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The University of Alabama at Birmingham

Vagus Nerve Stimultion for Treatment Resistant Major Depression: An Overview and Update

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Disclosure Statement

Matthew Macaluso, D.O. discloses the following over the last 24 months:

1) Received grant support from the following entities:

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PCORI, NIH/NIMH

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2) Served as a paid advisor with UAB's permission: CME Institute, NuSachi Labs, PharmaTher, Residents Medical, Tactical Mind Solutions, and the University of Missouri.

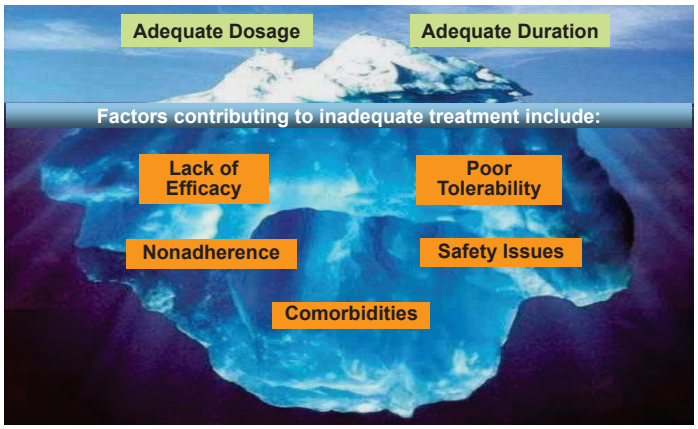
3) From April 2019 to June of 2020, Dr Macaluso was a member of the speaker bureau for Janssen pharmaceuticals (Spravato/esketamine).

4) Dr Macaluso has also received royalties from Springer Nature for textbooks published.

Objectives

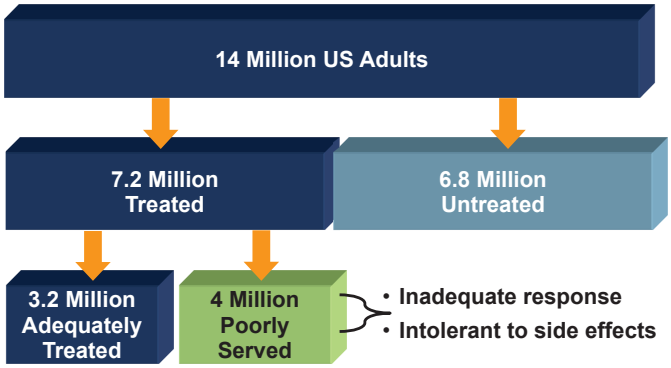
- 1) Review the problem and challenges associated with treatment resistant major depression.
- 2) Understand the history and use of VNS to date in the clinical treatment of depression.
- 3) Discuss the ongoing Medicare sponsored study of implantable VNS in depression and the investigator-initiated trial of non-invasive VNS conducted at UAB.

In MDD, "Adequate" Treatment Is Difficult to Achieve[1-3]



1. Nemeroff CB. *Depress Anxiety*. 1996/1997;4(4):169-181; 2. Oquendo MA et al. *J Clin Psychiatry*. 2003;64(7):825-833; 3. Oquendo MA et al. *Am J Psychiatry*. 1999;156(2):190-194.

A Significant Percentage of Patients With MDD Remain Poorly Served



Kessler RC et al. *JAMA*. 2003;289(23):3095-3105.

Remission Rates (RR)* in STAR*D by Treatment Level

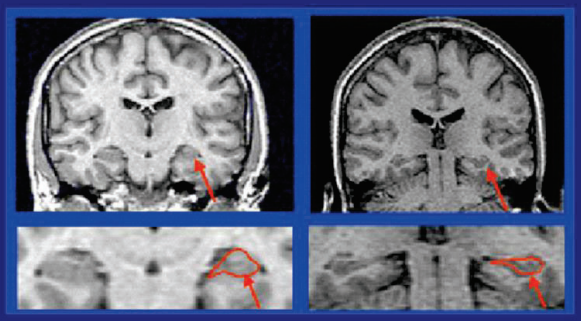
Level	RR Range	% Average RR	% Original Population Still Symptomatic**
1	28	28	72
2	18-30	25	54
3	12-25	18	44
4	7-14	11	39

* Remission = a score of ≤7 on a 17-item Hamilton Depression Rating Scale.

** Assumes every nonremitter went through the next treatment level rather than dropping out.

Brain atrophy in depression?

Atrophy of the Hippocampus in Depression



Normal Depression

Bremner JD, et al. *Am J Psychiatry*. 2000;157(1):115-118.

