Neurostimulation 2017: ECT, TMS, VNS

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Disclosures

Consultant
- **LivaNova**
- **Neuronetics**
- **Genomind**

Research Support
- **Neuronetics**

Speaker Bureau
- **Sunovion**
- **Neurocrine**
- **Takeda**

What is Neurostimulation?

- Modulation of the nervous system (either central or peripheral) by electrical or magnetic impulses.
- Commonly used technique in neurosurgery and neurology for a variety of uses including pain management, hearing and visual prostheses, and control of Parkinsonism
- Long history of psychiatric use related to electroconvulsive therapy
- More recently FDA cleared use of focal neurostimulation by vagus nerve stimulation and transcranial magnetic stimulation for depression
- On going research looking at the use of magnetic seizure therapy, deep brain stimulation and direct current stimulation

Why Do We Need Neurostimulation?

- Tendency to look at somatic therapies for depression being exclusively neurochemical, but the brain is as much electrical as it is chemical
- After four decades of antidepressant drug development we have drugs which affect serotonin and norepinephrine and to a lesser extent dopamine. Many other neurotransmitters are involved with mood disorders but we have no medications yet to target them
- We can alter neurochemicals by neurostimulation as well as altering aberrant neuronal activity
- Neurostimulation offers a non-systemic somatic approach to depression, often with an improved side effect profile

Neurostimulation Methods

FDA Cleared Methods
- Electroconvulsive Therapy (ECT)
- Vagus Nerve Stimulation (VNS)
- Repetitive Transcranial Magnetic Stimulation (rTMS)

Methods in Development
- Transcranial Direct Current Stimulation (tDCS)
- Deep Brain Stimulation (DBS)
- Synchronized Transcranial Magnetic Stimulation (sTMS)
- Magnetic Seizure Therapy (MST)
- Focal Electrically-Adminstered Seizure Therapy (FEAST)

Electroconvulsive Therapy (ECT)

Electroconvulsive Therapy (ECT)

- Oldest neurostimulation intervention, first used in 1938
- Highest response rate of response of any somatic therapy in TRD, up to 60%[1,2]
- Treatment is generalized and not focal
- Side effect burden is high--post-ictal confusion, memory loss, requires time off.
- Newer protocols may ease the potential side effect profile including-MST and FEAST, ?sub threshold ECT.
- More acceptable as an acute intervention than a chronic one
- High likelihood of relapse, 38-65% of responders are ill in six months[1,3]

–

1. Sackheim HA et. al., JAMA 2001;285:1299-307
2. Kellner CH et. al. Arch Gen Psych 2006;63:1337-44
3. Jelovac et al (2013). Relapse following successful ECT for major depression: a meta-analysis. *Neuropsychopharmacology* 38, 12, 2467-74.

Who benefits from ECT?

Lessons from 70 Years Experience

- More *severe*
- More *acute*
- *Older*

Max Fink

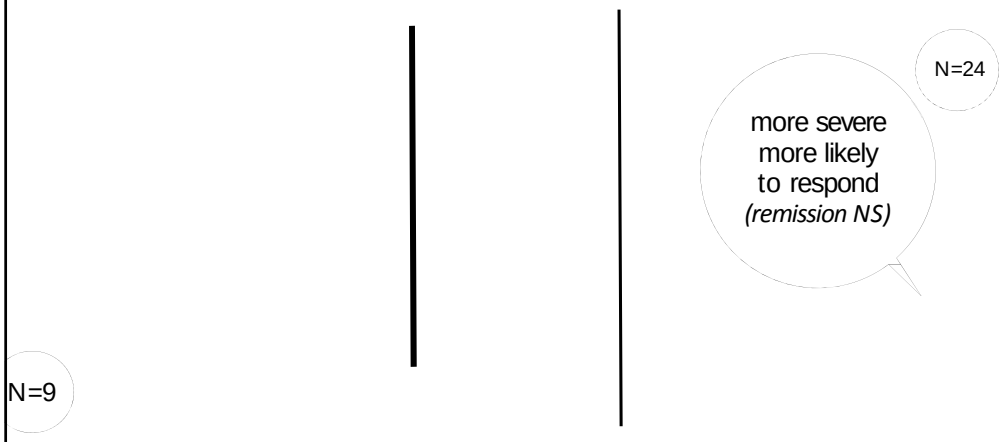
ECT Appropriateness Scale

2012

Severity - Heritability - Episodic nature

Severity

does (not) predict outcome

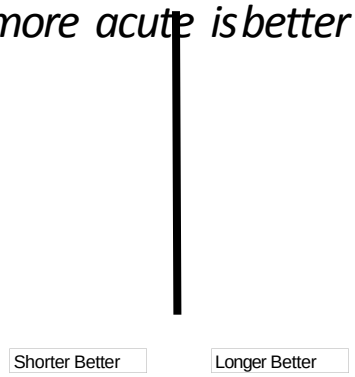


Haq et al. Response of depression to ECT - a meta-analysis of clinical predictors. J Clin Psychiatry 2015, 76, 1374-1384.

Van Diermen et al. PredicHon of ECT response and remission in major depression - a meta-analysis. Br J Psychiatry (in press)

Episode duration

more acute is better



N=7

Haq et al. Response of depression to ECT - a meta-analysis of clinical predictors. J Clin Psychiatry 2015, 76, 1374-1384.

Older Age

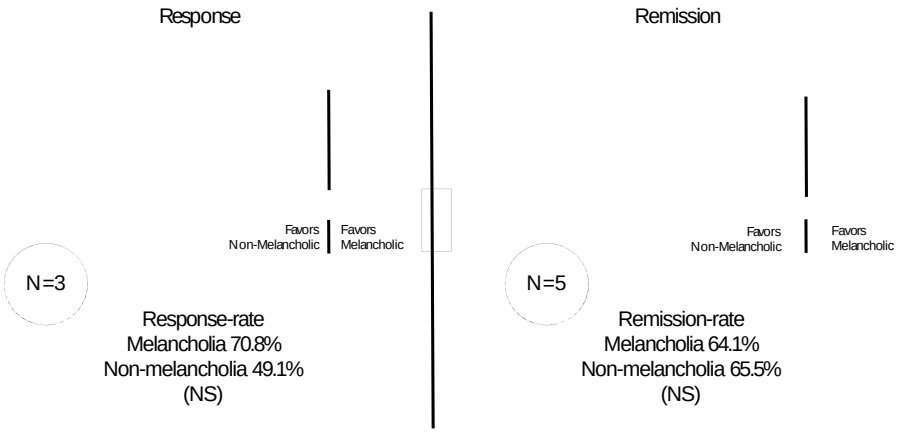
predicts response & remission

N=23

Van Diermen et al. Prediction of ECT response and remission in major depression - a meta-analysis. Br J Psychiatry (in press)

