NMDA Receptor Antagonism: A Novel Approach to Treating Depression

This presentation explores the role of NMDA receptor antagonism in treating depression. We will delve into WHY this shift in thinking is important and the mechanism of action therein. The discussion will cover Spravato, Auvelity, and Racemic Ketamine as "novel" therapeutic options.

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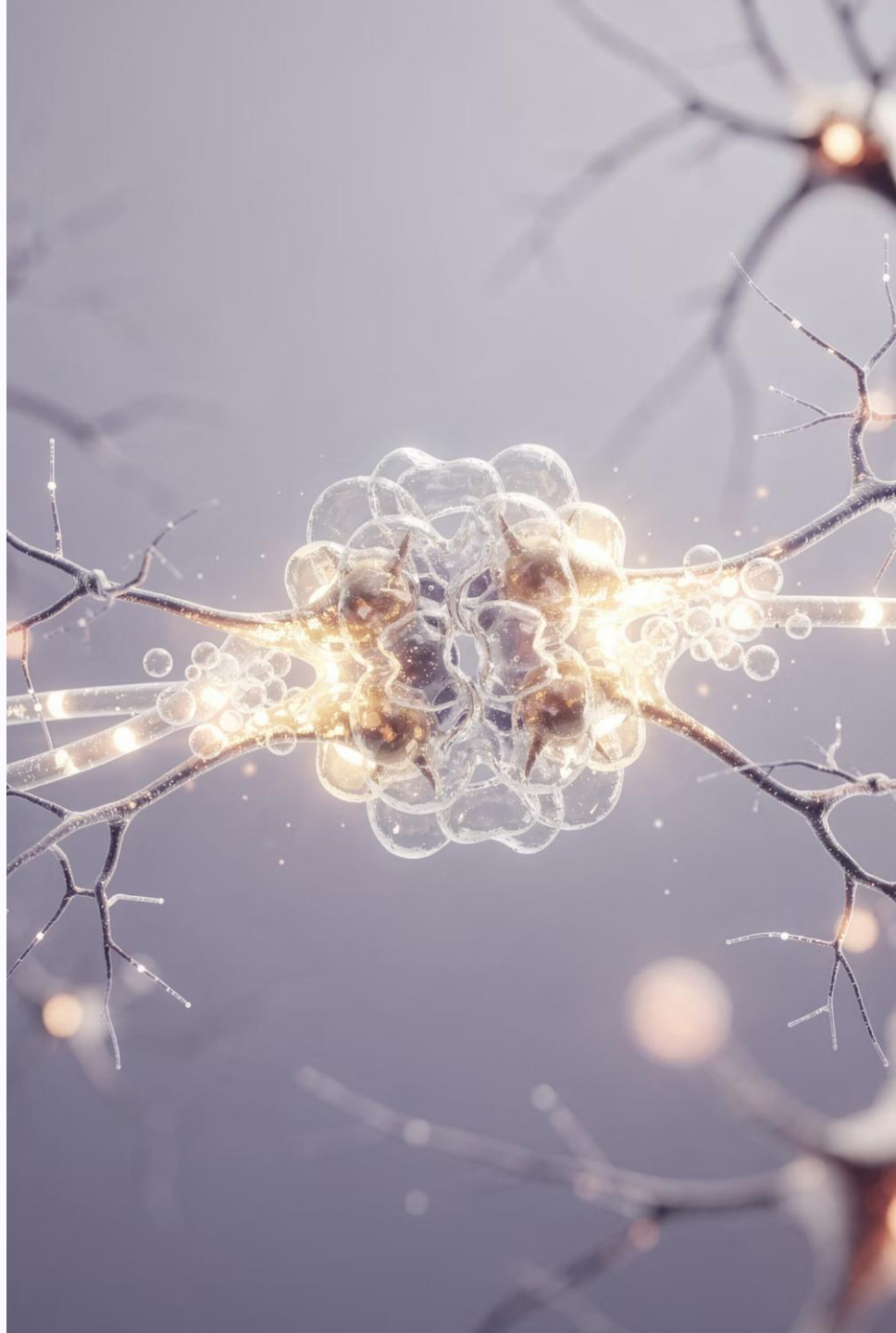
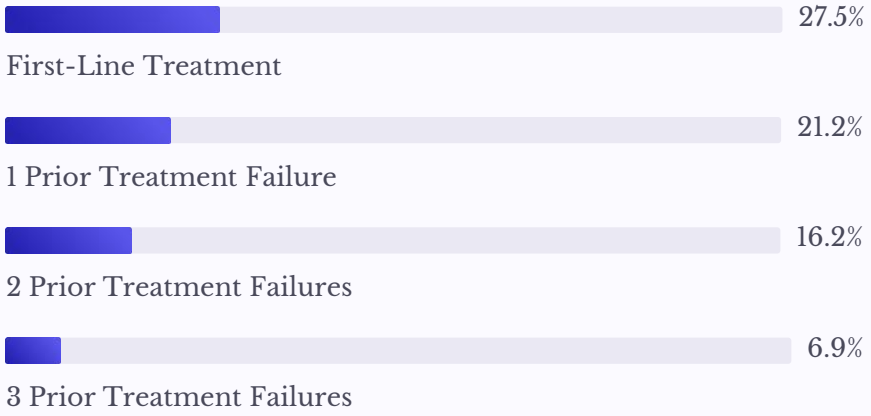


