Psych Congress Presents

MDD BOOTCAMP

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From Mechanisms to Modern Medicine: Reframing First-Line MDD Treatment

Faculty

Michael Asbach, DMSc, PA-C
Associate Medical Director
DENT Neurologic Institute
Assistant Adjunct Professor
Shenandoah University
Buffalo, New York

C. Brendan Montano, MD
Principal Investigator
CT Clinical Research
Internal Medicine Physician
Montano Wellness LLC
Cromwell, Connecticut

Rakesh Jain, MD, MPH
Clinical Professor
Texas Tech – Permian Basin
Lewisville, Texas

Faculty Disclosures

- **Michael Asbach, DMSc, PA-C**: Consultant – Axsome, Biogen, Bristol Myers Squibb, Intra-Cellular Therapies Inc, Janssen Pharmaceuticals, Neurocrine Biosciences; Speakers Bureau – AbbVie, Avanir Pharmaceuticals (ended) Axsome, Bristol Myers Squibb, Intra-Cellular Therapies Inc, Janssen Pharmaceuticals, Neurocrine Biosciences, Otsuka Pharmaceuticals
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- This CME activity includes brand names for participant clarity purposes only. No product promotion or recommendation should be inferred.

Learning Objectives

- Describe the role of glutamatergic and neuroplasticity-based strategies in informing first-line treatment approaches for MDD

- Apply current evidence for newly approved and emerging treatments to personalize early-stage management of MDD

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The State of MDD in 2026

Persistent Unmet Needs and Partial Response Rates

MDD: Ongoing Challenges

Persistent Depression Symptoms

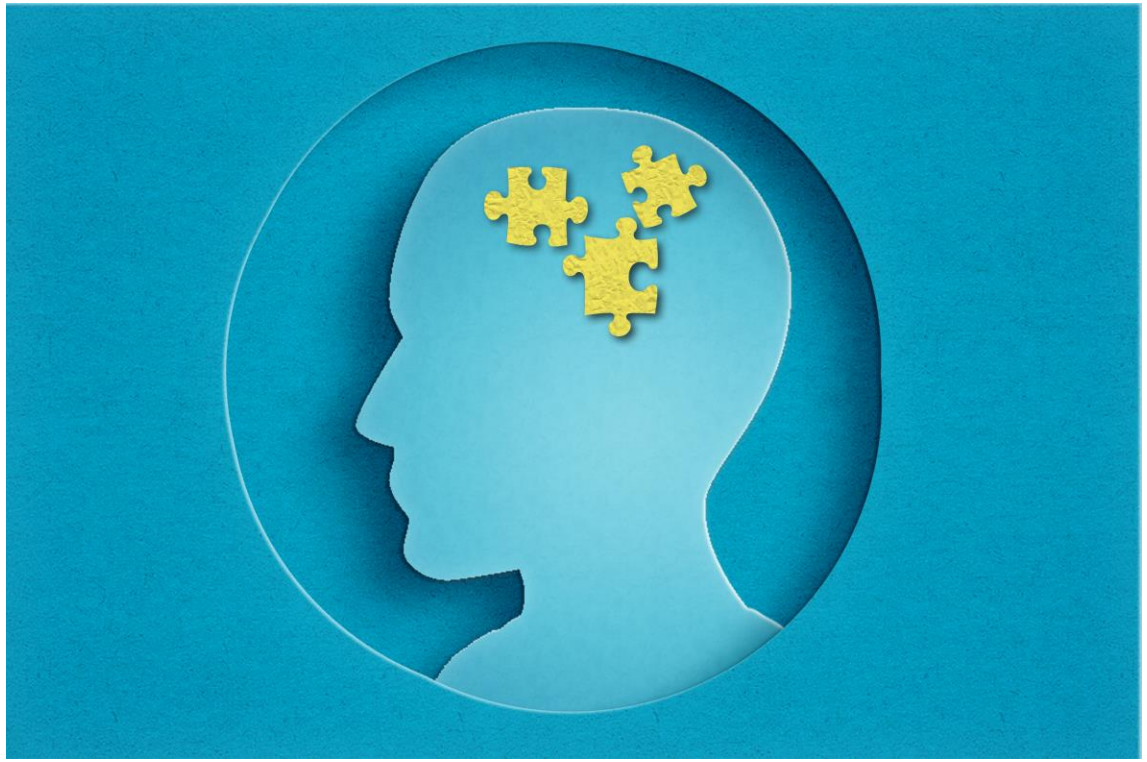
Many people with MDD continue to experience symptoms despite treatment, impacting daily life and well-being.

Limited Therapy Response

A substantial number of patients have only partial or inadequate responses to available therapies for MDD.

Unmet Treatment Needs

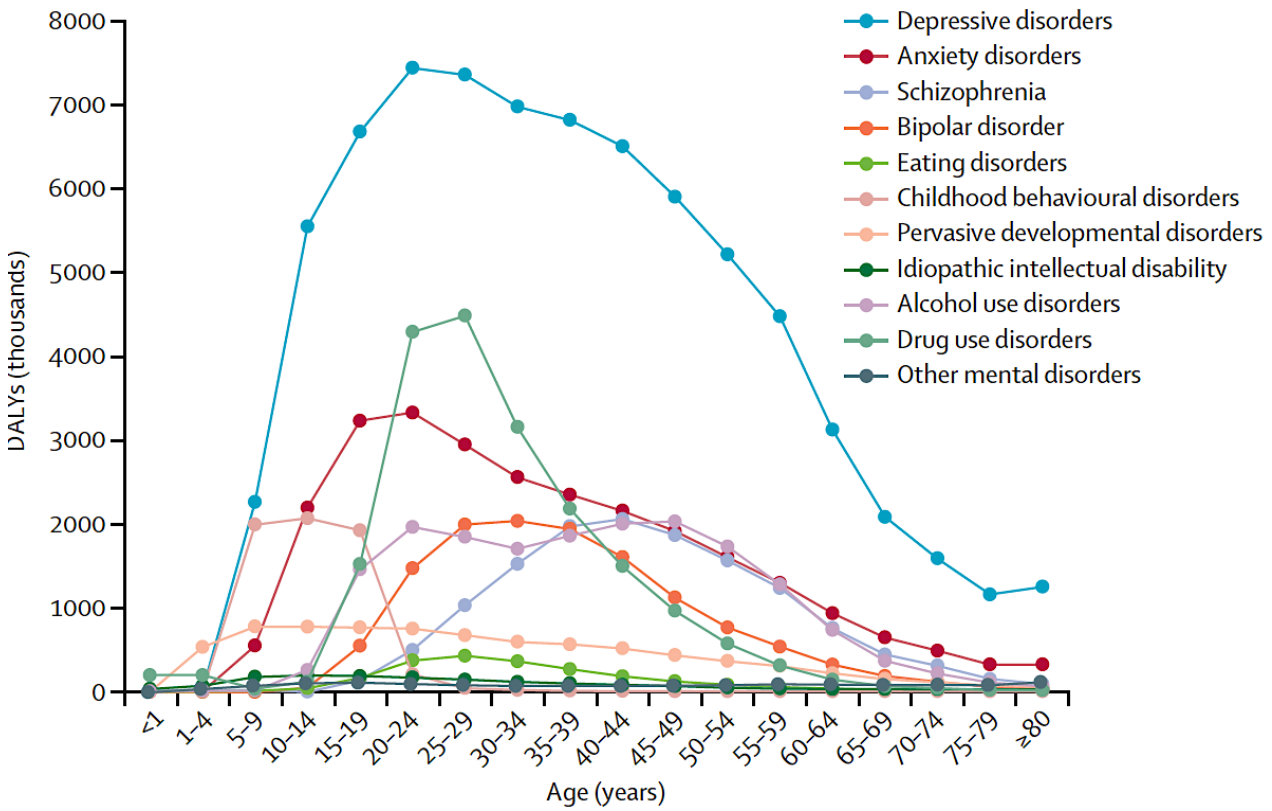
Improved efficacy, quicker relief, and better management of treatment-resistant depression are crucial ongoing needs.



MDD = major depressive disorder.

The Global Burden of MDD

Depression Accounts for the Greatest Disability Among All CNS Disorders



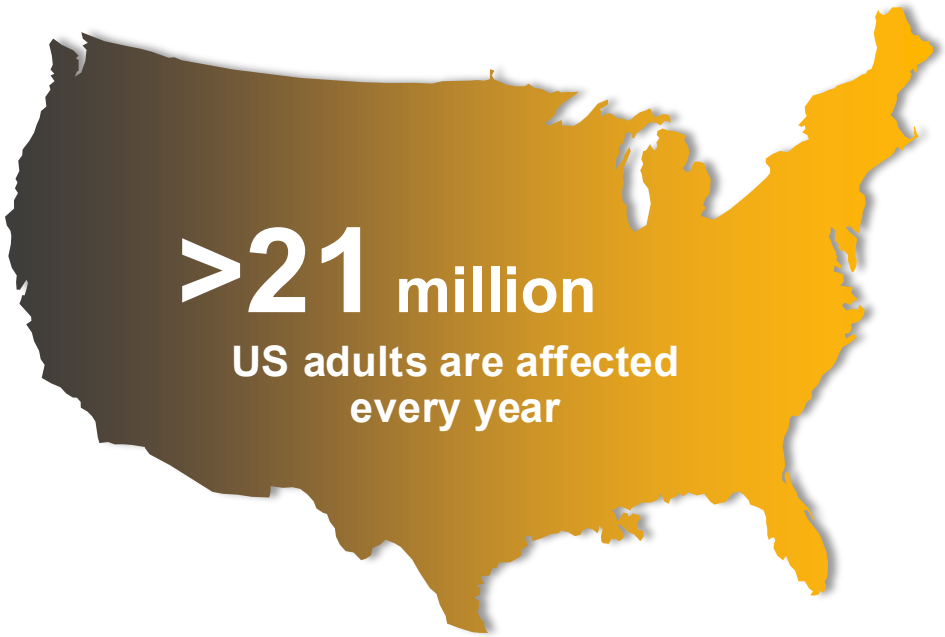
gure 3: Disability-adjusted life years (DALYs) for each mental and substance use disorder in 2010, by age

- Among the most common and disabling conditions worldwide
- 70 million years lost to disability
- 1 million suicides annually and rising
- 1 in 3 patients do not respond to available treatments

CNS = central nervous system; DALY = disability-adjusted life year.

Whiteford HA, et al. *Lancet.* 2013;382(9904):1575-1586. Greenberg PE, et al. *Pharmacoeconomics*. 2021;39:653-665. Egede LE. *Gen Hosp Psychiatry*. 2007; 29(5):409-416.

MDD Poses a Substantial Burden



MDD: A Silent Crisis

75% of people with MDD have **comorbidities**

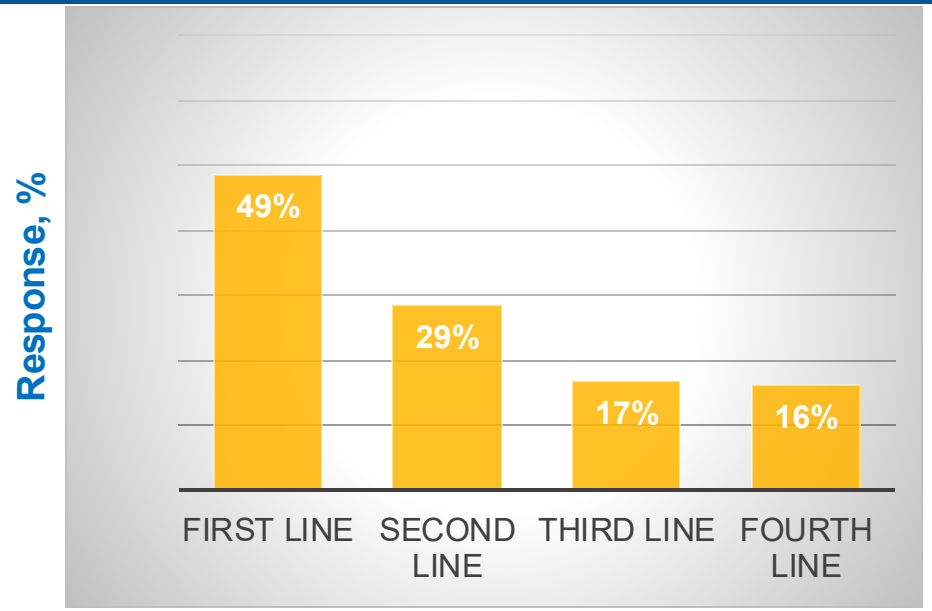
~50% of adults go **untreated**

20× higher **suicide** risk than the general population

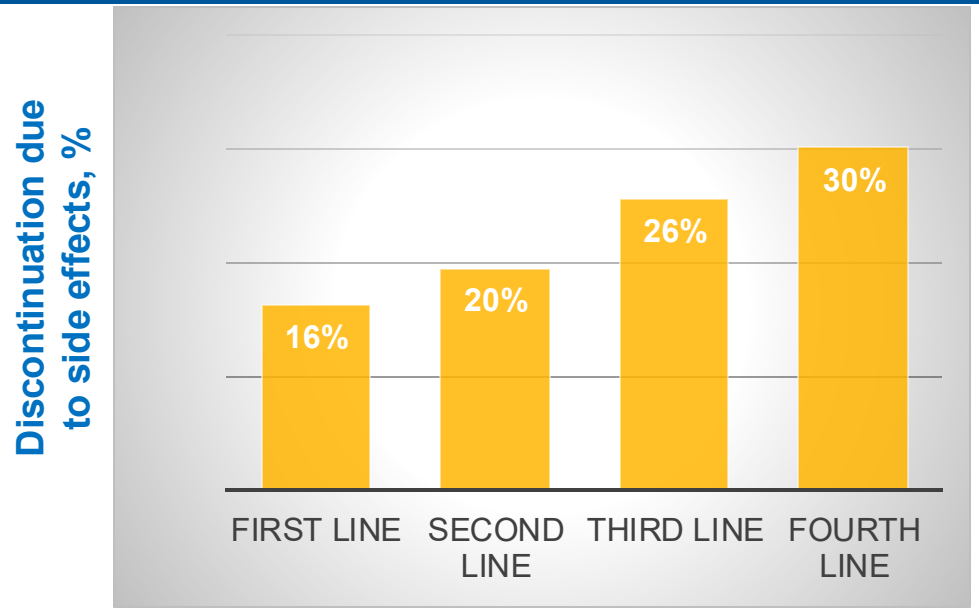
GBD 2021 Diseases and Injuries Collaborators. *Lancet*. 2024;403(10440):2133-2161. Bhatia R. Anxiety and Depression Association of America. November 2, 2020. Updated August 21, 2025. Accessed February 7, 2025. https://adaa.org/understanding-anxiety/depression/facts-statistics. Hasin DS, et al. *JAMA Psychiatry*. 2018;75(4):336-346. Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917. Chesney E, et al. *World Psychiatry*. 2014;13(2):153-160.

