Beyond Medications:

The Expanding Role of Interventional Psychiatry in Treatment-Resistant Mental Illness

Mental Health Association of East Tennessee
2025 Fall Psychiatric Symposium
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Disclosures

Brittany Albright, MD:

- Advisory Board – AbbVie, Bristol Myers Squibb, Eli Lilly, Johnson & Johnson, Neurocrine
- Consultant – AbbVie, Axsome, Johnson & Johnson, Osmind, Precision Genetics
- Speaker's Bureau – AbbVie, Alkermes, Axsome, Johnson & Johnson

Learning Objectives

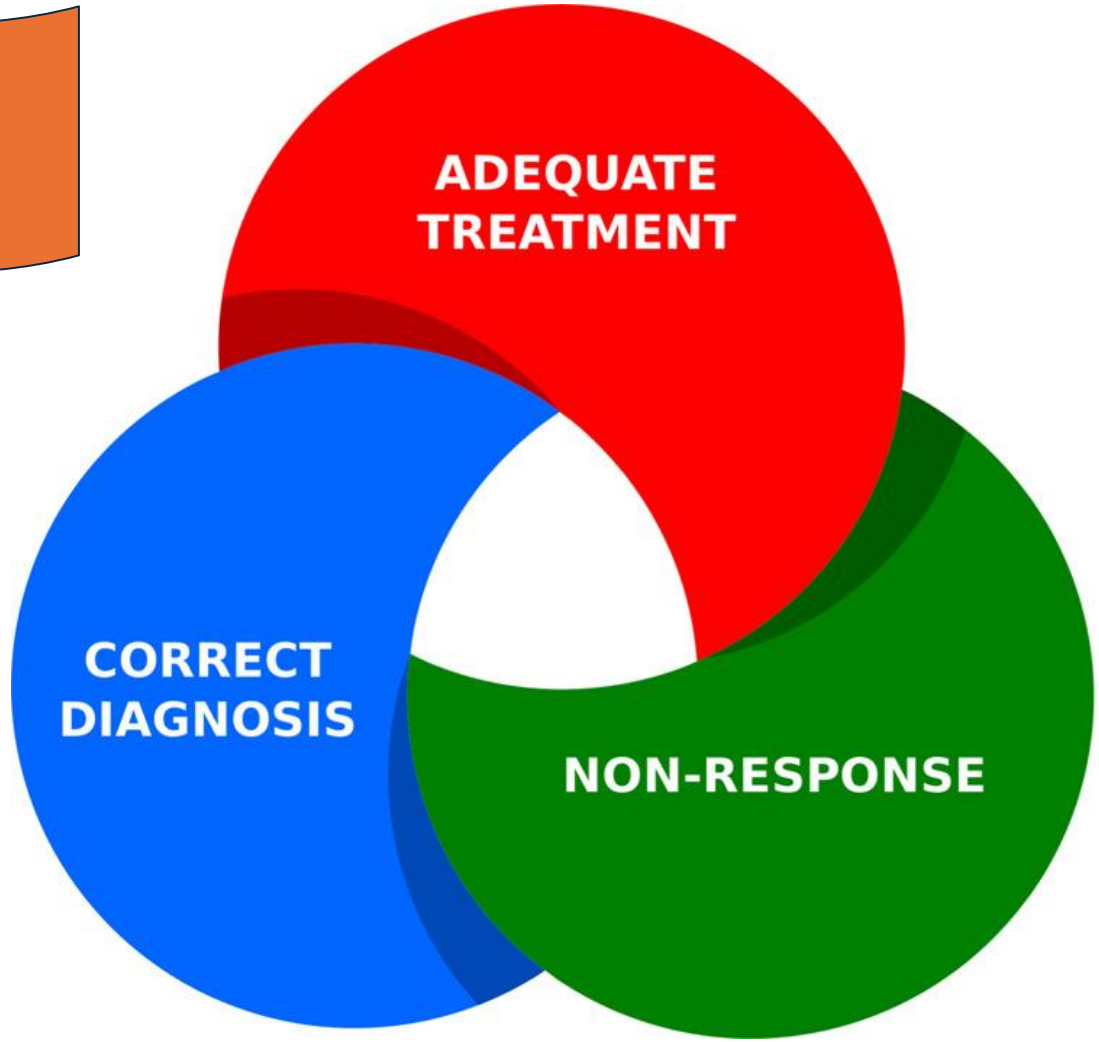
- Examine the growing role of interventional psychiatry
- Analyze mechanisms of action, research evidence, and optimal patient selection for interventional treatments
  - Electroconvulsive therapy (ECT)
  - Transcranial magnetic stimulation (TMS)
  - Vagus nerve stimulation (VNS)
  - Deep brain stimulation (DBS)
  - Ketamine and esketamine
- Discuss how to integrate interventional treatments with standard psychiatric care

ECT = electroconvulsive therapy; TMS = transcranial magnetic stimulation; VNS = vagus nerve stimulation; DBS = deep brain stimulation.

Despite decades of research, current pharmacotherapies and psychotherapies remain ineffective or intolerable for many patients with psychiatric disorders.

Treatment Resistance in Psychiatry

Treatment resistance affects 20%-60% of patients with psychiatric disorders

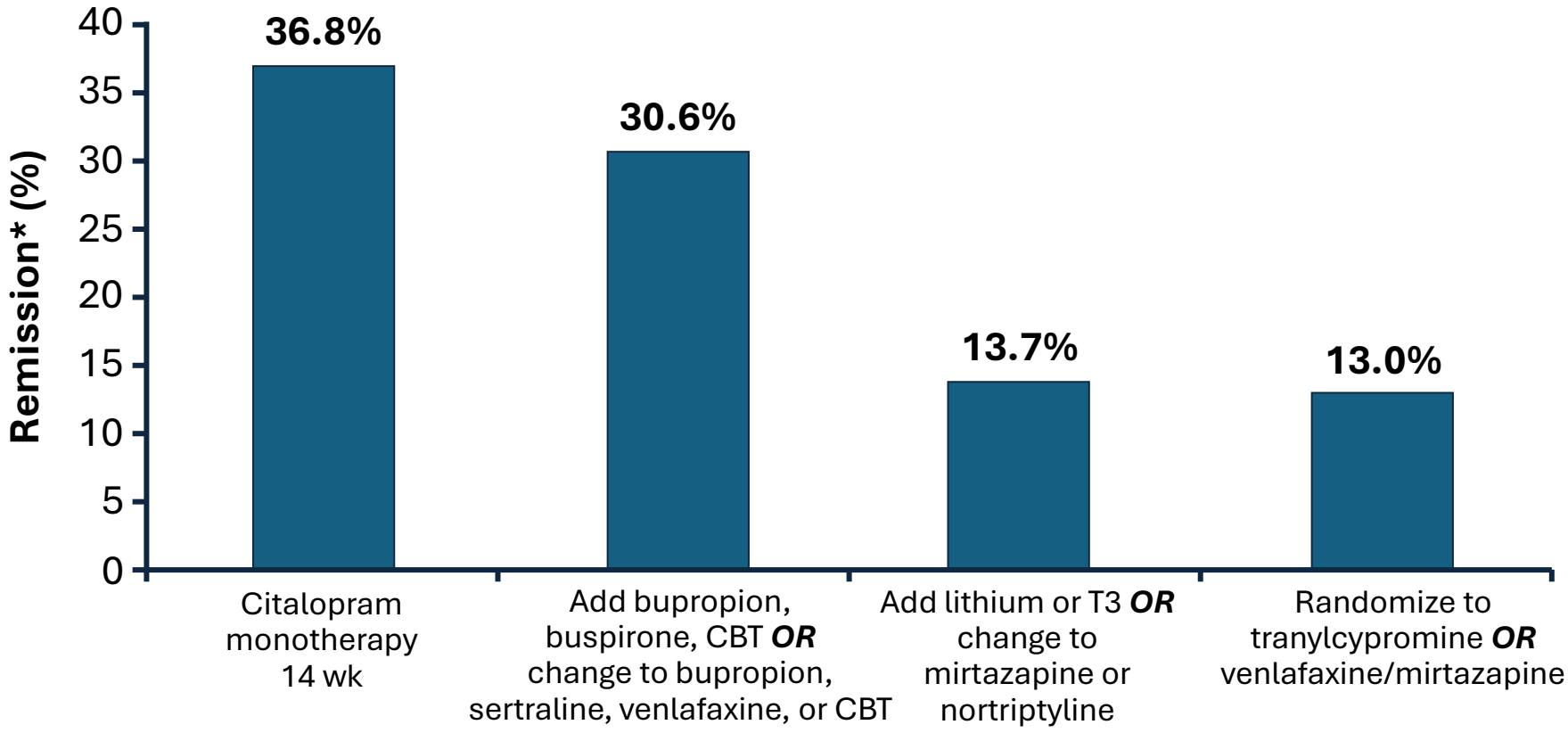


Reasons for Treatment Resistance

- Heterogeneity
- Absence of consensus criteria
- Poor understanding of neurobiology
- Under-investment
- Lack of treatments

Howes OD, et al. *Mol Psychiatry*. 2022;27(1):58-72.

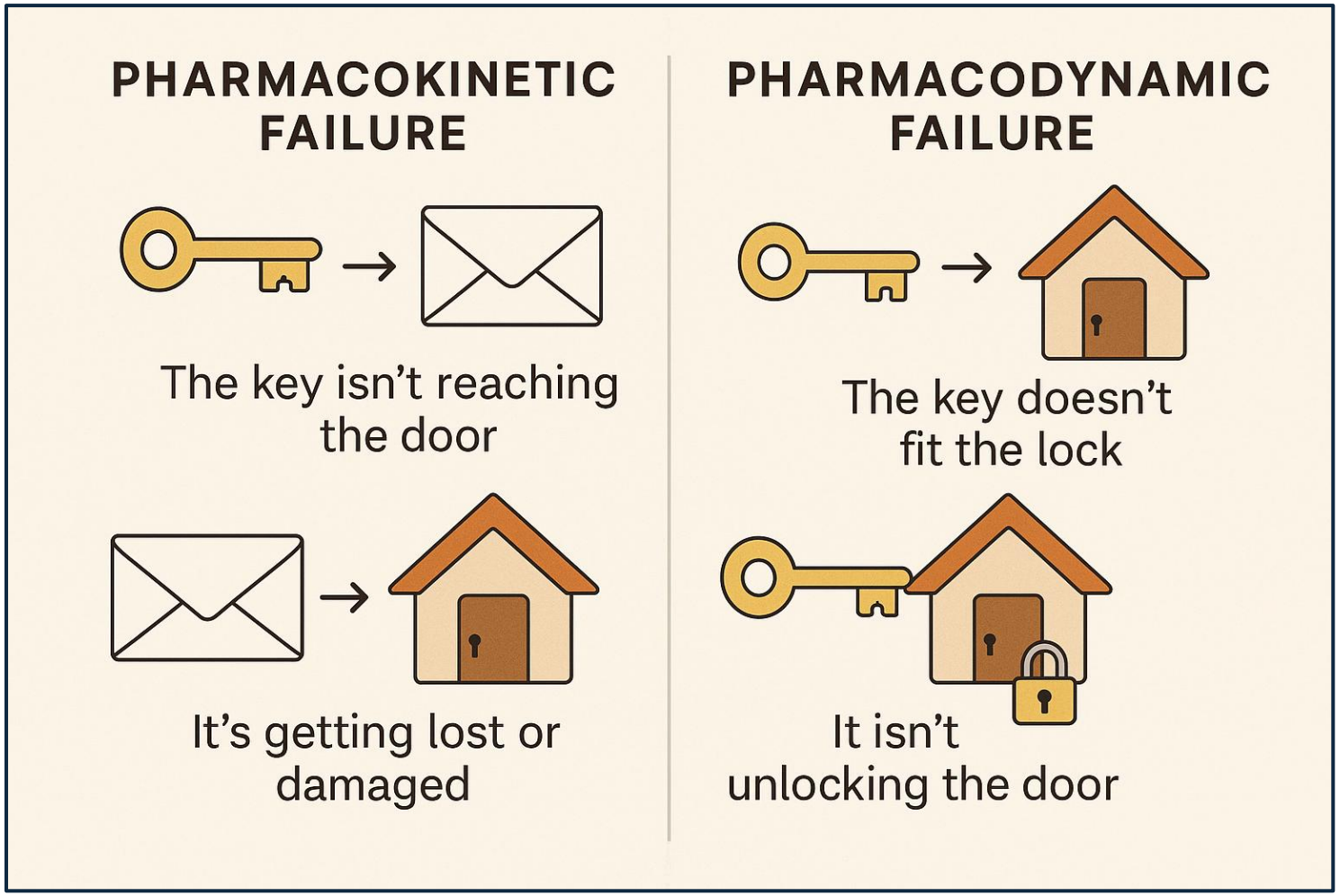
STAR*D: Antidepressant Efficacy Decreases with Successive Acute Treatments



*Remission defined as QIDS-SR-16 ≤5. STAR*D = Sequenced Treatment Alternatives to Relieve Depression; CBT = cognitive behavioral therapy.

Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917.

Pharmacokinetic or Pharmacodynamic Failure?



Pharmacokinetic failure: The drug is not **reaching the target site** at therapeutic levels (due to issues with absorption, distribution, metabolism, or elimination)

Pharmacodynamic failure: The drug **fails to exert its intended effect** (eg, receptor insensitivity, downstream signaling abnormalities)

OpenAI. Image. Accessed July 2025. https://openai.com/.

Impact of Treatment Resistance

Treatment-Resistant Schizophrenia

- Annual **direct** medical costs in the U.S. exceed **$34 billion**
- Hospitalization and total health resource utilization are **10× higher** than for non-TRS
- **Up to 80%** of schizophrenia-related healthcare costs are attributed to TRS
- Patients with TRS experience **greater functional impairment**
- **Quality of life** is estimated to be **20% lower** in TRS patients compared to non-TRS patients

Treatment-Resistant Depression

- Direct medical costs are estimated to be **2-6× higher** than those of other MDD patients
- Costs increase with **greater chronicity and severity**
- TRD patients are **twice as likely to be hospitalized** as non-TRD patients
- **Quality of life** is approximately **25-40% lower** in TRD patients compared to those in remission or treatment-responsive
- **30% of patients** with TRD **attempt suicide** during their lifetime

TRS = treatment-resistant schizophrenia; MDD = major depressive disorder.

Howes OD, et al. *Mol Psychiatry*. 2022;27(1):58-72.

Enter in...

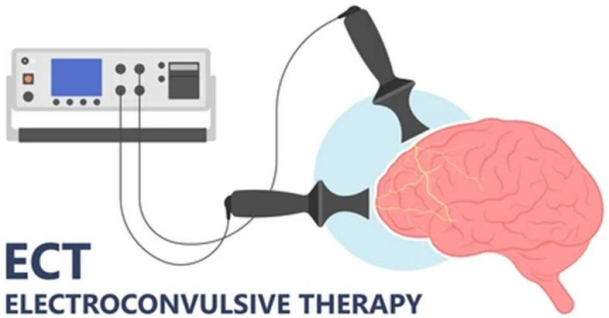
Interventional Psychiatry

University of Toronto, Psychiatry. Accessed July 2025. https://psychiatry.utoronto.ca/event/advancing-care-one-day-workshop-interventional-psychiatry-techniques.

What Is Interventional Psychiatry?

"We must recollect that all of our provisional ideas in psychology will presumably one day be based on an organic substructure."
~Sigmund Freud, *On Narcissism*

Interventional psychiatry refers to treatments that are **administered under medical supervision in a clinic or hospital**



Device-based neuromodulation therapies

Pharmacologic treatments given in-clinic

Williams NR, et al. *J Clin Psychiatry*. 2014;75(8):895-897. Nikayin S, et al. *J Neurol Sci*. 2022;434:120093. Ressler KJ, et al. *Nat Neurosci*. 2007;10(9):1116-1124. Dufor T, et al. *Int J Mol Sci*. 2023;24(22):16456.

Interventional Psychiatry: Circuit-Based

🧠 1. Circuit Dysfunction

- Interventional psychiatry targets **dysfunctional neural circuits**

⚡ 2. Precision Targeting of Brain Networks

- Neuromodulation targets **activity in defined brain circuits** rather than influencing global neurochemistry

🧬 3. Neuroplasticity and Network Rewiring

- These interventions work by **inducing plastic changes** and **circuit recalibration**

🎯 4. Objective Circuit-Based Biomarkers

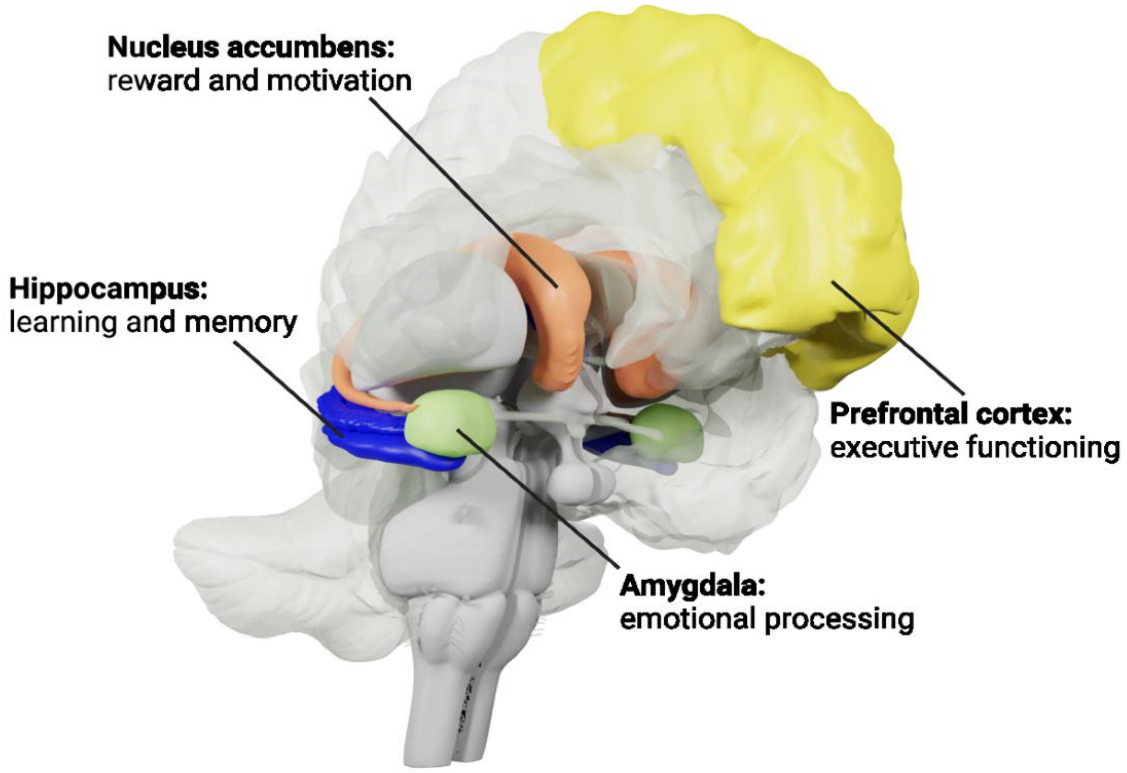
- Advances in neuroimaging and computational psychiatry enable **mapping of dysfunctional connectivity patterns**
- Future interventional treatments may be **guided by fMRI, EEG, or connectomic signatures**

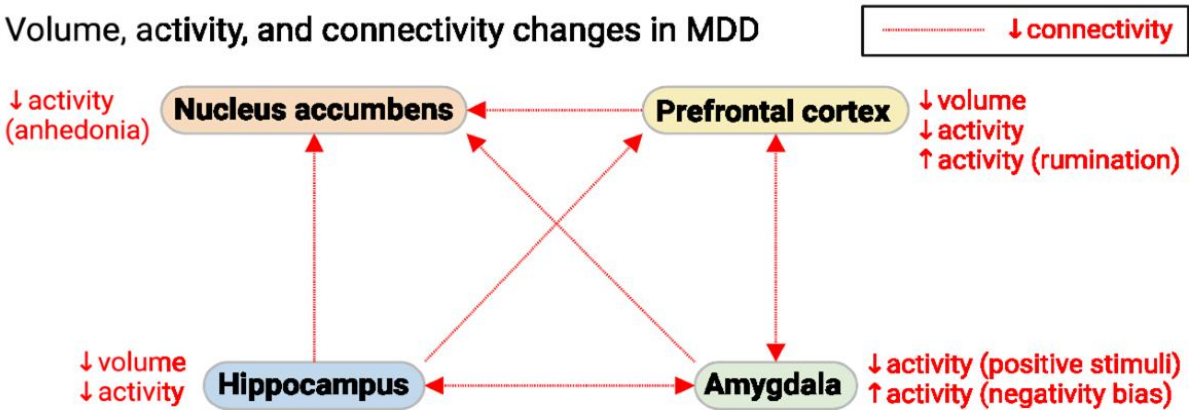
🚫 5. Overcoming Pharmacologic Limits

- Circuit-based interventions **bypass limitations of pharmacokinetics and pharmacodynamics**

fMRI = functional magnetic resonance imaging; EEG = electroencephalogram.

Circuits and Depression





MDD involves cognitive and emotional inflexibility with a persistent negativity bias.

Effective treatments enhance neuroplasticity, promoting adaptive processing.

