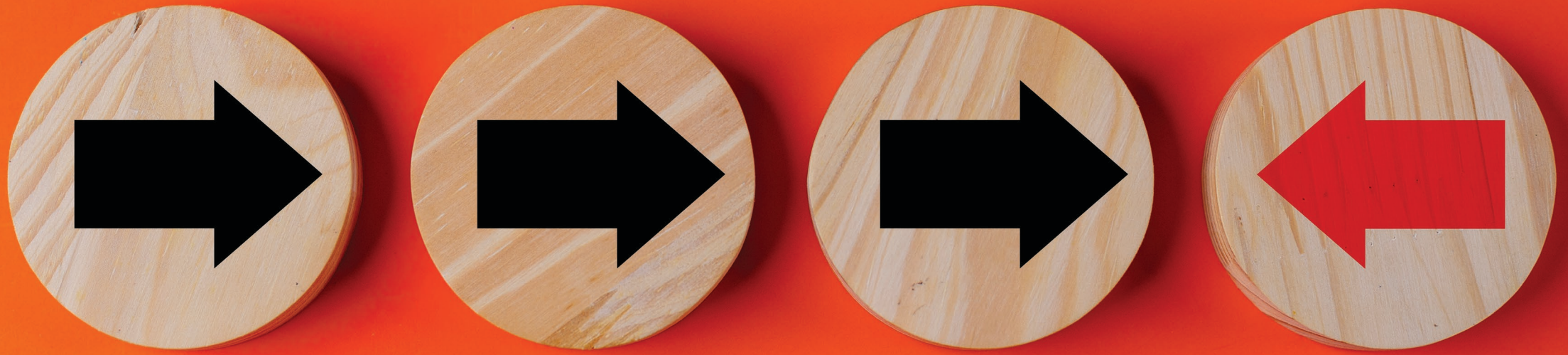
Finding a Way Forward in **"Treatment-Resistant Depression"** with Glutamatergic Agents



Supported by an independent educational grant from Janssen Pharmaceuticals, Inc., administered by Janssen Scientific Affairs, LLC: a Johnson & Johnson Company.

Faculty

Lisa Harding, MD

Assistant Clinical Professor
Department of Psychiatry Yale School of Medicine
New Haven, CT
Medical Director of Mood Institute
Milford and Southport, CT

Hara Oyedeji, APRN, PMHNP-BC, MSEd

Founder and Lead Clinician
Fortitude Behavioral Health, LLC
Baltimore, MD

Faculty Disclosures

Lisa Harding, MD

Advisory Board - AbbVie, COMPASS Pathways, GH Therapeutics, Johnson & Johnson, Otsuka; Consultant - AbbVie, GH Therapeutics, Johnson & Johnson, Otsuka; Grant/Research Support - COMPASS Pathways; Speaker's Bureau - COMPASS Pathways, GH Therapeutics, Johnson & Johnson

Hara Oyedeji, APRN, PMHNP-BC, MSEd

Advisory Board - Alkermes PLC, BMS; Consultant - Alkermes PLC; Speaker's Bureau - Alkermes PLC, BMS, Intracellular, Neurocrine Biosciences Inc, Otsuka Pharmaceuticals, Teva Pharmaceuticals

Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration)
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity
- This activity has been independently reviewed for balance

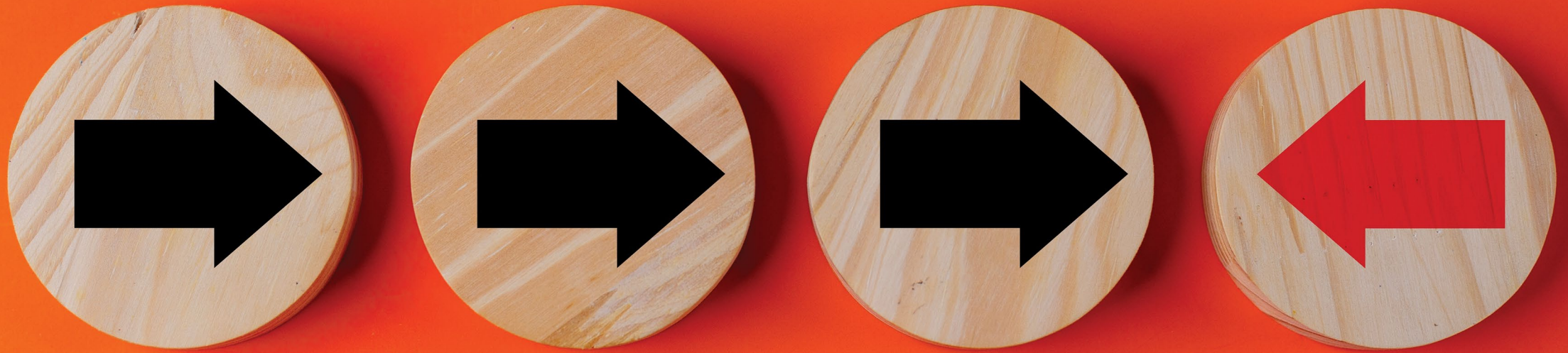
Learning Objectives

1. Assess the treatment limitations associated with conventional monoaminergic antidepressants in MDD and TRD

2. Evaluate the mechanism of action and latest clinical and real-world evidence and treatment implications associated with newer glutamatergic and neuromodulation therapies for TRD

3. Develop personalized treatment plans for patients with TRD according to the latest guidelines and the principles of patient-centered care and shared decision-making

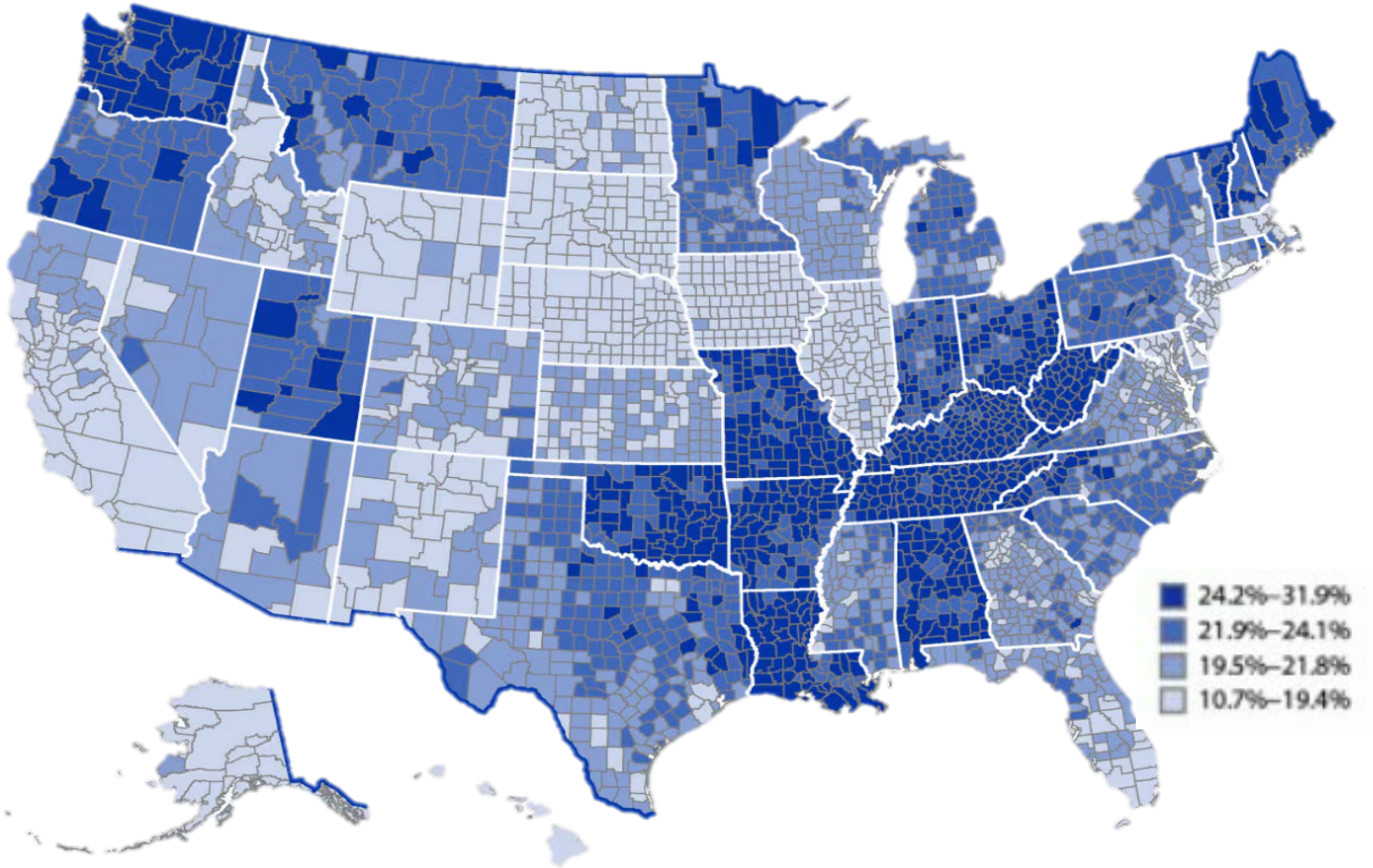
Understanding Treatment-Resistant Depression



MDD Is One of the Most Prevalent Mental Health Conditions

Worldwide
280 million people

Lifetime Prevalence
in adults in the US is
20.6%



Model-based county estimates of the % of adults age ≥18 years self-reporting a lifetime diagnosis of depression

MDD = Major depressive disorder. Hasin DS, et al. *JAMA Psychiatry.* 2018;75(4):336-46. Lee B, et al. *MMWR Morb Mortal Wkly Rep.* 2023;72:644-50. National Institute of Mental Health website. Major Depression. Accessed October 3, 2024. https://www.nimh.nih.gov/health/statistics/major-depression.

TRD Definition and Risks

DEFINITION	**2 or more unsuccessful trials of antidepressants at adequate dose for at least 6-8 weeks**

RISK FACTORS	➢ Early onset in childhood or adolescence
	➢ Depressive episodes that are
	  ➢ Relatively more frequent
	  ➢ Relatively more persistent
	➢ Comorbid conditions (e.g., stress reactivity, anxiety)

MORTALITY	➢ In a Finnish data registry study of more than 11,000 patients with treated MDD, 11% had TRD
	  ➢ Death due to suicide ~twice as high in TRD
	  ➢ Death due to accidental overdose ~2x as high in TRD

Cepeda MS, et al. *J Affect Disord*. 2018;234:308-15. Dudek D, et al. *Psychiatr Pol*. 2010;44(5):701-12. Gustafsson TT, et al. J Affect Disord. 2024;368:136-42. Souery D, et al. *J Clin Psychiatry*. 2007;68(7):1062-70. Warden D, et al. *J Clin Psychiatry*. 2007;68(12):1907-13.

Definition Matters Because Accurate Differential Diagnosis Is Essential

Inaccurate diagnosis may cause up to 50% of non-response or partial response

Differential Diagnosis

- ✓ Mental health mimics
  - ✓ Bipolar disorder
  - ✓ Comorbid mental health condition
  - ✓ Autism/ADHD
  - ✓ Negative symptoms of psychotic disorder
- ✓ Neurologic mimics
  - ✓ Parkinson's
  - ✓ Stroke
  - ✓ Migraine
  - ✓ TBI
  - ✓ Narcolepsy
  - ✓ ALS
  - ✓ Epilepsy
- ✓ Medical conditions
  - ✓ Cancer
  - ✓ Cardiovascular disease
  - ✓ Chronic pain
  - ✓ Hypothyroidism
  - ✓ Vitamin deficiencies
  - ✓ Diabetes
  - ✓ Sleep disorders
  - ✓ Infections
  - ✓ Anemia

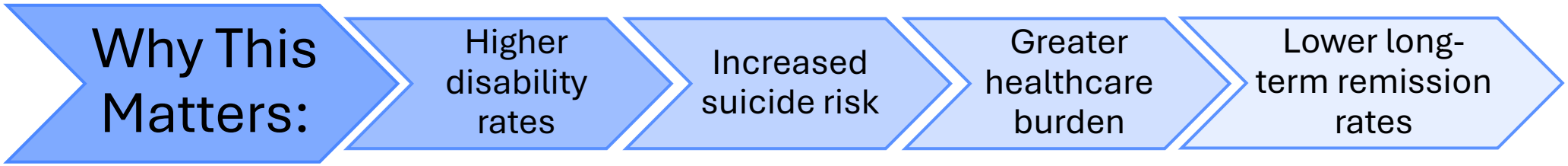
Remember to assess medication adherence!

Many medications can also cause depressive symptoms—be sure to assess

ADHD = Attention deficit hyperactivity disorder; ALS = Amyotrophic lateral sclerosis; Gaynes BN. *J Clin Psychiatry.* 2009;70(Suppl 6):10-5. McIntyre RS, et al. *World Psychiatry*. 2023;22(3):394-412.

