Vagus Nerve Stimulation 2019: Everything Old is New Again

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Consultant/Advisor:

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Speakers Bureau:

Sunovion Pharmaceuticals Inc.; Janssen

Agenda

1. **Overview of Treatment Resistant Depression (TRD)**
2. **Overview of Neurostimulation**
3. **Vagus nerve stimulation**

1. Overview
2. Status of current data
3. New Medicare funded clinical trial
4. Patient selection

DEPRESSION TREATMENT PARADIGM

Treatment Algorithm Snapshot

STAR*D Algorithm

Level 1

Initial treatment: **citalopram**

Level 2

Switch to: **bupropion (sustained-release), cognitive therapy, sertraline, venlafaxine (extended-release);** Or augment with: **bupropion (sustained-release), buspirone, cognitive therapy**

Level 2a

(Only for those receiving cognitive therapy in Level 2)
switch to: **bupropion (sustained-release) or venlafaxine (extended-release)**

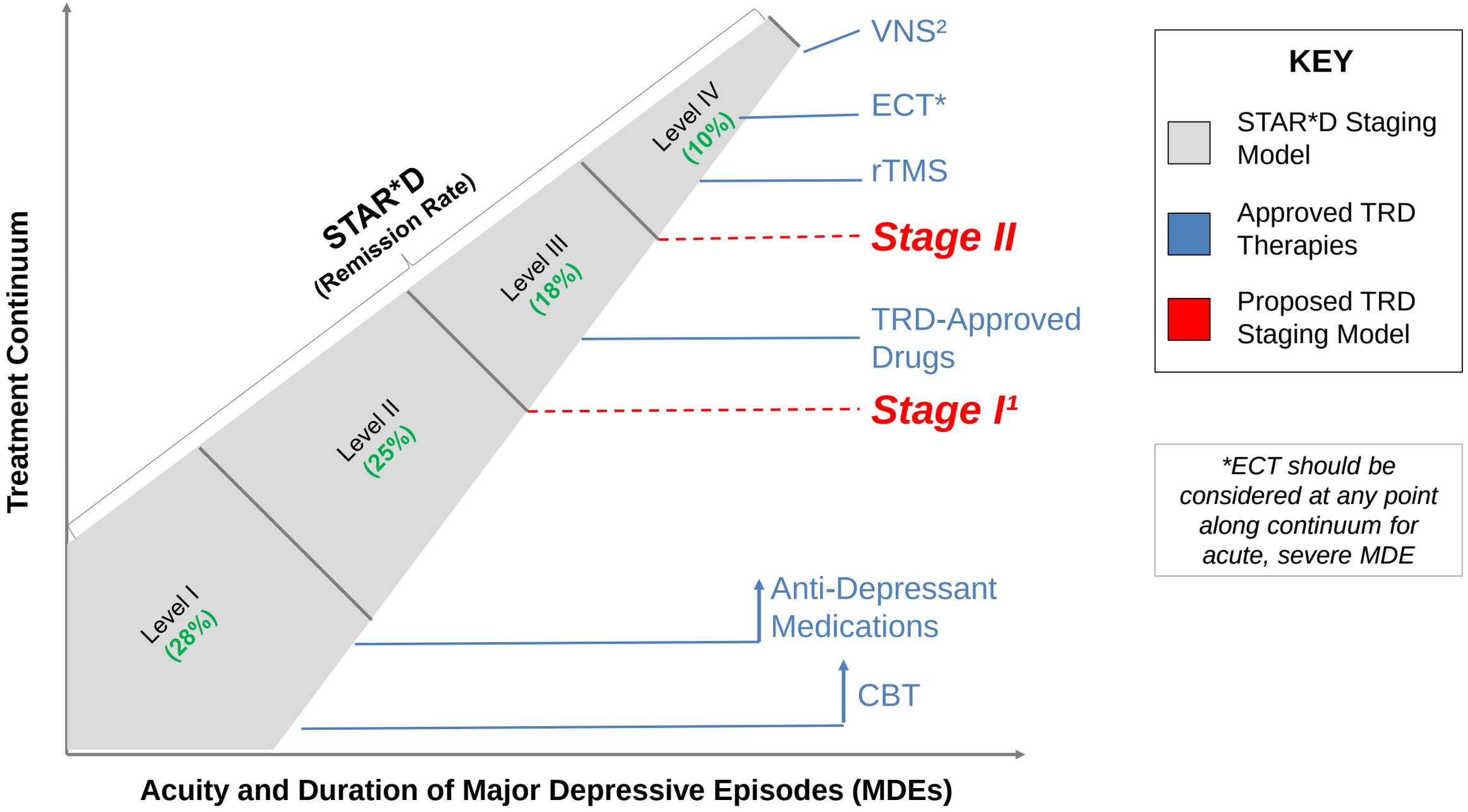
Level 3

Switch to: **mirtazapine or nortriptyline (Aventyl)**
or augment with: **lithium (Eskalith, Lithobid) or triioclothyronine (only with bupropion [sustained-release], sertraline, venlafaxine [extended-release])**

Level 4

Switch to : **tranylcypromine (Parnate) or mirtazapine combined with venlafaxine (extended-release)**

Major Depressive Disorder (MDD):
A Staged Approach to Determining Treatment Resistance



KEY

- STAR*D Staging Model
- Approved TRD Therapies
- Proposed TRD Staging Model

**ECT should be considered at any point along continuum for acute, severe MDE*

VNS: Vagus Nerve Stimulation
ECT: Electroconvulsive Therapy
rTMS: Repetitive Transcranial Magnetic Stimulation
CBT: Cognitive Behavioral Therapy

[1]**Studies:** Rizvi, 2014; Kubitz, 2013; Vieta & Colom, 2011; Albert, 2015
[1]**Guidelines:** VA/DoD, 2009; NICE, 2009; AHRQ, 2011; APA, 2010
[1]**Health Tech Assessments**: Oregon HERC, 2012; AHRQ, 2011; ICER-CEPAC, 2011
[2]**AHRQ**, 2011; APA, 2010

Applying This Definition of TRD Across Settings of Care for Medicare Beneficiaries

- Stage I TRD may be managed in the primary care setting; pharmacotherapy can be managed collaboratively with psychiatrist

- Stage II TRD should be managed by general or specialized psychiatry

- Clinical studies of Stage II (and higher) TRD treatments should be conducted in centers with specific training in managing patients with advanced TRD; for example:
  - Centers that have participated in clinical trials of TRD treatments
  - Centers that participated in STAR*D
  - Centers that treat TRD regularly and have experience with a broad spectrum of pharmacological and nonpharmacological treatments
  - National Network of Depression Centers

Definitions

Nonresponse--<25% reduction on depression rating scale
Partial response—25-50% reduction
Treatment response-->50% reduction
Remission—no dysfunction or minimal sx remain

N.B.—response is not remission
Most clinical trial give statistics for response, not remission
Responders at least three times as likely to experience a relapse in 12 months than remitters

Pharmacotherapy of Depression

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

Essentially we have no clear other targets for antidepressants (perhaps opiate receptors or NMDA antagonists)

At least a third of patients with depression do not have a sufficient response to antidepressant medications