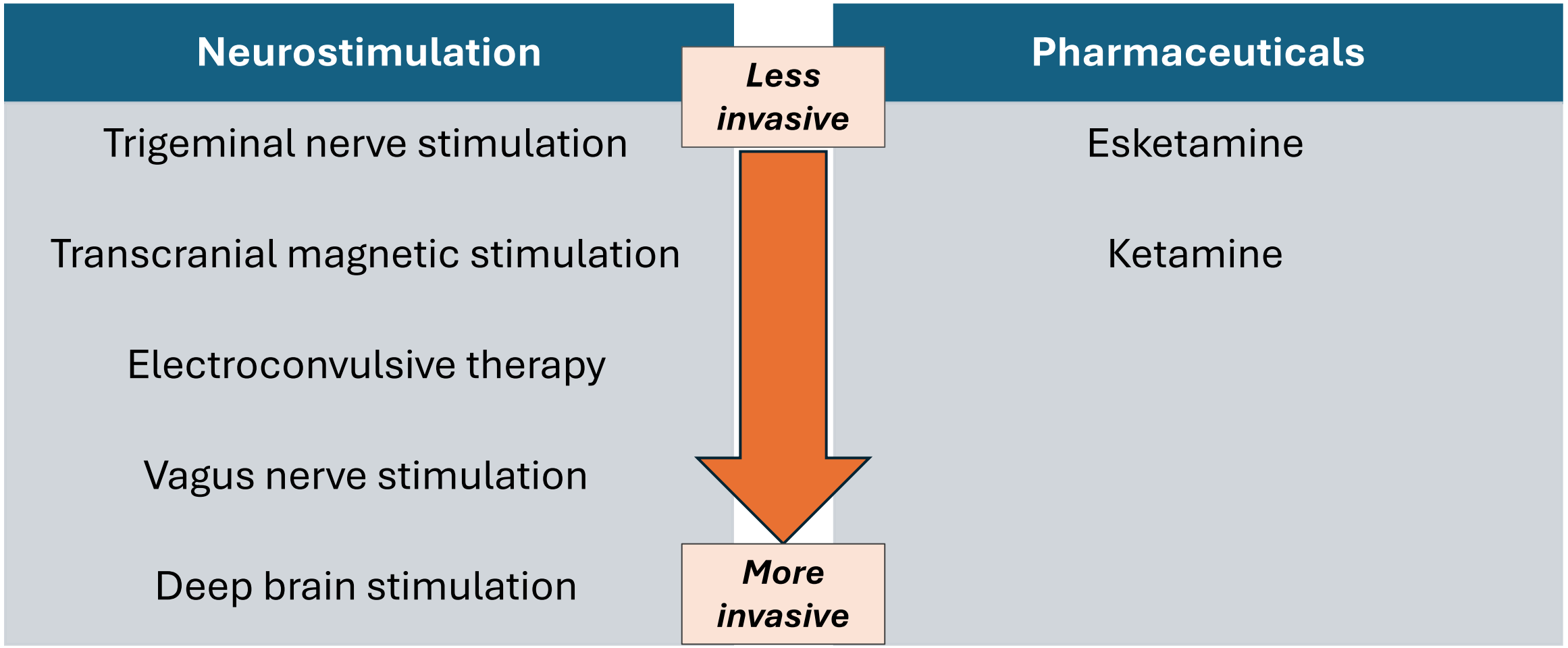
Mechanisms include **synaptic, network, and behavioral restoration**.

Treatment modalities

- Monoaminergic antidepressants
- **Novel agents** (eg, ketamine, psychedelics)
- **Psychotherapy**
- **Lifestyle modifications** (diet, exercise, meditation)
- **Neuromodulation** techniques

MDD = major depressive disorder. Page CE, et al. *Mol Psychiatry*. 2024;29(12):3802-3813.

Treatment Modalities in Interventional Psychiatry



Williams NR, et al. *Acad Psychiatry*. 2014;38(2):168-176.

FDA Approval vs FDA Clearance

What are the differences?

FDA clearance: Pathway used for low- to moderate-risk medical devices that are substantially equivalent to a legally marketed predicate device.

- Manufacturer must demonstrate that the new device is at least as safe and effective as the predicate device

FDA approval: Required for high-risk medical devices and new drugs.

- Involves a more rigorous review and submission of a premarket approval application for devices or a New Drug Application for drugs
- Manufacturer must provide substantial evidence of the device's/drug's safety and effectiveness through clinical trials

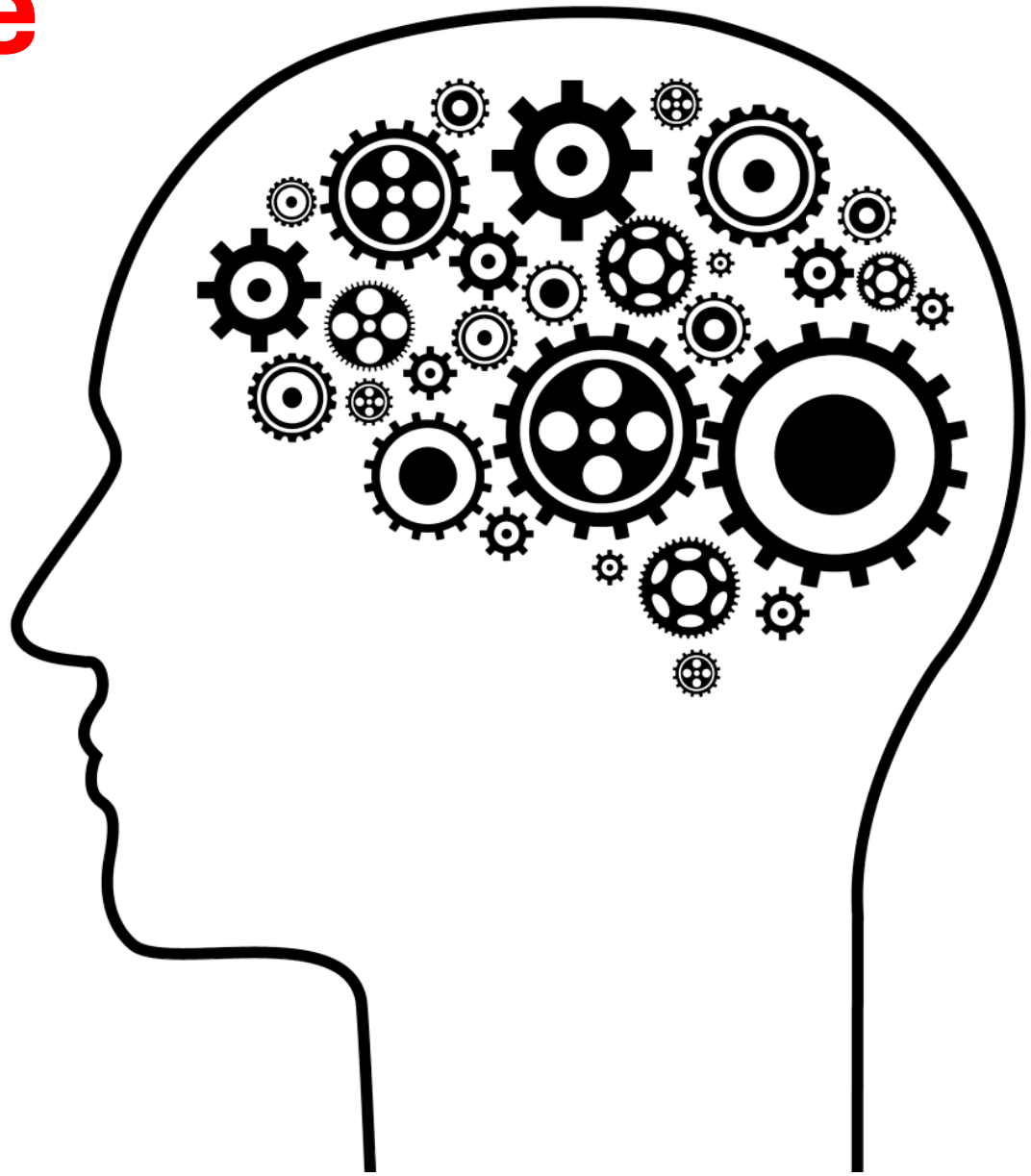
Distinct regulatory pathways used by the U.S. Food and Drug Administration (FDA) to evaluate medical devices and drugs:

FDA clearance is for low- to moderate-risk devices shown to be substantially equivalent to existing devices

FDA approval is for high-risk devices and new drugs that must demonstrate safety and efficacy through rigorous clinical testing

Jarow JP, et al. *Urologic Oncology*. 2015;33(3):128-32. Gassman AL, et al. *N England J Medicine*. 2017;376(7):674-682.

Electroconvulsive Therapy



Indicated for (per APA guidelines):

Treatment-Resistant Major Depression with or without Psychosis

Catatonia Irrespective of Precipitating Cause

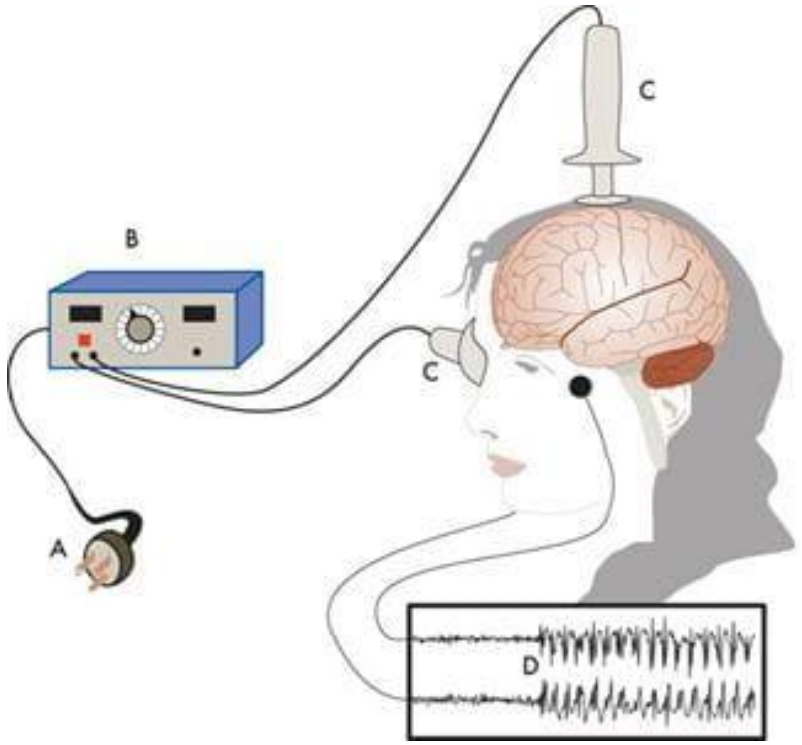
Bipolar Depression and Mania

Treatment Refractory Schizophrenia and Schizoaffective Disorder

APA = American Psychiatric Association.

Electroconvulsive Therapy (ECT)

Arguably the most effective treatment in psychiatry today and the most burdened…



60%-80%
of depressed patients achieve symptom reduction

50%
Reduction in suicide risk

- Uses an electrical current to induce a tonic-clonic seizure under general anesthesia
- An acute series consists of 3 weekly treatments for up to 4 weeks, with each session requiring at least 1 hour from pre-op to recovery
- Highly effective for mania, severe depression, psychosis, catatonia

ECT = electroconvulsive therapy.

Mutz J, et al. *BMJ*. 2019;364:l1079. Espinoza RT, Kellner CH. *N Engl J Med*. 2022;386(7):667-672. Kaster TS, et al. *Lancet Psychiatry*. 2022;9(6):435-446. Kim J, Widge AS. Neuromodulation Approaches to Depressive Disorders. Psychiatric Times. March 21, 2024. Accessed October 24, 2024. https://www.psychiatrictimes.com/view/neuromodulation-approaches-to-depressive-disorders. Medical University of South Carolina. Accessed July 2025. https://medicine.musc.edu/departments/psychiatry/divisions-and-programs/divisions/brain-stimulation-lab/ect.

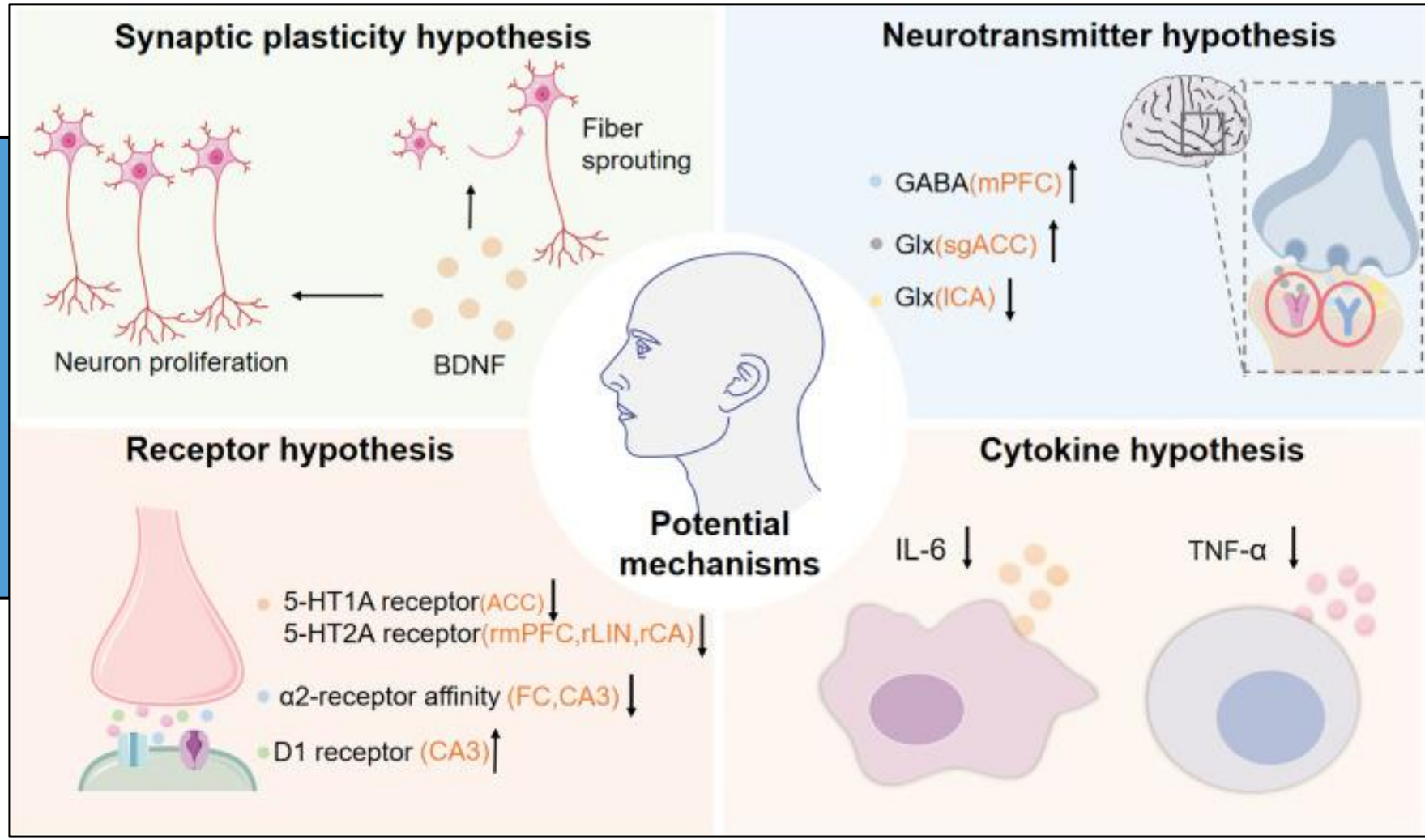
ECT: Potential Mechanisms of Action

Neurophysiological

Theory: Seizures cause changes in cerebral blood flow, regional metabolism, changes in blood–brain barrier

Neurochemical

- Theory: Seizures cause neurochemical changes

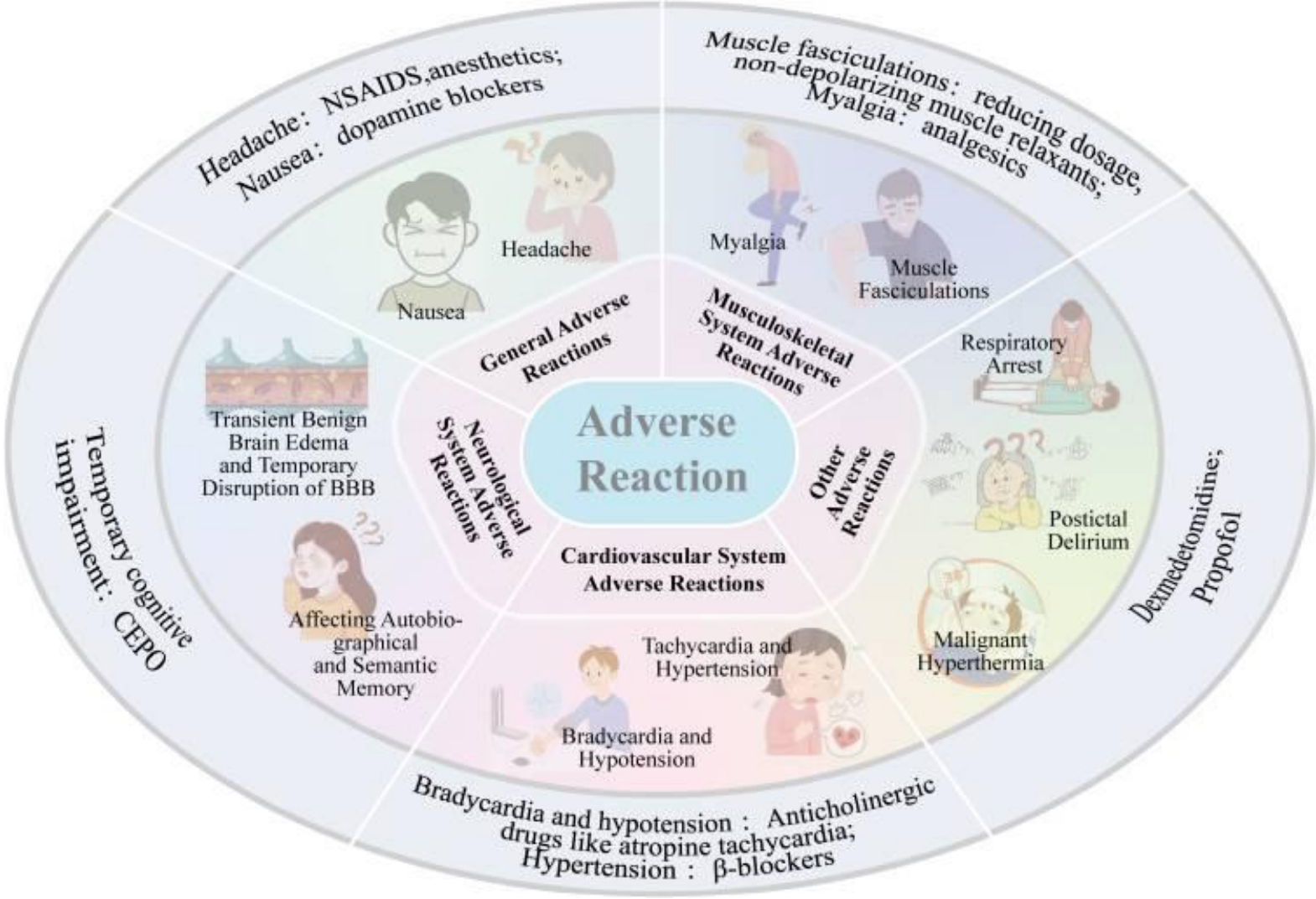


Rojas M, et al. *Int J Mol Sci*. 2022;23(13):6918. Dai X, et al. *Neuropsychiatr Dis Treat*. 2024;20:1491-1502.

ECT: Adverse Reactions

Most common side effects

- Myalgias
- Nausea
- Temporalis/masseter tenderness
- Headache
- Temporary cognitive side effects



NSAID = nonsteroidal anti-inflammatory drugs; CEPO = carbamylated erythropoietin; BBB = blood-brain barrier.

Pagnin D, et al. *J ECT*. 2004;20(1):13-20. Andrade C, et al. *Psychiatr Clin North Am*. 2016;39(3):513-530. Benbow SM, Crentsil J. *Psychiatric Bulletin*. 2004;28(8):289-291. Dai X, et al. *Neuropsychiatr Dis Treat*. 2024;20:1491-1502.

ECT: Patient Considerations

ECT leads to acute and quick vital sign changes during procedure; consider patient safety for general anesthesia

Appropriate patients	Contraindications	Relative risk considerations	Medications	Barriers to care	Pros
No age cut off Adolescent through geriatric	No absolute contraindications Can be used during pregnancy	Cardiac conditions Neurological disorders: Space-occupying lesions, elevated ICP, intracranial devices High-risk pregnancy	Consider down-titration of psychiatric anticonvulsants	Stigma Access Patient Transportation	Covered by insurance Outpatient or inpatient Most patients may continue to work during treatment course

ICP = intracranial pressure.

Williams NR, et al. *J Clin Psychiatry*. 2014;75(8):895-897. Pagnin D, et al. *J ECT*. 2004;20(1):13-20. Andrade C, et al. *Psychiatr Clin North Am*. 2016;39(3):513-530. Benbow SM, Crentsil J. *Psychiatric Bulletin*. 2004;28(8):289-291.

