



Time to Change the Target: Optimal Use of Glutamatergic Antidepressants in Treatment-Resistant Depression

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Learning Objectives

- Describe the **suboptimal outcomes** associated with conventional monoaminergic antidepressants in MDD/TRD
- Assess the evolving neurobiological understanding of the **glutamatergic system** and its role in MDD/TRD
- Evaluate the MOAs and the latest clinical and real-world evidence and **treatment implications** associated with newer glutamatergic and neuromodulation therapies for TRD
- Develop personalized treatment plans for patients with TRD according to the latest guidelines and the principles of patient-centered care and shared decision-making

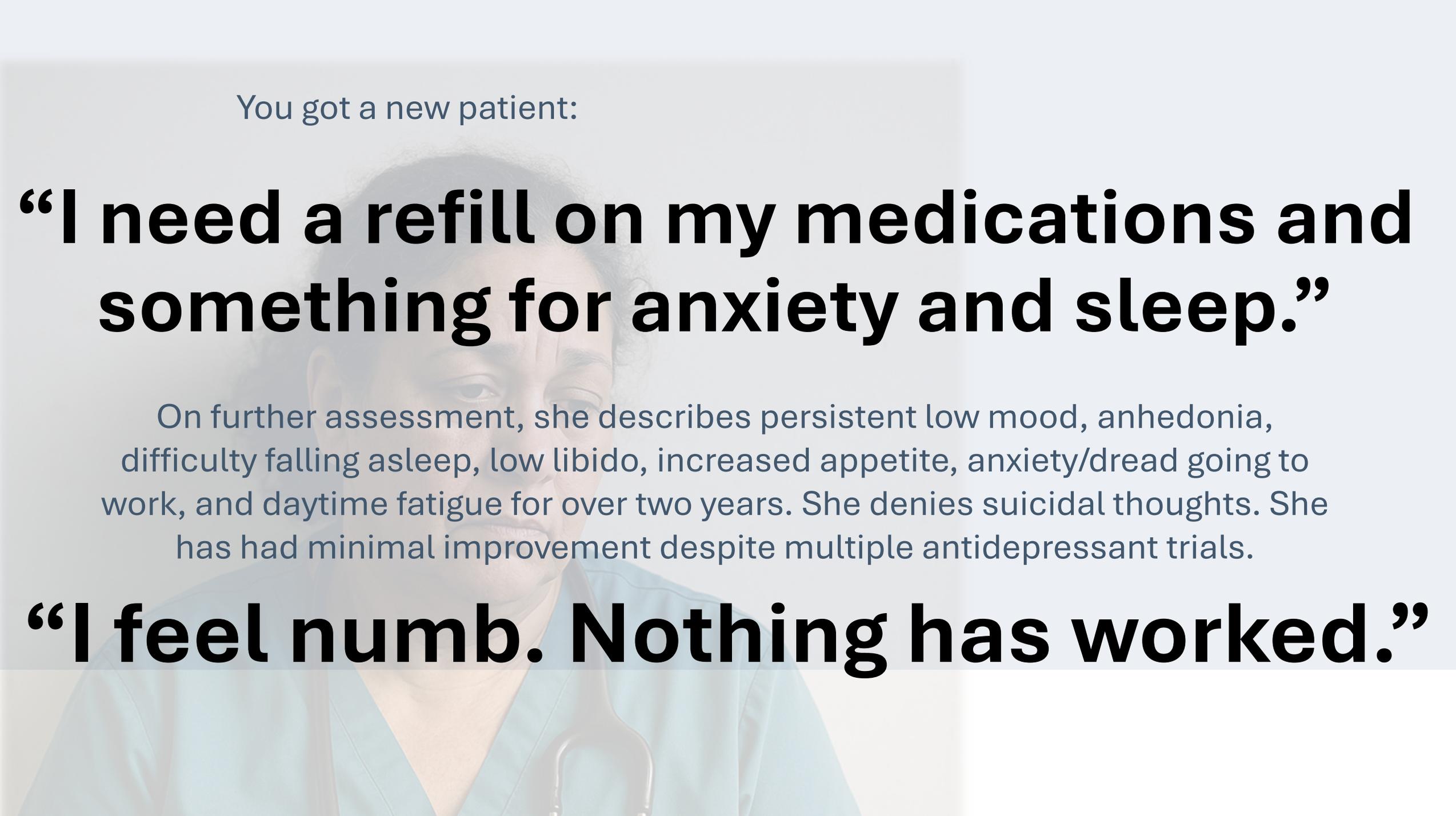
We are broken.

~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:

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

On further assessment, she describes persistent low mood, 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 anesthesiologist...

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.

47-year-old divorced female anesthesiologist...

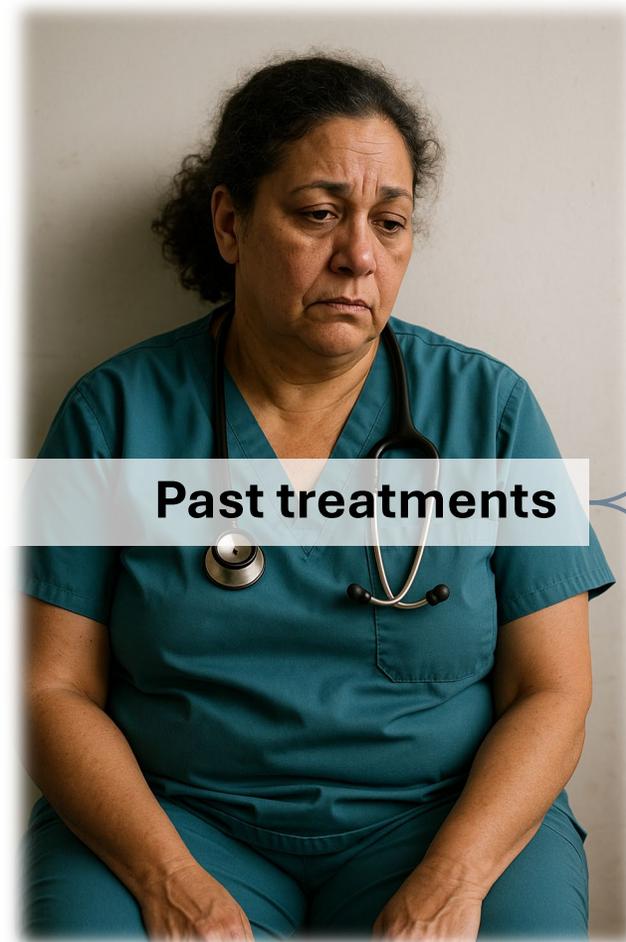
Current meds

Sertraline 150 mg daily (ongoing, >5 weeks, no significant response)
Seroquel 50mg QHS
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)?

TRD = Subset of MDD

- ≥ 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



Where did this TRD term come from? STAR*D



Key STAR*D Findings

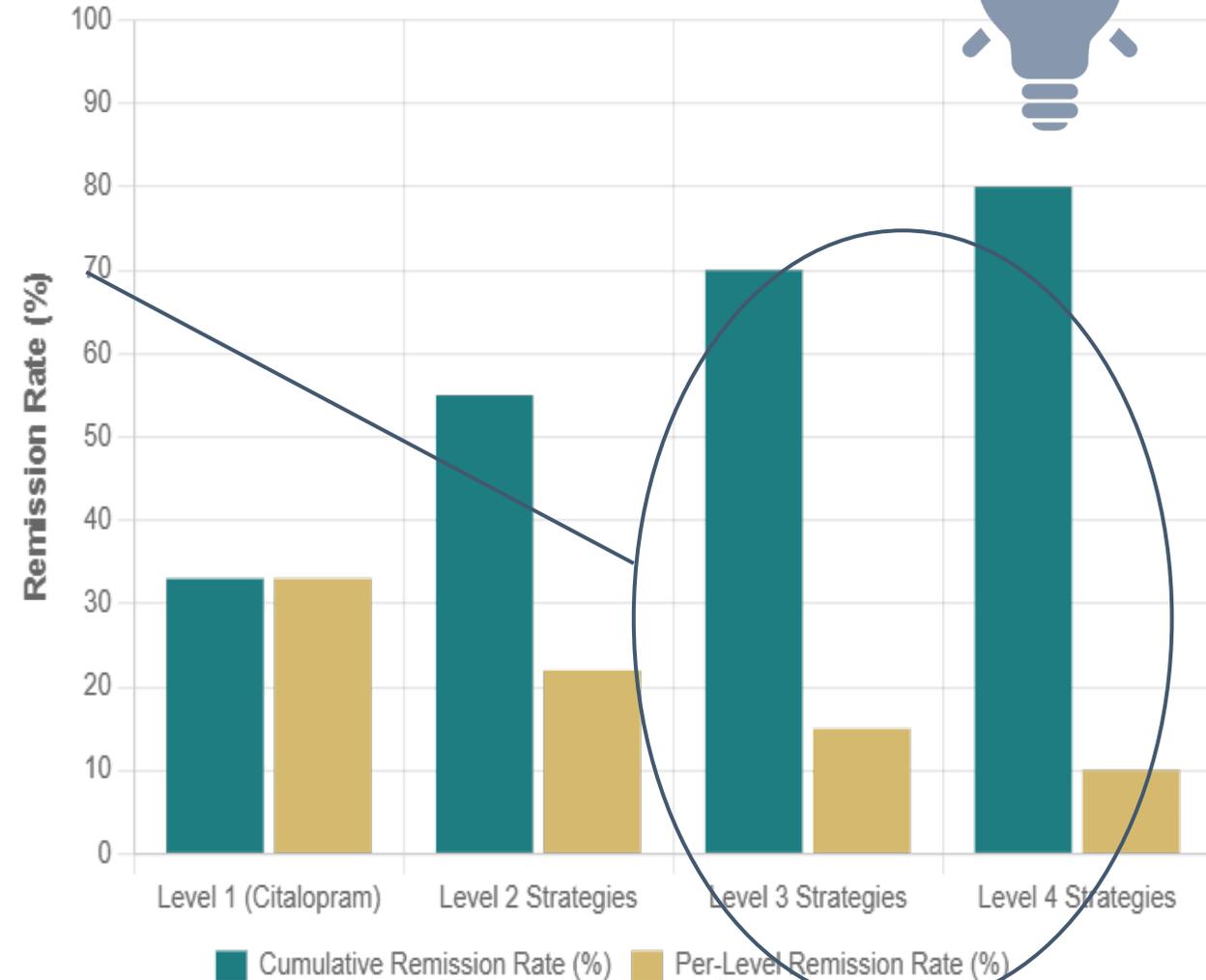
~**20%-30%** of patients fail to respond to 4 sequential treatment strategies

Remission rates **decrease** with each successive treatment step

- Level 1, citalopram: ~**33%** remission
- Level 2, switch/augment: ~**25%** remission
- Level 3, ~**14%** remission
- Level 4, ~**13%** remission

Implications for Clinical Practice

TRD represents a distinct subgroup requiring mechanism diversification beyond standard monoaminergic approaches



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

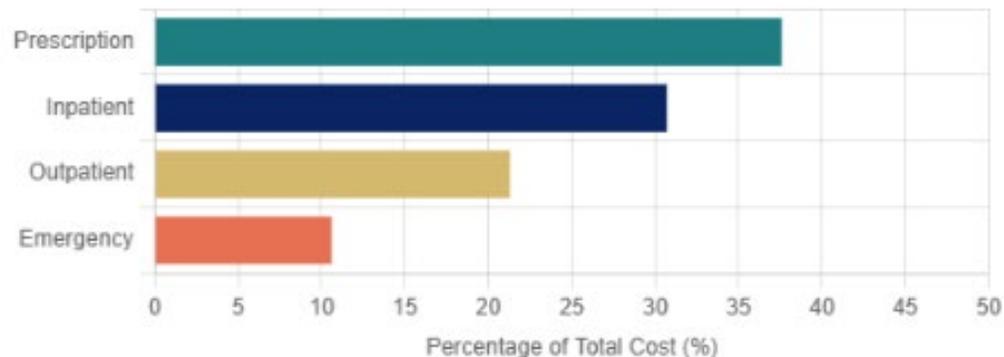
- Greater impairment in social and family functioning
- More persistent cognitive dysfunction
- Higher rates of comorbid anxiety and substance use

TRD: Significant Healthcare Utilization & Costs

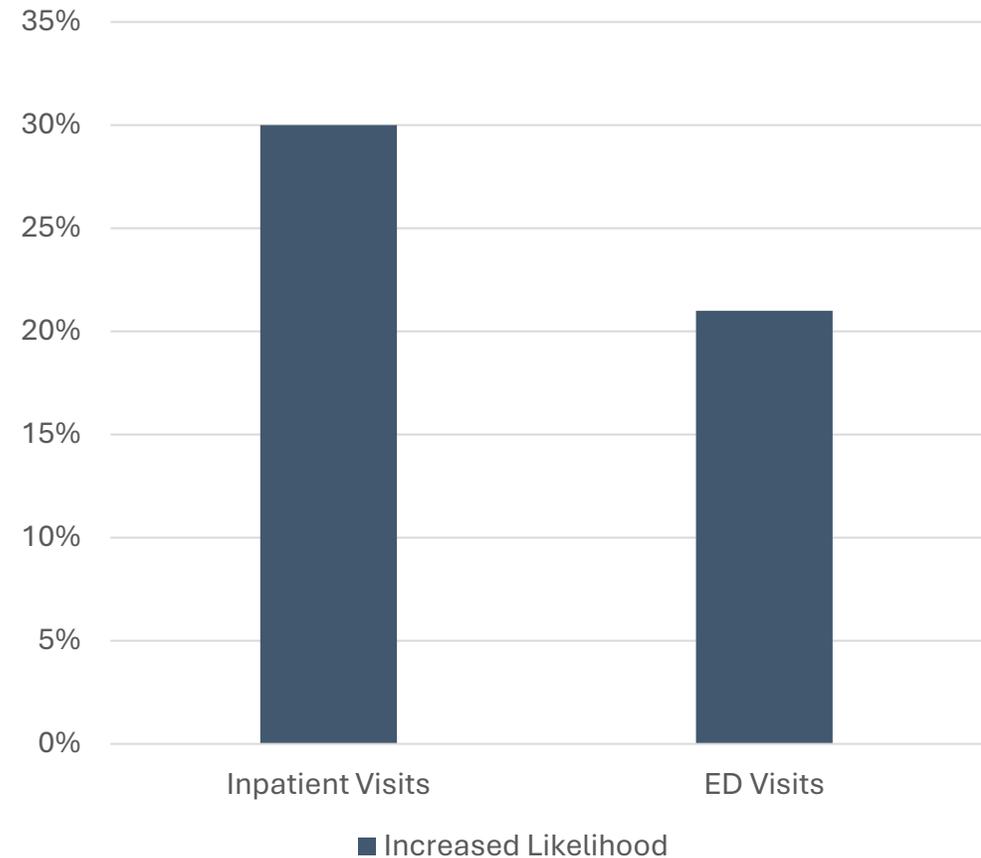
Annual Healthcare Cost (2018 US\$)

Non-TRD	TRD	Excess Cost
\$14,712	\$21,015	+\$6,303

Cost Drivers in TRD



Healthcare Utilization Increase (TRD vs non-TRD)

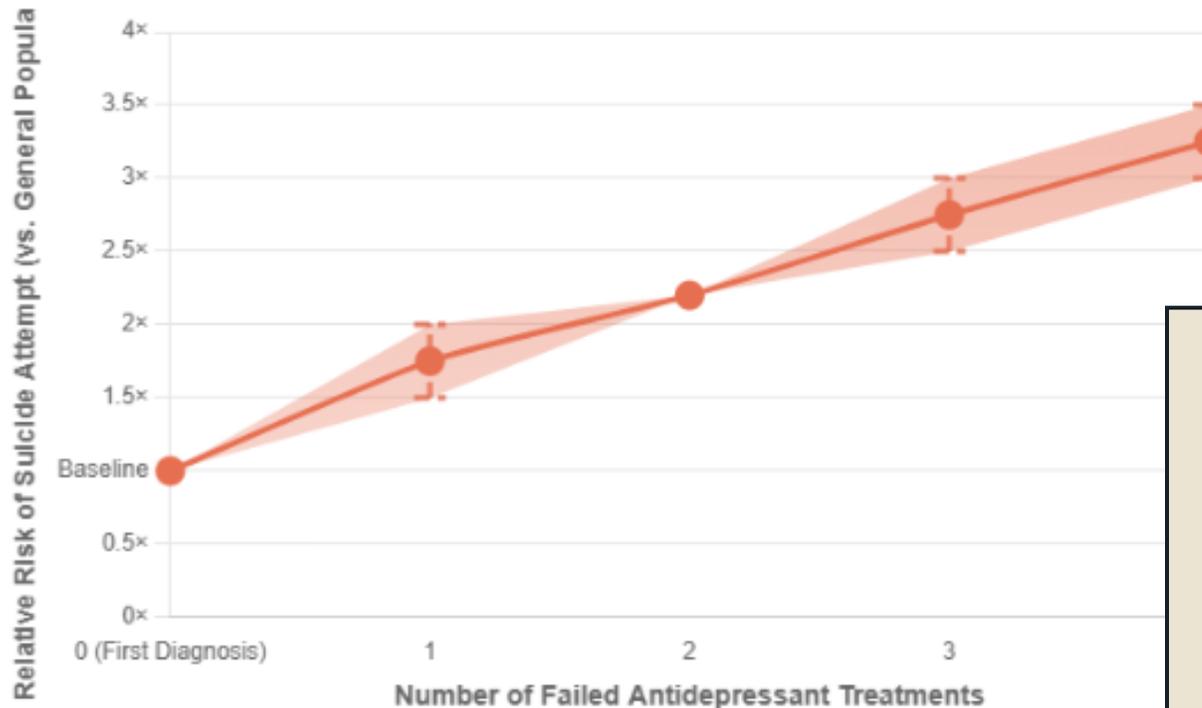


ED = emergency department.

Shah D, et al. *Pharmacoeconomics*. 2021;39(6):639-651. Pappa S, et al. *J Psychiatr Res*. 2024;180:511-518.