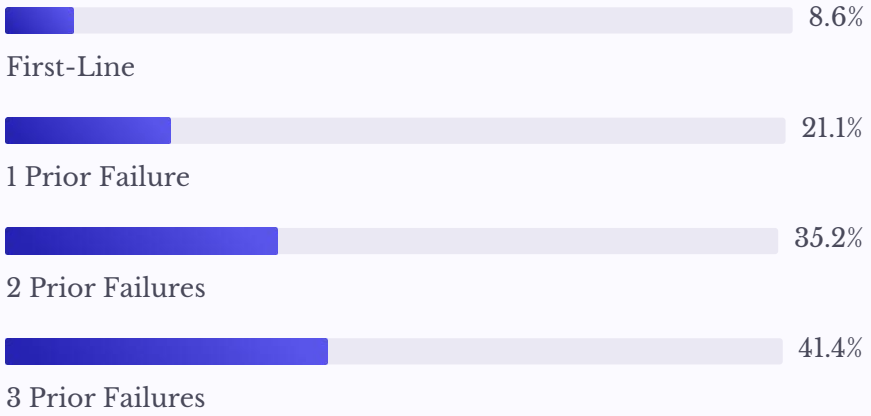
The STAR*D Study: Why Current Treatments Fall Short

The STAR*D study revealed a sobering reality — remission rates decline sharply with each successive antidepressant treatment attempt, while discontinuation rates climb.

Remission Rate by Treatment Step



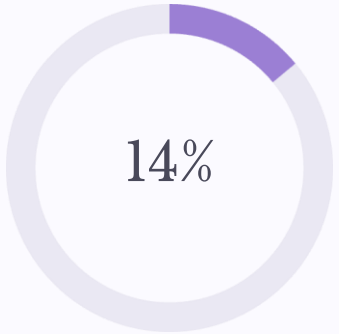
Discontinuation Rate by Treatment Step



These findings underscore the urgent need for novel mechanisms like NMDA receptor antagonism.

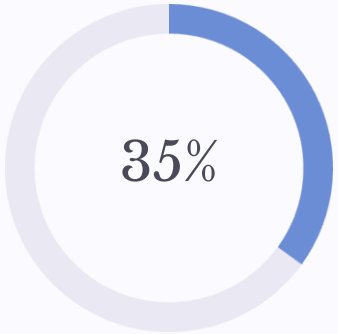
The Monoamine Hypothesis; Standard of Care?

Traditional antidepressants target monoamine neurotransmitters — serotonin, norepinephrine, and dopamine. Yet the STAR*D trial exposed critical limitations of this approach, with alarming rates of treatment failure, discontinuation, and relapse.