Melancholic features

do not predict outcome



Van Diermen et al. PredicHon of ECT response and remission in major depression - a meta-analysis. Br J Psychiatry (in press)

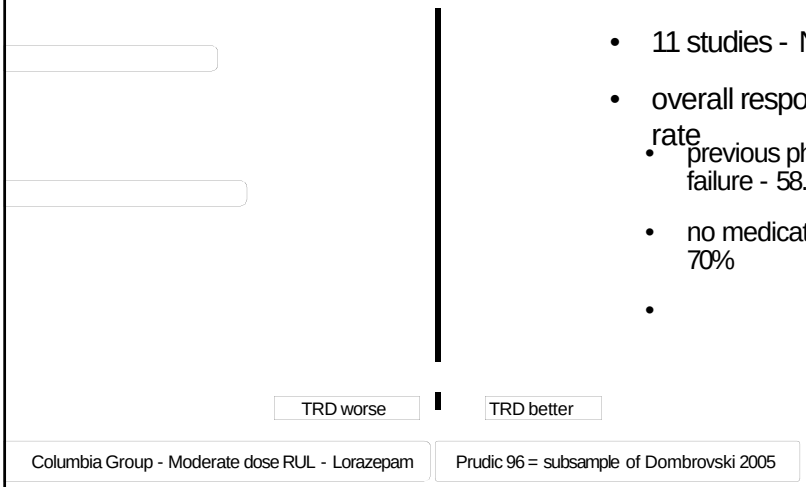
Psychotic Symptom

N=19

Van Diermen et al. Prediction of ECT response and remission in major depression - a meta-analysis. Br J Psychiatry (in press)

Medication Resistance

and response to subsequent ECT



- 11 studies - N=1175
- overall response rate
  - previous pharmacotherapy failure - 58.0%
  - no medication resistance - 70%
  -

Haq et al. Response of depression to ECT - a meta-analysis of clinical predictors. JClin Psychiatry 2015;76:1374-1384.

Relapse

following successful ECT - Meta-analysis - Treatment reducesrisk

3 *months*	6 *months*	12 *months*	24 *months*
27%	38% (17) 710	51% (8) 348	50% (3) 111
	37% (4) 146		

relapse rate % - number of studies - number of subjects

Jelovac et al (2013). Relapse following successful ECT for major depression: a meta-analysis. *Neuropsychopharmacology* 38, 12,2467-74.

Medication Resistance *Predicts* Relapse

relapse 2x rate of patients who did not receive adequate TCA trial pre-ECT

Inadequate pre-ECT pharmacotherapy (N=28)

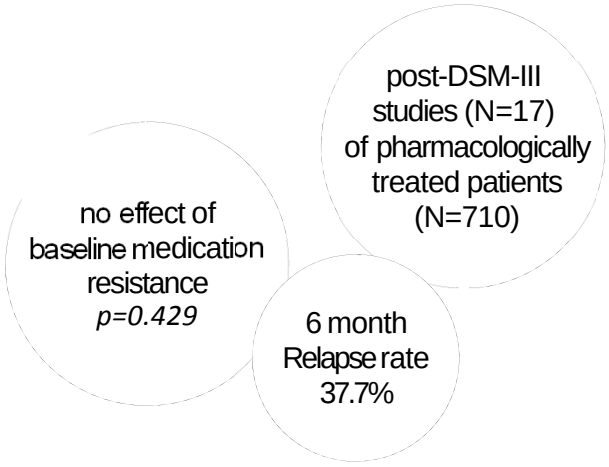
TCA-resistant (N=34)

Time after Treatment, weeks

- 12 month - relapse
  - *resistant patients* ***68.6%***
  - *patients who did not have adequate med trial before ECT* ***33.3%***
- *Higher HRSD scores* post-ECT associated with higher rate of relapse *likelihood ratio = 10.21, P=0.001*

Sackeim et al. A prospective, randomized, double-blind comparison of BL and RUL ECT at different stimulus intensities. *Arch Gen Psychiatry* 2000;57(5):425-34.

Medication Resistance *Does Not Predict* Relapse



Jelovac et al (2013). Relapse following successful ECT for major depression: a meta-analysis. *Neuropsychopharmacology* 38, 12, 2467-74.

Sackeim et al
Continuation Pharmacotherapy in the Prevention of Relapse Following ECT
JAMA 2001

MDD, HDRS-24 ≥ 21, no bipolars, no psychotropics (Lorazepam ≤ 3 mg/d)

159 remitters (54%)

N=84

Placebo, N=29	Nortriptyline, N=27 75-125 ng/mL	Nortriptyline + Lithium N=28 0.5-0.9 mEq/L
6 M		
84%	= 60%	> 39%
Relapse		

Most relapse in NT-Li group occurred in the first 5 weeks!

Kellner et al. Continuation ECT vs pharmacotherapy for relapse prevention in major depression: a multisite study from CORE. *Arch Gen Psychiatry* 2006, 63, 1337-1344.

Unipolar, Ham ≥ 21, 30% delusional

N=184

Nortriptyline + Lithium N=95	0.53	C-ECT, N=89
6 M		
32% 6.8 weeks		**37%** 8.9 weeks
Relapse		

M-ECT

alternatives

M-TMS

after successful ECT

Longitudinal changes in QIDS

- N=6
- bilateral TMS 1-2/W
- 5/6 maintained response status from 6-13 months

Noda et al. rTMS to maintain treatment response to ECT in depression: a case series.
Frontiers in psychiatry 2013, 4, 73

VNS

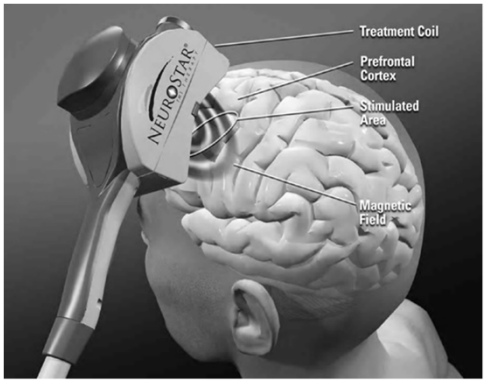
after successful (M-)ECT

Aaronson, et. al. AJP (2017)

Repetitive Transcranial Magnetic Stimulation (rTMS)

Transcranial Magnetic Stimulation (TMS)

- Application of electromagnetic induction described by Michael Faraday in 1839
  - Faraday's Law: a time-varying magnetic field induces an electric current that runs perpendicular to the time-varying motion of the magnetic field[1,2]
- Clinical application: Pulsed magnetic fields can induce electrical currents in brain tissues and neurons[3]



1. Faraday M. In: *Experimental Research in Electricity*. Vol 1. London Quaritch; 1839:1-15; 2. Barker AT. *J Clin Neurophysiol*. 1991;8(1):26-37; 3. Barker AT et al. *Lancet*. 1985;11(8437):1106-1107.

