# Neuro-modulatory Devices in Epilepsy Treatment
# Approved Alternative Surgical Therapies

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Cleveland Clinic Epilepsy Update & Review

DISCLOSURES:

Grant/Research Support:

- NIH RO1 (RO1NS089212) A Brain Atlast for Mapping Connectivity in Focal Epilepsy
- NIH RO1 (RNS097719A) Nomogram to Predict Seizure Outcome
- NeuroPace Long term Treatment Trial & Post Approval Study
- Medtronic Post Approval Study
- Brain Sentinel

Speaker's Bureau:

- NeuroPace

Consultant:

- NeuroPace

Major Shareholder:

- None

# Objectives

Review neuromodulatory therapy in epilepsy and their efficacy, adverse effects and safety data for:

- Vagus nerve stimulation
- Brain responsive neurostimulation
- Deep brain stimulation of the anterior nucleus of thalamus

# Neuromodulation

## Targets for Stimulation

- Cerebellum
- Hippocampus
- Subthalamic Nucleus
- Caudate Nucleus
- CentroMedian Nucleus
- Anterior Nucleus of the Thalamus
- Various individualized cortical sites
- Vagus Nerve
- Trigeminal Nerve

## Types of Stimulation

- Open Loop
- Closed Loop

## Safety of Stimulation

- **Electrical stimulation of brain tissue**
  - **Less than 30μC/cm$^2$/phase**

Nune G et al. Curr Treat Opions Neurol 2012

# Neuro-Modulation

**Versus Medicine/Surgery**

- Lack typical systemic or neurological sided effects
- Stimulation related side effects
  - Intracranial stimulation
  - VNS stimulation
- Surgically implanted
  - Surgical complications
  - Battery replacement
  - Less invasive
  - Reversible

**Versus Medicine/Surgery**

- Improvement of efficacy over time

Nune G et al. Curr Treat Opions Neurol 2012

# Parameters of Stimulation

- Anode/Cathode contacts
- Stimulation Frequency
- Stimulation Duration
- Stimulation Intensity
- Stimulation Field
- Pulse Duration

# Vagus Nerve Stimulation (VNS)

# VNS

- FDA approval in 1997
- Indicated for adjunctive therapy for drug resistant partial epilepsy
  - Commonly used in generalized epilepsy
  - Approved for depression
    - But not reimbursed
- In adults and adolescents over 4 years (approved June 2017)
- More than 100,000 patients implanted

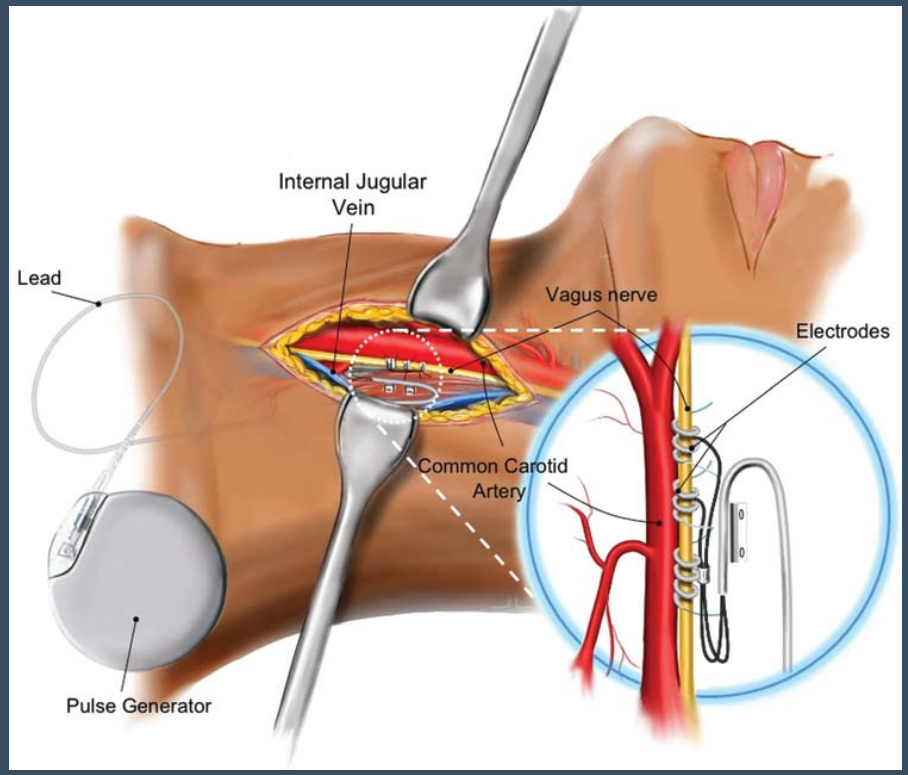
Wheless JW et al. Epilepsy Behav 2018

# Mechanism

- Unknown
- Vagus nerve parasympathetic nerve also part of the interoceptive pathway
- Stimulation ascending via brainstem nuclei and diffusely modulating cortical excitability
  - Patients with good efficacy showed decrease metabolic activity on functional imaging studies bilaterally during ON stimulation

Krishna V et al. Neurosurg Clin N Am 2016

# Vagus Nerve Stimulation




- Open Loop
  - Optional cardiac detection (closed loop adjunct)
    - Provides stimulation to tachycardia (at least 20%)
    - AspireSR model
    - June 2015
  - Patient activated by magnet
- Subcutaneous implantation
  - Generator in left subclavicular fossa
  - Electrode left vagus

