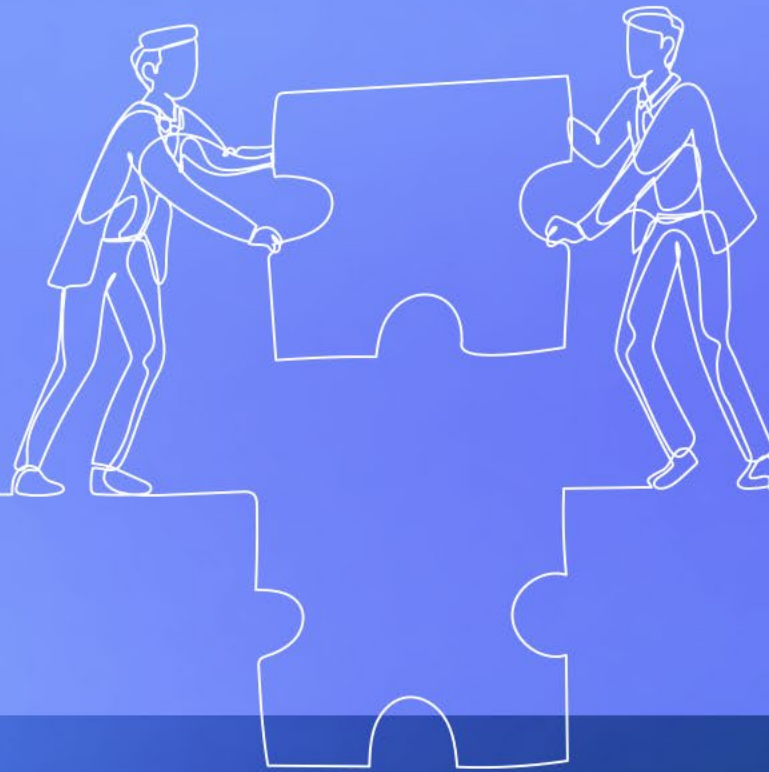




Could Glutamatergic Modulation be the Keystone of ***Durable Change in Treatment-Resistant Depression?***

MasterClass

Supported by an educational grant from Johnson & Johnson.

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Faculty Disclosures

Brittany B. Albright, MD, MPH, DABOM: Advisory Board — AbbVie, Bristol Myers Squibb, Compass Pathways, Definium Therapeutics, Eli Lilly, Johnson & Johnson, Neurocrine Biosciences, Vistagen; Consultant — AbbVie, Aidvance, Almatica, Axsome, Definium Therapeutics, Johnson & Johnson, Osmind, Precision Genetics; Speakers Bureau — AbbVie, Alkermes, Axsome, Bristol Myers Squibb, Johnson & Johnson, Tonix Medicines

Michael Asbach, DMSc, PA-C: Consultant — Axsome Therapeutics, Biogen, Bristol-Meyers-Squibb, Intracellular, Johnson & Johnson Innovative Medicine, Neurocrine Biosciences Inc; Speakers Bureau — AbbVie Inc, Axsome Therapeutics, Bristol-Meyers-Squibb, Intracellular, Johnson & Johnson Innovative Medicine, Neurocrine Biosciences Inc, Otsuka Pharmaceutical Development & Commercialization Inc (Terminated, December 31, 2025)

Disclosure

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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

Characteristics and Burden of TRD

Michael Asbach, DMSc, PA-C

What Is Treatment-Resistant Depression?



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





How Common Is TRD?

30–31%

of MDD episodes meet
TRD criteria (STAR*D-
based)

11%

of episodes in a Swedish
cohort (N=158,169) using
a stricter ≥ 3 -treatment
definition

8%

met TRD criteria in a UK
NHS study (N=110,406)

552 days

median time from MDD
onset to TRD

Why do the estimates vary?

Prevalence depends heavily on the TRD definition (≥ 2 vs ≥ 3 failed trials) and the population studied

Takeaway: TRD is a mainstream problem, not an edge case:

~1 in 3 MDD episodes fail sequential first-line therapy, and it takes ~18 months to get there.

The unmet need is large and often recognized late

MDD = major depressive disorder; TRD = treatment-resistant depression; STAR-D = Sequenced Treatment Alternatives to Relieve Depression; NHS = National Health Service.

McIntyre RS, et al. *World Psychiatry*. 2023;22(3):394-412; Lundberg J, et al. *JAMA Psychiatry*. 2023;80(2):167-175; Pappa S, et al. *J Psychiatr Res*. 2024;180:511-518.

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

Clinical Course Comparison

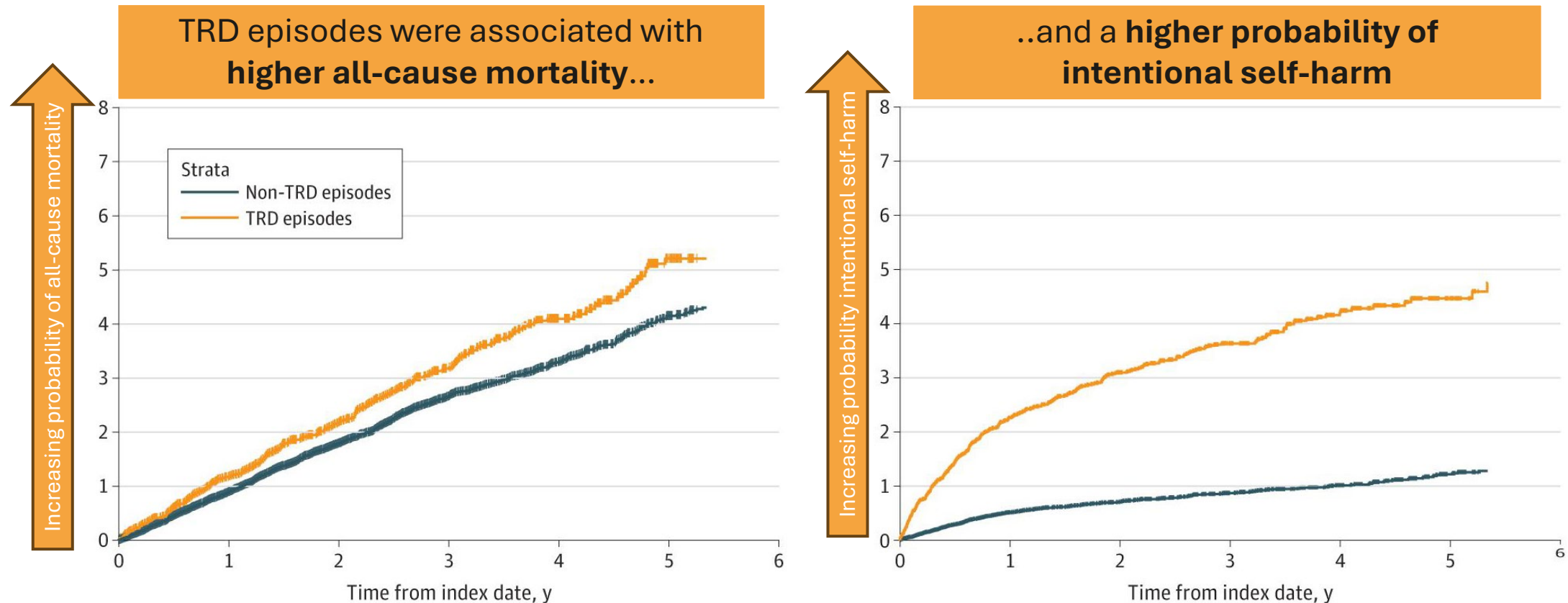
- More chronic, persistent course, longer episodes, and earlier onset
- Higher relapse rates (67%-80% within 1 year)
- Shorter inter-episode recovery periods
- Increased treatment complexity over time



Quality of Life Impact

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

Divergent Outcomes Over Time: Mortality and Self-Harm In Individuals with TRD



Cumulative probability of all-cause mortality (A) and intentional self-harm (B) separates early and widens over ~5 years.

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; 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.

The Evidence Gap:

Few Therapies Are Studied in True TRD

Approved for FDA-defined TRD	EVIDENCE GAP	Studied in inadequate ADT response (not true TRD)		
Olanzapine-fluoxetine combination Only atypical antipsychotic combination approved specifically for TRD		<i>A critical distinction:</i> inadequate response to one ADT ≠ FDA-defined TRD (≥2 adequate failures) <ul style="list-style-type: none"> • Second-generation antipsychotics: pivotal trials evaluated inadequate response to <i>a single antidepressant</i> • DXM-BUP is approved for MDD, not TRD (TRD trial was negative) 		
Esketamine (intranasal) Approved for TRD and for MDD with acute suicidal ideation/behavior		Other commonly used augmentation (off-label)		
		LITHIUM	LAMOTRIGINE	BUPROPION
		Evidence supports augmentation, but not FDA approved for TRD; requires monitoring	Large RCT negative; no significant difference vs placebo	Commonly used; randomized evidence has not shown clear superiority over ADT monotherapy

ADT = antidepressant treatment; DXM-BUP = dextromethorphan-bupropion; RCT = randomized controlled trial.

McIntyre RS, et al. *JAMA Psychiatry*. 2026;83(7):741-750; Edwards SJ, et al. *Health Technol Assess*. 2013;17(54):1-190; Barbee JG, et al., *J Clin Psychiatry*. 2011;72(10):1405-1412; Henssler J, et al., *JAMA Psychiatry*. 2022;79(4):300-312; Nuñez NA, et al. *J Affect Disord*. 2022;302:385-400.



Key Learning Points

- TRD is defined as **nonresponse to at least 2 qualifying trials of monoaminergic antidepressants**
 - TRD occurs in **at least 30% of people with MDD**
- **Rule out pseudo-resistance first:** diagnosis, bipolarity (up to 25%), and adherence ($\approx 46\%$ non-adherent)
- **TRD is higher-acuity:** $>2x$ lost workdays, $>4x$ self-harm, higher mortality, worse QoL at equal severity
- **The toolkit is thin:** Only OFC and esketamine are studied/approved in FDA-defined TRD
- **Remission remains elusive:** A clear rationale for mechanistically novel treatments

Understanding the Glutamatergic System

Michael Asbach, DMSc, PA-C

Thinking Beyond The Monoaminergic Model: Two Complementary Systems

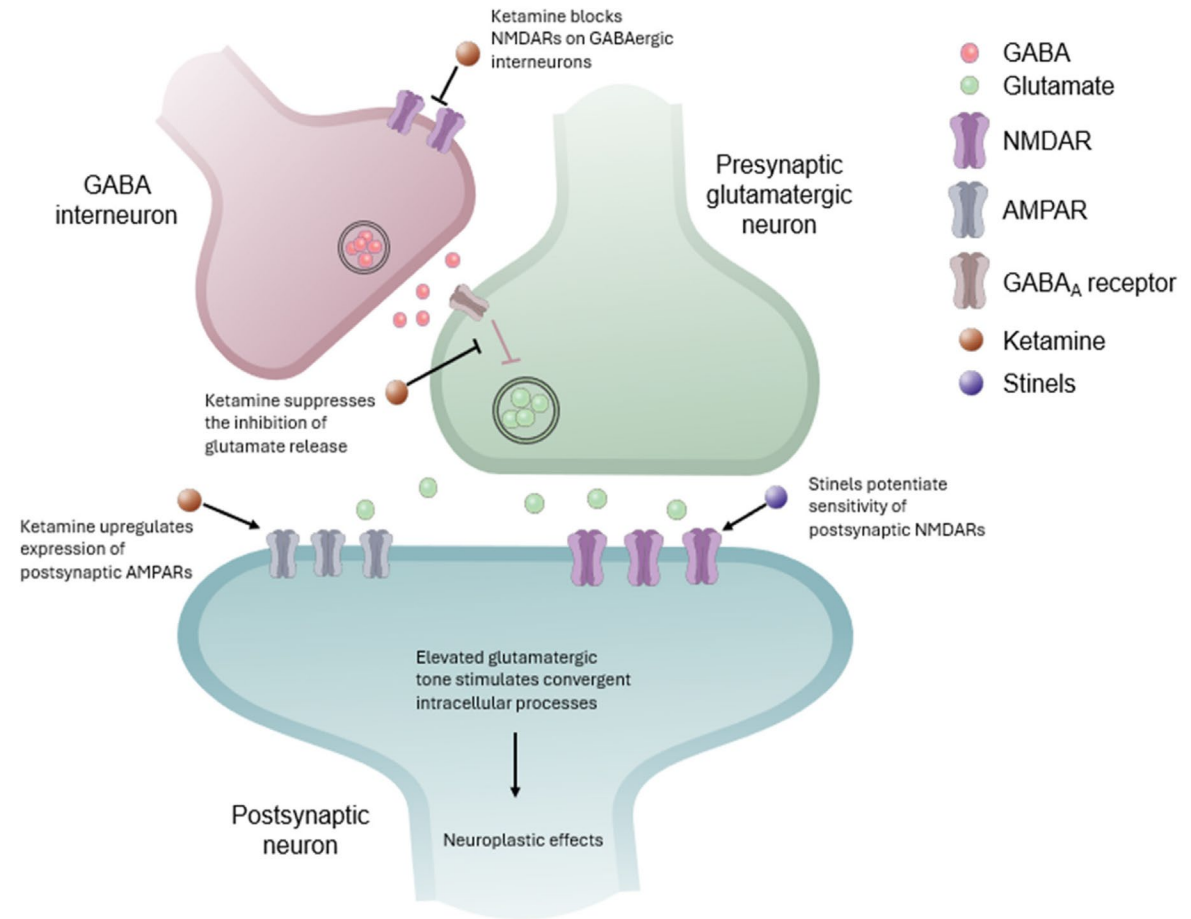
Neurotransmitter Comparison

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

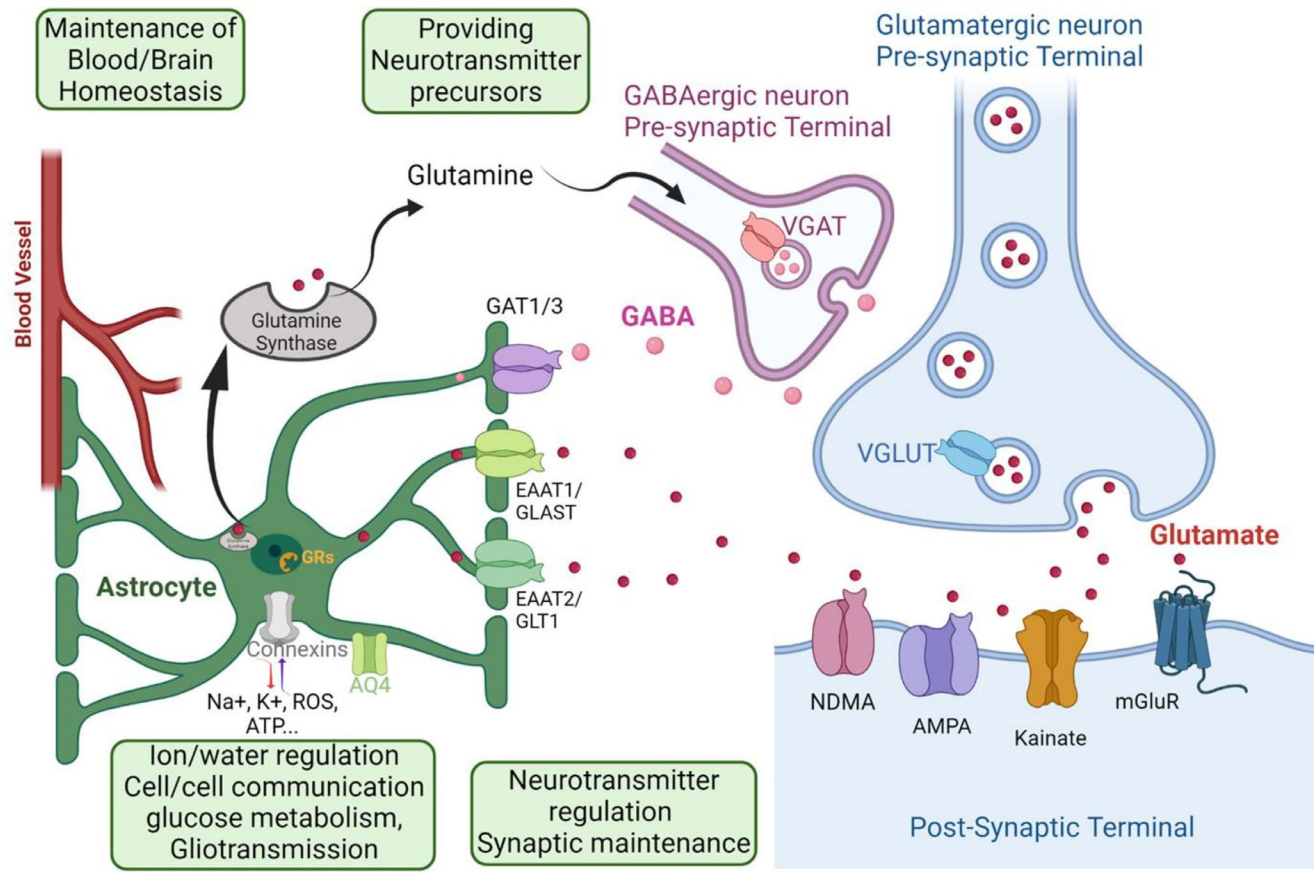
Healthy Mood Circuits Require Coordinated Excitation, Inhibition, and Glutamate Clearance

- **Glutamatergic pyramidal neurons provide excitatory output**
 - Supporting information processing, learning, reward, and adaptation
- **GABAergic interneurons regulate timing and intensity**
 - Filtering noise, synchronizing circuits, and preventing excessive excitation
- **Astrocytes maintain the extracellular environment**
 - Clearing and recycling glutamate through EAAT2/GLT-1
- **Healthy function depends on dynamic E/I balance**
 - Depression may involve region-specific disruption rather than globally high or low glutamate

When inhibitory control and glutamate clearance fail, signaling becomes mistimed and maladaptive, contributing to cellular stress and impaired plasticity.



