



Neuromodulation

Mohamad Z. Koubeissi, MD
Professor of Neurology
Director, Epilepsy Center
The George Washington University



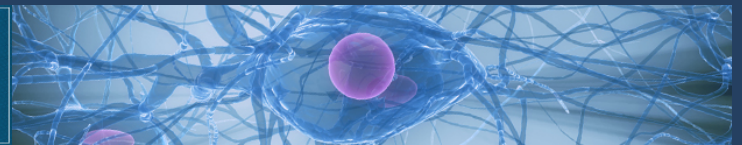
2023 **GW**
Epilepsy Board Review
& Best Practices

DISCLOSURES

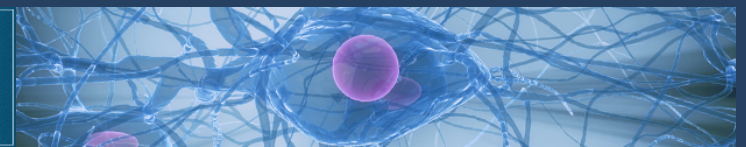
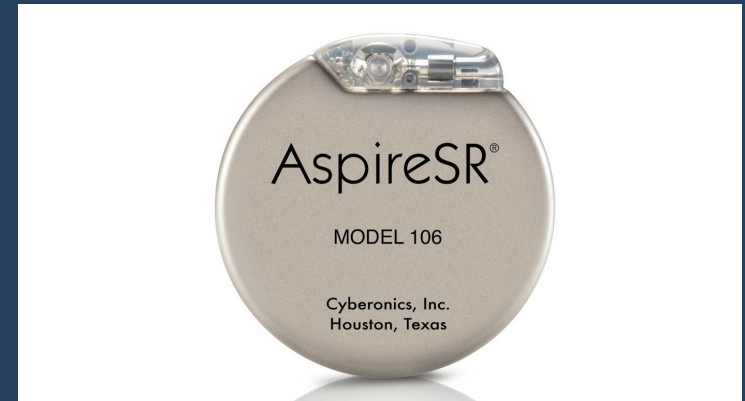
- **Disclosure of Financial Relationships:
None related to the current talk**

VNS Therapy: US indication for use

- The VNS Therapy System is indicated for use in epilepsy in the US as
 - An adjunctive therapy in intractable focal epilepsy
 - Above 4 years of age
 - Also approved for depression



- Autostimulation in those with heart rate increases with seizures
- Amount of stimulation can be adjusted at different times of the day
- Autostimulation can be given when the device detects tachycardia
- The device can be set to detect if a person is lying flat after a seizure.



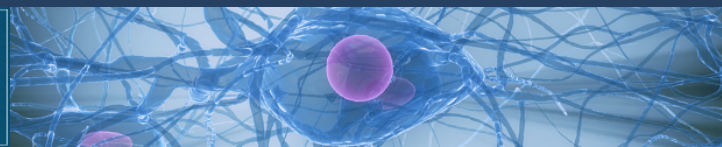


Evidence-Based Guideline Update: Vagus Nerve Stimulation for the Treatment of Epilepsy

Report of the Guideline Development Subcommittee of the American Academy of Neurology

George L. Morris III, MD, FAAN¹; David Gloss, MD²; Jeffrey Buchhalter, MD, FAAN³; Kenneth J. Mack, MD, PhD, FAAN⁴; Katherine Nickels, MD⁴; Cynthia Harden, MD⁵

- >50% seizure reduction in 55% (95% CI 50%–59%) of 470 children with partial or generalized epilepsy (13 Class III studies).
- >50% seizure reduction in 55% (95% CI 46%–64%) of 113 patients with LGS (4 Class III studies).
- Increase in $\geq 50\%$ seizure frequency reduction rates of $\sim 7\%$ from 1 to 5 years postimplantation (2 Class III studies).
- Improvement in standard mood scales in 31 adults with epilepsy (2 Class III studies).



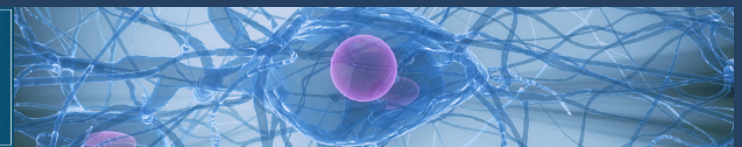


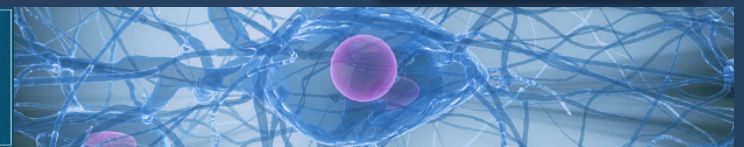
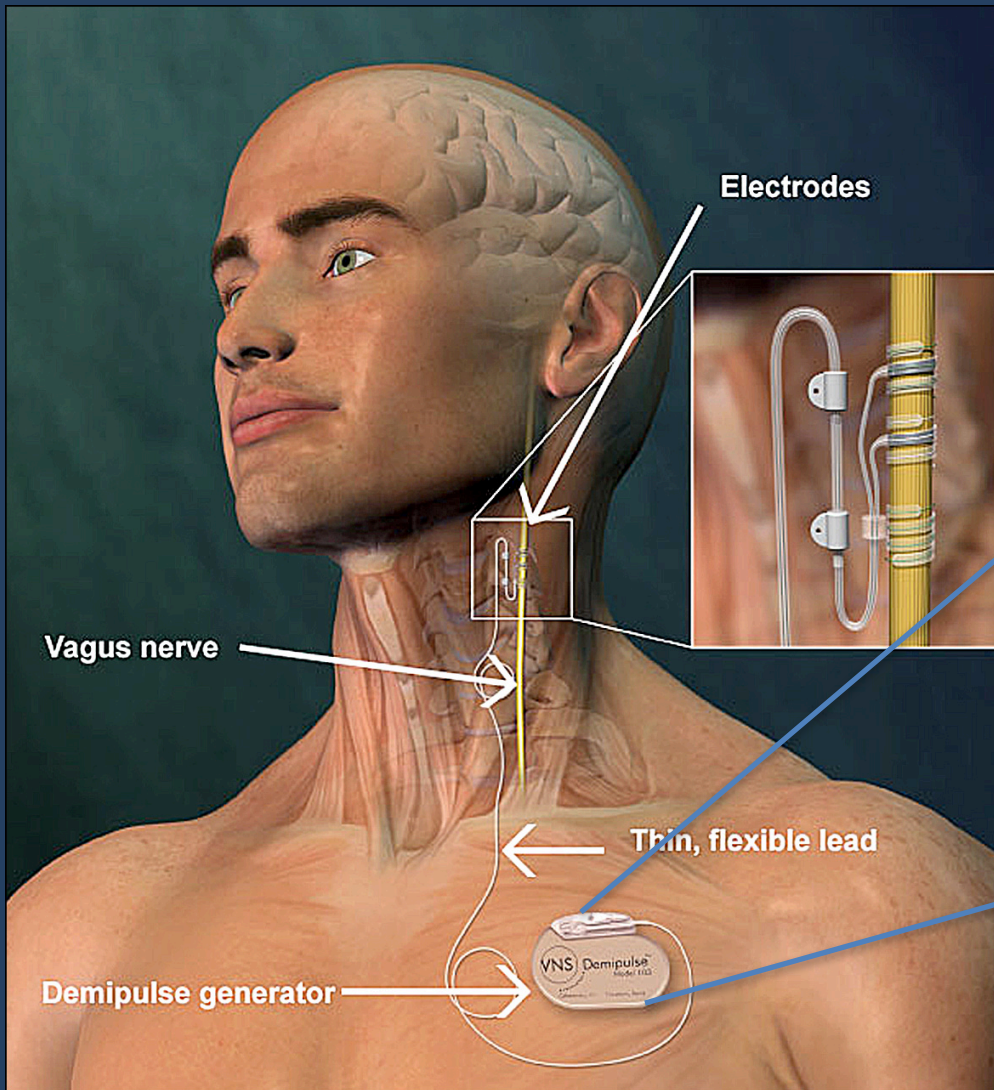
Evidence-Based Guideline Update: Vagus Nerve Stimulation for the Treatment of Epilepsy

Report of the Guideline Development Subcommittee of the American Academy of Neurology

George L. Morris III, MD, FAAN¹; David Gloss, MD²; Jeffrey Buchhalter, MD, FAAN³; Kenneth J. Mack, MD, PhD, FAAN⁴; Katherine Nickels, MD⁴; Cynthia Harden, MD⁵

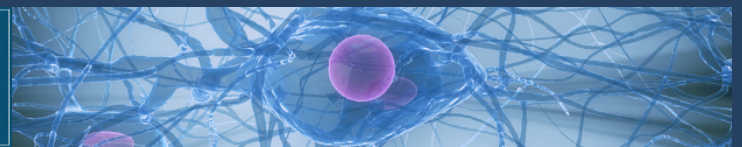
- Infection risk at VNS site in children is increased relative to that in adults (odds ratio 3.4, 95% CI 1.0–11.2).
- VNS is possibly effective for seizures (both partial and generalized) in children, for LGS-associated seizures, and for mood problems in adults with epilepsy. VNS may have improved efficacy over time.
- **RECOMMENDATIONS:** VNS may be considered for seizures in children, for LGS-associated seizures, and for improving mood in adults with epilepsy (Level C). VNS may be considered to have improved efficacy over time (Level C). Children should be carefully monitored for site infection after VNS implantation