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Review Article

Vagus Nerve and Vagus Nerve Stimulation, a Comprehensive Review: Part II

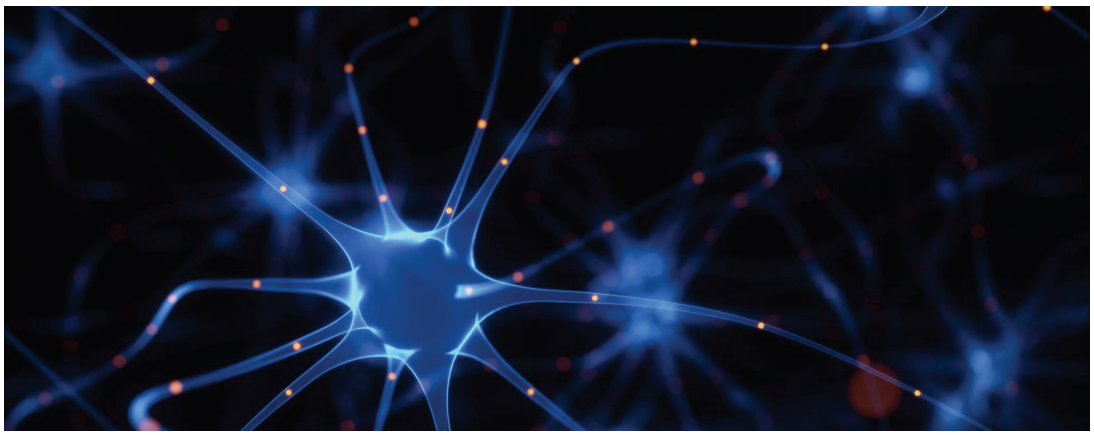
Hsiangkuo Yuan, MD, PhD; Stephen D. Silberstein, MD

The development of vagus nerve stimulation (VNS) began in the 19th century. Although it did not work well initially, it introduced the idea that led to many VNS-related animal studies for seizure control. In the 1990s, with the success of several early clinical trials, VNS was approved for the treatment of refractory epilepsy, and later for the refractory depression. To date, several novel electrical stimulating devices are being developed. New invasive devices are designed to automate the seizure control and for use in heart failure. Non-invasive transcutaneous devices, which stimulate auricular VN or carotid VN, are also undergoing clinical trials for treatment of epilepsy, pain, headache, and others. Noninvasive VNS (nVNS) exhibits greater safety profiles and seems similarly effective to their invasive counterpart. In this review, we discuss the history and development of VNS, as well as recent progress in invasive and nVNS.

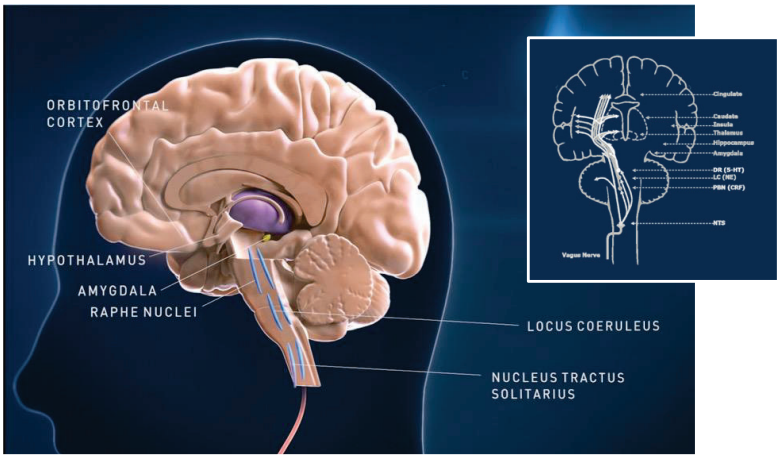
Key words: vagus nerve, vagus nerve stimulation

(*Headache* 2015;00:00-00)

Mechanism of Action of VNS Therapy®



Anatomical Connections of the Vagus Nerve



Pardo JV, et al. *Neuroimage* 2008;42(2):879-889.

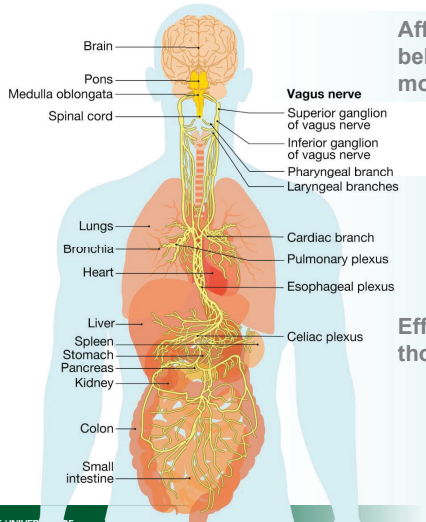
Rationale for VNS Treatment

- **Neuroanatomic connections** of afferent and efferent vagus nerves[1]
- **VNS Therapy effects on neural networks** based on imaging studies[1] and ΔFɔsB in animals[2]
- **Mood improvements** in epilepsy patients[3]
- **Anti-inflammatory** cholinergic network effects[4,5]
- **Effects of VNS Therapy** on neurotransmitters/neuroreceptors, including NE, 5-HT, GABA, glutamate, and BDNF/TrkB, implicated in depression[6-10]
- **Preclinical evidence** of antidepressant activity (forced swim test)[11]
- **Anticonvulsants** in mood disorders[12]

*See full indication on cover slide.

