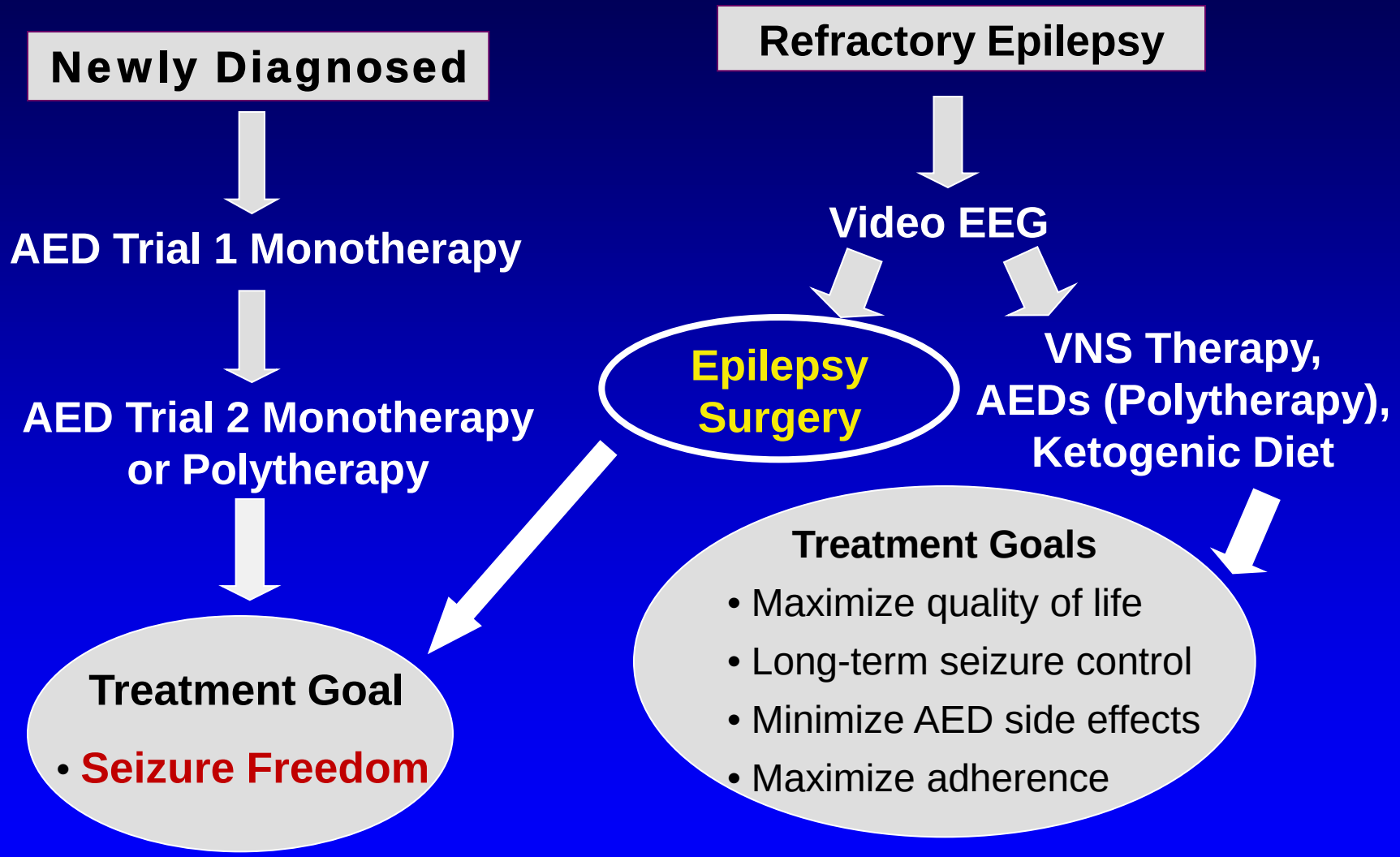
Identifying Candidates for Vagus Nerve Stimulation (VNS) Therapy

James W. Wheless, M.D.
Professor and Chief of Pediatric Neurology
Le Bonheur Chair in Pediatric Neurology
University of Tennessee Health Science Center
Director, Le Bonheur Comprehensive Epilepsy Program
& Neuroscience Institute
Le Bonheur Children's Hospital
Memphis, TN USA

Treatment Goals for Epilepsy



Kwan P, et al. *Epilepsia* 2009; doi: 10.1111/j.1528-1167.2009.02397. Gilliam F. Neurology 2002;58:s9-s19. Wheless JW. Neurostimulation Therapy for Epilepsy. In: Wheless JW, Willmore LJ, Brumback RA, eds. Advanced Therapy in Epilepsy. Hamilton, Ontario: BC Decker, Inc. 2008. Faught E, et al. Epilepsia 2009;50(3):501-509.

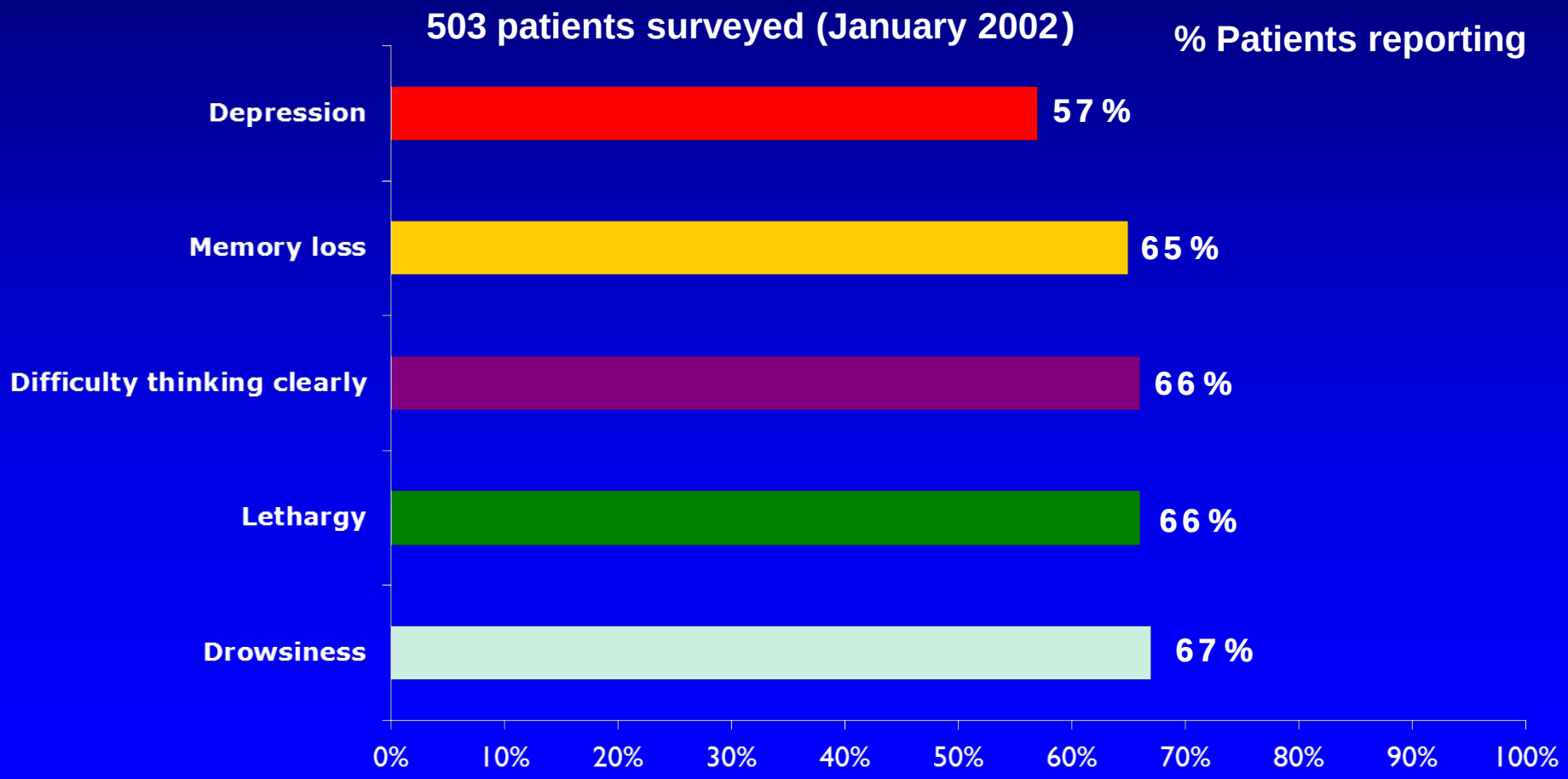
Side Effects Are a Concern for Patients on Multiple Anti-Epileptic Drugs

- ~ 90% of patients with refractory epilepsy or their caregivers (n=703) agreed that small improvements in seizure control and ability to think clearly mean a lot on a day-to-day basis
- Most would like to find a treatment that would allow them to reduce their number of medications
- **Most would change their current treatment if offered a new treatment that might maintain their current level of seizure control, but without the negative side effects they are currently experiencing**

Wheless JW. Epilepsy Behav. 2006;8:756-764.

Substantial Cognitive Effects are Associated with Epilepsy and its Treatment

Intractable Epilepsy Survey

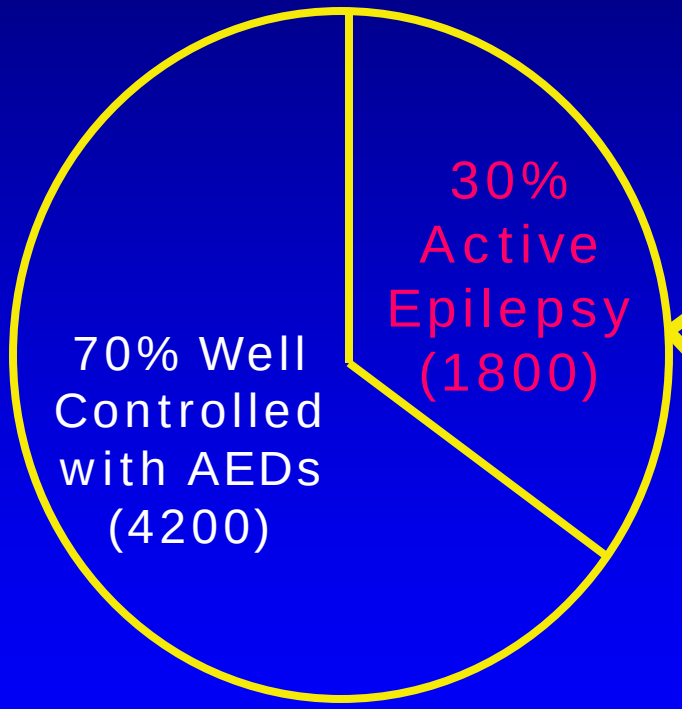


Wheless JW, et al. Epilepsy Behav 2006;8:756-764.

Are There Candidates for VNS Therapy?