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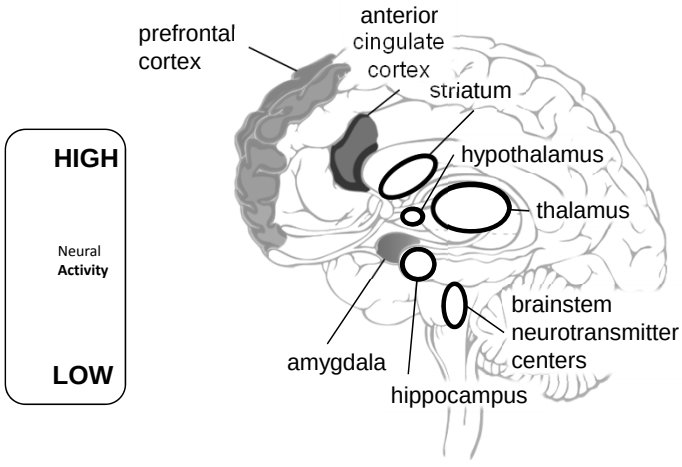
Major Depressive Disorder

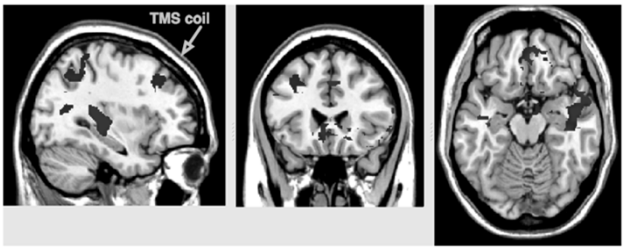


In MDD, some areas of the brain are hypoactive and others are hyperactive.

Biological Effects of TMS

Acute Effects

- Induces electric current
- Depolarizes neurons in superficial cortex
- Leads to local and trans-synaptic changes in brain activity



Example:

Left prefrontal TMS

23 depressed individuals

Activation demonstrated at site of stimulation and also at synaptically connected cortical and subcortical regions

Li X et al. *Biol Psychiatry.* 2004;55(9):882-890; Teneback CC et al. *J Neuropsychiatry Clin Neurosci*. 1999;11(4):426-435; Epstein CM et al. *Neurology*. 1990;40(4):666-670.

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Biological Effects of TMS

Chronic Effects

Specific outcome is dependent upon stimulation parameters
Alteration of monoamine concentrations
Beta-receptor, serotonin-receptor modulation
Induction of neurogenesis genes (eg, BDNF)
Plasticity, LTD/LTP effects
Local GABA, glutamate effects
Stimulation of the dorsolateral prefrontal cortex (DLPFC) alters functional activity of the anterior cingulate (AC) and deeper limbic regions

Lisanby SH, Belmaker RH. *Depress Anxiety*. 2000;12(3):178-187; Kim EJ et al. *Neurosci Lett*. 2006;405(1-2):79-83; Shajahan PM et al *Prog Neuropsychopharmacol Biol Psychiatry*. 2002;26(5):945-954; Teneback CC et al. *Neuropsychiatry Clin Neurosci*. 1999;11(4):426-435; Epstein CM et al. *Neurology*. 1990;40(4):666-670; George MS et al. *NeuroReport*. 1995;6(14):1853-1856.; Post A, Keck, ME *J. of Psych Rsch.* 2001.

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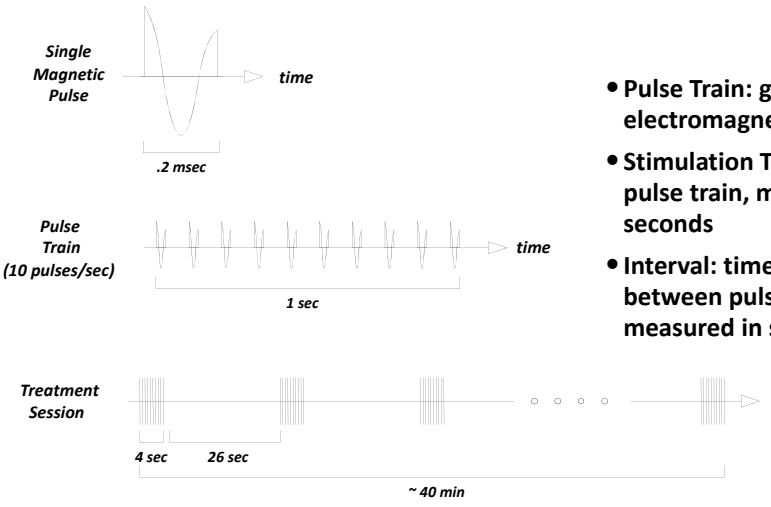
Key TMS Terms



- **Pulse Train: group of electromagnetic pulses**
- **Stimulation Time: duration of pulse train, measured in seconds**
- **Interval: time period between pulse trains, measured in seconds**

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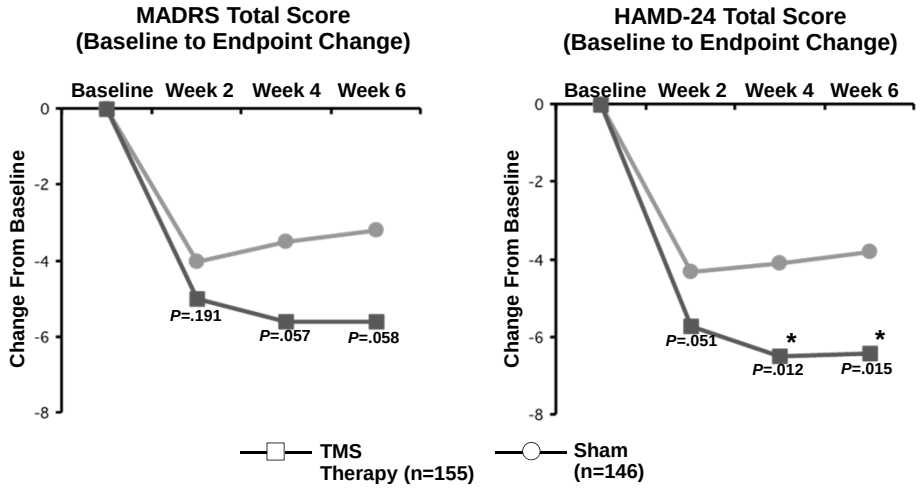
TMS Therapy: Overall Efficacy in RCT



*** *P*<.05.**
LOCF, LS mean.

O'Reardon JP et al. *Biol Psychiatry*. 2007;62(11):1208-1216.