1. George MS, et al. *Biol Psychiatry*. 2000;47(4):287-295. 2. Naritoku DK, et al. *Epilepsy Res*. 1995;22(1):53-62. 3. Harden CL, et al. *Epilepsy Behav*. 2000;1(2):93-99.
4. Tracy KJ. *Nature*. 2002;420(6917):853-859. 5. Tracy KJ. *J Clin Invest*. 2007;117(2):289-296. 6. Ben-Menachem E, et al. *Epilepsy Res*. 1995;20(3):221-227.
7. Krahl SE, et al. *Epilepsia*. 1998;39(7):709-714. 8. Walker BR, et al. *Epilepsia*. 1999;40(8):1051-1057. 9. Furmaga H, et al. *PLoS One*. 2012;7(5):e34844.
10. Follesa P, et al. *Brain Res*. 2007;1179:28-34. 11. Krahl SE, et al. *J Psychiatr Res*. 2004;38(3):237-240. 12. Meador KJ. *J Clin Psychiatry* 2003;64 Suppl 8:30-34.

Gross Anatomical Distribution of the Vagus Nerve

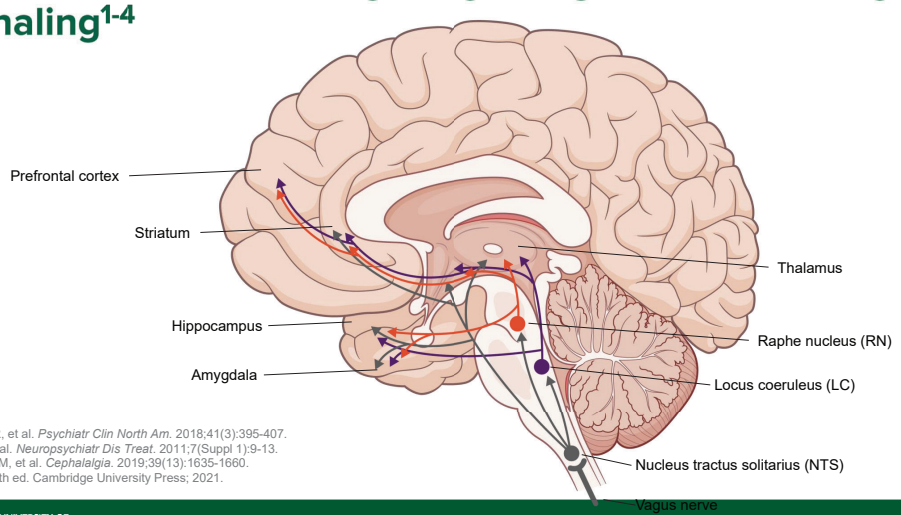


Afferent pathway to the brain to areas believed to be responsible for seizures, mood, appetite, memory, and anxiety.

Efferent pathways to the viscera of the thorax and abdomen.

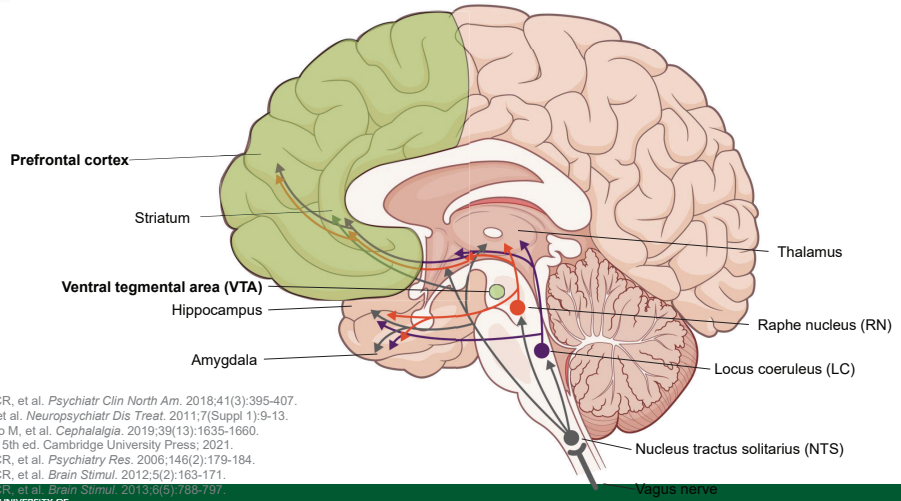
Henry TR. *Neurology*. 2002;58(suppl 4):S3-S14.