Early Experiments in Cats

Year	Authors	Results
1938	Bailey and Bremer	EEG fast activity in orbitofrontal cortex
1952	Zanchetti <i>et al.</i>	Blocked interictal spiking
1961	Magnes <i>et al.</i>	EEG desynchronization
1967	Chase <i>et al.</i>	EEG synchronization or desynchronization in the thalamus and cortex

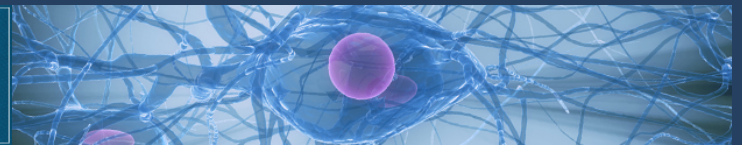


Historical Overview VNS Therapy

- 1985 First Animal Studies (J. Zabara, Temple University)
- 1987 Cyberonics founded by Reese Terry
- 1988 First Human Implant (Dr. Kiffin Penry)
- 1992 First Randomized Active Control Study
- 1994 European Community Approval
- 1996 Second RCT complete (5 total completed studies [N=454])
- 1997 PMA submitted (January)
- 1997 USA (FDA) Commercial Approval (July)

Possible Mechanism of Action

- 80% of vagal fibers are afferent
- Activation of the reticular formation
- Stimulation of locus ceruleus and noradrenergic pathways
- Changes in some neurotransmitters or neuropeptides
- Long-term learning through synaptic structural changes
- Indirect thalamic stimulation
- Desynchronization of EEG rhythms



VNS Therapy evaluated in five clinical trials

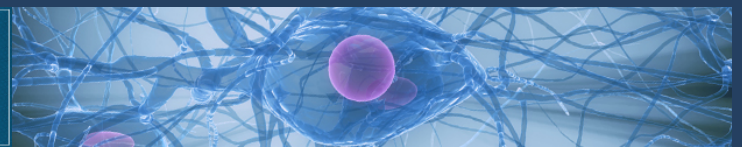
- E01-E05 evaluated the safety, tolerability, and efficacy of VNS Therapy
 - 454 patients received VNS Therapy, with 440 available for assessment of long-term (3-year) treatment
 - Medication changes were allowed in the extension phase

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



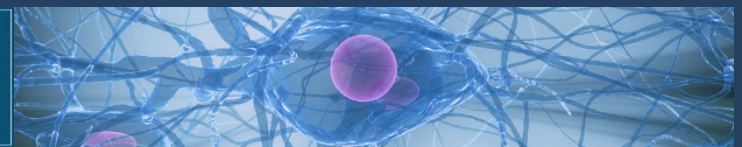
SCHOOL OF MEDICINE
AND HEALTH SCIENCES

The Department of Neurology



VNS Therapy evaluated in five clinical trials

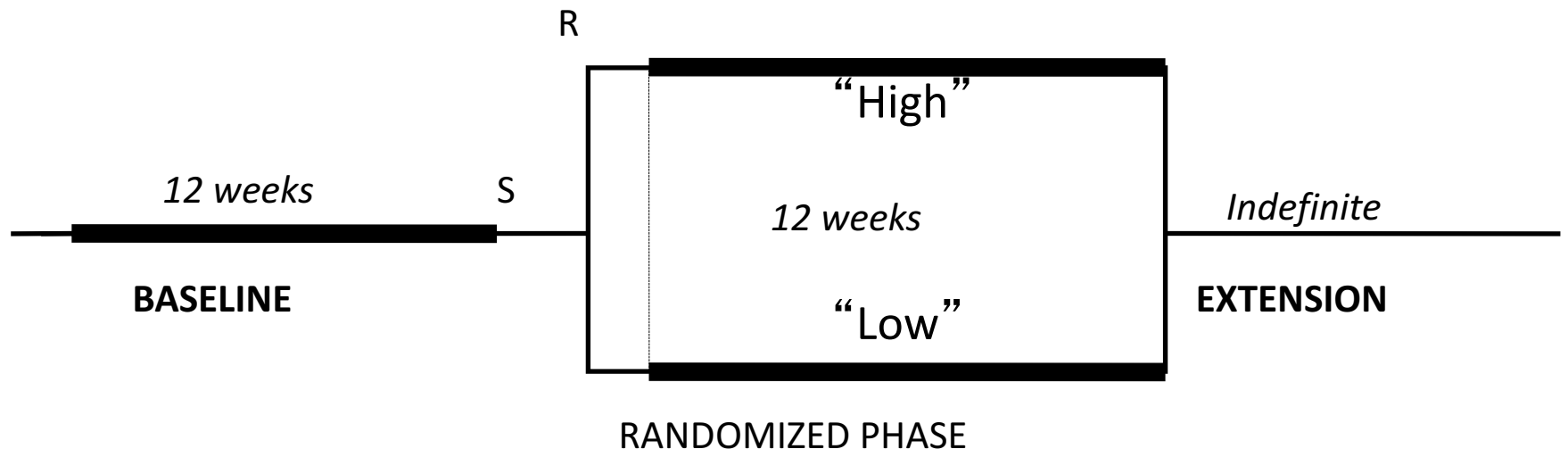
Study	Design	Seizure type	N	Time frame
E01/E02	Pilot, single blind	Partial	14	1988-1990
E03	Randomized, double blind, active control	Partial	114	1990-1992
E04	Compassionate use	All	124	1991-1995
E05	Randomized, double blind, active control	Partial	199	1995-1996



VNS Therapy Clinical Trials Study Design

Hypothesis: “High”-level stimulation would reduce overall seizure frequency to a greater degree than “low”-level stimulation

Design:

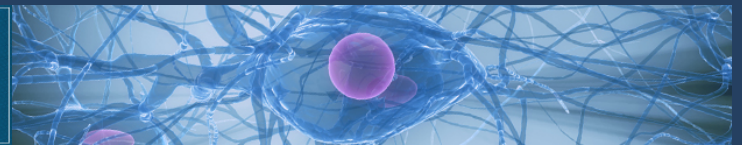


1	2	3	4	5	6	7	8	Visit
0	1	2	3	4	5	6	7	Month

VNS Therapy Clinical Trial: E03

- Multicenter (21)
- Inclusion criteria:
 - 12 years of age or older
 - Refractory focal epilepsy
 - 6 or more seizures per month
 - 1–3 medications

Vagus Nerve Stimulation Study Group. *Neurology*. 1995;45:224-230.



VNS Therapy Clinical Trial: E03

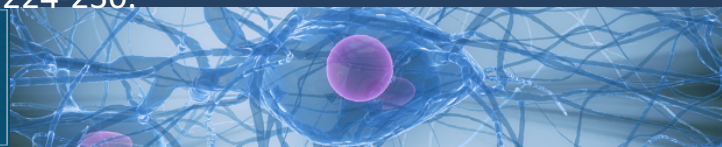
- Number of patients: 114
 - High-stimulation group, n=54
 - Low-stimulation group, n=60
- Years of seizure disorder (mean)
 - High-stimulation group: 23 years
 - Low-stimulation group: 20 years
- Median # of seizures per day (baseline) = 0.73

Vagus Nerve Stimulation Study Group. *Neurology*. 1995;45:224-230.



