A TMS Investigational Device for Migraine relief

Lightweight device, intended for home use, delivers fixed pulse, has over use limits in place

TMS future as clinical treatment

- Currently FDA reviewing application for approval for TMS as a treatment for major depression
- TMS clinically available in Canada, Australia, Israel & Europe
- Available off-label in some centers in the US
- TMS is a safe intervention & may be promising option for a number of psychiatric & neurological disorders

Magnetic Seizure Therapy (MST)

Investigational

Magnet-induced stimulus (like rTMS)

High Intensity

Target "antidepressant regions"

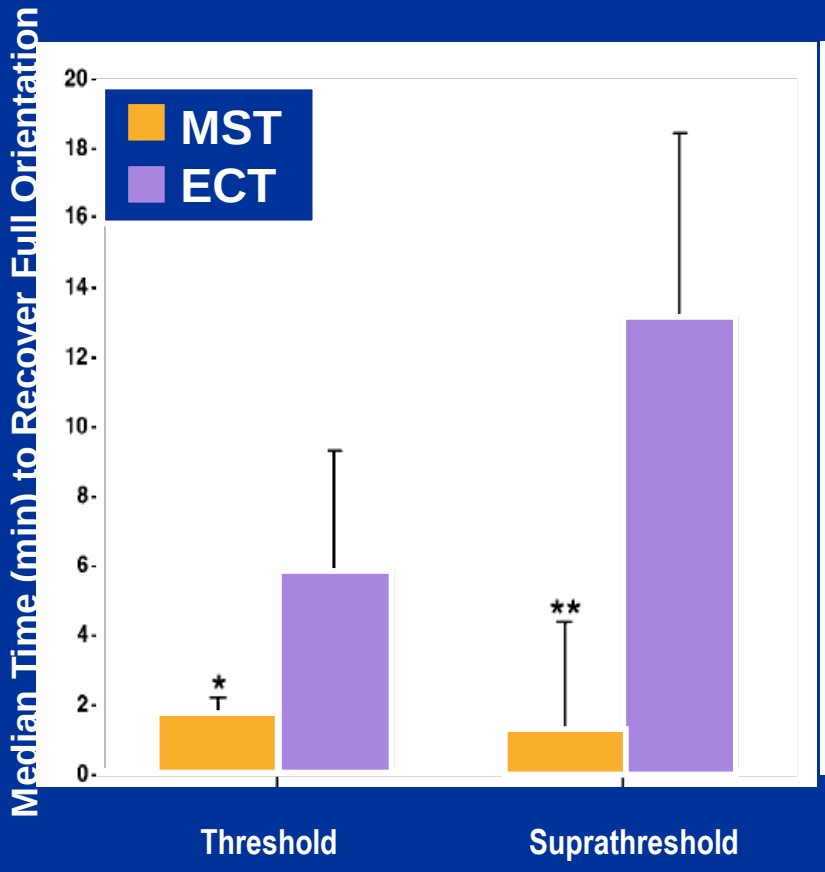
Fewer side effects

3 sessions/week

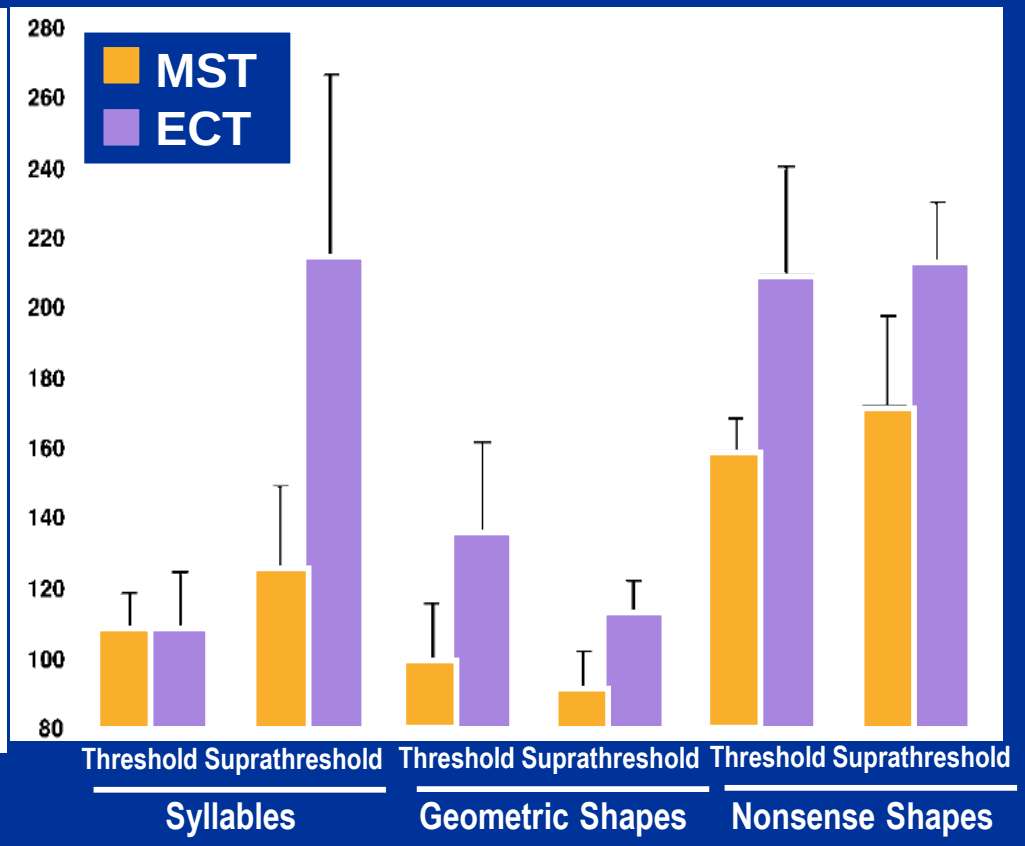
Same as ECT

- Anesthesia
- Tonic clonic seizure
- Monitor EEG, vitals

MST: Shorter Period of Post-Ictal Disorientation and Inattention



*Threshold MST v.ECT, p<.004



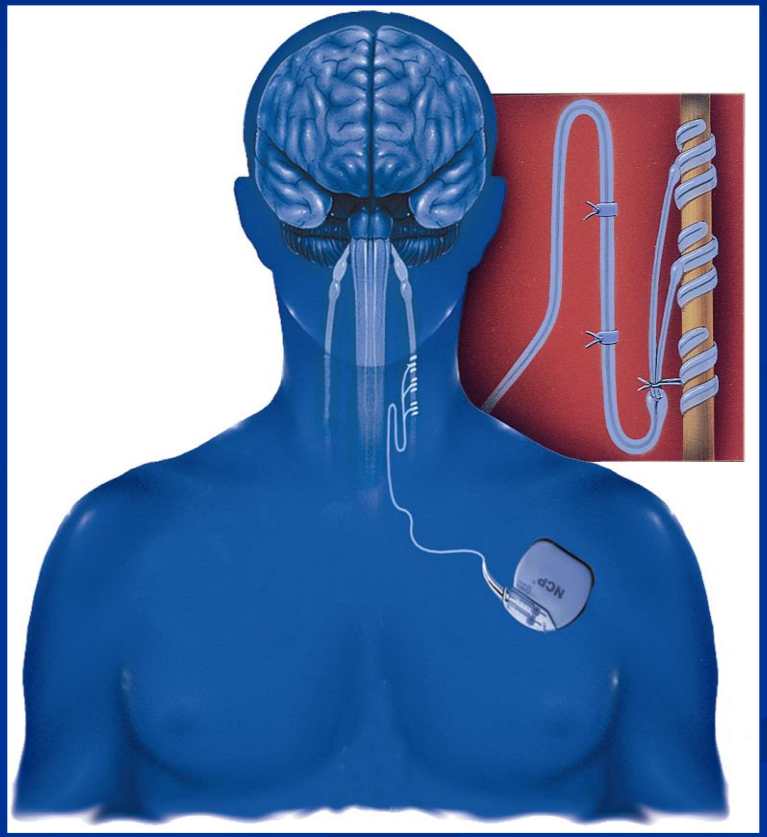
Faster following MST, p<.01

Lisanby SH et al. *Neuropsychopharmacology.* 2003.