Memphis, TN 1,000,000

Active Epilepsy* 6,000



1/4 to 1/3 Epilepsy Surgery Candidates (450 – 600)

2/3 to 3/4 Are Candidates for Other Therapies: VNS, Ketogenic Diet, Experimental AEDs (1200-1350)

* Active epilepsy prevalence 6/1,000 (Engel J. Neurol, 1998; 51: 1243-1244)

USA-FDA Device Evaluation

	VNS Therapy	DBS – Anterior N. of Thalamus	Responsive Neurostimulation	Epilepsy Surgery
Efficacy	Yes	Yes	Yes	Yes
Quality of Life	Yes	Yes	Yes	Yes
Pharmacoeconomics	Yes	No	?	?
Risks				
Serious	No	Yes	Yes	Yes
Non-Serious	Yes	Yes	Yes	Yes

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm (FDA Document # 1772)

Neurostimulation: Evidence-Based Medicine

Device or Surgery	Blinded, Controlled, Randomized Trials	Randomized, Clinical Trials	Observational Studies
Epilepsy Surgery	0	2	Yes
Gamma Knife Radiosurgery	0	1	Yes
VNS Therapy	**3**	**2**	**Yes**
Intercept	1	0	Yes
RNS System	1	0	Yes

Barbara NM et al, Ann Neurol, 2009; 65(2): 167-75
Wiebe S et al, Can J Neurol Sci, 2006; 33(4): 365-371
Wiebe S. Epilepsia, 2003; 44 (Suppl. 7): 38-43
Englott DJ et al. J Neurosurg, 2011; 115: 1248-1255
Engel J et al. JAMA, 2012; 307(9): 922-930

VNS Approved Indications - Epilepsy

Epilepsy (1994)
The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients whose epileptic disorder is dominated by partial seizures (with or without secondary generalization) or generalized seizures that are refractory to antiepileptic medications.

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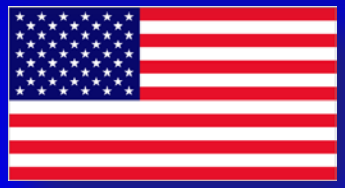

Epilepsy (1997):
The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures that are refractory to antiepileptic medications

Epilepsy (2010)
The Vagus Nerve Stimulation Device VNS System is an electric stimulation device that stimulates the vagus nerves, used as an adjunctive therapy to reduce the frequency of epileptic seizures for drug-resistant refractory epilepsy patients (except for the patients for whom a craniotomy will be effective).

VNS Approved Indications – Depression

Depression (2001)
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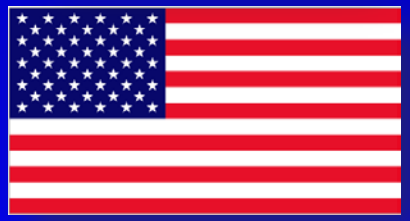


Depression (2005):
The VNS Therapy System is indicated for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments

Depression
Not approved yet

Patient Profile (Hannah L.)

- 19 year-old female
- Unremarkable past medical history
- March 2005 (seizure onset)
  - viral illness, febrile, lethargic
  - generalized tonic clonic seizures
  - admitted to local hospital
    - seizures, fever, change of mental status
    - CSF pleocytosis
    - Diagnosis: viral encephalitis

Treatment History

- Refractory seizures
  - average two partial seizures with secondary generalization/week
  - longest seizure-free interval 1 month
  - seizure duration 2-3 minutes
  - semiology: aura (cephalic) → stare off → head deviates to either side → tonic clonic activity

- Prior treatments:
  - phenytoin, carbamazepine, lamotrigine, topiramate, levetiracetam, oxcarbazebine, gabapentin, and zonisamide

History

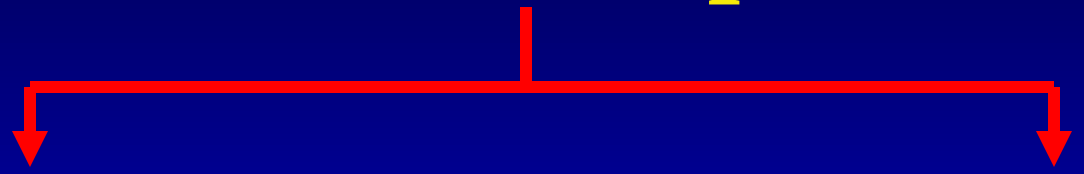
- Co-morbidity: poor memory, ↓ school performance
- Current treatment
  - Levetiracetam 500mg – 2 am, 2 hs, (serum level 26.4 mcg/ml)
  - Topiramate 100mg – 1 ½ am, 1 hs (serum level 8.7 mcg/ml)

What do you do next?

Evaluation

- MRI: subtle increase size of the temporal horn of left lateral ventricle without signal change
- V-EEG (scalp):
  - interictal: diffuse slowing (mild) (7-8 Hz wake)
    focal slowing, bi-temporal
    sharp waves, independent T_3 and T_4
  - ictal: 5 seizures (2 right temporal, 2 left temporal, 1 bilateral)
- Neuropsychology: bi frontal-temporal dysfunction (L>R)

Treatment Options

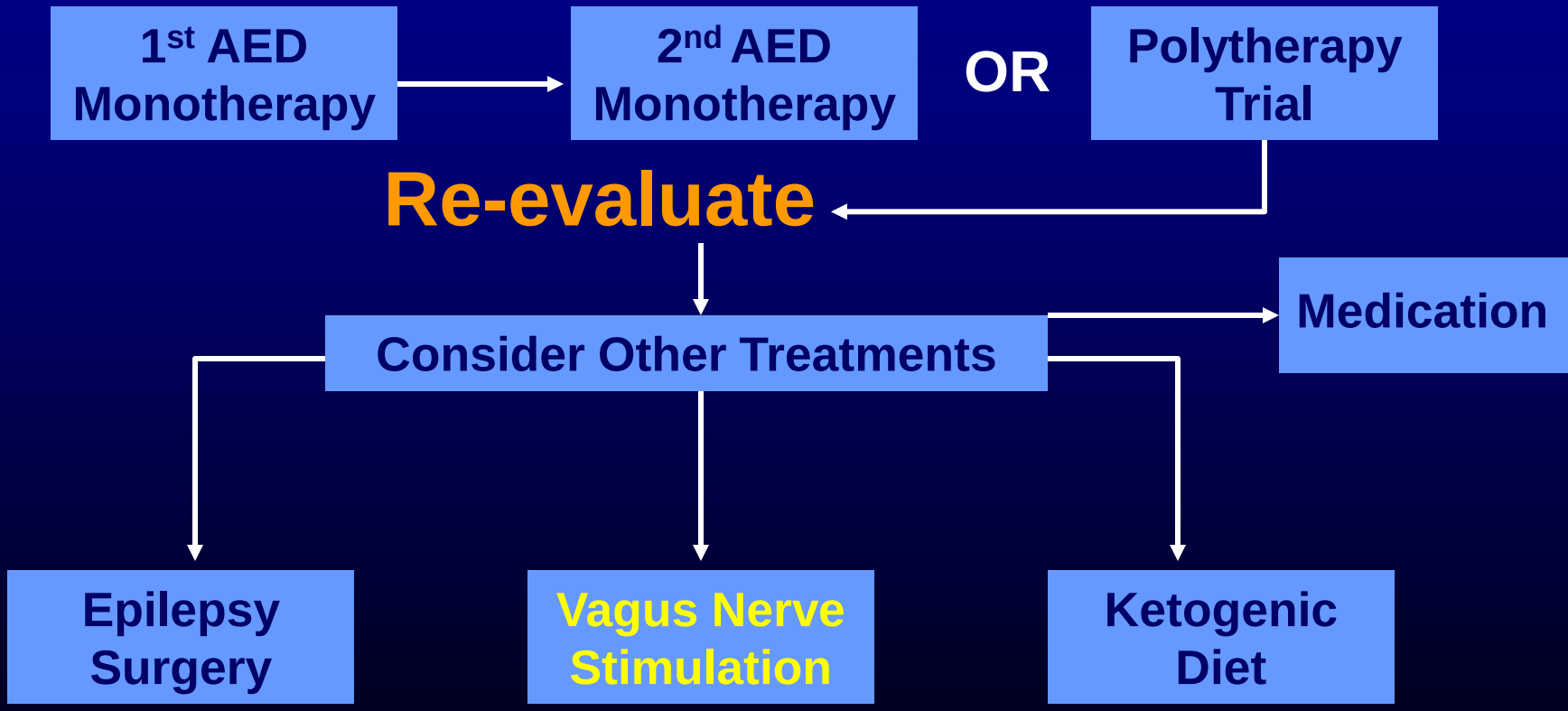


Other Anti-Epileptic Drugs **VNS Therapy**

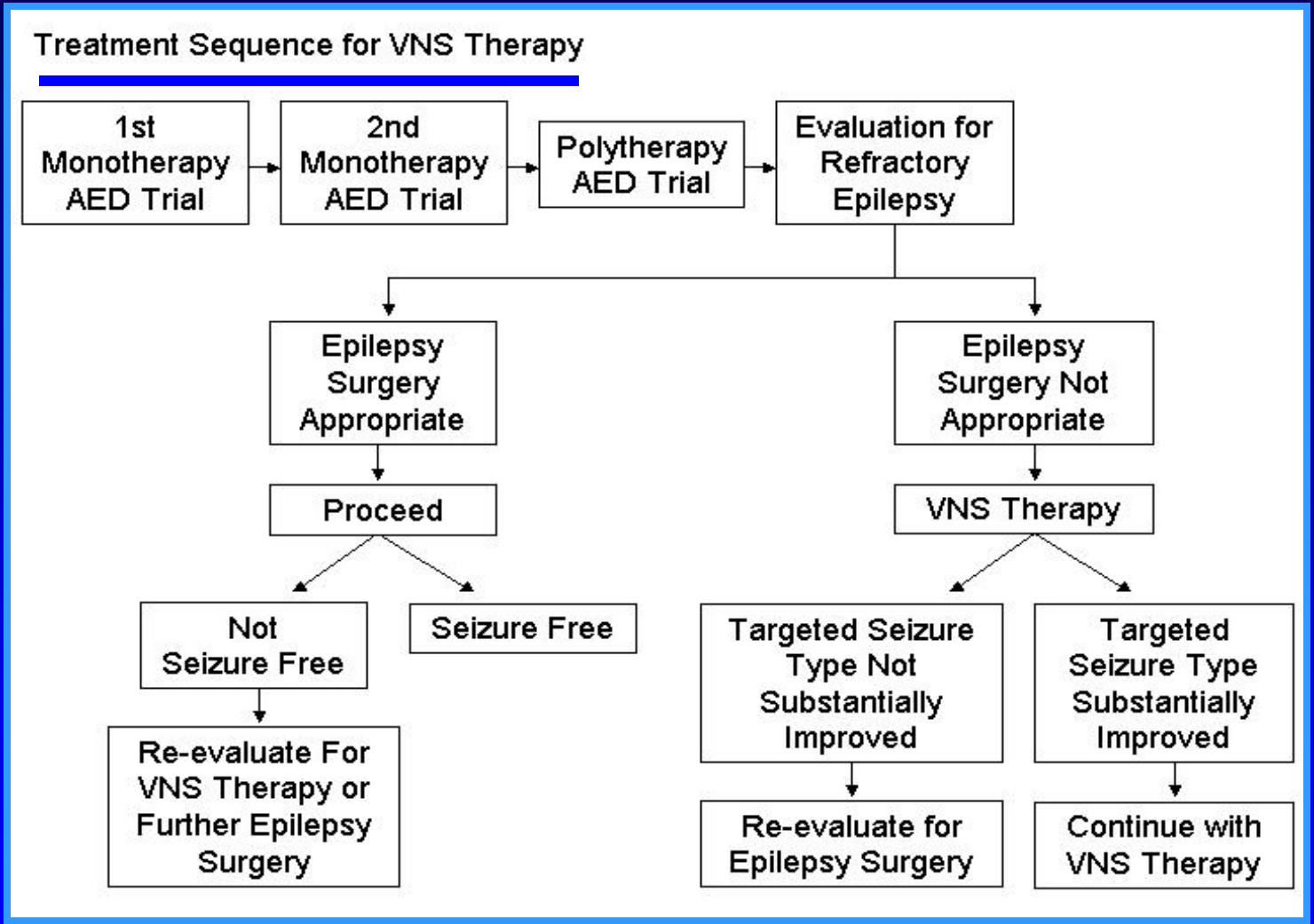
- **VNS therapy added to topiramate & levetiracetam**
- **last 22 months**
  - **No secondary GTC seizures**
  - **1 complex partial seizure every 4 to 6 weeks**

Pharmacoresistant Epilepsy

What do you do when AEDs fail?