Monoaminergic Antidepressants Have Not Been a Successful Strategy for Many Patients

Response rates*,†



Discontinuation due to side effects*



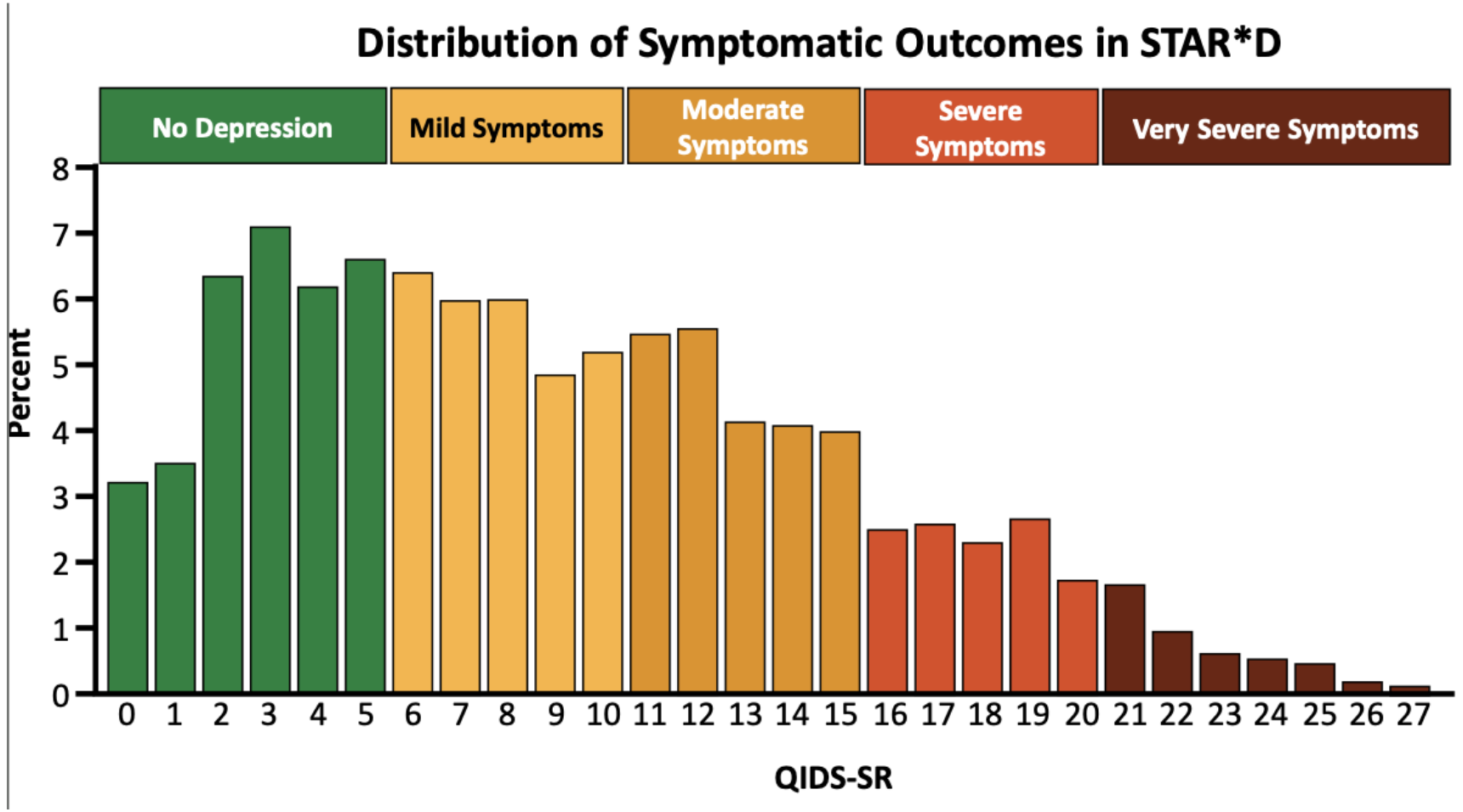
*Based on the STAR*D trial (N=4041); †Response defined as ≥50% reduction in QIDS-SR-16 score. Remission defined as QIDS-SR-16 score ≤5, corresponding with an HRSD score of 7.

HRSD = Hamilton Rating Scale for Depression; QIDS-SR-16 = Quick Inventory of Depressive Symptomatology-Self-Report-16 item; STAR*D = Sequenced Treatment Alternatives to Relieve Depression.

Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917. Cain RA. *Prim Care*. 2007;34(3):505-519, vi.

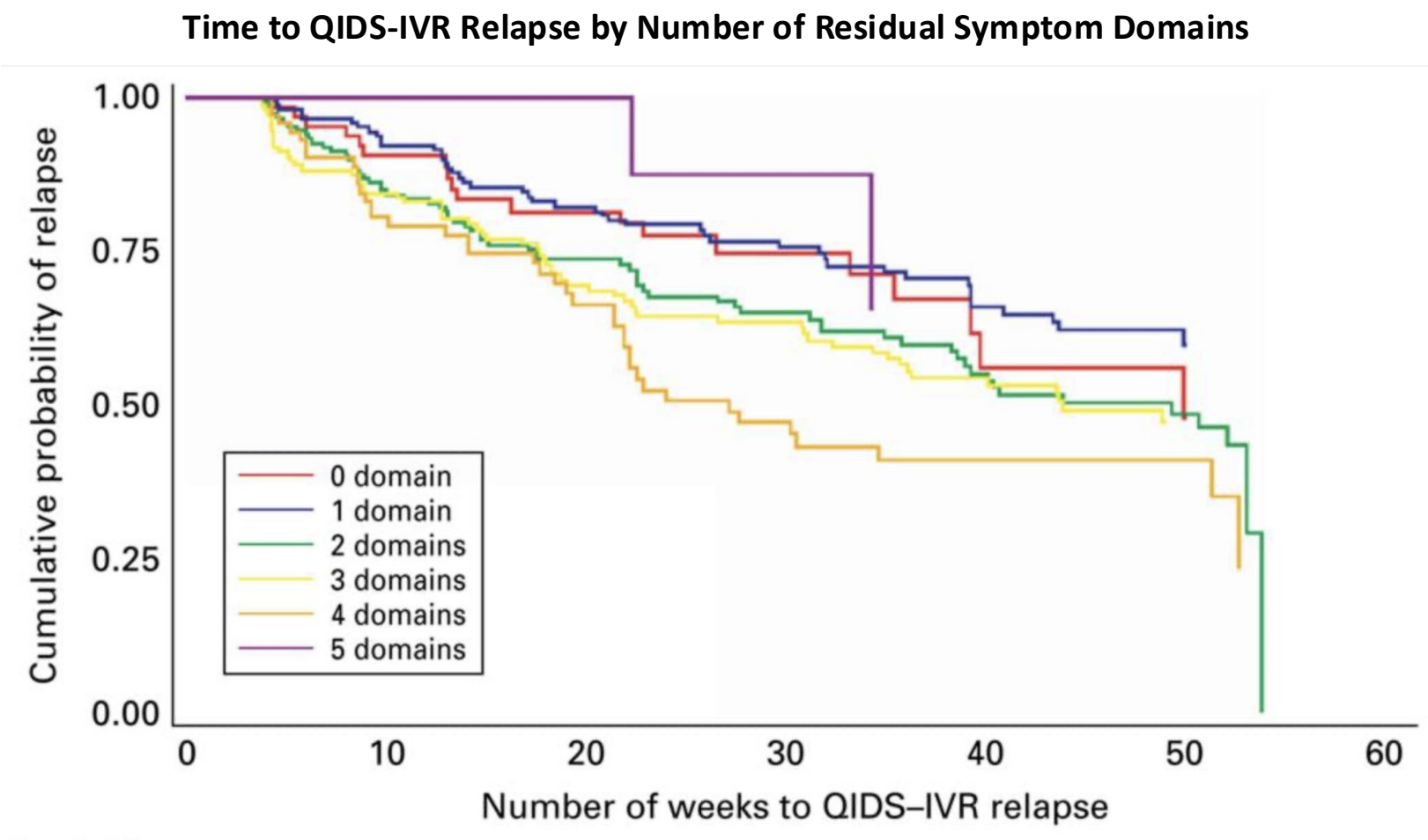
STAR*D Citalopram Exit Scores

Degree of depression following ≤14 weeks of Citalopram



Trivedi MH, et al. *Am J Psychiatry*. 2006;163(1):28-40.

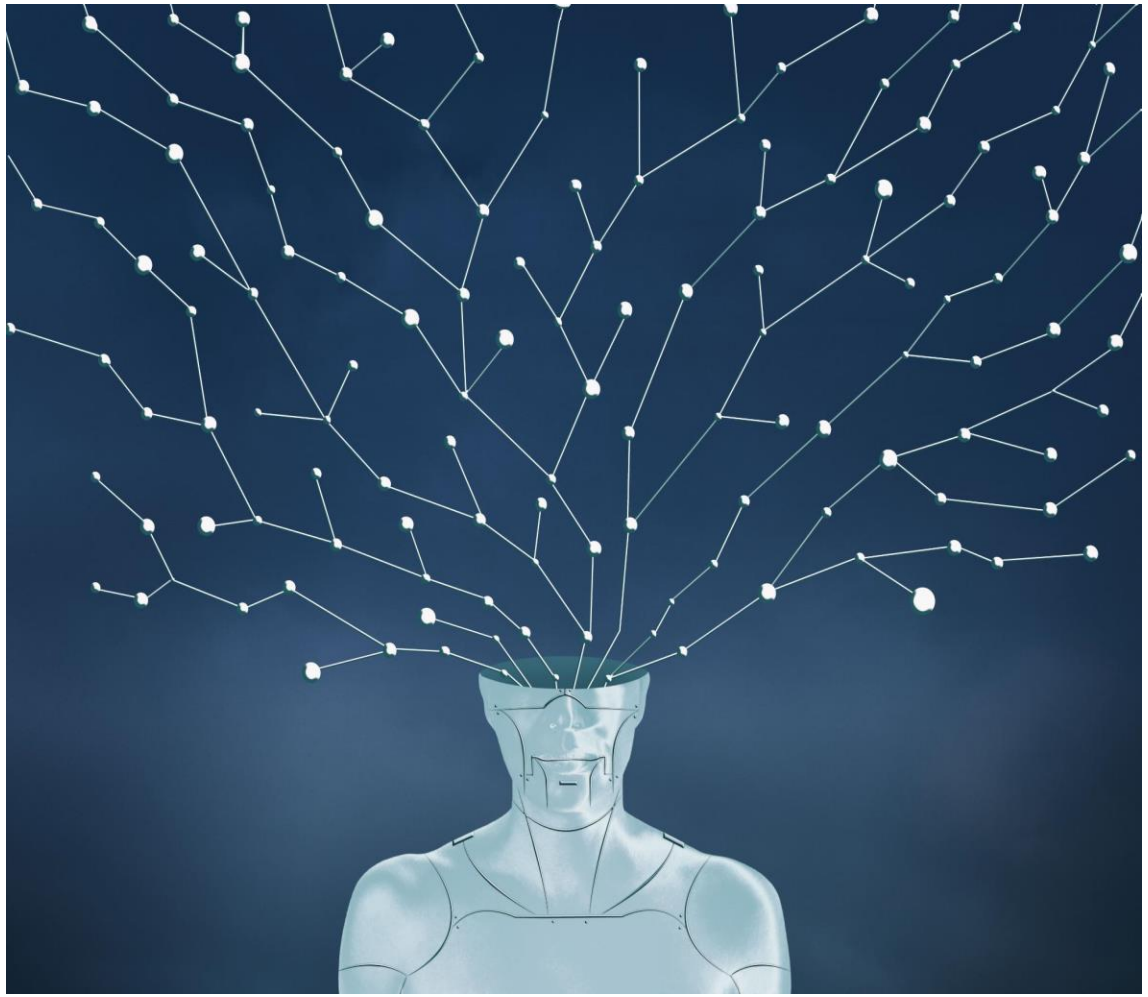
STAR*D: Residual Symptoms Predict Relapse



- **STAR*D follow-up:** Many patients had *residual depressive symptoms* even after response or remission.
- **Implication:** Partial remission isn't full recovery; complete symptom resolution is needed.
- **Clinical advice:** Aim for full remission, monitor residual symptoms regularly, and consider additional therapies for persistent symptoms.

QIDS-IVR = Quick Inventory of Depressive Symptomatology interactive voice response.
Nierenberg AA, et al. *Psychol Med*. 2010;40(1):41-50.

Limits of Monoamine Models



Partial Symptom Relief

Monoamine treatments often leave cognitive and emotional symptoms unresolved, providing only partial benefit for many patients.

Delayed Treatment Onset

Medications like SSRIs and SNRIs usually require four to eight weeks before noticeable effects appear.

Low Response Rates

About 30%–40% of patients do not respond to traditional monoamine-based therapies, highlighting their limitations.

Oversimplification of Depression

The model ignores depression's biological complexity, lacks biomarker guidance, and relies on trial-and-error treatment.

SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor.