This information concerns a use that has not been approved by the U.S. Food and Drug Administration

Vagus Nerve Stimulation (VNS)

- FDA approved for epilepsy; FDA approved for TRD July, 2005
- Implanted in over 30,000 patients worldwide
- Pulse generator implanted in left chest wall area, connected to leads attached to left vagus nerve
- Mild electrical pulses applied to CN X for transmission to the brain



Vagus Nerve Stimulation (VNS)

Intermittent, cycled stimulation

- 30 sec on/5 min off
- 24/7 continuous cycles

In-office programming (dosing) by the treating physician

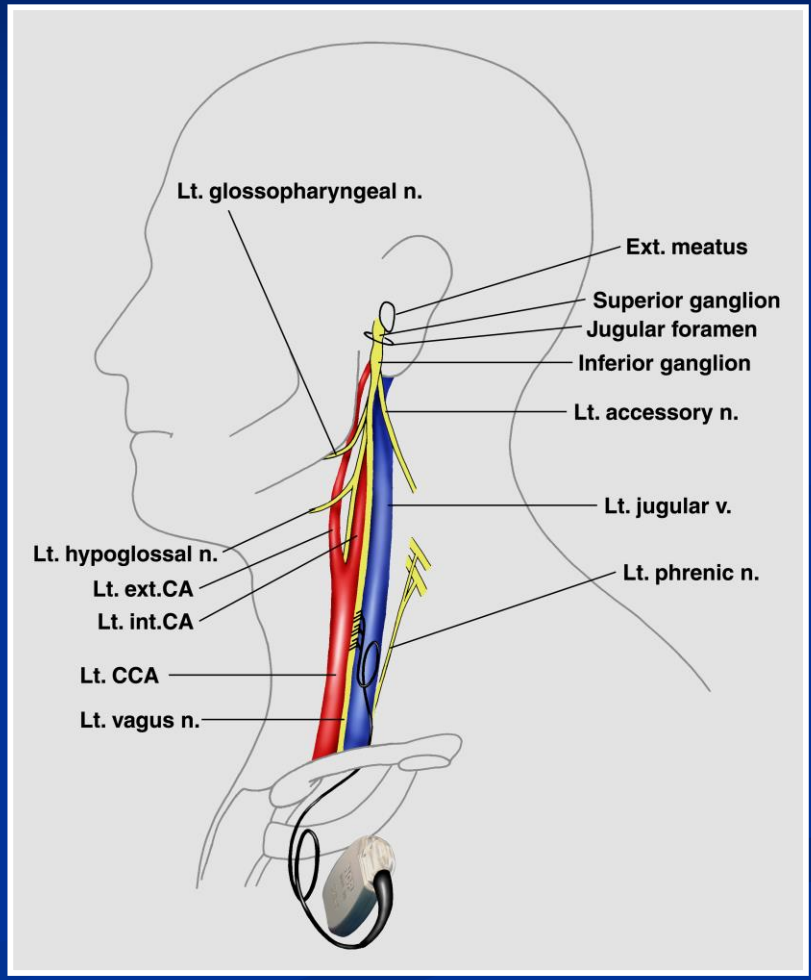
Fact that it is an implant helps adherence/compliance

Cervical Vagus Nerve Anatomy

~80% afferent fibers, mostly unmyelinated

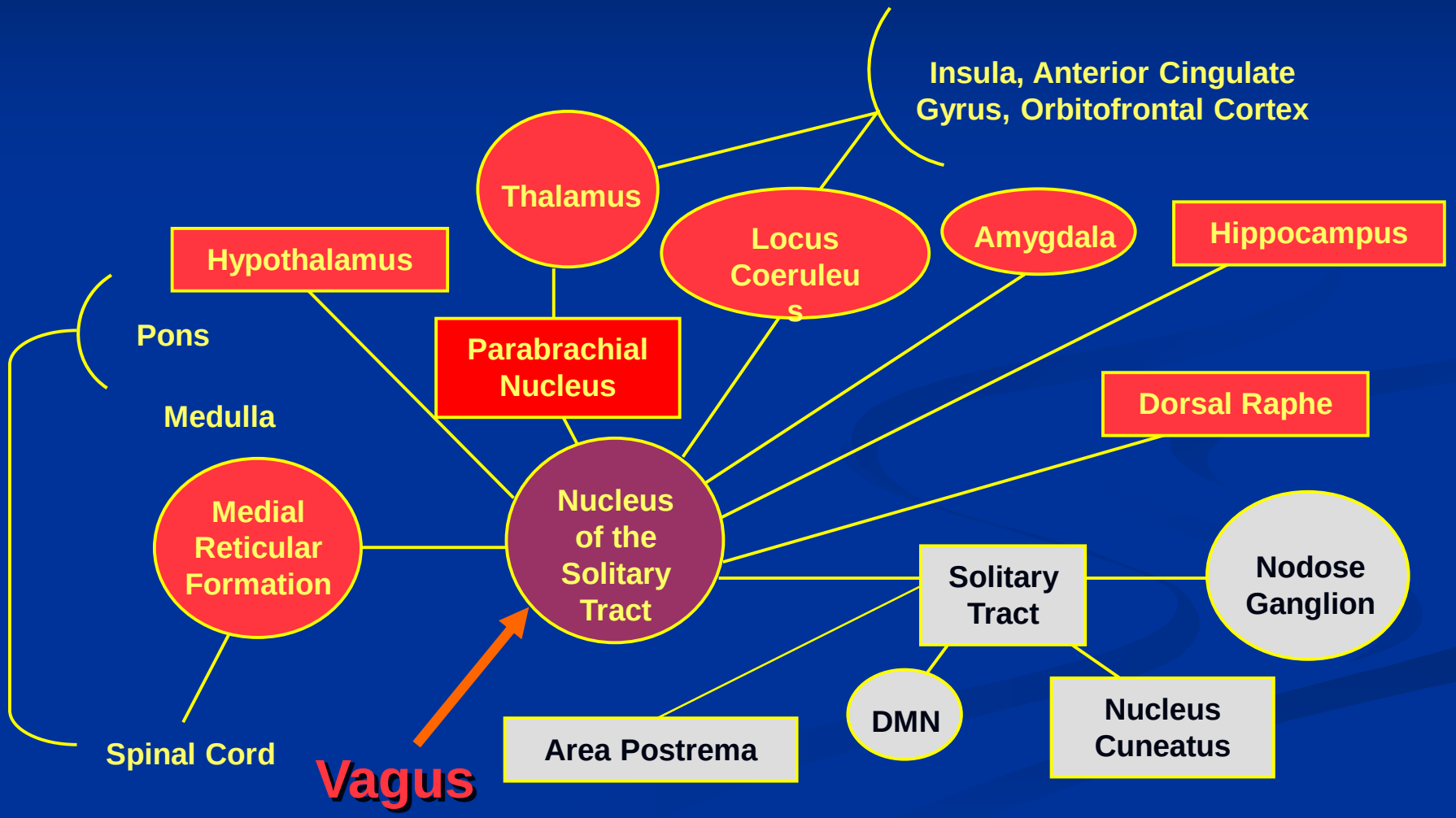
~20% efferent fibers, mostly unmyelinated parasympathetic fibers to thoraco-abdominal viscera