TRD: Greater Disability, Suicidality, and Mortality

Suicide Risk Increases with Treatment Failure



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

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

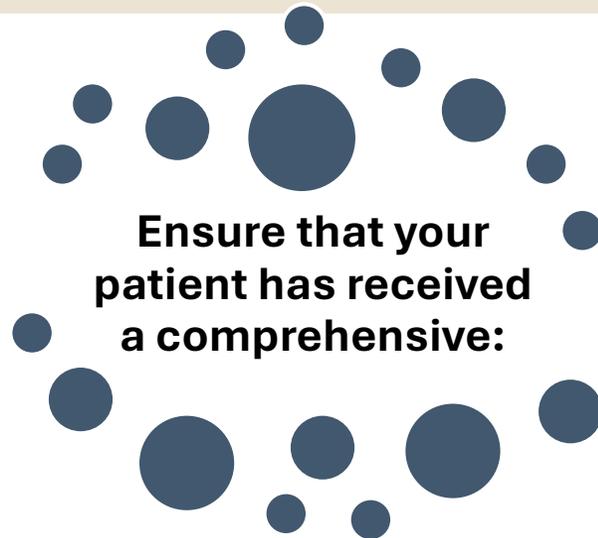
At least 30% of persons with MDD have TRD.



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.



- 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)



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

PHQ9 = Patient Health Questionnaire-9

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.

TRD: Differential Diagnosis

NEUROLOGIC MIMICS

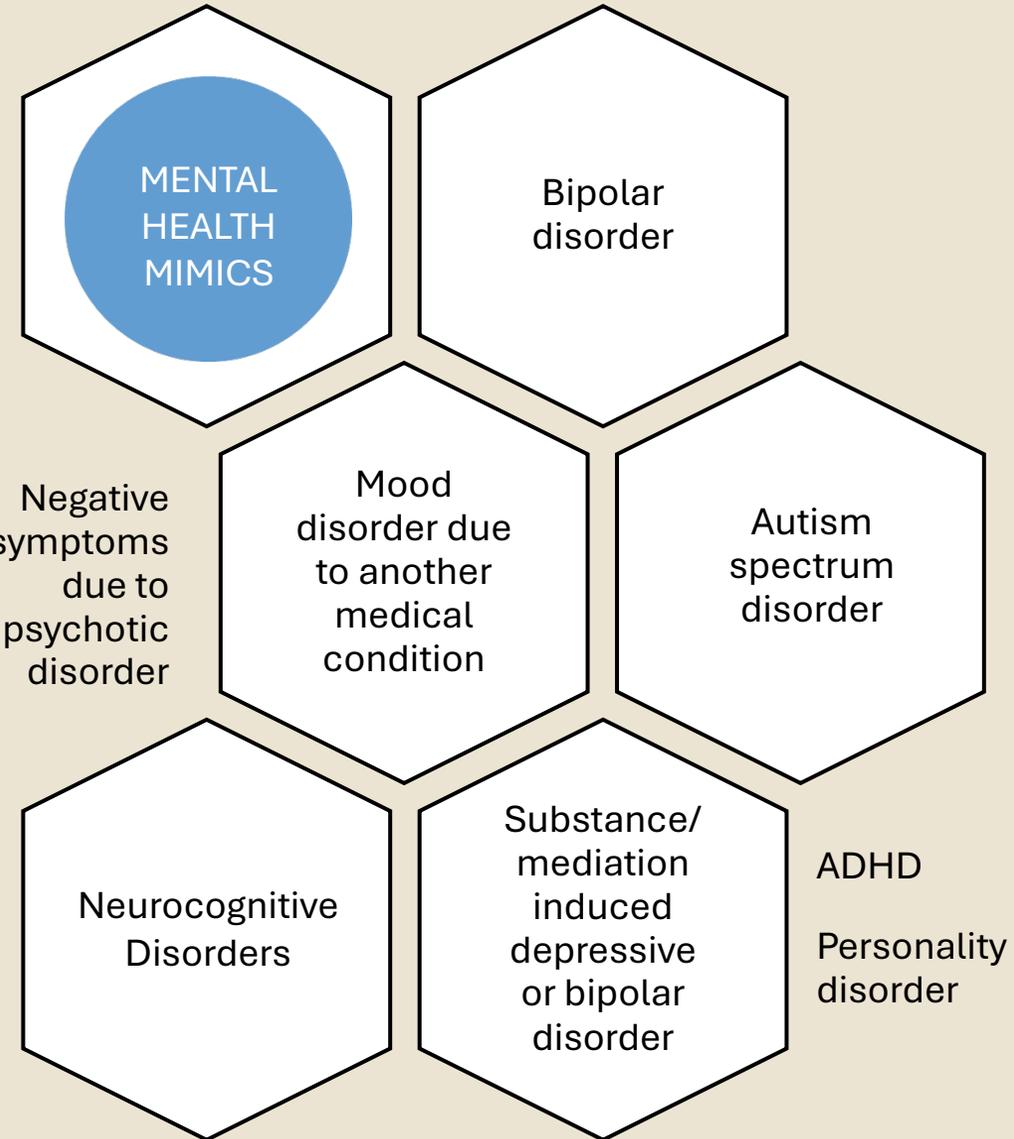
PARKINSON'S DISEASE
STROKE
MIGRAINE
TRAUMATIC BRAIN INJURY
NARCOLEPSY
AMYOTROPHIC LATERAL SCLEROSIS
EPILEPSY

MEDICAL MIMICS

CANCER
CHRONIC PAIN
HYPOTHYROIDISM
VITAMIN DEFICIENCIES
DIABETES
CARDIOVASCULAR DISEASE
OBSTRUCTIVE SLEEP APNEA
OTHER SLEEP DISORDERS
INFECTIONS
MENOPAUSE
ANEMIA

MEDICATION MIMICS

OPIOIDS
CALCIUM CHANNEL BLOCKERS
CORTICOSTEROIDS
INTERFERON ALPHA
BENZODIAZEPINES
RESERPINE
SOME ANTICONVULSANTS
CANNABIS



Key Learning Points

Definition, Prevalence, Burdens, Diagnosis



Prevalence of TRD ~30% amongst those with MDD

- Additionally, 1 in 5 depression patients will not achieve remission despite 4 trials

Diminishing returns

- The STAR*D remission cascade highlights early attrition with each subsequent treatment step

High economic burden

- TRD drives \$6K annual excess cost per patient versus MDD, with significantly increased suicide risk (x2.2++)

Rule out pseudoresistance

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

Additional medical findings for our patient

- Her PHQ9 score = 18
- BP 135/89
- Labs significant for mildly elevated TSH
- Pt in perimenopause
- Ordered sleep apnea test = moderate obstructive sleep apnea → started CPAP

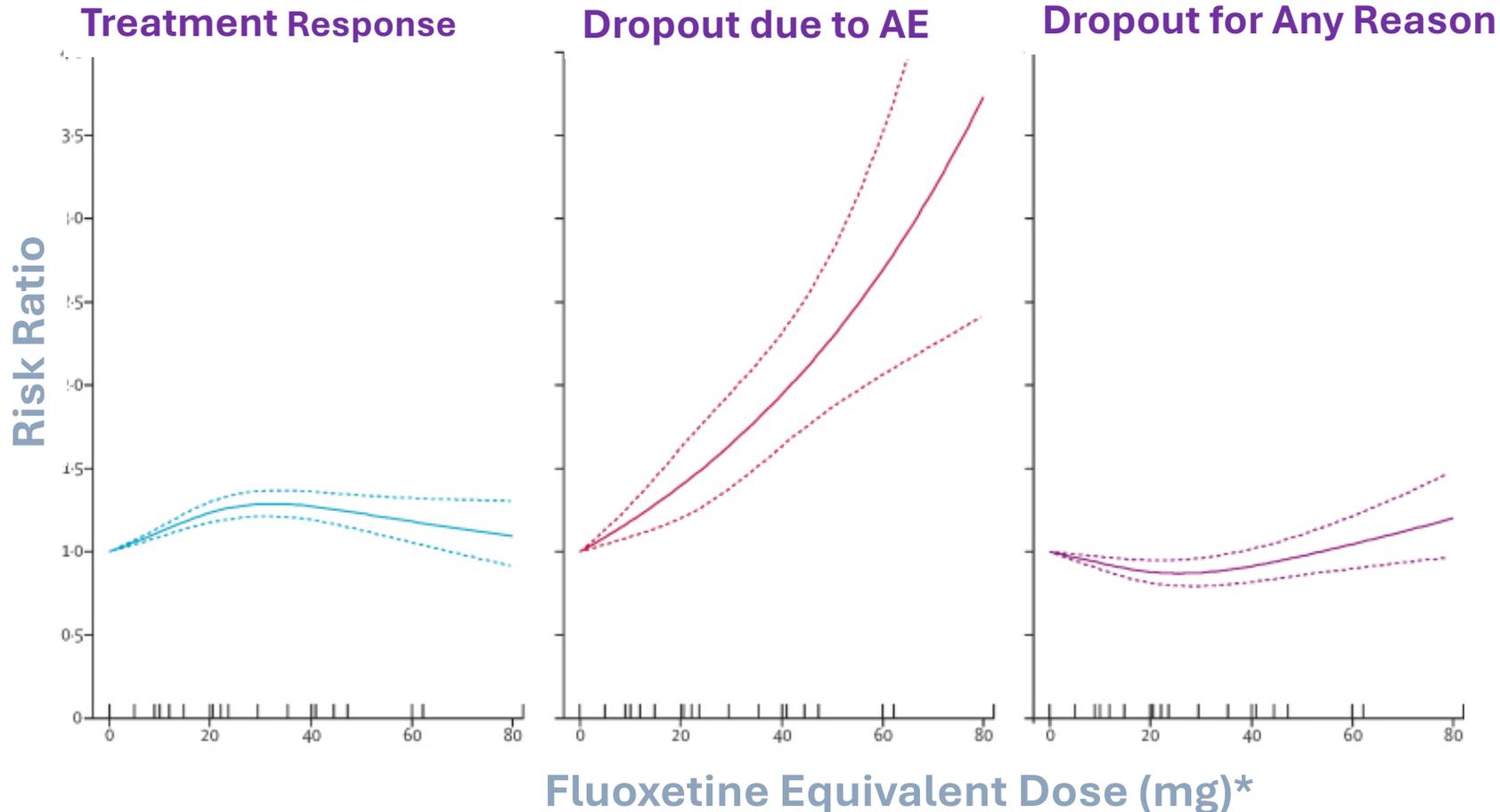
What do we do next for her?

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



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

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

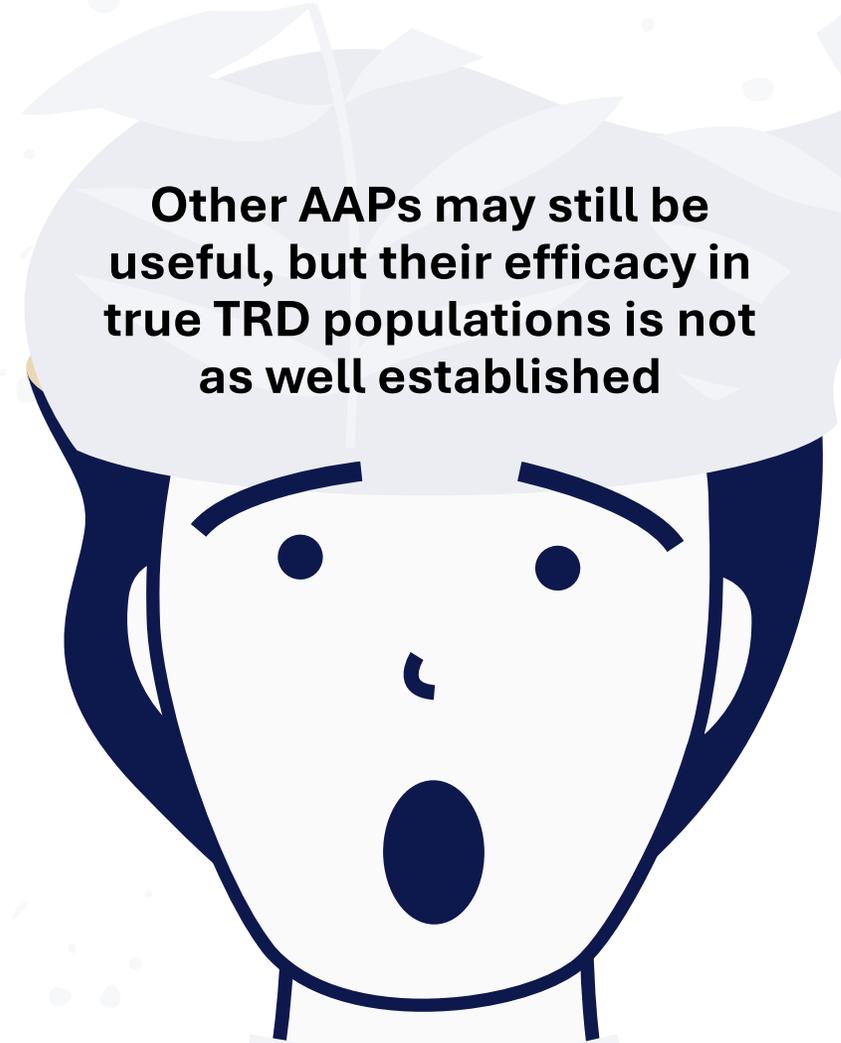
- Cognitive problems
- Depressed mood
- Eating problems
- Mood dysfunction
- Psychomotor effects
- Suicidality
- Decreased motivation
- Fatigue



Adverse effects

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

What about adding an adjunct atypical antipsychotic?



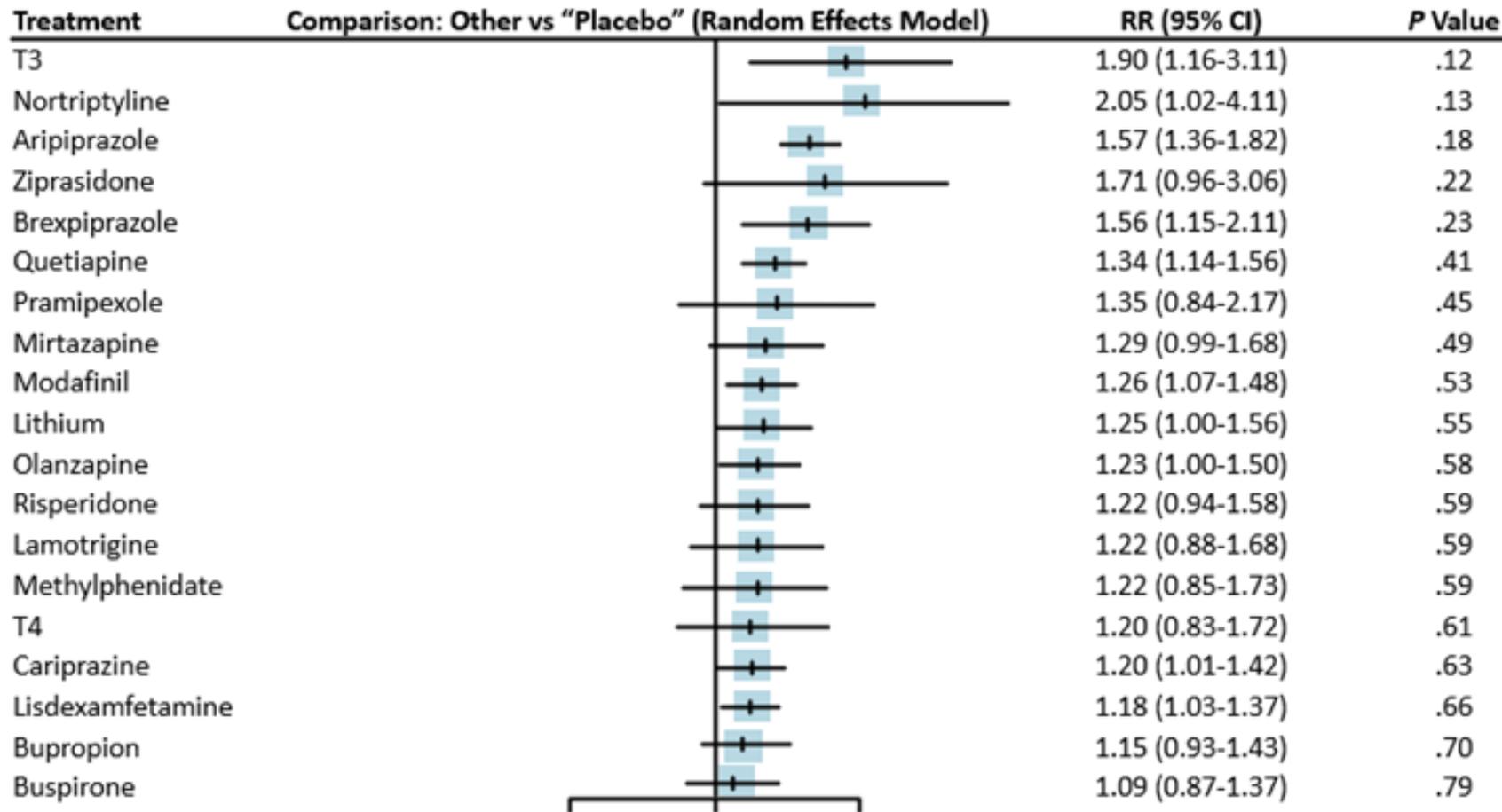
Other AAPs may still be useful, but their efficacy in true TRD populations is not as well established

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.

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

Meta-Analysis of Adjunctive Treatment with Augmentation Medications in TRD



Pairwise analysis for relative risk of depression response

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

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

- **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

What about olanzapine/fluoxetine combination (OFC)?

