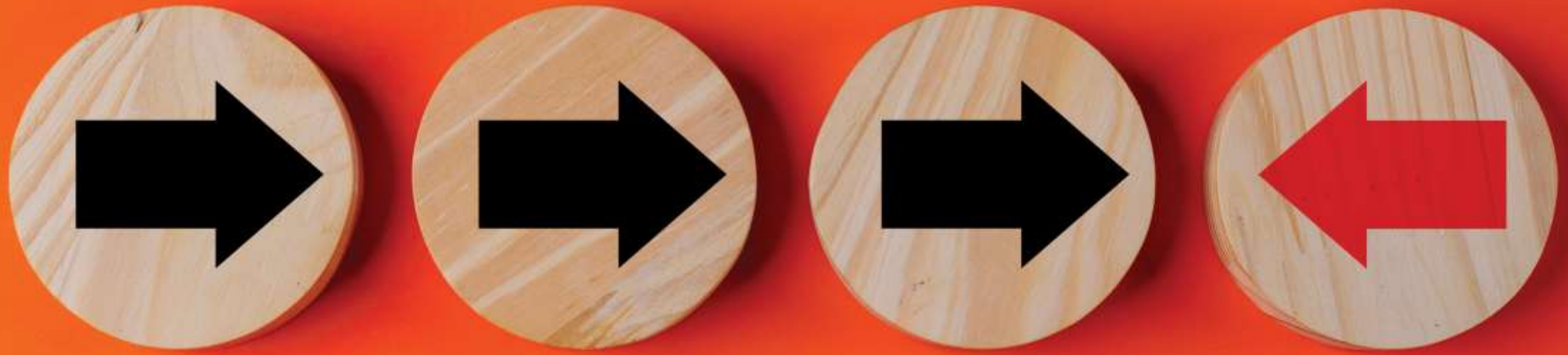
Treating "Treatment-Resistant Depression: Bringing Hope with Glutamatergic Antidepressants



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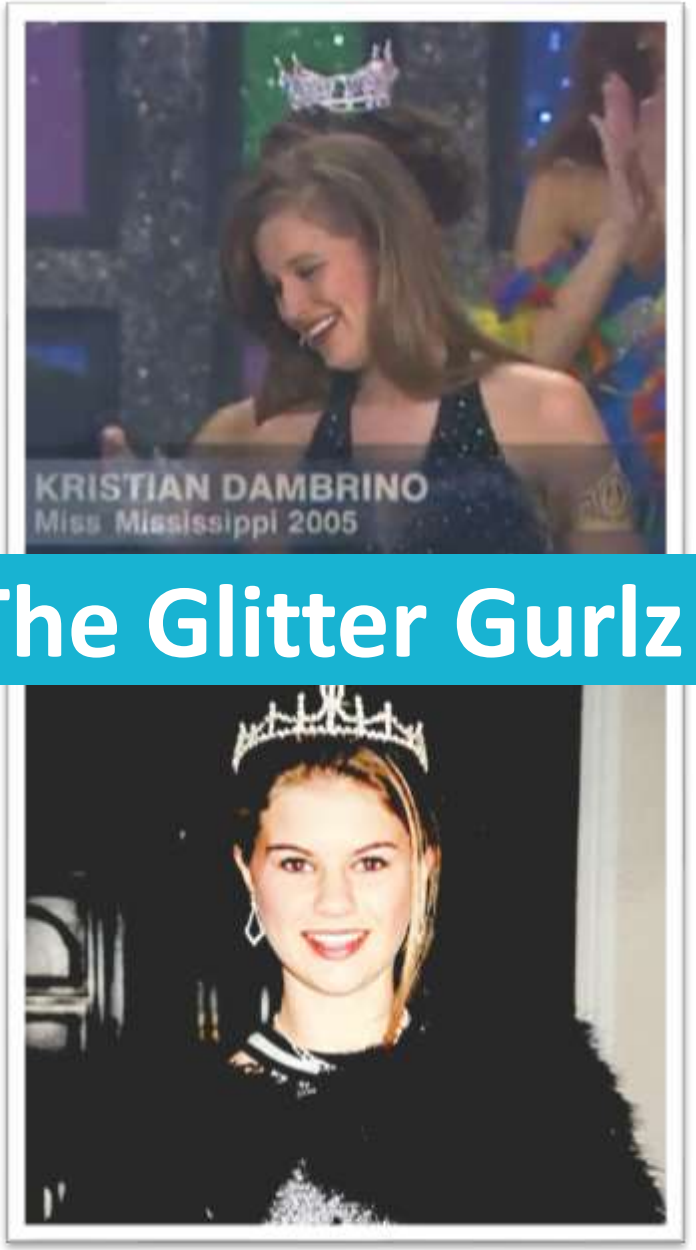


Disclosure

- 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)

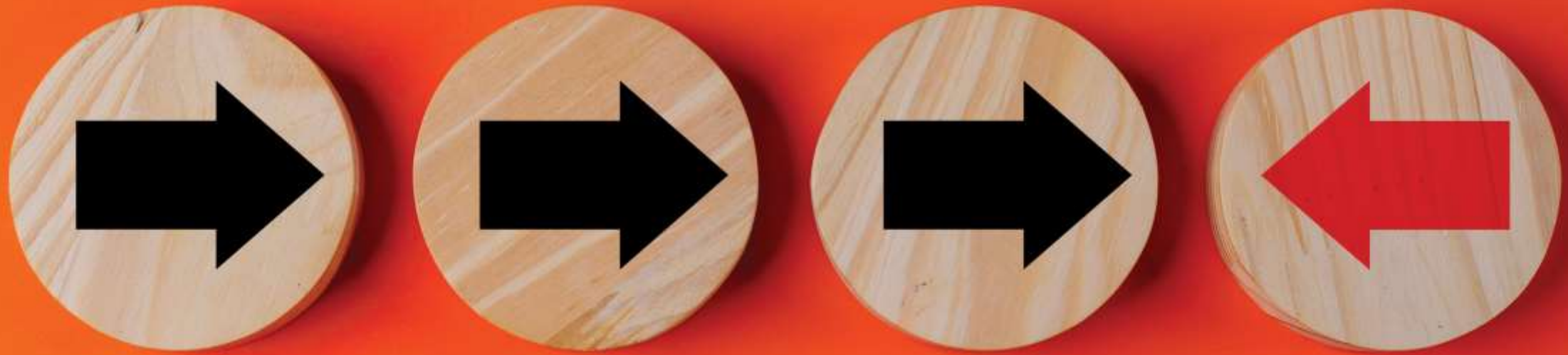
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity

- This activity has been independently reviewed for balance

Learning Objectives

- Describe the shortcomings associated with monoaminergic antidepressants for patients with major depressive disorder (MDD), including delayed response, nonresponse, and treatment resistant depression (TRD)
- Evaluate the mechanism of action and latest clinical and real-world data associated with newer glutamatergic and neuromodulation therapies for TRD
- Implement patient-centered strategies for personalized treatment planning, including shared decision-making, in patients with TRD

Understanding Treatment-Resistant Depression

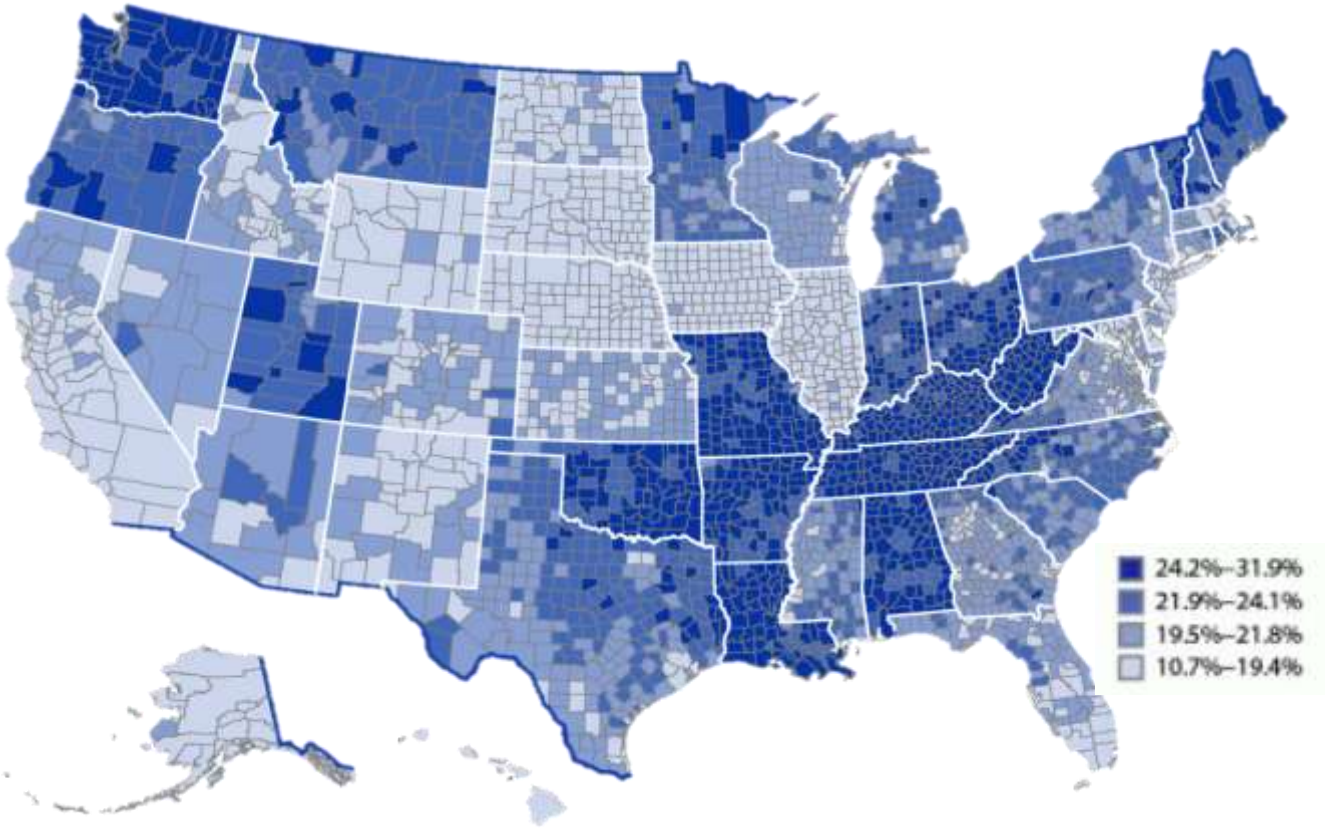


What Is Your *Why*?

Seriously – you could be at Disney right now and you are learning about a very *depressing* topic instead…

America: Land of the Free and *Depressed*

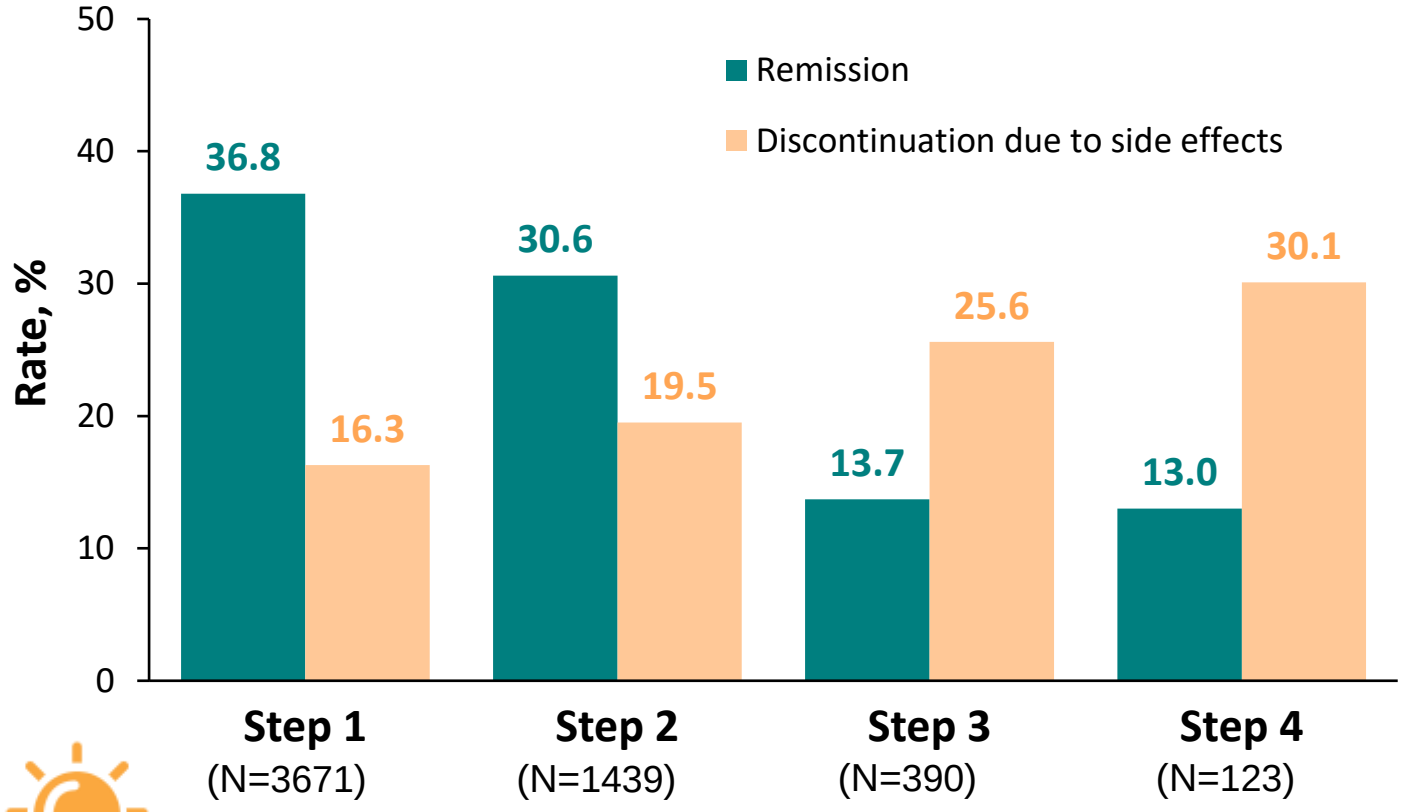
Even Disney Characters Experience Depression!