SCHOOL OF MEDICINE
AND HEALTH SCIENCES

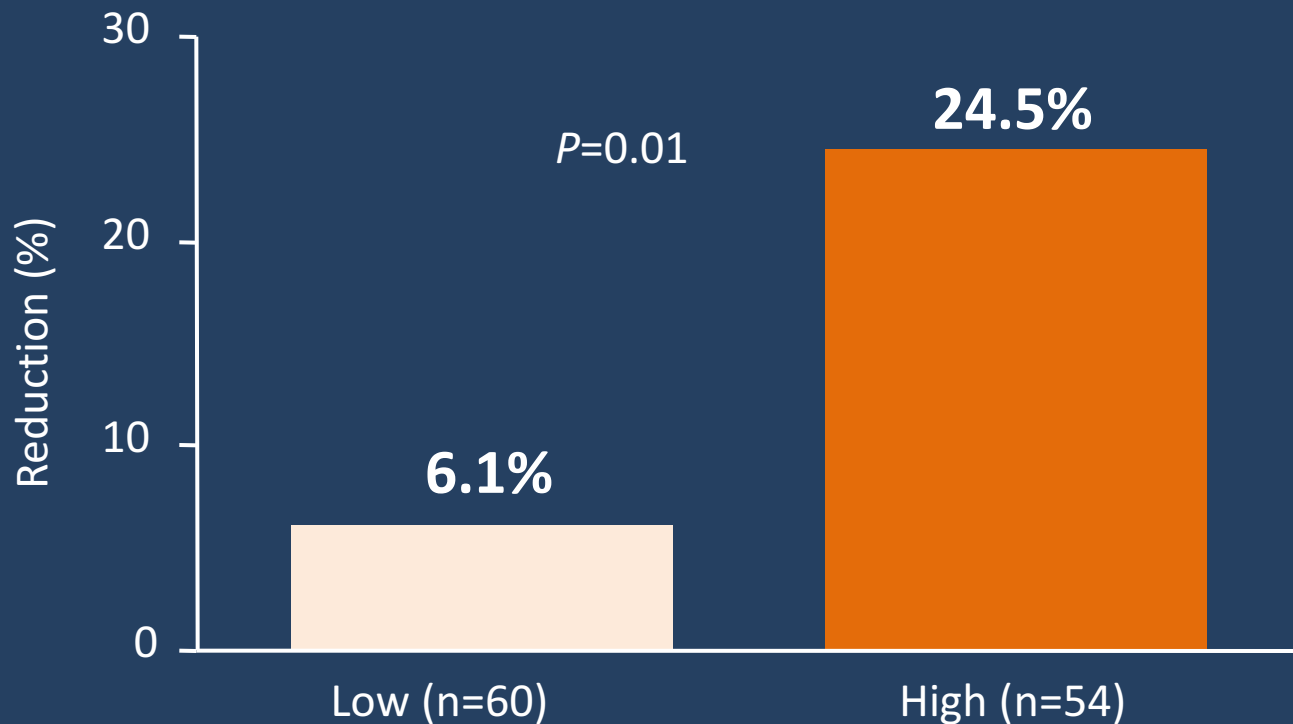
The Department of Neurology



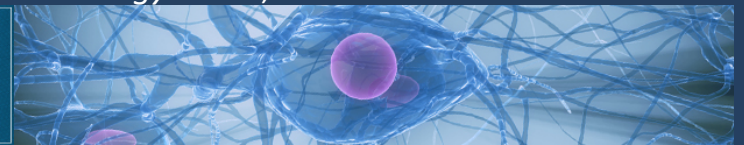
VNS Therapy Clinical Trial: E03

Seizure Reduction

Mean Decrease in Seizure Frequency Versus Baseline



Vagus Nerve Stimulation Study Group. *Neurology*. 1995;45:224-230.

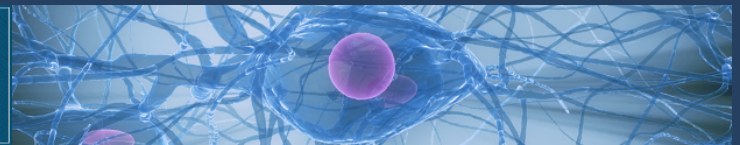


VNS Therapy Clinical Trial: E03

Adverse Events

- Adverse events (occurring in $\geq 5\%$ of patients)
 - Hoarseness 37%
 - Throat pain 11%
 - Coughing 7%
 - Dyspnea 6%
 - Paresthesia 6%
 - Muscle pain 6%

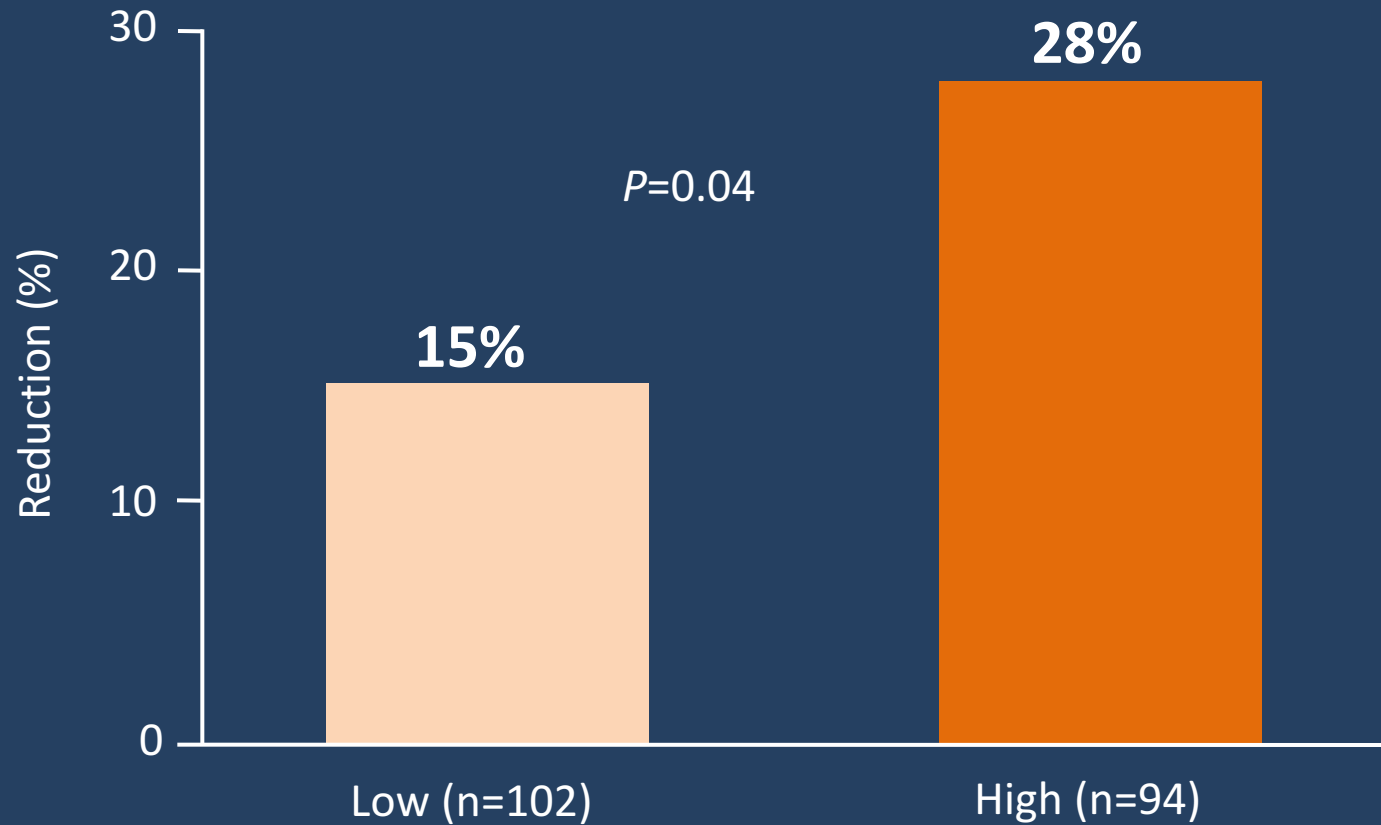
Vagus Nerve Stimulation Study Group. *Neurology*. 1995;45:224-230.



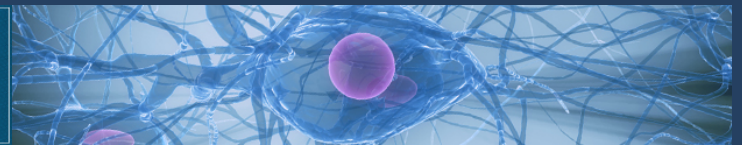
VNS Therapy Clinical Trial: E05

Seizure Reduction

Mean Decrease in Seizure Frequency Versus Baseline



Handforth A, et al. *Neurology*. 1998;51:48-55.