Some myelinated fibers to striated muscles of the pharynx and larynx

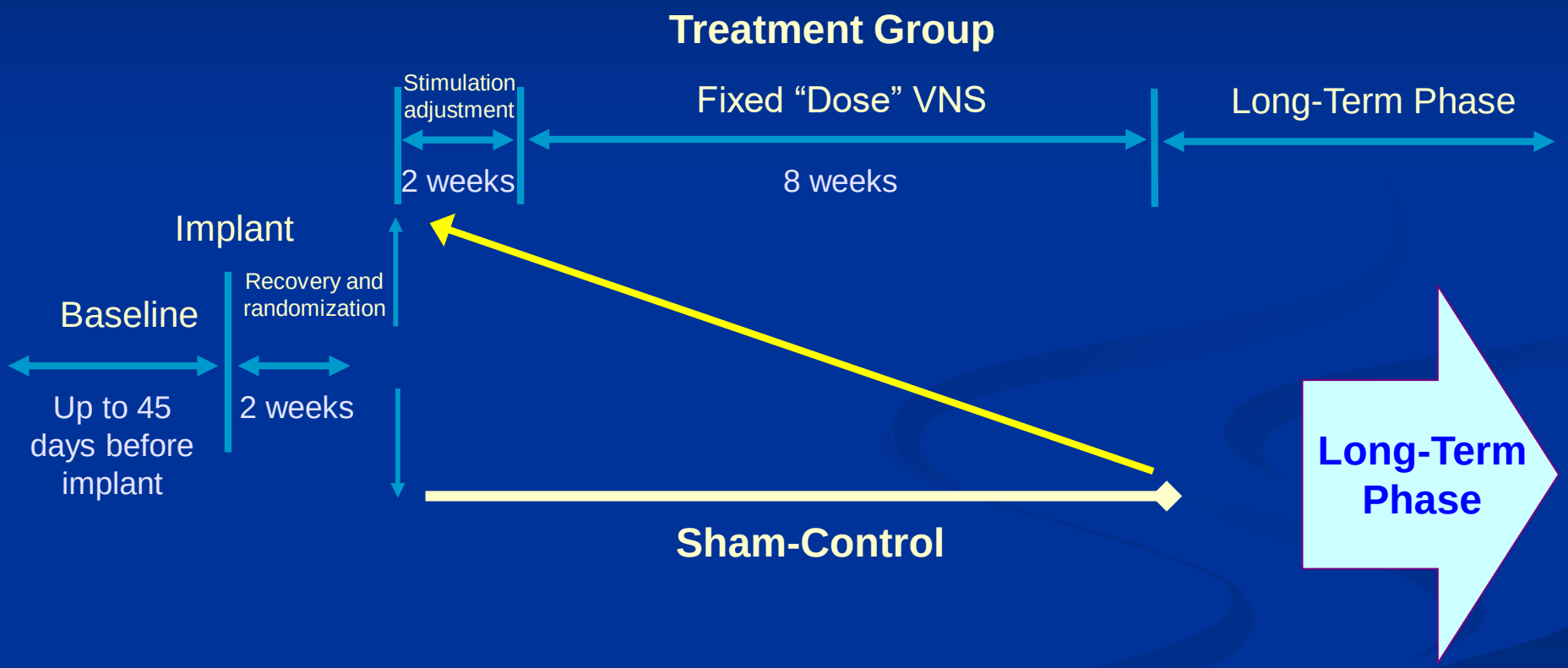


Henry TR. *Neurology.* 2002;59(suppl 4):S3-S14.