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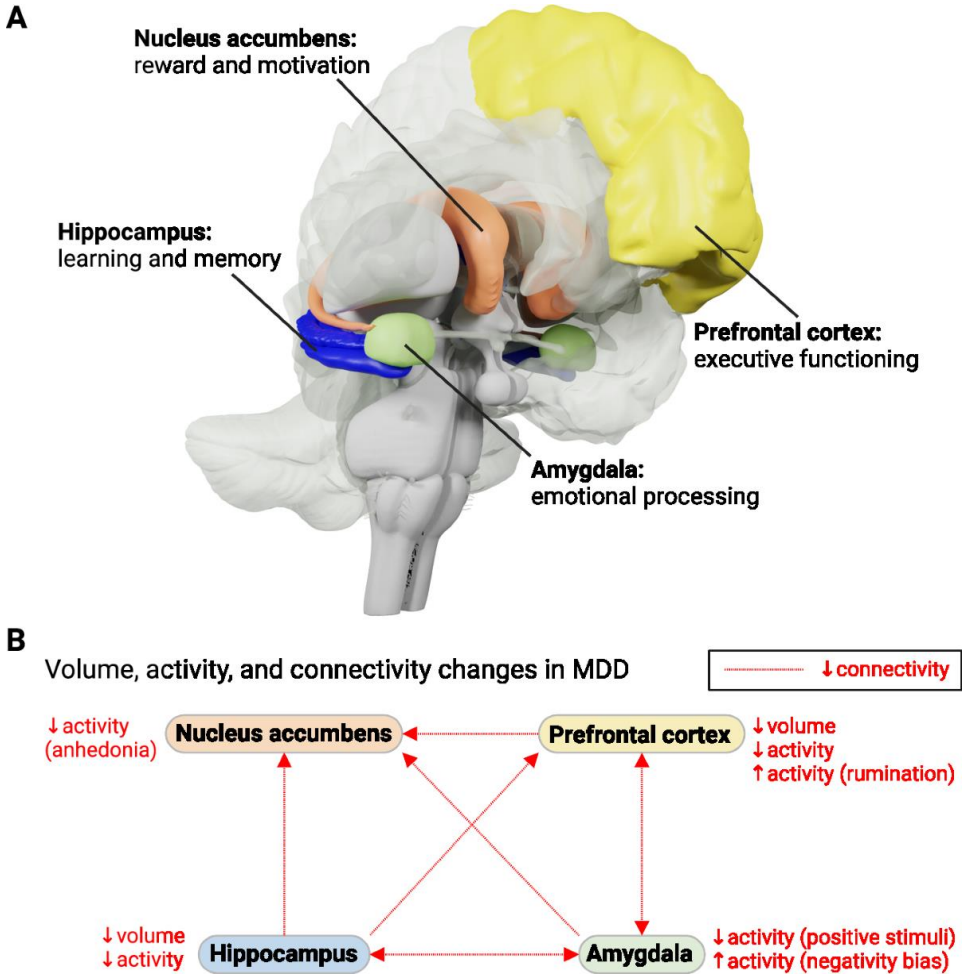
Emerging Mechanistic Insights into Glutamatergic Strategies

Depression as a Disorder of Neuroplasticity and Brain Circuit Remodeling



Modern understanding

- Major depressive disorder (MDD) involves *dysfunctional brain circuits*
  - Regions become "stuck" in maladaptive patterns of activity and connectivity

Result

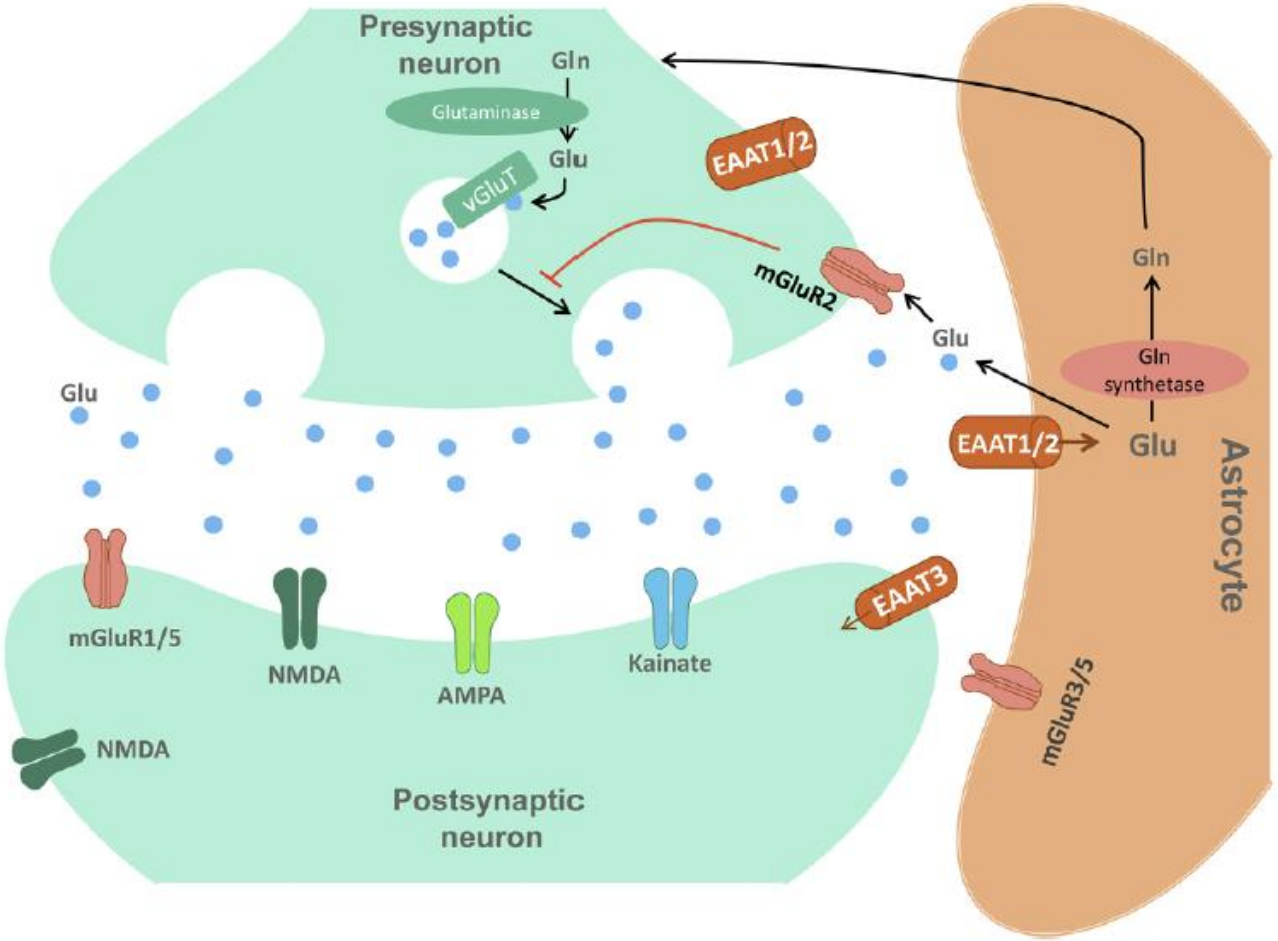
- Reduced flexibility and weakened communication across emotion–reward–cognition networks, contributing to symptoms like anhedonia and persistent negative affect

Treatment goal

- Restore *network flexibility* through neuroplasticity

Page CE, et al. *Mol Psychiatry*. 2024;29(12):3802-3813.

The Basic Glutamate Synapse



1. Glutamate (Glu) is stored in presynaptic vesicles. Once released, it activates postsynaptic ionotropic (AMPA, NMDA, and kainate) and metabotropic (mGluR1/5) glutamate receptors.
2. Astrocytes rapidly remove glutamate from the synapse through glutamate transporters (EAAT 1-2) in order to avoid glutamate spillover leading to extrasynaptic effects.
3. In the astrocyte, glutamate is converted to glutamine (Gln), which is the immediate precursor for neuronal synthesis of glutamate. Further, neuronal glutamate transporters (EAAT3) and presynaptic mGluR2 autoreceptors limit synaptic glutamate availability.

Fullana N, et al. *Neuropharmacology*. 2020;166:107914.

Glutamate and Synaptic Remodeling in Depression

Chronic stress and inflammation in MDD

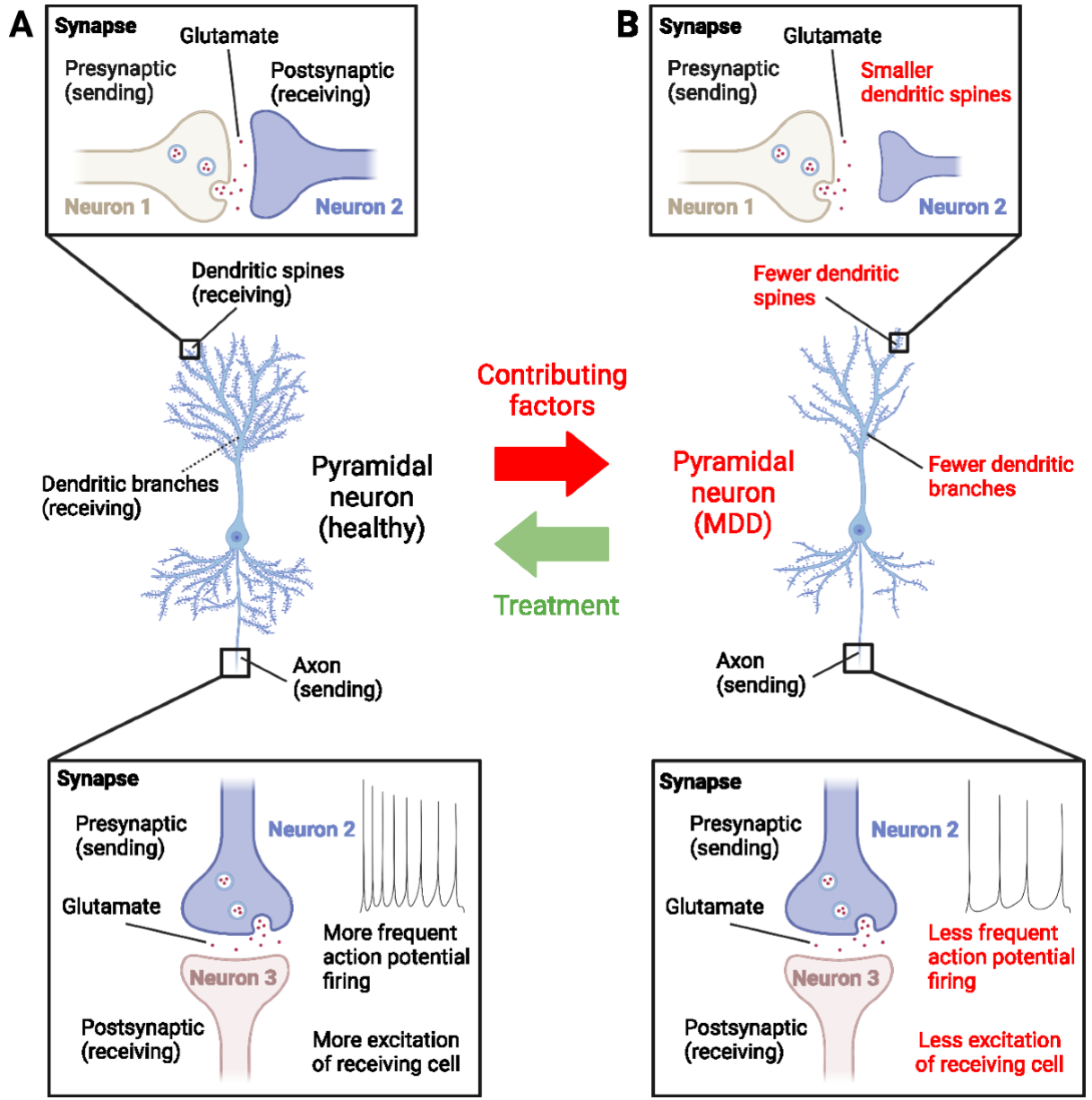
- Increase extrasynaptic glutamate, disrupting normal excitatory signaling
- Lead to excessive NMDA receptor activation and presynaptic mGlu receptor changes
- Increase inhibitory GABA signaling while suppressing healthy synaptic glutamate transmission
- Reduce postsynaptic AMPA receptor activity, decreasing BDNF release and impairing mTOR signaling
- Ultimately result in fewer and smaller dendritic spines, reduced dendritic branching, and weakened synaptic connectivity

Consequences

- Impaired neuroplasticity and synaptic maintenance
- Loss of network connectivity and structural resilience associated with depression

Treatment mechanisms

- SSRIs, ketamine, and psychedelics help restore glutamatergic balance
- Enhance BDNF–TrkB and mTOR signaling pathways
- Promote synapse formation, dendritic regrowth, and network repair



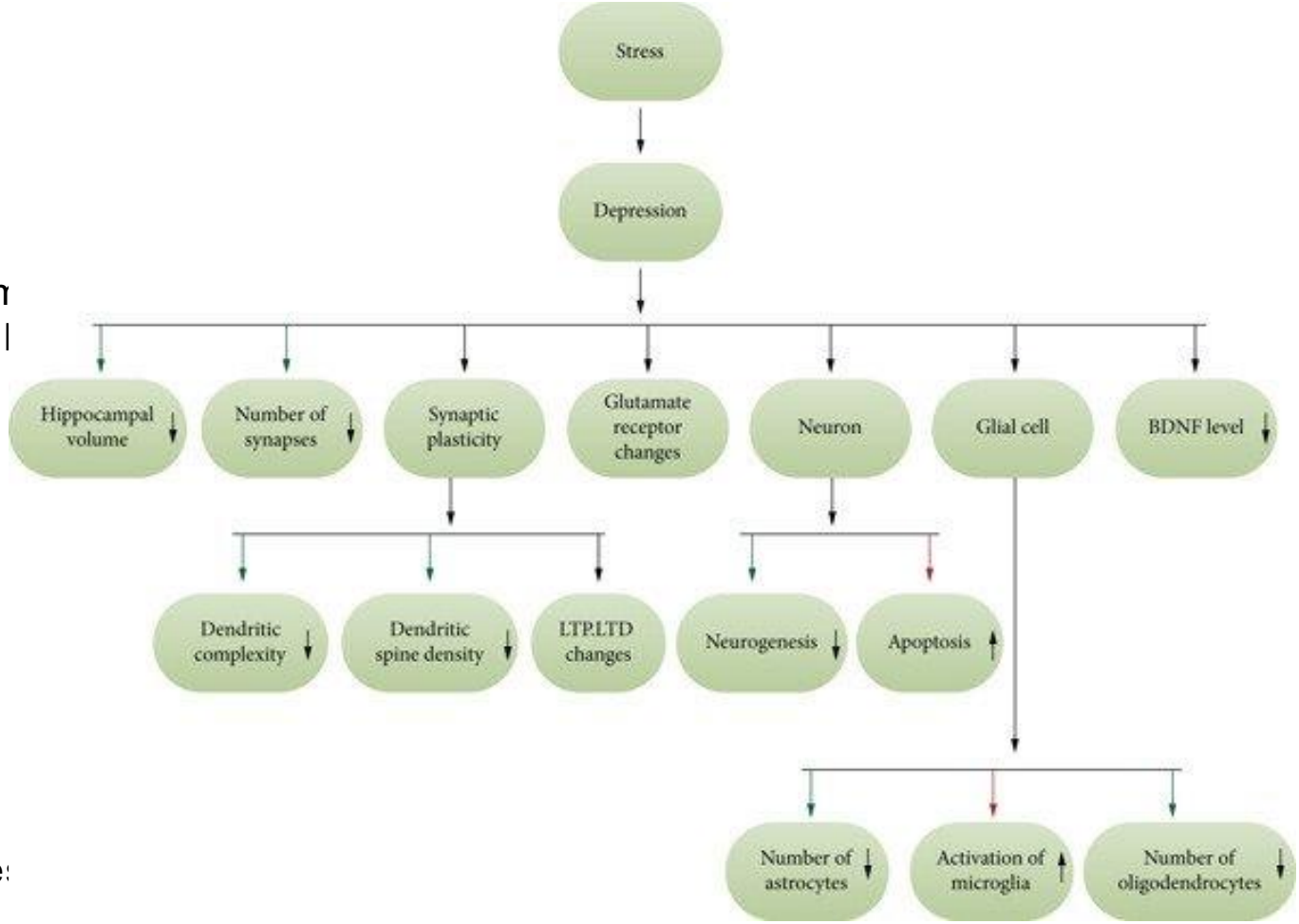
BDNF = brain-derived neurotrophic factor.