The Glutamate/GABA-Glutamine Cycle: Astrocytes Provide the Metabolic Foundation



Created with BioRender.com

1. Glutamate is released

- Excitatory neurons communicate across the synapse

2. Astrocytes clear extracellular glutamate

- EAAT2/GLT-1 prevents excessive extrasynaptic accumulation

3. Glutamate is converted to glutamine

- Glutamine synthetase supports safe recycling

4. Glutamine returns to neurons

- Replenishing glutamate and GABA neurotransmitter pools

5. The cycle maintains E/I balance

- Astrocytic dysfunction can impair both excitation and inhibition

E/I = excitatory/inhibitory.

Bansal Y, et al. *Int J Mol Sci.* 2024;25(12):6357; Andersen JV. *J Neurochem.* 2025;169(3):e70029.

CNS Processes Regulated by Glutamate

Emotional processing

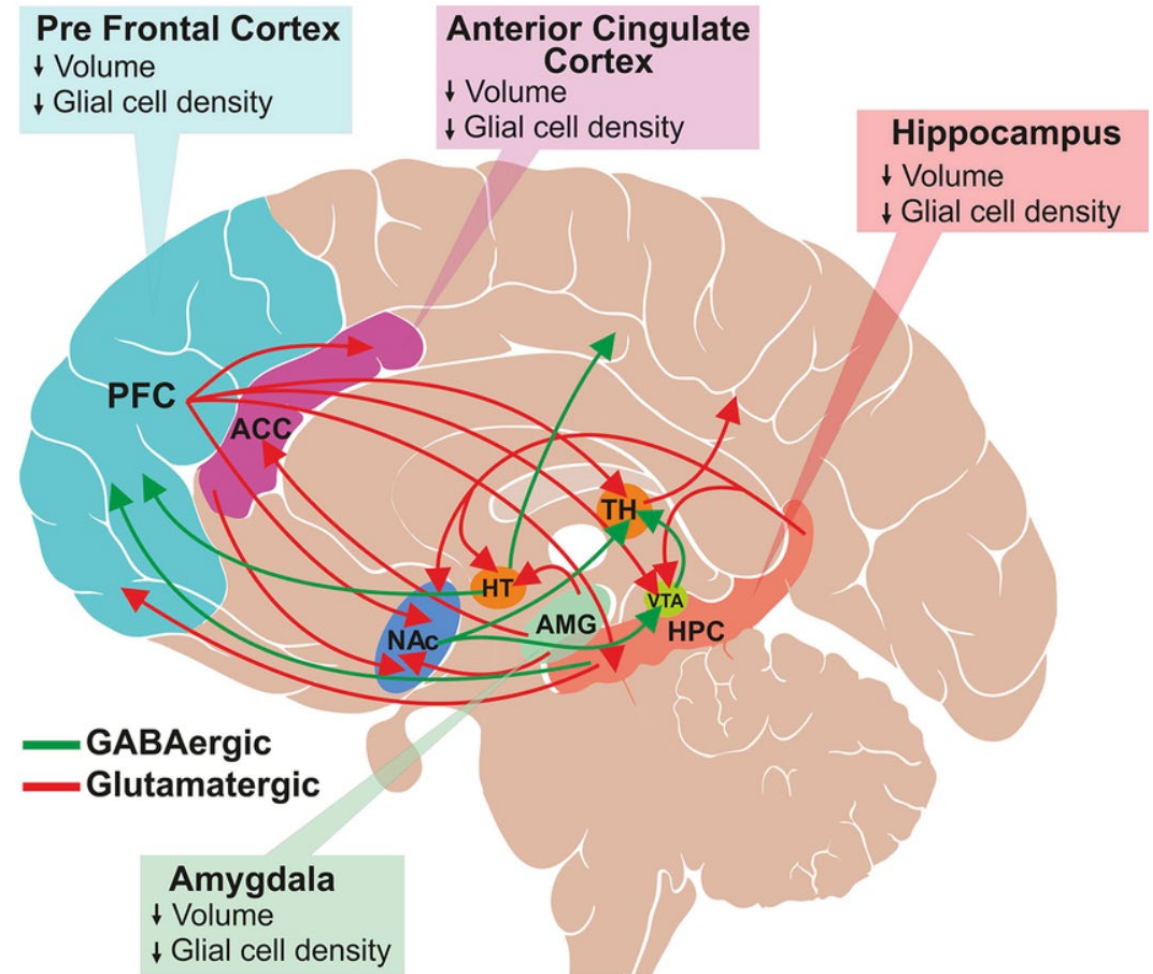
- Amygdala fear extinction pathways
- Nucleus accumbens reward signaling

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.

Glutamate Helps the Brain Detect and Pursue **Reward**

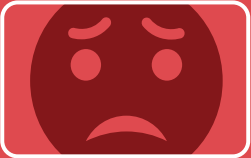
Evidence for Glutamate's Involvement in Reward:



Lower glutamate in reward-related regions is associated with diminished reward responsiveness



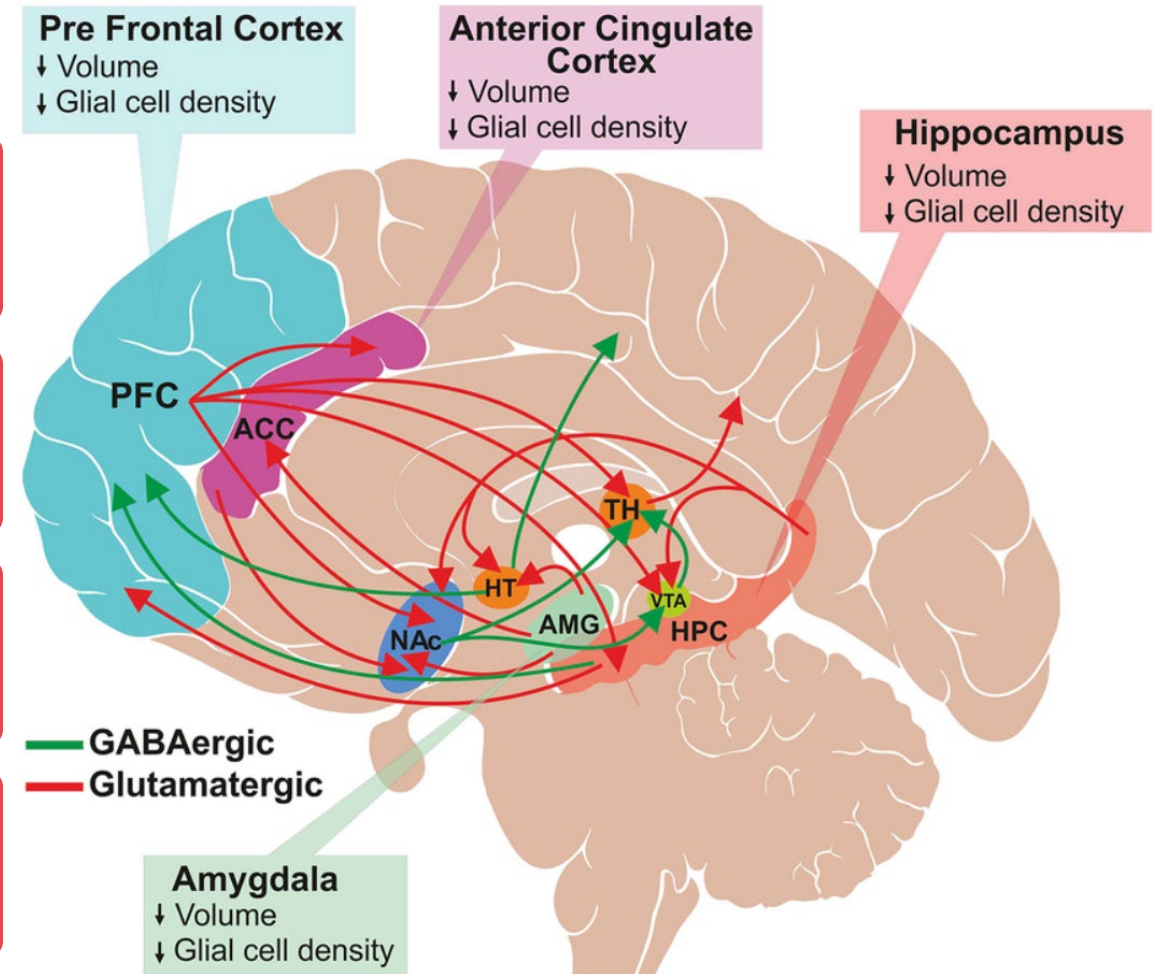
Ventral striatal dysfunction may contribute to anhedonia and reduced motivation



Chronic stress alters AMPA, NMDA, and metabotropic glutamate signaling in reward circuits



Impaired astrocytic glutamate regulation can further disrupt reward processing



Glutamate Supports Working Memory and Cognitive Flexibility

dlPFC glutamate rises during working-memory performance

Parietal glutamate levels are associated with working-memory capacity

NMDA and AMPA signaling support flexible updating of behavior

Chronic stress can blunt prefrontal glutamate release and thalamic input

Glutamatergic dysfunction may contribute to **cognitive rigidity, impaired decision-making, and executive dysfunction** in MDD

dlPFC = dorsolateral prefrontal cortex;

Woodcock EA, Anand C, Khatib D, Diwadkar VA, Stanley JA. *Front Psychiatry*. 2018;9:66. Zacharopoulos G, Kadosh Cohen R. *Neuroscience*. 2021;457:12-19. Jett JD, Bulin SE, Hatherall LC, McCartney CM, Morilak DA. *Neuroscience*. 2017;346:284-297.

NMDA and AMPA Receptors Are the Central Therapeutic Players

NMDA

Ionotropic · Ca^{2+}

Voltage- and ligand-gated
Extrasynaptic sites can drive excitotoxicity
Location matters as much as subunit
A key antidepressant target

AMPA

Ionotropic · fast

Mediates fast excitatory transmission

Downstream AMPA activation is required for rapid antidepressant synaptogenesis

Kainate

Ionotropic

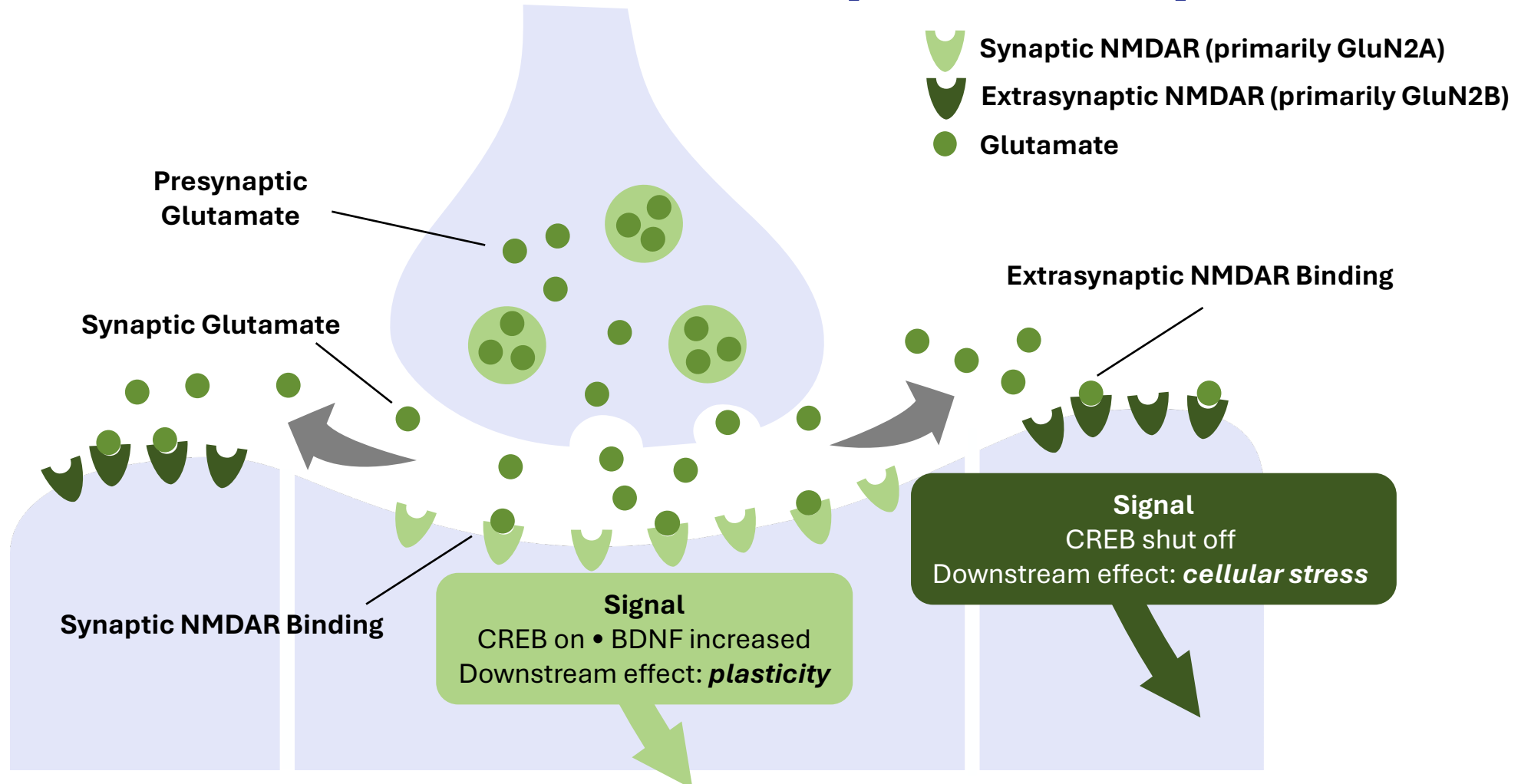
Modulates pre- and post-synaptic excitability and network oscillations

mGluR

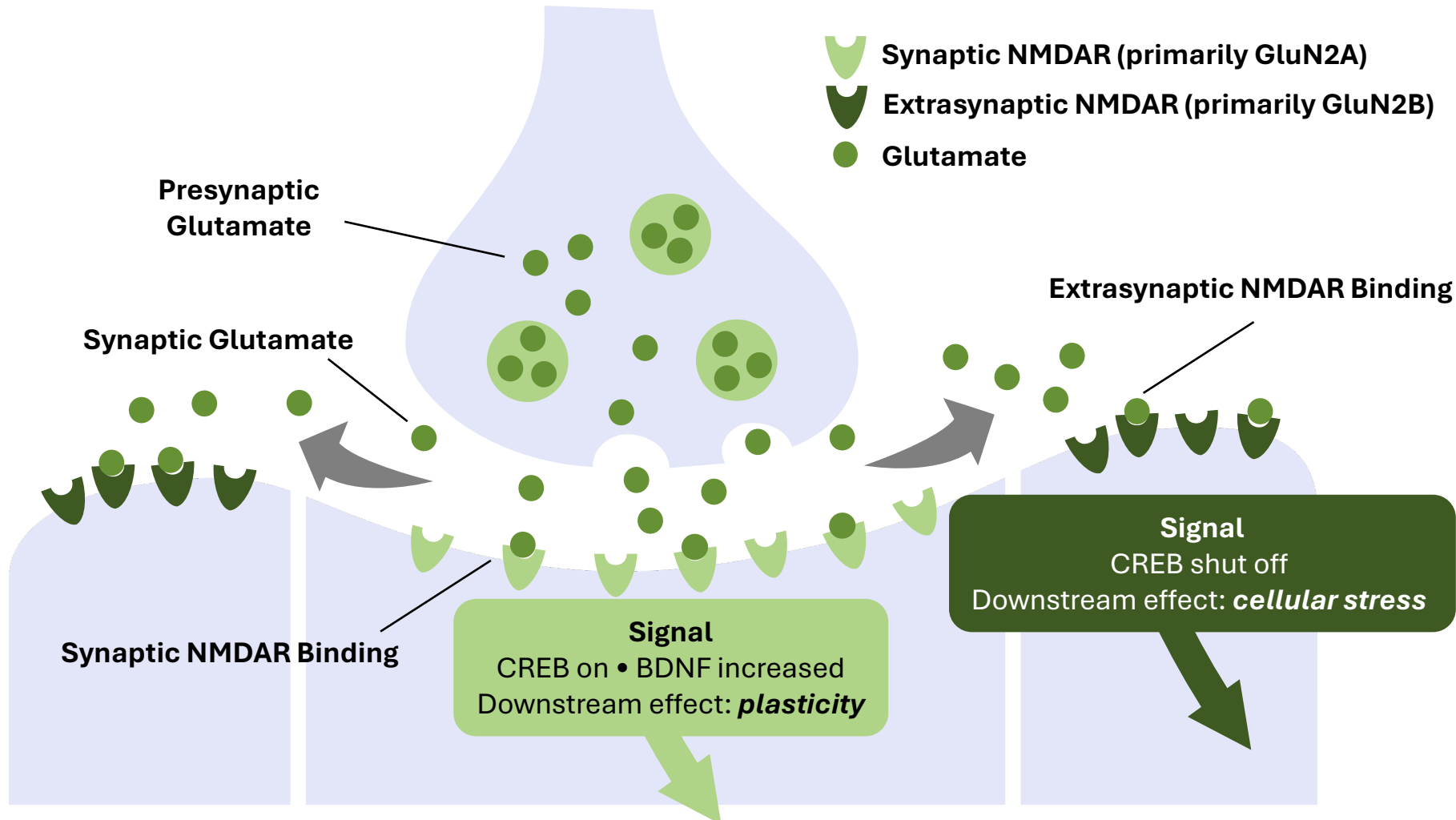
Metabotropic

G-protein coupled (Groups I–III); tune glutamate release and astrocytic Ca^{2+} /neurotrophic support

NMDAR Signaling Outcomes Depend on Location, Pattern, and Receptor Composition



NMDAR Signaling Outcomes Depend on Location, Pattern, and Receptor Composition



KEY FACTORS:

Location:

Synaptic ↔ Extrasynaptic

Pattern:

Brief & patterned ↔
Sustained & excessive

Receptor Composition:

GluN2A/GluN2B
composition

How Chronic Stress Disrupts Glutamate Homeostasis



More glutamate enters the extracellular space

- Stress can increase presynaptic release

Clearance becomes less efficient

- Inflammation and astrocytic dysfunction may reduce EAAT2/GLT-1 activity

Glutamate reaches extrasynaptic receptors

- Spillover shifts signaling away from tightly regulated synaptic transmission

Cellular stress pathways are engaged

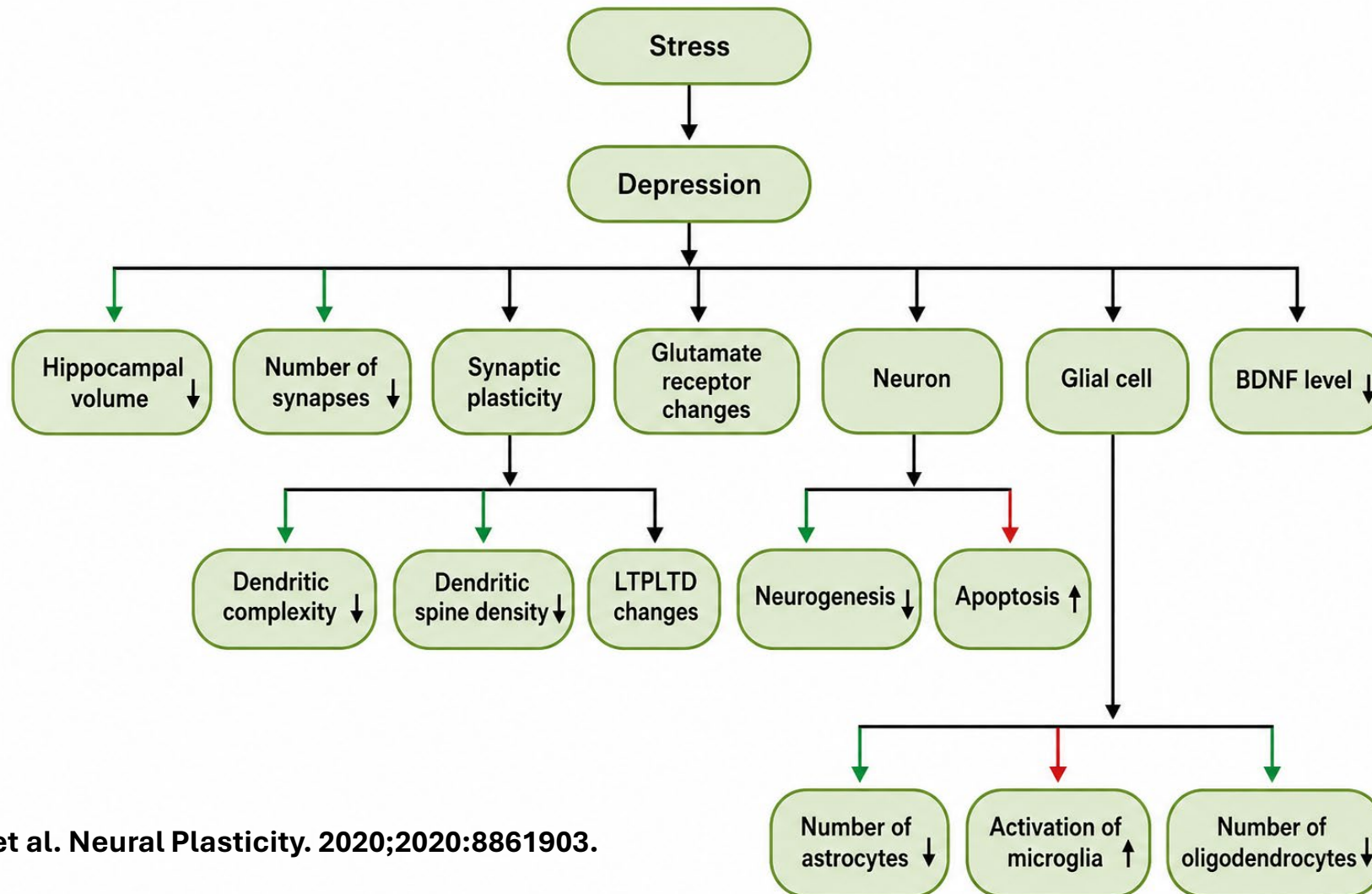
- Calcium loading, oxidative stress, mitochondrial dysfunction, and CREB suppression

Plasticity deteriorates

- Dendritic retraction, spine loss, and impaired circuit connectivity

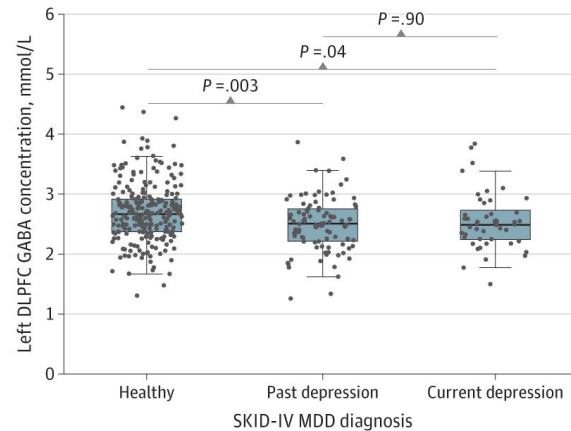
The common denominator:
the brain becomes ***less able to update its responses to experience***

Chronic Stress Reduces the Brain's Capacity to Adapt

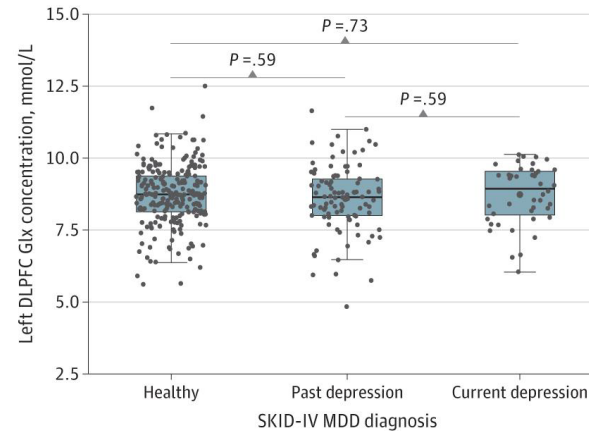


Prefrontal GABA and Glutamate Are Also Altered in Human Population with MDD

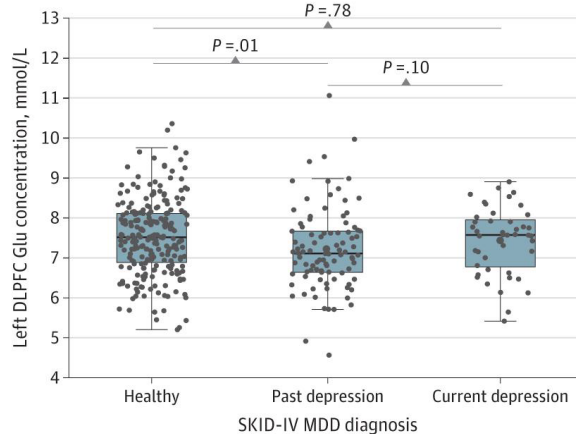
A GABA concentrations



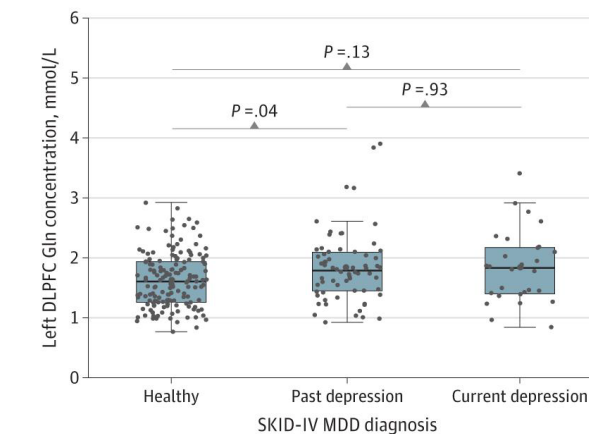
B Glx concentrations



C Glu concentrations



D Gln concentration



What to note

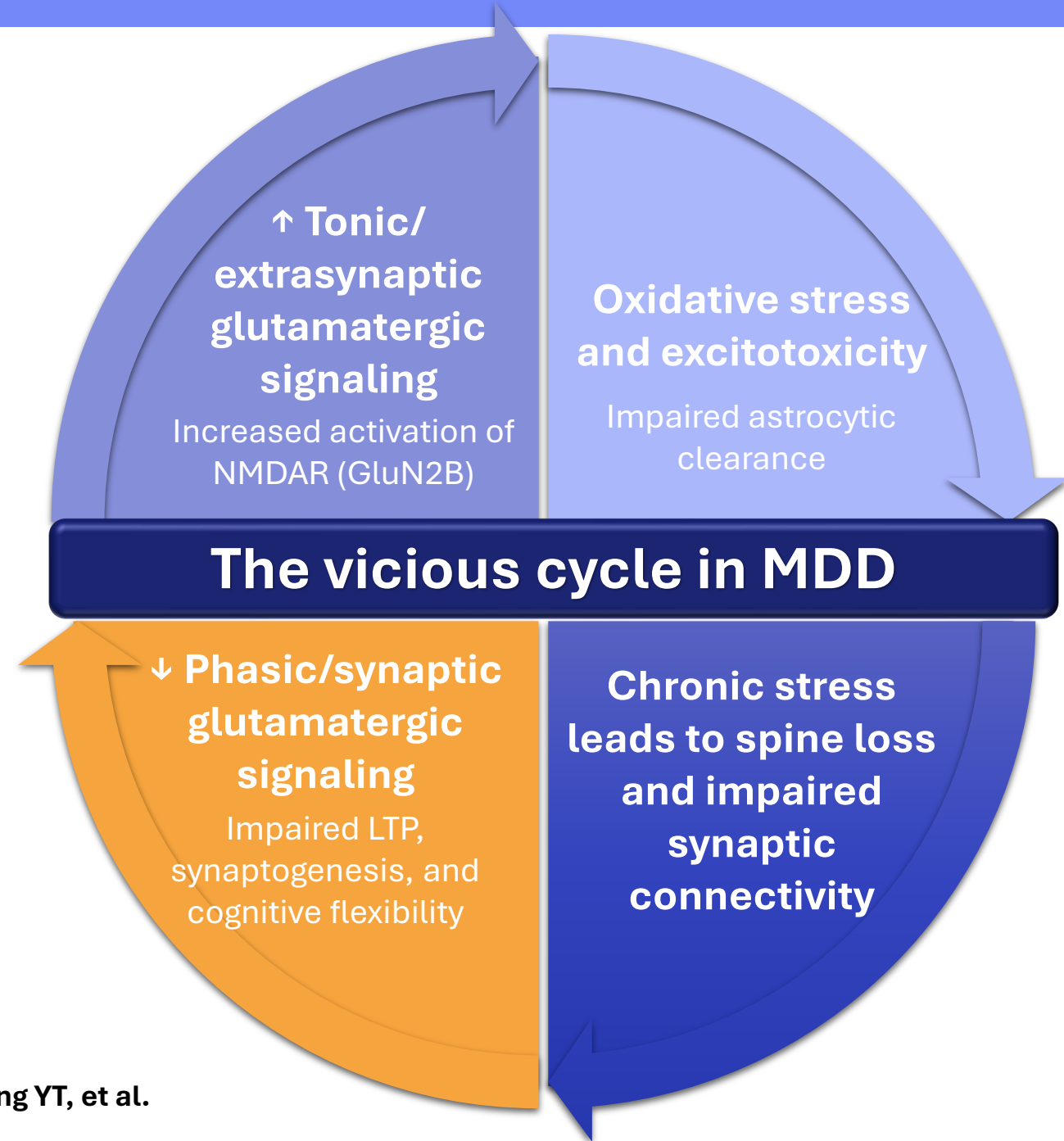
- Community sample examining left dlPFC metabolites
- GABA and glutamate were lower in past MDD
- Glutamine was higher in past MDD
- Pattern is consistent with altered glutamate–glutamine cycling

These findings suggest an altered balance between excitatory and inhibitory neurotransmitters

MDD May Reflect an Imbalance Between Maladaptive and **Healthy** Glutamatergic Signaling



MDD may be characterized by *too much maladaptive signaling* and *too little healthy signaling*





Key Learning Points

- **MDD is a disorder of synaptic plasticity** — not simply monoamine deficiency
- **Excitation/Inhibition balance is disrupted → GABA deficit → glutamatergic disinhibition**
- **Chronic stress is the driver:** the brain becomes less able to update its responses to new experiences
- **Location matters:** extrasynaptic vs synaptic; the NMDA paradox
- **Both excess and deficiency coexist** in this model, restoring AMPA:NMDA throughput is the guiding therapeutic principle

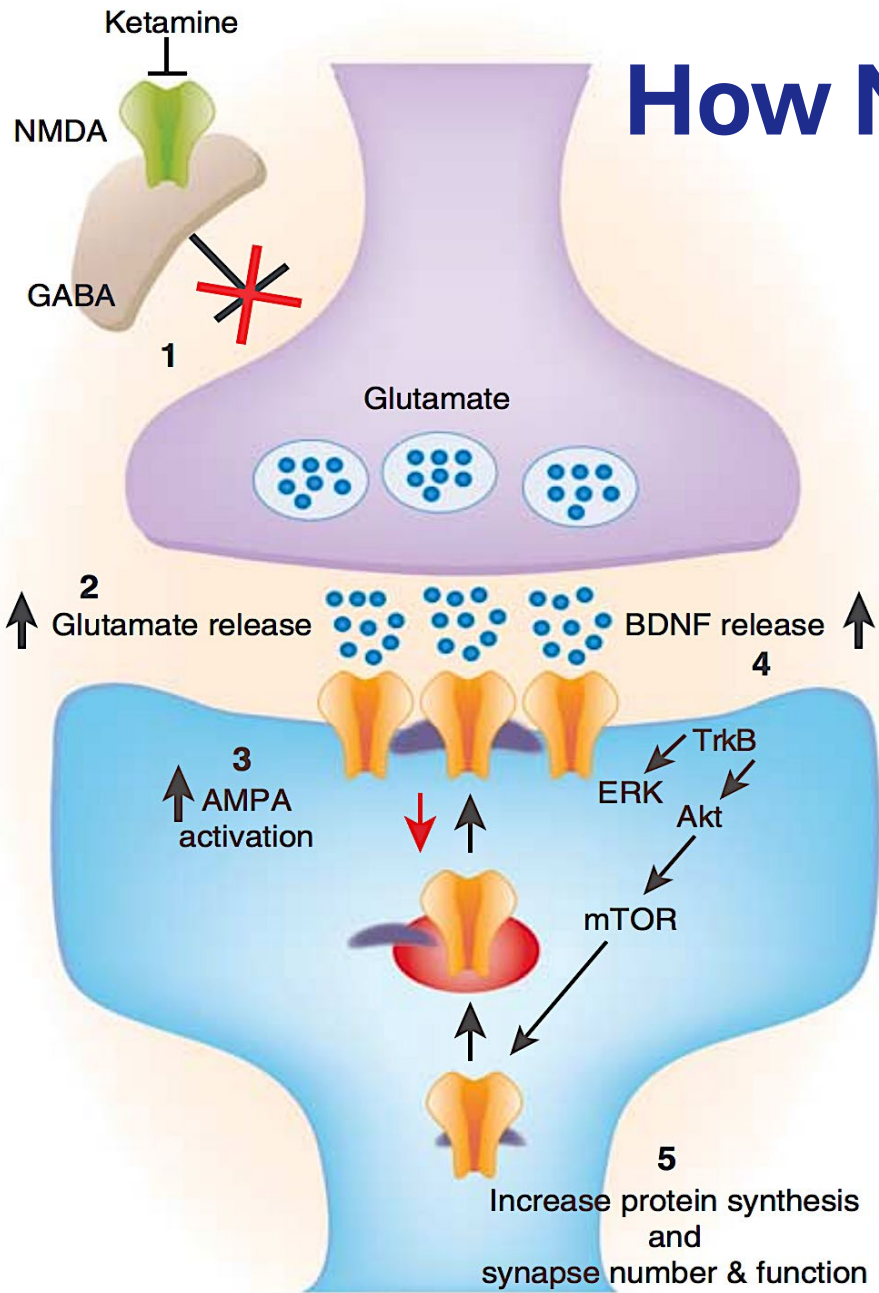


Glutamatergic Signaling as a Therapeutic Target in TRD

Brittany Albright MD, MPH, DABOM

Speed & Precision Matter +

Goal = Remission • ○



How NMDA Receptor 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

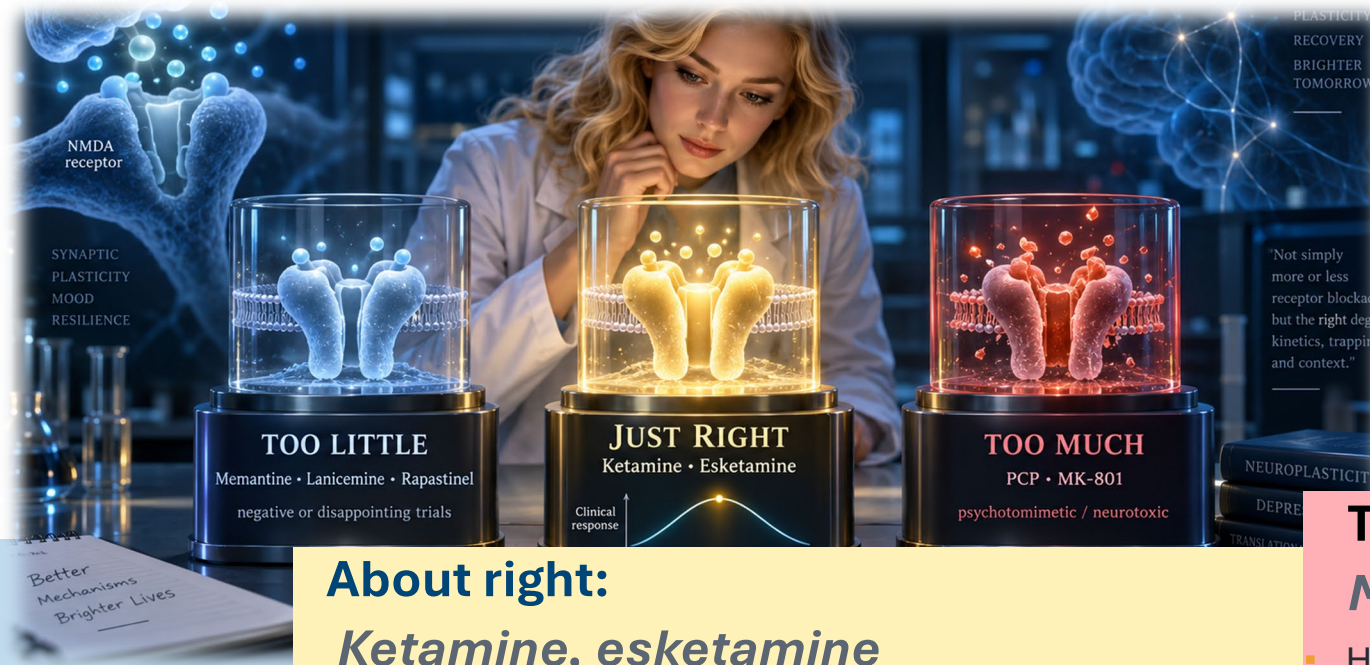
Leads to increased AMPA receptor stimulation