NEUROSTIMULATION

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**

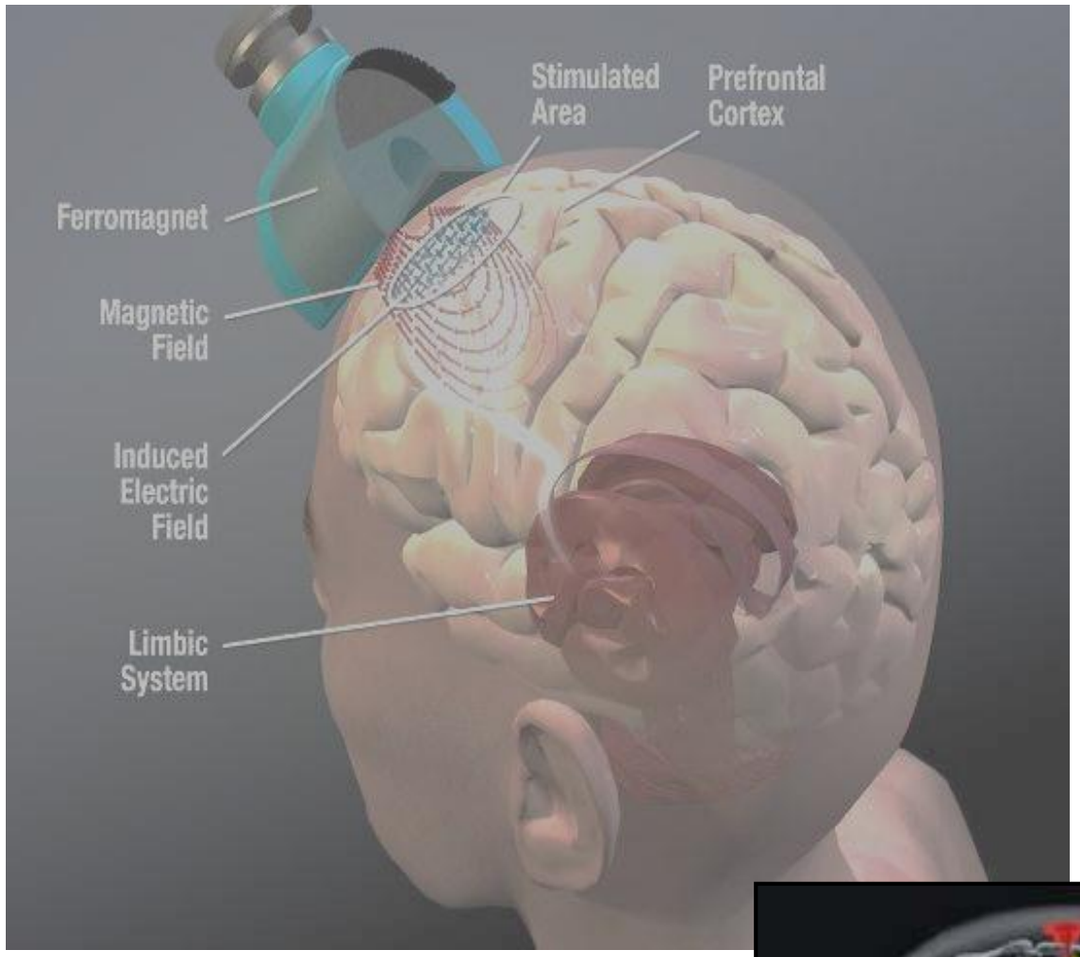
Neurostimulation Methods

FDA Cleared Methods

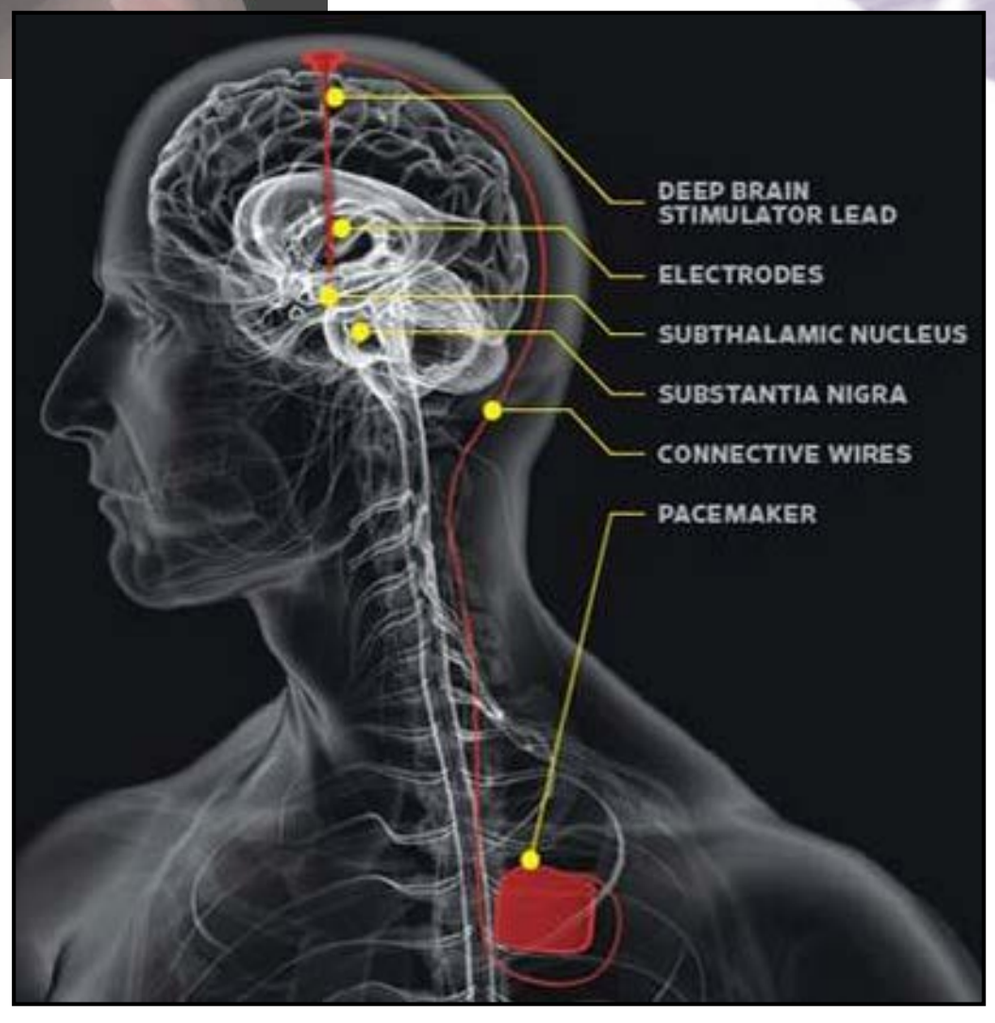
- Electroconvulsive Therapy (ECT)
- Vagus Nerve Stimulation (VNS)
- Repetitive Transcranial Magnetic Stimulation (rTMS)

Methods in Development

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

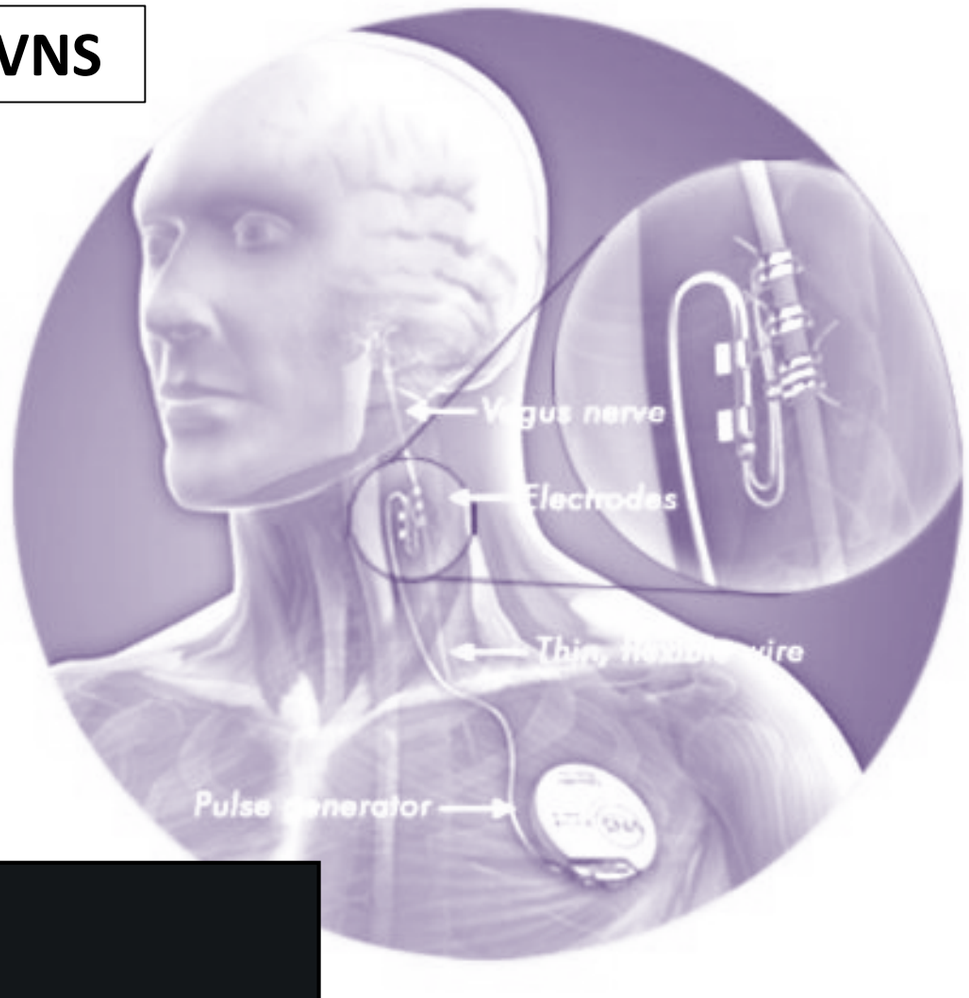

Stimulated Area
Prefrontal Cortex
Ferromagnet
Magnetic Field
Induced Electric Field
Limbic System

TMS


DEEP BRAIN STIMULATOR LEAD
ELECTRODES
SUBTHALAMIC NUCLEUS
SUBSTANTIA NIGRA
CONNECTIVE WIRES
PACEMAKER

DBS

VNS


Vagus nerve
Electrodes
Pulse generator

Neuromodulation in Depression

	ECT	TMS	VNS	tDCS	DBS
Efficacy in Severe	yes	Not much	yes	none	Open label only
Durability of Response	High relapse ?mainten.	Moderate relapse ?mainten.	good	none	possibly
Efficacy with episode >5 yr	Yes, Mostly anecdotal	No evidence	good	none	yes
Bipolar evidence	yes	Early anecdotal	good	minimal	?

