New Mechanisms, New Possibilities: Exploring Innovations in Psychopharmacology for Depression and Associated Symptoms

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Faculty

Craig Chepke, MD, DFAPA

Medical Director,
Excel Psychiatric Associates
Huntersville, NC
Adjunct Associate Professor of Psychiatry,
Sandra & Leon Levine Psychiatry Residency Program at Atrium Health
Charlotte, NC

Veronica Ridpath, DO

University of South Carolina SOM
Clinical Assistant Professor
Department Chair, Psychiatry and Substance Use Disorders
HopeHealth
Florence, SC

Faculty Disclosures

- **Craig Chepke, MD, DFAPA:** Advisory Board—AbbVie, Acadia, Alkermes, Axsome, Biogen, Bristol Myers Squibb, Corium, Idorsia, Intra-Cellular, Johnson & Johnson, Lundbeck, Moderna, Neurocrine, Noven, Otsuka, Sage, Sumitomo, Teva; Advisory Board (spouse): Bristol Myers Squibb, Otsuka; Consultant—AbbVie, Acadia, Alkermes, Axsome, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Corium, Intra-Cellular, Johnson & Johnson, Lundbeck, MedinCell, Moderna, Neurocrine, Noven, Otsuka, Sage, Sumitomo, Supernus, Teva; Research/Grant Support—Acadia, Axsome, Harmony, Neurocrine, Teva; Speaker's Bureau—AbbVie, Acadia, Alkermes, Axsome, Boehringer Ingelheim, Bristol Myers Squibb, Corium, Intra-Cellular, Johnson & Johnson, Lundbeck, Merck, Neurocrine, Noven, Otsuka, Sumitomo, Teva

- **Veronica Ridpath, DO:** Speaker Bureau– Abbvie, Alkermes, Axsome, Neurocrine, Teva, Intra-Cellular Therapies. Advisory Board– Otsuka

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- ✓ 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)
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- ✓ This activity has been independently reviewed for balance

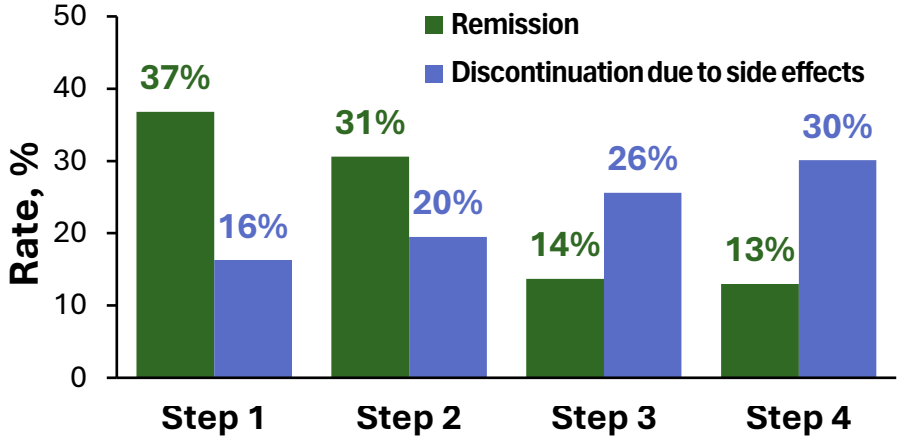
Learning Objectives

- Outline the limitations of traditional pharmacotherapies for depression and associated symptoms
- Describe the mechanisms of action (MOA) of novel/investigational pharmacotherapies for depression and associated symptoms
- Evaluate clinical evidence and implications associated with novel/investigational pharmacotherapies for depression and associated symptoms

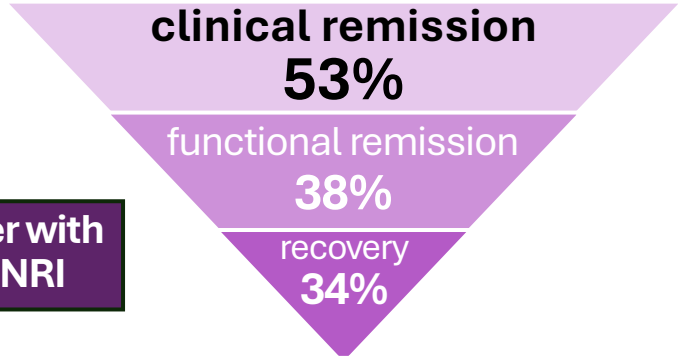
The Importance of Continual Innovation in Psychopharmacology

The Reason We Need Innovation…

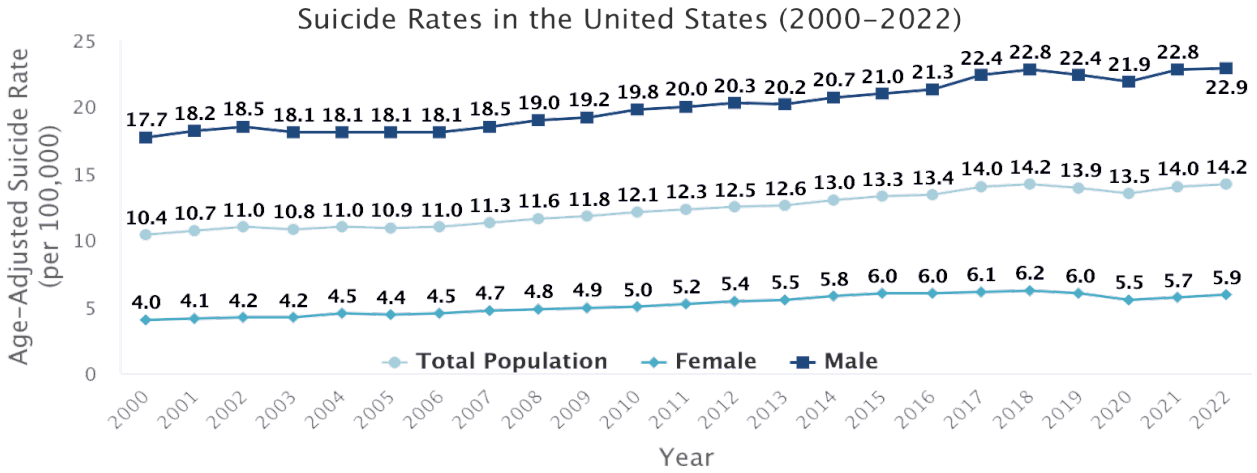
Each successive treatment in STAR*D brought lower remission rates and increased intolerance



Among 1297 people with MDD after 16 weeks of an SSRI/SNRI in an observational study:



Only 1 in 3 recover with the first SSRI/SNRI



And suicide rates continue to rise:

≈49,000 deaths in 2023

~1 Life Lost Every 11 Minutes

SS = selective serotonin; SN = selective norepinephrine; RI = reuptake inhibitor; STAR*D = Sequenced Treatment Alternatives to Relieve Depression.

Rush AJ, et al. *Am J Psychiatry.* 2006;163(11):1905-1917. Voineskos, et al. *Neuropsych Dis Treat.* 2020;16:221-234. Ishak, et al. *Depress Anxiety.* 2014;31:707-716. Novick D, et al. *Patient Prefer Adherence.* 2017;11:1859–1868. https://www.nimh.nih.gov/health/statistics/suicide. Accessed 5-28-25.

Glutamate in MDD: NMDA Receptor Antagonism

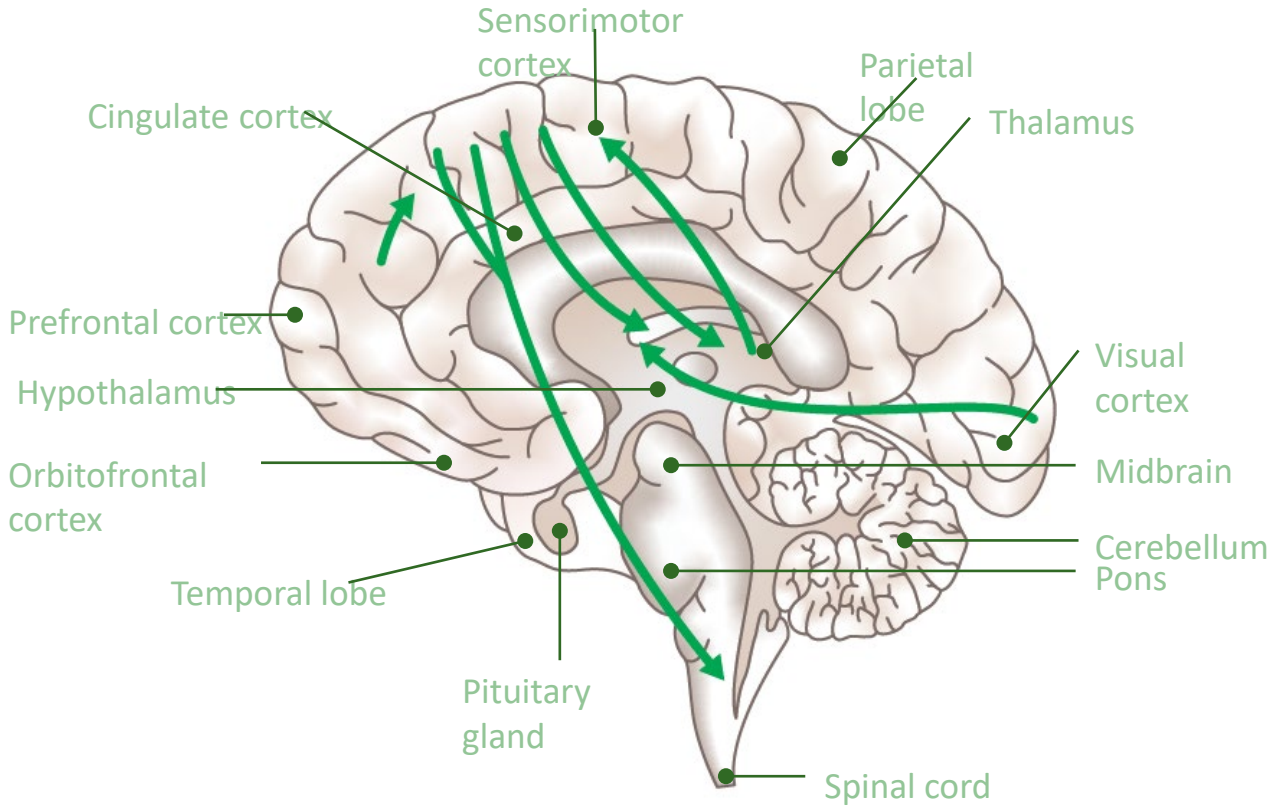
NMDA = *N*-methyl-D-aspartate; MDD = major depressive disorder.

Glutamate Is THE #1 Most Common Neurotransmitter in the Brain

DID YOU KNOW?

- **Glutamate comprises ~40% of all neurotransmitters in the brain**
- **Glutamate is responsible for the majority of all action potentials in the brain. 85% of synapses are glutamatergic**
- **Glutamate is a vital neurotransmitter involved in:**
  - **Cognition**
  - **Affect/Mood**
  - **Learning**
  - **Memory**

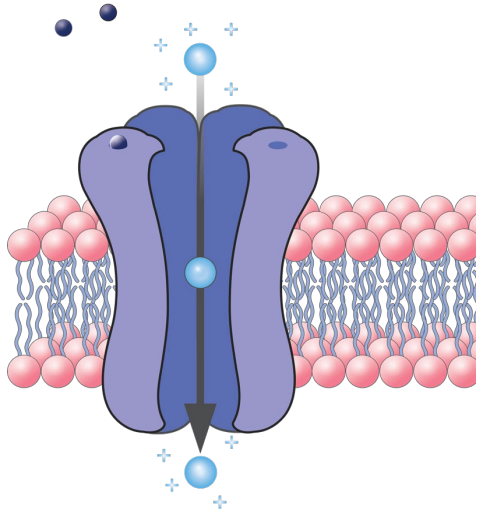
C.A.L.M.



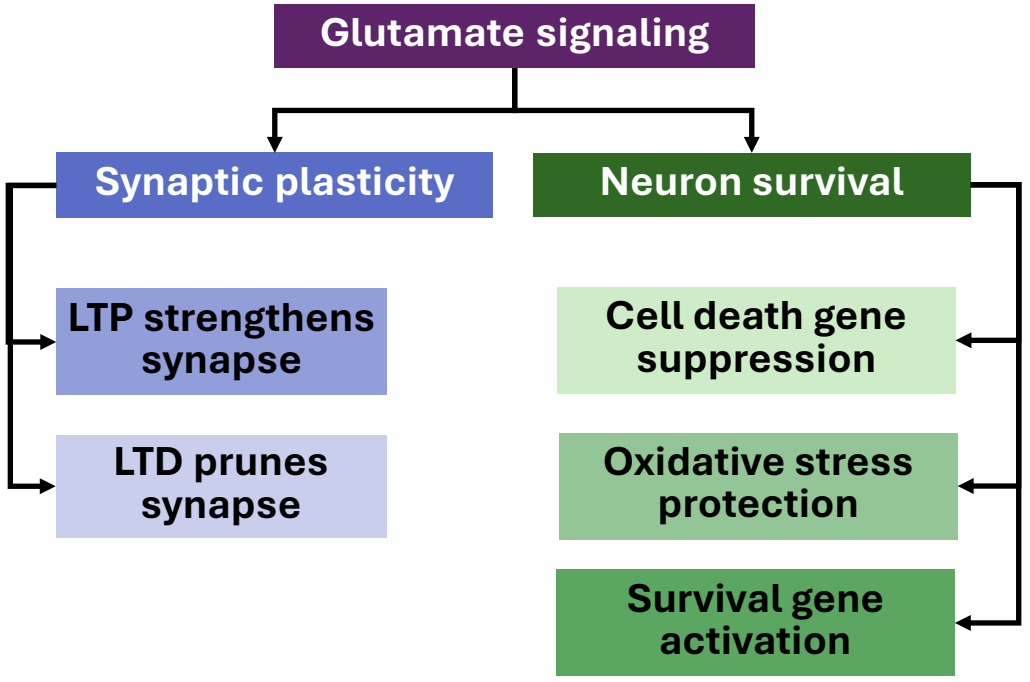
Well – Does Glutamate Have Our Attention Now?!

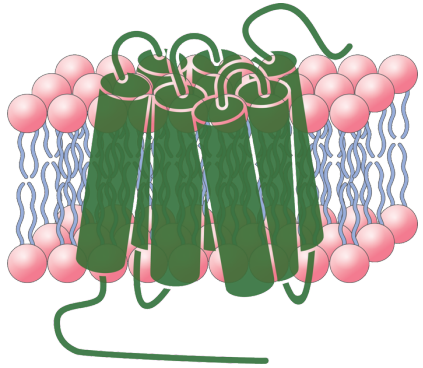
Stahl SM. *Stahl's Essential Pharmacology*. 4th ed. Cambridge University Press; 2013. Duman RS. *Dialogues Clin Neurosci*. 2014;16(1):11-27.

Also – Glutamate's Ionotropic NMDA and AMPA Receptors are the Drivers of Neuroplasticity in the Brain



Ionotropic Glu receptors, including **NMDA** receptor, change nerve cells activation thresholds





Metabotropic G-protein-coupled **mGlu receptor** leads to changes in DNA expression

Remember!

