121 (4.6)	200 (7.6)	1012 (38.4)	1301 (49.4)	2634





Englot D et al, J Neurosurg 115: 1249-1255, 2011

PuLsE STUDY

Ryvlin P et al. *Epilepsia 55(6):893-900, 2014*

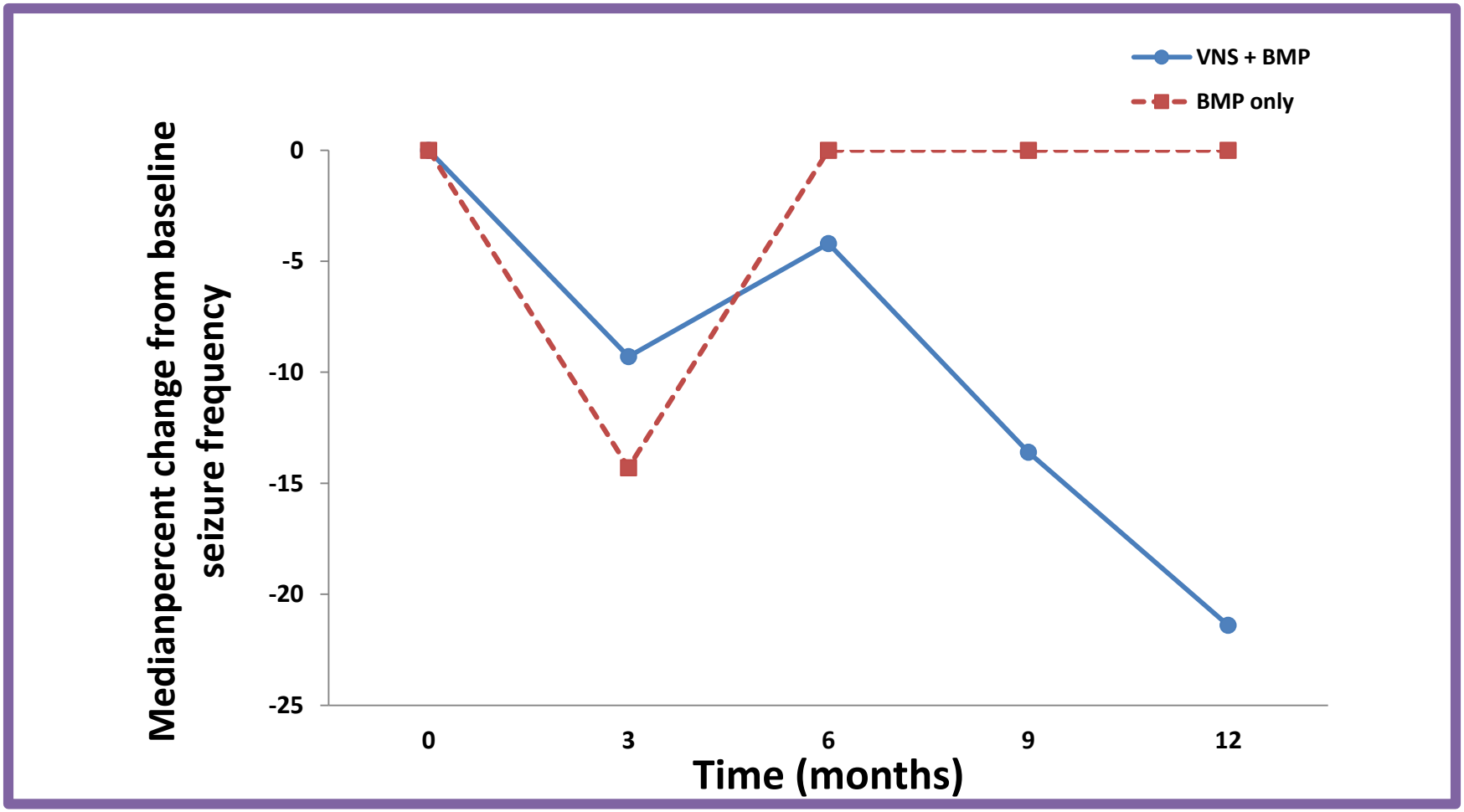
Study :

The Long-Term Effect of Vagus Nerve Stimulation of Quality of Life in Patients with Pharmacoresistant Epilepsy: The PuLsE (Open Prospective Randomized Long-Term Effectiveness) Trial

Objective :

The purpose of this study was to evaluate whether VNS Therapy as an adjunct to best medical practice (VNS+BMP) is superior to BMP alone in improving long-term health-related QOL

