Vagus Nerve Stimulation for the Treatment of Epilepsy

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Ideal Epilepsy Therapy

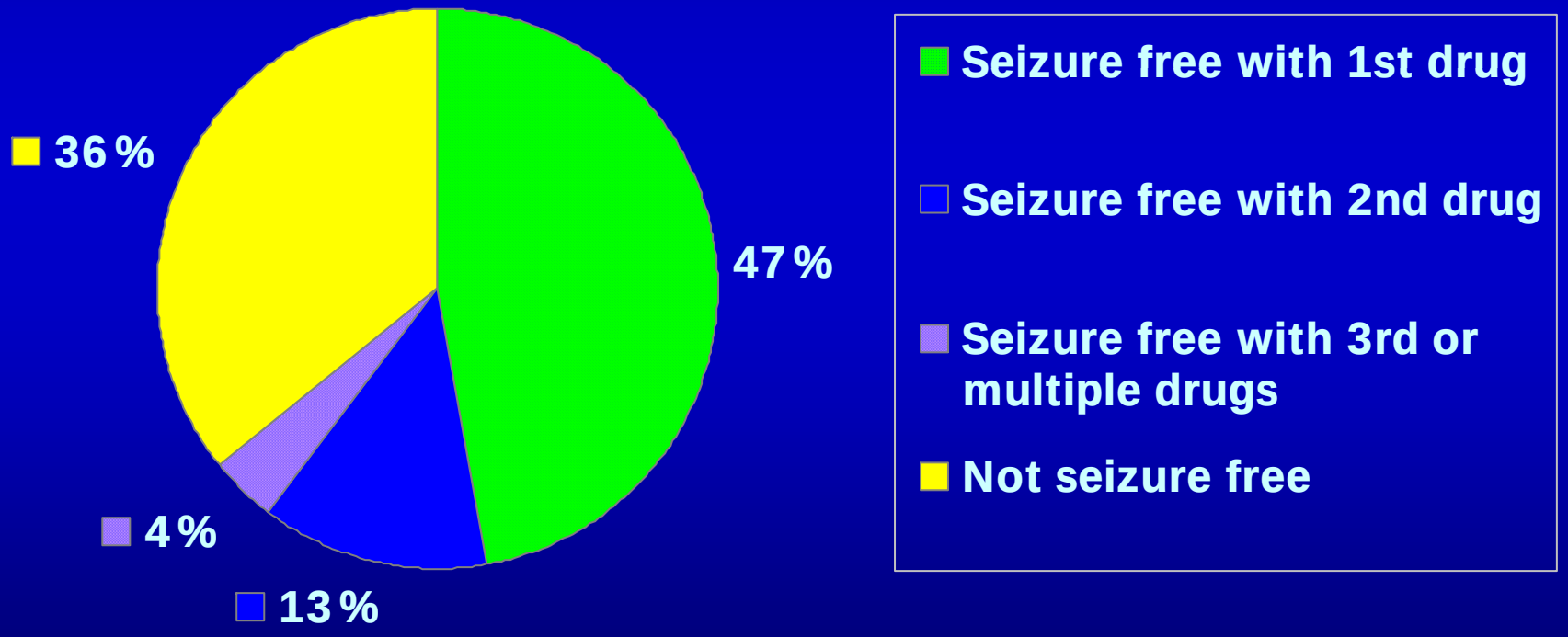
- Long-term antiseizure effect
- Long-term antiepileptogenic effect
- Safe
- No AEs that impair QOL
- Treatment effects that improve QOL
- 100% compliance
- No interactions with other therapies

Goals of Epilepsy Therapy

- **Optimal Quality of Life (QOL)**
  - **No seizures**
  - **No adverse effects (AEs) from therapy**
  - **No depression**

Success With Antiepileptic Drug (AED) Regimens

Previously Untreated Epilepsy Patients (N=470)



Kwan P, Brodie MJ. *N EJM* 2000;342:314-319.

Identifying Medically Refractory Epilepsy

- **Response to first AED is a powerful prognosticator of refractory epilepsy**
- **Only 11% of patients whose first AED failed because of inadequate seizure control ever achieve seizure freedom**
- **Compared with patients whose first AED failed because of intolerable side effects (41% seizure-free) or idiosyncratic reaction (55% seizure-free)**

Kwan P, Brodie MJ. *N EJM* 2000;342:314-319.

Medically Refractory Epilepsy

- **Persistent seizures despite “appropriate” trials of antiepileptic medications**
  - **Failure of 3 drug trials**

Or

- **Intolerable AEs**
- **36% of all newly treated patients with epilepsy**

Impact of Refractory Epilepsy

- Cognitive and memory impairment[1]
- Excessive AED burden[2]
- Increased mortality (accidental, SUDEP)[3]
- Higher depression rates[4]
- Psychosocial dysfunction[2]
- Reduced lifetime income[5]
- Increased healthcare utilization[6]

[1] Meador KJ. Neurology 2002;58(suppl 5):S21-S26.
[2] Kwan P, Brodie MJ. NEJM 2000;342:314-319.
[3] Annegers JF et al. Epilepsia 1998;39:206-212.
[4] Harden CL. Neurology 2002;59(suppl 4):S48-S55.
[5] Van Ness PC. Arch Neurology 2002;59:732-735.
[6] Griffiths R, et al. Epilepsia 1999;40:351-358.

Potential AED Adverse Effects

- Impaired cognition
- Somnolence
- Dizziness
- Ataxia
- Diplopia
- Gastrointestinal effects
- Weight gain
- Alopecia
- Gingival hyperplasia
- Hepatic failure
- Aplastic anemia, agranulocytosis, thrombocytopenia
- Rash, Stevens-Johnson
- Teratogenicity
- Pancreatitis

Vagus Nerve Stimulation (VNS)

Origin of VNS Hypothesis

Time	Investigator(s)	Model	Animal	Result
1938	Bailey & Bremer	N/A	Cats	Orbital frontal cortex EEG fast activity
1952	Zanchetti, et al	Strychnine	Cats	Blocked interictal (EEG) spiking
1961	Magnes, et al	N/A	Cats	Desynchronized EEG
196 7	Chase, et al	N/A	Cats	Synchronized/de-synchronized EEG in thalamus and cortex

Historical Overview of VNS

- **1985 First animal studies (J. Zabara, Temple University)**
- **1988 First human implant (K. Penry, B.J. Wilder, E. Ramsay)**
- **1994 European community approval**
- **1996 5 completed controlled studies (N=454)**
- **1997 USA (FDA) commercial approval**
- **2005 30,000+ patients treated worldwide**

VNS Indication for Use

"...indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures, which are refractory to antiepileptic medications."