VNS: Afferent Pathway to the Brain

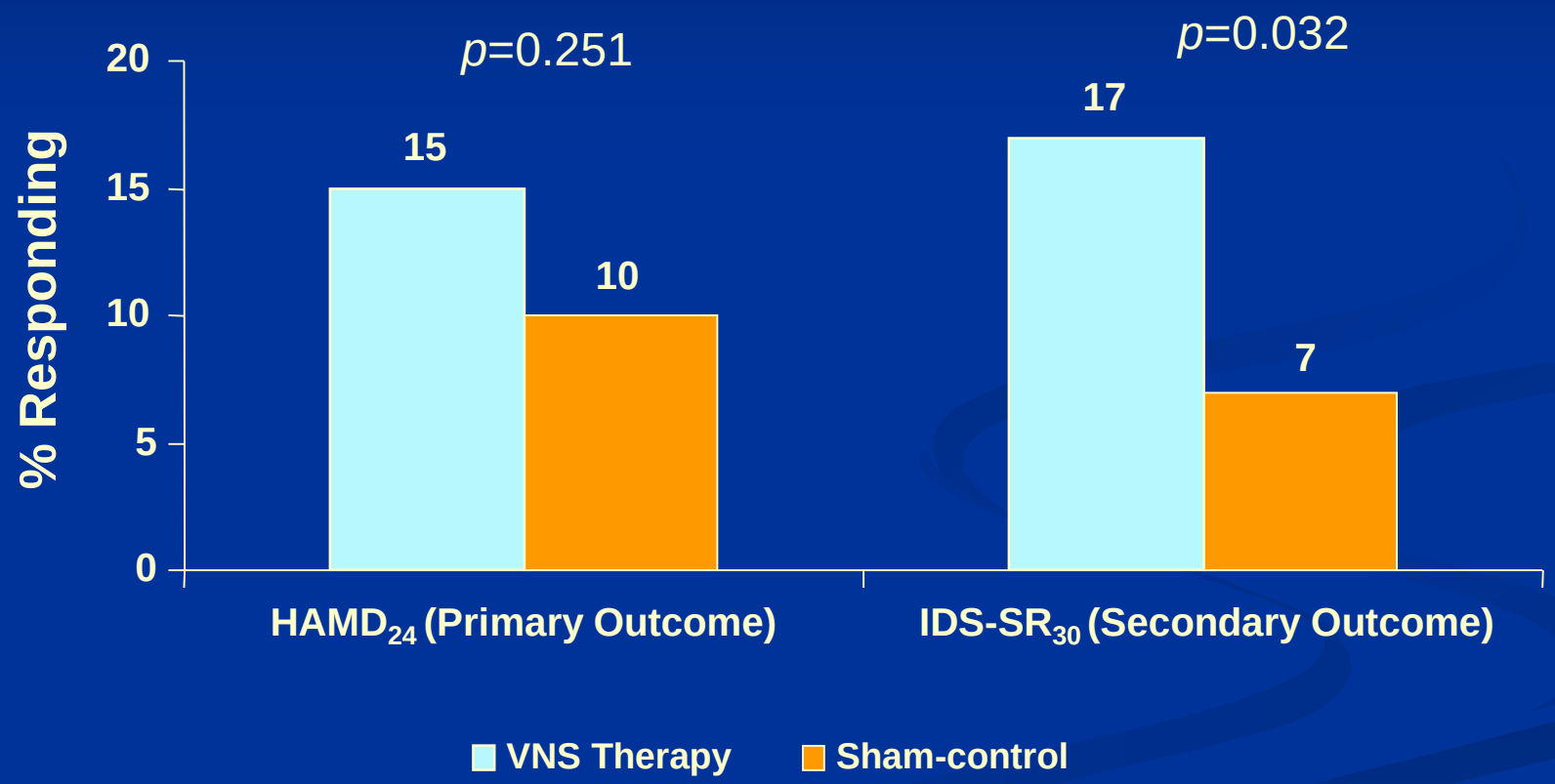


VNS Pivotal Study Design



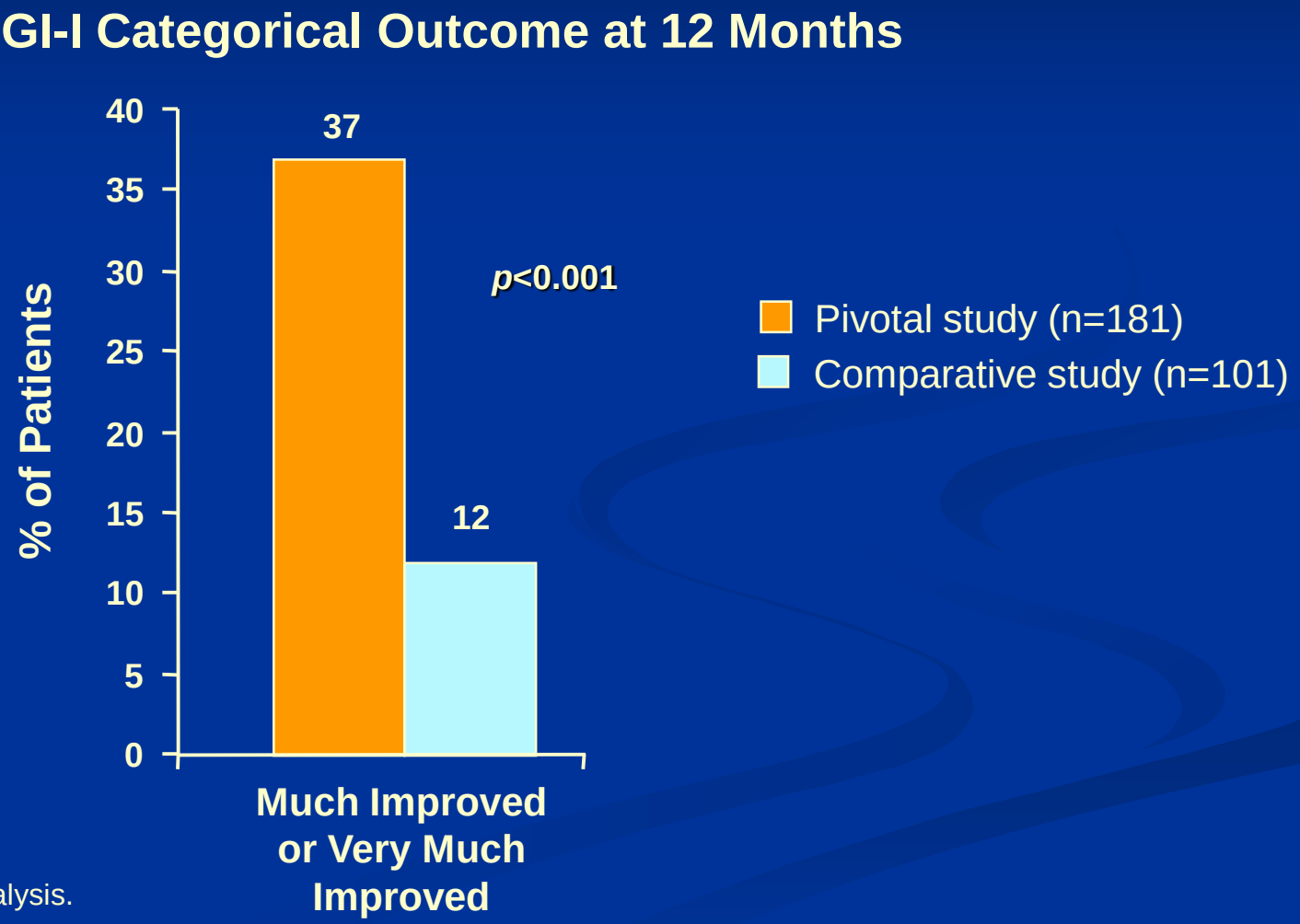
Rush AJ, et al. *Biol Psychiatry*. 2005;58:347-354.

Acute outcome at 12-weeks



Rush AJ, et al. *Biol Psychiatry*. 2005;58:347-354.