Treatment Sequence for VNS Therapy



Wheless JW. Neurostimulation Therapy for Epilepsy. *Advanced Therapy in Epilepsy*. Hamilton, Ontario: BC Decker, Inc. 2009

VNS Therapy: Intractable Partial Onset Seizures

Consider VNS Therapy if:

- Non-lesional MRI, symptomatic or cryptogenic epilepsy (especially extra-temporal lobe, partial onset seizures)
- Normal interictal EEG, or bilateral independent or multifocal epileptiform discharges on EEG
- Contraindication to epilepsy surgery (i.e., memory, ictal zone overlaps eloquent cortex,etc.)

VNS Therapy: Intractable Partial Onset Seizures

Consider VNS Therapy if:

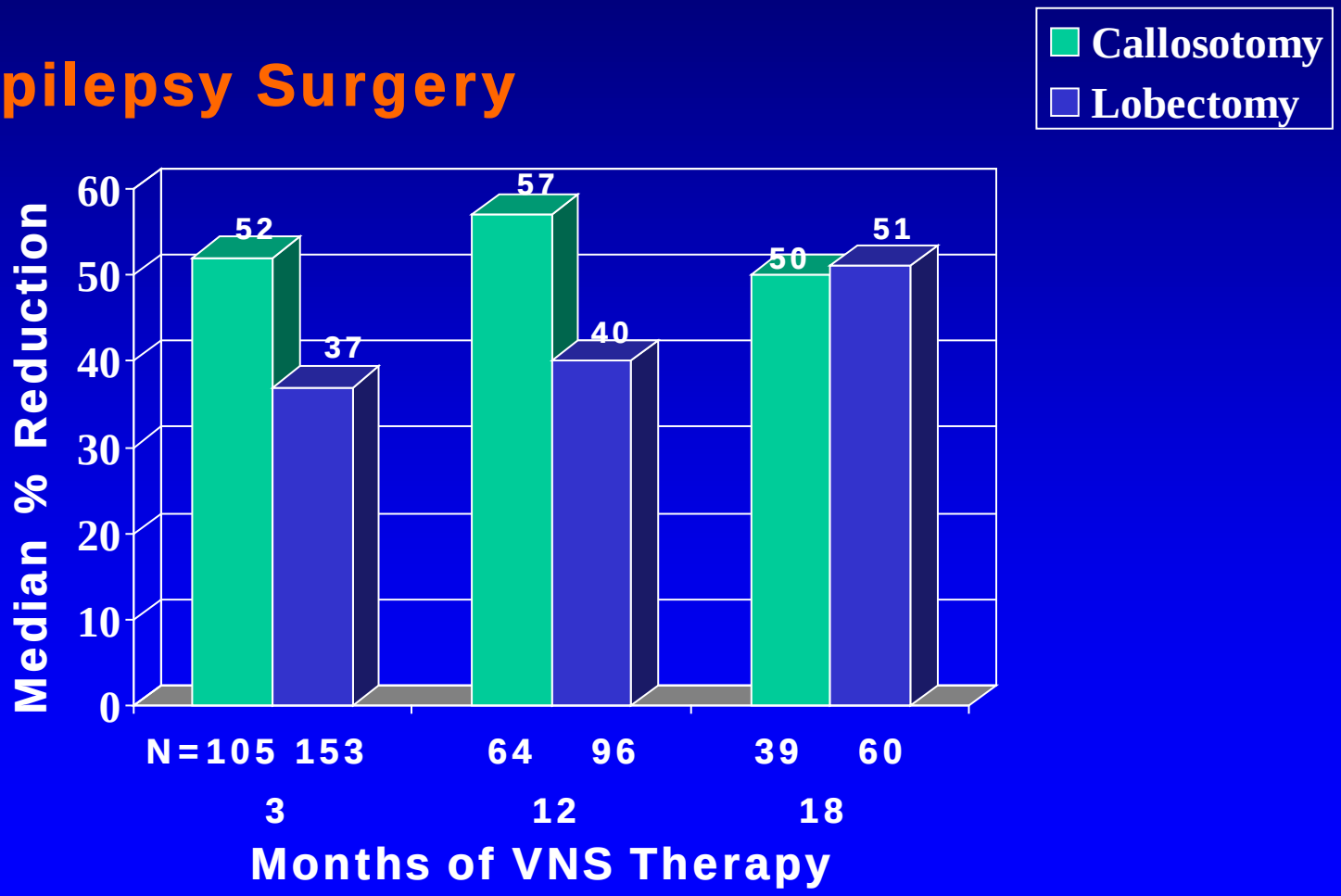
- Partial onset seizures of independent hemisphere onset
- Symptomatic generalized epilepsy

Identifing Candidates for VNS Therapy

- Intractable Seizures
  - Etiology
  - Co-morbid conditions
    (mood disorder/depression)
  - History of anti-epileptic drug adverse events
  - Adherence issues
  - Failure of prior epilepsy surgery
- Efficacy of VNS Therapy