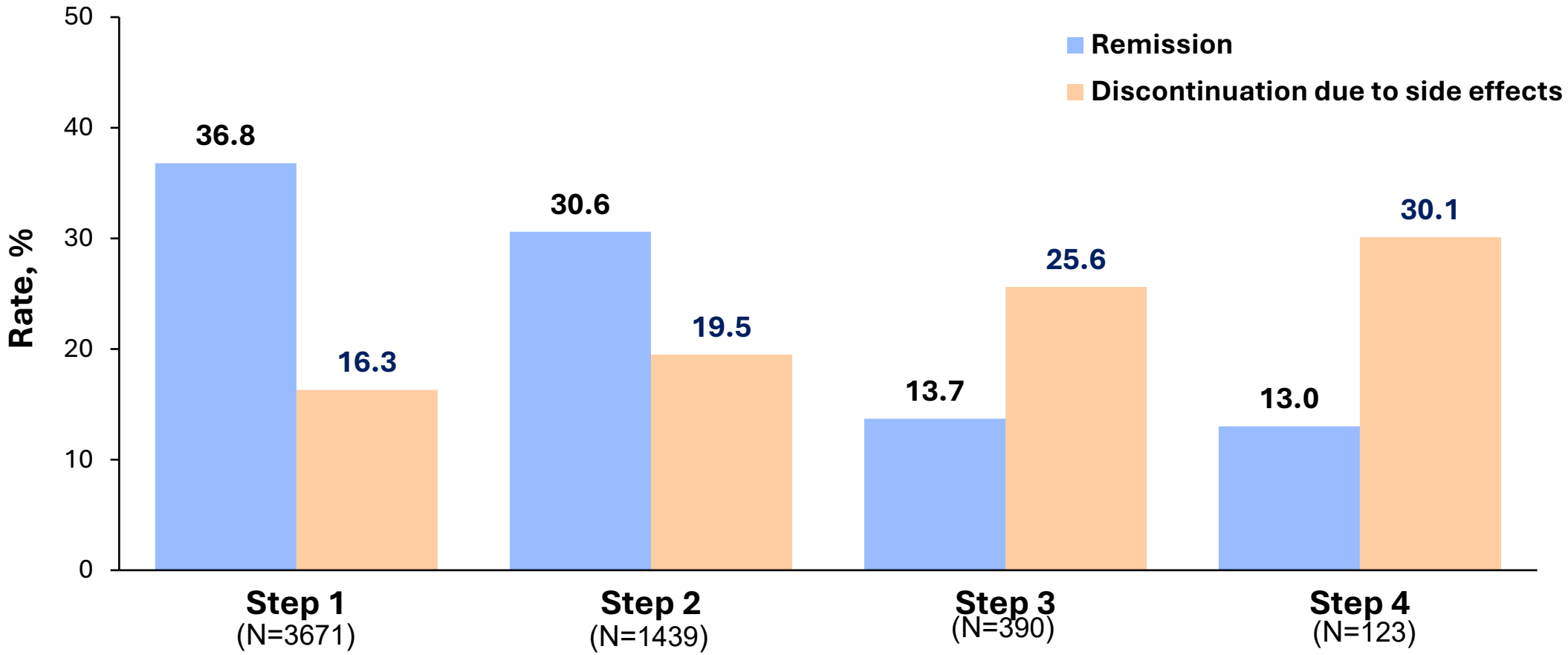
Why We Care = Burden of TRD

The Burden of TRD			
Medication-treated depression	MDD	TRD	Total
Unemployment	$8.7M	$9.6M	$18.3M
Productivity	$19.6M	$9.3M	$28.8M
Health care	$19.8M	$25.8M	$45.6M
TOTAL FINANCIAL BURDEN OF TRD			**$92.7M**



Oliveira-Maia AJ, et al. *Adv Ther*. 2024;41(1):34-64. Zhdanava M, et al. *J Clin Psychiatry*. 2021;82(2):20m13699.

How STAR*D Informs TRD: The Critical Drop-Off



The **biggest drop-off** in remission rates occurs between **Step 2 and Step 3**, emphasizing the **difficulty in achieving remission beyond two unsuccessful treatments**

STAR*D = Sequenced Treatment Alternatives to Relieve Depression. Rush AJ, et al. *Am J Psychiatry.* 2006;163(11):1905-17. Voineskos ,et al. *Neuropsychiatric Dis Treat*. 2020;16,:221-34.

Limitations of Monoaminergic Antidepressants

An observational study examined the recovery rates of MDD patients (N=1297)

At **Week 16** after initiating, or switching to, an SSRI or SNRI antidepressant

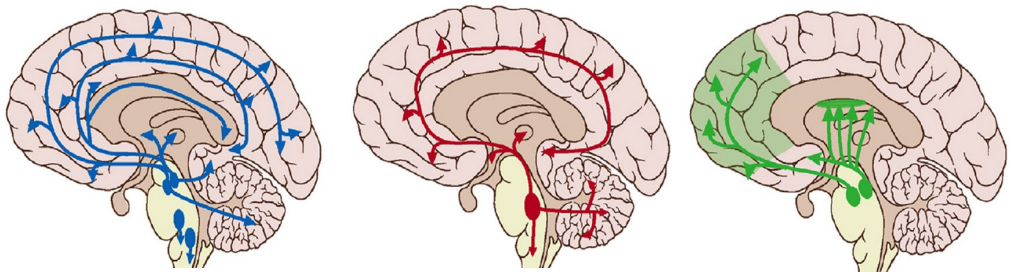
- **53%** showed **clinical remission**
- **38%** showed **functional remission**
- **34.2%** showed **recovery**

May take weeks to become effective

- Partial response is common with residual symptoms
  - Cognitive issues
  - Blunted affect/decreased motivation
  - Appetite/eating problems
  - Fatigue
  - Psychomotor effects
- Adverse effects
  - Sexual dysfunction
  - Weight gain
  - Insomnia
  - Emotional blunting
  - Low response and recovery rates

SNRI = Selective serotonin inhibitor; SSRI = Selective serotonin reuptake inhibitor. Conradi HJ, et al. *Psychol Med*. 2011;41:1165–74. Culpepper L, et al. *Am J Med*. 2015;128:S1-S15. Haroon E, et al. *Neuropsychopharm-acology*. 2017;42(1):160-177. Kadriu N, et al. *Biol Psychiatry*. 2019;86(9):730-743. Masdrakis VG, et al. *Acta Neuropsychiatrica*. 2023;35(4):189-204. McClintock SM, et al. *J Clin Psychopharmacol*. 2011;31:180-6. Ishak, et al. *Depress Anxiety*. 2014;31:707-16; Novick D, et al. *Patient Prefer Adherence*. 2017;11:1859-68.

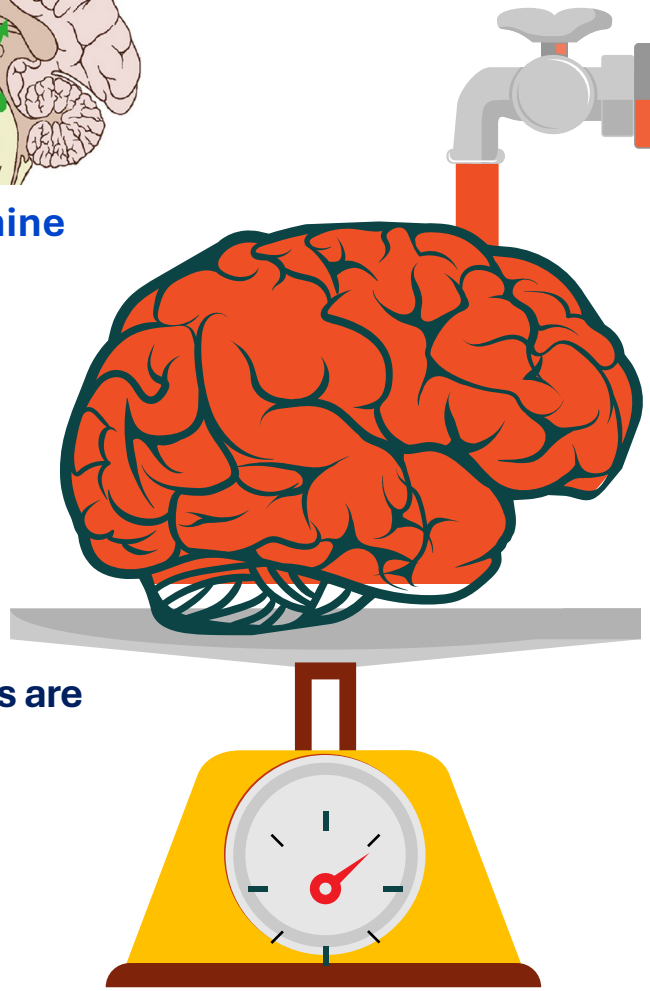
What About Glutamate?



Serotonin Norepinephrine Dopamine

Monoamine cell bodies are **mostly in the brainstem and midbrain** and project to the cortex to influence glutamatergic neurons at monoamine receptors

1%-2%
Of cortical synapses are monoaminergic



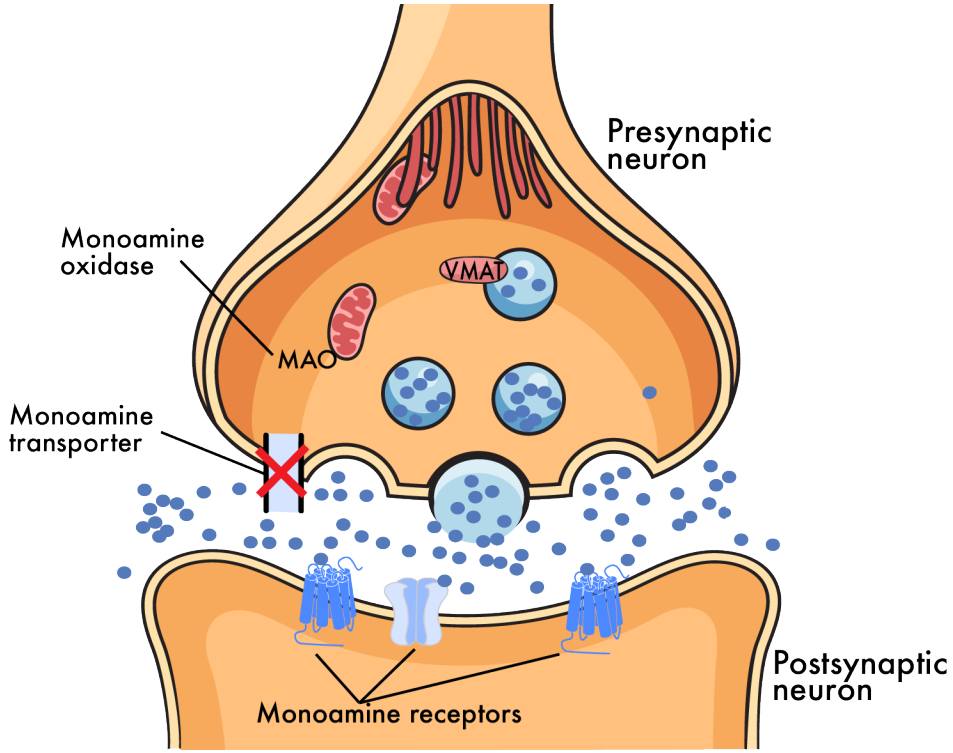
~85%

Of cortical synapses are glutamatergic

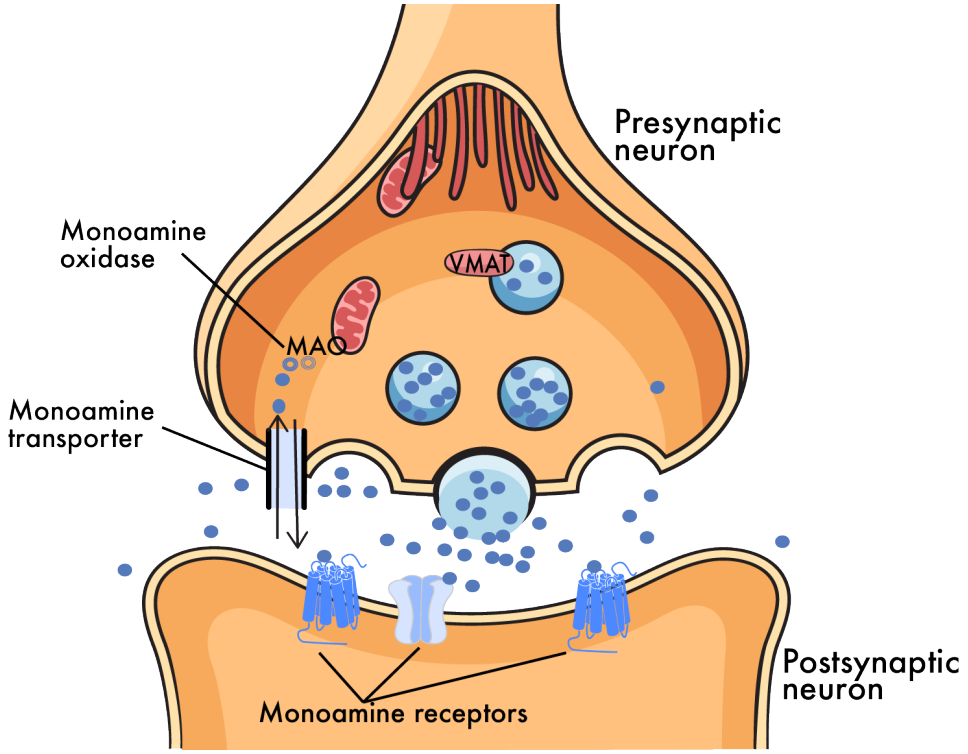
- **Most widespread excitatory neurotransmitter in the brain**
- Significant role in **learning, cognition, and mood**
- Involved in synaptogenesis and neuroplasticity
- Can be **neurotoxic in excess**
- Glutamate and GABA form the primary components of the cortex

Froböse MI, et al. *Curr Opin Behav Sci*. 2018;22:121-127. Ng J, et al. *Nat Rev Neurol*. 2015;11(10):567-584. Inoshita M, et al. *Neuropsychiatr Dis Treat*. 2018;14:945-953. Stahl SM. *Stahl's Essential Psychopharmacology*. (5th ed.) Cambridge University Press; 2021.