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

National Institute of Mental Health website. Major Depression. Accessed October 3, 2024 https://www.nimh.nih.gov/health/statistics/major-depression. Hasin DS, et al. *JAMA Psychiatry.* 2018;75(4):336-346. Lee B, et al. *MMWR Morb Mortal Wkly Rep.* 2023;72:644–650.

How STAR*D Informed 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**

Step1	Citalopram	
	Path A	Path B
Step 2	Add bupropion or buspirone or switch to bupropion, sertraline, or venlafaxine	Switch to or add cognitive therapy
Step 3	Add lithium or T3 or switch to nortriptyline or mirtazapine	Use 2A options
Step 4	Switch to tranylcypromine or venlafaxine with mirtazapine	Use Step 3A
		Use Step 4A

What Makes it TRD?

- Subset of MDD
- ≥2 qualifying unsuccessful monoaminergic antidepressant trials within the same depressive episode

✓ **From the same or different classes**
✓ **Of adequate duration (6-8 weeks)**
✓ **Of adequate/therapeutic dose**

STAR*D = Sequenced Treatment Alternatives to Relieve Depression; T3, triiodothyronine.

Rush AJ, et al. *Am J Psychiatry.* 2006;163(11):1905-17. Voineskos ,et al. Neuropsychiatric Disease and Treatment. 2020;16,:221–234.

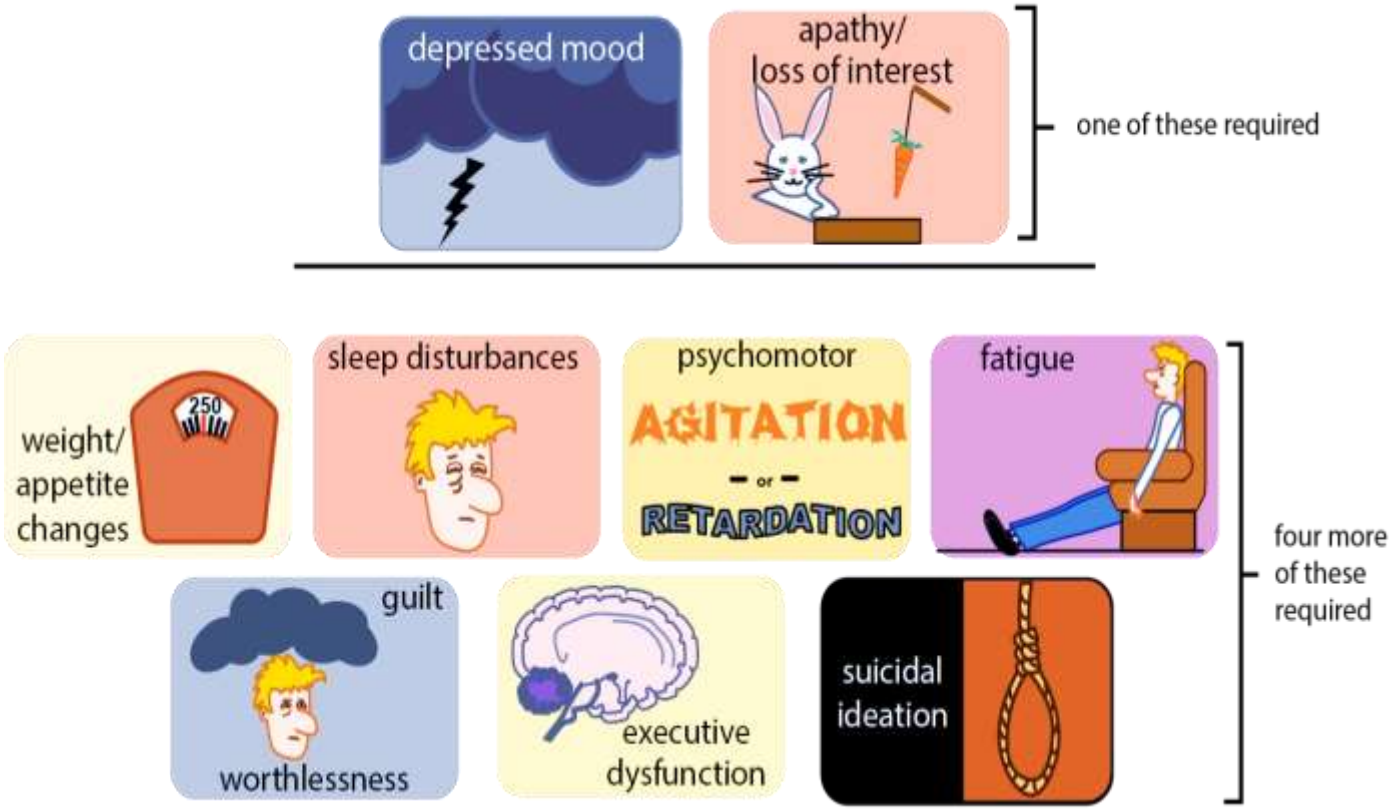
What (Kinda) Rhymes with TRD? Heterogeneity.

MDD is a **highly heterogeneous syndrome with** weak correspondence to its neurobiological + genetic substrates

DSM-5 recognizes at least **256 unique symptom presentations** meeting MDD1 criteria

MDD is **unstable over time** and the longitudinal course differs widely among patients

~**75% of MDD patients have at least 1 comorbid neuropsychiatric illness,** and transdiagnostic mechanisms contribute to the biology underlying variable presentations



American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Publishing; 2013.
Image Reference: https://www.neiglobal.com/Members/MonthInPsychopharmPost/tabid/509/topic/20795/Default.aspx

Risk Factors for and Risks of TRD

Early-onset depression (pre-adulthood) linked to higher treatment resistance

- **More persistent, recurrent episodes** that require **stronger treatment interventions**
- Associated with **higher chronicity and lower response to monoaminergic antidepressants**

Remission becomes less likely as the number of depressive episodes increases

- Recurrent episodes are linked to **progressive neural changes, including**
  - **Glutamate dysregulation**
  - **Reduced neuroplasticity**
- Chronic, recurrent depression leads to higher TRD rates and poorer treatment outcomes

Often complicated by comorbidities, including GAD, panic disorder, and OCD

- Increased stress reactivity, HPA-axis dysregulation, and differential neurotransmitter involvement
- Anxiety reduces the likelihood of remission, even in those with initial treatment response

GAD = generalized anxiety disorder; HPA = hypothalamic-pituitary axis; OCD = obsessive-compulsive disorder. Cepeda MS, et al. *J Affect Disord.* 2018;234:308-315. Dudek D, et al. *Psychiatr Pol.* 2010;44(5):701-712. Souery D, et al. *J Clin Psychiatry.* 2007;68(7):1062-1070. Warden D, et al. *J Clin Psychiatry*. 2007;68(12):1907-1913.

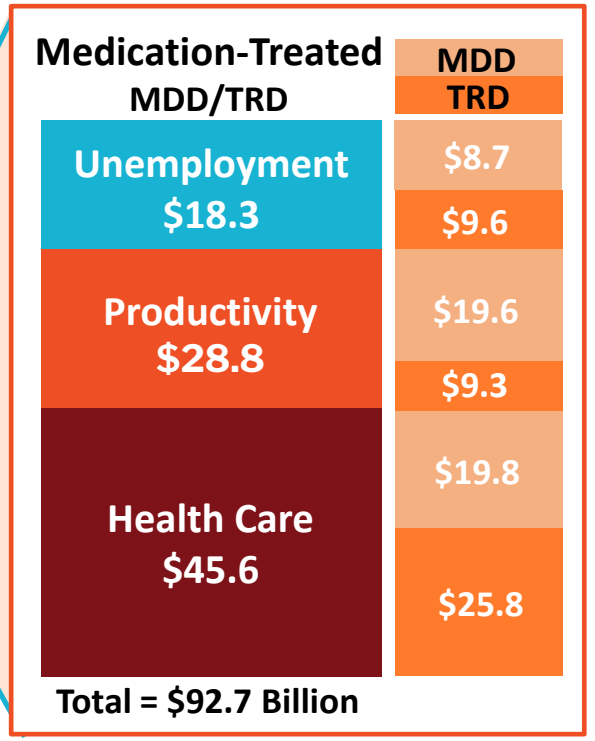
Why We Care = Burden of TRD

Definition
Lack of response to at least two adequate antidepressant trials

Prevalence
30.9% of medication-treated MDD patients develop TRD
- 20 studies (14 to 411patients)
- 8.9 M treated, 2.8M have TRD

High disease burden
Long-term illness (1.4-16.5 years)
Annual cost burden = $92.7 Billion

Low remission rates
Longer-term follow-up shows improvement



Why This Matters:
- Higher disability rates
- Increased suicide risk
- Greater healthcare burden
- Lower long-term remission rates

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

Cause-Specific Mortality in TRD

TRD was associated with a **17% higher risk** for all-cause mortality than non-TRD MDD.
Increased mortality risk was **driven largely by suicide and accidental overdose**, nearly twice as high.

METHODS:

- Data from 176,942 individuals diagnosed with MDD and treated with an antidepressant in Finnish registries
- ~ 11% of the participants had TRD
- The outcomes were all-cause and cause-specific mortality

TAKEAWAYS:

- Median time to TRD was 8 months, and 959 and 7662 deaths were observed in the TRD and non-TRD groups, respectively.
- **Mortality due to suicides was 1.9 times higher in TRD than in non-TRD.**
- **Mortality due to accidental poisonings was 1.8 times higher in TRD than in non-TRD.**

Gustafsson TT, et al. *J Affect Disord.* 2024;368:136-142.

Accurate Differential Diagnosis Is Essential

TRD is a clinical diagnosis with no laboratory test, genetic test, or neuroimaging study

Mental health mimics		
Bipolar disorder		
Mood disorder due to another medical condition		
Autism	**ADHD**	
Neurocognitive disorders		
Negative symptoms due to psychotic disorder		

Neurologic mimics	Medical mimics	Medication mimics
Parkinson's disease Stroke Migraine TBI Narcolepsy ALS Epilepsy	Cancer Chronic pain Hypothyroidism Vitamin deficiencies Diabetes CVD OSA or other sleep disorder Infections Anemia	Opioids Ca^{2+} channel blockers Corticosteroids Interferon alpha Benzodiazepines Reserpine Some anticonvulsants Cannabis

Inaccuracy of the MDD diagnosis is a common reason for pseudo-resistance.
It is estimated that ~half of individuals with MDD are not correctly diagnosed

Ensure patient has a comprehensive

- ✓ Medical and laboratory evaluation
- ✓ Psychiatric evaluation
- ✓ Psychosocial evaluation including collateral from loved ones

Assess if patients received **minimally adequate trials with 2 or more antidepressants** of adequate dose and duration (at least 6-8 weeks)

Assess medication adherence

ADHD = Attention deficit hyperactivity disorder; ALS = Amyotrophic lateral sclerosis; CVD = cardiovascular disease; OSA = obstructive sleep apnea.

Gaynes BN. *J Clin Psychiatry.* 2009;70(Suppl 6):10-5. McIntyre RS, et al. *World Psychiatry*. 2023;22(3):394-412.

Limitations of Conventional Monoamine Antidepressants

Delayed onset and high non-response rates

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

Frequent residual symptoms

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

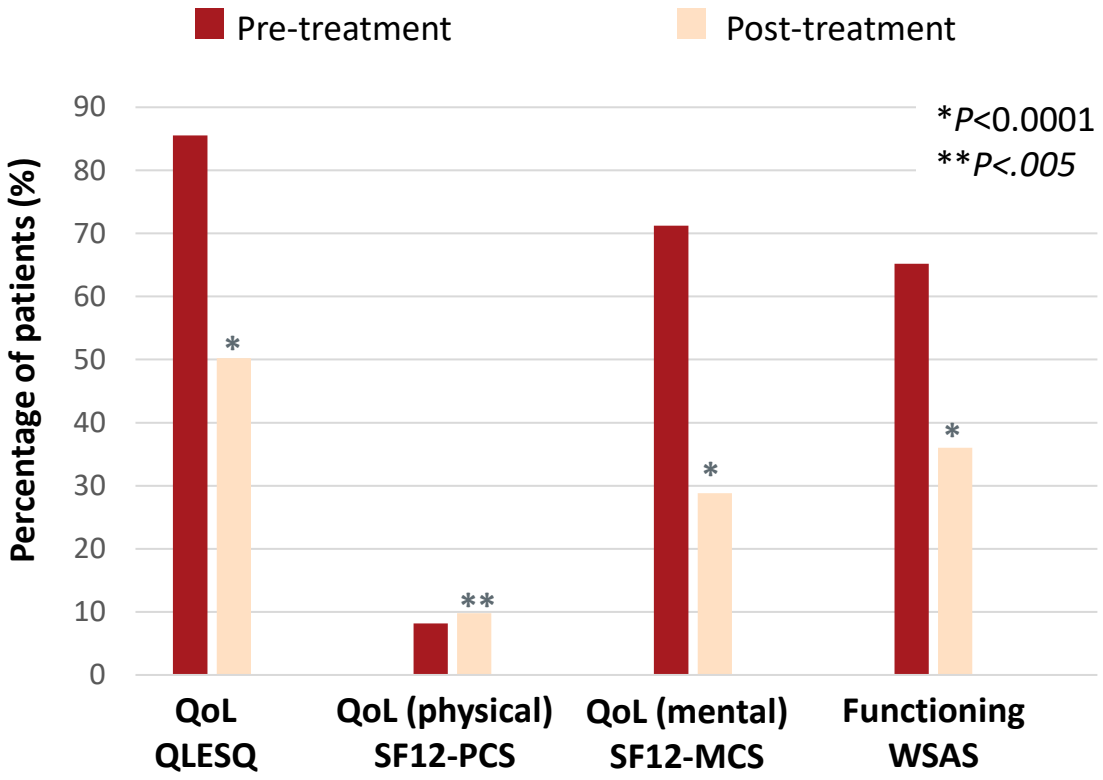
Adverse effects

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

Conradi HJ, et al. *Psychol Med*. 2011;41:1165–74. 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.

