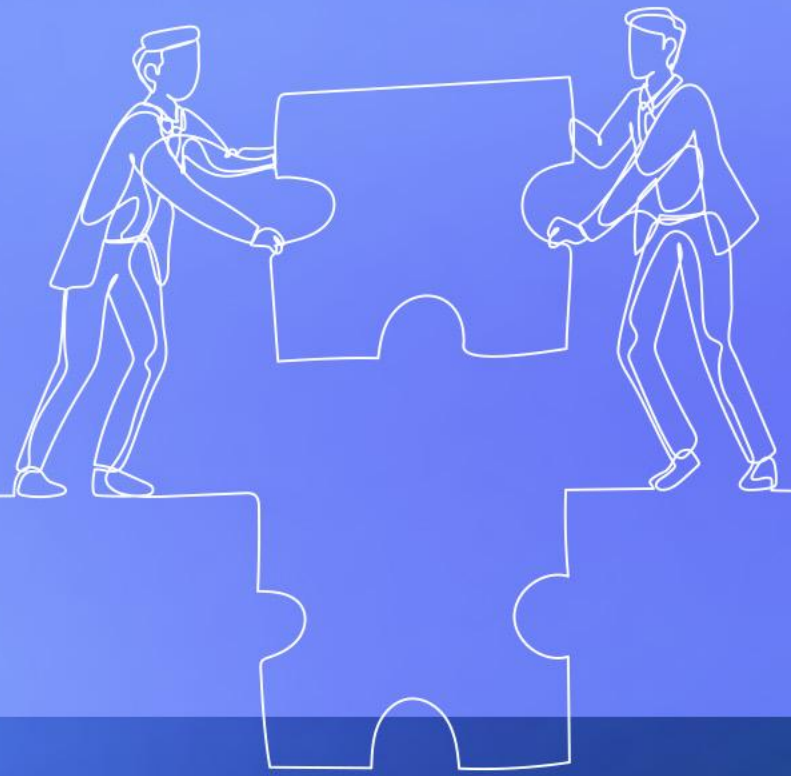


Could Glutamatergic Modulation be the Keystone of Durable Change in Treatment-Resistant Depression?

MasterClass

Supported by an educational grant from Johnson & Johnson.

Faculty

Hara Oyedeji, DNP, PMHNP-BC, MSEd

Founder and Lead Clinician,
Fortitude Wellness Group
Owings Mills, MD

Brittany Albright, MD, MPH, DABOM

Affiliate Assistant Professor,
Medical University of South Carolina
Owner and CEO,
Sweetgrass Psychiatry
Mount Pleasant, SC

Faculty Disclosures

Hara Oyedeji, DNP, PMHNP-BC, MSEd: Advisory Board– AbbVie, Alkermes, Bristol Myers Squibb, Intra-Cellular Therapies, Johnson & Johnson, Karuna, Neurocrine Biosciences, Otsuka, Sage Therapeutics, Sunovion, Teva Pharmaceuticals; Consultant– AbbVie, Alkermes, Biogen, Bristol Myers Squibb, Intra-Cellular Therapies, Johnson & Johnson, Karuna, Neurocrine Biosciences, Otsuka, Sage Therapeutics, Sunovion, Teva Pharmaceuticals; Speaker's Bureau– Alkermes, Axsome Therapeutics, Bristol Myers Squibb, Johnson & Johnson, Luye Pharma Group, Neurocrine Biosciences, Teva Pharmaceuticals

Brittany Albright, MD, MPH: Advisory Board – AbbVie, Bristol Myers Squibb, Definium Therapeutics, Eli Lilly, Johnson & Johnson, Neurocrine Biosciences; Consultant – AbbVie, Johnson & Johnson, Osmind EHR, Precision Genetics; Speaker's Bureau – AbbVie, Alkermes, Axsome, Bristol Myers Squibb, Johnson & Johnson

Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration)

- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity

- This activity has been independently reviewed for balance

- This CME activity includes brand names for participant clarity purposes only. No product promotion or recommendation should be inferred

Learning Objectives

- Identify the limitations of monoaminergic antidepressants, including delayed onset, incomplete efficacy, and residual symptoms, and the need for novel therapeutic mechanisms
- Evaluate the current understanding of the role of the glutamatergic system in the pathophysiology of MDD and its implications for treatment targets
- Assess the mechanisms of action and most recent clinical data associated with current and emerging glutamatergic treatments for MDD, and evidence that demonstrates their effects on the pathophysiology of MDD and TRD
- Apply evidence-based strategies to optimize treatment outcomes and address unmet needs in patients with TRD

MDD = major depressive disorder; TRD = treatment-resistant depression

Characteristics and Burden of TRD

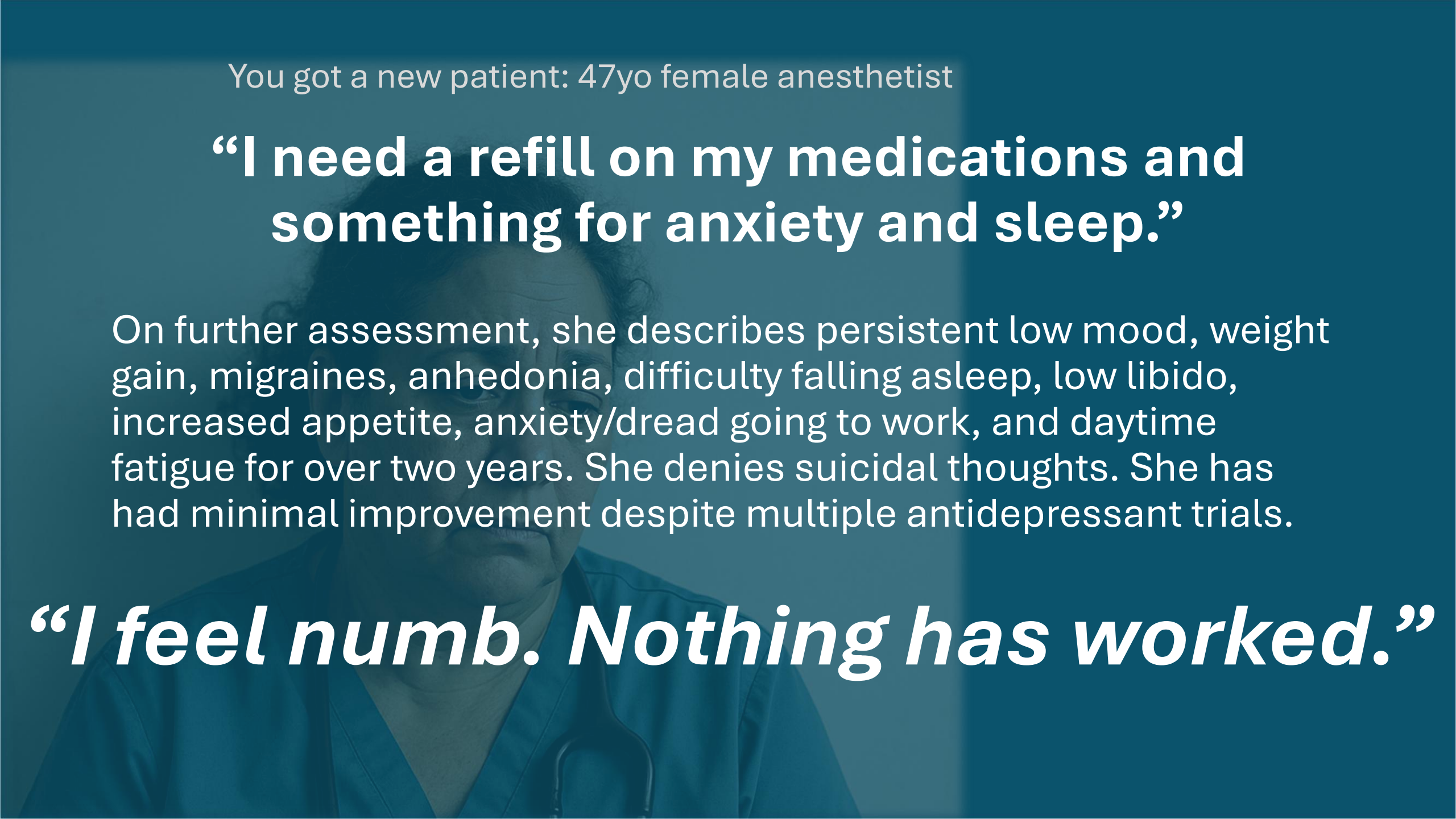
We are broken.

~21 million (8.3%) adults in US had a major depressive episode in 2021.

MDD is one of the leading causes of disability in the US and the world.

Suicide was the 11th leading cause of death in 2023.

Our traditional treatments are ineffective for the majority of our patients with major depression.



You got a new patient: 47yo female anesthetist

“I need a refill on my medications and something for anxiety and sleep.”

On further assessment, she describes persistent low mood, weight gain, migraines, anhedonia, difficulty falling asleep, low libido, increased appetite, anxiety/dread going to work, and daytime fatigue for over two years. She denies suicidal thoughts. She has had minimal improvement despite multiple antidepressant trials.

“I feel numb. Nothing has worked.”

47-year-old divorced female nurse anesthetist

Past medical history / Review of systems

At least 2-3 mixed migraine/tension headaches per month.

Recently transient unilateral vision changes.

Past year – experiencing hot flashes, irregular menses.

10 lb weight gain past 6 months – BMI 30, Prediabetes

Past psychiatric history

First depressive episode at age 24, treated successfully with sertraline.

Recurrent major depressive episodes since age 40, with increasing frequency and severity.

No history of mania, psychosis, hospitalization, prior suicide attempts.

Current psychiatric symptoms

Depressed mood most days, anhedonia, social withdrawal.

Significant fatigue, sleep disruptions, and catastrophic thinking/anxiety.

Impaired concentration.

No suicidal ideation but feels hopeless that things will get better.

No psychotic features.

Substance use

Drinks 2-3 seltzer alcohol drinks every evening after work.

No tobacco use.

No drug use.

Psychosocial history

Lives alone; divorced, has pets.

Employed full time; able to hide symptoms at work.

Limited social supports.

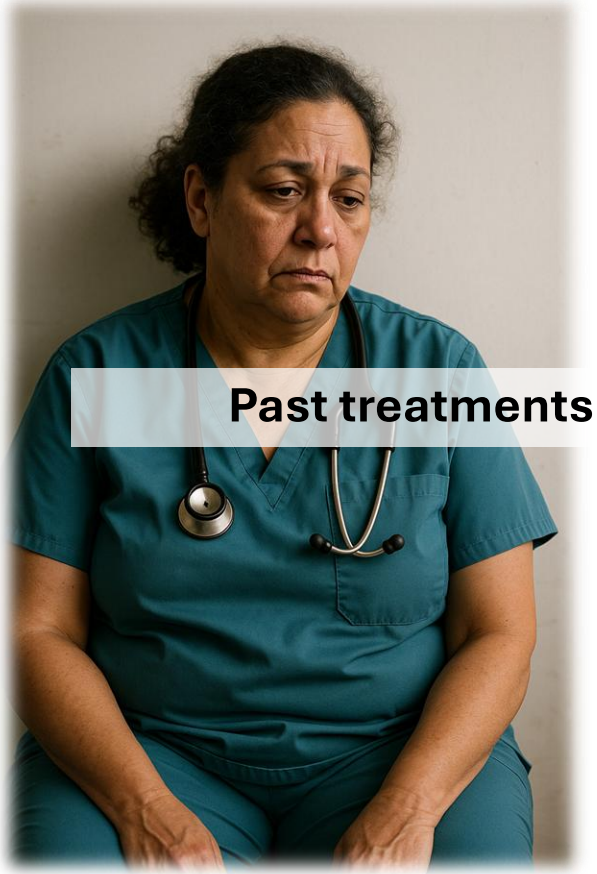
Has witnessed trauma at work.

No exercise routine.

No spiritual practice.

BMI = body mass index

47-year-old divorced female nurse anesthetist



Current meds

- Sertraline 150 mg daily (ongoing, x8 weeks, no significant response)
- Seroquel 50mg QHS x 2 years (has had weight gain, noticing mild involuntary oral movements)
- Sumatriptan 100mg PRN migraine

Past treatments

- Escitalopram 20 mg daily (8 weeks, inadequate response)
- Bupropion XL 300 mg daily (8 weeks, discontinued due to insomnia)
- Mirtazapine 30 mg nightly (8 weeks, partial response, discontinued due to weight gain)
- Amitriptyline 50mg QHS for headaches (6 months, discontinued due to inefficacy and daytime fatigue)
- Venlafaxine XR 225 mg daily (8 weeks, no significant improvement)
- Cognitive behavioral therapy (16 sessions, adjunctive, partial symptomatic relief)

QHS = every night at bedtime; PRN = as needed; XL/XR = extended release.

Could she have Treatment Resistant Depression (TRD)?

Definition

- ≥2 qualifying unsuccessful monoaminergic antidepressant trials within the same depressive episode
- From the same or different classes
- Of adequate duration (6-8 weeks)
- Of adequate/therapeutic dose

At least 30% of persons with MDD have TRD

Han C, et al. *Neuropsychiatr Dis Treat*. 2020;16:2929-2941.

Why care about TRD vs MDD? Because it is worse...

Clinical Course Comparison

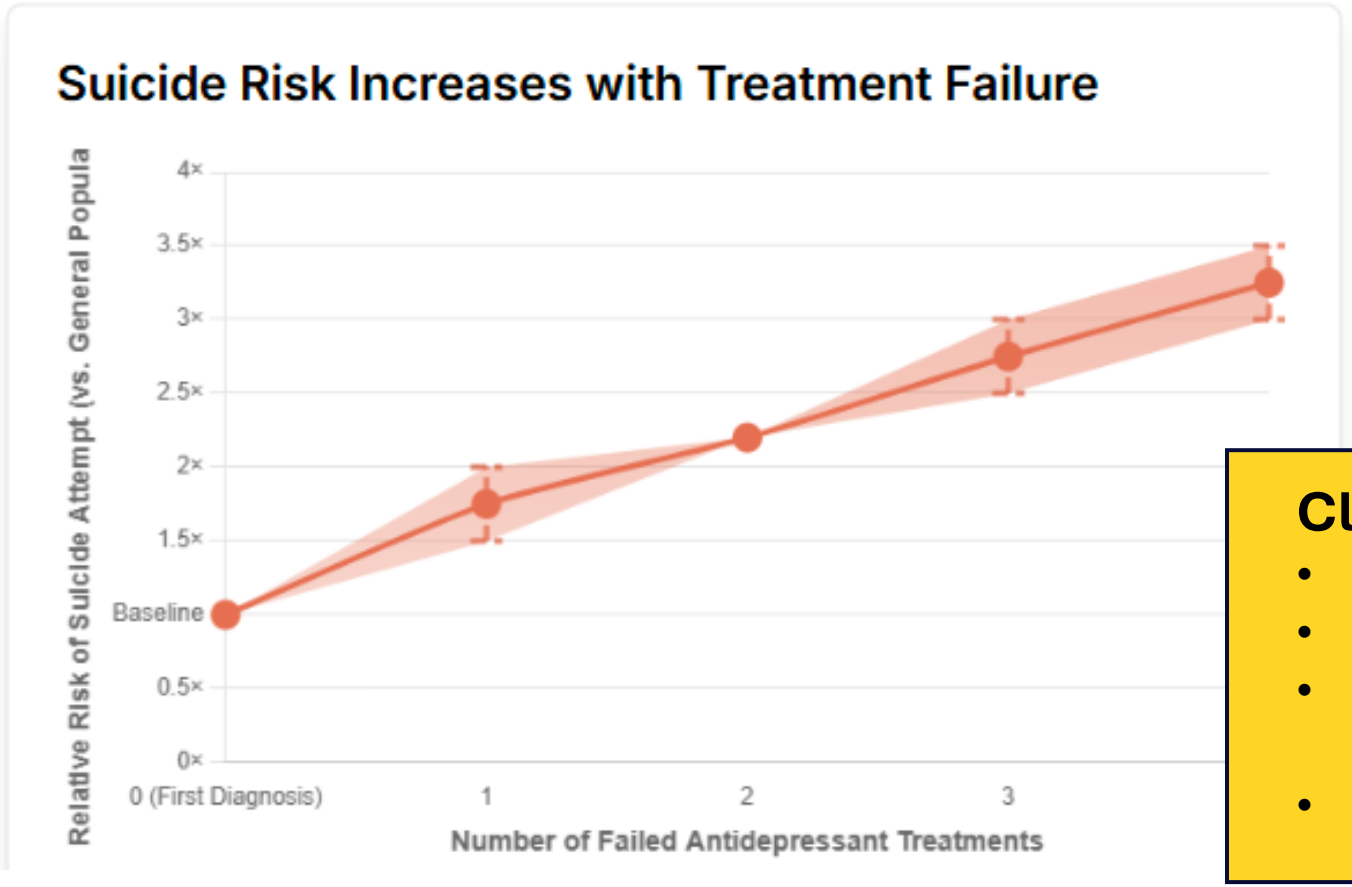
- More chronic, persistent course, longer episodes, and earlier onset
- Higher relapse rates (67%-80% within 1 year)
- Shorter inter-episode recovery periods
- Increased treatment complexity over time

Quality of Life Impact

- Greater impairment in social and family functioning
- More persistent cognitive dysfunction
- Higher rates of comorbid anxiety and substance use

Caraci F, et al. *Pharmacol Rev*. 2018;70(3):475-504. Fekadu A, et al. *J Affect Disord*. 2009;116(1-2):4-11.

TRD: Greater Disability, Suicidality, and Mortality



2.2x **Increased suicide mortality**

- Relative risk vs non-TRD depression

1.8x **All-cause mortality**

- Higher risk of death from any cause

3.1x **Disability claims**

- More likely to utilize disability benefits

Clinical Risk Assessment

- Monitor suicidality at **every visit**
- Risk increases with **each failed treatment**
- Consider **rapid-acting interventions** for acute suicidal ideation
- Implement **safety planning** early in treatment course

Bergfeld IO, et al. J *Affect Disord*. 2018;235:362-367. de Leon VC, et al. *J Affect Disord*. 2025;374:619-629. Gronemann FH, et al. *J Psychiatr Res*. 2021;135:197-202. O'Connor EA, et al. *JAMA*. 2023;329(23):2068-2085. Pfeiffer PN, et al. *Suicide Life Threat Behav*. 2013;43(4):356-365.