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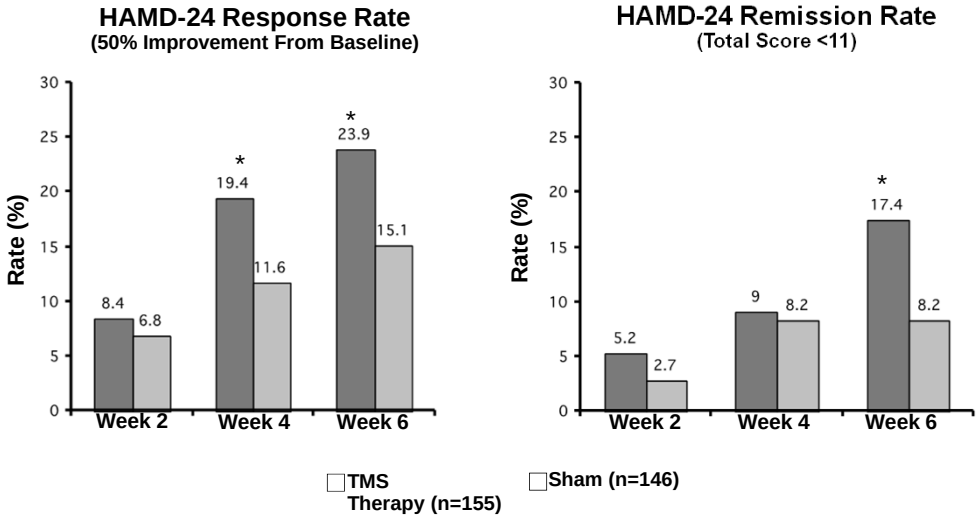
Response and Remission Rates in the Overall Population



*** *P*<.05.**

O' Reardon JP et al. *Biol Psychiatry*. 2007;62(11):1208-1216.

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Naturalistic TMS Outcomes Study

Goal

- Define real world outcomes associated with TMS therapy across a broad spectrum of patients and practitioners

Patient Population & Sites

- 307 evaluable unipolar, non-psychotic MDD patients in acute phase
- 42 sites comprised of institutions and private practice

Study Design Phases

- Acute phase *(clinician determined care based on clinical progress)*
- Long-term outcomes at 12 months

Patient Treatment

- Clinical care initiated per current labeled guidelines

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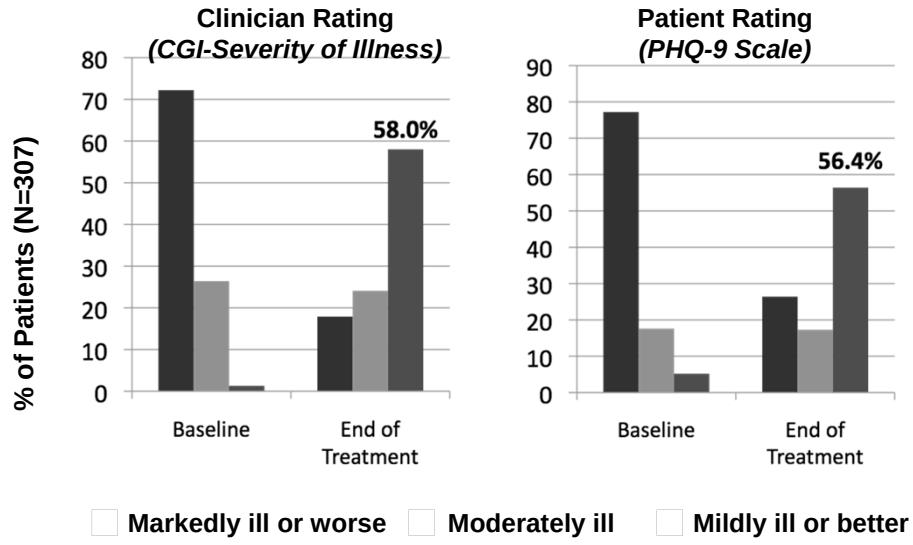
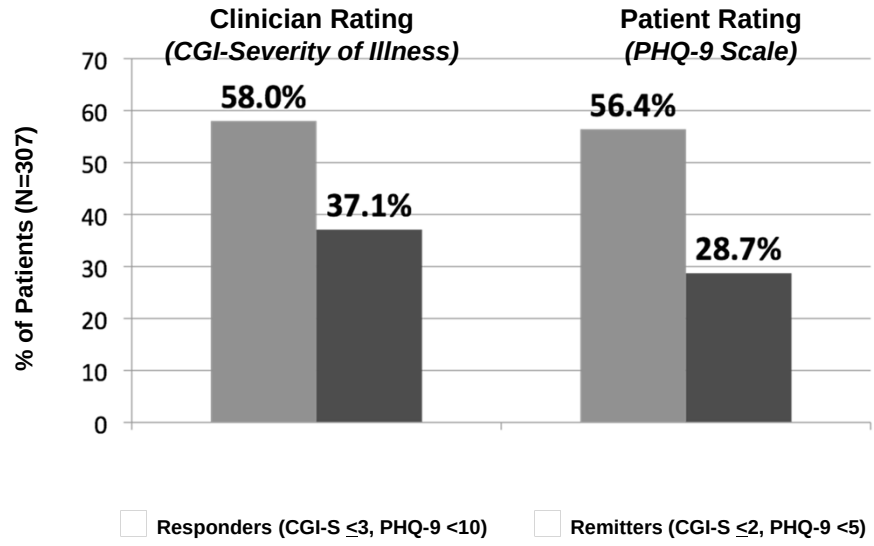
Carpenter LL, et.al. Depress Anxiety; 2012: 29(7)587-96

Comparison of End of Acute Treatment Clinical Status: Clinician- and Patient-Assessed Outcomes



LOCF Analysis of intent-to-treat population

Comparison of End of Acute Treatment Clinical Status: Clinician- and Patient-Assessed Outcomes



LOCF Analysis of intent-to-treat population

Clinical Results at Sheppard Pratt TMS Program

Open since April 2009
Treated about 300 patients
Patients have all failed 2 to 6 antidepressants in current episodes
15% had bipolar depression (type I or II)
60 % response rate and 30% remission rate by MADRS scores
Most patients get 30 treatments over 6 weeks
Almost all (except as required by study) on antidepressant medication
30% of patients (40% of responders) go on a maintenance protocol
No patient was unable to complete a course of treatment due to intolerable side effects
About half of patients pre-medicate with NSAID or acetaminophen
Several maintenance patients in remission for up to 7 years

Aaronson ST unpublished data

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Rationale for TMS in Bipolar Depression

Can offer a brief, episode related support which is easily adjustable based on response and adverse event

Well tolerated non-systemic therapy

Major risk is inducing manic or mixed symptoms.

Treatment can be stopped or adjusted accordingly.