***FDA Physician's Manual*.**

Mechanisms of Action (MOA) of VNS

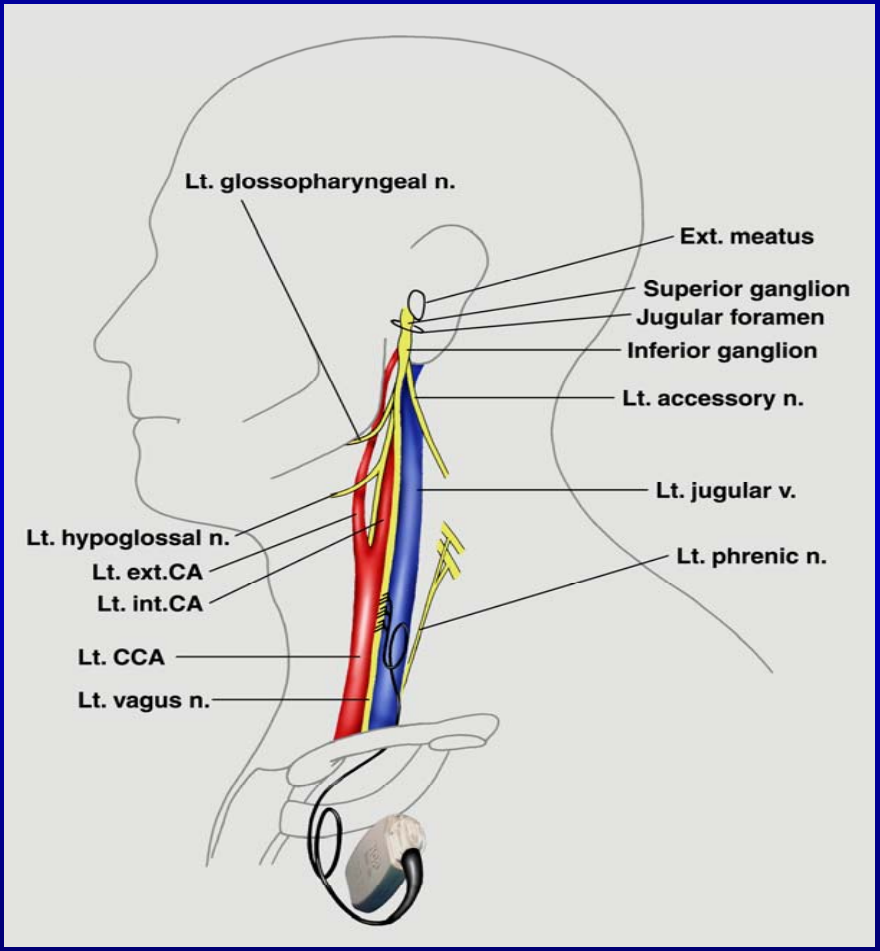
Mechanisms of VNS Therapy

- **Exact MOA is unknown**
- **Multiple actions of VNS therapy are supported by research in:**
  - **Human brain anatomy**
  - **Animal models of epilepsy**
  - **Human electroencephalogram (EEG), cerebrospinal fluid (CSF), functional brain imaging**

Vagus Nerve: Cranial Nerve X

Left cervical vagus nerve

- **80% afferent fibers, mostly myelinated**
- **20% efferent fibers, mostly unmyelinated parasympathetic fibers to viscera, with myelinated fibers to vocal muscles**



Henry TR. *Neurology* 2002;59(suppl 4):S3-S14.

Vagus Nerve and Central Anatomy

- **Left cervical vagus nerve has 80% afferent fibers, which are myelinated and activated by VNS therapy**
- **Vagus nerve's parasympathetic efferents are unmyelinated and not activated much by VNS therapy**
- **Left vagus nerve synapses bilaterally on nucleus of the solitary tract (NTS) in medulla**
- **NTS projects to brain stem nuclei that supply serotonin and norepinephrine to the entire brain**
- **NTS has widespread projections to limbic, reticular, and autonomic cerebral structures**

Animal Studies in Epilepsy Models

Time	Investigator	Model	Animal	Result
1984-85	Zabara	Strychnine/PTZ	Dog	Interrupts seizures
1985-86	Lockard	Alumina Gel	Monkey	Reduces seizure rate
1989-90	Woodbury/ Woodbury	3-MPA/PTZ	Rat	Interrupts seizure
1989-90	Woodbury/Woodbury	MES	Rat	Inhibits tonic & clonic seizures
1992	McLachlan	Penicillin G	Rat	Decreased interictal spiking
1993	McLachlan	PTZ	Rat	Decreased seizure duration
1996	Naritoku & Takaya	PTZ	Rat	Dose response demonstrated & effect is persistent
1998	Krahl	MES	Rat	Reduces seizure severities
1999	Fernandez-Guardiola	Kindling	Cat	Prevents stage VI kindling

Locus Ceruleus Lesions Suppress the Seizure-Attenuating Effects of VNS

- **VNS demonstrated an anticonvulsant effect in rats against maximal electroshock**
- **Chronic and acute chemical lesioning of the locus ceruleus (LC) was then performed**
- **After lesioning LC, VNS was no longer effective**
- **Conclusions**
  - **LC is involved in anticonvulsant effect of VNS**
  - **Effect of VNS may require norepinephrine release, a neuromodulator that has anticonvulsant effects**

Krahl S, et al. *Epilepsia* 1998;39:709-714.

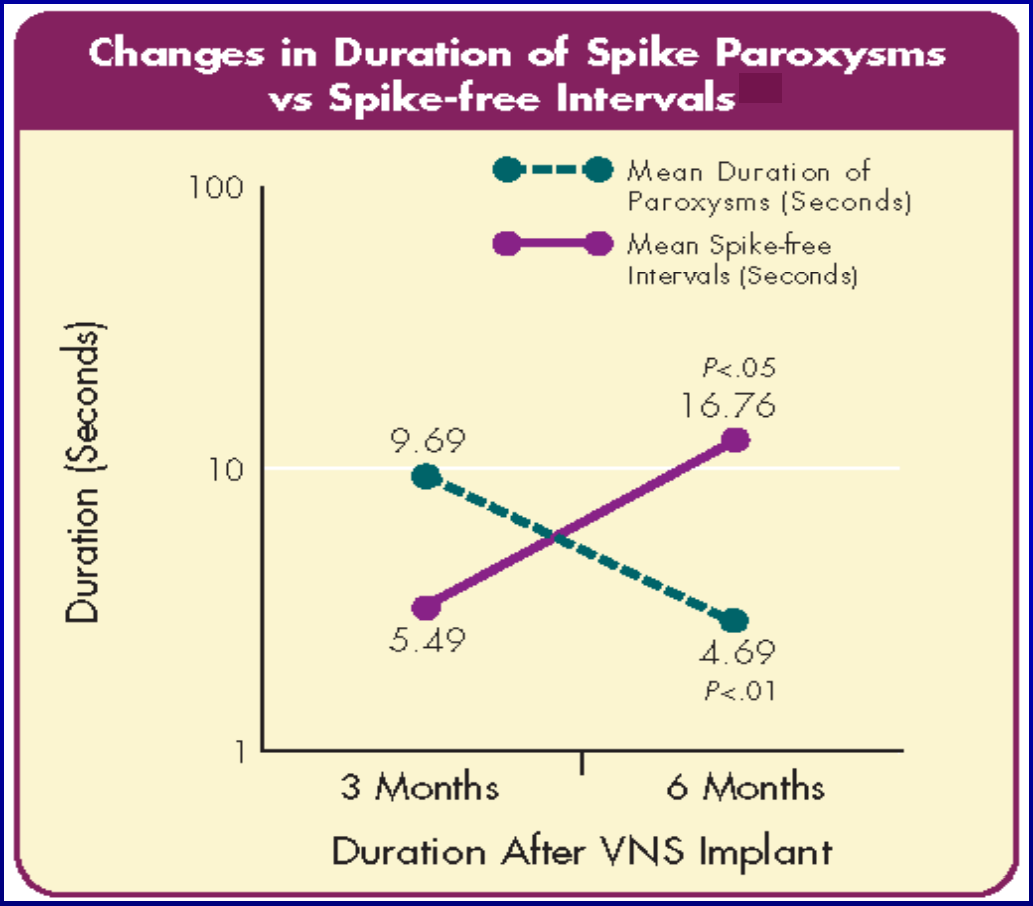
Conclusions from VNS Studies in Animal Models

- **Acute, abortive effects[1]**
  - **VNS terminates seizures when applied after seizure onset**
- **Acute, prophylactic effects[2]**
  - **Seizure frequency and severity are reduced between trains of VNS**
- **Chronic, progressive prophylactic effects[3]**
  - **Seizure frequency and severity are further reduced after chronic, long-term VNS**

[1]McLachlan RS, et al. *Epilepsia* 1993;34:918-923.
[2]Takaya M, et al. *Epilepsia* 1996;37:1111-1116.
[3]Lockard JS. *Epilepsia* 1990;31(suppl 2):S20-S26.