Page CE, et al. *Mol Psychiatry*. 2024;29(12):3802-3813.

Depression Related Changes in the Glutamate Synapses

1. Novel glutamatergic therapies aim to restore healthy synaptic signaling and enhance neuroplasticity.
2. NMDA receptor antagonists (e.g., ketamine/esketamine) increase synaptic glutamate release, enhancing downstream AMPA receptor activation. AMPA stimulation increases BDNF release and activates intracellular TrkB-mTOR pathways, promoting synaptogenesis and structural recovery.
3. Other investigational approaches include:
    - AMPA potentiators (AMPA-PAMs) → enhance excitatory throughout
    - mGlu receptor modulators → rebalance glutamatergic tone
    - Neuroplasticity-targeted agents → directly influence intracellular signaling pathways

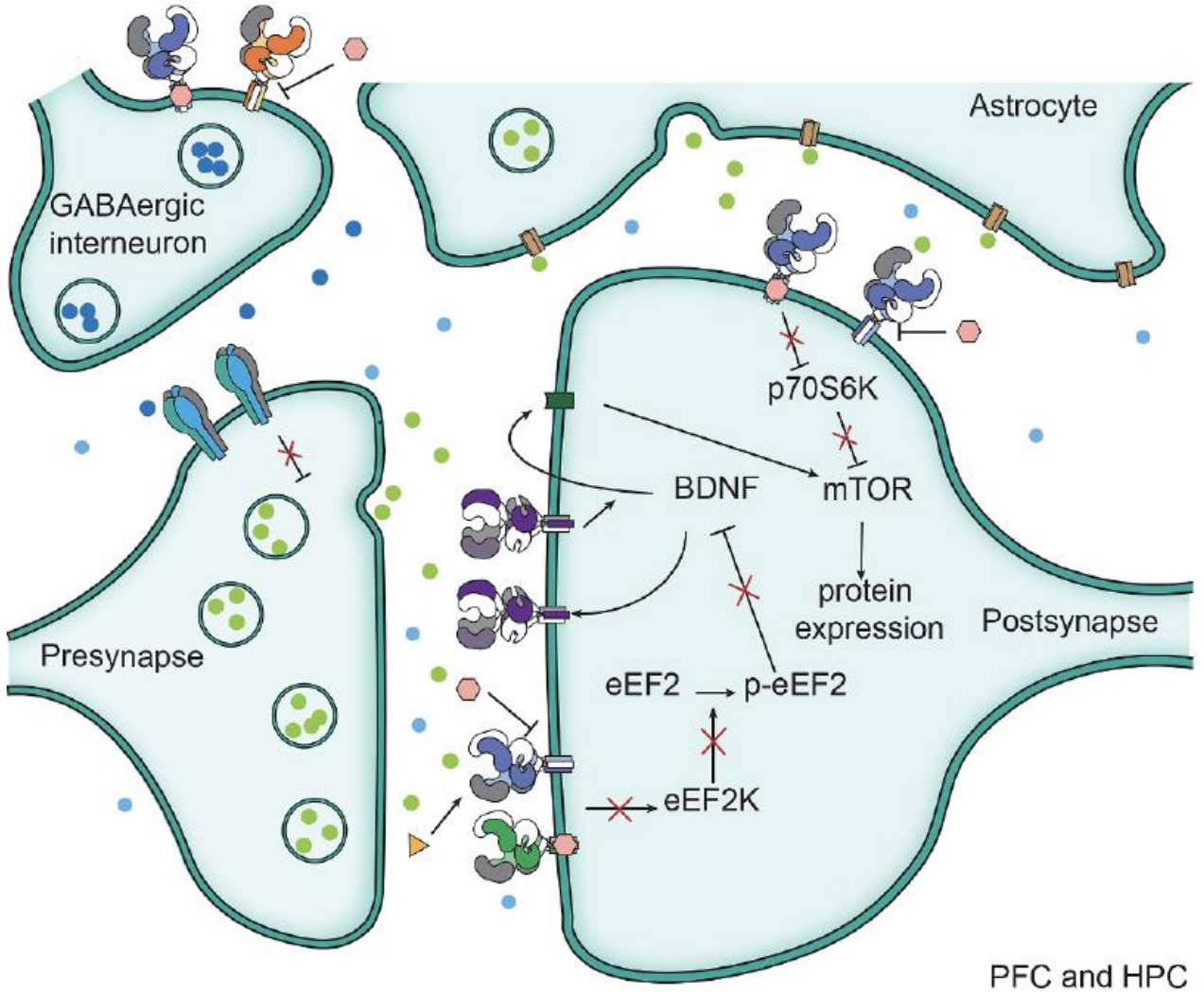
Restoration of synaptic connectivity may explain the rapid antidepressant effects observed with glutamatergic therapies compared with traditional monoaminergic antidepressants.



mTOR = mechanistic target of rapamycin.
Freudenberg F, et al. *Pharmacol Res*. 2025;220:107918.

Mechanisms of Ketamine Antidepressant Effects

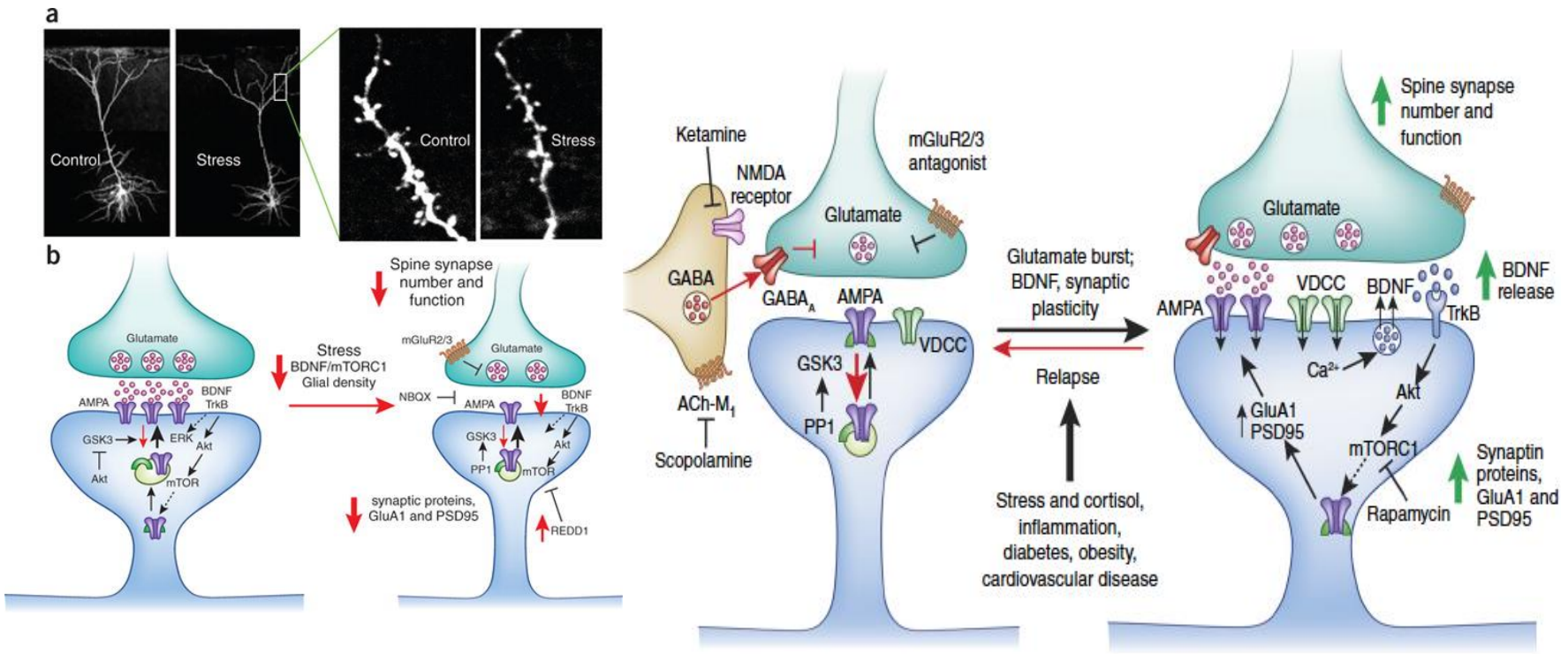
1. Ketamine blocks NMDA receptors on GABA interneurons, increasing glutamate release.
2. Increased glutamate stimulates AMPA receptors, enhancing BDNF release and activating TrkB/mTOR signaling pathways linked to neuroplasticity.
3. Ketamine also reduces resting NMDA-mediated signaling, increasing BDNF translation through eEF2 pathway modulation.
4. Blockade of extrasynaptic GluN2B NMDA receptors further activates mTOR signaling and supports synaptic plasticity.



Lv S, et al. *Neuropharmacology*. 2023;225:109378.

Evidence of BDNF and Downstream Mechanisms Having Antidepressant Effects

NMDA Receptor, Glutamate Burst, and Neuroplasticity



Duman RS, et al. *Nat Med*. 2016;22(3):238-249.

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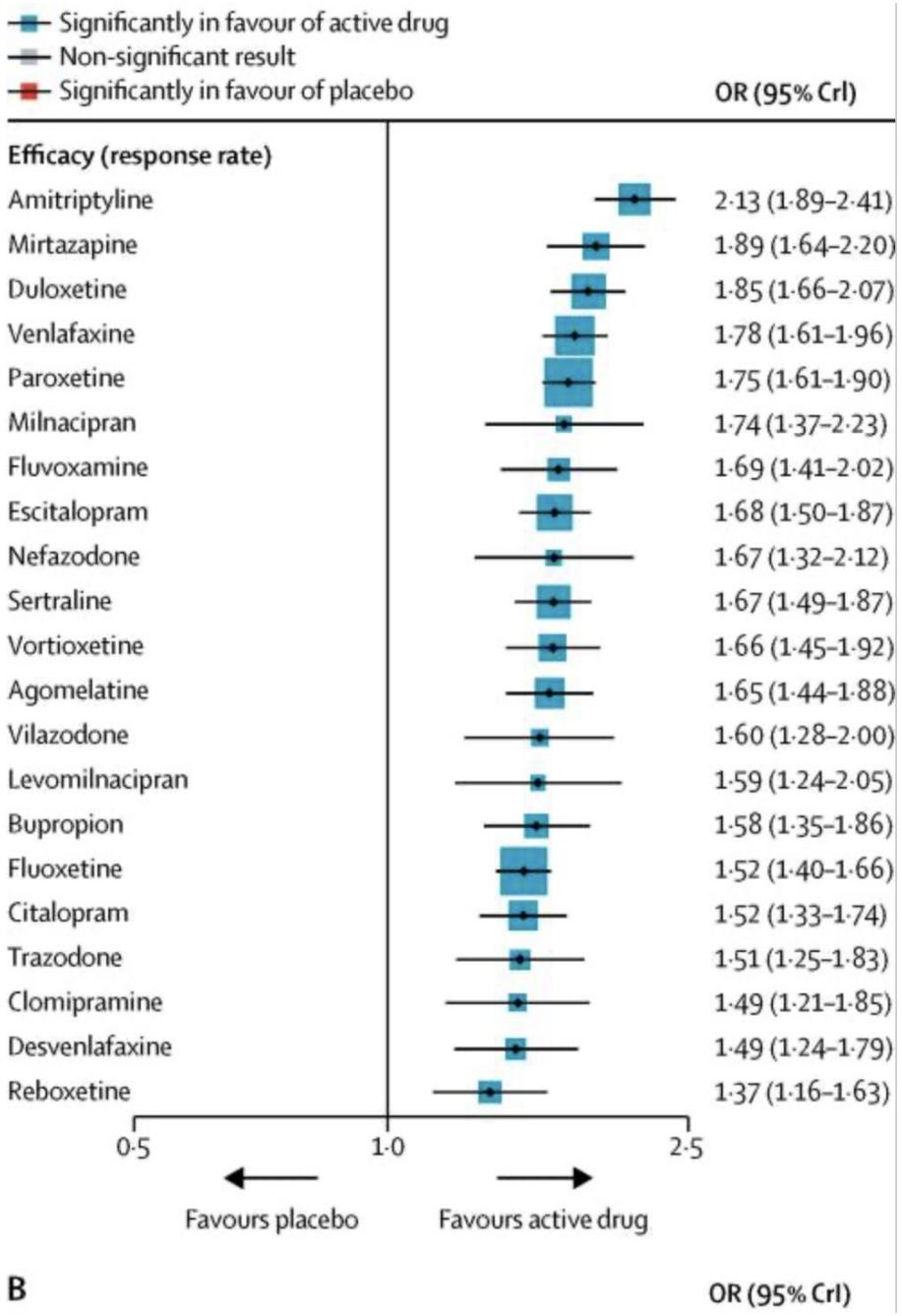
Modernizing First-Line Care