Leads to a release of BDNF

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

Not All NMDA Receptor Antagonists Work in MDD: The Goldilocks Problem

The efficacy of NMDA receptor antagonists in treating MDD depends on a precise balance of binding affinity and kinetics



Also failed in MDD trials: *lanicemine, esmethadone, rapastinel, apimostinel, AV-101, basimglurant, decogurant, riluzole*

Too little: *Memantine*

- Low affinity, fast on and off
- Blocks only during prolonged pathological firing, then detaches so normal signals pass
- Filters excitotoxic noise but never starts the plasticity cascade: no antidepressant effect

About right: *Ketamine, esketamine*

- Moderate affinity, intermediate kinetics
- Blocks long enough to trigger AMPA, BDNF and mTORC1 synaptic repair
- Clears fast enough to avoid sustained toxicity: rapid antidepressant response

Too much: *MK-801, phencyclidine*

- High affinity, slow off-rate, drug trapped in the channel
- Blockade persists well past the therapeutic window
- Psychotomimetic effects and neurotoxicity

BDNF = brain-derived neurotrophic factor. NMDA = N-methyl-D-aspartate.

Zarate CA Jr, et al. Am J Psychiatry. 2006;163(1):153-155. Autry AE, et al. Nature. 2011;475(7354):91-95. Gideons ES, et al. Proc Natl Acad Sci U S A. 2014;111(23):8649-8654. Henter ID, et al. CNS Drugs. 2021;35(5):527-543.

Ketamine

A potent non-competitive NMDA receptor antagonist that rapidly modulates glutamatergic circuits & downstream synaptic plasticity

NOT approved for TRD, all psychiatric indications are off label

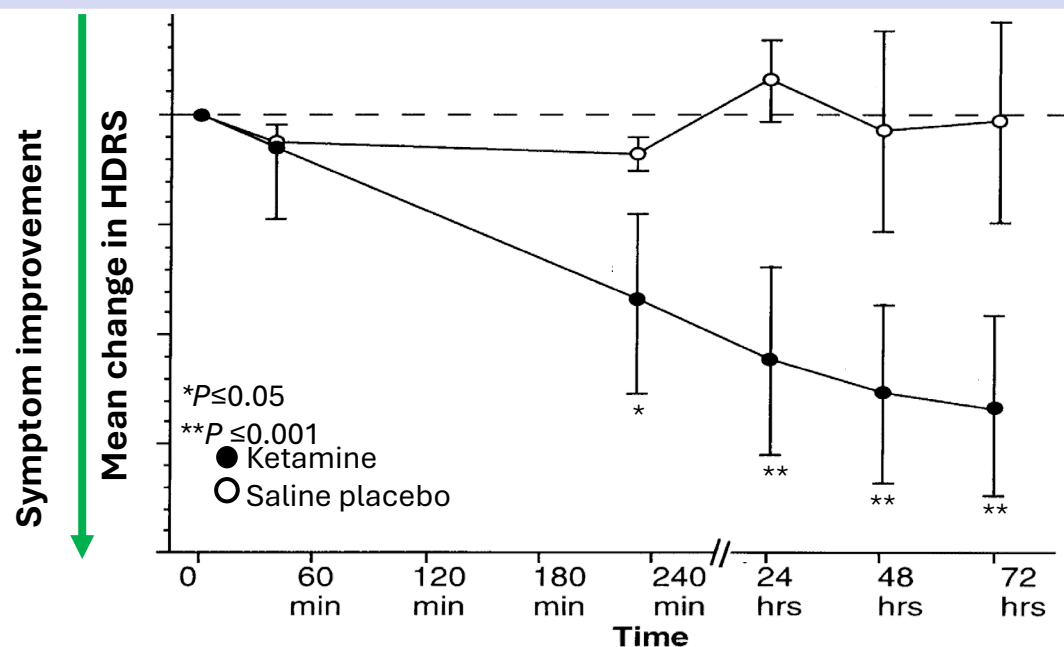
Studies have demonstrated ketamine is associated with:

- Rapid reduction in suicidal ideation
- Improvements in anhedonia and quality-of-life measures

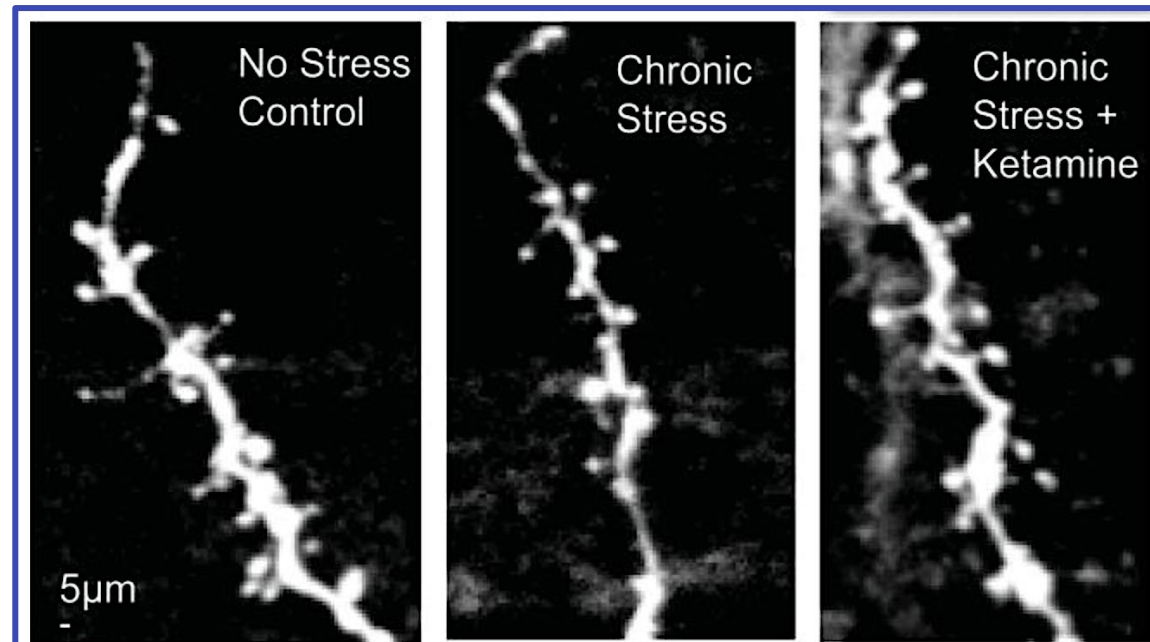
Ketamine for Major Depression

Onset of antidepressant effect within hours of a single IV infusion

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 rodent pyramidal neurons.

HDRS = Hamilton Depression Rating Scale.

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

Ketamine Is Generally Tolerated Acutely, Requires Careful in Office Monitoring

Adverse effects are usually acute and transient

- Dissociation and perceptual change
- Transient hypertension and tachycardia, typically 10–20 mmHg systolic, peaking around 30–50 minutes
- Dizziness and lightheadedness
- Headache
- Nausea
- Blurred or double vision
- Sedation and fatigue in the hours afterward
- Anxiety during the infusion

Bioavailability:

IV ~100% * IM ~ 93% * PO ~ 16-24%

The FDA has warned of potential risks with compounded ketamine, particularly at-home use without onsite monitoring, including sedation, dissociation, hemodynamic and respiratory effects, misuse, and urinary toxicity.

Long-term safety data remains incompletely characterized

AE = adverse event. IM = intramuscular. IV = intravenous.

Short et al. *Lancet Psychiatry*. 2018;5:65-78; Wan et al. *J Clin Psychiatry*. 2015;76:247-252; Sanacora et al. *JAMA Psychiatry*. 2017;74:399-405; FDA. Compounded Ketamine Risk Alert. 2023; ANSM. CPC Kétamine. 2026.

Esketamine

**The only FDA-approved ketamine enantiomer for treatment resistant depression;
self administered intranasally under a REMS program**

Studies have demonstrated esketamine treatment is associated with:

- Reduced relapse risk back into depression (maintenance treatment)
- Reduction in depressive symptoms in suicidal patients
- Improvements in anhedonia and anxiety (post hoc analyses)

REMS = risk evaluation mitigation strategy

Canuso CM et al. Am J Psychiatry 2018;175(7):620-30; Oraee S et al. J Psychiatr Res 2024;180:371-9; Nikolin S et al. EClinicalMedicine 2023;62:102127.

Esketamine: The Approved Glutamatergic Option

Indications in adults

- Treatment-resistant depression, as monotherapy or with an oral antidepressant
- Depressive symptoms in MDD with acute suicidal ideation or behavior, with an oral antidepressant

Safety guardrails

- Observe at least 2 hours in office; recheck BP & O2 saturation near 40 minutes
- Contraindicated in aneurysmal vascular disease, AV malformation, or prior intracerebral hemorrhage
- No driving until the next day after restful sleep



Dosing and course

- 56 mg or 84 mg intranasally; 28 mg per device
- Twice weekly for 4 weeks, then weekly, then weekly or every 2 weeks
- Reassess benefit after the 4-week induction

BOXED WARNINGS

Risk for sedation, dissociation, and respiratory depression

Abuse and misuse: Schedule III controlled substance

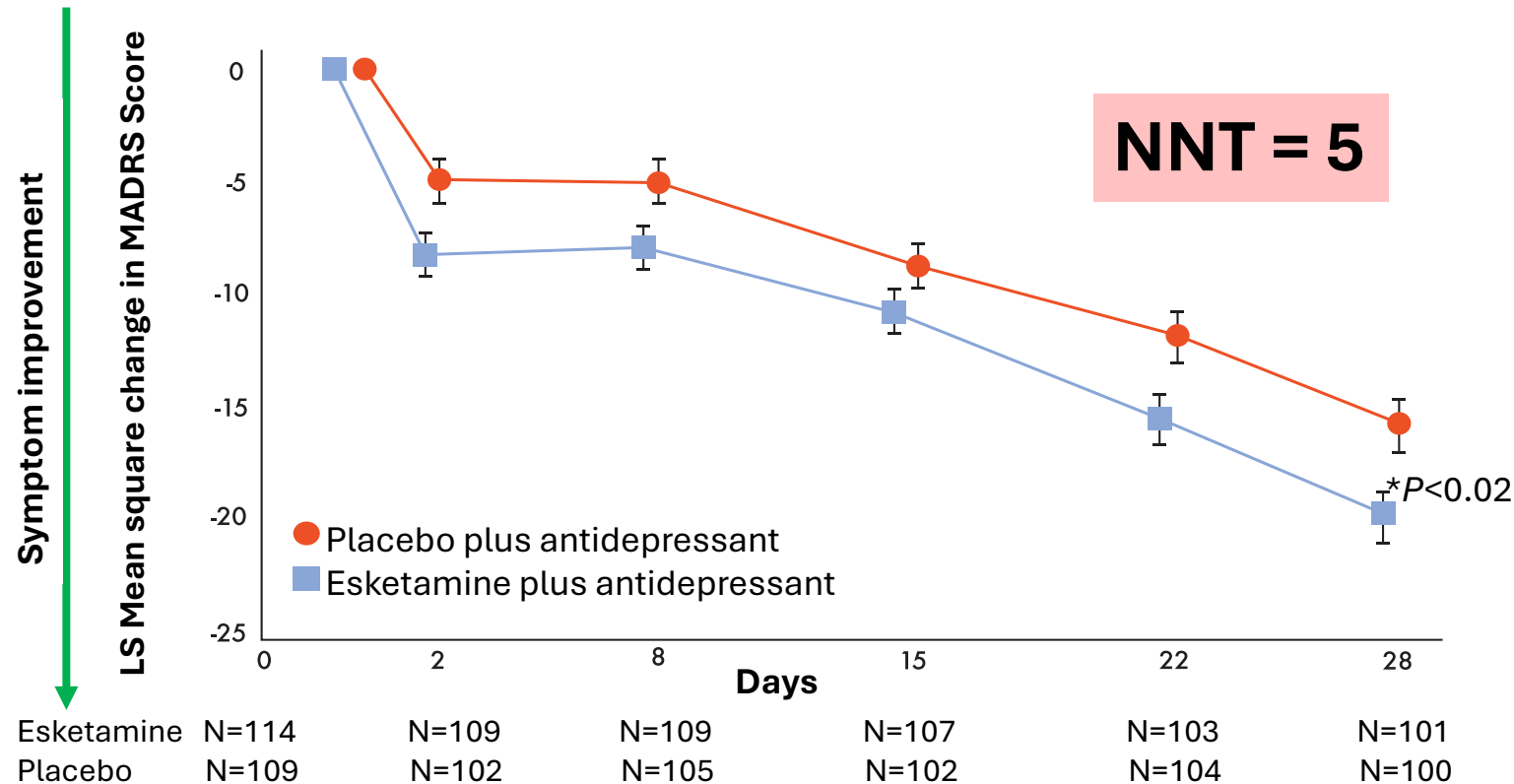
Suicidal thoughts and behaviors in young adults and adolescents: monitor closely; it is not shown to prevent suicide

Because of these risks it is available only through a restricted REMS program.



Esketamine Efficacy in TRD & MDSI Trials

TRANSFORM-2: esketamine + SSRI/SNRI decreased depressive symptoms significantly more than placebo + SSRI/SNRI at week 4



Monotherapy, Phase 4:

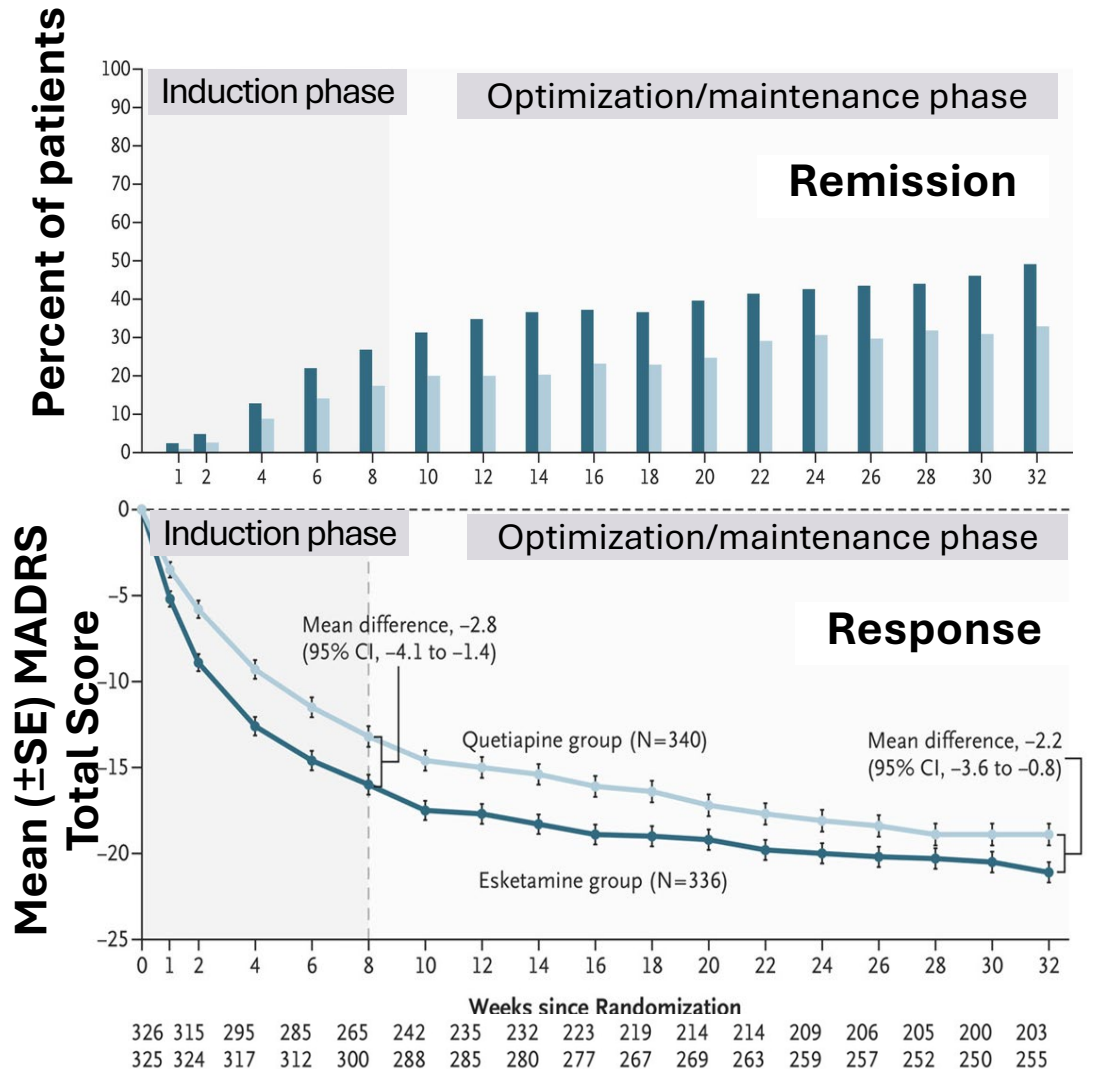
- MADRS fell 5 points (56 mg) and 7 points (84 mg) more than placebo at day 28
- Effect size 0.48 and 0.63; both $P<0.001$

ASPIRE-I: MDD with active SI

- 84 mg plus standard of care separated from placebo by 24 hours ($P=0.006$)
- Effect size 0.28 to 0.30; suicidality fell in both arms

MADRS = Montgomery-Åsberg Depression Rating Scale. NNT = number needed to treat. SSRI = selective serotonin reuptake inhibitor. SNRI = serotonin norepinephrine reuptake inhibitor. MDD = major depressive disorder. SI = suicidal ideation. MDSI = Major depression w/ suicidal ideation
Popova V, et al. Am J Psychiatry. 2019;176(6):428-438. Janik A, et al. JAMA Psychiatry. 2025;82(9):877-887. Fu DJ, et al. J Clin Psychiatry. 2020;81(3):19m13191.