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



Blocking monoamine transporters increases the amount and duration of monoamines in synapse



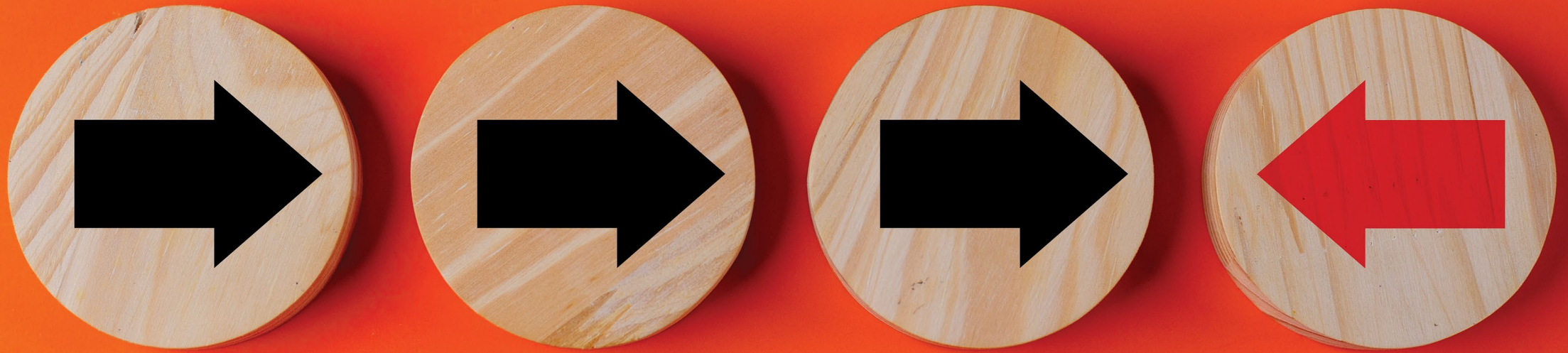
The success of monoamine transport blocking SSRIs/SNRIs, although limited, suggested monoamine deficit causes depression

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

Key Learning Points

- In the STAR*D trial, remission rates dropped the most **after adding or switching to a second drug**
- An observational follow-up study of the STAR*D showed **34.2% of patients recovered 16 weeks after** after initiating, or switching to, an (SSRI/SNRI) antidepressant
- TRD is defined as **2 or more unsuccessful antidepressant trials during the same depressive episode** at an effective dose for at least 6 to 8 weeks
- Patients with TRD have **higher suicide** and **mortality** rates and increased healthcare costs compared with patients with MDD

Current and Emerging Treatments for Treatment-Resistant Depression



Olanzapine/Fluoxetine Combination

Mechanisms of Action

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

Effects

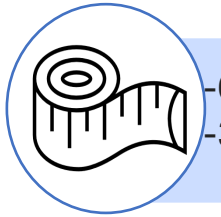
- Systematic review showed combination provides earlier response vs fluoxetine alone
  - Higher response/remission rates also seen
- Long-term open label studies show sustained efficacy for up to 76 weeks

Monaminergics do work for 1 in 3 people with MDD, so continued improvement of these may make sense for improving TRD treatment

Tamayo JM, et al. *Arch Neuroscien*. 2015;20 (1):3-19. Bobo WV et al. *Neuropsychiatr Dis Treat*. 2009;5:369-83.

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

1% of patients discontinued treatment due to weight gain

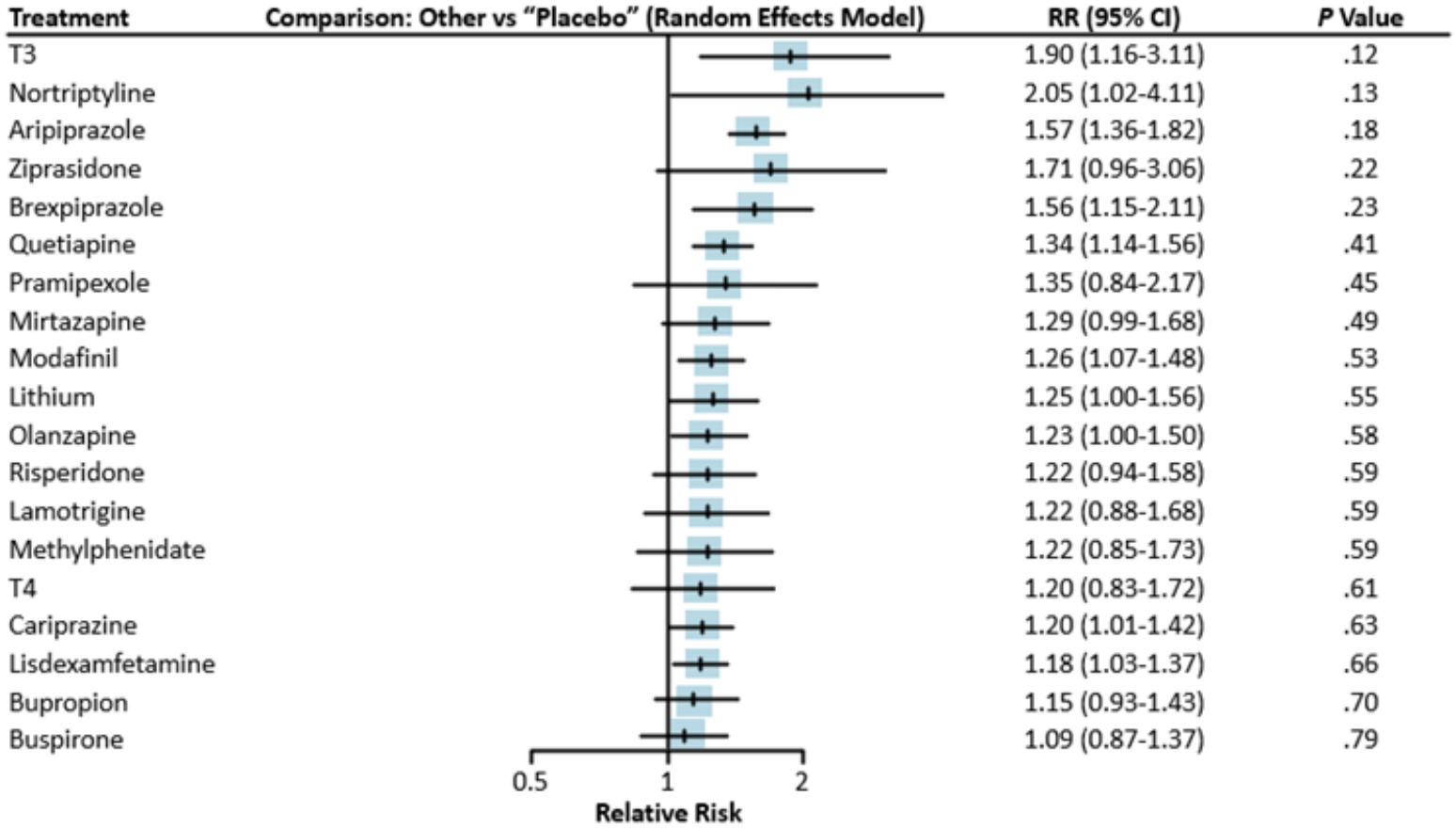
Treatment-Emergent Adverse Events Occurring in ≥ 5% of OFC Patients and at Least Twice that of Placebo			
Event	Combination	Fluoxetine	Olanzapine
Weight increase	28%	7%	34%
Increased appetite	24%	6%	29%
Dry mouth	19%	7%	21%
Somnolence	16%	7%	14%
Fatigue	14%	9%	16%
Peripheral edema	11%	1%	7%
Tremor	10%	6%	5%
Sedation	9%	3%	11%
Hypersomnia	6%	2%	8%
Attention disturbance	6%	3%	6%

All adverse events significantly higher with combination vs fluoxetine alone, except attention disturbance

Tremor was the only adverse event to occur significantly more with the combination than with olanzapine alone

Bobo WV. *Expert Review of Neurotherapeutics*. 2010;10(5):651-70. Eli Lilly and Company. Symbyax® (olanzapine and fluoxetine hydrochloride) Prescribing Information. Drugs@FDA: FDA Approved Drugs. Accessed January 10, 2023. www.accessdata.fda.gov/scripts/cder/daf/.Madhukar HT, et al. *J Clin Psychiatry*. 2009;70(3):387-396.

Meta-Analysis of Adjunctive Treatment with Antidepressants



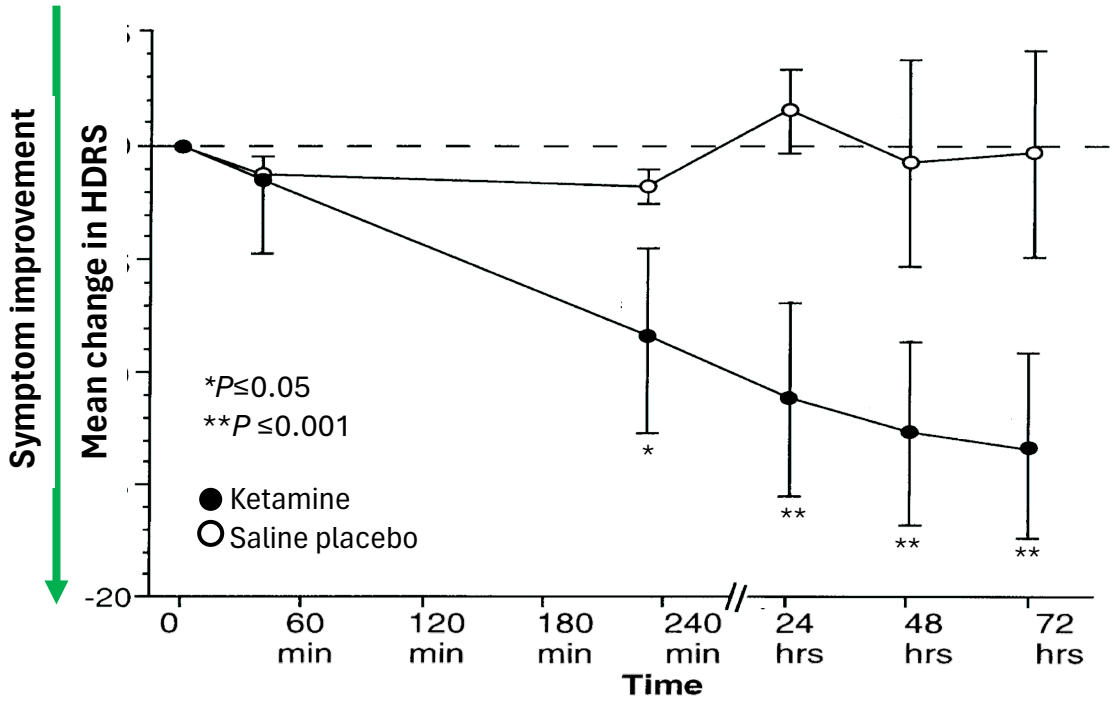
- Atypical antipsychotics had higher response rates than lithium or T_3
- Second-generation antipsychotics were among the most effective, but carry a higher burden of side effects
- Meta-analysis supports tailoring adjunctive treatment to the individual patient—highlighting the need for precision in TRD

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

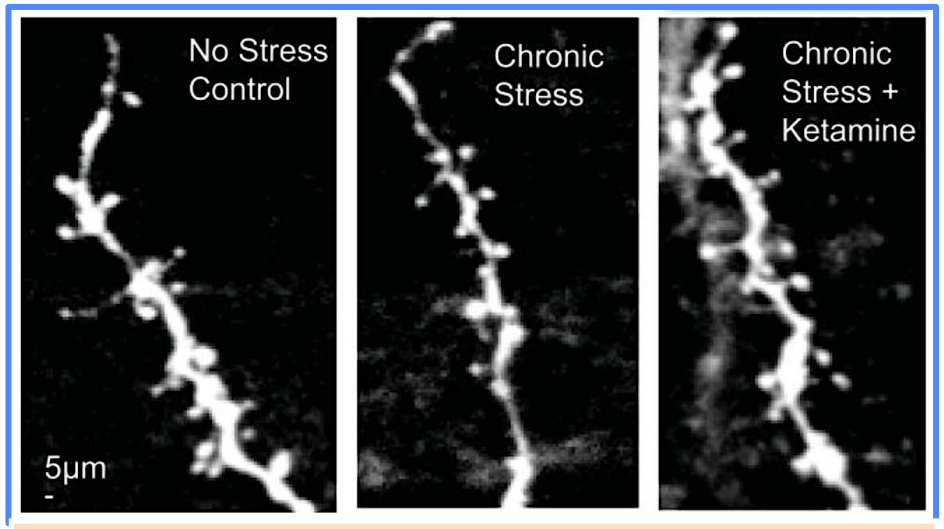
And What About Glutamate Again?

Ketamine is a potent NMDA receptor antagonist

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



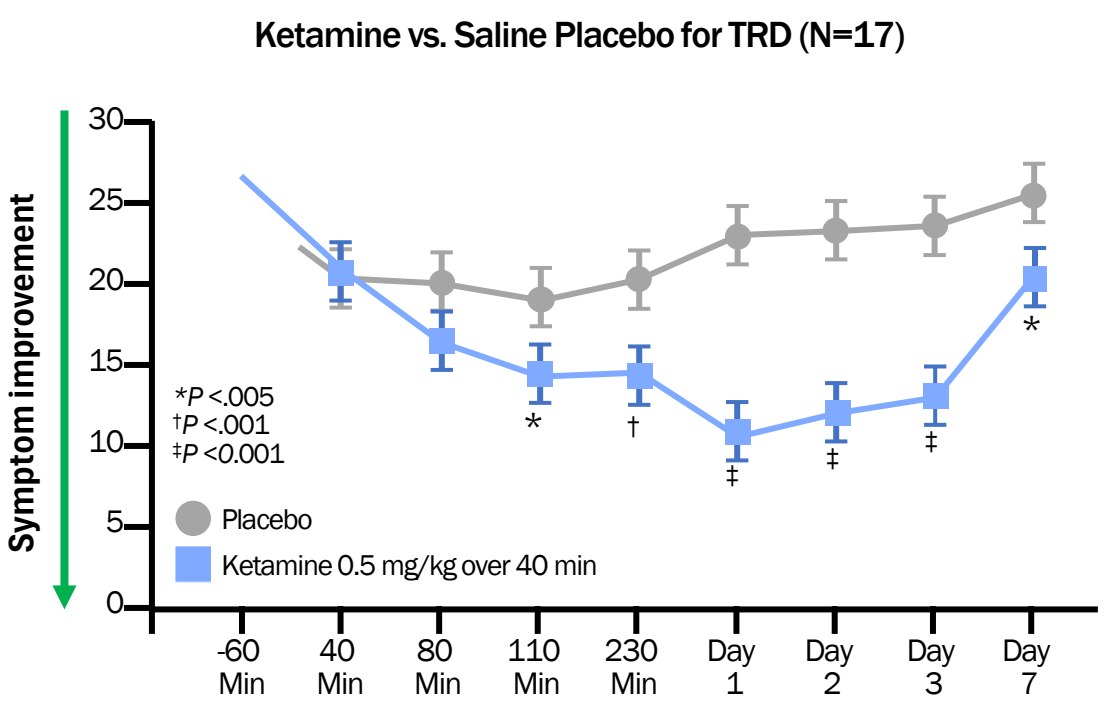
The ketamine group separated from placebo at 4 hours and the effect was sustained for ≥ 3 days

