Interventional Psychiatry

Southern Psychiatric Association

ECT, Ketamine/Esketamine, VNS, TMS for Major Depressive Disorder

Wagner | Farooqui | Cochran

Disclosures

Eveleigh Wagner MD

- NeuroScience & TMS Treatment Center, Staff Psychiatrist
- NSTMS Center Clinic receives Research funding from LivaNova as part of a clinical trial
- Clinical TMS Society member
  - PULSES committee

Outline & Objectives

- Prevalence, Statistics, Course of MDD
- Treatment As Usual review
  - Outcomes
- Interventional Neuromodulation Treatment Options for MDD
  ECT, Ketamine/Esketamine, VNS, TMS
  - FDA Clearances/Approvals
  - Mechanisms of Action

What we won't talk about

- Non-FDA cleared Neuromodulation for other disorders; other FDA cleared indications for TMS (OCD, or Smoking cessation); ECT for Catatonia nor Psychosis; Trigeminal Nerve Stimulation for ADHD; Neuromodulation being researched (tDCS & tACS), nor DBS

Prevalence & Impact of Depression

- Major Depressive Disorder is Common
- Globally, more than 280 million people of all ages suffer from depression.[1]
- Depression is a leading cause of disability worldwide and is a major contributor to the overall global burden of disease.

[1] Institute of Health Metrics and Evaluation. Global Health Data Exchange (GHDx). https://vizhub.healthdata.org/gbd-results/ (Accessed 4 March 2023); Image modified Sasha Freemind Unsplash.com

Depression: Incidence & Risk Factors

- Incidence of Depression is high
- Risk Factors
  - Female > males
  - Race: highest among Mixed or Biracial, Native American Indian/Alaskan Native, Caucasian
  - 18-25 year olds
  - Poverty and Low Education
  - Southern states have high rates & also higher rates of obesity, heart disease, stroke, sleep disorders, as well as Lower access to care which may be related.

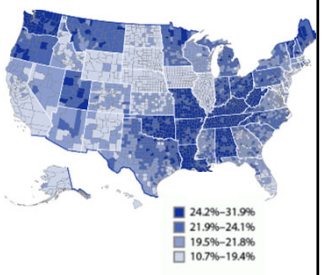
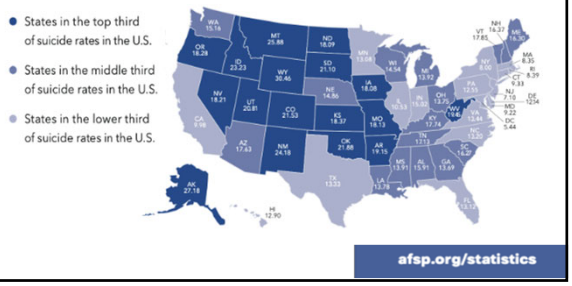


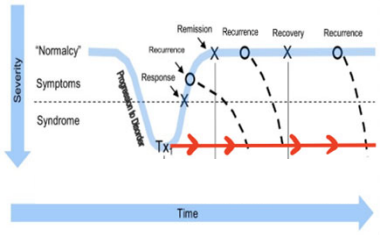
Image from June 2023 MMWR from CDC

Depression, like cancer, can kill you. Suicide is a public health problem in US



Depression is Recurrent
Like cancer, our goal should be to get and keep remission.

- Many fail to get remission first trial (up to 60%).
- After 1 episode, Recurrence is common >60%, after 2 episodes = 70%, 3+ = 90%
- If patient only responds, higher likelihood to have recurrence
- Patients can suffer for long periods of time.



Nierenberg 2015; Judd et al 2000; Thase 2009; Papakostas 2009; Monroe et al 2011; modified from Kupfer 1991

Results from Treatment as Usual (TAU) for MDD

<u>The Good</u> (STAR*D data)

With first treatment standard medication, just above **30% remit** with medication alone.
Additional **30% respond**, but don't remit….

Fava, 2003

Results from Treatment as Usual (TAU) for MDD

<u>The BAD</u>

With first treatment standard medication, *30% FAIL to show clinical response to treatment.*[1]

With additional treatment trials, remission potential continues to fall & side effects increase.[1]

Rates of discontinuation are high; *>40% patients discontinue treatment in 3 months*

Fava, 2003

Results from Treatment as Usual (TAU) for MDD

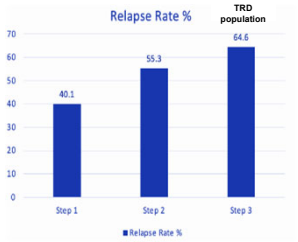
The Ugly

'Under-treatment' is very common *(underdosed and inadequate)* throughout US & World

- In US, some studies show 20-30% of patients received inadequate treatment
- Often non-psychiatrist underdosage
- collaborative relationships may be best solution
- Rural and undeveloped areas = patients receive minimally adequate treatment or no treatment.

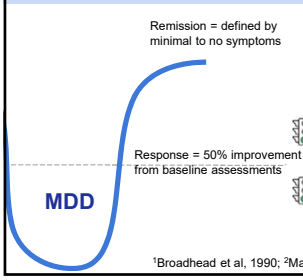
JB Weilburg et al. 2003

Results from STAR*D with TAU



Rush AJ et al.2006

Where do Interventional Neuromodulation Treatments Fit within the algorithm for MDD?