VNS versus Treatment as Usual

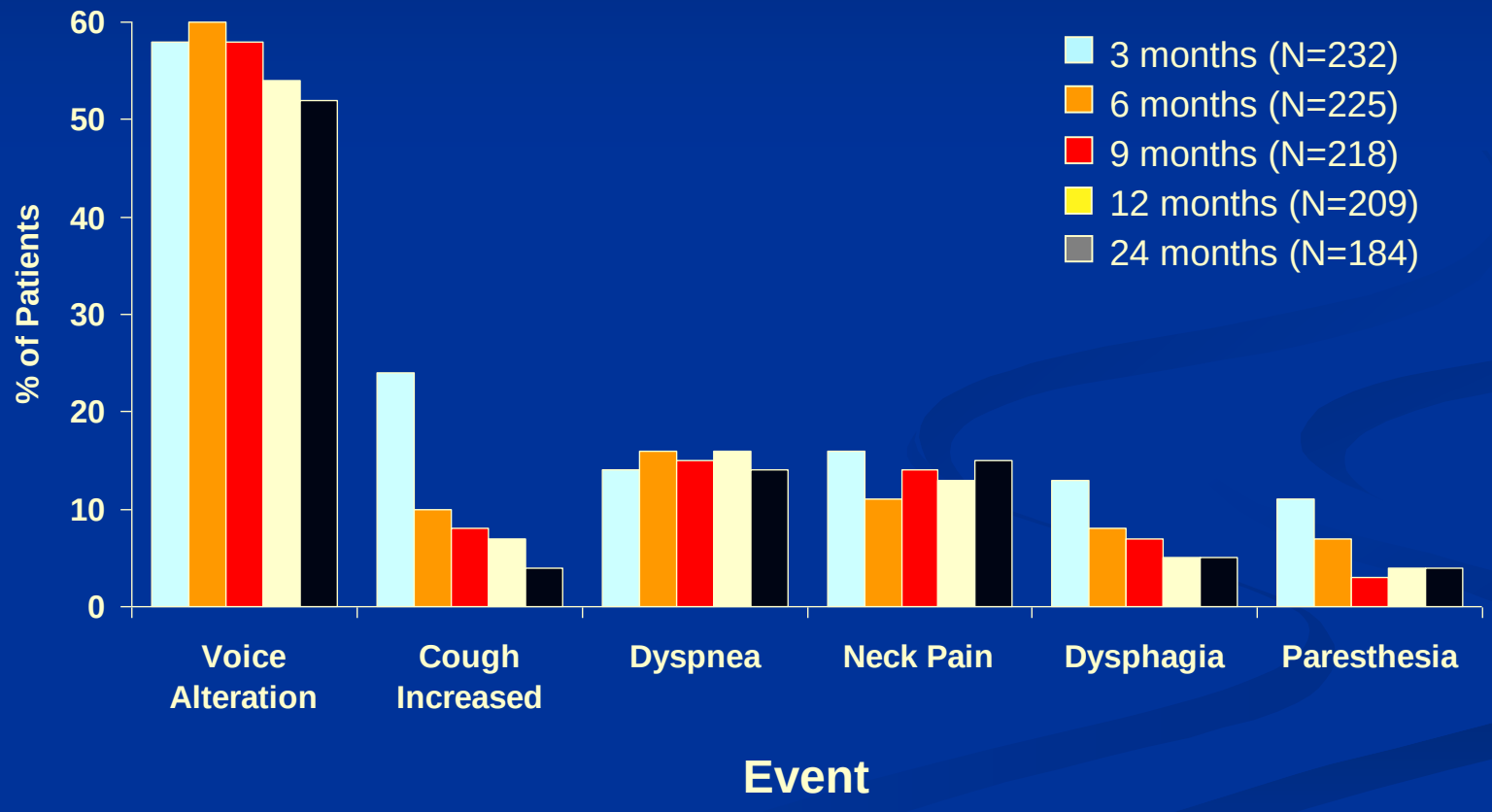


Evaluable observed analysis.

George MS, et al. *Biol Psychiatry*. 2005;58:364-373.

Safety profile of VNS

Most Frequently Reported Stimulation-Related AEs at 3 Months (≥10%)



1. Rush AJ, et al. *Biol Psychiatry*. 2005;58:355-363. 2. Cyberonics, Inc. *Depression Physician's Manual.* Houston, Tex; 2005.

VNS Advantages

- ✓ Well tolerated with high adherence rates
- ✓ Implant so guaranteed treatment delivery
- ✓ No cognitive impairment, or related stigma
- ✓ No weight gain, no known metabolic issues, no sexual dysfunction side effects

Disadvantages/Controversies

- Surgery is an obstacle for some patients, and overall costs upfront are high relative to pharmacotherapy and psychotherapy
- Controversy associated with FDA approval, given failed pivotal trial, has limited access in practice for patients – Medicare has decided against covering VNS for TRD
- May be a disincentive for future development of neuromodulation devices in psychiatry

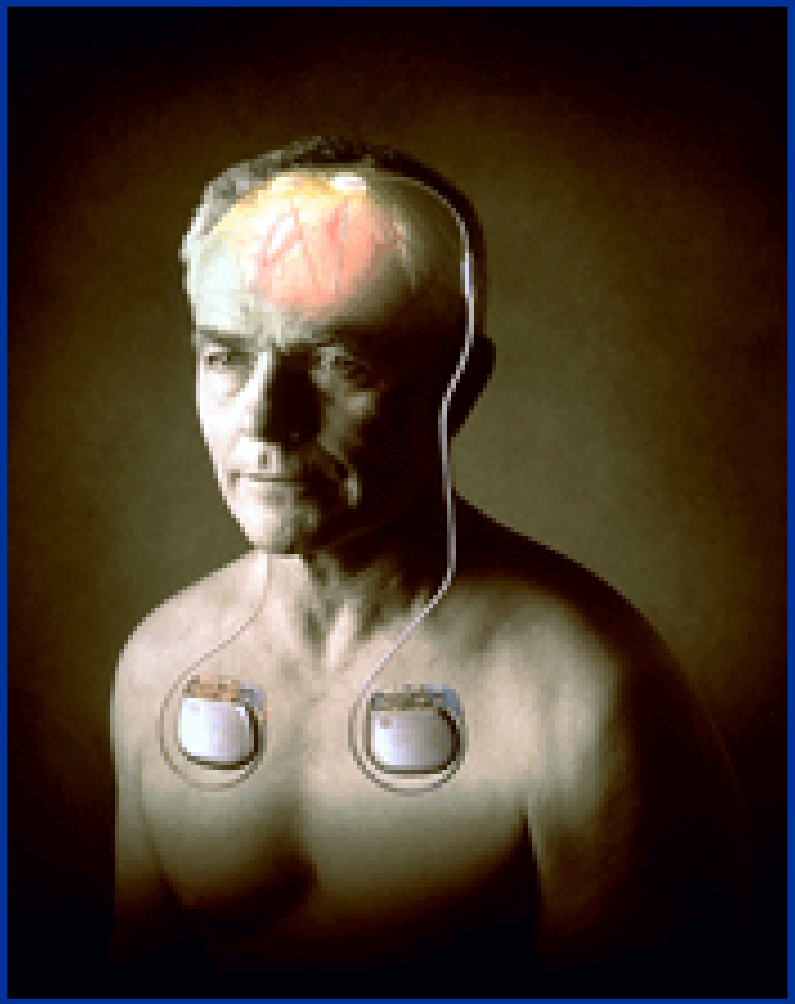
CMS denial of VNS coverage

- "CMS does not believe there is a treatment effect directly attributable to VNS therapy based on the current evidence"[1]
- "The pivotal randomized, controlled trial of VNS, subsequent to a pilot study, failed"[1]
- Medicare, however, has covered VNS for epilepsy since 1999, where evidence for efficacy is similar to TRD

1. www.cms.hhs.gov/MCD/viewdraftdecisionmemo.asp?id=195, accessed 2/13/07

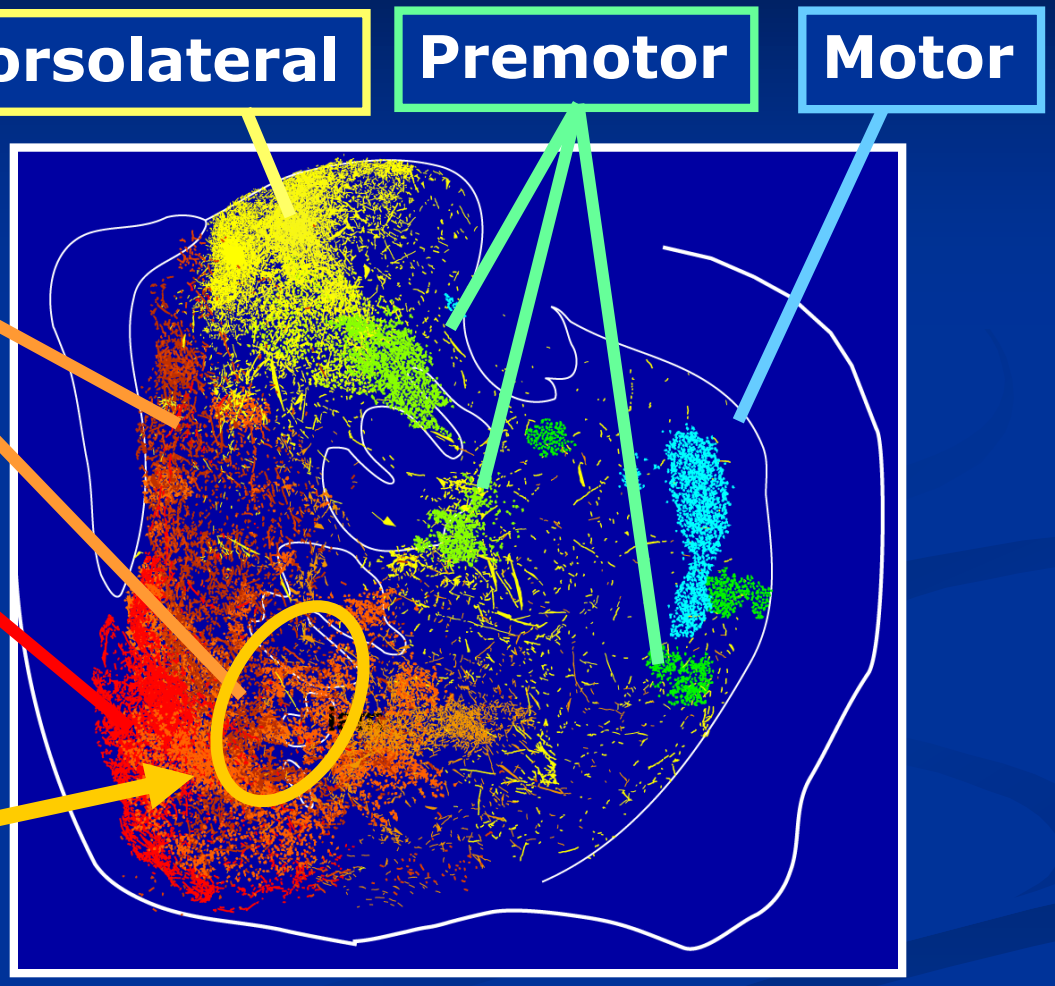
Deep Brain Stimulation (DBS)