ECT--Electroconvulsive Therapy, TMS—Transcranial Magnetic Stimulation, VNS—Vagus Nerve Stimulation, tDCS—transcranial Direct Current Stimulation, DBS—Deep Brain Stimulation

VAGUS NERVE STIMULATION (VNS)

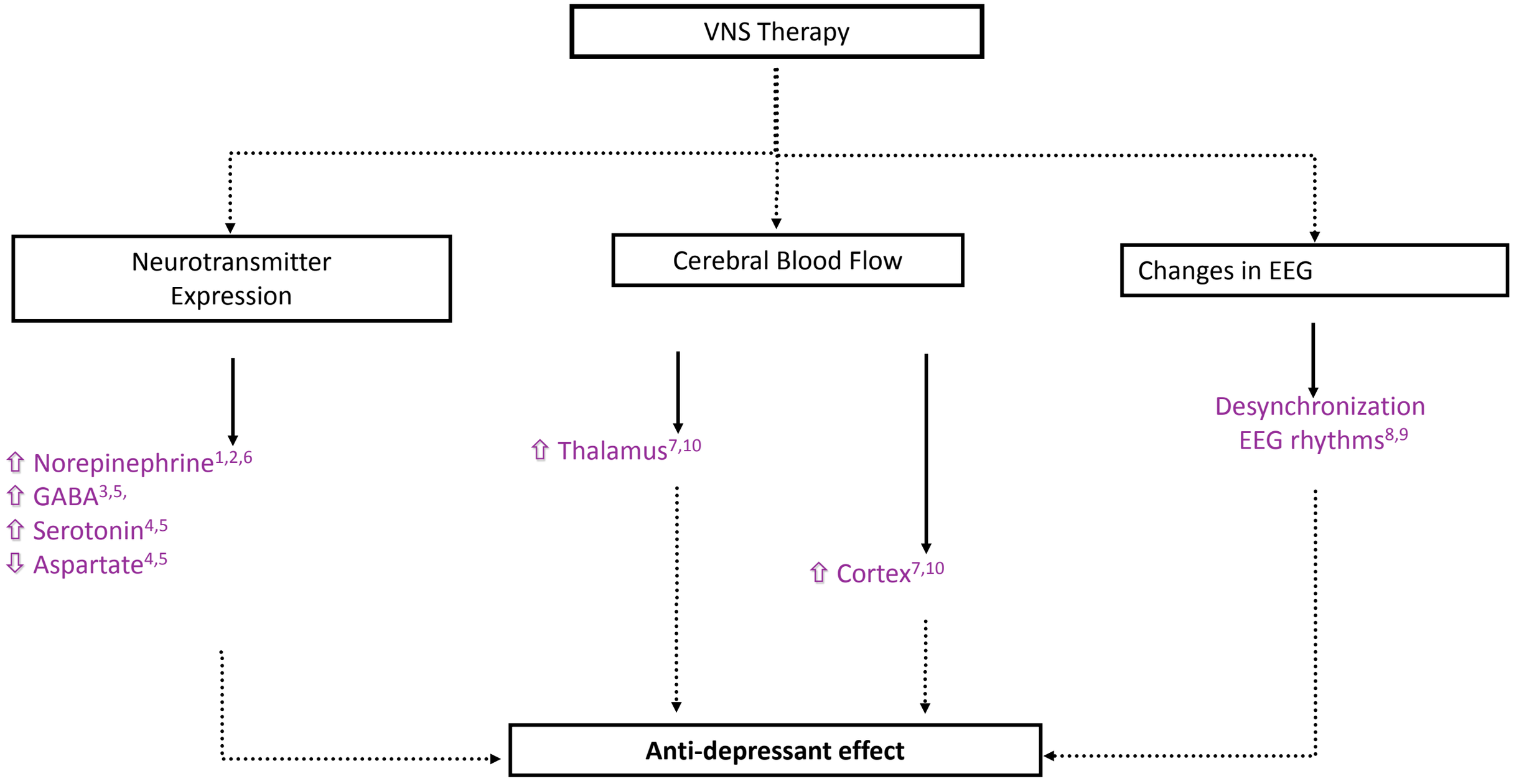
Vagus Nerve Stimulation (VNS)

- Device implanted in the upper chest, leads tunneled under the skin and wrapped around the left vagus nerve in the neck.

- Device sends small electrical current for 30 seconds every 5 minutes

- Treatment delivered 24/7 unless interrupted by a magnet placed over the device

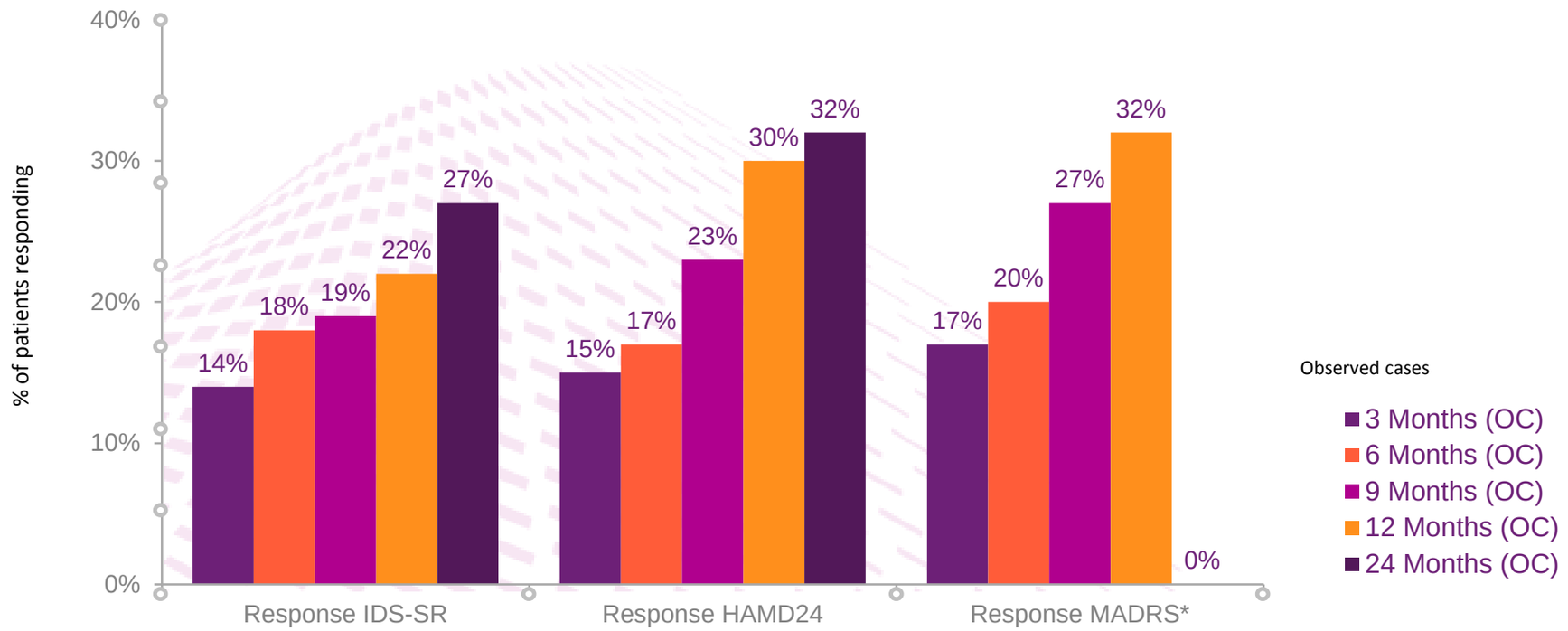
VNS Therapy Mechanism of Action



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

D-02 Study

Long-term Phase – Outcomes



Rush AJ, et al. Biol Psychiatry. 2005;58:355-363.