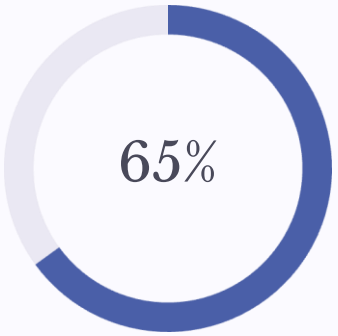
Remission Rates

Star*D Step 3



Discontinuation Rates

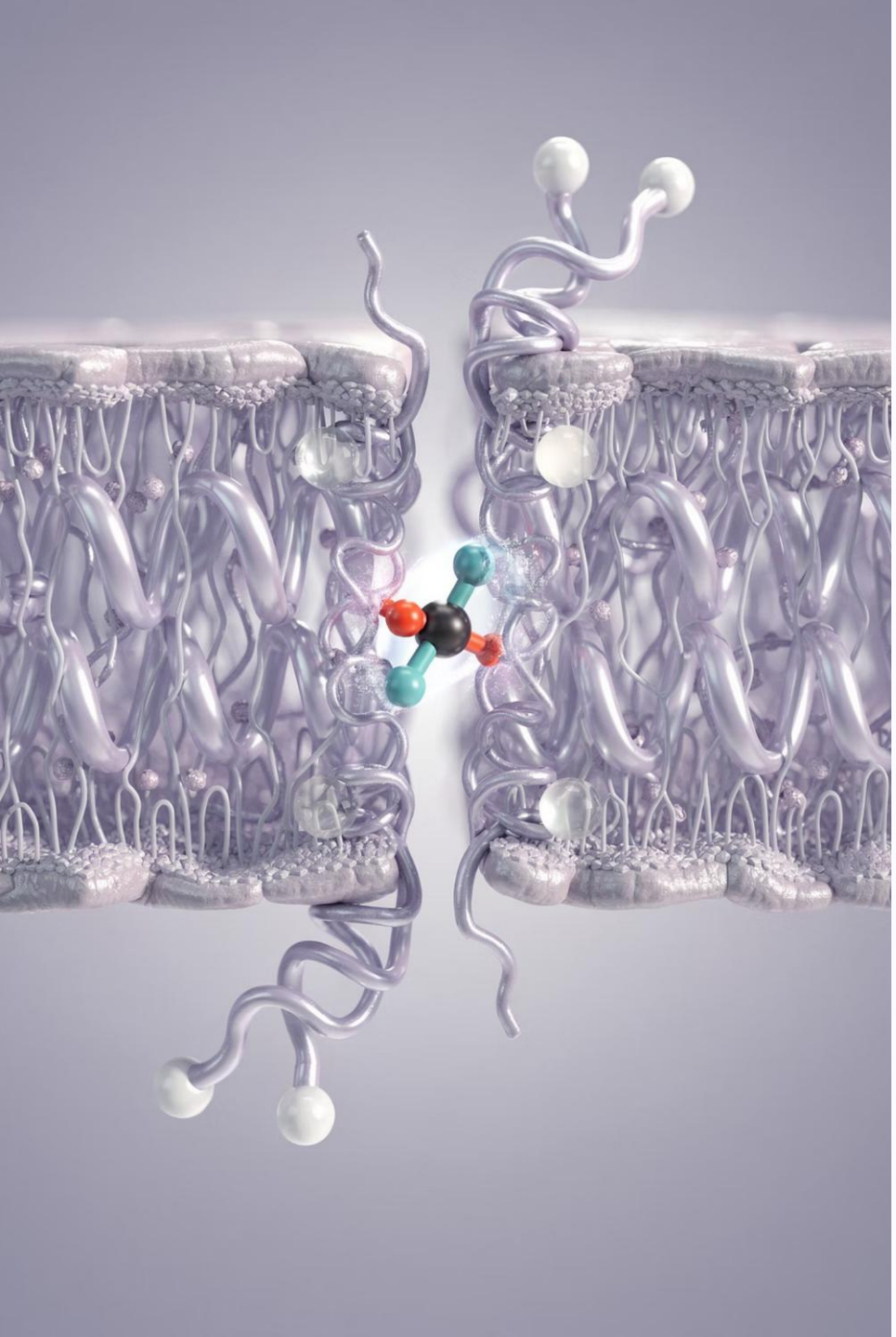
Star*D Step 3



Relapse Rates

Star*D Step 3

Nearly two-thirds of patients relapse, and fewer than 1 in 7 achieve remission by Step 3 — highlighting the ceiling of monoamine-based therapy.



NMDA Receptor Antagonism: A New Approach

NMDA receptor antagonists block or reduce receptor activity. This helps restore glutamate balance in the brain. This offers a different approach to traditional antidepressants. Traditional antidepressants primarily target serotonin, dopamine, and norepinephrine.

Blocks NMDA Receptor

Prevents glutamate from fully activating the receptor.

Modulates Glutamate Release

Alters the way neurons communicate.

Restores Balance

Helps modulate glutamate levels in the brain.

Understanding Glutamate Receptors

NMDA receptors are glutamate-gated ion channels in the brain. They play a critical role in synaptic plasticity as well as in learning and memory. **Dysregulation** is implicated in depression symptomatology.