Efficacy of Antidepressants

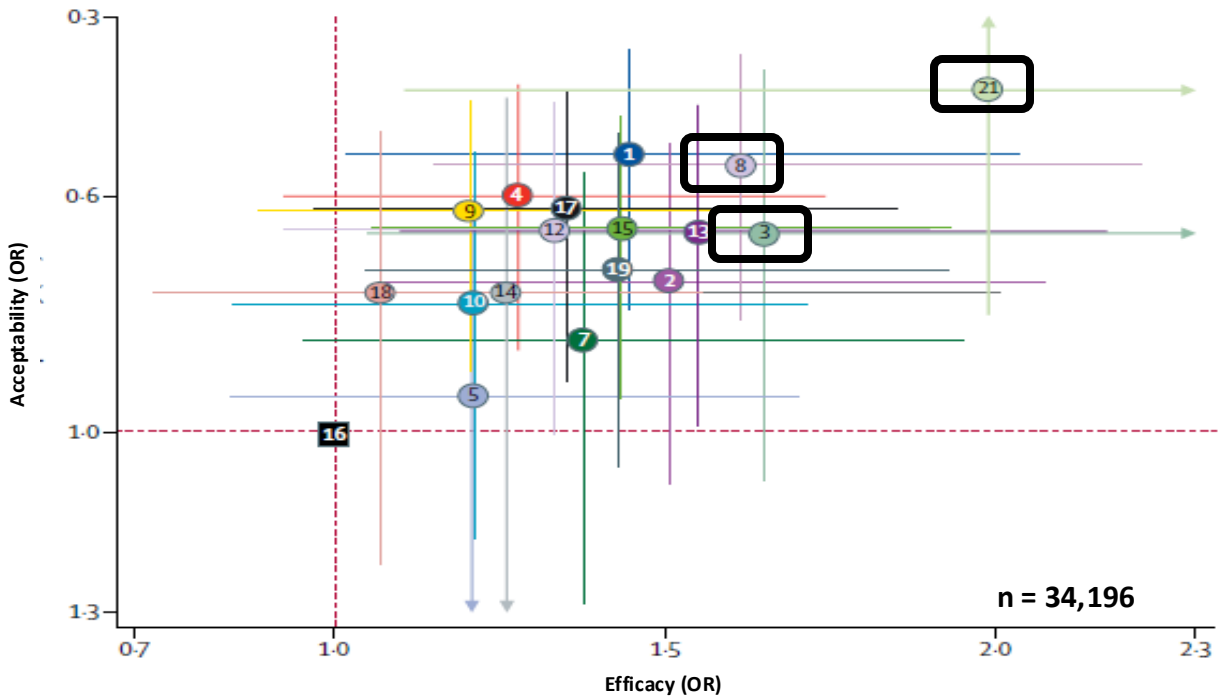
1. Analyzed 522 double-blind RCTs with over 116,000 participants
2. All antidepressants outperformed placebo
3. Effect sizes were modest and varied
4. Escitalopram, mirtazapine, paroxetine, agomelatine, and sertraline showed higher efficacy
5. Differences between agents are small despite statistical superiority
6. Emphasized need for precision approaches and new mechanisms



RCT = randomized controlled trial.
Cipriani A, et al. *Lancet*. 2018;391(10128):1357-1366.

Depression: A Quick Look at the Data

Head-to-Head Studies of Efficacy and Acceptability



In head-to-head studies, 3 antidepressants had the most favorable profile for efficacy and acceptability:

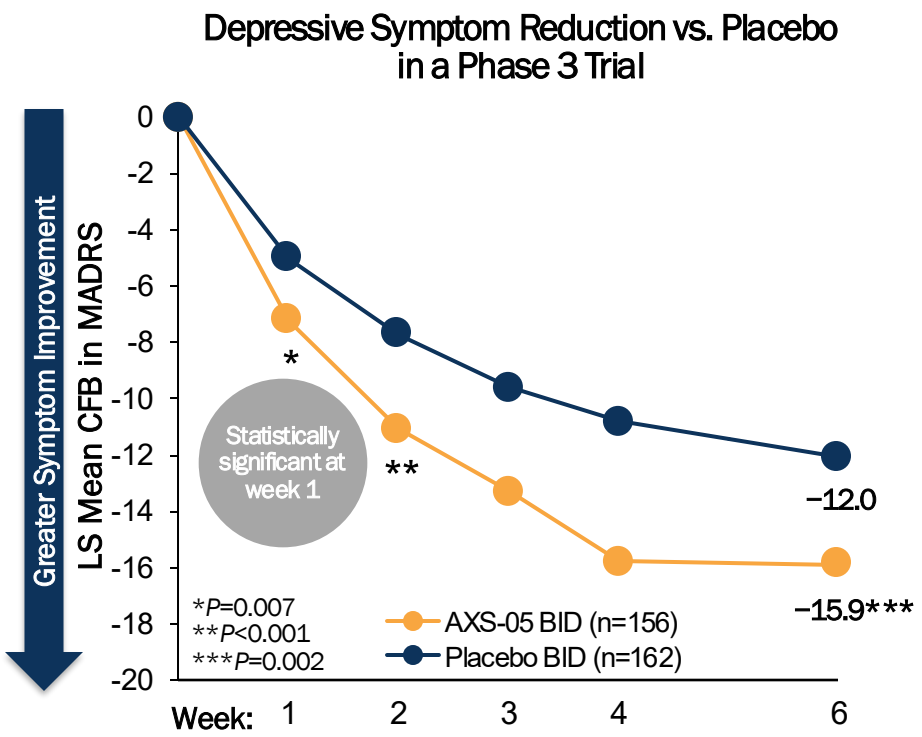
1. Vortioxetine (21) had the greatest net clinical benefit
   - Highest OR for efficacy
   - Lowest OR for all-cause discontinuation
2. Escitalopram (8)
3. Bupropion (3)

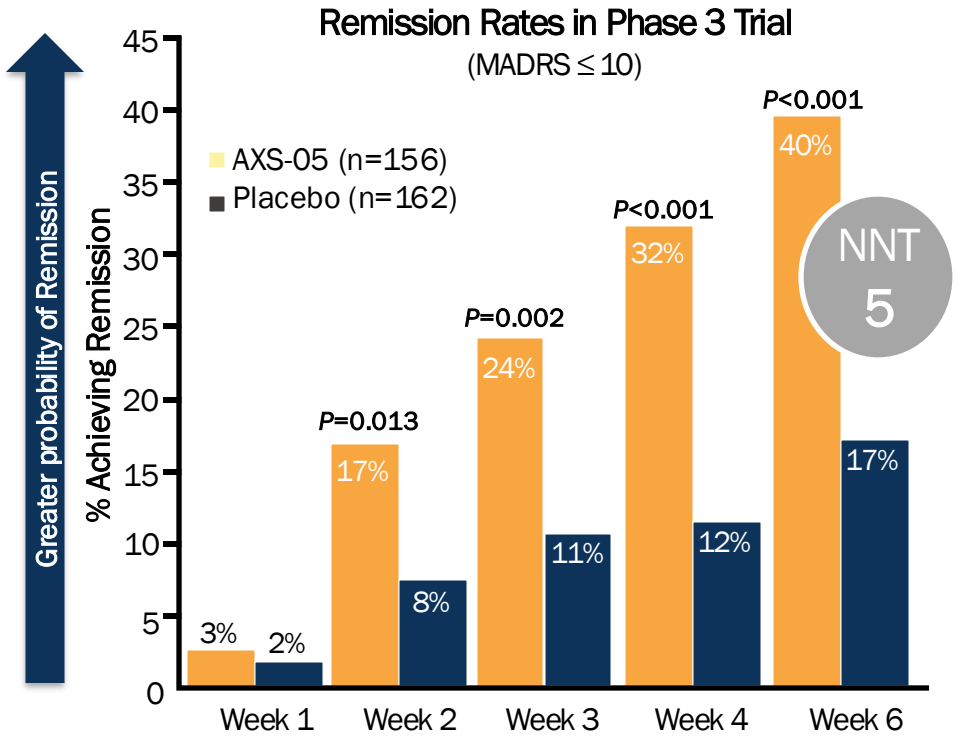
1, agomelatine; 2, amitriptyline; 3, bupropion; 4, citalopram; 5, clomipramine; 6, desvenlafaxine; 7, duloxetine; 8, escitalopram; 9, fluoxetine; 10, fluvoxamine; 11, levomilnacipran; 12, milnacipran; 13, mirtazapine; 14, nefazodone; 15, paroxetine; 16, reboxetine; 17, sertraline; 18, trazodone; 19, venlafaxine; 20, vilazodone; 21, vortioxetine.

OR = odds ratio.

Cipriani A, et al. *Lancet*. 2018;391(10128):1357-1366.

DXM-BUP Efficacy

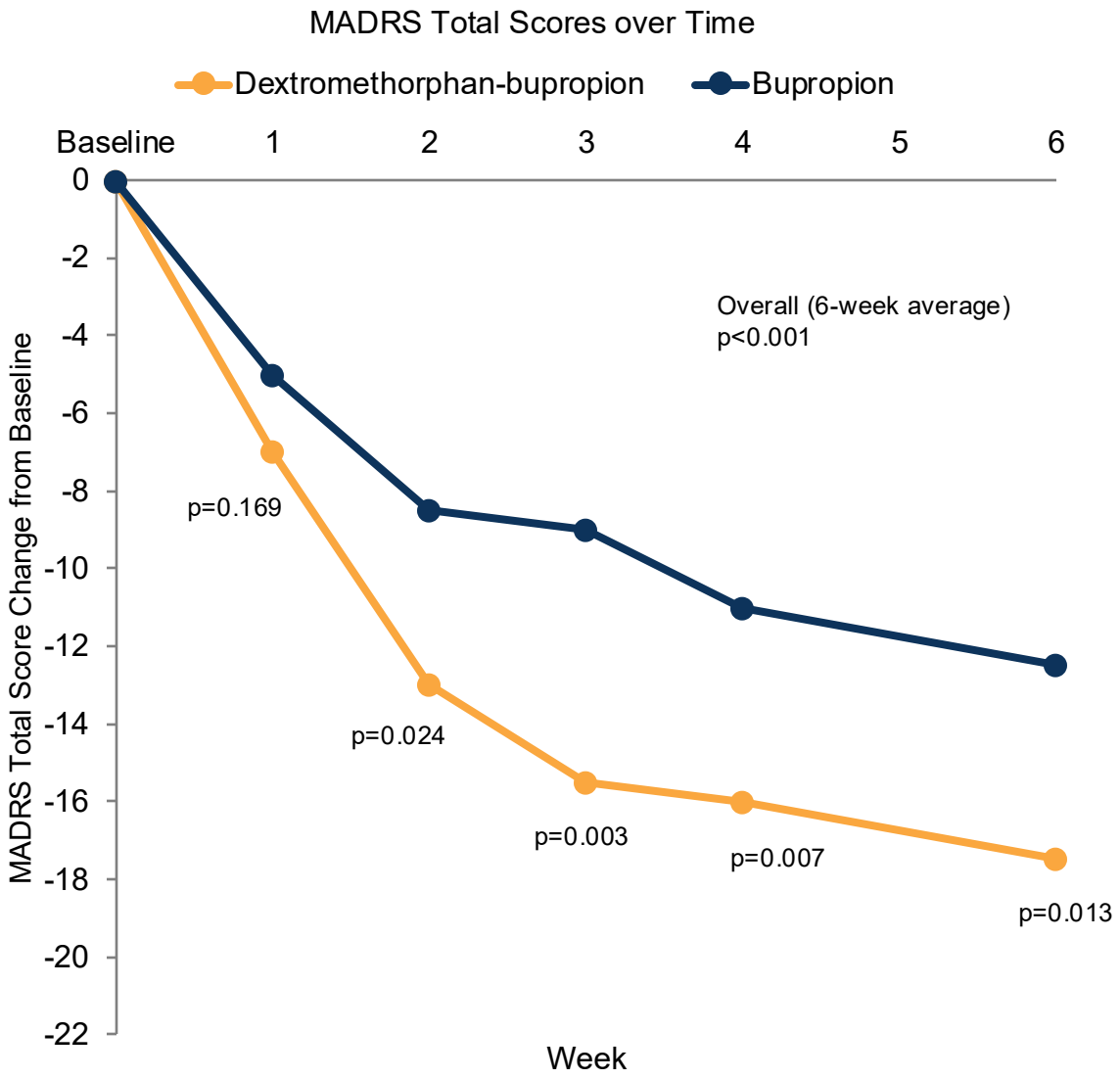


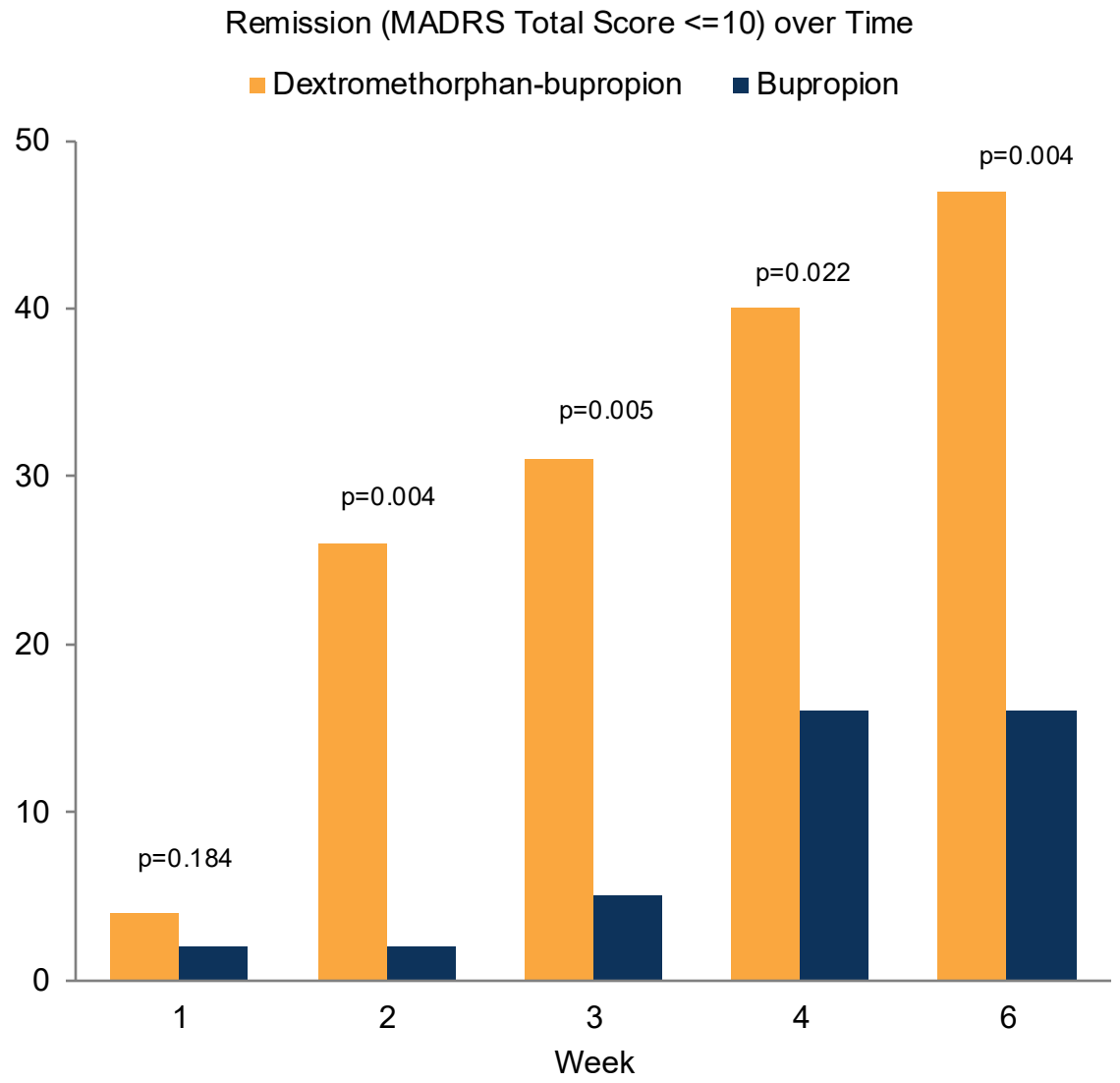


LS = least squares; CFB = change from baseline; MADRS = Montgomery-Asberg Depression Rating Scale; NNT = number needed to treat.