TRD represents not just treatment failure, but a distinct clinical entity with **greater chronicity, higher disability,** and **substantial societal burden** compared to responsive depression.

At least 30% of persons with MDD have TRD.

Fekadu A, et al. *Journal of Affective Disorders*. 2009;116(1–2): 4-11. McIntyre RS, et al. *World Psychiatry*. 2023;22(3):394-412.

But does my patient really have TRD?

Inaccuracy of the MDD diagnosis is a common reason for pseudo-resistance.

It is estimated that ~half of individuals with MDD are not correctly diagnosed.

Ensure that your patient has received a comprehensive:

- Medical and laboratory evaluation
- Psychiatric evaluation & PHQ9
- Psychosocial evaluation including collateral from loved ones
- Assess recent stressors, trauma history

Assess all prior medication trials & if patients received minimally adequate treatment with 2 or more antidepressant medications of adequate dose and duration (at least 6-8 weeks)

Assess if patients were adherent to past medication trials

TRD is a clinical diagnosis – there's no laboratory test, genetic test, or neuroimaging study

PHQ9 = Patient Health Questionnaire-9; TRD = treatment resistant depression.

McIntyre RS, et al. *World Psychiatry*. 2023;22(3):394-412. Steffens DC. *N Engl J Med*. 2024;390(7):630-639. Gaddey HL, et al. *Am Fam Physician*. 2024;109(5):410-416. Manning JS. *J Clin Psychiatry*. 2010;71 Suppl 1:10-5. Dodd S, et al. *World J Biol Psychiatry*. 2021;22(7):483-494.

Additional Medical Findings For Our Patient

- Her PHQ-9 score = 19; BP 141/89; BMI = 30
- Labs significant for mildly elevated TSH, mildly elevated %CDT, mildly elevated LDL & Ha1c
- Pt in perimenopause, menses are irregular
- On exam, she is withdrawn with a flat facial expression, slow speech, and very mild involuntary oral and tongue movements, AIMS score = 6
- Ordered sleep apnea test = moderate obstructive sleep apnea → started CPAP

What do we do next for her?

Try another monoamine antidepressant??
Increase her sertraline from 150mg to 200mg?

BP = blood pressure; TSH = thyroid-stimulating hormone; pt = patient; CPAP = continuous positive airway pressure. AIMS = Abnormal Involuntary Movement Scale; PHQ-9 = Patient Health Questionaire; %CDT = Carbohydrate-deficient transferrin; BMI = body mass index

Key Learning Points

Definition, Prevalence, Burdens, Diagnosis

Treatment resistant depression (TRD) is a subset of depression

- ≥2 qualifying unsuccessful monoaminergic antidepressant trials within the same depressive episode of adequate dose and duration

Diminishing returns

- Increased treatment complexity with greater impact on quality of life

Greater Disability, Suicidality, and Mortality

- 2.2 x increased suicide mortality, 1.8 x all-cause mortality, 3.1 x disability claims

Rule out pseudoresistance

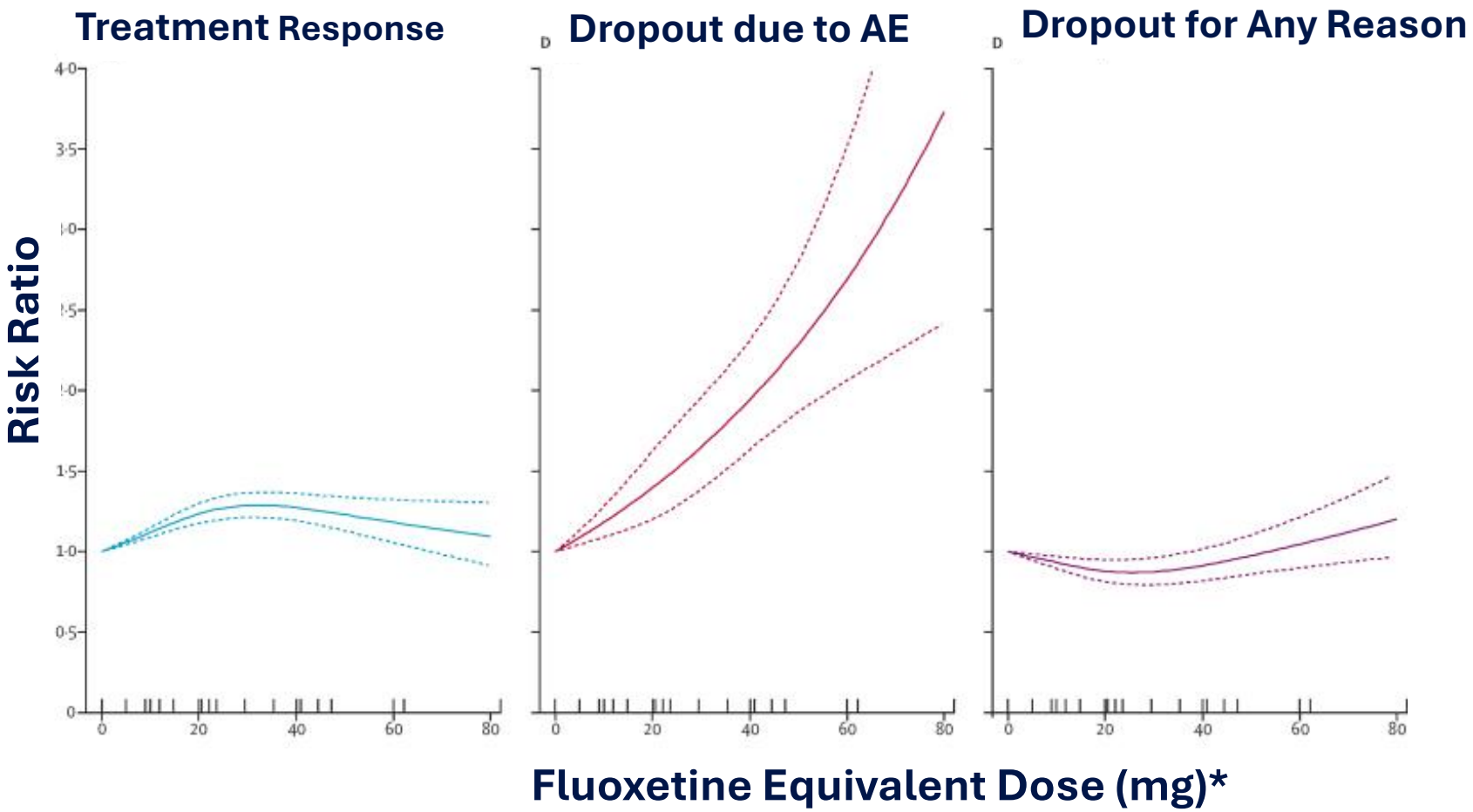
- Screen for misdiagnosis, non-adherence, and medical comorbidities before labeling TRD

- **Medical issues:** Address underlying medical issues, including metabolic disease, sleep apnea & perimenopause symptoms
- **Alcohol use:** Use motivational interviewing & psychoeducation surrounding her alcohol use; discuss treatment options if she is unable to reduce her use
- **Psychotherapy:** She declines this option
- **Medications:** Discontinue quetiapine due to concerns about tardive dyskinesia

What do we do next?

Just increase the SSRI dose, right?

Meta-analysis of dose outcome relationships for SSRIs



SSRIs studied included: citalopram, escitalopram, paroxetine, and sertraline

Each tick on the x-axis represents the dose examined in a treatment group

*Doses of citalopram, escitalopram, paroxetine, and sertraline were converted to fluoxetine equivalents

SSRI = selective serotonin reuptake inhibitor; AE = adverse effect.

Furukawa, TA et al. *Lancet Psychiatry*. 2019;6(7):601-609.

Limitations of Conventional Monoamine Antidepressants

Delayed onset and high non-response rates

- Can take weeks to reach efficacy
- Function may remain diminished
- Quality of life improvement is partial

Frequent residual symptoms

- Cognitive problems
- Depressed mood
- Eating problems
- Mood dysfunction
- Psychomotor effects
- Suicidality
- Decreased motivation
- Fatigue

Adverse effects

- Sexual dysfunction
- Weight gain
- Insomnia
- Emotional blunting or apathy (anhedonia)

Conradi HJ, et al. *Psychol Med*. 2011;41:1165–1174. Culpepper L, et al. *Am J Med*. 2015;128:S1-S15. Haroon E, et al. *Neuropsychopharm-acology*. 2017;42(1):160-177. Kadriu N, et al. *Biol Psychiatry*. 2019;86(9):730-743. Masdrakis VG, et al. *Acta Neuropsychiatrica*. 2023;35(4):189-204. McClintock SM, et al. *J Clin Psychopharmacol*. 2011;31:180-186.

What About Adding an Adjunct Antipsychotic?

While adding AAPs as adjunct may be a strategy used in TRD, OFC is the only FDA-approved combination with an atypical

In a 2024 systematic review and meta-analysis of cariprazine for MDD, most trials involved participants with only one unsuccessful antidepressant trial in the same depressive episode.

Other AAPs may still be useful, but their efficacy in true TRD populations is not as well established

Approved by the FDA as an adjunctive therapy for MDD after inadequate response to antidepressant: aripiprazole, lumateperone, brexpiprazole, cariprazine, quetiapine XR → **NOT APPROVED FOR TRD**

AAP = atypical antipsychotics; OFC = olanzapine fluoxetine combination; XR = extended release.

Jha MK, Mathew SJ. *Am J Psychiatry*. 2023;180:190-199. Ali E, et al. *Asian J Psychiatr*. 2024;95:104005.

Olanzapine/Fluoxetine Combination (OFC)?

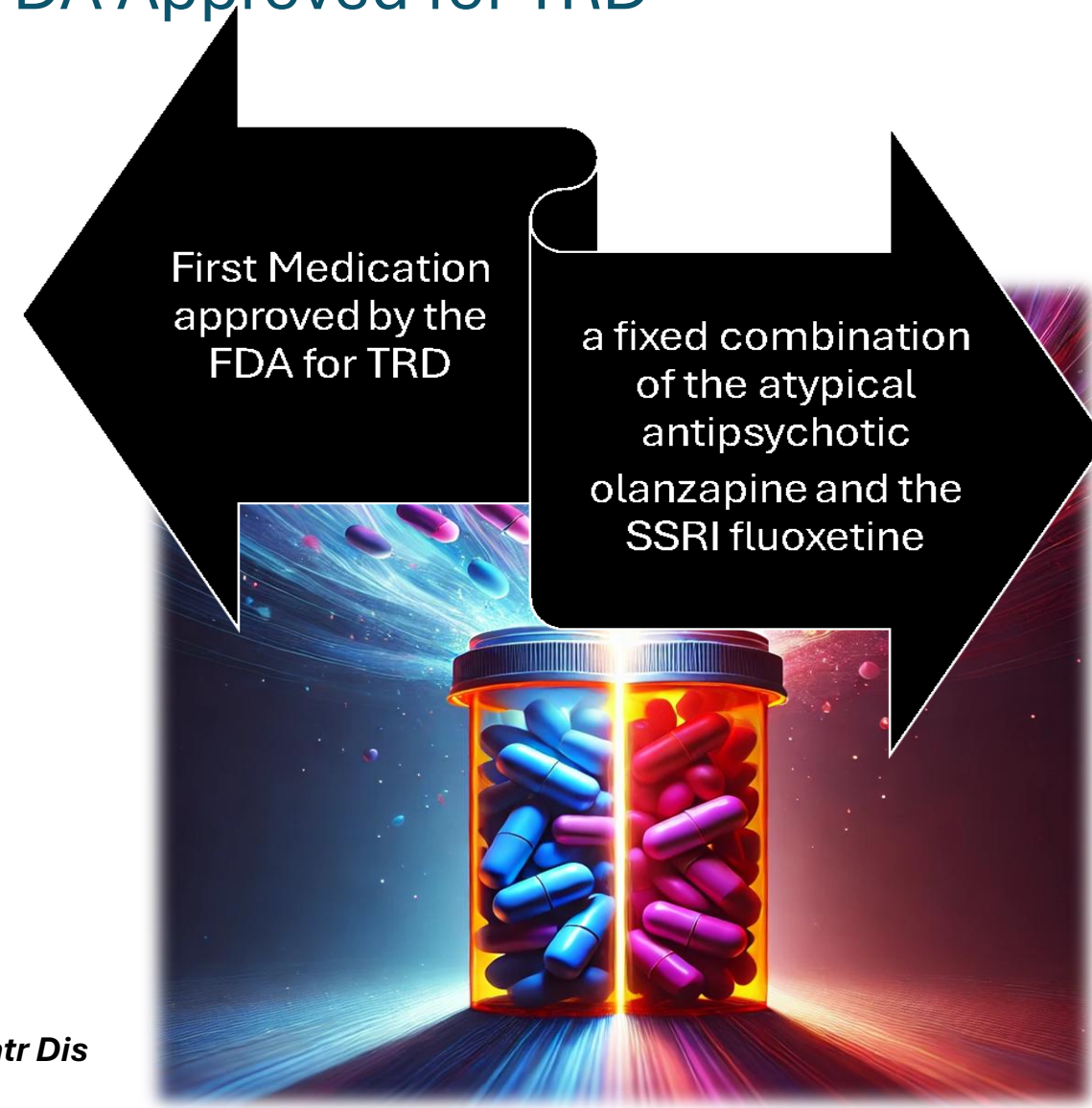
Monoaminergic Combination Treatment FDA Approved for TRD

Mechanisms of Action

- Olanzapine is a dopamine D_2 and serotonin 5-HT_{2A} receptor antagonist
- Fluoxetine is an SSRI
- Combination may have dual mechanism

Effects

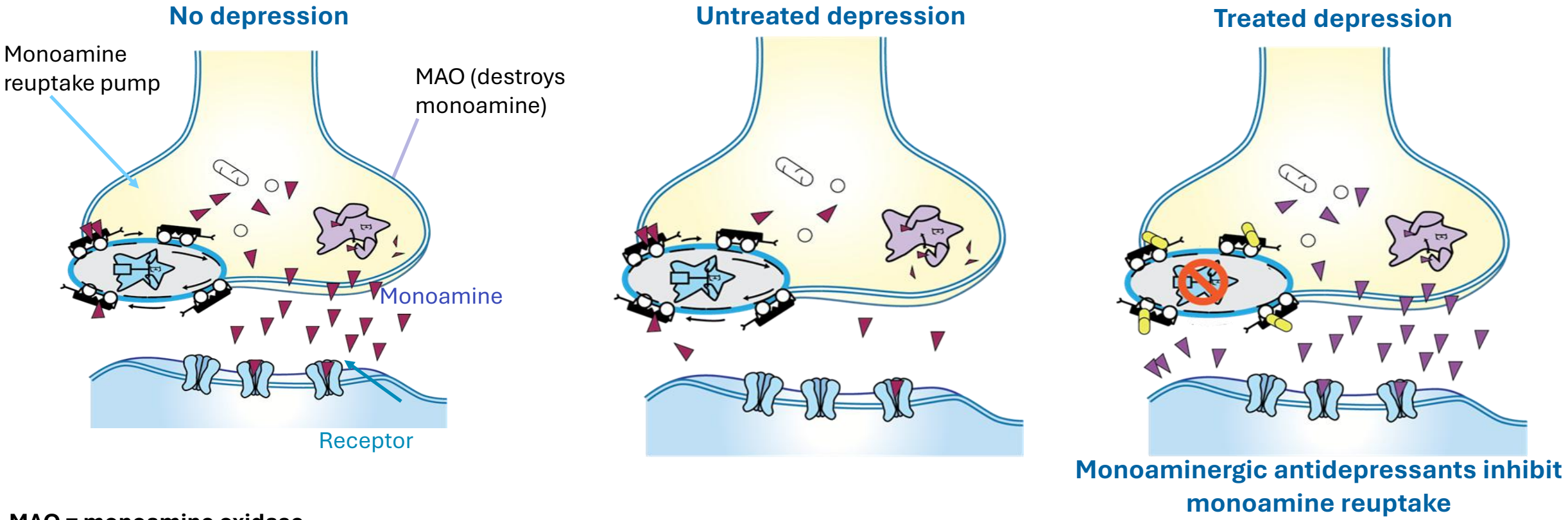
- In a systematic review, treatment with OFC vs fluoxetine treatment alone was associated with earlier improvement and higher rates of response and remission
- Long-term open-label studies show sustained efficacy for up to 76 weeks



Tamayo JM, et al. *Arch Neuroscien*. 2015;20 (1):3-19. Bobo WV, et al. *Neuropsychiatr Dis Treat*. 2009;5:369-383.

Is the Monoamine Hypothesis Too Simplistic to Explain "Monoamine Resistant Depression"?

Monoaminergic treatment success, though limited, suggests *monoamine deficit causes depression*



MAO = monoamine oxidase.

Malhi GS, et al. *Lancet*. 2018;392(10161):2299-2312. Stahl SM. *Essential Psychopharmacology. 2nd ed*. Cambridge University Press; 2000.

Moving Beyond Monoamines for “Monoamine” TRD

Exploring the Glutamatergic System in Depression

Glutamate vs Monoamine Neurobiology

Neurotransmitter Comparison		
Feature	**Monoamines**	**Glutamate**
Abundance	~10% of synapses	~60% of synapses
Signal speed	Slow, modulatory	Fast, direct
Receptor diversity	Moderate (7-14 subtypes)	High (>30 subtypes)
Synaptic plasticity	Days to weeks	Minutes to hours
Clinical effect onset	2 to 6 weeks	Hours to days

The **glutamate model** emphasizes rapid synaptic modulation and neuroplasticity, potentially enabling faster symptom relief.

Clinical implications

- Faster onset potential
- Different mechanism
- More precise targeting options

Greengard P. *Science*. 2001;294(5544):1024-1030. Hansen KB, et al. *Pharmacol Rev*. 2021;73(4):298-487. Niciu MJ, et al. *J Neural Transm (Vienna)*. 2014;121(8):907-924. Ren L. *Prog Neuropsychopharmacol Biol Psychiatry*. 2024;129:110910.