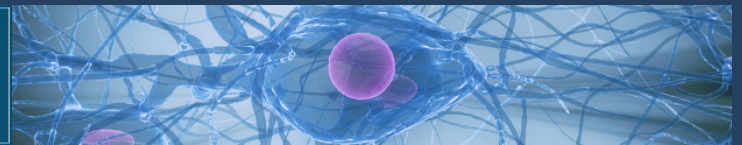


VNS Therapy Clinical Trial: E05

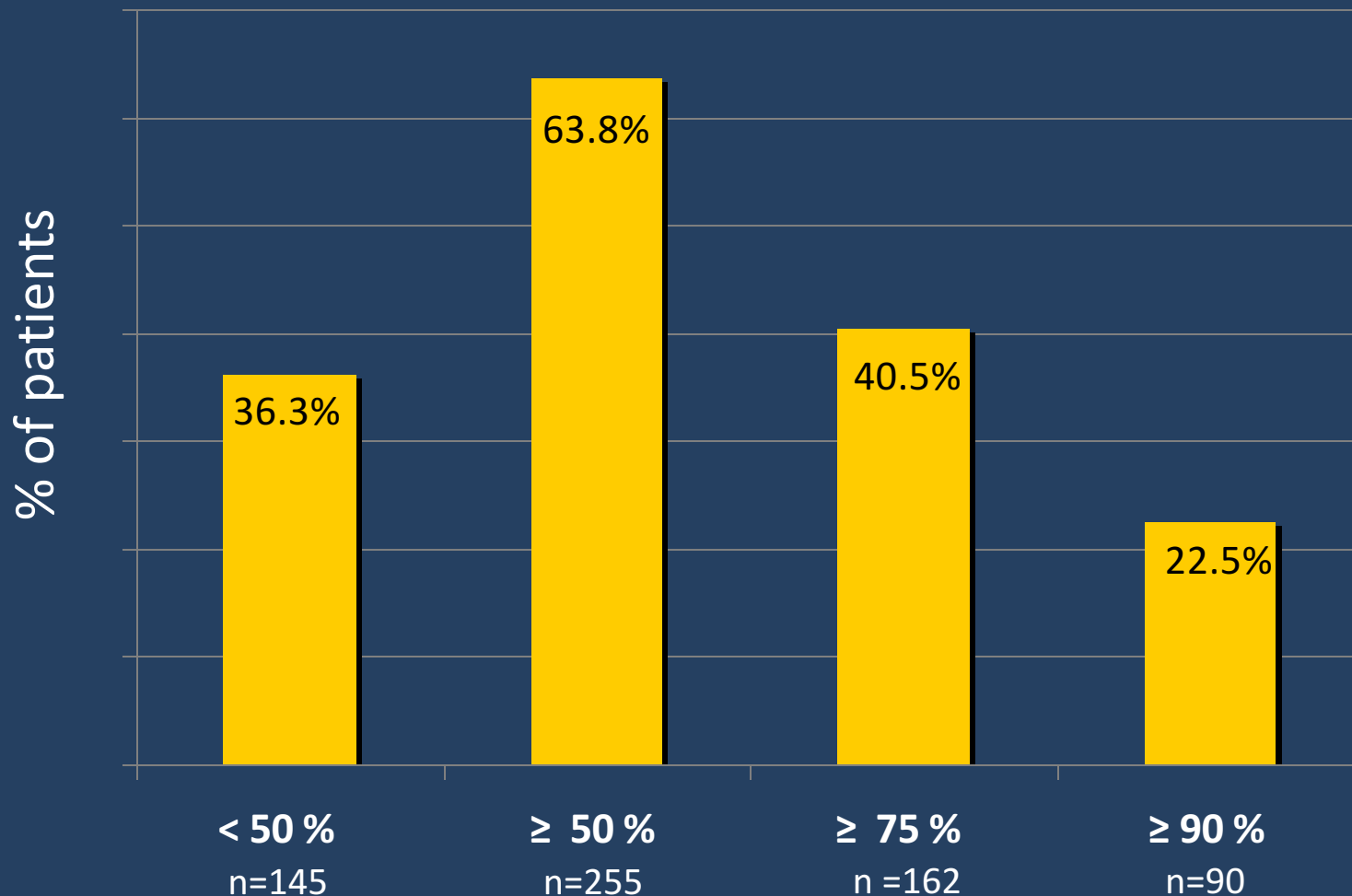
Adverse Events

- Adverse events (occurring in $\geq 10\%$ of patients)
 - Voice alteration 66%
 - Cough 45%
 - Pharyngitis 35%
 - Dyspnea 25%

Handforth A, et al. *Neurology*. 1998;51:48-55.



Responder rates (avg 5 years of follow up)

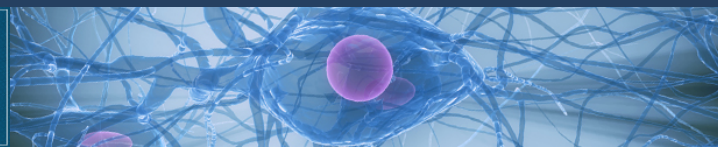


Elliott RE, et al. Epilepsy & Behavior 20: 57-63, 2011



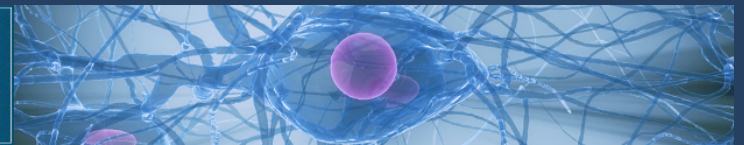
SCHOOL OF MEDICINE
AND HEALTH SCIENCES

The Department of Neurology



Conclusion from NYU data

- Responder Rate of VNS is **60%** when used as part of a multimodality treatment plan including aggressive medication regimens and epilepsy surgery
 - *(more than 60% of patients with treatment-resistant epilepsy experienced at least a 50% reduction in seizure burden)*



VNS Therapy in Patients < 18 Years

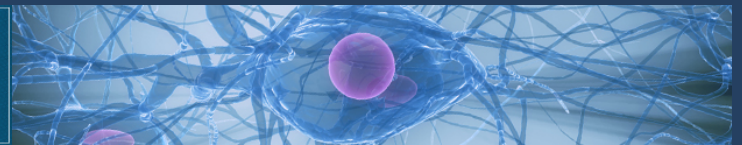
29% of all patients treated with VNS Therapy are younger than 18 years

70.5% of them were developmentally delayed

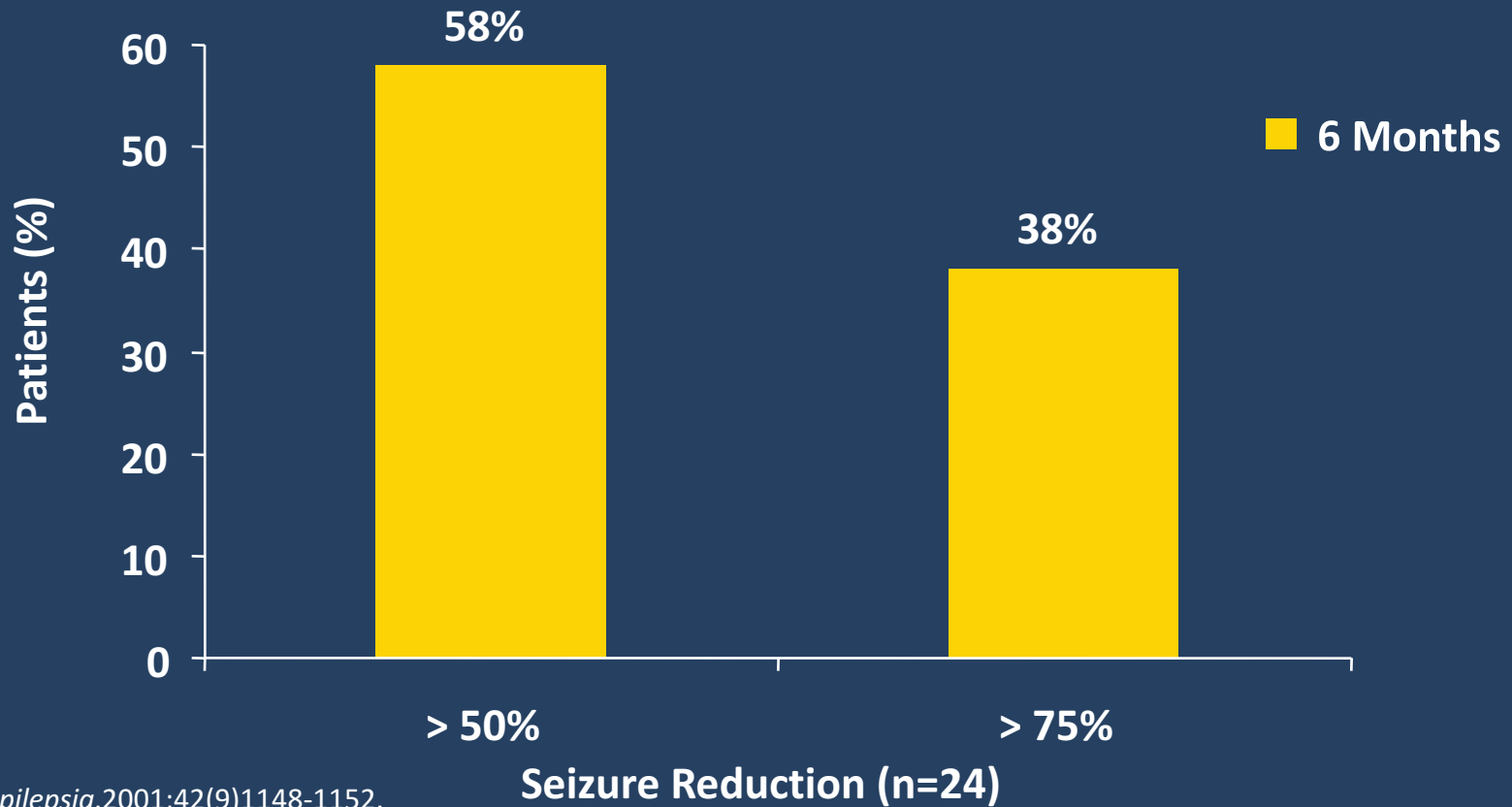
61% of these patients had at least a 50% reduction in seizure frequency at 12 months**

Wheless J. et al. *Neurology* 2002;59 (Suppl 4) S21-S25.

**2002 Patient Outcome Registry Data (N=125).



VNS Long-Term Seizure Control Response Rates in Pediatric Patients With Lennox-Gastaut Syndrome

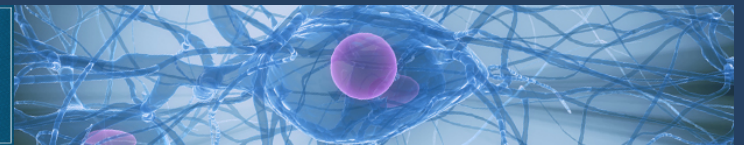


Frost M. *Epilepsia*.2001;42(9)1148-1152.