VNS Stimulates the Vagus Afferent Network, Which Includes Regions Associated With Abnormal Activity in Depression, Noradrenergic Signaling, and Serotonergic Signaling[1-4]



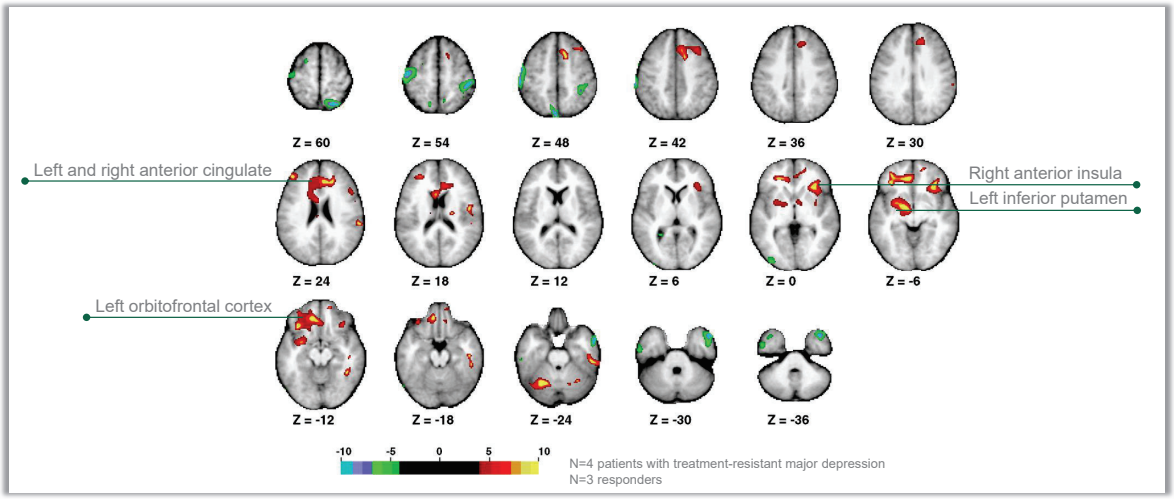
1. Conway CR, et al. *Psychiatr Clin North Am*. 2018;41(3):395-407.
2. Moret C, et al. *Neuropsychiatr Dis Treat*. 2011;7(Suppl 1):9-13.
3. Vila-Pueyo M, et al. *Cephalalgia*. 2019;39(13):1635-1660.
4. Stahl SM. 5th ed. Cambridge University Press; 2021.

Changes in Brain Activity in Regions Associated With Mood Regulation Were Observed After Acute and Chronic VNS[1-7]



1. Conway CR, et al. *Psychiatr Clin North Am*. 2018;41(3):395-407.
2. Moret C, et al. *Neuropsychiatr Dis Treat*. 2011;7(Suppl 1):9-13.
3. Vila-Pueyo M, et al. *Cephalalgia*. 2019;39(13):1635-1660.
4. Stahl SM. 5th ed. Cambridge University Press; 2021.
5. Conway CR, et al. *Psychiatry Res*. 2006;146(2):179-184.
6. Conway CR, et al. *Brain Stimul*. 2012;5(2):163-171.
7. Conway CR, et al. *Brain Stimul*. 2013;6(5):788-797.

PET Images Following Acute VNS (Pilot Data)



Conway CR, et al. *Psychiatry Res*. 2006;146(2):179-184.

VNS Is FDA Approved

VNS Therapy has been FDA approved 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

It has been prescribed for over 4,000 TRD patients in the United States and studied in several clinical trials

History

July 2005
- VNS approved to treat subjects with treatment-resistant depression by FDA
- Coverage determined by local Medicare Administrative Contractors

2006
- Formal request for non-coverage decision (NCD) to include coverage of VNS Therapy for TRD

May 4, 2007
- CMS determined VNS for TRD non-covered: sufficient evidence to conclude that VNS Therapy was not reasonable and necessary for TRD

May 30, 2018
- Formal request to reconsider NCD to remove non-coverage of VNS for TRD

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Evidence Base for VNS Therapy

Established Evidence for VNS in TRD

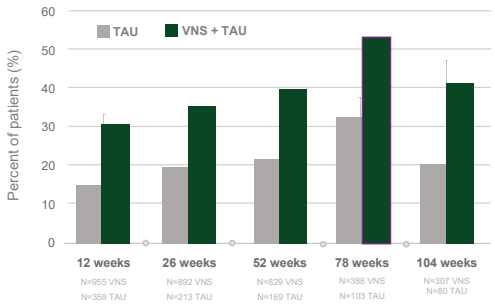
Study[1]	VNS + TAU - N	TAU - N	Study Duration	Study Design
D-01	60	-	2-year	Single-arm, open-label
D-02	235	110	2-year	RCT, sham-controlled for 12 weeks, then single-arm, open-label
D-03	74	-	2-year	European, single-arm, open-label
D-04	-	124	2-year	Single-arm, open-label
D-21	331	-	1-year	RCT of VNS Therapy dosing for 22 weeks, then single-arm open-label
D-23	335	301	5-year	Two-arm, open-label, registry
Total 2013 Meta-Analysis	1035	425	Various	
Final D-21 and D-23[2]				
D-21	159	-	5-year	
D-23	335	301	5-year	
Total 2017 Long-Term Study	494	301	5-Year	