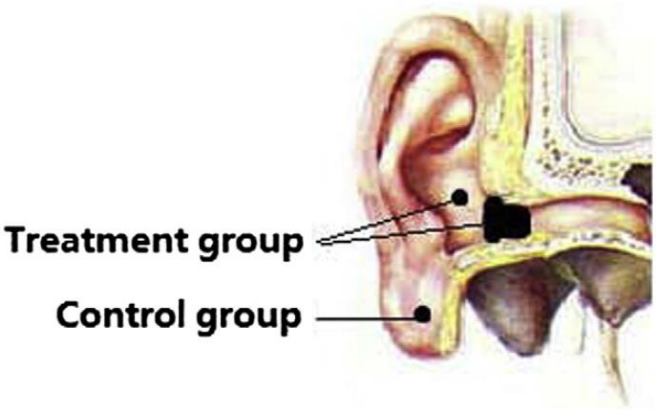
Median Percent Change in Total Seizure Frequency From Baseline



A controlled trial of transcutaneous vagus nerve stimulation for the treatment of pharmacoresistant epilepsy

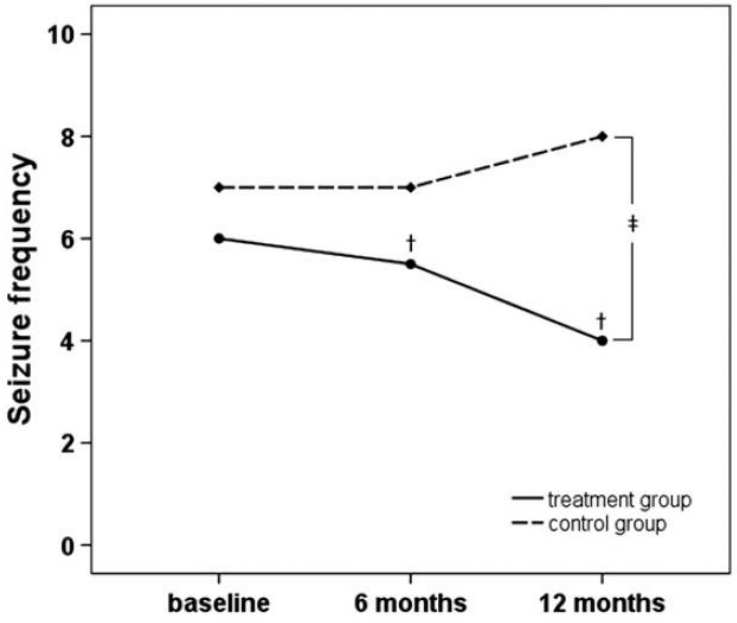
Liu Aihua, Song Lu, Li Liping, Wang Xiuru, Lin Hua, Wang Yuping *

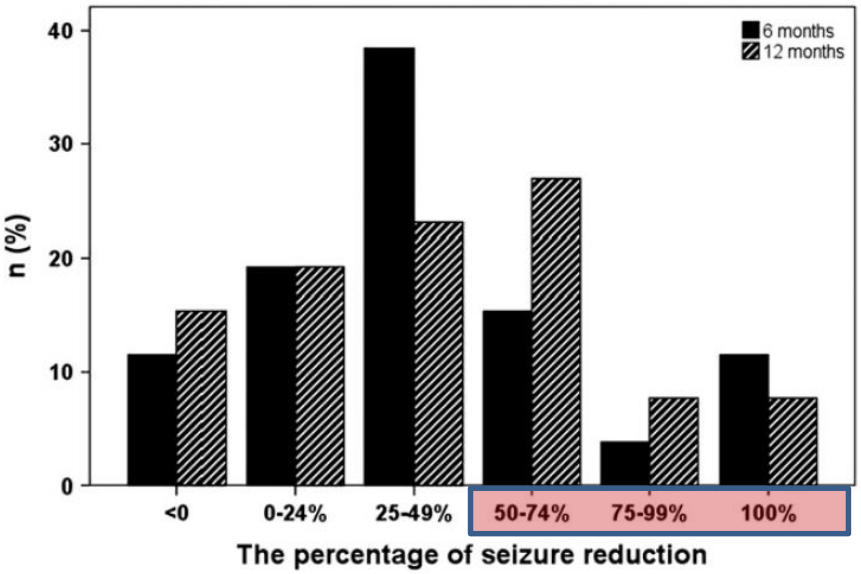
The Department of Neurology, Xuanwu Hospital, Capital Medical University, No. 45, Changchun Street, Xicheng District, Beijing 100053, China