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

D-21 Dosing Study

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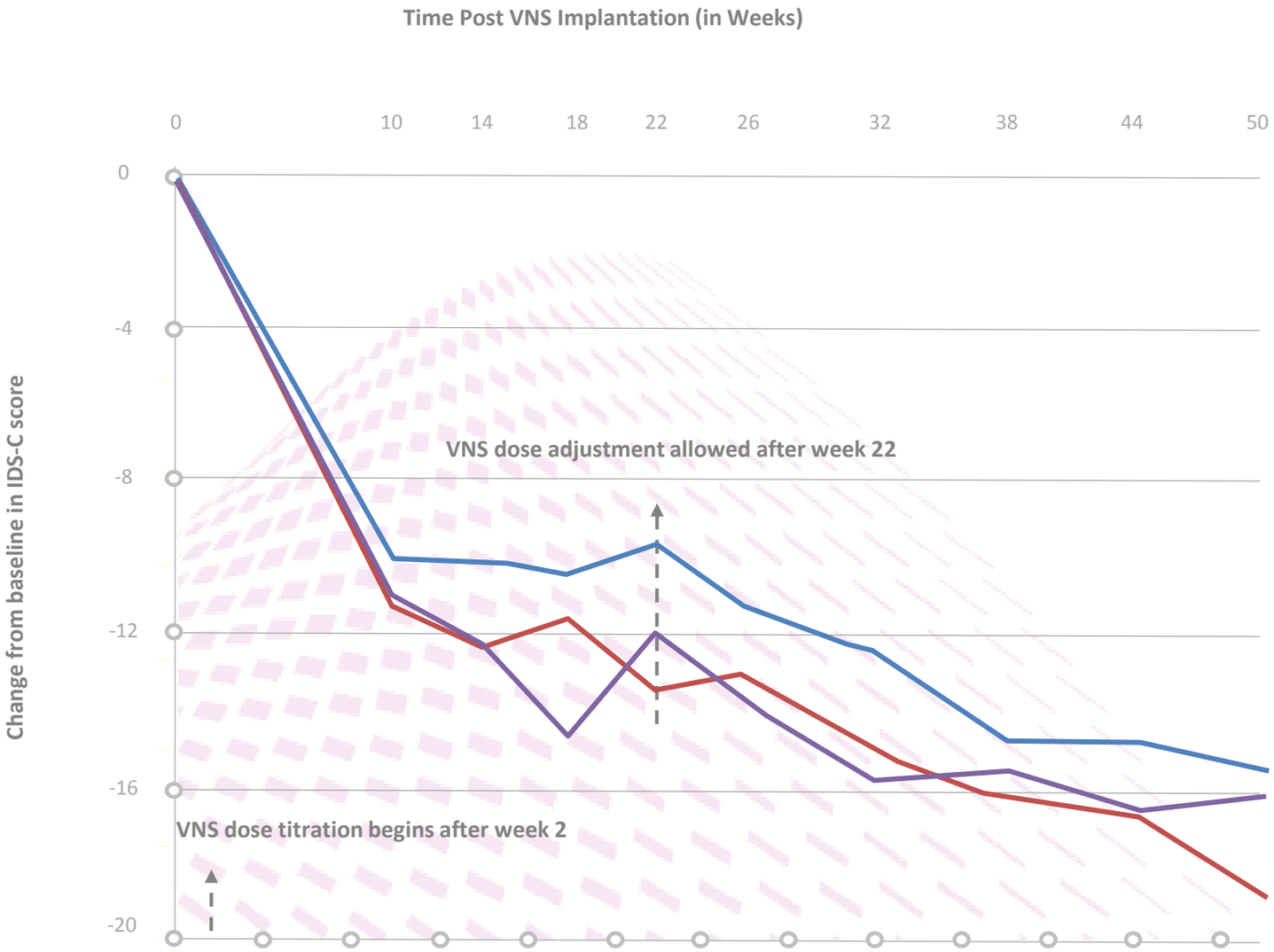

Adjusted sample for those patients in each treatment group who attained their assigned dose during acute phase

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

LOW dose (n=74)

MEDIUM dose (n=76)

HIGH dose (n=63)

Aaronson et al. Brain Stimulation, .2012

Five Year Study of VNS in TRD and Bipolar Depression

D-23 VNS Registry

5-year, prospective, open-label, non-randomized, observational registry study at 61 centers

Patients with unipolar or bipolar depression comparing **494** patients in the VNS arm (including D-21 rollover patients) and 301 in the 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).

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)

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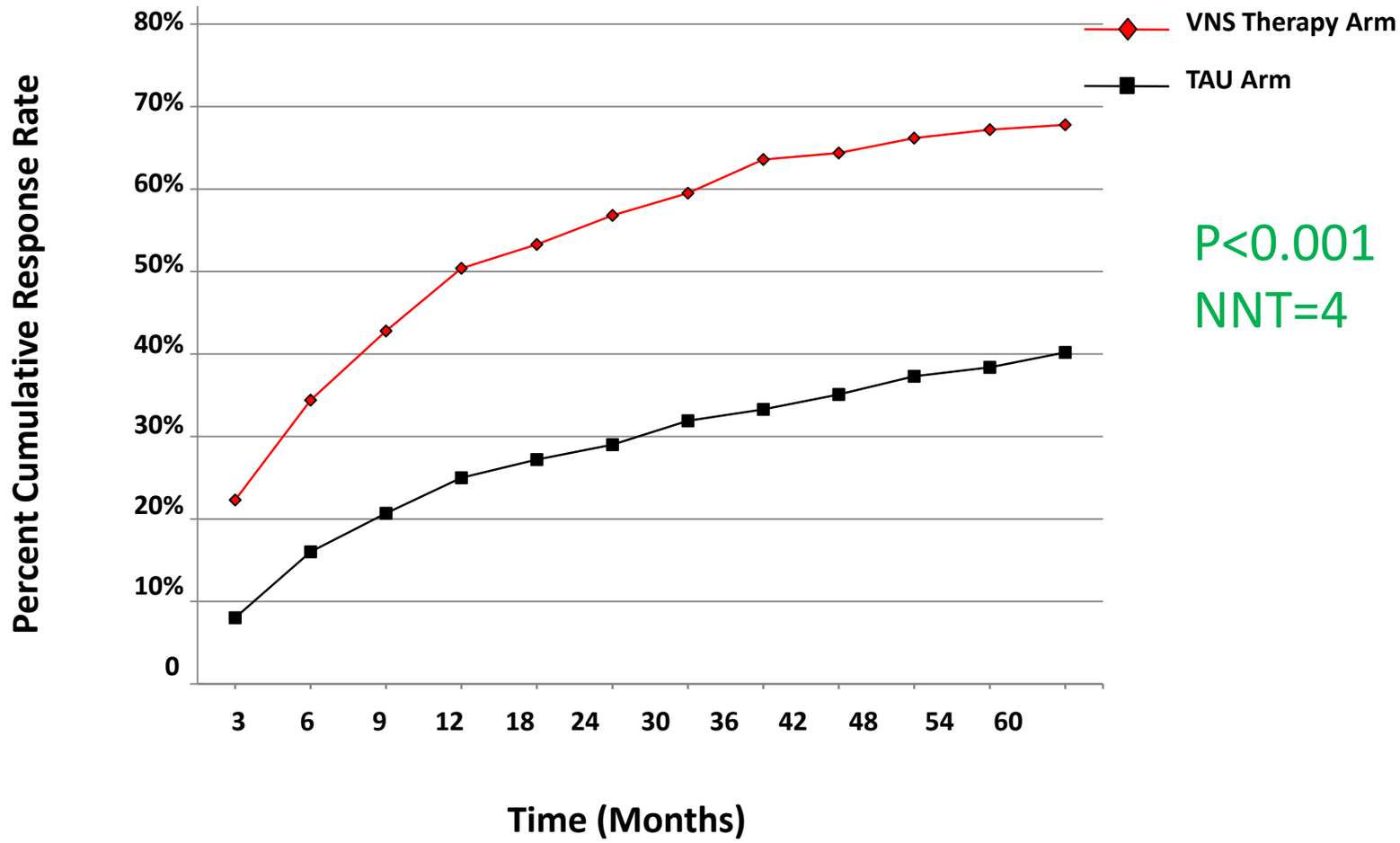
D-23 VNS Registry - US
Patient Demographics

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%

Final Clinical Study Report: Treatment-Resistant Depression Registry (D-23)
Submitted to the FDA on August 1, 2015