ESCAPE-TRD: Esketamine vs Quetiapine-XR



51%

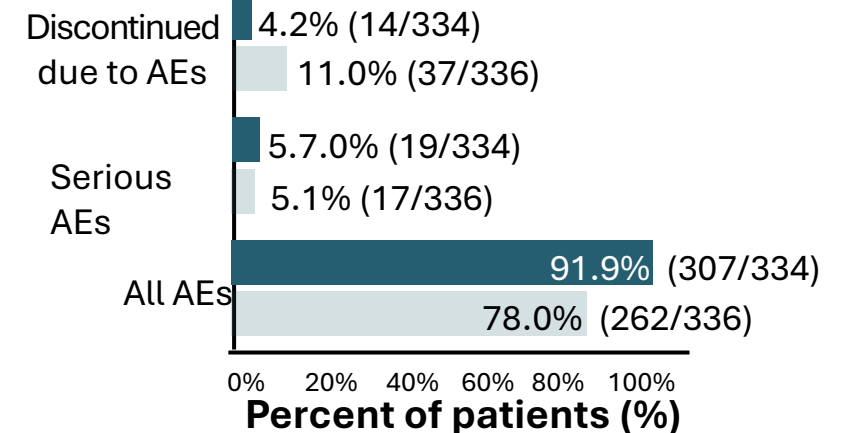
More likely to achieve remission (week 8) OR=1.74 (95% CI: 1.20-2.52) $P=.003$

72%

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

SAFETY AND TOLERABILITY

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



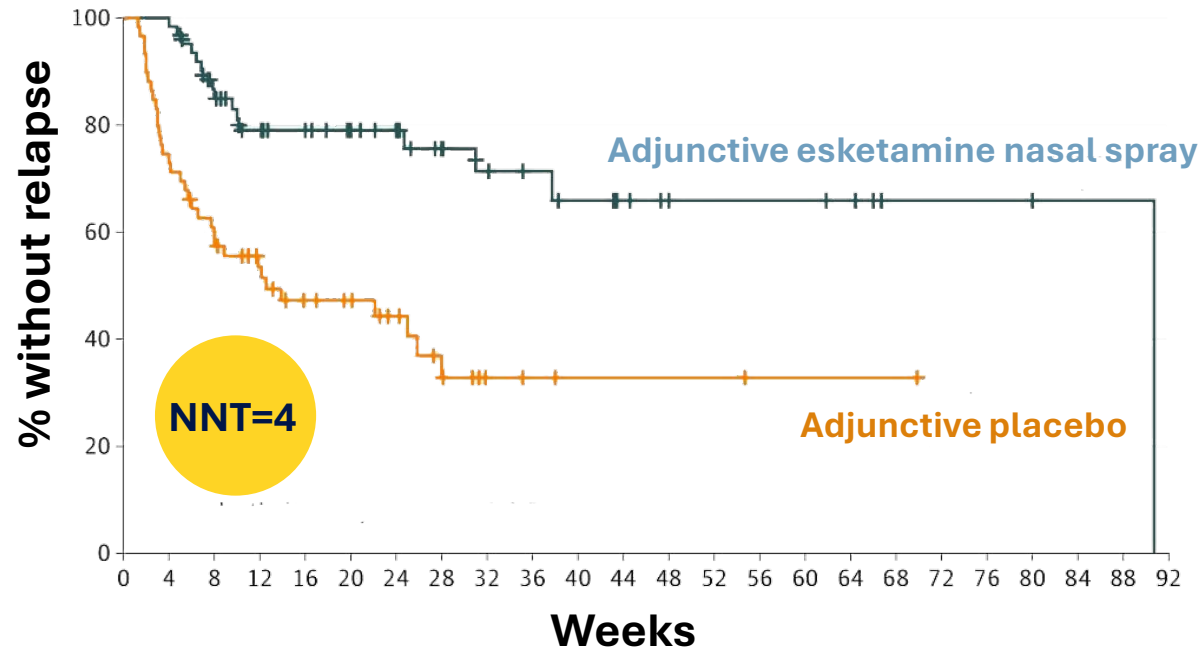
LIMITATIONS

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

SUSTAIN-1: Esketamine + Oral ADT Extend Time to Relapse into Depressive Episode

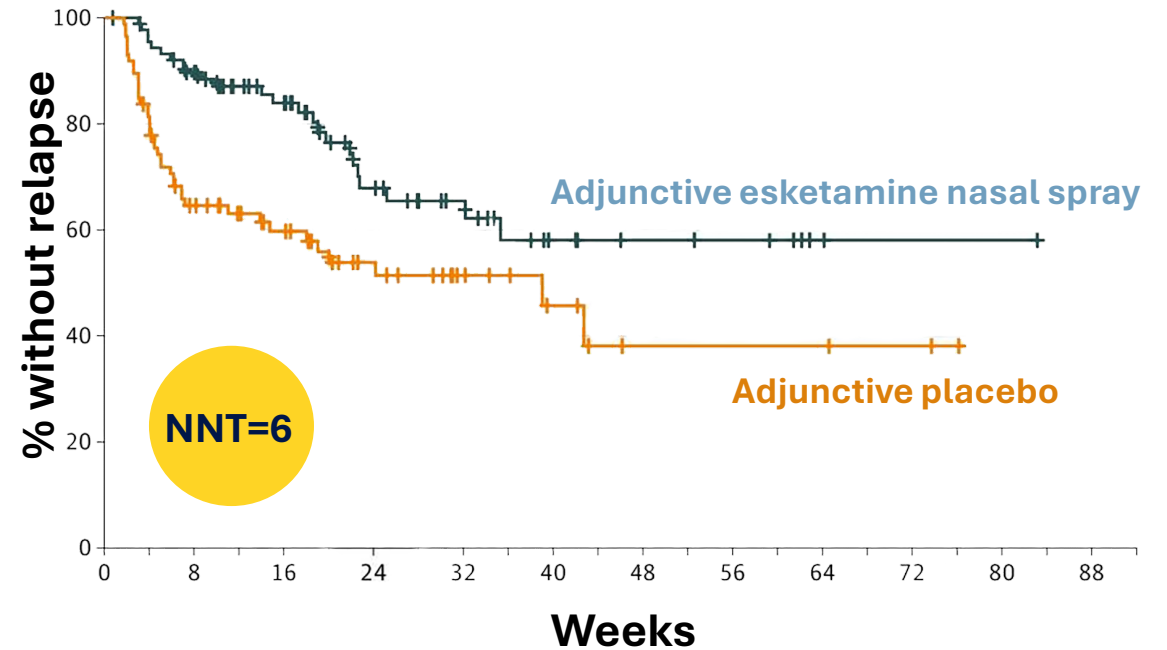
Patients who responded to treatment were

70% 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), $P=.001$



Esketamine Safety Over Up to 6.5 Years: SUSTAIN-3

Adverse event		Incidence
Headache		36.9%
Dizziness		33.9%
Nausea		33.6%
Dissociation		25.5%
Nasopharyngitis		23.8%
Somnolence		23.1%
Dysgeusia		20.2%
Back pain		20.0%
Discontinued due to AEs		6.4%

What 6.5 years showed

- 1148 adults with TRD, up to 6.5 years of dosing, 3777 cumulative patient-years; mean exposure 42.9 months
- 97% of adverse events on a dosing day resolved the same day
- No new concerns for blood pressure, renal or urinary problems, or suicidality; no impaired cognition, cystitis, or hepatotoxicity
- Improvement from induction persisted through maintenance

Open-label, single-arm extension of six phase 3 parent studies. No placebo arm, so these incidences are not comparative. AE = adverse event.

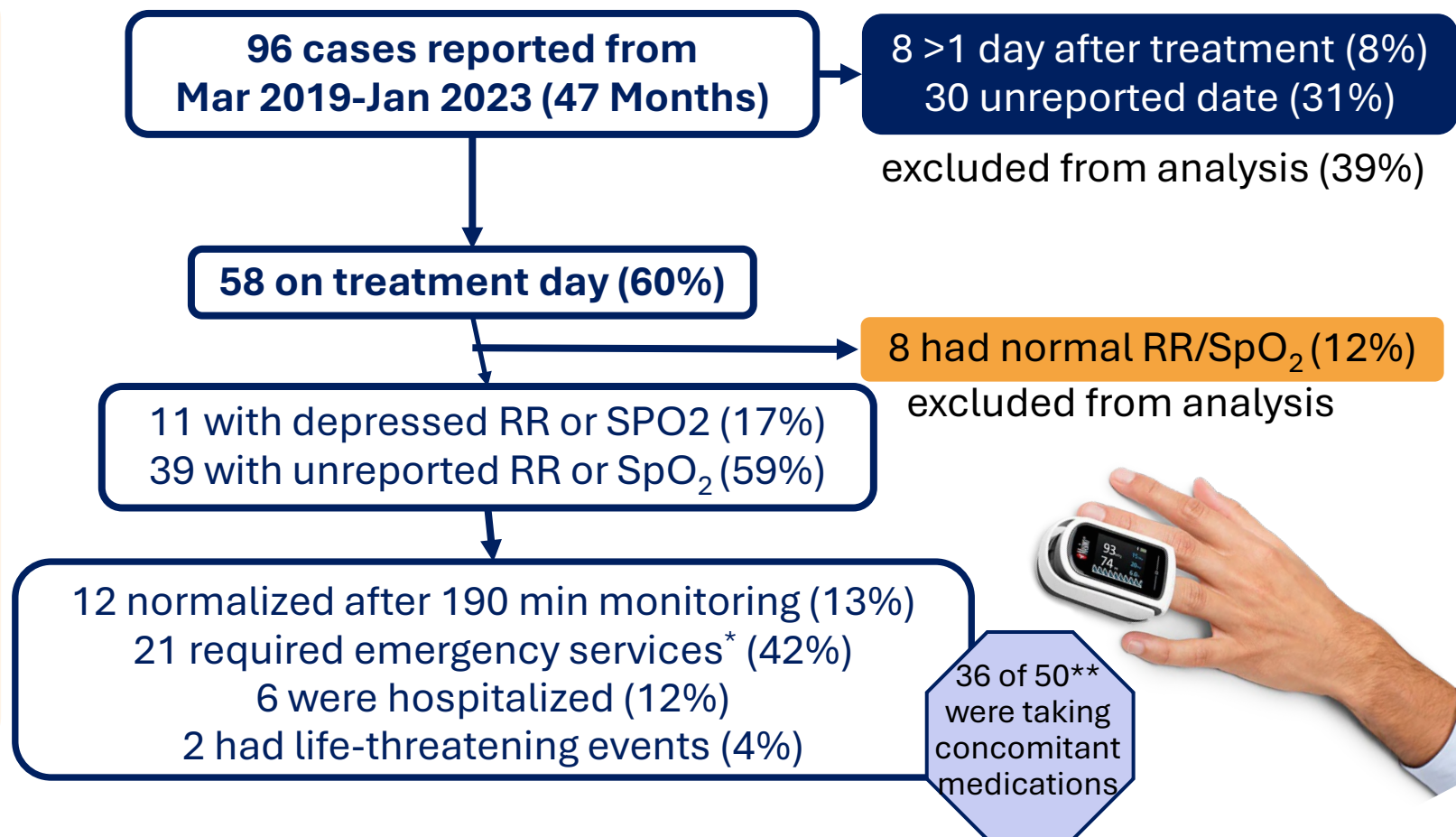
Zaki N, et al. Int J Neuropsychopharmacol. 2025;28(6):pyaf027.

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



*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.

Dextromethorphan- Bupropion

First oral NMDA-receptor antagonist and sigma one receptor agonist FDA-approved for MDD (Aug 2022) but not demonstrated to be effective for TRD

Dextromethorphan-Bupropion Is Glutamatergic

Dextromethorphan the glutamatergic agent

- **Non-competitive NMDA receptor antagonist**
- **Sigma-1 (σ_1) receptor agonist**
modulates Ca^{2+} , BDNF, neuroplasticity

Bupropion the pharmacokinetic enabler

- **CYP2D6 inhibitor**
raises & prolongs DXM plasma levels ~20-fold
- **Weak NE / DA reuptake inhibitor**
adds modest monoaminergic activity

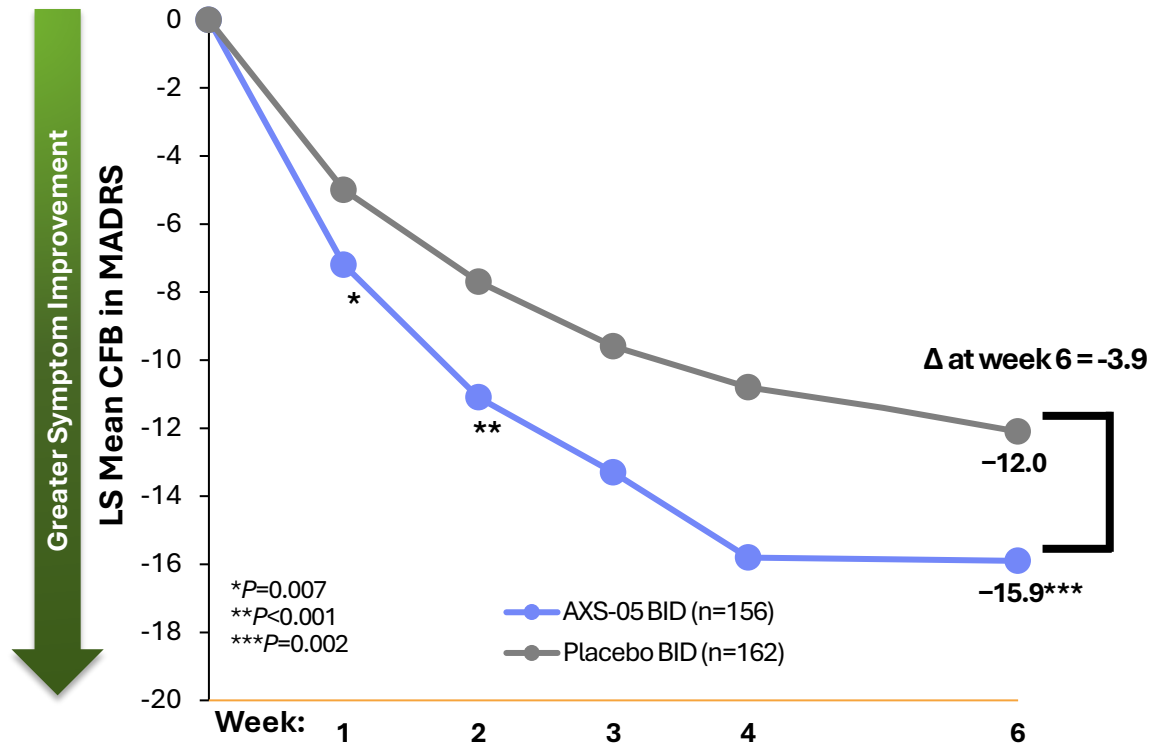
Downstream glutamatergic effect

- Increases glutamate release by decreasing presynaptic inhibition
- Redirects synaptic glutamate toward AMPA receptors
- Dampens extrasynaptic NMDA-mediated excitotoxicity
- Sigma-1 activity may fine tune monoamine and glutamate signaling, reduce neuroinflammation, and promote neuronal repair

Engages the same AMPA-BDNF-mTORC1 cascade orally, without need for in office monitoring