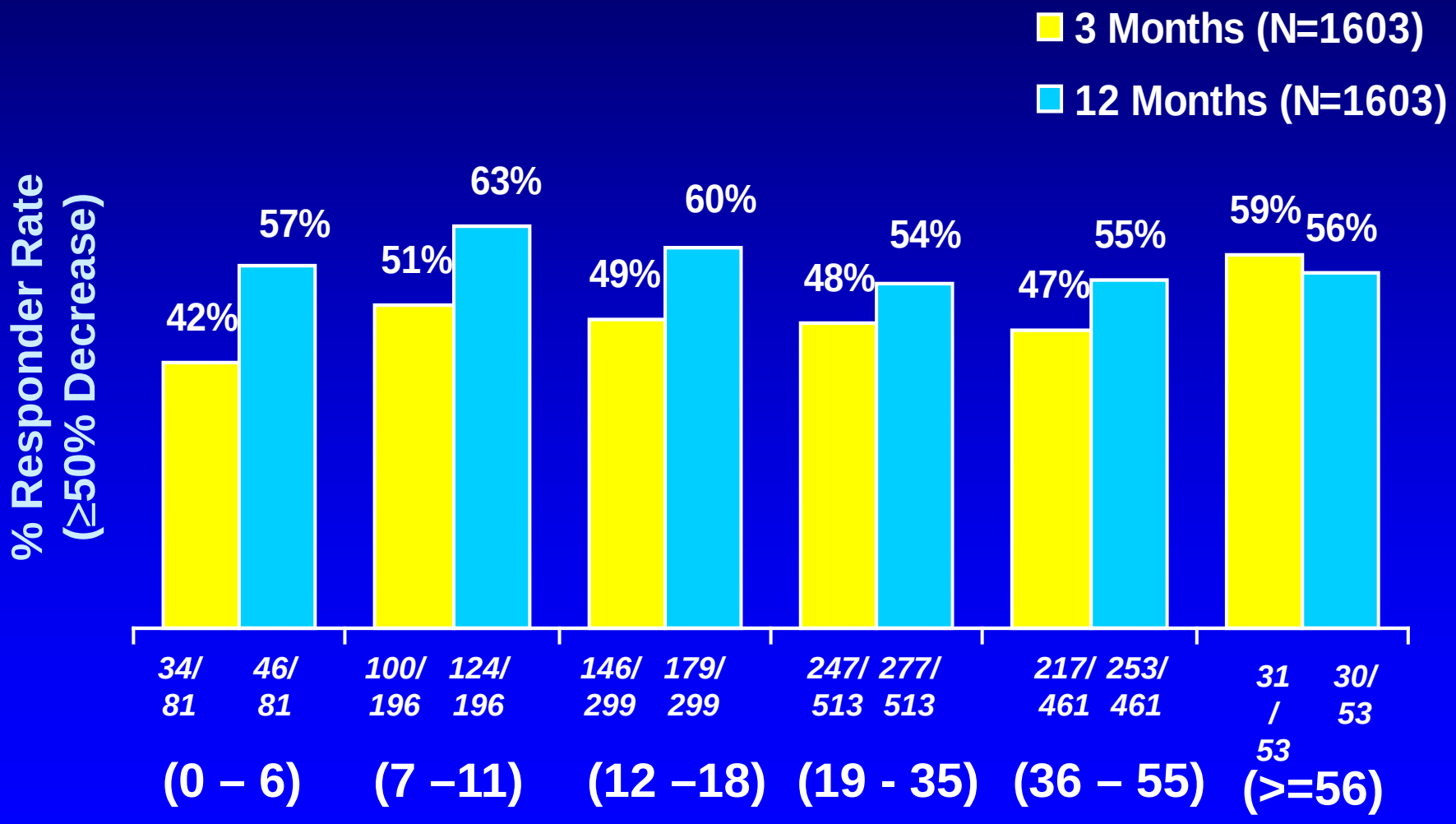
VNS Therapy : Special Population

Prior Epilepsy Surgery



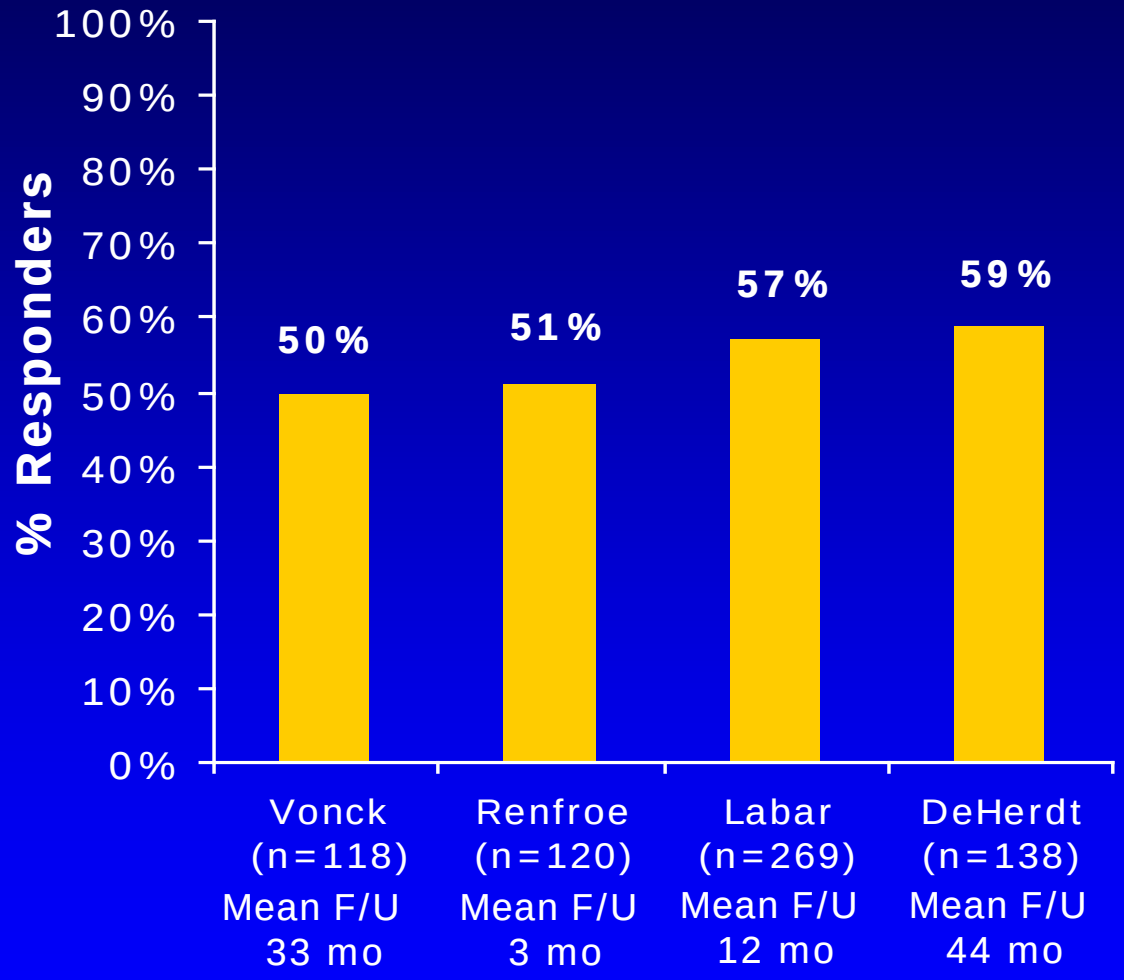
Amar AP et al. Neurosurg, 2004, 55(5): 1086-1093

VNS Effectiveness by Age Group (Years)



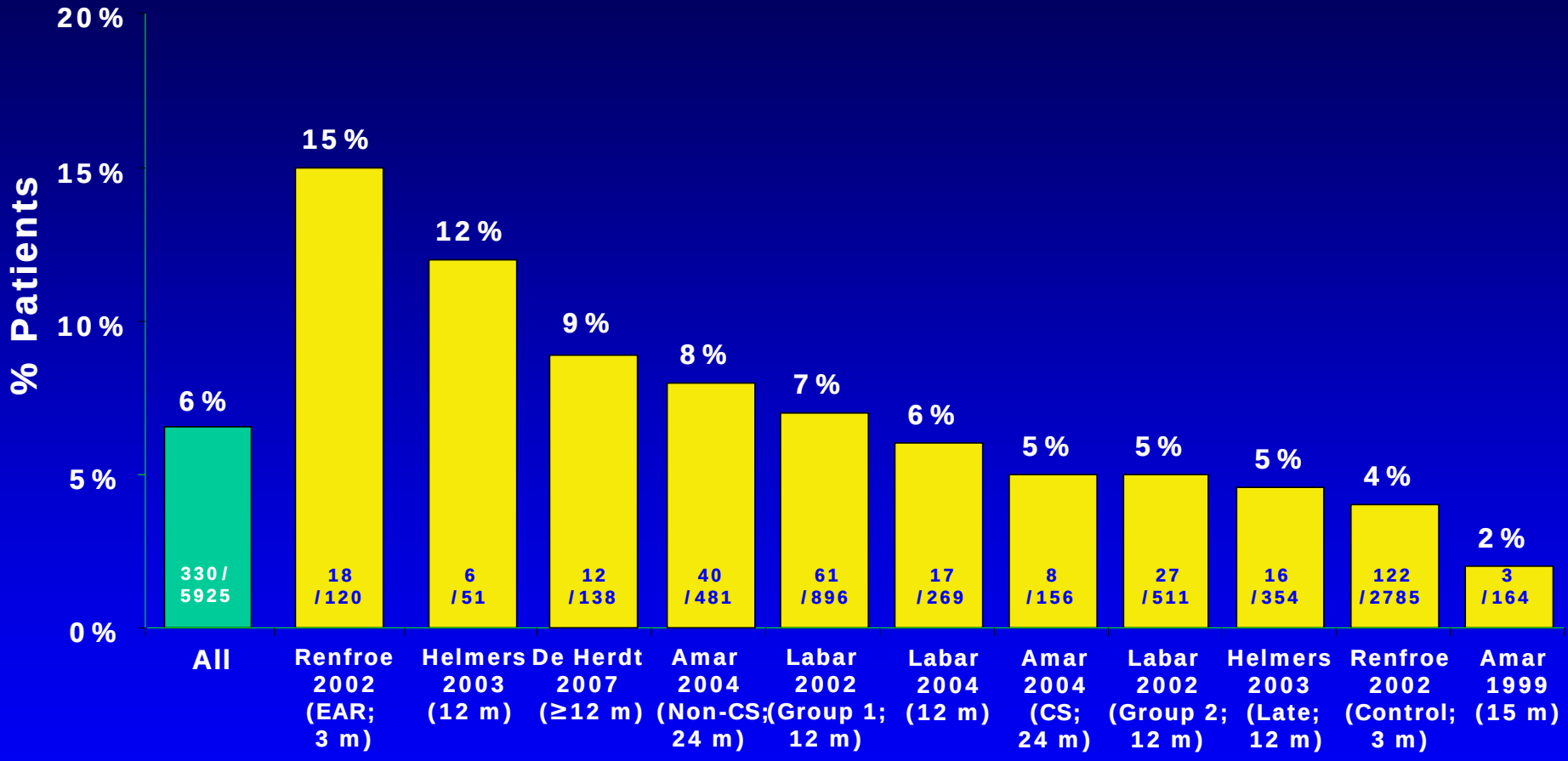
Cyberonics, 1/25/02

Average VNS Therapy Real-World Responder Rate is ~50%



1. De Herdt V, et al. *Eur J Paediatr Neurol* 2007;11:261-9. 2. Labar DR. *Seizure* 2004;13:392-8. 3. Renfroe JB and Wheless JW. *Neurology* 2002;59(suppl 4):S26-S30. 4. Vonck K, et al. *J Clin Neurophysiol* 2004;21:283-9.

VNS Therapy Seizure-Free Rates



1. Renfroe JB and Wheless JW. *Neurology* 2002;59(suppl 4):S26-S30. 2. Helmers SL, et al. *Neurologist* 2003;9:160-4. 3. De Herdt V, et al. *Eur J Paediatr Neurol* 2007;11:261-9. 4. Amar AP, et al. *Neurosurgery* 2004;55:1086-93. 5. Labar DR, et al. *Neurology* 2002;59:S38-43. 6. Labar DR. *Seizure* 2004;13:392-8. 7. Amar AP, et al. *Stereotact Funct Neurosurg* 1999;73:104-8. 8.Ghaemi K et al. Seizure,2010;19:264-268(6.9%).

VNS Therapy Earlier Use Study

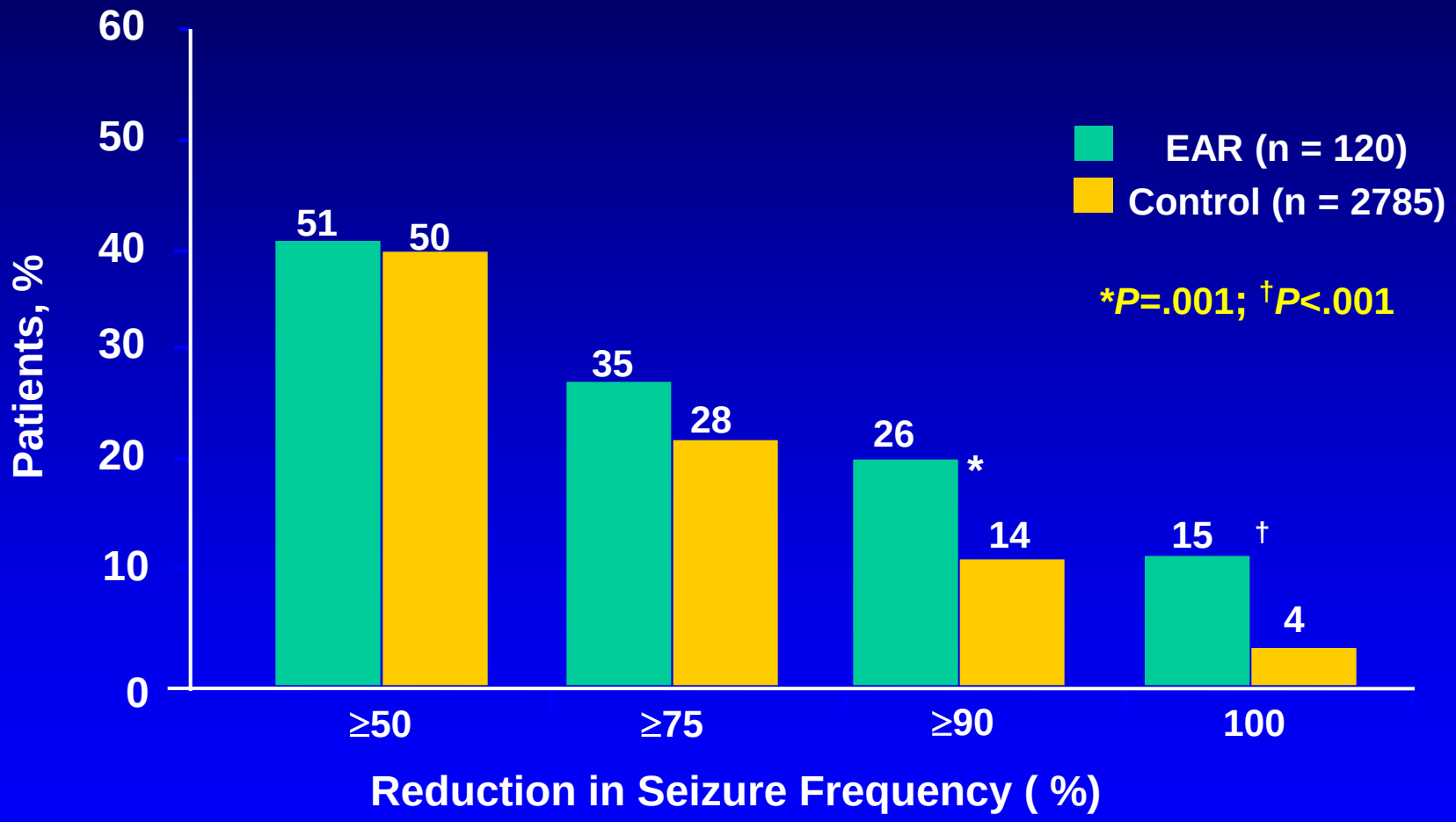
- Multicenter study
- Early Adjunctive Registry (EAR group)
  - n = 120
  - Prospectively enrolled
  - **≤5 years of epilepsy at VNS implantation**

    OR
  - **≤4 standard AEDs before VNS implantation**
- Control group
  - n = 2785
  - Retrospectively extracted from Patient Outcome Registry data
- Seizure and quality-of-life data collected at baseline and 3 months
- Patient demographics
  - EAR n = 120, Control n = 2785
  - Mean age: control = 28.9 years, EAR = 18.7 years
  - Years of epilepsy (mean): control = 21.7 years, EAR = 5.9 years

Renfroe JB and Wheless JW. *Neurology.* 2002;59(suppl 4):S26-S30.