Iosifescu DV, et al. *J Clin Psychiatry*. 2022;83(4):21m1434. Tabuteau H, et al. *Am J Psychiatry*. 2022;179(7):490-499.

Dextromethorphan/Bupropion vs Bupropion in MDD

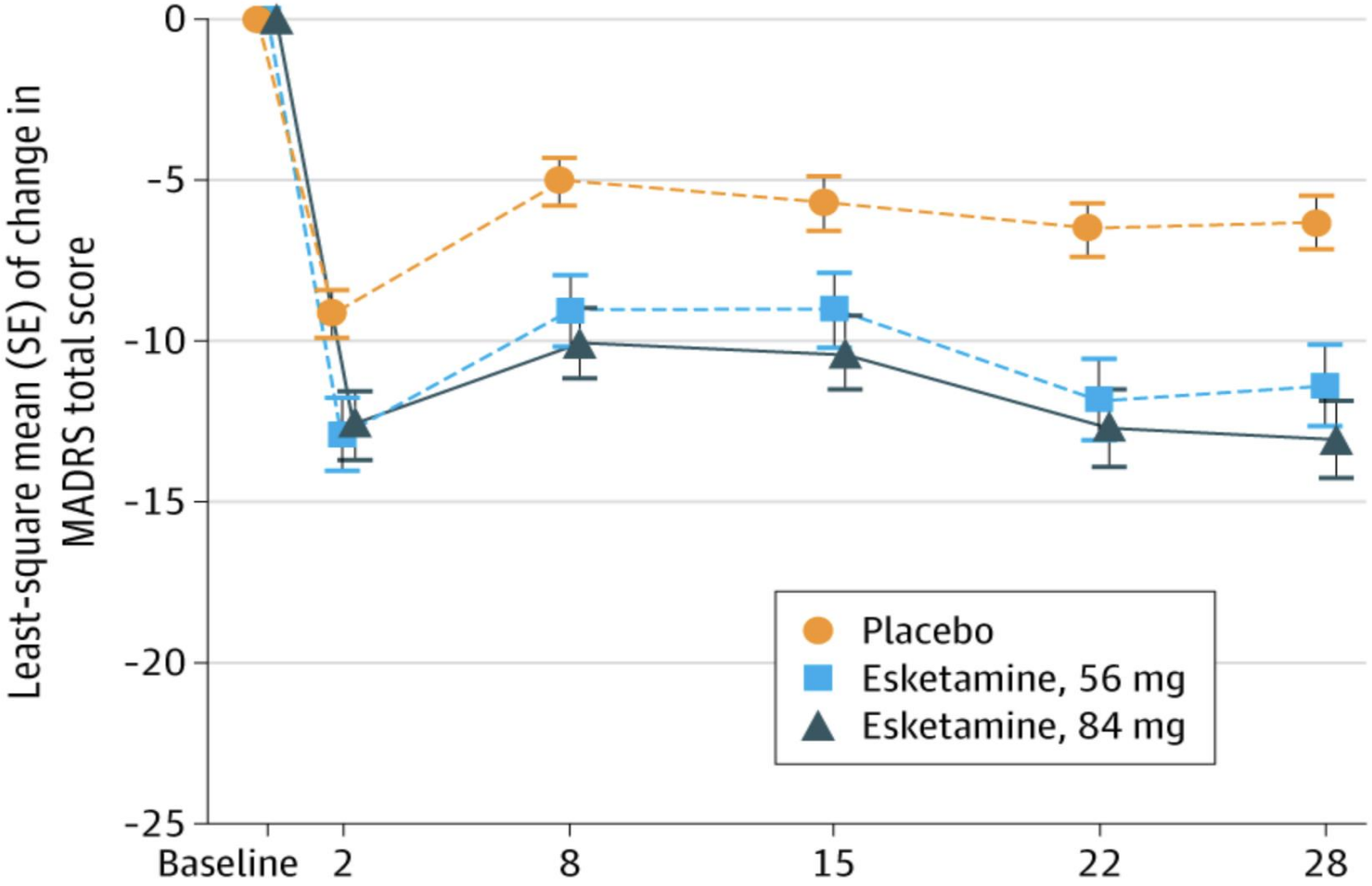




Tabuteau H, et al. *Am J Psychiatry*. 2022;179(7):490-499.

Esketamine Monotherapy in TRD

Both esketamine doses produced significant symptom reduction within 24 hours (day 2)

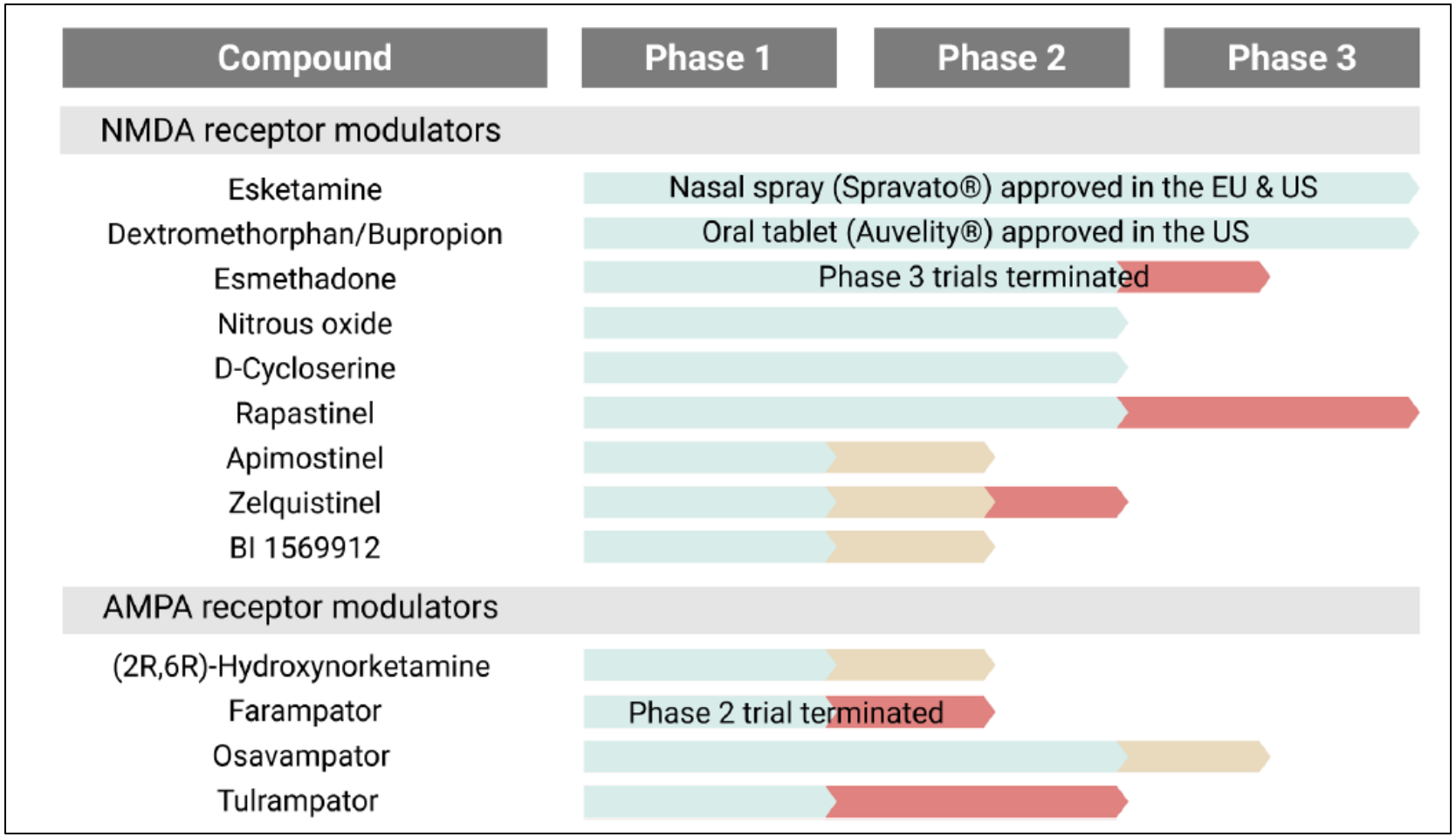


Effect size (84mg): 0.63

TRD = treatment-resistant depression.

Janik A, et al. *JAMA Psychiatry*. 2025;82(9):877-887.

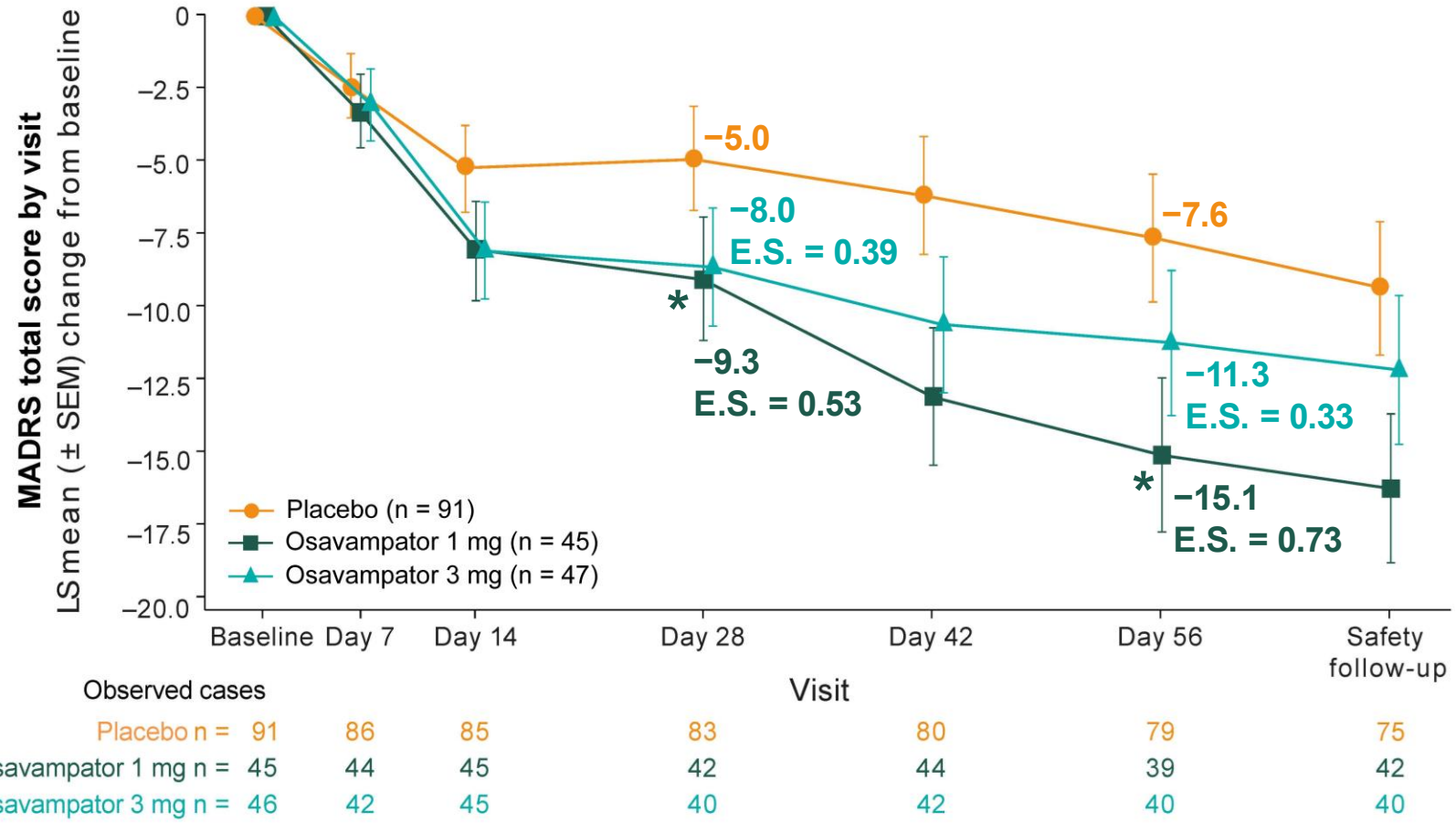
Ionotropic Glutamate Receptor Modulators Studied for MDD



Green indicates successful passage of the clinical phase (ie, positive data available). Yellow indicates ongoing trials or trials where data has not yet been published. Red indicates failed clinical trials or trials that were prematurely terminated, with further development halted. Of the indicated substances, approval has only been obtained for intranasal esketamine (Spravato®, EU and US) and dextromethorphan/bupropion (Auvelity®; US only).

Freudenberg F, et al. *Pharmacol Res*. 2025;220:107918.

Osavampator Demonstrated Statistically Significant and Clinically Meaningful Improvements in Depression Severity and Was Well Tolerated in Adults with MDD



Primary (DAY 28) and secondary (DAY 56) efficacy endpoints met

Response rates at DAY 56:

Placebo	1 mg	3 mg
31.6%	56.4%*	41.5%

Remission rates at DAY 56:

Placebo	1 mg	3 mg
22.8%	48.7%*	31.7%

Both doses were well tolerated, with no serious AEs or AEs of special interest reported.