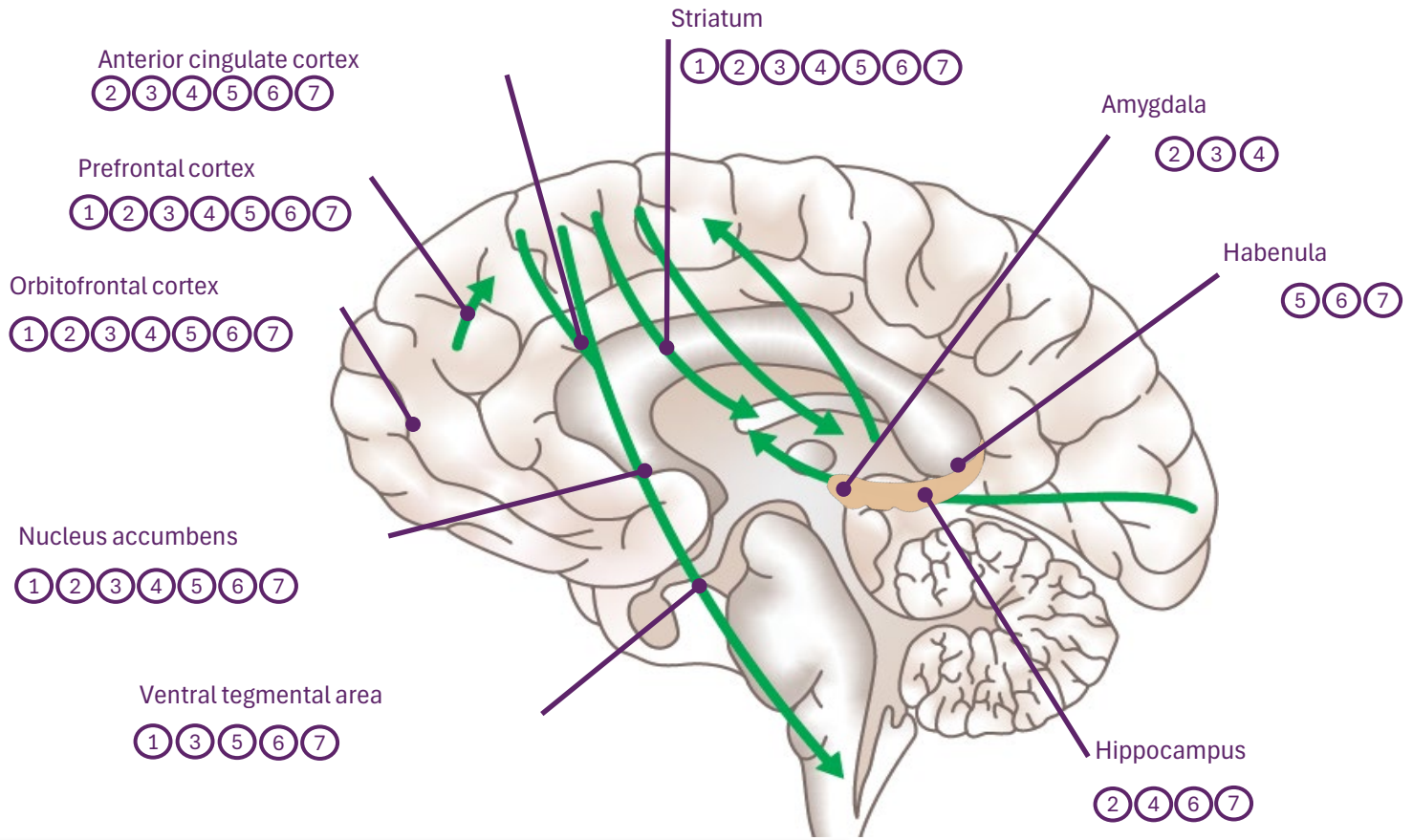
1. Neuroplasticity is very important in recovery from various psychiatric disorders
2. Glutamate is vital in the creation of neuroplasticity

LTD = long-term depression; LTP = long-term potentiation.

Jourdi H, et al. *J Neurosci*. 2009;29(27):8688-8697. Malenka RC, Nicoll RA. *Trends Neurosci*. 1993;16(12):521-527. Wang S, et al. *Brain Sci*. 2022;12(10):1329.

Additionally – Glutamate Has a Major Role in Anhedonia Symptoms of MDD

1. Subjective anhedonia
2. Anticipation
3. Motivation/effort
4. Valuation
5. Expectation
6. Consummatory pleasure
7. Learning/feedback integration



Remember!

1. Anhedonia is found in about 70% of patients with MDD
2. Anhedonia's presence complicates the severity of MDD and is a marker of poorer response to SSRIs

Wang S, et al. ***Prog Neuropsychopharmacol Biol Psychiatry*****. 2021;110:110289.**

Let’s Focus for a Minute on the Amazing NMDA Receptor

Given the Potential for Neurotoxicity, NMDA Receptors are Among the Most Tightly Regulated in the Human Brain

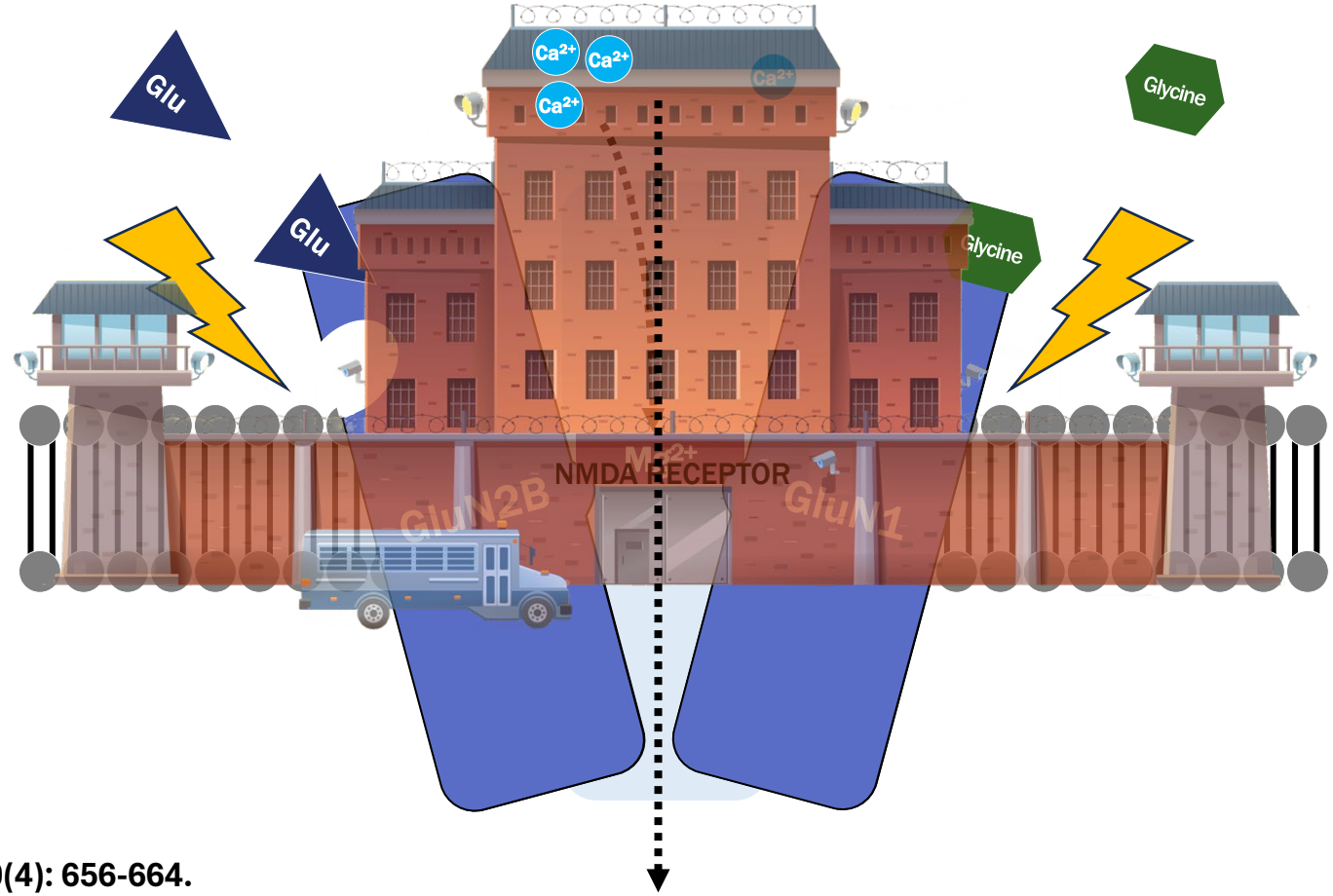
Given the potential for neurotoxicity, NMDA receptors are among the most tightly regulated in the human brain.

For one, they are the only ones that require co-agonists for activation.

Co-Agonists

Opening the NMDA receptor's ion channel requires:

- ✓ Glutamate **x2**
- ✓ Glycine **x2 (or D-serine x2)**
- ✓ Membrane depolarization to remove Mg^{2+} plug

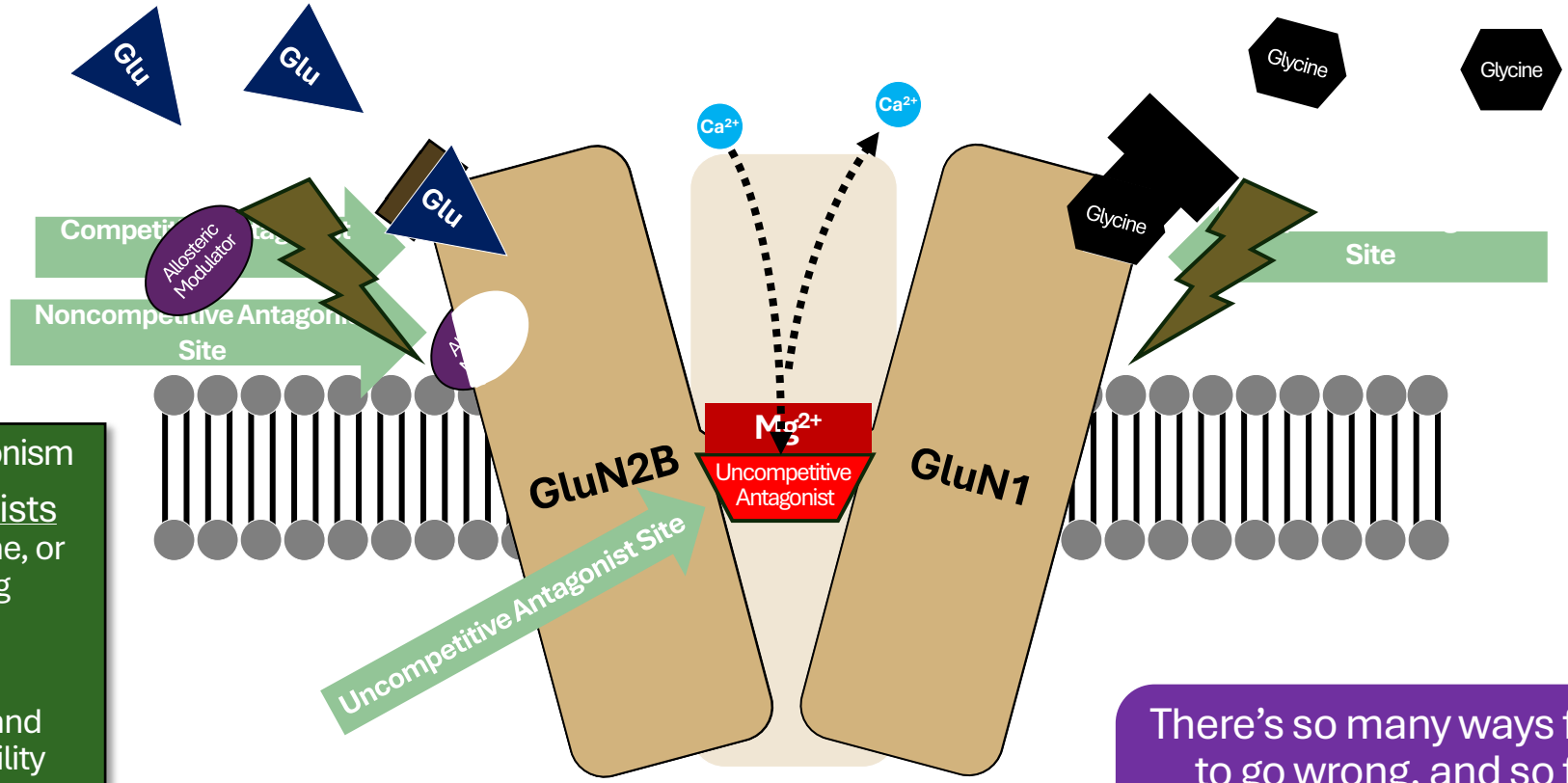


Niciu, MJ. *Pharmacology Biochemistry and Behavior*. 2012;100(4): 656-664.
Duman, RS. *F1000Res*. 2018;7:F1000 Faculty Rev-659.

The NMDA Receptor Can be Modulated in Many Ways

The NMDA Receptor's elaborate set of checks and balances might guard against inadvertent activation…

but it also provides multiple avenues to inhibit its function



Types of NDMA-R Antagonism

Competitive antagonists
Prevent glutamate, glycine, or D-serine from binding

Noncompetitive antagonists
Bind at allosteric sites and modulate open probability

Uncompetitive antagonists
Block the ion channel completely

There's so many ways for NMDA Receptors to go wrong, and so few to get it right…

It's no wonder so many investigational NMDA antagonists have been unsuccessful!

Niciu, MJ. *Pharmacology Biochemistry and Behavior*. 2012;100(4):656-664. Duman RS. *F1000Res*. 2018;7:F1000 Faculty Rev-659.

Good News for Patients and Clinicians!

We Now Have Two FDA-Approved Treatment Options in MDD that are Primarily Glutamate Based Interventions

Let's Examine Both Briefly...

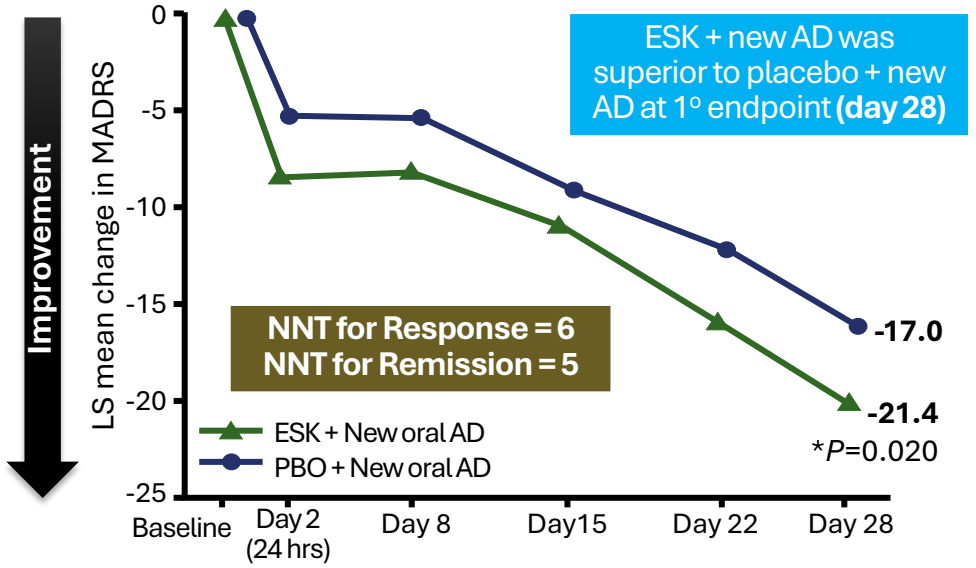
The Noncompetitive NMDA Antagonist Esketamine Has Shown Efficacy in Clinical Trials of "TRD"

The S-enantiomer of ketamine has 2X to 4X greater potency than the R-enantiomer for the NMDA receptor

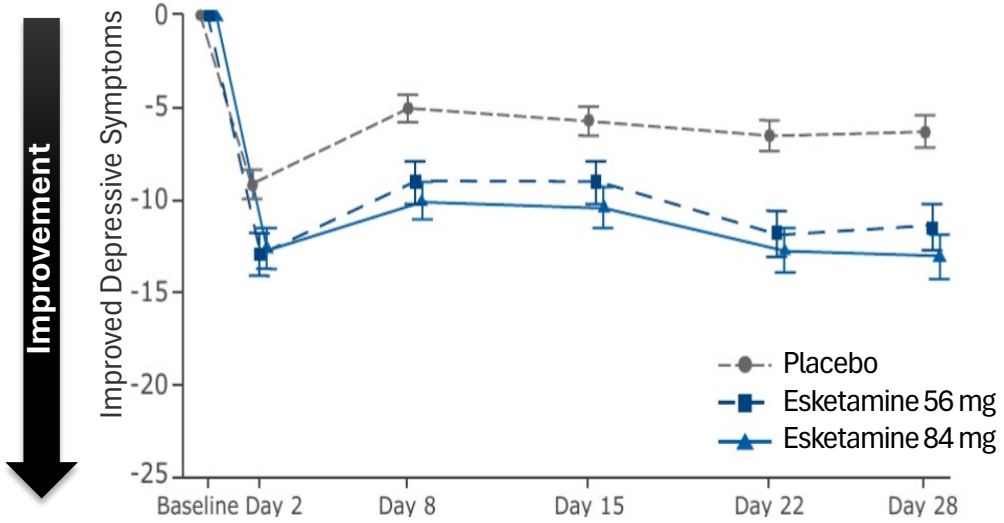
Self-administered by nasal spray device to delivers the dose to the optimal area for mucosal absorption

Most participants in flexible-dose studies received 84 mg esketamine *(56mg is comparable to 0.5 mg/kg ketamine)*

Treatment Resistant Depression - Adjunct



Treatment Resistant Depression - Monotherapy



Esketamine rapidly and robustly improved depressive symptoms in populations of difficult-to-treat MDD

TRD = treatment-resistant depression; ESK = esketamine; AD = antidepressant; MADRS = Montgomery-Åsberg Depression Rating Scale; NNT = number needed to treat.