	Treatment group (n = 26)	Control group (n = 21)	*P*-value
Age (years)[1]	34.5 (26.5, 41.3)	29.0 (24.5, 42.0)	0.668
16–30[2]	12 (46.2)	11 (52.4)	0.862
31–45	8 (30.8)	5 (23.8)	
46–60	6 (23.1)	5 (23.8)	
Duration of epilepsy (years)[3]	19.7 ± 11.1	17.6 ± 9.6	0.496
≤10[2]	5 (19.2)	5 (19.0)	0.943
11–20	11 (42.3)	10 (47.6)	
21–30	6 (23.1)	5 (23.8)	
≥31	4 (15.4)	2 (9.5)	
Epilepsy type[2]			0.741
Simple partial seizure	17 (65.4)	15 (71.4)	
Complex partial seizure	3 (11.5)	3 (14.3)	
Generalized seizures	6 (23.1)	3 (14.3)	
MRI[2]			0.805
Normal	17 (65.4)	13 (61.9)	
Abnormal	9 (34.6)	8 (38.1)	
EEG[2]			0.528
Normal	10 (38.5)	10 (47.6)	
Abnormal	16 (61.5)	11 (52.4)	
The number of AEDs[1]	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	0.981
Seizure frequency[1]	6.0 (4.8, 25.0)	7.0 (4.0, 11.5)	0.829
Stimulation intensity (mA)[1]	6.0 (5.0, 6.3)	6.0 (5.0, 6.5)	0.918
SAS scores[3]	43.3 ± 8.5	38.1 ± 7.0	0.031*
SDS scores[3]	49.2 ± 7.3	48.1 ± 7.2	0.581
LSSS scores[3]	13.9 ± 3.9	14.8 ± 4.4	0.471
QOLIE-31 scores[3]	109.2 ± 11.8	111.4 ± 10.4	0.492

Epilepsy and Behavior, 2014



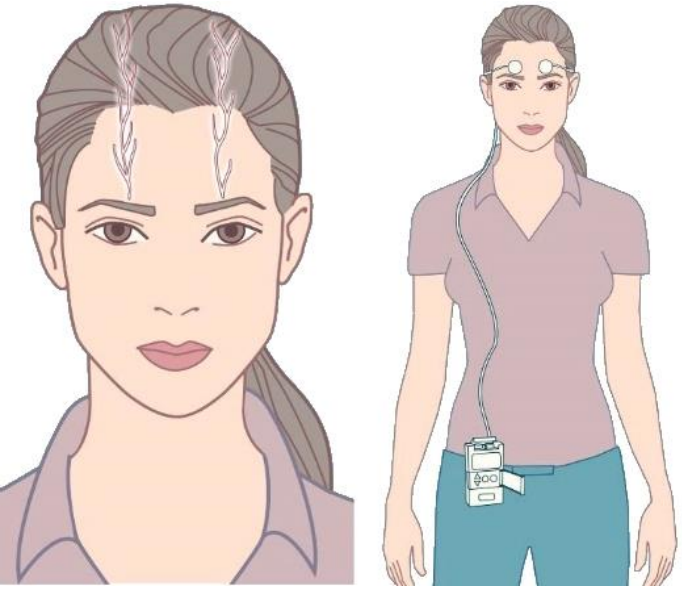


Multiple linear regression analysis of t-VNS efficacy.

	Coefficient (95% CI)	*P*-value
Age (years)	−0.45 (−1.45, 0.55)	0.372
Duration of epilepsy (years)	1.36 (0.21, 2.52)	0.022*
Seizure type		
Simple partial seizure	Ref.	
Complex partial seizure	−17.61 (−52.69, 17.48)	0.316
Generalized seizures	12.35 (−15.65, 41.35)	0.377
MRI		
Normal	Ref.	
Abnormal	8.11 (−16.99, 33.21)	0.517
EEG		
Normal	Ref.	
Abnormal	−2.20 (−26.71, 22.32)	0.857
The number of AEDs	6.60 (−12.70, 25.90)	0.493
Seizure frequency	1.41 (0.46, 2.36)	0.005*
Stimulation intensity (mA)	−3.78 (−12.77, 5.22)	0.400

Randomized controlled trial of trigeminal nerve stimulation for drug-resistant epilepsy

Christopher M. DeGiorgio, Jason Soss, Ian A. Cook, et al.