ECT remains the gold standard for severe, treatment resistant psychiatric illness, but it is underutilized due to patient and clinician stigma…

Transcranial Magnetic Stimulation

FDA-Cleared for:

Treatment-Resistant Depression in Adults and Adolescents
Anxious Depression
Smoking Cessation
Migraines
Obsessive Compulsive Disorder

Transcranial Magnetic Stimulation

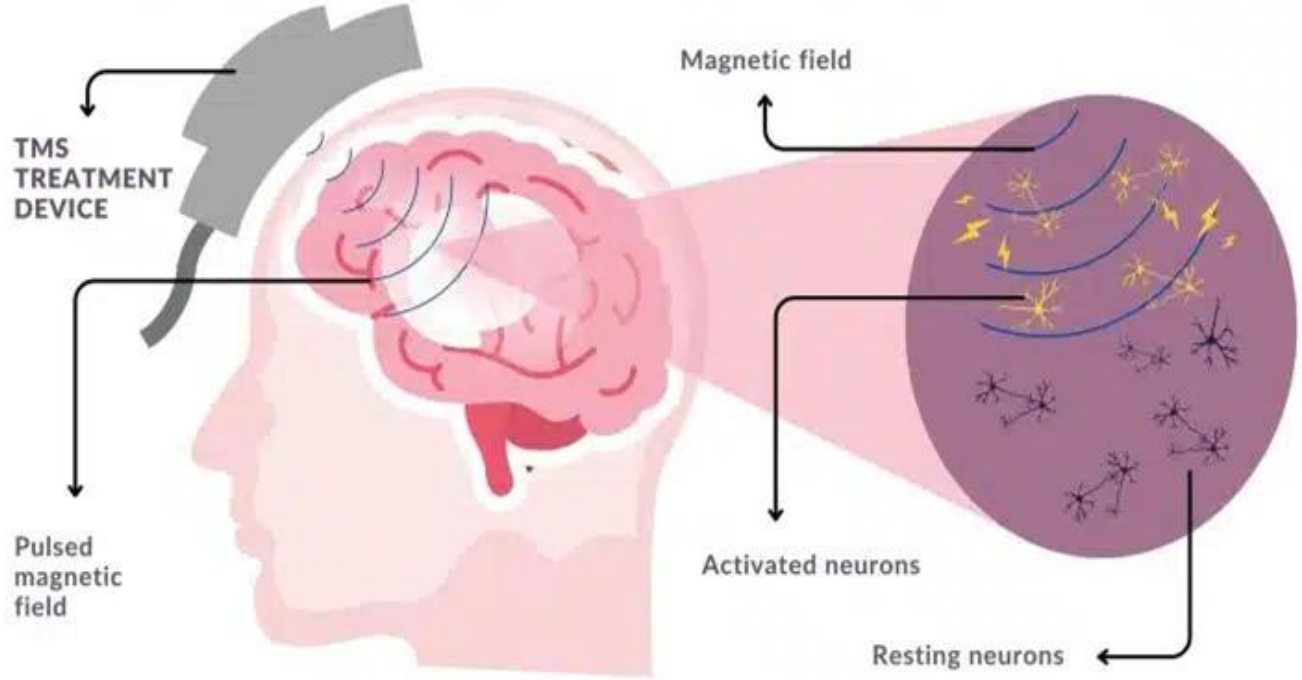
FDA cleared for TRD in adult patients in 2008 and adolescents in 2024

TMS Dosing Fundamentals

- Involves identifying the motor threshold and selecting the stimulation type (eg, iTBS vs standard), coil (H-coil vs figure-8), and schedule (daily vs accelerated)
- Incorrect dosing can lead to ineffective treatment or increased seizure risk.

Clinical Protocols and Treatment Schedules

- FDA-cleared protocols define parameters including intensity, coil, and frequency
- Standard courses run daily for 4-6 weeks; **accelerated protocols** may deliver up to 10 sessions per day over 5 days



Coils generate repetitive changing magnetic fields, which create an electric field, increasing neural excitability and activity.

TMS = transcranial magnetic stimulation; iTBS = intermittent theta burst stimulation.

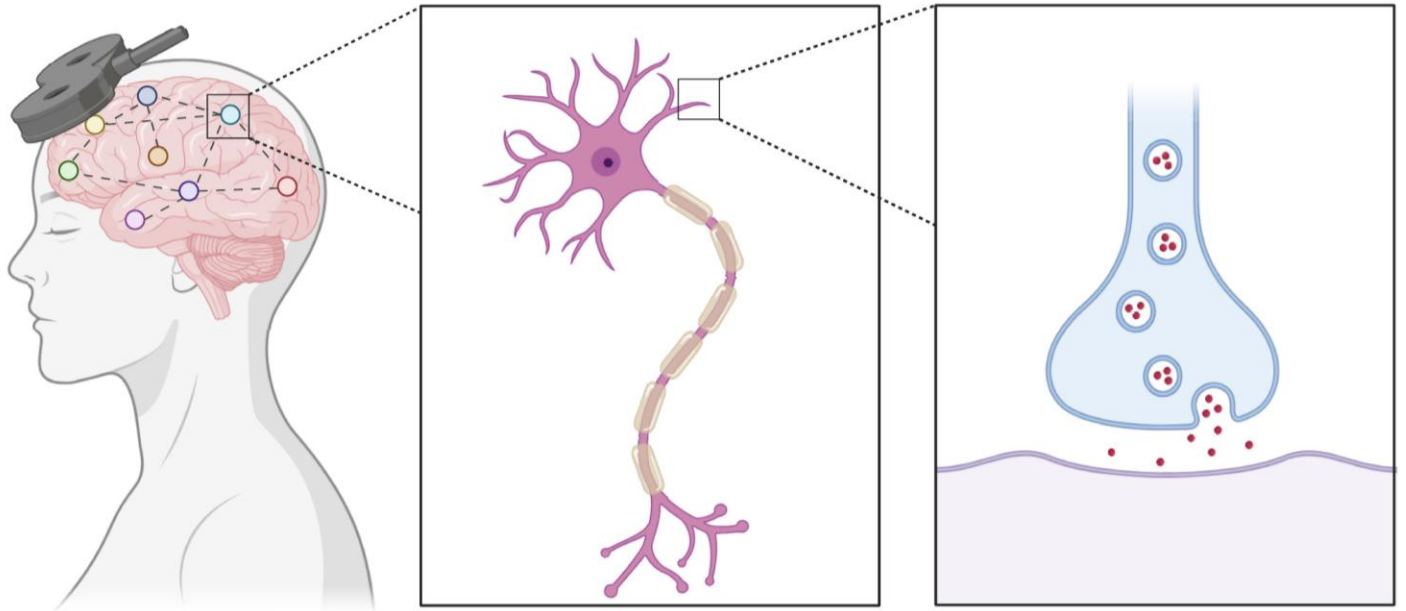
Roth Y, et al. *J Clin Neurophysiol*. 2002;19(4):361-370. McClintock SM, et al. *J Clin Psychiatry*. 2018;79(1):16cs10905. Menon SN, et al. *Front Psychiatry*. 2024;15:1397102. Neuralia TMS. Image. Accessed July 2025. https://www.neuraliatms.com.au/tms-therapy/for-depression/.

TMS: Mechanism of Action

TMS Modulates Neuroplasticity via Synaptic and Network-Level Mechanisms

TMS (transcranial magnetic stimulation) influences **long-term potentiation (LTP)**- and **long-term depression (LTD)**-modulating synaptic strength

Effects are dependent on **stimulation parameters, brain state, and network connectivity**, suggesting complex interactions between stimulation and endogenous neural activity



Circuit	Neural	Synapse
• Altered activity • Altered functional connectivity • Altered white matter integrity and connectivity • Increased gray matter thickness and volume	• HF rTMS/iTBS: ↑ excitability / ↓ inhibition	• Increased BDNF release • Altered DA release • Altered 5-HT synthesis • Altered 5-HT receptor availability • Altered GABA and glutamate

LTP = long-term potentiation; LTD = long-term depression. Fitzsimmons SMDD, et al. *Biol Psychiatry*. 2024;95(6):592-600.

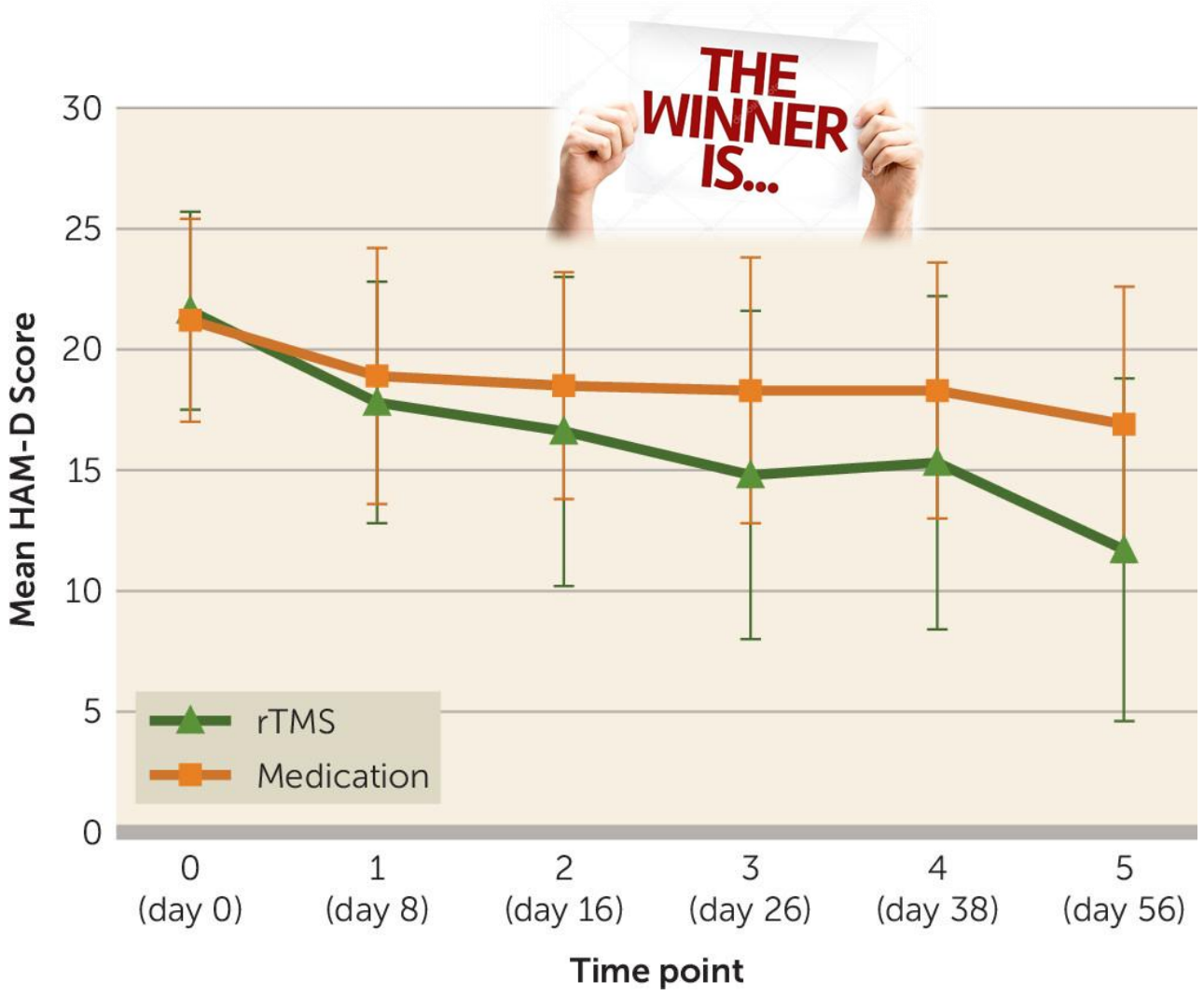
rTMS Compared with Switching Antidepressant

METHODS

- 89 patients with unipolar nonpsychotic TRD
- Randomly assigned to psychotherapy plus
  - rTMS ~3 times weekly
  - Antidepressant switch

RESULTS

- Significantly larger reduction in depressive symptoms with rTMS vs new medication
- **Higher response rate with rTMS** (37.5%) vs new medication (14.6%)
- **Higher remission rate with rTMS** (27.1%) vs new medication (4.9%)
- Larger decrease in anxiety and anhedonia symptoms with rTMS
- No differences in rumination, cognitive reactivity, or sleep disorders



HAM-D = Hamilton Depression Rating Scale.

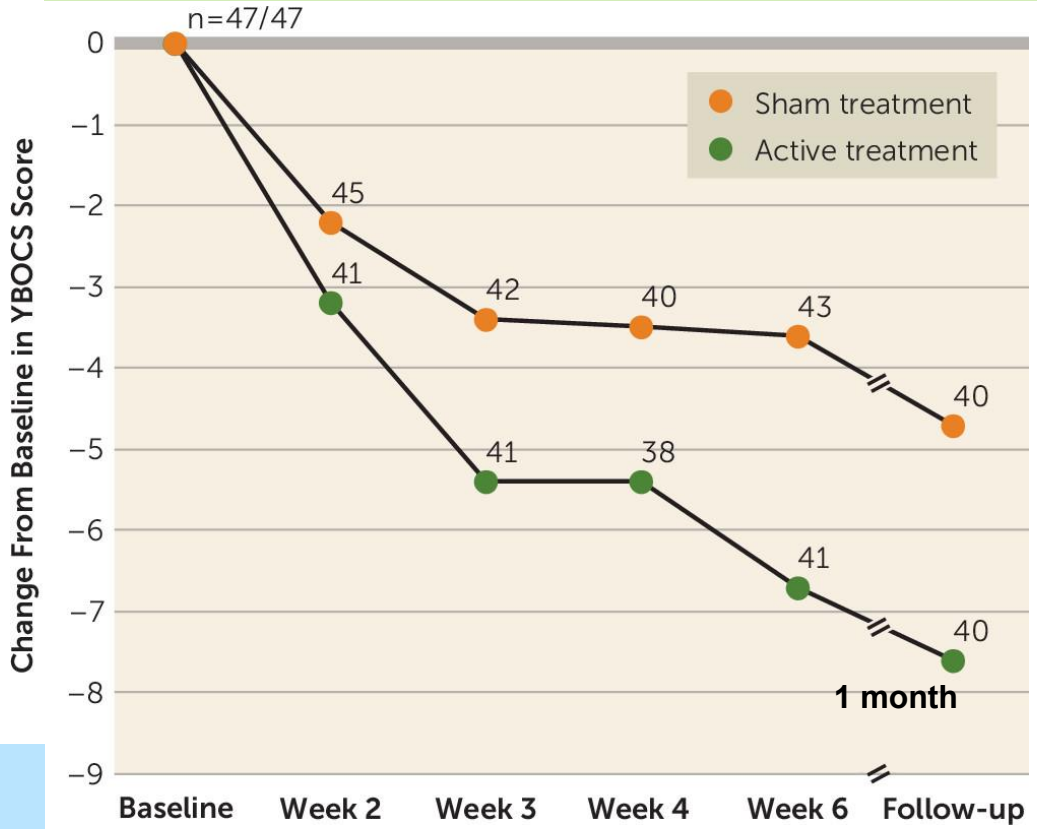
Dalhuisen I, et al. *Am J Psychiatry*. 2024;181(9):806-814.

Deep TMS: FDA Cleared for OCD

Randomized, double blind, sham-controlled trial

99 patients received 6 weeks daily treatment of high-frequency deep TMS targeting the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC) + OCD symptom provocation

Change from baseline in mean YBOCS score for the active and sham dTMS treatment groups:



Response rates: 38.1% (active) vs 11.1% (sham) at end of treatment
Sustained benefit: 45.2% (active) vs 17.8% (sham) at 1-month follow up

mPFC = medial prefrontal cortex; ACC = anterior cingulate cortex; dTMS = deep transcranial magnetic stimulation. YBOCS = Yale-Brown Obsessive Compulsive Scale

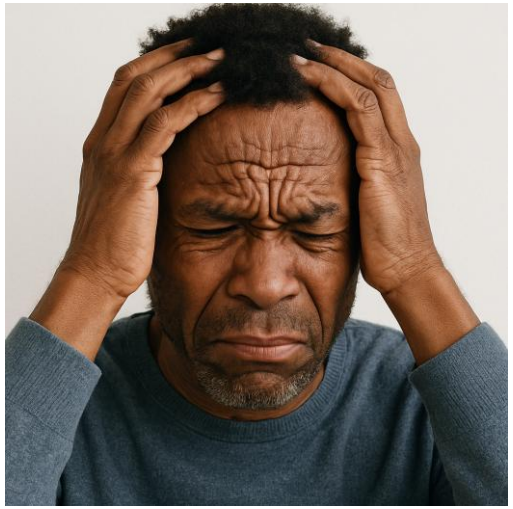
Carmi L, et al. *Am J Psychiatry*. 2019;176(11):931-938. Vidrine R. Psychiatric Times. April 7, 2020. Accessed July 2025. https://www.psychiatrictimes.com/view/integrating-deep-transcranial-magnetic-stimulation-ocd-treatment-algorithm.

rTMS for Generalized Anxiety Disorder?

Preliminary studies suggest that in GAD, high frequency, rTMS may reduce:

NOT FDA-CLEARED

- Excessive worry
- Somatic tension
- Avoidance and hyperarousal
- Emotional dysregulation



Most common target = right dorsolateral prefrontal cortex

- Meta-Analysis of 6 studies encompassing 152 GAD patients: 97 received active treatment and 55 received sham treatment
- rTMS produced a standardized mean difference of −1.857 (confidence interval: −2.219 to −1.494; P<.001) with a prediction interval of −2.55 to −1.16
- **Results suggest a robust effect of rTMS in GAD in the context of limited, heterogeneous studies**

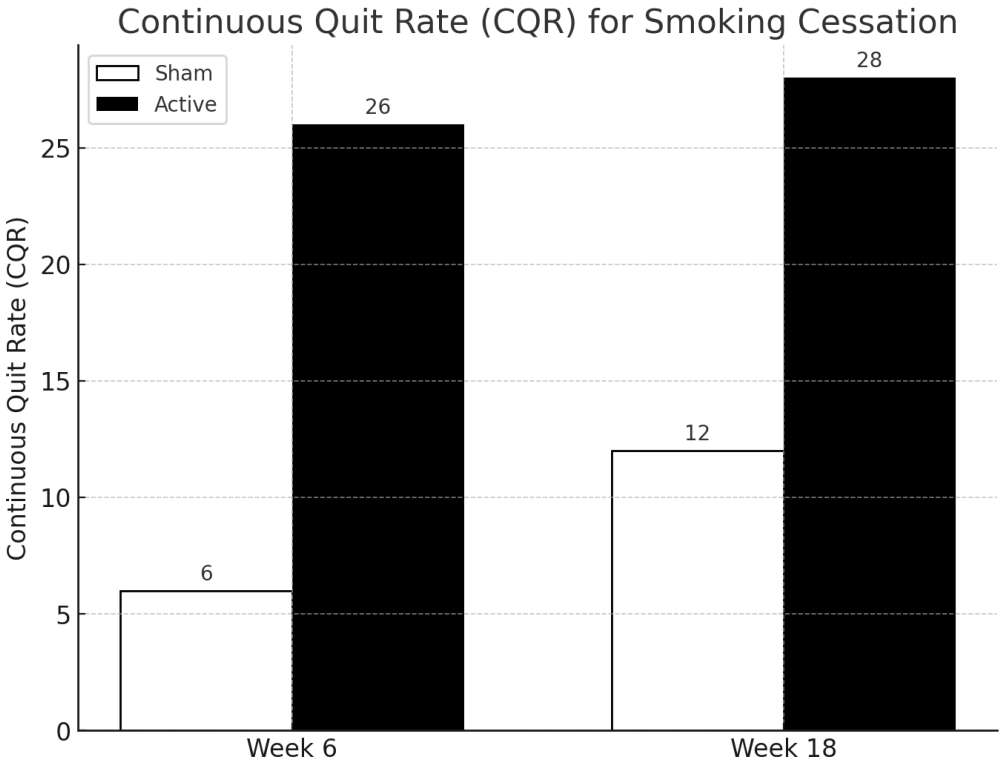
GAD = generalized anxiety disorder.

Parikh TK, et al. *Int J Neuropsychopharmacol*. 2022;25(2):144-146. Dilkov D, et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2017;78:61-65.

rTMS: FDA Cleared for Smoking Cessation

Safe and effective intervention in chronic smokers

- Large, multicenter RCT
- Adults age 22-70
  - Met DSM-5 criteria for tobacco use disorder
  - Chronic smokers (>10 cigarettes/day for >1 year)
  - Had made at least one prior failed attempt to quit (68% had made at least 3 failed attempts)
- 3 weeks of daily rTMS
  - Targets lateral prefrontal cortex and insula during cue-induced craving
  - Followed by once weekly rTMS for 3 weeks

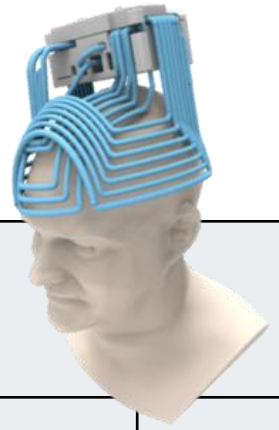


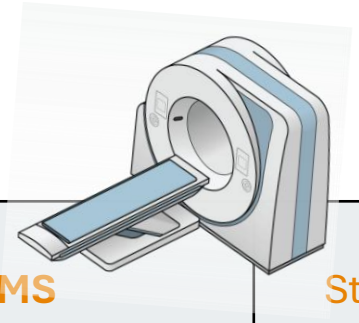
Active treatment more than doubled the quit rate and significantly reduced craving and cigarette consumption relative to sham

RCT = randomized controlled trial; CQR = continuous quit rate.

Zangen A, et al. *World Psychiatry.* 2021;20(3):397-404.