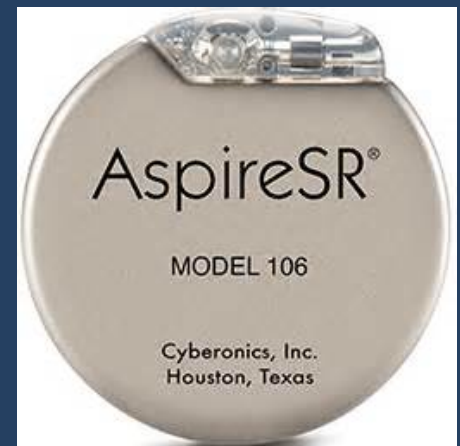
GW

SCHOOL OF MEDICINE
AND HEALTH SCIENCES

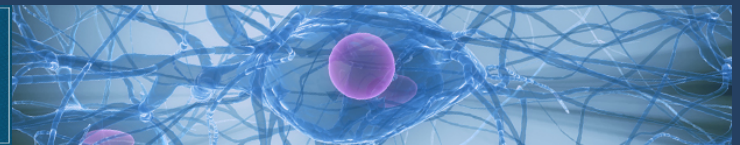
The Department of Neurology



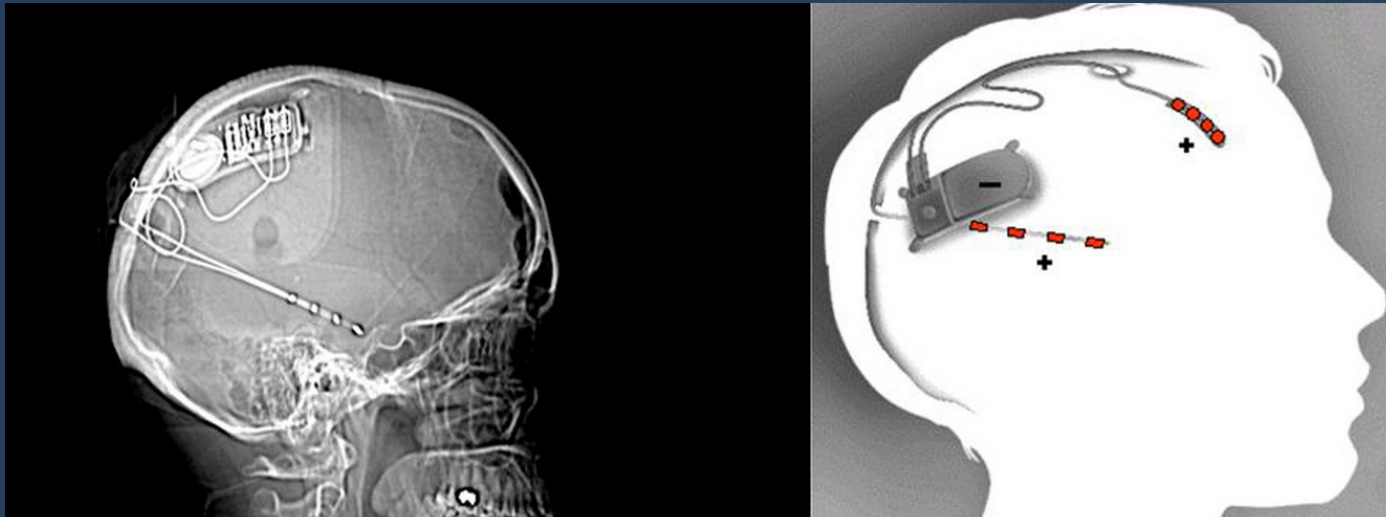
Aspire SR



- Clinical studies of AspireSR:
 - Some seizure cessation, improvement of seizure severity, and improved postictal recovery
- 82% of patients with epilepsy may have an increase in their heart rate associated with a seizure
- Side effects (> 5%): dysphonia, convulsion, headache, oropharyngeal pain, depression, dysphagia, dyspnea, exertional dyspnea, stress, and vomiting

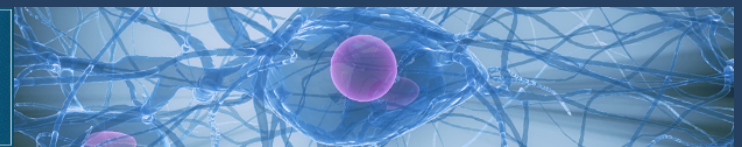


Responsive Neurostimulation



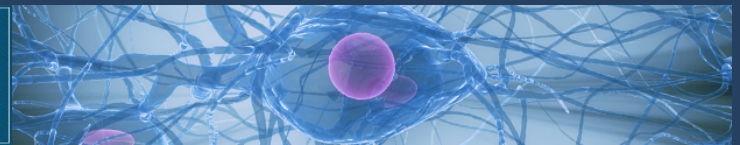
- Bursts of stimulation can interrupt seizures and ADs
- Multicenter, double-blind RCT in 191 patients: Seizure reduction of 37.9% vs. 17.3% in controls
- 29% of patients (and 53% of patients at 2 years) showed >50% seizure reduction

Jobst 2010 Epilepsy Res

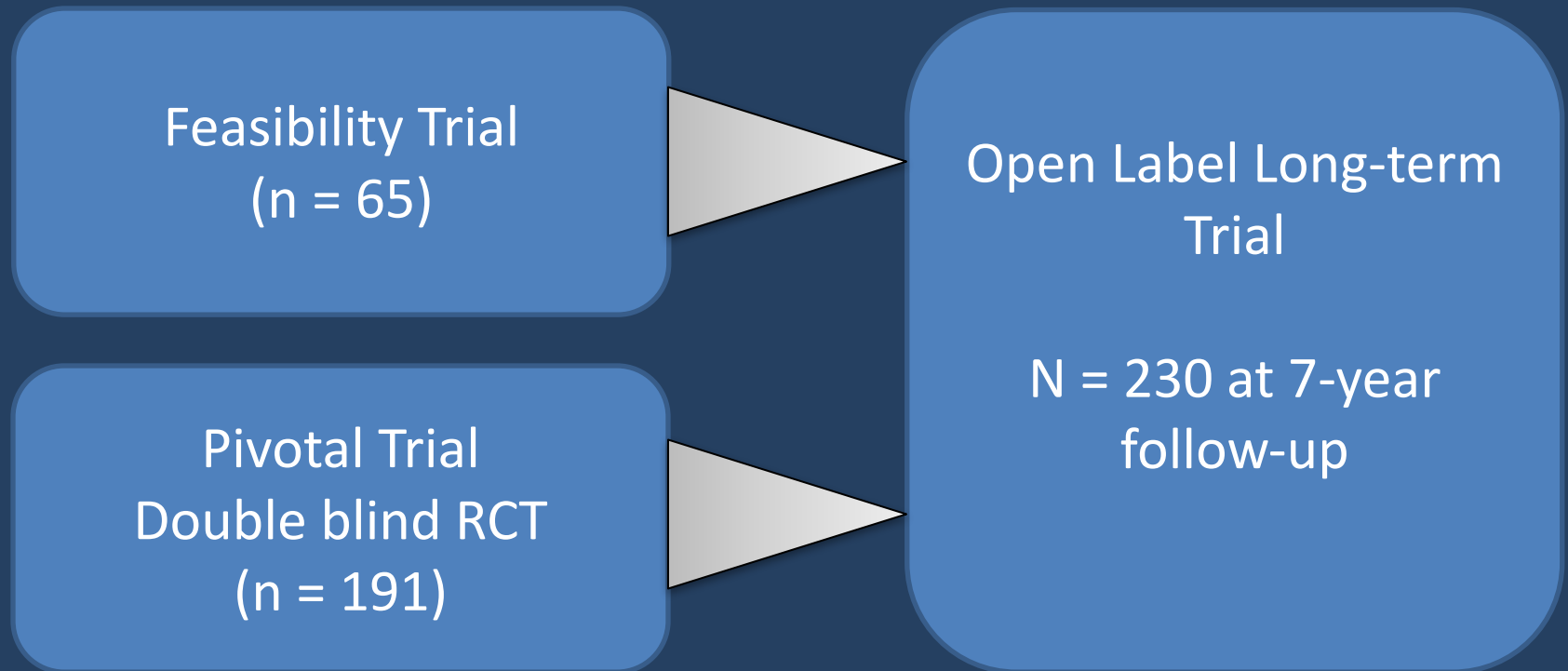


FDA Indication

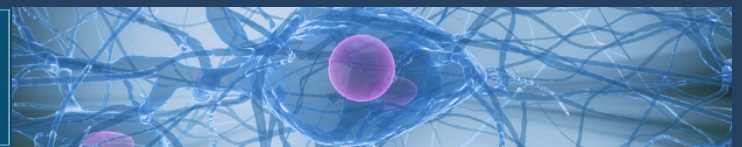
- The RNS[®] System is an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than 2 epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and/or secondarily generalized seizures). The RNS[®] System has demonstrated safety and effectiveness in patients who average 3 or more disabling seizures per month over the three most recent months (with no month with fewer than two seizures), and has not been evaluated in patients with less frequent seizures.