VNS Therapy Earlier Use Study

Reduction in Seizure Frequency at 3 Months



32% of patients with complex partial seizures were seizure free at 3 months

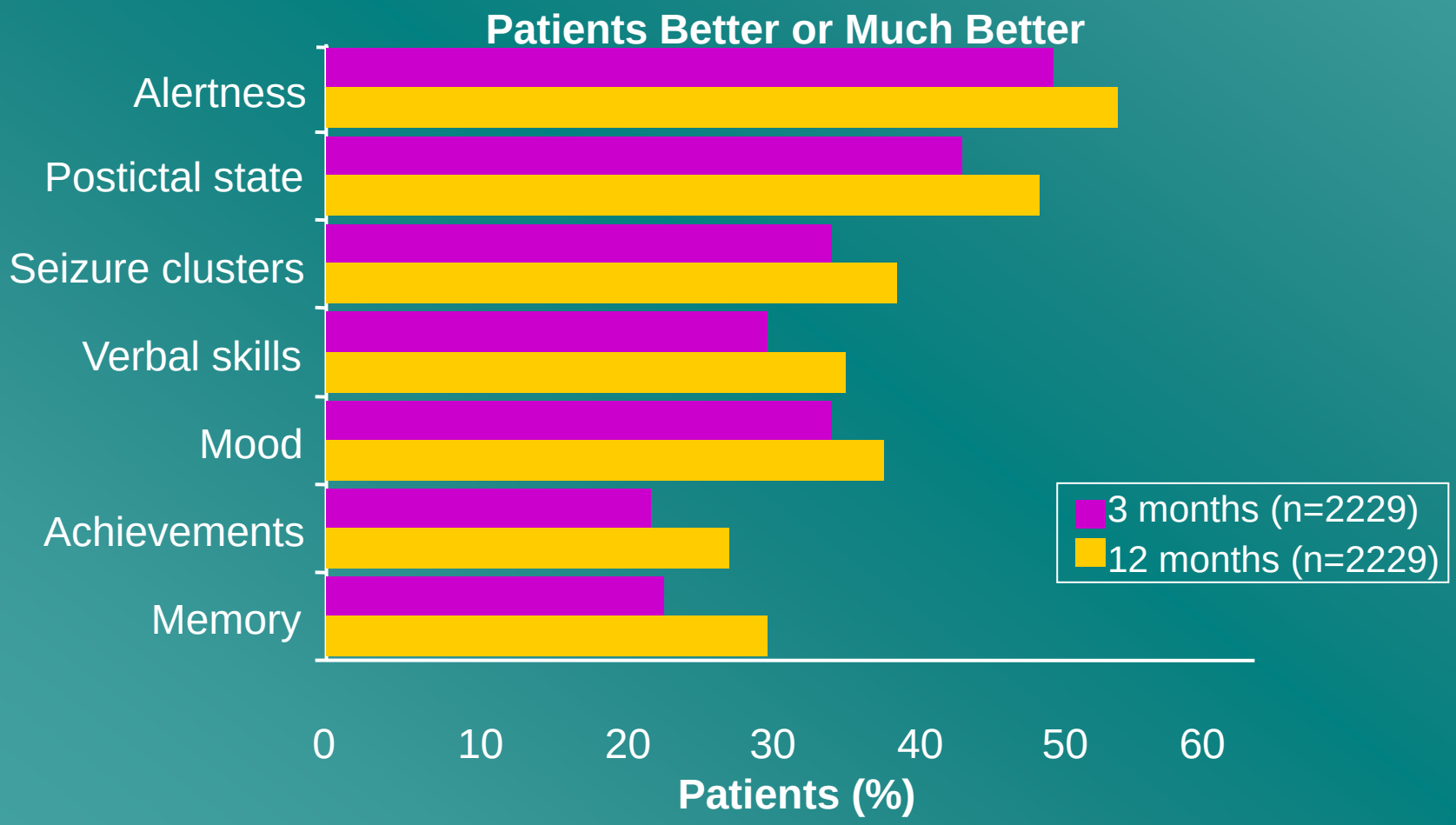
Renfroe JB and Wheless JW. *Neurology.* 2002;59(suppl 4):S26-S30.

VNS Therapy Earlier Use Study
Quality-of-Life Measures at 3 Months

*P=0.030; †P<0.002

Renfroe JB, Wheless JW. *Neurology.* 2002;59(suppl 4):S26-S30.

VNS Therapy Quality of Life Patient Outcome Registry



Cerebellar Stimulation

Level IV

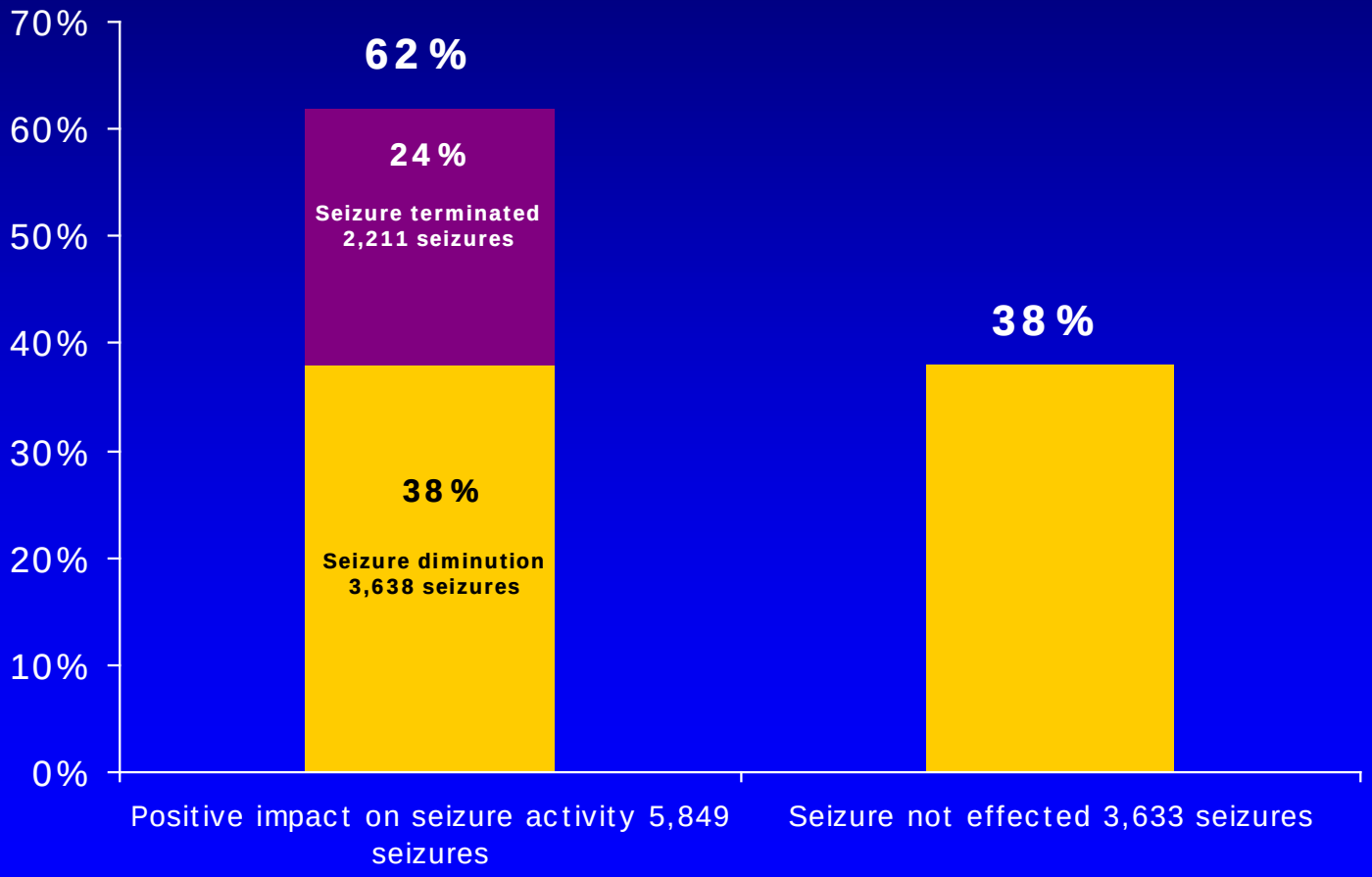
- Cooper, Arch Neurol., 1976; 33: 559.
  - N = 15 (Adult), 10/15 (67%) improved, up to 3 years
  - **Alert, reduced anxiety & depression**
- Cooper, Trans Am. Neurol. Assoc., 1973; 98: 192.
  - N = 7 (Adult), 6/7 (86%) improved, up to 8 months
- Cooper, Appl. Neurophysiol., 1977/78; 40: 124
  - N = 32 (Adult), 18/32 (56%) improved

Level I

- Van Buren, J. Neurosurg., 1978; 48: 407
  - N = 5 (Adults), none changed
  - **Alert, improved functional status**