Popova V, et al. *Am J Psych*. 2019;176(6):428-438. Esketamine [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals; 2022. Janik A, et al. American Society of Psychopharmacology Annual Meeting. Poster presentation. May 28, 2024. McIntyre RS, et al. *Am J Psychiatry*. 2021;178.5: 383-399.

Esketamine Has A Substantial Database in TRD

Adjunctive esketamine provided rapid and superior improvement of depressive symptoms in TRD, as soon as 24 hours and sustained over 1.5 years

STABLE RESPONSE

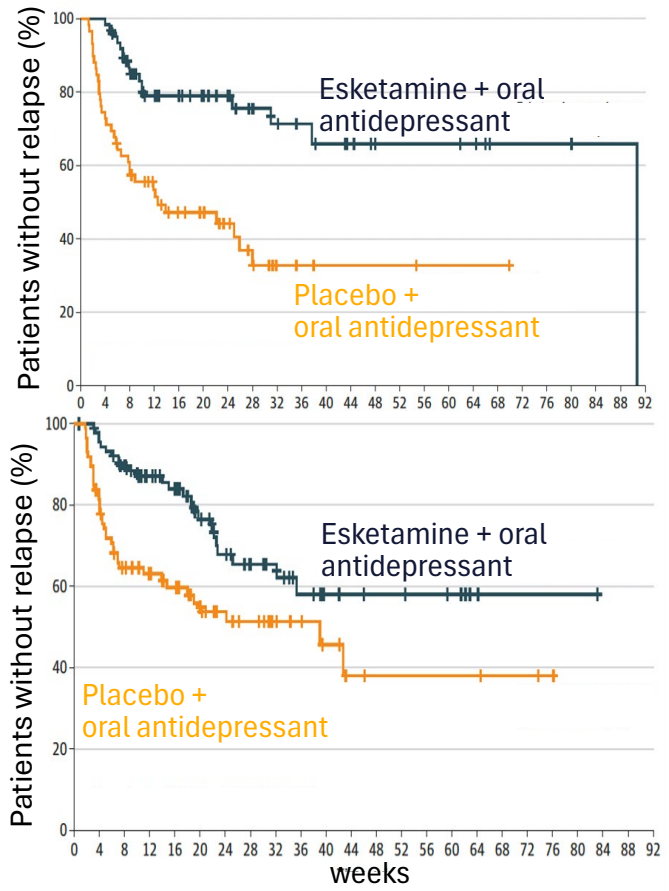
70%

Less likely to relapse (95% CI: 0.16-0.55) *P*=0.001

STABLE REMISSION

51%

Less likely to relapse (95% CI: 0.29-0.55) *P*=0.003



Most Common AEs in Short-Term TRD Studies

≥ 5% and ≥ 2x PBO + oral AD	ESK + oral AD (N=346)	PBO + oral AD (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%
Blood pressure increased	10%	3%
Vomiting	9%	2%
Feeling drunk	5%	0.5%

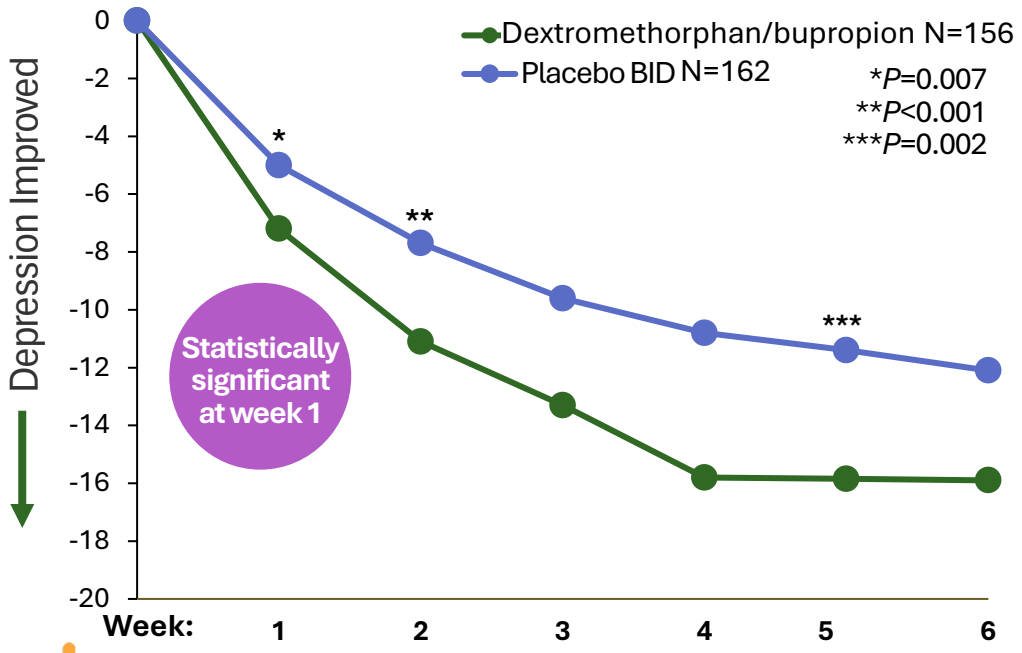
Sexual dysfunction not observed at ≥ 2%
Mean body weight change was similar to PBO + oral AD

LS = Least squares.

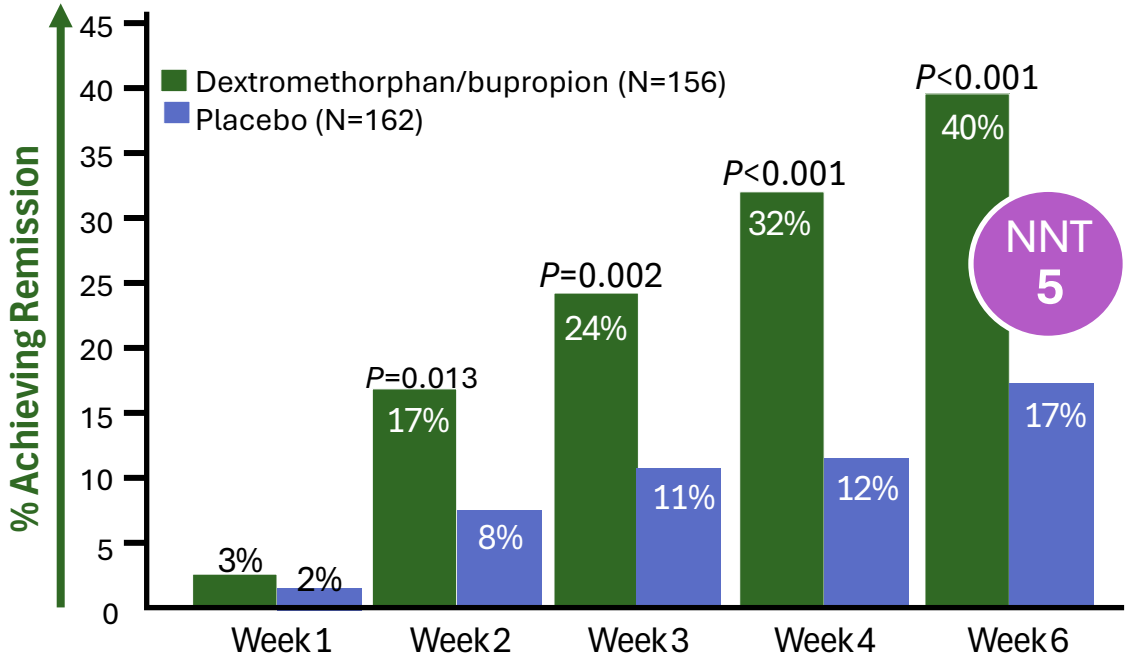
Daly E, et al. *JAMA Psychiatry*. 2019;76(9):893-903. del Casale A, et al. *JAMA Psychiatry*. 2025:e250200. Janik A, Qiu X, Lane R, et al. American Society of Psychopharmacology Annual Meeting. Poster presentation. May 28, 2024. Popova V, et al. *Am J Psychiatr*. 2019;176(6):428-38.

Dextromethorphan/Bupropion: Uncompetitive NMDA Antagonism Powers A Rapid-Acting Oral Antidepressant

Dextromethorphan/Bupropion Reduced Depressive Symptoms Rapidly in Phase 3 Trial



Dextromethorphan/Bupropion Also Substantially Improved Remission Rates

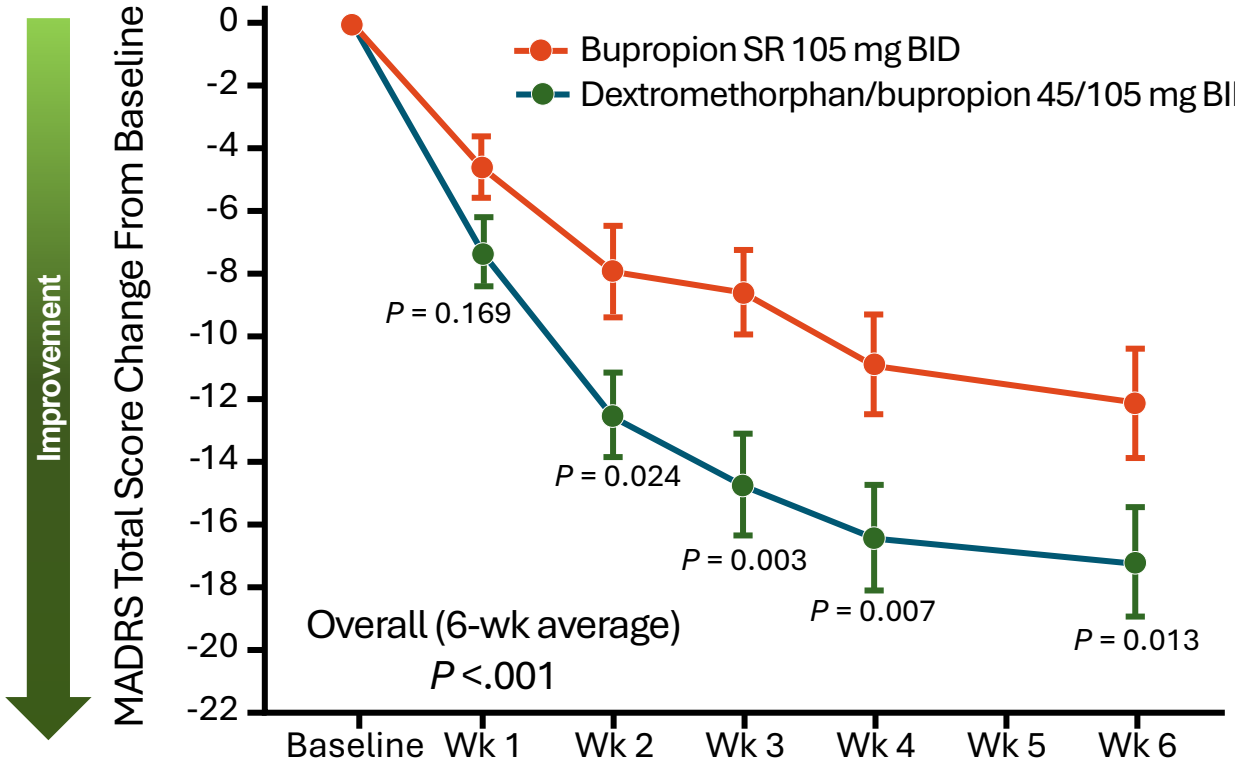


Dextromethorphan/bupropion is the first oral antidepressant to show statistical significance vs placebo in symptom reduction at week 1 and remission at week 2.

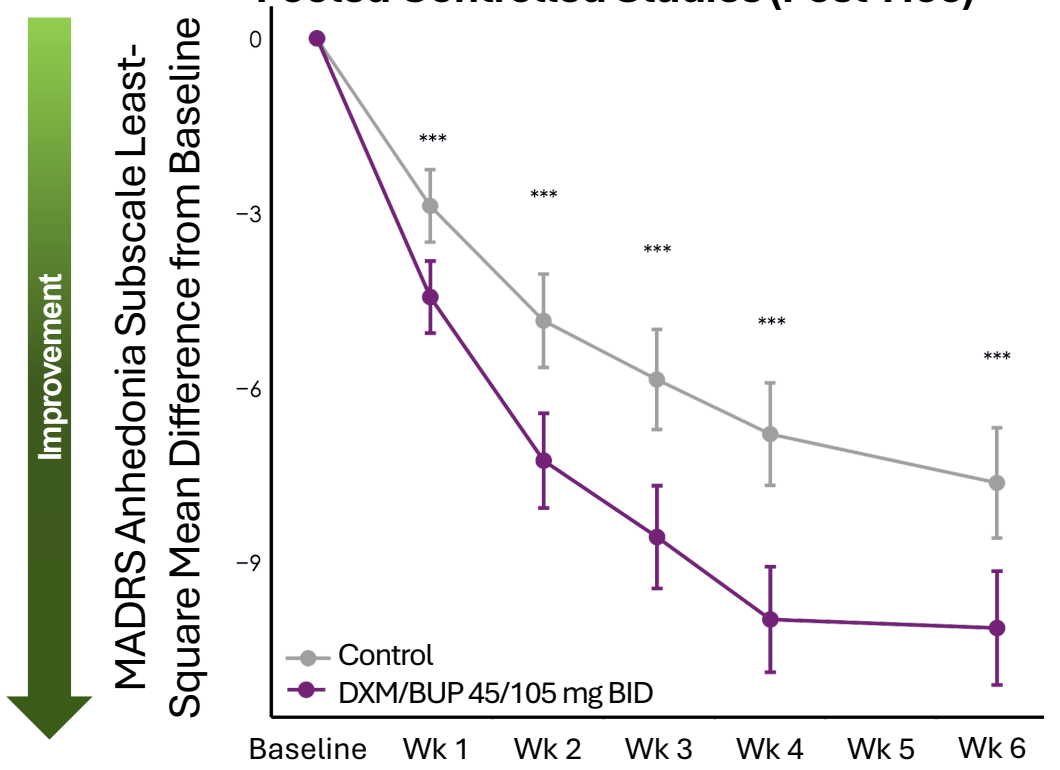
Iosifescu DV, et al. *J Clin Psychiatry*. 2022;83(4):21m1434. Tabuteau H, et al. *Am J Psychiatry*. 2022;179(7):490-499.