1 Ionotropic Receptors

Allows ions like calcium to flow into the neuron.

2 NMDA & AMPA

Both play key roles in antidepressant effects

Introducing Spravato (Esketamine)

Spravato (esketamine) is an NMDA receptor antagonist. It is approved for treatment-resistant depression as adjunctive and monotherapy. Also, it is approved for depressive symptoms in adults with suicidal thoughts. It is administered as a nasal spray.

1. ## Nasal Spray

   Administered intranasally for rapid absorption.

2. ## Treatment-Resistant Depression

   Approved for patients who haven't responded to 2 or more medication treatments.

3. ## Suicidal Ideation

   Offers a new approach for individuals with severe depressive symptoms.

4. ## Administered over a 2 hour period under the supervision of a REMS certified HCP

Mechanism of Action: How Spravato Works

Spravato works by blocking the NMDA receptor. This leads to increased release of Glutamate and downstream upregulation of brain-derived neurotrophic factor (BDNF). BDNF promotes neuronal growth and synaptic connections. This is thought to be one of the four “Pillars” of the newly formed Depression Hypothesis.

1

Blocks NMDA

Esketamine binds to the NMDA receptor.

2

BDNF Release

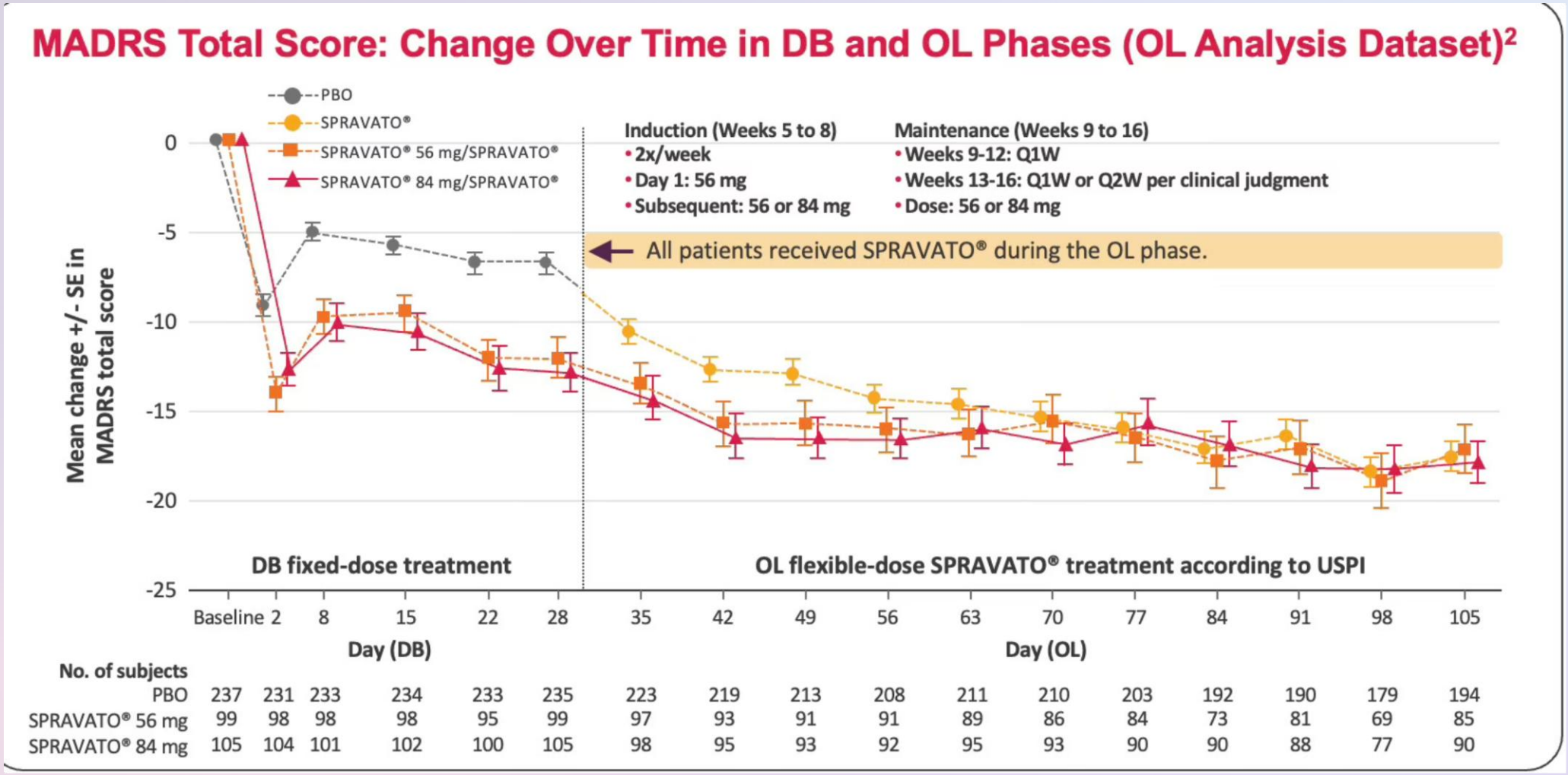
Increases the release of BDNF.