Efficacy in Routine Practice

Reference	N	Location/Coil	Freq/Intensity	# Sessions	Outcomes	AE
Dell'Osso 2009	11	R-DLPFC Figure 8	1Hz 110%MT 300 pulses	15 over 3 wks	4/11 remit 6/11 resp HDRS	No mania
Harel 2011	19	L-DLPFC H-coil	20Hz 120%MT 1680 pulses	20 over 4 wks	52.6% remit 63.2% resp HDRS	No mania 1 general sz
Connolly 2012	20	L-DLPFC Figure 8	10 Hz 120% MT 3000 pulses	30 over 6 wks	15% remit 35% resp CGI	No serious AE
Aaronson 2016	39	L-DLPFC Figure 8	10 Hz 120% MT 3000 pulses	Up to 30 over 6 wks	BP I: 44% Remit 72% Resp BP II: 27% Remit 67% Resp MADRS	Agitation: 17% BPI 5% BPII No mania

Aaronson Study

Analyzed outcomes for 39 patients with bipolar depression (18 type 1, 21 type 2)

All patients on at least one mood stabilizer

Treated with standard protocol, 5 treatments a week, 3000 pulses LDPFC, at 10 Hz

MADRS scores collected at baseline, week 4, week 6 or as clinically indicated

Observed for possible activation to hypomania

Other Findings

17% (3/18) Bipolar 1 patients stopped after sessions 5, 5 and 9 for overstimulation

5% (1/21) Bipolar 2 patient stopped after 11 sessions due to overstimulation

For patients with ECT hx, 1 of 6 responded and remitted, 2 had a partial response

Average time to remission was 22.5 sessions for BP1, 22.6 for BP2

Vagus Nerve Stimulation

KC1

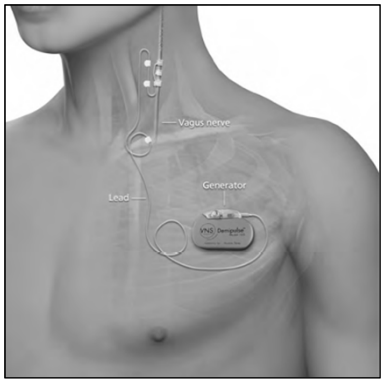
What is VNS Therapy® ?

Mild pulses applied to the left vagus nerve in the neck send signals to the brain

Automatic **intermittent stimulation**

Simple **in-office dose adjustment**

Assured **treatment compliance**



Physician Manual

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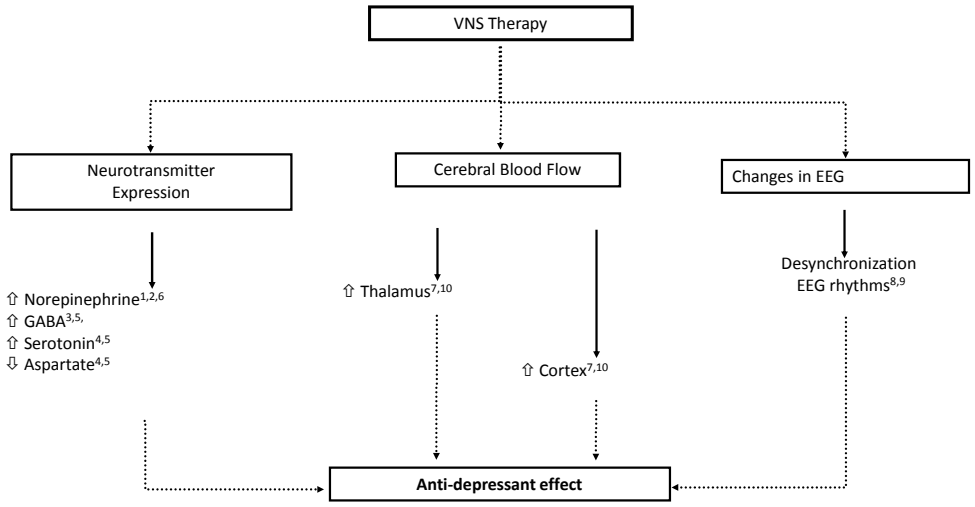
VNS Therapy Mechanism of Action



1. Roosevelt RW, et al. *Brain Res* 2006;1119(1):124-32. 2. Hassert DL, et al. *Behavioral Neuroscience* 2004;118(1):79-88. 3. Woodbury DM and Woodbury JW. *Epilepsia* 1990;31 (Suppl. 2):S7-S19. 4. Hammond BM, et al. *Brain Research* 1992;583:300-3. 5. Ben-Menachem E, et al. *Epilepsy Res* 1995;20:221-7. 6. Krahl S, et al. *Epilepsia.* 1998;39:709-714. 7 Henry TR, et al. *Epilepsia*. 2004;45(9):1064-1070. 8. Wang H et al., *J Neurosci.* 2009 ;in press. 9. Koo B. *J Clin Neurophysiol.* 2001;18:434-441. 10.Vonck K, et al. *Seizure* 2008; 17(8):699-706

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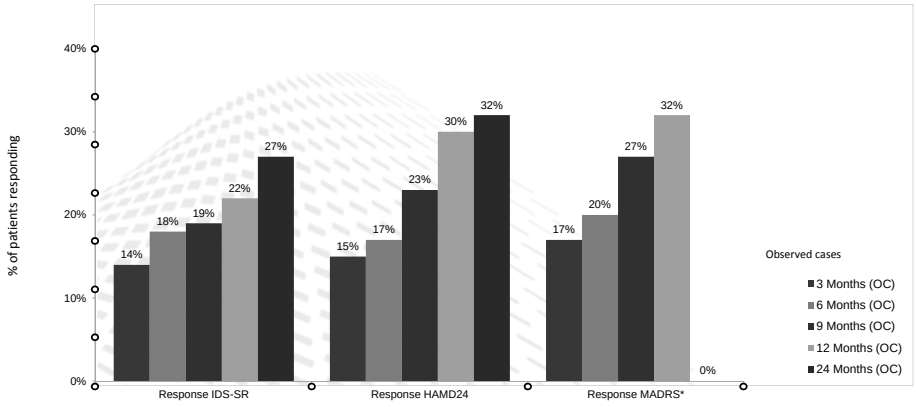
Slide 41

KC1 SP - Update image with Demipulse; update reference
Kimberly Cooper, 5/25/2015

D-02 Study
Long-term Phase – Outcomes



This graph reports the available population for each assessment at each visit.
*Montgomery-Åsberg Depression Rating Scale (MADRS) data not available for 24-month group.

Rush AJ, et al. Biol Psychiatry. 2005;58:355-360.
Depression Physician's Manual. Cyberonics®, Inc. Houston, Tx.