Effect of VNS Therapy on Human EEG

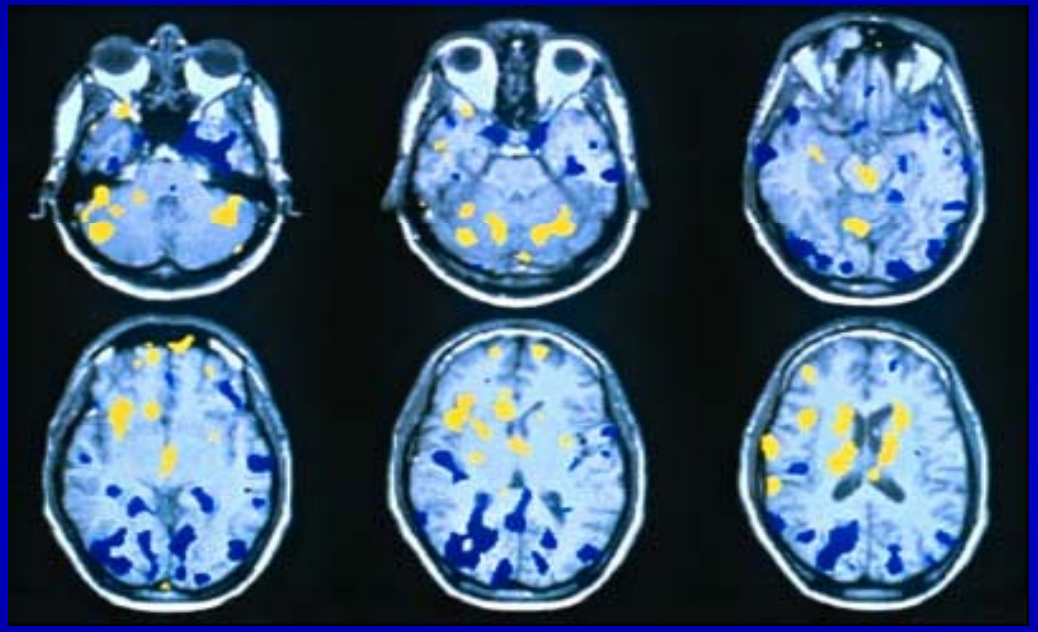
- **VNS therapy induces progressive EEG changes in the form of clustering of epileptiform activity followed by progressively increased periods of spike-free intervals**



Koo B. *J Clin Neurophysiol* 2001;18:434-441.

VNS Therapy Modulates Blood Flow in Key Brain Structures

- **Significant bilateral changes in blood flow observed during VNS therapy[1]**
- **Increased blood flow in the thalamus has been shown to have significant correlation with long-term seizure control (*P*<0.001)[2]**



[1]Henry TR, et al. *Epilepsia* 1998;39:983-990.
[2]Henry TR, et al. *Neurology* 1999;52:1166-1173.

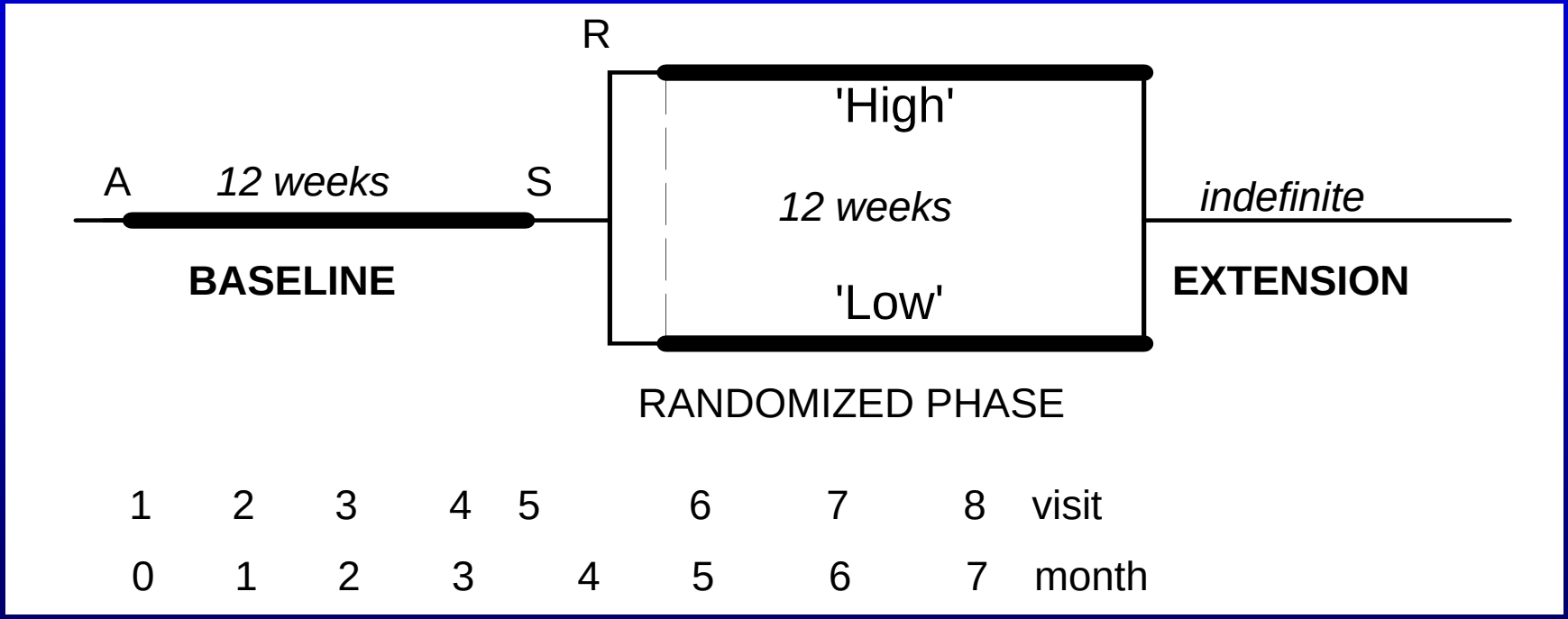
Efficacy of VNS

VNS Clinical Studies

Study	Design	Seizure Type	# of Patients	Dates
E01/E02	Pilot, Single Blind	Partial	16	1988-90
E03	Blinded, Randomized, Double Blinded, Active Control	Partial	115	1990-92
E04	Compassionate Use	All	124	1991-95
E05	Blinded, Randomized, Double Blinded, Active Control	Partial	199	1995-96

1st and 2nd Controlled VNS Studies: Hypothesis & Design

"High" level stimulation would reduce overall seizure frequency to a greater degree than "Low" level stimulation.

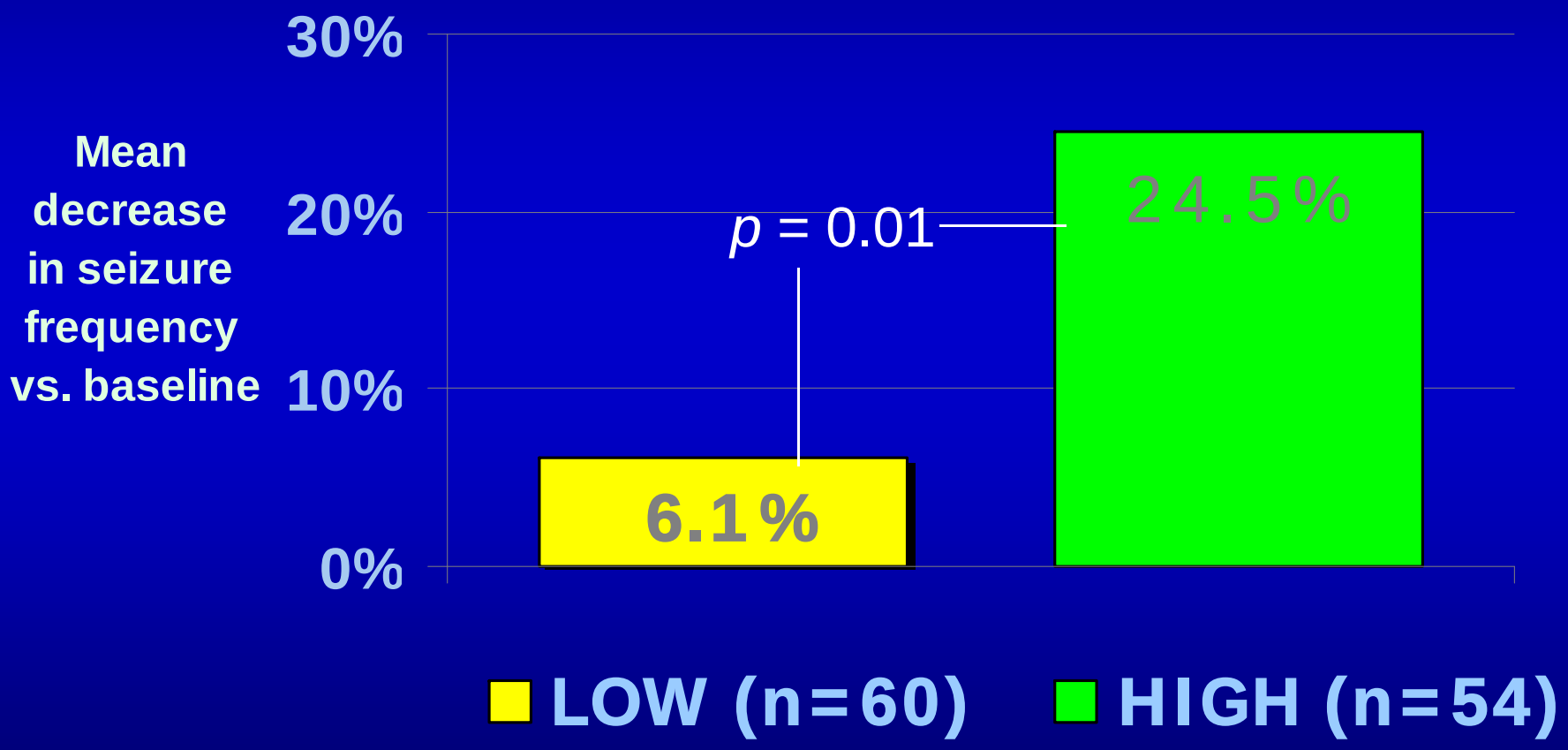


High vs. Low (Active Control) Stimulation Parameters

	HIGH	LOW
Current	1.5 mA	1.0 mA
Frequency	30 Hz	1 Hz
Pulse width	500 usec	130 usec
On time	30 sec	30 sec
Off time	5 min	90 min