TMS: Different Modalities





	Traditional TMS	Deep TMS	SAINT Stanford Accelerated Intelligent Neuromodulation Therapy
Coil / Placement	figure-8 coil (located using general anatomical measurements)	patented H-Coil inside a padded helmet (stimulating a broad area)	figure-8 coil (located at a custom target using functional MRI data)
Intensity / Dose	120% of motor threshold (MT) 3000 pulses pulses reach a depth of 0.7–1.1 cm	pulses reach a depth of 1.8–3.5 cm	intermittent theta-burst stimulation (iTBS) 1,800 pulses a session
Schedule	One ~19 min session per day for 36+ treatments	One session per day for 20+ days	10 sessions (~10 min each) per day for 5 days; 50 min between sessions
FDA-Cleared	Yes	Yes	Yes

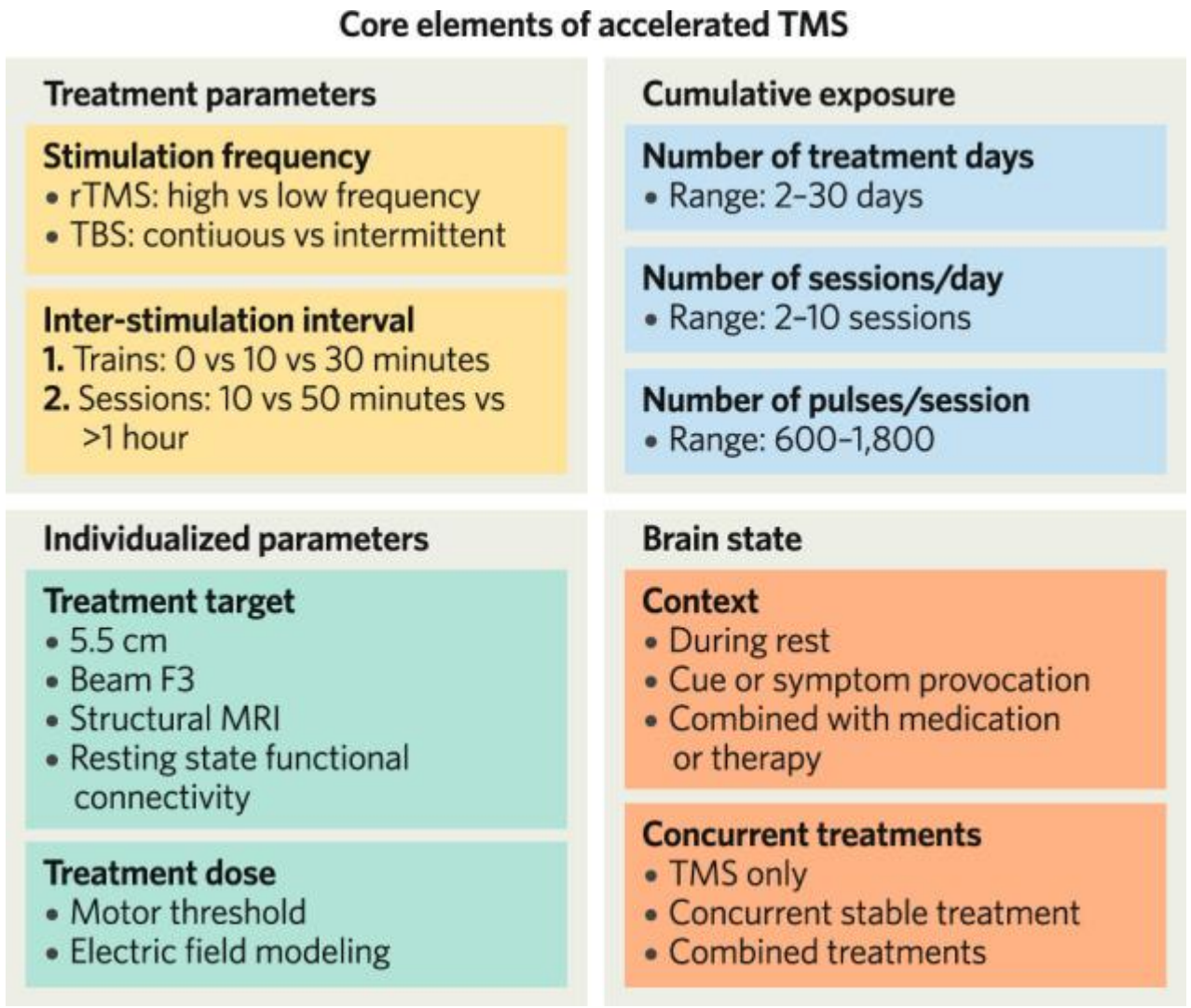
MT = motor threshold.

Cole EJ, et al. *The American Journal of Psychiatry.* 2020;177(8):716-726. BrainsWay. Image. Accessed July 2025. https://www.brainsway.com/how-does-it-work/build-deep-vs-traditional-tms/. Magnus Medical. Image. Accessed July 2025. https://www.magnusmed.com/.

The Future of TMS Is Accelerated

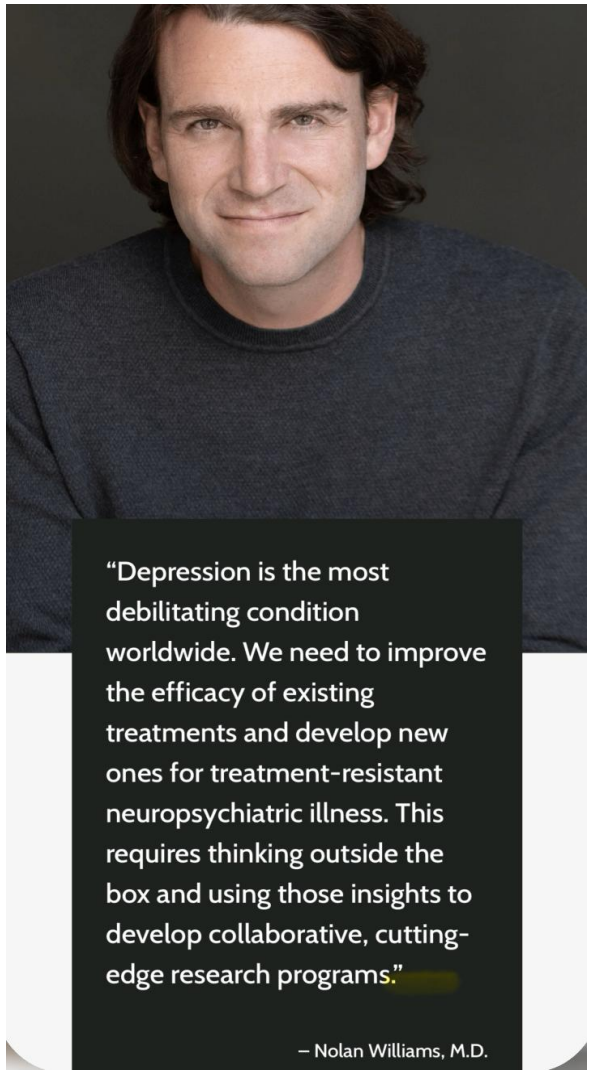
Accelerated protocols generally involve

- **Multiple sessions per day** (eg, 5-10 daily)
- Delivered over a **short course (1-5 days)**
- Typically use **iTBS** due to its brevity and neuroplasticity effects



van Rooij SJH, et al. *Neuropsychopharmacology*. 2024;49(1):128-137.

SAINT Intermittent Theta Burst 5 Day TMS Protocol



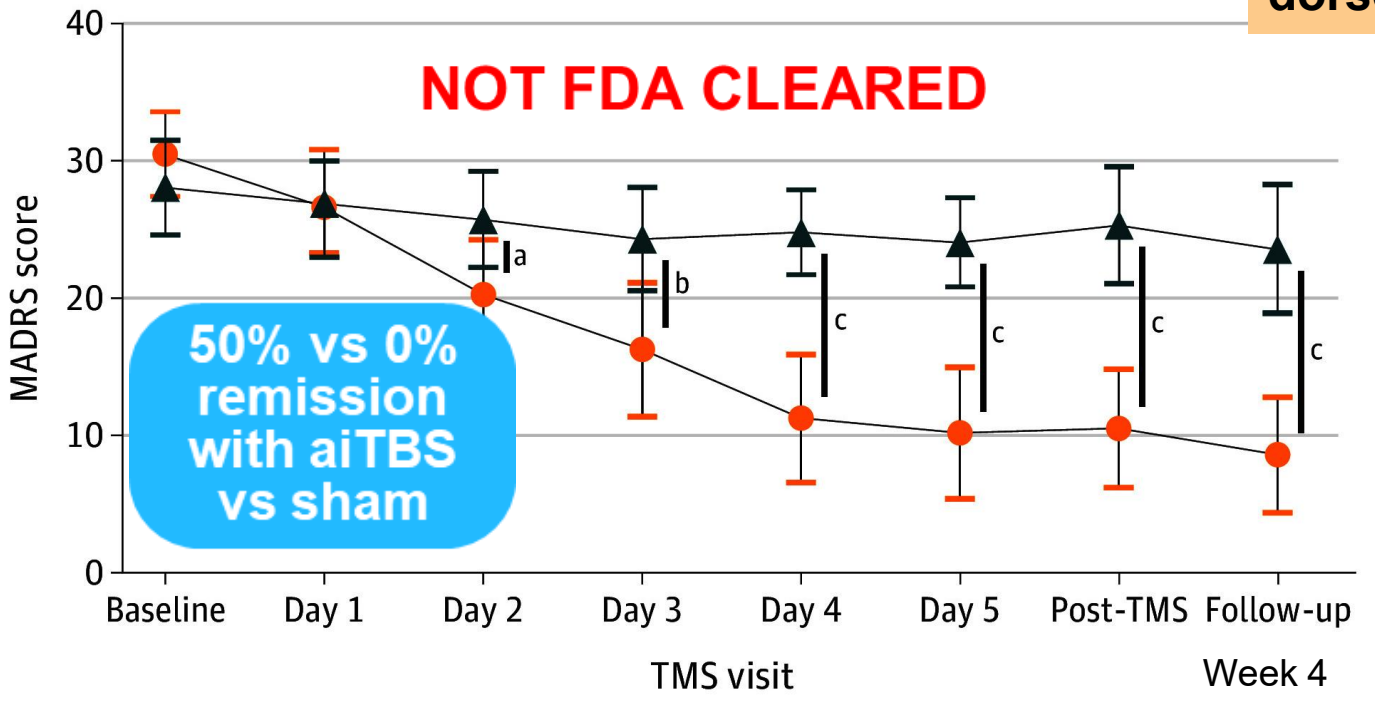
- 10-minute session, followed by 50-minute rest
- 10-times/day for 5 days
- 19 of 21(90%) participants achieved remission within 3 to 5 days

In a small, open-label study, SAINT iTBS significantly reduced depressive symptoms and suicidal ideation in patients with TRD within 5 days, with no negative cognitive side effects.

Magnus Medical. Image. Accessed November 17, 2024. https://www.magnusmed.com/. Cole EJ, et al. *Am J Psych*. 2020;177(8):716-726. Nolan Williams. Image. Accessed October 11, 2025. https://nolanrwilliams.com/

Accelerated Intermittent Theta Burst Stimulation For Treatment-Resistant Bipolar Depression

MADRS scores before and after an iTBS in participants with treatment-resistant bipolar depression



Randomized, double-blind, sham-controlled design using neuronavigated aiTBS applied over the left dorsolateral prefrontal cortex

- All patients were receiving mood stabilizers, optional antidepressants, and no anti-seizure medication
- Intervention included 5 days with 10 sessions per day (active vs sham aiTBS) at 1 session per hour with 18,000 pulses per day at 90% resting motor threshold
- After 5 days of treatment, **50% of participants in the active aiTBS group experienced remission** compared with none in the sham group

[a]*P*<.05; [b]*P*<.01; [c]*P*<.001.

MADRS = Montgomery-Åsberg Depression Rating Scale; aiTBS = accelerated intermittent theta burst stimulation.

Sheline YI, et al. *JAMA Psychiatry*. 2024;81(9):936-941.

Accelerated Intermittent Theta Burst Stimulation For Treatment-Resistant Depression

Randomized, triple-blinded, sham-controlled design using novel protocol of aTBS applied over the LDLPFC

POPULATION

16 Men, 84 Women

Adults with treatment-resistant depression in an acute depressive episode

Mean (SD) age, 41.7 (8.8) y

SETTINGS / LOCATIONS

1 Clinic in São Paulo, Brazil

INTERVENTION

100 Patients randomized

50 Active accelerated theta-burst stimulation (aTBS)
3 Sessions of 1200 pulses each, 30 min apart, per day (total of 45 sessions) targeting the left dorsolateral prefrontal cortex (BeamF3 method)

50 Sham aTBS
Same setup as active group, but without active stimulation

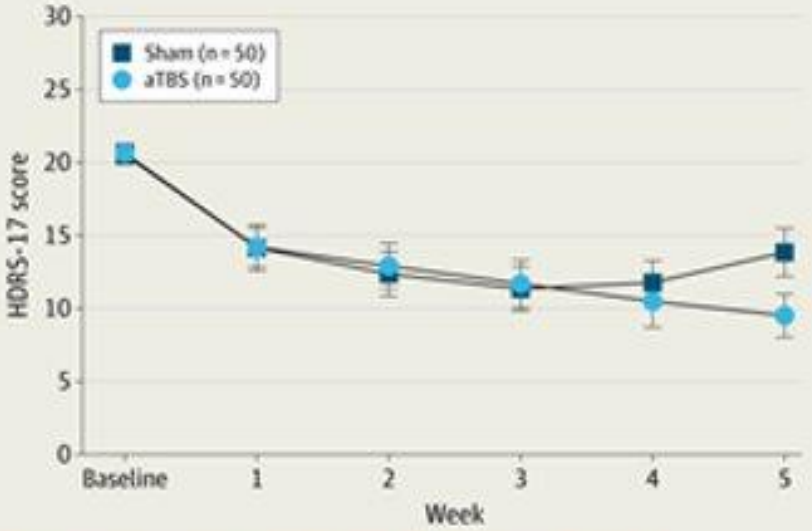
Both interventions were well tolerated, with similar rates of adverse events.

PRIMARY OUTCOME

Hamilton Depression Rating Scale (HDRS-17) score change at week 5 (range 0-52), with lower scores indicating less depression

FINDINGS

The aTBS group showed a greater mean reduction in HDRS-17 scores compared to the sham group



Mean improvement
54.7% vs 31.9% with aTBS vs sham (P<.001)

aTBS = accelerated theta burst stimulation; LDLPFC = left dorsolateral prefrontal cortex.

Ramos MRF, et al. *JAMA Psychiatry*. 2025;82(5):442-450.

Future of TMS? One Day Protocol for TRD

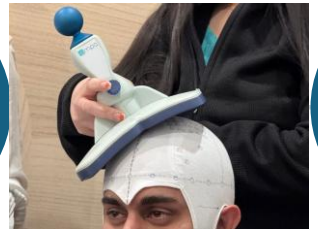
Traditional TMS requires weeks; ONE-D delivers full treatment in one day

1

ONE-D TMS Protocol

- 600-pulse **(iTBS)** per session
- Intensity: **120% of motor threshold (MT)**
- **Left dorsolateral prefrontal cortex (DLPFC)**
- **20 sessions delivered every 30 minutes** over **9.5 hours (1 day)**

2



Pharmacologic Enhancement *(Off-label)*

- **D-cycloserine (125 mg)** and **Lisdexamfetamine (20 mg)**
- Both agents administered **1 hour before TMS treatment**

3

Study Population

- **32 adults** with medication-resistant unipolar depression
- All participants were **TMS-eligible**

Scale at Week 6	Response Rate	Remission Rate
HDRS-17	90%	74%
BDI-II	94%	71%
PHQ-9	90%	58%
GAD-7	93%	77%

Gradual, exponential improvement over 6 weeks.

No discontinuations or serious adverse events

+Mild scalp discomfort

ONE-D = optimized, neuroplastogen-enhanced depression; HDRS = Hamilton Depression Rating Scale; BDI = Beck Depression Inventory; PHQ = Patient Health Questionnaire; GAD = Generalized Anxiety Disorder scale.

Vaughn DA, et al. *Research Square*. 2024 [Epub ahead of print]. DOI:10.21203/rs.3.rs-5679327/v1. Muir OS. The Frontier Psychiatrists. April 7, 2025. Accessed July 2025. https://thefrontierpsychiatrists.substack.com/p/the-scalable-depression-solution.

TMS: Practical Considerations

Adverse Effects

- No cognitive side effects
- **Common**
  - Headache
  - Scalp discomfort
  - Lightheadedness
- **Rare**
  - Activation/induction of mania/ hypomania
  - Hearing loss if no ear protection used
  - Vaso-vagal syncope
  - Seizure (<0.003%)

Downsides:

Not available in every community
Can be costly even with insurance
Scheduling multiple treatments may be challenging

Strengths:

FDA-Cleared for TRD
Covered by most insurances
No medications required
Side effects are mild
Brief treatments
Can drive to/from treatments
Noninvasive

McClintock SM, et al. *J Clin Psychiatry*. 2018;79(1):16cs10905. Centers for Medicare and Medicaid Services (CMS). Accessed July 2025. https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?LCDId=33398.

TMS is noninvasive and is indicated and effective for adults and adolescents with TRD, adults with treatment-resistant OCD, and for smoking cessation.

TMS carries a favorable side effect profile.

TMS is covered by insurance.

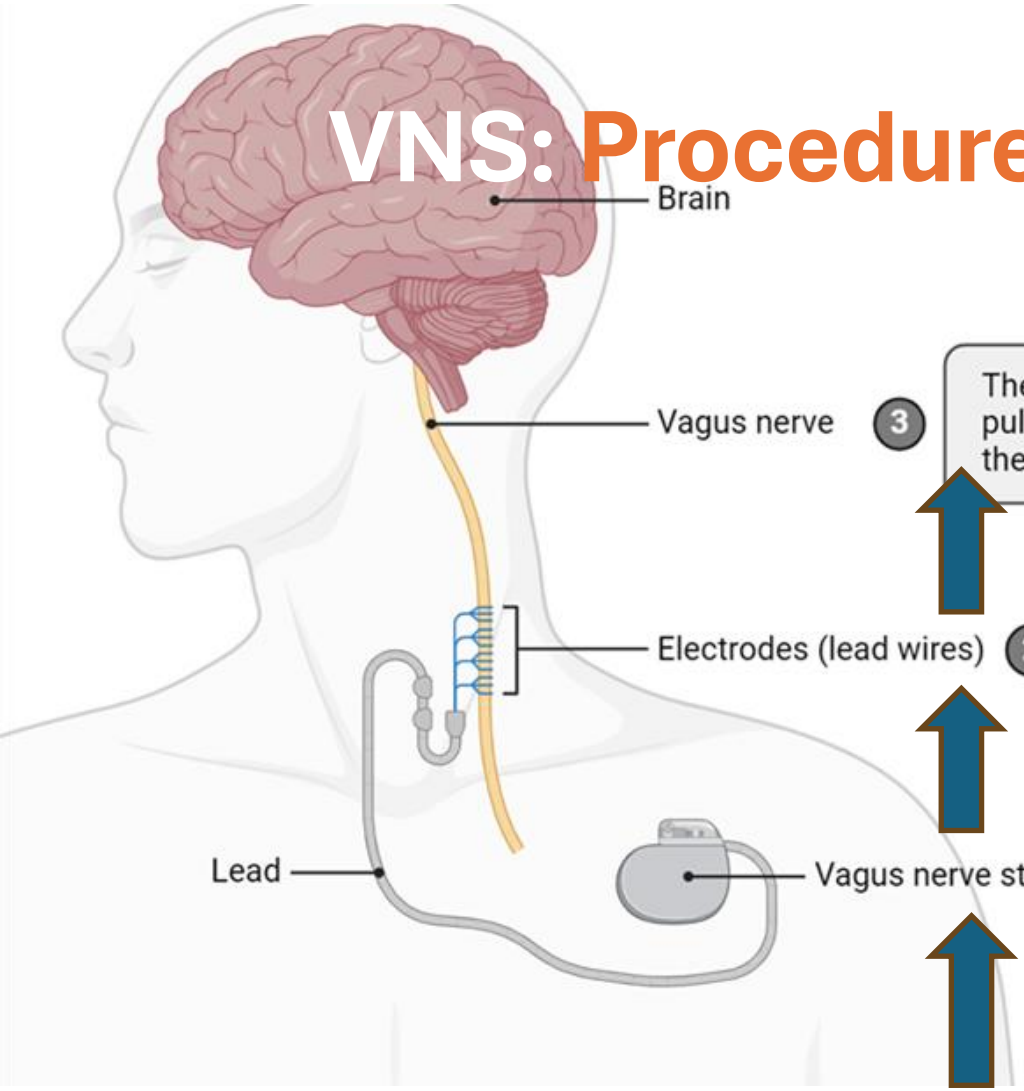
Vagus Nerve Stimulation

FDA-Indicated for:

Treatment-Resistant Depression

*Clinical trials ongoing for Bipolar Depression

VNS: Procedure and Mechanism of Action



1. The stimulator is implanted in the upper left chest.
2. Lead wires attached to the stimulator are wrapped around the left vagus nerve
3. The stimulator sends electrical pulses through the vagus nerve to the brain through wires for therapy
4. Afferent conduit of the vagus nerve interacts with brainstem, subcortical, and cortical regions involved in mood regulation.
5. Cerebral blood flow & activity changes in mood regulation regions such as the anterior insular cortex, prefrontal cortex, and others.
6. In animal models, chronic VNS results in increased activation of serotonergic and noradrenergic neuronal firing patterns.

STEP 1: Neurosurgeon creates small incisions to implant the generator and two small flexible wires in a 45-90 min outpatient procedure

VNS = vagus nerve stimulation.

Kamel LY, et al. *J Neurol Sci*. 2022;434:120171. Jiang W. Image. bioRender. Accessed July 2025. https://www.biorender.com/template/vagus-nerve-stimulation-vns.