CNS Processes Regulated by Glutamate

Emotional processing

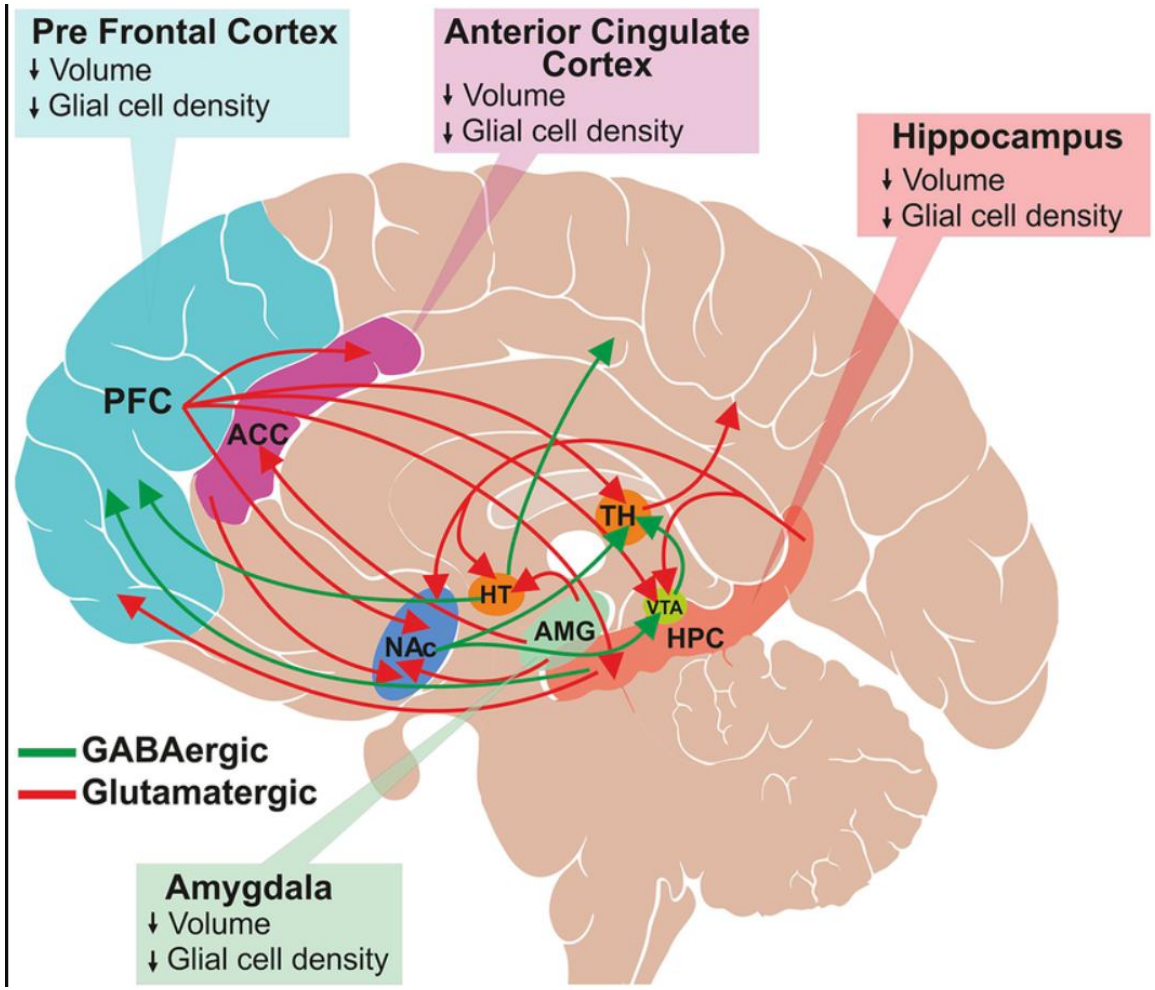
- Amygdala fear extinction pathways
- Nucleus accumbens reward signaling

Cognitive function

- Working memory (dorsolateral PFC)
- Attention and cognitive flexibility
- Executive function regulation

Neuroplasticity

- Long-term potentiation (LTP)
- Synaptic pruning and remodeling
- Dendritic spine formation

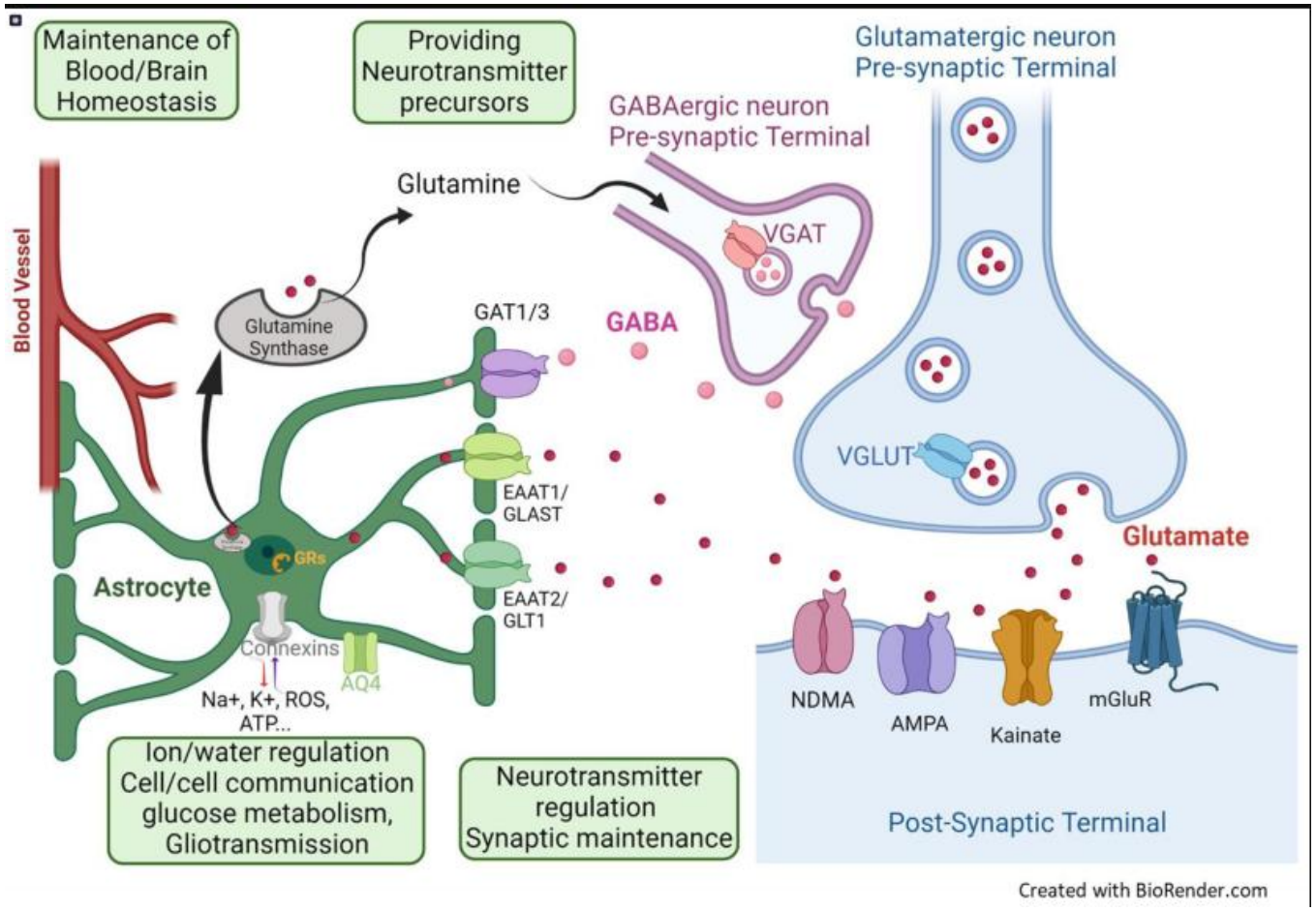


PFC = prefrontal cortex; LTP = long-term potentiation.

Duman RS, et al. *Neuron*. 2019;102(1):75-90. Halaris A, Cook J. *Adv Exp Med Biol*. 2023;1411:487-512. McGrath T, et al. *Nutrients*. 2022;14(5):917. Sarawagi A, et al. *Front Psychiatry*. 2021;12:637863.

Role of Astrocytes in Glutamate/GABA Balance

- **Glutamate-GABA cycle**
  - Uptake of synaptic glutamate, conversion to glutamine, transfer to neurons for GABA synthesis
- **Excitotoxicity prevention**
  - Removal of excess glutamate to prevent neuronal damage via EAAT1/2 transporters
- **Synaptic modulation**
  - Release of gliotransmitters (D-serine, ATP) that regulate synaptic strength
- **Energy support**
  - Glycogen storage and lactate provision to neurons during high activity



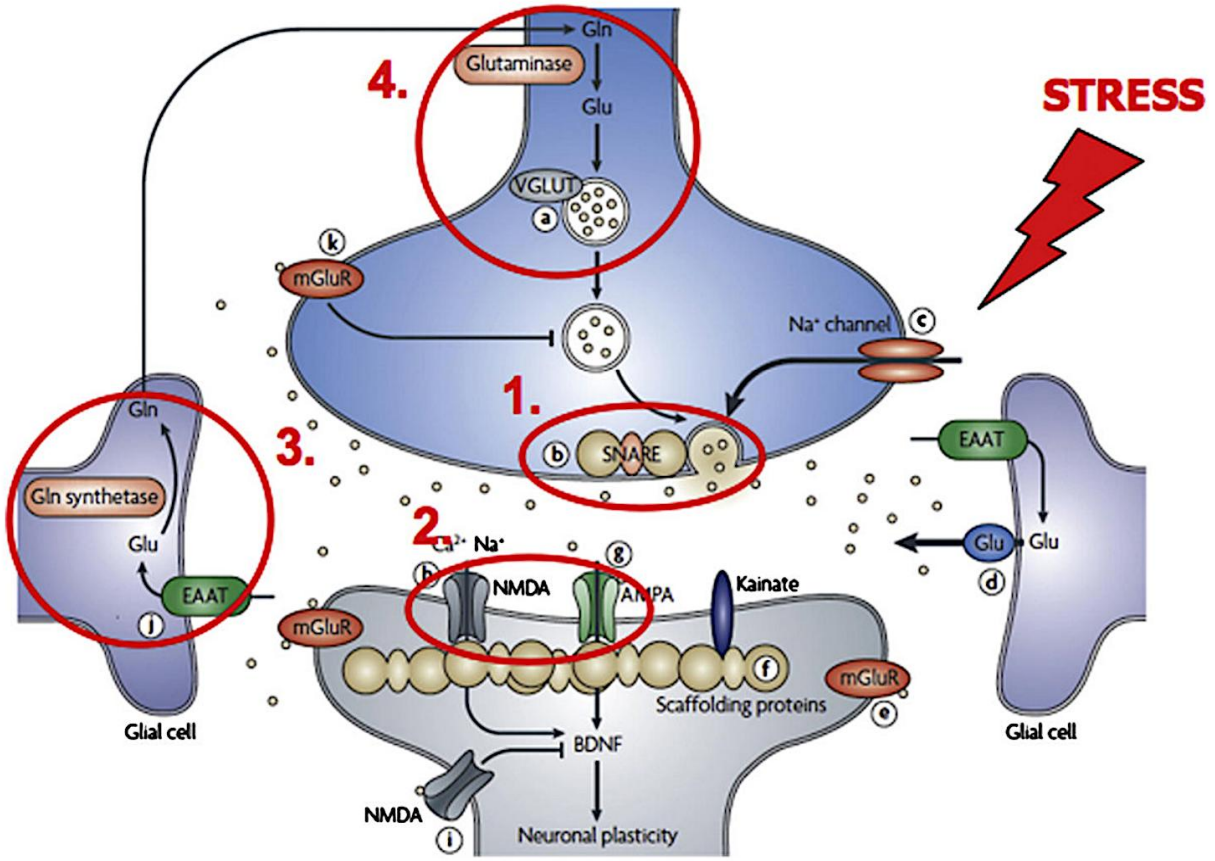
ATP = adenosine triphosphate.

Li S, et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2025;141:111475. Musazzi L, et al. *Biol Psychiatry*. 2013;73(12):1180-1188. McGrath T, et al. *Nutrients*. 2022;14(5):917. Bansal Y, et al. *Int J Mol Sci*. 2024;25(12):6357.

Stress Disrupts Glutamate at Multiple Levels

NORMAL FUNCTIONING

1. Presynaptic release of glutamate
2. Postsynaptic ionotropic receptors for glutamate (NMDA and AMPA receptors)
3. Reuptake of glutamate by glial glutamate membrane transporters
4. Glutamate metabolism and recycling by the glutamate/glutamine cycle



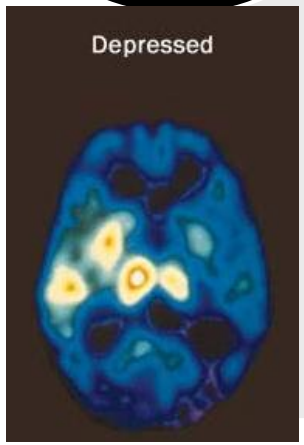
STRESS

- Increases glutamate release
- Alters trafficking / expression/function of ionotropic glutamate receptors
- Alters clearing of glutamate from the synapse
- Reduces glutamate/ glutamine cycling and glial cell density

Sanacora G, et al. *Neuropharmacology*. 2012;62(1):63-77.

Stress, Glutamate & Synaptic Plasticity

THIS IS YOUR BRAIN **NOT ON** GLUTAMATERGIC DRUGS



Reduced Neural Connectivity

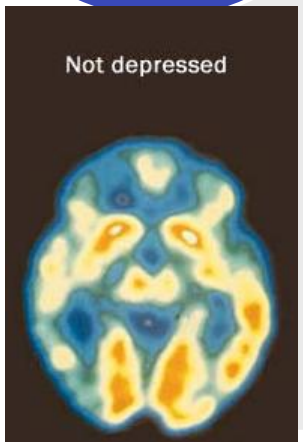
-**Dendritic spine loss** (30%-40% reduction)

-**Suppressed** BDNF signaling

-**Impaired glutamate** regulation → excitotoxicity

-**Circuit dysfunction** in cognitive and emotional networks

THIS IS YOUR BRAIN **ON** GLUTAMATERGIC DRUGS



Enhanced Synaptic Connectivity

-**Rapid dendritic spine regrowth** within 24 hours

-**Enhanced BDNF and mTOR activation**, boosting neuroplasticity

-**Restored glutamate balance** through NMDA receptor modulation

-**Reconnected neural circuits** for better mood regulation

Minutes	1 hour	2-4 hours	24 hours	7 days
• NMDA blockade	• Glutamate surge	• BDNF release	• Spine growth	• Network reset

Duman RS, et al. *Neuron*. 2019;102(1):75-90. Khoodoruth MAS, et al. *Front Psychiatry*. 2022;13:886918. Tomasetti C, et al. *Curr Pharm Des*. 2019;25(4):381-387.

Key Learning Points

- Conventional monoaminergic antidepressants show diminishing returns in TRD
- Glutamatergic signaling is disrupted by chronic stress, contributing to suppressed downstream signaling and impaired neural connectivity
- Effective TRD treatment may require restoring neuroplasticity by targeting glutamate pathways

Glutamatergic Signaling as a Therapeutic Target in MDD

Glutamate Is the Target, But Mechanism Matters

Unsuccessful Trials of Glutamatergic Medications in MDD: Memantine, Lamotrigine

Agent	Mechanism of Action	Trial Results	Key Takeaway
Memantine	Low-affinity NMDA receptor antagonist	No consistent separation from placebo (mono- or adjunctive)	**Weak NMDA blockade** may not trigger meaningful synaptic plasticity
Lamotrigine	Reduces presynaptic glutamate release; sodium channel blockade	Mixed/negative results in unipolar TRD	**Reducing glutamate release alone** is likely insufficient for reducing depressive symptoms

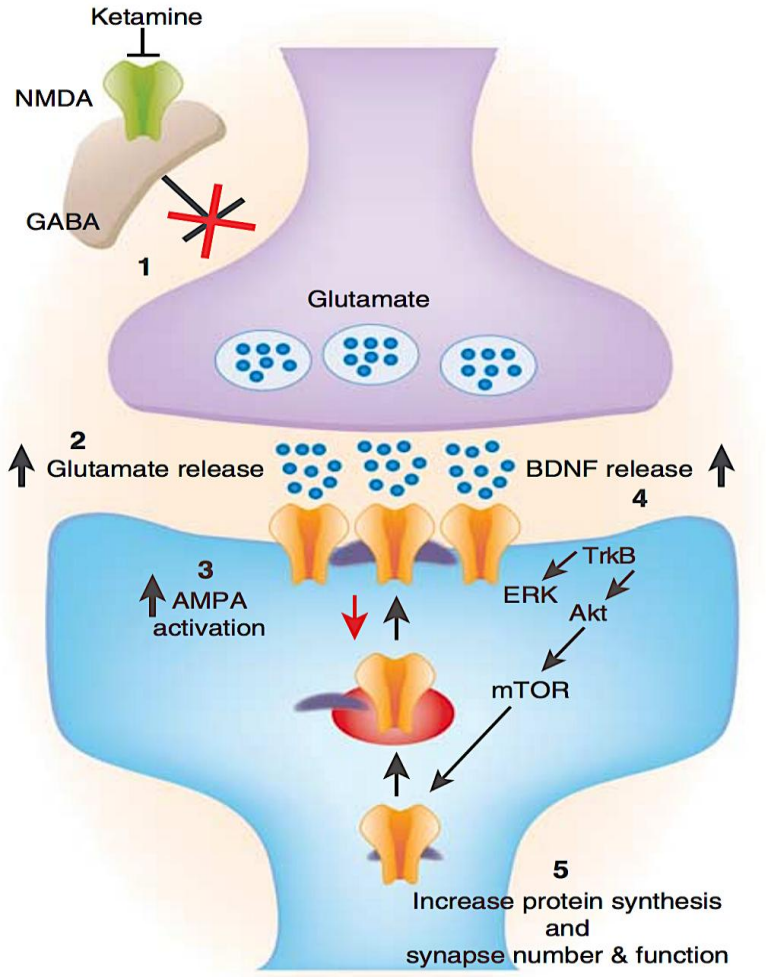
Simply targeting glutamate <u>is not enough</u>

Antidepressant efficacy may depend on rapid downstream neuroplastic change

Zarate CA Jr, et al. *Am J Psychiatry*. 2006;163(1):153-155; Sanacora G, et al. *Am J Psychiatry*. 2014;171(6):660-668; Barbee JG, et al. *J Clin Psychiatry*. 2011;72(10):1405-1412.