Monoaminergic Combination Treatment FDA Approved for TRD

Mechanisms of Action

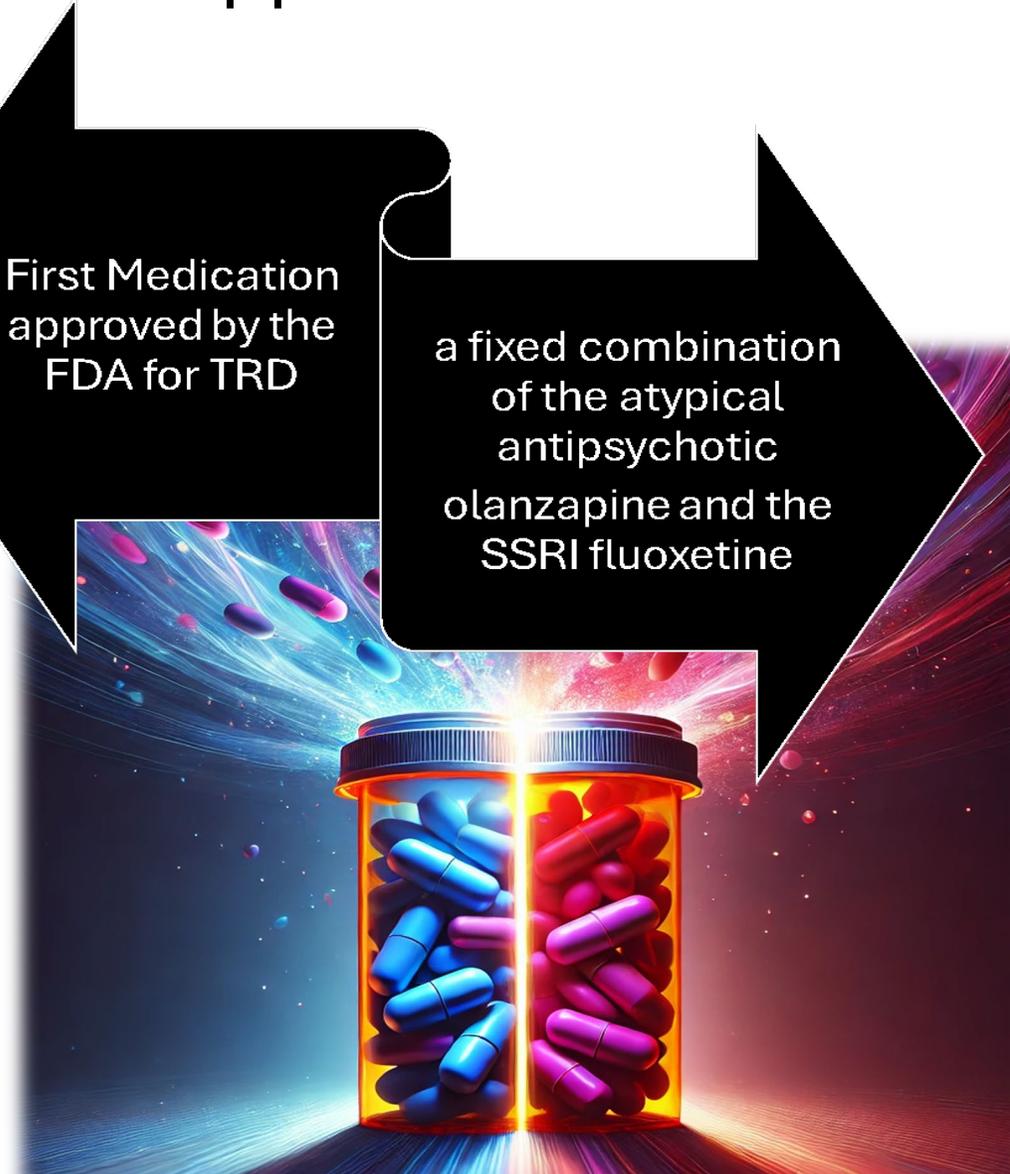
- Olanzapine is a dopamine D₂ and serotonin 5-HT_{2A} receptor antagonist
- Fluoxetine is an SSRI
- Combination may have dual mechanism

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

First Medication approved by the FDA for TRD

a fixed combination of the atypical antipsychotic olanzapine and the SSRI fluoxetine



Adverse Events Seen in Clinical Trials of Olanzapine/Fluoxetine Combination



In long-term studies (>48 weeks) mean weight gain was 14.7 lb



-66% gained 7% of their body weight
-33% gained 15% of their body weight



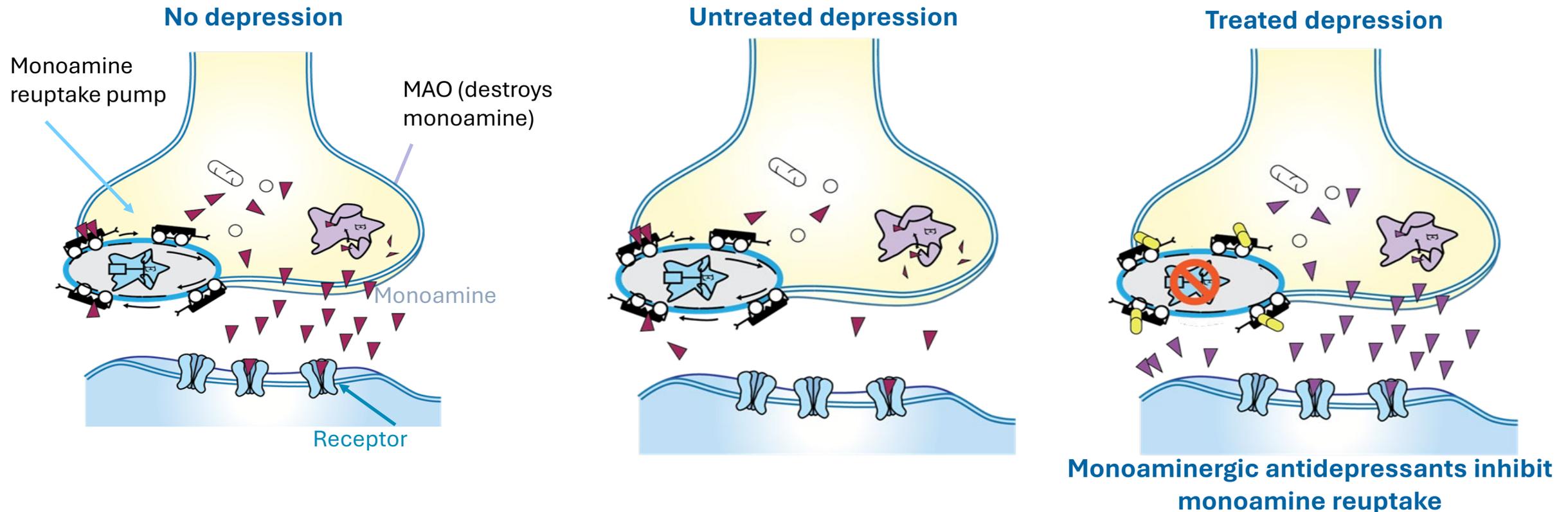
Discontinuation rates for any reason ranged 4.5%-47% in randomized clinical trials

Treatment-Emergent Adverse Events Occurring in $\geq 5\%$ of OFC Patients and at Least Twice that of Placebo

Event	Combination	Fluoxetine	Olanzapine
Weight increase	28%	7%	34%
Increased appetite	24%	6%	29%
Dry mouth	19%	7%	21%
Somnolence	16%	7%	14%
Fatigue	14%	9%	16%
Peripheral edema	11%	1%	7%
Tremor	10%	6%	5%
Sedation	9%	3%	11%
Hypersomnia	6%	2%	8%
Attention disturbance	6%	3%	6%

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 “Monamine” TRD:

Exploring the Glutamatergic System in Depression



Glutamate vs Monoamine Neurobiology

Neurotransmitter Comparison

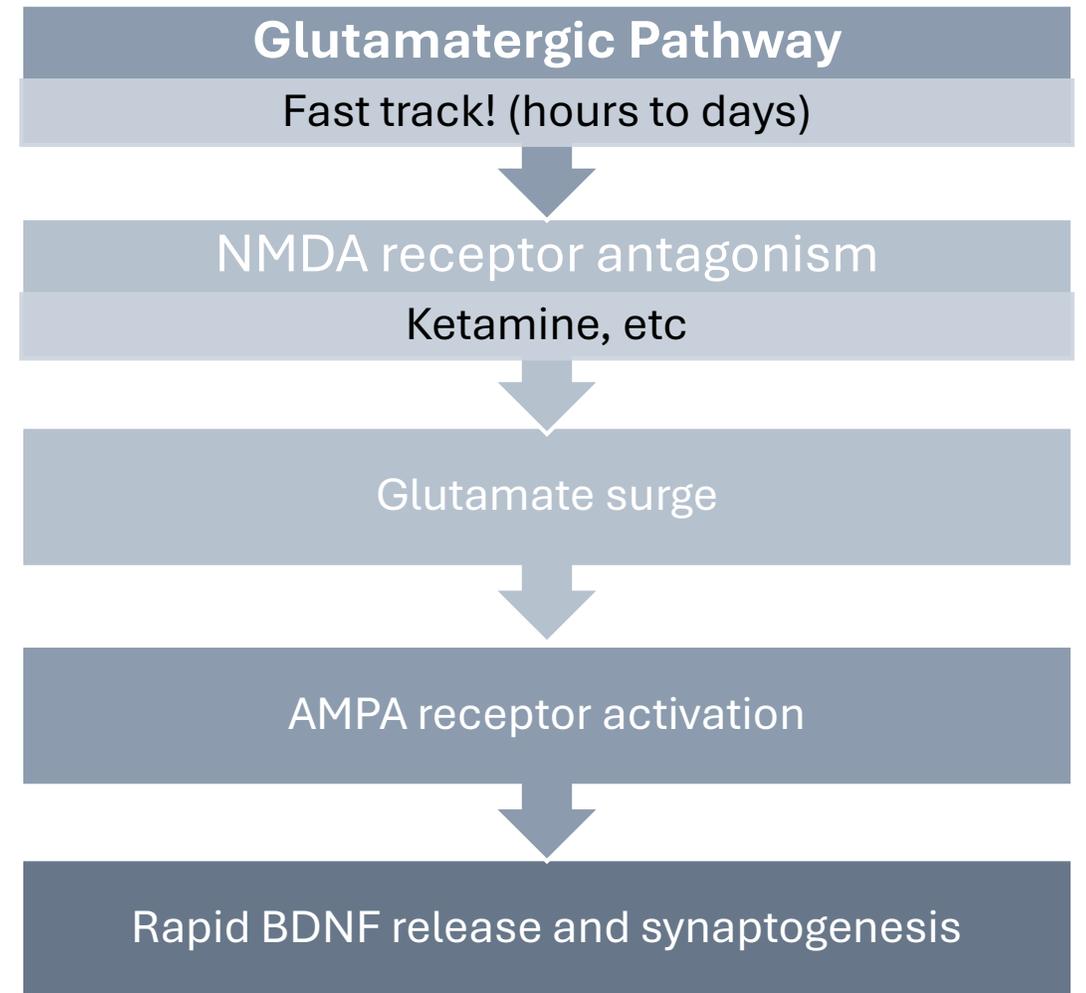
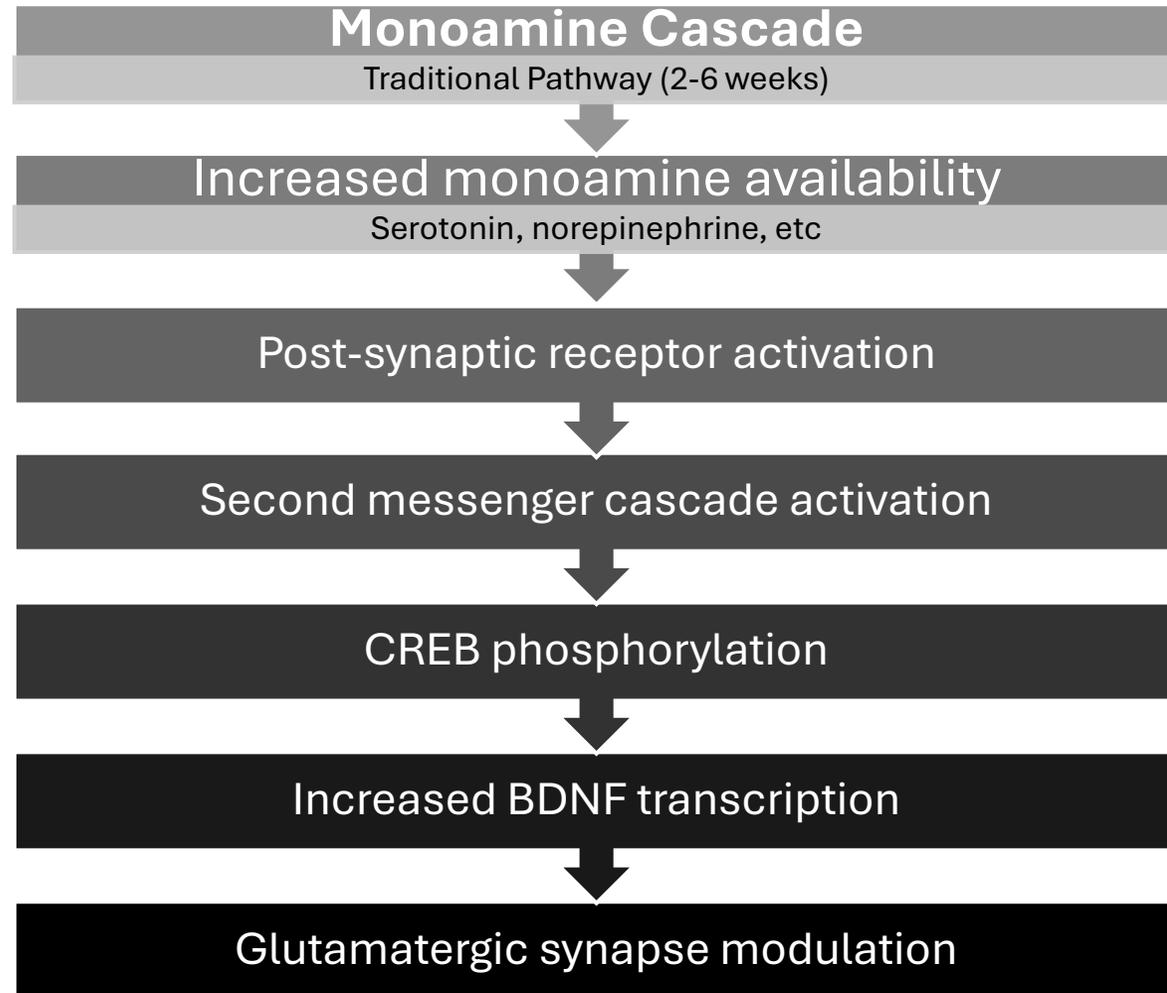
Feature	Monoamines	Glutamate
Abundance	~10% of synapses	~60% of synapses
Signal speed	Slow, modulatory	Fast, direct
Receptor diversity	Moderate (7-14 subtypes)	High (>30 subtypes)
Synaptic plasticity	Days to weeks	Minutes to hours
Clinical effect onset	2 to 6 weeks	Hours to days

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

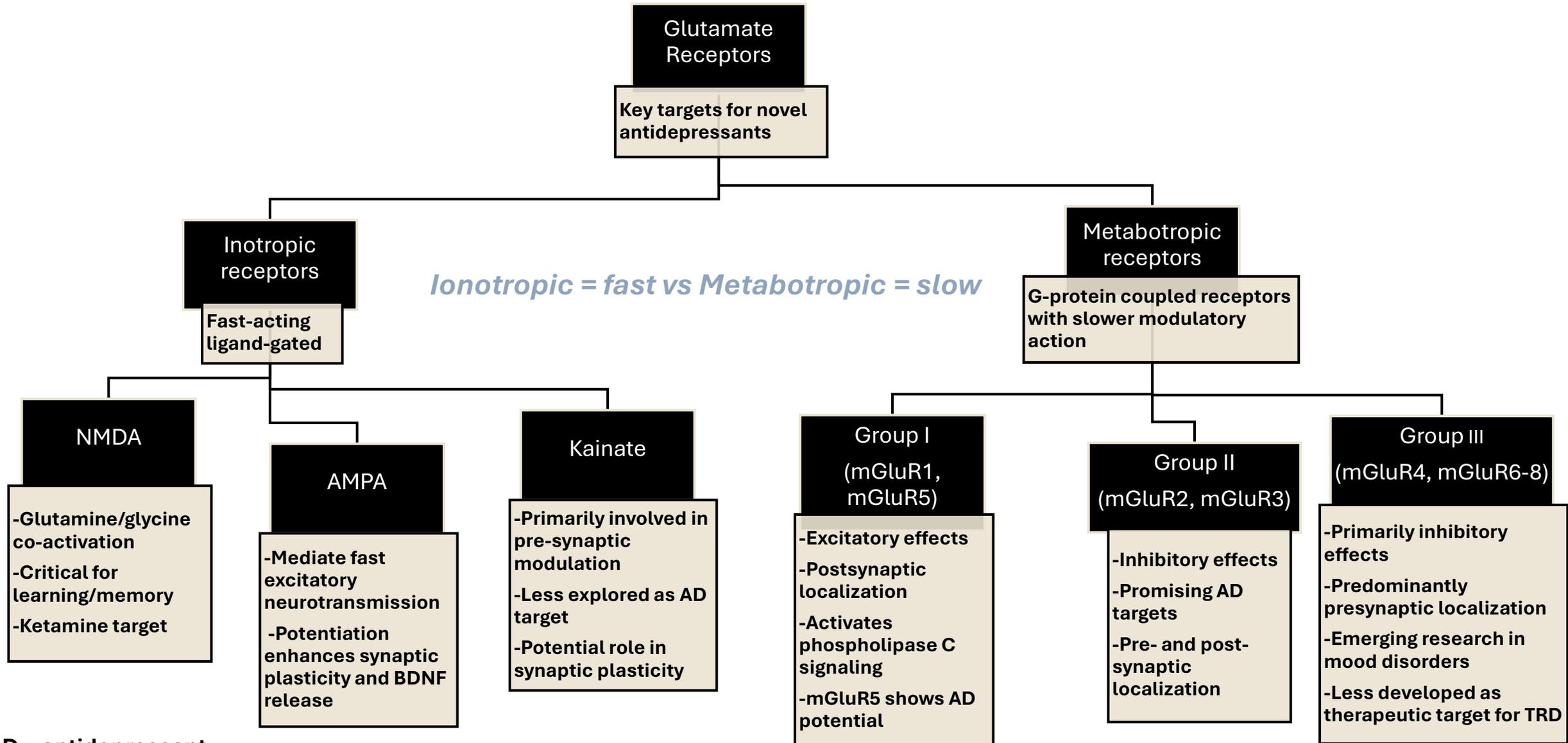
Antidepressant Mechanisms: Monoamines vs Glutamate



CREB = cAMP responsive element binding protein; BDNF = brain-derived neurotrophic factor; NMDA = N-methyl-D-aspartate; AMPA = α -amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid.

Niciu MJ, et al. *J Neural Transm (Vienna)*. 2014;121(8):907-924. Tomasetti C, et al. *Curr Pharm Des*. 2019;25(4):381-387. Duman RS, et al. *Eur J Neurosci*. 2021;53(1):126-139.

Glutamate Receptor Types



AD = antidepressant.

Freudenberg F, et al. *Pharmacol Res.* 2025;220:107918. Niciu MJ, et al. *J Neural Transm (Vienna).* 2014;121(8):907-924. Xia CY, et al. *Pharmacol Ther.* 2021;226:107875.