1 = Best Evidence = Combo of Evidence Based Psychotherapy & Medication[1,2,3,4]

2 = If no remission, augment or switch medication

3 = If no remission, after 2 trials; best option is to augment, OR start an Interventional Treatment

4 = Interventional Treatments

[1]Broadhead et al, 1990; [2]March et al, 2009; [3]Thase et al, 1997; [4]Pampallona, et al 2004

- Despite the predominance of pharmaceutical agents for the treatment of depression, the monoamine transmitters are only part of the picture of dysfunction when there is Depression.
- Sophisticated forms of brain imaging like positron emission tomography (PET), single-photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), and Human Connectome Project are permitting scientists to understand the working brain
- This technology is leading towards understanding which brain regions regulate mood. Areas such as the prefrontal cortex, cingulate cortex, amygdala, the thalamus, and the hippocampus are important in the brain illness that is depression.

The Brain is an Electrochemical organ

We can therapeutically alter brain activity through targeted delivery of an electrical stimulus or a chemical stimulus

- Central, peripheral or Autonomic Nervous System can be modulated
- Direct Electrical or Indirect Electrical effects
- Pharmacological Neuromodulation (pumps)
- Implanted devices vs external devices
- We have Neuromodulation options for Pain, movement disorders, spasticity, epilepsy, sensory deprivation, urinary incontinence, gastric dysfunction, pancreatitis/visceral disorders, MDD, Bipolar Disorder, OCD, Smoking Cessation

ECT = Electroconvulsive Therapy

Electroconvulsive Therapy

A brief electrically induced generalized seizure

Oldest neuromodulation,
- first use of electricity for ECT occurred in Italy on April 11, 1938
- December 2018, FDA regulated ECT devices

The FDA regulation limited ECT to:
- treatment of catatonia
- a severe major depressive episode associated with major depressive disorder or bipolar disorder
- patients age 13 yrs+, who are treatment-resistant or those who require a rapid response treatment due to the severity of their psychiatric or medical condition.

Unique considerations of ECT

- Quickest way to treat severe recurrent depression with:
  - MDD or Bipolar Disorder
  - Psychotic depression in pregnancy
  - Catatonia
- Covered by most Insurance including Medicare, Medicaid
- Frequently started inpatient; may be outpatient procedure with maintenance phase
- Requires Anesthesia & Monitored setting
- Rare risk of long term memory problems

Modernization & Effectiveness of ECT

- Anesthesia (vital sign monitoring, pre-operative evaluation, respiratory support, recovery, medications)
- Improved ECT technology (EEG monitoring, delivery of electrical stimulus, reliability of machines)
- Effective for depression with psychotic or catatonic features, catatonia, and psychotic depression in pregnancy (MDD or Bipolar depression).
- Safe and effective for geriatric patients (especially those with Parkinson's)
- Remission rates have been reported as high as 80-90%.
  - In severely treatment resistant depression, rates reported to be 50-60%

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Slide 17

1 removed comments about ultrabrief pulse as it is on another slide
Michelle Cochran, 10/8/2023

ECT DEVICES

Thymatron

MECTA 5000q

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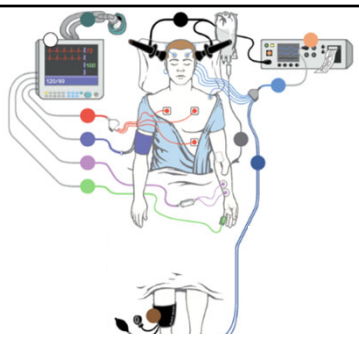

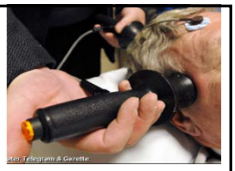

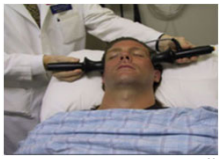

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Adapted from Gouvernement du Québec, Ministère de la Santé et des Services Sociaux

Theoretical Mechanism of Action

- Release of neurotransmitters; most receptor systems
  - Serotonin
  - Dopamine
  - Norepinephrine and epinephrine
  - GABA/glutamate/glutamine
  - Opioid
- Brain Metabolism affected
- Connectivity between different brain regions restored
- Increase BDNF

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No Contraindications, Considerations.