Characteristics of a VNS Patient

Characteristic	VNS + TAU (n=1035)	TAU (n=425)
Female (%)	66.2	69.7
Age (years)	47.8	48.7
Bipolar Depression (%)	22.3	20.2
Duration of illness (years)	**25.9**	**27.7**
Length of Current Episode (years)	6.9	7.6
Baseline MADRS score (>30 = Severe)	**33.0**	**29.4**
Baseline CGI Severity	**5.2**	**4.7**
# Prior Failed Medication Classes	**6.9**	**5.9**
% ECT (lifetime)	**56.1**	**39.5**
Mean # Hospitalizations (lifetime)	**3.4**	**1.9**
Mean # Suicide attempts (lifetime)	1.3	1.2

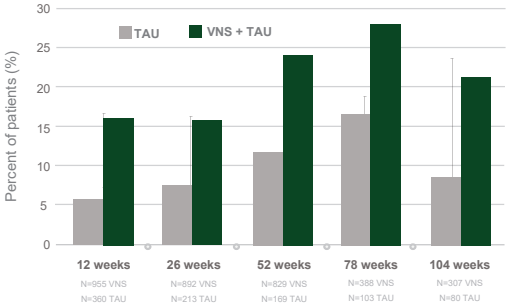
VNS Response and Remission Rates Increase Over Time

Percent of Patients Achieving Response
(MADRS): Observed Cases



Odds ratio (OR) of response with VNS + TAU over TAU = 3.2
(CI_{95} 2.1, 4.7) (repeated measures model)

Percent of Patients Achieving Remission
(MADRS): Observed Cases

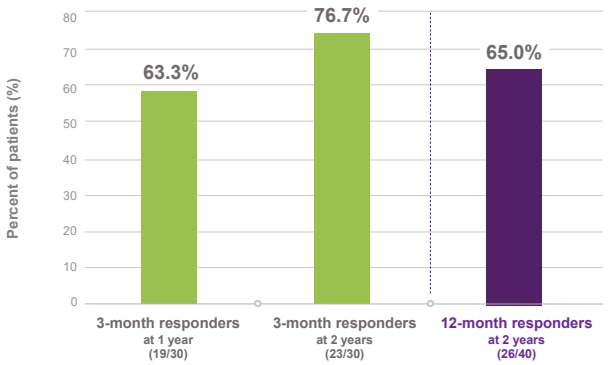


Odds ratio (OR) of remission with VNS + TAU over TAU = 5.0
(CI_{95} 2.9, 7.8) (repeated measures model)

MADRS, Montgomery-Åsberg Depression Rating Scale.
Data on File. LivaNova USA, Inc.

Of the Patients Who Responded to Therapy, a Majority Had Sustained Response Over 1 Year With VNS

Percent of Patients Who Maintained Response* (Observed Data)



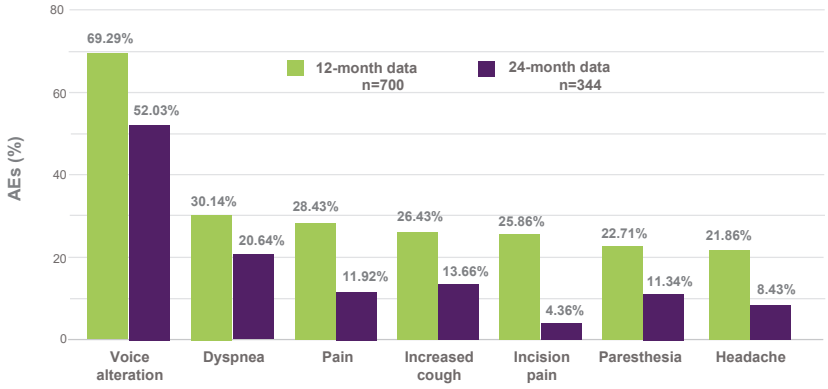
***Response:**
≥50% improvement from BL $HAMD_{24}$

Maintained response:
≥40% reduction from BL

Sackeim HA, et al. *Int J Neuropsychopharmacol.* 2007;10(6):817-826.