How NMDA Receptor Allosteric Antagonists Work

Esketamine, Ketamine, Dextromethorphan: A Receptor and Intracellular Cascade Story



Proposed mechanism of NMDA antidepressant action through a blockade of GABAergic inhibition …

Causes a surge in glutamate release

Leads to increased AMPA receptor stimulation

Leads to a release of BDNF

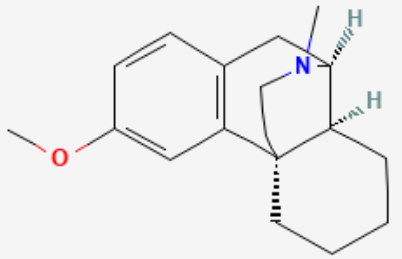
Activates downstream neurotrophic signaling to increase synaptic protein synaptogenesis, restoring synaptic functioning

Sanacora G, et al. *Neuropsychopharmacology*. 2015;40(2):259-267.

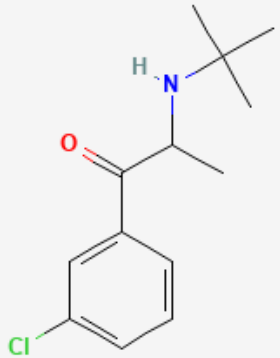
Dextromethorphan-Buproprion is Glutamatergic

Exploring the Key Components

Dextromethorphan



Bupropion



NMDA receptor antagonist

Sigma-1 receptor agonist

1. Increases glutamate release by decreasing presynaptic inhibition
2. Redirecting synaptic glutamate to AMPA
3. Removing inhibitory signal of extrasynaptic NMDA receptors

1. Fine-tunes monoamine and glutamatergic signaling
2. Reduces neuroinflammation and promotes neuronal repair and regeneration
3. Helps degrade misfolded proteins and dampen glutamate excitotoxicity

(Relatively) weak inhibitor of NE and DA reuptake

Increases and prolongs the plasma concentration of DXM

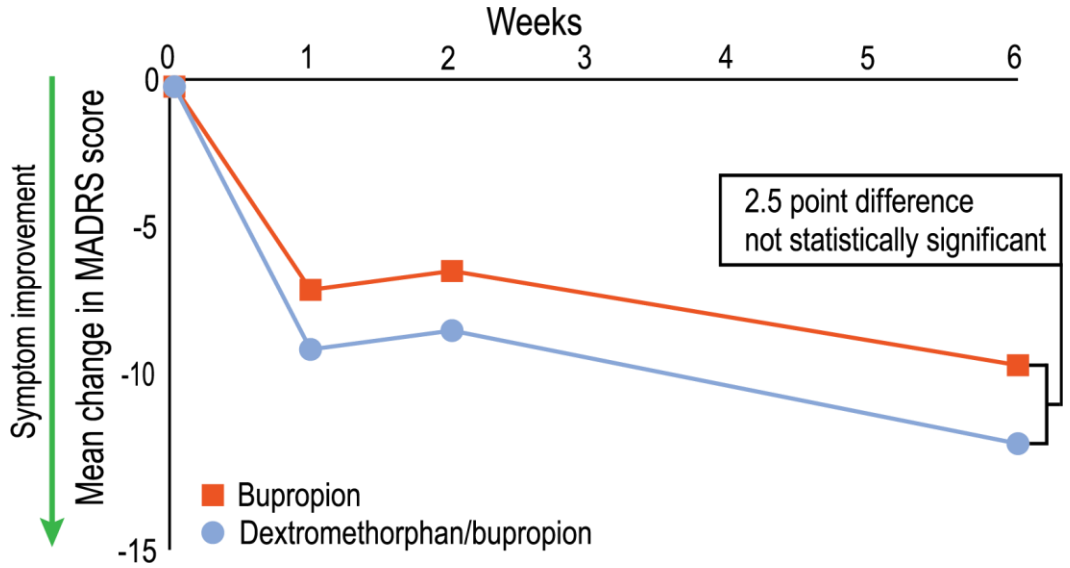
DXM-BUP = dextromethorphan/bupropion; NMDA = N-methyl-D-aspartate; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NE = norepinephrine; DA = dopamine.

Stahl SM. CNS Spectr. 2019;24(5):461-466.

Dextromethorphan/Bupropion Was Studied for TRD

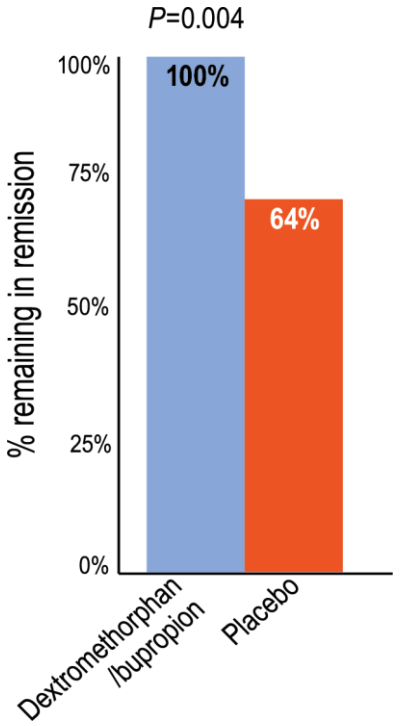
Dextromethorphan is a noncompetitive NMDA receptor antagonist and bupropion slows metabolism of dextromethorphan

Phase 3 STRIDE 1 trial of dextromethorphan/bupropion vs bupropion alone for patients with TRD



- Numeric improvements in anxiety and cognition also seen
- Most common AEs with combination were dizziness/nausea
- Discontinuation: 2.6% with combination, 1.9% with bupropion alone

Phase 2 MERIT trial of dextromethorphan/bupropion vs placebo for patients with TRD in remission



- All previously achieved remission with open-label dextromethorphan/bupropion
- Double blind switch to placebo or continuation (N=22 each)
- Continuation vs switch to placebo was significantly less likely to result in relapse over 6 months

Globe Newswire. Axsome Therapeutics [press release]. 2020. Accessed May 12, 2025. https://www.biospace.com/axsome-therapeutics-announces-topline-results-of-the-stride-1-phase-3-trial-in-treatment-resistant-depression-and-expert-call-to-discuss-clinical-implications. Globe Newswire. Axsome Therapeutics [press release]. 2021. Accessed May 12, 2025. https://www.globenewswire.com/news-release/2021/08/09/2276951/33090/en/Axsome-Therapeutics-Announces-AXS-05-Achieves-Primary-and-Key-Secondary-Endpoints-in-the-MERIT-Phase-2-Trial-in-Treatment-Resistant-Depression.html.

Dextromethorphan/Bupropion Safety and Tolerability

AEs >5% and >2x the Rate of Placebo

	AXS-05	Placebo
Dizziness	**16%**	**6%**
Nausea	**13%**	**9%**
Headache	**8%**	**4%**
Diarrhea	**7%**	**3%**
Somnolence	**7%**	**3%**
Dry mouth	**6%**	**2%**
Sexual dysfunction	**6%**	**0%**
Hyperhidrosis	**5%**	**0%**

Discontinuation due to Adverse Events:
4% AXS-05
0% Placebo

Weight Change
-0.60 lbs AXS-05
+0.73 lbs Placebo

Median Duration of AEs for AXS-05 in Pooled Controlled Studies

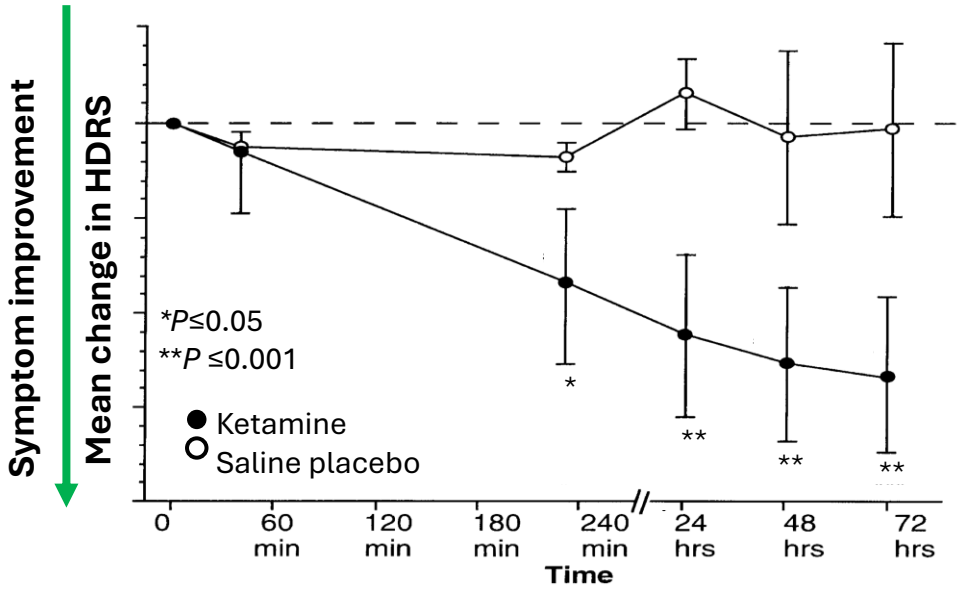
Dizziness	**5 days**
Nausea	**6 days**
Headache	**2.5 days**
Diarrhea	**4 days**
Somnolence	**5 days**
Dry mouth	**12.5 days**
Sexual Dysfunction	**3 days**

AUVELITY® (dextromethorphan hydrobromide and bupropion hydrochloride) Prescribing Information. Drugs@FDA: FDA-Approved Drugs. Accessed September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/215430s008lbl.pdf. Chepke C, et al. AXS-05 in Major Depressive Disorder: Pooled Data from Two Six-Week Controlled Trials (GEMINI and ASCEND). Poster presented at: Psych Congress Elevate; May 30-June 2, 2024; Las Vegas, NV.

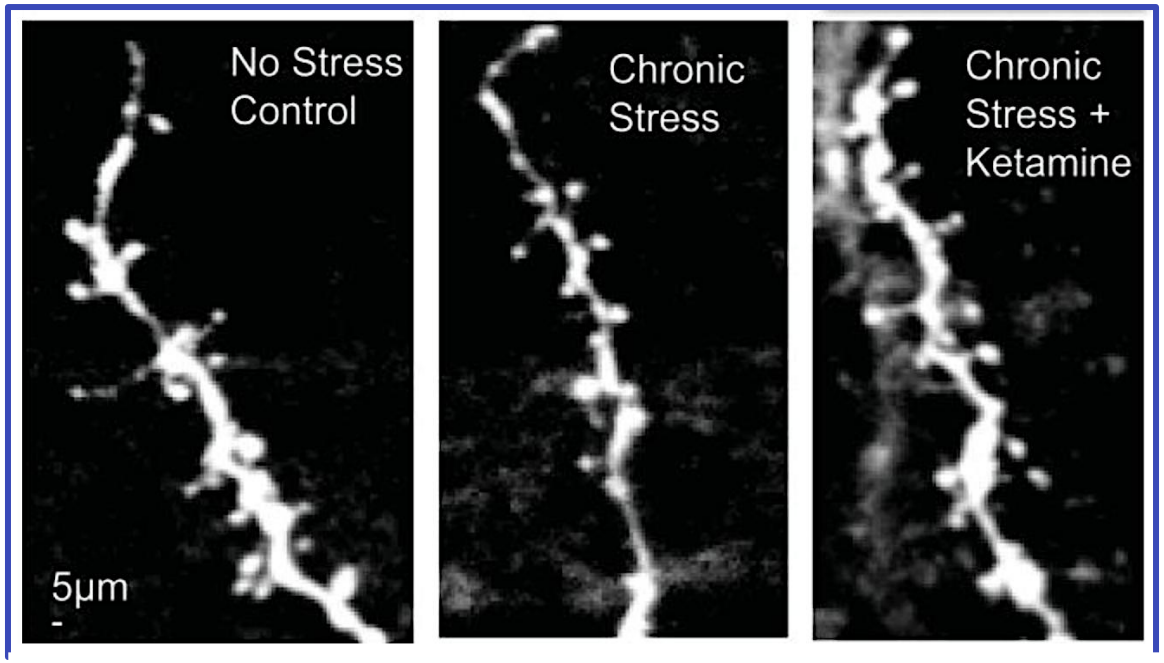
Ketamine for Major Depression

A potent NMDA receptor antagonist NOT approved for TRD

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

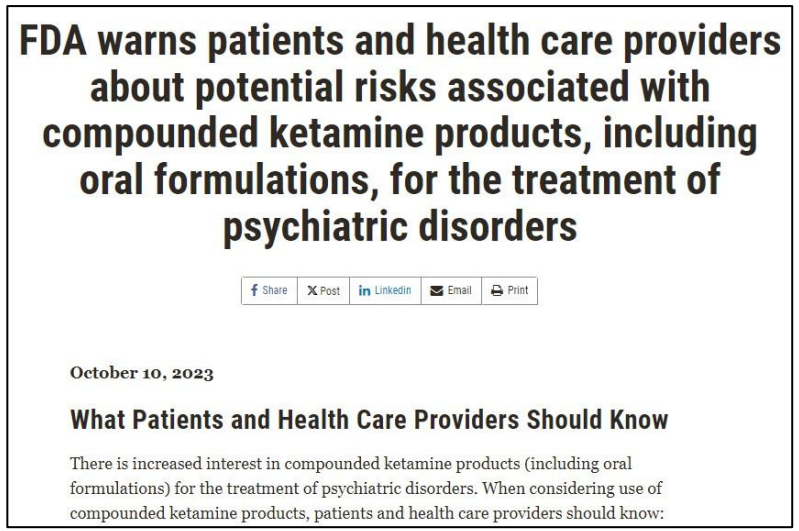


High-powered microscopy demonstrated that a single dose of ketamine could produce rapid synaptogenesis in rat pyramidal neurons.

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.

FDA Compounded Ketamine Warnings:



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 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

- **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

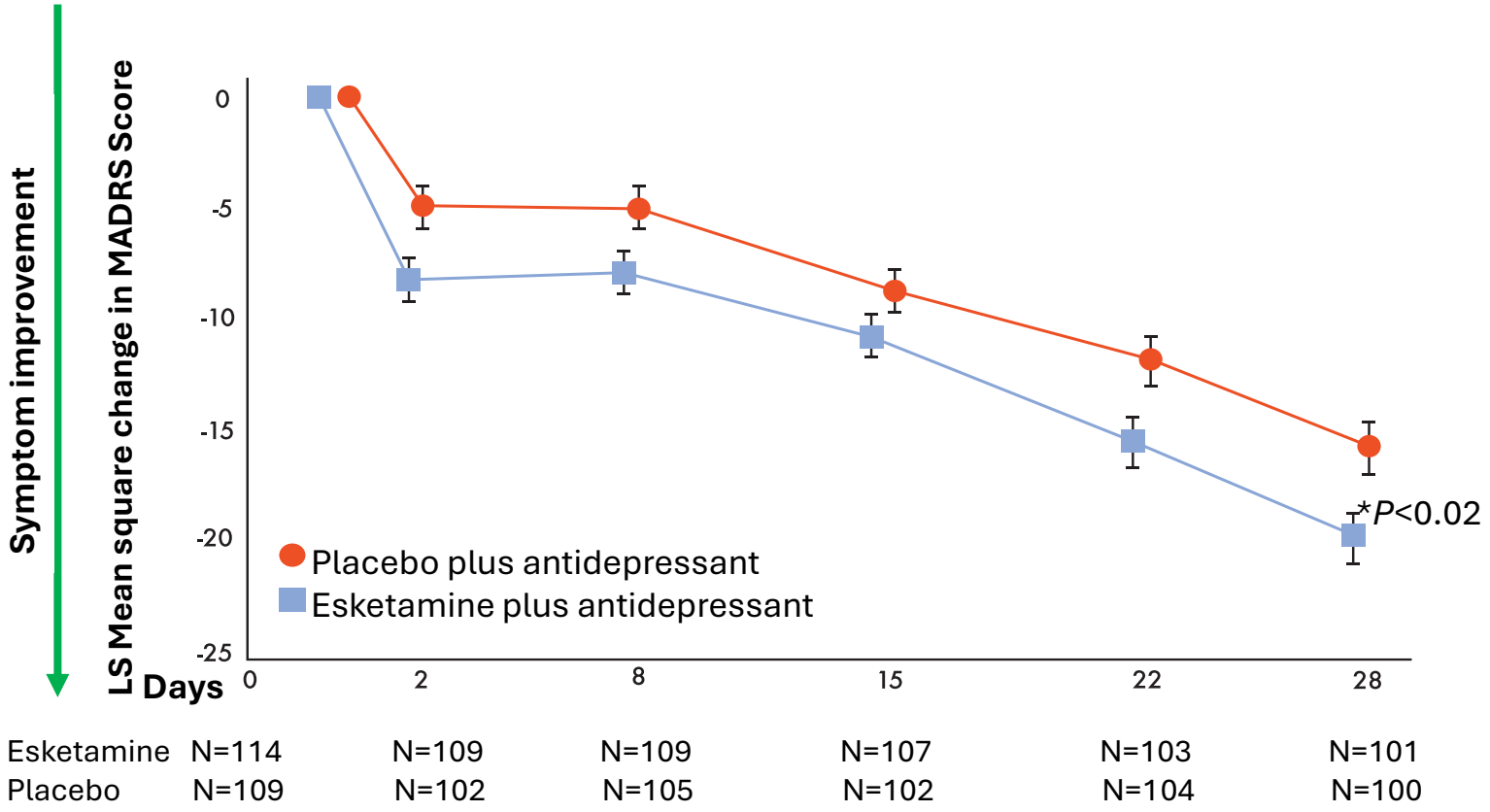
REMS = risk evaluation mitigation strategy

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

Glutamatergic Signaling and NMDA Receptor Modulation in Difficult-to-Treat Depression

Trial of Esketamine for Adjunctive TRD Treatment

In the TRANSFORM-2 trial, adjunctive esketamine decreased depressive symptoms significantly more than adjunctive placebo at week 4