Fridley J et al. Neurosurg Focus 2012

Nune G et al. Curr Treat Opions Neurol 2012

**TABLE 1: Summary of Class I, II, and III evidence of VNS efficacy in treating epilepsy***

| Study | No. of Cases | Seizure Type | Notes | Follow-Up | No. of Centers | Median or Mean % Seizure Reduction | % Patients w/ >50% Reduction† |
|---|---|---|---|---|---|---|---|
| Class I evidence — Blinded randomized control | | | | | | | |
| Ben-Menachem et al., 1994 | 114 | partial | high vs low stim comparison | 3 mos | multi | 25 vs 6 | 31 |
| Handforth et al., 1998 | 196 | partial | high vs low stim comparison | 3 mos | multi | 28 vs 15 | 23 |
| Amar et al., 1998 | 17 | partial | high vs low stim comparison | 3 mos | single | 71 vs 6 | 57 |
| Class II evidence — Non-blinded randomized control | | | | | | | |
| Scherrmann et al., 2001 | 28 | mixed | 2 stim paradigms | NR | single | 30 overall | 45 |
| DeGiorgio et al., 2005 | 61 | partial | 3 stim paradigms | 3 mos | multi | 26 overall | 29 |
| Class III evidence — Prospective observational clinical studies | | | | | | | |
| Ben-Manachem et al., 1999 | 64 | mixed | | 3–64 mos | single | NR | 45 |
| Parker et al., 1999 | 15 | mixed | children w/ encephalopathy | 1 yr | single | 17 | 27 |
| Labar et al., 1999 | 24 | gen | | 3 mos | single | 46 | 46 |
| DeGiorgio et al., 2000 | 195 | mixed | | 12 mos | multi | 45 | 35 |
| Chavel et al., 2003 | 29 | partial | | 1–2 yrs | single | 53 | 54‡ |
| Vonck & colleagues, 1999 & 2004 | 118 | mixed | | >6 mos | multi | 55 | 50 |
| Majoie & colleagues, 2001 & 2005 | 19 | mixed | children w/ encephalopathy | 2 yrs | single | 20.6 | 21 |
| Huf et al., 2005 | 40 | NR | adults w/ low IQ | 2 yrs | single | 26 | 28 |
| Kang et al., 2006 | 16 | mixed | children | >1 yr | multi | 50 | 50 |
| Ardesch et al., 2007 | 19 | partial | | >2 yrs | single | 25§ | 33§ |

* gen = generalized; multi = multiple; NR = not reported; stim = stimulation.
† Refers to "high" stimulation group only.
‡ At 1 year.
§ At 2 years.

Responder Rate

Therapeutic Sham

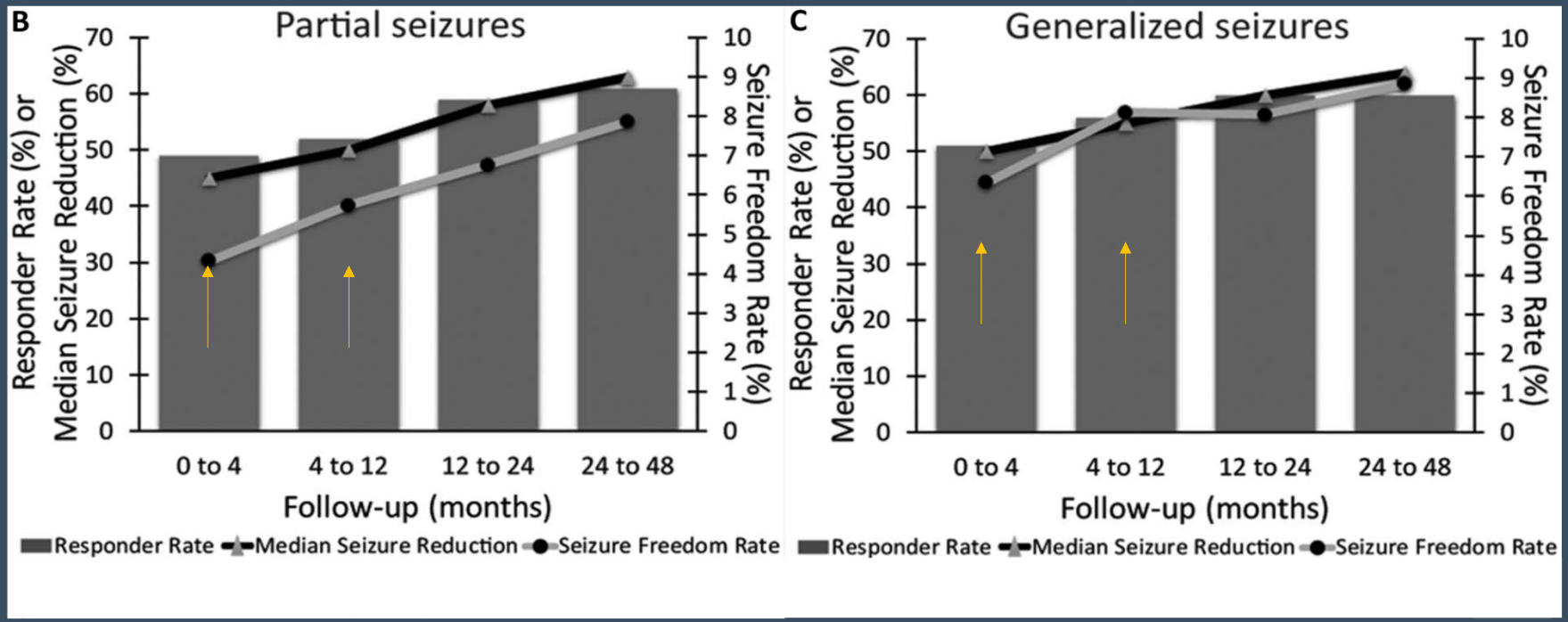
**TABLE 1.** *Stimulation parameters*

| Parameter | High Typical | High Range | Low Typical | Low Range |
|---|---|---|---|---|
| Output current (mA) | 1.5 | 0.25–3.0 | 1.25 | 0.25–3.0 |
| Frequency (Hz) | 30 | 20–50 | 1 | 1–2 |
| Pulse Width (μs) | 500 | 500 | 130 | 130 |
| On time (s) | 30 | 30–90 | 30 | 30 |
| Off time (min) | 5 | 5–10 | 90 | 60–180 |
| Magnet parameters | | | | |
| Output current (mA) | 1.5 | 0.5–3.0 | 0 | 0 |
| On time (s) | 30 | 30–90 | NA | NA |
| Pulse width (μs) | 500 | 500 | NA | NA |

NA, Magnet output was set to 0 in the low group: no current delivered.