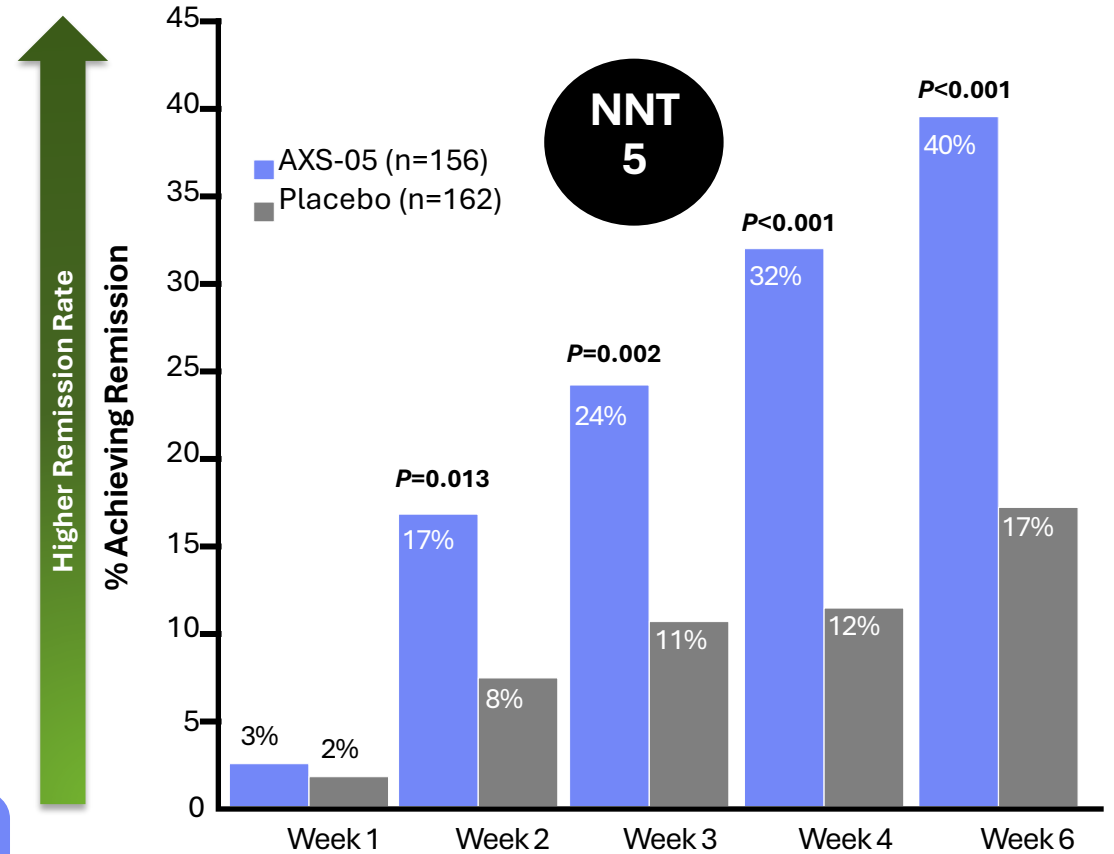
DXM-BUP: Phase 3 Clinical Data Summary in MDD

Depressive Symptom Reduction



AXS-05 is the only oral antidepressant to show statistical significance vs. placebo in symptom reduction at week 1 & remission at week 2

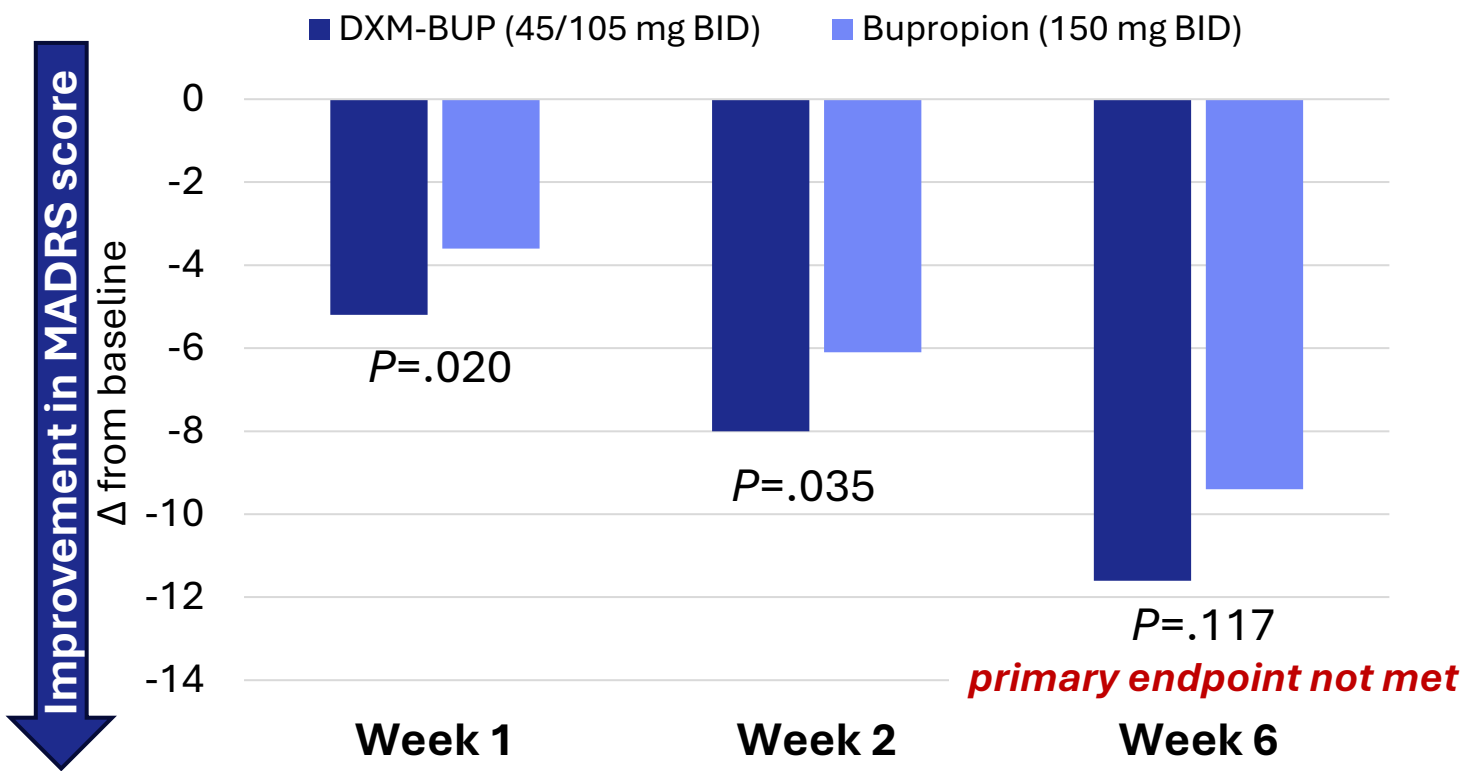
Depression Remission Rates (MADRS ≤ 10)



But what about TRD?

DXM-BUP Showed Early Improvement in TRD, But Did Not Meet the Primary Endpoint

Phase 3 RCT for **N=312 adult patients with confirmed TRD**, who had failed 2-3 prior treatments



Secondary findings:

- Average MADRS improvement across 6 weeks favored DXM-BUP: -8.6 vs -6.7; $P=.031$
- Week 6 QIDS-SR-16 remission: 18.2% vs 8.2%; $P=.012$
- Improvements in self-reported cognition and anxiety also favored DXM-BUP

Short-term tolerability :

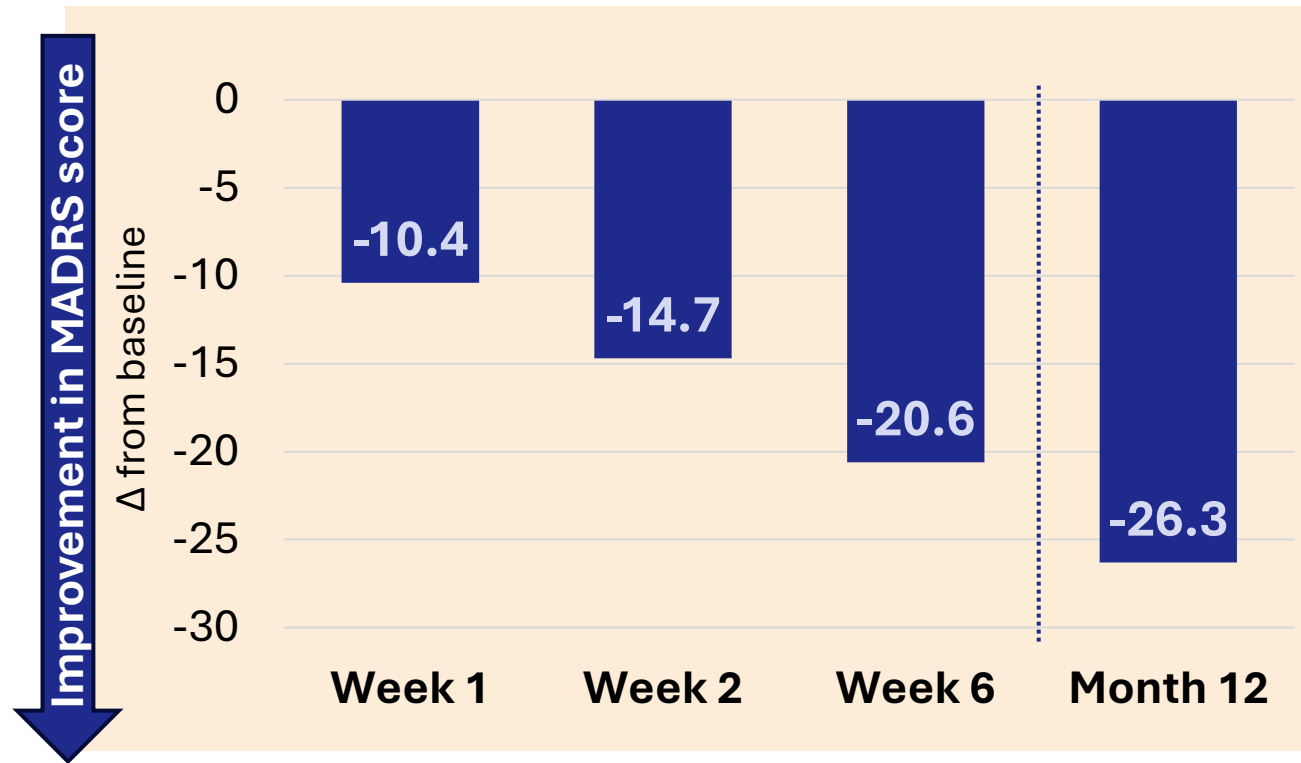
- Most common AEs: dizziness and nausea
- AE-related discontinuation: 2.6% vs 1.9%
- Three SAEs occurred with DXM-BUP: migraine, overdose, and suicidal ideation occurring more than 1 week after treatment cessation
- No reported signal for psychotomimetic effects, weight gain, or sexual dysfunction

MADRS=Montgomery Åsberg Depression Rating Scale. AE = adverse event.

Axsome Therapeutics. STRIDE-1 Phase 3 topline results. March 30, 2020. NCT02741791. (sponsor-reported topline results; not peer reviewed)

COMET-TRD Suggests Rapid and Sustained Improvement, Yet Findings Remain Exploratory

Sub-study of N = 70 individuals with ongoing depressive symptoms despite use of ≥ 2 antidepressant treatments during the current episode



High response rates were reported at Month 12

- Clinical response: **72%**
- Remission: **62%**
- Marked/moderate CGI-I improvement: **79%**
- Functional response on SDS: **70%**

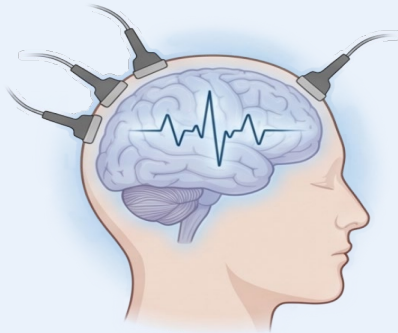
Safety and Tolerability:

- Most common AEs: **dizziness, nausea, and headache**
- No new safety signal was reported
- Open-label design, no comparative efficacy
- Attrition, selective retention, and a sponsor-defined TRD subgroup may inflate longer-term outcomes

Other Approaches to Modulate Neuroplasticity

Neurostimulation Therapies for TRD

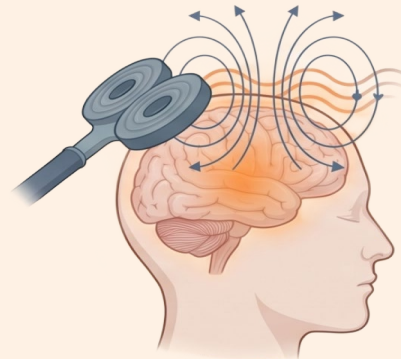
Electroconvulsive Therapy (ECT)



Remains the most effective treatment for severe and psychotic depression as well as the gold-standard treatment for TRD.

May cause temporary confusion, headaches, muscle aches, nausea, retrograde amnesia/memory loss.

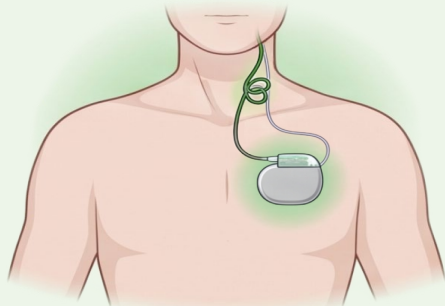
Transcranial Magnetic Stimulation (rTMS)



FDA-cleared noninvasive neurostimulatory technique that involves the application of a strong, pulsed magnetic field to the left dorsolateral prefrontal cortex.

Most common AEs are headache, discomfort at stimulation site; rare seizure risk ~0.003%

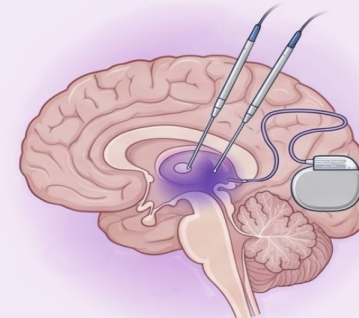
Vagus Nerve Stimulation (VNS)



Approved since 2005 as adjunctive therapy after four or more failed treatments

RECOVER (N=493): primary MADRS endpoint missed, but clinician- and patient-rated symptoms, function, and quality of life favored active stimulation

Deep Brain Stimulation (DBS)



Investigational therapy targeting subcallosal cingulate; ~half responded in long-term open-label follow-up; the sham-controlled trial stopped for futility

Risks include infection, intracerebral hemorrhage (1-3%), neuropsychiatric changes.

AE = adverse event. McIntyre RS, et al. *World Psychiatry*. 2023;22(3):394-412. Saelens J, et al. *Neuropsychopharmacology*. 2025;50(6):913-919. Kasper S, et al. *JATROS*. 2022;Special issue: *Neurology & Psychiatry*. Silberbauer LR, et al. *N Engl J Med*. 2023;389(10):960. Lam RW, et al. *Can J Psychiatry*. 2024;69(9):641-687. Kavakbasi E, et al. *J Affect Disord*. 2025;378:39-46. Cole EJ, et al. *Am J Psychiatry*. 2022;179(2):132-141. Conway CR, et al. *Brain Stimul*. 2025;18(3):676-689. Woodham RD, et al. *Nat Med*. 2024;30:2879-2887. Crowell AL, et al. *Am J Psychiatry*. 2019;176(11):949-956.

ECT for Efficacy, TMS for Tolerability

ECT

- Ranked first of 25 treatments in a TRD network meta-analysis (OR 12.86 vs sham)
- Response up to 80%, remission up to 60%
- Raises hippocampal volume, BDNF and VEGF; restores network connectivity
- Needs anesthesia; cognitive side effects; over 50% relapse by 6 months without continuation

rTMS

- Response 29% vs 10% and remission 19% vs 5% against sham
- No anesthesia, no seizure, no cognitive impairment
- 5 sessions per week over 6 weeks
- Smaller effect than ECT
- Possibly longer remission without maintenance treatments vs ECT

Accelerated iTBS (SAINT)

- fMRI-guided target; 10 sessions a day for 5 days instead of 6 weeks
- 79% remission vs 13% with sham
- FDA cleared 2022
- Insurance coverage is spotty

ECT stays the benchmark for severity.

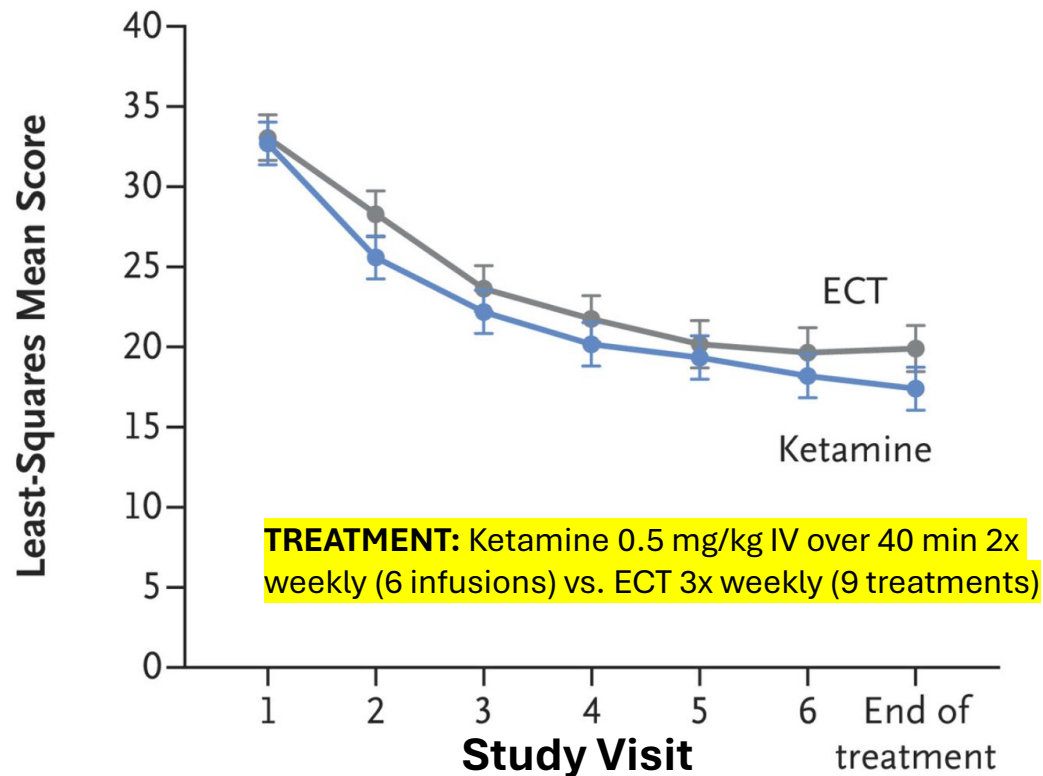
rTMS trades some efficacy for tolerability and convenience.