Low Response to Conventional Antidepressants

STAR*D: Patient-reported pre- and post-SSRI-treatment QoL and functioning severity scores (N=2280)



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

A follow-up at **Week 16** after initiating, or switching to, an SSRI or SNRI antidepressant found:

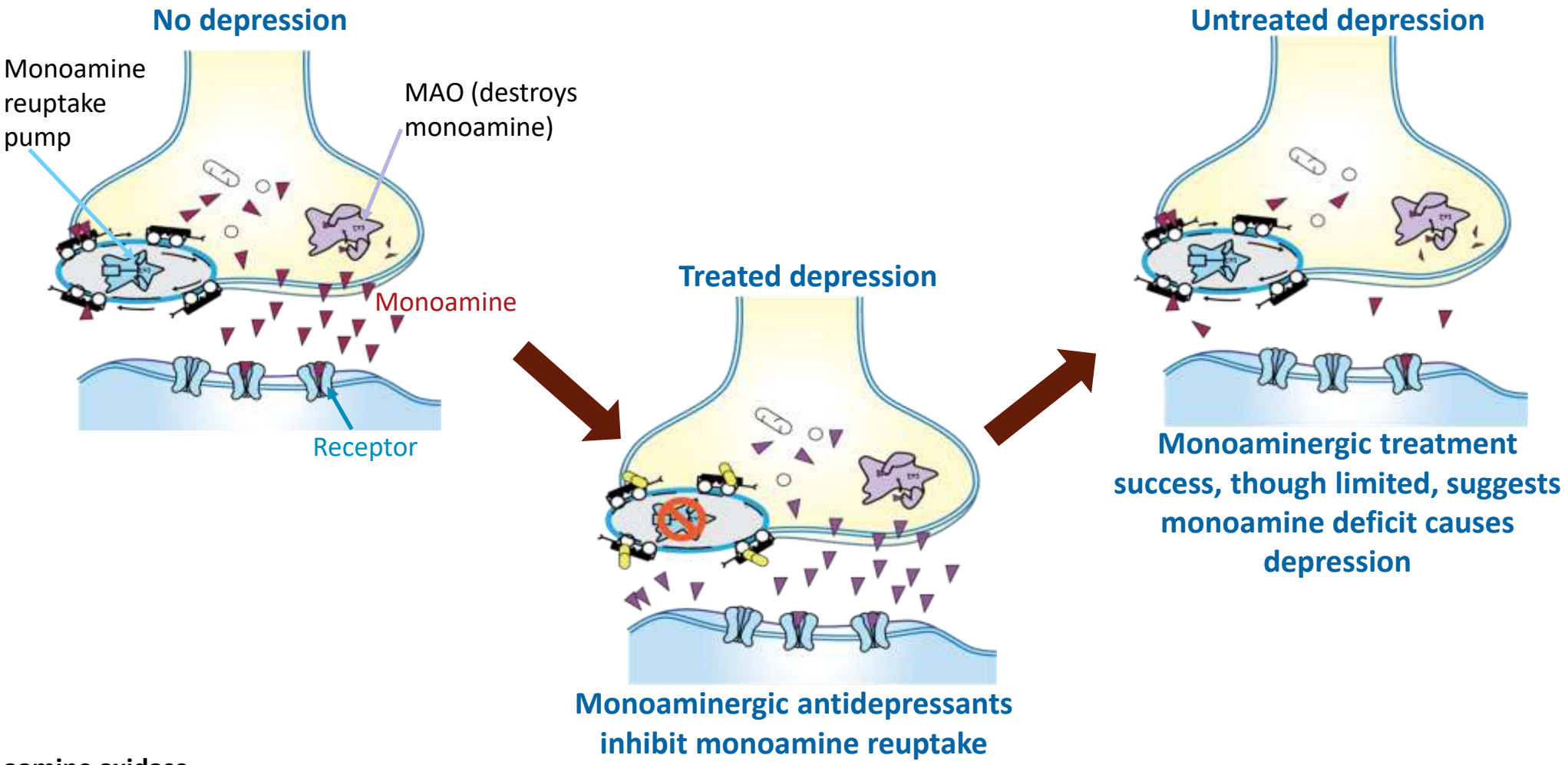
- **52.9%** showed **clinical remission**
- **37.7%** showed **functional remission**
- **34.2%** showed **recovery**

Patients still had decreased quality of life and functional impairments

Q-LES-Q = quality of life, enjoyment, and satisfaction questionnaire—short form; SF-12 PCS = 12-item version of the medical outcomes study—short form, physical component scale; MCS = mental component scale; SSRI = selective serotonin reuptake inhibitor; QoL = quality of life; STAR*D = Sequenced Treatment Alternatives to Relieve Depression; WSAS = work and social adjustment scale.

Ishak, et al. *Depress Anxiety*. 2014;31:707–16; Novick D, et al. *Patient Prefer Adherence*. 2017;11:1859–68.

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



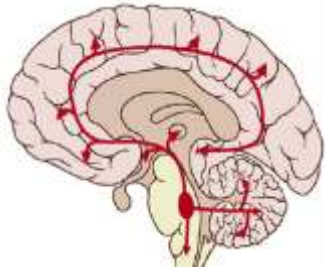
MAO = monoamine oxidase

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

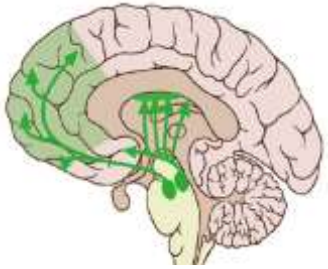
What About Glutamate?

Monoaminergic cells are less widespread

Serotonin



Norepinephrine

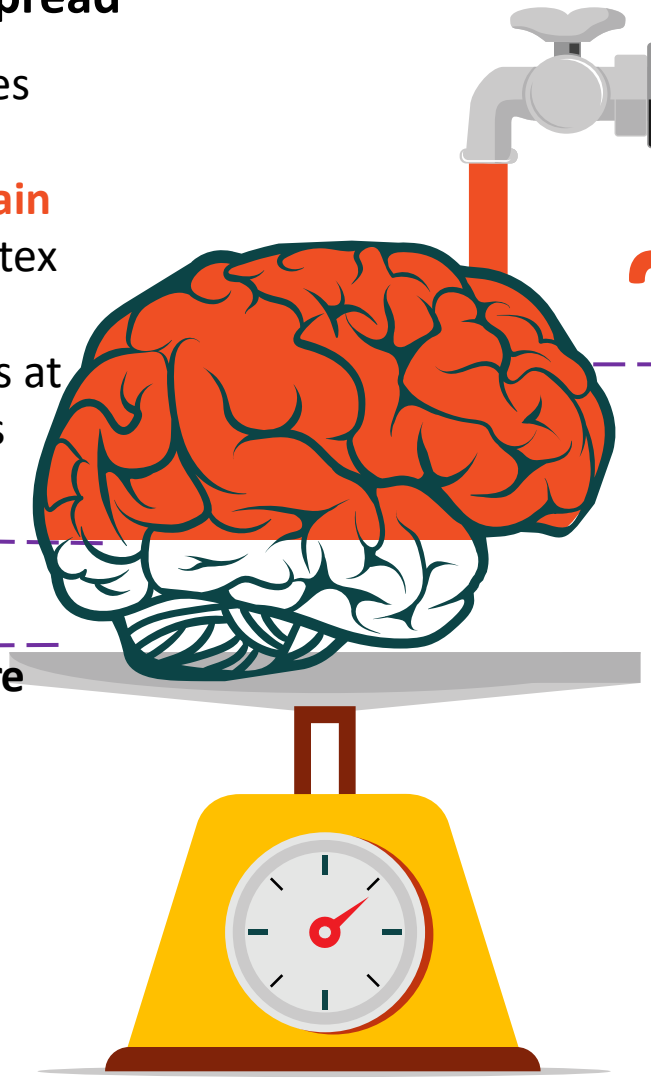


Dopamine

- 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

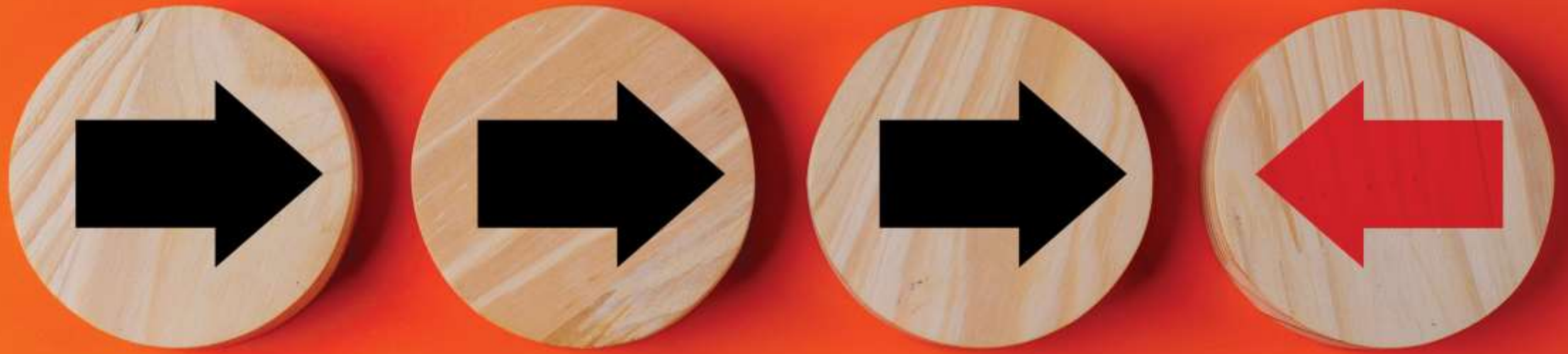
- **Most widespread excitatory neurotransmitter in the brain**
- Significant role in **learning, cognition, and mood**
- Involved in synaptogenesis and neuroplasticity
- Can be **neurotoxic in excess**
- Glutamate and GABA form the primary components of the cortex.

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. Stah's Essential Psychopharmacology. (5th ed.) Cambridge University Press; 2021.

Key Learning Points

- In the STAR*D trial, the biggest drop in remission rates was **after the second drug added or switched to**, and even after four drugs were tried, approximately one-third of patients did not reach remission
- An observational follow-up study of the STAR*D showed that only **34.2% of patients showed recovery** from MDD at Week 16 after initiating, or switching to, an antidepressant (SSRI/SNRI)
- TRD diagnosis requires **≥2 qualifying unsuccessful antidepressant trials within the same depressive episode**, from the same or different classes, with at least the minimum effective antidepressant dose for 6 to 8 weeks
- Patients with TRD (compared with MDD) have worse clinical outcomes, higher suicide and mortality rates, higher medication side effect burdens, and increased healthcare costs

Current and Emerging Treatments for Treatment-Resistant Depression



Monoaminergic Combination Treatment Approved for TRD

Olanzapine/Fluoxetine Combination

First Medication approved by the FDA for TRD

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

Olanzapine/Fluoxetine Combination

How does it work? Does it work?

Mechanism of action:
Olanzapine modulates dopamine & serotonin (5-HT2A, D2 antagonism) while fluoxetine boosts serotonin through reuptake inhibition
—a dual mechanism that may improve treatment response in TRD

In a systematic review, treatment with OFC vs fluoxetine treatment alone was associated with **earlier improvement and higher rates of response and remission**

The efficacy of OFC is **sustained during longer-term treatment**, as demonstrated by open-label studies lasting up to 76 weeks

Weight gain, increased appetite, and changes in metabolic parameters were commonly reported by participants treated with OFC

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

OFC = olanzepine/fluoxetine combination

Tamayo JM, et al. *Arch Neuroscien.* 2015;20 (1):3-19. Bobo WV et al. *Neuropsychiatric Disease and Treatment.* 2009;5:369–383.

Olanzapine/Fluoxetine: Adverse Events

In long-term OFC studies (at least 48 weeks), the mean weight gain was 6.7 kg (14.7 lb)

With long-term exposure body weight gain was 7%, 15%, and 25% for 66%, 33%, and 10% of patients, respectively

1.2% of patients discontinued due to weight gain

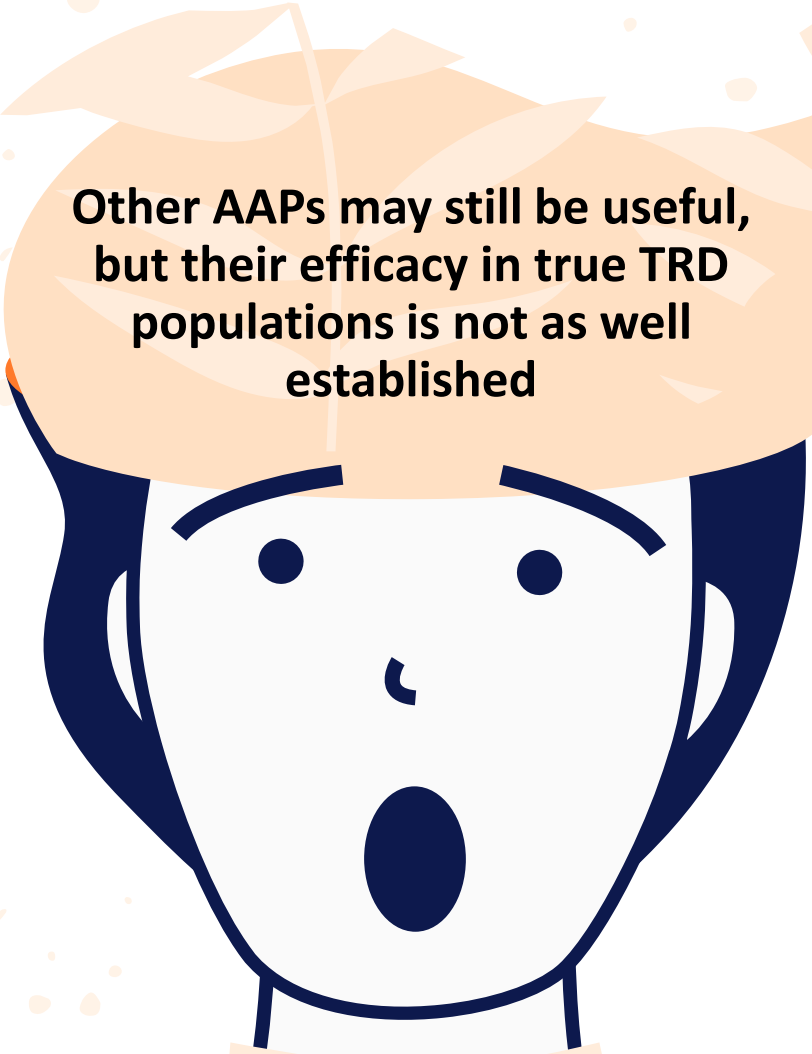
Treatment-Emergent Adverse Events Occurring in ≥ 5% of OFC Patients and at Least Twice that of Placebo

					p-value	
Event	OFC (%)	Fluoxetine (%)	Olanzapine (%)	Overall	OFC vs Fluoxetine	OFC vs Olanzapine
Weight Increased	27.9	7.1	33.5	<0.001	<0.001	0.091
Increased appetite	24.3	6.3	29.2	<0.001	<0.001	0.128
Dry mouth	18.6	6.5	21.2	<0.001	<0.001	0.376
Somnolence	15.6	6.5	13.5	<0.001	<0.001	0.426
Fatigue	14.0	9.4	16.0	0.024	0.051	0.428
Peripheral edema	11.2	1.1	7.4	<0.001	<0.001	0.074
Tremor	9.7	6.3	5.4	0.047	0.075	0.026
Sedation	8.5	2.8	10.6	<0.001	<0.001	0.333
Hypersomnia	6.1	2.0	8.3	<0.001	0.005	0.270
Attention disturbance	5.5	3.4	6.6	0.142	0.181	0.553

OFC = olanzapine/fluoxetine combination.