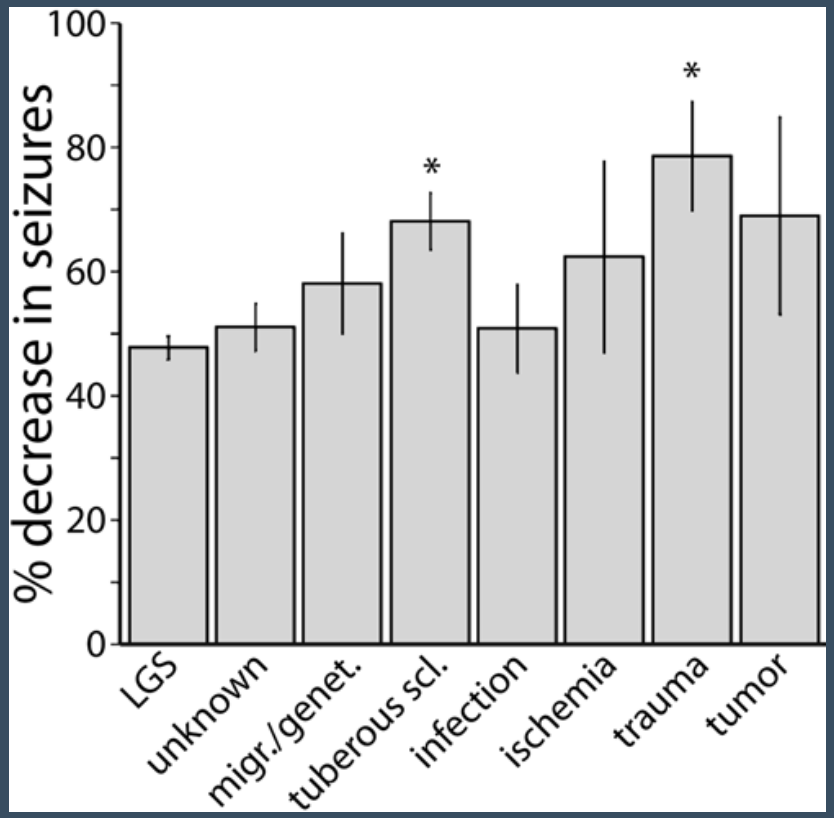
Englot DJ et al. J Neurosurg 2011

# Seizure Free, Responder Rate, Engle Classification




Englot DJ et al. J Neurosurg 2016

# Efficacy



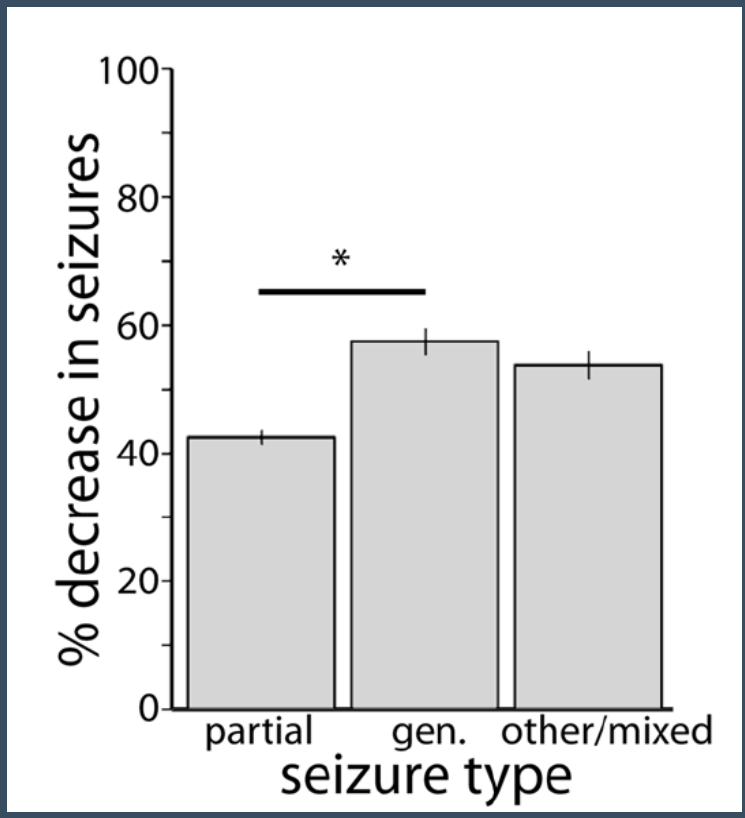




**TABLE 2: Seizure outcomes reported by Engel class**

| | 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 |

* Only individuals for whom Engel classification could be determined are tallied.