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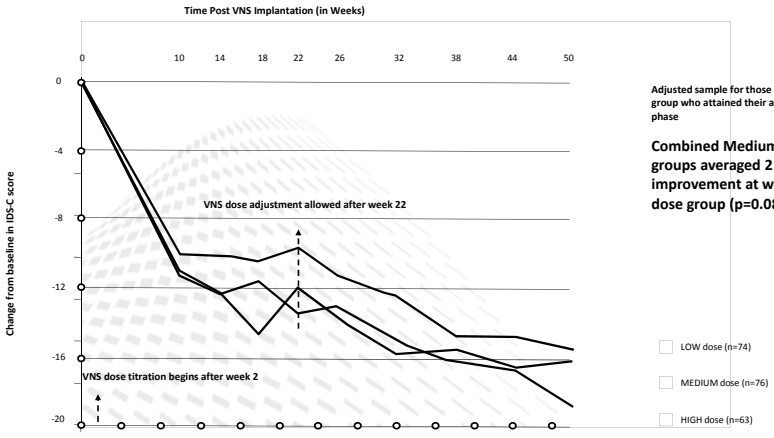
D-21 Dosing Study
Change in Baseline IDS-C Scores



Adjusted sample for those patients in each treatment group who attained their assigned dose during acute phase

Combined Medium and High dose groups averaged 2 points more improvement at week 22 than Low dose group (p=0.089)

Aaronson et al. Brain Stimulation, 2012

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D-23 VNS Registry

- Long term observational study of patients with unipolar or bipolar depression comparing 500 patients who received a VNS implant with 300 patient who received treatment as usual (TAU) at the same medical centers
- Patients that completed the D-21 Dose Finding Study were also eligible to enroll (rollover) in the TRD Registry and be included within the VNS Therapy group
- The study design permitted subjects to choose which treatment arm they were in at screening, either VNS or TAU
- Subjects were followed for five years
- Study data was collected for the registry between January 2006 and June 2014 (ClinicalTrials.gov Identifier: NCT00320372).

[45] Aaronson et al, AJP 2017

Patient Baseline Demographics

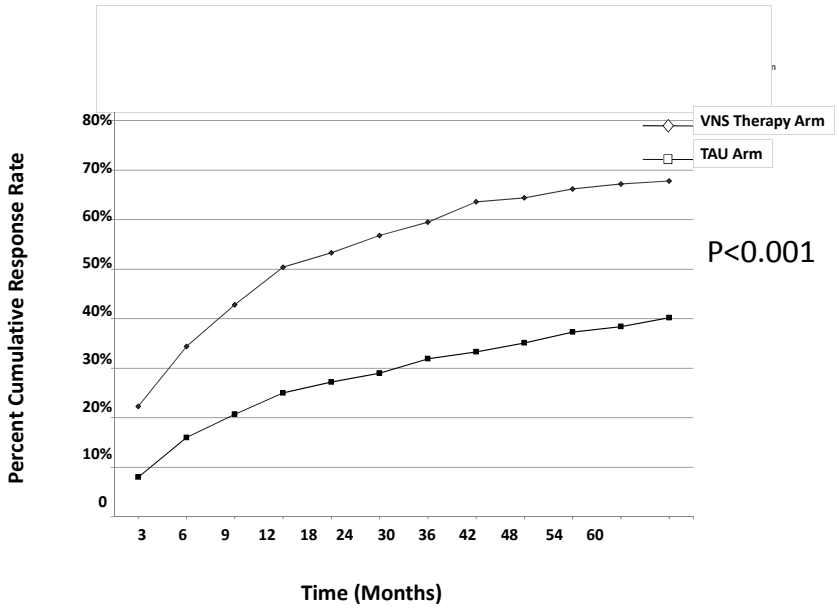
Parameter	VNS (N=494)	TAU (N=301)	Total (N=795)
Age at baseline in years, mean (SD)	48.9 (10.12)	49.9 (11.07)	49.3 (10.50)
Female, n (%)	350 (70.9%)	211 (70.1%)	561 (70.6%)
Caucasians, n (%)	478 (96.8%)	274 (91.0%)	752 (94.6%)
Age at initial onset of depression (years), mean (SD)	20.9 (11.80)	21.1 (11.39)	20.9 (11.64)
Age at initial diagnosis of depression (years), mean (SD)	28.9 (10.79)	29.5 (11.90)	29.1 (11.22)
Number of failed treatments for depression, mean (SD)	8.2 (3.3)	7.3 (2.9)	7.9 (3.2)
Prior use of electroconvulsive therapy, n (%)	280 (56.7%)	120 (39.9%)	400 (50.3%)
Psychiatric hospitalizations within 5 years prior to enrollment, mean (SD)	3.0 (4.57)	1.9 (4.73)	2.6 (4.66)
Suicide attempts over lifetime, mean (SD)	1.8 (4.0)	1.2 (2.4)	1.6 (3.5)

D-23 VNS Registry - US
Patient Demographics

Parameter	VNS D-23 + D-21 (n=494)	TAU (n=301)	Overall (n=795)
Recurrent MDD (Moderate)	12.8%	22.9%	16.6%
Recurrent MDD (Severe)	45.5%	31.6%	40.3%
Single MDD (Moderate)	3.2%	10.0%	5.8%
Single MDD (Severe)	11.3%	12.0%	11.6%
Bipolar I Depressed (Moderate)	5.1%	7.0%	5.8%
Bipolar I Depressed (Severe)	12.6%	4.0%	9.3%
Bipolar II Depressed	9.5%	12.6%	10.7%

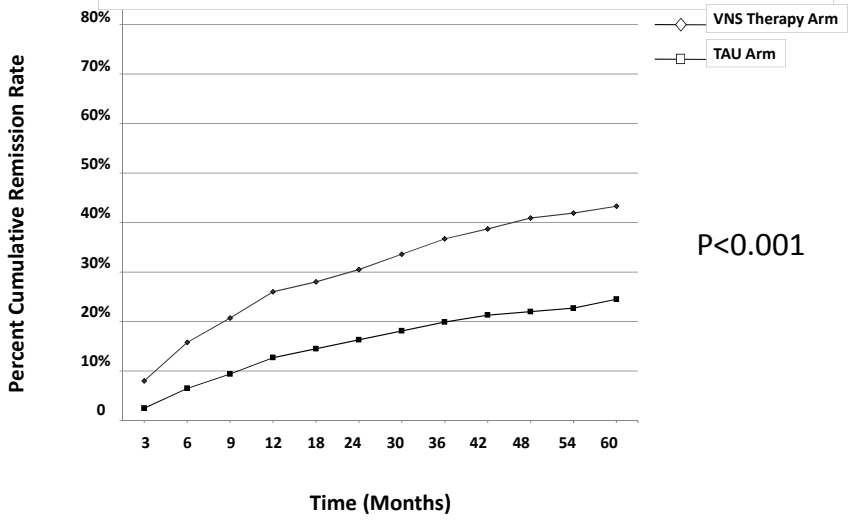
Treatment Response for the Entire Study Cohort