3

Neuronal Growth

Promotes neuronal growth and connections.

Clinical Trials: Evidence of Efficacy



Introducing Auvelity (Dextromethorphan/Bupropion)

FDA approved in August 2022 for Major Depressive Disorder (MDD) in adults, Auvelity stands as the first and only oral NMDA receptor antagonist approved for MDD.

1 Unique Combination

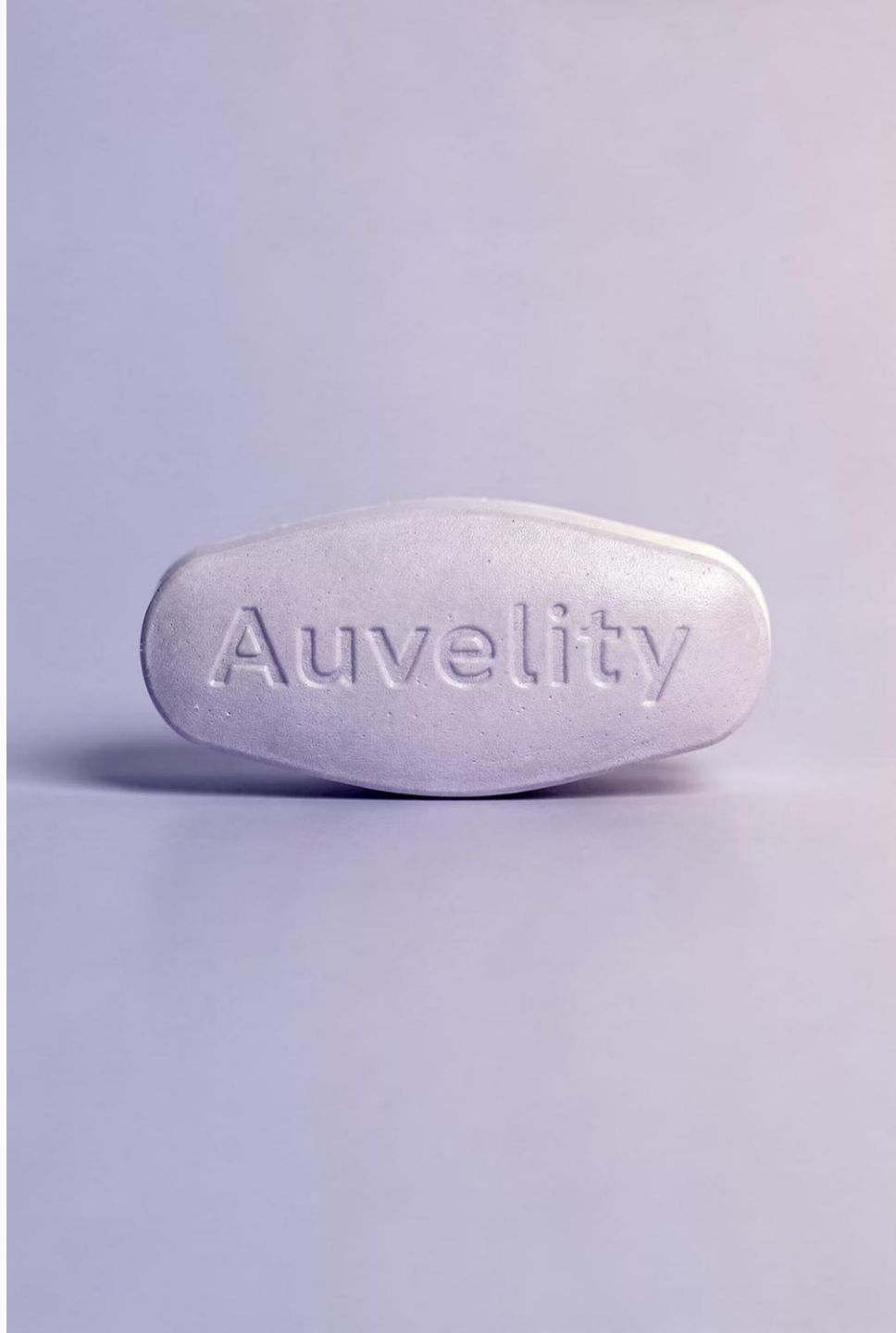
Combines dextromethorphan (an uncompetitive NMDA receptor antagonist and sigma-1 receptor agonist) with bupropion (a CYP2D6 inhibitor that extends DXM's half-life from 4 to 22 hours).