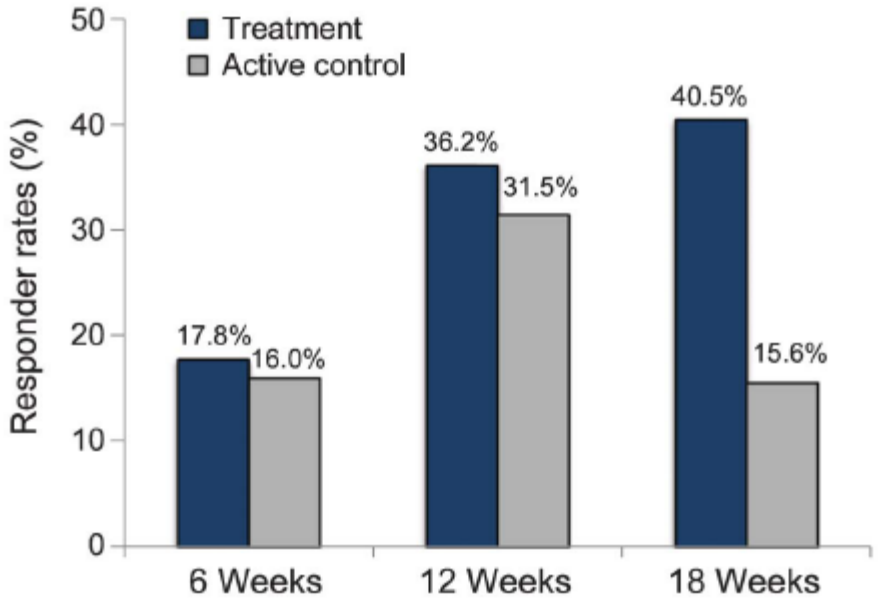


	Treatment	Active control
No.	25	25
Age, y, mean (range)	33.1 (20-58)	34.2 (19-52)
M/F	9/16	14/11
Seizure frequency, median (SD)	8.7 (56.2)	4.8 (20.8)
Duration of epilepsy, y (SD)	21.5 (9.7)	23.7 (12.1)
Beck Depression Inventory, mean (SD)[a]	16.7 (9.6)	12.0 (10)
UCLA, %	56	52
USC, %	44	48

Neurology, 2013

Randomized controlled trial of trigeminal nerve stimulation for drug-resistant epilepsy

Christopher M. DeGiorgio, Jason Soss, Ian A. Cook, et al.

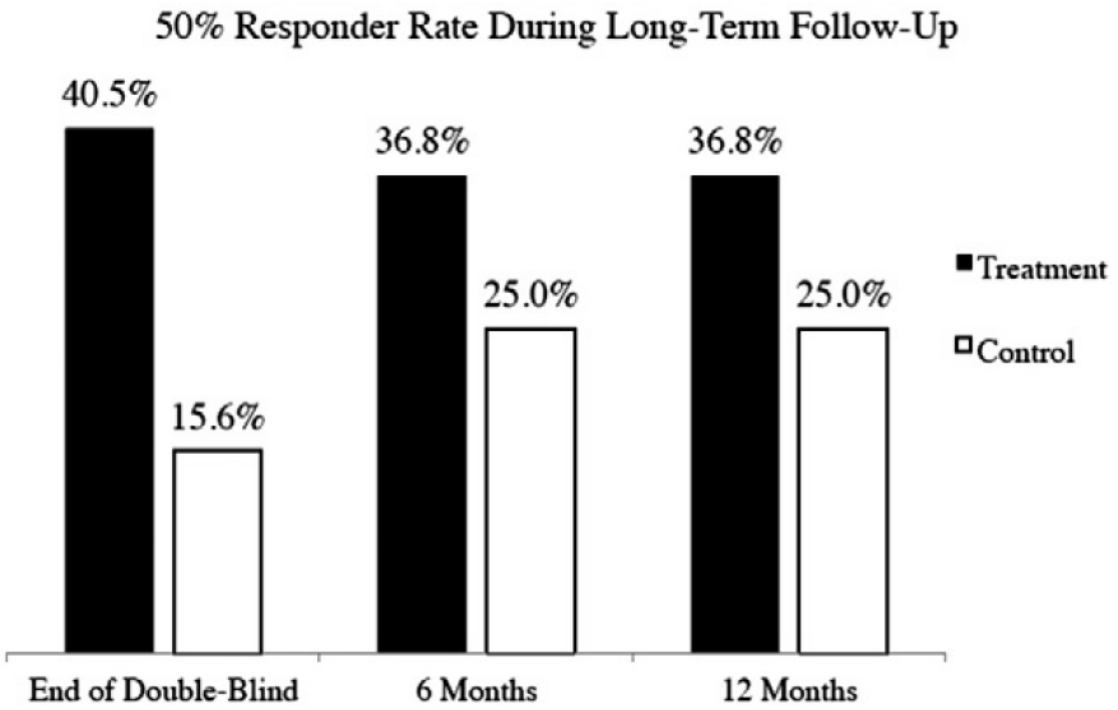


Non-significant primary end points

A prospective long-term study of external trigeminal nerve stimulation for drug-resistant epilepsy