- FDA Approved for Parkinson's and Tremor
- Investigational for OCD, TRD
- Stereotactic Target from MRI
- Two chest-wall Pulse Generators
- Burr holes in skull for electrode placement
- Stimulation parameters programmed by computer, through "wand"



This information concerns a use that has not been approved by the U.S Food and Drug Administration

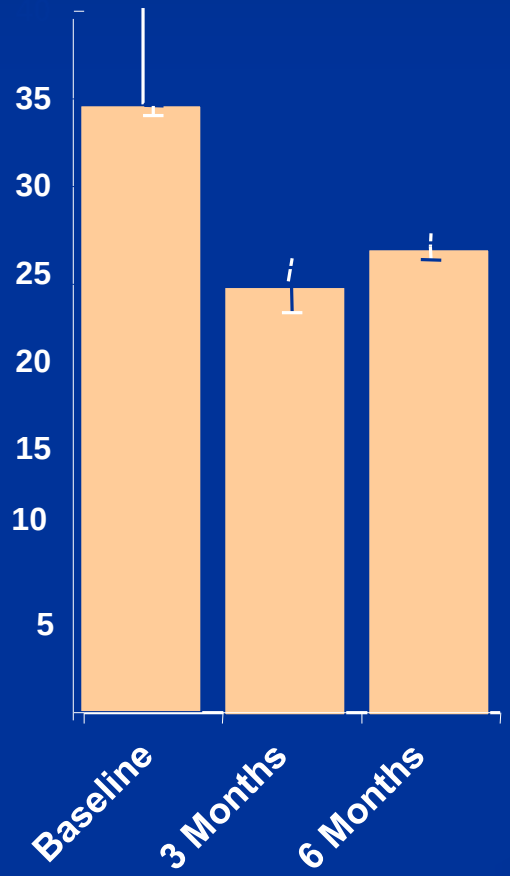
DBS Targets - Anterior Limb of the Internal Capsule/Ventral Striatum



Haber SB et al. *J of Neuroscience*. 1995.

Brown experience with DBS for OCD (n=10)

YBOCS Severity Improvement During DBS in Intractable OCD



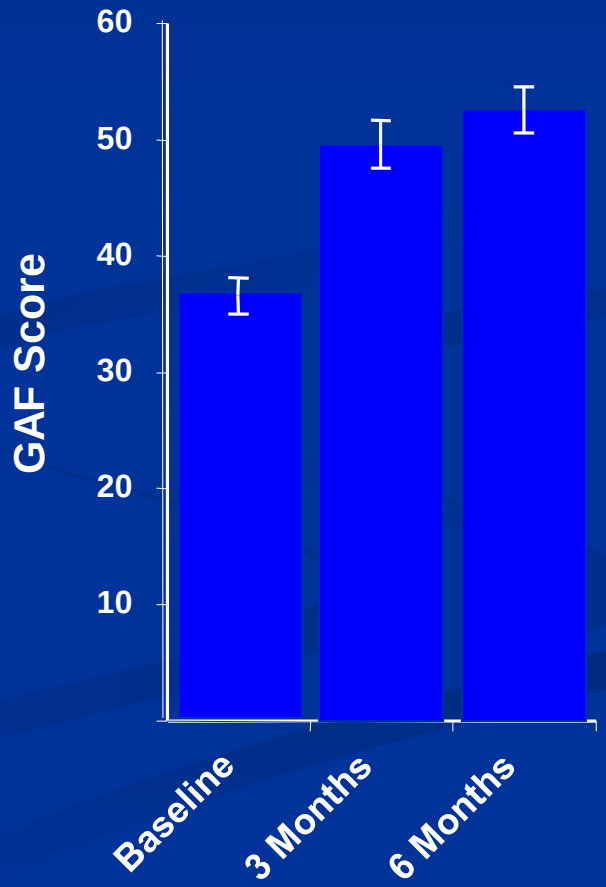
35% ⇓ YBOCS

3/10 (6 months)

25% ⇓ YBOCS

5/10 (6 months)