- No “Absolute” Contraindications
- Specific considerations should be made for:
  - Space-occupying cerebral lesion
  - Recent ACS
  - Recent intracranial bleed or current unstable aneurysm
  - Severe pulmonary conditions

Pre-procedural medical work-up

Basic:
- Labs: CBC, CMP
- EKG
- CXR

Additional:
- Specialty consults (pulmonary, cardiologist)
- Brain CT
- Spine X-Rays

Side Effects

Most common side effect: Headache & Muscle Soreness

Associated risk of general anesthesia

Other potential side effects
- Cardiac arrhythmia
- Prolonged seizure
- Postictal delirium
- Nausea
- Dental complications
- Memory issues

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Side Effects: Memory Issues

- Short term memory loss during the course of ECT
- Ultra-brief pulse gives limited short term memory problems that generally resolve in 6+ wks; rare risk of long term memory problems
- Long term memory or cognitive disturbance are not typical of ECT but more consistent with prolonged psychiatric illness.
- Patients can actually see improved long term cognition post- ECT due to treatment of underlying severe depression

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Treatment Overview

Team: Psychiatrist, Anesthesiologist/CNA, and ECT nurse

- Patient responsibilities: NPO overnight, transportation, arriving on time for pre-op (IV placement and monitoring set up)
- Administration
  - Anesthetic agents and muscle relaxants
  - Oxygenation + bag/mask
  - Placement of electrodes and delivery of stimulus
  - 1 - 2 min seizure
  - Recovery 30 - 40 minutes

Course of ECT

- Average # 6 - 15 Treatments in Acute Phase, rarely 20+
- Acute Phase: Tx scheduled two to three times per week
- Once clinical determination of remission or substantial improvement is reached; switch to Maintenance Phase
  - Maintenance Phase per clinical judgment

    Example Maintenance Schedule:

    Typically once per week for 1-2 months ->
    every other week for 1-2 months ->
    monthly for 2-3 months, ? indefinitely

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ECT Disadvantages

- Poor Durability long-term, patients are very likely to relapse w/in 6 months
- Access limitations→ hospital centers
- Patients need secure transport to and from treatment
- Stigma

Ketamine & Esketamine

Disclosures

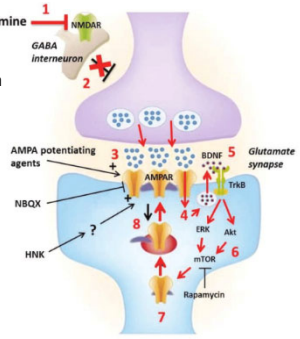
Ali A. Farooqui, MD

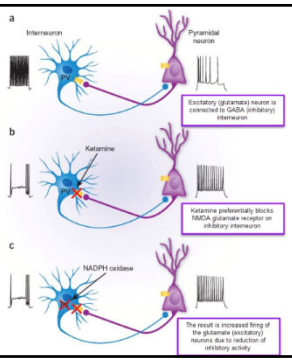
- Integrative Psychiatry, PLLC
- Clinical Faculty, University of Louisville Department of Psychiatry and Behavioral Sciences
- Psychiatric Director, Louisville Metro Department of Corrections
- Consultant, Jefferson, Oldham, Shelby County Courts (civil and criminal)
- Select Professional Memberships:
  - Kentucky Psychiatric Medical Association, Chairman of Scientific Committee
  - National Networks of Depression Centers (NNDC), Ketamine Taskforce, Psychedelics Taskforce
  - American Society of Ketamine Physicians, Psychotherapists & Practitioners, Member
  - Clinical Transcranial Magnetic Stimulation Society, Member
  - Greater Louisville Medical Society, Physician Wellness Committee
- Industry Consulting and Speaking Engagements:
  - Abbvie
  - Bioxcel
  - Magstim

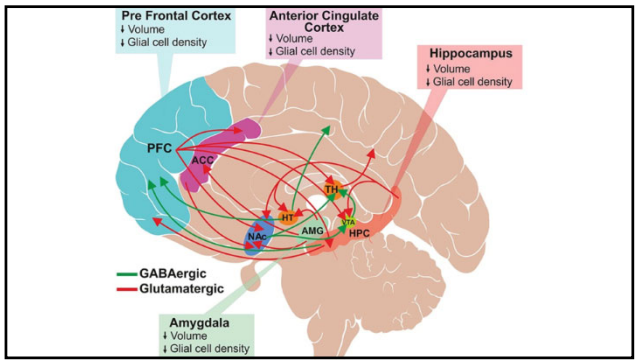
How ketamine/esketamine work

- Noncompetitive antagonist at the N-methyl-D-aspartate (NMDA) receptor – Blocks Glut
- Excites opioid receptors within the insular cortex, putamen, and thalamus.
- EEG activity in the hippocampus is dissociated from that in the thalamo-neocortical system

Proposed Mechanism of Action







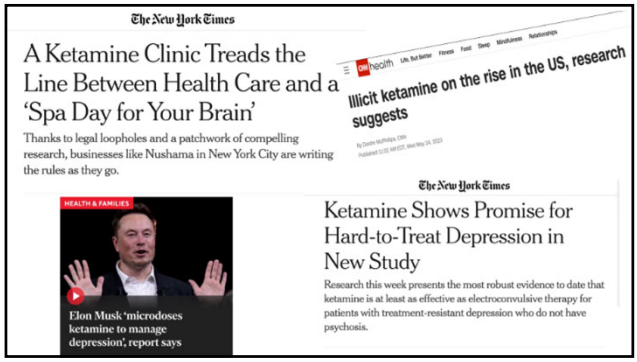
"Why is this important for my patients?"