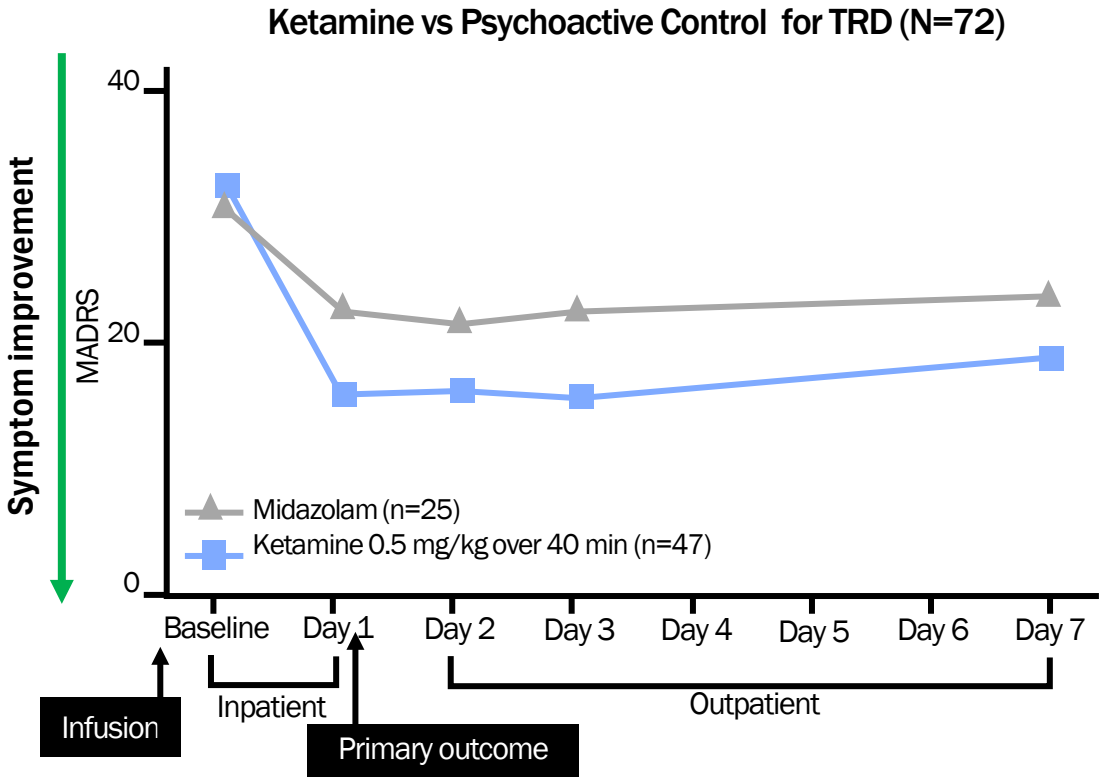


Later, high-powered microscopy demonstrated that a single dose of ketamine could produce rapid synaptogenesis in rat pyramidal neurons.

IV = intravenous; HDRS = Hamilton Depression Rating Scale. Berman RM, et al. *Biol Psychiatry*. 2000;47(4):351-4. Sanacora G, et al. *JAMA Psychiatry*. 2017;74(4):399-405. Li N, et al. *Biological Psychiatry*. 2011;69(8):754-61.

Additional Studies Suggested Potential of Ketamine





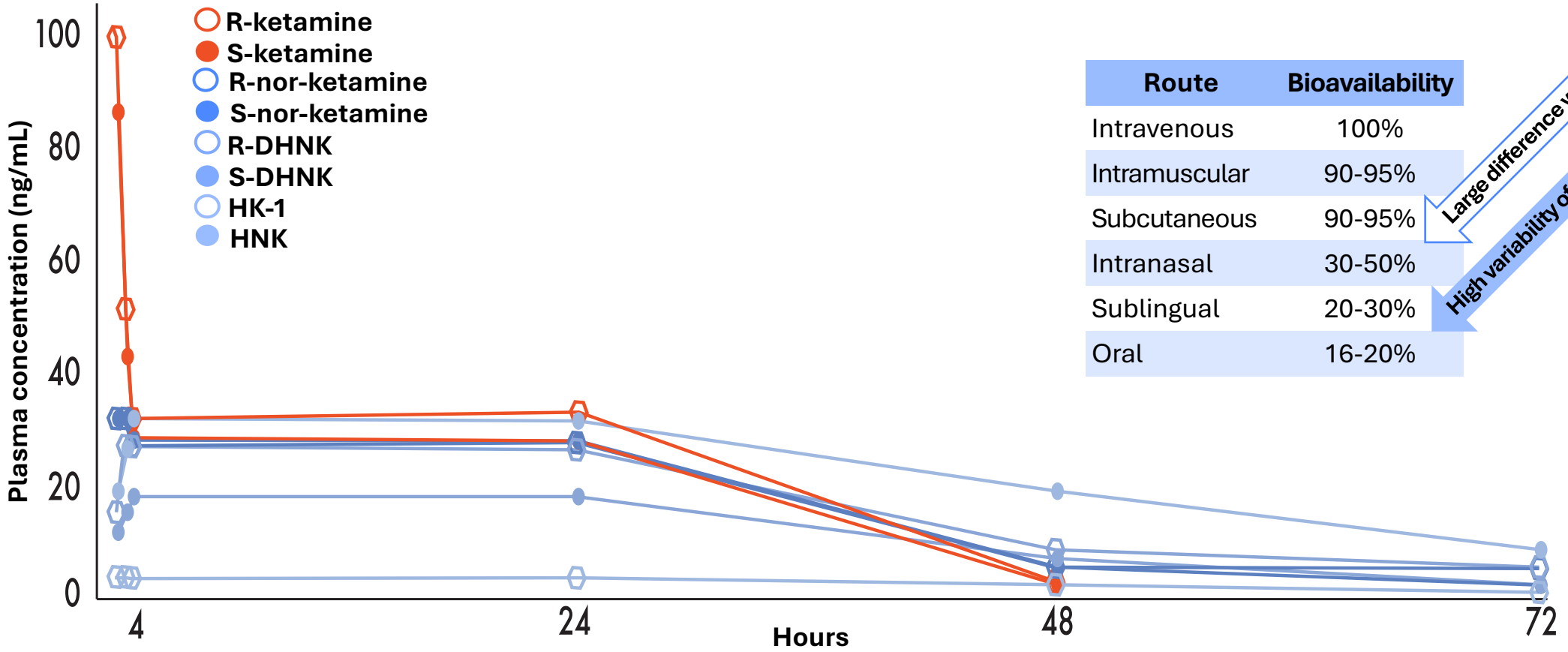
Adverse events more common with ketamine than placebo: perceptual disturbances, confusion, elevations in blood pressure, euphoria, dizziness, and increased libido.

Adverse events more common with ketamine within 4 hours of infusion: dizziness, blurred vision, headache, nausea or vomiting, dry mouth, poor coordination, poor concentration, and restlessness.

HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery-Åsberg Depression Rating Scale. Zarate CA, et al. Archives of general psychiatry. 2006;63(8): 856-64. Murrough,JW, et al. *American Journal of Psychiatry*. 2013;170(10): 1134-42.

Pharmacokinetics of Ketamine

Ketamine and its metabolites rise to a peak concentration in just over 1 hour, then rapidly decline.



Route	Bioavailability
Intravenous	100%
Intramuscular	90-95%
Subcutaneous	90-95%
Intranasal	30-50%
Sublingual	20-30%
Oral	16-20%

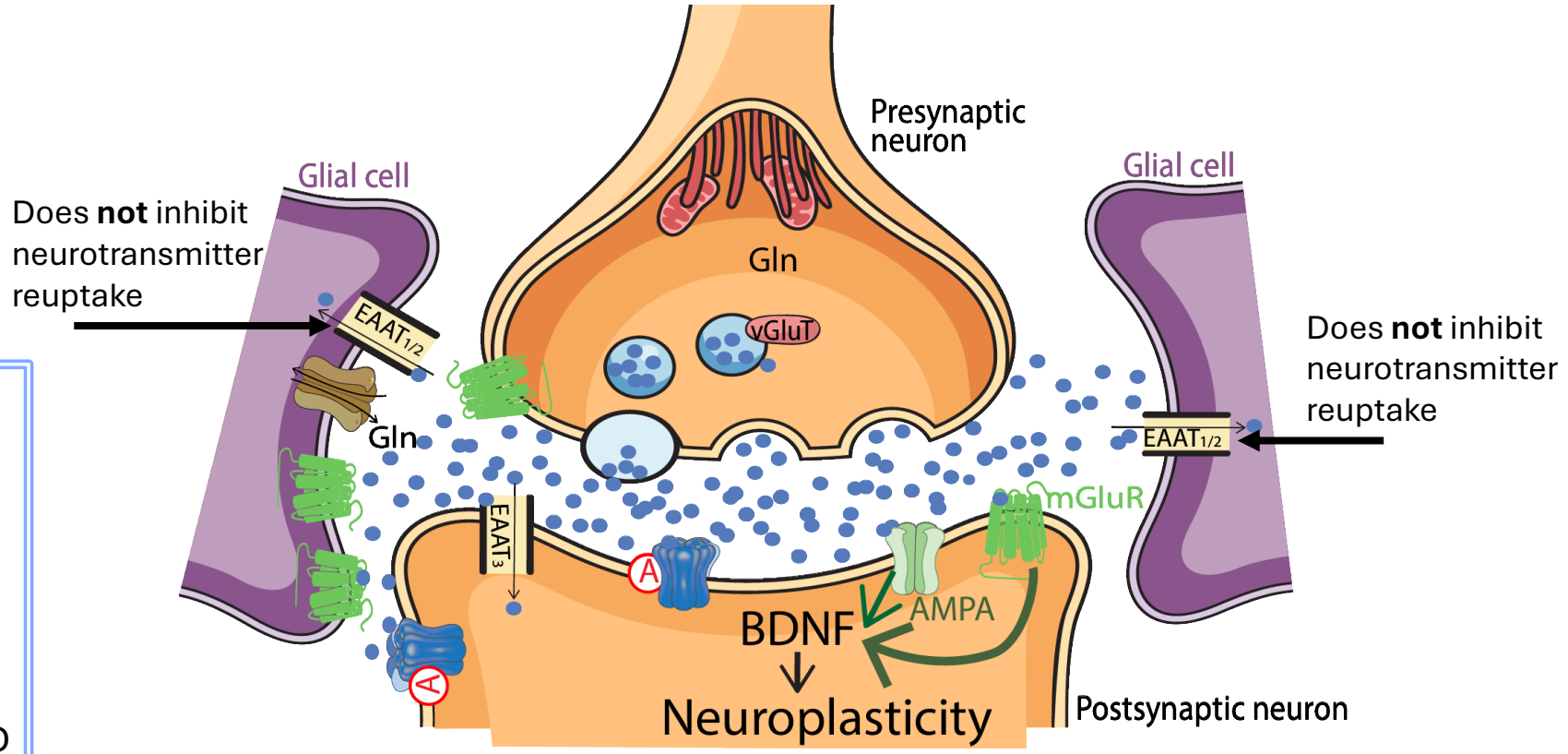
Large difference with mode of administration

High variability of solid/liquid oral forms

Fourcade EW, et al. The Basic and Clinical Pharmacology of Ketamine. In: Sanjay JM, Karate CA Jr (Eds). *Ketamine for Treatment-Resistant Depression: The First Decade of Progress*. 2016: 13-29, Adis. Marland S, et al. *CNS Neurosci Ther. 2013;19(6):381-9*. McIntyre RS, et al. *Am J Psychiatry*. 2021;178(5):383-99. Zhao X, et al. *Br J Clin Pharmacol*. 2012;74(2):304-14.

Esketamine, Ketamine, and Dextromethorphan Are NMDA-Receptor Allosteric Antagonists

- Esketamine is approved for TRD
- Ketamine is used off-label for TRD
- Dextromethorphan (with bupropion) was being evaluated in TRD



- Antagonists bind NMDA receptor, initially reducing glutamate transmission
- Increases glutamate reuptake and release
- Other glutamate receptors more activated and increase neuroplasticity

Globe Newswire. Axsome Therapeutics [press release]. 2020. Accessed May 12, 2025. https://www.biospace.com/axsome-therapeutics-announces-topline-results-of-the-stride-1-phase-3-trial-in-treatment-resistant-depression-and-expert-call-to-discuss-clinical-implications. Niciu, MJ. *Pharmacology Biochemistry and Behavior*. 2012;100(4): 656-664. Duman RS. *F1000Res*. 2018;7:F1000 Faculty Rev-659.