Functional Improvement During DBS in Intractable OCD



DBS for OCD: Adverse Effects

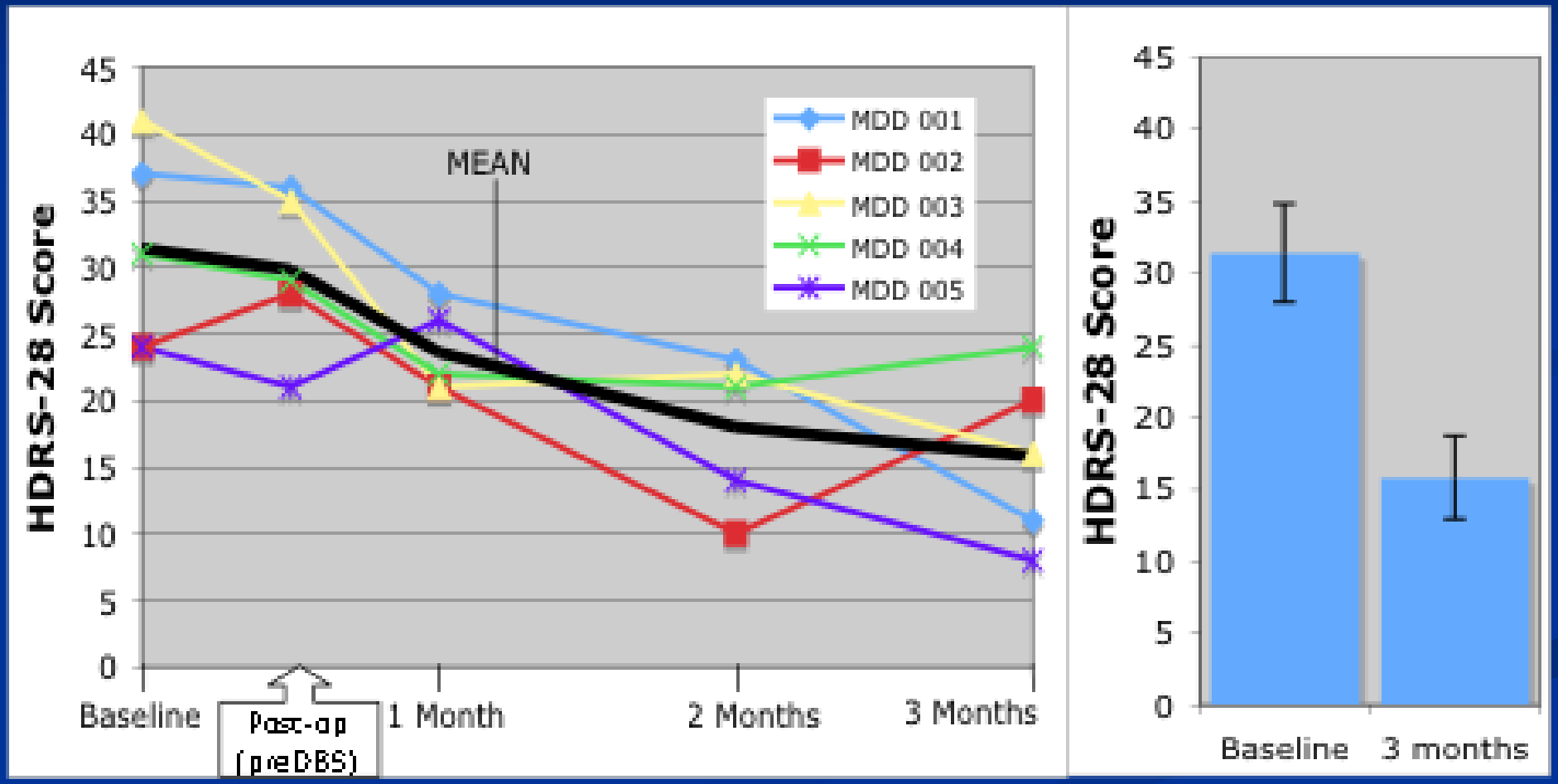
- Surgical
  - Small hemorrhage without symptoms or sequelae
  - Superficial infection
  - Single intraoperative seizure
- Stimulation
  - Hypomania (4/10)
  - Sensorimotor effects (facial)
  - Insomnia
  - Autonomic
  - Memory flashbacks
  - Panic
- OFF effects
  - Symptom return
- No AEs were persistent

DBS for TRD: pilot Study n=5

	AGE	SEX	HANDED-NESS	DIAGNOSIS DSM-IV	DURATION OF MDD	MEDS/ECT RESPONSE
001	54	Male	Right	Severe/chronic unipolar MDD, w/ melancholia	36 years	None
002	60	Male	Right	Severe bipolar I disorder, MDD w/ melancholia	35 years	No sustained benefit
003	51	Female	Left	Unipolar MDD w/ melancholia	19 years	None
004	51	Female	Right	Unipolar MDD w/ melancholia	9 years	Intermittent benefit
005	43	Female	Right	Severe unipolar MDD, single episode, w/ melancholic features	6 years	Minimal, short-lived improvement

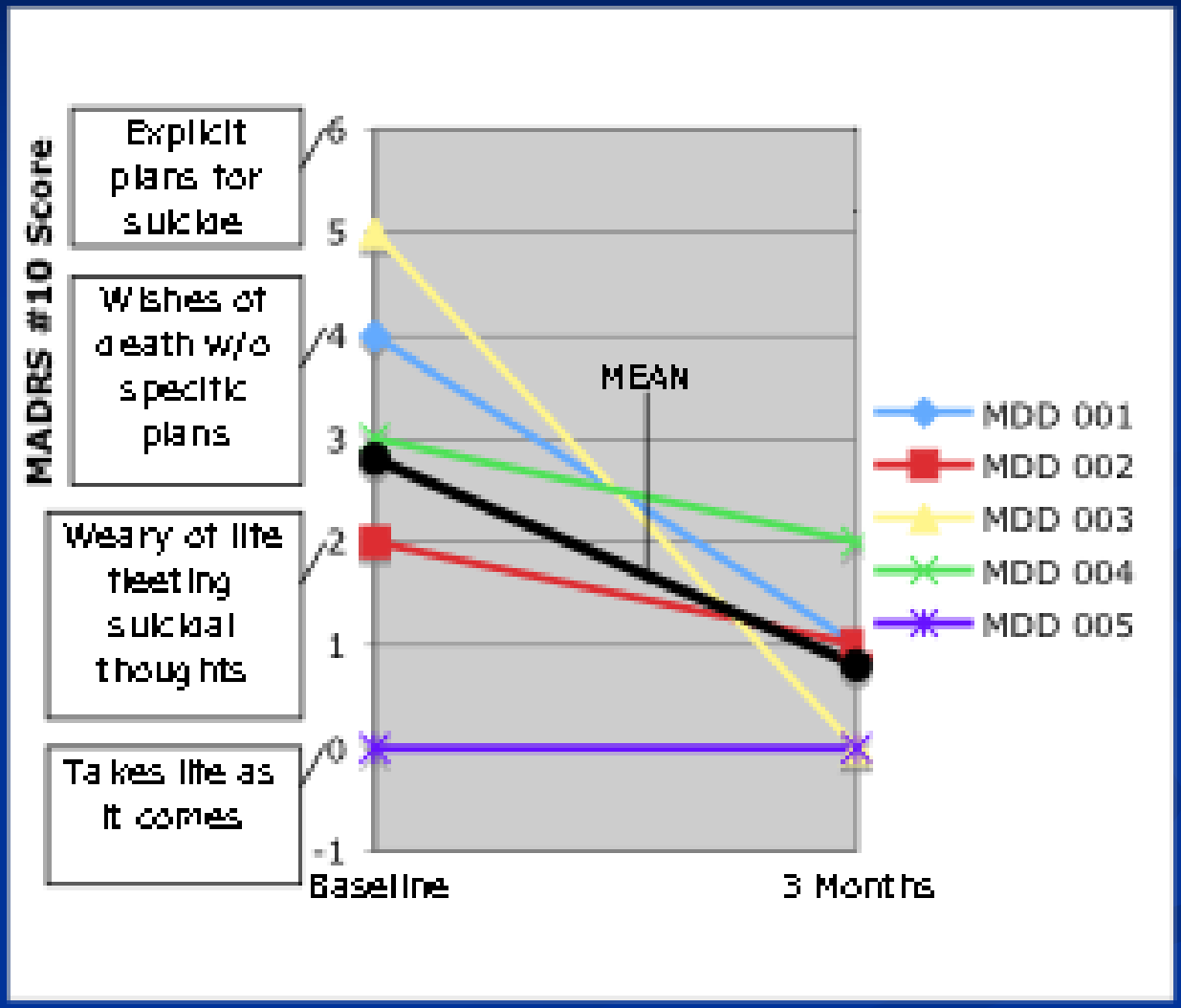
Greenberg BD et al, Neuropsychopharmacology 29:s32, 2004