VNS: Treatment Logistics

Stimulator Activation Timeline

- Typically 2 – 4 weeks post-implantation

Programming

- Done by a neurologist/psychiatrist in-office using specialized tools: hand-held computer, software, and programming wand

Programming Features

- Adjusts strength, duration, and timing of impulses (typical = 30 sec stimulation on, 5 min off)

Patient Control

- Provided to the patient with a handheld magnet
  - Deliver extra stimulation (sweeping over pulse generator site)
  - Temporarily turn stimulation off (holding magnet in place)
  - Resumes stimulation upon magnet removal

Continuous Operation

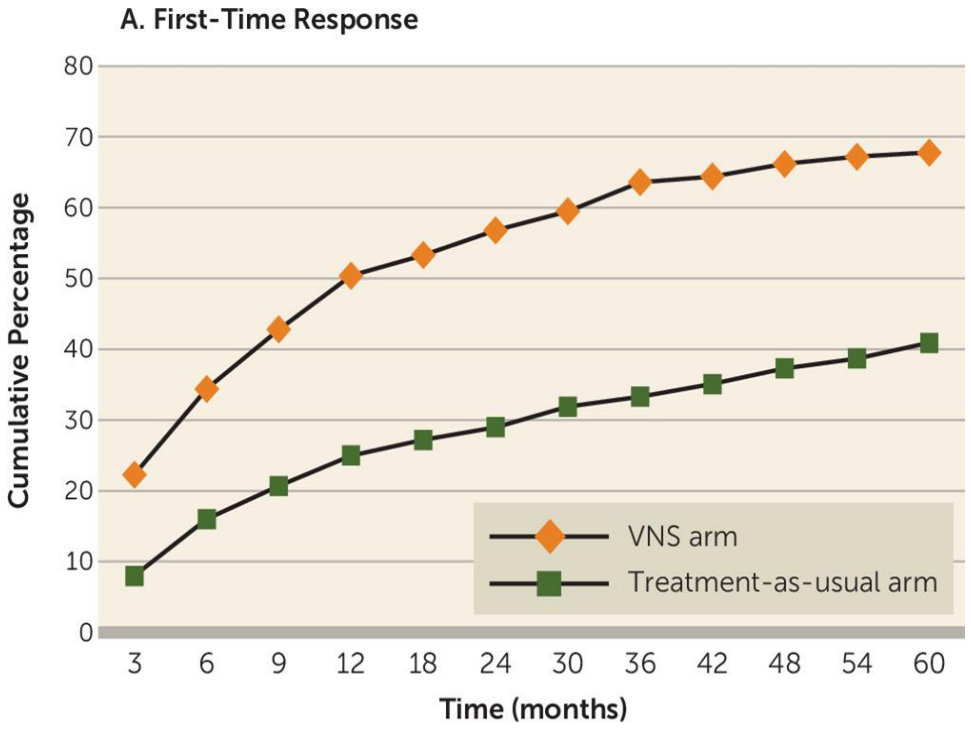
- The device runs on a set cycle unless manually adjusted

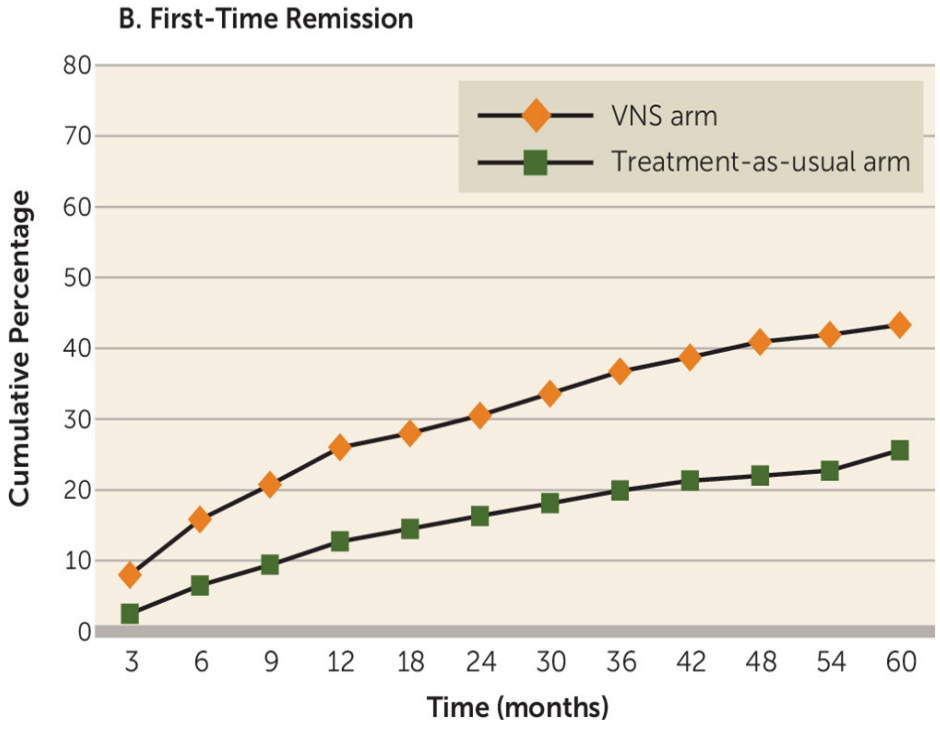
FDA APPROVED FOR TRD IN 2005

American Association of Neurological Surgeons (AANS). April 9, 2024. Accessed November 16, 2024. https://www.aans.org/patients/conditions-treatments/vagus-nerve-stimulation/.
The Royal Children's Hospital Melbourne. Image. Accessed July 2025. https://www.rch.org.au/neurology/patient_information/vagus_nerve_stimulation/.

VNS: Efficacy and Safety

Treatment as Usual With or Without Adjunctive VNS





Most Common AEs
- Voice alteration
- Cough
- Dyspnea
- Dysphagia
- Neck pain
- Paresthesia

Antidepressant benefits of VNS in TRD occurred over several months and were long-lasting: 67.6% 5-yr response, 43.3% remission (median time to response: 12 months)

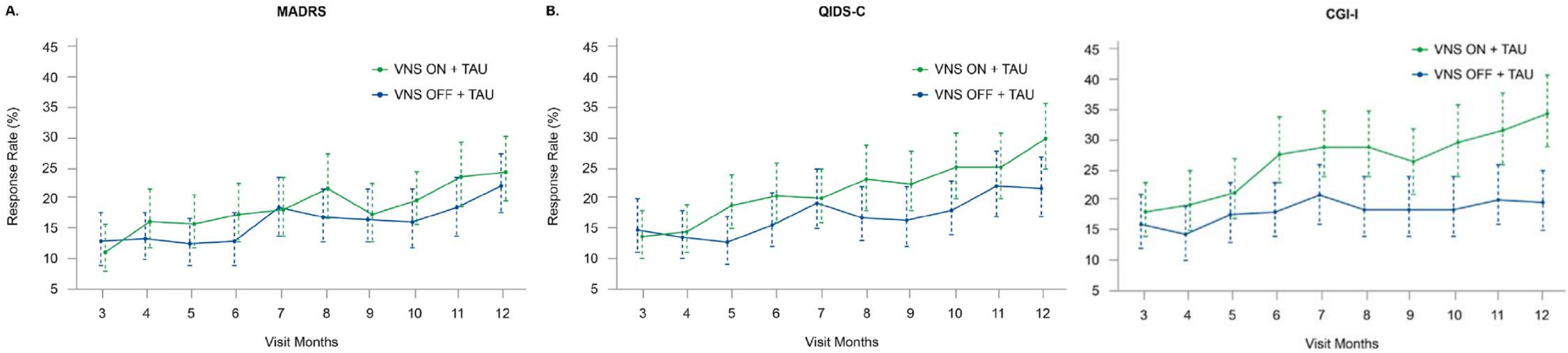
AE = adverse effect.

Aaronson ST, et al. *Am J Psychiatry*. 2017;174(7):640-648. Rush AJ, et al. *Biol Psychiatry*. 2005;58(5):347-354. Ben-Menachem E. *J Clin Neurophysiol*. 2001;18(5):415-418.

VNS in TRD:

A 1-Year Randomized, Sham-Controlled Trial

Response rates by visit month:



Active VNS (vs sham) demonstrated significantly more percent time in

- ✓ response by QIDS-SR (25.2 % vs 19.8 % sham) and CGI-I (26.7 % vs 18.2 % sham)
- ✓ partial response (PR; symptom improvement ≥30 %) on the CGI-I (53.8 % vs 39.8 % sham) and QIDS-C (39.6 % vs 30.7 % sham)

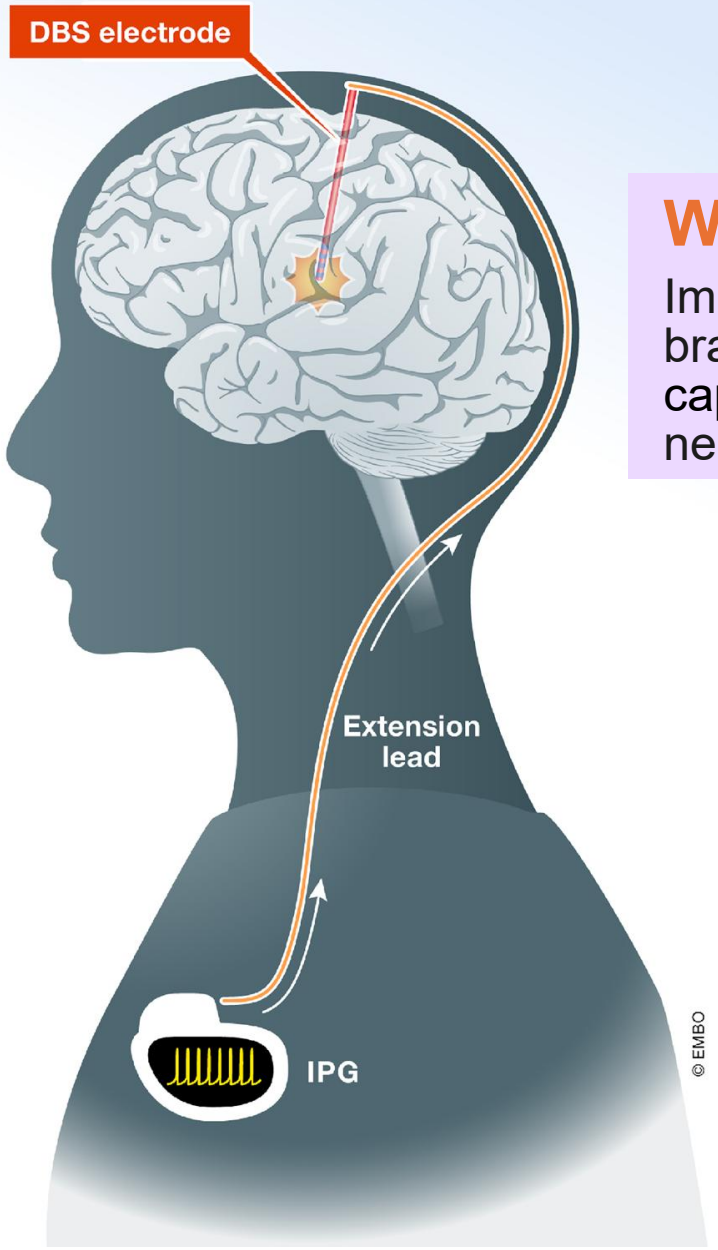
CGI-I = Clinical Global Impression–Improvement; QIDS-C = Quick Inventory of Depressive Symptomatology–Clinician; QIDS-SR = Quick Inventory of Depressive Symptomatology–Self-Report; TAU = treatment as usual.
Conway CR, et al. *Brain Stimul*. 2025;18(3):676-689.

Deep Brain Stimulation

FDA-Approved for:

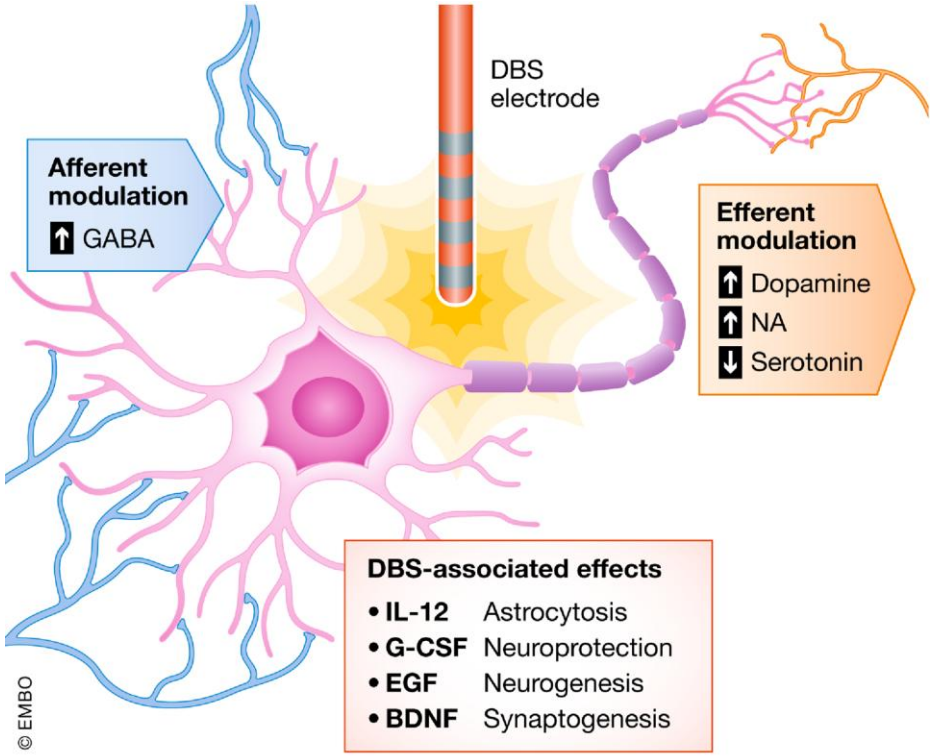
Obsessive Compulsive Disorder

DBS: Procedure & Effects



What is happening here?

Implanted neurostimulation device - -> generates electrical fields in targeted deep brain (For OCD -> typically bilateral stimulation of the anterior limb of the internal capsule) - -> altered firing pattern of neural circuits --> changes in neurotransmitter dynamics and protein expression



Molecular Effects:

Inhibitory and excitatory neurotransmitters are up- or downregulated as afferent or efferent fibers are located in the volume of tissue activated

DBS = deep brain stimulation; IPG = internal pulse generator.

Jakobs M, et al. *EMBO Mol Med*. 2019;11(4):e9575. Borron BM, Dougherty DD. *Focus (Am Psychiatr Publ)*. 2022;20(1):55-63.

Deep Brain Stimulation for OCD

FDA Approval

2009 for chronic, severe treatment-resistant OCD under a Humanitarian Device Exemption as an adjunct to medications in adult patients who have failed at least 3 SSRIs

Efficacy

Systematic review found DBS was an effective and safe alternative for **2 out of 3** severe, treatment-resistant OCD patients who received it

Unknowns

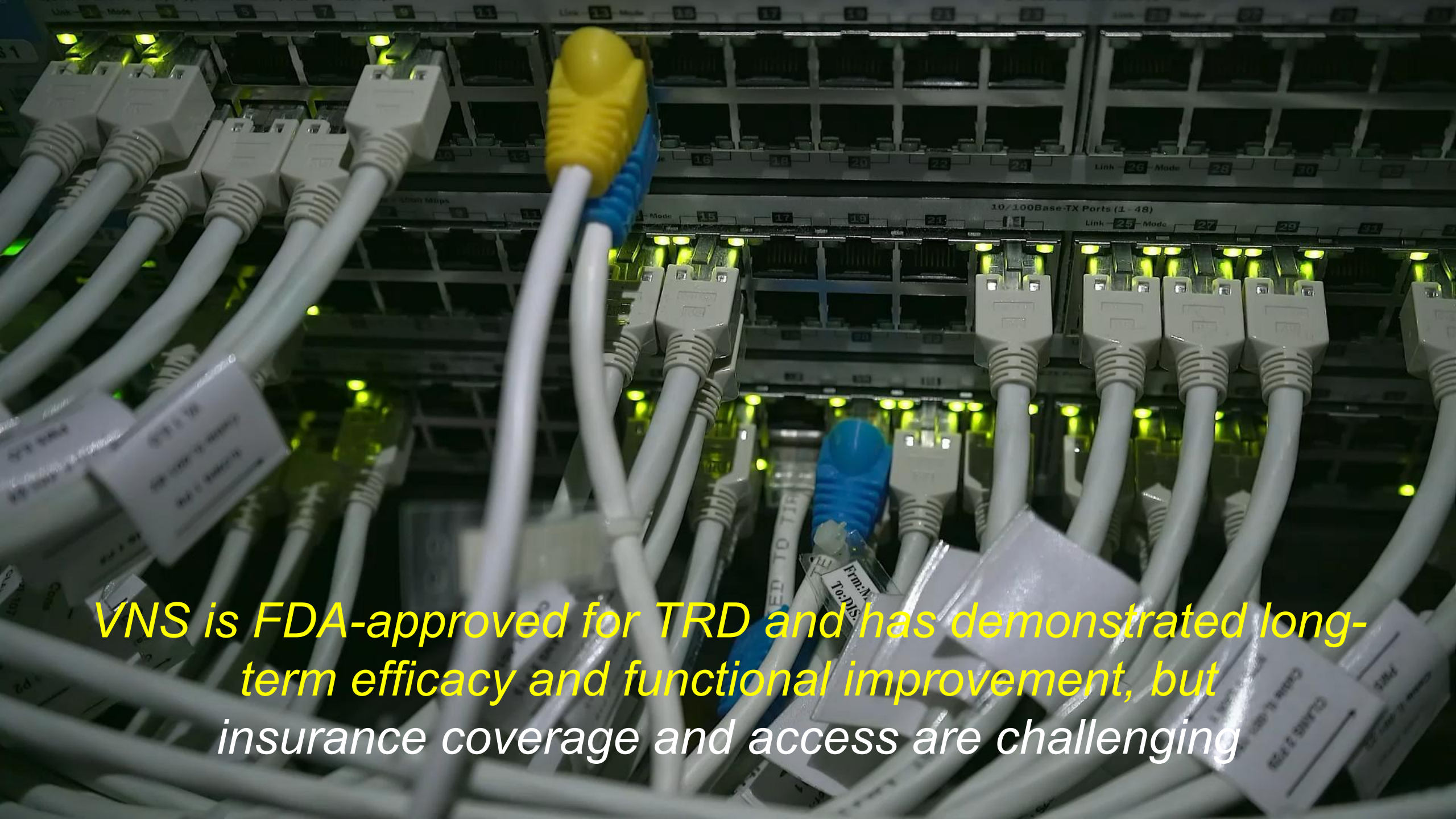
- Full risks and benefits
- Optimal anatomical targets
- Best stimulation parameters
- Long-term effects
- The possibility of establishing clinical or biological factors associated with response

Barriers

- Invasive neurosurgery with limited availability outside of major academic medical centers
- Limited insurance approval

SSRI = selective serotonin reuptake inhibitor.

Mar-Barrutia L, et al. *World J Psychiatry*. 2021;11(9):659-680. Borron BM, Dougherty DD. *Focus (Am Psychiatr Publ)*. 2022;20(1):55-63.



VNS is FDA-approved for TRD and has demonstrated long-term efficacy and functional improvement, but
insurance coverage and access are challenging

Ketamine

FDA-Indicated for:

Anesthesia ONLY

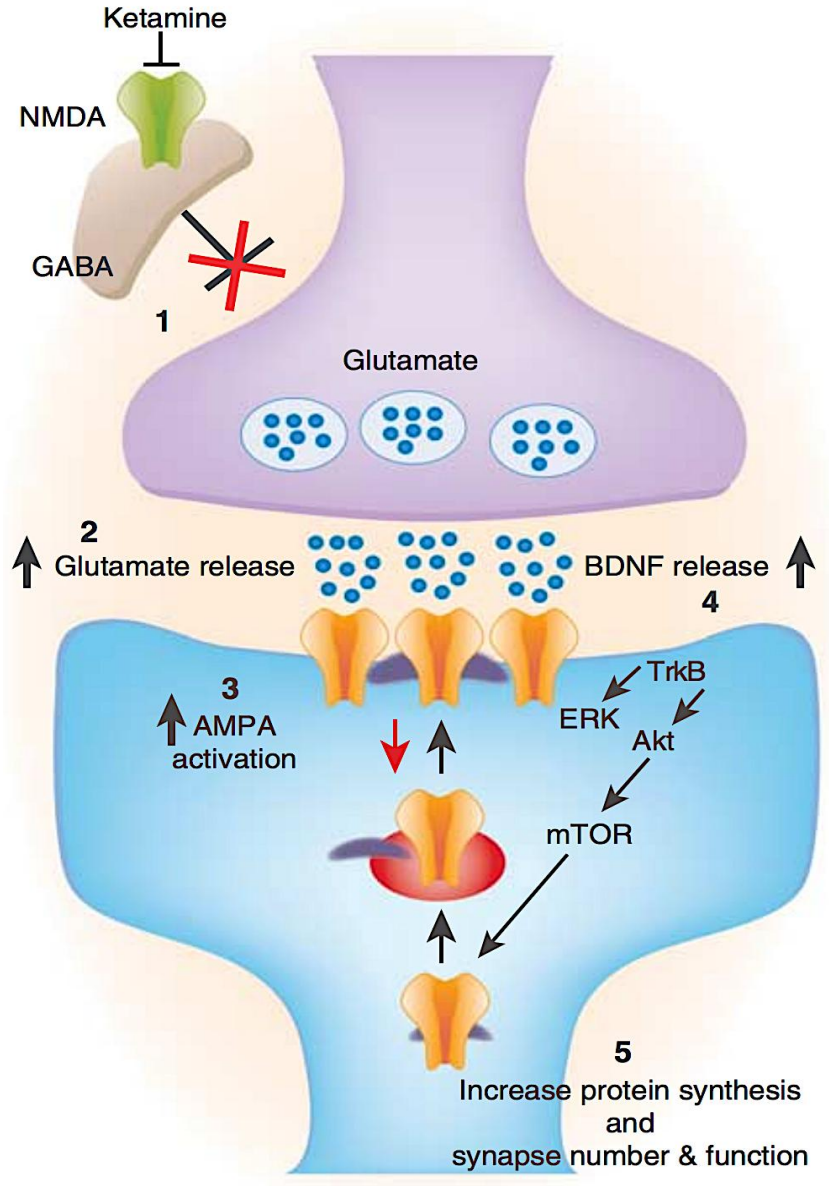
No Indication for Psychiatric Conditions

NMDA Receptor Antagonist

Trigger rapid synaptic plasticity: → By blocking NMDA receptors, these agents induce a glutamate surge that activates AMPA receptors and promotes brain-derived neurotrophic factor (BDNF) release.