Meta-Analysis With Long-Term Adverse Event (AE) Profile of Patients on VNS

Side Effects (>20%) of VNS Therapy

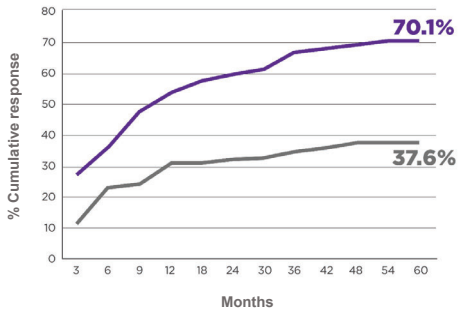


Additional AEs (>10%): neck pain, pharyngitis, depression, dysphagia, incision-site reaction, nausea, device-site pain, hypertonia, device-site reaction, insomnia

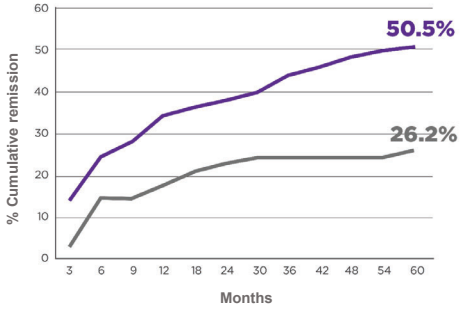
Berry SM, et al. *Med Devices (Auckl).* 2013;6:17-35.

Sustained Antidepressant Efficacy That Increases Over Time With Therapeutic Benefit to 5 Years Following Implantation

5-Year Cumulative First-Time Response Rate (*P*<0.0001)



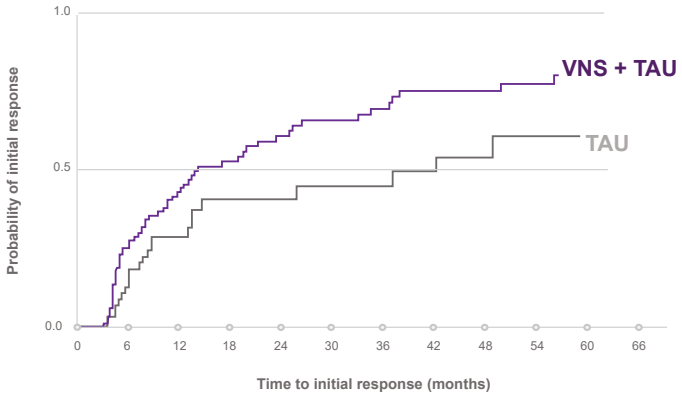
5-Year Cumulative First-time Remission Rate (*P*<0.0001)



VNS + TAU TAU

TAU, treatment as usual.
McAllister-Williams RH, et al. *Int J Bipolar Disorder.* 2020;8(1):13.

Effect of VNS + TAU in Bipolar Depression: Time to Response

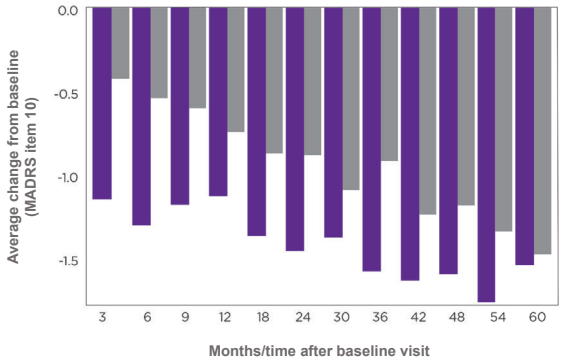


TAU, treatment as usual.

McAllister-Williams RH, et al. *Int J Bipolar Disorder.* 2020;8(1):13.

Effect of VNS + TAU on Suicidality in Bipolar Depression

VNS + TAU demonstrated significantly greater reduction in suicidality across the study visits vs TAU alone based on MADRS item 10 (*P*<0.001)



Patients with available suicidality data on MADRS item 10 by visit

treatment	3m	6m	9m	12m	18m	24m	30m	36m	42m	48m	54m	60m
VNS + TAU	89	77	66	67	61	62	52	53	48	44	32	40
TAU	52	46	36	34	25	21	16	18	19	20	13	16

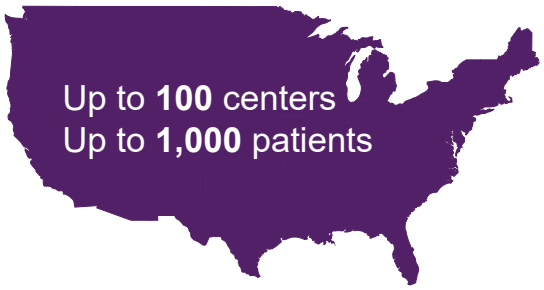
Mean change in suicidality score from baseline based on MADRS item 10

MADRS, Montgomery-Åsberg Depression Rating Scale; TAU, treatment as usual.