Limited resources

Limited expertise

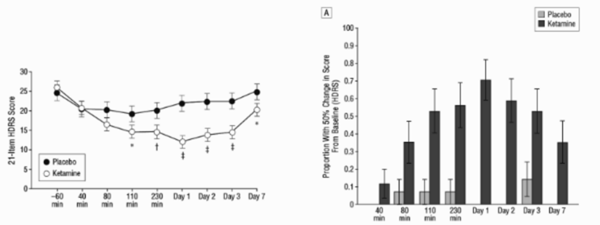
Patients will get the services– one way or another

Ketamine and Neuromodulation is a hot-topic



A Randomized Trial of an *N*-methyl-D-aspartate Antagonist in Treatment-Resistant Major Depression

Arch Gen Psychiatry. 2006;63:856-864



A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression

Jaskaran B. Singh, M.D., Maggie Fedgchin, Pharm.D., Ella J. Daly, M.D., Peter De Boer, Ph.D., Kimberly Cooper, M.S., Pilar Lim, Ph.D., Christine Pinter, M.S., James W. Murrough, M.D., Gerard Sanacora, M.D., Richard C. Shelton, M.D., Benji Kurian, M.D., Andrew Winokur, M.D., Maurizio Fava, M.D., Husseini Manji, M.D., Wayne C. Drevets, M.D., Luc Van Nueten, M.D.

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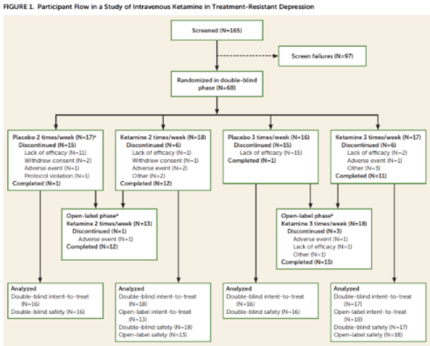
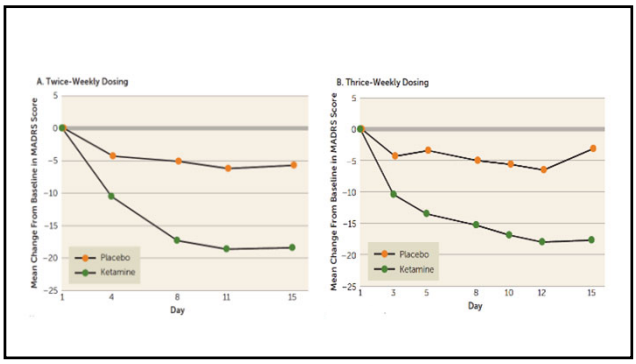
FIGURE 1. Participant Flow in a Study of Intravenous Ketamine in Treatment-Resistant Depression





Acute and longer-term outcomes using ketamine as a clinical treatment at the Yale Psychiatric Hospital

J Clin Psychiatry 2018;79(4):17m11731

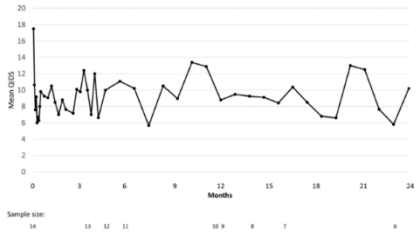
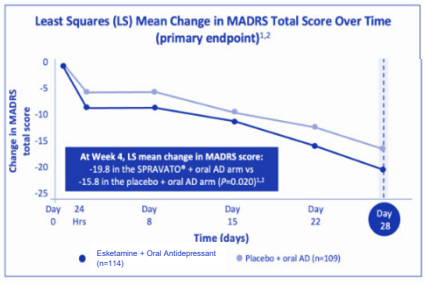


Figure 2.
Longer term outcomes of patients who have received continuation/maintenance ketamine treatment (n=14). The sample size decreases over time, reflecting where patients are in their current treatment and does not indicate that they have dropped out of treatment.

Esketamine + Oral Antidepressant (AD)



= First TX 56 mg + AD

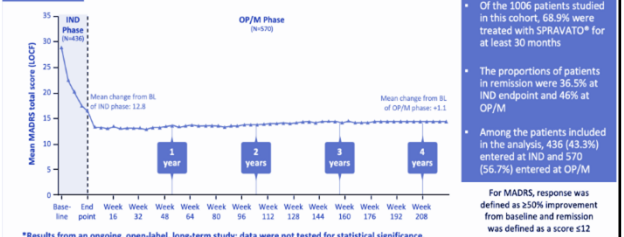
= Ongoing 84 mg + AD

Esketamine + oral AD studied >1700 pts

- 6 Short term 4 wk trials
  - 1 low dose 28mg study failed (geriatric)
  - Remainder showed superior benefit over placebo w 56 -> 84mg measured by MADRS change
- Most of benefit in 1st 24 hrs.
- Maintenance of effect data now out 4.5 years

1. Esketamine/SPRAVATO® [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; July 2020. 2. Popova V et al. *Am J Psychiatry*. 2019;176(6):428-438.doi:10.1176/appi.ajp.2019.19020172

MADRS Scores Were Consistent Through Interim Analysis at 4 Years*



- Of the 1006 patients studied in this cohort, 68.9% were treated with SPRAVATO® for at least 30 months
- The proportions of patients in remission were 36.5% at IND endpoint and 46% at OP/M
- Among the patients included in the analysis, 436 (43.3%) entered at IND and 570 (56.7%) entered at OP/M

For MADRS, response was defined as ≥50% improvement from baseline and remission was defined as a score ≤12

*Results from an ongoing, open-label, long-term study; data were not tested for statistical significance.