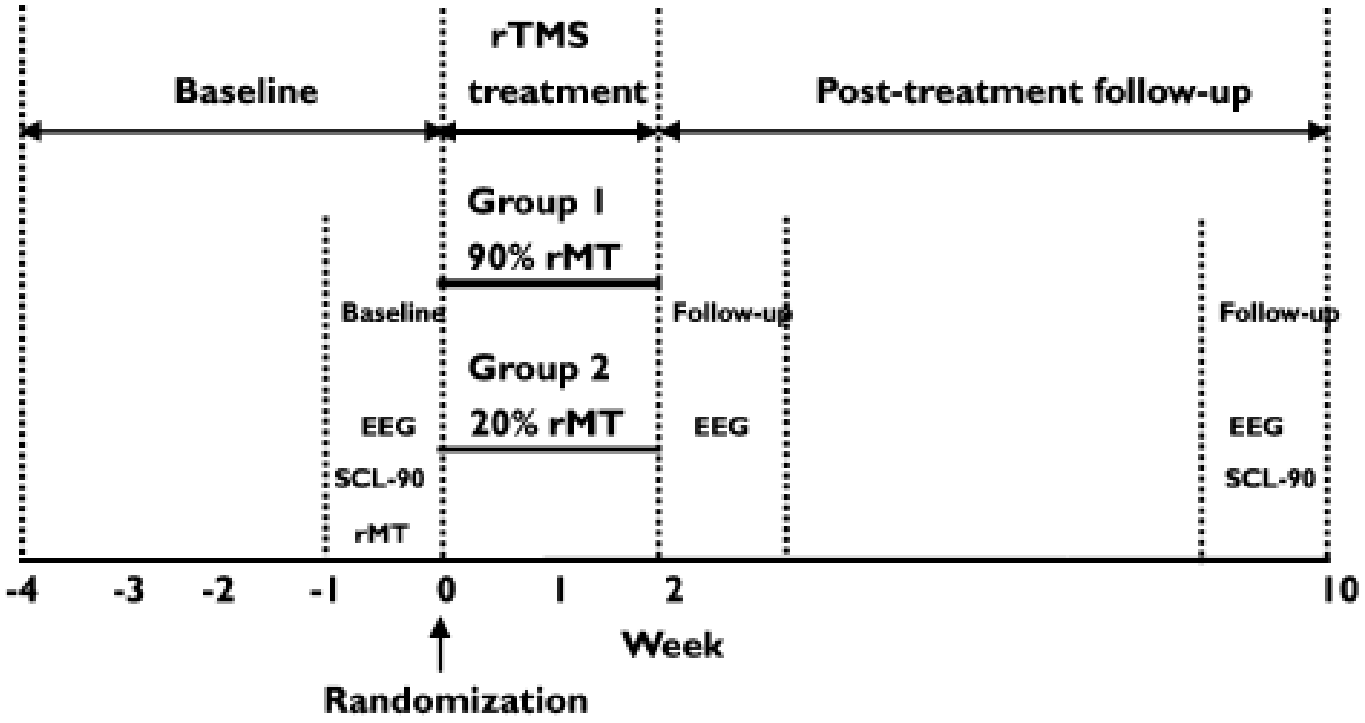
Jason Soss [a], Christi Heck [b], Diana Murray [a], Daniela Markovic [d], Sandra Oviedo [b], Guadalupe Corrale-Leyva [b], Steven Gordon [a], Colin Kealey [c], Christopher DeGiorgio [a,c,*]

[a] Olive View/UCLA Medical Center, UCLA Department of Neurology, USA
[b] USC Department of Neurology, USA
[c] NeuroSigma, Inc., USA
[d] UCLA Department of Biomathematics, USA