Enhance synaptogenesis: → NMDA antagonism initiates downstream signaling (eg, mTOR pathway), leading to increased dendritic spine growth and synaptic connectivity.

Facilitate rapid circuit-level reorganization: → This plasticity enables rebalancing of dysfunctional fronto-limbic circuits, supporting faster recovery of mood and cognitive function.



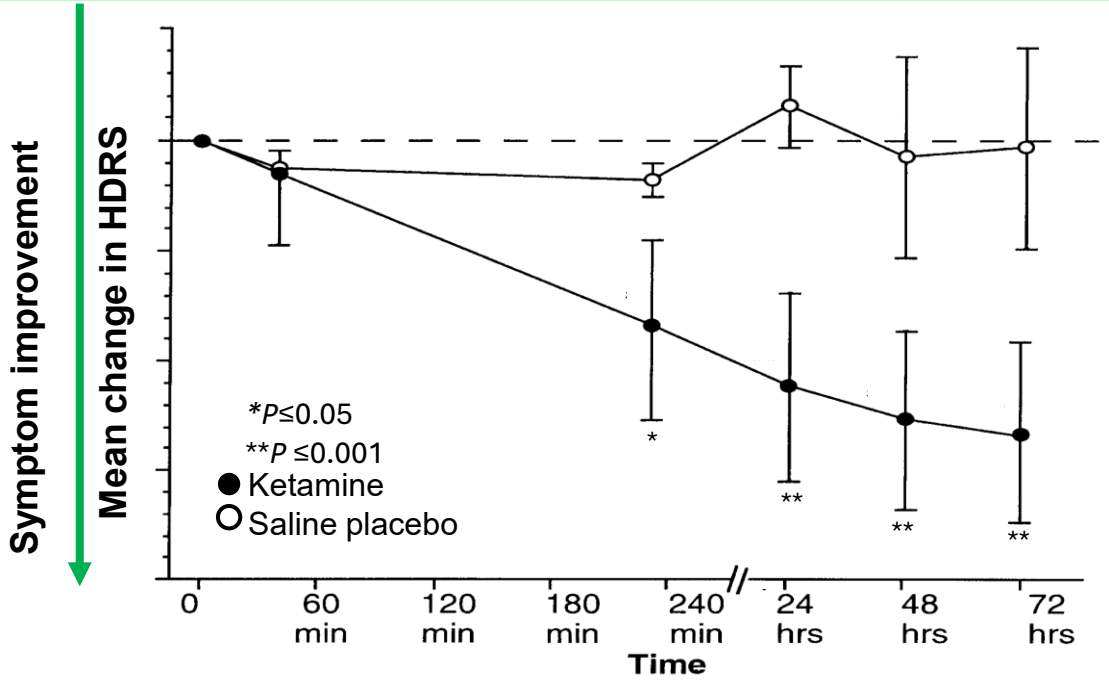
BDNF = brain-derived neurotrophic factor; NMDA = N-methyl-D-aspartate; mTOR = mammalian target of rapamycin.

Page CE, et al. *Mol Psychiatry*. 2024;29(12):3802-3813. Sanacora G, et al. *Neuropsychopharmacology*. 2015;40(2):259-267.

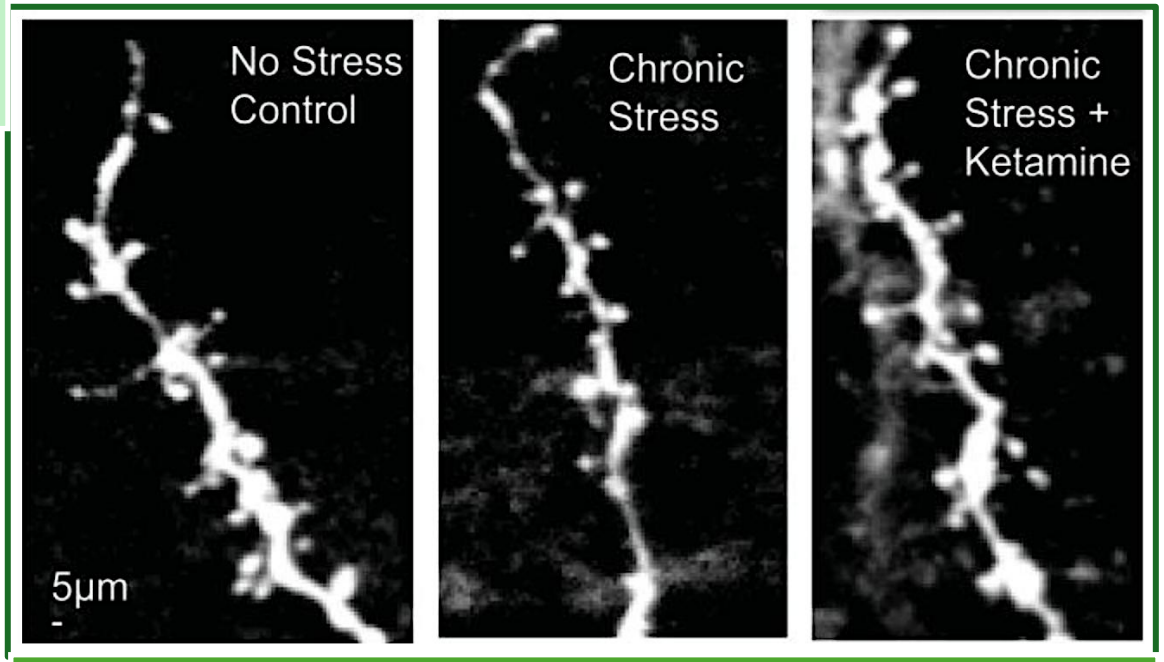
Ketamine for Major Depression

A potent NMDA receptor antagonist NOT approved for psychiatric indications

Double-blind crossover study comparing a single IV infusion of racemic ketamine 0.5 mg/kg or IV saline to 8 patients with depression



The ketamine group separated from placebo at 4 hours and the effect was sustained for ≥ 3 days



High-powered microscopy demonstrated that a single dose of ketamine could produce rapid synaptogenesis in rat pyramidal neurons.

HDRS = Hamilton Depression Rating Scale. Berman RM, et al. *Biol Psychiatry*. 2000;47(4):351-354. Sanacora G, et al. *JAMA Psychiatry*. 2017;74(4):399-405. Li N, et al. *Biological Psychiatry*. 2011;69(8):754-761.

Ketamine

Mechanism of Action

- NMDA receptor antagonist → enhances glutamate transmission and synaptic plasticity

Clinical Uses

- All off-label in psychiatry, backed by clinical studies
- Treatment-Resistant Depression (TRD)
- Bipolar depression
- PTSD, anxiety disorders
- Substance use disorders (alcohol, opioid, cocaine)
- Eating disorders

Forms of Administration

- Intravenous, intramuscular, intranasal, oral

Benefits

- Rapid reduction in depressive symptoms (hours to days)
- Reduction in acute suicidal thoughts

Considerations

- Short duration of effect without maintenance
- Need for monitoring due to potential dissociation, blood pressure elevation, and misuse risk
- Best delivered within a structured treatment program

Important!

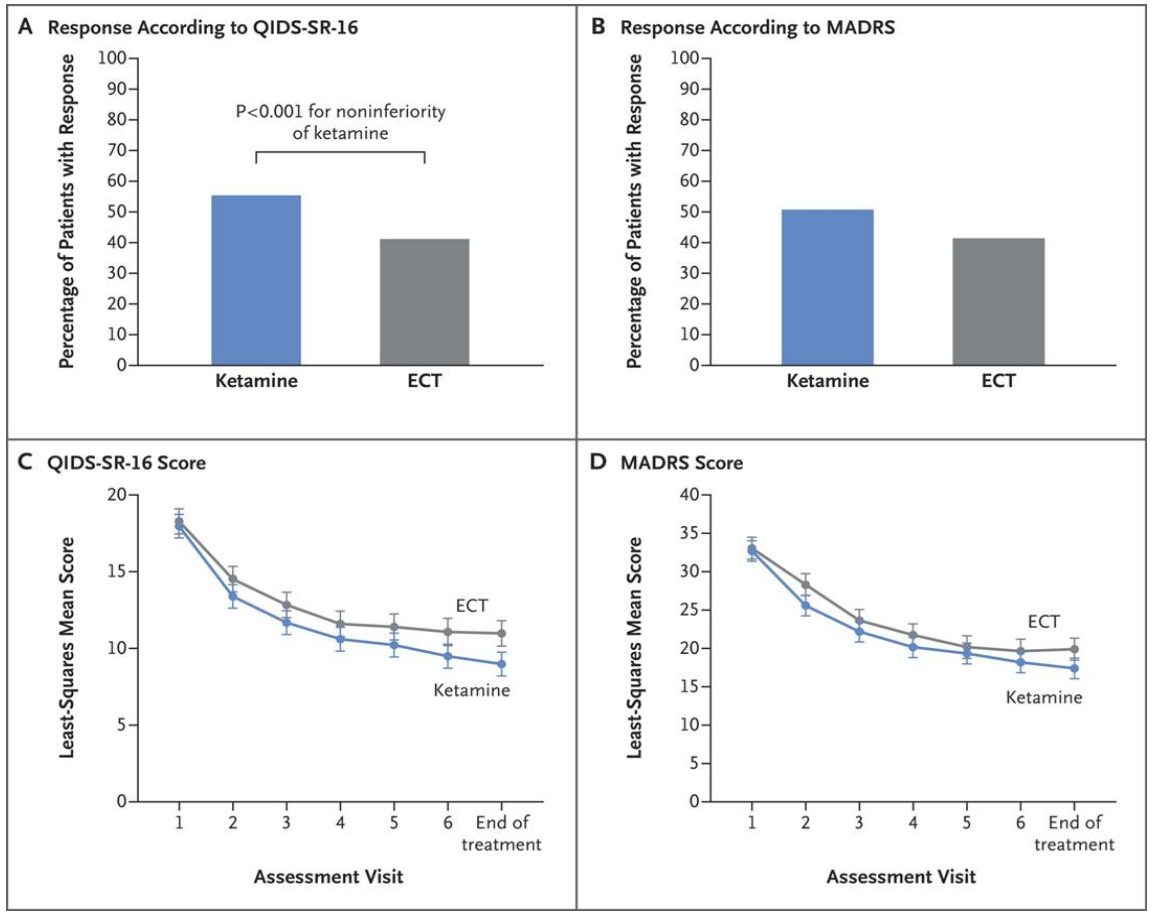
- ✓ Follow state and federal DEA guidelines; Pro tip = follow esketamine REMS
- ✓ Always monitor patients in medical settings by trained healthcare professionals
- ✓ Common side effects: dissociation, dizziness, sedation, elevated blood pressure, nausea, vomiting, anxiety, headache, perceptual disturbances
- ✓ Use with caution in any patients with a history of substance use disorder
- ✓ Typical dose = 0.5 mg of ketamine per kg (patient weight)

PTSD = posttraumatic stress disorder; REMS = Risk Evaluation and Mitigation Strategy.

Walsh Z, et al. *BJPsych Open*. 2021;8(1):e19. Yavi, M, et al. *Discov Ment Health*. 2022;2(1):9.

Ketamine vs ECT for TRD

Response to Ketamine and ECT According to the QIDS-SR-16 and MADRS during the Initial 3-Week Treatment Phase



Conclusions

- Among adults with TRD without psychosis, IV ketamine was noninferior to ECT in this 3-week study
- The incidence of moderate or severe adverse events, including musculoskeletal adverse events, was higher in the ECT group than in the ketamine group
- More patients withdrew from the ECT group than from the ketamine group before treatment

Shi ZM, et al. *J Affect Disord*. 2025;371:45-53. Anand A, et al. *N Engl J Med*. 2023;388(25):2315-2325.

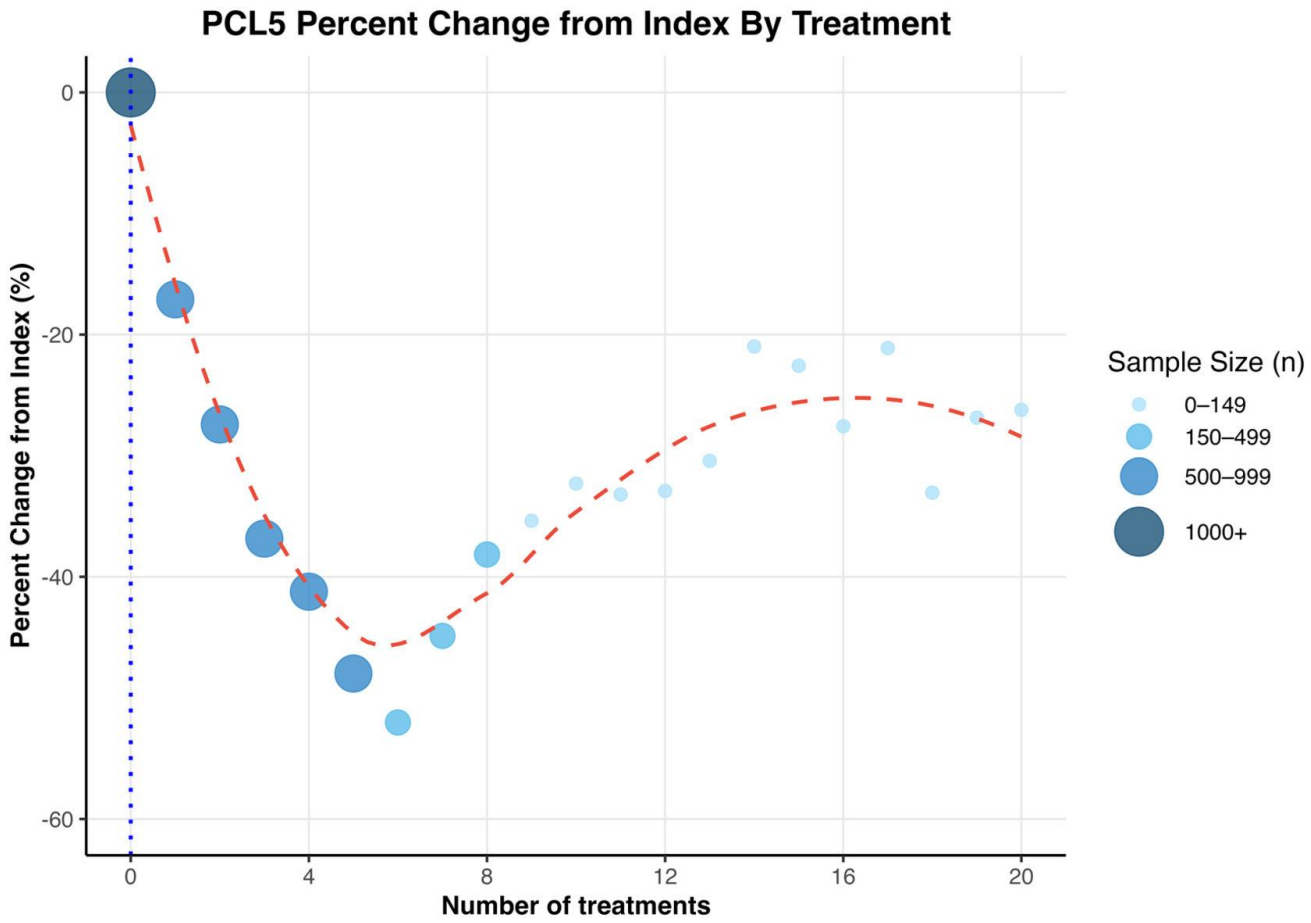
Ketamine & PTSD: Real World Retrospective Study

In a large real-world sample of 8,136 PTSD patients (87 % with comorbid depression), Ketamine Intravenous Therapy (KIT) significantly reduced PTSD and depression symptoms.

Greatest symptom reductions occurred within the first 3 treatments, typically at doses of 0.6-0.8mg/kg.

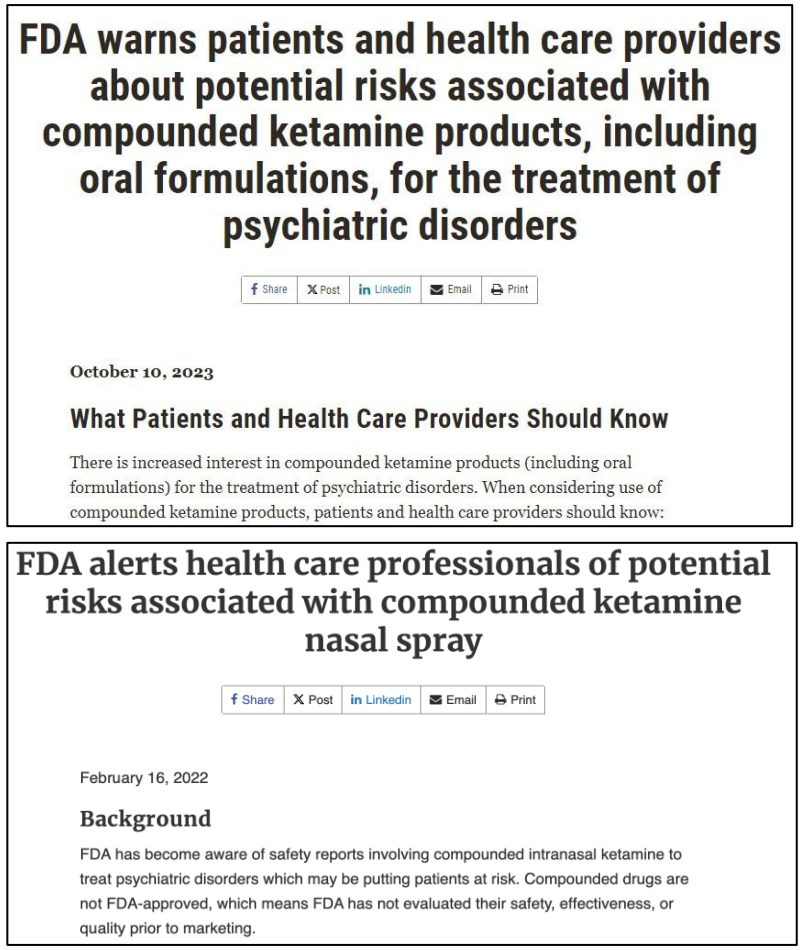
A logarithmic model best described symptom change, suggesting **diminishing returns with additional treatments** beyond the early phase.

Sensitivity analyses on PTSD patients without comorbid MDD confirmed that KIT effectively reduced PTSD symptoms, demonstrating direct therapeutic benefits beyond treating co-occurring depression.



PTSD = post traumatic stress disorder. McInnes, L. A., Worley, M., Shih, E., et al. "A Retrospective Analysis of Ketamine Intravenous Therapy for PTSD and Comorbid Depression in Outpatient Psychiatric Patients." Psychiatry Research, 2025.

FDA Compounded Ketamine Warnings: Just don't…



FDA warns patients and health care providers about potential risks associated with compounded ketamine products, including oral formulations, for the treatment of psychiatric disorders

Share | Post | Linkedin | Email | Print

October 10, 2023

What Patients and Health Care Providers Should Know

There is increased interest in compounded ketamine products (including oral formulations) for the treatment of psychiatric disorders. When considering use of compounded ketamine products, patients and health care providers should know:

FDA alerts health care professionals of potential risks associated with compounded ketamine nasal spray

Share | Post | Linkedin | Email | Print

February 16, 2022

Background

FDA has become aware of safety reports involving compounded intranasal ketamine to treat psychiatric disorders which may be putting patients at risk. Compounded drugs are not FDA-approved, which means FDA has not evaluated their safety, effectiveness, or quality prior to marketing.

- Ketamine is not FDA-approved for the treatment of any psychiatric disorder
- Compounded drugs are not FDA–approved
- Use of compounded ketamine without monitoring by onsite health care providers …may put patients at risk for serious adverse events, misuse, and abuse
- In addition to the concerns regarding the short-term use of compounded ketamine, the overall benefit-risk profile of ketamine for the treatment of psychiatric disorders is unknown

FDA. Accessed September 10, 2024. https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-professionals-potential-risks-associated-compounded-ketamine-nasal-spray. FDA. Accessed September 10, 2024. https://www.fda.gov/drugs/human-drug-compounding/fda-warns-patients-and-health-care-providers-about-potential-risks-associated-compounded-ketamine.