Primary Efficacy Endpoint: Percentage of First-Time Responders Over Time



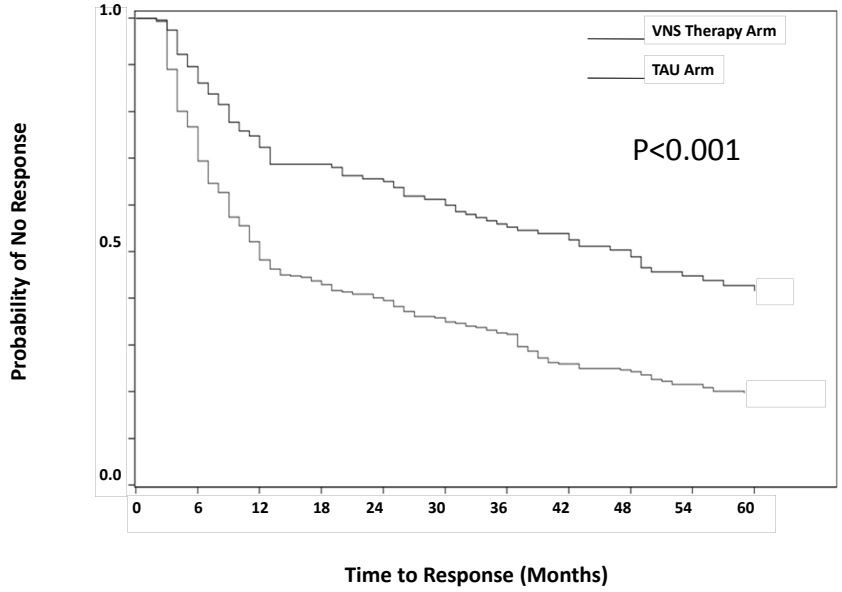
P<0.001

Percentage of First-Time Remitters over Time

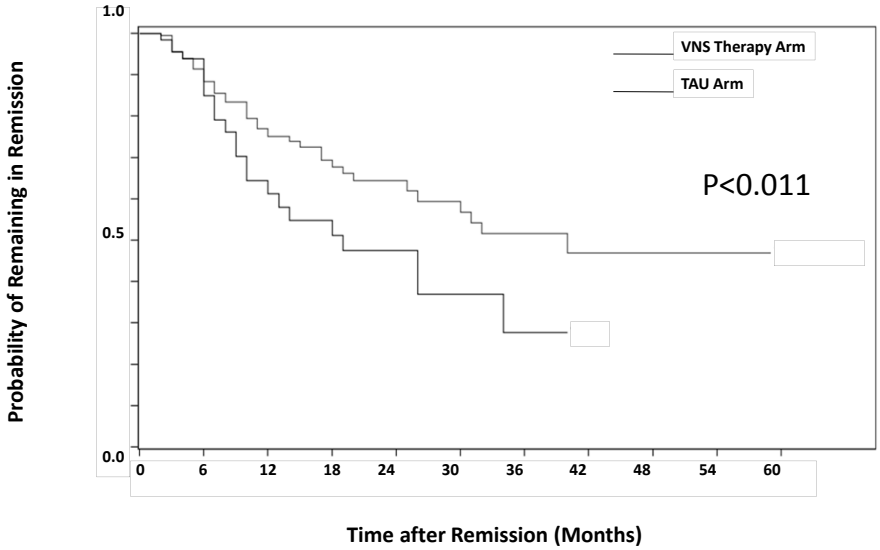


P<0.001

Time-to-First Response based on MADRS



Time to First Recurrence in Patients who Achieved Remission based on MADRS



Subanalysis of ECT Treated Patients

- ECT treated patients represent the most treatment resistant group
- Data was collected about ECT exposure and response
- A total of 290 VNS patients and 109 TAU patients had a history of at least one adequate course of ECT

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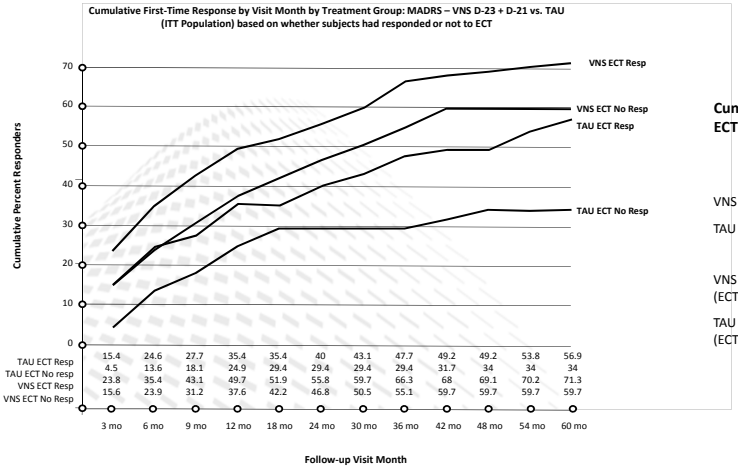
D-23 VNS Registry - US
MADRS – Response by History of Prior Response to ECT

Exploratory Analysis – **Response** based on MADRS



Cumulative Response Rate Based on ECT Response (yes/no)

VNS (ECT resp)	(n=129)	71.3%
TAU (ECT resp)	(n=37)	56.9%
		NNT=6
VNS (ECT nonresp)	(n=65)	59.7%
TAU (ECT nonresp)	(n=15)	34.0%
		NNT=5

Data on File Livo Nova

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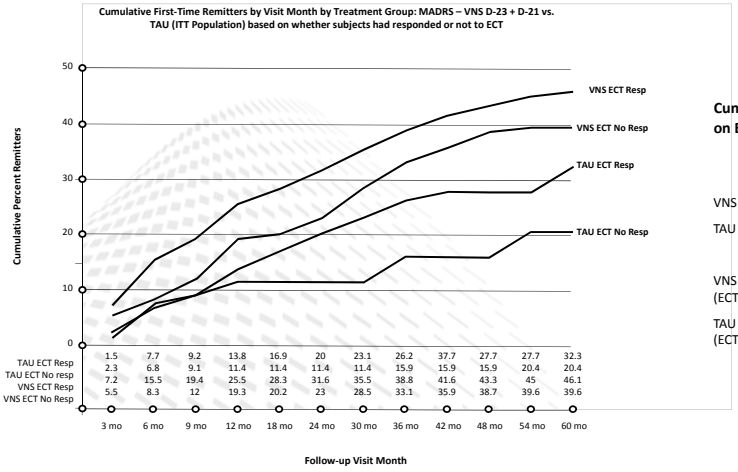
D-23 VNS Registry - US
MADRS – Remission by History of Prior ECT Response