Challenges of Ketamine and Esketamine

Schedule III controlled substance

Esketamine

- REMS certification of staff, provider and site required
- Patient must be monitored for at least 2 hours
- REMS paperwork must be submitted for every treatment
- Driving restrictions
- Standardized doses
- Self-administered nasal spray

Risks

- Sedation
- Dissociation
- Respiratory depression

Ketamine

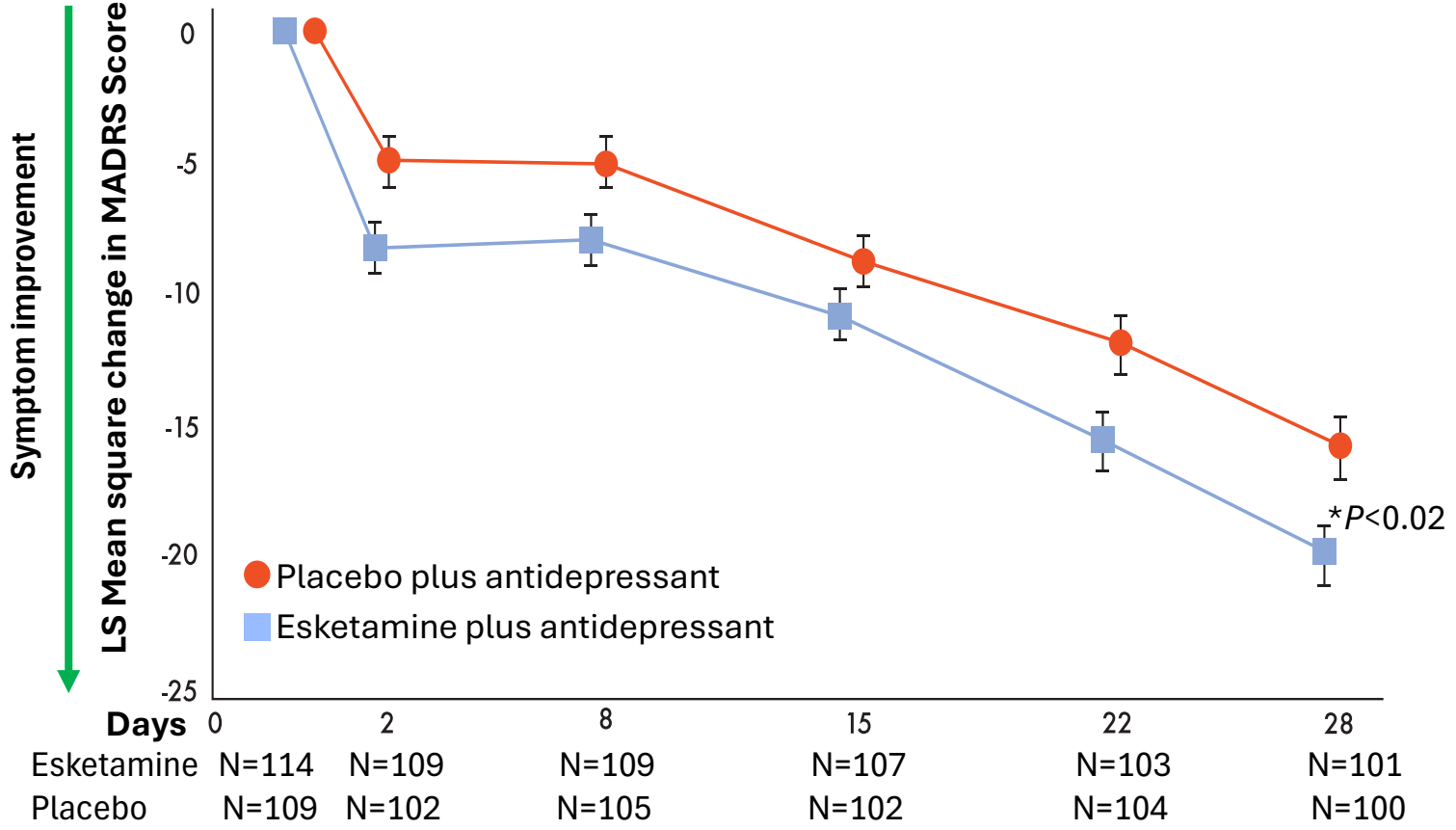
- Not FDA-approved for any mental health condition
- Insurance reimbursement may not be available
- No standardized monitoring
- No standardized dosing
- At-home dosing raises the risk of nonmedical use/diversion

Although both treatments may be extremely useful, both have challenges to work through

Esketamine [prescribing information]. Drugs@FDA: FDA-Approved Drugs. Accessed May 10, 2025. McIntyre RS, et al. *Am J Psychiatry*. 2021;178(5):383-99.

Trial of Esketamine for Adjunctive TRD Treatment

In the TRANSFORM-2 trial, adjunctive esketamine decreased depressive symptoms significantly more than adjunctive placebo and 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%

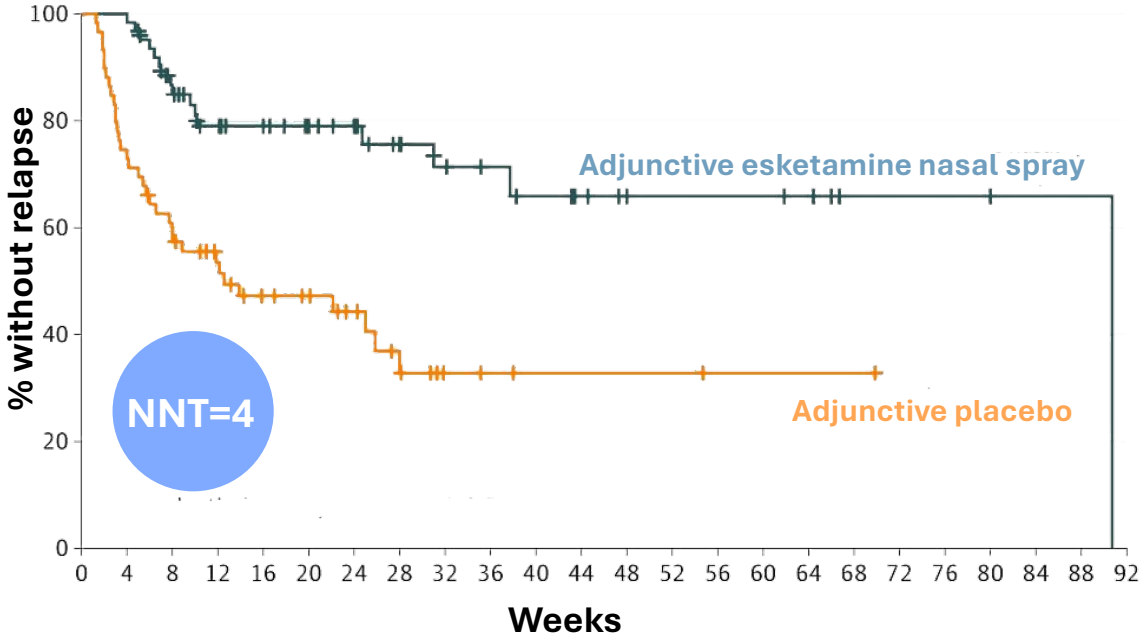
Popova V, et al. *Am J Psychiatry*. 2019;176(6):428-38.

Esketamine for Adjunctive TRD Treatment Response and Remission in SUSTAIN-1 Trial

Patients who responded to treatment were

70% **less likely to relapse**

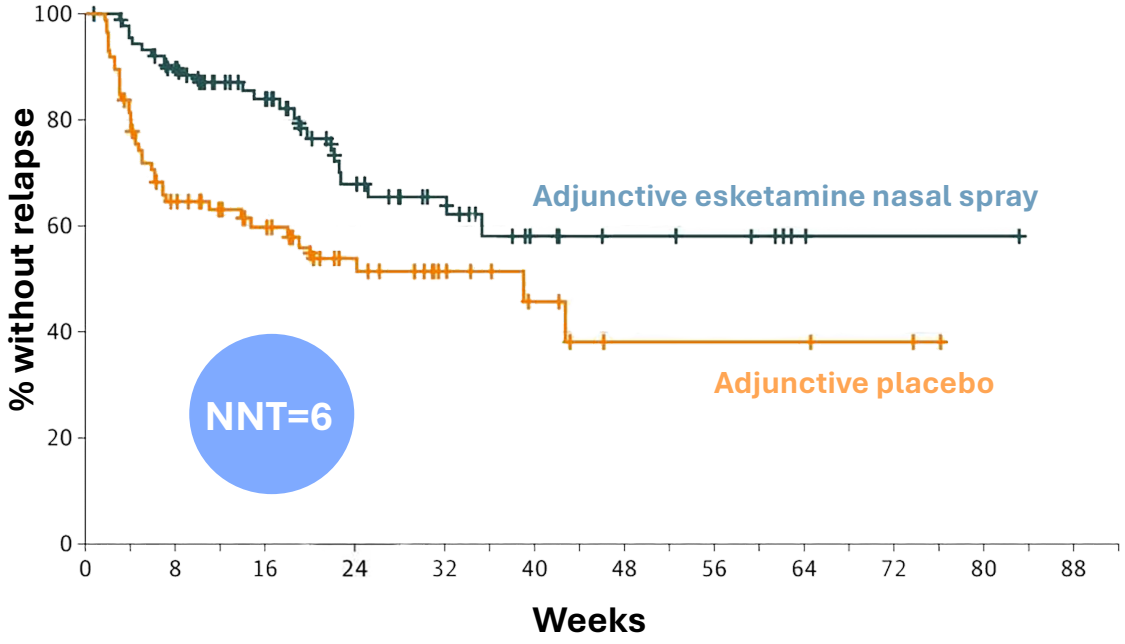
HR=0.30 (95% CI: 0.16-0.55), *P*=.003



Patients who reached remission were

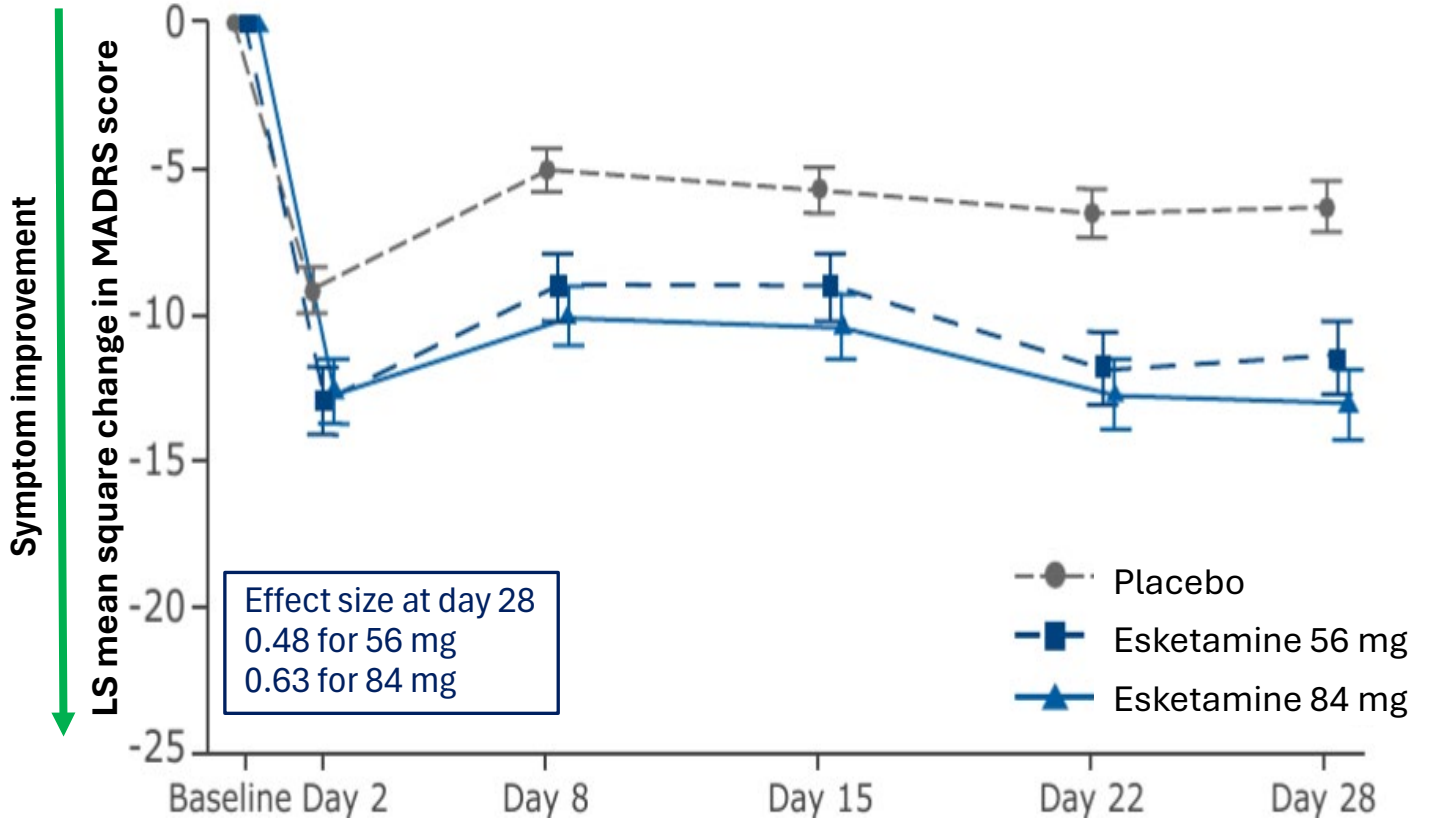
51% **less likely to relapse**

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



Daly E, et al. *JAMA Psychiatry*. 2017;76(9):893-903.