Englot DJ et al. J Neurosurg 2011

# Adverse Effects

**TABLE 3: Incidence of adverse effects of VNS for epilepsy**

| Parameter | Ben-Menachem et al., 1994 | Handforth et al., 1998 | DeGiorgio et al., 2000 |
|---|---|---|---|
| no. of patients | 114 | 196 | 195 |
| follow-up (mos) | 3 | 3 | 12 |
| adverse effect (% cases) | | | |
| hoarseness | 37 | 62 | 55 |
| cough | 7 | 21 | 15 |
| paresthesia | 6 | 25 | 15 |
| pain | 6 | 17 | 15 |
| dyspnea | 6 | 16 | 13 |
| headache | 2 | 20 | 16 |
| infection | NR | 4 | 6 |

Serious adverse effects: Vocal cord paralysis 1%; infection 1.5%

Englot DJ et al. J Neurosurg 2011

# VNS Stimulation Parameters

- Begin 0.25mA
  - Gradually increase 0.25mA steps
  - Up to 1-1.5mA or more
- Frequency 20-30Hz
- Pulse width 250-500 μs
- 30 seconds on
- 5 minutes off

- Side effect may improve
  - Reduction of pulse width to 250μs
  - Reduction of frequency to 20hz
- Improve efficacy
  - Increase duty cycle by reducing off time
    - Do not exceed 50% duty cycle

Nune G et al. Curr Treat Opions Neurol 2012

# Responsive Neural Stimulation (RNS)

# Responsive Neural Stimulation

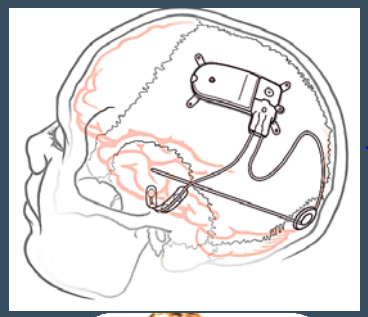
- Medically refractory focal epilepsy
  - Failure of more than 2 ASD
- 18 years or older
- FDA approved 2013
- Implantation
  - Device within the skull
  - Combination of 1-2 depths or subdural strips over seizure focus
- No more than two (2) ictal onsets

- Closed loop
- Stimulation usually does not cause appreciable symptoms
- Stores ECoG
- Seizure detections algorithms programmed

Nune G et al. Curr Treat Opions Neurol 2012

# The RNS® System

**Neurostimulator and Leads**



**Programmer**

**Patient Data Management System (PDMS)**


**Remote Monitor**

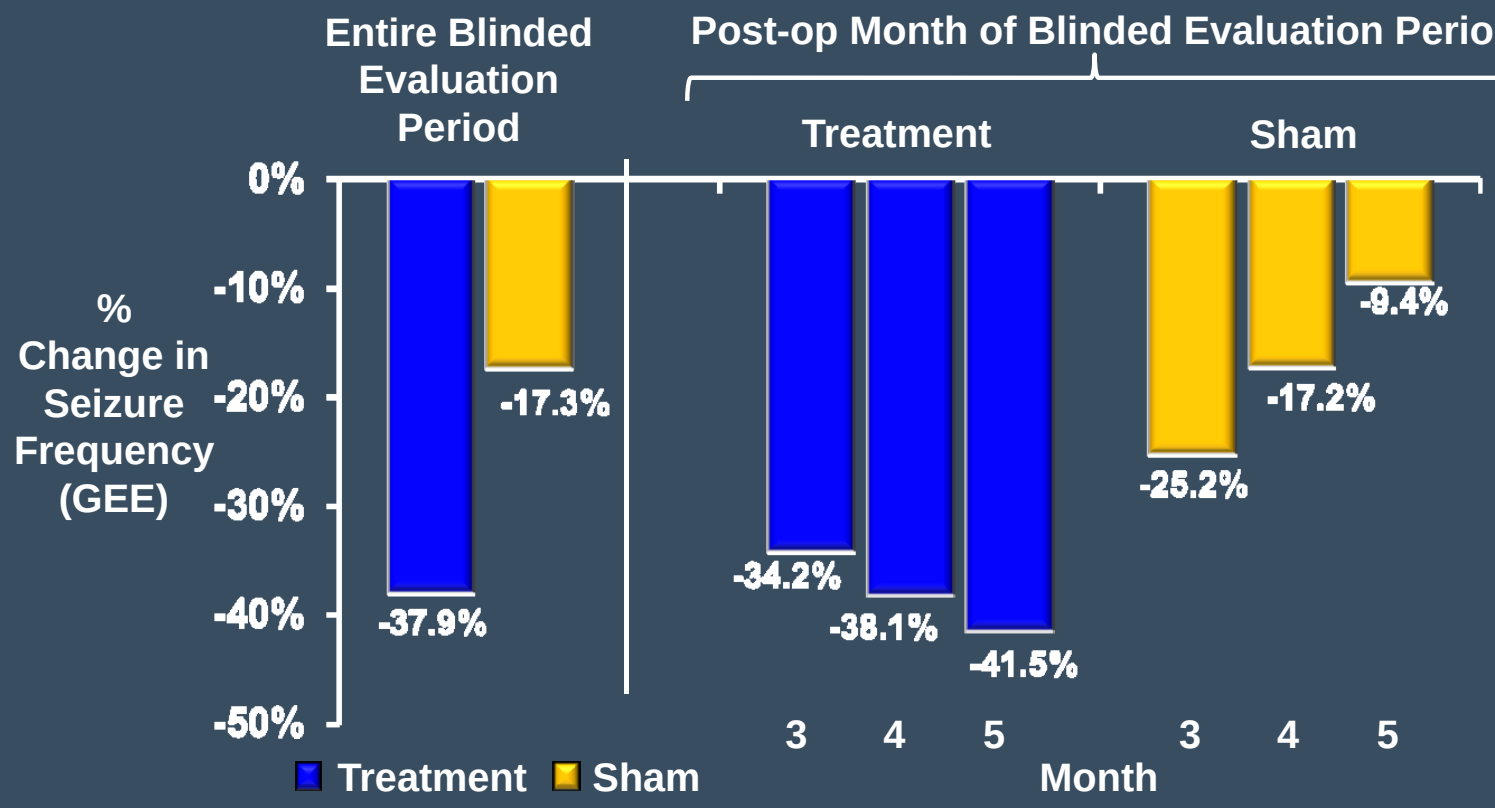
# RNS Stimulation Parameters

- Five sequential stimulations
  - Rapid succession
  - Each two bursts
- Starting 1mA
  - Adjust up to 3μC/cm$^2$/phase
- Pulse width 160μs
- Frequency 200 Hz
- Burst duration 100ms