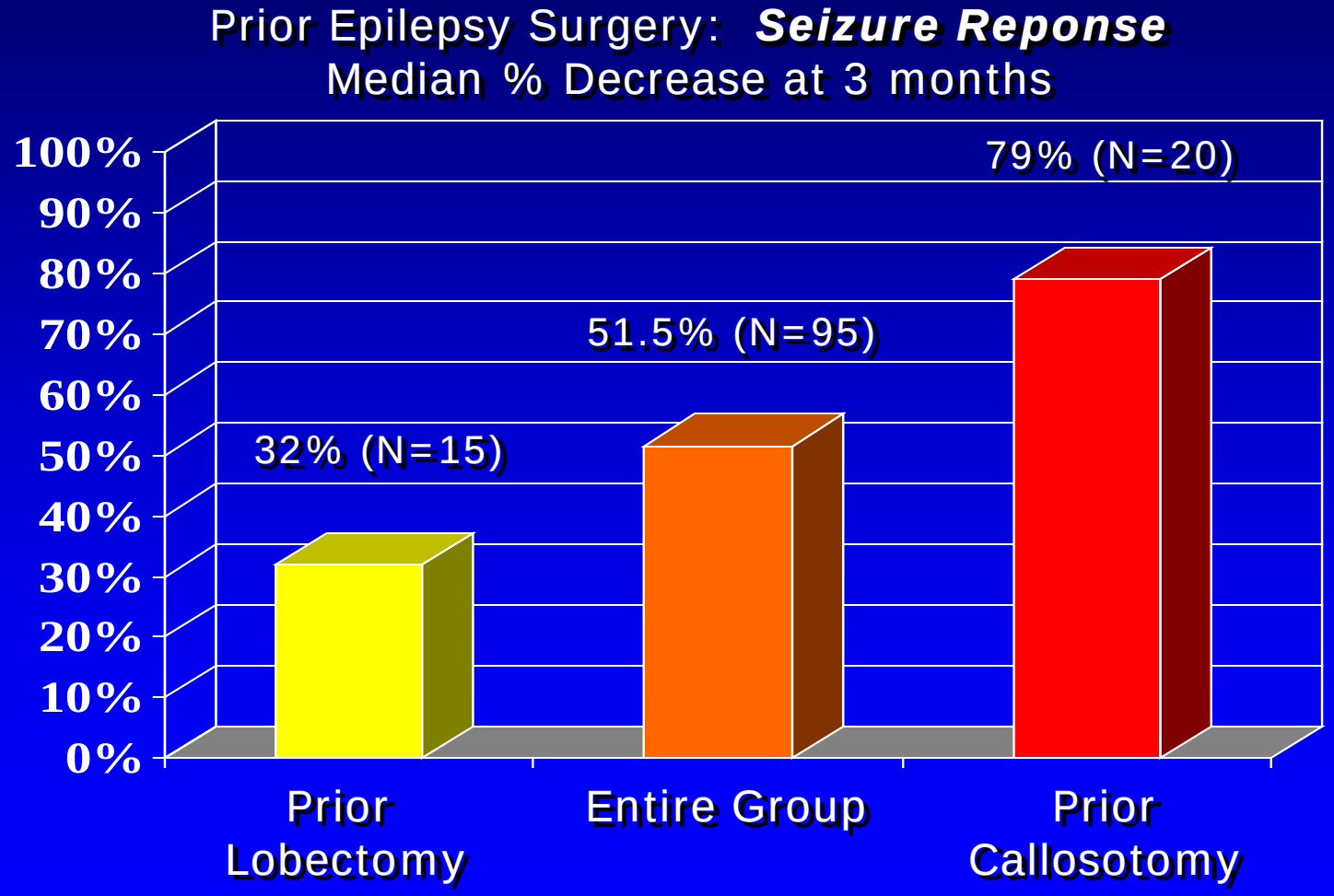
Many Patients Are Able To Stop or Decrease the Severity/Duration of Their Seizures Using the VNS Therapy Magnet

Effect of Magnet-Activated Stimulation in 9,482 Seizures



Morris GL, et al. Epilepsy and Behavior 2003;(4):740-745.

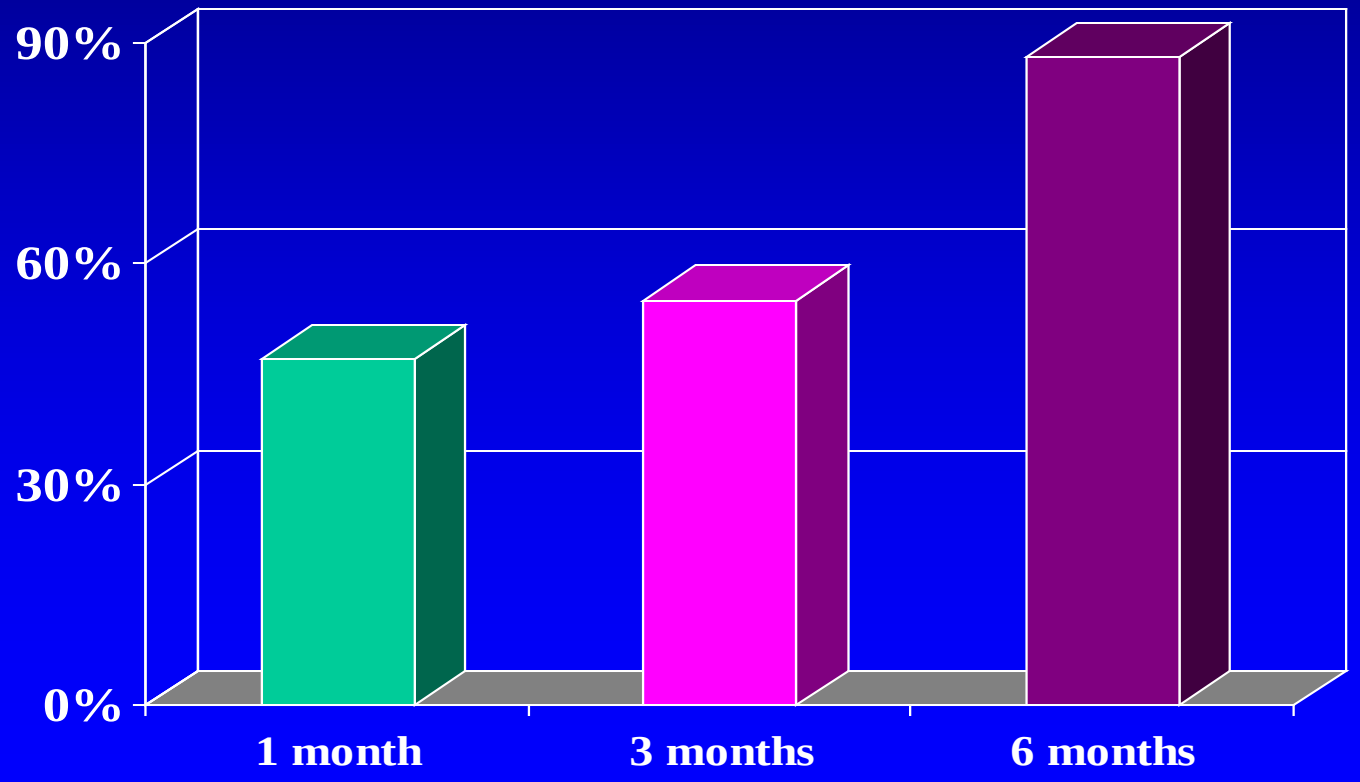
VNS in Pediatric Patients with Refractory Epilepsy



Helmers SL, Wheless JW et al; J. Child Neurol., 2001: 843-848

VNS in Lennox-Gastaut Syndrome

Drop Attacks (N=33) Median Seizure Reduction



Frost M, Wheless JW et al, Epilepsia 2001: 1148-1152

VNS Therapy: Lennox-Gastaut Syndrome

Author, Year	N	Responder Rate (>50% ↓)	or	Median % (Sz Reduction)
Hornig G W, 1997	6	83% with > 90% ↓		
Lundgren J, 1998	4	50%		
Parker APJ, 1999	9			34%
Hosain S, 2000	13	46%		
Majoie HJM, 2001	16	25%		
Frost M, 2001	46	43%		
Benifla M, 2006	10	40%		
Rychlicki F, 2006	8			33%
Rossignol E, 2009	5	80%		
Shahwan A, 2009	9	78%		
Kostov K, 2009	30			60.6%
Cersosimo R 2011	46	65%		

1 Hornig GW et al, Southern Med J, 1997; 90(5): 484-88. 2 Lundgren J et al, Epilepsia, 1998; 39(8): 809-813
3 Parker APJ et al, Pediatrics, 1999; 103: 778-782. 4 Hosain S et al, J Child Neurol, 2000; 15: 509-512
5 Majoie HJ et al, J Clin Neurophysiol, 2001; 18(5): 419-428. 6. Frost M et al, Epilepsia, 2001; 42(9): 1148-1152
7 Benifla M et al, Childs Neuro Syst, 2006; 22: 1018-1026. 8. Rychlicki F et al, Seizure 2006; 15: 483-490
9 Rossignol E et al, Seizure, 2009; 18: 34-37. 10 Shahwan A et al, Epilepsia, 2009. 11. Kostov K et al, Epil & Behav, 2009;16:321-324. 12. Cersosimo RO et al. Epileptic Disord, 2011; 13(4): 382-388.

Symptomatic Generalized Seizures: VNS Therapy or Corpus Callosotomy

Center	Seizure Type(s)	Number / Procedure	Responder Rates
You SJ, 2008[1] Seoul, Korea (Retrospective) (Children)	Drop Attacks (LGS) N=24	14 Callosotomy 10 VNS	64.3% 70%
Nei M, 2006[2] Philadelphia, PA (Prospective) (Adults)	GTC (N=71) Tonic/Atonic (N=26)	53 Callosotomy 25 VNS	80%- GTC 78%- Atonic/Tonic 50%- GTC 67%- Atonic/Tonic

[1] You SJ et al, Brain & Develop, 2008; 30: 195-199

[2] Nei M et al, Epilepsia, 2006; 47(1): 115-122

Factors to Consider in the Decision of VNS Therapy vs. Corpus Callosotomy

	VNS Therapy	Corpus Callosotomy
High Frequency Seizure		✓
Tall, heavy child		✓
Unable to tolerate complications	✓	
Interictal EEG – bilateral, independent spikes	✓	

With either procedure, judge outcome by response after 6 months .