Phase 4 Study of Esketamine Monotherapy for TRD



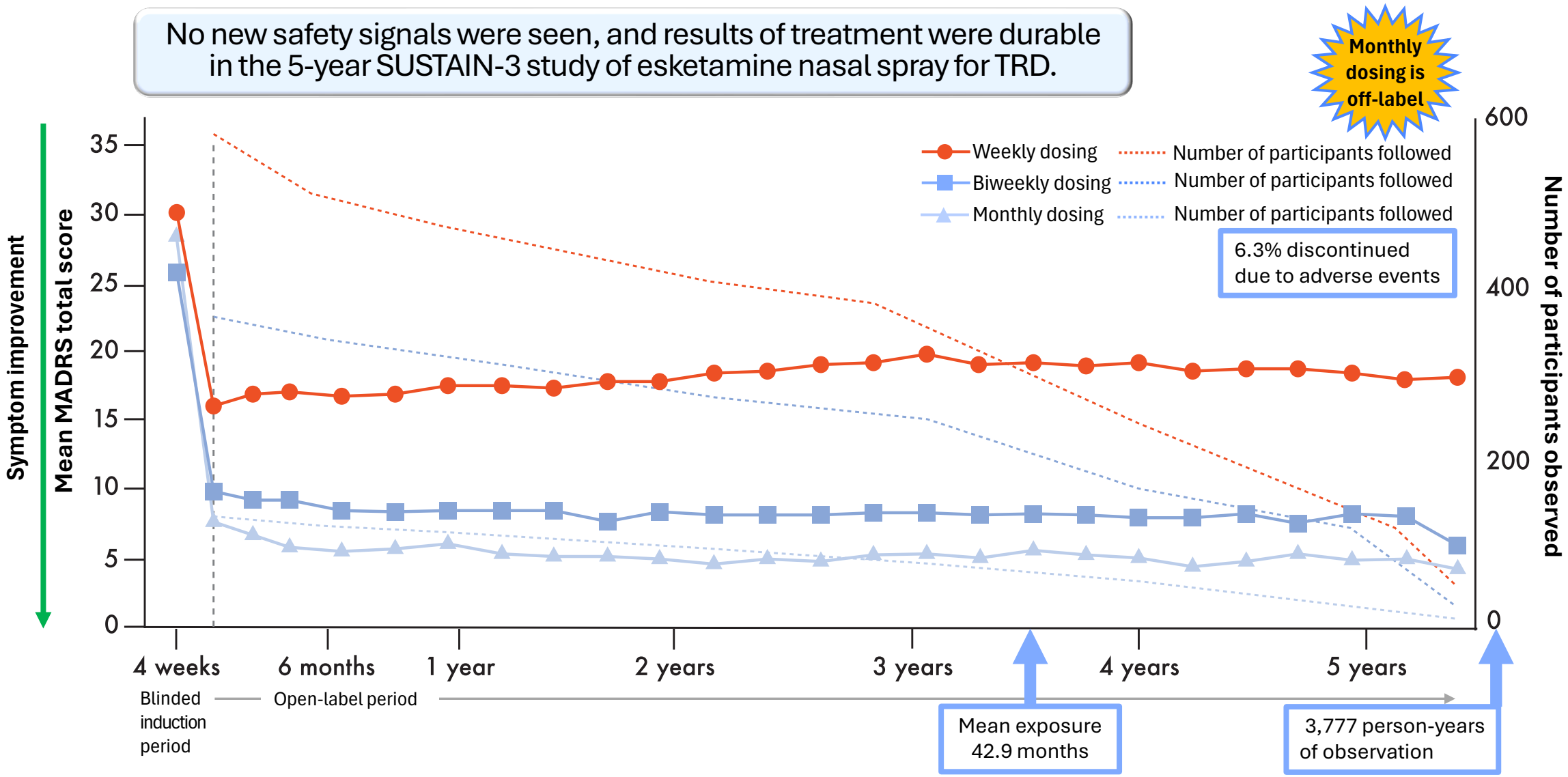
Treatment of TRD with esketamine nasal spray 56 mg or 84 mg reduced MADRS scores by 5 and 7 points, respectively, compared with placebo.

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

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

Long-Term Safety Study of Esketamine for TRD

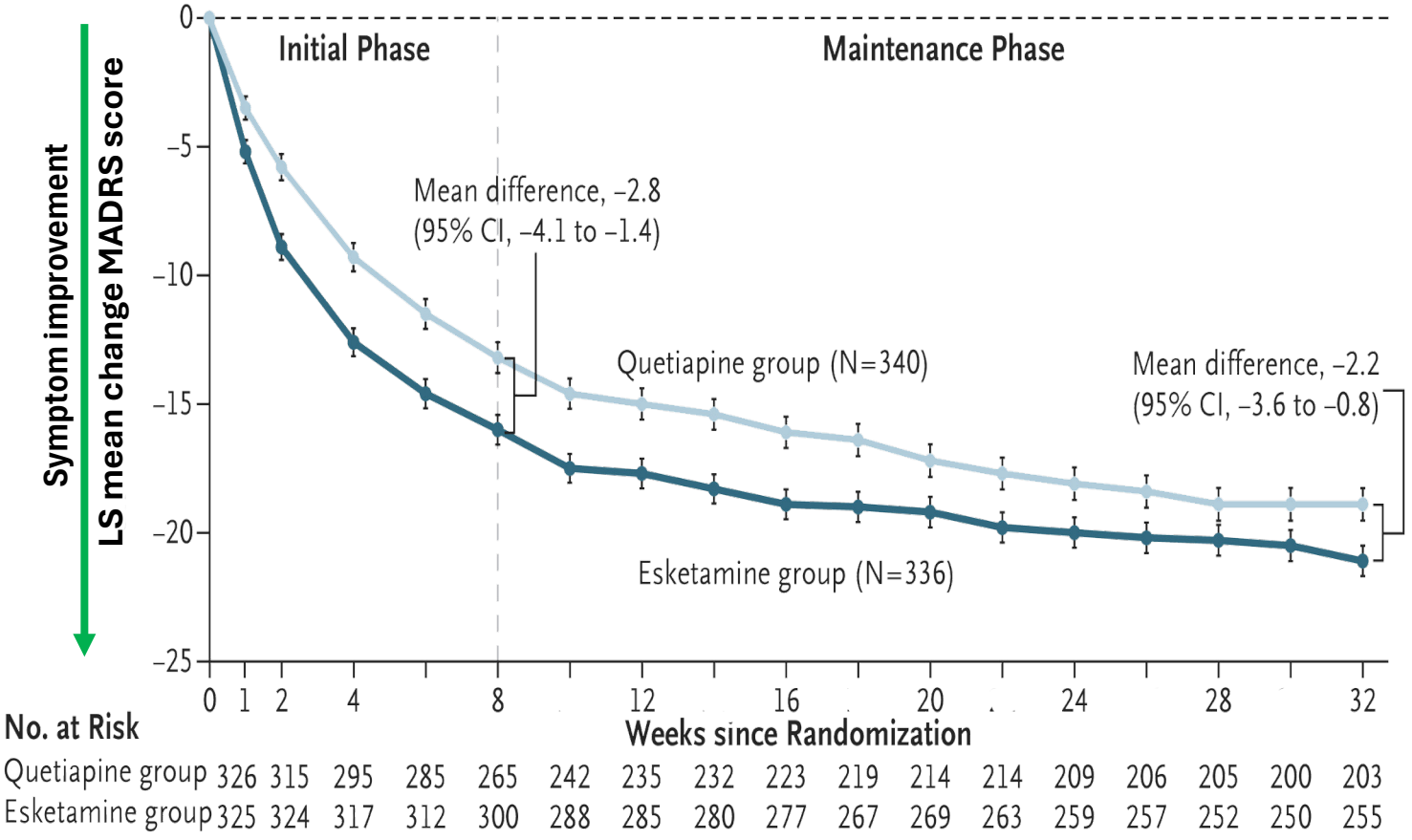
No new safety signals were seen, and results of treatment were durable in the 5-year SUSTAIN-3 study of esketamine nasal spray for TRD.



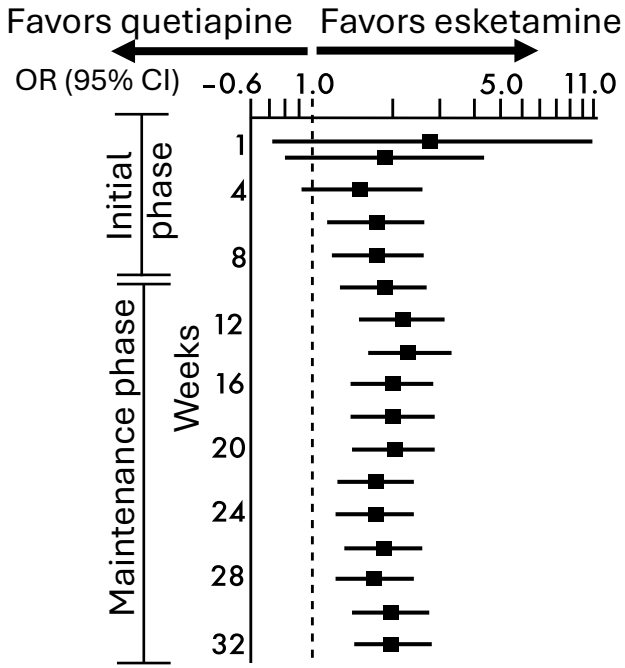
Zaki N, et al. *Neuropsychopharmacol.* 2023;48:1225–1233. Zajecka J, et al. Presented at 2024 Psych Congress Elevate.

Open-Label Head-to-Head Study of Adjunctive Esketamine vs Adjunctive Quetiapine-XR

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



Esketamine treatment was superior to quetiapine at all time points



More adverse events with esketamine

	Esketamine	Quetiapine
All AEs	92%	78%
Serious AEs	6%	5%
D/C due to AEs	11%	4%

Reif A, et al. *N Engl J Med*. 2023;389:1298-309.

Appropriate Risk Management for Esketamine

Real-world respiratory depression after esketamine treatment

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

→ 8 >1 day after treatment (8%)
30 unreported date (31%)
excluded from analysis (39%)

58 on treatment day (60%)

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

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

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

36 of 50** were taking concomitant medications

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 cries could not be attributed to these

DEA = Drug Enforcement Administration; RR = Respiratory rate; SpO2 = oxygen saturation; Chepke C. et al. Int J Neuropsychopharmacol.2024; 27(12): pyae058.

Comparison of Glutamatergic Agents Used for Depression

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

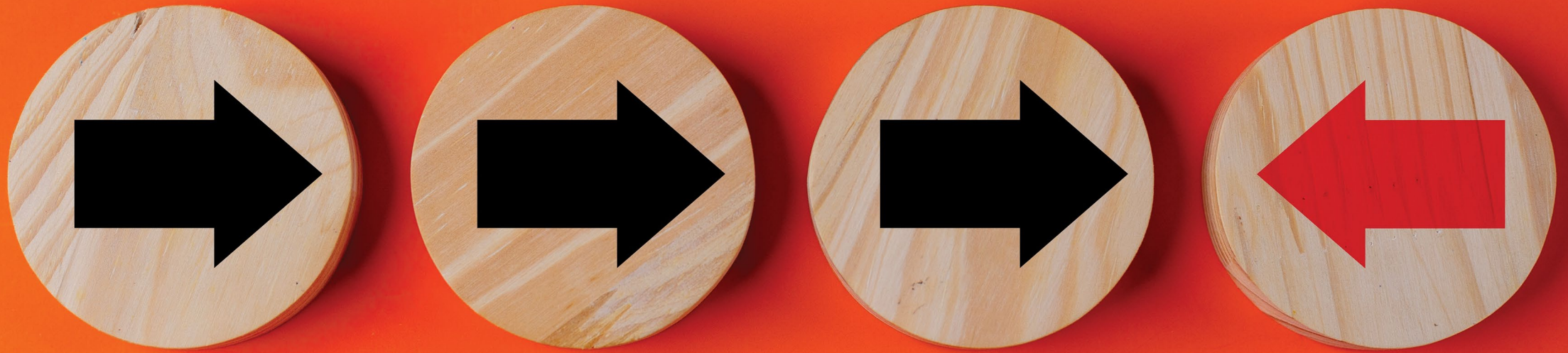
Key Learning Points

- ✓ **Olanzapine** is a **dopamine D_2** and **serotonin 5-HT_{2A}** receptor **antagonist** and **fluoxetine** is an **SSRI**, that in combination are thought to have a **dual mechanism** of action

- ✓ In the phase 4 clinical trial that led to the approval of intranasal **esketamine as monotherapy for TRD**, doses of **56 mg** and **84 mg**, respectively, reduced MADRS scores by **5 and 7 points more than placebo**

- ✓ In a head-to-head, open-label trial of **adjunctive intranasal esketamine** resulted in a **72% higher likelihood** of being **relapse-free at week 32 compared with quetiapine-XR**

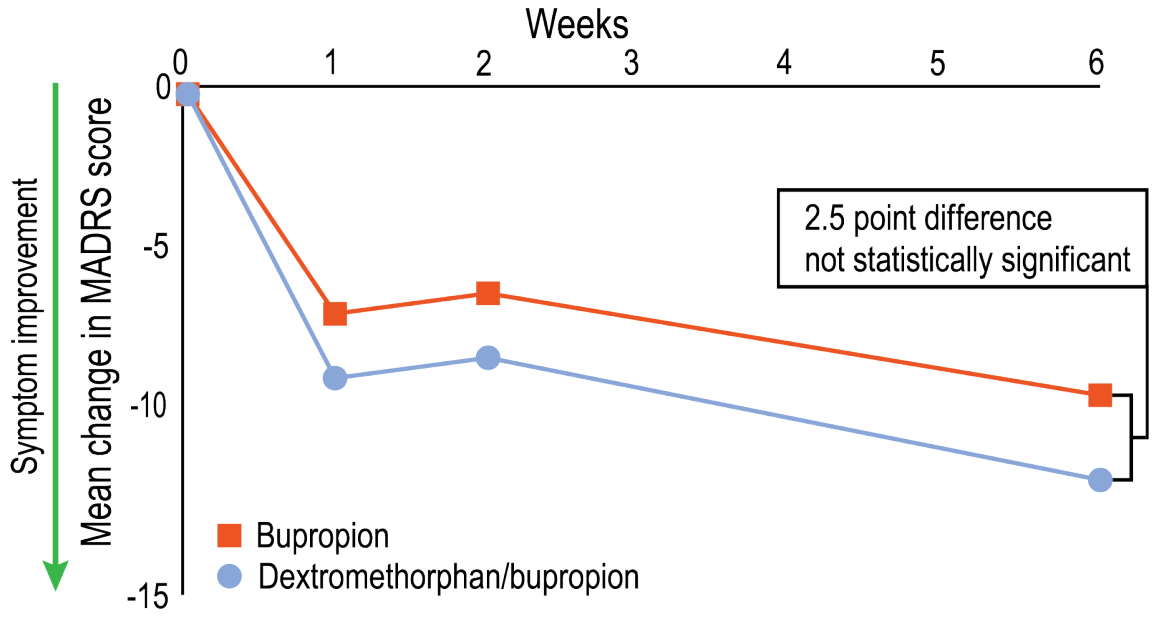
Other Treatment Considerations for Treatment-Resistant Depression



Dextromethorphan/Bupropion Was Studied for TRD

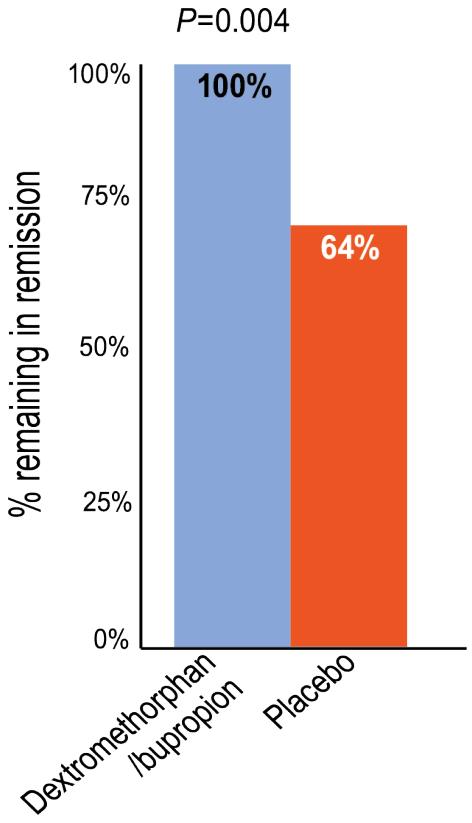
Dextromethorphan is a noncompetitive NMDA receptor antagonist and bupropion slows metabolism of dextromethorphan