Esketamine

FDA-Indicated for:

Treatment-Resistant Depression in Adults as Monotherapy or with Oral Antidepressant

Major Depressive Disorder with Suicidal Ideation

Esketamine Is a Glutamatergic Antidepressant

Schedule III controlled substance (CIII) FDA approved for adults with TRD Mar 2019, MDD with suicidal ideation Aug 2020, and MONOTHERAPY in Jan 2025

BOXED WARNINGS: Due to the risks of sedation, dissociation, respiratory depression, abuse and misuse, as well as suicidal ideation in adolescents and young adults, esketamine is only available at certified treatment centers through a restricted distribution program

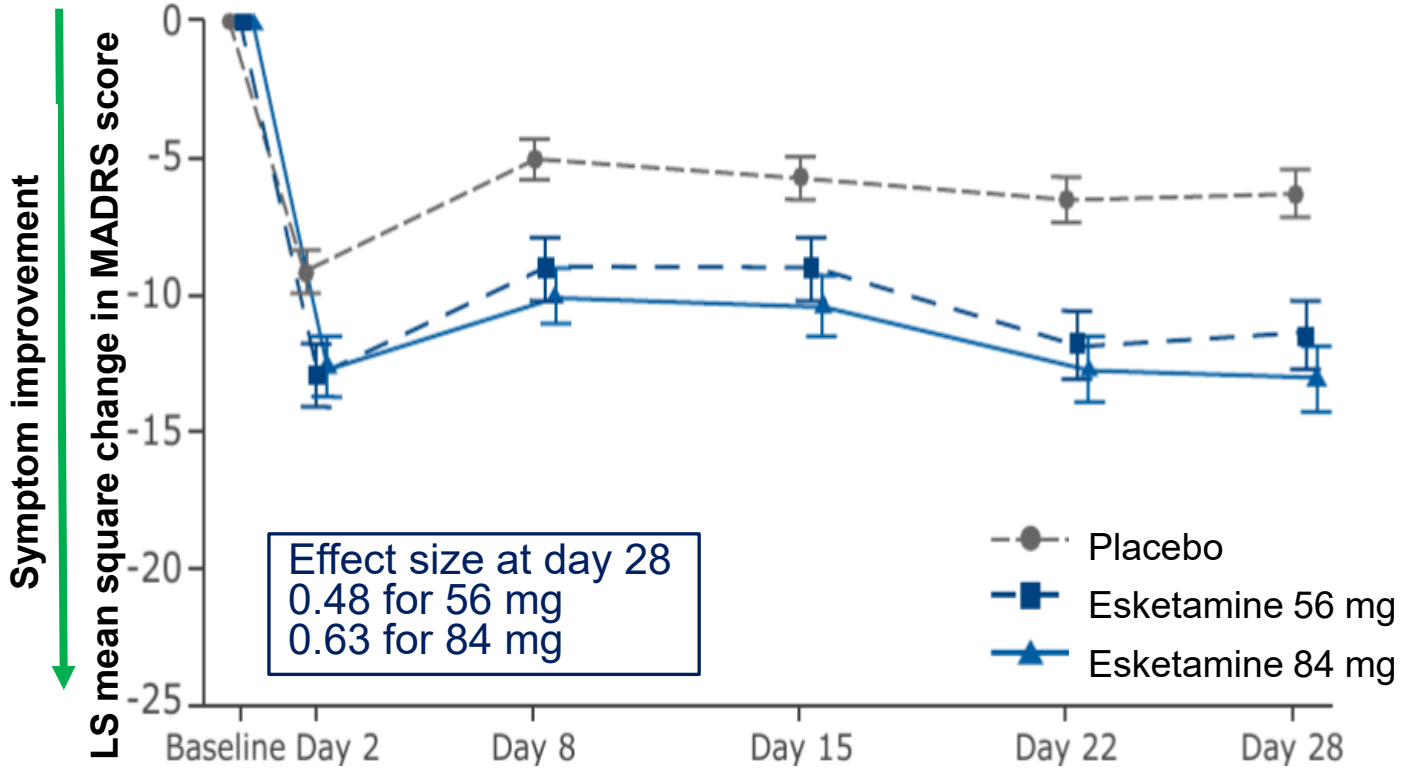
Self-administered nasal spray 28 mg each

- **Requirements**: Patients must be monitored in a certified treatment center by a licensed healthcare provider (MD, DO, APRN, PA-C) for at least 2 hours after administration- with submission of patient monitoring form submitted within 7 days
- **Monitoring**: Measure pulse ox and blood pressure prior to dosing, 40 minutes post-dose and subsequently as clinically warranted until values decline, in addition to 2 hours post first dose. Do not start dose until BP < 140/90
- **Contraindications**: aneurysmal vascular disease, arteriovenous malformation, history of intracerebral hemorrhage
- **REMS:** Patients, health care setting and pharmacy must be certified
- **Restrictions:** Patients cannot drive or operate heavy machinery for the rest of the day

REMS = risk evaluation mitigation strategy

Drugs@FDA: FDA Approved Drugs. Accessed February 27, 2025. www.accessdata.fda.gov/scripts/cder/daf/.

Esketamine Monotherapy for TRD: Phase 4 Trial



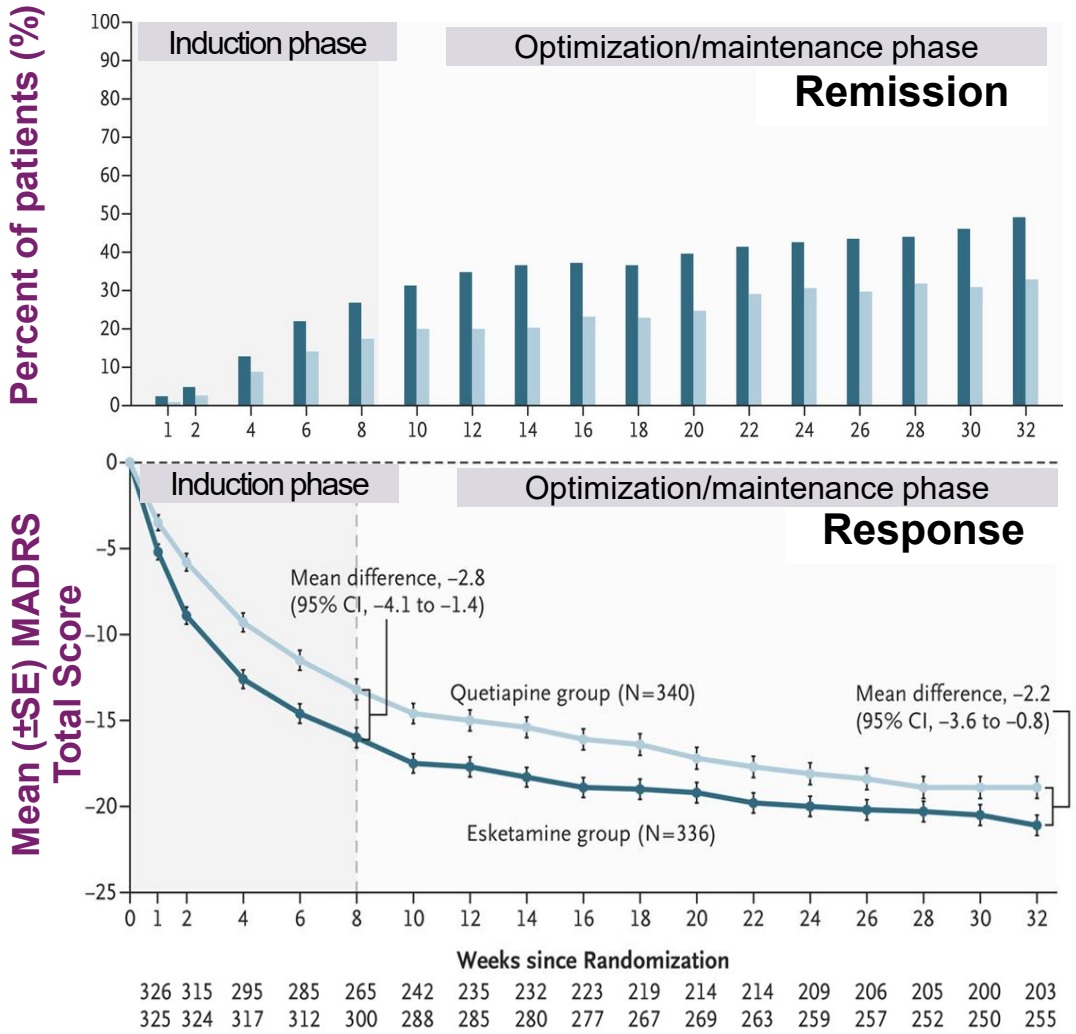
Treatment of TRD with esketamine nasal spray 56 mg or 84 mg reduced MADRS scores by 5 and 7 points, respectively, compared with placebo.

Adverse Events in Double-Blind Phase	Esketamine		Placebo
	56 mg (N=105)	84 mg (N=121)	N=250
Nausea	23%	26%	8%
Dissociation	22%	26%	3%
Dizziness	21%	22%	7%
Headache	18%	20%	9%
Feeling drunk	8%	7%	1%
Anxiety	5%	8%	1%
Fatigue	8%	6%	4%
Vomiting	5%	8%	<1%
Insomnia	6%	4%	4%
Somnolence	6%	3%	1.6%
D/C due to AEs	<1%	1%	4%

D/C = discontinuation.

Janik Aet al. Presented at 2024 Am Soc Clin Psychopharmacol meeting. Accessed May 10, 2025. https://www.jnjmedicalconnect.com/media/attestation/congresses/neuroscience/2024/ascp/efficacy-and-safety-of-esketamine-nasal-spray-as-monotherapy-in-adults-with-treatmentresistant-depre.pdf

Adjunctive Esketamine Superior to Adjunctive Quetiapine-XR



51%

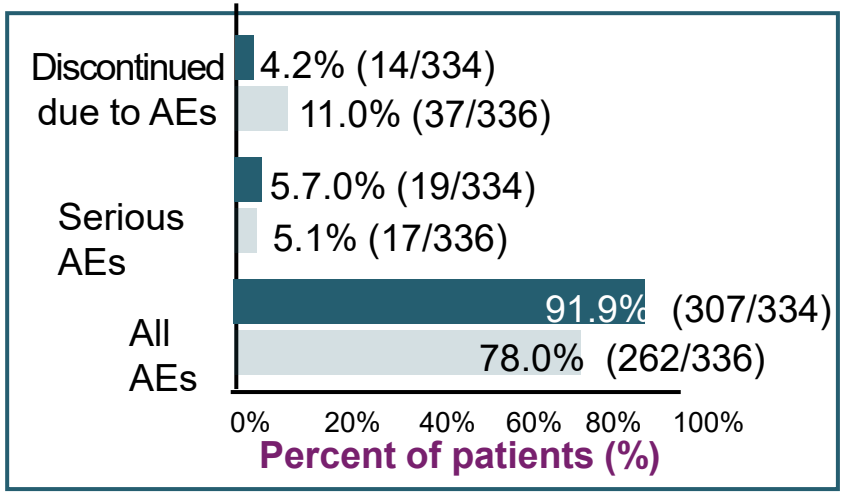
More likely to achieve remission (week 8) OR=1.74 (95% CI: 1.20-2.52) *P*=.003

72%

More likely to remain relapse-free (week 32) OR=1.72 (95% CI: 1.15-2.16)

SAFETY AND TOLERABILITY

- More AEs with esketamine
- Similar rates of serious AEs
- Fewer discontinued treatment with esketamine than quetiapine



LIMITATIONS

- Open-label study
- Quetiapine may not represent outcomes of all antipsychotics

Reif A, et al. *N Engl J Med*. 2023;389:1298-1309.

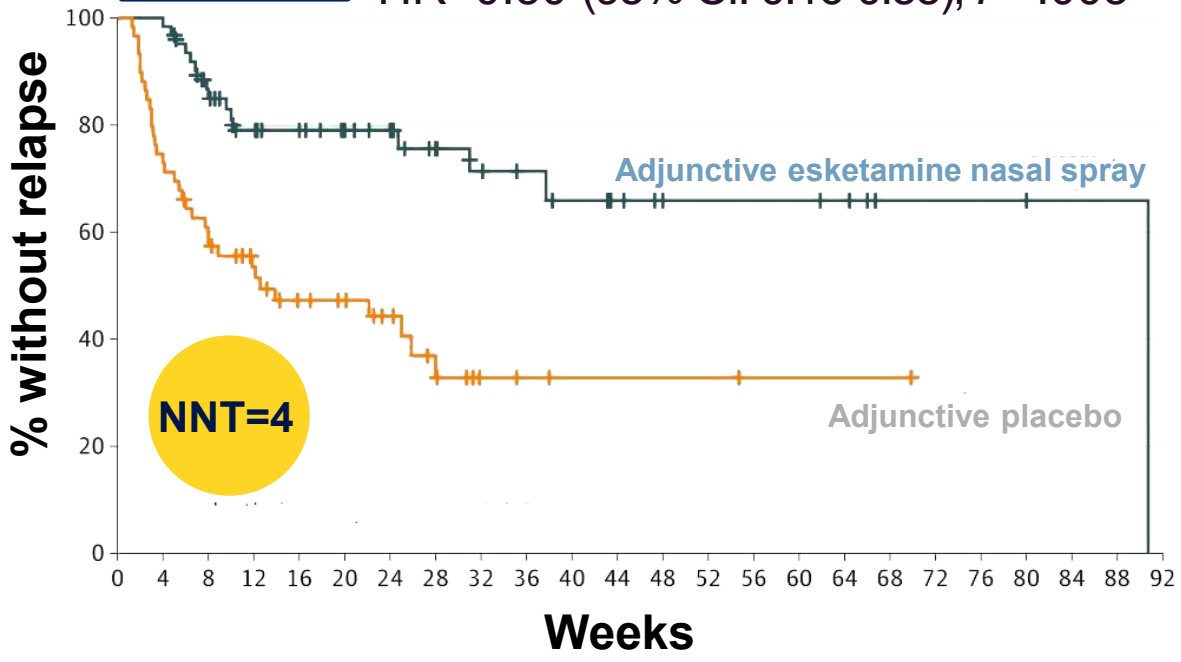
Should Patients Remain on Esketamine Indefinitely?

Response and Remission in SUSTAIN-1 Trial

Patients who responded to treatment

70% were less likely to relapse

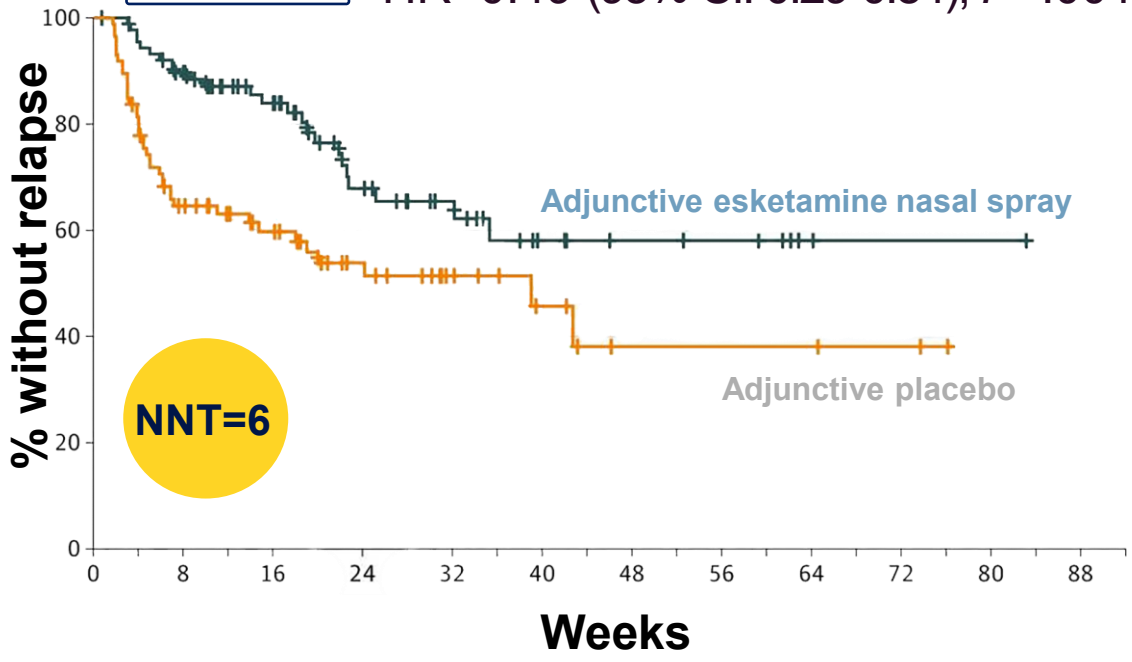
HR=0.30 (95% CI: 0.16-0.55), *P*=.003



Patients who reached remission

51% were less likely to relapse

HR=0.49 (95% CI: 0.29-0.84), *P*=.001



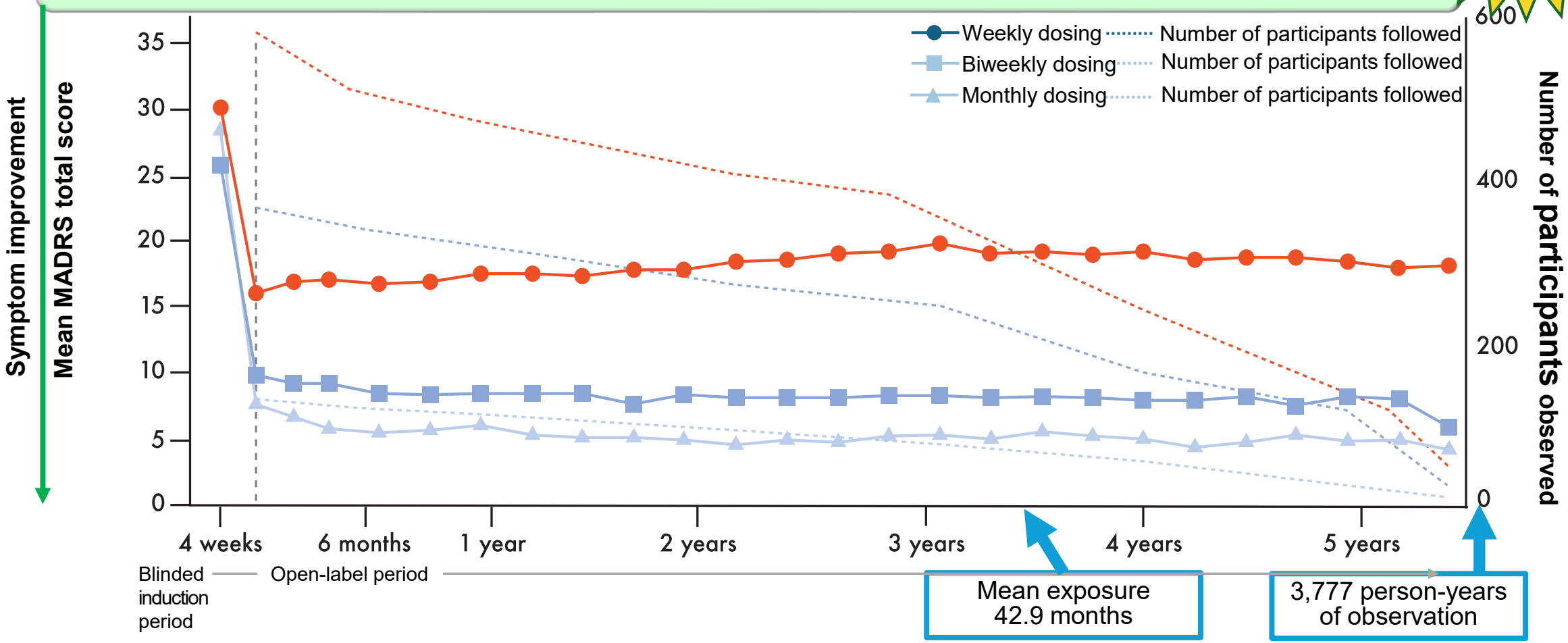
HR = hazard ratio.

Daly E, et al. *JAMA Psychiatry*. 2019;76(9):893-903.

5 Year Long-Term Safety Study of Esketamine

Monthly dosing is off-label

No new safety signals were seen, and results of treatment were durable in the 5-year SUSTAIN-3 study of esketamine nasal spray for TRD.



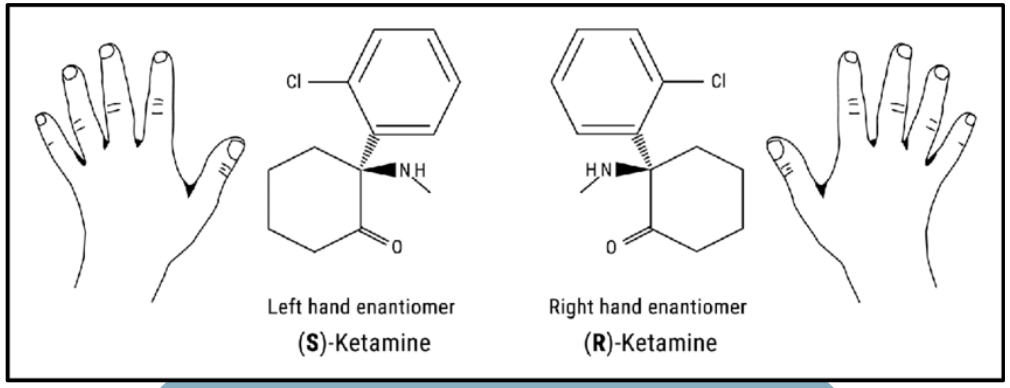
Zaki N, et al. *Neuropsychopharmacol.* 2023;48:1225-1233. Zajecka J, et al. Presented at: 2024 Psych Congress Elevate; May 30 - June 2, 2024; Las Vegas, NV.