- Polarity of electrodes can be configured
  - Close bipolar within electrode (+-+- and +-+-)
  - Wide bipolar across electrode (+++ and ----)
  - From electrode to generator cover

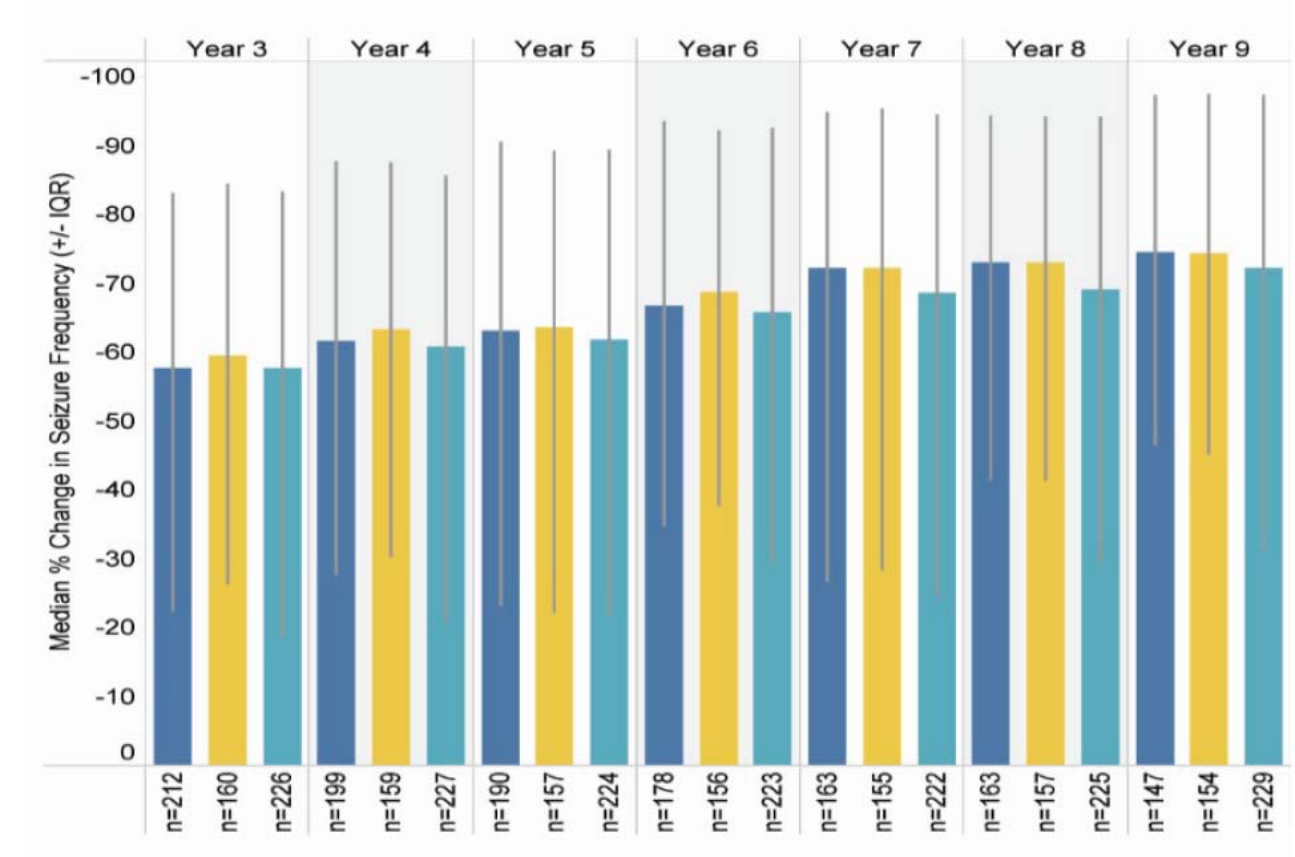
Nune G et al. Curr Treat Opions Neurol 2012

# Primary Effectiveness Endpoint




Morrell M et al. Neurology 2011

# 75% Median Seizure Reduction at Year 7




Analysis

- At least 91 days diary
- Constant cohort
- LOCF

In year 7, 35% of patients had seizure reduction of ≥90%

Similar response regardless of

- Number of seizure foci
- Seizure onset location
- MRI abnormality
- Prior epilepsy surgery
- Prior VNS
- Prior intracranial monitoring