Treatment Response for the Entire Study Cohort

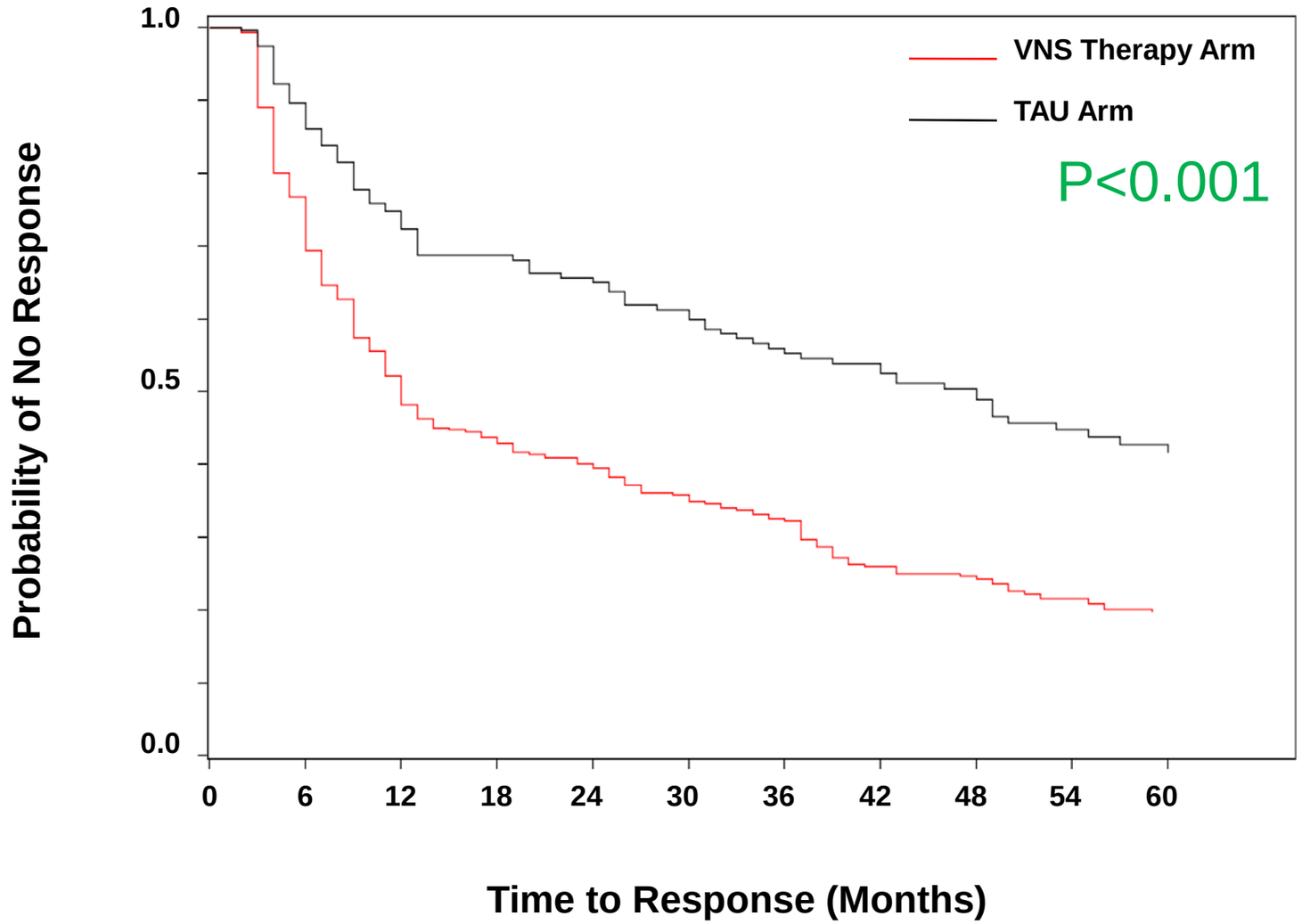
Primary Efficacy Endpoint: Percentage of First-Time Responders Over Time



P<0.001

NNT=4

Time-to-First Response based on MADRS

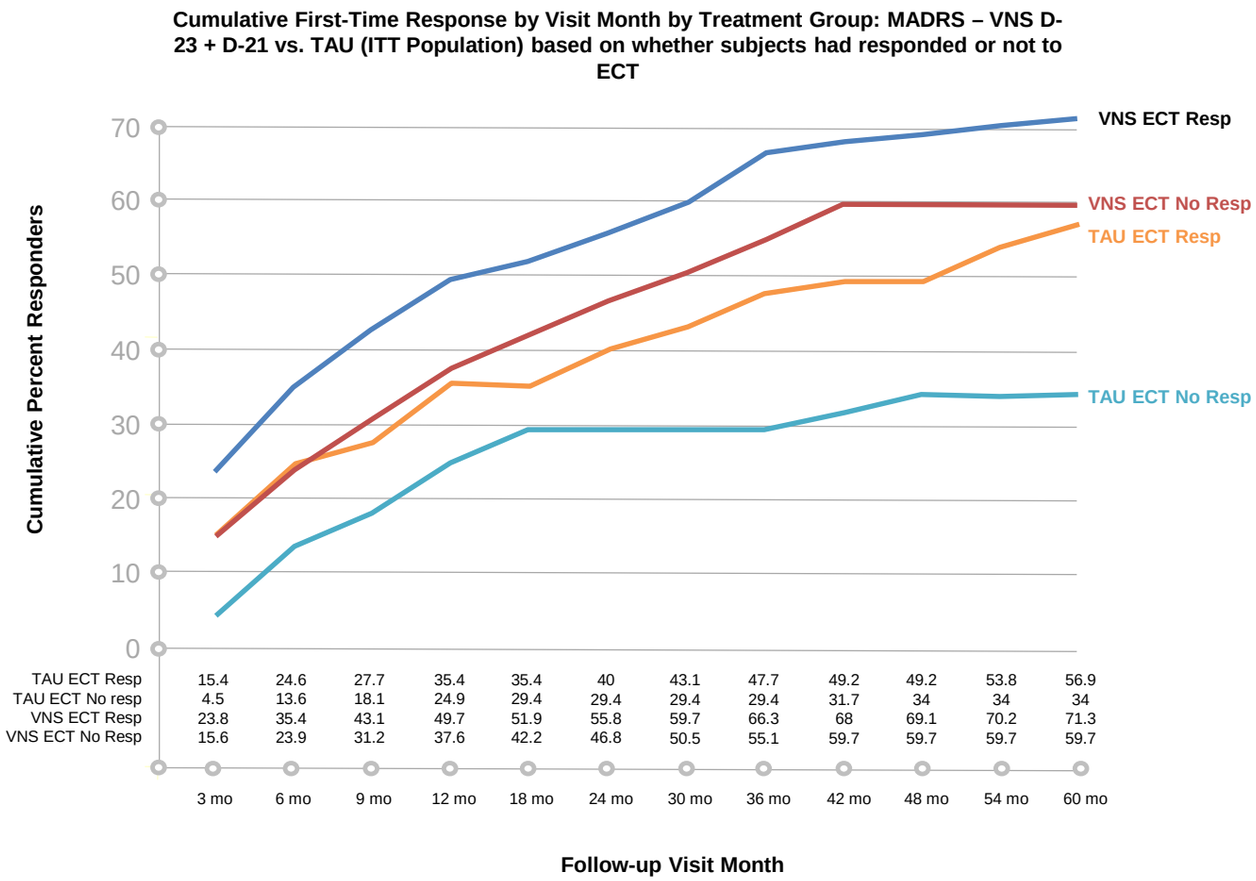


Subanalysis of ECT Treated Patients

- 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

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

Exploratory Analysis – **Response** based on MADRS



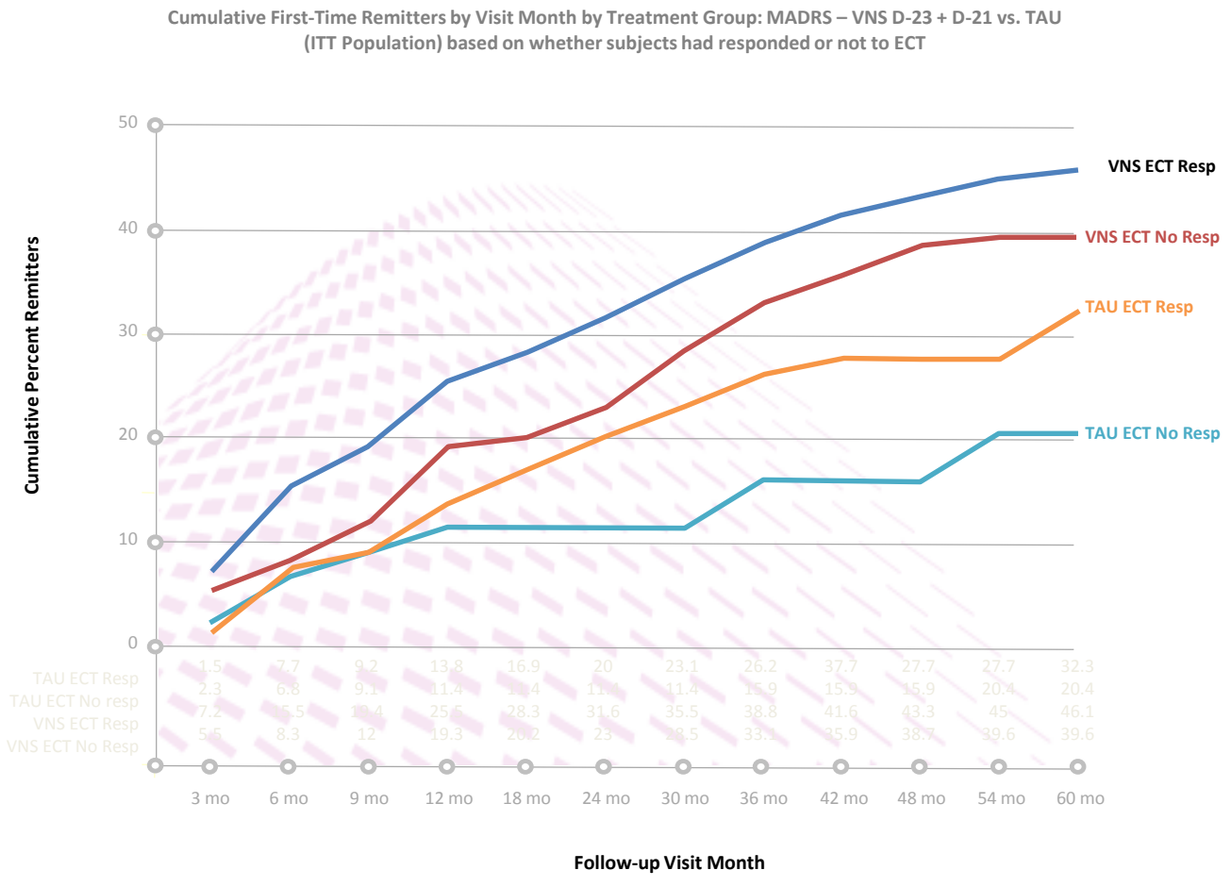
Cumulative Response Rate Based on ECT Response (yes/no)