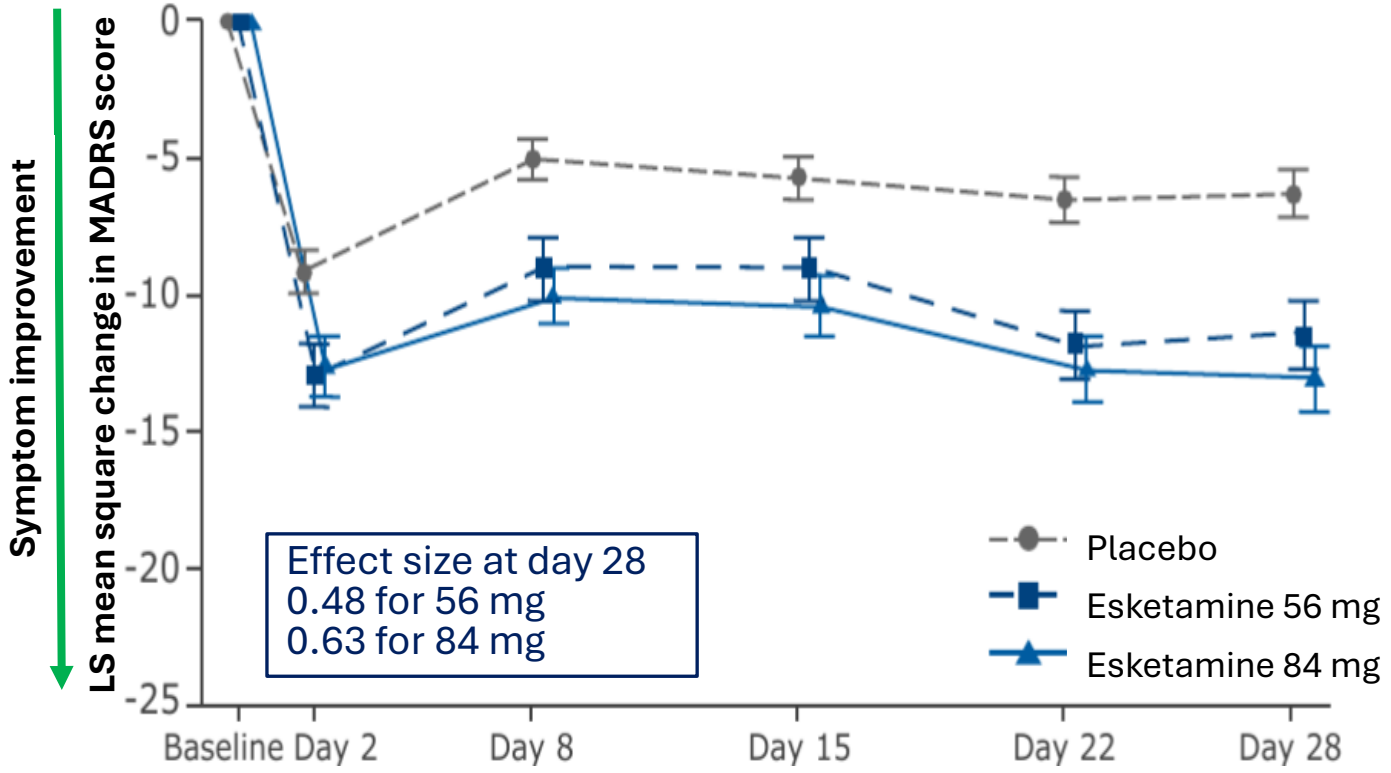
MADRS = Montgomery–Åsberg Depression Rating Scale.

Popova V, et al. *Am J Psychiatry*. 2019;176(6):428-438.

Most Common Adverse Events Observed in TRANSFORM-2 Trial

	Esketamine (N=114)	Placebo (N=109)
Dissociation	26%	4%
Nausea	26%	6%
Vertigo	26%	3%
Dysgeusia	24%	12%
Dizziness	21%	5%
Headache	20%	17%
Somnolence	13%	6%
Blurred vision	12%	3%
Paresthesia	11%	1%
Anxiety	10%	5%
Increased blood pressure	10%	0%
Insomnia	10%	5%
Vomiting	10%	2%
Diarrhea	9%	9%

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.

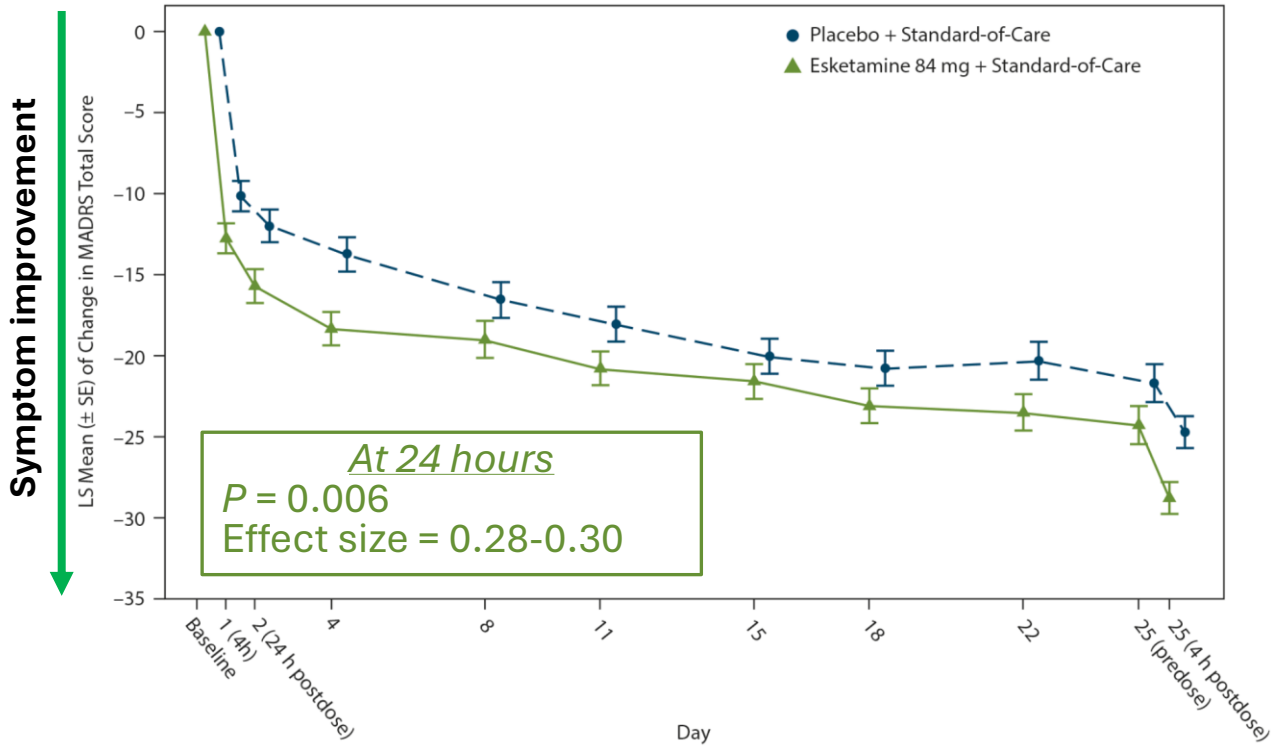
Adverse Events in Double-Blind Phase

	Esketamine 56 mg (N=105)	Esketamine 84 mg (N=121)	Placebo 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

Esketamine Demonstrated Significant Symptom Reduction at 24 Hours in MDD With Active Suicidal Ideation



During the double-blind phase, both groups experienced a reduction in **depressive symptoms** and **suicidality**

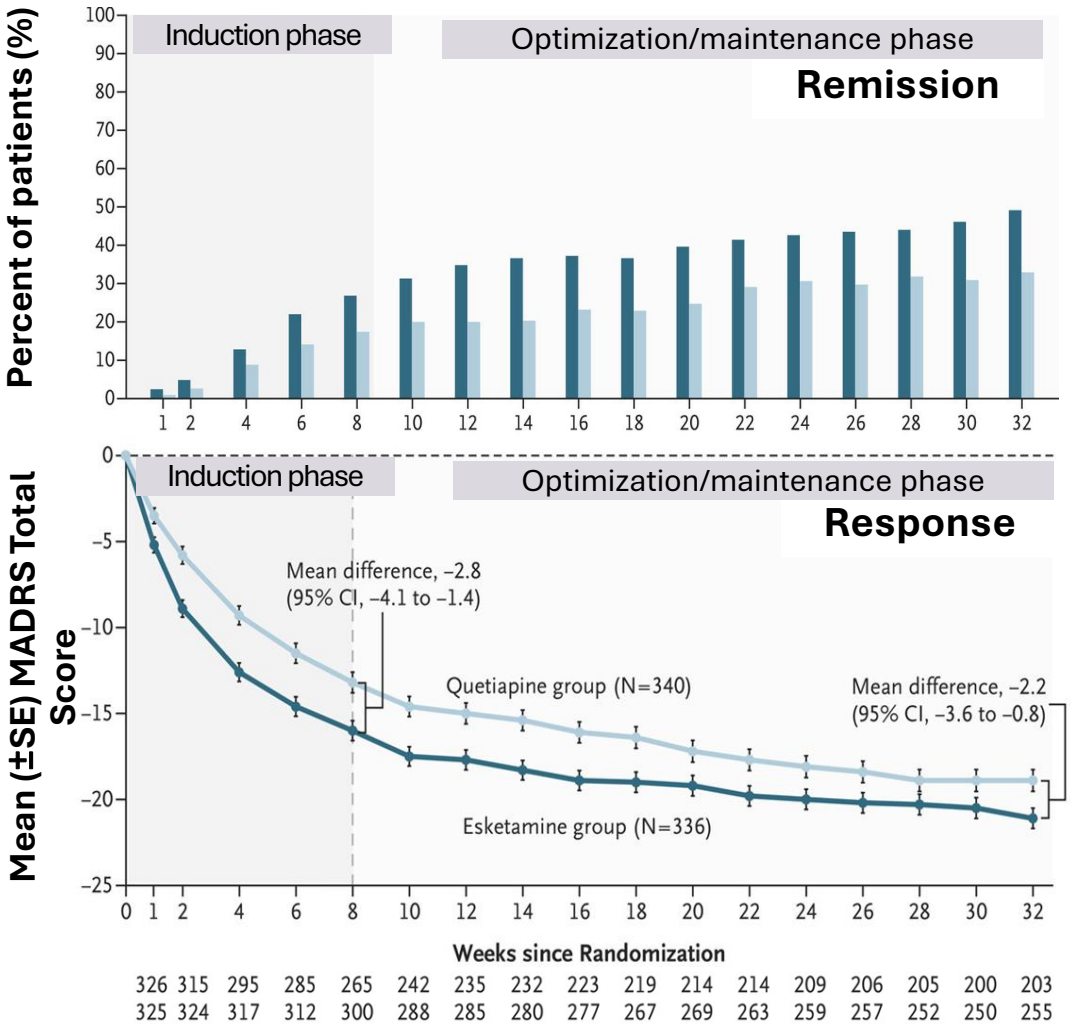
Adverse Events in Double-Blind Phase (ASPIRE-I)		
Event (≥5%)	**Esketamine 84mg** + Standard-of-Care*	**Placebo** + Standard-of-Care
	N=113	**N=112**
Dizziness	35%	9%
Dissociation	29%	4%
Nausea	20%	13%
Headache	19%	18%
Somnolence	19%	10%
Increased BP	17%	5%
Dysgeusia	14%	10%
Constipation	13%	5%
Vision blurred	9%	5%
Hypoesthesia	7%	2%
Vomiting	7%	6%
Insomnia	6%	6%
Sedation	6%	2%
Vertigo	6%	1%
Anxiety	5%	9%
Dizziness postural	5%	2%

*initial psychiatric hospitalization and newly initiated or optimized oral antidepressant[s] therapy

BP = blood pressure

Fu DJ, et al. J Clin Psychiatry. 2020;81(3):19m13191. Published May 12, 2020.

Adjunctive Esketamine Superior to Adjunctive Quetiapine-XR



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

51%

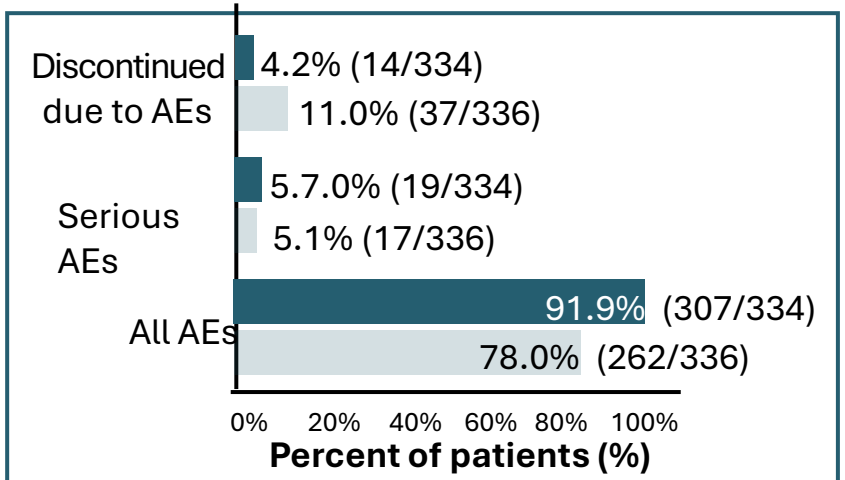
More likely to achieve remission (week 8) OR=1.74 (95% CI: 1.20-2.52) *P*=.003

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

Esketamine Treatment & Relapse Prevention

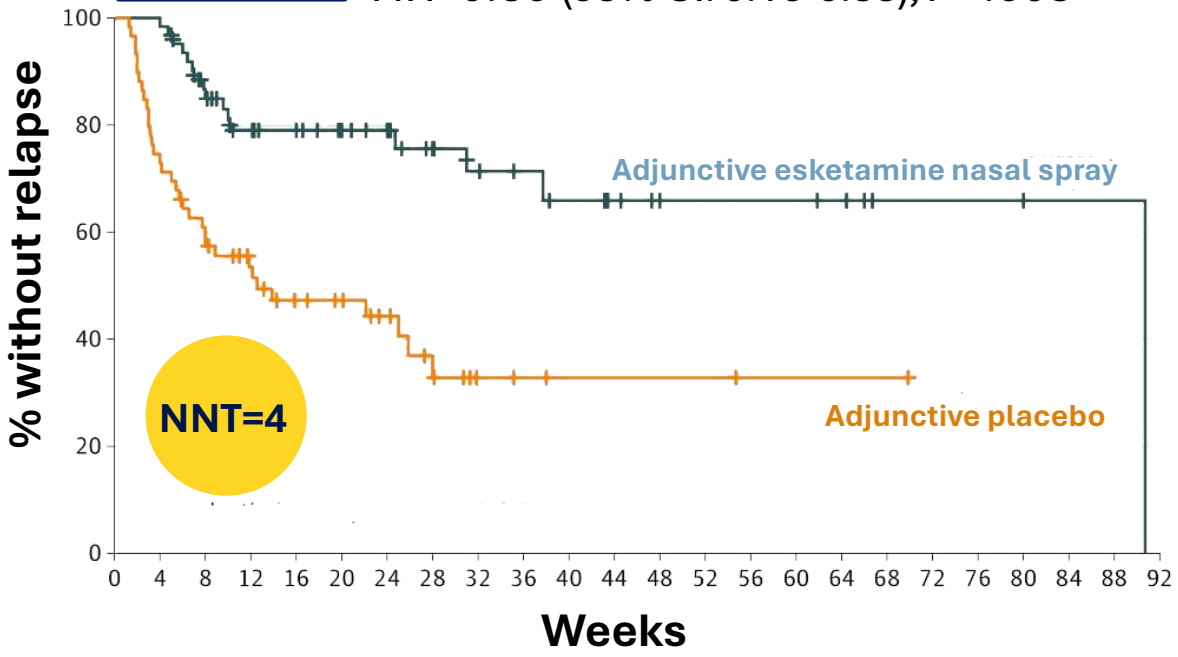
Response and Remission in SUSTAIN-1 Trial

Should patients be on esketamine maintenance therapy?