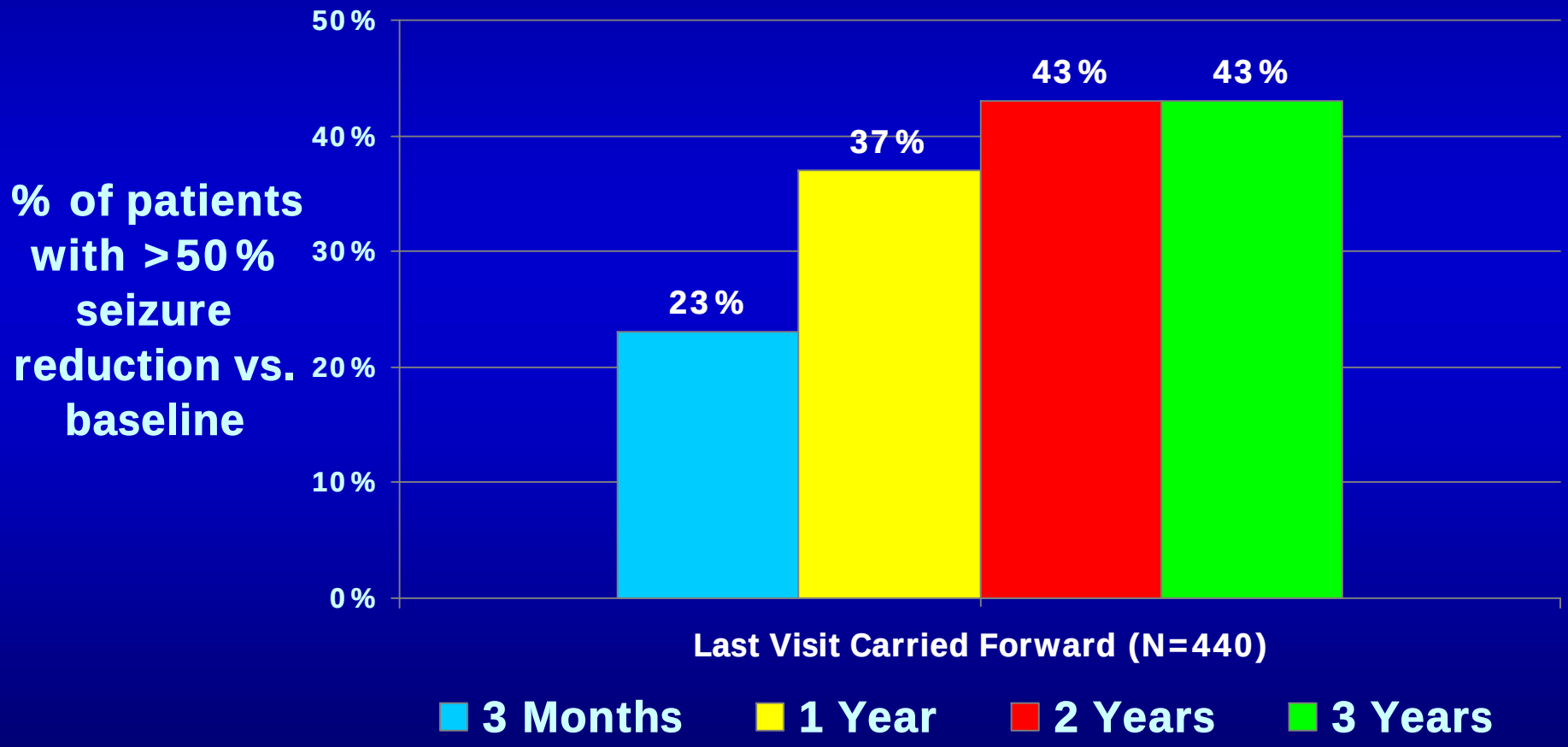
Salinsky MC et al. *Neurology* 1995;45:224-230.

1st Controlled VNS Study Results (E03)



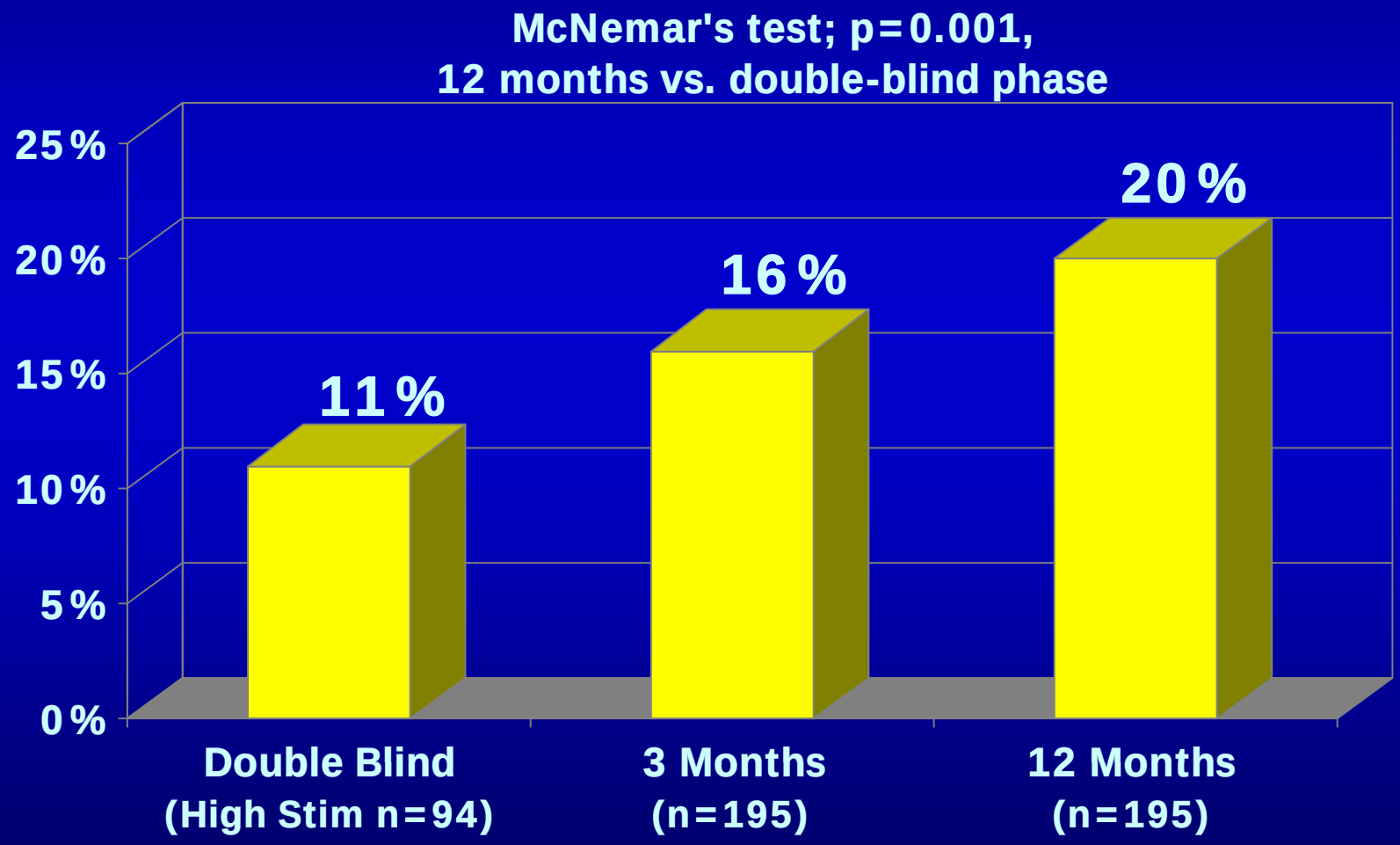
Salinsky MC et al. *Neurology* 1995;45:224-230.