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.

What About Other Atypical Antipsychotic Meds?



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

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

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

AAP = atypical antipsychotics. Jha MK, Mathew SJ. *Am. J. Psychiatry.* 2023;180:190–199.; Ali E, et al. *Asian Journal of Psychiatry.* 2024;95.

Esketamine

In Conjunction with an Oral Antidepressant or as Monotherapy for Adults with TRD

Esketamine Is a Glutamatergic Antidepressant NMDA Receptor Antagonist

Schedule III controlled substance (CIII) FDA approved for adults with TRD Mar 2019, MDD with suicidal ideation Aug 2020, and MONOTHERAPY in Jan 2025

BOXED WARNINGS: Due to the risks of sedation, dissociation, respiratory depression, abuse and misuse, as well as suicidal ideation in adolescents and young adults, esketamine is only available at certified treatment centers through a restricted distribution program

Self-administered nasal spray 28 mg each

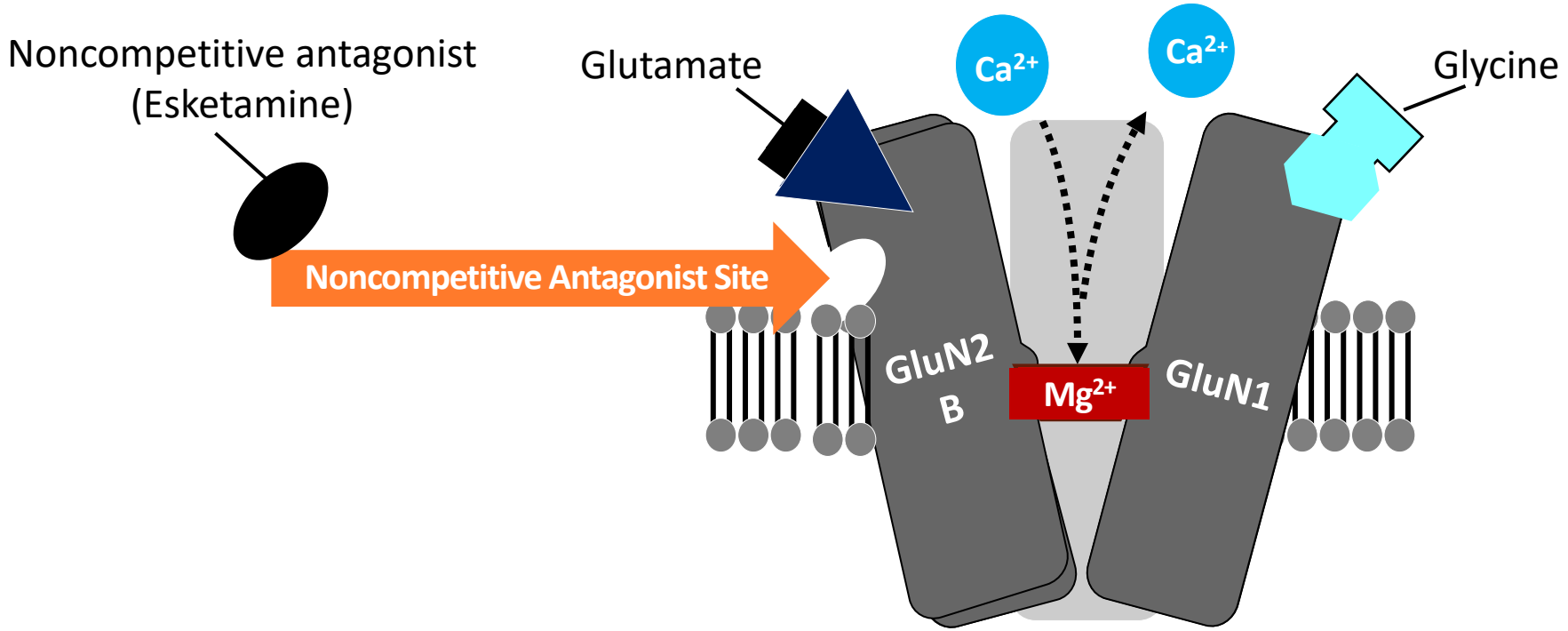
- **Requirements**: Patients must be monitored in a certified treatment center by a licensed healthcare provider (MD, DO, APRN, PA-C) for at least 2 hours after administration- with submission of patient monitoring form submitted within 7 days
- **Monitoring**: Measure pulse ox and blood pressure prior to dosing, 40 minutes post-dose and subsequently as clinically warranted until values decline, in addition to 2 hours post first dose. Do not start dose until BP < 140/90
- **Contraindications**: aneurysmal vascular disease, arteriovenous malformation, history of intracerebral hemorrhage
- **REMS:** Patients, health care setting and pharmacy must be certified
- **Restrictions:** Patients can not drive or operate heavy machinery for the rest of the day

NMDA = N-methyl D-aspartate. REMS = Risk evaluation mitigation strategy

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

Esketamine is a Glutamatergic Antidepressant

Does NOT Inhibit Neurotransmitter Reuptake



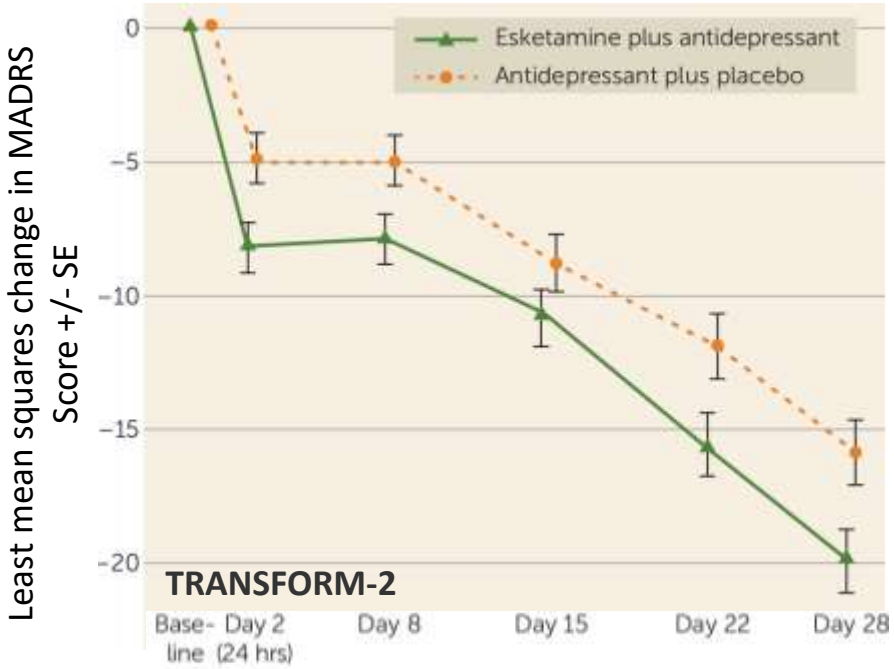
Esketamine is the S-enantiomer of racemic ketamine-think "mirror image"

A nonselective, noncompetitive antagonist of the ionotropic NMDA glutamate receptor

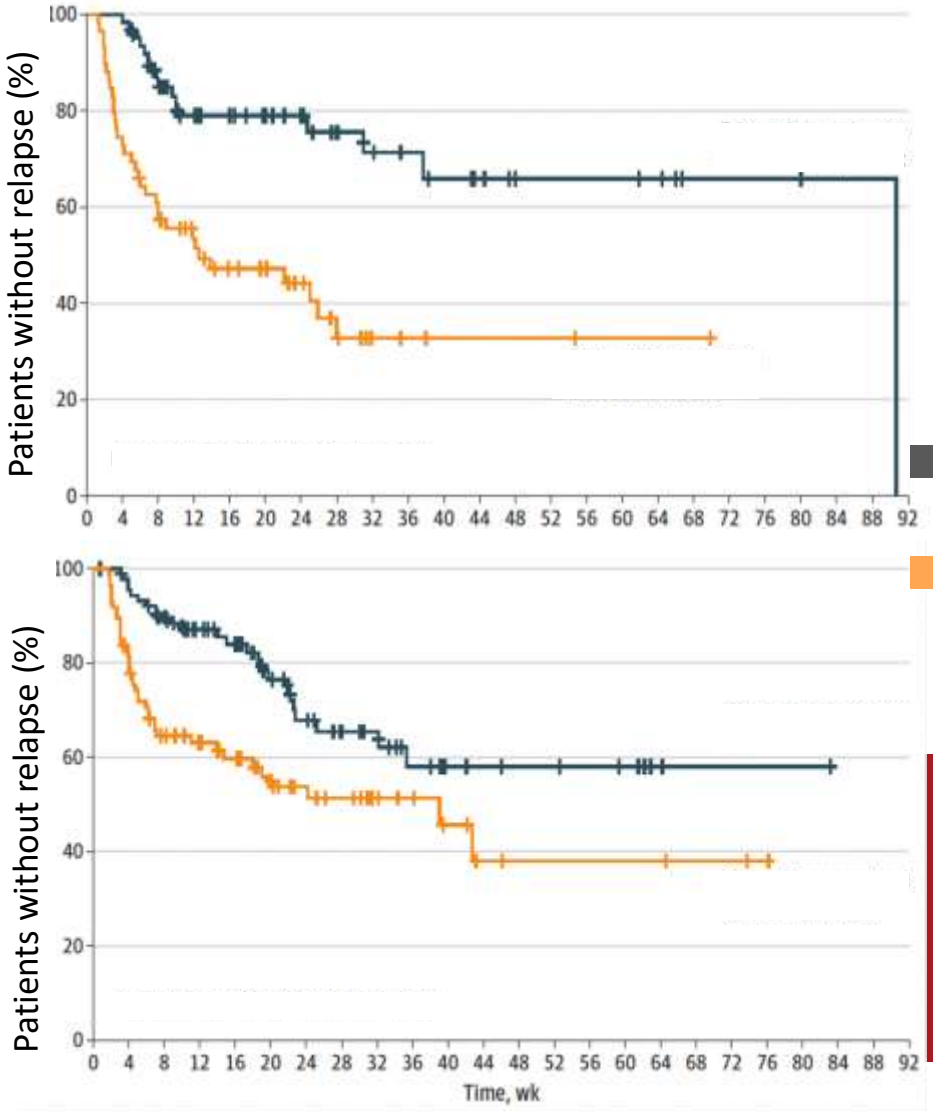
Binds at allosteric site to modulate the probability of an open ion channel

Ca^{2+} = calcium ion; GluN1 = glycine-binding type 1 NMDA receptor subunit; GluN2B = glutamate-binding type 2B NMDA receptor subunit; Mg^{2+} = magnesium ion. Niciu, MJ. *Pharmacology Biochemistry and Behavior*. 2012;100(4): 656-664. Duman RS. F1000Res. 2018;7:F1000 Faculty Rev-659.

Efficacy of Adjunctive Esketamine



- Rapid and superior improvement in depressive symptoms at week 4
- Difference between esketamine vs placebo observed at 24 hours
- Improvement seen in both groups from 24 hours to 4 weeks
- Relatively consistent difference between groups over time



Stable Response

70%

Less likely to relapse HR=0.30 (95% CI: 0.16-0.55) *P*=.001

Stable Remission

51%

Less likely to relapse HR=0.49 (95% CI: 0.29-0.84) *P*=.003

Popova V, et al. *The American Journal of Psychiatry.* 2019;176(6):428-438. Daly E, et al. *JAMA Psychiatry*. 2017;76(9):893-903.