Patients who responded to treatment

70% were less likely to relapse

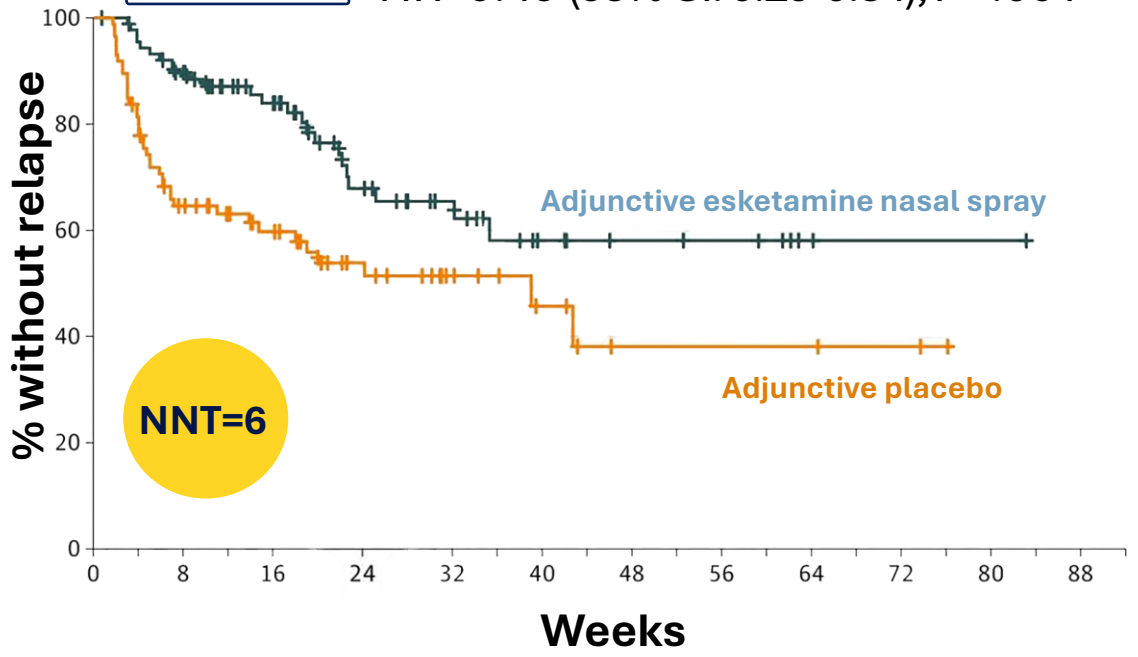
HR=0.30 (95% CI: 0.16-0.55), *P*=.003



Patients who reached remission were

51% less likely to relapse

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



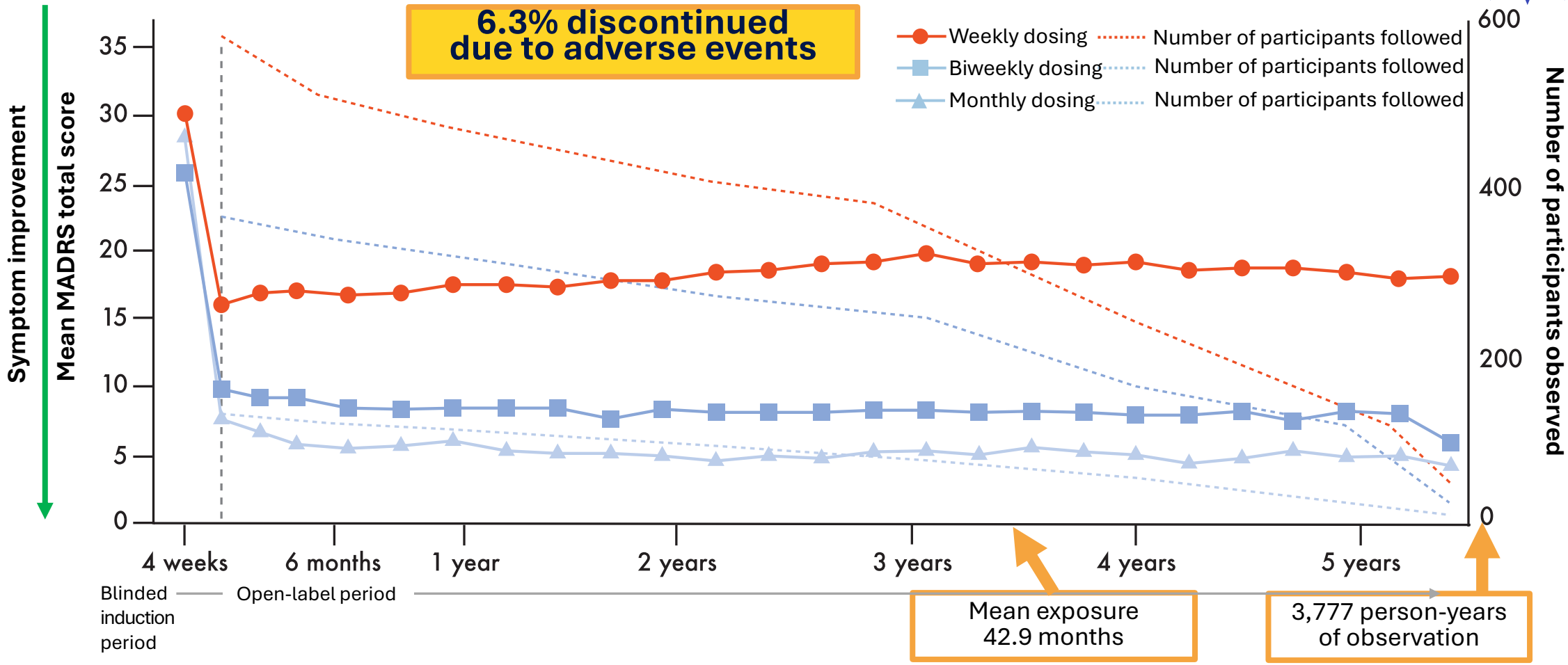
HR = hazard ratio.

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.

Up to 6.5 Years of Esketamine Safety Data

- Phase 3, open-label, single-arm long-term extension study (SUSTAIN-3) conducted from 2016 -2022 in 1,148 patients on esketamine maintenance treatment (weekly, every other week, or every 4 weeks) + oral AD
- **No new safety signals were identified during long-term treatment with intermittently-dosed esketamine**
- There were 9 (0.8%) deaths, none considered related to esketamine. There was 1 completed suicide
- Improvement in depression generally persisted among participants who remained on maintenance treatment

6.4% of patients discontinued due to adverse events	**5.3% of patients discontinued due to lack of efficacy**

Most Common Adverse Events	
Headache	**37%**
Dizziness	**34%**
Nausea	**34%**
Dissociation	**26%**
Nasopharyngitis	**24%**
Somnolence	**23%**
Dysgeusia	**20%**
Back pain	**20%**
Anxiety	**19%**
Arthralgia	**16%**
Diarrhea	**16%**
Vomiting	**16%**
Urinary tract infect	**16%**
Increased BP	**15%**
No sexual side effects or weight gain	

Zaki N, et al. *Int J Neuropsychopharmacol*. 2025;28(6):pyaf027.

Appropriate Risk Management for Esketamine

What REMS requires in practice

- ❑ REMS clinic certification
- ❑ DEA log
- ❑ Patient-specific enrollment paperwork
- ❑ Confirmation of patient's ride home
- ❑ Annual staff training
- ❑ Blood pressure cuff
- ❑ Pulse oximeter
- ❑ Emergency plan for respiratory crisis or symptomatic hypertensive crisis

Real-world respiratory depression after esketamine treatment

96 cases reported from Mar 2019-Jan 2023 (47 Months)

8 >1 day after treatment (8%)
30 unreported date (31%)

excluded from analysis (39%)

58 on treatment day (60%)

8 had normal RR/SpO_2 (12%)
excluded from analysis

11 with depressed RR or SPO2 (17%)
39 with unreported RR or SpO_2 (59%)

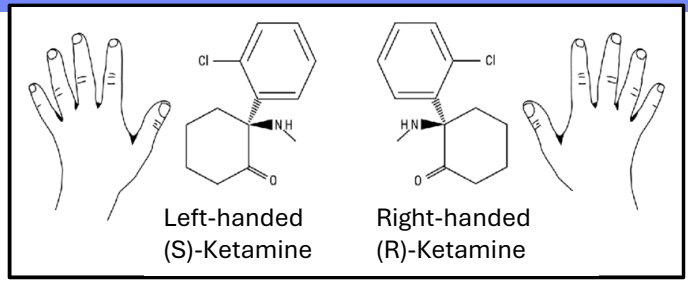
12 normalized after 190 min monitoring (13%)
21 required emergency services* (42%)
6 were hospitalized (12%)
2 had life-threatening events (4%)

36 of 50** were taking concomitant medications

***included emergency visits, oxygen, medication, tactile/verbal stimulation, CPR, and rescue breathing; ** mostly benzodiazepines and other antidepressants, although respiratory cries could not be attributed to these.**
RR = respiratory rate; SpO2 = oxygen saturation.
Chepke C, et al. *Int J Neuropsychopharmacol*. 2024;27(12):pyae058.

Comparison of Glutamatergic Agents

Used for Treatment Resistant Depression



	Dextromethorphan/ bupropion	Esketamine	Ketamine
Approved for TRD?	No	Yes	No
Indication	MDD	TRD	Anesthesia
Mechanism of action	NMDA receptor antagonist	NMDA receptor antagonist	NMDA receptor antagonist
Administration	Oral	Nasal spray	Intravenous, intramuscular, sublingual, oral
Key clinical evidence	GEMINI, ASCEND, COMET	TRANSFORM, SUSTAAIN-1/3, ESCAPE-TRD	Small clinical trials, meta-analyses
Safety considerations	Dizziness, GI effects, lowers seizure threshold	Dissociation, sedation, respiratory and elevated blood pressure (BP)	Dissociation, sedation, respiratory depression, elevated BP, misuse/diversion concerns
Limitations	Not approved for TRD	Available in office only with REMs certification and protocols, requires monitoring of vital signs	Not FDA approved, no standardized dosing or monitoring protocols, no long-term safety data, insurance, and liability issues

Esketamine Prescribing Information. Drugs@FDA: FDA-Approved Drugs. Accessed May 10, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/211243s019lbl.pdf. McIntyre RS, et al. *Am J Psychiatry*. 2021;178(5):383-399. Singh B, et al. *J Clin Psychiatry*. 2023;84(2):22m14548.

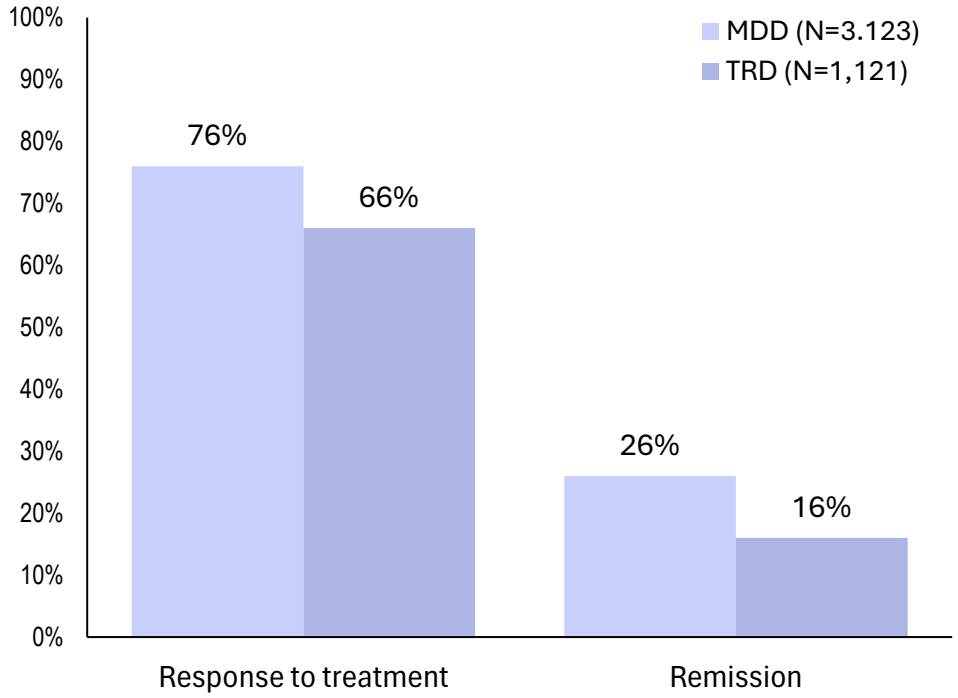
Other Approaches to Modulate Neuroplasticity

in Treatment Resistant Depression

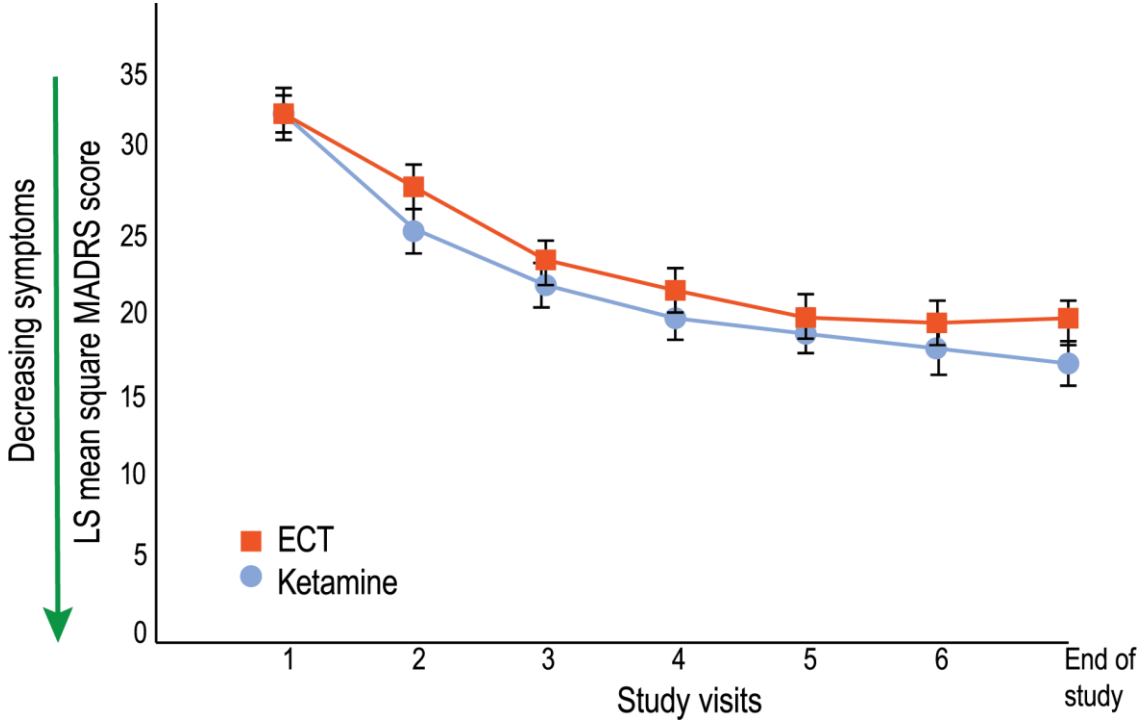
Electroconvulsive Therapy (ECT) for TRD

Hospital & outpatient-based treatment that uses an electrical current to induce a tonic-clonic seizure under general anesthesia

Swedish registry study shows high response rates to ECT in patients with TRD or MDD, with response and remission rates 10% higher in MDD vs TRD



Clinical trial of ECT vs ketamine showed similar MADRS score reduction in patients with TRD with ECT vs ketamine



Anand A, et al. *N Engl J Med*. 2023;388:2315-2325. Nygren A, et al. *BJPsych Open*. 2023;9(2):e35.

Electroconvulsive Therapy: Safety & Efficacy

- ✓ Consider patient safety for general anesthesia
- ✓ Consider current medications and potentially down-titrate psychiatric anticonvulsants / benzodiazepines

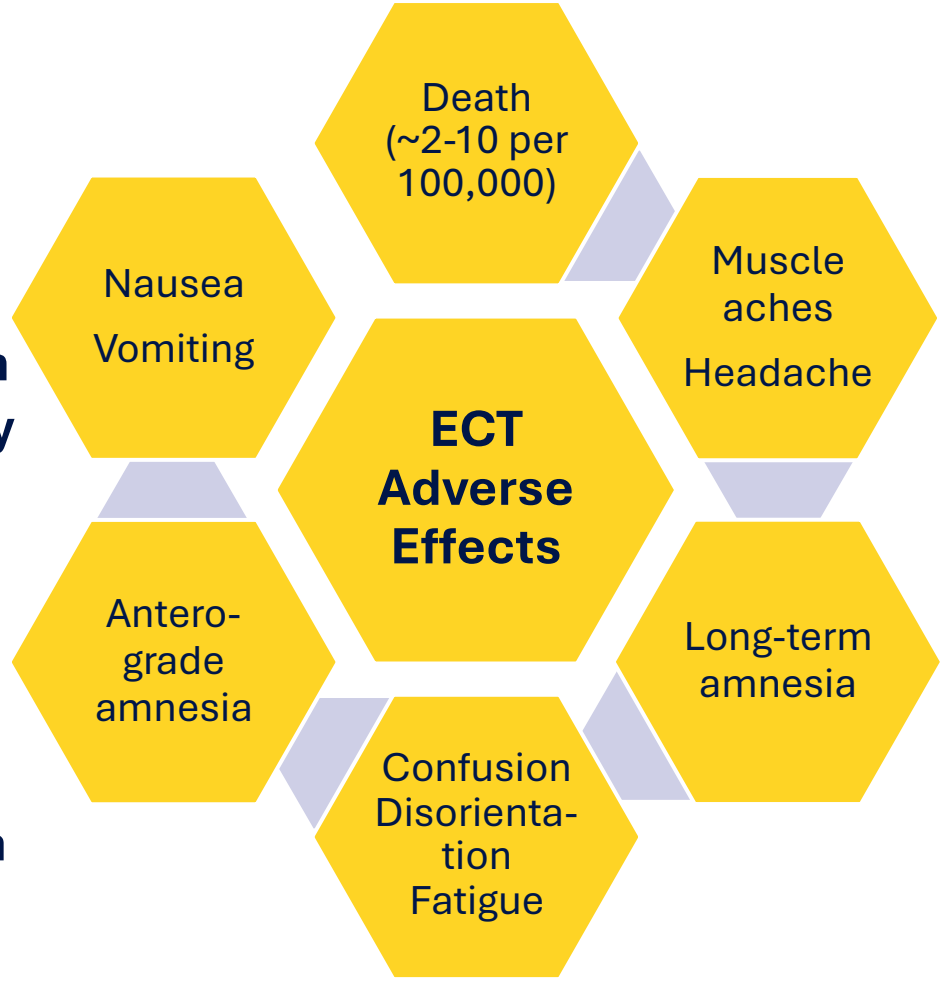
✓ **Contraindications** include intracranial mass, elevated ICP, cerebral aneurysm, recent MI or CVA, high-risk pregnancy

✓ **An acute series is 3 weekly treatments for up to 4 weeks, with each session requiring at least 1 hour from pre-op to recovery**

✓ One of the most rapid and effective treatments for MDD

- ✓ Even in TRD, response rates can exceed 60% to 80%
- ✓ Maintenance ECT (monthly or weekly) is possible for those who respond and then relapse
- ✓ Meta-analysis shows superiority to placebo, stimulated ECT, and several classes of antidepressants

✓ **Preferred treatment for MDD with psychosis and/or catatonia**



ICP = intracerebral pressure; MI = myocardial infarction; CVA = cerebrovascular accident.

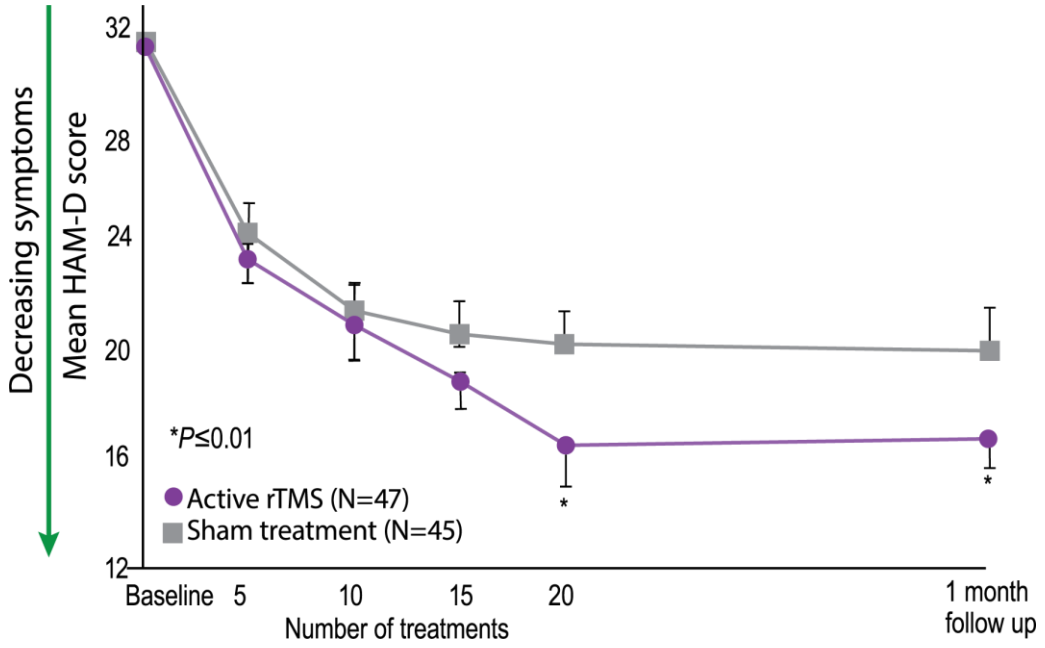
Mutz J, et al., *BMJ*. 2019;364:l1079. Kim J, et al. *Psychiatric Times*. 2024;41(3). Pagnin D, et al. *J ECT*. 2004;20(1):13-20. Andrade C, et al. *Psychiatr Clin North Am*. 2016;39:513. Benbow SM, Tench D. *Int Psychogeriatr*. 2007;19(5):985-987.