Cognitive and Emotional Processes Regulated by Glutamate

Emotional processing

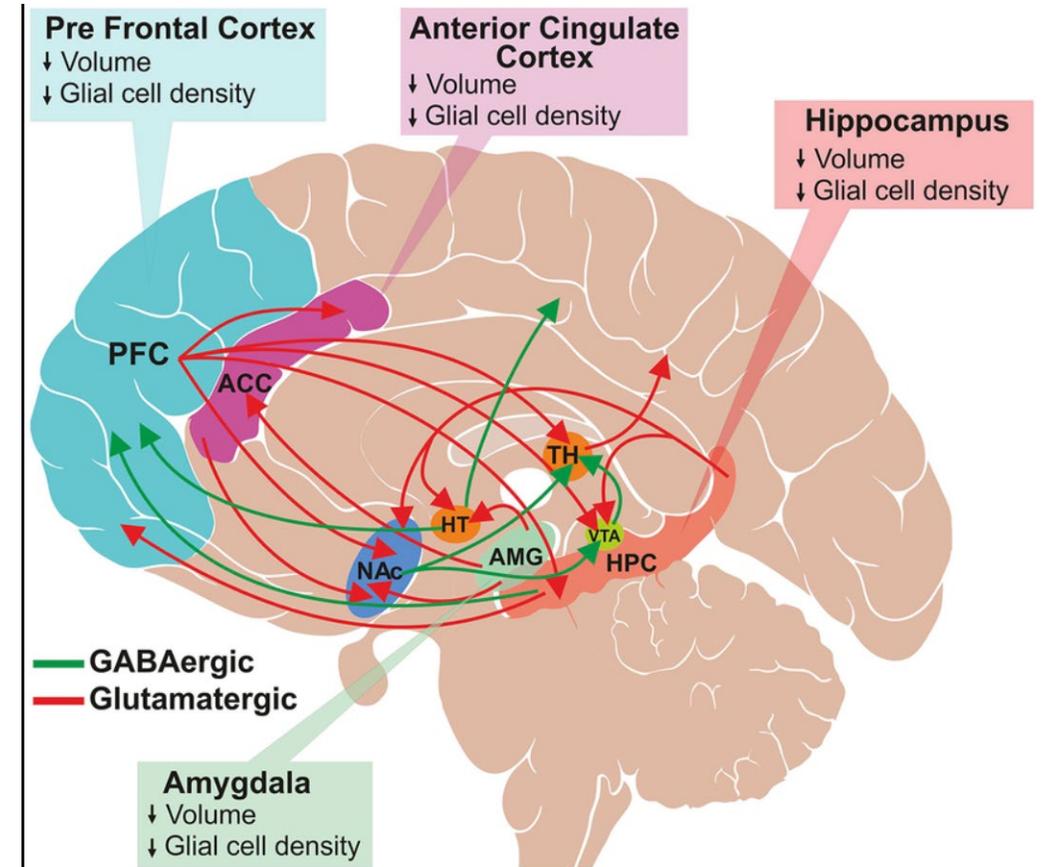
- Amygdala fear extinction pathways
- Nucleus accumbens reward signaling

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

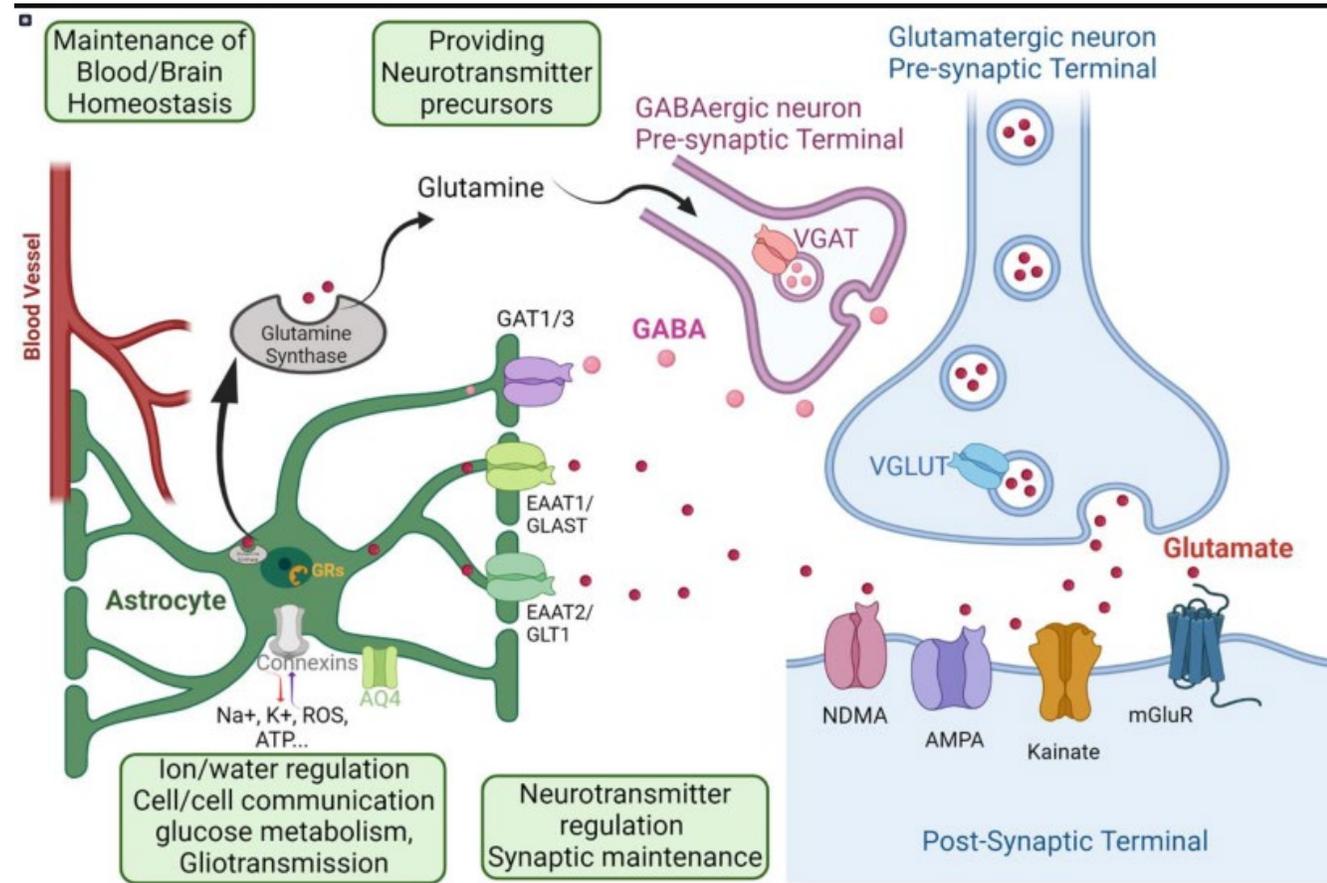


PFC = prefrontal cortex; LTP = long-term potentiation.

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



Created with BioRender.com

ATP = adenosine triphosphate.

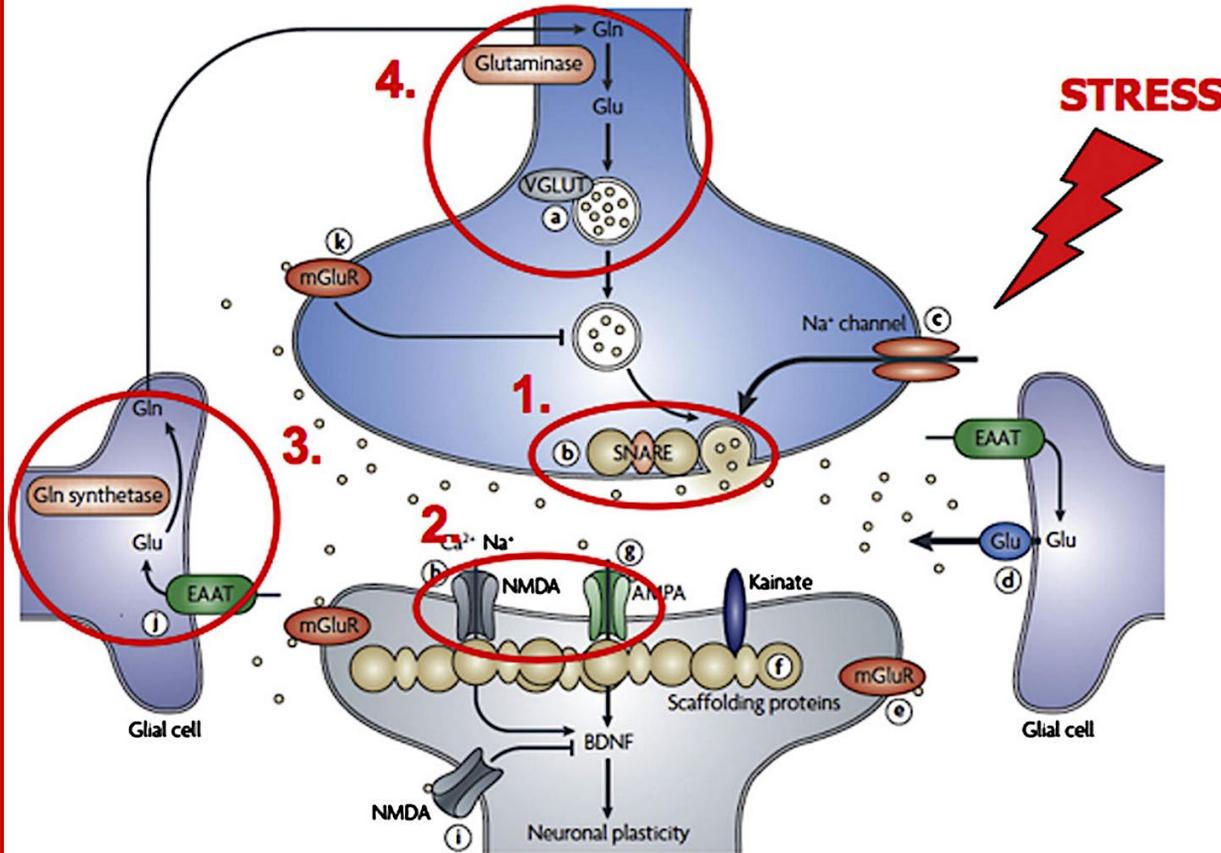
Li S, et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2025;141:111475. Musazzi L, et al. *Biol Psychiatry*. 2013;73(12):1180-1188. McGrath T, et al. *Nutrients*. 2022;14(5):917. Bansal Y, et al. *Int J Mol Sci*. 2024;25(12):6357.

Glutamate and Stress

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

Glutamatergic Dysfunction in Depression

Human Neuroimaging

- **Increased** glutamate in the anterior cingulate cortex (MRS studies)
- **Decreased** prefrontal Glx ratio in TRD
- Normalization of glutamate levels with successful treatment
- Ketamine normalizes glutamate connectivity patterns

Post-Mortem Studies

- **Decreased** NMDA receptor subunit expression
- Altered AMPA:NMDA receptor ratio
- **Decreased** glutamate transporter density in PFC
- **Decreased** glial cell density in mood regions

Animal Models

- Stress-induced glutamate surge in PFC and hippocampus
- Ketamine rapidly reverses stress-induced synaptic deficits
- NMDA-NR2B knockout shows antidepressant phenotype

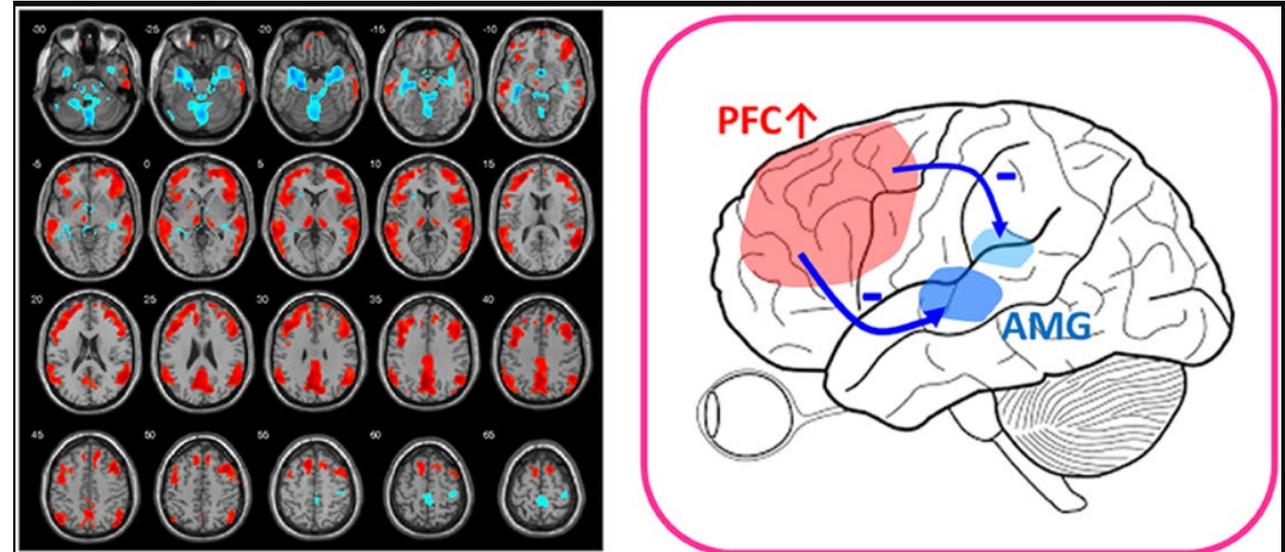


Figure 1. After vs before changes of glucose metabolism in response to low-dose ketamine in treatment-resistant depressives (FWE-corrected, $p < 0.001$). **Patients showed decreased glucose metabolism in limbic structures, such as amygdala (AMG) and hippocampus (shown in blue color), and increased function in prefrontal cortex (PFC) (shown in red color) after ketamine treatment.** The placebo group lacked the PFC activation. The findings of prefronto-amygdala changes in response to ketamine provided supports that low-dose ketamine could reverse glutamatergic dysfunction of the mood circuit.

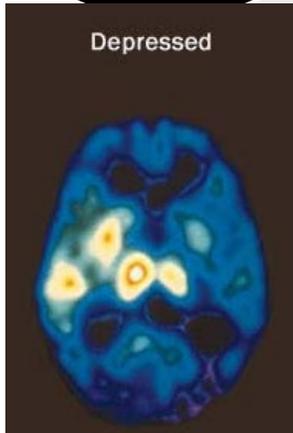
MRS = magnetic resonance spectroscopy.

Halaris A, Cook J. *Adv Exp Med Biol.* 2023;1411:487-512. Kim YK, Na KS. *Prog Neuropsychopharmacol Biol Psychiatry.* 2016;70:117-126. Niciu MJ, et al. *J Neural Transm (Vienna).* 2014;121(8):907-24. Li CT, et al. *Psychiatry.* 2019;9:767.

Stress, Glutamate & Synaptic Plasticity

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

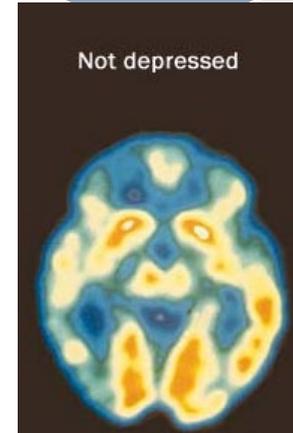
Reduced Neural Connectivity



- 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

- NMDA blockade

1 hour

- Glutamate surge

2-4 hours

- BDNF release

24 hours

- Spine growth

7 days

- Network reset

Effects of Deficient or Excessive Glutamate Signaling

✓ Deficient Glutamate

Mechanism

Reduced glutamate release, altered receptor expression

Clinical Features

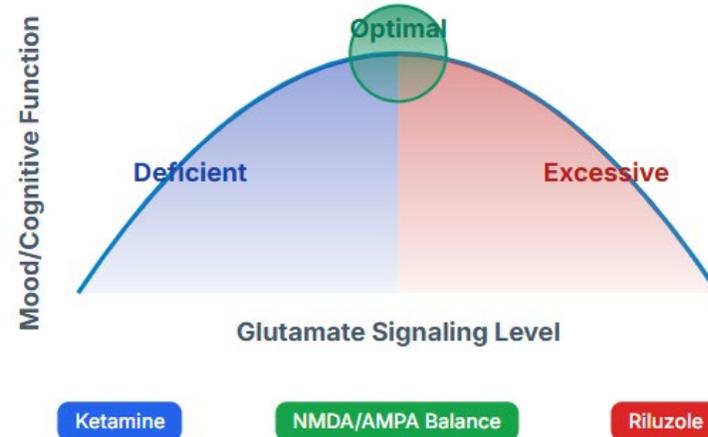
Chronic TRD, anhedonia, cognitive slowing

Effects

Impaired LTP, reduced neuroplasticity

Treatment Strategy

Ketamine (transient glutamate surge)



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

↑ Excessive Glutamate

Mechanism

Reduced astrocytic uptake, excess glutamate release

Clinical Features

Acute stress, early depression stages, anxiety

Effects

Excitotoxicity, synapse damage, oxidative stress

Treatment Strategy

Riluzole, lamotrigine, NAC

✓ Optimal Glutamate

Balance

Appropriate AMPA:NMDA receptor ratio

Clinical Features

Normal mood regulation, cognitive function

Effects

Healthy synaptic plasticity and LTP

Signaling

Balanced glutamate release and uptake

Key Learning Points

The Glutamatergic System in Depression

Receptor diversity

- The complex receptor landscape allows for targeted interventions with diverse mechanisms and effects

Rapid modulation

- Glutamatergic interventions enable rapid synaptic plasticity, unlike the slower monoaminergic effects

Stress disruption

- Chronic stress disrupts glutamatergic homeostasis and synapse integrity through multiple mechanisms

Novel therapeutics

- Glutamatergic agents (eg, esketamine) target this pathway with proven efficacy in TRD