VNS Therapy: Stimulation Parameters

Decisions to make:

- Magnet strength, duration (icing on the cake)
- Stimulation strength (dose amount)
- Stimulation on/off time (dosing frequency)
- Stimulation pulse width, frequency (AE control)

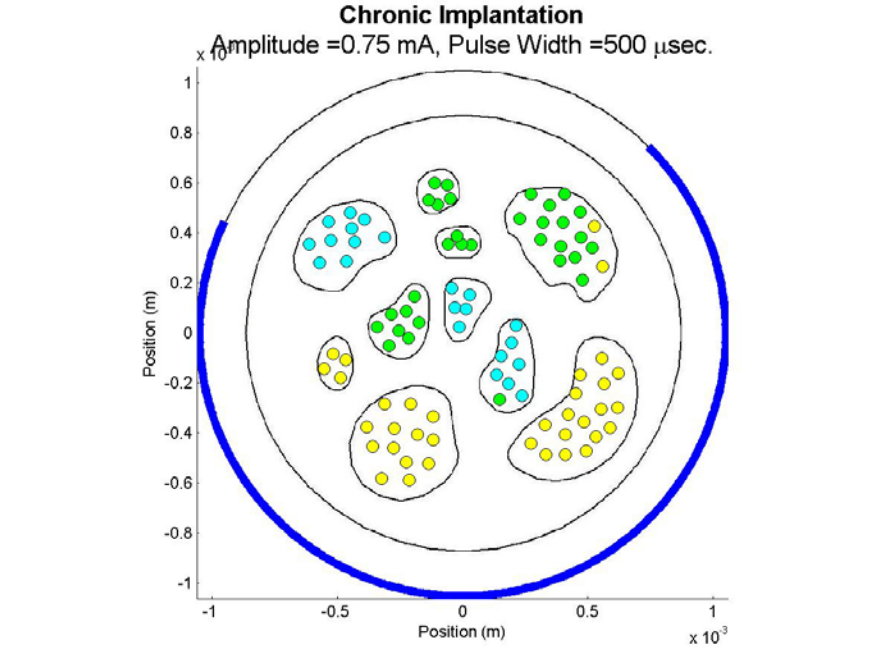
VNS PULSE GENERATOR PARAMETERS

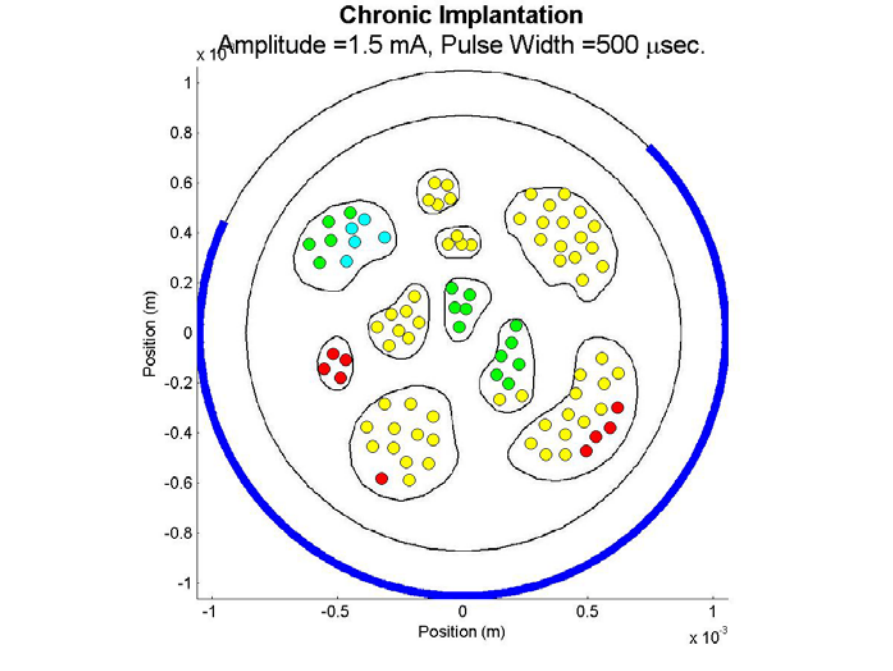
- Dose adjustment **goal** is to maximize the therapeutic effect while minimizing side effects.

Stimulation Variables
Ranges

Parameter	Units	Range	Suggested
Output current	milliamps	0–3.5	>1.50
Signal frequency	hertz	1–30	20
Pulse width	microseconds	130–1000	250
ON-time	seconds	7–60	7 (14)
OFF-time	minutes	0.2–180	0.3 (0.5)
Magnet Settings			
Output current	milliamps	0–3.5	>1.75
Pulse width	microseconds	130–1000	250
ON-time	seconds	7–60	14

Chronic Activation





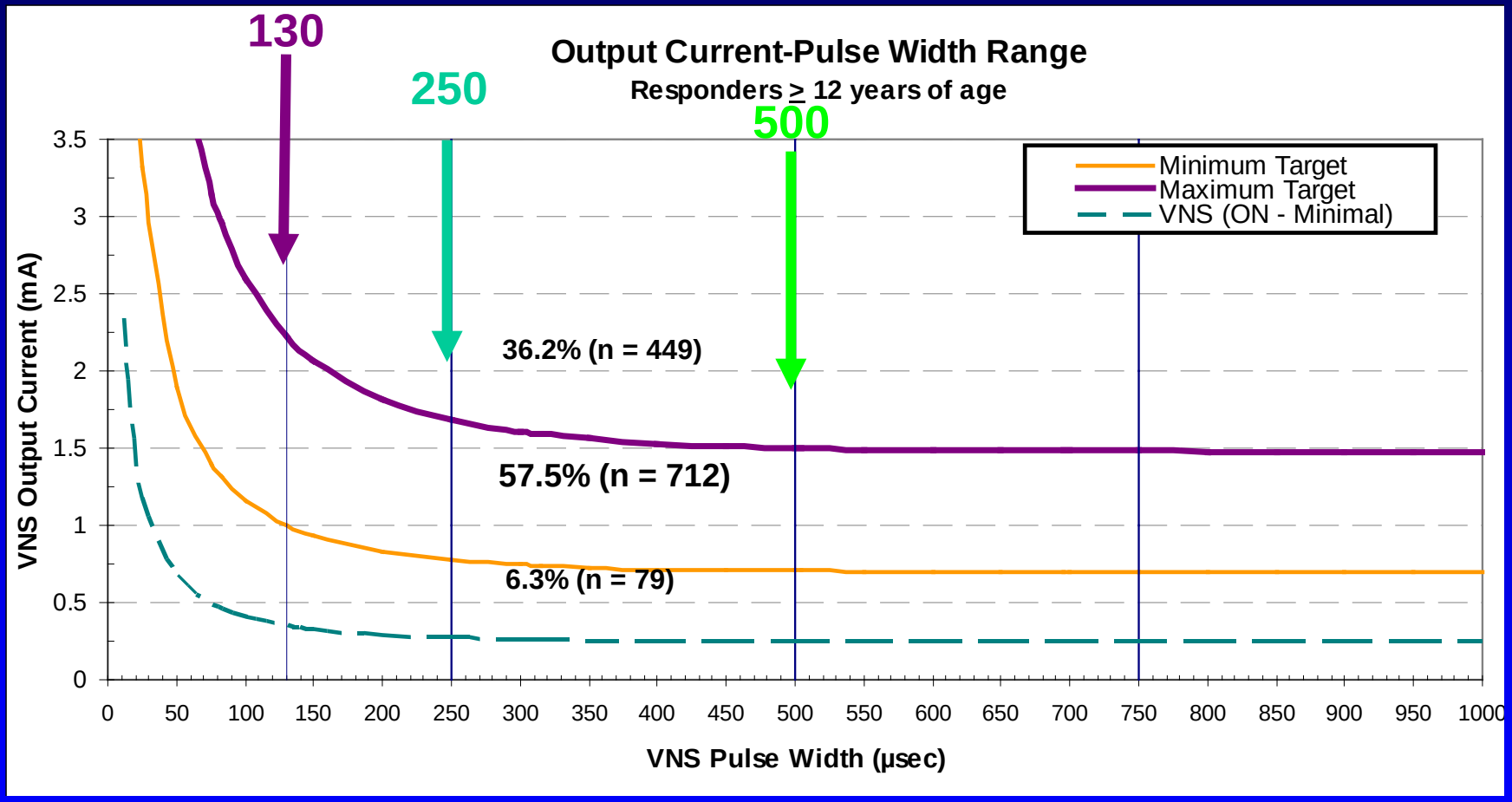
0.75 mA, 500 μsec | **1.50 mA, 500 μsec**

• 1 μ • 2 μ • 3 μ • 5 μ • 10 μ

Output (mA)	PW (μsec)	Percent stimulated (Chronic Model)				
		1 to 1.9 μ	2 to 2.9 μ	3 to 4.9 μ	5 to 9.9 μ	10 to 20 μ
0.75	500	0%	40%	76%	**100%**	**100%**
1.50	500	10%	77%	**94%**	**100%**	**100%**

Helmers SL et al. Acta Neurol Scand, 2012

VNS Parameters: Pulse Width



*Minimum line derived from intraoperative measurements by Evans et al. (2004); Maximum line derived from Epilepsy Patient Registry of responders

Stimulation Variables
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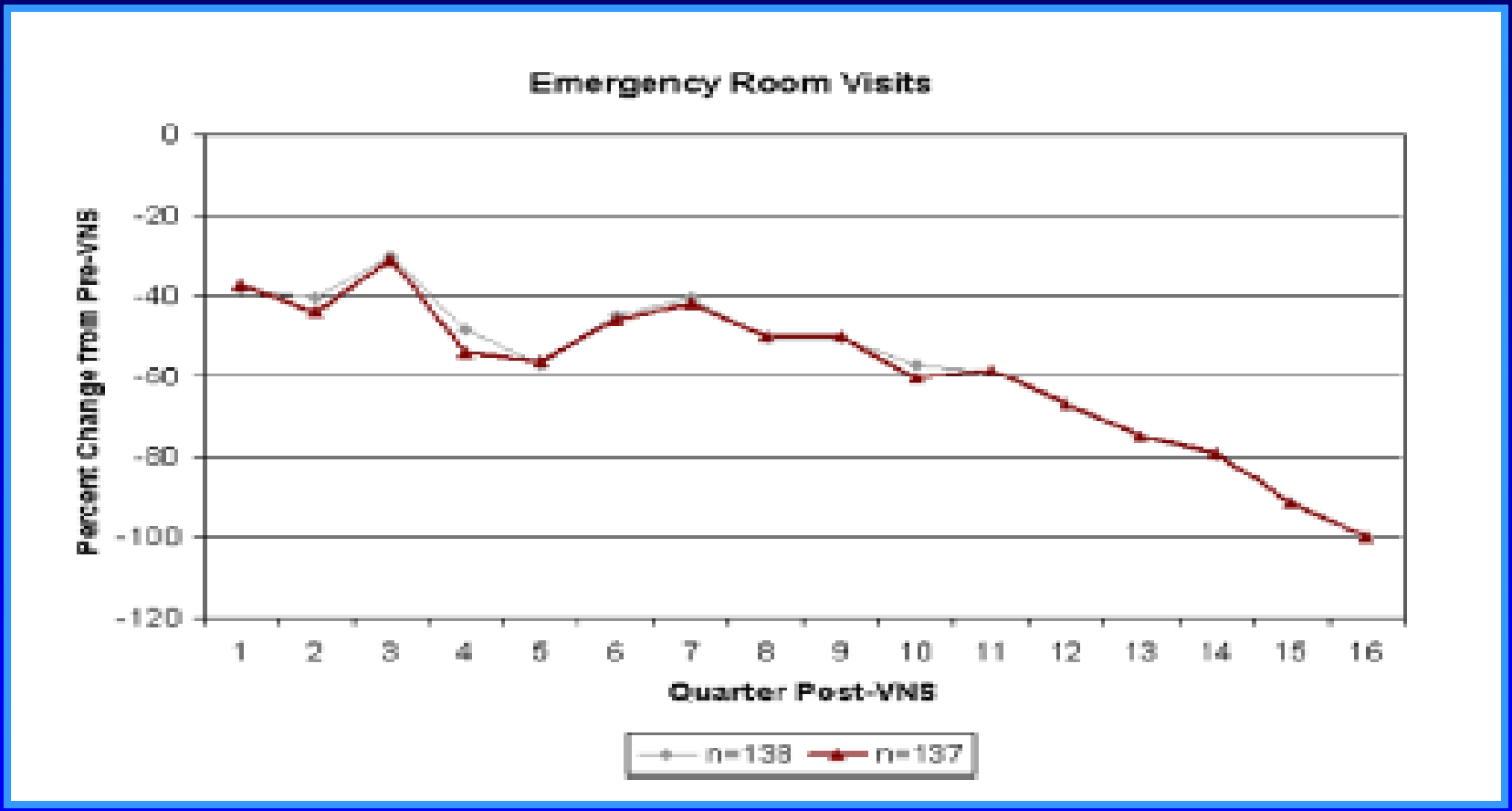
Magnet Settings			
Output current	milliamps	0–3.5	>1.75
Pulse width	microseconds	130–1000	250
ON-time	seconds	7–60	14