VNS Long-Term Responder Rates (E01-E05)



Morris GL, Mueller WM. *Neurology* 1999;53:1731-1735.

VNS Long-Term Efficacy: % of Patients with >75% Seizure Reduction (E05)



DeGiorgio CM et al. *Epilepsia* 2000;41:1195-1200.

VNS Long-Term Efficacy: Seizure Frequency Reduction vs. Baseline

- **26% at 1 year, 30% at 5 years, 52% at 12 years using "last visit carried forward" analysis (n=25 of 47)[1]**
- **28% at 1 year, 72% at 5-7 years (n=26 of 28)[2]**

[1] Uthman BM, et al. *Neurology* 2004;63:1124-1126.
[2] Spanaki MV, et al. *Seizure* 2004;13:587-590.

AAN Position Statement

"…sufficient evidence exists to rank VNS for epilepsy as safe and effective, based on a preponderance of Class 1 evidence*."

Fisher RS, Handforth A. *Neurology* 1999;53:666-669.

Class 1 evidence: Provided by one or more well-designed randomized, controlled clinical trials.

Adverse Effects of VNS

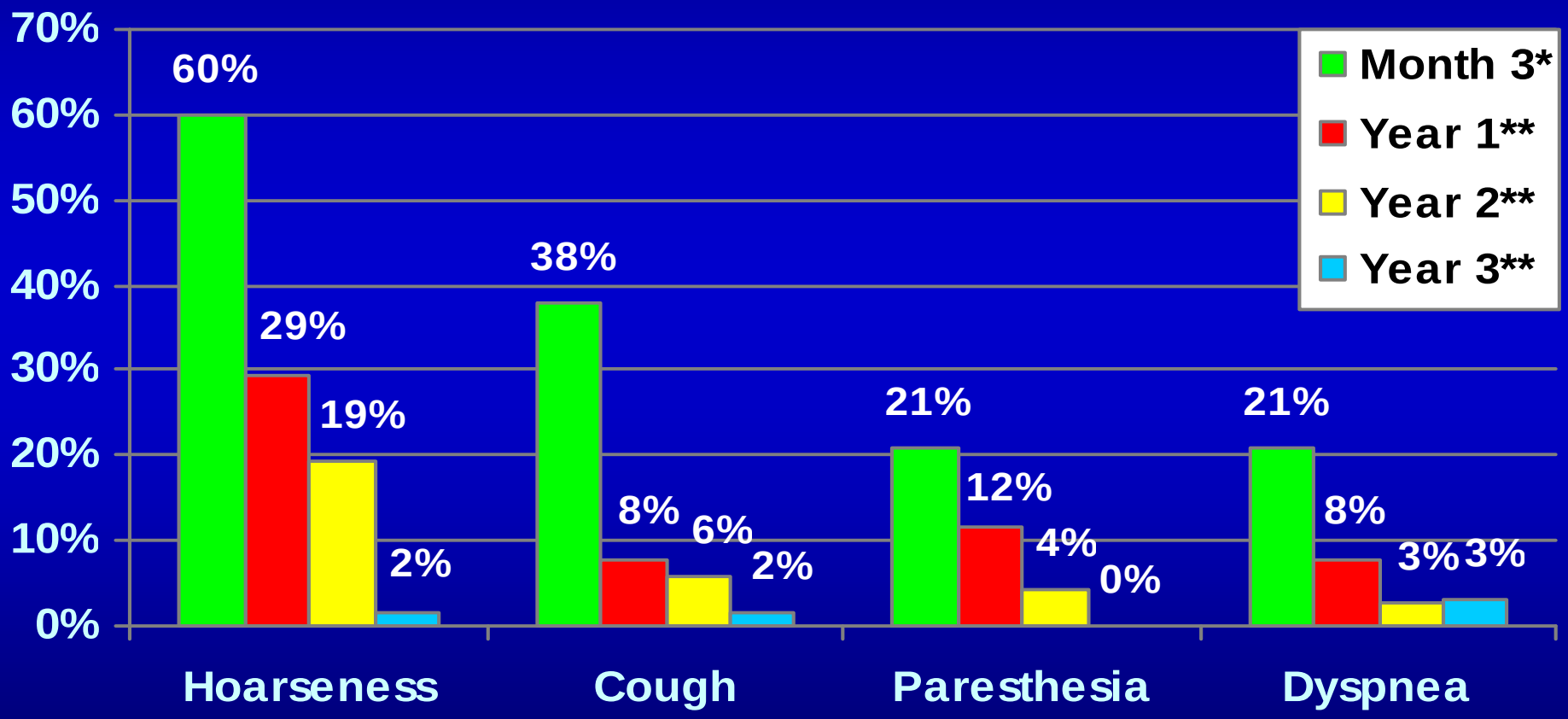
VNS Adverse Effects

- Typically during stimulation “on time”
- May lessen over time
- May be reduced or eliminated with parameter adjustments
- Similar across all age groups

Common Side Effects of VNS Therapy

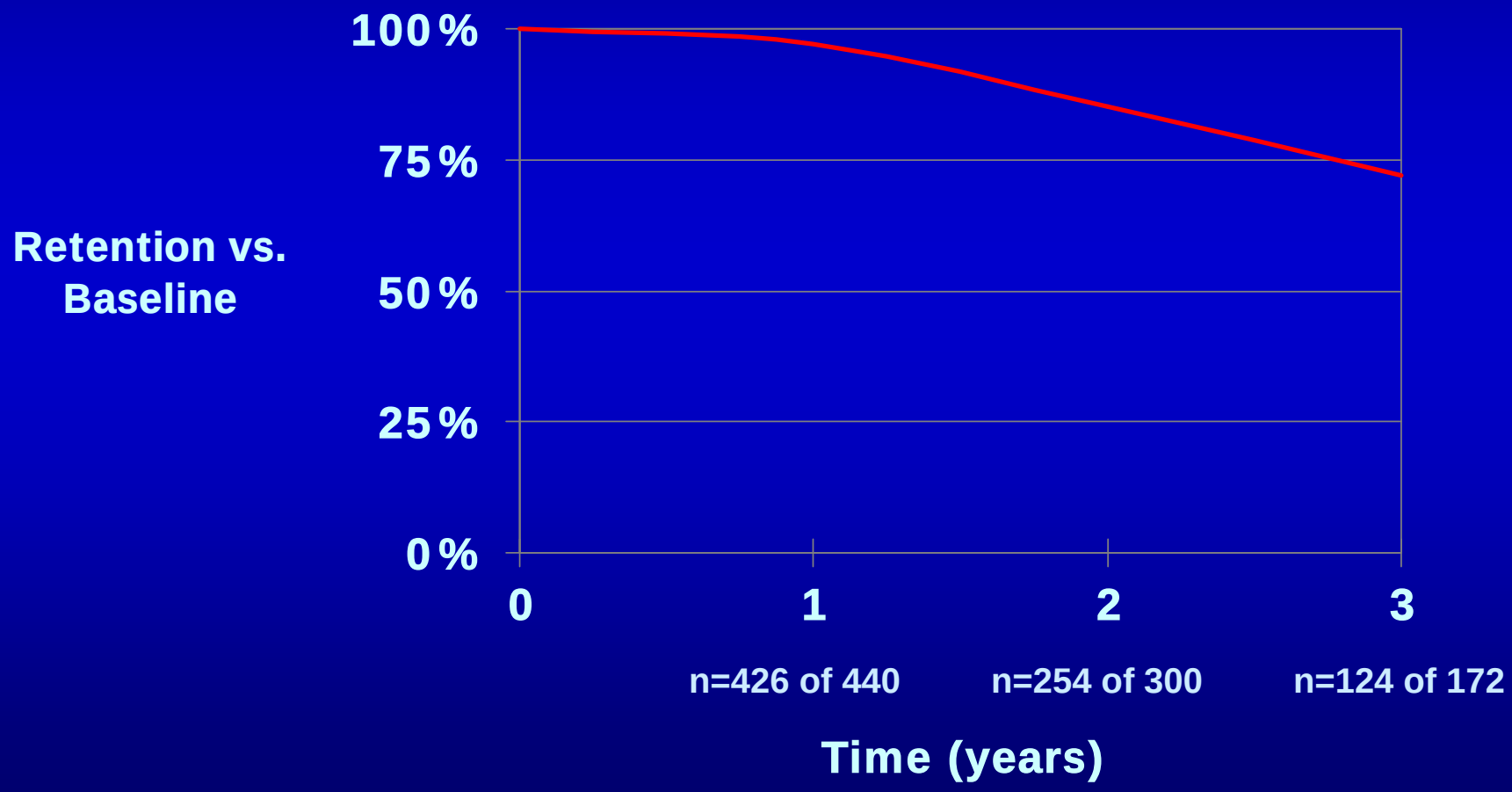
- Temporary hoarseness/changes in voice tone
- Cough
- Tickling in the throat
- Shortness of breath
- Most common adverse effect from implant surgery is infection