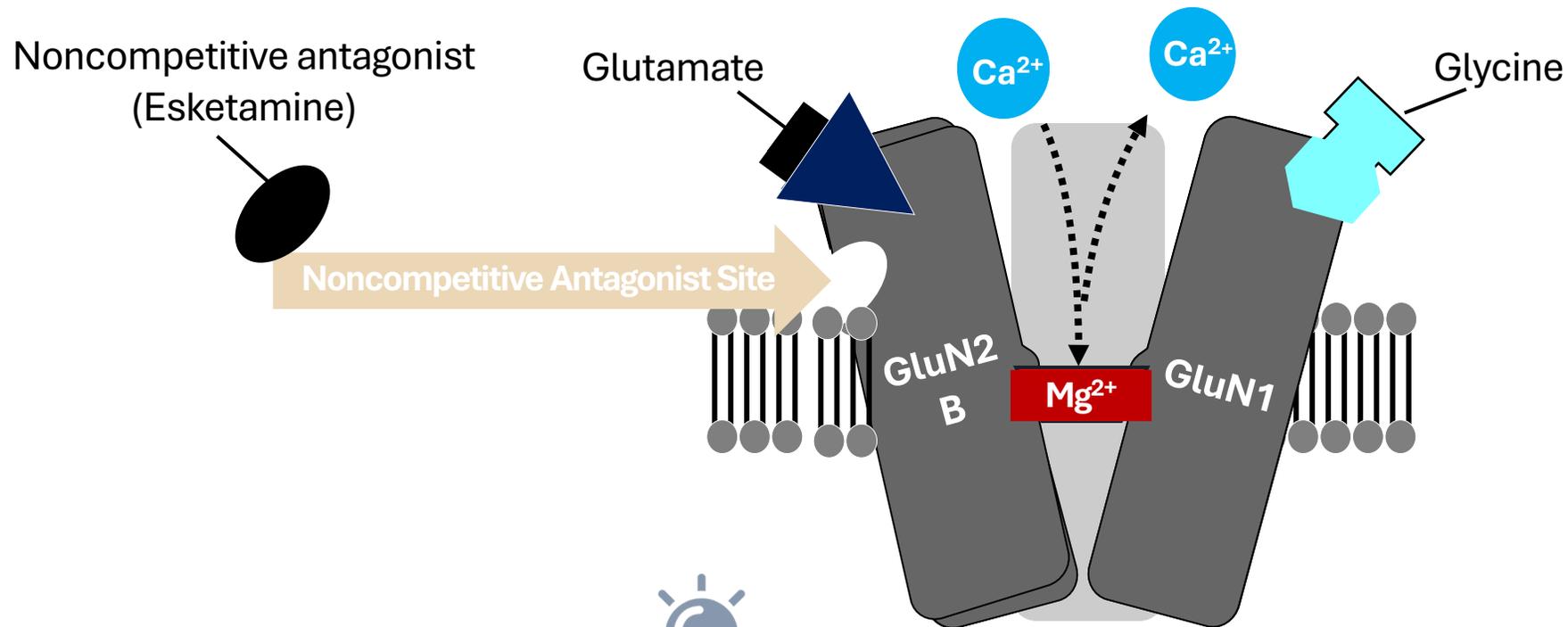
Targeting Glutamate Receptors in TRD

Translating Science into Action: *What else can we offer our patient?*



Ketamine & Esketamine are Glutamatergic Modulators

They do NOT Inhibit Neurotransmitter Reuptake



Esketamine is the S-enantiomer of racemic ketamine—think “mirror image”

A nonselective, noncompetitive antagonist of the ionotropic NMDA glutamate receptor

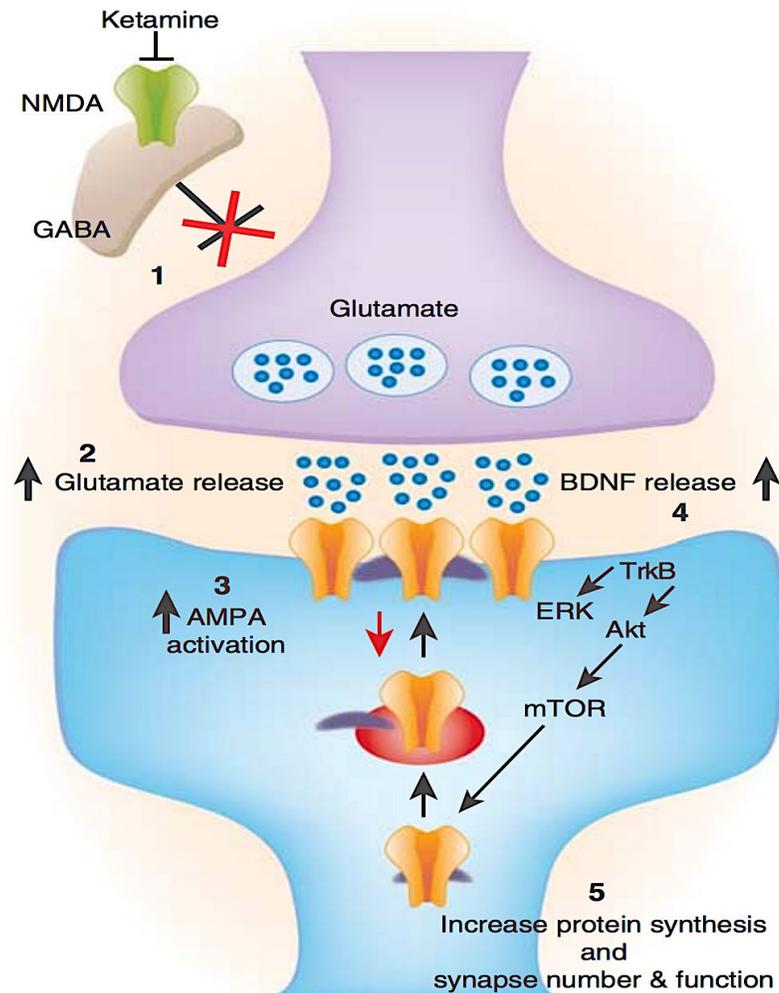
Binds at allosteric site to modulate the probability of an open ion channel

Ca^{2+} = calcium ion; GluN1 = glycine-binding type 1 NMDA receptor subunit; GluN2B = glutamate-binding type 2B NMDA receptor subunit; Mg^{2+} = magnesium ion.

Niciu MJ. *Pharmacology Biochemistry and Behavior*. 2012;100(4):656-664. Duman RS. *F1000Res*. 2018;7:F1000 Faculty Rev-659.

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

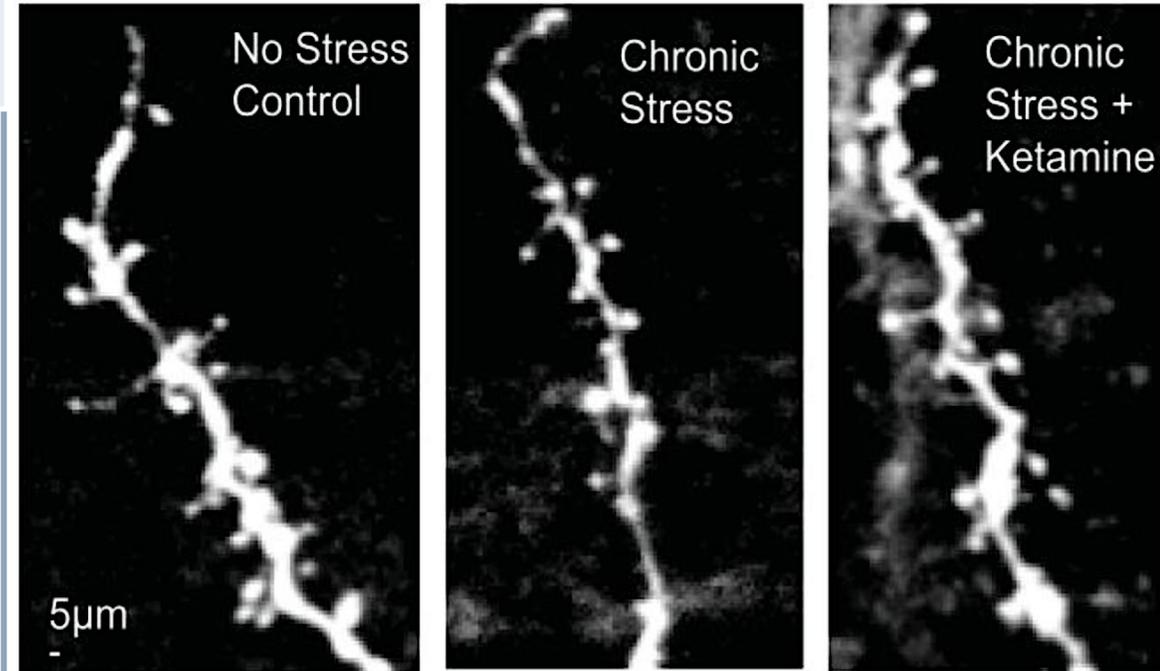
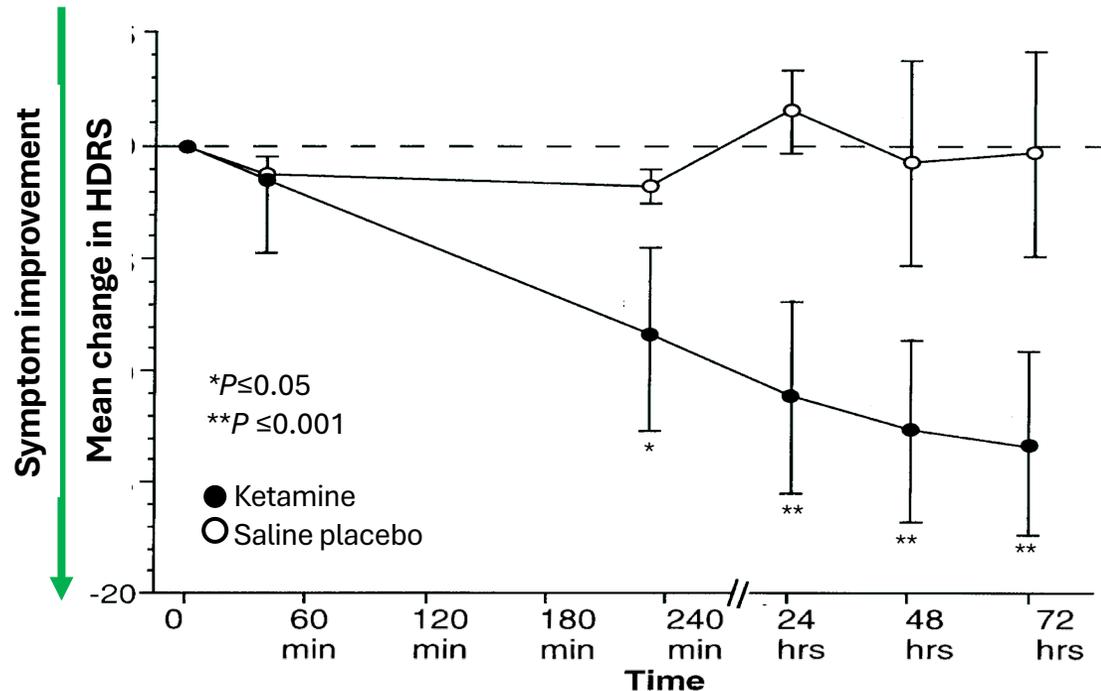
Leads to a release of BDNF

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

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



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

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

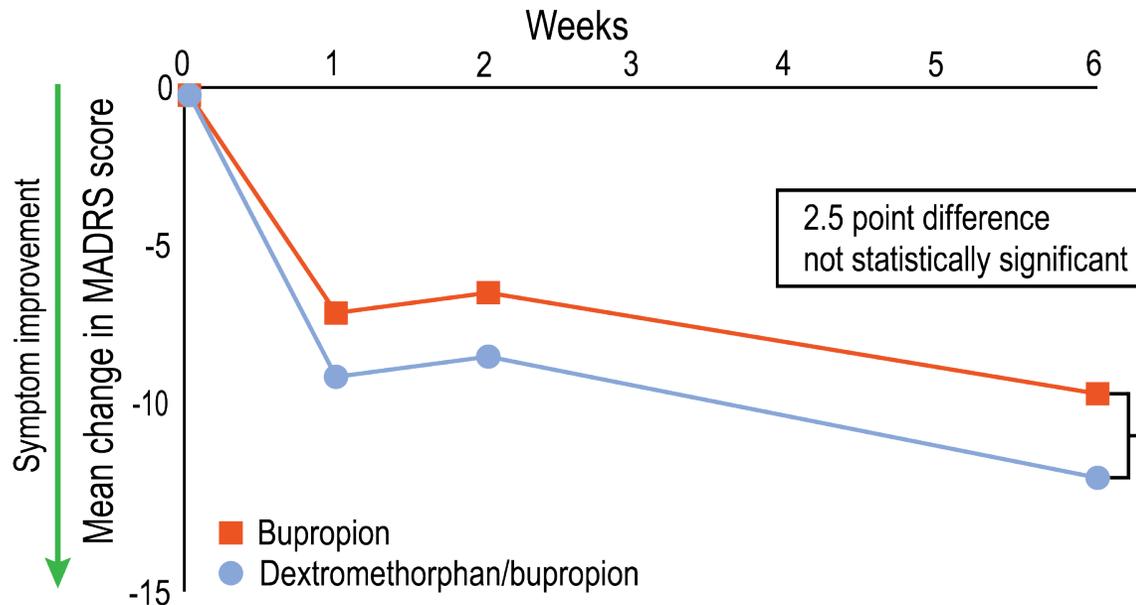
HDRS = Hamilton Depression Rating Scale.

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.

Dextromethorphan/Bupropion Was Studied for TRD

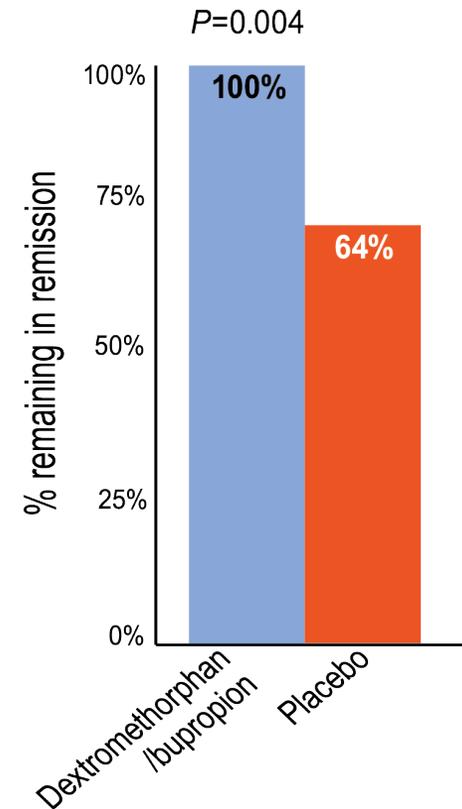
Dextromethorphan is a noncompetitive NMDA receptor antagonist and bupropion slows metabolism of dextromethorphan

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

Esketamine Is a Glutamatergic Antidepressant NMDA Receptor Antagonist

**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 can not drive or operate heavy machinery for the rest of the day



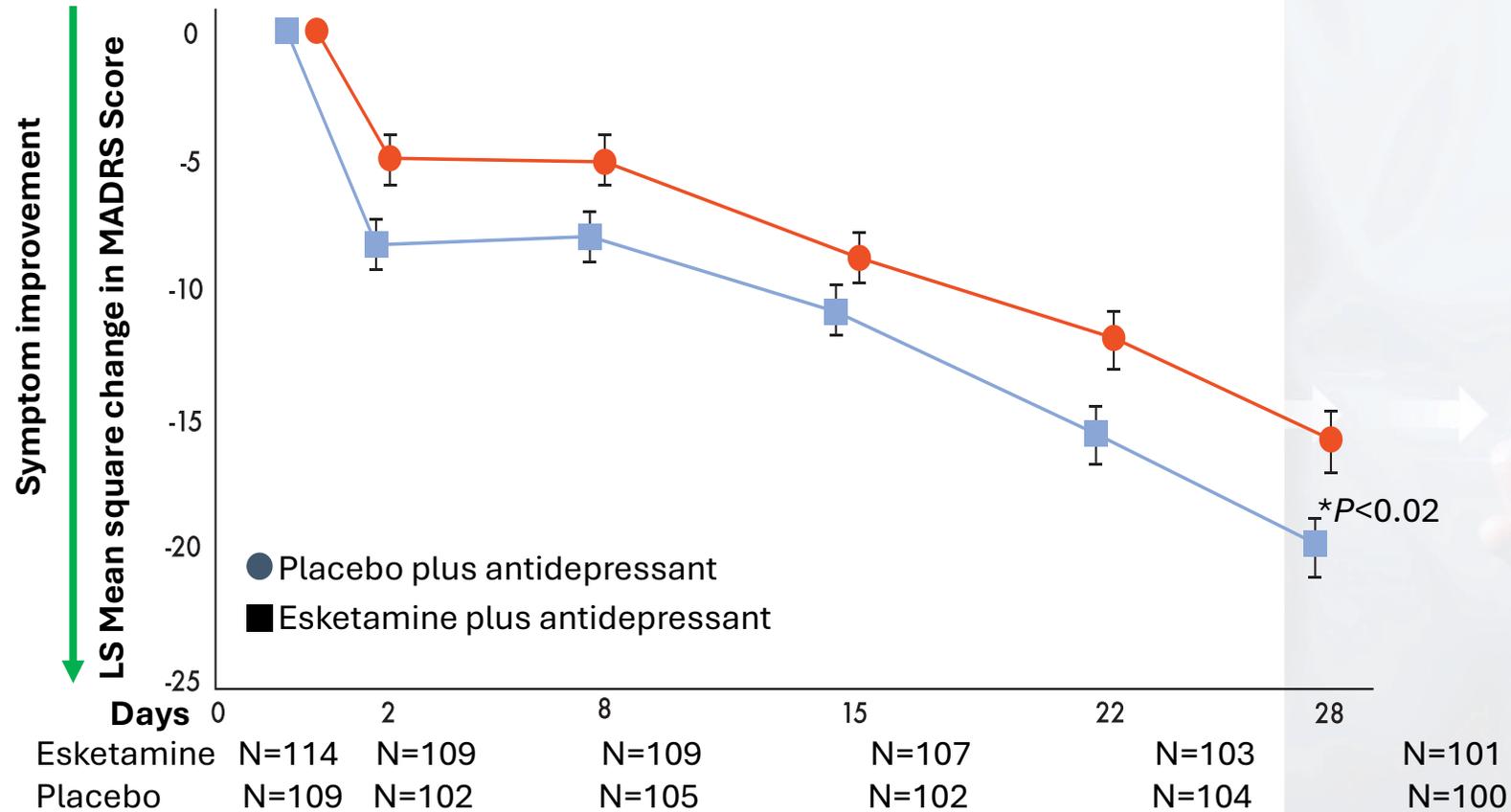
**Self-administered nasal spray
28 mg each**