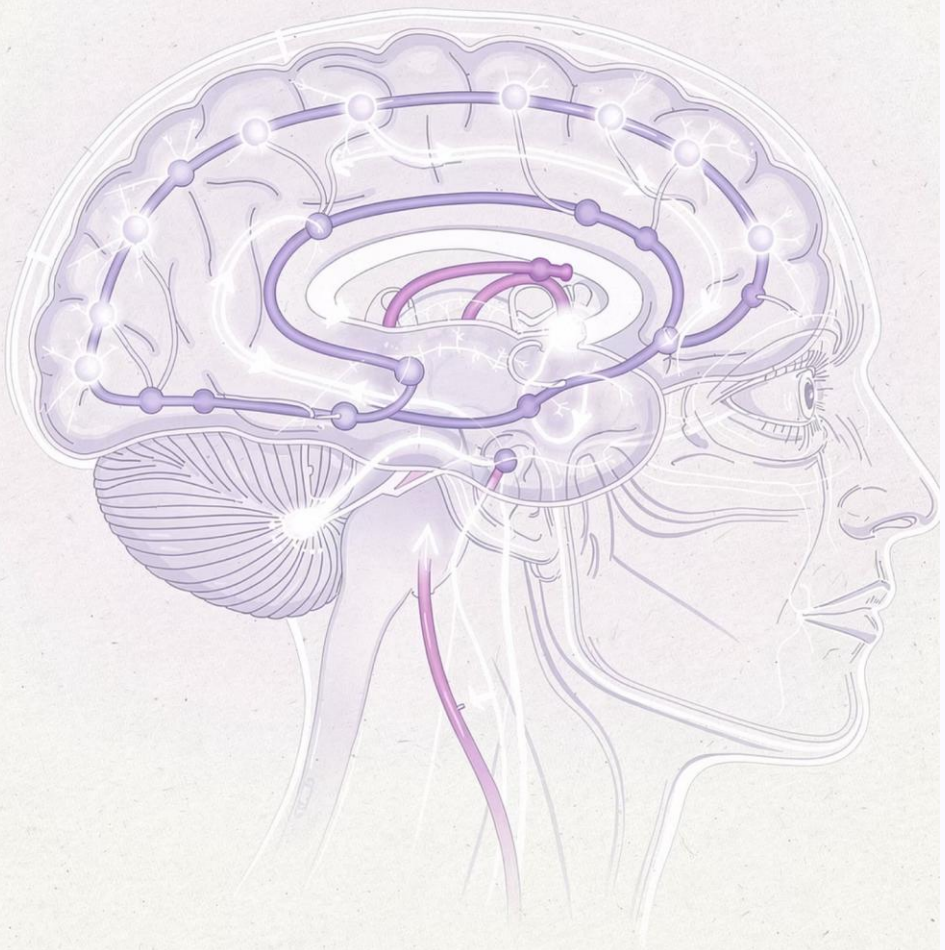
2 Novel Mechanism

Represents the first new oral non-monoamine mechanism approved for depression in over 60 years, targeting glutamate pathways.

3 Rapid Efficacy

Demonstrated statistically significant efficacy versus placebo starting as early as one week into treatment.





Auvelity: Mechanism of Action

Auvelity provides a unique dual-pathway approach, combining the actions of dextromethorphan (DXM) and bupropion to address depression through both glutamatergic and monoaminergic systems.

1

Dextromethorphan: NMDA Antagonism

Blocks NMDA receptors, restoring **glutamate balance** and **synaptic functioning**.

2

Dextromethorphan: Sigma-1 Agonism

Modulates mood, stress response, **inflammation**, and cognitive function.