Accelerated iTBS compresses 6 weeks of treatment into 5 long days.

iTBS = intermittent theta-burst stimulation. OR = odds ratio. ECT = electroconvulsive therapy. rTMS = repetitive transcranial magnetic stimulation
Saelens J, et al. Neuropsychopharmacology. 2025;50(6):913-919. Berlim MT, et al. Psychol Med. 2014;44(2):225-239. Cole EJ, et al. Am J Psychiatry. 2022;179(2):132-141.

Ketamine Was Noninferior to ECT for TRD Response, & Had Better Cognitive Outcomes

Similar MADRS score reduction in patients with TRD with ECT vs ketamine during initial 3-week treatment phase

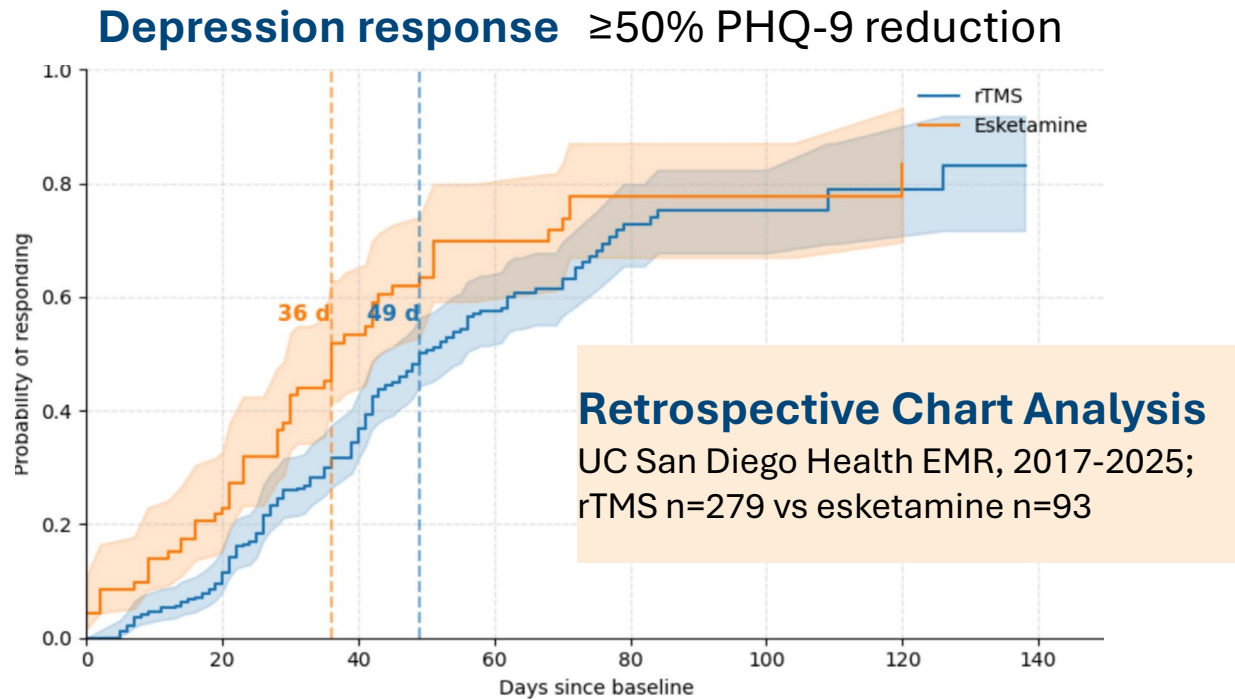
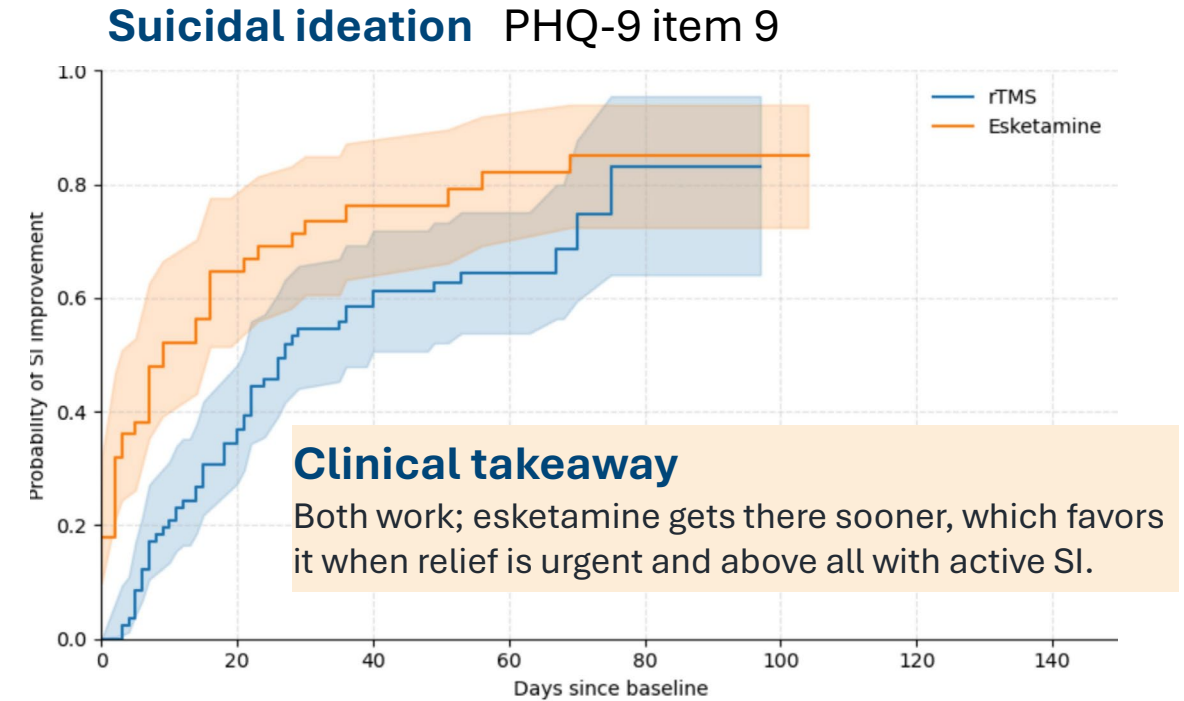


55.4% vs 41.2%

response (ketamine vs ECT); noninferior, $P < 0.001$

- Largest head-to-head trial in nonpsychotic TRD across 5 US academic centers (open label)
- ~89% outpatient; excluded psychotic features
- **ECT was worse for all cognitive tasks ($P < 0.001$); short-term memory favored ketamine**
- **Caveats:** ECT may perform better in inpatient/very severe depression; early ECT advantage converged by end of treatment

rTMS vs Intranasal Esketamine in TRD



Speed of Response

36 vs 49 days

IPTW Cox HR 1.62 (95% CI 1.16-2.26; $P=.005$)

Cumulative Response

68.8% vs 59.4%

Remission 45.2% vs 40.1%;
differences numerical, curves
converge by about 90 days

Suicidal Ideation

9 vs 26 days

Median time to SI improvement
($P=.001$); by day 5, 40.0% vs 9.7%
had improved

Predictors of Response

rTMS only

Anxiety (HR 0.69) and
benzodiazepine use (HR 0.73)
predicted slower response

Exercise: Solid Effect in MDD, Untested in TRD

What the evidence shows:

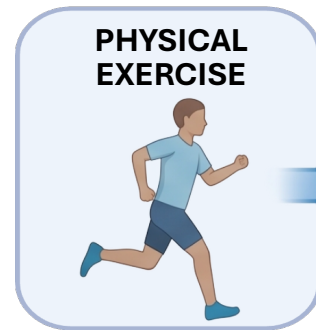
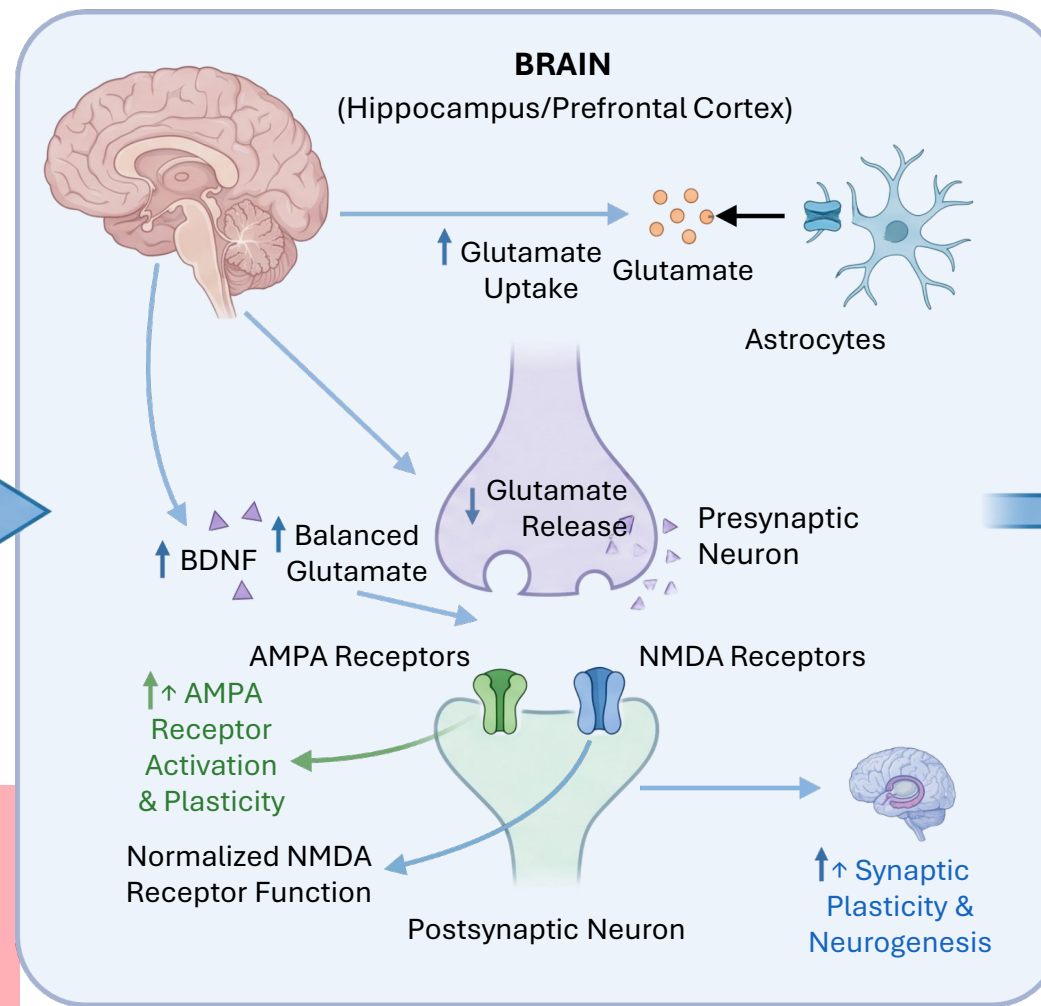
- **Better than no treatment, by a moderate to large margin.** The effect is larger than the usual antidepressant-vs-placebo difference, but the comparator was no treatment, not placebo.

(SMD -0.67 across 92 randomized trials)

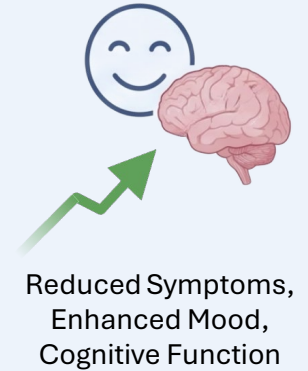
- **About as effective as an antidepressant or psychotherapy.**

In head-to-head comparisons exercise was not significantly different from either.

- **Shared mechanisms:** Raises BDNF, hippocampal neurogenesis and dendritic spines. Raises amygdala, thalamus and accumbens volume; anti-inflammatory; normalizes the HPA axis



MAJOR DEPRESSION IMPROVEMENT



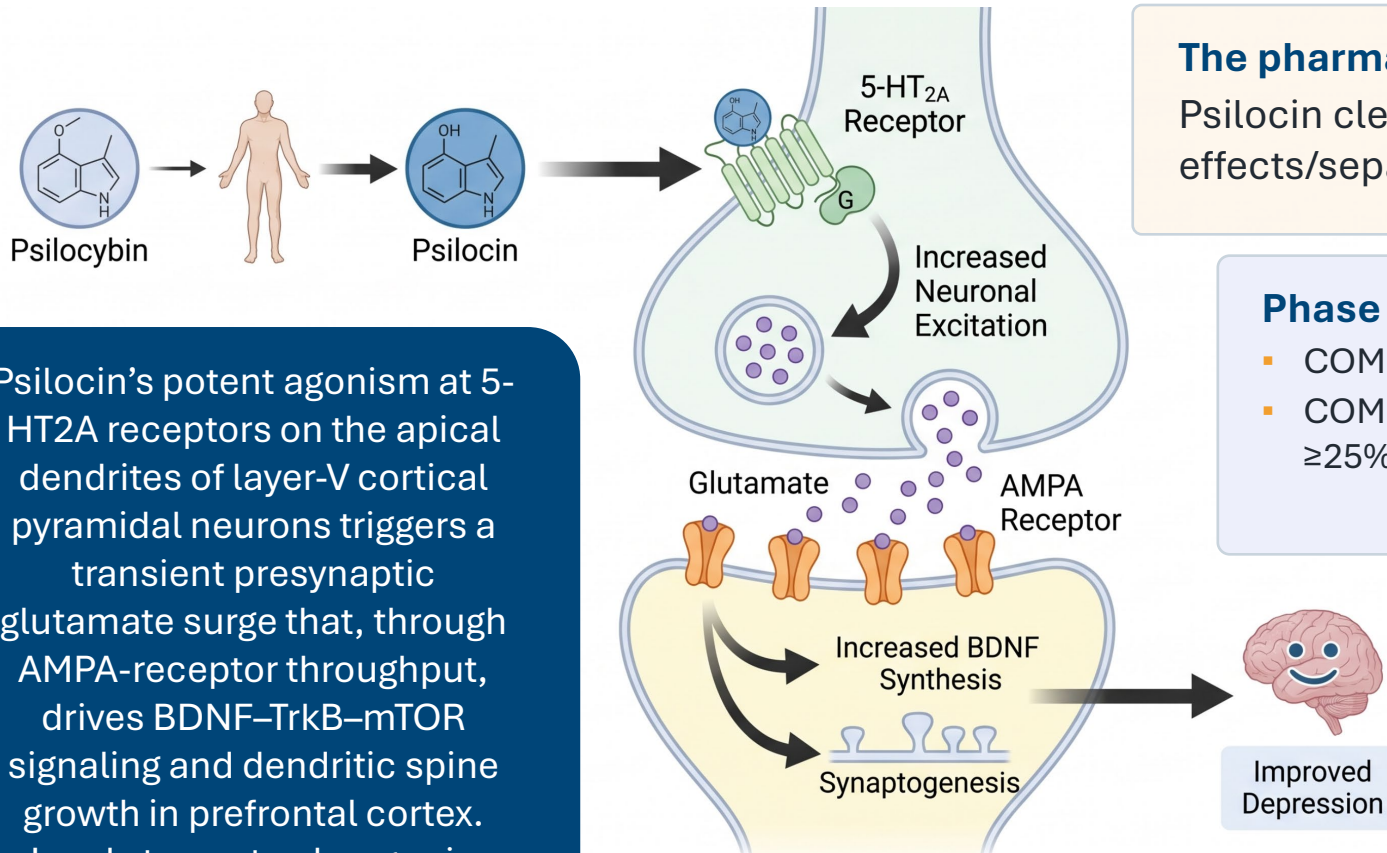
Limitations

- Low-certainty evidence; adherence undermined by depression itself
- Not adequately studied in TRD

HPA = hypothalamic-pituitary-adrenal. LTP = long-term potentiation. SMD = standardized mean difference. BDNF = brain derived neurotrophic factor. Image created using BioRender.com

Clegg AJ, et al. Cochrane Database Syst Rev. 2026 (92 RCTs). Kandola A, et al. Neurosci Biobehav Rev. 2019. Brüche W, et al. Front Psychiatry. 2021.

Future Directions: Psilocybin in TRD



Psilocin's potent agonism at 5-HT_{2A} receptors on the apical dendrites of layer-V cortical pyramidal neurons triggers a transient presynaptic glutamate surge that, through AMPA-receptor throughput, drives BDNF-TrkB-mTOR signaling and dendritic spine growth in prefrontal cortex. Leads to acute changes in cortical network connectivity and downstream plasticity.

The pharmacokinetic paradox:

Psilocin clears in about 24 hours, yet some effects/separation were still present at 26 weeks.

Phase 3: both met the primary endpoint

- COMP005 (n=258): 25 mg vs placebo, MADRS -3.6, $P < 0.001$
- COMP006 (n=581): -3.8 for 25 vs 1 mg, $P < 0.001$; 39% at $\geq 25\%$ reduction

Safety & questions:

- AEs on dosing days (73%), 83% resolve within 24 hours
- SAEs 2-5%; serious suicidal ideation <1%
- Functional unblinding
- Absolute response/remission rates are unreleased

BDNF = brain-derived neurotrophic factor. MADRS = Montgomery-Åsberg Depression Rating Scale. SAE = serious adverse event.

5-HT_{2A} = serotonin 2A receptor. mTOR = mechanistic target of rapamycin. TrkB = tropomyosin receptor kinase B.

Figure: BioRender. Aghajanian & Marek. Neuropharmacology 1997. Shao LX, et al. Neuron 2021. Compass COMP005/006; ASCP 2026. Raison CL et al. JAMA 2023;330(9):843-53.