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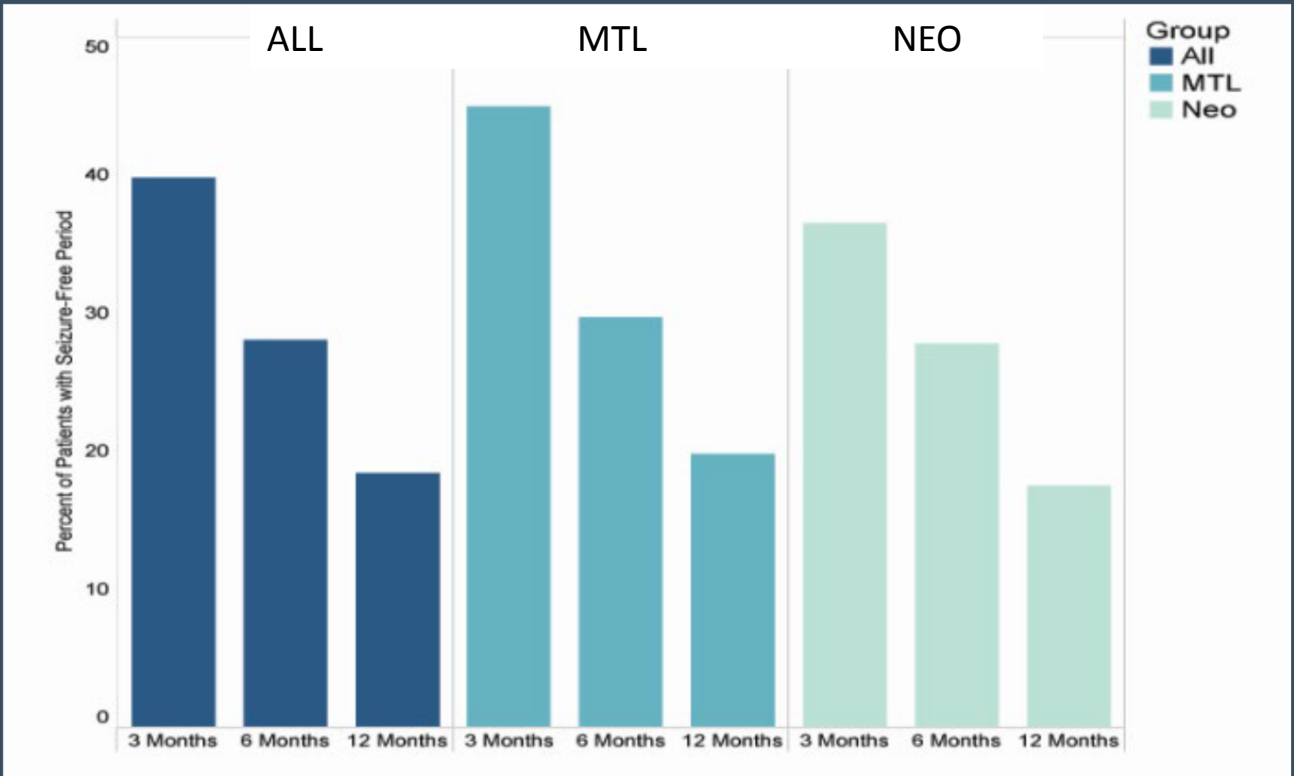
# Meaningful Seizure Free Periods




28% (72/256) had at least 1 period of ≥ 6 months of seizure freedom

18% (47/256) had at least 1 period of ≥ 12 months of seizure freedom

- These patients had an average of 3.2 years as the longest consecutive period of seizure freedom

# Pivotal Study: SAEs Affecting ≥ 2.5% of Subjects, 2 Yrs Post-Implant

| | % Subjects with events (# subjects) | % Subjects with Device-Related[1] Events (# subject) |
|---|---|---|
| **Related to the implanted device** | | |
| Implant site infection | 3.7% (7) | 3.7% (7) |
| Device lead revision | 3.7% (7) | 2.1% (4) |
| Device lead damage | 2.6% (5) | 2.6% (5) |
| **Related to seizures** | | |
| Complex partial seizures increased | 5.2% (10) | 3.1% (6) |
| Tonic-clonic seizures exacerbated | 3.7% (7) | 0.5% (1) |
| Tonic-clonic seizures increased | 3.7% (7) | 2.6% (5) |
| **Other serious adverse events** | | |
| EEG monitoring | 7.3% (14) | 0.5% (1) |
| Death | 3.1% (6) | 0.5% (1) |
| Therapeutic agent toxicity[2] | 2.6% (5) | -- |

[1] Includes device-related and device-relation uncertain
[2] Four related to antiepileptic medication and 1 to acetaminophen toxicity

Morrell M et al. Neurology 2011

- The risk for infection is 4.1% with each RNS neurostimulator procedure
  - Over 1895 patient-implant years, serious device-related implant site infection was reported in 12.1%
  - All but one of the infection involved only soft tissue and cultures most often indicated skin flora
  - No instances of meningitis or brain parenchymal infection
- Non-seizure related hemorrhage occurred in 7 patients (2.7%)

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# Cognition, Mood and Quality of Life