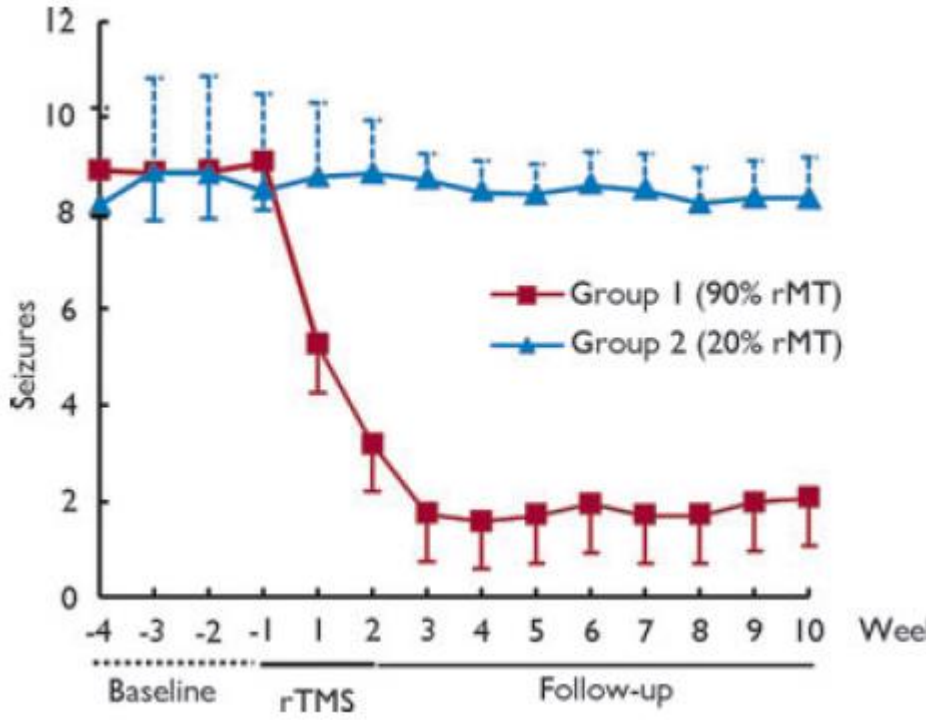


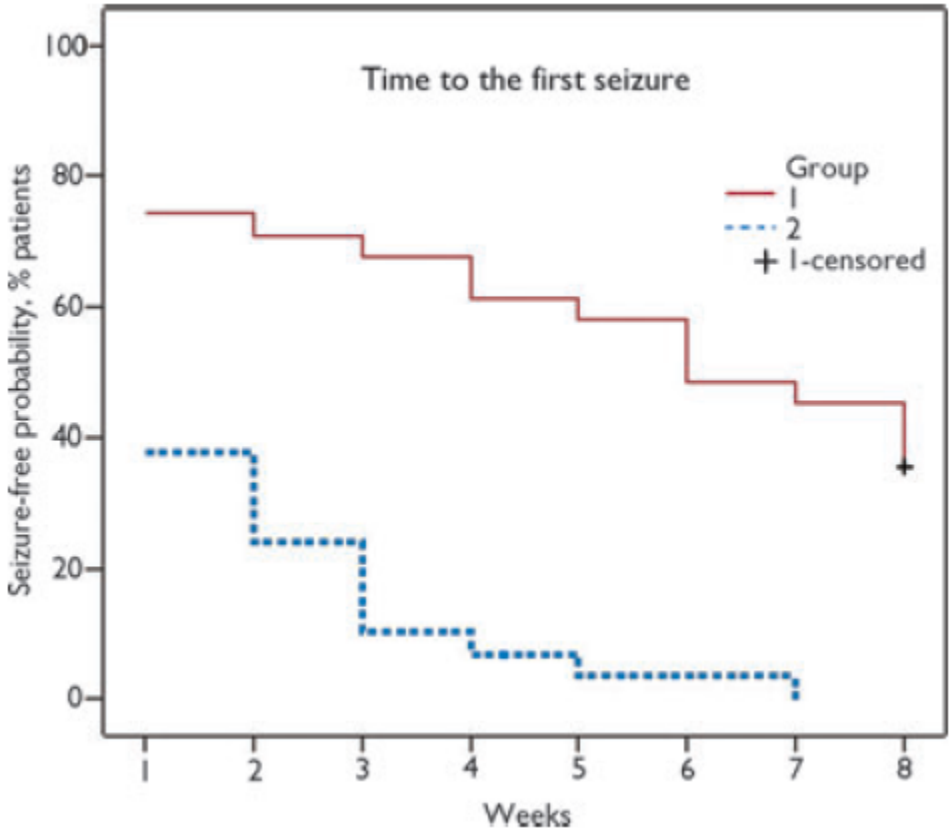
Epilepsy and Behaviour 2015

Low-frequency repetitive transcranial magnetic stimulation for the treatment of refractory partial epilepsy: A controlled clinical study