McAllister-Williams RH, et al. *Int J Bipolar Disorder.* 2020;8(1):13.

RECOVER
A VNS Therapy® Clinical Trial

The RECOVER Study

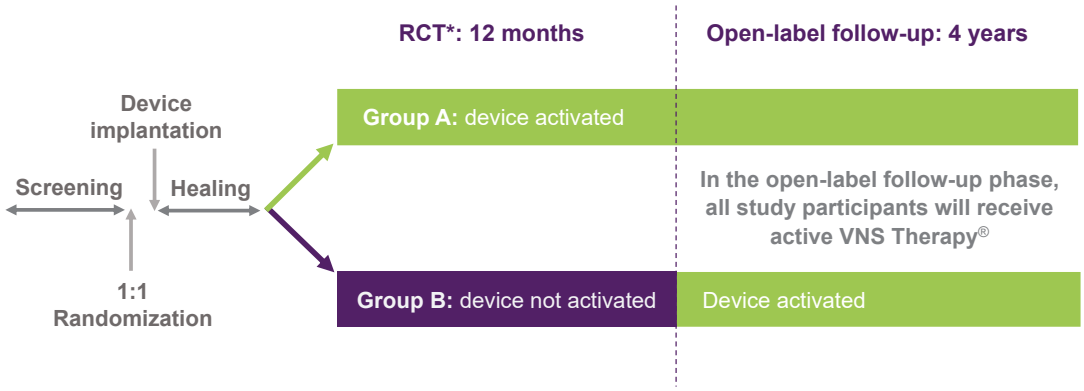


- **Prospective multicenter RCT:** up to 1,000 TRD patients (unipolar or bipolar) will take part at up to 100 medical centers across the United States
- All participants will continue to take their usual treatment(s) for depression

All study-related costs specific to the device and the implant procedure are provided at no expense to the patient

Programming sessions and office visits are covered during the first 12 months of the study

The RECOVER Study: Design



*RCT period will be double-blind (only device programmers will be unblinded). Blinding must be continued at each site until the last patient at that site reaches the end of the RCT.

The RECOVER Study: Overview

Clinical Study Objective

Compare VNS Therapy® vs No Stimulation control in subjects with treatment-resistant depression (TRD)

Rate of MADRS Response

1) Defined as total # of months in response divided by total months of expected study participation
2) 50% reduction in baseline MADRS total score at 12 months

Prospective | Multicenter | Blinded | RCT

Primary Endpoint

50% improvement on MADRS over 12 months

Study Size and Analysis Plan

1) RCT Phase up to 1,000 patients
2) Longitudinal Registry Phase up to 5,800 patients
3) Medicare participants reimbursed by CMS
4) Incorporate adaptive design
5) First interim analysis 250 evaluable unipolar subjects

The RECOVER Study: Key Inclusion Criteria

- 18 years or older
- Documented diagnosis of **MDD or bipolar depression**: either chronic (≥2 years) or recurrent (≥4 prior episodes, at least 2 months apart) according to *DSM-5*
- Insufficient response to ≥4 adequate trials of antidepressant treatment **in the current episode** (including antidepressant medication, augmenting agents, psychotherapy, rTMS, ECT, and esketamine)
- Continued use of mood stabilizer if bipolar

Description	ICD-9 Code	ICD-10 Code
MDD, Single Episode, Moderate	296.22	F32.1
MDD, Single Episode, Severe	296.23	F32.2
MDD, Recurrent Episode, Moderate	296.32	F33.1
MDD, Recurrent Episode, Severe	296.33	F33.2
Bipolar I, Current or Most Recent Episode Depressed, Moderate	296.52	F31.32
Bipolar I, Current or Most Recent Episode Depressed, Severe	296.53	F31.4
Bipolar II	296.89	F31.81

The RECOVER Study: Key Exclusion Criteria

- Acute suicidality or recent suicide attempt
- History of substance abuse (past 12 months)
- History of psychosis
- Severe personality disorder
- Deep brain stimulation implant
- Dementia

The RECOVER Study: Endpoints and Protocol Requirements

Main endpoint:

50%
improvement on MADRS
over 12 months

- **Participants may continue to see their current psychiatrist** and regular physician for routine care outside of the study
- **All current therapies can—and should—be continued**, meaning even those in the control arm will still receive standard of care
  - Changes to these treatments should be avoided as much as possible during the randomized clinical trial portion of the study (first year)

Investigator Initiated Trial

- electroCore provided 5 devices for a pilot study in depression.
- Device is approved in migraine and cluster headache.
- Open label study in TRD. One or more treatment failures.