VNS Therapy: Effect on Healthcare Utilization



n = 138 denotes all patients in analysis
n = 137 excludes patients with high utilization (outliers)

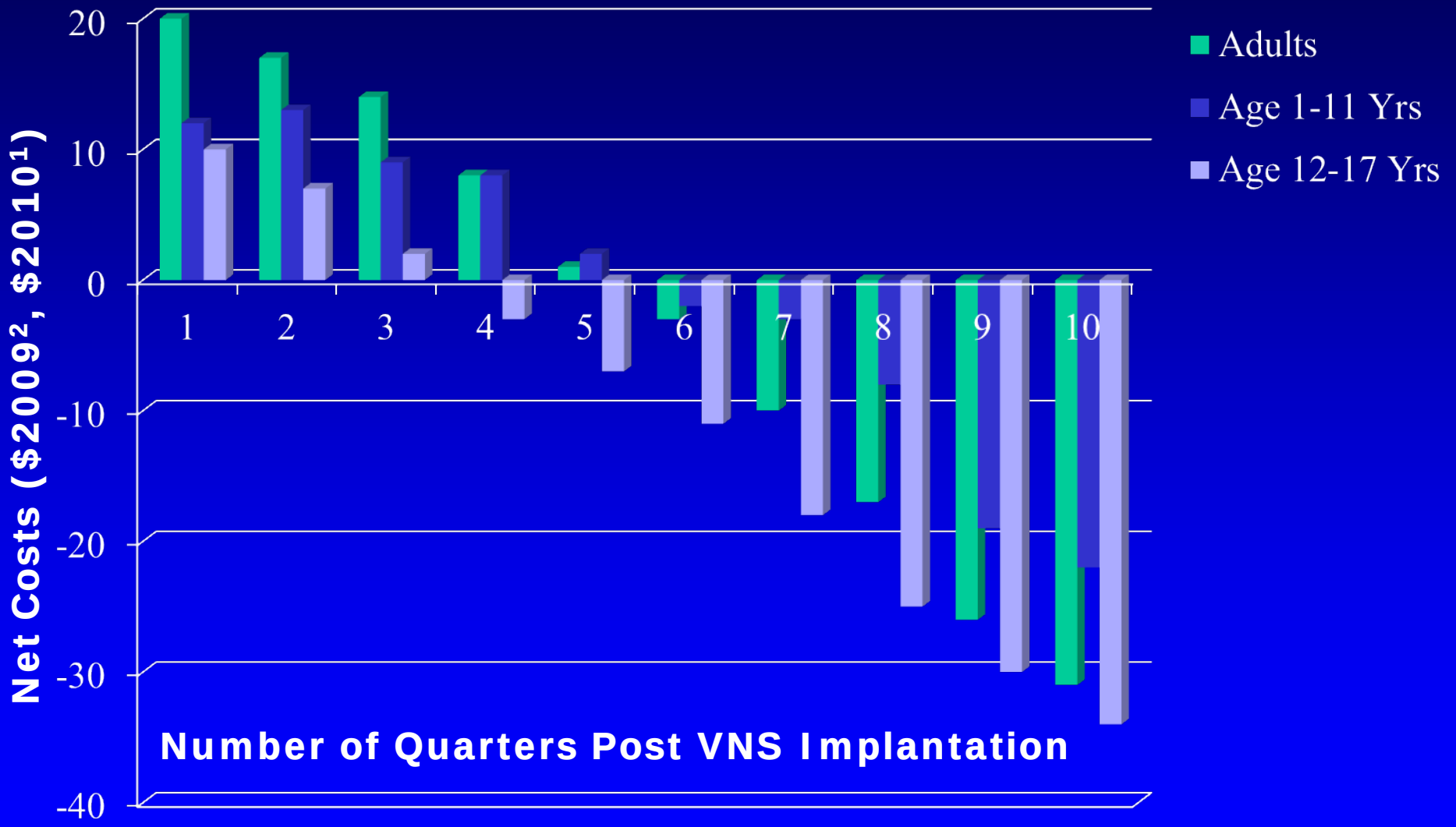
Bernstein AL, et al. *Epilepsy Behav*. 2006;10(1):134-137.

Clinical & Economic Impact of Vagus Nerve Stimulation

	Children[1] (1-11 Yrs) (N=238)	Adolescents[1] (12-17 Yrs) (N=207)	Adults[2] (N=1655)
AED Usage	• by 1	• by 0 .6	• by 0 .3
Seizure –Related Hospitalizations	•	•	•
ED Visits	•	•	•
Head Traumas	•		•
GTC Status Epilepticus		•	•
Fractures			•
Average F/U Period (mo.)	28.3	29.8	30.4

[1]Helmers SL et al. Eur J of Paediatric Neurol, 2012
[2]Helmers SL et al. Epil & Behav, 2011; 22(2): 370-375

Clinical & Economic Impact of Vagus Nerve Stimulation



[1]Helmers SL et al. Eur J of Paediatric Neurol, 2012

[2]Helmers SL et al. Epil & Behav, 2011; 22(2): 370-375

VNS Therapy: Candidates - Take Home Message

Features Which Help Identify Candidates

Seizure Type

- Drop Attacks (astatic events)
- Symptomatic generalized tonic-clonic seizures
- Simple partial → complex partial / secondary GTC
- Partial onset seizures (non-lesional)
- Refractory primary generalized epilepsy (JME, Absence)

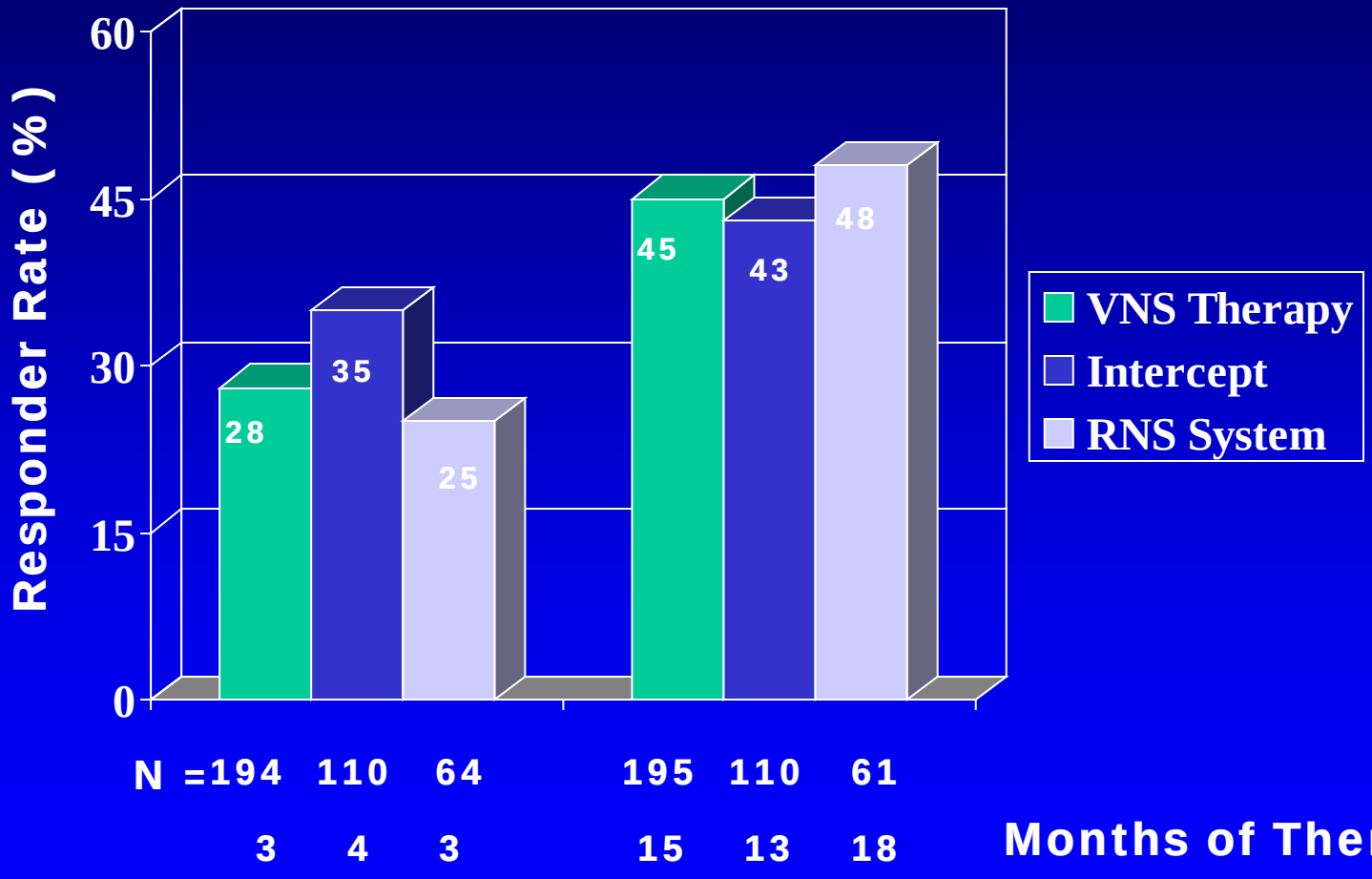
Patient Factors

- Sensitive to Antiepileptic Drug (AED) side effects.
- Co-morbid depressed mood.
- Poor adherence with AED regimen.
- Frequent ED visits / Hospitalizations
- Failed prior epilepsy surgery

VNS Therapy: How to Gauge If the Device Is Helping?

- Targeted seizure type is improved.
- Antiepileptic drug burden is decreased
- Decreased emergency department visits or injuries secondary to seizures
- Improved quality of life (more alert, post-ictal phase shorter, magnet responsive, etc.)
- Patient thinks continuing with VNS Therapy is worthwhile!

Neurostimulation for Epilepsy: Efficacy



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I hope this has stimulated your thinking about the treatment of epilepsy.

Thank you !

Questions ?