Other Trials & Analyses of Demonstrate Advantages of DXM/BUP Compared to Bupropion and for Anhedonia

Phase 2 Study of Dextromethorphan/Bupropion and Bupropion



MADRS Anhedonia Subscale Improvements in Pooled Controlled Studies (Post-Hoc)



Tabuteau H, et al. *Am J Psychiatry*. 2022;179:490. McIntyre RS, et al. Effects of AXS-05 in Improving Anhedonia and Interest-Activity Symptoms of MDD and the Associated Improvements in Functional Impairment. Poster Presented at the American Society of Clinical Psychopharmacology. May 28-31, 2024, Miami Beach, FL.

Dextromethorphan-Bupropion Was Generally Well Tolerated In Controlled Studies

AEs ≥5% and ≥2x Rate of Placebo

	DXM-BUP	Placebo
Dizziness	**16%**	**6%**
Nausea	**13%**	**9%**
Headache	**8%**	**4%**
Diarrhea	**7%**	**3%**
Somnolence	**7%**	**3%**
Dry mouth	**6%**	**2%**
Sexual dysfunction	**6%**	**0%**
Hyperhidrosis	**5%**	**0%**

Discontinuation due to Adverse Events:
4% AXS-05
0% Placebo

Weight Change
-0.4 lbs AXS-05
+1.0 lbs Placebo

Median Duration of AEs for AXS-05 in Pooled Controlled Studies

Dizziness	**5 days**
Nausea	**6 days**
Headache	**2.5 days**
Diarrhea	**4 days**
Somnolence	**5 days**
Dry mouth	**12.5 days**
Sexual Dysfunction	**3 days**

TE = treatment emergent; AE = adverse event; D/C = discontinuation.

Iosifescu DV, et al. *J Clin Psychiatry*. 2022;83(4):21m14345. Chepke C, et al. AXS-05 in Major Depressive Disorder: Pooled Data from Two Six Week Controlled Trials (GEMINI and ASCEND). Poster Presented at Psych Congress Elevate. May 30-June 2, 2024, Las Vegas NV.

Key Learning Points

- ✓ Approximately **one in three (34%)** of **patients recover** from MDD after treatment **with SSRI** or **SNRI**
- ✓ **Glutamate receptors** are **more prevalent** in brain regions involved in MDD and anhedonia and offer multiple **targets for treatment**
- ✓ **NMDA** and **AMPA** receptors are the drivers of **neuroplasticity** in the brain
- ✓ **Lucky for our patients and us – TWO different, glutamate-based interventions are available to help a wide variety of our patients with MDD (Dex+Bup in MDD, and Esk in TRD)**
- ✓ **Both have efficacy as early as one week** after starting treatment

GABA-A Receptor Positive Allosteric Modulation

Veronica Ridpath, DO

GABA is Connected to Glutamatergic and Monoamine Signaling

Serotonergic neurons in the dorsal raphe nucleus project into the prefrontal cortex (PFC) to regulate the GABA-ergic and glutamatergic signal balance

This then regulates the excitability of the serotonergic neurons in the dorsal raphe through a feedback loop

Chronic stress appears to impact somatostatin-expressing GABAergic neurons, providing reduced dendritic inhibition of glutamatergic pyramidal neurons, particularly in the hippocampus and medial prefrontal cortex

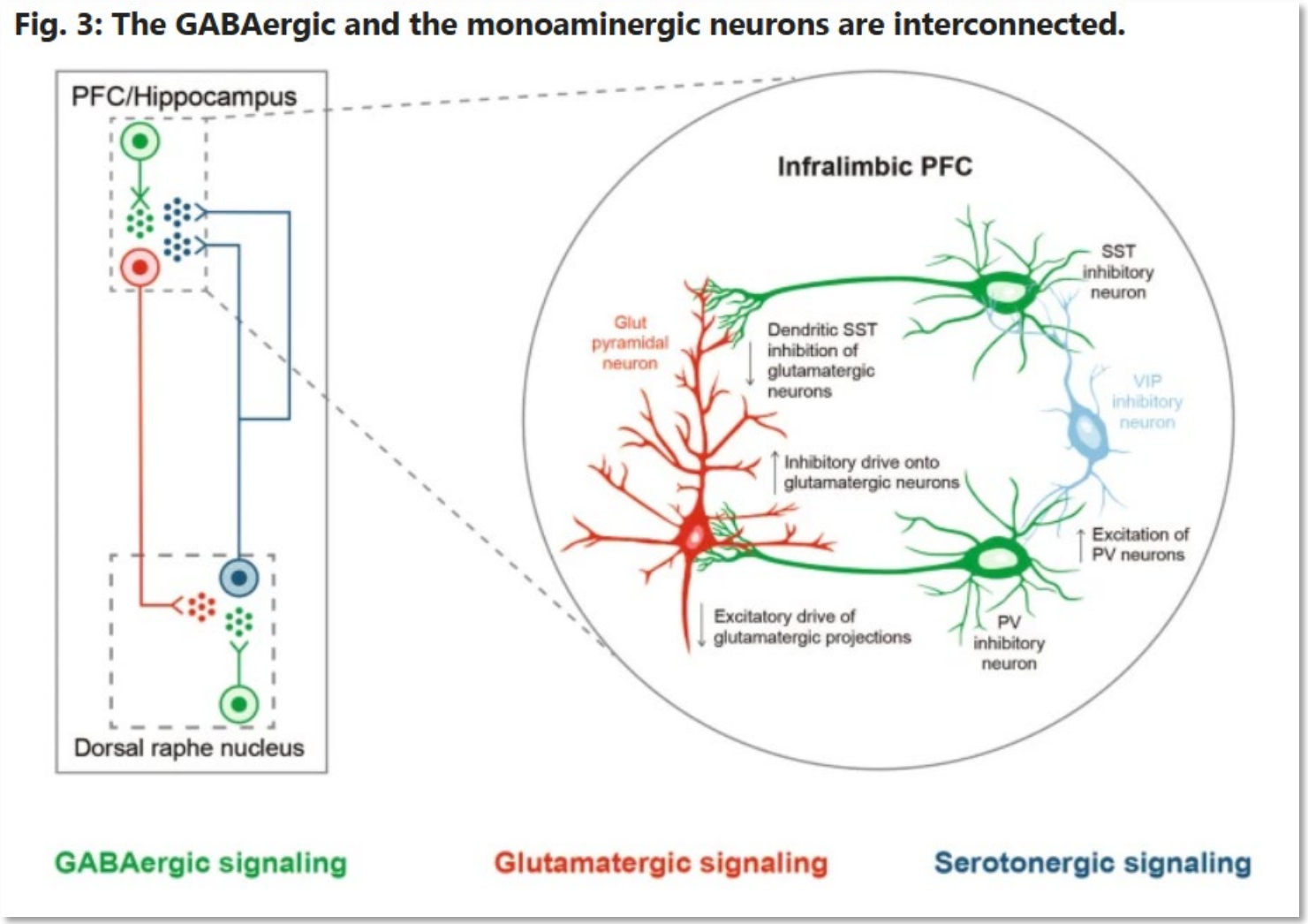


Image: Cutler AJ, et al. Figure 3. *Transl Psychiatry*. 2023;13(1):228.

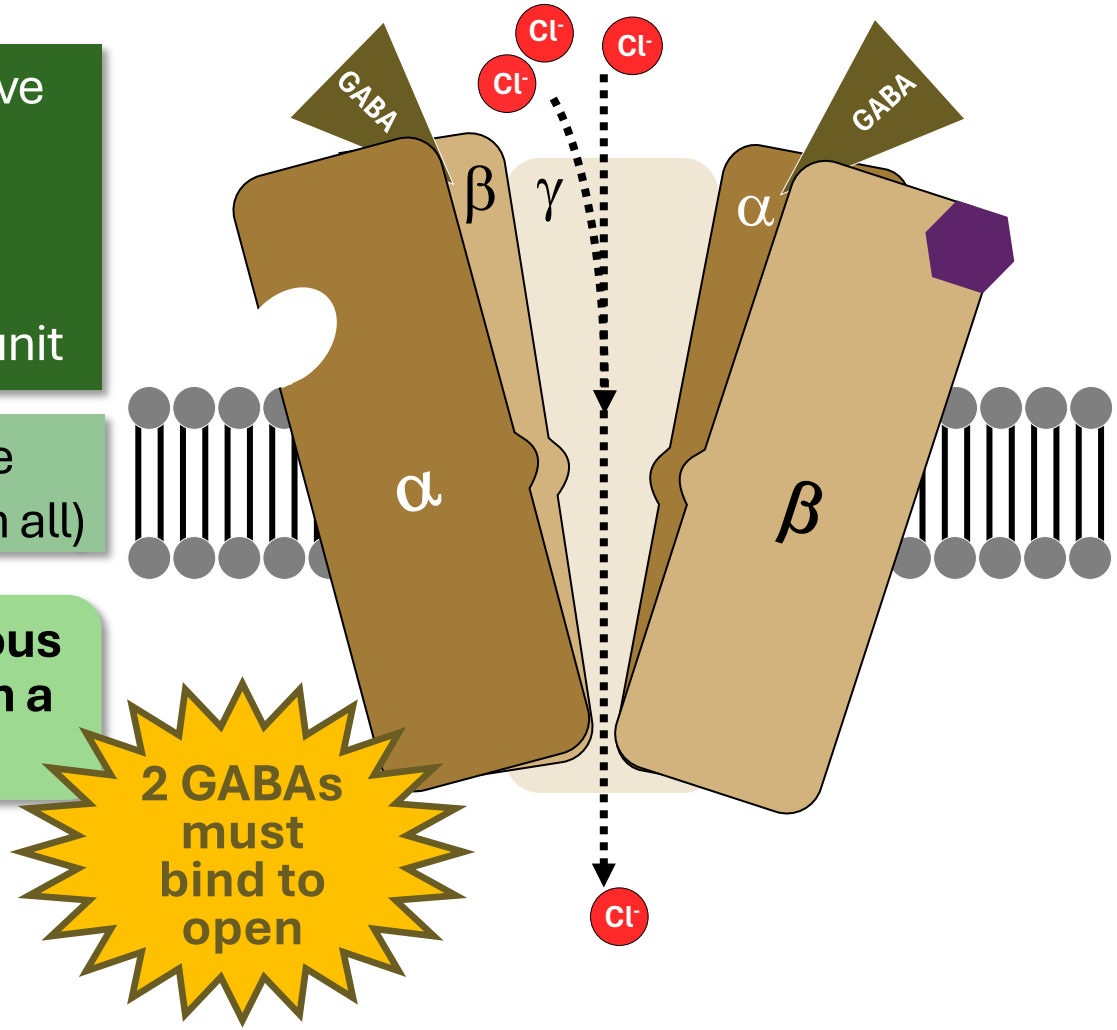
Duman R, et al. *Neuron*. 2019;102(1):75-90.

GABA-A Receptors Have High Functional Diversity

GABA-A receptors have
5 subunits:
two α subunits
two β subunits
one δ, γ, ε, θ, or π subunit

Some subunits have multiple isoforms (19 in all)

This allows tremendous functional diversity in a single receptor



With γ2 subunit

Ubiquitous throughout the brain, mostly at synapses with comparatively low affinity for GABA

Mediate phasic inhibition:
Rapid, transient conductance

With δ subunit

Found in cerebellum, dentate gyrus, thalamus, striatum, and cortex, away from synapse with comparatively high affinity for GABA

Mediate tonic inhibition:
Persistent conductance

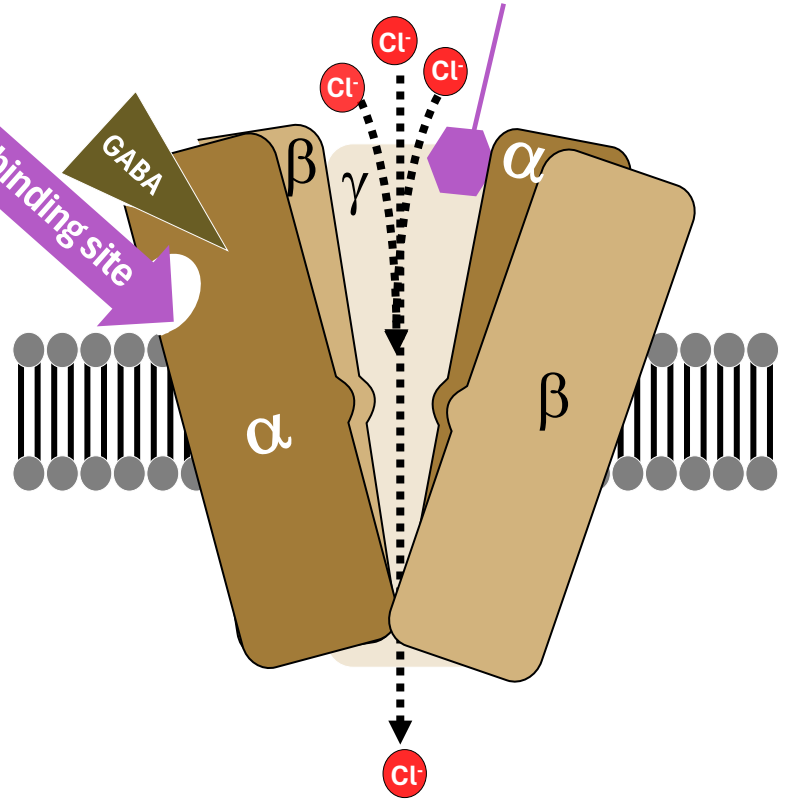
GABA = Gamma-aminobutyric acid.

Gunn BG, et al. *Front Neurosci.* 2011;5:131.

There Are Multiple Sites and Mechanisms for GABA-A Receptor Modulation

Positive allosteric modulator binding site is different from neurotransmitter binding site, when PAM is present, GABA activity is increased

Benzodiazepine is a positive allosteric modulator on α subunits 1, 2, 3, 5 but not 4 or 6



Exogenous modulation with medications varies with subunit isoforms

α1: sedatives, anticonvulsants
α2: anxiolytics
α3: muscle relaxants
α1 and α5: cognition, memory

β2: anesthetic sedation
β3: anesthetic immobilization

Neuroactive steroids are endogenous GABA-A receptor modulators produced in the brain

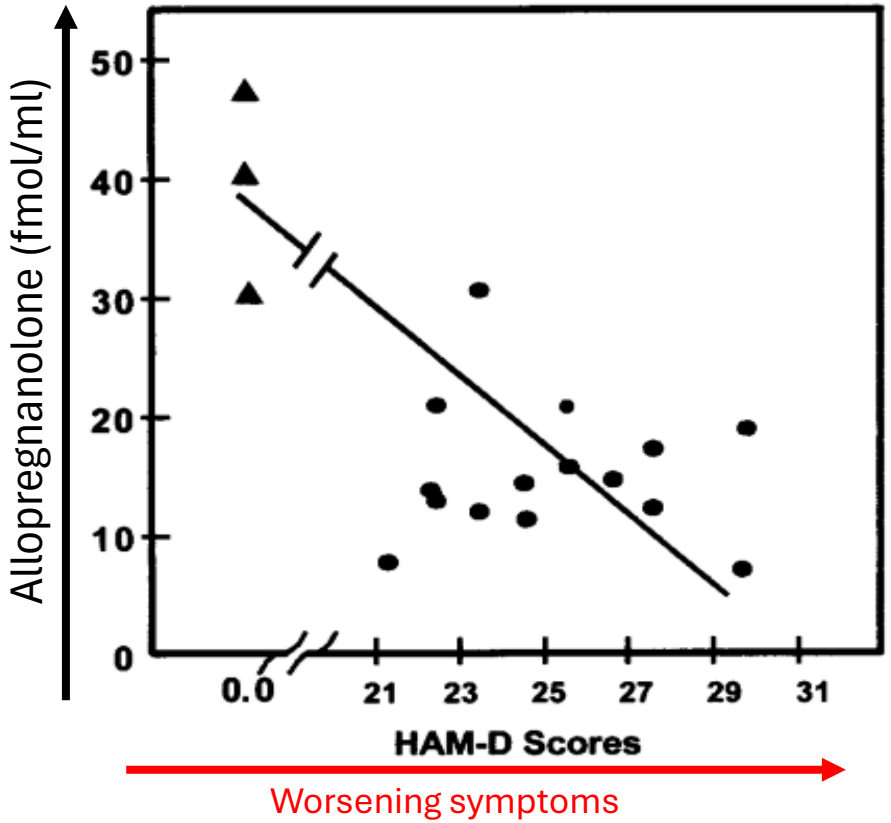
- **Pregnenolone**
- Epiallopregnanolone
- Epipregnanolone
- Tetrahydrodeoxycorticosterone
- Androsterone
- Pregnenolone sulfate
  7α-hydroxypregnenolone
- Dehydroepiandrosterone
- Progesterone
- Corticosterone
- **Allopregnanolone**
- Androstenedione
- Testosterone
- Estradiol-17β

GABA = Gamma-aminobutyric acid; PAM = positive allosteric modulation.