VNS Long-Term Adverse Effects (E01-E05)



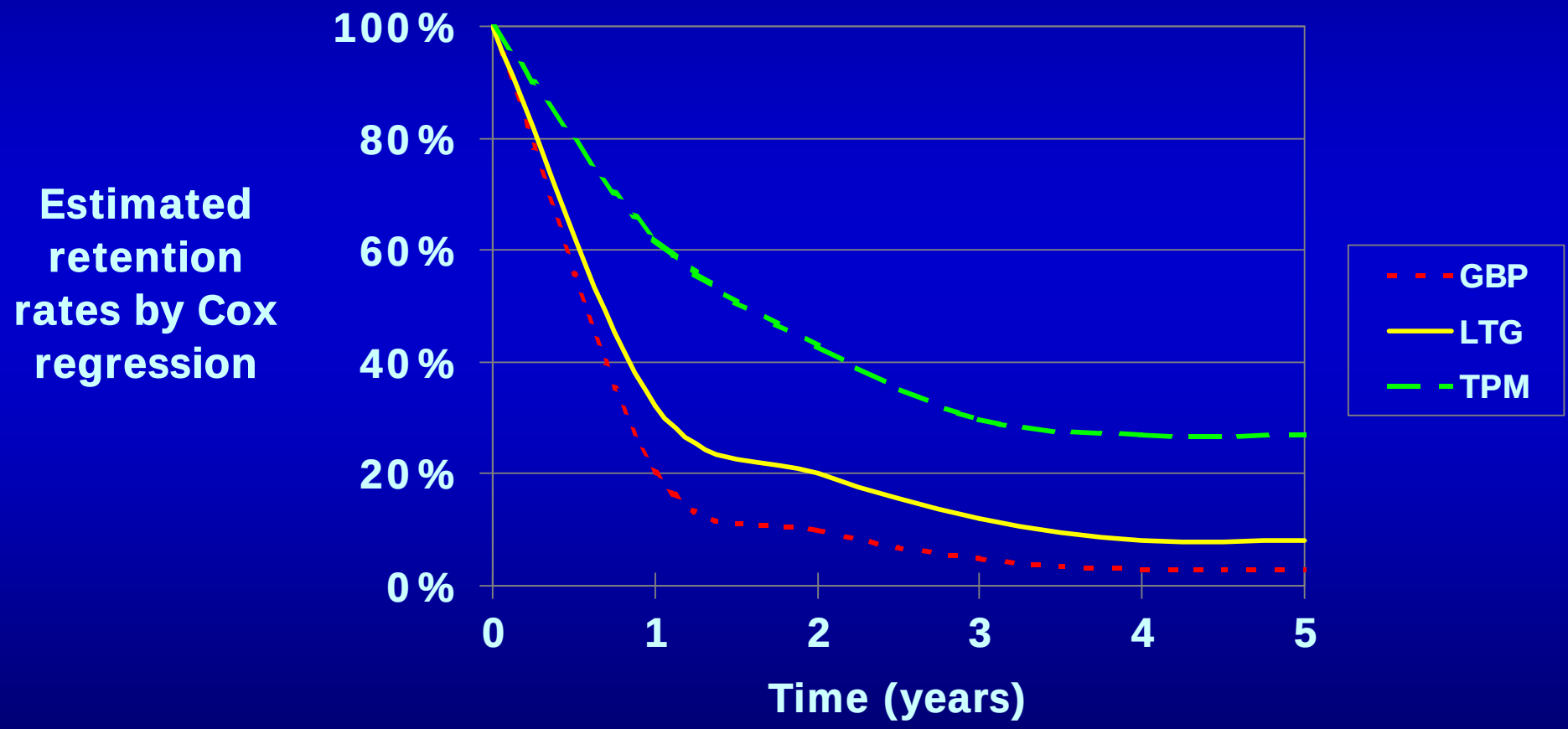
*3-month results (High stimulation only, n=152). *FDA Physician's Manual*.
**Year 1,2 and 3 results (all study patients, N=440). Morris GL, Mueller WM. *Neurology* 1999;53:1731-1735.

VNS Retention Rates (E01-E05)



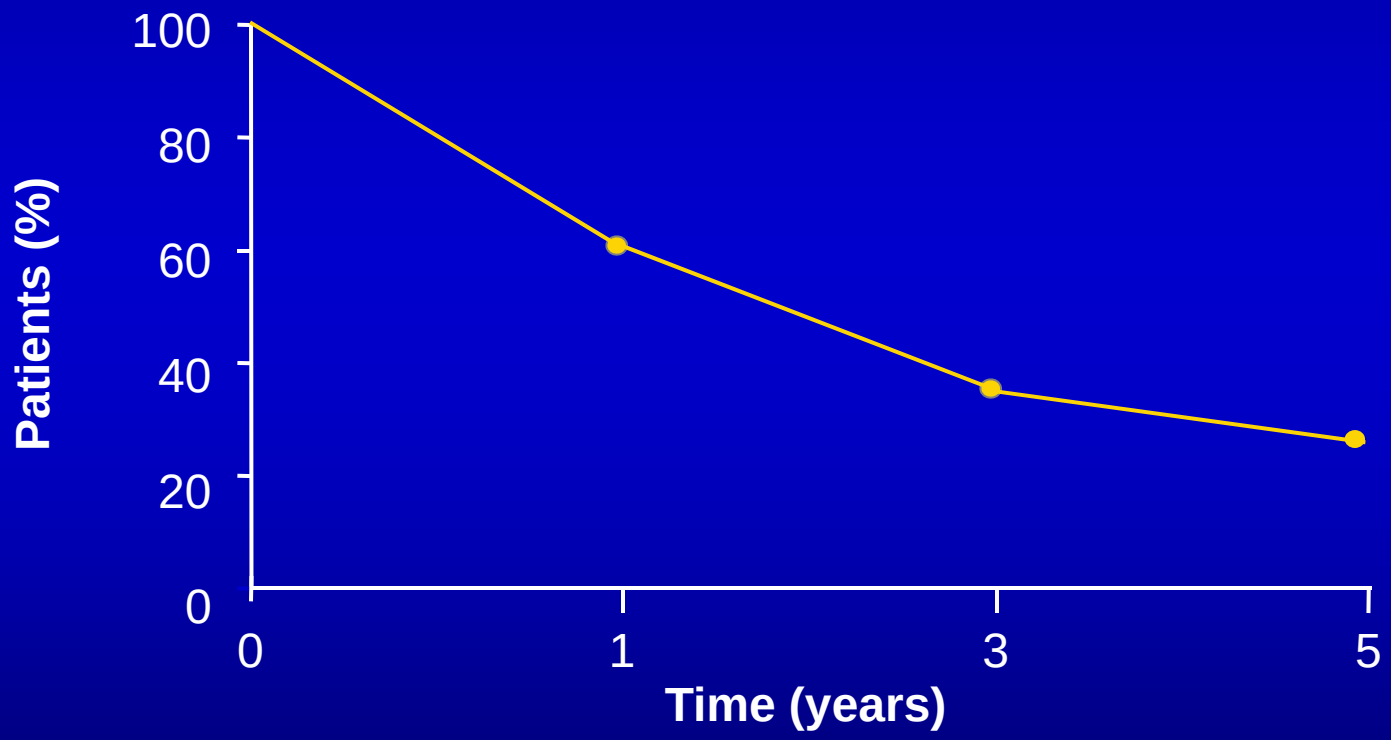
Morris GL, Mueller WM. *Neurology* 1999;53:1731-1735.