REMS = risk evaluation mitigation strategy

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

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



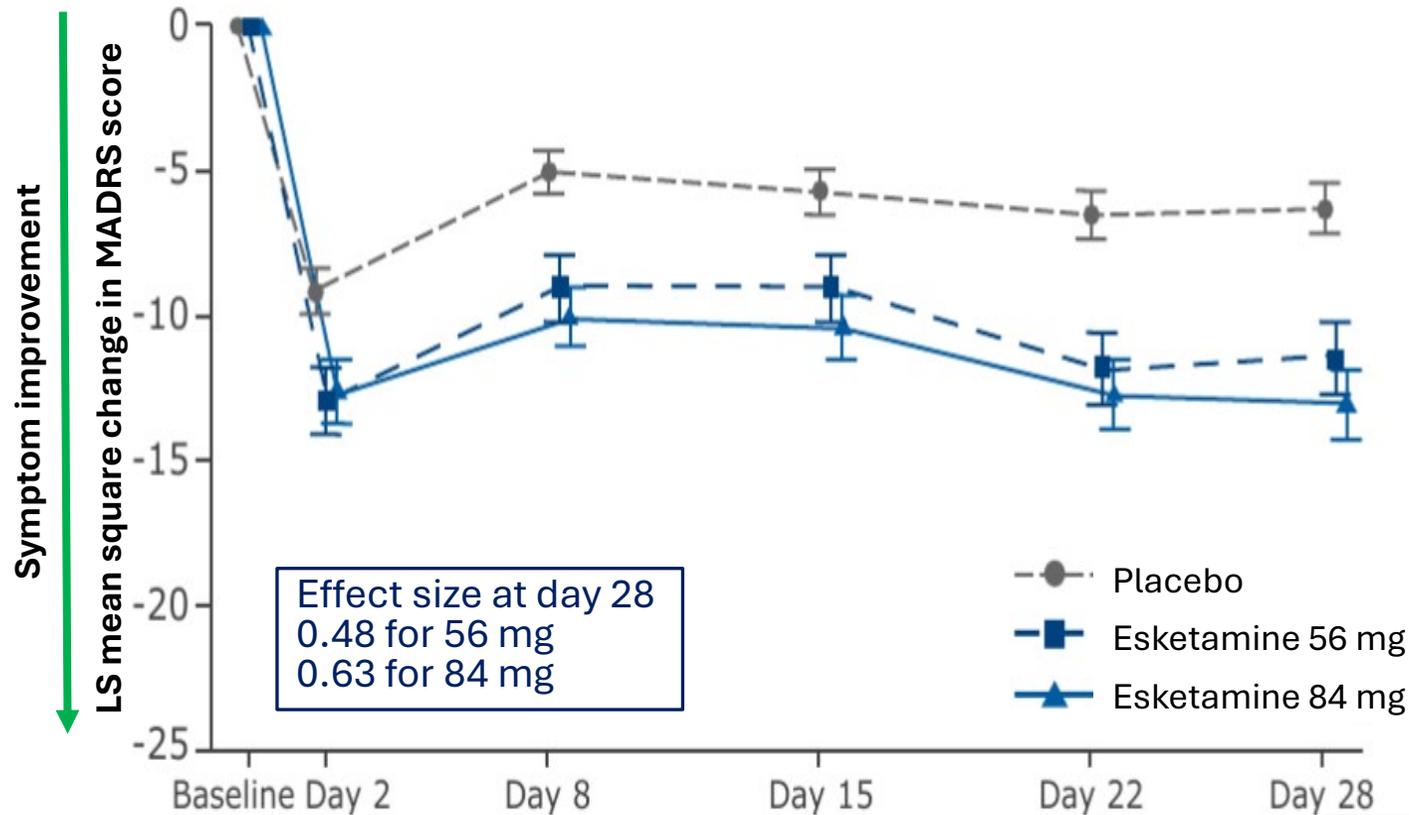
Most Common Adverse Events Observed in TRANSFORM-2 Trial

	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%

MADRS = Montgomery-Åsberg Depression Rating Scale.

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

Esketamine Monotherapy for TRD: Phase 4 Trial



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%

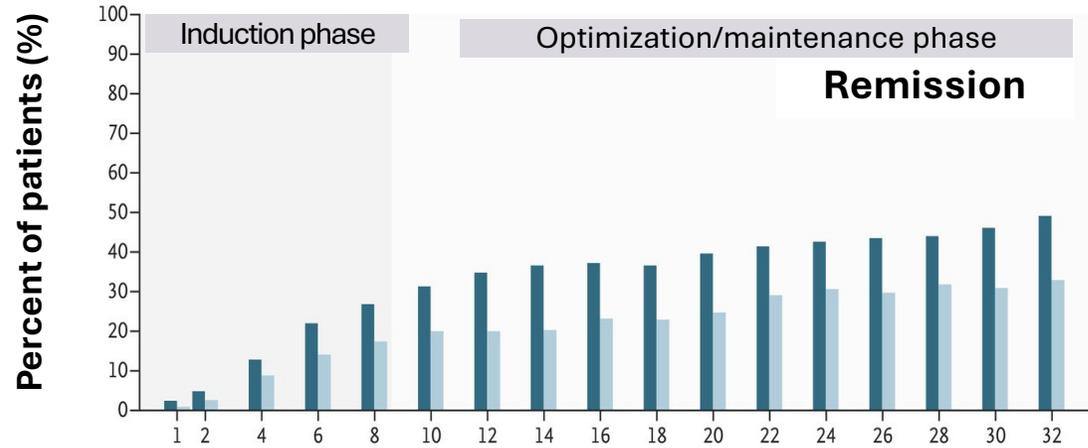
Treatment of TRD with esketamine nasal spray 56 mg or 84 mg reduced MADRS scores by 5 and 7 points, respectively, compared with placebo.

D/C = discontinuation.

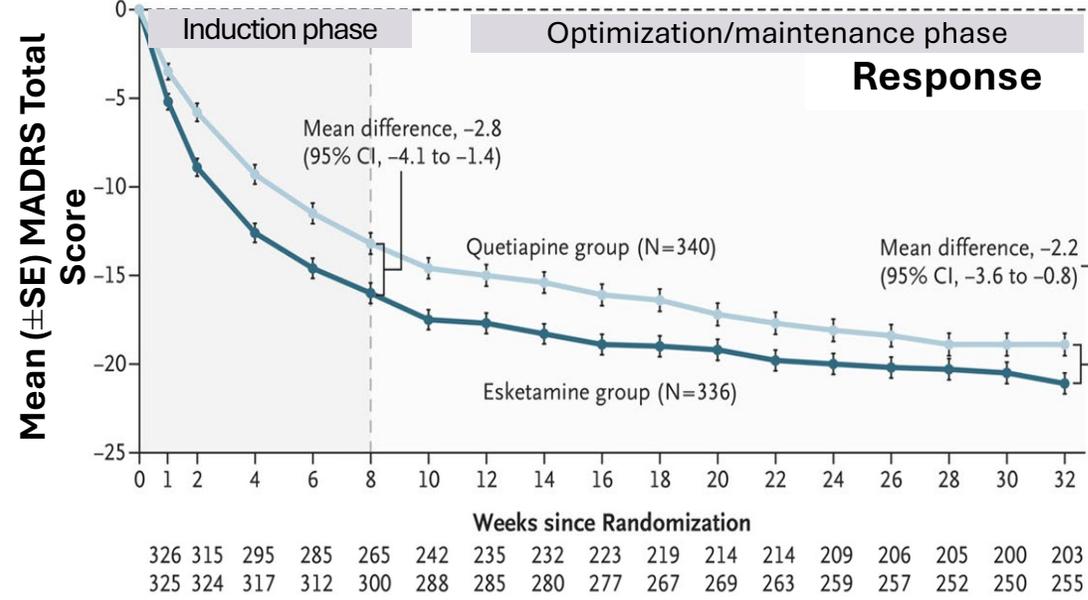
Janik Aet al. Presented at 2024 Am Soc Clin Psychopharmacol meeting. Accessed May 10, 2025.

<https://www.jnjmedicalconnect.com/media/attestation/congresses/neuroscience/2024/ascp/efficacy-and-safety-of-esketamine-nasal-spray-as-mono-therapy-in-adults-with-treatment-resistant-depre.pdf>

Adjunctive Esketamine Superior to Adjunctive Quetiapine-XR



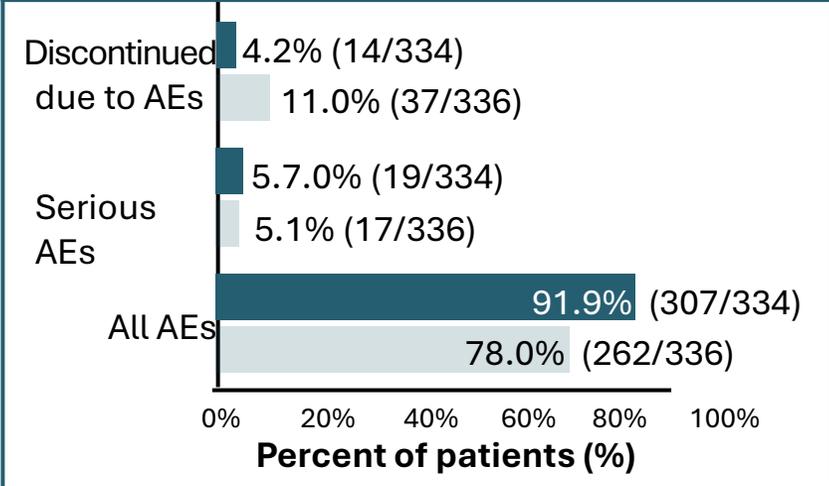
51%
 More likely to achieve remission (week 8) OR=1.74 (95% CI: 1.20-2.52) P=.003



72%
 More likely to remain relapse-free (week 32) OR=1.72 (95% CI: 1.15-2.16)



SAFETY AND TOLERABILITY



LIMITATIONS

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

■ Adjunctive esketamine nasal spray ■ Adjunctive quetiapine-XR

Esketamine Treatment & Relapse Prevention

Response and Remission in SUSTAIN-1 Trial

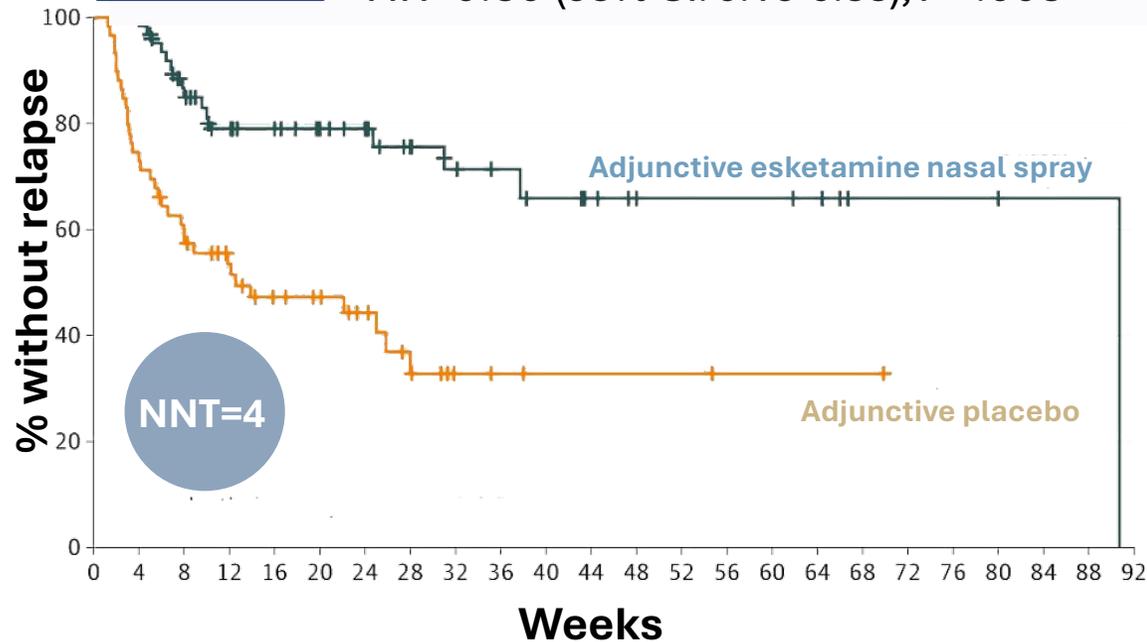
Should patients be on esketamine maintenance therapy?

Patients who responded to treatment

70%

were less likely to relapse

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

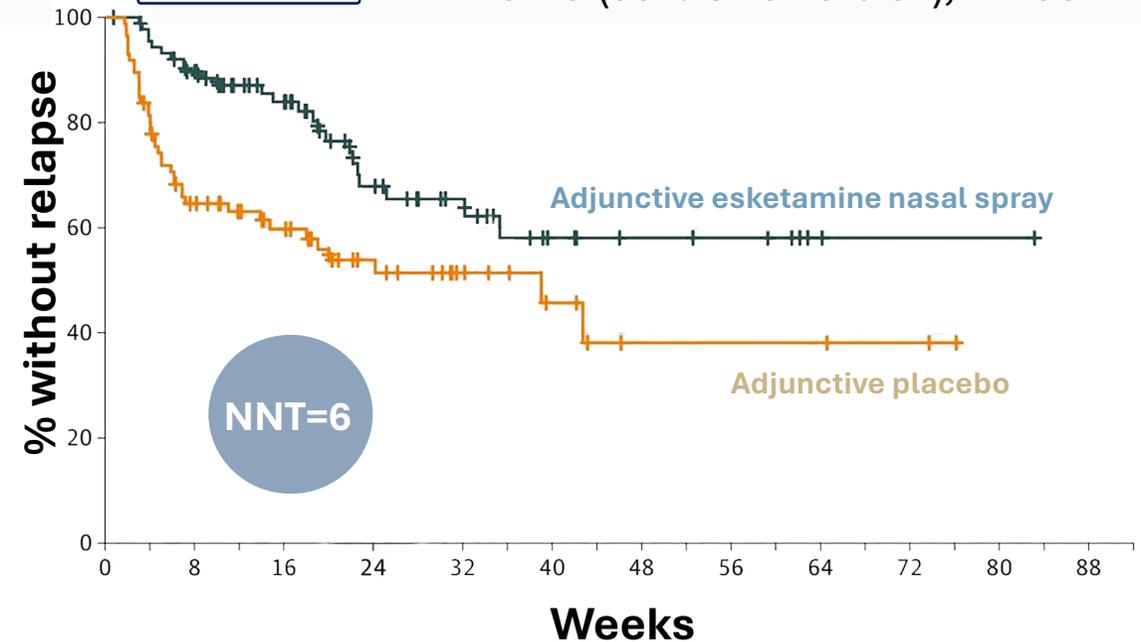


Patients who reached remission

51%

were less likely to relapse

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



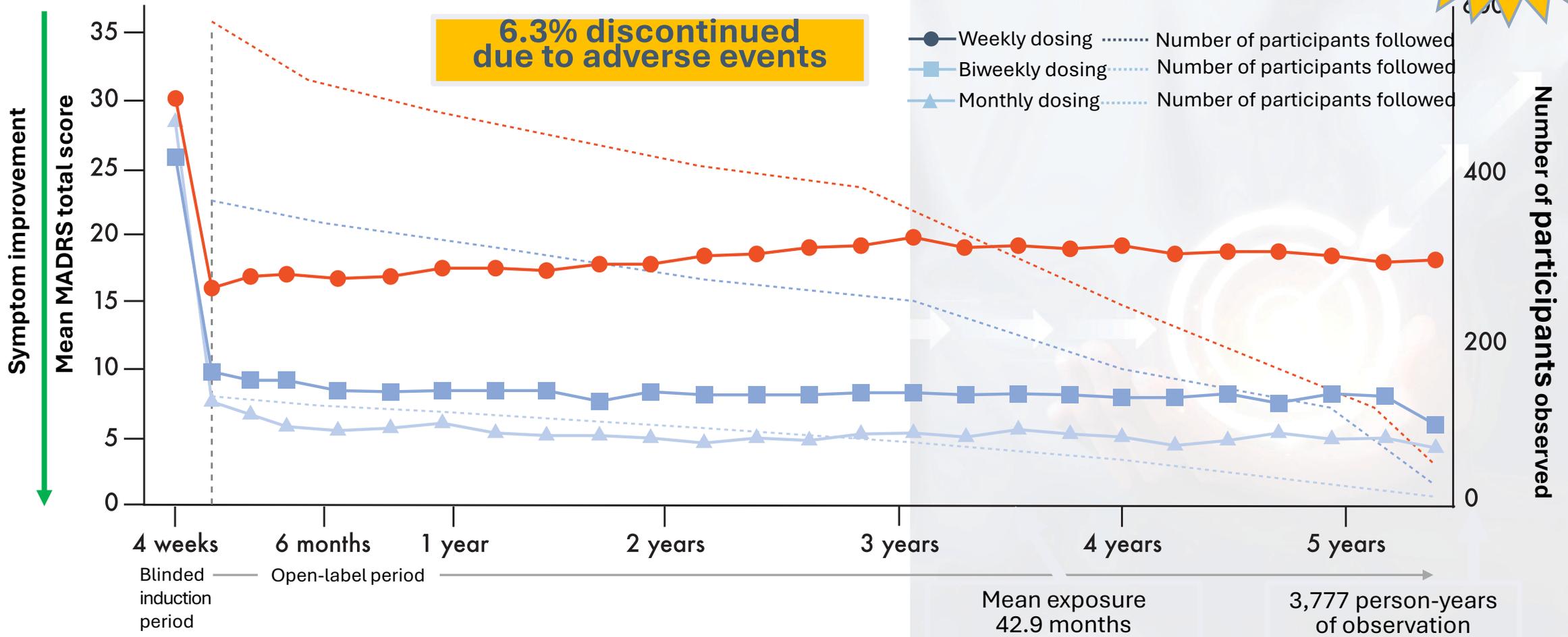
HR = hazard ratio.

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

5 Year Long-Term Safety Study of Esketamine

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.