BL = baseline; IND = open-label induction phase; LOCF = last observation carried forward; OP/M = open-label optimization/maintenance phases.

Zaki N, Fu DJ, Daly E, et al. Long-term efficacy of esketamine nasal spray in adults with treatment-resistant depression: a subgroup analysis of the ongoing SUSTAIN-3 study. Presented at: Neuroscience Education Institute Congress; November 4-7, 2021; Colorado Springs, CO.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression

A. Anand, S.J. Mathew, G. Sanacora, J.W. Murrough, F.S. Goes, M. Altinay, A.S. Aloysi, A.A. Asghar-Ali, B.S. Barnett, L.C. Chang, K.A. Collins, S. Costi, S. Iqbal, M.K. Jha, K. Krishnan, D.A. Malone, S. Nikayin, S.E. Nissen, R.B. Ostroff, I.M. Reti, S.T. Wilkinson, K. Wolski, and B. Hu

Design

- 403 patients underwent randomization
- Five clinical sites
- 200 patients were assigned to the ketamine group
- 203 patients were assigned to the ECT group.
- 38 patients withdrew before initiation of the assigned treatment
- Ketamine was administered to 195 patients
- ECT was administered to 170 patients

Treatments

Three weeks
- Ketamine 2x per week
- ECT 3x per week

Total treatments
- Ketamine = 6
- ECT = 9 (supported by PRIDE Phase 1)

Treatments

1:1 randomization

Ketamine
- IV, 0.5mg/kg, 40 mins
- Dose modification allowed

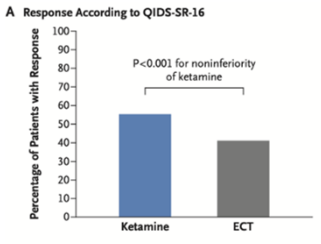
ECT
- R unilateral
- Ultra brief pulse
- 6x Sz threshold

Primary Outcome

Ketamine:
108 of 195 patients (55.4%)

ECT:
70 of 170 patients (41.2%)

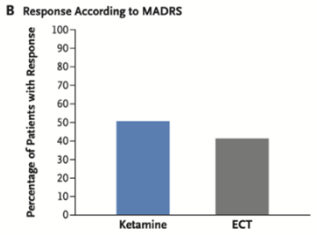
Intent to treat:
55.4% ketamine and 41.6% ECT

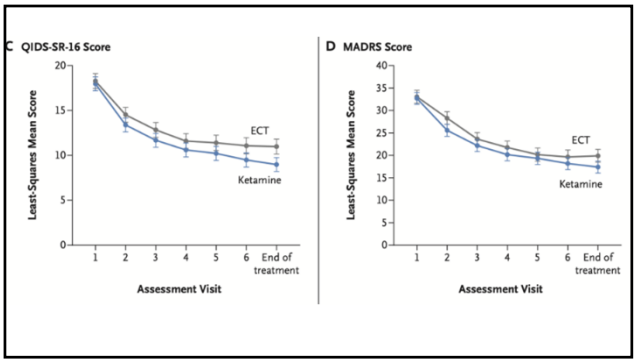


Secondary Outcome

Ketamine:
99 of 195 patients (50.8%)

ECT:
70 of 169 patients (41.1%)





6 Month Follow-Up

Relapse (QIDS-SR-16 score greater than 11)

Month 1: 19.0% ketamine, 35.4% ECT
Month 3: 25.0% ketamine, 50.9% ECT
Month 6: 34.5% ketamine, 56.3% ECT

Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta-analysis

Anees Bahji[a,b], Gustavo H. Vazquez[b], Carlos A. Zarate Jr[c,*]

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[b] Department of Public Health Sciences, Queen's University, Kingston, ON, Canada
[c] Section on Neurobiology and Treatment of Mood Disorders, Division of Intramural Research Program, National Institute of Mental Health, 10 Center Drive, MSC 1282 Building 10/3CRC, Room 7-5342, Bethesda, MD 20892, USA

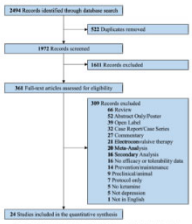


Fig. 1. PRISMA flow diagram outlining the systematic review process.

Journal of Affective Disorders 278 (2021) 542–555

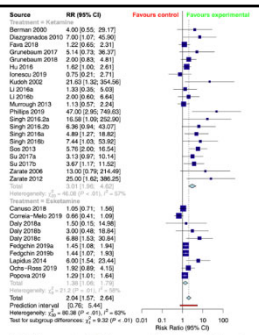


Fig. 2. Subgroup meta-analysis of response rates in the treatment of depression with racemic ketamine versus esketamine.