Esketamine Safety and Tolerability

- 184 patients (18%) experienced serious TEAEs
- Serious TEAEs that occurred in >5% of patients
  - Depression (n=16)
  - Suicide attempt (n=15)
  - Suicidal ideation (n=9)
  - COVID-19 (n=7)
- Six deaths (0.6%) occurred due to TEAEs
  - Investigator assessment considered none esketamine-related

4.6% of patients discontinued due to adverse events

Most TEAEs (93.7%) occurred and resolved on day of dosing

Most Common Adverse Events in Pivotal Trials of Esketamine vs Placebo Plus Oral Antidepressant		
	Esketamine (N=346)	**Placebo** (N=222)
Dissociation	**41%**	**9%**
Dizziness	**29%**	**8%**
Nausea	**28%**	**9%**
Sedation	**23%**	**9%**
Vertigo	**23%**	**3%**
Hypoesthesia	**18%**	**2%**
Anxiety	**13%**	**6%**
Lethargy	**11%**	**5%**
BP increased	**10%**	**3%**
Vomiting	**9%**	**2%**
Feeling intoxicated	**5%**	**0.5%**
Incidence 5% and at least twice that of placebo+ oral antidepressant		

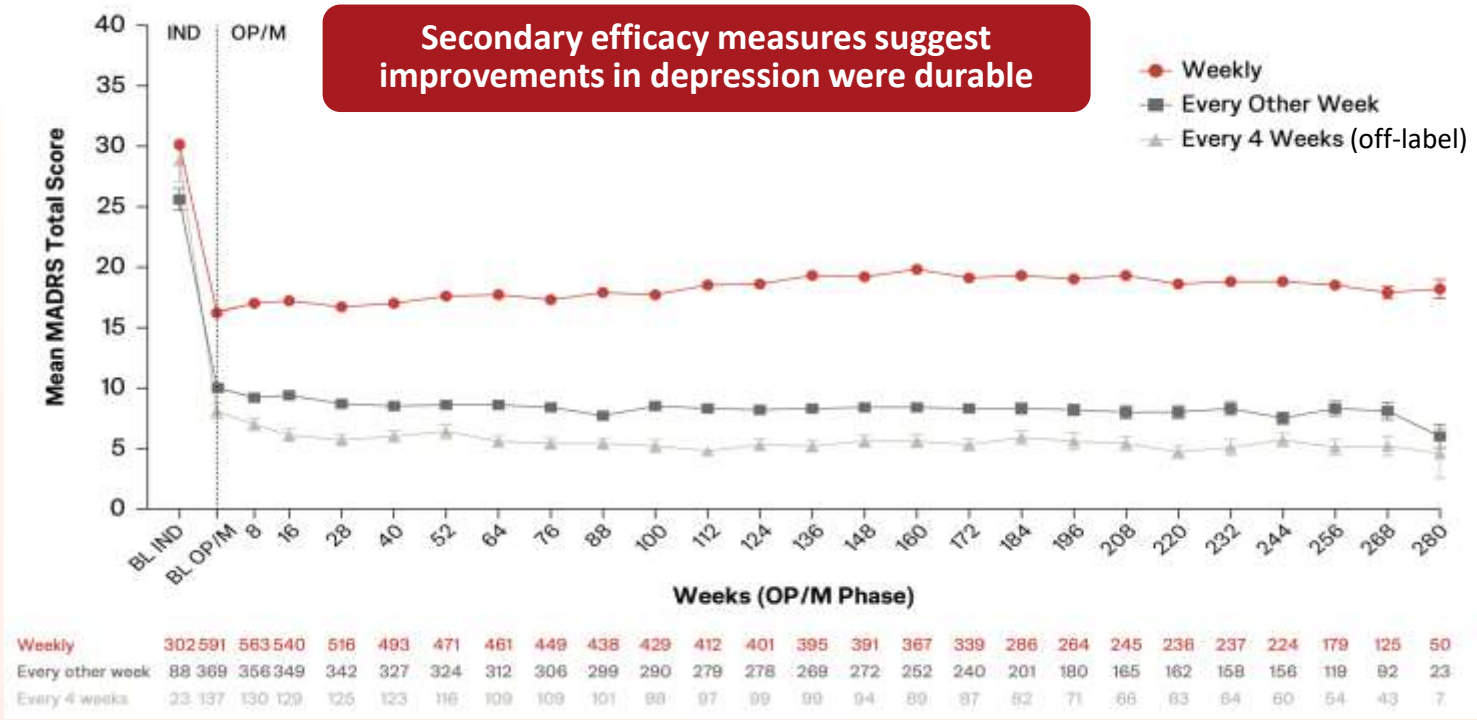
TEAEs = Treatment-emergent adverse events. BP=blood pressure

Popova V, et al. *Am J Psychiatry.* 2019;176(6):428-438. Zaki N, et al. *Neuropsychopharmacology.* 2023;48:1225–1233.

Esketamine Long-Term Safety Study up to 5+ Years

- Eligible participants from 6 previous studies entered either a 4-week induction or directly into optimization/maintenance
- Intranasal esketamine + oral antidepressant dosing was flexible
  - Twice weekly in induction
  - Weekly (54%), every other week (34%), or every 4 weeks (12%) in optimization/maintenance, individualized to depression severity

Secondary efficacy measures suggest improvements in depression were durable



AEs in Optimization/Maintenance (N = 1110)

Headache	369 (33.2%)
Dizziness	342 (30.8%)
Nausea	332 (29.9%)
Dissociation	257 (23.2%)
Nasopharyngitis	251 (22.6%)
Somnolence	246 (22.2%)
Dysgeusia	208 (18.7%)
Vertigo	196 (17.7%)
Back pain	189 (17.0%)
Anxiety	175 (15.8%)
Vomiting	161 (14.5%)
Diarrhea	155 (14.0%)
Urinary tract infection	148 (13.3%)
Blood pressure increased	141 (12.7%)
Upper respiratory infection	131 (11.8%)
Insomnia	122 (11.0%)
Influenza	115 (10.4%)
Vision blurred	114 (10.3%)

Safety results were consistent with the safety and tolerability established in pivotal trials of esketamine with an oral antidepressant

Zaki N, et al. *Neuropsychopharmacology.* 2023;48:1225–1233. Zajecka J, et al. Long-Term Safety and Efficacy of Esketamine Nasal Spray by Dosing Frequency in Adults With Treatment-Resistant Depression: Analysis of the SUSTAIN-3 Study. Presented at Psych Congress Elevate; May 30-June 2, 2024; Las Vegas, Nevada

Real-World Safety of Esketamine:
Acute Central Respiratory Depression

96 Cases of Acute Respiratory Depression Reported (Mar 2019-Jan 2023)

On day of dosing	60% (58/96)	8 >1 day after dosing 30 unreported date of event or dosing
SpO_2 or RR unreported or depressed	86% (50/58)	8 normal SpO_2 saturation or RR recorded 11 depressed SpO_2 or RR reported 39 unreported SpO2 and RR
Serious events	70% (35/50)	**No fatalities** **6 hospitalizations** **2 life-threatening events**
Medical interventions*	64% (32/50)	42% (21/50) needed emergency services 24% (12/50) needed only prolonged monitoring (>120-190 min)
Concomitant CNS depressants**	72% (36/50)	Mostly benzodiazepines (18/36) and antidepressants (16/36)

*included emergency visits, oxygen, medication, tactile/verbal stimulation, CPR, and rescue breathing; **cannot attribute respiratory depression to these

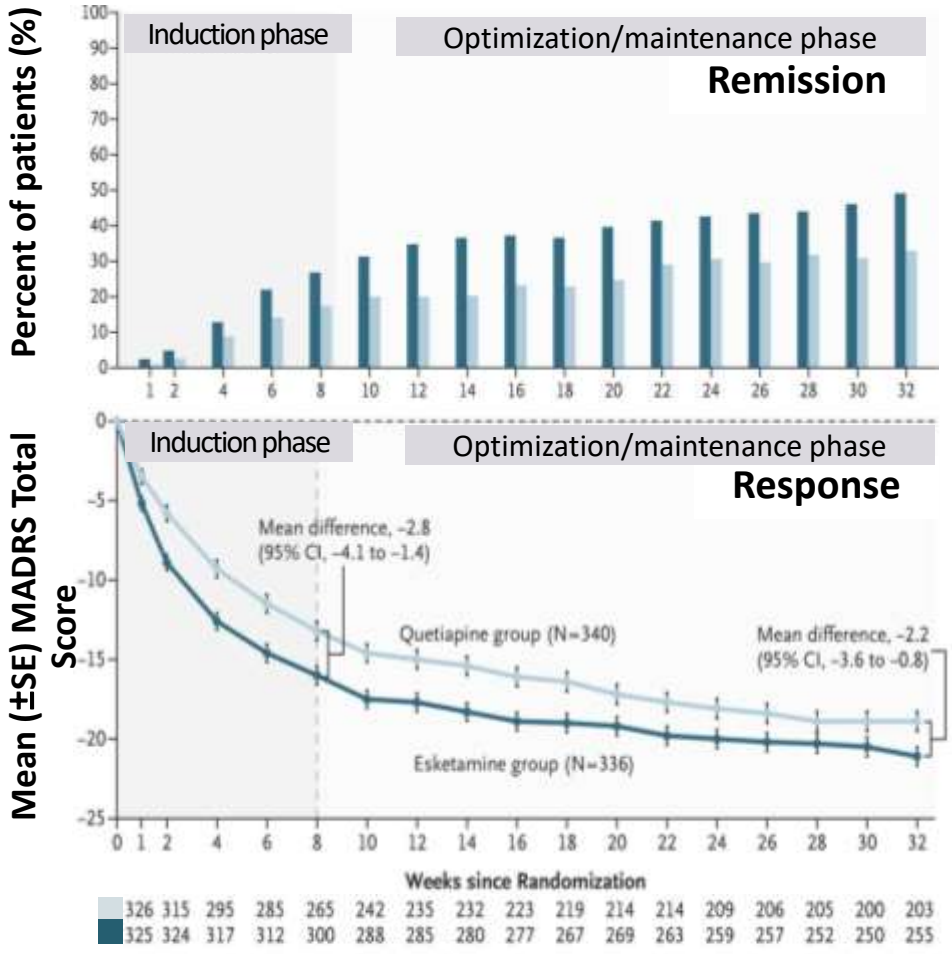
Clinic Safety Requirements

- REMS clinic certification
- DEA log
- Patient-specific enrollment paperwork
- Confirmation of patient ride home
- Clinical procedures in place with annual staff training
- Comfortable chair or couch
- Blood pressure cuff
- Pulse oximeter
- Emergency plan
  - Activate if hypertensive or respiratory crisis occurs
  - Asymptomatic hypertension needs no treatment because of short half life of esketamine

RR = Respiratory rate; SpO2 = oxygen saturation; DEA = Drug Enforcement Administration.

Chepke C. et al. International Journal of Neuropsychopharmacology 27.12 (2024): pyae058.

Adjunctive Esketamine Superior to Adjunctive Quetiapine-XR



51%

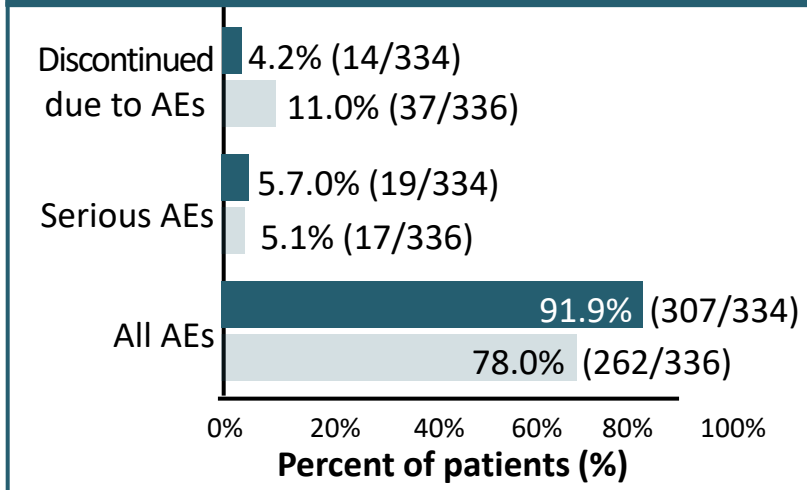
More likely to achieve remission (week 8) OR=1.74 (95% CI: 1.20-2.52) *P*=.003

72%

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

SAFETY AND TOLERABILITY

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



LIMITATIONS

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

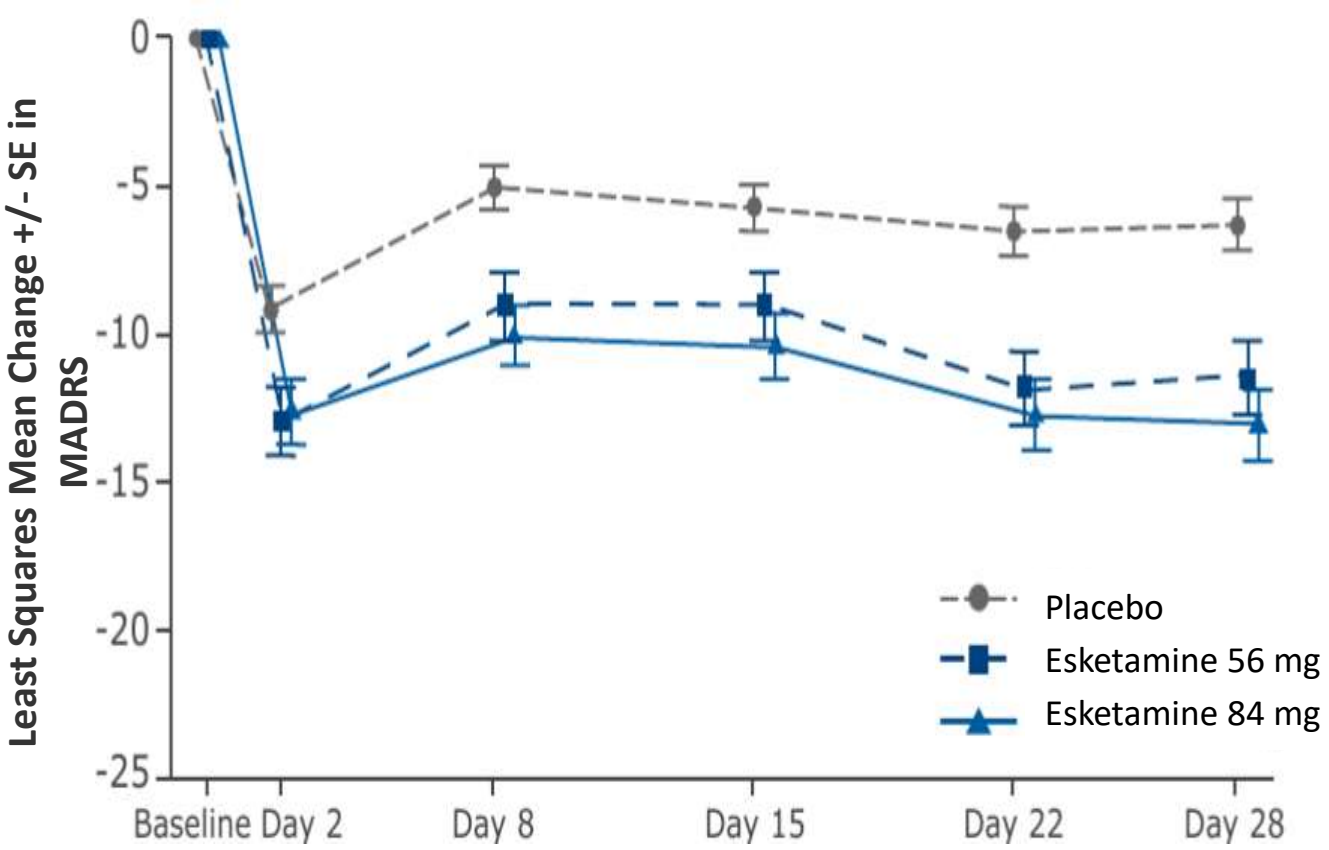
AEs = Adverse events. Reif A, et al. *N Engl J Med.* 2023;389:1298-309.