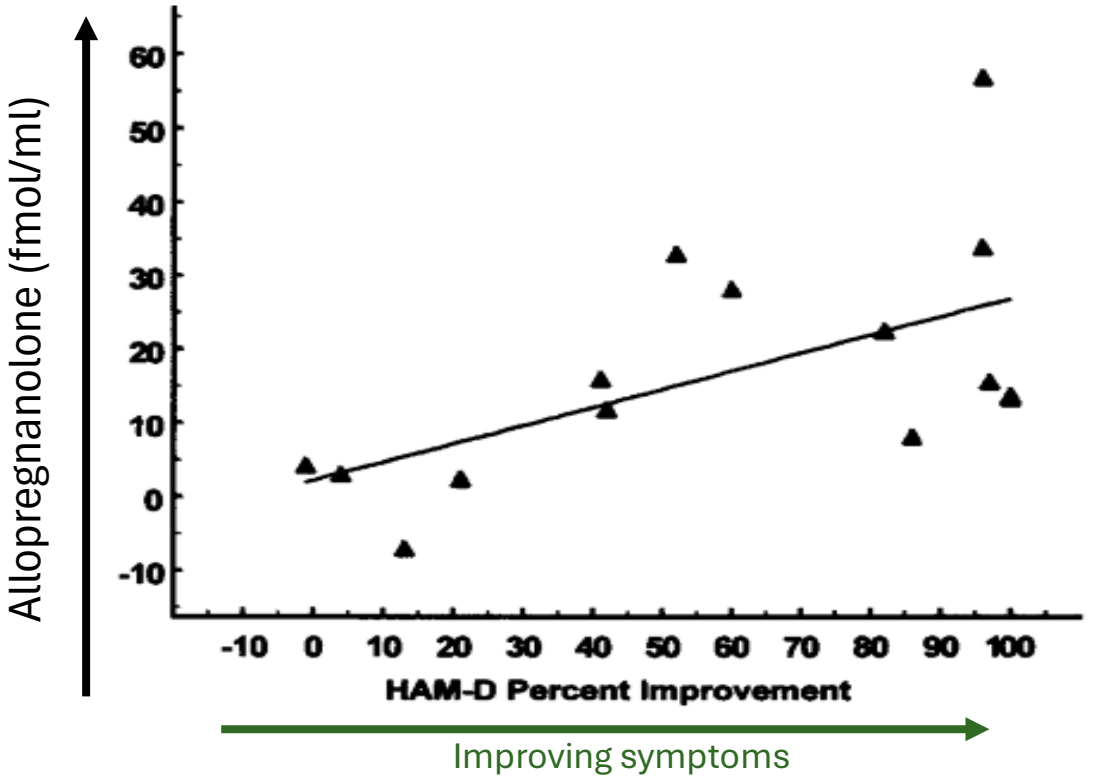
Gunn BG, et al. *Front Neurosci.* 2011;5:131. Kim JJ, Hibbs RE. *Trends Biochem Sci*. 2021;46(6):502-517. Jacob T. *Front Mol Neurosci.* 2019;24:12:179. Reynolds DL, et al. *J Neurosci*. 2003;23(24):8608-17. Sigel E. *Cur Top Med Chem*. 2002;2:833–839.

Lower Levels of Endogenous Allopregnanolone Associated with MDD

Severity of depression correlated negatively with increasing allopregnanolone in CSF at baseline [r=0.081; P=0.01]



Treatment with fluoxetine or fluvoxamine correlated with increase in allopregnanolone in CSF and MDD symptom improvement [r=0.58; P=0.023]

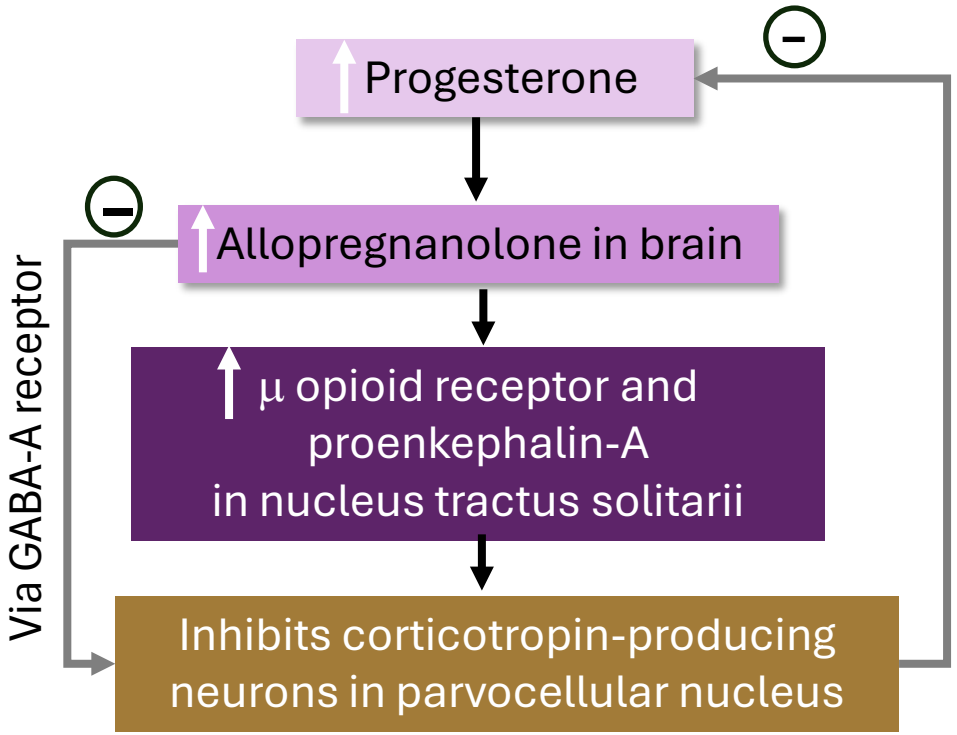


BZDs affect synaptic GABA-A receptors where allopregnanolone impacts both synaptic ***and*** **extra-synaptic** receptors. Murine models with delta subunit (present on extracellular GABA-A receptors) knockout mice show loss of antidepressant efficacy to allopregnanolone, suggesting extra-synaptic activation is necessary for antidepressant effect. In human studies, addition of BZDs to antidepressant treatment does not improve response.

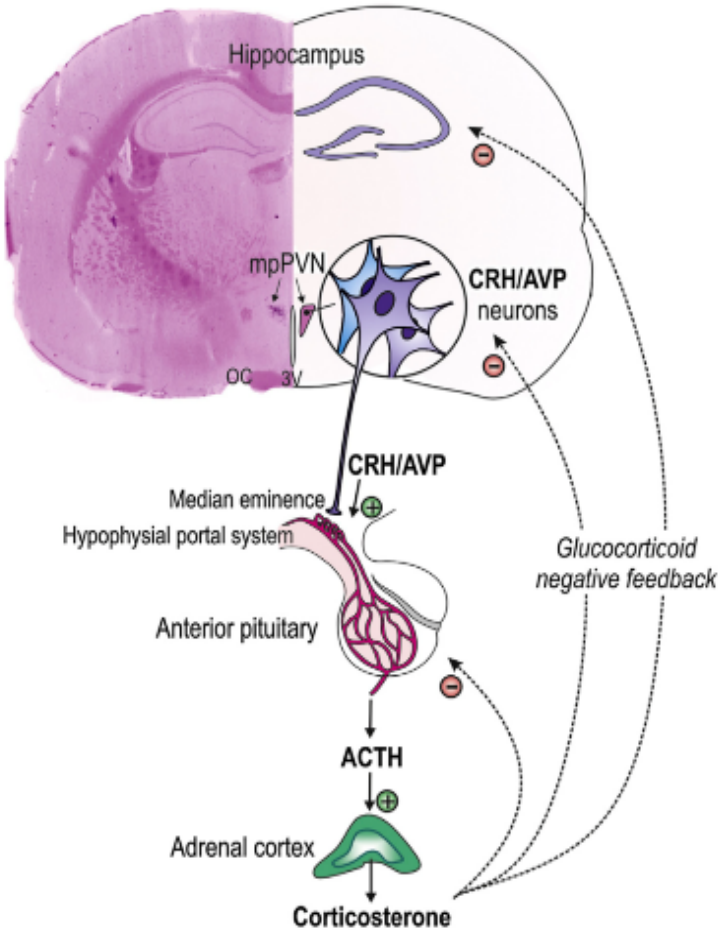
CSF = cerebrospinal fluid; HAM-D = Hamilton Rating Scale for Depression; BZDs= benzodiazepines.

Uzunova V, et al. *Proc Natl Acad Sci U S A*. 1998;95(6):3239-44. Takasu K. et al. *Front Cell Neurosci*. 2024;17:1274459. Ogawa Y et al. *Cochrane Database Syst Rev*. 2019;(6):CD001026.

The Neurosteroid Allopregnanolone Plays a Role in Regulating Stress Hormone Production



Allopregnanolone may also play a role in neuroplasticity by increasing production of neurotrophic factors (e.g., BDNF)



Synthetic allopregnanolone, brexanolone, was approved for treatment of PDD

Administered by IV infusion

Discontinued

Replaced by zuranolone, an oral neuroactive steroid that also acts as a GABA-A receptor PAM

Pathogenesis of PMDD is presumed to be due to altered stress response during the luteal phase, and ***decreased sensitivity*** to allopregnanolone

ACTH = adrenocorticotropin hormone; AVP = arginine vasopression; CRH = corticotropin releasing hormone; mpPVN = medial parvocellular paraventricular nucleus of hypothalamus; BDNF = brain-derived neurotrophic factor; PPD = postpartum depression; PMDD = premenstrual dysphoric disorder.

Brunton PJ. *J Steroid Biochem Mol Biol*. 2016;160:160-8. Hantsoo L et al. *Neurobiol Stress*. 2020;12:100213.

GABA-A Modulation Promotes Sleep

Long known that benzodiazepines and other GABA-A modulators (e.g., zolpidem) induce sleepiness

- Decrease time to fall asleep (sleep latency)
- Increase total sleep time
- Induce NREM sleep

Conversely, inhibition of GABA-ergic neurons in the CNS promotes wakefulness

GABA supplementation has been studied as a target for stress and sleep

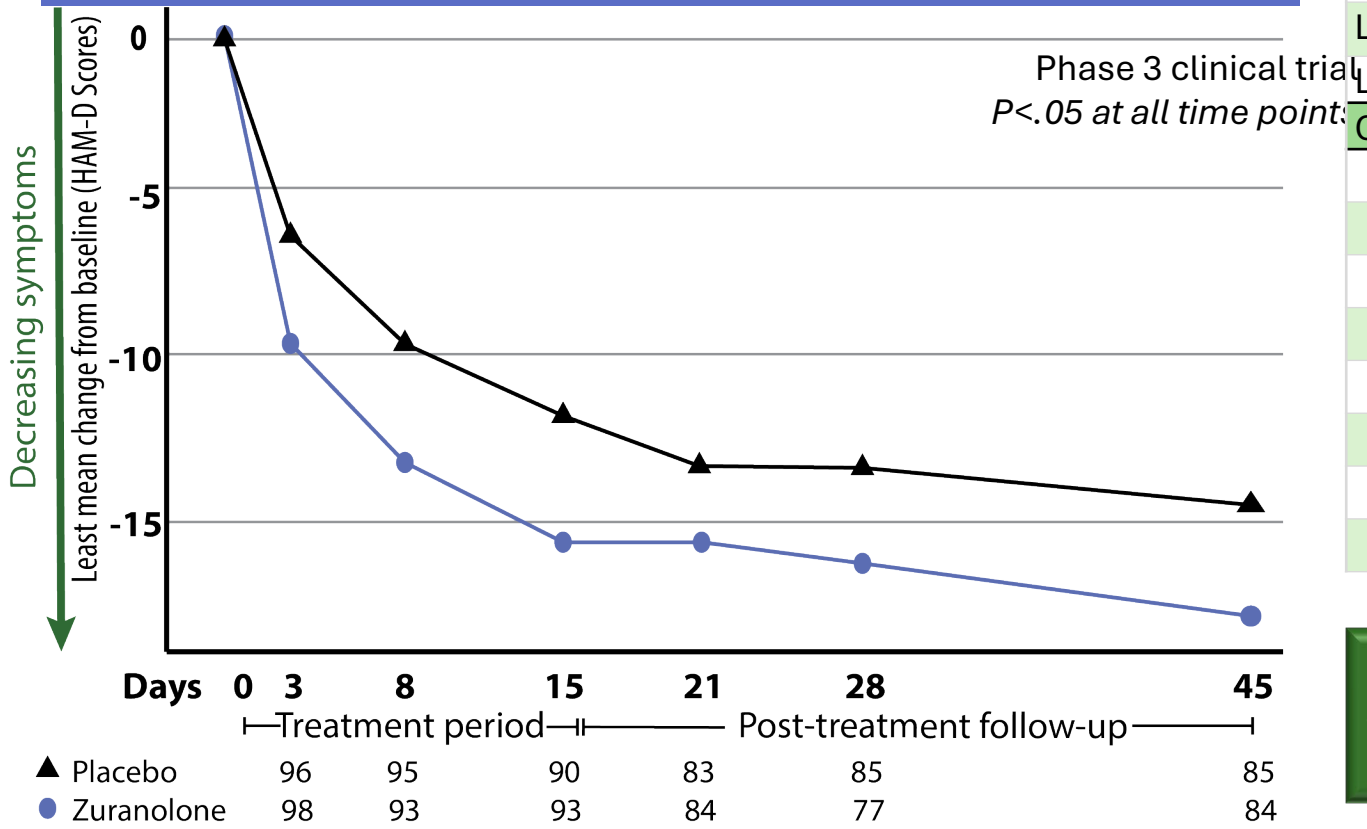
- A systematic review of 14 human studies showed improvement in sleep latency, but no benefit in total sleep time or number of awakenings
- Coadministration with l-theanine enhances sleep promoting effects
- As with all supplements, regulation and labeling is variable. Drowsiness and low blood pressure can develop from supratherapeutic dosing.
- Natural sources of dietary GABA include fermented foods, soy, brown rice, cruciferous vegetables etc.

NREM = non-rapid eye movement.

Byun JI, et al. *J Clin Neurol*. 2018;14(3):291-295. Winsky-Sommerer R. *Eur J Neurosci*. 2009;29:1779–94. Hepsomali P, et al. *Front Neurosci*. 2020;14:923. Kim S, et al. *Pharm Biol*. 2019;57(1):65-73.