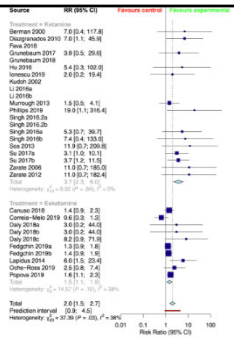
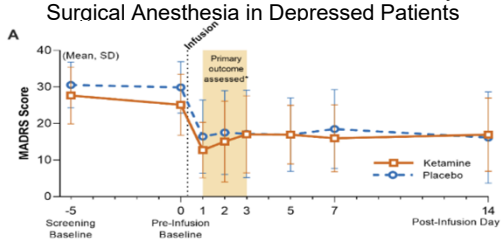


Fig. 3. Subgroup meta-analysis of remission rates in the treatment of depression with ketamine versus esketamine.

The Experience vs. The Medication

Randomized Trial of Ketamine Masked by Surgical Anesthesia in Depressed Patients



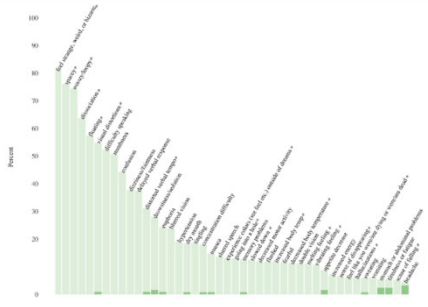
Comparison

Ketamine	Esketamine
Approved as: Anesthetic Agent	Approval as: TRD treatment, MDD with Suicidal ideation
IV, IM, and compounded to oral & intranasal versions; Schedule per prescriber	Intranasal, Specific schedule (2x/wk X 4 wks-> 1X/wk X4-8 wks, then taper to every 1-4.5 weeks ongoing)
Inexpensive, but not covered by insurance, so this treatment is Private Pay only; likely will never receive a new indication as it is generic only Often patients cannot afford maintenance and switch to Esketamine	Expensive, and covered by most insurance when 2 -3 + medications & augmenters don't give achieve remission Copay coupon reductions are available so patients pay very little for treatments and medication
No Current Federally mandated program; ASKP is producing guidelines for care	REMS program

Side effects

Esketamine
Dissociation (41%), Dizziness (29%), Vertigo (23%), Sedation (23%), Lethargy (11%), feeling drunk (55)
Nausea (28%), Vomiting (9%)
Hypoesthesia of nasal or pharyngeal areas (18%), Anxiety (13%)
Blood Pressure increases (10%), Headache (20%)
Dysgeusia (19%), nasal irritation (7%), throat irritation (7%)

Side effects - IV/IM Ketamine



VNS = Vagus Nerve Stimulation

Disclosures

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- NeuroScience & TMS Treatment Center, Chief Medical Officer
- Clinical Faculty, Dept of Psychiatry, Vanderbilt University Medical Center
- Owner & Operator: *Train Your Brain: Your record of Care with TMS,* www.TMSworkbook.com
- Research funding from LivaNova as part of a clinical trial
- Speaker, Janssen Pharmaceuticals: Spravato - 2023
- Past Paid consultant & speaker: Neuronetics/NeuroStar (2012-2013, 2019-2020)
- Clinical TMS Society (CTMSS), former Board Member and executive member
  - Inaugural Class of CTMSS Fellows (FCTMSS)
  - Education Committee co-chair - developed PULSES conference;
  - Appointed PULSES Director 2022 to present,
  - Member of Annual committee (past co-chair)
- American Psychiatric Association - Assembly member as ACROSS rep from CTMSS to APA; Vice President of TN Psychiatric Association; DB rep lobbying
- Membership in AFSP3

VNS: Vagus Nerve Stimulation

VNS Therapy is FDA-approved (2005) 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

Previous clinical research with VNS Therapy

A recent 5-year prospective study found patients **using VNS Therapy + TAU*** results in:

*TAU = Treatment As Usual

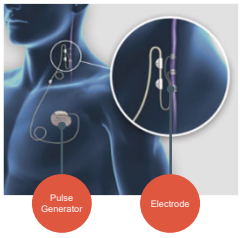
- **65%** Higher Cumulative **Response** Rate vs TAU Alone[1]
- **68%** Improvement in **Remission** vs TAU Alone[1]
- Reduced 60-Month All Cause **Mortality**[1]
- **2/3** Patients had a **Durable** 2-Year Response[2]

No risk of non-adherence with VNS Therapy,
unless the patient chooses to stop stimulation with optional magnet placement.

[1]Aaronson et al *AmJ Psychiatry* 2017; 174:640–648;
[2]Sackeim et al *Int J Neuropsychopharmacol.* 2007;10:817-826.

About the implantation procedure

- Surgery done under general anaesthesia on an outpatient basis and takes <1–2 hours
- Procedure requires a small incision on the chest & one on the side of the neck
- VNS Therapy device (pulse generator) is placed under the skin below the collarbone
- Access to the vagus nerve is created through a natural crease in the left side of the neck
- Electrodes are wrapped around vagus nerve in neck & connected to the pulse generator
- Incisions are allowed to heal for about two - four weeks before the device is turned on.



Trained surgeons implant the device, so it is discrete and comfortable

VNS Safety profile

- Device Stimulation typically occurs for a period of 30 seconds, every 5 minutes but the device may be programmed differently.
- Most common side effects (adverse events - AEs) from stimulation include:
  - voice changes (hoarseness),
  - prickling or tingling in the skin,
  - sore throat, and
  - shortness of breath
- Vast majority of AEs decrease with continued VNS Therapy. Most notable exception is voice alteration which can persist.
- Most commonly reported AE from the implantation procedure is infection (<1%)
- Importantly, unlike other treatments for TRD, VNS Therapy has not been associated with memory impairment or sexual dysfunction and there are no drug or food interactions

Source: LivaNova VNS Therapy System Physician's Manual.