Monthly dosing is off-label



Up to 6.5 Years of Data: Esketamine Safety and Tolerability

- 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



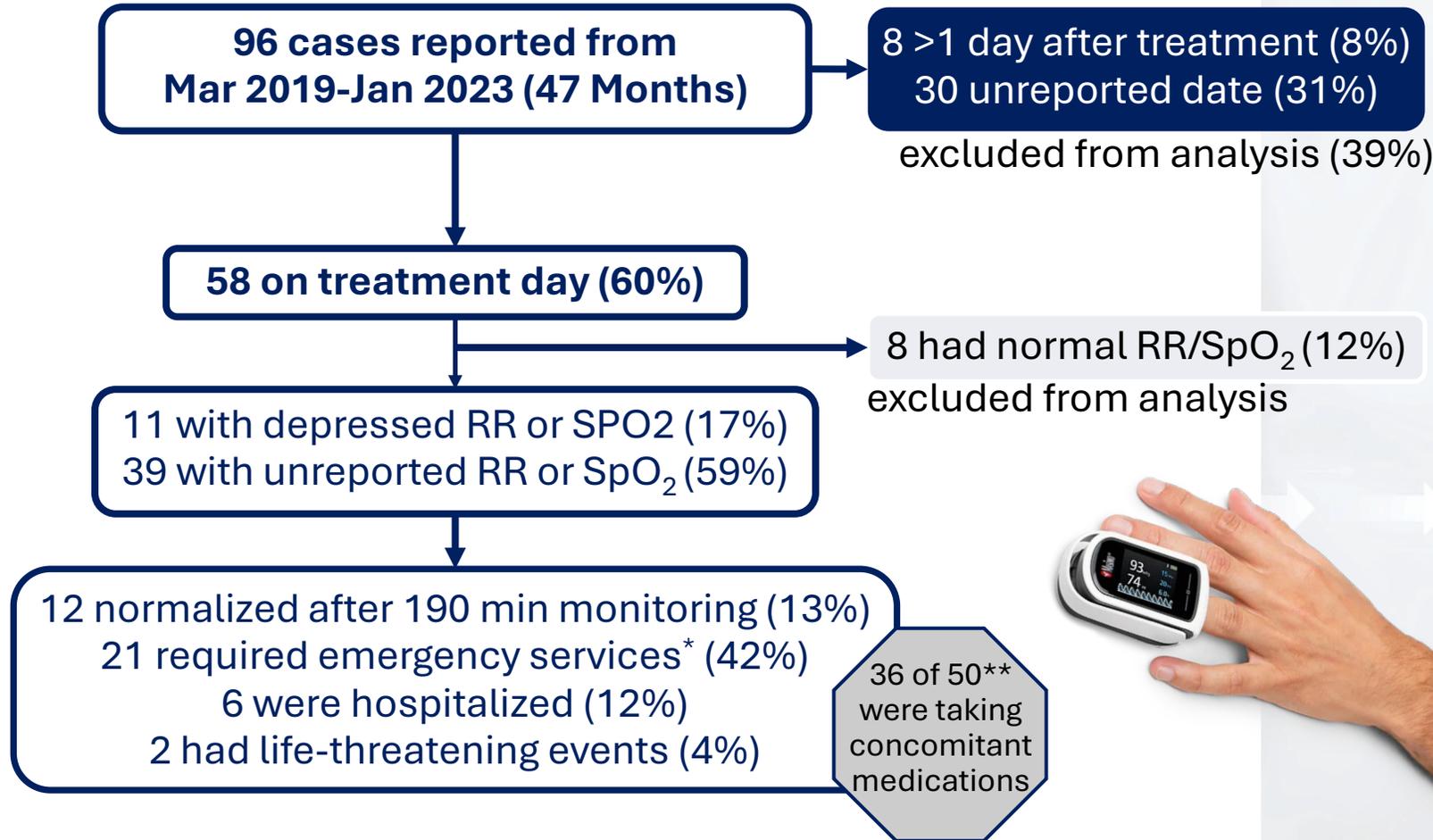
6.4% of patients discontinued due to adverse events

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	

Appropriate Risk Management for Esketamine

Real-world respiratory depression after esketamine treatment



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



*included emergency visits, oxygen, medication, tactile/verbal stimulation, CPR, and rescue breathing; ** mostly benzodiazepines and other antidepressants, although respiratory crises could not be attributed to these.

RR = respiratory rate; SpO2 = oxygen saturation.

Chepke C, et al. *Int J Neuropsychopharmacol.* 2024;27(12):pyae058.

Initiating Esketamine Earlier in TRD: Early Response Predicts Later Response Higher Chance of Success and Potential to Alter Treatment Course

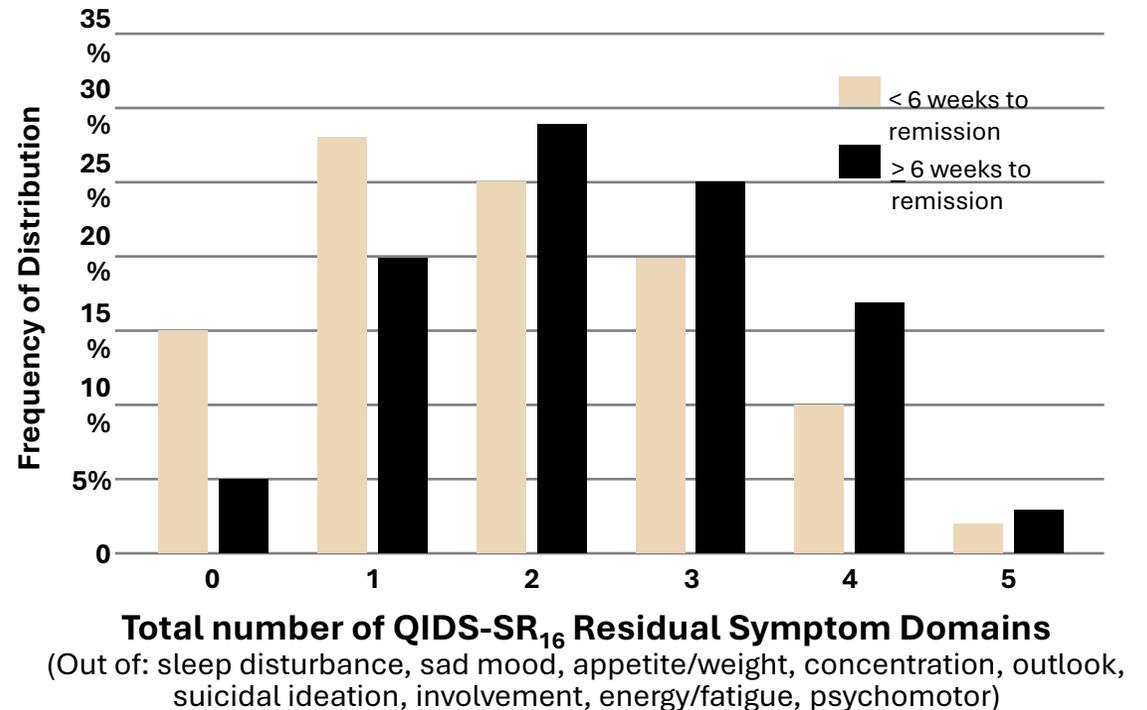
Esketamine may be appropriate after 2 well-defined unsuccessful antidepressant trials.

Compared to Those Lacking Early Improvement

Those with **20% improvement** at week 2 were **6x more likely to achieve remission** in a meta-analysis of mostly 6-week controlled trials

Those with **30% improvement** at week 4 were **~3x more likely to achieve remission** at week 14 in an open-label naturalistic study

STAR*D participants who reached remission in first 6 weeks had fewer residual symptoms compared to those who reached remission after 6 weeks.

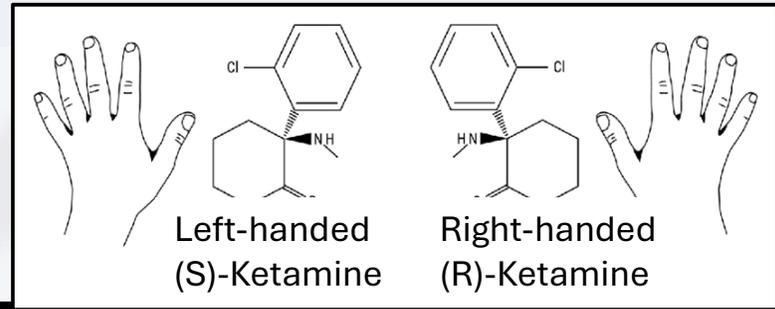


QIDS-SR=Quick Inventory of Depressive Symptomatology-Self Report.

Belanger HG, et al. *J Clin Psychopharmacol.* 2023;43(1):46-54. Szegedi A, et al. *J Clin Psychiatry.* 2009;70(3):344-353. Nierenberg AA, et al. *Psychol Med.* 2010;40(1):41-50.

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, SUSTAIN-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.

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

[f Share](#) [X Post](#) [in 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

[f Share](#) [X Post](#) [in 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>.

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 the SUSTAIN-3 open-label, long-term extension study of adjunctive intranasal esketamine, only **4.6% 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)**
- ✓ 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

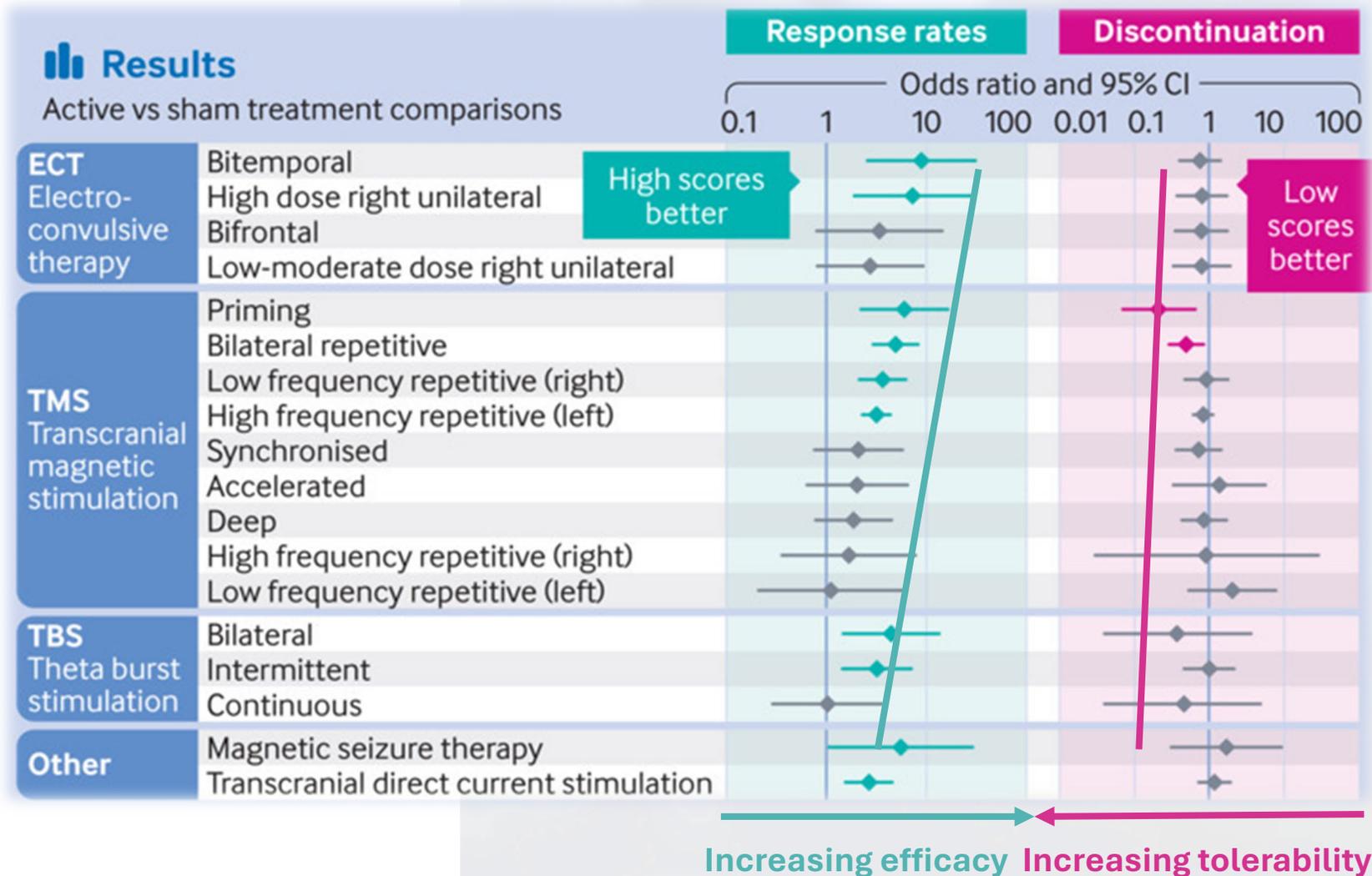
**Other Treatment
Considerations/
Neuromodulation for:
Treatment-Resistant
Depression**



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



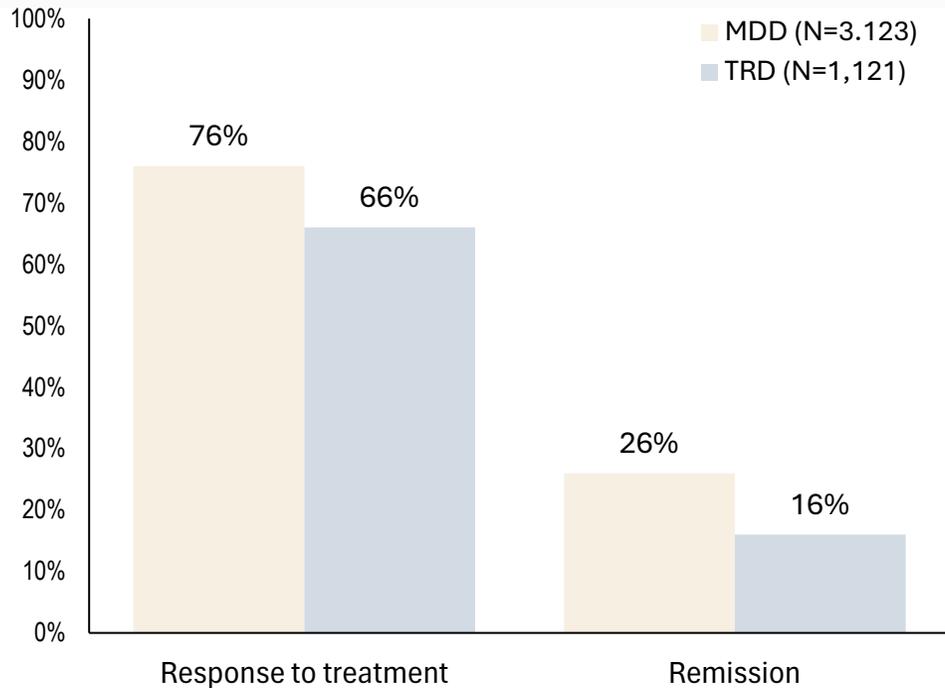
ECT = electroconvulsive therapy; TMS = transcranial magnetic stimulation; TBS = theta burst stimulation.

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

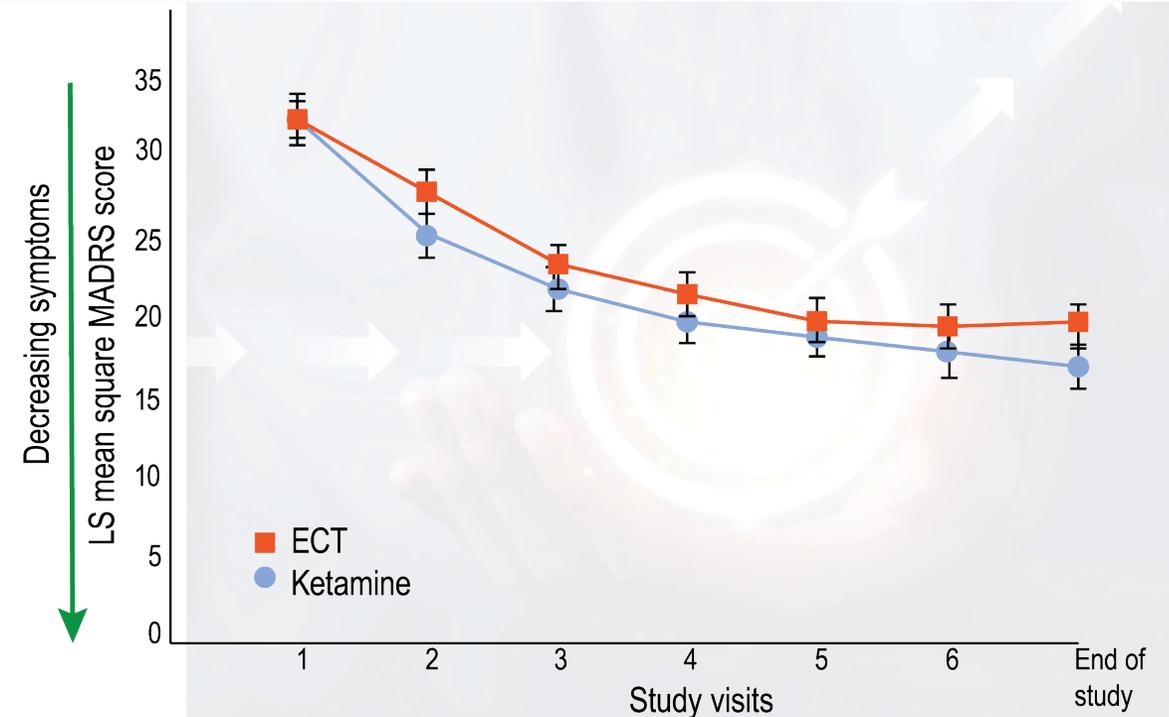
Electroconvulsive Therapy (ECT) for TRD

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

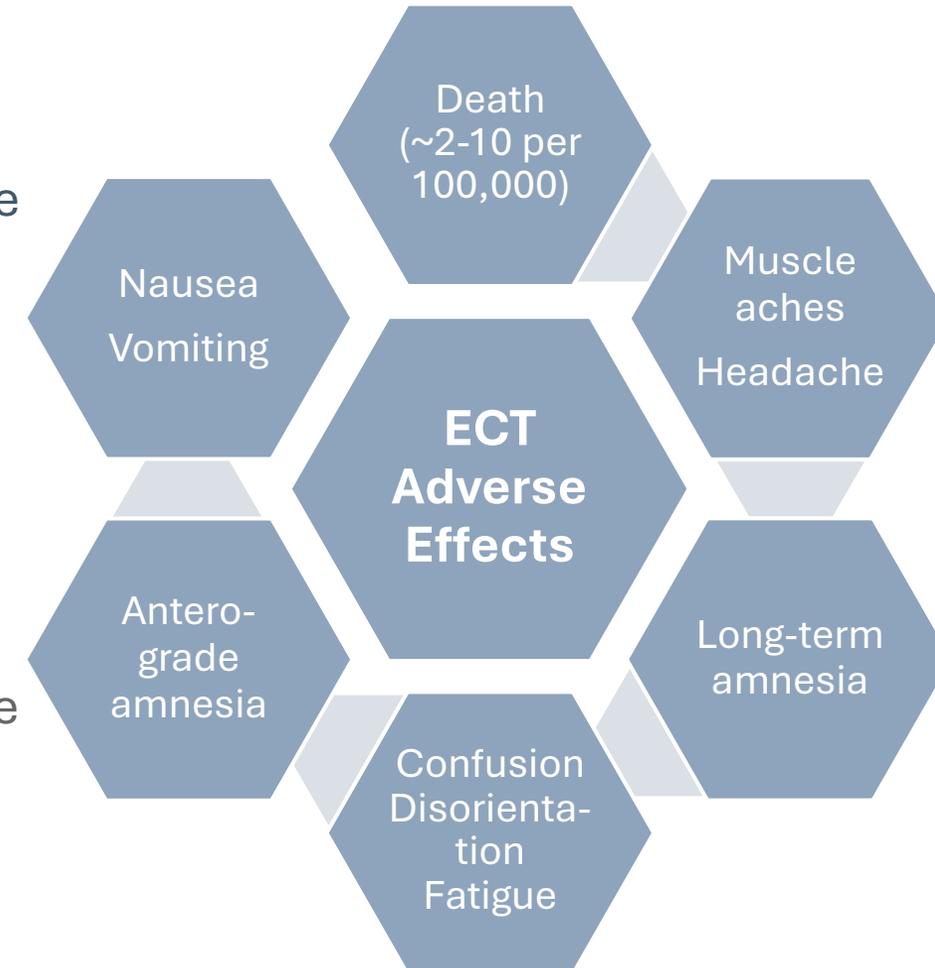


Clinical trial of ECT vs ketamine showed similar MADRS score reduction in patients with TRD with ECT vs ketamine



Electroconvulsive Therapy: Safety & Efficacy

- ✓ Acute vital sign changes occur during procedure
- ✓ 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.