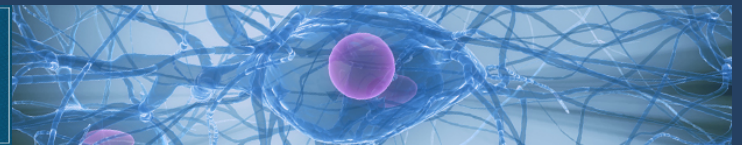
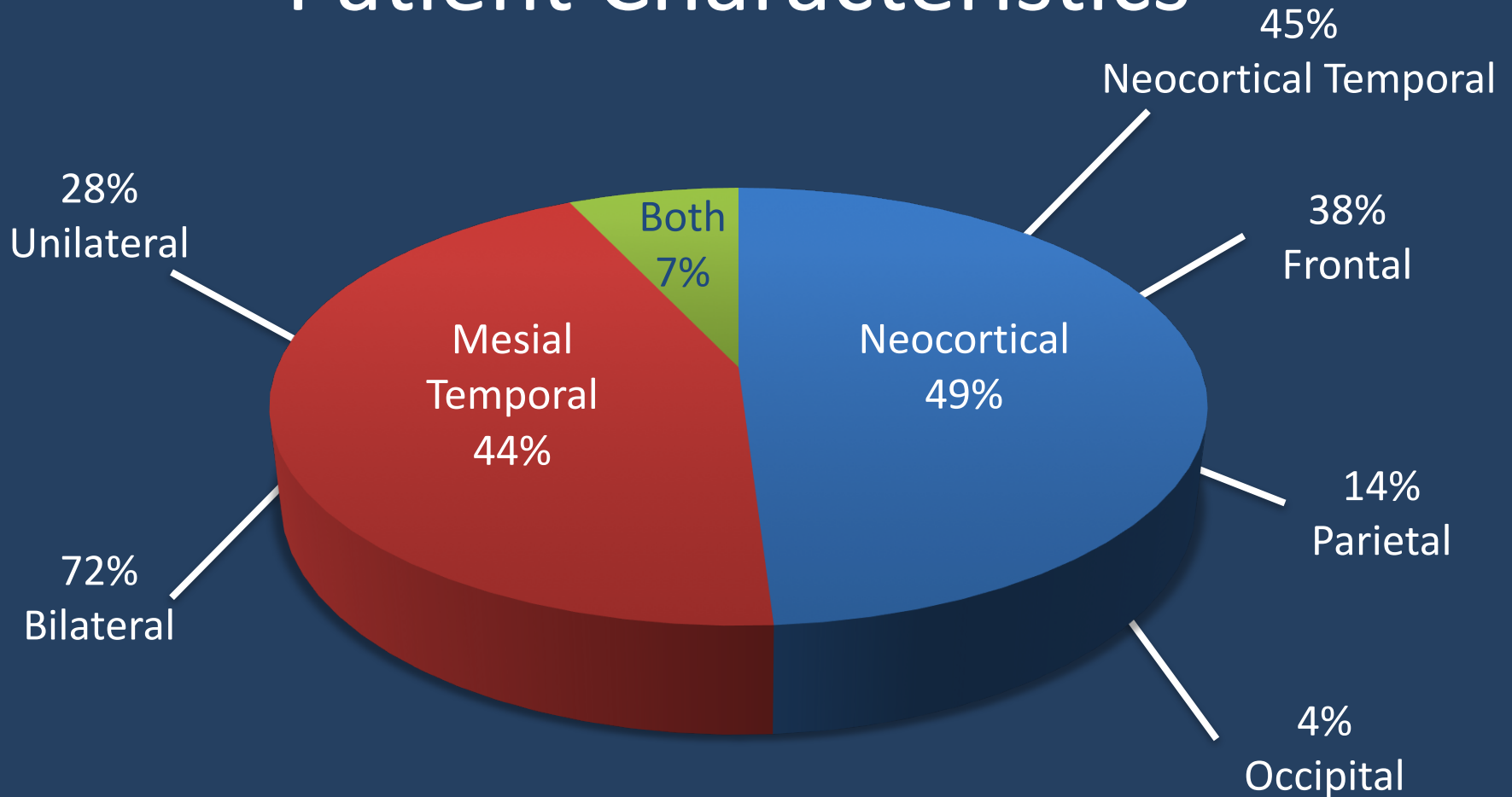
Clinical Trials



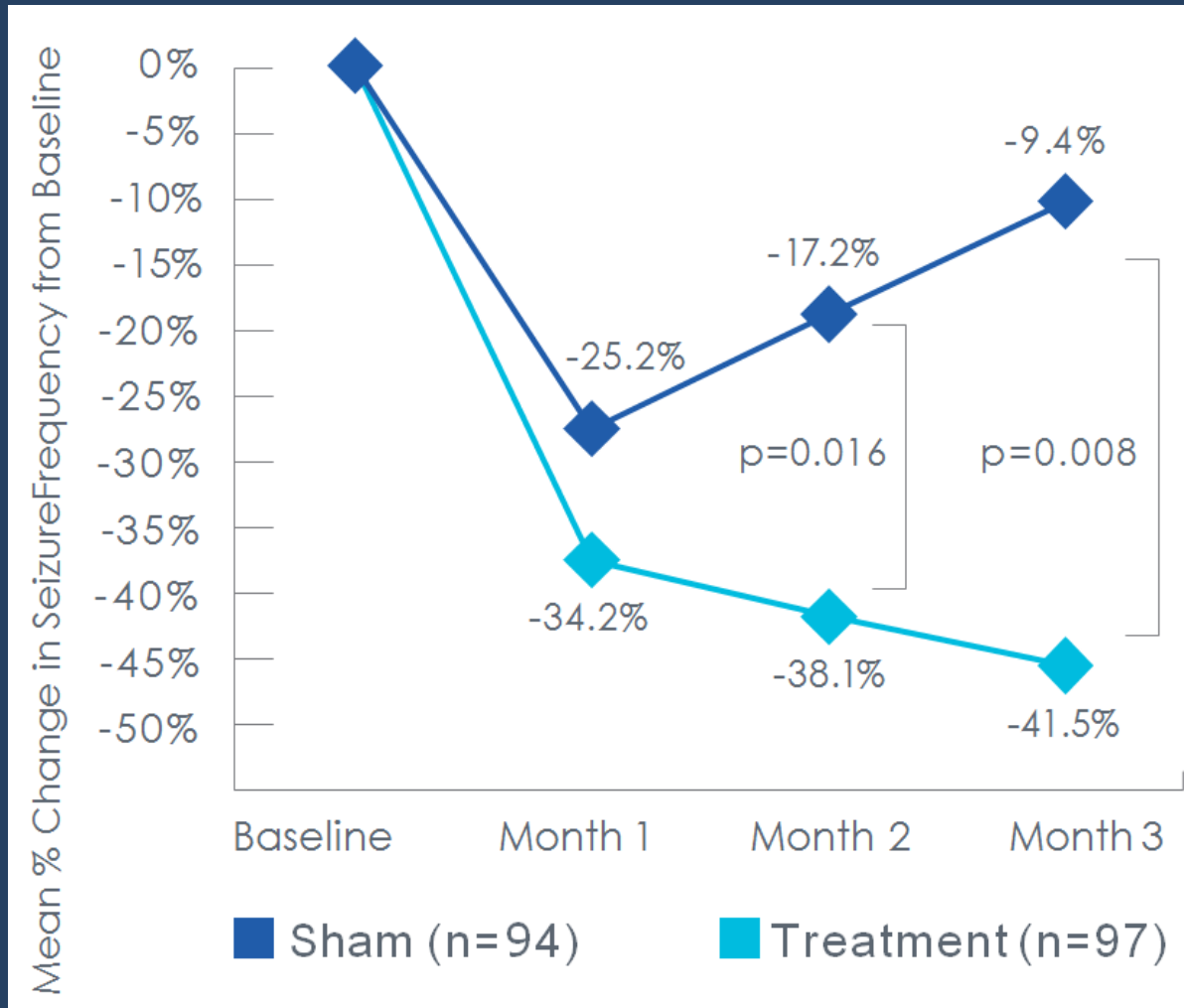
Safety and efficacy of RNS: Class I Evidence



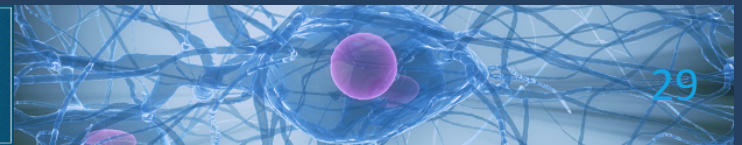
Patient Characteristics



RNS System Pivotal Trial



Morrell M et al., *Neurology* (2011)