Zuranolone Efficacy and Safety for Treating PPD: Results of SKYLARK Study

Statistically significant **improvement in PPD symptoms with zuranolone** vs placebo **seen as early as day 3** and were maintained a month after treatment ended



Treatment-Emergent Adverse Events		
	Zuranolone 50 mg/day N=98	**Placebo N=98**
Leading to dose reduction	16%	1%
Leading to treatment discontinuation	4%	2%
Leading to withdrawal from trial	1%	1%
Occurring in 5% of more of either group		
Somnolence	27%	5%
Dizziness	13%	10%
Sedation	11%	1%
Headache	9%	13%
Diarrhea	6%	2%
Nausea	5%	6%
UTI	5%	4%
COVID-19	5%	0%

No serious or severe AEs related to study treatment. Somnolence generally resolved within 7 days from first dose and majority of AE resolved by 5 days from last dose

Post-hoc analysis using MADRS anhedonia subscale data showed nominally significant improvements in anhedonia at day 8, maintained at day 15 and 45.

Deligiannidis KM, et al. *Am J Psychiatry*. 2023;180(9):668-75. Chepke C, et al. Improvement in anhedonia symptoms with zuranolone in patients with postpartum depression (PPD): A Post Hoc Analysis of the Phase 3 SKYLARK Study. Poster presented at: APA Annual Meeting. Los Angeles, CA, USA; May 17-21, 2025.

Key Learning Points

- ✓ **GABA-A receptors** have a **broad range of diverse types** due to their pentameric structure that combines three or more subunit types that have multiple isoforms
- ✓ The diversity of GABA-A receptor types creates **multiple opportunities** for **positive allosteric modulation (PAM)**
- ✓ **Neurosteroids** produced in the brain **act as GABA-A PAMs**
- ✓ The synthetic **neuroactive steroid zuranolone** is approved for and **rapidly improves symptoms of PPD**

Sigma-1 Receptor Agonism

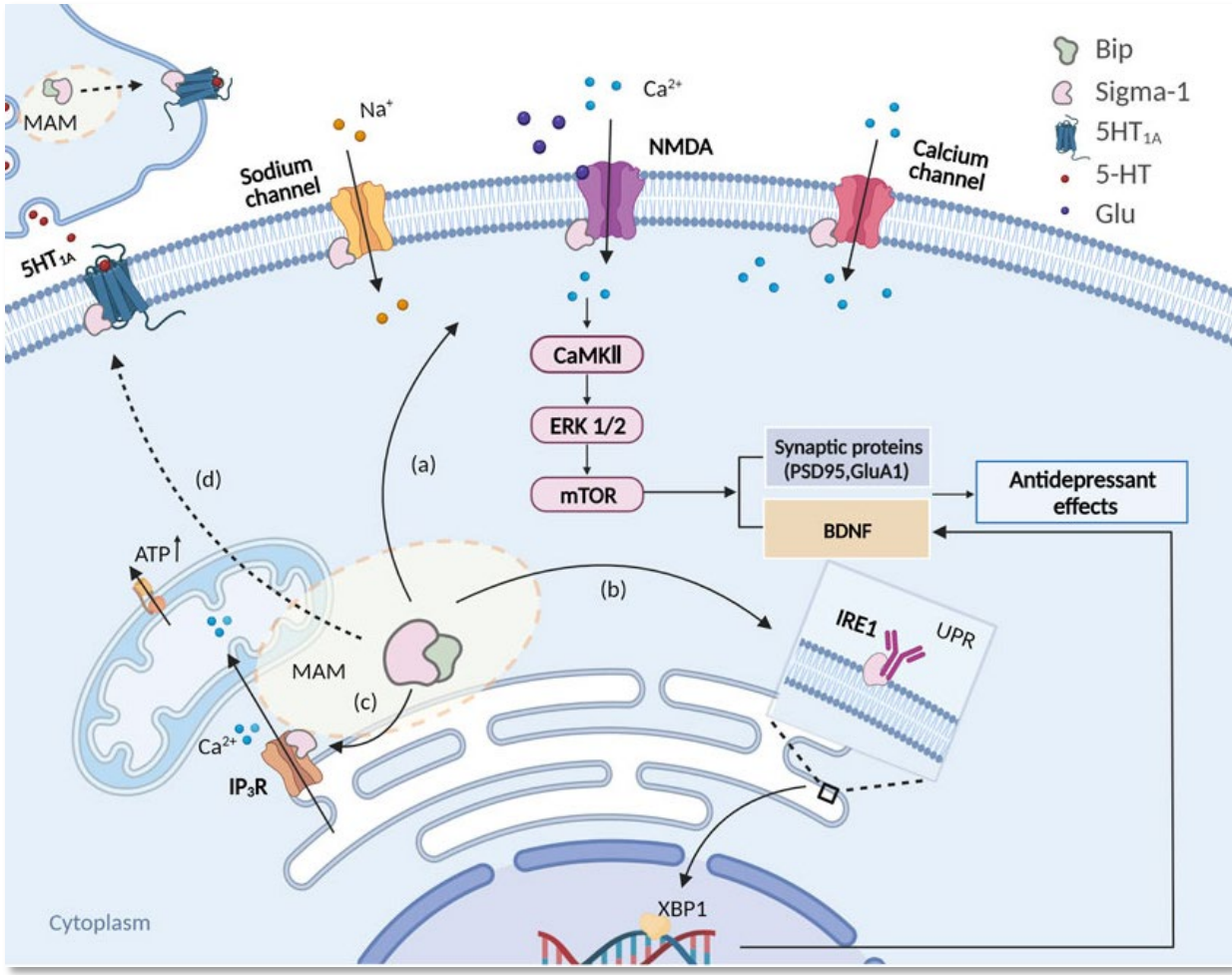
Why Talk About Sigma-1 When It Is Not a Neurotransmitter Receptor?

What is Sigma-1?

- Multifunctional, ligand-operated receptor found at endoplasmic reticulum in the hippocampus, amygdala, and other brain regions-initially characterized as an opioid receptor
- Stimulation (agonism) causes sigma-1 to travel into the cytoplasm where it can bind many proteins, including neurotransmitter receptors, including both ion-channel receptors and GPCRs at cell membrane as a chaperone

Clinical Implications of Sigma-1 Agonism

- Neuroprotection
- Modulation of Neurotransmission
- Anti-inflammatory Effects



Ren P et al. Figure 1. Schema of intracellular signaling pathways involved in the antidepressant-like effects of sigma-1 receptors. *Front Pharmacol*. 2022;13:925879.

GPCR = G-protein coupled receptor.

Balasuriya D, et al. *J Neurosci*. 2013;33(46):18219-24. Kekuda R, et al. *Biochem Biophys Res Commun*. 1996;229:553–558. Mavylutov T, et al. *Protein Cell*. 2018;9(8):733-737. Schmidt HR, et al. *Nature*. 2016;532(7600):527-530. Zhang B, et al. *Neuropharmacology*. 2017;116:387-398.

Sigma-1 Modulates Glutamate and Monoamine Signal Transmission

Sigma-1 Agonism and Glutamate

- Affects glutamate transmission (cell-type and location dependent for increase vs decrease)
- Increases NMDA receptor production and delivery to cell membrane
- Affects intracellular Ca2+ levels that influence the threshold for glutamate release
- Affects the balance of glutamate-GABA recycling and transmission
- Induces synaptic plasticity (LTP) via NMDA and AMPA receptors

Sigma-1 Agonism and Monoamines

- Affects norepinephrine transmission indirectly and increases serotonin transmission
- Interacts with dopamine and serotonin receptors in response to antidepressants
- Affects intracellularCa2+ levels that influence the threshold for monoamine release
- Modulates the conformation of the dopamine transporter
- Increases dopamine transmission induced by stimulants
- Enhances dopamine binding to D1 and D2 dopamine receptors

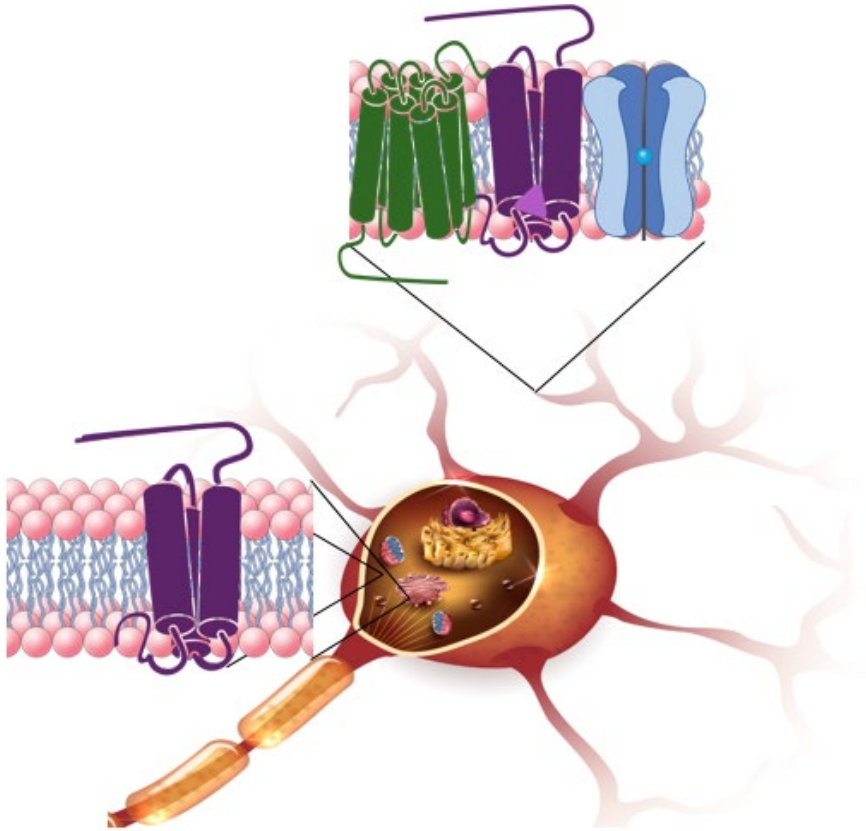
Beggiatto S, et al. *Cell Signal*. 2017;40:116–124. Hong WC, et al. J Biol Chem. 2017;292:11250–61. Monnet FP, et al. *Proc Natl Acad Sci USA*. 1995;92:3774–3778. Pabba M, et al. *J Neurosci*. 2014;34:11325–38. Pozdnyakova N, et al. *Exp. Neurol*. 2020;333:113434. Salaciak K, et al. *Neurosci Biobehav Rev*. 2021;132:1114-1136. Sambo DO, et al. *Nat Commun*. 2017;8:2228.

Evidence that Sigma-1 Plays a Role in MDD

Preclinical evidence

- Sigma-1 “knock-out” rodents exhibit depression-like behavior (interestingly, neurosteroids appear to be protective in this model)
- In animals with depression-like behavior, administering sigma-1 agonists reduces symptoms
- The effect of quetiapine in an animal model of depression is increased by sigma-1 agonists and reduced by sigma-1 antagonists

Sigma 1 agonists including dextromethorphan-bupropion reduced MDD symptoms in multiple clinical trials



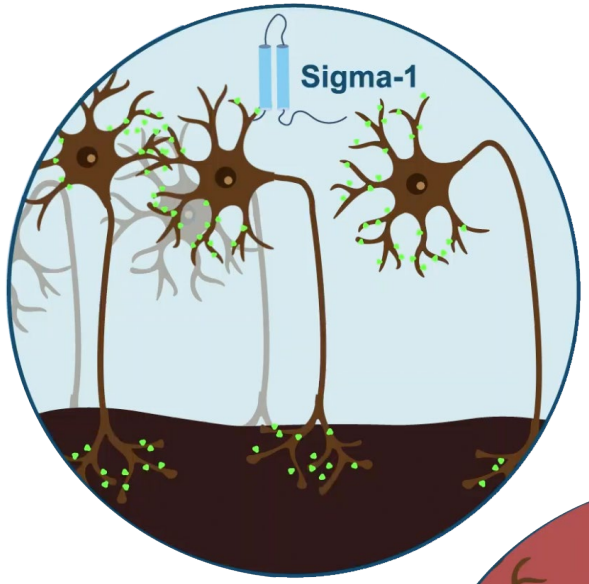
Binding of the antidepressant fluvoxamine to sigma 1 in humans was shown in dynamic PET study

Lab studies show many antidepressants bind sigma-1: fluvoxamine, sertraline, fluoxetine, escitalopram, citalopram, paroxetine

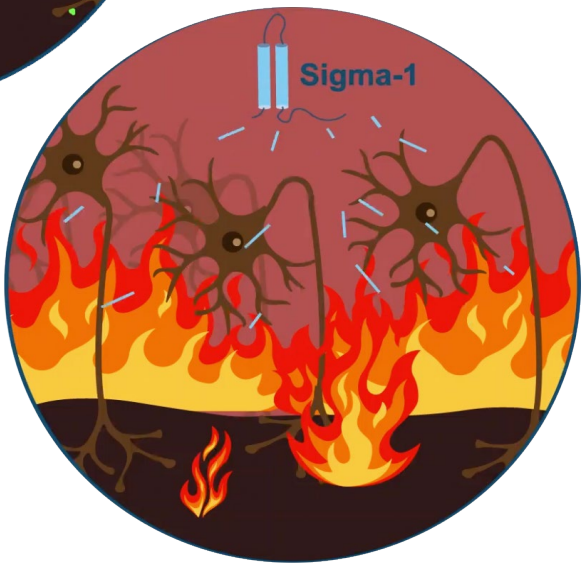
Balasuriya D, et al. *J Neurosci*. 2013;33:18219–24. Hayashi T, Su TP. *Exp Opin Ther Targets*. 2008;12(1):45–58. Ishikawa M, et al. *Biol Psychiatry*. 2007;62(8):878-883. Kotagale NR, et al. *Eur J Pharmacol*. 2013;702(1-3):180-186. Lucas G, et al. *Int J Neuropsychopharmacol*. 2008;11(4):485–495. Ngo-Anh TJ, et al. *Nat Neurosci*. 2005;8:642–649. Sabino V, et al. *Behav Brain Res*. *2009;*198(2):472–476. Shirayama Y, et al. *Neurosci Lett*.1994;165(1–2):219–222.

Sigma-1 Receptor May Also Be Anti-Inflammatory

- Enhances cell survival with reduction of oxidative stress and apoptosis through modulating cellular calcium homeostasis, excitotoxicity and clearance of reactive oxygen species
- Reduces pro-inflammatory cytokine production and inflammation-related hyperalgesia
- In conditions like sepsis, sigma-1 can interact with the endoplasmic reticulum stress response pathway to reduce inflammatory cascade



Visual metaphor



Neuroprotective Effects

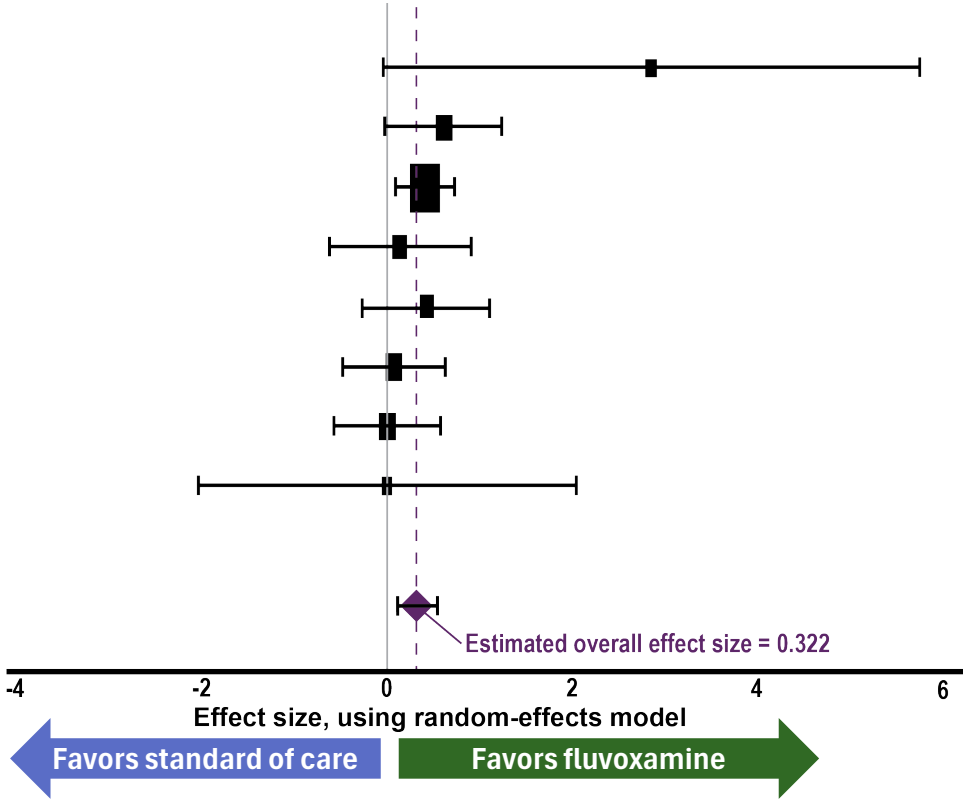
Sigma 1 receptors modulate Ca2++ in the endoplasmic reticulum → Endoplasmic reticulum Ca2++ affects protein folding → Avoidance of protein misfolding and aggregation= neuroprotection

Francardo V, et al. *Brain*. 2014;137(Pt 7):1998-2014. Hayashi T, et al. *Cell*. 2007;131(3):596-610. Nguyen L, et al. *Adv Exp Med Biol*. 2017;964:133-152. Wu Z, et al. *J Neurochem*. 2015;134(5):904-914. Zhang Y, et al. *J Neuroinflammation*. 2015; 12:29.