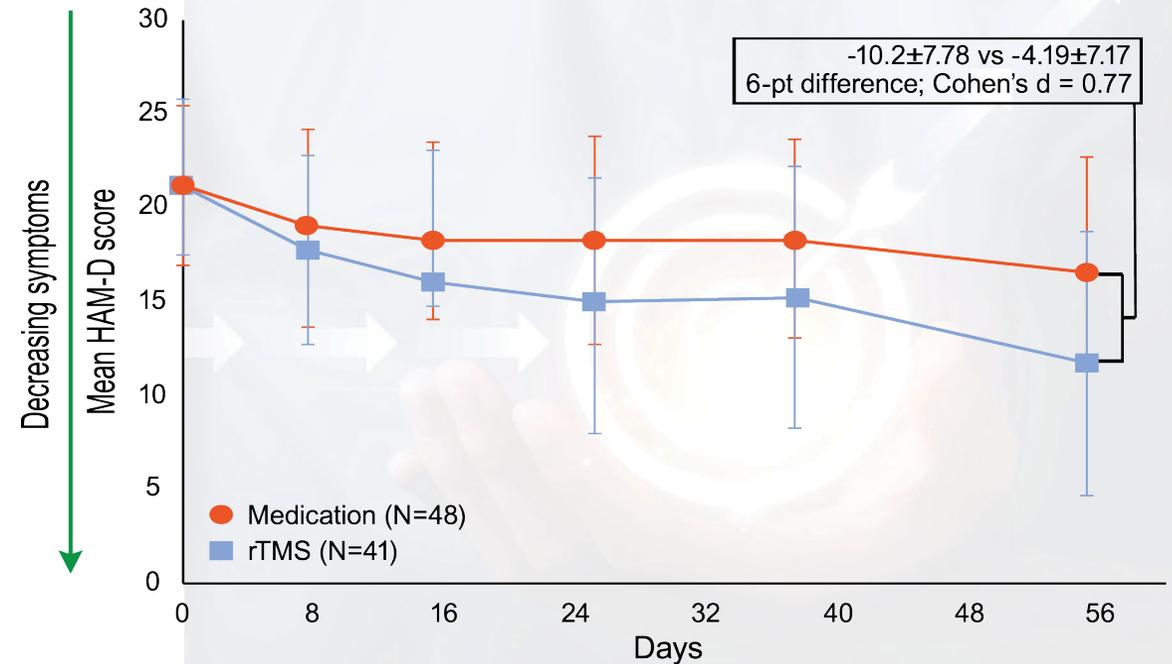
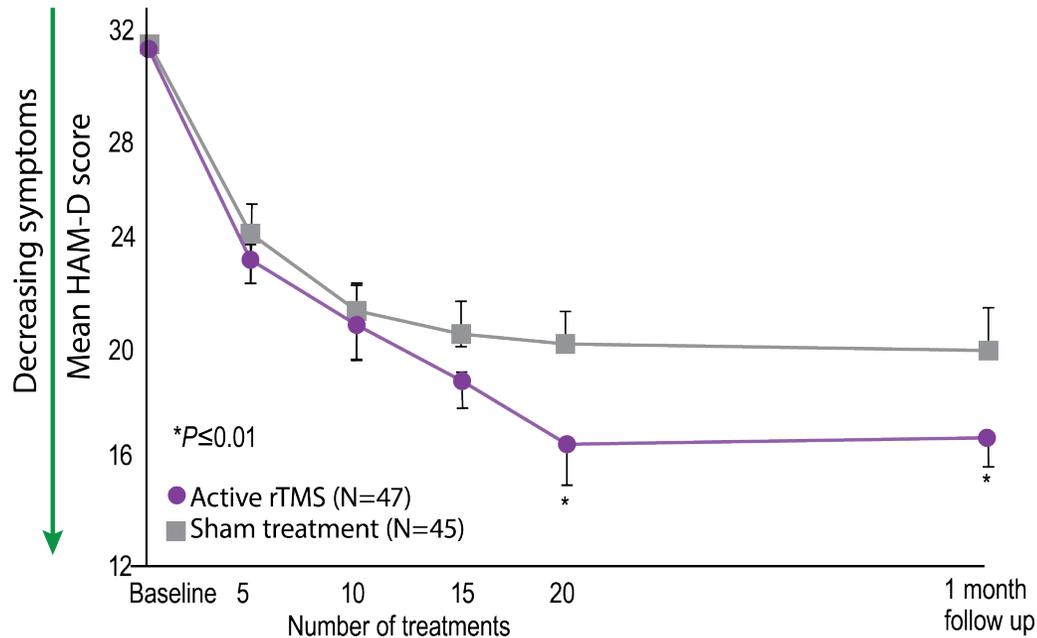
Repetitive Transcranial Stimulation for TRD

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

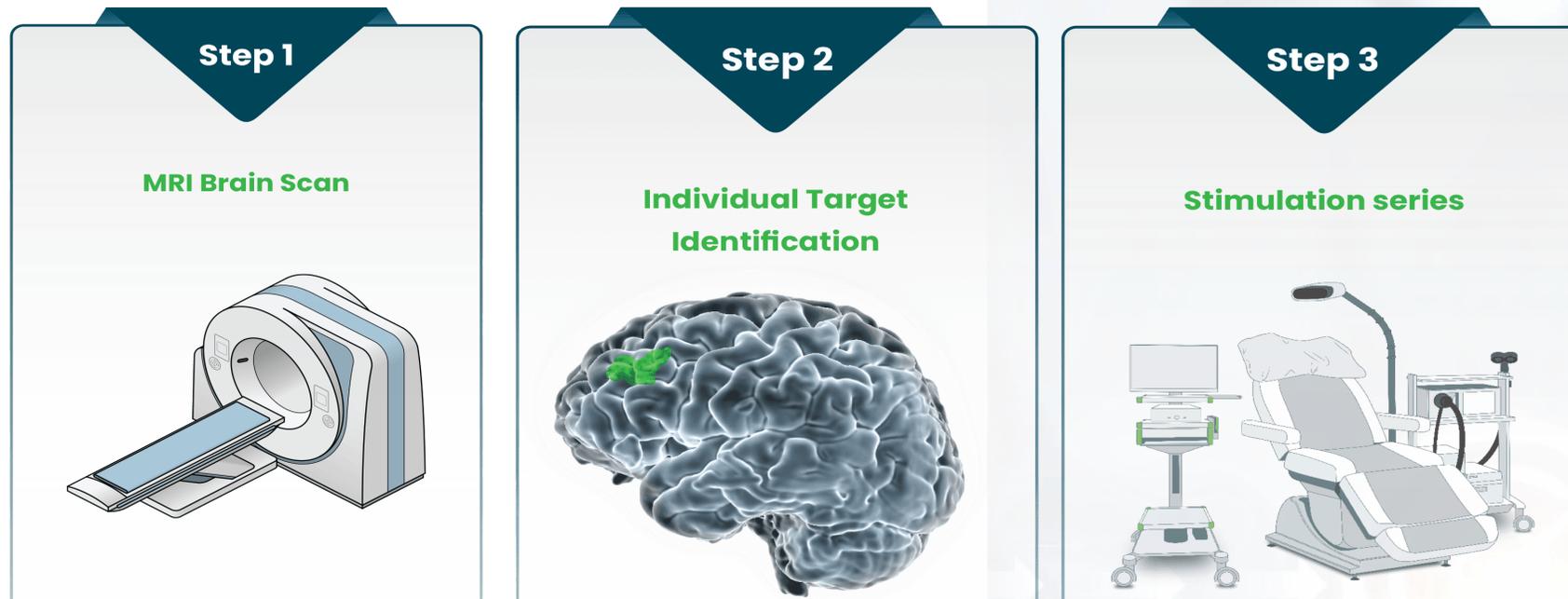


Meta-analysis of 17 studies confirms efficacy of rTMS

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.

Vagus Nerve Stimulation

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



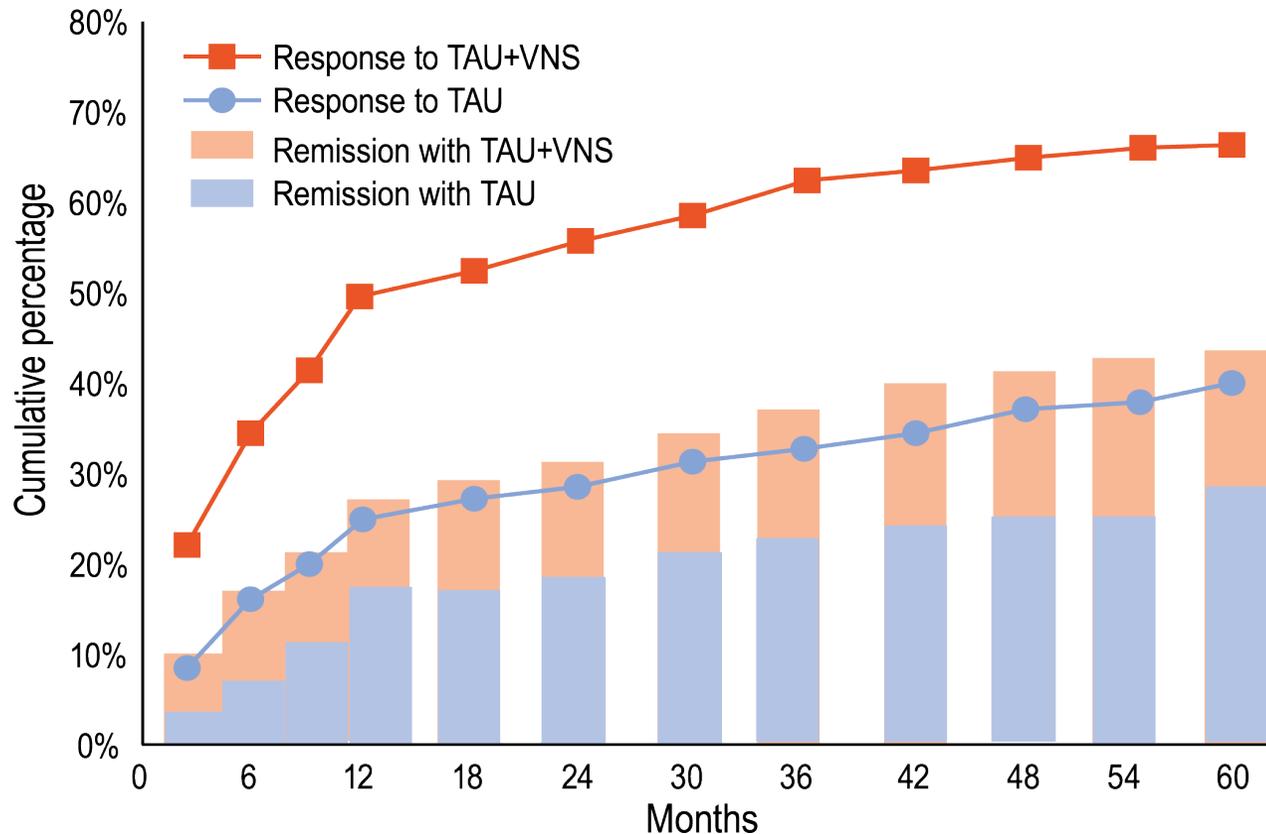
**FDA APPROVED
FOR TRD IN 2005**

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.

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.

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

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

Important limitations for patients' consideration

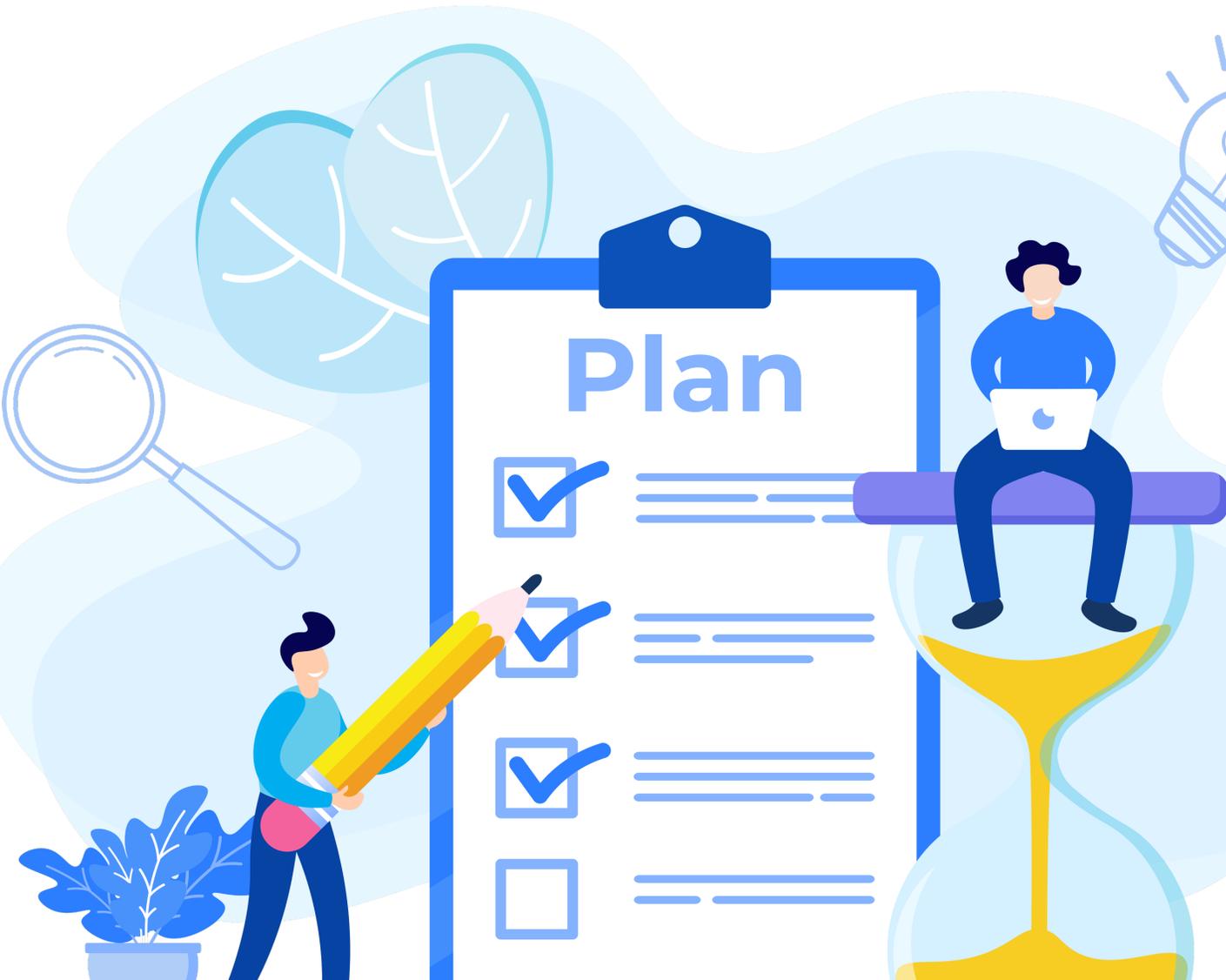
Treatment	Rationale	Limitations
Ketamine	Acute efficacy established in TRD. Beneficial effects on suicidality. Rapid onset of symptomatic improvement	Insufficient long-term efficacy, tolerability and safety data. Access to treatment limited in many jurisdictions. Specialized personnel required for safe 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.
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.

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?**

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

Q&A



Resource Slides

Esketamine Administration, Dose, and Schedule



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

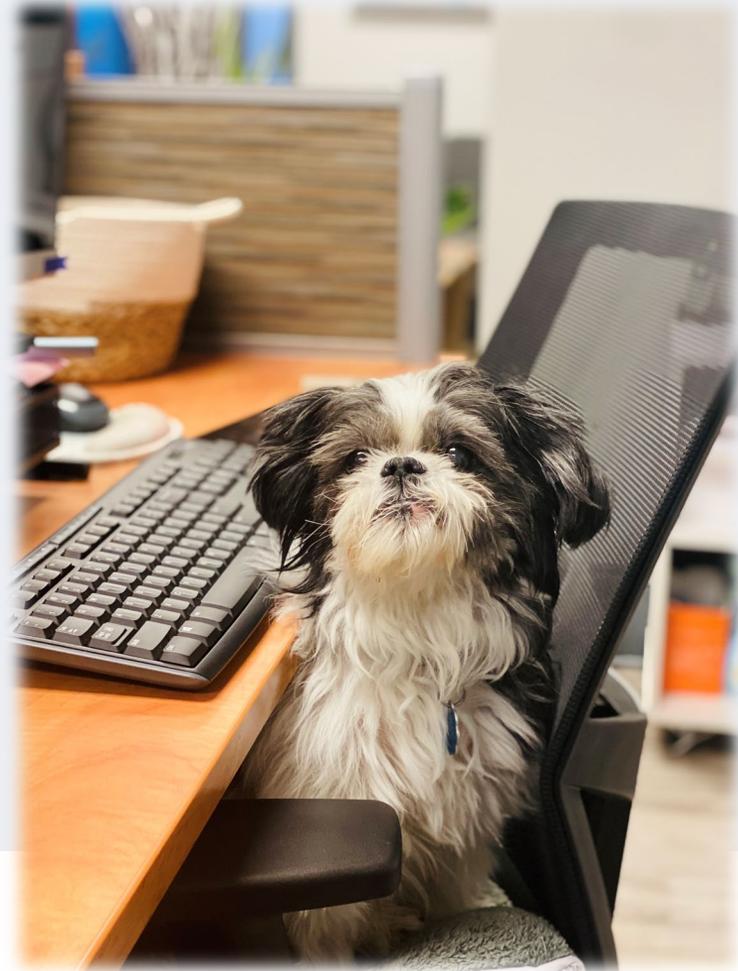
Maintenance phase weeks 9+

- 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

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

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 <u>not</u> generally be treated due to short $t_{1/2}$ 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