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

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

Exploratory Analysis – **Remitter** based on MADRS



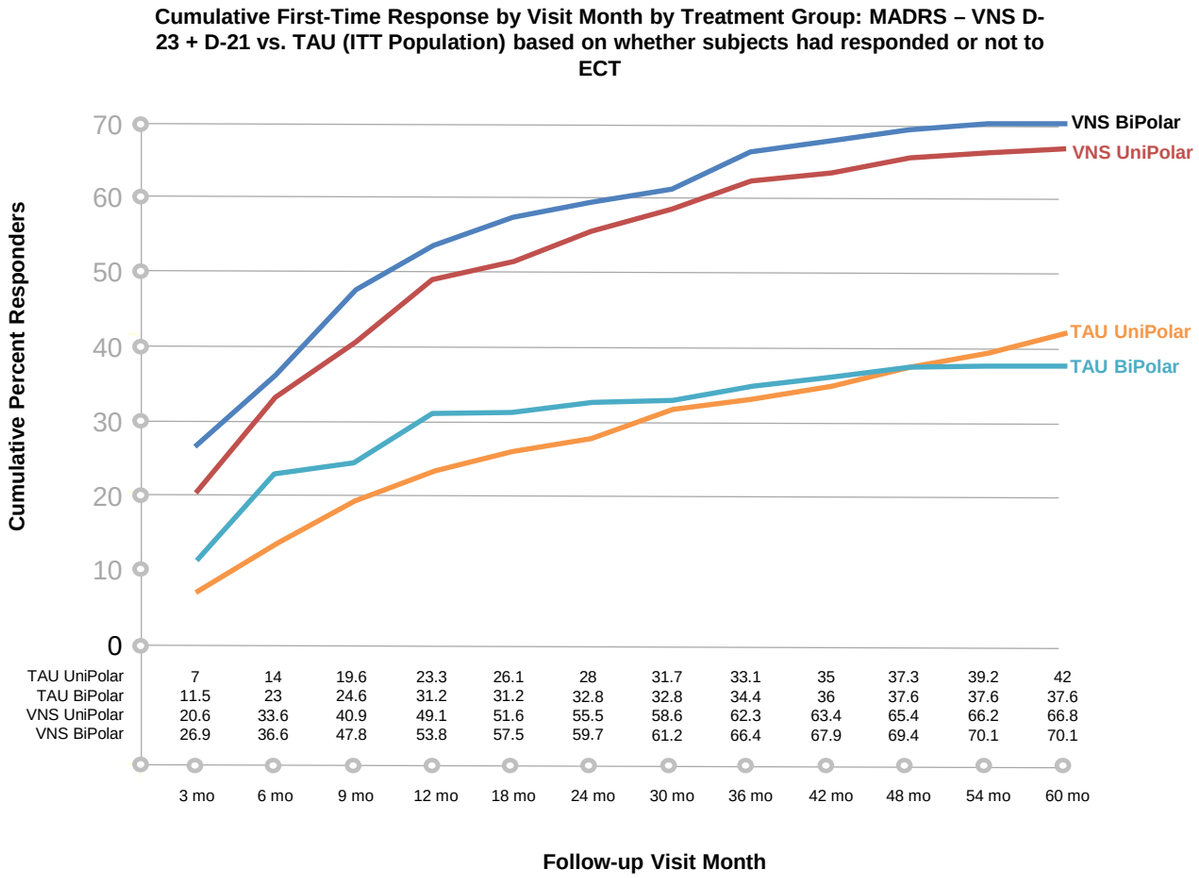
Cumulative Remission Rate Based on ECT Response (yes/no) at 5 years

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

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

Exploratory Analysis – **Response** based on MADRS



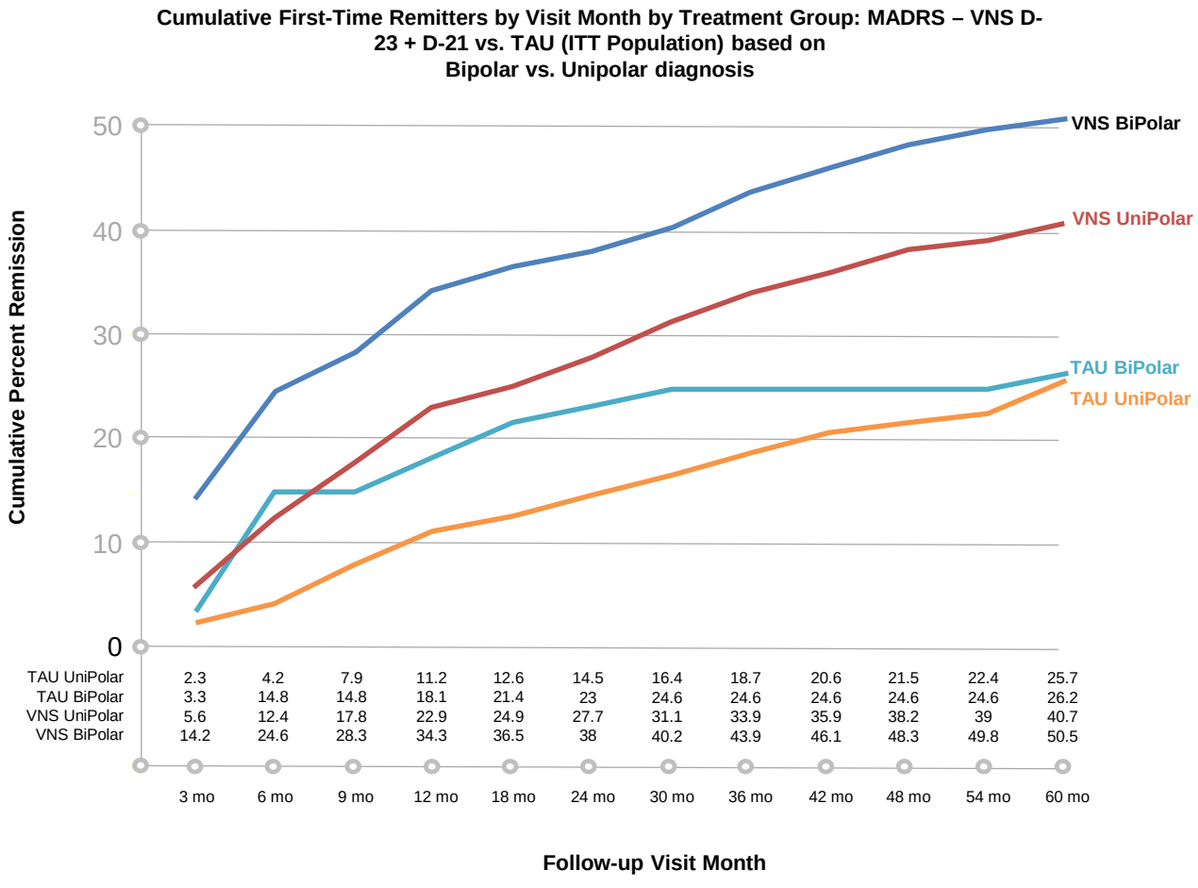
Cumulative Response Rate Based on Diagnosis (UP vs. BP) at 5 years