Future Directions: Osavampator, an Oral AMPA-PAM

Targets the AMPA step directly:

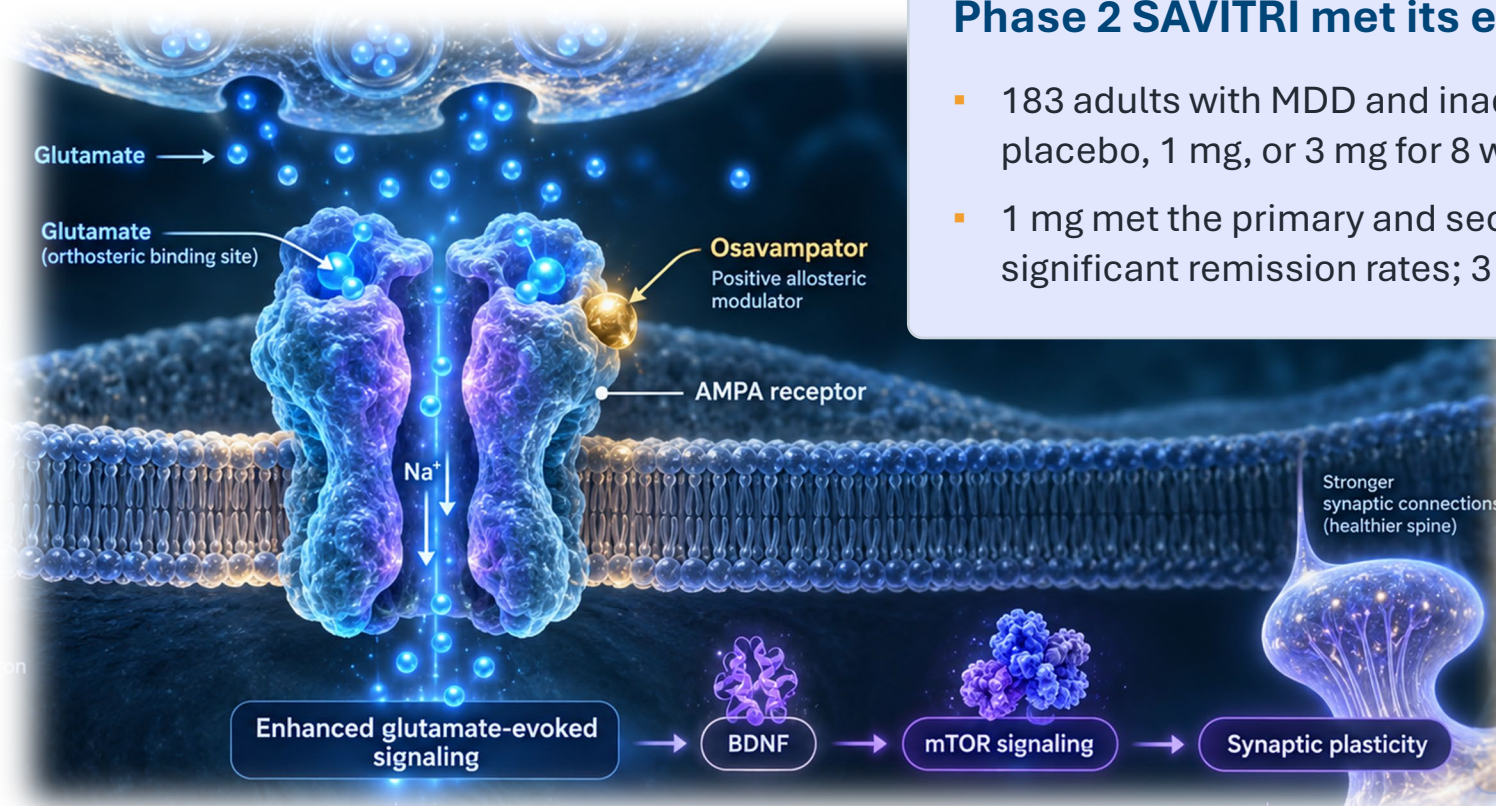
- Selective positive allosteric modulator of the AMPA receptor: no NMDA blockade = no dissociation
- Acts at the step ketamine reaches indirectly, testing whether AMPA potentiation drives the antidepressant effect
- Oral, once daily, adjunctive to ongoing antidepressant treatment

Phase 2 SAVITRI met its endpoints:

- 183 adults with MDD and inadequate response to ADT, randomized 2:1:1 to placebo, 1 mg, or 3 mg for 8 weeks; 88% completed
- 1 mg met the primary and secondary endpoints at days 28 and 56 and produced significant remission rates; 3 mg was only nominal

What to watch:

- Well tolerated at both doses with no serious adverse events reported
- Five phase 3 trials of the 1 mg dose are enrolling, with primary completion expected in 2027
- Studied in MDD with inadequate response, not specifically in TRD



AMPA-PAM = positive allosteric modulator of the AMPA receptor. ADT = antidepressant treatment. Image created using ChatGPT.

Hara H, et al. Pharmacol Biochem Behav. 2021;211:173289. Dijkstra F, et al. Transl Psychiatry. 2022;12(1):408.

Neurocrine Biosciences. Phase 2 SAVITRI (NCT05203341), Psych Congress 2025. Suzuki A, et al. Neuropharmacol. 2023 Jan 1;222:109308.



Key Learning Points

- **Ketamine is rapid and, when repeated, durable:** noninferior to ECT with a cognitive advantage in ELEKT-D
- **Esketamine is the approved TRD/MDSI option:** delivered under a REMS with in-office monitoring
 - In a head-to-head trial as adjunctive treatments vs quetiapine XR, esketamine was associated with being 72% more likely to remain relapse free at week 32
- **DXM-bupropion is oral and rapid... for MDD, not TRD:** STRIDE-1 was negative; can be taken as an outpatient - no REMS
- **Exercise & neuromodulation are complementary:** combine to open and consolidate the neuroplasticity window
- **The pipeline targets the same cascade:** psilocybin and oral AMPA modulators are in phase 3, testing plasticity without NMDA blockade

Faculty Discussion: Impact of Glutamatergic Agents on the Management of TRD

Practical Clinical Matters: eg, Access, Patient Monitoring, Billing/Coding

Discussing Treatment Options with Patients

Case Study Discussion

Practical Clinical Matters

Access & setting

Esketamine: certified REMS site, chair time, monitoring, acquisition of medication

IV ketamine often off-label/cash-pay.

PO ketamine not proven for TRD and is unsafe for at home use.

Patient monitoring

Baseline & periodic BP; observe for sedation/dissociation ≥ 2 h (esketamine); screen bipolar/mania;

Warnings for seizure risks (DXM-bupropion; TMS).

Billing , coding, documentation

Esketamine has specific billing codes

Coverage and prior-authorization vary by payer.

Be prepared for REMS, DEA, and chart audits

Continuity & maintenance

Plan for in-office dosing. tapering-frequency maintenance and relapse prevention;

Coordinate time off work and transportation as no same-day driving

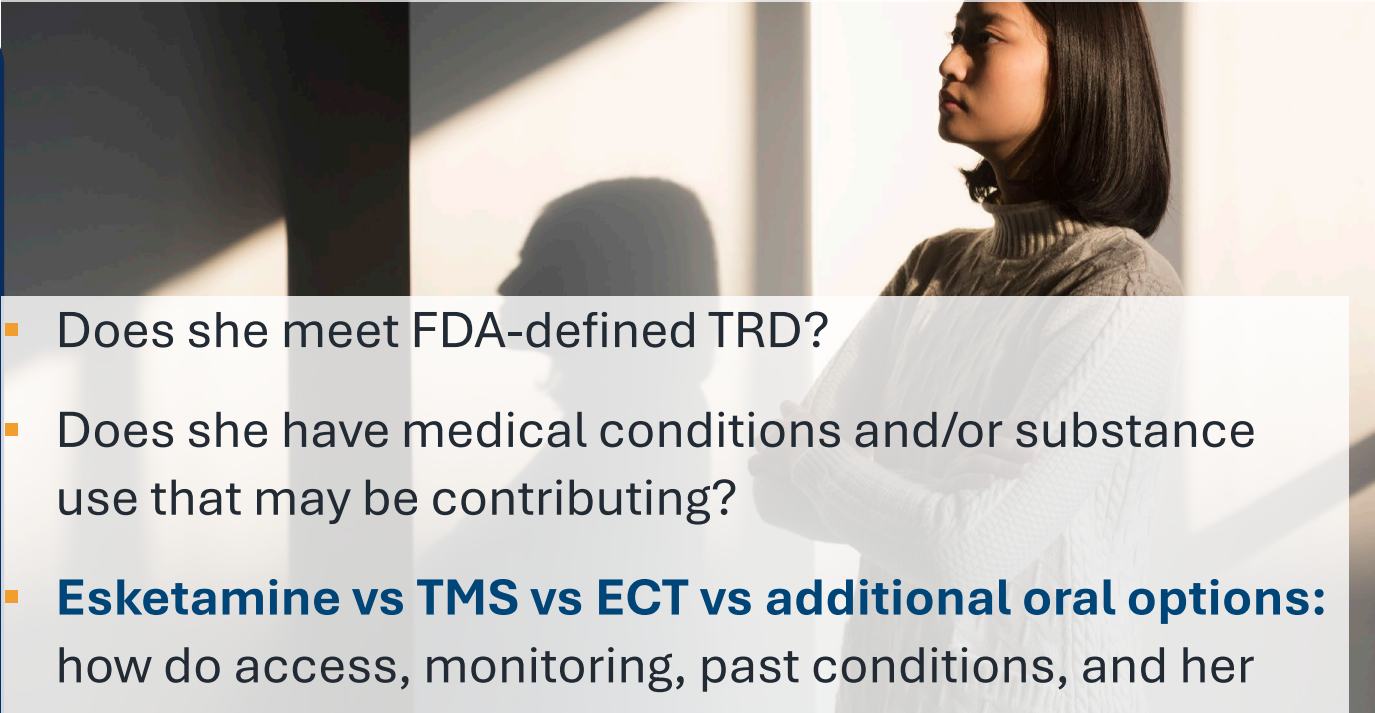
Discussing Treatment Options With Patients



- **Set expectations on onset:** glutamatergic agents can work within days
but durability depends on a maintenance plan
- **Explain side effects & monitoring:** dissociation is transient and expected with (es)ketamine; arrange transportation for in-office dosing
- **Match the option to the patient:** logistics, cost, and medical contraindications to in-office esketamine vs neuromodulation vs trial of another oral medication
- **Address anhedonia and emotional blunting explicitly:** treatment nonadherence is tied to psychological side effects and residual symptoms and patients may not report them spontaneously
- **Frame as part of multimodal care:** pair pharmacotherapy with psychotherapy & exercise to consolidate the neuroplasticity window
- **Discuss substances of abuse** and concomitant CNS medication considerations: ideally would hold psychostimulants and CNS depressant medications on treatment days

Case : 35yo Woman with Recurrent MDD + Epilepsy

- Current episode 14 months; PHQ-9 = 19
- Adequate trials of an SSRI and an SNRI at full dose/duration → non-remission
- Prominent anhedonia, anxiety symptoms, emotional blunting, 2 missed workweeks this quarter, passive suicidal ideation
- No psychosis; screens negative for mania hx; adherent by pharmacy refill data
- Wants to keep working; asks about 'the nasal spray'

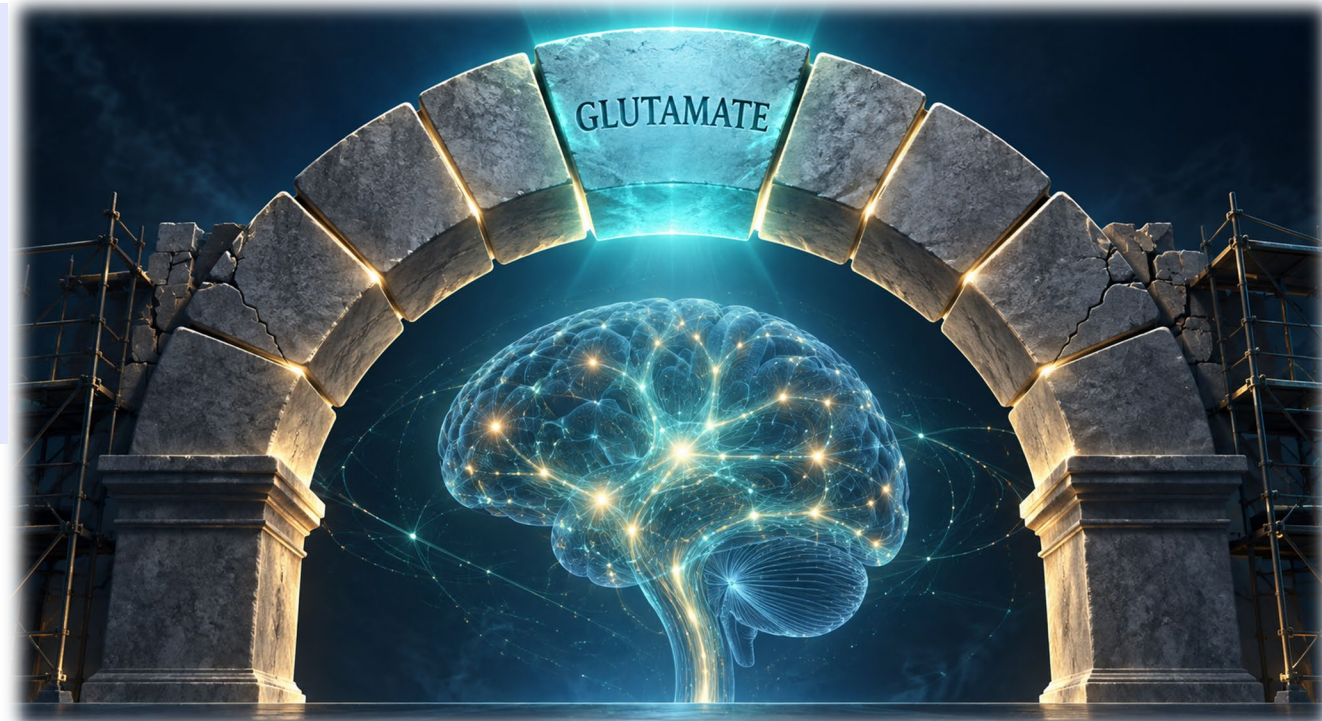
- 
- Does she meet FDA-defined TRD?
 - Does she have medical conditions and/or substance use that may be contributing?
 - **Esketamine vs TMS vs ECT vs additional oral options:** how do access, monitoring, past conditions, and her work schedule factor in?
 - How will you address anhedonia/emotional blunting specifically?
 - What maintenance and psychosocial plan delays time to relapse?

Conclusion: Glutamate Is a Keystone, Not the Only One

- Depression is a disorder of impaired synaptic and circuit plasticity
- Agents that shift signaling from NMDA toward AMPA and trigger synaptogenesis act within days and hold with repeated dosing
- Glutamate sits on a monoamine-glutamate continuum, so durable change is multimodal

What this means in practice

- Ketamine and esketamine are available today but only esketamine is FDA approved for TRD
- Psilocybin and oral AMPA modulators are in phase 3
- Memantine, lamotrigine and riluzole are not substitutes: there is no class effect
- Dextromethorphan-bupropion is effective for MDD, no studies to prove efficacy for TRD



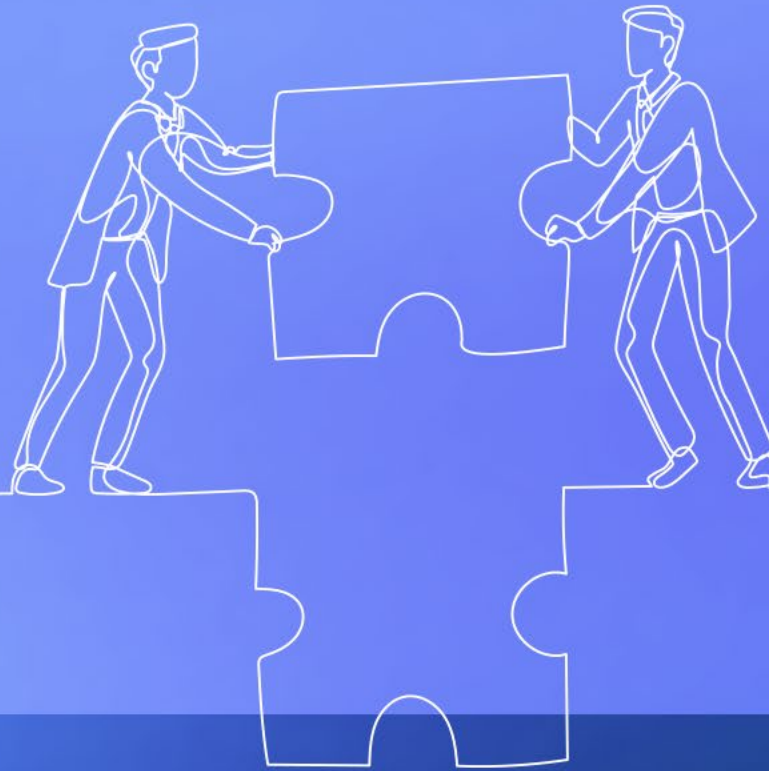
What is still unresolved

- How long benefit holds once maintenance dosing stops
- No head-to-head trials against the emerging pipeline
- In-office administration, monitoring and REMS limit access

Anand A, et al. *N Engl J Med*. 2023;388(25):2315-2325. Zaki N, et al. *Int J Neuropsychopharmacol*. 2025;28(6):pyaf027. Kishi T, et al. *J Alzheimers Dis*. 2017;57(1):113-121. McIntyre RS, Jain R. *CNS Drugs*. 2024;38(11):869-890.

Practical Take-Aways

- Confirm true TRD before escalating diagnosis: rule out bipolarity, confirm adherence & adequacy of prior trials
- Treat patients with TRD to remission! Target residual symptoms anhedonia and emotional blunting matter to patients, ask directly
- Glutamatergic agents act on plasticity with rapid onset, but plan for maintenance treatments and relapse prevention
- Choose treatments based on shared decision making: coverage, cost, logistics, contraindications, monitoring time all matter
- Think multimodal: combine pharmacotherapy, neuromodulation, exercise, and psychotherapy!



Q&A