Esketamine as Monotherapy for TRD

Significantly greater improvement was seen with both esketamine doses compared with placebo at 24 hours and 28 days (*P*<.001)

Participants treated with esketamine had larger mean decreases in MADRS total score from baseline to day 28 compared with those treated with placebo (*P*<.001).

In a post hoc analysis, esketamine treatment led to larger improvements vs placebo on all MADRS items



In this placebo-controlled trial, remission rates (MADRS total score ≤12) were higher in the 56-mg and 84-mg esketamine groups compared with placebo at all timepoints in the double-blind period.

Janik A, Qiu X, Lane R, et al. American Society of Psychopharmacology Annual Meeting. Poster presentation. May 28, 2024.

Tolerability of Esketamine for TRD Monotherapy

TEAEs Most Frequently Observed* During Double-Blind Period			
	Placebo	Esketamine	
	N=250 (%)	56 mg (N=105)	84 mg (N=121)
Nausea	21 (8.4)	24 (22.9)	32 (26.4)
Dissociation	7 (2.8)	23 (21.9)	32 (26.4)
Dizziness	18 (7.2)	22 (21.0)	27 (22.3)
Headache	22 (8.8)	19 (18.1)	24 (19.8)
Feeling drunk	2 (0.8)	8 (7.6)	8 (6.6)
Anxiety	3 (1.2)	5 (4.8)	10 (8.3)
Fatigue	11 (4.4)	8 (7.6)	7 (5.8)
Vomiting	1 (0.4)	5 (4.8)	10 (8.3)
Insomnia	9 (3.6)	6 (5.7)	5 (4.1)
Somnolence	4 (1.6)	6 (5.7)	3 (2.5)

*Incidence ≥5% in either treatment group. NB: events that occurred at the same frequencies within a group are listed in alphabetical order

Discontinuations during the double-blind period due to TEAEs were 0.5%, 1.2%, and 4.2% in the placebo, 56-mg esketamine, and 84-mg esketamine groups, respectively.

Janik A, Qiu X, Lane R, et al. American Society of Psychopharmacology Annual Meeting. Poster presentation. May 28, 2024.

2025 Esketamine Meta-Analysis: Key Flaws

01 Excluded monotherapy trials – ignored key studies that demonstrate esketamine's full efficacy

02 Included trials with subtherapeutic doses (28 mg) – lower doses do not reflect real-world treatment effects

03 Short-term data for a chronic condition – 28-day trials cannot assess long-term efficacy for a persistent illness

04 Misinterpreted relapse rates – withdrawal effects are common in antidepressants and do not indicate dependence

05 Ignored real-world evidence – clinical practice shows robust improvements, lower hospitalization rates, and reduced suicidality

Fountoulakis KN, et al. *Am J Psychiatry*. 2025;182(3):259-275.

Esketamine Administration, Dose, and Schedule

Induction phase (weeks 1-4)
- 56 mg twice weekly
- May increase to 84 mg after day 1

Early maintenance phase weeks 5-8
- 56 or 84 mg once weekly

Maintenance phase weeks 9+
- 56 or 84 mg weekly or every other week
- Dosing less frequently than every two weeks is off-label but can be acceptable if response maintained

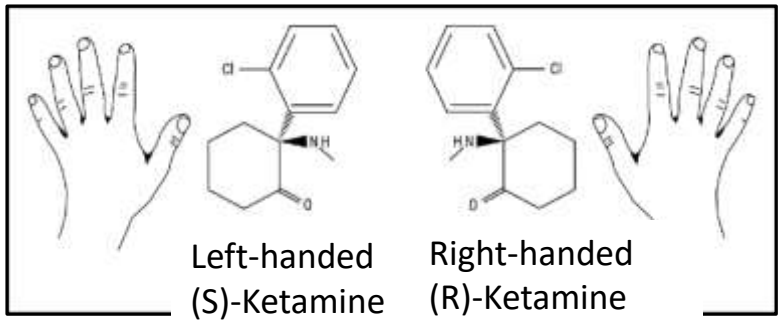
Medication Administration and Adverse Event Mitigation

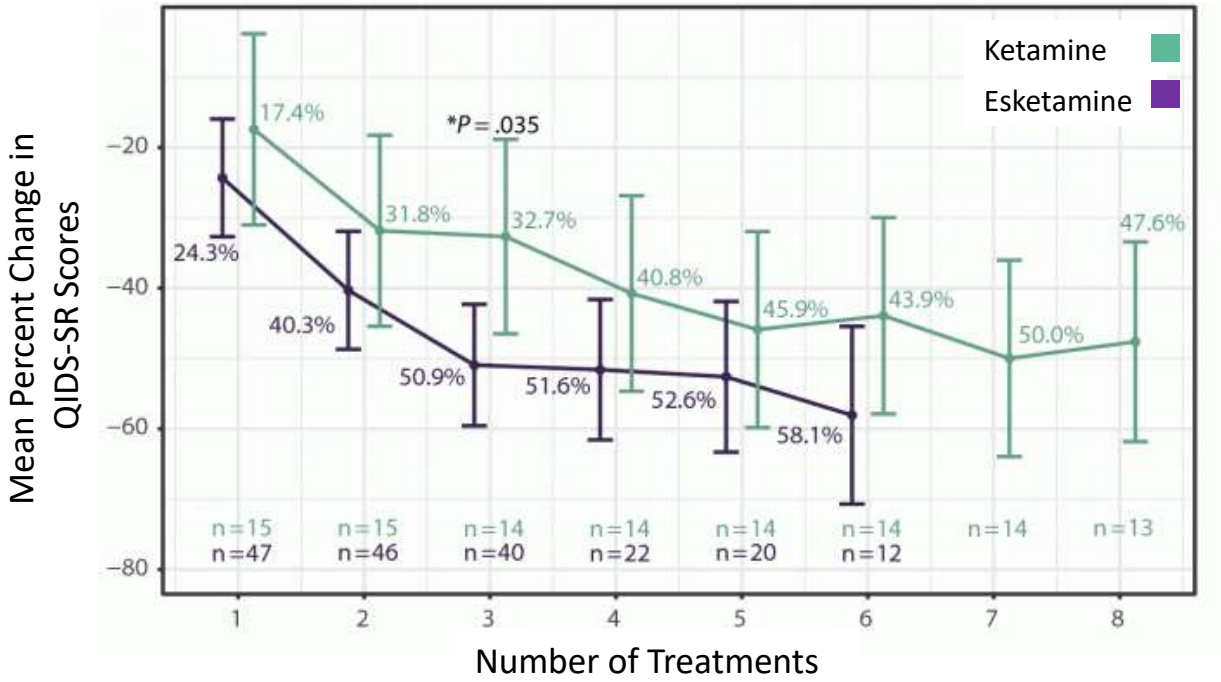
1. Ensure adherence to REMS (i.e., certification, post-administration monitoring, paperwork) and controlled substance requirements
2. Recommend patients do not eat 2 hours before or drink 30 minutes before treatment (consider pretreatment with anti-emetic (e.g., ondansetron)
3. Ensure patient's blood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

Bozymski KM, et al. *The Annals of Pharmacotherapy.* 2020;54(6): 567-576. doi:10.1177/1060028019892644

Esketamine and Ketamine: What's the Difference?

	Intranasal Esketamine	Intravenous Ketamine
FDA Approved for TRD	Yes	No
Covered by insurance	Yes	Not really
Long term safety data	Yes	No
REMS Protocol	Yes	No
Standardized doses	Yes	No
Malpractice liability	Lower	Higher
Procurement cost	High	Low





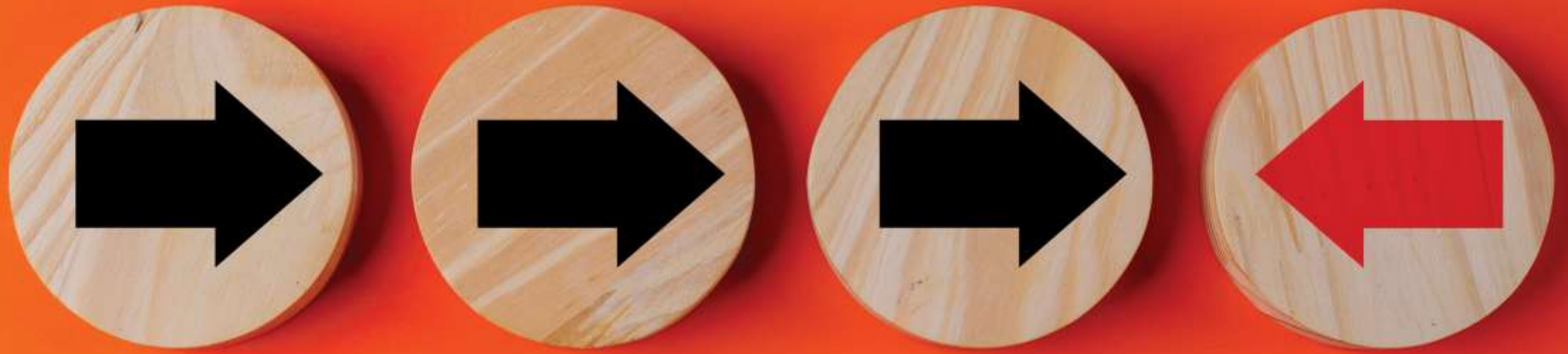
- No head-to-head RCT has compared intranasal esketamine to intravenous ketamine for TRD
- A single-site observational study of intranasal esketamine vs intravenous ketamine showed similar response rates for TRD during acute/induction phase
- Significantly fewer esketamine treatments were needed to achieve a response

Singh B, et al. *J Clin Psychiatry*. 2023 Feb 1;84(2):22m14548.

Key Learning Points

- ✓ Olanzapine/fluoxetine combination therapy is thought to act via a dual mechanism that may improve response to treatment: olanzapine modulates dopamine and serotonin receptors (antagonists) and fluoxetine inhibits serotonin reuptake
- ✓ In the SUSTAIN-3 open-label, long-term extension study of adjunctive intranasal esketamine, only **4.6% of patients discontinued treatment** because of treatment-emergent adverse events
- ✓ In a head-to-head, open-label trial of intranasal esketamine vs quetiapine XR as adjunctive treatment with an SSRI/SNRI, **participants treated with adjunctive intranasal esketamine had 72% higher odds of remaining relapse-free at week 32 (for those in remission at week 8)**
- ✓ In a placebo-controlled trial of intranasal esketamine monotherapy for TRD, higher remission rates were seen in the **56-mg and 84-mg esketamine groups** compared with the placebo group during the double-blind study phase

Other Treatment Considerations for Treatment-Resistant Depression



Dextromethorphan/Bupropion Combination

Recently approved for MDD with rapid onset ~
Clinical trials under investigation for TRD but NOT approved

	Phase 3 STRIDE 1 randomized, double-blind, active control	Phase 2 MERIT randomized, double-blind, placebo control
Objective	Assess efficacy and safety of dextromethorphan/bupropion vs bupropion alone for TRD	Evaluate dextromethorphan/bupropion vs placebo in preventing TRD relapse after achieving stable remission
Inclusion criteria	Adults with MDD • Inadequate response (<50% symptom reduction) to 1 or 2 prior antidepressants	Adults with TRD • From COMET open-label study, including STRIDE-1 • Did not respond after trials of at least 2 antidepressants before entering COMET
Primary endpoint	Change in MADRS total score	Time to relapse
Key secondary endpoint	Change in Clinical Global Impressions-Severity and change in HAM-D score at 6 weeks	Proportion without relapse
Findings	Treatment with dextromethorphan/ bupropion resulted in a 2.2-point greater reduction in MADRS total score compared with bupropion SR (150 mg, twice daily) but was not statistically significant	Significant reduction in time to relapse compared with placebo

Jones A, et al. Poster presented at: American College of Neuropsychopharmacology Annual Meeting; 2021 Dec 5-8; San Juan, Puerto Rico.

Few Medication Options for TRD

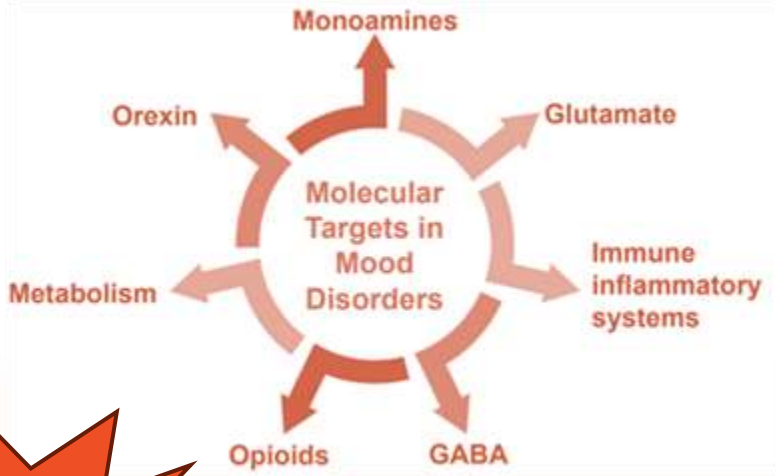
WHAT IS IN THE PIPELINE?