3

Bupropion: CYP2D6 Inhibition

Extends DXM's half-life from 4 to 22 hours, maintaining therapeutic levels.

4

Bupropion: NE/DA Reuptake Inhibition

Enhances norepinephrine and dopamine activity, contributing to antidepressant effects.

5

Multimodal Activity

Simultaneously targets glutamatergic, anti-inflammatory, synaptogenesis, and **all three monoaminergic pathways** for comprehensive antidepressant action.

Spravato vs. Auvelity: Key Comparisons

Dimension	Spravato	Auvelity
Drug Class	Esketamine (S-enantiomer of ketamine), NMDA antagonist	Dextromethorphan/Bupropion, NMDA antagonist + sigma-1 agonist + monoamine reuptake inhibitor
FDA Indication	Treatment-Resistant Depression (TRD) AND Major Depressive Disorder (MDD) with acute suicidal ideation	MDD in adults (Not approved for TRD)
Route of Administration	Intranasal, in-office only (REMS program required)	Oral tablet, taken at home
Onset of Action	Rapid, within hours to days	Rapid, statistically significant at 1 week
Dosing	Twice weekly for 4 weeks, then weekly for 4 weeks, then every 1-2 weeks	Once daily for 3 days, then twice daily
Controlled Substance	Schedule III	Not a controlled substance
REMS Required	Yes (must be administered in certified healthcare setting)	No

Choosing the Right NMDA Antagonist for Your Patient

Clinical decision framework

Choose Spravato when:

- Patient has Treatment-Resistant Depression (TRD) — failed 2+ antidepressants
- Patient has acute suicidal ideation (MDD with SI)
- Clinic has REMS certification and monitoring infrastructure
- Rapid, supervised treatment is preferred
- Patient cannot take oral medications reliably

Choose Auvelity when:

- Patient has MDD (not necessarily TRD)
- Patient prefers oral, at-home treatment
- Avoiding controlled substance scheduling is a priority
- Clinic lacks REMS infrastructure
- Patient has failed or is intolerant to traditional antidepressants and wants a novel mechanism

Both share NMDA antagonism but serve different patient populations and practice settings.

How about Racemic Ketamine?

Racemic Ketamine is an intravenous medication. It has shown promise in treating patients with major depressive disorder (MDD), suicidal thoughts or actions, and PTSD. Some new evidence for OCD and SUDs.

IV Administration

Administered as an intravenous infusion under medical supervision.

NMDA Receptor Antagonist

A novel mechanism of action compared to traditional antidepressants.

Rapid Relief

May provide relief from depressive symptoms within hours.

Potential Side Effects: What to Watch For

Common side effects include dissociation, sedation, and increased blood pressure. Nausea and vomiting can also occur. Almost all are transient and return to baseline within same day of dosing. Serious adverse events are rare but should be monitored. Patients should be educated about these risks.

Spravato	Auvelity
Sedation	Dizziness
Dissociation	Nausea
Increased Blood Pressure	Dry Mouth
Nausea/vomiting	Increased Blood Pressure

Glutamate vs. Traditional Monoamine Antidepressants

Glutamate Modulators (i.e. Spravato/Auvelity) offer a different mechanism of action. It targets the NMDA receptor, unlike traditional monoamine medications (i.e. SSRIs and SNRIs). It has a more rapid onset of action. Traditional antidepressants can take weeks to show effects.