Esketamine vs Ketamine

No head-to-head RCT comparing intravenous (IV) ketamine and intranasal (IN) esketamine for TRD

	IN Esketamine	IV Ketamine
FDA-Approved: TRD	Yes	No
Covered by insurance	Yes	Not really
Long-term safety data	Yes	No
REMS Protocol	Yes	No
Standardized doses	Yes	No
Malpractice liability	Lower	Higher
Cost to procure the medication	High	Low

Ketamine = racemic mixture of (R) and (S) enantiomers

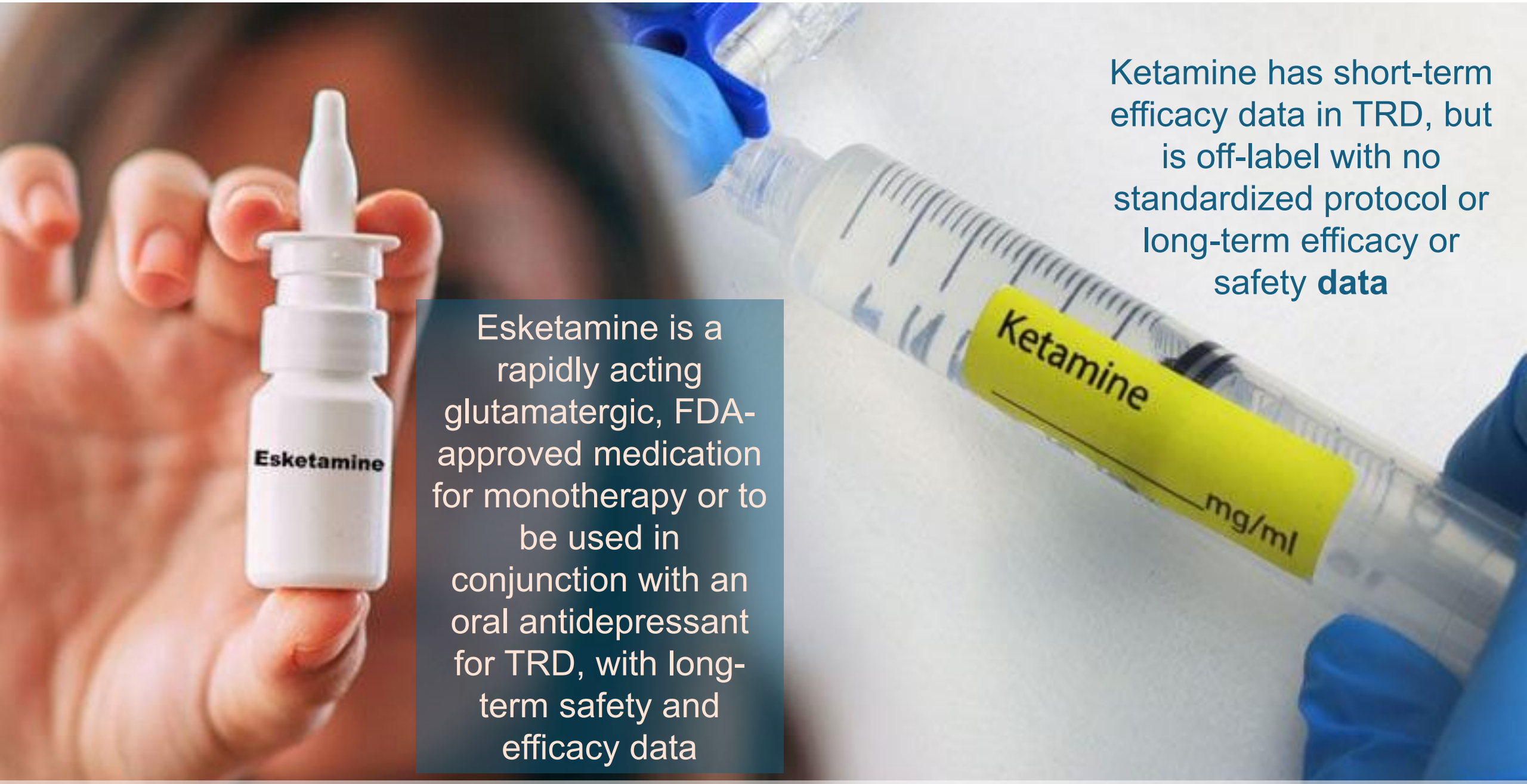


Esketamine = isolated (S)-enantiomer of ketamine

- 4-fold greater affinity from NMDA receptor
- 2-fold greater potency
- Faster clearance/recovery
- Greater therapeutic index
- Less cognitive and concentration impairment
- Less lethargy and agitation

RCT = randomized controlled trial.

Singh B, et al. *J Clin Psychiatry*. 2023;84(2):22m14548. Muller J, et al. *Ther Adv Psychopharmacol*. 2016;6(3):185-192.



Esketamine is a rapidly acting glutamatergic, FDA-approved medication for monotherapy or to be used in conjunction with an oral antidepressant for TRD, with long-term safety and efficacy data

Ketamine has short-term efficacy data in TRD, but is off-label with no standardized protocol or long-term efficacy or safety **data**

TRD = treatment resistant depression.

Image: https://www.medscape.com/viewarticle/ketamine-vs-esketamine-critical-differences-explained-2024a10001is?form=fpf

External Trigeminal Nerve Stimulation for ADHD

A cell phone-sized device that connects to a disposable patch placed on the child's forehead at bedtime

Device sends low stimulating pulses to the trigeminal nerve

Pulsing effects are mild, non-intrusive, feel like tingling on skin

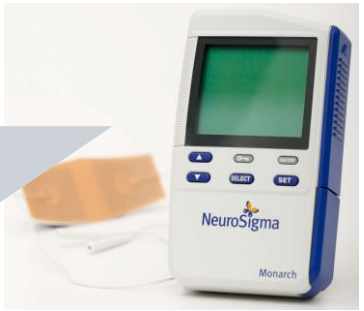
Patch removed in morning upon awakening

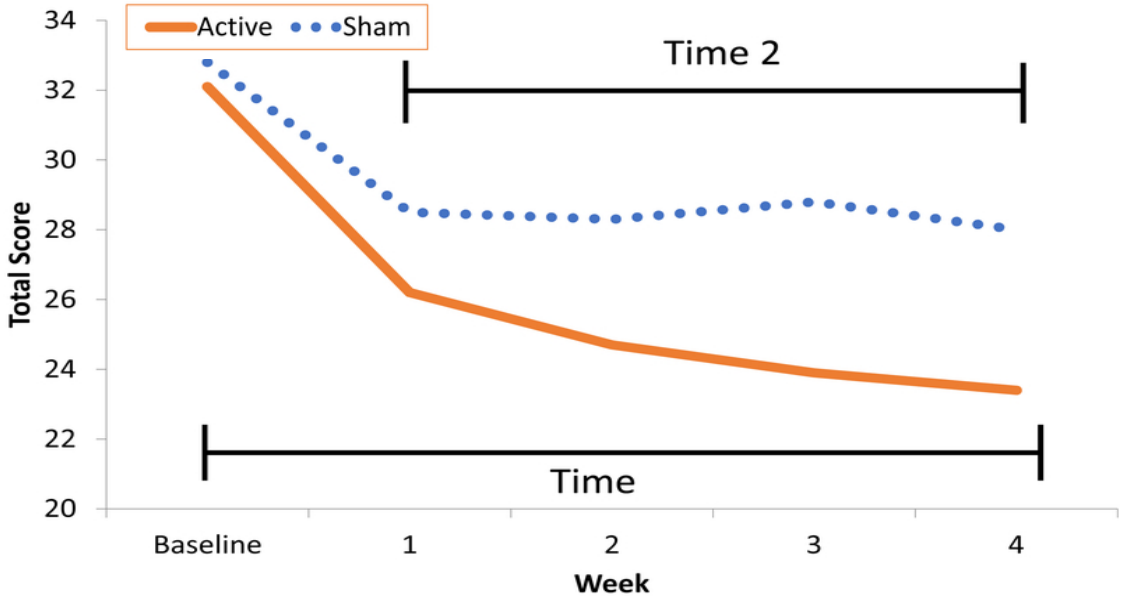
2019 **First FDA-Cleared Device for ADHD!**

- Monotherapy in children ages 7-12 years
- **Prescription-only** device for at-home use
- Carries **minimal risk** and is **well tolerated**

52% of children who used eTNS vs 14% of placebo group had significantly reduced impulsivity, hyperactivity, and inattention, as measured by ADHD rating scales

4-week, blinded, placebo-controlled trial, parent-supervised treatment





ADHD = attention deficit/hyperactivity disorder; TNS = trigeminal nerve stimulation.

McGough JJ, et al. *J Am Acad Child Adolesc Psychiatry*. 2019;58(4):403-411.e3. ABC News. Image. Accessed May 2025. https://abcnews.go.com/Politics/parents-cautious-fda-approved-device-kids-adhd/story?id=62630944.

Prism for Chronic PTSD

- **Adjunctive** Amygdala-Derived-EEG-fMRI-Pattern (EFP) neurofeedback for chronic PTSD
  - **31.89% had remission rate at 3-month follow-up**
  - **66.7% responded to treatment at 3 months**
  - Prospective, single-arm, open-label trial to assess safety and efficacy (N=63)
- **During a session**
  - Patient wears EEG headset
  - Watches a computer simulation with agitated avatars
  - EEG measures brain activity in real-time
  - Patient is instructed to identify an experience, memory, or emotion to make the avatars sit down
- **Mechanism of action**
  - Targets amygdala dysregulation with real-time EEG-based biofeedback
  - Patients learn to self-regulate emotional brain activity by receiving visual feedback linked to their brain signals

Cons:

- Unfavorable financial model with a monthly equipment lease fee
- Covered by insurance: No
- Time commitment: 15 sessions (45 min each) over 8 weeks

Pros:

- System is easy to use
- No medications needed
- FDA cleared: 2023
- Side effects: Tend to be mild – fatigue, headache

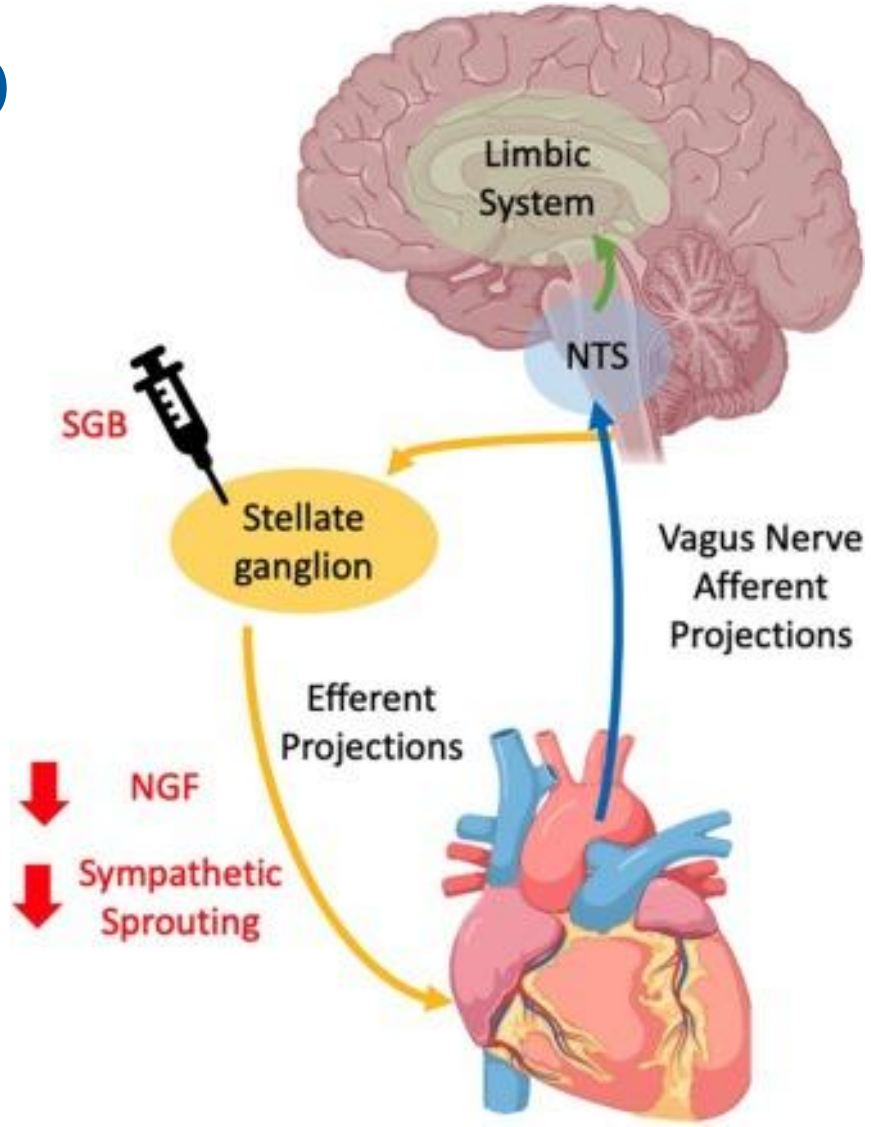
First FDA-Cleared Device for PTSD (2023)!

EFP = EEG-fMRI-Pattern.

Fruchter E, et al. *Psychiatry Res.* 2024;333:115711. Nature. Image. June 24, 2021. Accessed July 2025. https://www.nature.com/articles/d41586-021-01664-x.

Stellate Ganglion Block for PTSD

- SGB is a local anesthetic injection in the neck to reset the “fight or flight” system
  - Safely used for 100 years for pain conditions & for PTSD since 2010
- **50% reduction in PTSD and Anxiety symptoms for >80% of patients within hours**
  - Effects last 6-12 months on average
- Over 40 articles in the peer-reviewed literature (Level 1b evidence supports)
  - *Twice the effect as placebo in a large trial published in JAMA Psych 2020*
- SGB does *not replace, but rather <u>enhances</u>* standard treatments for anxiety and post-traumatic stress.



*not typically covered by insurance

SGB = stellate ganglion block. JAMA Psychiatry 2020;77(2):130-138. Image: Kim S, et al. Medical Hypotheses 2022; 162: 110833. Accessed Nov 11, 2025.

What Is in the Pipeline?

Interventional Psychiatry Pipeline

Phase 2 Clinical Trials	Phase 3 Clinical Trials
GH001 – Inhalation-based formulation of mebufotenin for TRD, single dose	Transcranial direct current stimulation – MDD
BPL-003 – Intranasal mebufotenin (5-MeO-DMT) for TRD, single dose	COMP360 – Synthetic psilocybin for TRD
COMP360 – Synthetic psilocybin for PTSD	CYB003 – Deuterated oral psilocin for MDD
VLS-01 – Buccal film DMT for TRD	CYB004 – Deuterated IM DMT for GAD
Facial botulinum toxin – MDD	Subcutaneous Ketamine – TRD
	MM120 – Synthetic LSD for GAD and MDD

DMT = N, N-dimethyltryptamine; LSD = lysergide D-tartrate.

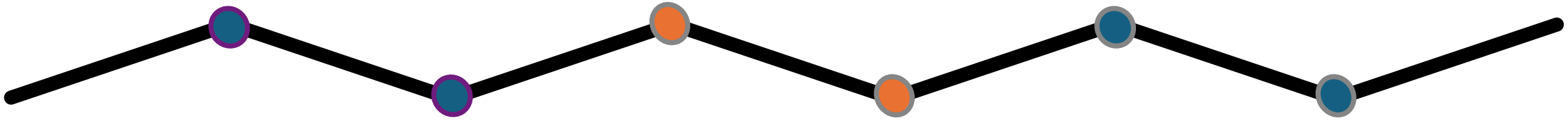
Cybin. Accessed July 2025. https://ir.cybin.com/investors/news/news-details/2024/Cybin-Initiates-PARADIGM-A-Multinational-Pivotal-Phase-3-Program-Evaluating-CYB003-for-the-Adjunctive-Treatment-of-Major-Depressive-Disorder-and-Reports-Second-Quarter-Financial-Results/default.aspx. McIntyre RS, et al. *Lancet*. 2020;396(10265):1841-1856. Loo C, et al. *Br J Psychiatry*. 2023;223(6):533-541. Loo C, et al. *Br J Psychiatry*. 2024;225(2):349. Husain MI, et al. *BJPsych Open*. 2023;9(4):e134. Beckley Psytech. Accessed July 2025. https://www.beckleypsytech.com/our-work/clinical-trials/ongoing-clinical-trials. Principium Psychiatry. Accessed July 2025. https://www.principiumpsychiatry.com/blog/the-uses-of-botox-to-treat-anxiety-and-depression/. McIntyre R. Image. Neuroscience Education Institute. Accessed July 2025. https://www.neiglobal.com/.

Barriers to Implementation of Interventional Psychiatry

Lack of Training and Certification

Limited Clinical Infrastructure Requires significant investment in equipment, staffing, space

Reimbursement and Insurance Challenges



Referral Gaps Interdisciplinary collaboration is limited

Lack of Biomarkers/Patient Selection

Limited Access In Underserved Populations

Menon SN, et al. *Front Psychiatry*. 2024;15:1397102.

TRD: Discussing Treatment Options

Important Limitations for Patients' Consideration

Treatment	Rationale	Limitations
Ketamine	Acute efficacy established in TRD. Beneficial effects on suicidality. Rapid onset of symptomatic improvement	Insufficient long-term efficacy, tolerability and safety data. Access to treatment limited in many jurisdictions. Specialized personnel required for safe administration. Long- term safety profile in TRD not established(e.g., abuse liability, gateway activity)
Esketamine	Acute and maintenance efficacy established in TRD. Beneficial effects on suicidality. Rapid onset of symptomatic improvement. Superiority to SGA (i.e., quetiapine XR) in acute and maintenance treatment of TRD.	Must be administered in a REMS-certified clinic; may be limited access in rural areas. Need insurance prior authorization. 2x per week x4 weeks - Can be challenging for patients with time and transportation constraints.
ECT	Highly effective in acute and maintenance treatment of TRD. Non-inferiority to IV ketamine suggested by available evidence. Efficacy in TRD across the age span.	Relative lack of availability in many contexts.Stigma and lack of acceptability to many patients, Tolerability concerns (e.g., memory deficits).
rTMS	Shown to be effective in TRD. More acceptable to patients than ECT. Accelerated protocol demonstrates significant remission rates within one week Tolerability advantages compared to ECT(i.e., persistent cognitive deficits not observed).	Relative lack of availability in many jurisdictions.Inferiority to ECT in TRD with non-accelerated protocols.Insufficient long-term data in TRD
VNS	Proven efficacy in TRD in persons with extensive antidepressant failure histories.Treatment does not need to be administered on a daily basis	Not available in most countries globally. Complexity of procedure limits scalability. Complications of implant. Cost of treatment.

TRD = treatment resistant depression. SGA = second-generation antipsychotic; XR = extended release.

McIntyre RS, et al. *World Psychiatry*. 2023;22(3):394-412.

Choosing a Neuromodulation Intervention

Kim J, Widge AS. Neuromodulation Approaches to Depressive Disorders. Psychiatric Times. March 21, 2024. Accessed October 24, 2024. https://www.psychiatrictimes.com/view/neuromodulation-approaches-to-depressive-disorders.

Noninvasive Intervention	Pros	Cons
TMS ■ FDA-approved, office-based treatment using electromagnetic conduction to stimulate areas of the brain (typically the dorsolateral prefrontal cortex)	■ Pairs well with behavioral activation, as it provides daily structure for patients ■ Patients can continue daily routine (work, driving) ■ Minimal adverse effects ■ Good option in severe depression without psychosis or acute suicidality if patients worry about ECT adverse effects	■ Usually time-intensive, requiring 4 to 8 weeks of daily treatment (except SAINT protocol requiring 5 days) ■ Small risk for seizures
Invasive Interventions	**Pros**	**Cons**
VNS ■ FDA-approved treatment using a surgically implanted stimulator to deliver repetitive stimulation to the left cervical vagus nerve	■ May be effective in a population with severe TRD including bipolar depression ■ Good option in patients who respond to ECT but quickly relapse (also effective in ECT non-responders)	■ Carries surgical risks as well as risks for dysphagia and dysphonia ■ May require a long period of treatment before a response is seen ■ Not yet covered by most insurance
DBS ■ Experimental treatment with growing body of evidence using a surgically implanted stimulator in brain regions thought to be part of a mood-regulation network	■ Some evidence for benefit in severe TRD ■ Faster onset of effect compared with TMS and VNS (but not ECT) ■ Durable effect for responders	■ Expensive, invasive, and only available at very specialized centers
Other emerging neuromodulation interventions under study: transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and magnetic seizure therapy (MST)		

Treatment should be individualized to each patient, and patient choice and autonomy are critically important

COMORBIDITIES?

Psychiatric and Medical

SUPPORT SYSTEMS

Occupational, family, friends

COLLABORATING PROVIDERS

Who is involved in care?

FINANCIAL STRAIN?

Is treatment sustainable given costs?

Patient-Specific Treatment Considerations

Key Takeaways

We can share hope with our patients with multiple treatments FDA-approved for treatment-resistant psychiatric conditions, including esketamine, ketamine, TMS, ECT, DBS, eTNS, stellate ganglion block, VNS, plus many in the pipeline.

Neuromodulation strategies should be considered for appropriate patients who remain treatment-resistant after trialing pharmacotherapies and psychotherapies

Patients with treatment-resistant psychiatric conditions should be thoroughly assessed with a comprehensive medical and psychiatric assessment. Treatment decisions should be patient-centered using shared decision-making strategies

“Know all the theories, master all the techniques, *but as you touch a human soul, be just another human soul.”*

~CARL JUNG


Questions?