Long-Term Retention Rates for AEDs in Patients with Refractory Epilepsy



Lhatoo SD, Wong, et al. *Epilepsia* 2000;41:1592-1596.

Long-term Retention Rates with Levetiracetam



Retention rates estimated by Kaplan-Meier method.

Krakow K, et al. *Neurology* 2001;56:1772-1774.

Safety of VNS

VNS Safety Profile

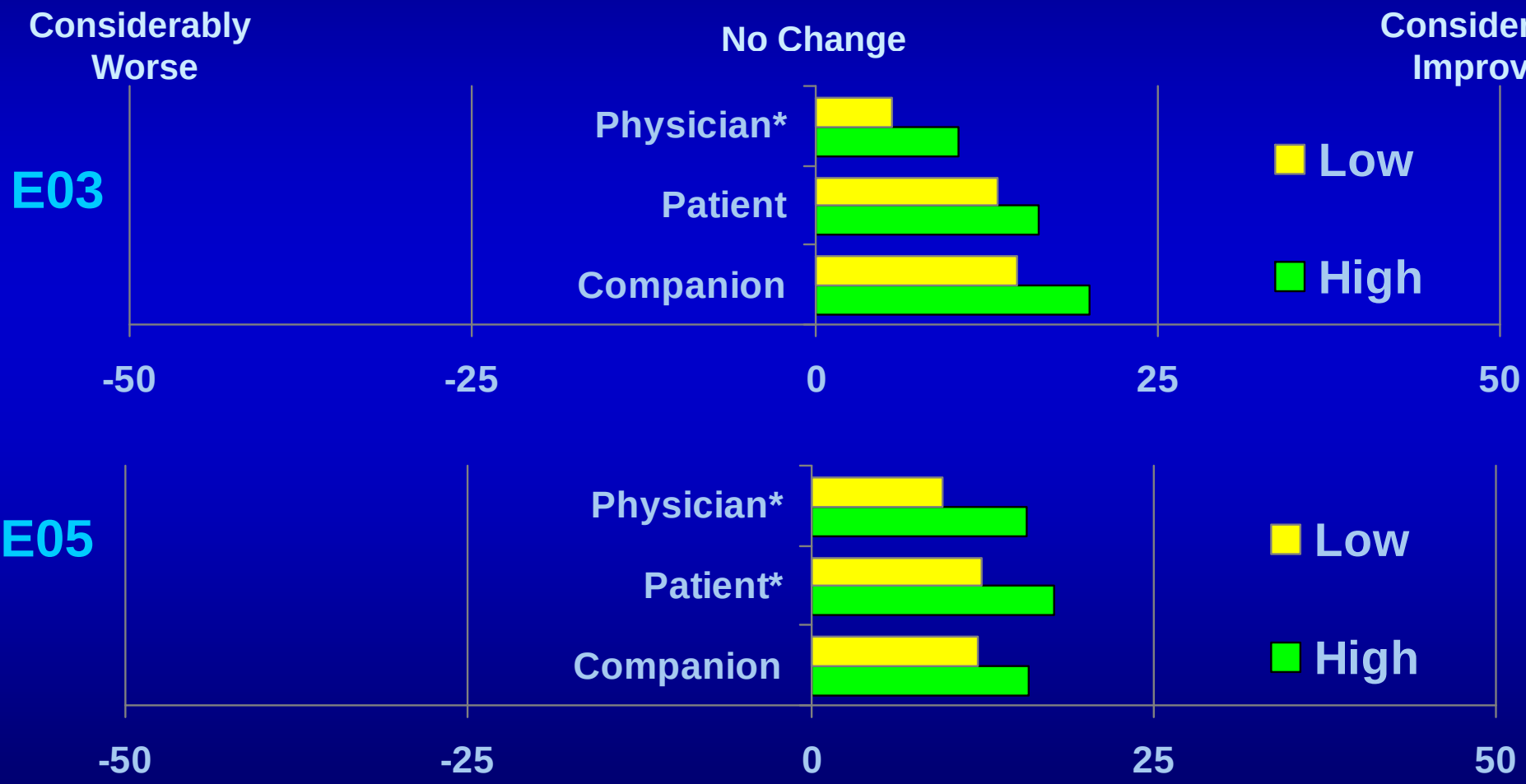
- **No idiosyncratic reactions**
- **No deaths attributed to VNS**
- **No increase in Sudden, Unexpected Death in Epilepsy (SUDEP)**

Quality of Life (QOL) with VNS

Quality of Life

AEs with VNS	AEs NOT seen with VNS
❖ Hoarseness	❖ Sedation
❖ Paresthesia	❖ Depression
❖ Cough	❖ Fatigue
❖ Dyspnea	❖ Dizziness
	❖ Insomnia
	❖ Confusion
	❖ Cognitive impairment
	❖ Weight gain
	❖ Sexual dysfunction

Controlled VNS Studies: Effect on Overall Well-Being



In Press. Dodrill C, Morris GL et al. ***Epilepsy & Behavior***.

** Between-group analysis P<0.05.*

Technical Aspects of VNS Therapy

Vagus Nerve Stimulation

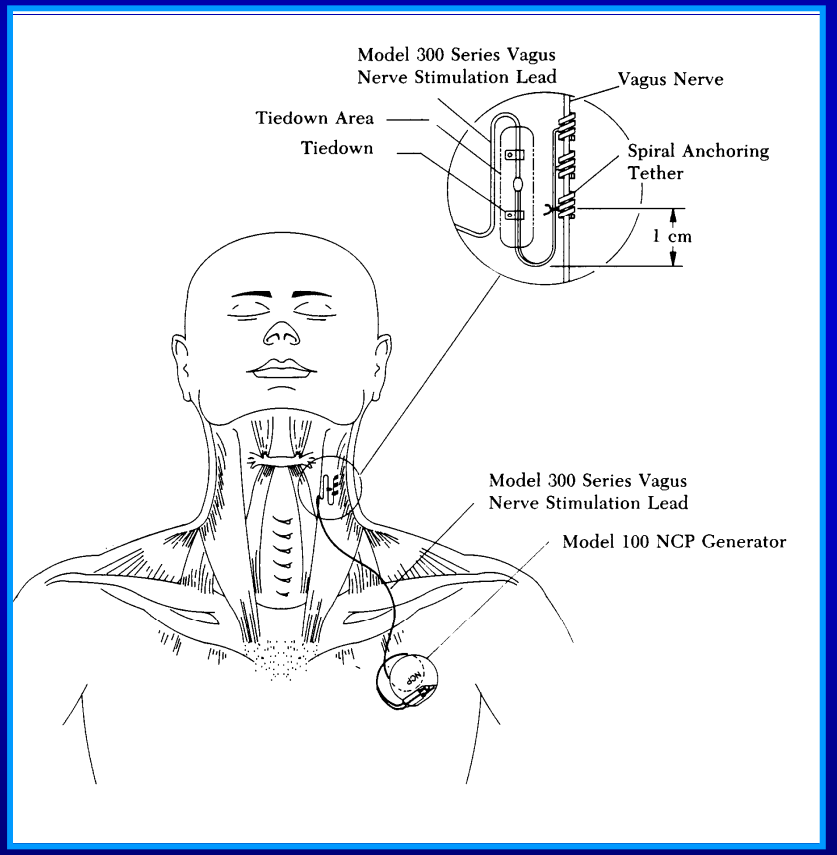
- **Intermittent electrical stimulation of the left cervical vagus nerve**
- **Why the cervical vagus nerve?**
  - **Easy access**
  - **Few pain fibers**
  - **80% afferent fibers**
  - **Widespread anatomic projections in the brain**
  - **Left vagus has less cardiac innervation than the right**

VNS Pulse Generator & Lead

- Pacemaker-like pulse generator
- Bipolar lead with two stimulating electrodes
- Intermittent stimulation
  - 30 sec on/5 min off
  - 24 hours/day
- On-demand therapy mode
- 6.9 mm thick
- Weighs 25 grams
- 6 to 11-year battery life