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



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

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



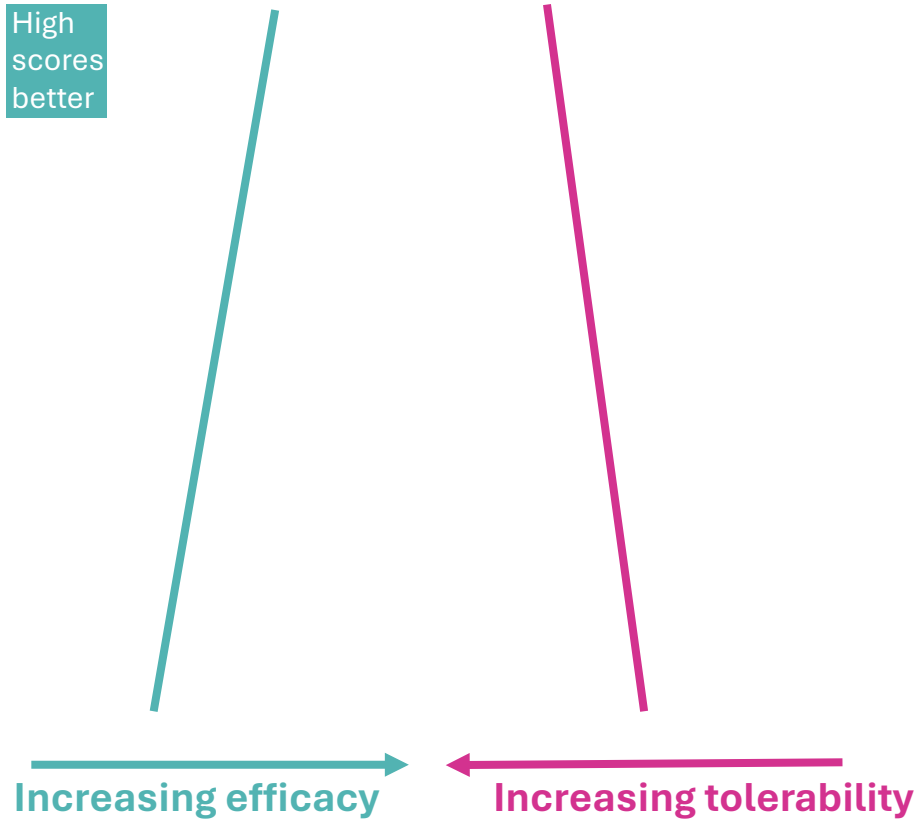
- All previously achieved remission with open-label dextromethorphan/bupropion
- Double blind switch to placebo or continuation (N=22 each)
- Continuation vs switch to placebo was significantly less likely to result in relapse over 6 months

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

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

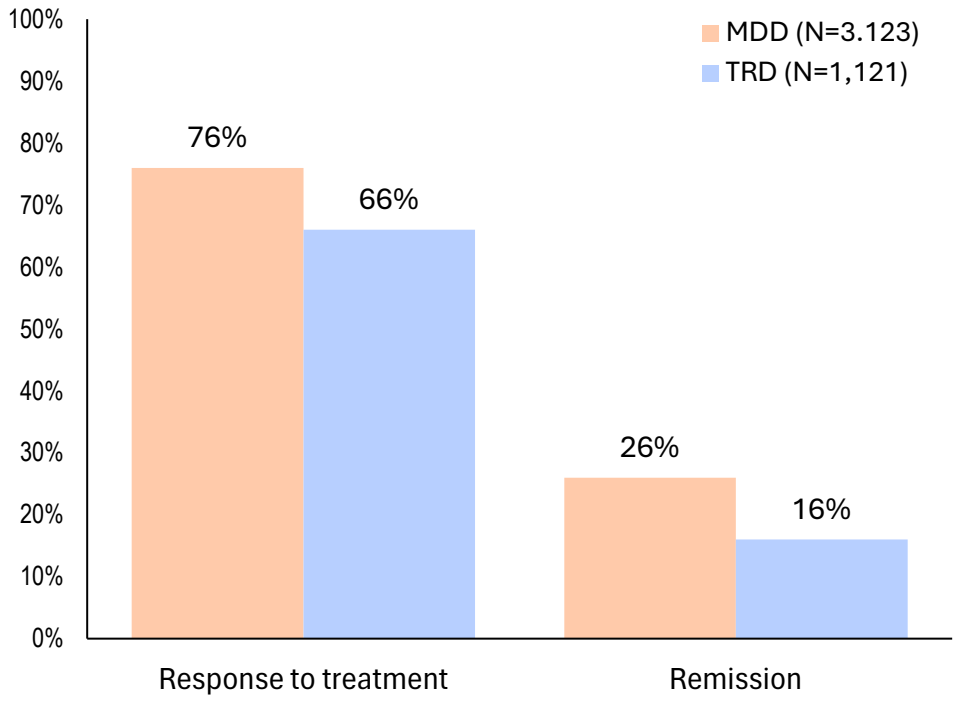


Mutz J, et al. *BMJ*. 2019;364:l1079.

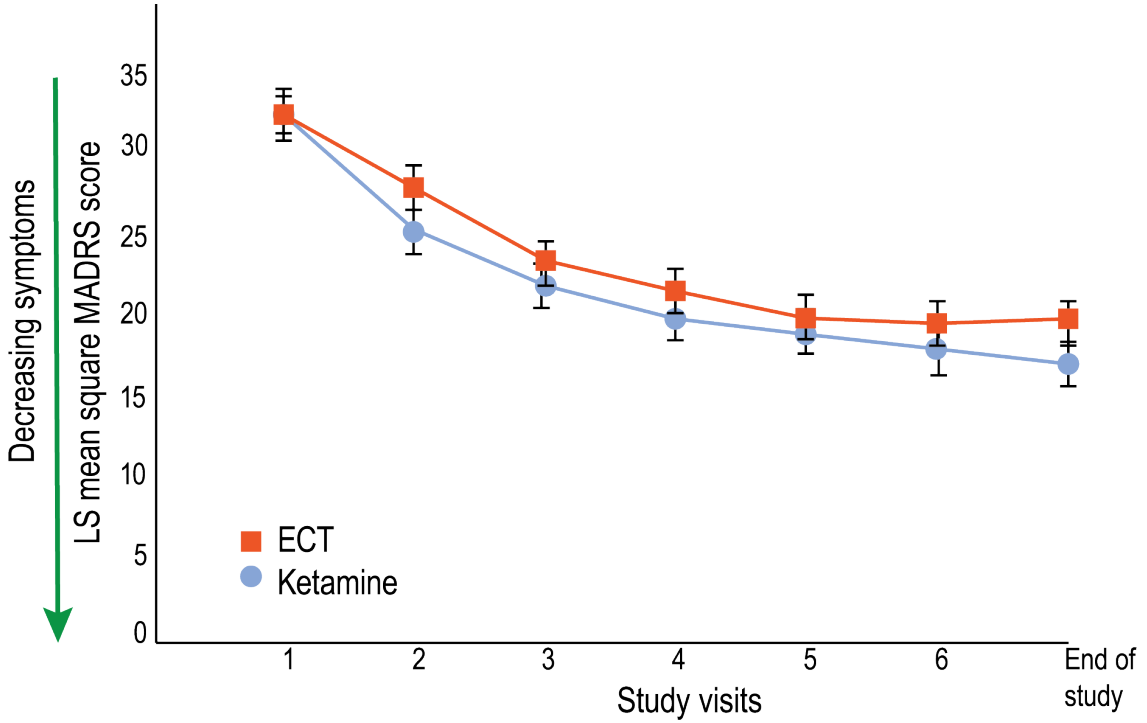
Electroconvulsive Therapy (ECT) for TRD

Noninvasive, requires anesthesia, pretreatments, and brief in-patient stay

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



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



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

Safety and Tolerability of ECT

Data for AEs in ECT is scarce

2016 Narrative Review of ECT AEs			
Adverse event		**Rate**	**Notes**
Muscle pain		Common	Can be pre-treated with muscle relaxants
Headache		26%-85%	Transient
Anxiety, confusion, restlessness, disorientation, cognitive complaints		8%-20%	All reported neurologic AEs are reported as transient
Seizures		1%-2%	
Other neurologic (aphasia, hemiparesis)		<1%	
Cardiovascular (e.g., asystole, ECG anomalies, myocardial infarction)		2%-55%	More common with cardiovascular disease
Psychiatric	Treatment-emergent mania	3%-10%	
Nausea due to anesthesia is frequent, varies by, can be pre-treated			

AEs Reported in 2023 Trial Comparing ECT to Ketamine		
	ECT	Ketamine
Headache	7%	8%
Gastrointestinal	5%	7%
Hypertension	2%	3%
Muscle pain	5%	0.5%
Suicidal ideation	2%	1%
Any AE	32%	25%

- German single-site study of 157 patients treated with >3,000 ECT sessions over 3 years (any mental health disorder
  - 30% of patients had a mild adverse event
  - 1.9% had a serious adverse event
  - 6.1% of ECT sessions resulted in an AE
  - 67% had depression

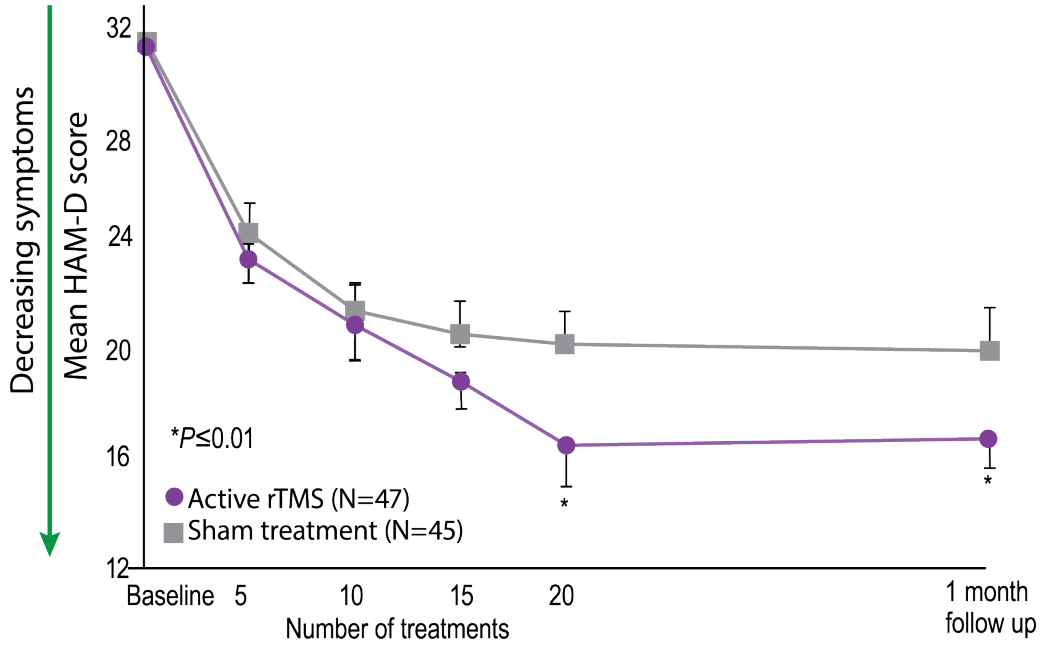
Andrade C, et al. *Psychiatr Clin N Am. 2016;39* :513–30. Nygren A, et al. *BJPsych Open*. 2023;9(2):e35. Anand A, et al. *N Engl J Med*. 2023;388:2315-25.