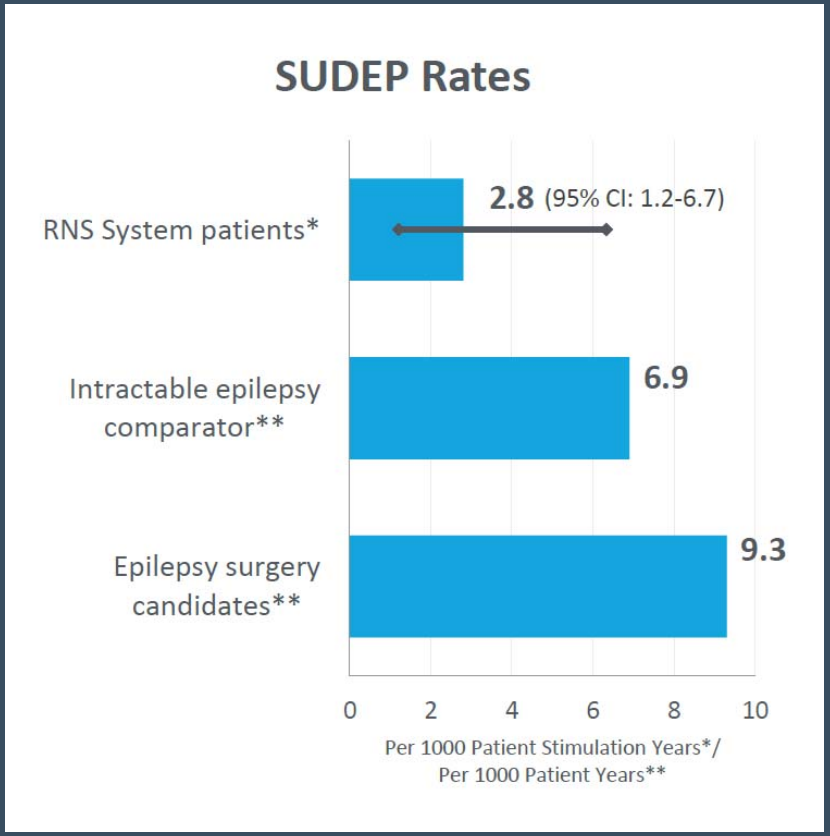
Pivotal Study

- No adverse effects on cognition[1]
  - No difference between Treatment and Sham at end of Blinded Evaluation Period
  - No deterioration in any group scores, including memory
- No adverse effects on mood[2]
  - No difference between Treatment and Sham at end of Blinded Evaluation Period
  - No deterioration at any time point in group scores
- Clinically significant improvements in Quality of Life[3]
  - Blinded Period: 36.6% Treatment; 39.1% Sham
  - Open Label: 38% 1 year; 44% 2 years

Morrell M et al. Neurology 2011

# Safety SUDEP Rate

- Rate of probable or definite SUDEP combined was **2.8 per 1000** patient stimulation years (95% CI: 1.2-6.7) and 3.2 per 1000 patient implant years (95% CI: 1.4-7.0).

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# Deep Brain Stimulation (DBS)

# Deep Brain Stimulation

- DBS provides open loop stimulation
- Bilateral anterior nucleus of the thalamus stimulation
- DBS of other targets remains inconclusive

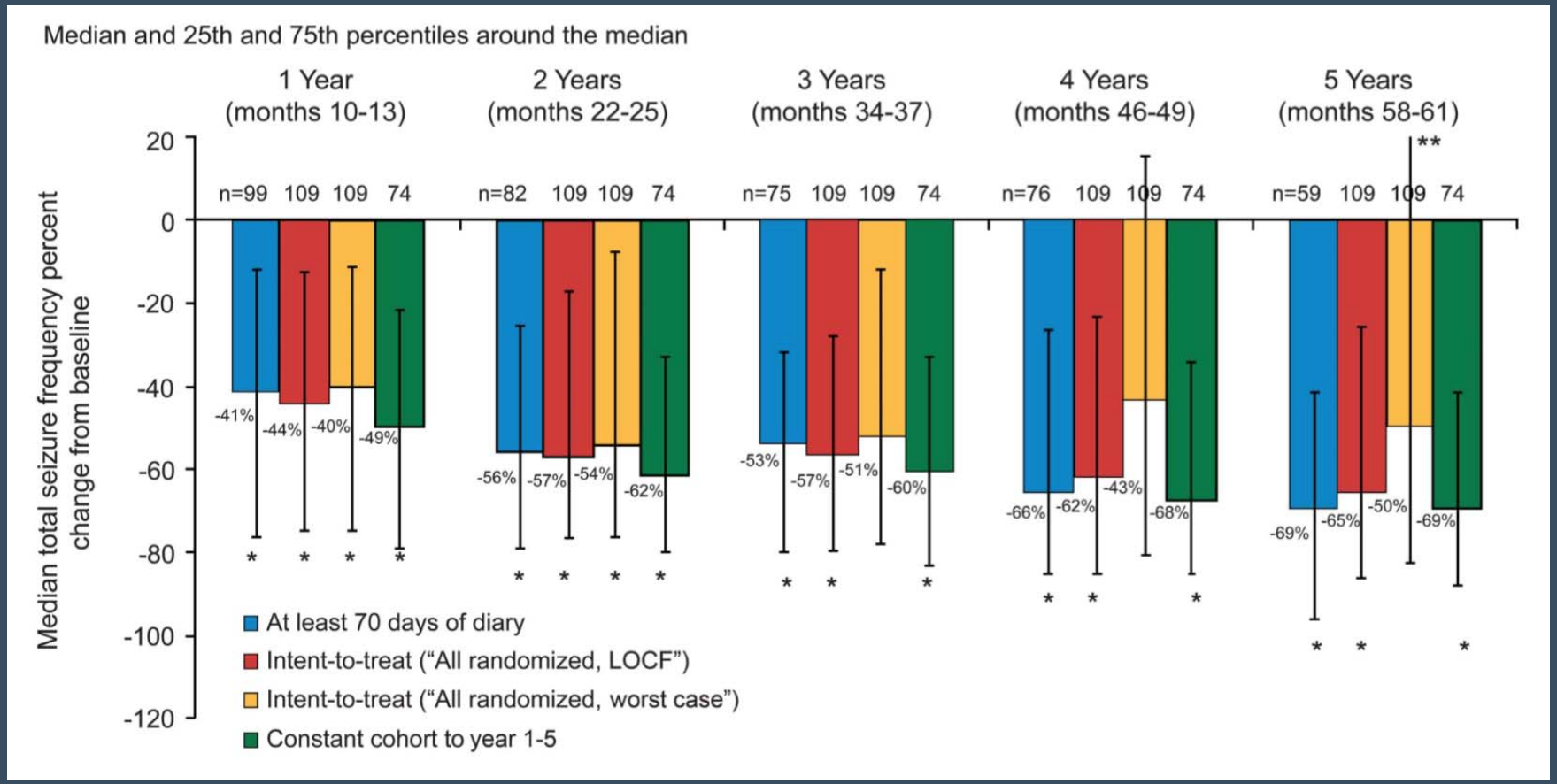
- Approved in Europe (September 2010), Canada (March 2012), Australia (2015)
- Approved in USA (April 2018)
  - Patients 18 years and older
  - Focal / Partial Epilepsy
  - Medically intractable (failed more than 3 AEDs)