Anti-inflammatory Properties of Antidepressants

Meta-analysis of 7 placebo-controlled clinical studies showed the SSRI fluvoxamine has small effect on reducing clinical deterioration in COVID-19

Included placebo-controlled studies				
Study	**Standard of care (n/N)**	**Fluvoxamine n/N**	**Weight**	**Log OR (95% CI)**
Stop COVID	6/72 (8.3%)	0/80 (0%)	0.52	2.85 (-0.05, 5.75)
COVID Out	48/291 (16.5%)	15/156 (9.6%)	11.56	0.62 (0.00, 1.23)
Together	119/756 (15.7%)	79/741 (10.7%)	42.15	0.41 (0.09, 0.74)
Stop-COVID 2	15/275 (5.5%	13/272 (4.8%)	7.55	0.14 (0.62, 0.90)
Active-6 ARM E	21/586 (3.6%)	14/589 (2.4%)	9.32	0.42 (-2.6, 1.11)
Active-6 ARM B	26/588 (4.4%)	27/646 (4.2%)	14.46	0.07 (-0.48, 0.62)
McCarthy et al	23/614 (3.7%)	26/674 (3.9%)	13.38	0.00 (-0.57, 0.57)
Soe et al	2/23 (8.7%)	2/23 (8.7%)	1.06	0.00 (02.04, 2.04)
Pooled	**260/3205 (8.1%)**	**176/3181 (5.5%)**	**Pooled**	**0.32 (0.11, 0.53)**



Retrospective analysis of those taking SSRIs with or without sigma-1 agonism at time of COVID-19 detection showed SSRIs reduced the risk for long-COVID (RR 0. 71 [*P*<0.001] and 0.79 [*P*<0.005], respectively).

Prasanth MI, et al. *Sci Rep*. 2024;14(1):13462; Erratum in: *Sci Rep*. 2024;14(1):13462.

Dextromethorphan Is Also a Sigma-1 Agonist

Dextromethorphan (DXM) → Is rapidly metabolized to → **Dextrorphan (DXO)**

DXM Binds sigma-1 ten times **weaker** than **DXO**

DXM Binds NMDA **ten times weaker** than **DXO**

DXM Binds mu opioid and M1 **weaker** than **DXO**

→ Responsible for enhanced safety and behavioral profile of DXM vs. DXO due to reduction in phenyclidine (PCP)-like effects and reduced mu-opioid agonism

DXM Also has serotonin transporter (SERT) activity

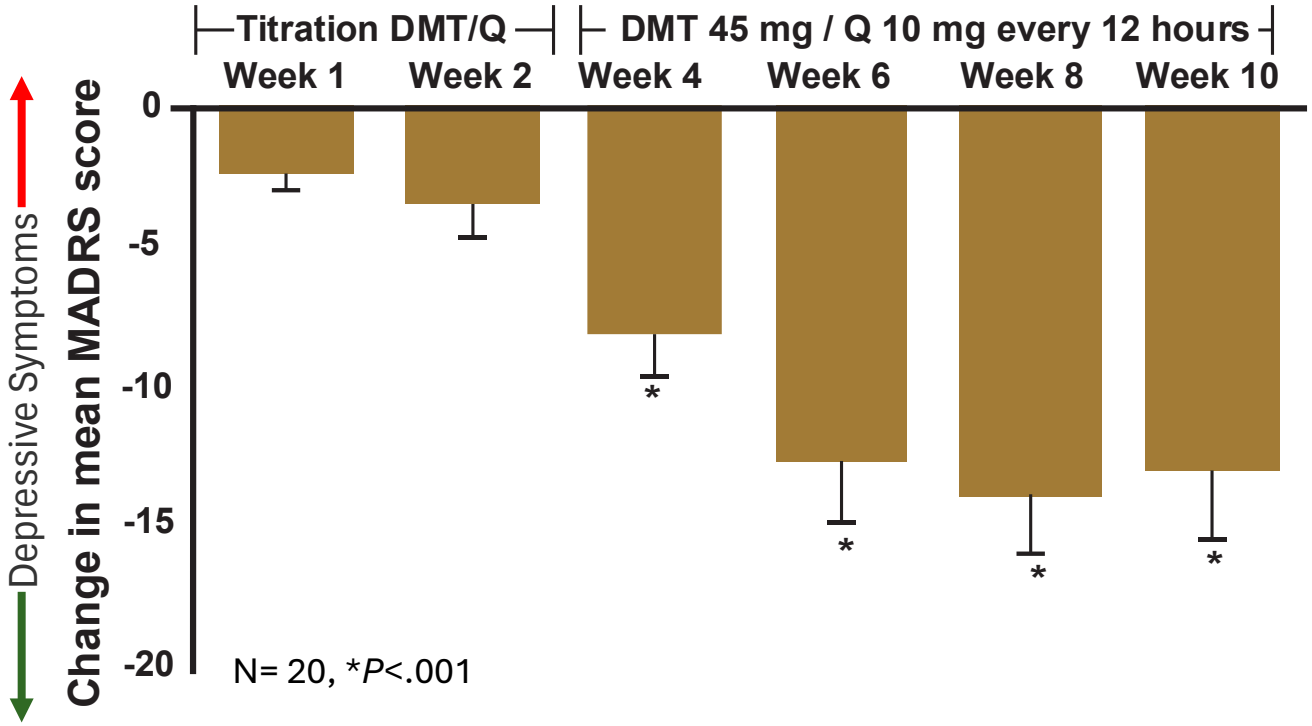
Silva AR, Dinis-Oliveira RJ. *Drug Metab Rev.* 2020;52(2):258-282. Taylor CP, et al. *Pharmacol Ther.* 2016;164:170-182.

Phase 2a, Open-Label Trial of Dextromethorphan with Metabolic Inhibitor Quinidine for TRD

DXM with quinidine showed potential for treating MDD

-1.5	points on MADRS (clinically meaningful)
45%	response rate
35%	remission rate

HOWEVER-Quinidine (Q) is not an ideal metabolic inhibitor due to QTc prolongation and faster elimination half life compared to bupropion (6-8 hours vs 15 hours)



Murrough JW, et al. *J Affect Disord*. 2017;218:277-283. McCarthy B, et al. Clin Psychopharmacol Neurosci. 2023;21(4):609-616.

Phase 3 Study of Dextromethorphan/Bupropion (AXS-05) for Alzheimer's Disease Agitation

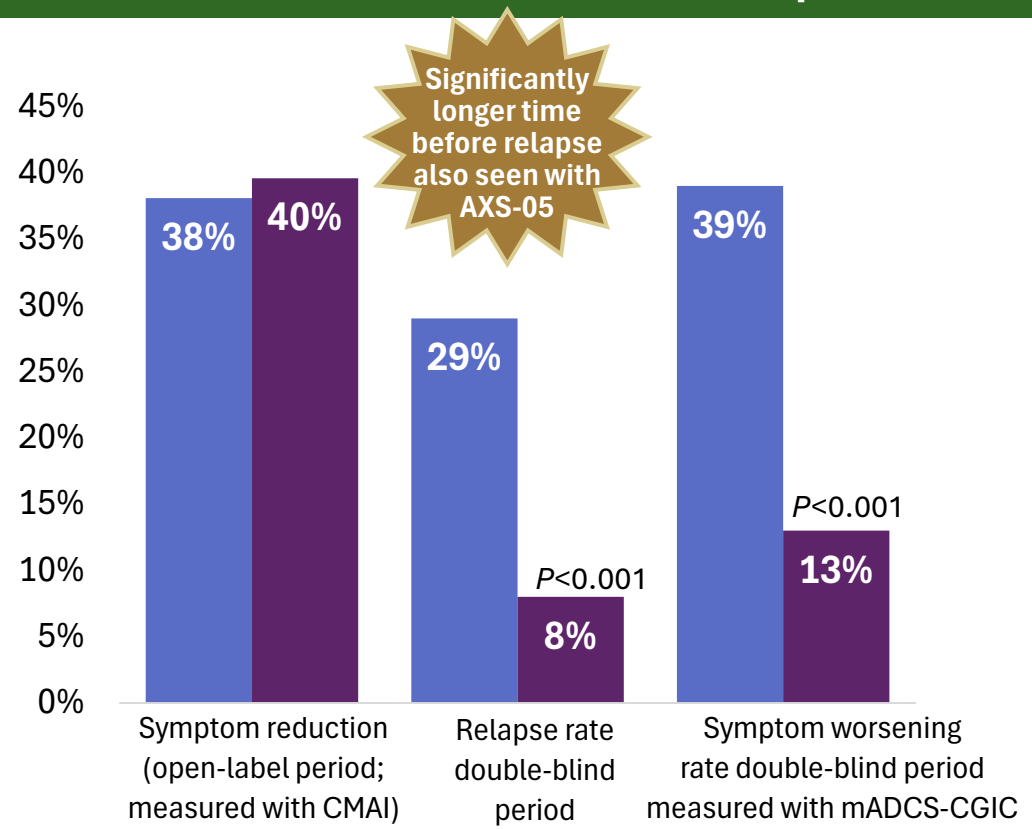
After up to 12 months of open-label treatment with AXS-05, continuing AXS-05 vs placebo reduced time to and rate of relapse and rate of symptom worsening,

70% had **≥30%**

symptom reduction after 8 weeks open-label treatment

3-4x
(HR=0.276; *P*<0.001)

less likely to relapse with AXS-05 vs placebo



Adverse events in double-blind period

- 29% vs 32% with AXS-05 vs placebo
  - 05 in AXS-05 group discontinued
  - 1.2% in placebo group discontinued
- None occurred in >3.7% of participants
- Two falls occurred in AXS-05 group
  - 1 considered related to study medicine
- Two serious adverse events (urinary retention, cellulitis) in placebo group
- No sedation or cognitive decline observed (measured with MMSE)

CMAI = Cohen Mansfield Agitation Inventory; mADCS-GCI = Modified Alzheimer' Disease Cooperative Study-Clinical Global Impression of Change.

Axsome Therapeutics announces successful completion and results of phase 3 clinical program of AXS-05 in Alzheimer's disease agitation. News Release. Globe Newswire; Dec 30, 2024. Accessed May 4, 2025. https://www.globenewswire.com/news-release/2024/12/30/3002588/33090/en/Axsome-Therapeutics-Announces-Successful-Completion-and-Results-of-Phase-3-Clinical-Program-of-AXS-05-in-Alzheimer-s-Disease-Agitation.html.

Key Learning Points

- ✓ **Sigma-1 receptors** are located in the endoplasmic reticulum membrane and **migrate to the cell membrane when activated by agonists**
- ✓ Activated **sigma-1 receptors modulate glutamate and monoamine** neurotransmission and are thought to play a role in MDD
- ✓ **Sigma-1** also has **anti-inflammatory activity**, likely through effects on protein production at endoplasmic reticulum Ca^{2+} balance, which **may** also **partly explain sigma-1 agonists** and **other antidepressants mechanisms of action**

Serotonin 2B ($5\text{-}HT_{2B}$) Receptor Antagonism

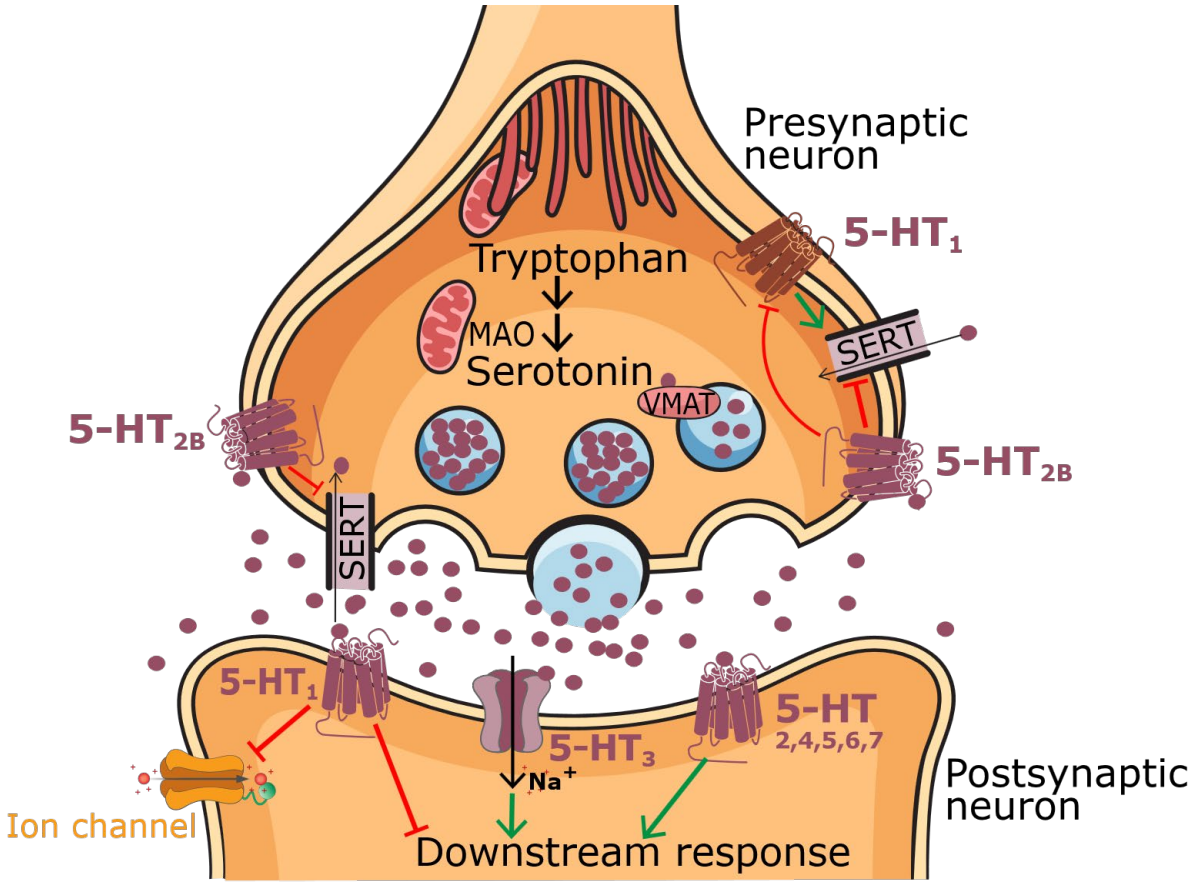
Serotonin 5-HT_{2B} Receptor Modulates Serotonin Reuptake and Transmission