Exploratory Analysis – **Remitter** based on MADRS



Cumulative Remission Rate Based on ECT Response (yes/no) at 5 years

VNS (ECT resp)	(n=83)	46%
TAU (ECT resp)	(n=21)	33%
		NNT=8
VNS (ECT nonResp)	(n=43)	40%
TAU (ECT nonResp)	(n=9)	21%
		NNT=5

Data on File Livo Nova

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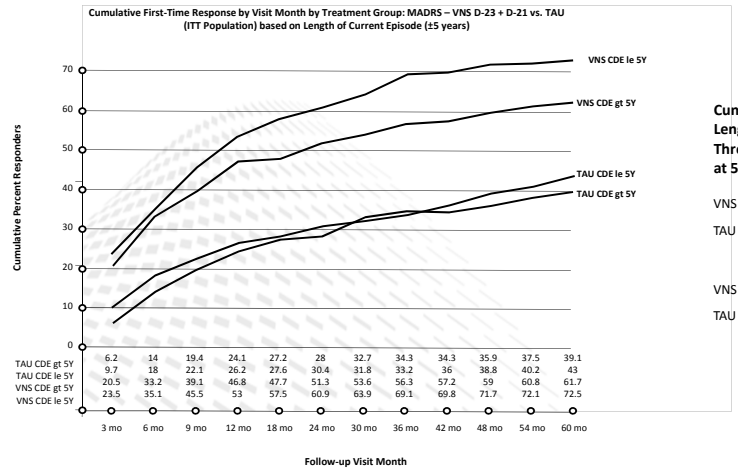
D-23 VNS Registry - US
MADRS – Response by Length of Current MDE

Exploratory Analysis – **Response** based on MADRS



Cumulative Response Rate Based on Length of Current MDE (5 year Threshold) at 5 Years

VNS (<5 yrs)	(n=194)	72.5%
TAU (<5 yrs)	(n=62)	43.0%
		NNT=3
VNS (≥ 5yrs)	(n=136)	61.7%
TAU (≥ 5yrs)	(n=50)	39.1%
		NNT=4

Data on File Livo Nova

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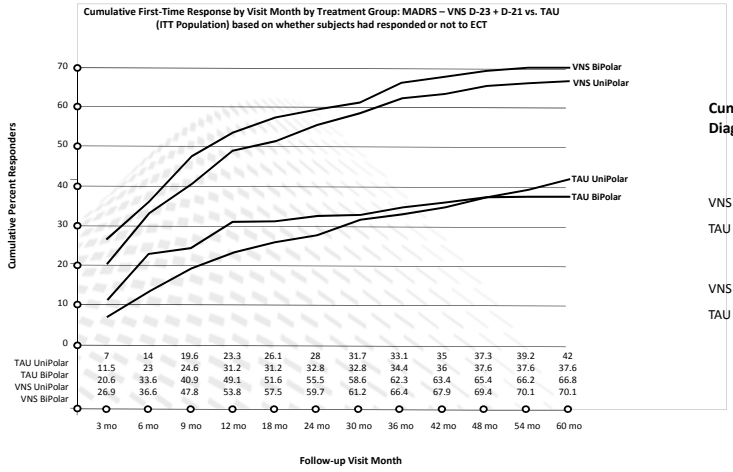
D-23 VNS Registry - US
MADRS – Response by Bipolar vs. Unipolar Diagnosis

Exploratory Analysis – **Response** based on MADRS



Cumulative Response Rate Based on Diagnosis (UP vs. BP) at 5 years

VNS (UP)	(n=237)	66.8%
TAU (UP)	(n=90)	42.0%
		NNT=4
VNS (BP)	(n=94)	70.5%
TAU (BP)	(n=23)	37.6%
		NNT=3

Data on File Livo Nova

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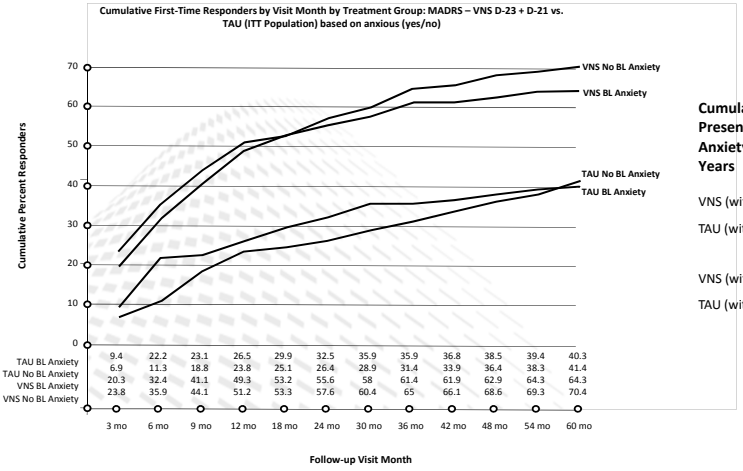
D-23 VNS Registry - US
MADRS – Response by Anxious (yes/no)

Exploratory Analysis – **Response** based on MADRS



Cumulative Response Rate Based on Presence/Absence of DSM-IV Anxiety Disorders (AD) (MINI) at 5 Years

VNS (without AD)	(n=198)	70.4%
TAU (without AD)	(n=66)	41.4%
		NNT=4
VNS (with AD)	(n=133)	64.3%
TAU (with AD)	(n=47)	40.3%
		NNT=4

Data on File Livo Nova

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D-23 VNS Registry - US
Mortality

Variable	VNS + TAU	TAU
Total number of deaths	7	8
Patient Year Exposure	1985.1	926.5
All-cause mortality/1000 person years	3.53	8.63
Suicides	2	2
Suicides/1000 person years	1.01	2.20
Cause of death	• Two were accidental overdoses • One each for complications due to diabetes, homicide and one for unknown reasons	• Four of the deaths were considered cardiac related (myocardial infarction, heart attack, hypertensive heart disease, and cardiopulmonary arrest secondary to possible complication of liver cancer) • Two were considered natural deaths (anoxic encephalopathy and cerebral hemorrhage)
Response	Three of the VNS patients were considered responders at last recorded visit (accidental overdose of opiates; suicide; and homicide)	None of the TAU patients were considered responders at last recorded visit

Final Clinical Study Report: Treatment-Resistant Depression Registry (D-23)
Submitted to the FDA on August 1, 2011

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Overview of VNS Studies in Depression

- Hard to figure out the appropriate parameters for an intervention that takes 6 months to see a response
- Minimal levels of stimulation may provide a cumulative response that is effective enough to not provide an adequate sham
- VNS offers a chronic, but not acute, treatment option that is not available from any other neuromodulation modality
- It may provide particular support for ECT responders for chronic maintenance
- Remarkable durability of response persists over five years
- Current status by CMS of VNS as not covered needs to be revisited

Aaronson ST et al. *Brain Stimul.* 2012;6(4):631-640.
Aaronson ST et al *AJP* 2017 Mar 31:appiajp201716010034