- Both doses had an AE profile comparable to placebo.
- The most common AE was headache.

SAVITRI enrolled adults with MDD and inadequate response (≤ 50% improvement) to 1–5 prior oral antidepressant treatments.
Osavampator is investigational and not approved in any country.

***P*<0.05.**
AE = adverse event; ES = effect size.
Singh JB, et al. Presented at Psych Congress 2025; September 17-21, 2025; San Diego, CA; Poster #33.

Drugs Targeting BDNF and Related Downstream Mechanisms Under Investigation for Antidepressant Efficacy

ALTO-100 (NSI-189) – exact mechanism of action is unknown. However, it is thought to work indirectly by enhancing BDNF signaling and increasing neuroplasticity and neurogenesis in the hippocampus. The drug dose-dependently increases hippocampal volume at sufficiently high doses in rodents.

Alto Neuroscience Reports Topline Results from a Phase 2b Trial Evaluating ALTO-100 as a Treatment for Major Depressive Disorder

October 22, 2024

– Treatment with ALTO-100 did not demonstrate improvement in depressive symptoms compared to placebo in patients with a memory-based cognitive biomarker –

Allen BD, et al. *Radiat Res*. 2018;189(4):345-353. Alto Neuroscience. October 22, 2024. Accessed September 1, 2025. https://investors.altoneuroscience.com/news/news-details/2024/Alto-Neuroscience-Reports-Topline-Results-from-a-Phase-2b-Trial-Evaluating-ALTO-100-as-a-Treatment-for-Major-Depressive-Disorder/default.aspx.

Drugs Targeting BDNF and Related Downstream Mechanisms under Investigation for Antidepressant Efficacy

Supernus (*SPN-820, NV-5138)* is a novel, first-in-class intracellular modulator of mTORC1 for the treatment of depression.

Very early phase clinical trial just completed (Clinicaltrials.gov NCT06235905)

Supernus Announces Topline Results from Phase 2b Study in Adults with Treatment Resistant Depression

February 18, 2025 16:25 ET | Source: Supernus Pharmaceuticals, Inc.

- *Study did not demonstrate statistically significant improvement on primary endpoint of reduction in depressive symptoms as measured by MADRS total score compared to placebo*

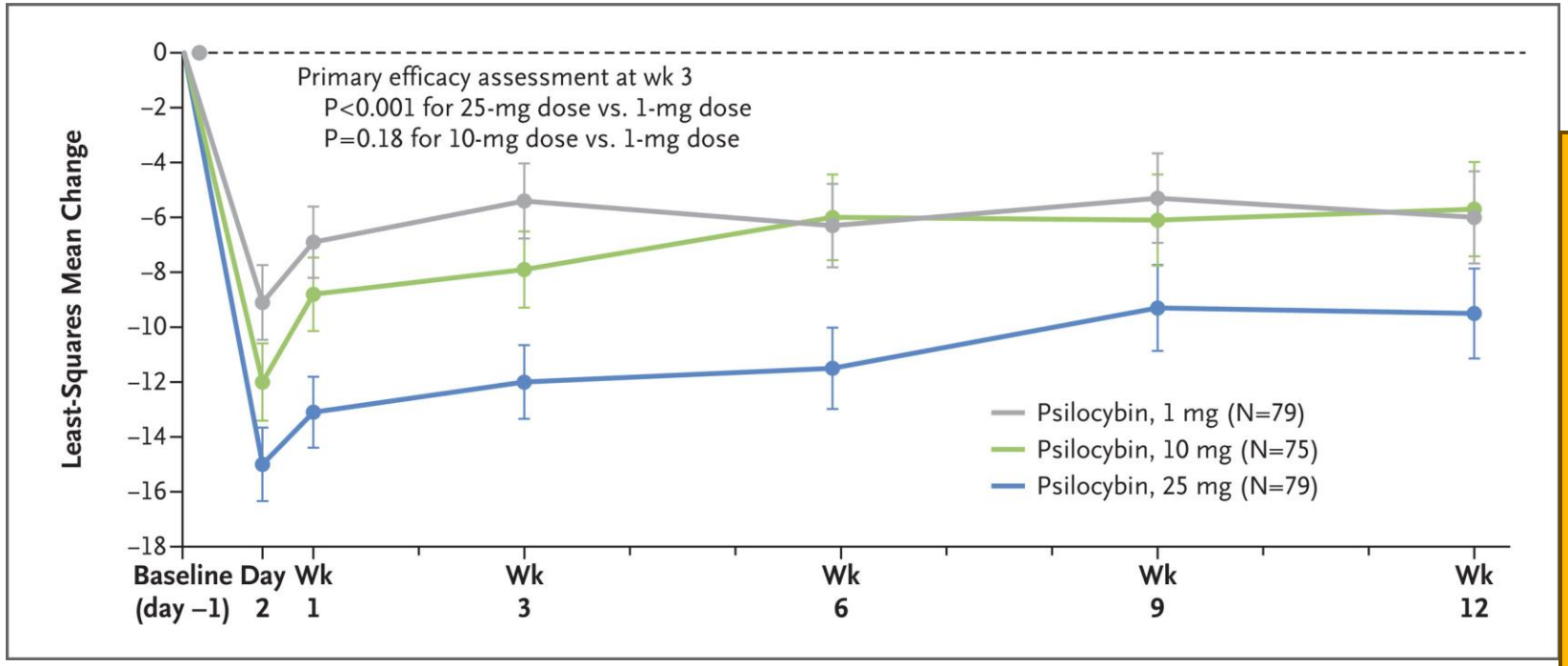
ROCKVILLE, Md., Feb. 18, 2025 (GLOBE NEWSWIRE) -- Supernus Pharmaceuticals, Inc. (Nasdaq: SUPN), a biopharmaceutical company focused on developing and commercializing products for the treatment of central nervous system (CNS) diseases, announced today that the Phase 2b study of SPN-820 in adults with treatment-resistant depression (TRD) did not demonstrate a statistically significant improvement on the primary endpoint of change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score to Week 4 (SPN-820 [LS mean ± Standard Error]: -12.3 ± 0.96 vs. placebo: -11.9 ± 0.96; p = not significant). There was no treatment difference between SPN-820 and placebo in the change from baseline to Week 4 for the secondary endpoints. The safety profile of SPN-820 was consistent with previous clinical trials, showing few adverse events.

Sengupta S, et al. *Sci Rep*. 2019;9(1):4107. Supernus Pharmaceuticals. February 18, 2025. Accessed September 1, 2025. https://www.globenewswire.com/news-release/2025/02/18/3028344/0/en/Supernus-Announces-Topline-Results-from-Phase-2b-Study-in-Adults-with-Treatment-Resistant-Depression.html.

Biased $5HT_{2A}$ Receptor Agonists: Can They Harness the Efficacy of Psilocybin?

Single-Dose Psilocybin (COMP360): Phase II

- Phase 2, double-blind, multicenter RCT (N=233)
- Adults with treatment-resistant MDD (2–4 prior antidepressant failures)
- Randomized to COMP360 psilocybin 25 mg, 10 mg, or 1 mg (control) with brief psychological support



Goodwin GM, et al. *N Engl J Med*. 2022;387:1637-1648.

Efficacy Results

- At Week 3, 25 mg reduced MADRS by −12.0 vs −5.4 for 1 mg (P<0.001); 10 mg was not significant.
- Response rates: 37% (25 mg) vs 18% (1 mg); remission: 29% vs 8%
- Effects decreased over time; 12-week sustained response: 20% vs 10%

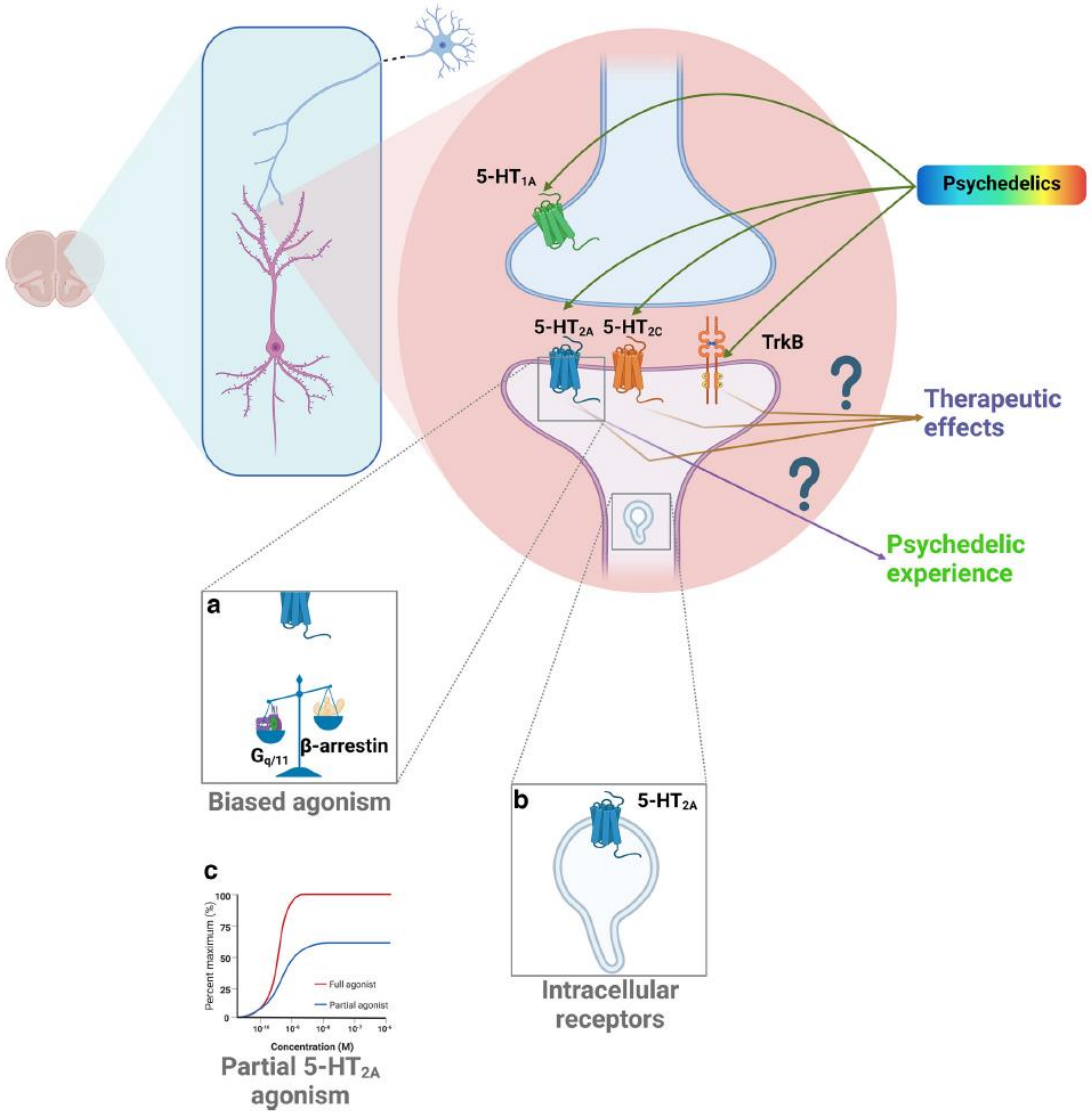
Safety Findings

- Adverse events occurred in 77%, mainly headache, nausea, dizziness/fatigue.
- Suicidal thoughts appeared across all doses, requiring close monitoring.

Clinical Implications

- Demonstrates a rapid, single-dose, non-monoaminergic antidepressant
- Emphasizes 5-HT2A-driven neuroplasticity as a treatment target
- February 2026 - Comp005 and comp006 top line results positive.

How Psychedelics Work



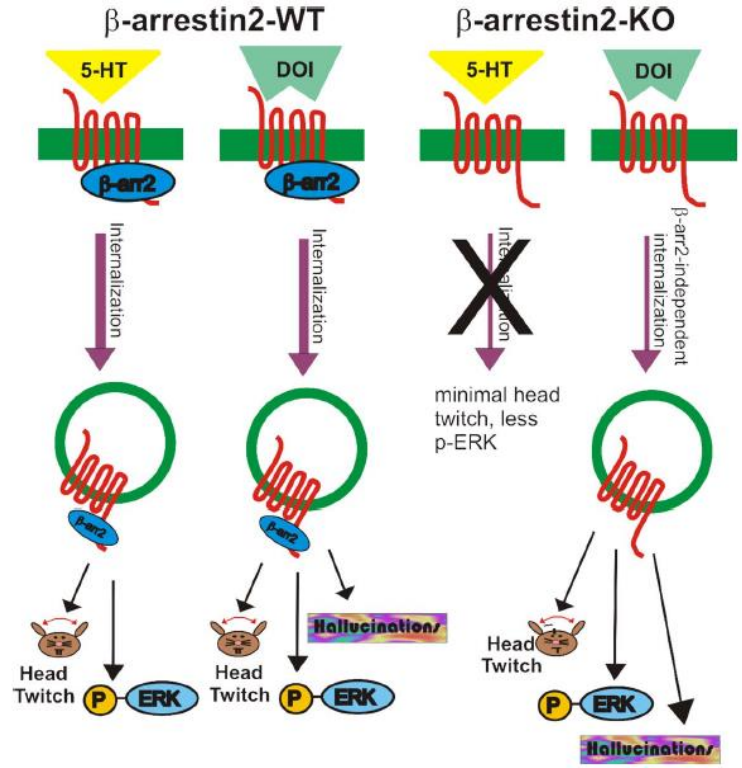
1. LSD and psilocybin bind to multiple 5-HT receptors, and are agonists of varying potency at all of these receptors.
   - 5-HT_{2A} receptor activation leading to changes in neuronal growth is not well defined, but appears to involve TrkB, mechanistic target of rapamycin (mTOR), and AMPA receptor signaling.
2. The psychedelic, antidepressant, and neuroplasticity effects in animal models are blocked by 5-HT_{2A} antagonists (eg, ketanserin), leading to the conclusion that 5-HT_{2A} receptor stimulation must be a core aspect of the MOA.
3. **Issue:** Why don't certain 5-HT_{2A} agonists (eg, lisuride) induce psychedelic effects or exhibit antidepressant properties?
   - **Answer:** The actions of psychedelics occur at intracellular 5HT_{2A} receptors, not those on the cell surface, so lipophilicity correlates with plastogenicity.
   - **Question:** Psychedelics exhibit effects on G-protein–dependent and independent intracellular pathways, but are both necessary for antidepressant actions? (Does one need to trip?)