Side Effects

**Average Stimulation
Duration**

**Stimulation Related
Side Effects**

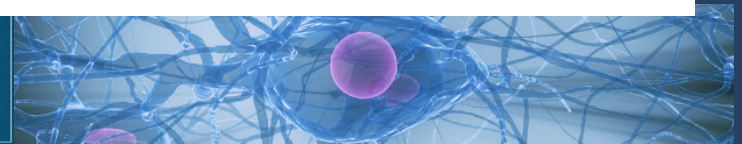
Assessed at 1 Year

RNS[®] SYSTEM

< 6 min/day²

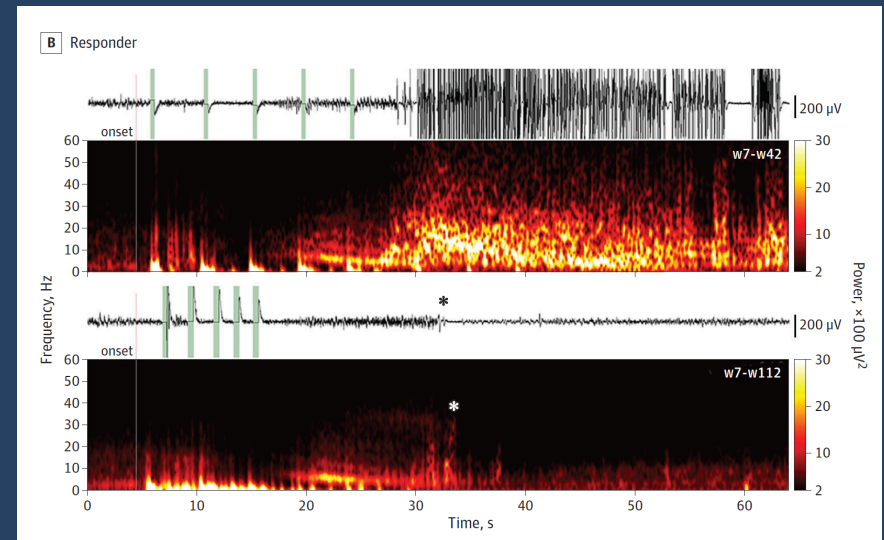
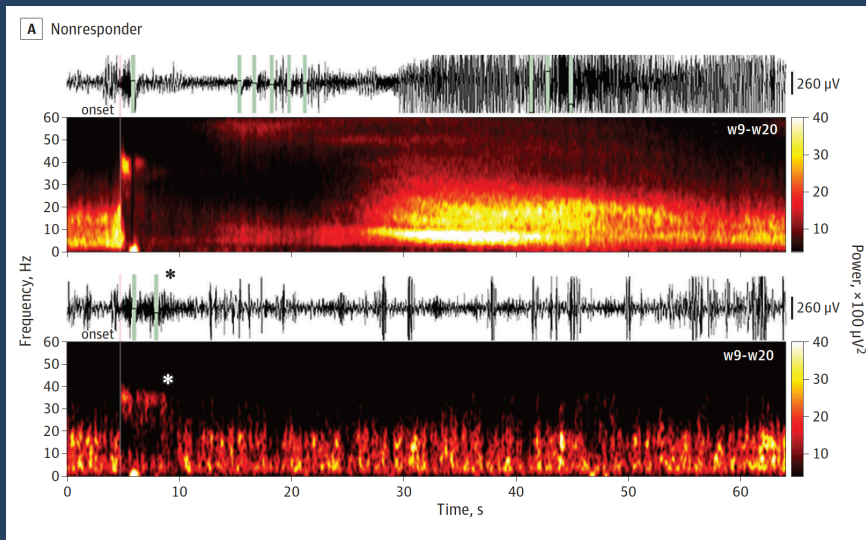
Mostly single events⁵

- Dysesthesia (4%)
- Photopsia (4%)
- Paresthesia (1%)
- Muscle twitching (0.5%)

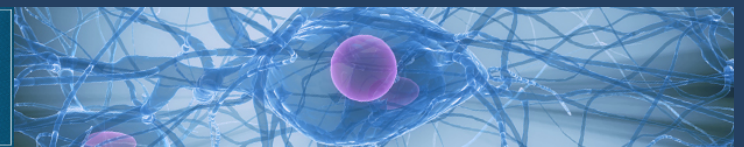


Association of Closed-Loop Brain Stimulation Neurophysiological Features With Seizure Control Among Patients With Focal Epilepsy

Vasileios Kokkinos, PhD; Nathaniel D. Sisterson, BA; Thomas A. Wozny, MD; R. Mark Richardson, MD, PhD

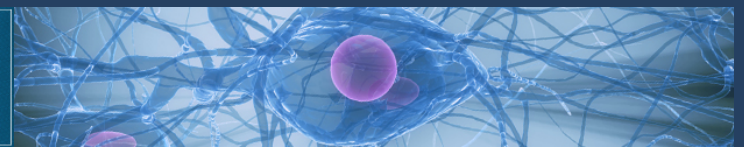
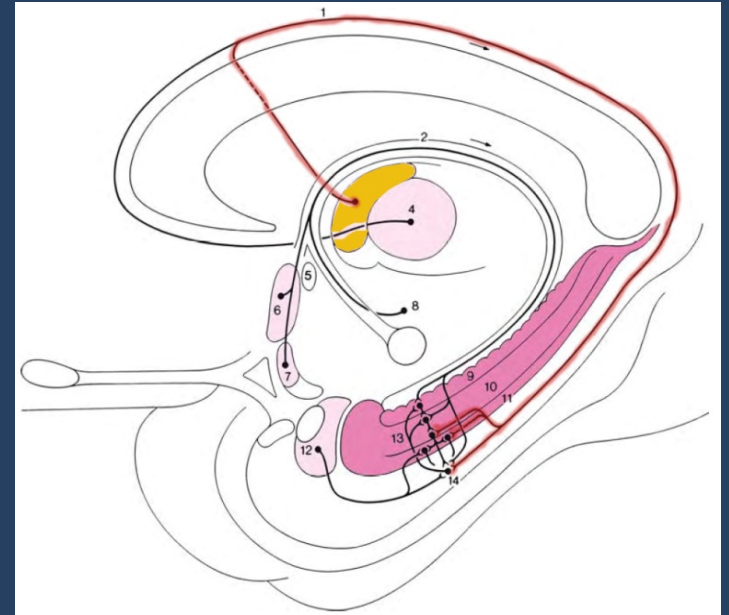


Kokkinos et al. *JAMA Neurol.* 2019



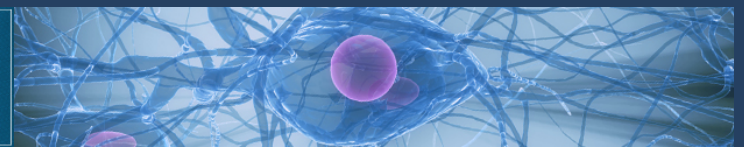
Anterior Thalamic Nucleus Stimulation

- Broad connections
- MTT interruption prevents PTZ seizures in guinea pigs
- Cooper *et al.* (1984): seizure reduction in 5 of 6 patients
- Open label trials suggested 50% seizure reduction

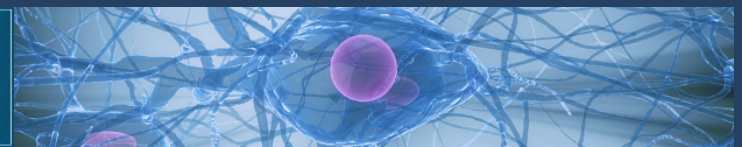
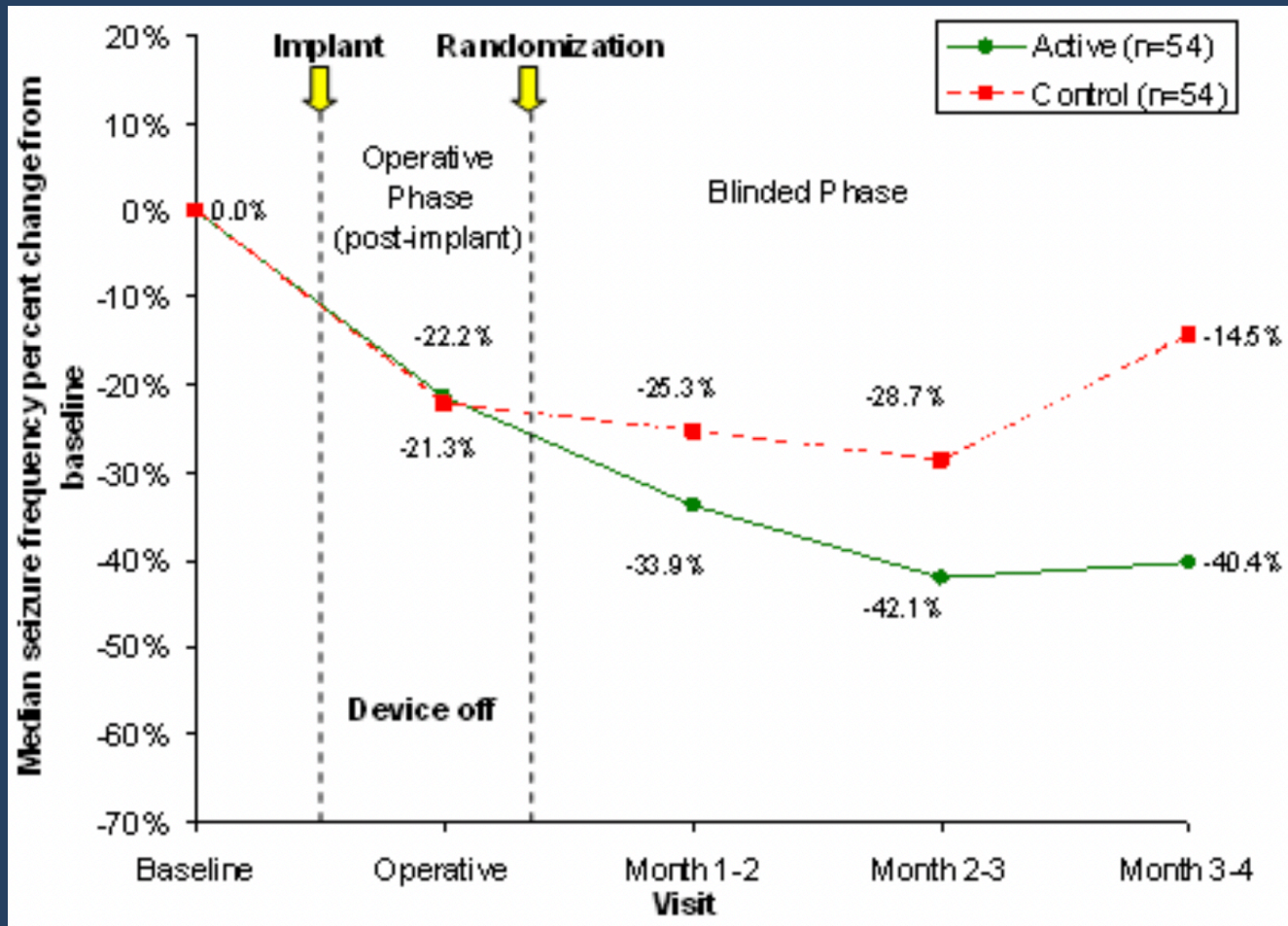