Depression Improvement During DBS in Intractable Depression



Greenberg BD et al, Neuropsychopharmacology 29:s32, 2004

Reduced Suicidality During DBS



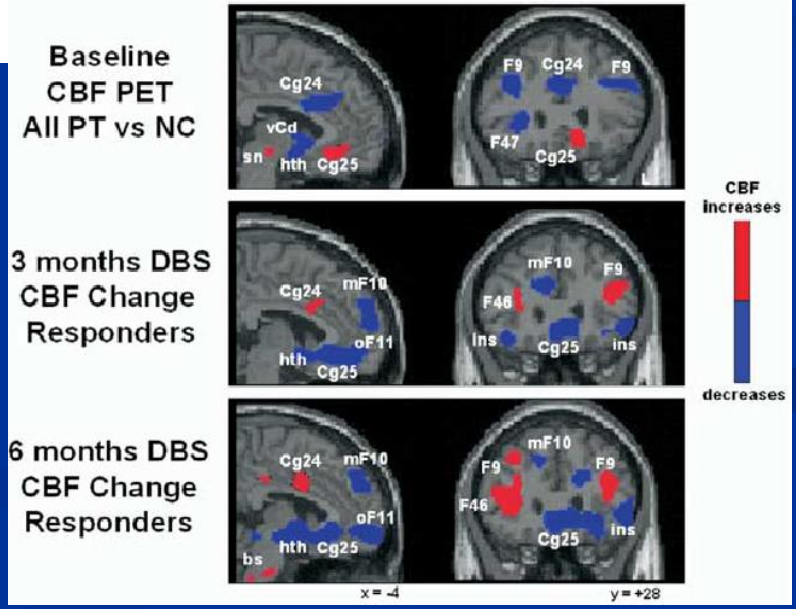
Greenberg BD et al, Neuropsychopharmacology 29:s32, 2004

DBS: Subgenual Cingulate (Cg25) Region

Table 2. Hamilton Depression Rating Scale, HDRS-17, Scores over Time for Each Subject

Time	Hamilton Score[a]					
	Pt 1[b]	Pt 2[c]	Pt 3[b]	Pt 4[c]	Pt 5[b]	Pt 6[b]
Preop baseline	29	22	29	24	26	25
1 week postop (acute stimulation)	5	10	12	18	17	12
2 weeks postop (DBS off)	9	13	23	18	22	n/a
1 month	10	14	17	20	22	12
2 months	13	11	12	18	10	12
3 months	2	15	14	25	7	14
4 months	4	9	12	24	6	12
5 months	5	18	7	23	8	n/a
6 months	5	15	9	23	6	12

[a] Clinical response: decrease HDRS score >50%. Clinical remission: absolute HDRS score <8.
[b] Clinical responders.
[c] Clinical nonresponders.

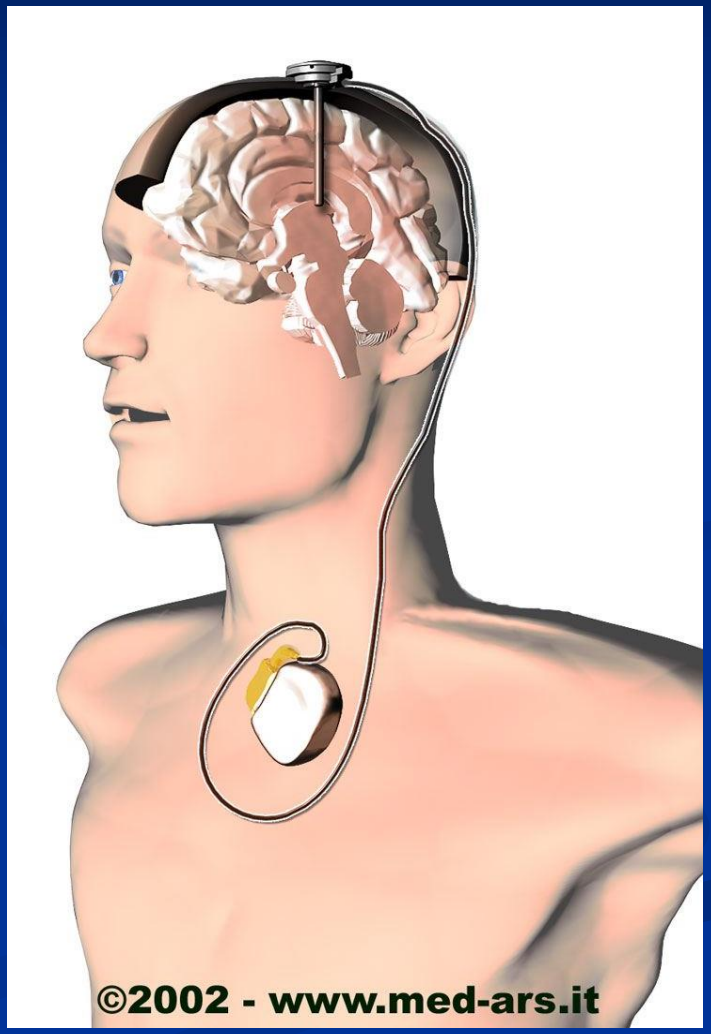


Mayberg HS et al. *Neuron*. 2005.

Deep Brain Stimulation (DBS)

Limitations

- Limited, short-term, open-label data in psychiatry
- Considerable Surgical Risk
- Cosmesis
- Targets and stimulation parameters not established
- MRI contraindication
- Risk of hypomania
- Battery Life



Neuromodulation overview

- ECT non-invasive, hospital procedure, requires anesthesia, safe, very efficacious, but stigmatized, no clear neurology application
- TMS is non-invasive, office based, most flexible, possible multiple applications, very acceptable to patients, but is it robust enough?
- VNS bottom-up modulation, limited surgery, but efficacy less than hoped for, & access problems
- DBS most invasive, only preliminary data to date (n~50), but looks robust

21st century neuromodulation therapies in psychiatry

- ✓ Psychiatry treatment may be at similar threshold as cardiology 25 years ago, in terms of potential for devices to improve our therapeutics
- ✓ Effective medications & psychosocial interventions help many but by no means all of our patients
- ✓ Devices have potential to help our severely ill patients and clearly warrant intensive research going forwards

Post-Lecture Exam Question 1

Magnetic Seizure Therapy (MST) differs from ECT in that:

a. the goal is not to induce a therapeutic seizure
b. the use of focused stimulation to produce a seizure
c. general anesthesia is not required
d. daily sessions of MST are needed to produce a therapeutic effect
e. it has a more benign profile in terms of cognitive adverse effects

Question 2

The most common side effect reports with VNS is:

a. weight gain
b. sexual dysfunction
c. cognitive impairment
d. hoarseness
e. chest pain

Question 3

Deep brain stimulation is currently FDA approved for the treatment of:

a. auditory hallucinations in schizophrenia
b. chronic neuropathic pain
c. obsessive compulsive disorder
d. parkinson's Disease
e. intractable migraine

Question 4

Transcranial Magnetic Stimulation (TMS) differs from Magnetic Resonance Imaging (MRI) technology in that:

a. the magnetic fields produced are much weaker in intensity
b. the rate of change of the magnetic field is higher with an MRI versus TMS
c. MRI technology activates neurons whereas TMS does not
d. scalp discomfort is common with TMS but not with an MRI

Question 5

Which of the following statements about ECT is not true?

a. ECT appears to be particularly efficacious in psychotic depression
b. ECT is not effective in the treatment of mania
c. ECT is effective in the treatment of bipolar depression
d. ECT is associate with retrograde memory impairments
e. ECT is effective in the treatment of pharmacotherapy-resistant major depression

Answers to Pre and Post-Lecture Exams

1. E
2. D
3. D
4. D
5. B