Repetitive Transcranial Stimulation for TRD

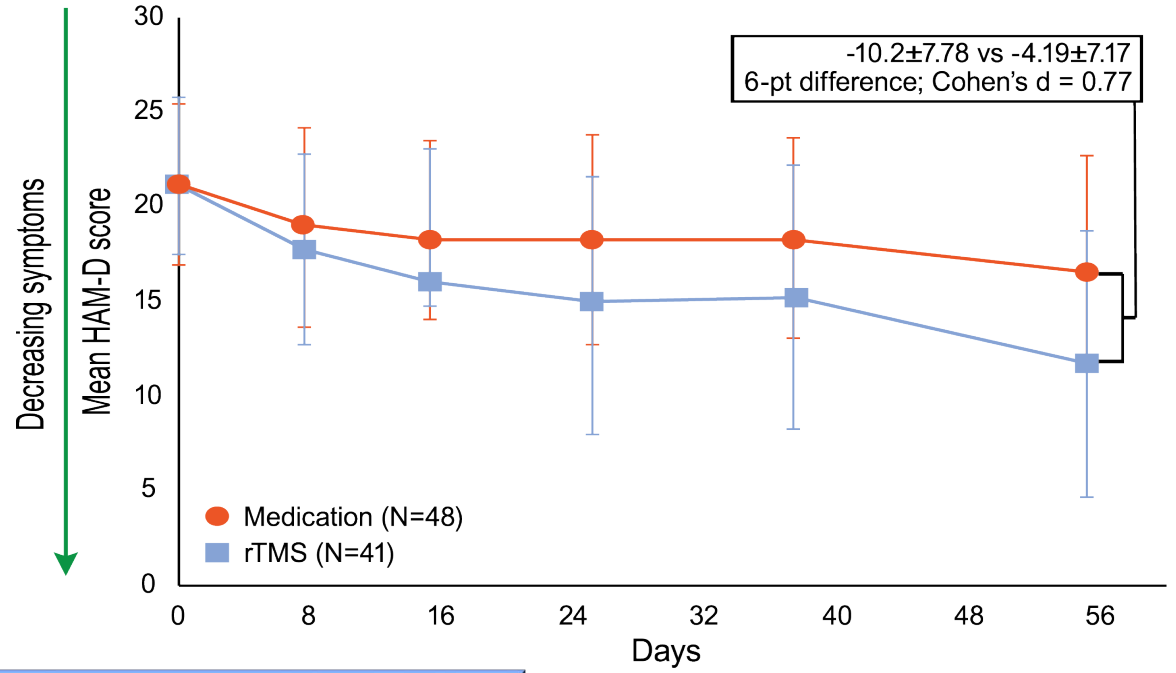
Noninvasive, out-patient treatment without anesthesia

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



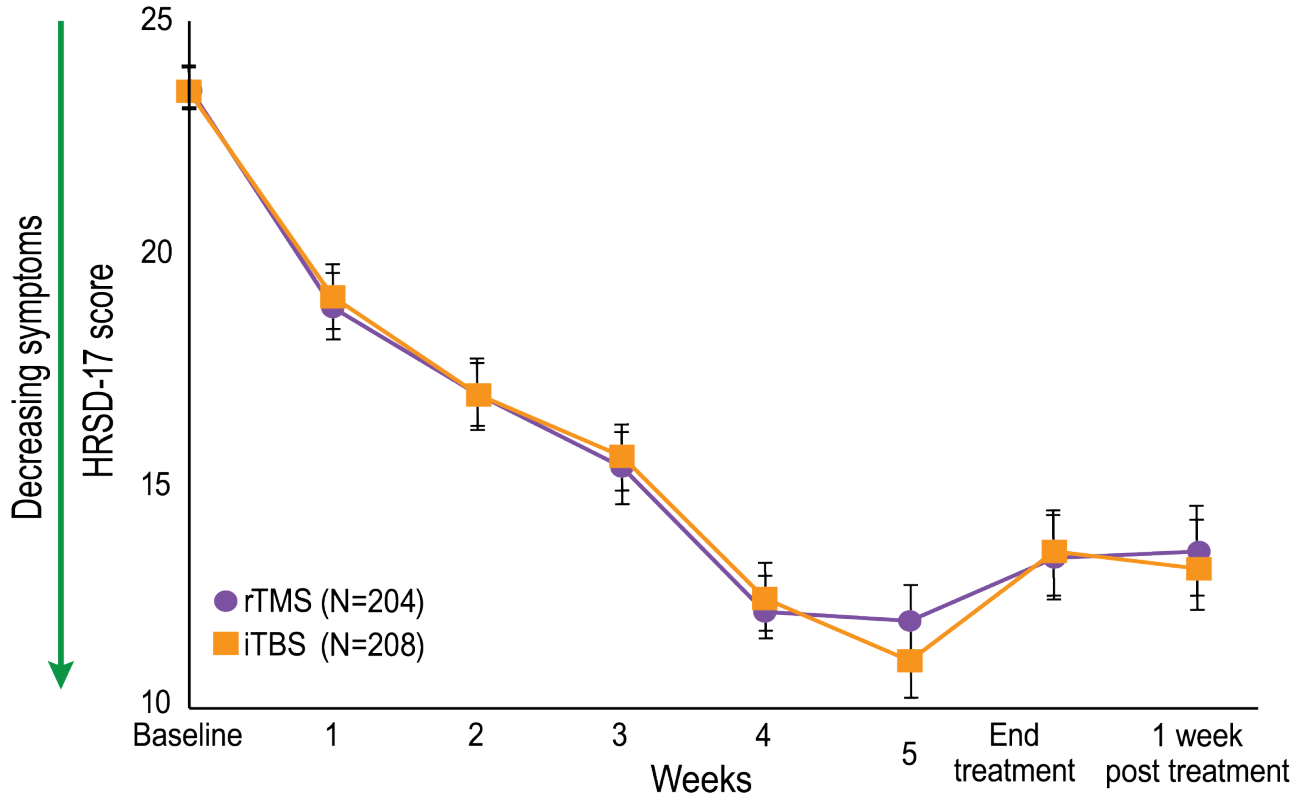
Meta-analysis of 17 studies confirms efficacy of rTMS

rTMS = Repetitive transcranial magnetic stimulation; TCA = Tricyclic antidepressant. Carpenter LL, et al. *Brain Stimul*. 2017;10:926–33.Dalhuisen I, et al. *Am J Psychiatry*. 2024;181(9):806-14. Morriss R, et al. Efficacy and Mechanism Evaluation, No. 12.02. Accessed May 12, 2025. https://www.ncbi.nlm.nih.gov/books/NBK612316/

Intermittent Theta Burst (iTBS) for TRD

rTMS with specific stimulation pattern localized over dorsolateral prefrontal cortex in shorter treatment sessions compared with rTMS

iTBS has been shown to be noninferior to rTMS in a large head-to-head trial



AEs of iTBS and rTMS in this trial

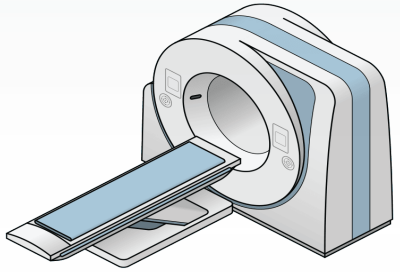
AE occurring in >2%	rTMS	iTBS
Headache	64%	65%
Nausea	11%	7%
Dizziness	4%	9%
Infection or other illness	23%	22%
Fatigue	7%	8%
Insomnia	7%	5%
Anxiety/agitation	4%	4%
Back or neck pain	3%	3%

Blumberger DM, et al. *Lancet*. 2018; 391: 1683–92

SAINT iTBS Protocol

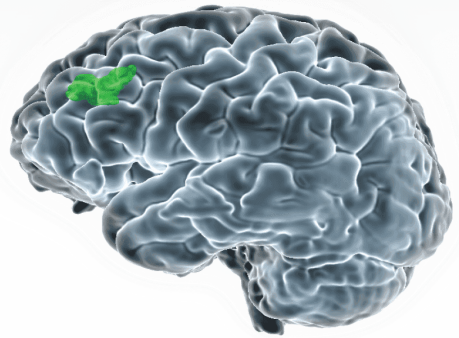
Step 1

MRI Brain Scan



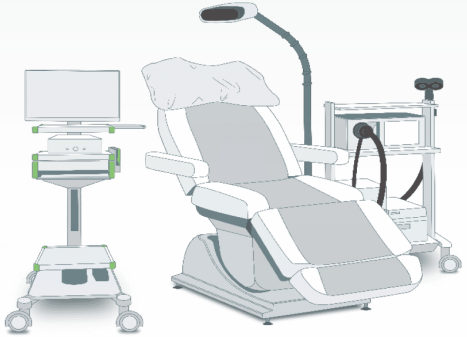
Step 2

Individual Target Identification



Step 3

Stimulation series



- 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.

iTBS = Intermittent theta burst. Image credit: Magnus Medical. Accessed November 17, 2024. https://www.magnusmed.com/.

Cole EJ, et al. *Am J Psych*. 2020;177(8):716-726.

Vagus Nerve Stimulation

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

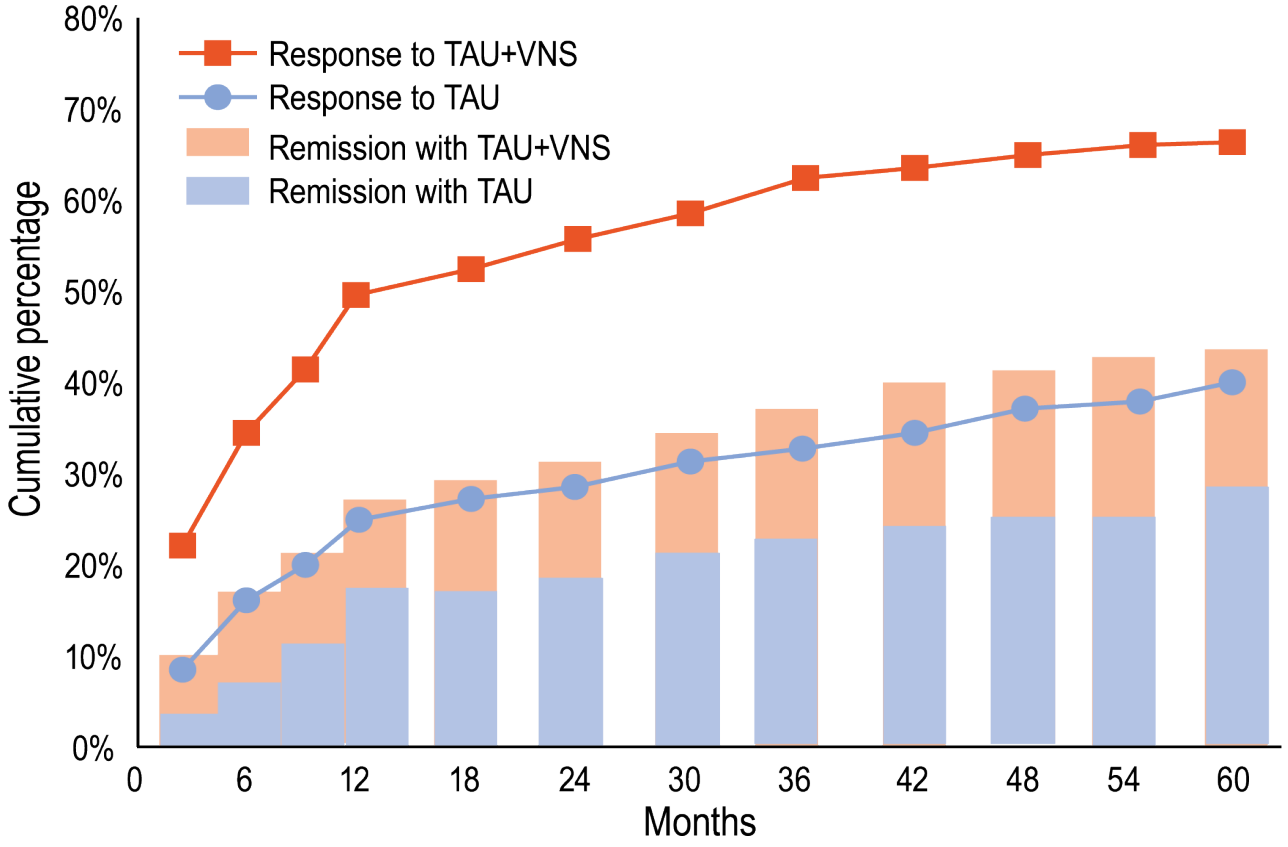
Runs on set cycle unless manually adjusted

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

Image: Accessed March 10, 2025. https://www.rch.org.au/neurology/patient_information/vagus_nerve_stimulation/
American Association of Neurological Surgeons. Vagus Nerve Stimulation. Accessed November 16, 2024. https://www.aans.org/patients/conditions-treatments/vagus-nerve-stimulation/. Kamel LY, et al. *J Neurol Sci.* 2022;434:120171.

Clinical Trial of Adjunctive Vagal 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%

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

- Across studies and indications, the most common AEs have been
  - Voice alteration
  - Cough
  - Dyspnea
  - Dysphagia
  - Neck pain
  - Paresthesia

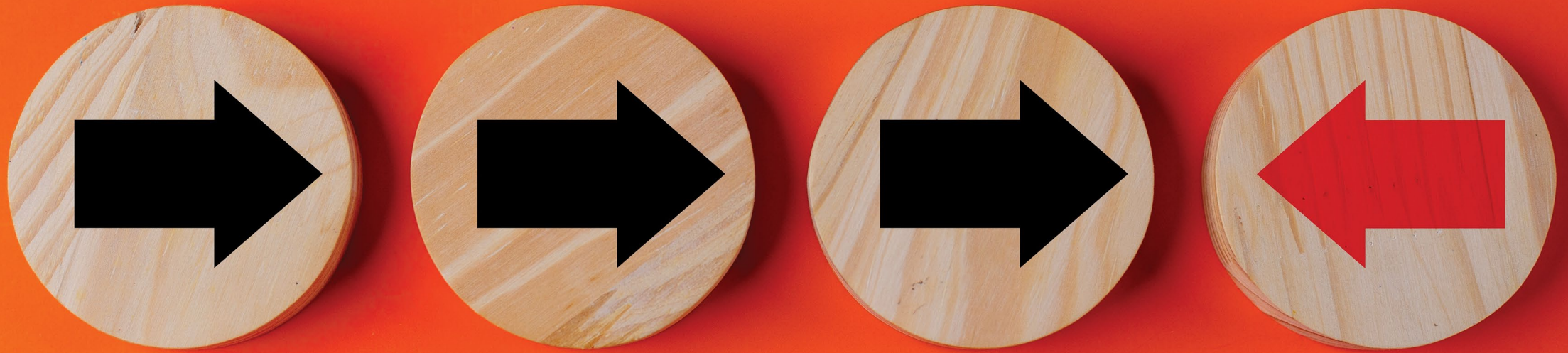
TAU = Treatment as usual; VNS = Vagal nerve stimulation. Aaronson ST. *Am J Psychiatry*. 2017;174:640.

Key Learning Points

- ✓ Clinical trials and meta-analyses show that **FDA-approved neuromodulation therapies are superior to sham treatment**

- ✓ **ECT, rTMS, iTBS, and VNS** are all **FDA-approved** for treatment of **TRD**

Panel Discussion
Personalized Treatment Planning in TRD



Patient-Specific Considerations

COMORBIDITES

Psychiatric and medical

SUPPORT SYSTEMS

Occupational, family, friends

TREATING OR REFERRING

Who is involved in care?

TREATMENT ACCESSIBILITY

Is treatment sustainable given costs?

Strategies for Shared Decision-Making

Two adequate trials of monoaminergic antidepressants and not in remission?

Time to discuss TRD options!

- ✓ Patient preferences
  - ✓ Medication with different MOA?
  - ✓ Neuromodulation?
- ✓ Be sure to discuss reimbursement, cost, convenience of both options
- ✓ Inform patient
  - ✓ Will you provide interventions
  - ✓ Or refer to a treatment center

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
  - Olanzepine/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

QUESTIONS?