Phase 3

- Single dose of synthetic psilocybin
  - Received FDA breakthrough status in 2019
- Subcutaneous ketamine injections (4 weeks)

Phase 2

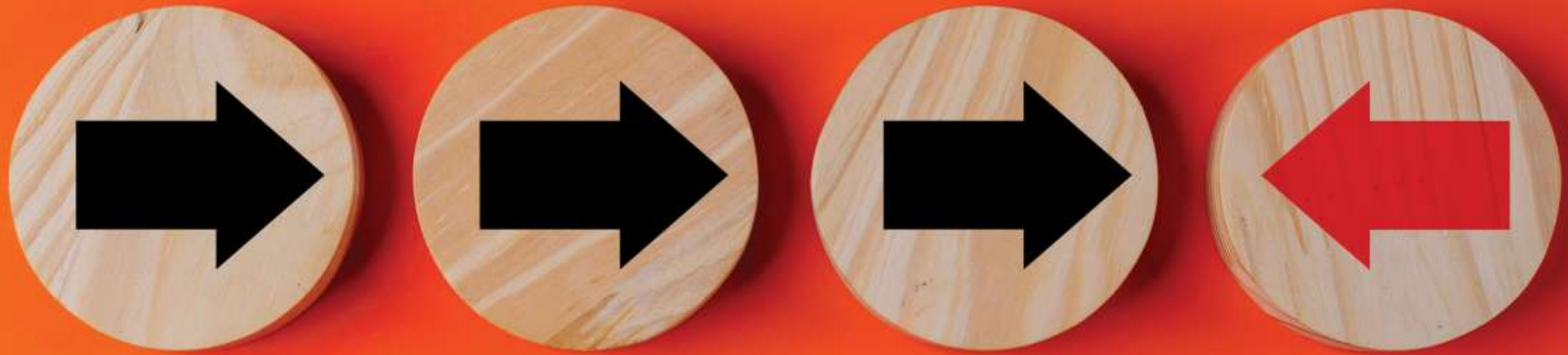
- Synthetic benzoate salt formulation of methylbufotenin (5-MeO-DMT) with psychological support
- Facial injection of botulinum toxin A
- Inhaled nitrous oxide
- Liafensine
  - First in class triple reuptake inhibitor (serotonin, norepinephrine, and dopamine)developed with artificial intelligence and whole genome sequencing
  - Failed in two clinical trials for TRD among non-biomarker selected participants
  - Phase 2b ENLIGHTEN showed safety and efficacy at 6 weeks, providing a 40% improvement in MADRS total score change compared with control (*P*=.006)



Precision medicine approach

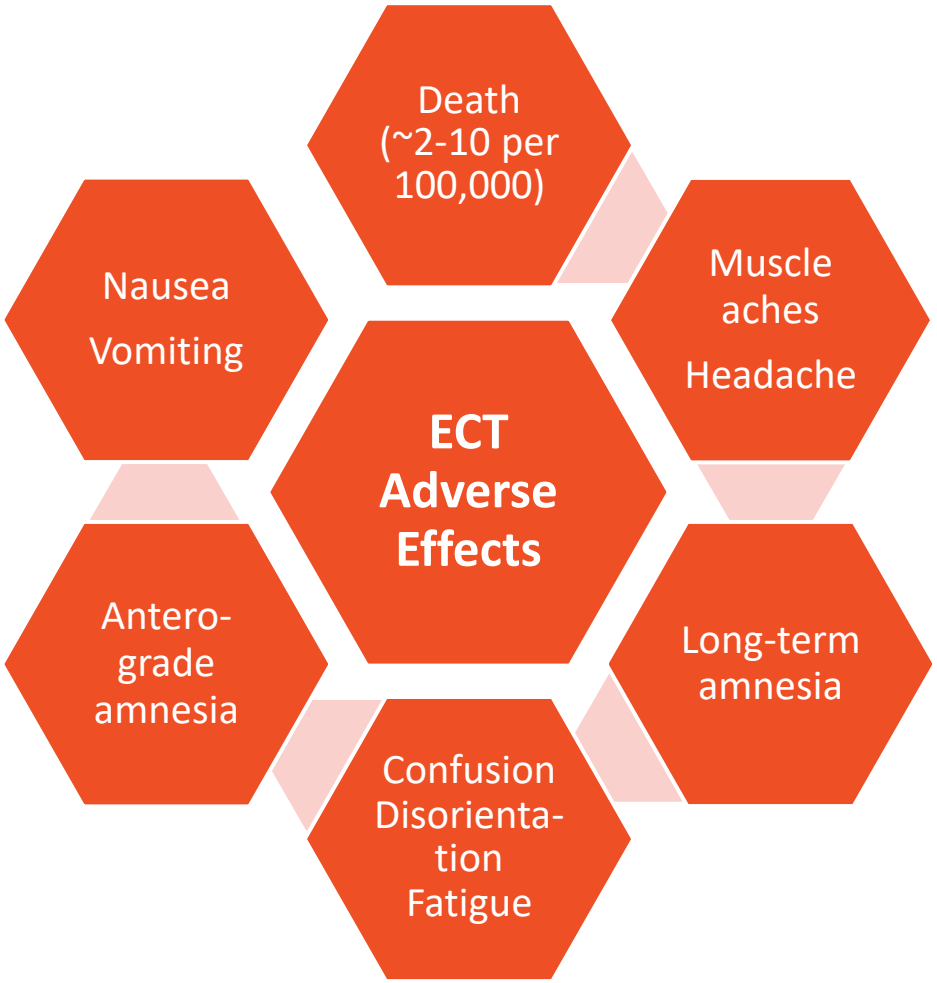
5-MeO-DMT = 5-methoxy-N,N-dimethyltryptamine. McIntyre RS et al. Lancet 2020;396(10265):1841-56. Loo C, et al. Br J Psychiatry. 2024;225(2):349. Husain MI, et al. BJPsych Open. 2023;25;9(4):e134. Image credit: R McIntyre, Neuroscience Educational Institute.

Neuromodulation Interventions for Treatment-Resistant Depression



Electroconvulsive Therapy

- ✓ **Hospital-based treatment that uses an electrical current to induce a tonic-clonic seizure under general anesthesia**
  - ✓ Acute vital sign changes occur during procedure
  - ✓ Consider patient safety for general anesthesia
  - ✓ Consider current medications and potentially down-titrate psychiatric anticonvulsants / benzodiazepines
- ✓ Contraindications include intracranial mass, elevated ICP, cerebral aneurysm, recent myocardial infarction or stroke, and high-risk pregnancy
- ✓ An acute series is 3 weekly treatments for up to 4 weeks, with each session requiring at least 1 hour from pre-op to recovery
- ✓ One of the most rapid and effective treatments for MDD
  - ✓ Even in TRD, response rates can exceed 60% to 80%
  - ✓ Maintenance ECT (monthly or weekly) is possible for those who respond and then relapse
  - ✓ Meta-analysis shows superiority to placebo, stimulated ECT, and several classes of antidepressants
- ✓ Preferred treatment for MDD with psychosis and/or catatonia



ECT = electroconvulsive therapy. Mutz J, et al., *BMJ.* 2019;364:l1079. Kim J et al., Psychiatric Times. March 21, 2024;41(3). Pagnin D, et al., *J ECT.* 2004;20(1):13-20.; Andrade. *Psychiatr Clin North Am.* 2016;39:513. Benbow SM, Int Psychogeriatr. 2007 Oct;19(5):985-7.

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression

Ana

CLINICAL PROBLEM

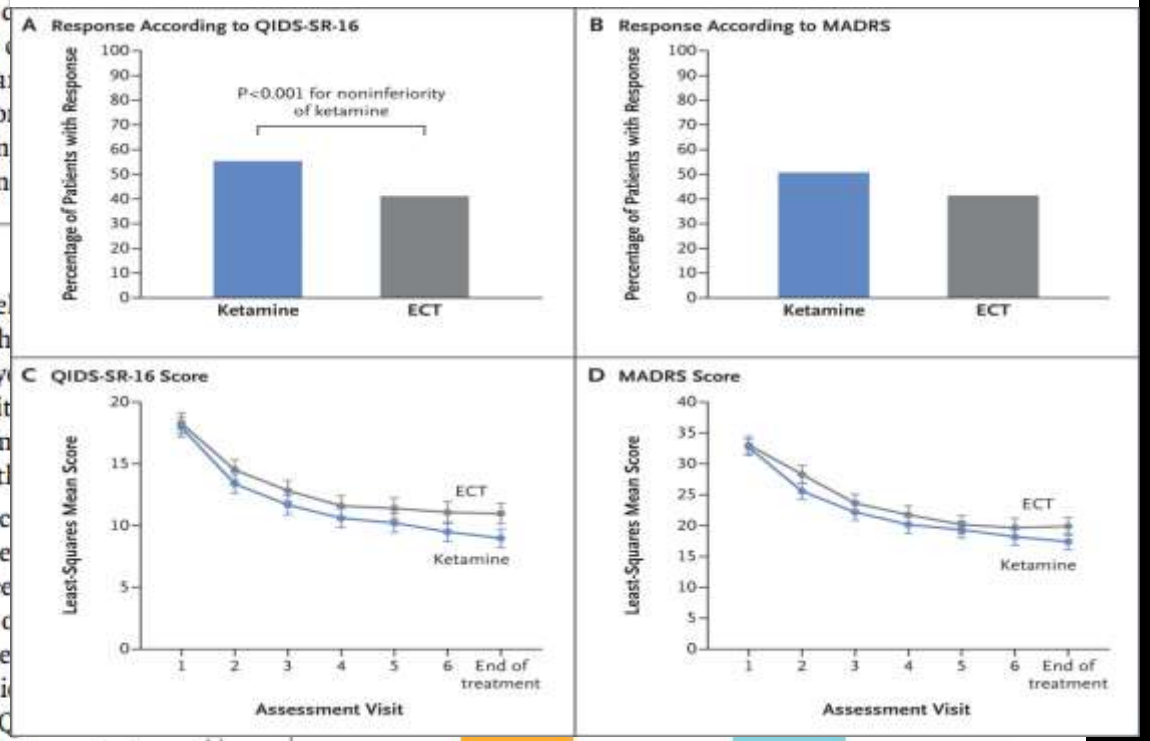
In more than a third of patients with major d
treatment with antidepressant drugs fails to
symptoms. Electroconvulsive therapy (ECT) a
thetic intravenous ketamine are both used fo
ment-resistant major depression, but the com
fectiveness of the two treatments remains un

CLINICAL TRIAL

Design: A prospective, multicenter, open-labe
ized, noninferiority trial compared subanesth
nous ketamine with ECT in adults 21 to 75 y
with treatment-resistant major depression wit
chosis who reported an unsatisfactory respon
equate trials of antidepressant treatment in t

Intervention: 403 patients were assigned to rec
of treatment with either ketamine (0.5 mg pe
of body weight over a 40-minute period twice
or ECT (three times per week). The primary
a response to treatment, defined as a decrease
line of ≥50% in the score on the 16-item Qui
of Depressive Symptomatology–Self-Report (
range, 0 to 27; higher scores indicate greater depression).
Secondary outcomes included quality of life, assessed on
a 16-item scale (range, 16 to 112; higher scores indicate
better quality of life).

Response to Ketamine and ECT According to the QIDS-SR-16 and MADRS During the Initial 3-Week Treatment



Conclusions:

- Among adults with TRD without psychosis, subanesthetic IV ketamine was noninferior to ECT in this 3-week study
- The incidence of moderate or severe adverse events, including musculoskeletal adverse events, was higher in the ECT group than in the ketamine group
- More patients withdrew from the ECT group than from the ketamine group before treatment

Shi ZM, et al. *J Affect Disord*. 2024:S0165-0327(24)01866-4. Anand A, et al. *N Engl J Med.* 2023;388:2315-2325.

Transcranial Magnetic Stimulation

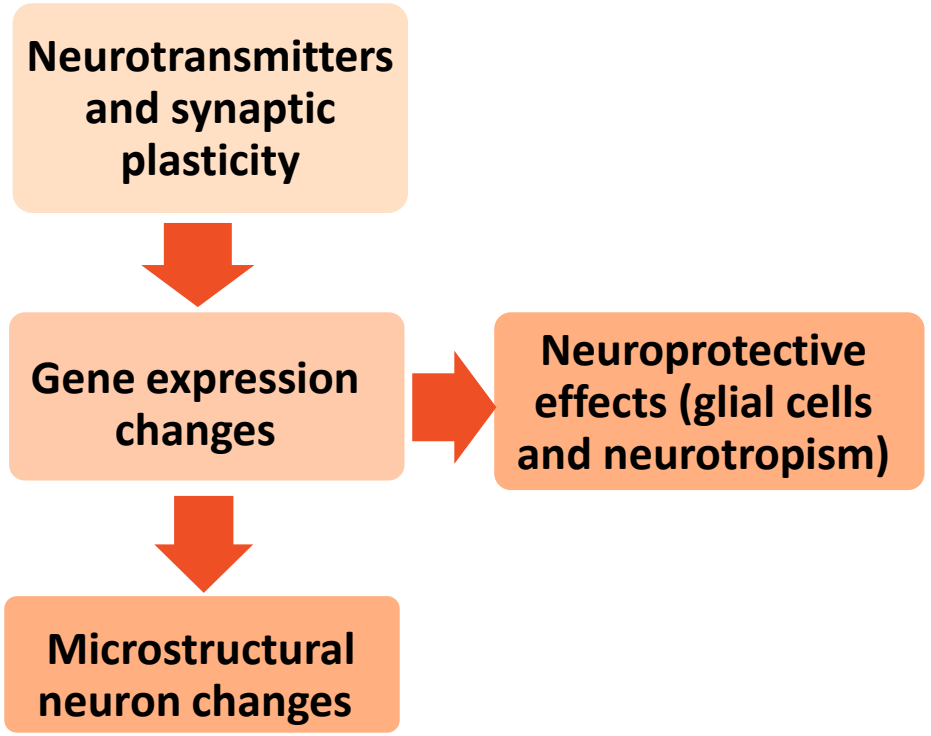
Typically, high-frequency stimulation of the left dorsolateral prefrontal cortex of the frontal lobe, other modalities, including deep stimulation with the "H-coil" and SAINT are also FDA-cleared

- Meta-analysis found repetitive transcranial magnetic stimulation was superior to sham stimulation for
  - Response (RR: 2.35 [95% CI, 1.70-3.25])
  - Remission (RR: 2.24 [95% CI, 1.53-3.27]) Raw
  - Remission rate = 30% (vs 6% sham controls)

- Open-label, naturalistic studies, compared to sham
  - ~60% of patients respond
  - ~60% who respond maintain response at 12 months
- Early improvement predicts response
- Older age, longer depressive episodes and prior ECT history lowers odds of response

Psychiatric medications may be continued, but TMS may work better for those who discontinue benzodiazepines and anticonvulsants

Possible Mechanisms of Action



SAINT = Stanford accelerated intelligent neuromodulation therapy. Chervyakov AV, et al. *Front Hum Neurosci.* 2015;9:303. Vida RG, et al. *BMC Psychiatry.* 2023;23(1):545. Dunner DL, et al. *J Clin Psychiatry*. 2014;75(12):1394–1401). Miller B. Predicting Response to rTMS in MDD. *Psychiatric Times*. 2024;41(10).