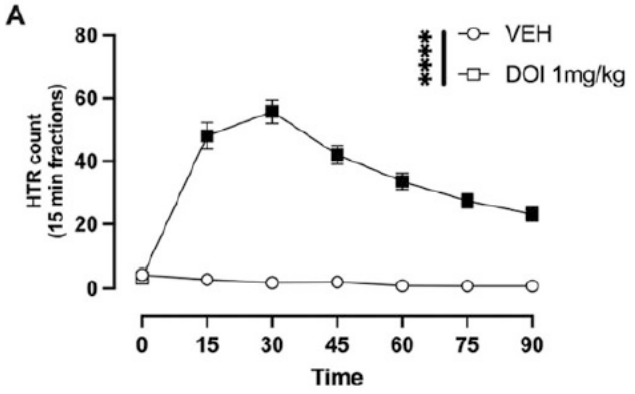
LSD = lysergic acid diethylamide; MOA = mechanism of action.

Cameron LP, et al. *J Neurosci*. 2023;43(45):7472-7482. Vargas MV, et al. *Science*. 2023;379:700-706.

The β Arrestin2 Pathway and Psychotropic Actions at G-Protein–Coupled Receptors: Example of Agonist Actions at $5HT_{2A}$ Receptors

1. **$5HT_{2A}$ Receptor Activation:** Agonists stimulate the G-protein pathway but also induce recruitment of the scaffolding protein Beta arrestin2 (βArr2) that results in internalization of the ligand-receptor complex.
2. **The role of βArr2:** The absence of βArr2 greatly attenuates many 5-HT–induced downstream events at 5-HT_{2A} receptors, including internalization, head twitch response.
3. **Animal correlate of hallucinations**
   - **βArr2 knockout (KO) mice:** Assays indicate that it is recruitment of the βArr2 pathway that is involved with the psychedelic properties of traditional $5HT_{2A}$ agonists (eg, LSD, psilocybin). The animal analog of the psychedelic property is the head twitch response (HTR): **βArr2 KO mice have minimal HTR from $5HT_{2A}$ agonists.**
   - **DOI:** The experimental ligand DOI (2,5-Dimethoxy-4-iodoamphetamine) is able to induce HTRs by βArr2 independent methods and is often used as a comparative model.





KO = knockout; HTR = head twitch response.

Abbas A, Roth BL. *Proc Natl Acad Sci USA*. 2008;105(3):831-832. Jaster AM, et al. *Methods Mol Biol*. 2023;2687:65-76.

Unlocking Psilocybin's Mechanism: The Search for Biased 5HT2A Agonists

Concept: Find a $5HT_{2A}$ biased agonist that lacks βArr2 recruitment to test the hypothesis that G-protein signaling achieves antidepressant effects. To accomplish this, investigators explored a virtual library of 75 million candidate structures against a model of the serotonin 5-HT_{2A} receptor, leading to synthesis and testing of 17 initial molecules. Structure-based optimization led to the 5-HT_{2A} agonists **(R)-69 and (R)-70.**

1. **CNS permeability:** (R)-69 and (R)-70 had substantial brain permeability in mouse PK studies, did **not** stimulate or inhibit locomotion, and **were not** associated with conditioned place preference (a measure of addiction).
2. **G_q activity:** In contrast to the psychedelic 5-HT_{2A} agonist LSD, which is arrestin-biased, the new agonists were G-protein-biased, activating Gq signaling at mid-nanomolar concentrations with high efficacy. **Behavioral assays indicated potent antidepressant activity that persisted for days after single doses in a manner comparable to that seen with ketamine or psilocin.**
3. **Low-level HTR:** Different doses of both (R)-69 and (R)-70 induced very low levels of HTRs and were significantly lower than LSD. Moreover, both (R)-69 and (R)-70 significantly blocked the HTRs induced by the potent 5-HT_{2A} agonist LSD (ie, via competitive inhibition). This partial blockade of LSD-induced HTRs with (R)-69 and (R)-70 indicates that these compounds are unlikely to be psychedelic at these doses.
4. **Prepulse inhibition:** (R)-69 and (R)-70 were found to exert no effects on prepulse inhibition (PPI) relative to LSD.

PK = pharmacokinetics; PPI = prepulse inhibition.

Kaplan AL, et al. *Nature*. 2022; 610(7932):582-591.

GM-2505: Human Data on a 5HT2A Agonist

1. **Method:** Phase 2a randomized, double-blind study evaluating GM-2505 (bretisilocin) in recurrent MDD patients (n=40) who were antidepressant free for 6 weeks. Patients were randomized to receive 10 mg GM-2505 or 1 mg GM-2505 via intravenous (IV) infusion on **Day 1**. All participants received an IV dose of 15 mg GM-2505 on **Day 15**.
2. **Efficacy**
   - **Day 14:** The initial 10 mg dose was superior to the 1 mg dose at day 14, with higher remission rates (**effect size 1.0**)
   - **Day 29:** High dose (10 mg + 15 mg) showed a -28.0 point change from baseline, with 94% achieving remission. A rapid effect seen within 24 hours, with a -18.5 point MADRS change from baseline
   - **Day 74:** Effects were less than day 29, but only by 10%
3. **Tolerability:** The 10 mg dose exhibited "robust psychedelic effects" and the 15 mg "maximal psychedelic effects," but these were shorter in duration than for traditional psychedelics. There were no serious AEs, no SI, and only transient increases in BP, HR.
4. **The future:** GM-200X program of non-hallucinogenic 5- HT_{2A} receptor agonists. Preclinical evidence suggests these compounds lack hallucinogenic effects while retaining the benefits, and might deliver long-term or subchronic maintenance therapy in addition to acute efficacy.

MADRS CHANGES FROM BASELINE AND REMISSION RATES

	ARM 1	ARM 2
GM-2505 DOSING	Day 1, 1 mg Day 15, 15 mg	Day 1, 10 mg Day 15, 15 mg
BASELINE	31.9	33.4
DAY 14	n=20	n=20
- CHANGE FROM BASELINE	-12.1	-21.6
- REMISSION	25 %	70 %
DAY 29	n=20	n=17
- CHANGE FROM BASELINE	-21.1	-28.0
- REMISSION	55 %	94 %
DAY 74 FOLLOW-UP	n=20	n=17
- CHANGE FROM BASELINE	-19.7	-25.1

SI = suicidal ideation; BP = blood pressure; HR = heart rate.

PR Newswire. May 27, 2025. Accessed May 27, 2025. https://www.prnewswire.com/news-releases/gilgamesh-pharmaceuticals-announces-positive-topline-phase-2a-results-for-gm-2505-in-major-depressive-disorder-mdd-302465404.html. Marek G, et al. Presented at: ASCP 2025 Annual Meeting – Abstracts; May 27-30, 2025; Scottsdale, AZ. Poster W63: Robust antidepressant efficacy of the novel 5-HT2A receptor agonist GM-2505 in a double blind, randomized, controlled phase 2a trial in patients with MDD, p. 200. Biopharma Dealmakers. September 2022. Accessed August 2025. https://www.nature.com/articles/d43747-022-00181-8.

Psych Congress Presents

Case Study

Melissa Is “Burned Out”

Meet Melissa

Is it just “burnout”?

“I just feel like I’m running on autopilot. I’m getting through each day, but I can’t remember the last time I felt like myself.”

- 36-year-old female project manager
- Married with two children, supportive spouse and stable home
- Increased workload, loss of engagement and meaning at work
- Moderate functional impairment (struggling with focus, motivation, enjoyment)

Clinical Presentation and Assessment

Clinical Presentation

- Low Mood
- Anhedonia
- Cognitive Slowing
- Poor Sleep (5–6 hours/night)
- **PHQ-9: 15/27**

Diagnosis

- **Major Depressive Disorder**
  single episode, moderate severity
- Specifier: Mild Anxious Distress

Patient Goals and Beliefs

- **Goal**: Restoration of Energy/Enjoyment
- **Therapy/Exercise**: Open, but anticipates difficulty with follow-through due to low motivation
- **Medication Beliefs:** Skeptical due to concerns of overprescription and side effects

PHQ = Patient Health Questionnaire.

CANMAT 2023 Framework – Initial Treatment Options

Approach	Lifestyle / Psychotherapy	SSRI / SNRI	Novel Mechanism Agent
Rationale	First-line for mild-to-moderate MDD; aligns with patient preference	Standard first-line for moderate MDD; robust evidence base	Rapid-acting, non-monoaminergic option; potential faster recovery
Advantages	Low side-effect risk, holistic wellness	Effective, accessible, covered by most plans	Faster onset (1–2 wks), cognitive and hedonic benefit
Limitations	Requires adherence and motivation	Side effects (sexual, weight), slower onset	Cost, access, limited long-term data
CANMAT Position	Step 1 (mild cases)	Step 1 for moderate severity	Step 1 or 2 for moderate MDD with functional impairment

Lam RW, et al. *Can J Psychiatry*. 2024;69(9):641-687.

MDE severity*	Summary recommendations for initial treatment selection
Mild with low safety risk.	• Psychotherapy and pharmacotherapy demonstrate similar benefits ●. – Psychotherapy (if readily accessible) is preferred because of fewer risks ◔. • Exercise, certain CAM treatments, or guided DHIs may be considered as monotherapy, especially if preferred by patients ◔.
Moderate, with low-moderate safety risk.	• Initial choice is between pharmacotherapy and psychotherapy ●. – Pharmacotherapy is slightly more efficacious in reducing depressed mood, guilt, suicidal thoughts, anxiety, and somatic symptoms during acute treatment ◔. – Structured psychotherapy, specifically CBT, is slightly more efficacious in the medium-term (6–12 months) ◔. • Combination of pharmacotherapy and psychotherapy may be considered ●. • Exercise, certain CAM treatments and/or DHIs may be considered as adjuncts to psychotherapy and/or pharmacotherapy, especially if preferred by patients ◔.
Severe, with moderate to high safety risk.	• For severe MDE without psychotic symptoms, use a combination of pharmacotherapy and psychotherapy ◔. • For severe MDE with psychotic symptoms, use a combination of antidepressant and antipsychotic medication ●. • For very severe and/or life-threatening situations, consider electroconvulsive therapy ◐.

● Level 1; ◔ Level 2; ◐ Level 3; ◔ Level 4.

Note. MDE = major depressive episode; CAM = complementary and alternative medicine; DHI = digital health intervention; CBT = cognitive-behavioural therapy. These recommendations are based on the severity of the illness (see conventions) and safety risk (see Q.2.c), but other factors should be considered,

Decisions: Forks in the Road

If Melissa starts with lifestyle-first:

- How long before reassessment? What outcomes to expect?

If she begins an SSRI (eg, sertraline, escitalopram):

- How to address side-effect concerns and set expectations?

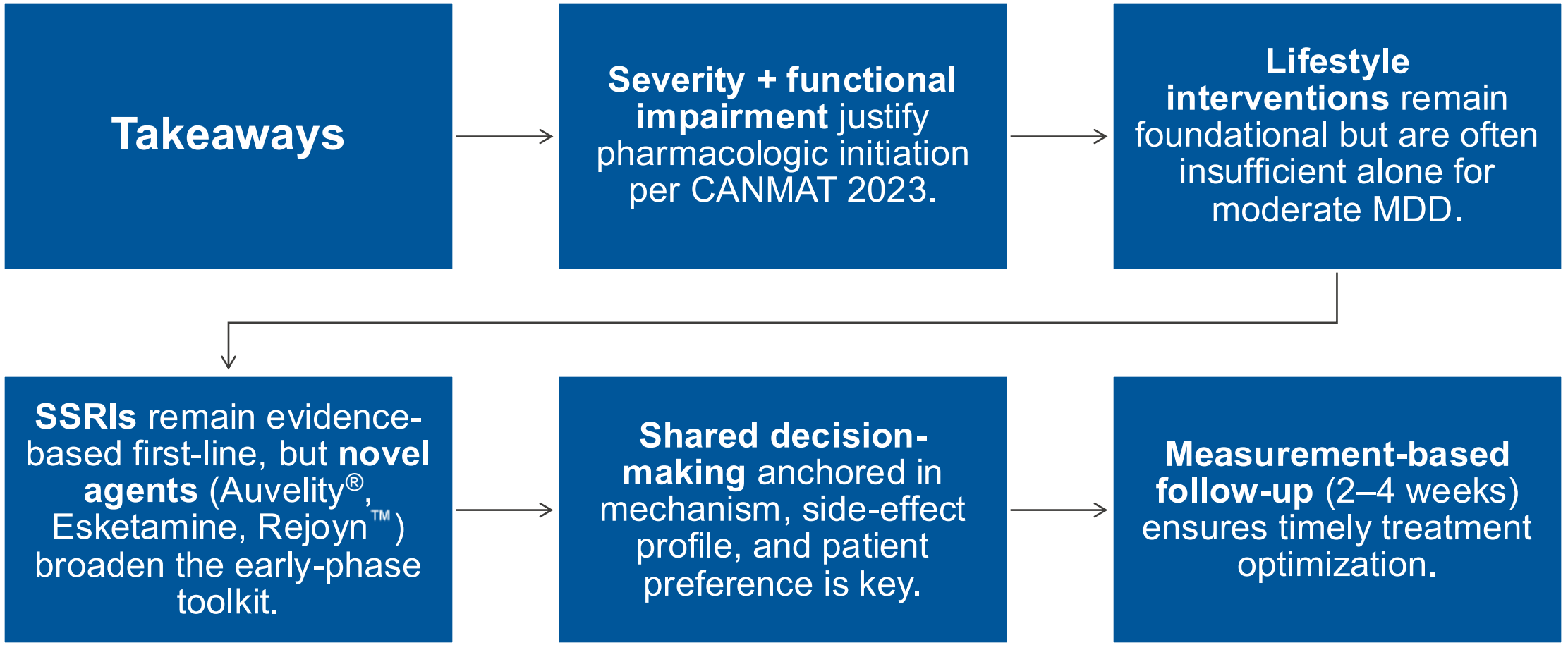
If she tries a novel agent (eg, DXM/BUP, Esketamine):

- What patient characteristics make this a reasonable choice?

At 4 weeks:

- If partial response: switch, augment, or intensify nonpharmacologic care?

Case Study Takeaways



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Q&A