VNS Implant Procedure

- Approximately 1 hour procedure
- General anesthesia
- Chest/axillary border incision for pulse generator
- Neck incision for lead
- Outpatient procedure

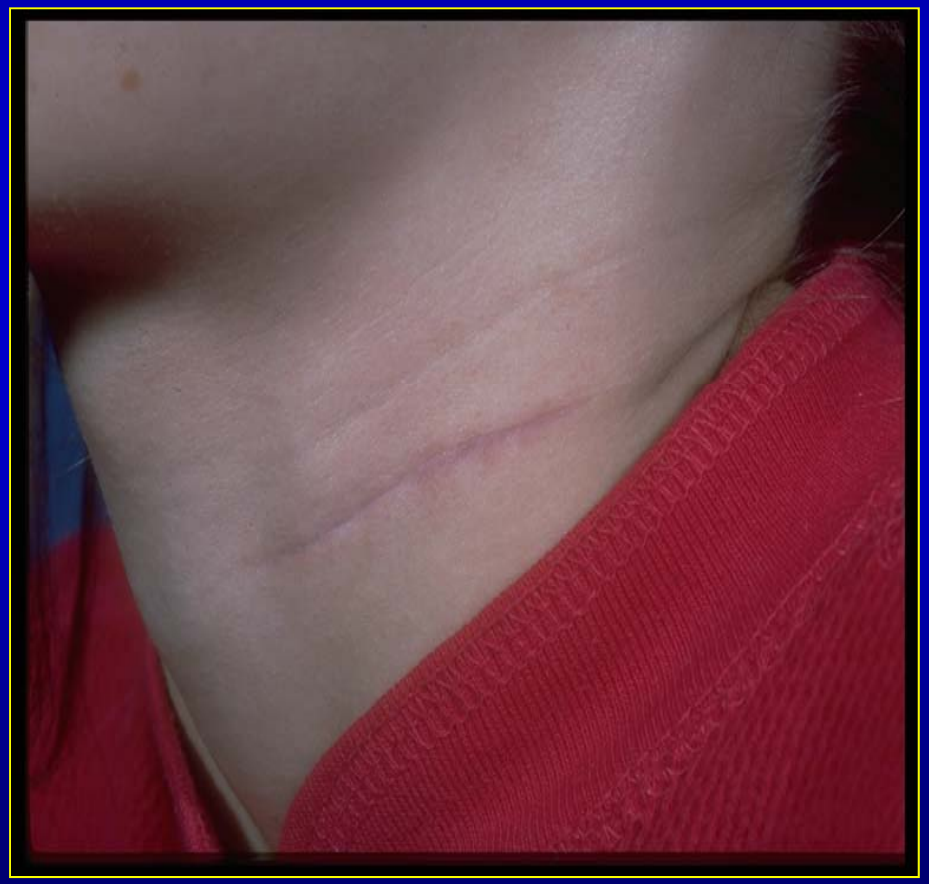


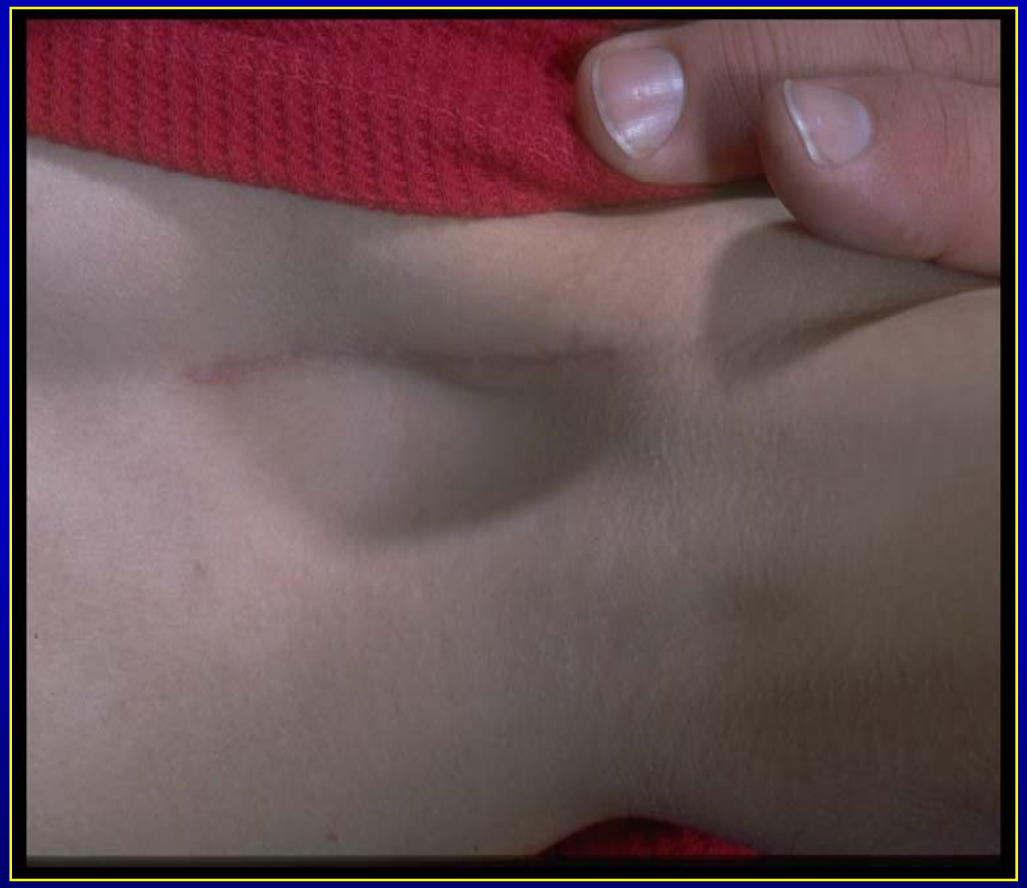
VNS Surgical Complications

Clinical Studies (N=454)[1]	
Infection without explant	1.8%
Infection with explant	1.1%
Hoarseness/temporary vocal cord paralysis	0.7%
Hypesthesia/lower left facial paresis	0.7%
All Patients (N=10,000+)	
Asystole during routine lead test	0.1%
Mortality	0.0%

[1]Bruce et al. Epilepsia 1998;39(Suppl 6):92-93.

VNS Implant: Post-Op Scars





Programming Components

- **Computer, Software & Wand communicate transcutaneously to the pulse generator**
- **Easy to use:**
  - **Training & equipment provided**
- **Used for:**
  - **Surgical implant**
  - **Routine office visits**

VNS Programmable Parameters

Parameter	Units	Range	Typical
Output current	milliamps	0 - 3.5	1.25
Signal frequency	hertz	1 - 30	30
Pulse width	microseconds	130 - 1000	500
Signal On time	seconds	7 - 60	30
Signal Off time	seconds/minutes	12 sec-180 min	5 min

Pulse Generator cycle is 24 hours per day.

On-Demand Stimulation: Magnet Activation

- **Pass magnet over the pulse generator to start on-demand mode**
- ***Potential* benefits:**
  - **Stop or shorten seizures/clusters**
  - **Decrease seizure severity**
  - **Improve post-ictal period**
  - **Sense of empowerment**
- **Tape magnet over pulse generator to stop stimulation**

Summary and Conclusions

VNS in Medically Refractory Epilepsy

- As adjunctive therapy in refractory epilepsy patients with a confirmed diagnosis
- Consider VNS after use of 3 appropriate AEDs along with the risk/benefit profile of all adjunctive therapies
- As an adjunct for patients experiencing intolerable AEs

VNS in Relation to Epilepsy Surgery

- **Not before ideal resective surgery candidates**
  - **MTLE with hippocampal sclerosis, lesional epilepsy**
- **Before more invasive palliative procedures such as callosotomy**
- **Before invasive monitoring and resections in nonlesional, extratemporal partial epilepsies??**

VNS Conclusions

- Offers seizure control which is maintained and, for some, improves over time
- Some patients report improvement in QOL
- May be useful in treating depression associated with medically refractory epilepsy
- No “Black Box Warning” regarding potential life threatening AEs

VNS Conclusions

- AEs are well-tolerated and, for some, decrease with time
- Unique advantages
  - 100% compliance
  - “On-demand” therapy results in increased patient and family control
  - No drug interactions