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

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

Exploratory Analysis – **Remitter** based on MADRS



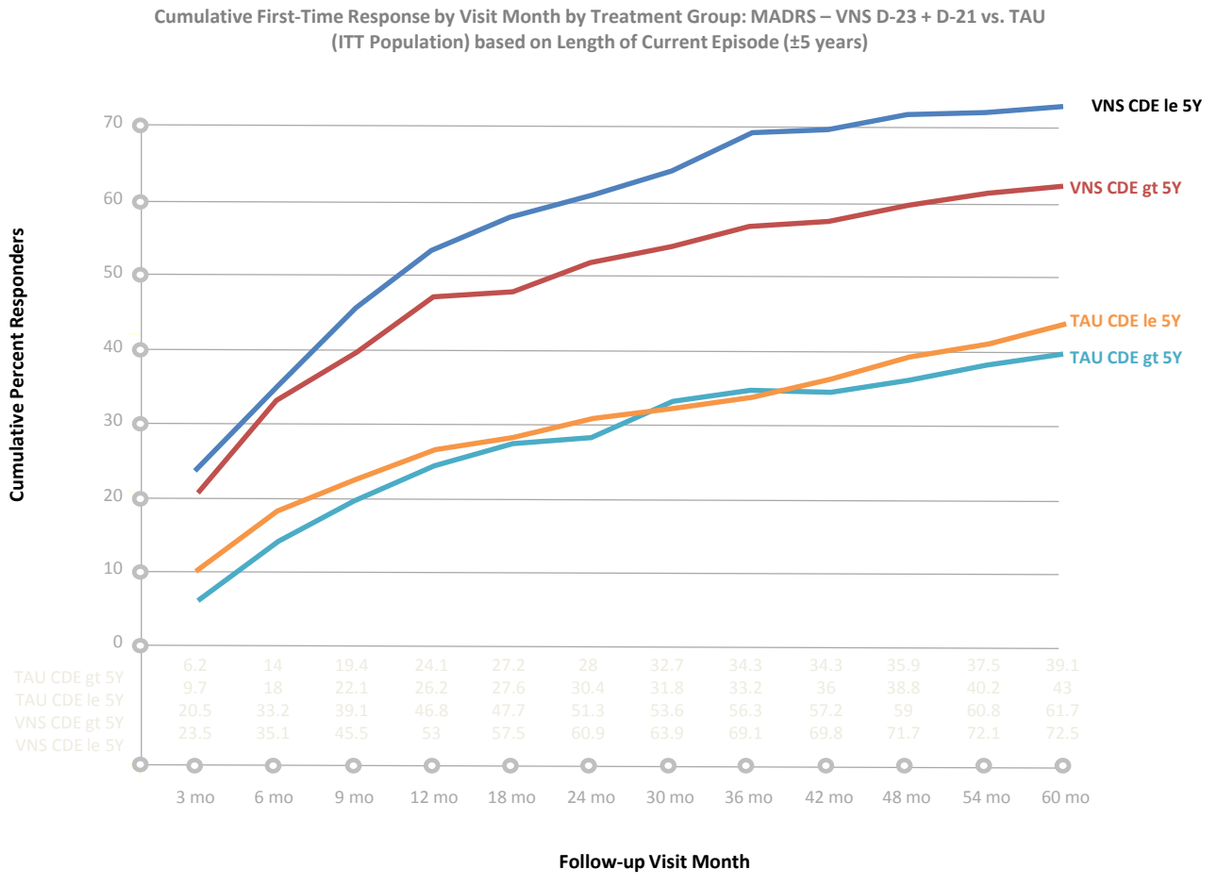
Cumulative Remission Rate Based on Diagnosis (UP vs. BP) at 5 years

VNS (UP)	(n=144)	40.7%
TAU (UP)	(n=55)	25.7%
		NNT=7
VNS (BP)	(n=68)	50.5%
TAU (BP)	(n=16)	26.2%
		NNT=4

Data on File Livo Nova

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

Exploratory Analysis – **Response** based on MADRS



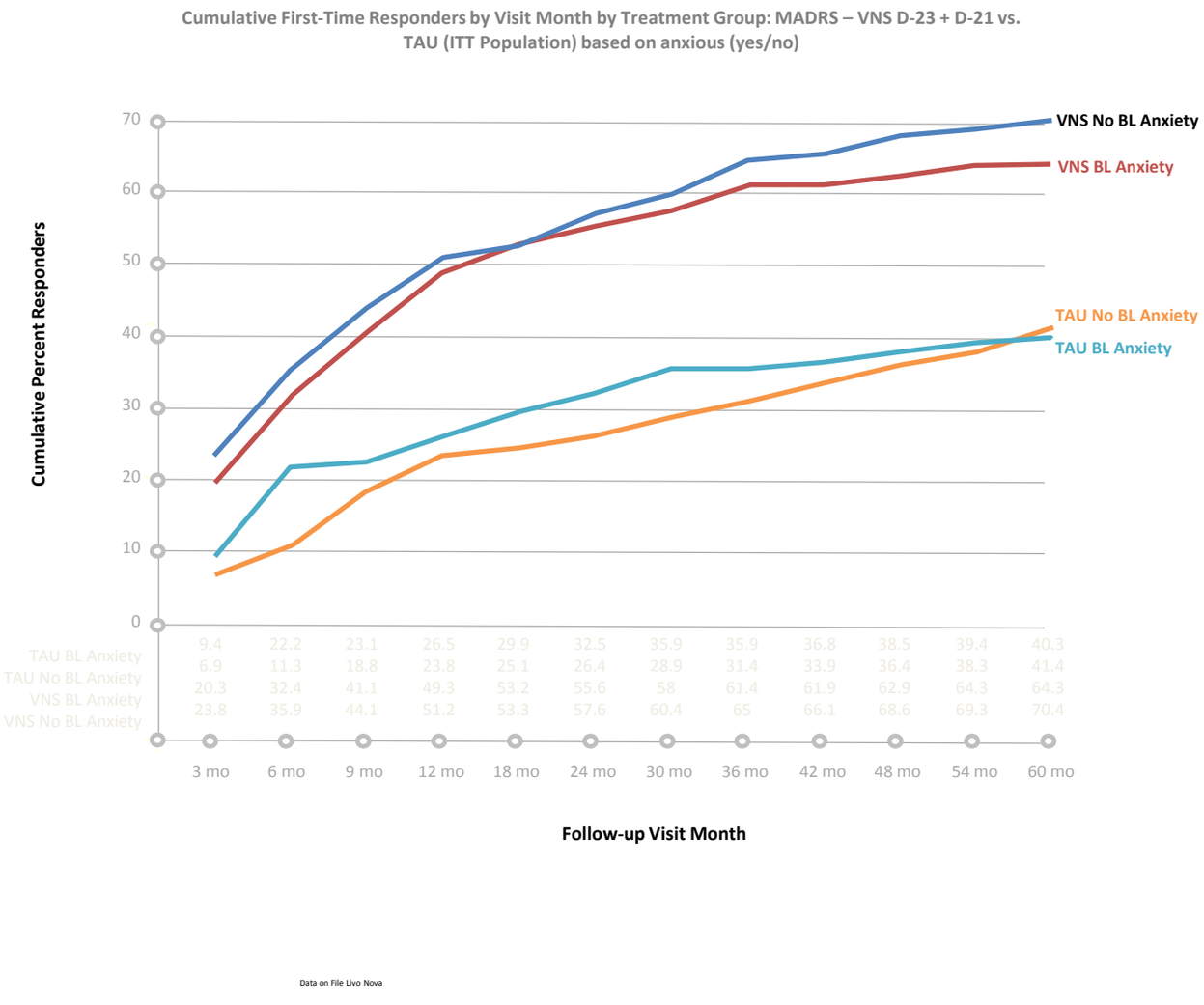
Cumulative Response Rate Based on Length of Current MDE (5 year Threshold) at 5 Years