The electroCore Device

https://www.electrocore.com/nVNS/

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Safety and tolerability of Transcutaneous Vagus Nerve stimulation in humans; a systematic review

J. Redgrave [a,*], D. Day [a], H. Leung [a], P.J. Laud [a], A. Ali [b], R. Lindert [a], A. Majid [a]

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[b] Department of Geriatrics and Stroke, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

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Safety
Adverse events

ABSTRACT

Background: Transcutaneous Vagus Nerve stimulation (tVNS) may be an alternative to surgically implanted VNS for epilepsy and other diseases. However, its safety and tolerability profile is unclear.
Objective: We performed a systematic review of treatment harms from tVNS in humans.
Methods: A systematic published and grey literature search was carried out to identify studies which deployed tVNS in human subjects. Study authors were contacted for safety/tolerability data if these were not available in the publication. Databases were searched from 1966 to May 2017. We noted study type, population, stimulation parameters, type and prevalence of side effects and/or serious adverse events (SAE). We also noted whether side effects/SAE were considered to be related to the tVNS and the proportion of participants dropping out of studies due to side effects.
Results: 51 studies were included comprising a total of 1322 human subjects receiving tVNS. The most common side effects were: local skin irritation from electrode placement (240 participants, 18.2%), headache (47, 3.6%) and nasopharyngitis (23, 1.7%). Whilst heterogeneity in overall side effect event rates between studies was not accounted for by the frequency (Hz) or pulse width (ms) of stimulation, a minority (35 participants (2.6%)) dropped out of studies due to side effects. Overall, 30 SAE occurred but only 3 were assessed by the relevant researchers to be possibly caused by tVNS.
Conclusion: tVNS is safe and well tolerated at the doses tested in research studies to date.

An Open Label Pilot Study of Non-Invasive Vagal Nerve Stimulation for Treatment Resistant Major Depressive Disorder

Matthew Macaluso, D.O., Michael Falola, M.D., Samantha White, B.A., Cassie Wicken, M.D., M.H.S.*
*presenter

Introduction

Major Depressive Disorder (MDD) is the leading cause of disability worldwide and one of the most economically burdensome conditions in the United States.

In the STAR^D Trial, thirty nine percent of patients continued to demonstrate clinically significant symptoms of MDD even after receiving up to four sequential antidepressant trials. New and effective alternatives to the currently available pharmacotherapies are needed for MDD.

Surgically implanted vagal nerve stimulation is FDA approved for the treatment of MDD due to its efficacy. Non-invasive vagal nerve stimulation (nVNS) devices are available for the treatment of migraines, but have not yet been studied for MDD.

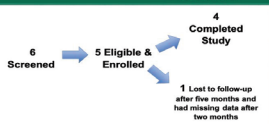
Objective

To assess the safety profile and preliminary efficacy of nVNS on MDD symptoms in adults who have failed at least one antidepressant trial.

Methods

This was an investigator initiated open-label trial of nVNS. Adults ages 18 to 75, in a current major depressive episode associated with MDD, who failed to respond to one or more adequate trials of antidepressant drugs, and did not meet exclusion criteria on screening assessment were enrolled.

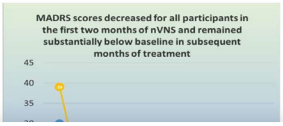
Results



Demographics	
Female: Male: Other	2: 3: 0
Mean Age	53 years
White Race	100%
Mean Education	16 years
Married or Life Partner	100%
Non-smoker	100%
Mean BMI	36.4

MDD Characteristics	Range	Mean	Median
Age of onset	7 – 42 years	20 years	16 years
Number of episodes	2 – 18	6.4	4
Duration of current MDD episode		23.8 months	13 months
History of suicidal thoughts with plan: 20%			
History of suicide attempt(s): 20%			

MDD Treatment History	Past (%)	Current (%)
SSRI	100	60
SNRI	100	0
TCA	20	40
Bupropion	80	20
Nefazodone	20	0
Benzodiazepine	20	80
MAOI or Esketamine	0	0
ECT	20	0
TMS	20	0



Compared to baseline, MADRS scores decreased by 15 to 36 points at last visit.

Results

Each of the five participants had previously failed at least two antidepressant trials and, at baseline visit they reported symptoms on MADRS consistent with moderate or severe depression.

At their last completed study visit, four subjects reported no depression and one reported mild depression. One hundred percent of participants reported a substantial decrease in MDD symptoms in the first two months of nVNS which was relatively sustained during the subsequent months of treatment.

Participants' MADRS scores at last study visit decreased by 15 to 36 points compared to baseline. These findings were not statistically significant given the small sample size.

Adverse Events

There were no serious adverse events related to nVNS. The only adverse event reported was one instance of mild neck soreness which resolved after changing the side to which stimulation was administered. One participant had a planned surgery that was unrelated to nVNS.

Conclusions

Each participant in this pilot study tolerated nVNS well and reported a substantial decrease in symptoms of MDD. Given these promising preliminary findings of a non-invasive, alternative to pharmacotherapy for MDD, future studies with larger cohorts and randomized and controlled designs are warranted.