Mechanism

Targets NMDA receptors vs Monoamines

Onset

Rapid onset of action vs delayed onset

Remission Rates

Approaches 70% vs <30% in TRD

The Future of NMDA Receptor Antagonism

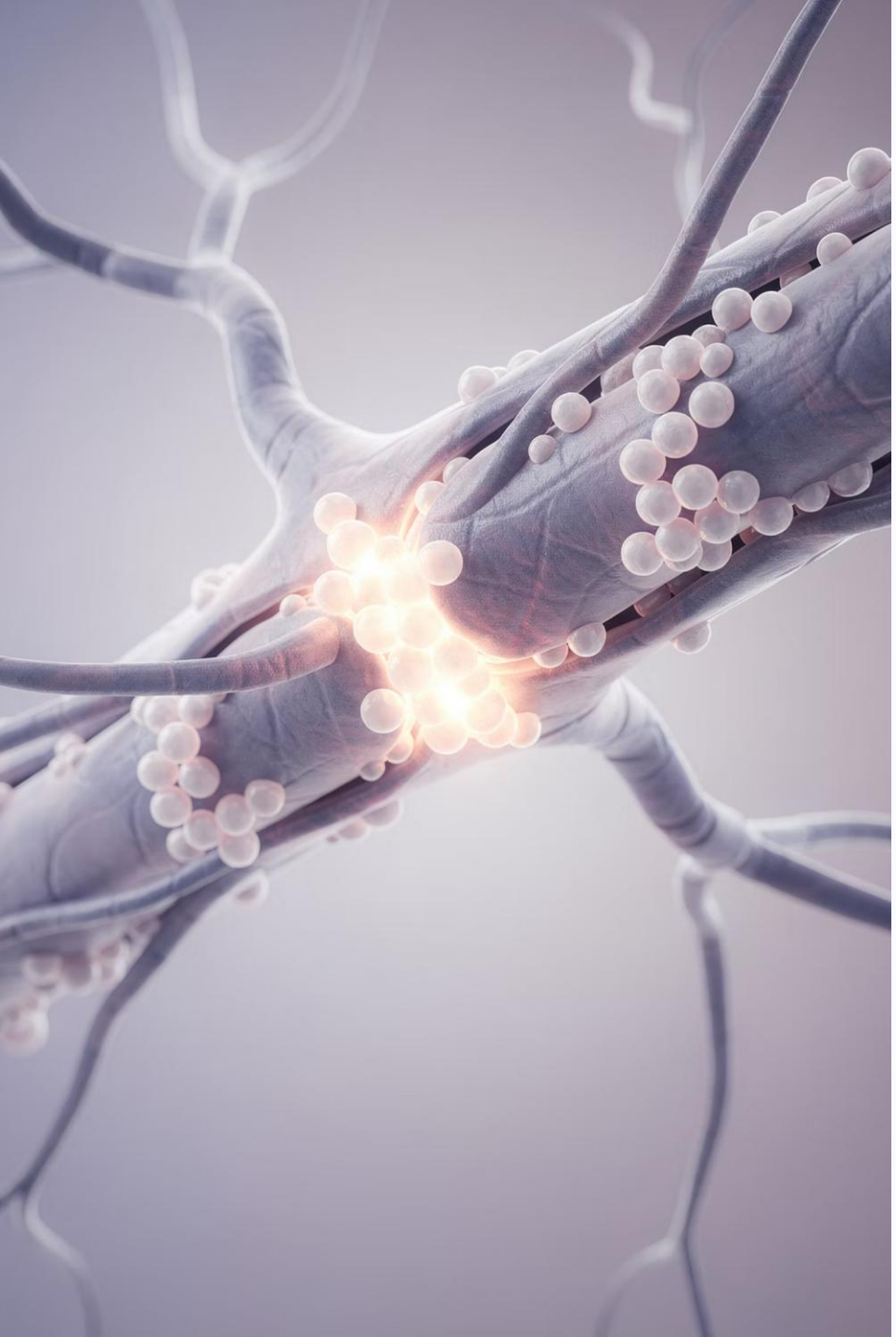
Research is ongoing to explore other NMDA receptor modulators. New compounds with improved safety profiles are being developed. This approach holds promise for treating other psychiatric disorders. Examples include anxiety and PTSD.

1 New Compounds

Pipeline of new compounds with similar mechanisms
*Psychedelics in late phase human studies (i.e. psylocibin)

2 Other Psychiatric Disorders

Promising approach for anxiety and PTSD.



Key Takeaways: NMDA Antagonism in Depression Treatment

Both Spravato and Auvelity represent a paradigm shift in depression treatment — moving beyond monoamines to target the glutamate system with rapid, meaningful results.

Novel Dual-Pathway Mechanisms

Spravato (esketamine) and Auvelity (dextromethorphan/bupropion) both target NMDA receptors, offering faster onset and higher efficacy than traditional monoamine-based antidepressants.

Right Drug, Right Patient

Spravato is indicated for TRD and MDD with acute suicidal ideation; Auvelity for MDD. Patient profile, practice setting, and REMS capability should guide selection.

Rapid Onset Advantage

Unlike traditional antidepressants that take 4–8 weeks, both Spravato and Auvelity demonstrate statistically significant antidepressant effects within days to 1 week — a critical advantage for patients in acute distress.

The Future is Glutamatergic+

With ongoing research into new NMDA modulators, this class is poised to expand its role across TRD, MDD, PTSD, and beyond.

Questions?!

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