Current Lack of Reimbursement limits patient access

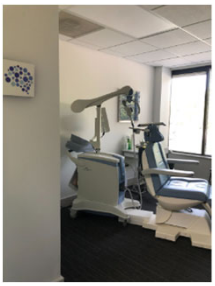
- Medicare beneficiaries with TRD were unable to access VNS Therapy outside of the RECOVER clinical study, however this is changing
- Patients with commercial insurance have limited access, but are having increasing success in obtaining coverage authorization by utilizing the LivaNova Patient Access Program
- The RECOVER study has been designed in partnership with many of the nation's top experts in treatment-resistant depression, ***and approved by Medicare,*** in order to provide additional robust evidence that VNS Therapy as an adjunctive treatment improves health outcomes for patients with TRD + for Bipolar Depression.

The RECOVER study

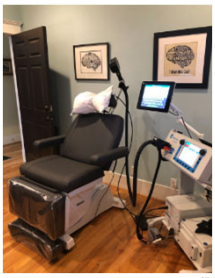
- Prospective multicenter RCT: up to 1,000 TRD patients (unipolar ***or bipolar***) at up to 100 medical centers across the United States
  - Unipolar TRD MDD Arm of study is closed now
  - Bipolar Depressed Arm is openly enrolling
- Participants will be randomized 1:1 into Group A (Active Treatment) or Group B (Device Off = Control) before device implantation
- Both groups receive surgery and get the device.
- Group A will begin treatment from the start of the study
  Group B has device turned on, after a 12-month delay
- All participants will continue to receive other usual treatment(s) for depression
- Refer from GA/TN/KY **615-224-9800** or support@hopeforyourbrain.com

TMS = Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS)



- TMS is the "newest" neuromodulation
- Received FDA clearance 2008 after one large RCT, & second RCT followed in 2010.
- Evidence for effectiveness is considerable
- Office-based



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FDA cleared TMS devices for [1]MDD, [2]OCD, [3]Smoking Cessation, [4]MDD with Anxious features in US

TMS

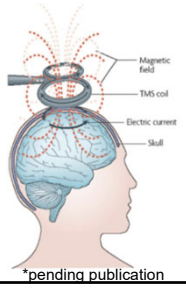
- TMS refers to the treatment that delivers repetitive, changing magnetic fields to the brain.
- The magnetic fields alter electrical & chemical functions in brain regions.

Original Outcome Studies with TMS

- showed approximately 30% response <u>without</u> medication in Treatment of MDD

More recent data

- shows improved rates in clinical settings (remission: 50-65% reported & response: 80-90% with skilled clinicians & supportive Behavioral Activation & CBT techniques + Meds + TMS treatment*



*pending publication

Theoretical Mechanism(s) of Action
Biological and Behavioral Effects of TMS

Effects Seen After Repeated TMS Applications:

- Specific outcome is dependent upon stimulation parameters
- Changes in blood flow and metabolism at the stimulation site
- Alteration of monoamine concentrations
- Beta-receptor, serotonin-receptor modulation
- Effects on thyroid hormones and HPA axis
- Evidence of induction of neurogenesis genes (eg, BDNF upregulation)
- Plasticity-like actions (ie, LTD/LTP-like effects)
- Local GABA & glutamate effects
- Increase in grey matter volume and hippocampal volume
- Changes in connectivity/activity of neural circuitry e.g., DLPFC-anterior cingulate cortex

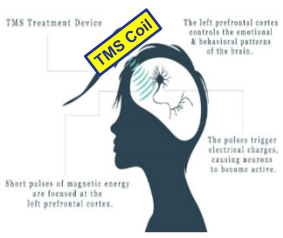
Lisanby SH, et al 2000; Kim EJ et al. 2006; Shajahan PM et al 2002; Teneback CC et al. 1999; Epstein CM et al. 1990; George MS et al. 1995; Czeh, B., et al. 2002.

TMS: Transcranial Magnetic Stimulation

- Initial FDA clearance for MDD, now there are TMS devices cleared for Migraine, OCD and Augmentation of Smoking Cessation.
- Very effective in outpatient treatment;
  - much higher response & remission rates than TAU for TRD
- Avg. course 36 treatment sessions; daily for ~30 min in office, for 4-6 weeks followed by 3 wks of tapering; tailored to reach remission
- Most insurance covers MDD treatment after second failed medication; patient's pay copays, deductibles, or co-insurance;
- Other indications, OCD is covered by a growing number of insurance companies

TMS Therapy Session

- Patient is awake and alert
  - No anesthesia or sedation needed
- No negative effects on thinking and memory
  - After treatment, patients can drive & return to work
- Some patients experience headache or mild to moderate pain or discomfort at or near the treatment area
- None of the side effects typical with antidepressant medications



TMS Therapy is a Well-Tolerated Antidepressant

list of most common adverse events with all coils (incidence > 5%)