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

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

Exploratory Analysis – **Response** based on MADRS



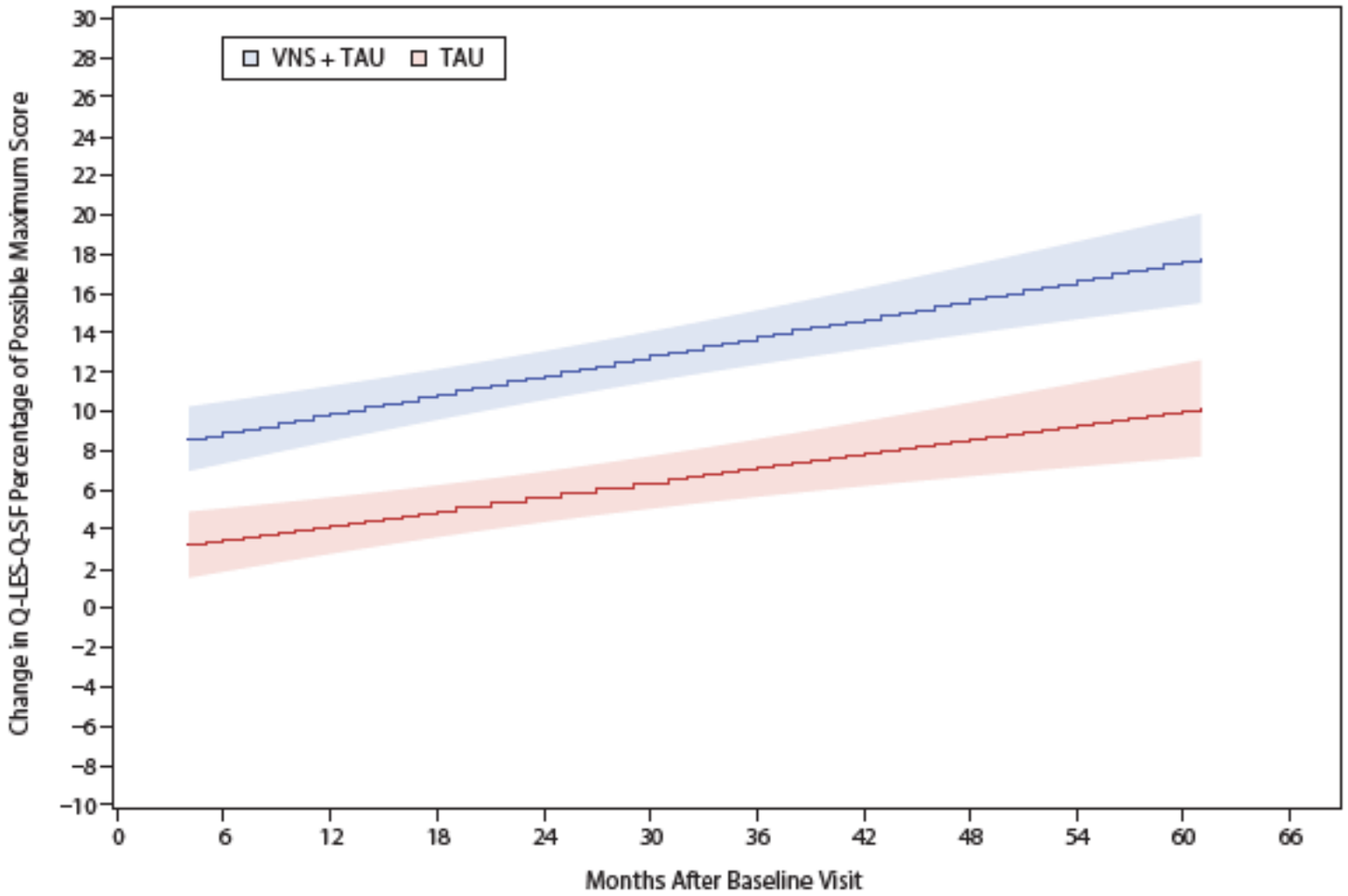
Data on File Livo Nova

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

Quality of Life

Months After Baseline Visit Plotted Against Estimated Change (With 95% Confidence Bands) in Q-LES-Q-SF Percentage Maximum Possible Score From Baseline.

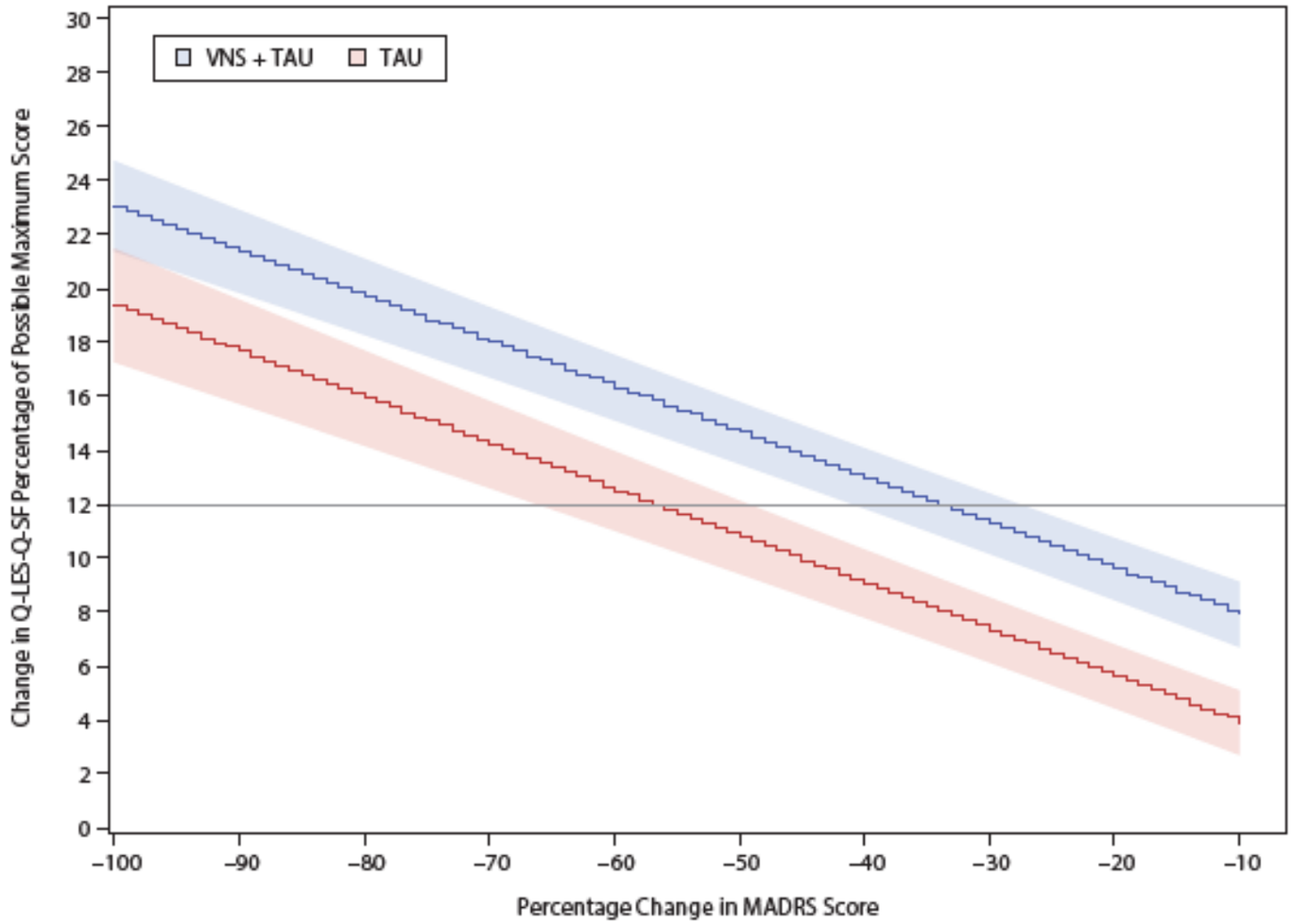


Abbreviations: Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire Short Form, TAU = treatment as usual (any antidepressant treatment[s]), VNS = vagus nerve stimulation, VNS + TAU = adjunctive VNS and any antidepressant treatments.

Conway CR, Kumar A, Xiong W, et al., 2018, *J Clinical Psychiatry*, August 2018.

Quality of Life Relationship with Depression Reduction

Percentage Change in MADRS Score From Baseline for VNS + TAU and TAU Plotted Against Estimated Change (With 95% Confidence Band) in Q-LES-Q-SF Percentage Maximum Possible Score From Baseline



The horizontal line = clinically significant change in Q-LES-Q-SF percentage of possible maximum score.

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire Short Form, TAU = treatment as usual (any antidepressant treatment[s]), VNS = vagus nerve stimulation, VNS + TAU = adjunctive VNS.

Conway CR, Kumar A, Xiong W, et al., 2018, *J Clinical Psychiatry*, August 2018.

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

Key Points About VNS

- **Large 800 patient, 5 year naturalistic study demonstrated significant efficacy of VNS over treatment as usual**
- **Quality of life improvements occurred sooner and at lower depression scale improvement for the VNS patients**
- **A non-coverage determination was made by the Centers for Medicare and Medicaid (CMS) in 2007 based on data available in 2005. The decision was adopted by commercial insurers.**
- **On the basis of the large naturalistic study, CMS agreed to fund a coverage with evidence development trial which will start enrollment in Fall 2019.**
- **VNS may provide unique chronic support for patients with severe treatment resistant depression.**
- **A key target may be patients requiring multiple courses of ECT or maintenance ECT**

Changing the Treatment Paradigm

While remission is the goal, how realistic is it?
What if response (50% drop in a depression rating scale score) is not achieved
Need to shift focus away from the quixotic search for a ”cure” to management of symptoms and optimizing the quality of life

Patient Selection Criteria: What makes a good VNS TRD patient?

View from 10,000 Feet

Looking for patients:

- With difficult to treat depression
- Who have clear biological targets
- Who are at low acute risk for self harm

May be unipolar or bipolar depressed

May be depressed in the current episode for months, years or decades

May have co-morbid anxiety

Must be Medicare eligible by age or disability

Difficult to Treat Depression

Have failed at least four treatments (at least 2 antidepressants of different classes)
Failures may include ECT (patients with a history of ECT exposure are of particular interest), phototherapy, TMS, psychotherapy or pharmacotherapy
Four failures must be in the current episode defined as the period since last in remission

Biological Targets

Bipolar disorder (more of a biological target than unipolar depression)
Neurovegetative symptoms (appetite changes, sleep changes, concentration difficulties, affective flattening)
Family history of mood disorder
Discreet episodes of depression (recurrent depression likely a better target than extended single episode)

Diagnostic Considerations

Depression can make a less overt personality disorder worse and can confound the current presentation

Lack of ability to engage in the evaluation in a thoughtful way suggests a poor prognosis as does secondary gain from being depressed

Evaluate the patient's ability to consider the risks and benefits of study participation and have realistic expectations

Acute Risk of Self Harm

VNS is a long term therapy for a chronic illness and takes months for an effect.
It cannot address immediate risks (not to mention that there is a 50% chance of not being randomized to active treatment)

Consider the course of illness. Suicide attempts, self injurious behavior, poor frustration tolerance.

Experiences from Practice

A history of temporary response to medications or neurostimulation is positively predictive of response to VNS

Realistic perspective by the subject is helpful

When dosing, titrate up to best tolerated parameters, there is a positive correlation between total delivered stimulation and outcome

Questions?

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