# DBS RCT and Long Term Efficacy

* Romanized to receive either 5V or 0V for 3 months double blind then conversion to 5V for all subjects

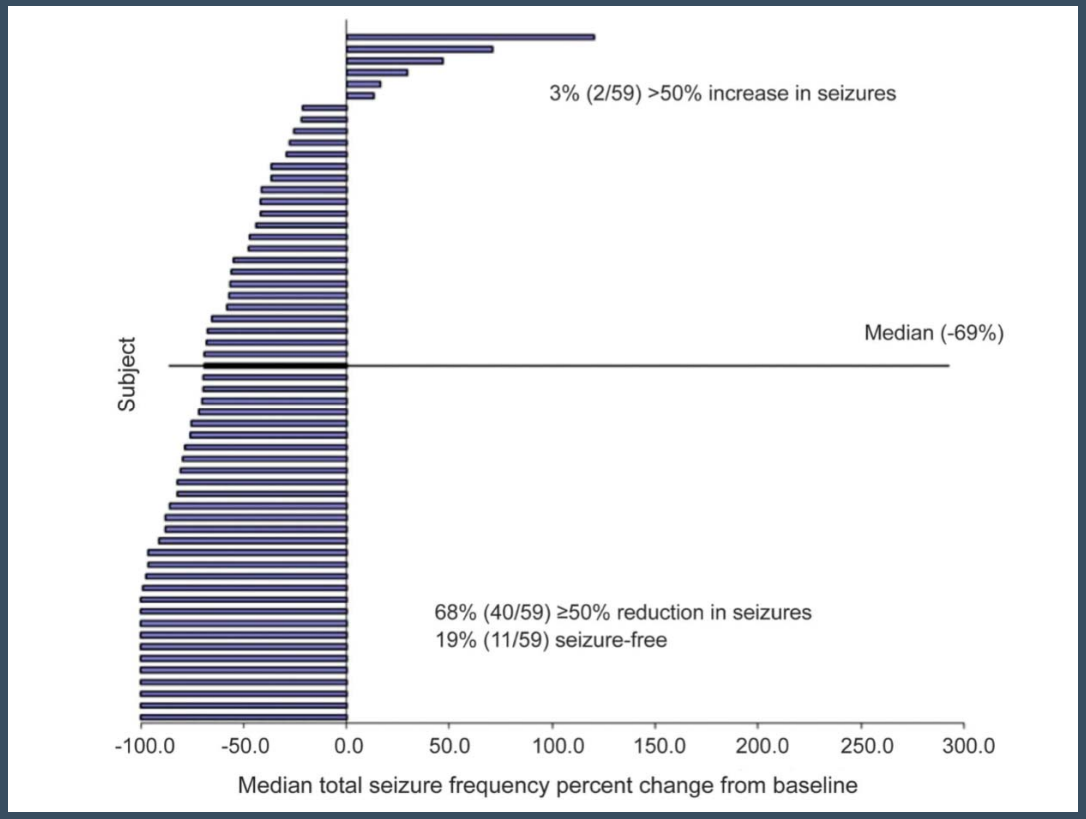
| **Randomized Control Trial*** | **Total # of Seizures: decreased by 40% at 3 months in DBS group and by 15% in patient not receiving DBS** | **Fisher RS, et al. Epilepsia. 2010 May; 51(5):899-908** |
|---|---|---|
| Five Year Follow up of Patients in RTC | Median percentage seizure reduction of 69% | Salanova V, et al. Neurology. 2015 Mar10; 84(10):1017-25. |
| Seven Year Follow up of Patients in RTC | Median percentage seizure reduction of 75% | Sandok E, et al. American Epilepsy Society Annual Meeting. 2016 Abst. 1.298. |

# Seizure Reduction Over Time




Salanova V, et al. Neurology. 2015 Mar10; 84(10):1017-25.

# Variation of Response 5 Years




- Median percentage reduction of seizure – 69%.
- Responder rate – 68%.
- Greater than 50% increase in seizures – 3%.
- Seizure free – 19%.

Salanova V, et al. Neurology. 2015 Mar10; 84(10):1017-25.

# DBS Serious Adverse Effects

35.5% Device Related SAE (39 out of 110 patients)

**Surgical SAE**

- Implant Site Infection – 10%
- Leads not at target – 8.2%

**Sudden Unexplained Death**

- 7 Deaths – none device related
  - 2 Definite SUDEP
  - 1 Probable SUDEP
  - 1 Possible SUDEP

**Cognitive SAE & Status Epilepticus**

- Depression 37.3%
  - 41 pts – of which 66% had H/O depression
  - 11.8% suicidal ideation (13 pts)
    - One completed suicide
- Memory Impairment 27.3%
  - 50% had H/O memory impairment
- Status Epilepticus 6.4%
  - 3 out of 7 pts not receiving stimulation

Salanova V, et al. Neurology. 2015 Mar10; 84(10):1017-25.

# Memory and Mood in Anterior Thalamic DBS for Epilepsy

- No significant cognitive declines or worsening memory
  - Blinded phase or at 7 years
- Higher scores of executive function and attention were measured at 7 years
- Memory and depression AEs were not associated with:
  - Objective measures
  - 7 year neurobehavioral outcome
  - Worsening quality of life measures
  - Demographic
  - Seizure  characteristics
  - Change in seizure frequency
  - Frequency of AEs

Tröster AI, et al. Seizure. 2017 Feb; 45:133-141.

# Conclusion

- Neuromodulatory therapy in epilepsy allows for adjunctive therapy for patients who are medically intractable and are not good candidates for epilepsy surgery
- Neuromodulation appears to have improved efficacy over time
- Safety data and adverse effects are different than those related to medications or surgery