Repetitive Transcranial Stimulation for TRD

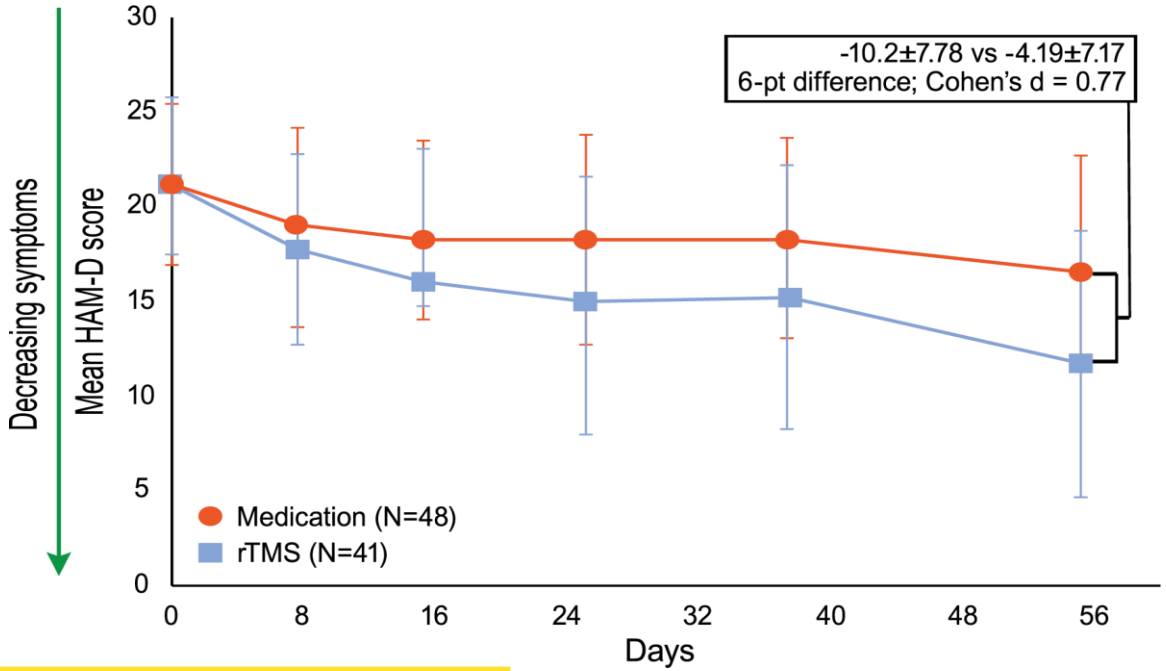
Noninvasive, out-patient treatment without anesthesia

AE data consistent with multiple trials across conditions for rTMS that show low rates of AEs, with transient headache (20%) and stimulation site pain (20%) most common

rTMS significantly reduced depressive symptoms compared with sham stimulation



Switching to rTMS vs switching to or augmenting with a TCA provided 6-point greater improvement on HAM-D

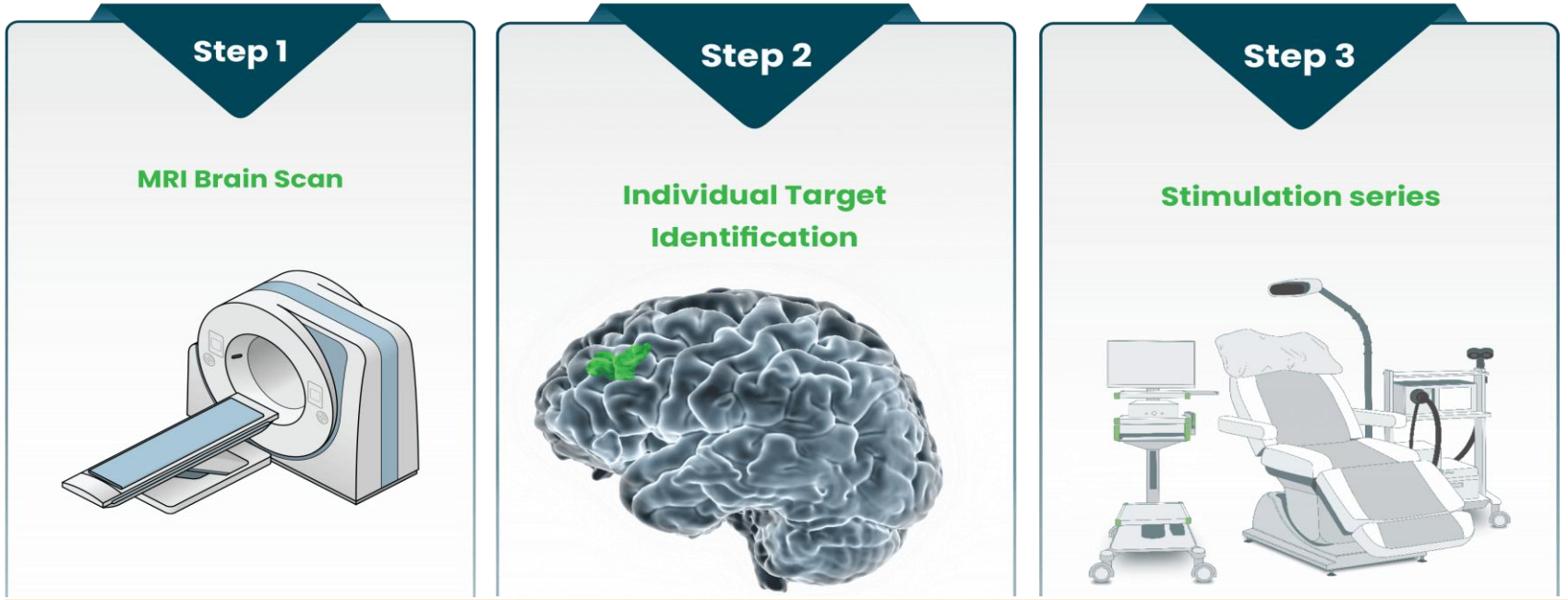


Meta-analysis of 17 studies confirms efficacy of rTMS

rTMS = repetitive transcranial magnetic stimulation; TCA = tricyclic antidepressant.

Carpenter LL, et al. *Brain Stimul*. 2017;10:926-933. Dalhuisen I, et al. *Am J Psychiatry*. 2024;181(9):806-814. Morriss R, et al. Efficacy and Mechanism Evaluation, No. 12.02. Accessed May 12, 2025. https://www.ncbi.nlm.nih.gov/books/NBK612316/.

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/

Vagus Nerve Stimulation for TRD

Mechanism of action

- May increase activity and blood flow in brain structures involved in mood
- In animal models, increases serotonergic and noradrenergic activity

Invasive neurosurgical procedure; stimulator implanted in neck at vagus nerve, controller implanted under chest skin

Stimulator activation

Two-four weeks post-implantation

Programming

By provider, in-office with handheld device, software and "wand"

Features

Can adjust strength, duration, frequency of stimulation

Patient Control

Handheld magnet can be used to pause or emergently deliver stimulation

Continuous operation

Runs on set cycle unless manually adjusted

FDA APPROVED FOR TRD IN 2005

The Royal Children's Hospital Melbourne. Image. Accessed March 10, 2025. https://www.rch.org.au/neurology/patient_information/vagus_nerve_stimulation/. American Association of Neurological Surgeons (AANS). Accessed November 16, 2024. https://www.aans.org/patients/conditions-treatments/vagus-nerve-stimulation/. Kamel LY, et al. *J Neurol Sci*. 2022;434:120171.

Key Learning Points

- Olanzapine/fluoxetine combination therapy is thought to act via a dual mechanism that may improve response to treatment: olanzapine modulates dopamine and serotonin receptors (antagonists) and fluoxetine inhibits serotonin reuptake
- In a placebo-controlled trial of intranasal esketamine monotherapy for TRD, higher remission rates were seen in the **56-mg and 84-mg esketamine groups** compared with the placebo group during the double-blind study phase
- In the SUSTAIN-3 open-label, long-term extension study of adjunctive intranasal esketamine, only **6.4% of patients discontinued treatment** because of treatment-emergent adverse events
- In a head-to-head, open-label trial of intranasal esketamine vs quetiapine XR as adjunctive treatment with an SSRI/SNRI, **participants treated with adjunctive intranasal esketamine had 72% higher odds of remaining relapse-free at week 32 (for those in remission at week 8)**
- Neuromodulation strategies should be considered for all patients who remain depressed after trialing pharmacotherapies

What are the next steps for our patient?

- How do we choose the optimal pharmacotherapy or neuromodulation therapy for TRD?
- What patient-specific factors are important to consider?
- How do we access these treatments? How do we refer to esketamine, TMS, ECT, or VNS?
- Should you start an esketamine treatment center or refer out?

Patient-Specific Considerations

COMORBIDITIES

Psychiatric, substance use and medical

SUPPORT SYSTEMS

Occupational, family, friends

TREATING OR REFERRING

Who is involved in care?

TREATMENT ACCESSIBILITY

Cost, convenience, accessibility, transportation, schedule/routine

TRD: Discussing Treatment Options with Our Patients

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.
Olanzapine/ Fluoxetine	The only SGA evaluated in patients failing two or more prior antidepressant treatments	Intolerable side effects for some. Requires daily adherence to oral medication.

SGA = second-generation antipsychotic. McIntyre RS, et al. *World Psychiatry*. 2023;22:394-412.

An Update On Our Patient...

She was referred to an esketamine treatment center

- She initially could not decide between TMS or esketamine but could not come in for 36 consecutive treatments and the nearest TMS clinic was 30 min away. She was also worried about headaches
- You checked the REMs certified esketamine treatment center located online and found a clinic 3 miles from her home. You contacted the clinic and faxed over your recent clinic notes
- The clinic contacted her and scheduled an intake appt
- Her insurance approved the treatment, she completed 12 sessions over 8 weeks, and is now in remission and completing maintenance treatments once every other week
- She still sees you regularly and you are working on tapering off the sertraline

Practical Take-Aways

- ✓ If remission is not achieved after two adequate trials of monoaminergic antidepressants, consider treatments proven effective for TRD
- ✓ Treatments that have been proven effective for TRD and approved for this indication by the FDA include
  - ✓ Olanzapine/fluoxetine, an oral agent that adds a dopaminergic agent to a monoaminergic treatment
  - ✓ Esketamine, a glutamatergic agent self-administered as a nasal spray in a REMs-certified treatment center
  - ✓ Neuromodulation therapies, including ECT, rTMS, iTBS, and VNS

Resource Slides

Effects of Deficient or Excessive Glutamate Signaling

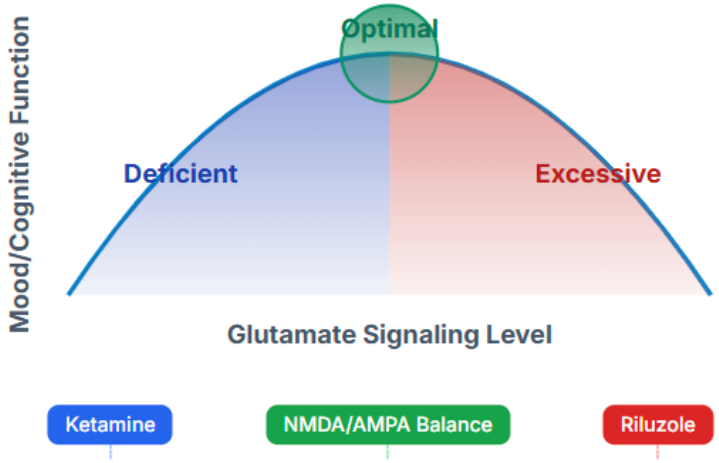
Deficient Glutamate

Mechanism
Reduced glutamate release, altered receptor expression

Effects
Impaired LTP, reduced neuroplasticity

Clinical Features
Chronic TRD, anhedonia, cognitive slowing

Treatment Strategy
Ketamine (transient glutamate surge)



The inverted U-shaped relationship between glutamatergic signaling and clinical outcomes

Optimal Glutamate

Balance
Appropriate AMPA:NMDA receptor ratio

Effects
Healthy synaptic plasticity and LTP

Clinical Features
Normal mood regulation, cognitive function

Signaling
Balanced glutamate release and uptake

Excessive Glutamate

Mechanism
Reduced astrocytic uptake, excess glutamate release

Effects
Excitotoxicity, synapse damage, oxidative stress

Clinical Features
Acute stress, early depression stages, anxiety

Treatment Strategy
Riluzole, lamotrigine, NAC

Amidfar M, et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2019;94:109668. Lener MS, et al. *Biol Psychiatry*. 2017;81(10):886-897. Rubio-Casillas A, Fernández-Guasti A. *Rev Neurosci*. 2016;27(6):599-622. Wang YT, et al. *Pharmacol Res*. 2021;171:105761. Yao R, et al. *Psychiatry Res*. 2020;284:112750. Duman RS, et al. Neuron. 2019;102(1):75-90.

Management of Adverse Events Associated with Esketamine

Medication Administration and Adverse Event Mitigation

1. Ensure adherence to REMS (ie, certification, post-administration monitoring, paperwork) and controlled substance requirements
2. Recommend patients do not eat 2 hours before or drink 30 minutes before treatment (consider pretreatment with anti-emetic (eg, ondansetron)
3. Ensure patient's blood pressure is controlled
4. Instruct patient to use the restroom and blow their nose
5. Check device expiration date and ensure indicator shows 2 green dots; do NOT prime device
6. Have patient recline head about 45°, insert tip into either nostril, close other nostril, push plunger entirely; repeat on other side
7. Check that indicator shows no green dots and instruct patient to rest comfortably and refrain from blowing nose for at least 5 min
8. Repeat steps 5-7 once (if 56 mg) or twice (if 84 mg)
9. Instruct patient to remain seated or lying down
10. Observe for at least two hours after last dose, checking blood pressure 40 min and 2 hours after each dose

Induction phase (weeks 1-4)

- 56 mg twice weekly
- May increase to 84 mg after day 1

Early maintenance phase weeks 5-8

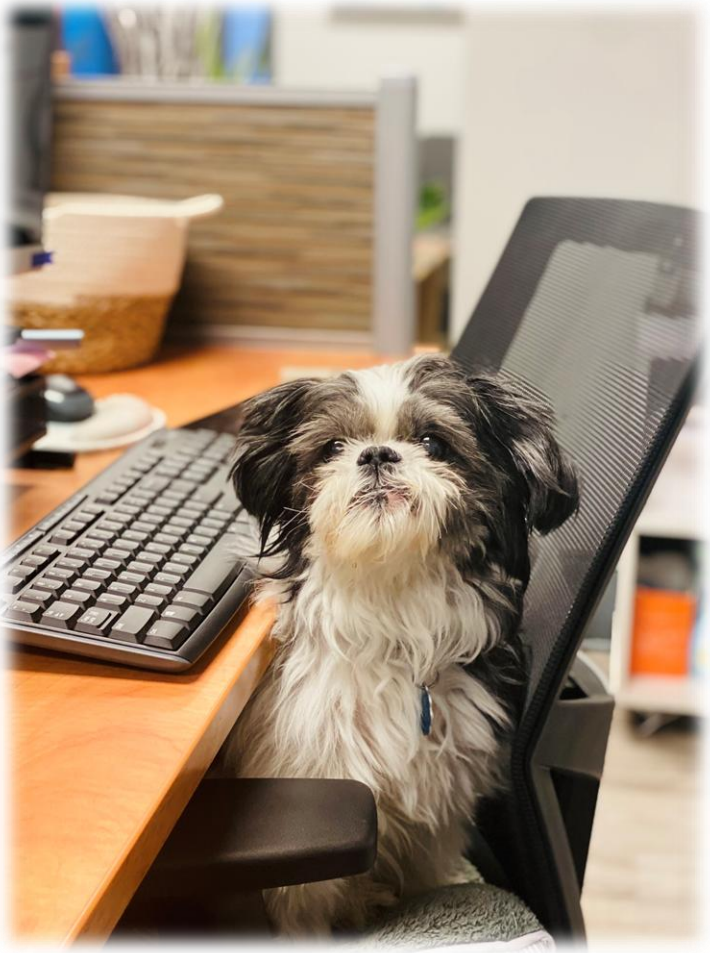
- 56 or 84 mg once weekly

Maintenance phase weeks 9+

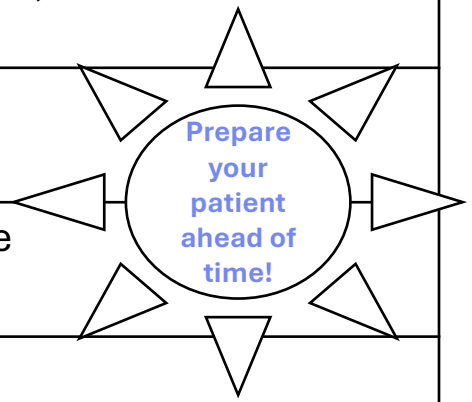
- 56 or 84 mg weekly or every other week
- Dosing less frequently than every two weeks is off-label but can be acceptable if response maintained

Bozymski KM, et al. *The Annals of Pharmacotherapy*. 2020;54(6): 567-576.