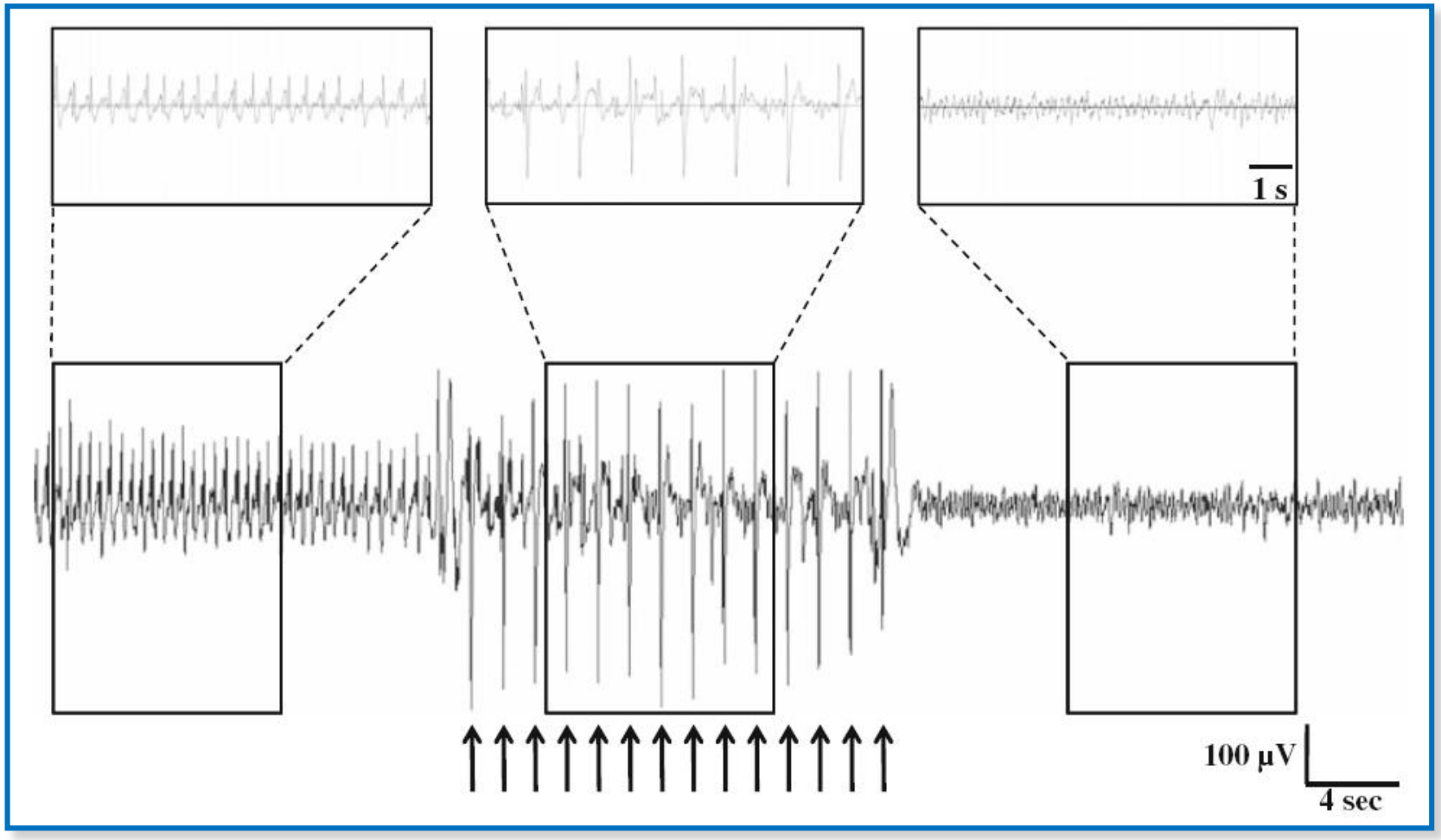


Wei Sun et al, Epilepsia 2012


12
10
8
6
4
2
0
Seizures
Group 1 (90% rMT)
Group 2 (20% rMT)
-4 -3 -2 -1 1 2 3 4 5 6 7 8 9 10
Wee
Baseline
rTMS
Follow-up


Time to the first seizure
100
80
60
40
20
0
Seizure-free probability, % patients
Group
1
2
1-censored
1 2 3 4 5 6 7 8
Weeks

Acute seizure treated with rTMS in rat

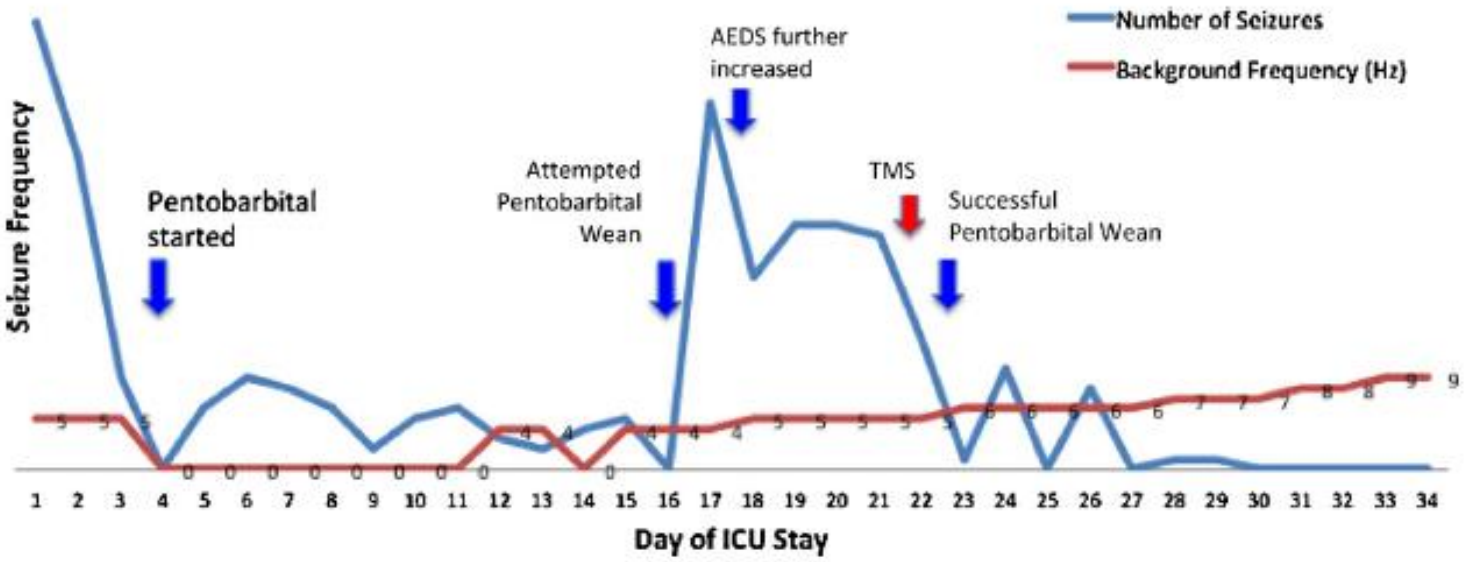


A 60-s tracing shows a representative KA-triggered seizure terminating with a 0.75 Hz rTMS train. Typical spikes of a KA seizure *(left)* were readily recognised by the TMS operator. Once a seizure was detected, rTMS *(arrow)* was initiated, and continued until spikes were no longer evident between the prominent rTMS artifact *(centre)*. After rTMS the EEG returned to baseline *(right)*