Anterior Thalamic Nucleus Stimulation

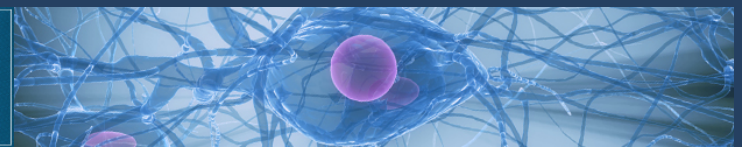
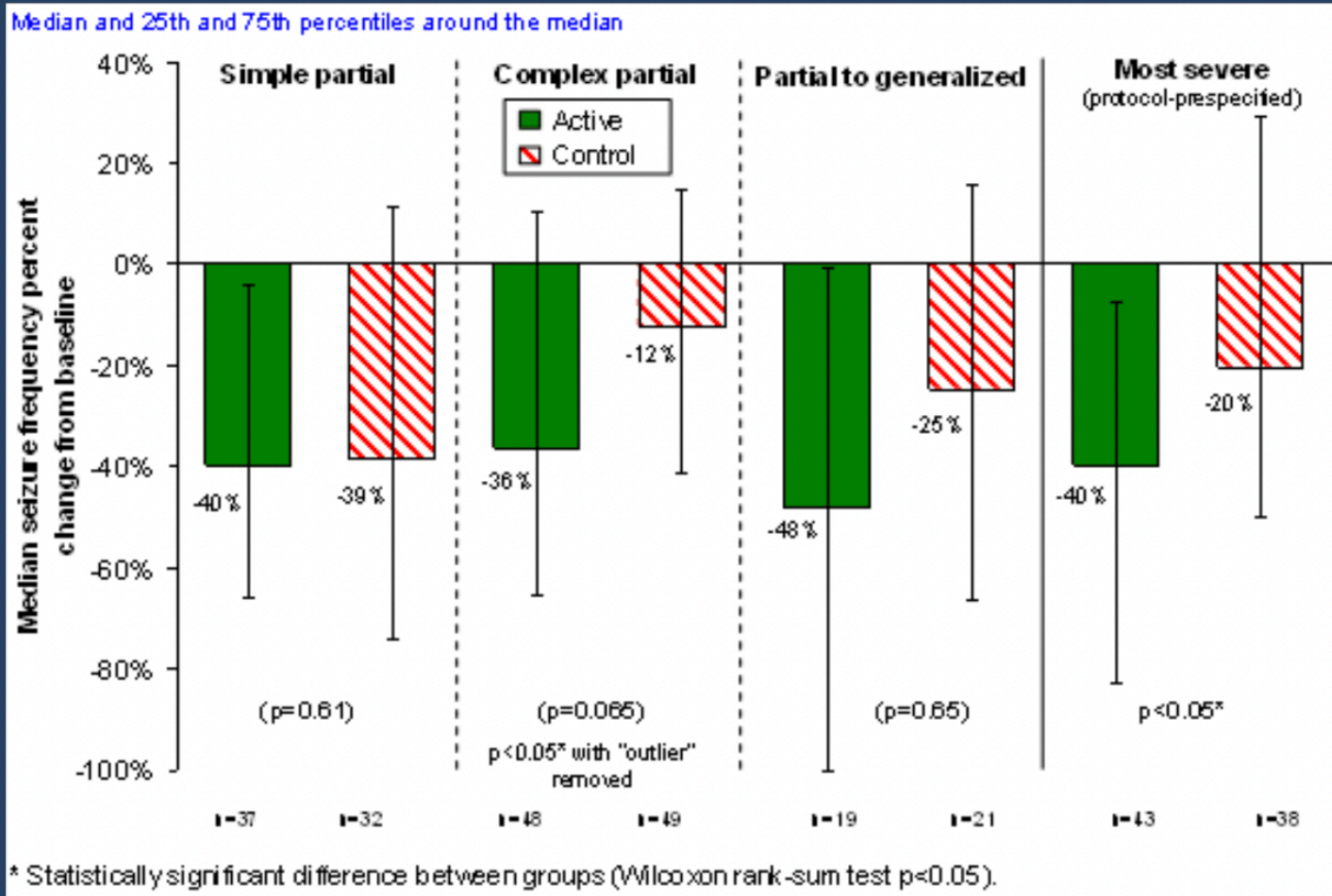
- SANTE Trial:
 - 110 patients with focal seizures
 - 3 months of stimulation: 29% more seizure reduction in DBS group in 3rd month
 - 40.4% seizure reduction (vs. 14.5% in controls)
- By two years: 54% of patients showed >50% reduction
- Depression and memory problems



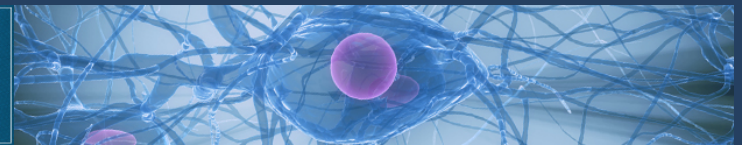
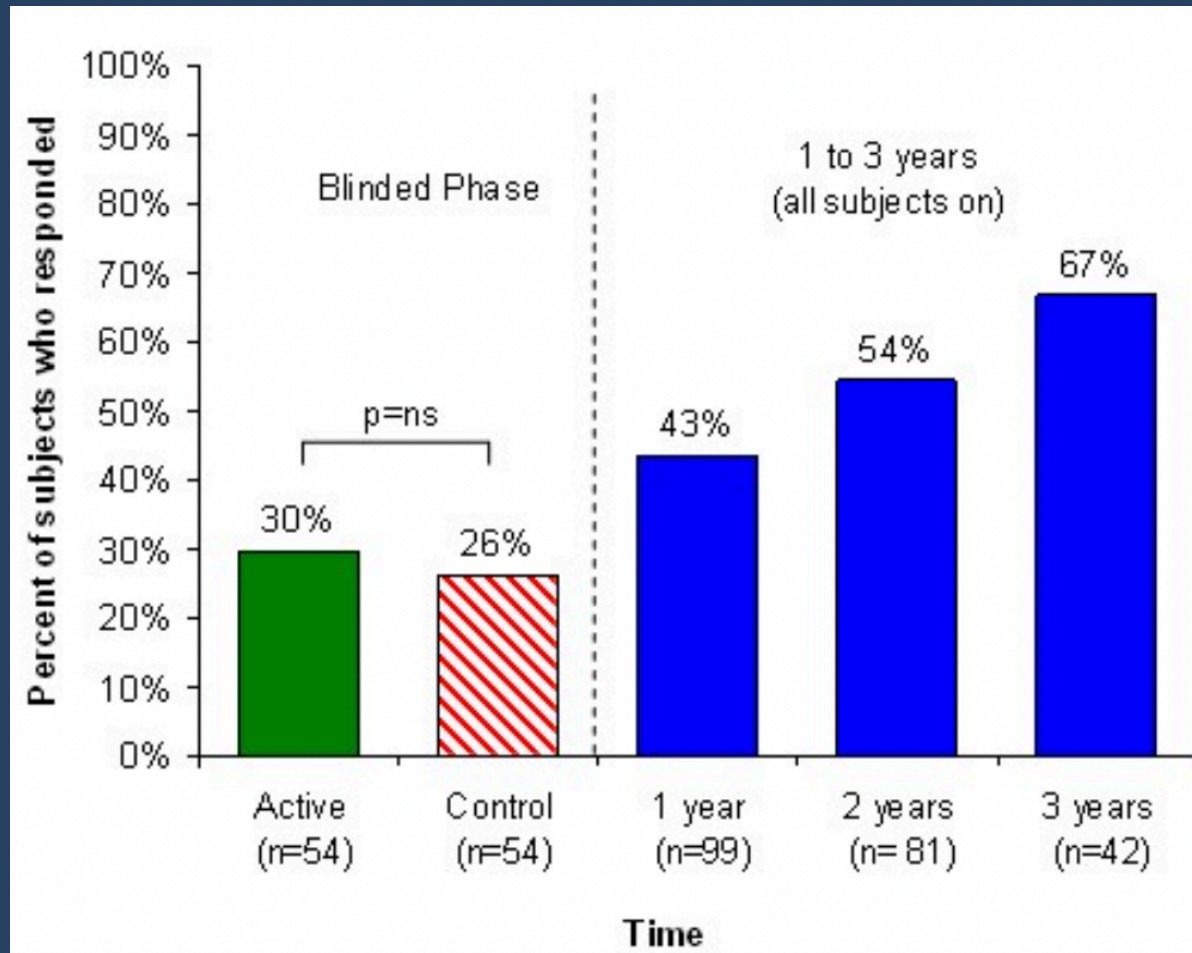
Blinded Phase



By Seizure Type



Over Time



Deep brain stimulation of anterior nucleus thalami disrupts sleep in epilepsy patients

***,¹Berthold R. Voges, †,¹Friedhelm C. Schmitt, ‡Wolfgang Hamel, *Patrick M. House, †,§Christian Kluge, ¶Christian K. E. Moll, and *Stefan R. Stodieck**

Epilepsia, 56(8):e99–e103, 2015

High-frequency electrical stimulation of the anterior thalamic nuclei increases vigilance in epilepsy patients during relaxed and drowsy wakefulness

Iancu Bucurenciu¹  | Anke Maren Staack¹ | Alireza Gharabaghi² | Bernhard J. Steinhoff¹

Epilepsia. 2020 May 9