Management of Adverse Events Associated with Esketamine

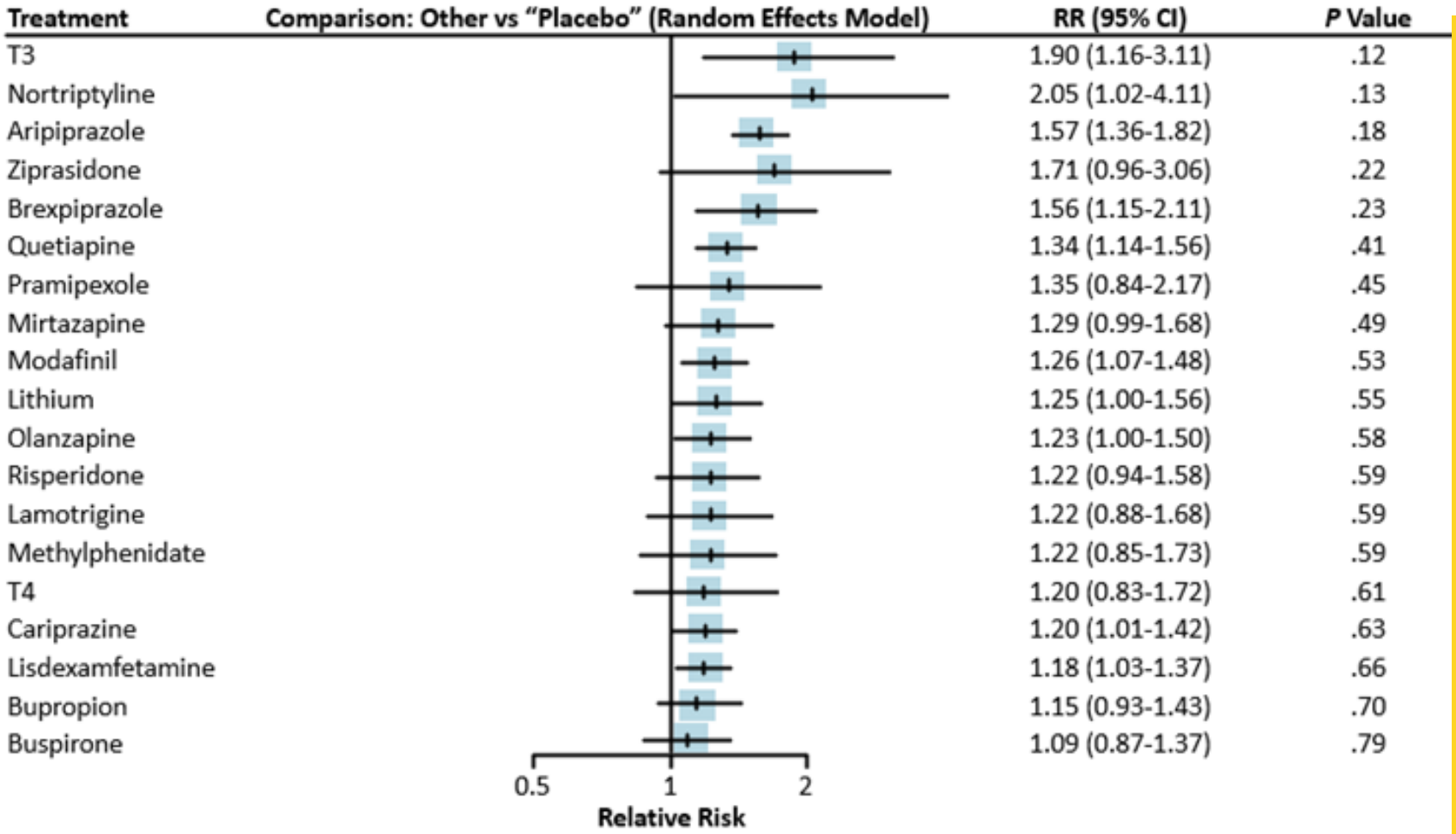


Adverse Event	Recommendations
Nausea, vomiting	Recommend not eating 2 hours prior to treatment, do not drink 30 min prior In some cases, may pretreat with an antiemetic, eg, ondansetron
Hypertension	Ensure blood pressure is controlled prior to treatment. Asymptomatic hypertension should not generally be treated due to short $t_{½}$ of esketamine. If hypertensive crisis occurs, activate emergency services Check BP prior to treatment, 40 min after first dose, and 2 hours after last dose
Deep sedation	Attempt to rouse Check vital signs, including pulse oximetry
Dissociation	Psychoeducation, Personnel reassuring presence Generally, would not administer anxiolytics
Dizziness	Keep patient seated/lying down Have patient use restroom prior to start of treatment to reduce need to do so after esketamine administration



McIntyre RS, et al. American Journal of Psychiatry. 2021;178(5): 383-399.

Meta-Analysis of Adjunctive Treatment with Augmentation Medications in TRD



Pairwise analysis for relative risk of depression response

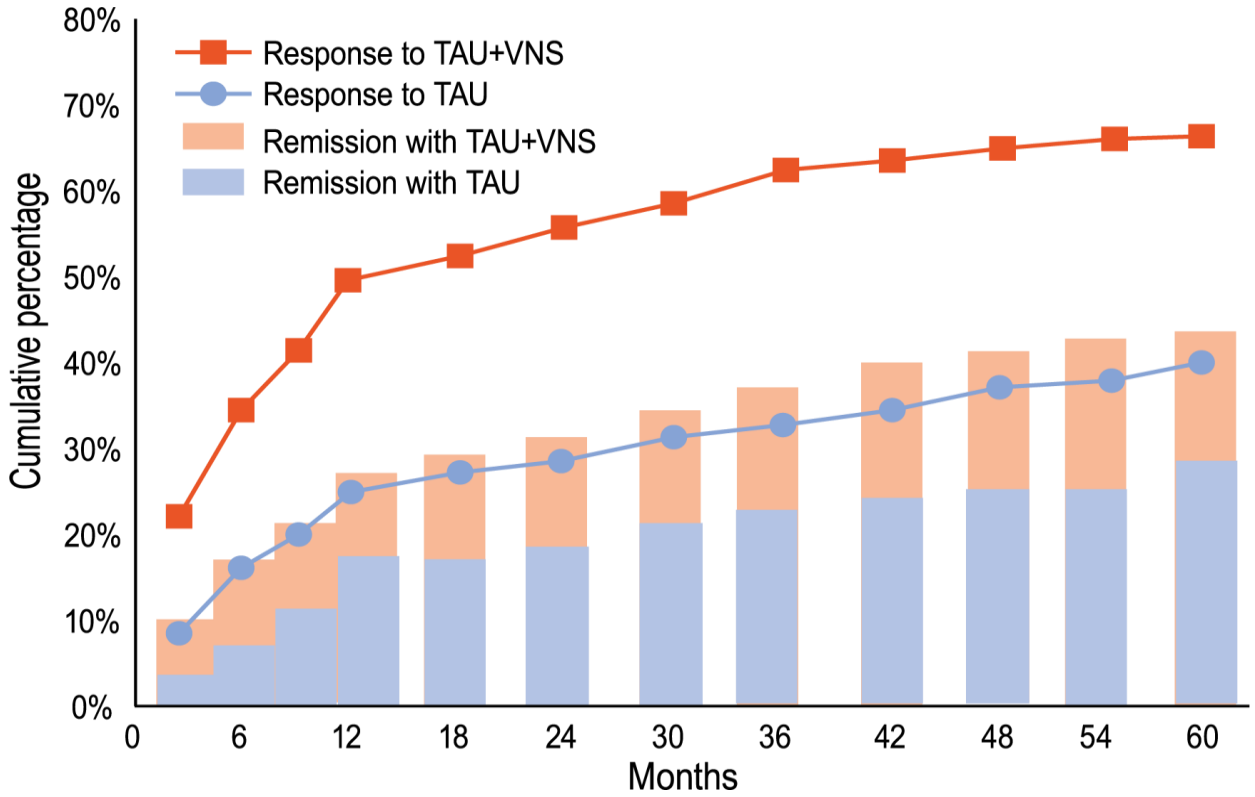
- **Findings:** T3, nortriptyline, aripiprazole, brexpiprazole, lithium, quetiapine, modafinil, olanzapine (fluoxetine), cariprazine, and lisdexamfetamine were more efficacious compared to placebo
- **All cause discontinuation**: significant findings for ziprasidone, mirtazapine, and cariprazine compared to placebo
- **Meta-analysis supports tailoring adjunctive treatment to the individual patient—highlighting the need for precision in TRD**

RR = relative risk; CI = confidence interval; T3 = triiodothyronine; T4 = thyroxine.

Nuñez NA, et al. *J Affect Disord*. 2022;302:385-400.

Adjunctive Vagus Nerve Stimulation for TRD

Approximately twice as many patients responded to treatment or reached remission with augmentive vagal nerve stimulation vs treatment as usual



Proportion with Highest Level of Side Effects on FISBER	TAU+VNS		TAU	
	Baseline	5 years	Baseline	5 years
Side effect frequency	24%	9%	18%	15%
Side effect intensity	10%	3%	6%	5%
Side effect burden	6%	2%	5%	3%

Most Common Adverse Effects

- Voice alteration
- Cough
- Neck pain
- Dysphagia
- Dyspnea
- Paresthesia

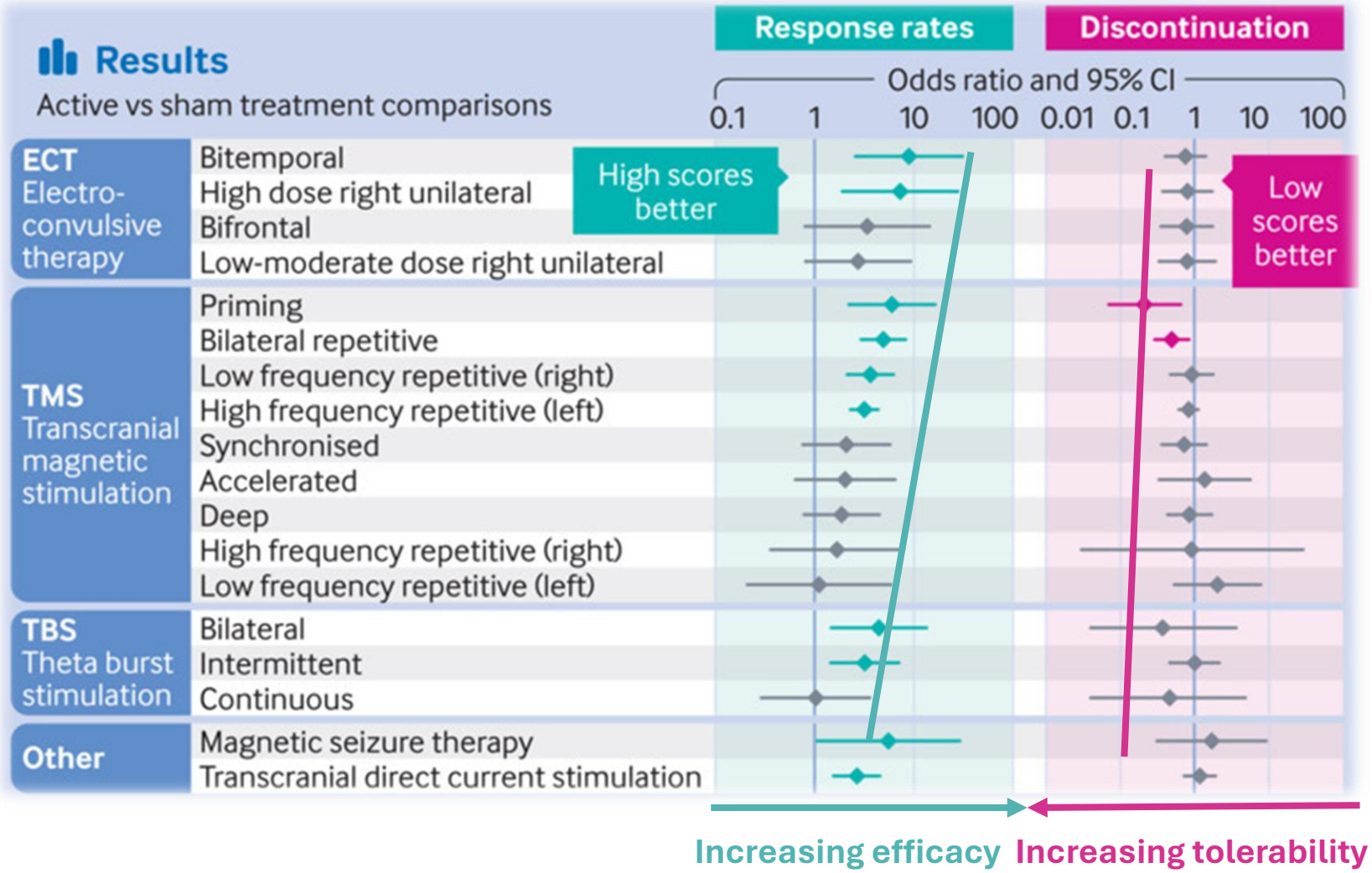
FIBSER = Frequency, Intensity, and Burden of Side Effects Rating Scale; TAU = treatment as usual; VNS = vagal nerve stimulation.

Aaronson ST. *Am J Psychiatry*. 2017;174:640.

Neuromodulation for TRD Treatment

Meta-analysis of **113 randomized, controlled clinical trials** in **6,750** patients with MDD or BPD showed favorable response rates and tolerability of neuromodulation treatments

- **81% of trials included only people with TRD**
- 59% of trials excluded patients with psychotic features
- 63% of trials were adjunctive treatment
- Did not examine specific AEs

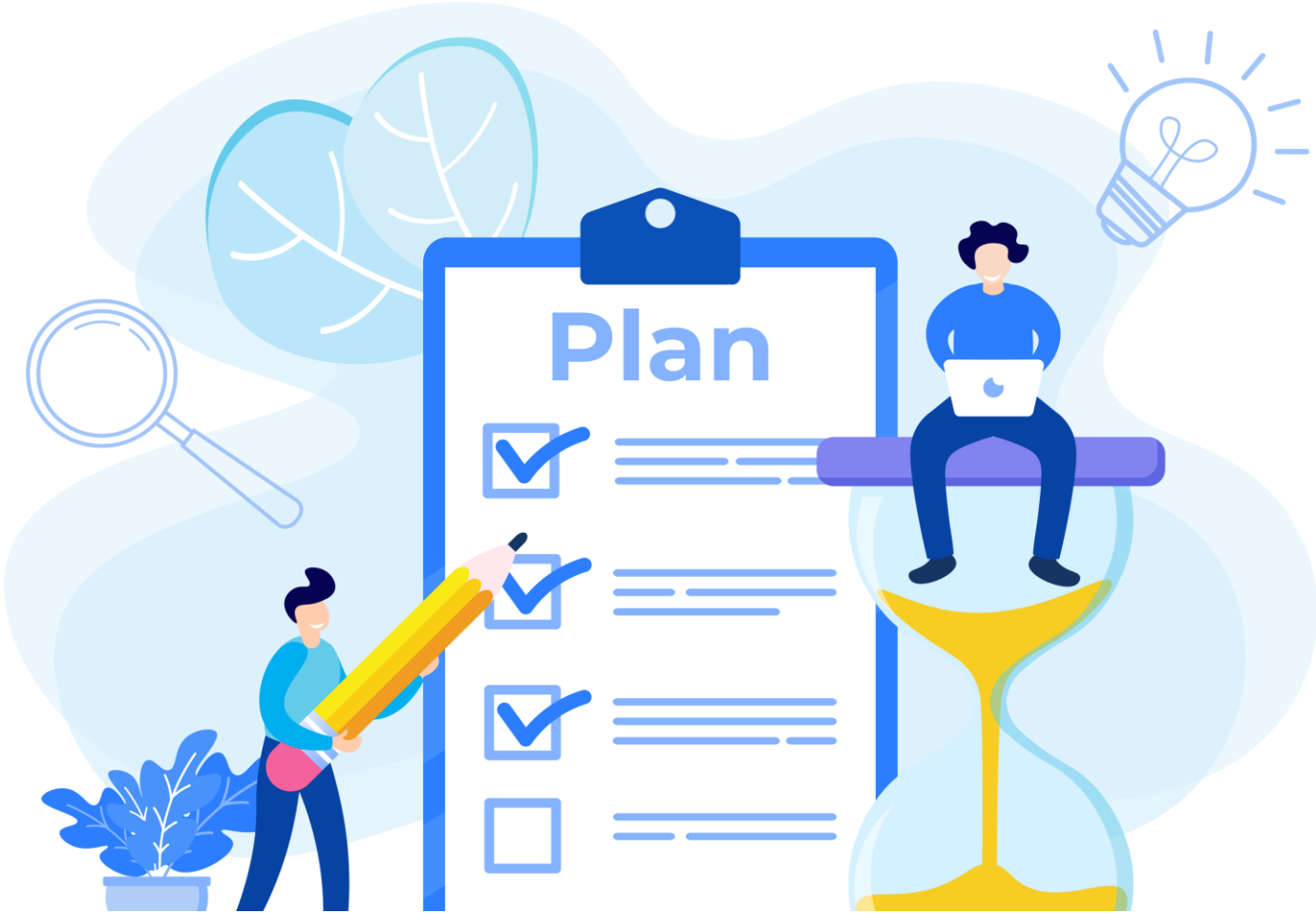


ECT = electroconvulsive therapy; TMS = transcranial magnetic stimulation; TBS = theta burst stimulation.

Mutz J, et al. *BMJ*. 2019;364:l1079.

Strategies for Shared Decision-Making

Two adequate trials of monoaminergic antidepressants and not in remission?



- **When is the right time to consider esketamine instead of another monoaminergic treatment?**
- **How do we decide between adjunctive esketamine vs esketamine monotherapy for TRD?**
- **When is it appropriate to consider other non-monoaminergic treatments for TRD?**

Key Learning Points

- ✓ Neuromodulation strategies should be considered for all patients who remain depressed after trialing pharmacotherapies
- ✓ TMS is noninvasive and is indicated and effective for patients who have trialed ≥1 medication for depression; TMS carries low AE profile
- ✓ ECT remains gold standard for MDD with psychotic features, but the AEs and invasiveness of the procedure remain challenges
- ✓ VNS is FDA-approved for TRD and has demonstrated long-term efficacy, but insurance coverage is challenging, and patients may have to have 4 or more unsuccessful treatments to qualify