TMS Side Effects:

- Scalp/Head Pain at Treatment Site
- Headache

No Systemic Side Effects:

Weight Gain	Nausea	Dry Mouth
Weight Loss	Nervousness/Anxiety	Sweating
Appetite changes	Sexual side effects	Tremor
Constipation	Impotence	Fatigue
Diarrhea	Weakness	Treatment Discontinuation symptoms

Reference: 510(k) applications for Neuronetics & Brainsway devices

Daily Checks to Avoid Rare Side effects for TMS

Patients are Screened Daily for:

- Number of sleep hours
- Any use of alcohol & other substances
- Medication changes
- Other changes

- Seizure is the most serious side effect associated with TMS
  - Risk < 0.1% per treatment
- Increased Auditory threshold or Hearing Loss
  - in RCT studies, a small proportion of adults experienced increased auditory threshold or permanent loss
  - ***all patients and staff are encouraged to wear hearing protection to 30db***

TMS is NOT ECT

- TMS is not a replacement for ECT: different modality; likely should be earlier in course of care for depression.
- ECT is still best for MDD with psychotic features, acute suicidality, or catatonia
- Some patients who fail ECT respond to TMS and vice versa[1]
- Head-to-head trials comparing ECT and TMS have not been completed with double blind due to the challenge of creating “double-dummy” sham design
- Durability may be greater with TMS (vs ECT), most ECT patients relapse in 6 months, for patients with remission TMS can maintain for year for 68%
- Re Introduction with TMS works if patient needs treatment again!

[1]H Sackeim 2016

Referring for Neuromodulation

How to refer?

- ECT - contact your local psychiatric hospital, ask if labs are needed, EKG?
- Ketamine/Esketamine - our opinion, learn to offer the esketamine in your office or locate a REMS certified office online, *www.spravato.com*
- VNS - refer to *www.clinicaltrials.org*; or email: *chai.lee@livanova.com*
- TMS - many offices that now offer TMS; our opinion, every psychiatrist should own a device and know how to use it.

What to expect?

- Most offices offer Screening for neuromodulation via trained staff
- Consultations in-network with the interventional psychiatrists
- Psychiatrists follow before, during and after care to optimize outcomes

	TMS	Esketamine Ketamine	ECT	VNS
FDA clearance (approval) w relation to MDD	18 yo + MDD, In MDD after 1+ medication fails *(often used w meds but studied w/out meds)*	Esk: 18yo + for TRD (2+ failures) *with oral antidepressant* Ket: (oral AD unnecessary)	13yo+ TRD, psychotic depression, and acutely suicidal	18 yo+ as adjunctive to treatment of MDD *(presumed to mean w medication)*
Course of Care	Typical: 5 days/wk for 5-7 wks, w/3 wk taper Avg # 36 Treatments	Esk: 2X/wk X 4wks, 1X/wk 4-8 wks, taper to maintain, *?indefinitely* Ket: 2X/wk until effect then taper to maintain	2- 3 X per week until effect, then taper to maintenance treatment phase	Implantation, heal for 4wks, then device turned on, programmed up to effect, then maintained
Outcomes	Remission 30-65% Response 50-85% *reported in literature and outpt offices*	Remission 30-60% Response 50-85% *reported in literature and outpt offices*	Remission 30-60% Response 50-85% *reported in literature and outpt offices*	Remission & Response pending study results Looks very promising
Durability	If effect, holds for 1 yr+; Maintenance Treatment not necessary nor yet proven to be effective	Maintenance Treatment - Most must continue with Treatment to maintain effect	Most patients relapse in 6 months, Maintenance used to maintain effect	Once implanted and titrated maintains effect until battery fades (approx 5 yrs)

	TMS	Esketamine Ketamine	ECT	VNS
Common Side Effects	Tapping sensation on head; Headache	Dissociation, nausea, sedation	Memory effects, anesthetic side effects	Buzzing sensation in upper chest during stimulation
Rare Side Effects	Seizure, vaso-vagal reactions	Blood pressure elev genitourinary probs (reported w/Ketamine abuse)	Serious memory impairment	Voice sounds "gravely" during stimulation Surgery: infection at surgical site.
Contra-indications	Ferromagnetic metal in head near coil	Aneurysms	No contraindications	If need to have MRI in the area of implantation

	TMS	Esketamine Ketamine	ECT	VNS
Highly suicidal patient	2-3 wks to help, not best for acutely suicidal patient w/ intent	also indicated for MDD + suiciality	Highly effective for suicidal patient generally within 4-20 treatments	12 + wks for benefit, not best for acutely suicidal patient
Costs	most payers cover when 2 or more fail for MDD; patients pay co-pays, coinsur, + deductibles	most payers cover after 3 + meds with augmentor; patients owe for medication + monitoring (copays, coinsur., + deductibles	Covered by payers Hospital & physician charges (copays, coinsur + deductibles	Free in study Long process to get approved if not in study 25,- 40,000 for surgery, then monitoring in doc appt
Other indications	OCD, and smoking cessation	MDD w suicidality - study didn't improve suicidality despite indication; did improve mood	psychotic depression, catatonia with depression,	Intractable seizures and epilepsy

Questions?

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