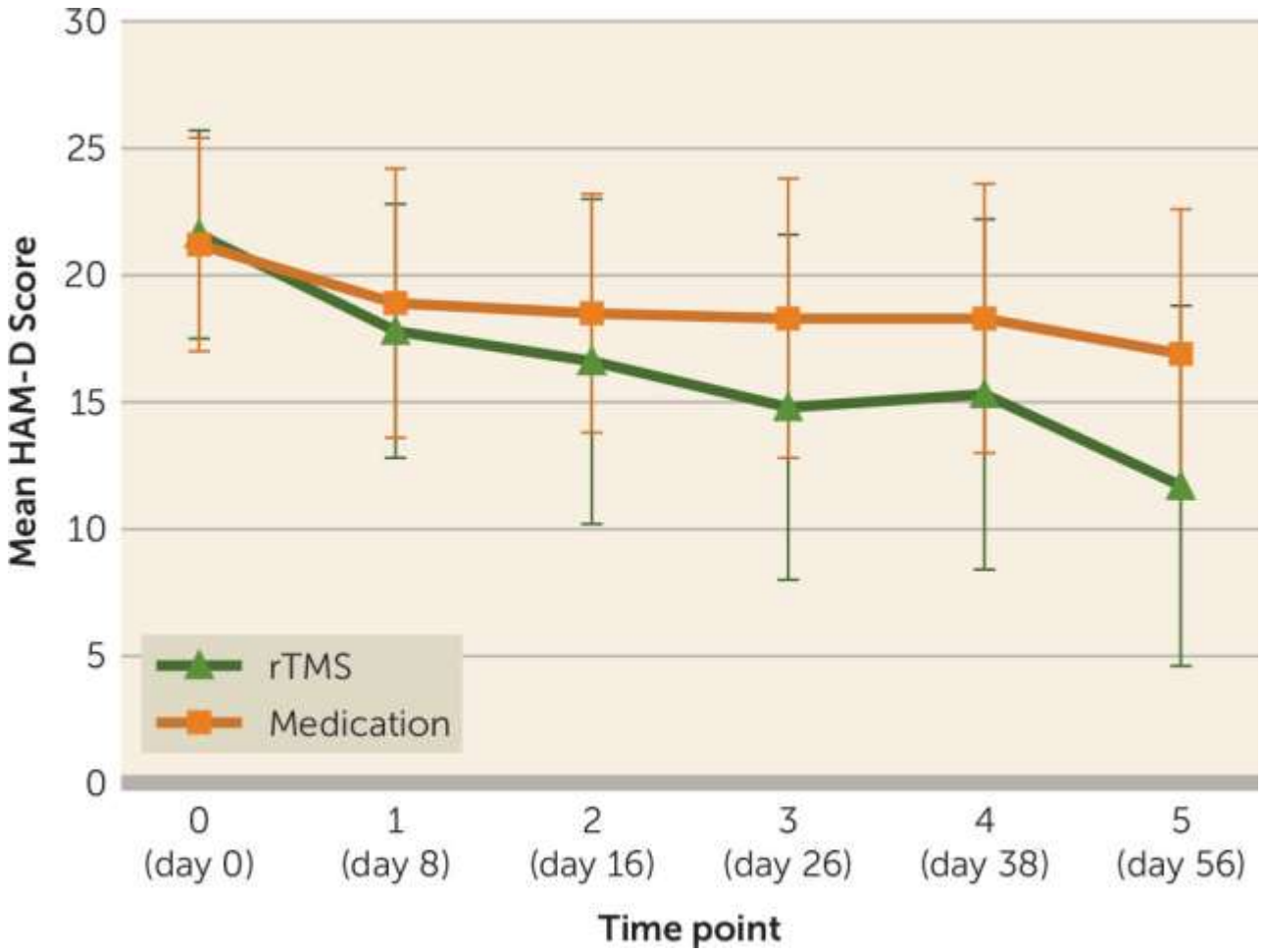
rTMS Compared with Switching Antidepressant

METHODS

- 89 patients with unipolar nonpsychotic TRD
- Randomly assigned to psychotherapy plus
  - rTMS ~3 times weekly
  - Antidepressant switch

RESULTS

- Significantly larger reduction in depressive symptoms with rTMS vs new medication
- Higher response rate with rTMS (37.5%) vs new medication (14.6%)
- Higher remission rate with rTMS (27.1%) vs new medication (4.9%)
- Larger decrease in anxiety and anhedonia symptoms with rTMS
- No differences in rumination, cognitive reactivity, or sleep disorders.



rTMS = repetitive transcranial magnetic stimulation. Dalhuisen I, et al. *Am J Psychiatry.* 2024;181(9):806-814.

SAINT iTBS Protocol

- 10-minute session, followed by 50-minute rest
- 10-times/day for 5 days
- 19 of 21(90%) participants achieved remission within 3 to 5 days

In a small, open-label study, SAINT iTBS significantly reduced MDD 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

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

Implantation done by neurosurgeon
Outpatient procedure (45-90 min)

Stimulator activation :

- Typically, 2–4 weeks post-implantation

Programming:

- Done by HCP in-office with hand-held computer, software, and programming wand

Programming features:

- Adjusts strength, duration, and timing of impulses (~30 sec on
  5 min off)

Patient Control:

- Via handheld magnet
  - Deliver extra stimulation (sweep over pulse generator site)
  - Temporarily turn off (hold magnet in place)
  - Resume stimulation upon magnet removal

Continuous operation:

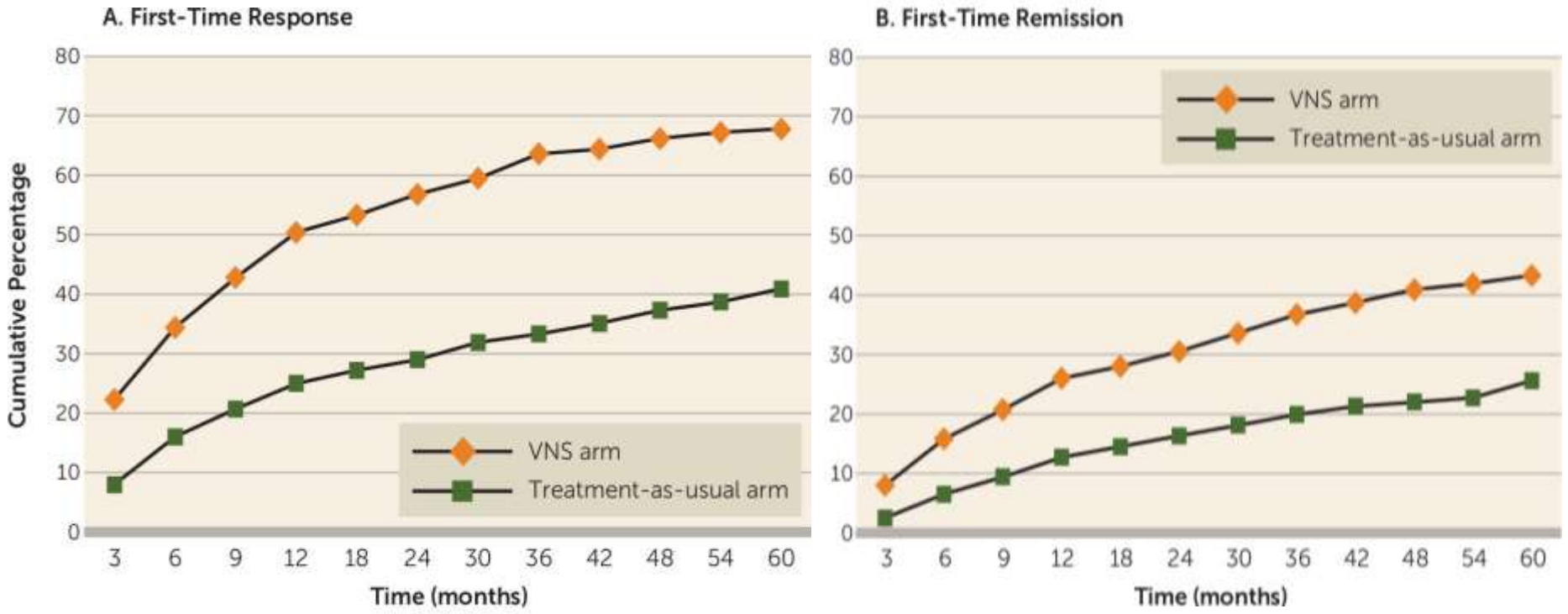
- Runs on set cycle unless manually adjusted

FDA APPROVED FOR TRD IN 2005

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.

Vagus Nerve Stimulation Efficacy and Safety

Treatment as Usual With or Without Adjunctive VNS



Most Common AEs:

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

Antidepressant benefits of VNS in TRD occurred over several months and were long-lasting: 67.6% 5-yr response, 43.3% remission (median time to response: 12 months)

Aaronson ST. *Am J Psychiatry*. 2017;174:640. Rush AJ. *Biol Psychiatry.* 2005;58(5):347. Ben-Menachem E. Vagus Nerve Stimulation, Side Effects, and Long-Term Safety. *Journal of Clinical Neurophysiology.* 2001;18 (5):415-418.

Choosing a Neuromodulation Intervention

Noninvasive Intervention	Pros	Cons
TMS ■ FDA-approved, office-based treatment using electromagnetic conduction to stimulate areas of the brain (typically the dorsolateral prefrontal cortex)	■ Pairs well with behavioral activation, as it provides daily structure for patients ■ Patients can continue daily routine (work, driving) ■ Minimal adverse effects ■ Good option in severe depression without psychosis or acute suicidality if patients worry about ECT adverse effects	■ Usually time-intensive, requiring 4 to 8 weeks of daily treatment (except SAINT protocol requiring 5 days) ■ Small risk for seizures
Invasive Interventions	**Pros**	**Cons**
VNS ■ FDA-approved treatment using a surgically implanted stimulator to deliver repetitive stimulation to the left cervical vagus nerve	■ May be effective in a population with severe TRD including bipolar depression ■ Good option in patients who respond to ECT but quickly relapse (also effective in ECT non-responders)	■ Carries surgical risks as well as risks for dysphagia and dysphonia ■ May require a long period of treatment before a response is seen ■ Not yet covered by most insurance
DBS ■ Experimental treatment with growing body of evidence using a surgically implanted stimulator in brain regions thought to be part of a mood-regulation network	■ Some evidence for benefit in severe TRD ■ Faster onset of effect compared with TMS and VNS (but not ECT) ■ Durable effect for responders	■ Expensive, invasive, and only available at very specialized centers
Other emerging neuromodulation interventions under study: transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and magnetic seizure therapy (MST)		

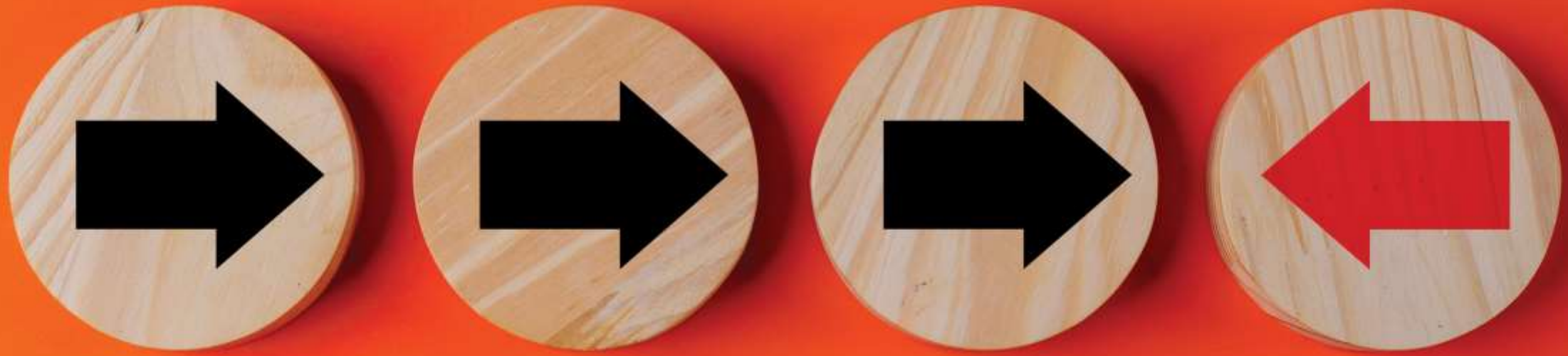
Kim J, Widge A. *Psychiatric Times.* 2024;41(3).

Key Learning Points

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

Discussion: Personalized Treatment Planning in TRD

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



COMORBIDITES?

Psychiatric and Medical

SUPPORT SYSTEMS

Occupational, family, friends

COLLABORATING PROVIDERS

Who is involved in care?

FINANCIAL STRAIN?

Is treatment sustainable given costs?

Patient-Specific Treatment Considerations

Is Earlier Treatment Better than More Treatment?

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

Accessing Treatments

- Referring to TMS/VNS/ECT
- Becoming an Esketamine Treatment Center vs. Referring to a Center

Practical Take-Aways

- Only 2/3 of patients with MDD are expected to reach remission with up to 4 treatment attempts.
- TRD is common, carries significant individual and societal burdens, and is defined as ≥2 qualifying unsuccessful antidepressant trials of adequate dose and duration within the same depressive episode
- Monoamines do play a role in MDD, but they do not explain all of the disease process. GABA and Glutamate both play a large role in MDD pathogenesis, and increasingly are targets of psychopharmacology
- We can share hope with our patients with multiple treatments FDA approved for TRD including olanzapine/fluoxetine, esketamine, TMS, ECT, and VNS.
- Through psychoeducation and shared decision making, we can develop effective TRD treatment plans with our patients.

Image credit: https://aepadillablog.wordpress.com/2015/08/13/pixars-inside-out-the-importance-of-sadness/

Questions?