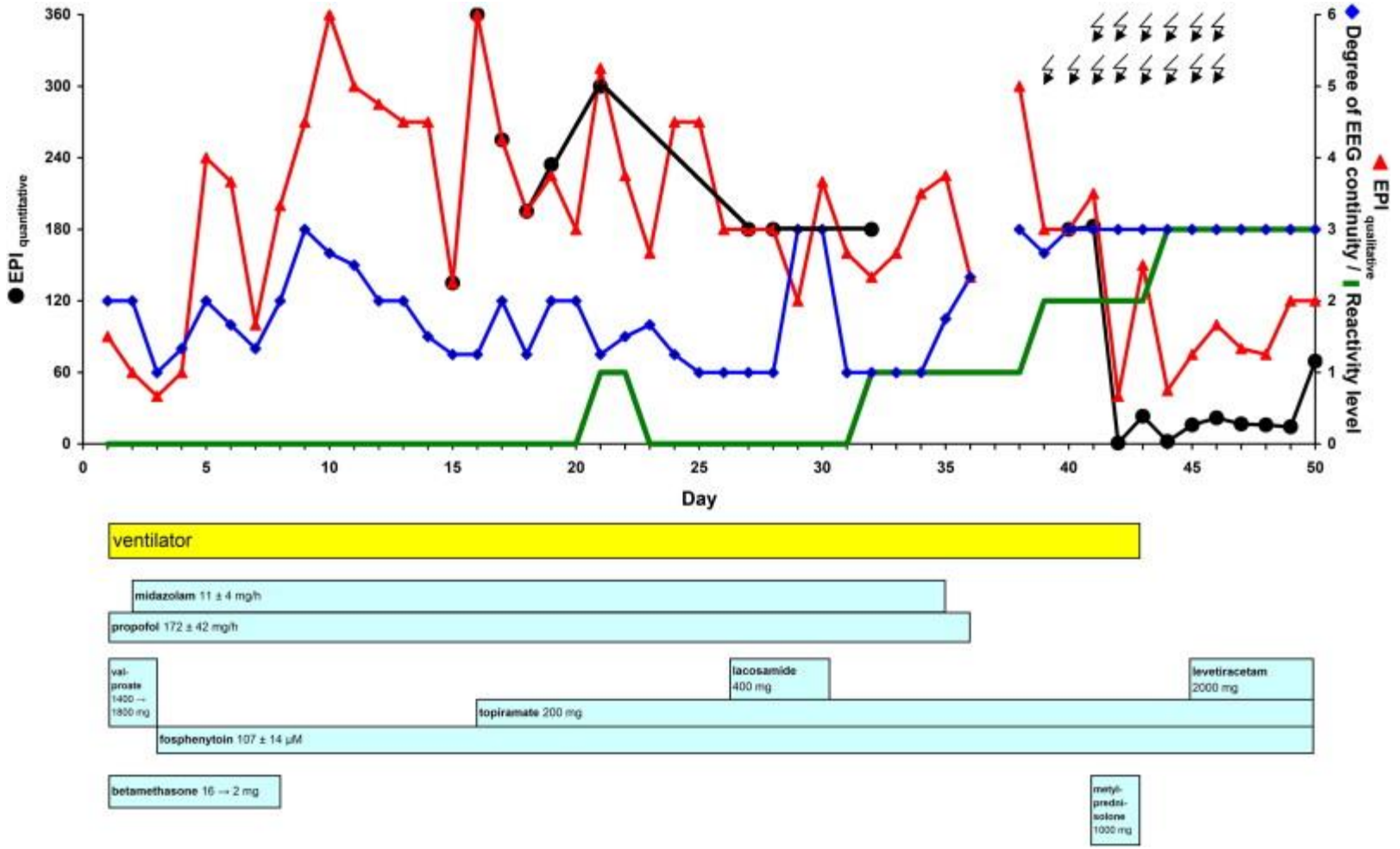
Rotenberg *Brain Topogr* 2010

Transcranial magnetic stimulation for refractory focal status epilepticus in the intensive care unit

Anli Liu [a,b], Trudy Pang [c,e], Susan Herman [c,e], Alvaro Pascual-Leone [c,e], Alexander Rotenberg [d,e,*]



Seizure 2013



Thordstein and Constantinescu, Epilepsy and Behav, 2012

Vagus nerve stimulation

- Indication : more than surgery screening failures (more than focal epilepsies)
- Early implantation : better efficacy ?

- Classic efficacy comparable to any other treatment modality in drug resistant epilepsy

- Other outcome measures needed in studies on drug resistant epilepsy : severity of seizures, QoL