Preclinical Evidence

- Chronic 5-HT_{2B} agonism mimics SSRI effects
- 5-HT_{2B} knockout or chronic blockade
  - Eliminates long-term effect of SSRIs, increases 5-HT_{1A} inhibitory activity
- 5-HT_{2B} is highly expressed on microglia and astrocytes and may be involved neuroinflammation

Clinical Evidence

- LSD and MDMA are 5-HT_{2B} agonists
- Genetic variations in *HTR2B* have been associated with impulsivity, aggression, schizophrenia, substance use disorder, and suicide
- Atypical antipsychotics used for adjunctive MDD treatment are 5-HT_{2B} antagonists



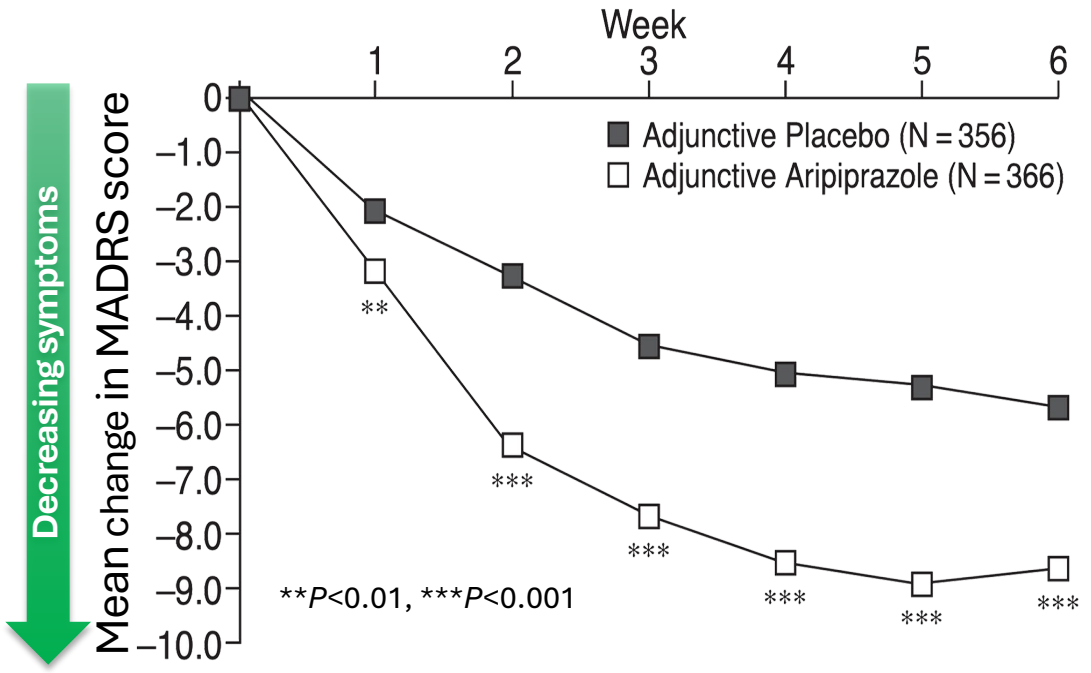
Benhadda A, et al. *iScience*. 2023;26(8):107401. Bevilacqua L, et al. *Nature*. 2010;468(7327):1061–66. Belmar A, et al. *Neuropsychopharmacol*. 2018; 43:1623–32. Brindley RL, et al. *Neuropharmacol*. 2017;110(Pt A):438-48. Diaz SL. In: Maroteaux et al., *5-HT2B Receptors*. Humana Press; 2021:349-66. Diaz SL, et al. *Mol Psychiatry*. 2012; 17:154–163. Doly S, et al. *J Neurosci*. 2008;28(11):2933–40. Hervas A, et al. *Psychiatr Genet*. 2014;24(4):158–163. Lin Z, et al. *Pharmacogenetics*. 2004;14(12):805–11. Montalvo-Ortiz JS, et al. In: Maroteaux et al., *5-HT2B Receptors*. Humana Press; 2021:291-304. Richardson-Jones JW, et al. *Neuron*. 2010;65(1):40-52. Montalvo-Ortiz JL, et al. *Mol Psychiatry*. 2018;23(12):2277–86. Zhu B, et al. *Personal Individ Differ*. 2012;53:1029–33

Atypical Antipsychotics Used for Adjunctive MDD Treatment Have 5-HT_{2B} Antagonist Activity

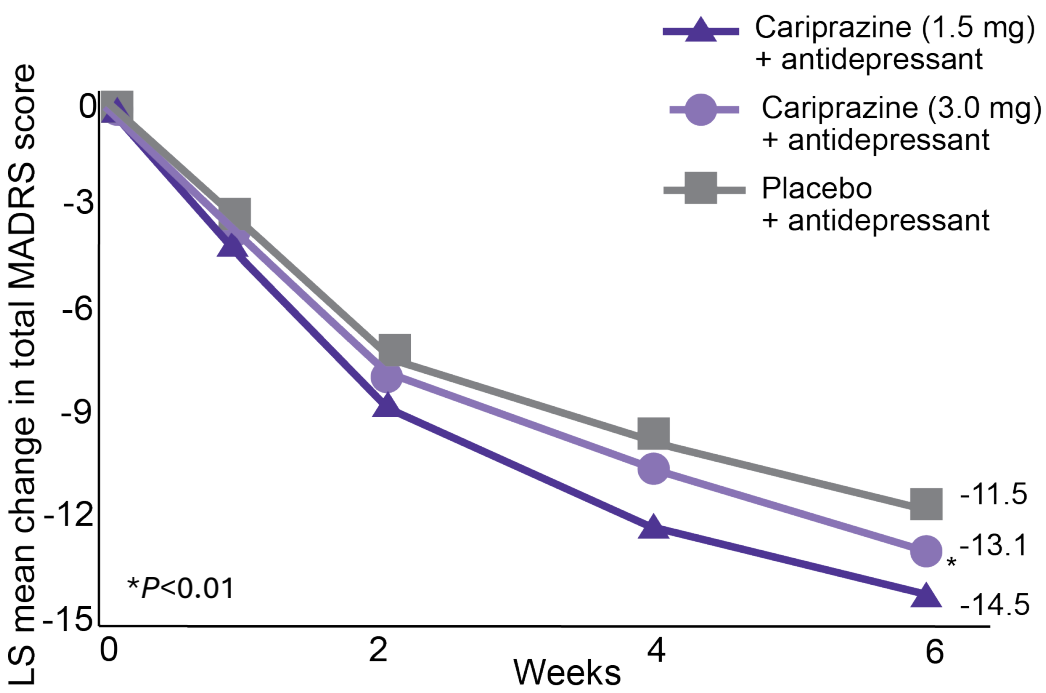
Atypical Antipsychotics Are Partial Dopamine Agonists and Serotonin Receptor Antagonists

Aripiprazole and cariprazine have particularly strong binding to the 5-HT2B receptor and are approved, effective adjunctive MDD treatments

Pivotal trial of aripiprazole for adjunctive MDD treatment



Pivotal trial of cariprazine for adjunctive MDD treatment

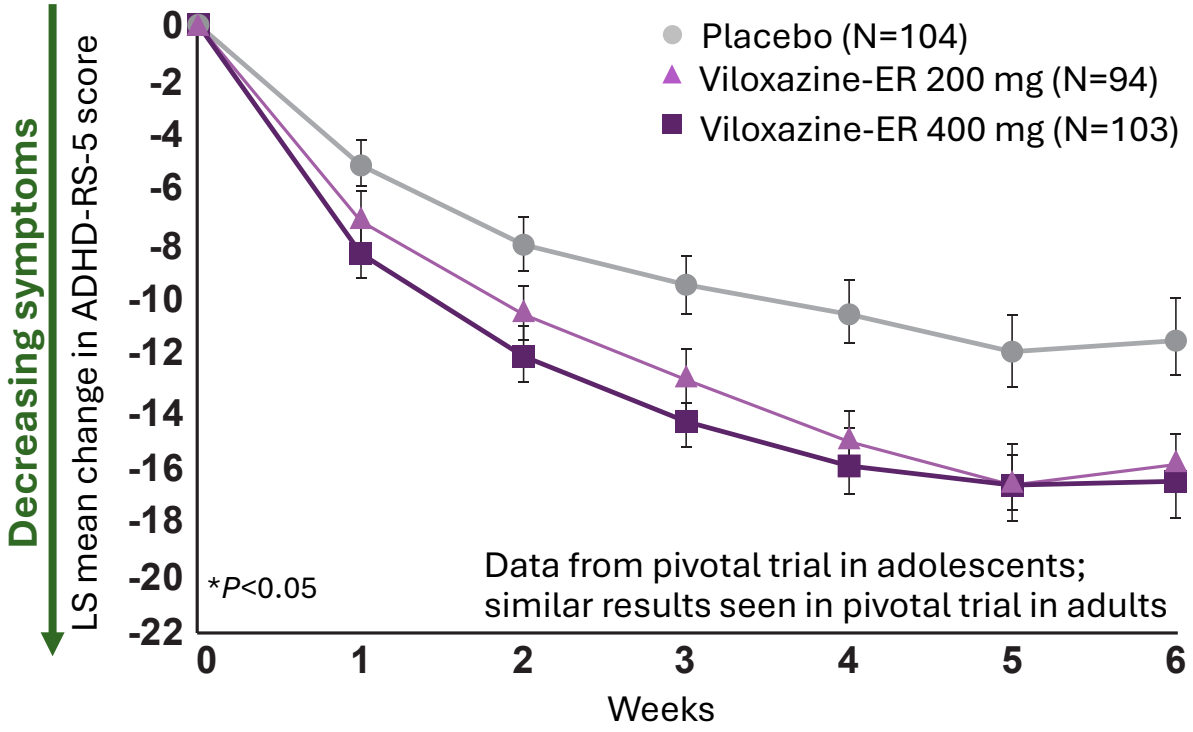


Vraylar (cariprazine) [package insert]. Madison, NJ: Allergan USA; 2022. Durgam, S, et al. *J Clin Psychiatry.* 2016;77(3):371-8. Abilify (aripiprazole) Prescribing Information. Drugs@FDA: FDA Approved Drugs. Accessed Jan 10, 2025. www.accessdata.fda.gov/scripts/cder/daf/.

Viloxazine, Now Approved for ADHD Was Used for Depression Outside United States

And has 5-HT2B antagonist activity in addition to being an NRI

Viloxazine is approved for ADHD in patients >6 years



Viloxazine was approved and used outside US for depression from late 1977-2002 when it was withdrawn from market for business reasons

- Viloxazine demonstrates partial agonism (functional antagonism) at 5HT2B and agonism at 5HT2C with high receptor occupancy
- No appreciable SERT activity
- Low incidence of cardiovascular adverse effects such as increased blood pressure suggests a moderate noradrenergic effect- so clinical effectiveness is not likely from norepinephrine alone
- In rat models, viloxazine increases norepinephrine, dopamine, and serotonin in the PFC

ADHD-RS-5 = ADHD Rating Scale-5; ADHD = Attention deficit hyperactivity disorder.

Yu C, et al. *J Exp Pharmacol*. 2020;12:285-300. Nasser A, et al. *CNS Drugs*. 2022;36(8)897-915. Nassar A, et al. *J Clin Pharmacol*. 2021;41(4):370-80. Garcia-Olivares J, et al. *J Exp Pharmacol*. 2024;16:13-24.

Key Learning Points

- ✓ **Serotonin 5-HT_{2B} receptors** are present on dendrites near cell body where they **act as autoreceptors**, regulating serotonergic neurons
- ✓ **Serotonin 5-HT2B receptors** are also **present on postsynaptic targets** where they **drive downstream effects in other neurons**
- ✓ **Long-term effects of SSRIs** depend on **5-HT_{2B} activity**
- ✓ Several medications that act as **5-HT2B antagonists reduce depressive symptoms**

Trace Amine Associated Receptor-1 (TAAR-1) Agonism

Craig Chepke, MD, DFAPA

Wait… Wait just a minute!

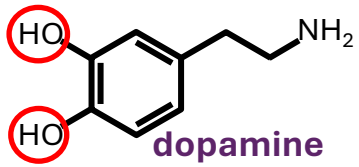
‘What is a TAAR?!’

TAAR – A Primer: Trace Amine Associated Receptors

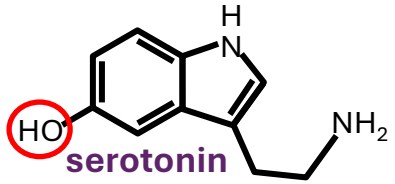
Trace Amines are structurally related to monoamine neurotransmitters, but found at much lower concentrations in the brain

- **Trace amines were discovered in 1876 and were thought to be merely metabolites of monoamines**

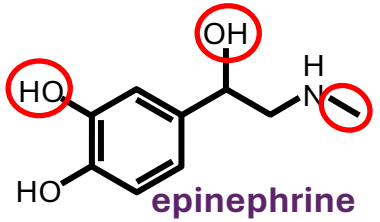
Monoamines



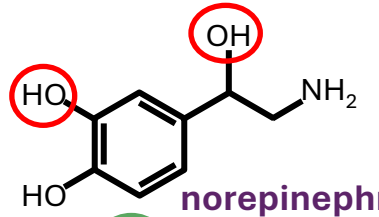
dopamine



serotonin

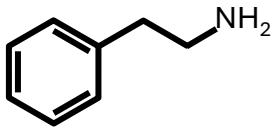


epinephrine

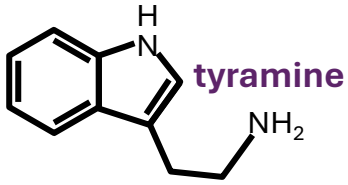


norepinephrine

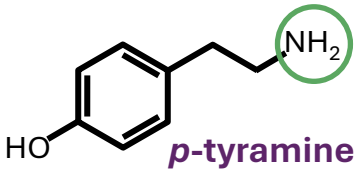
Trace Amines



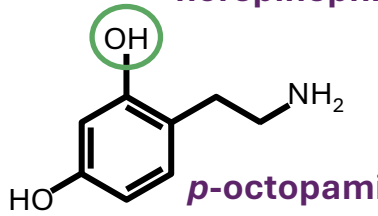
β-phenylethylamine



tyramine



p-tyramine



p-octopamine

- **TAARs** are found intracellularly when inactive and were discovered in 2001
- 26 TAARs have been identified, 6 are functional in humans
- TAAR1 is the most highly implicated in neuropsychiatric disease

Borowsky B, et al. *Proc Natl Acad Sci USA*. 2001;98:8966-71. Bunzow JR, et al. *Mol Pharmacol*. 2001;60:1181-1188. Berry MD, et al. *Pharmacol Ther*. 2017;180:161-180. Espinoza S, et al. *Neuropsychopharmacol*. 2015; 40:2217-2227. Gainetdinov RR, et al. *Pharmacol Rev*. 2018;70(3):549-620. Grandy DK. *Pharmacol Ther*. 2007;116(3):355-390.Huey J, et al. *FASEB J*. 2022; Published online May 13, 2022. Walling DP, et al. *J Clin Psychopharmacol*. 2019;39(6):575-582. Pei Y, et al. *Front Neurosci*. 2016;10:148.

TAAR1 Modulates Monoamine and Glutamate Signal Transmission

TAAR1 Effect on Monoamines

Activating TAAR1 may enhance the functional effects of 5-HT_{1A} receptor agonism

TAAR1 forms heterodimers with the 5-HT_{1B} autoreceptor

TAAR1 is mostly found in the limbic system, and is co-expressed with D_2 receptors in the VTA, NAc, DRN, and mPFC

TAAR1 Effect on Glutamate

TAAR1 activation reduces glutamate transporter levels on astrocytes, **increasing** synaptic glutamate availability*

TAAR1 activation increases cortical activity in mice with reduced glutamate function (NMDA receptor knockout)*

*Trace amines also bind monoamine and NMDA receptors directly, which might partially explain some of these observations

DRN = dorsal raphe nuclei.

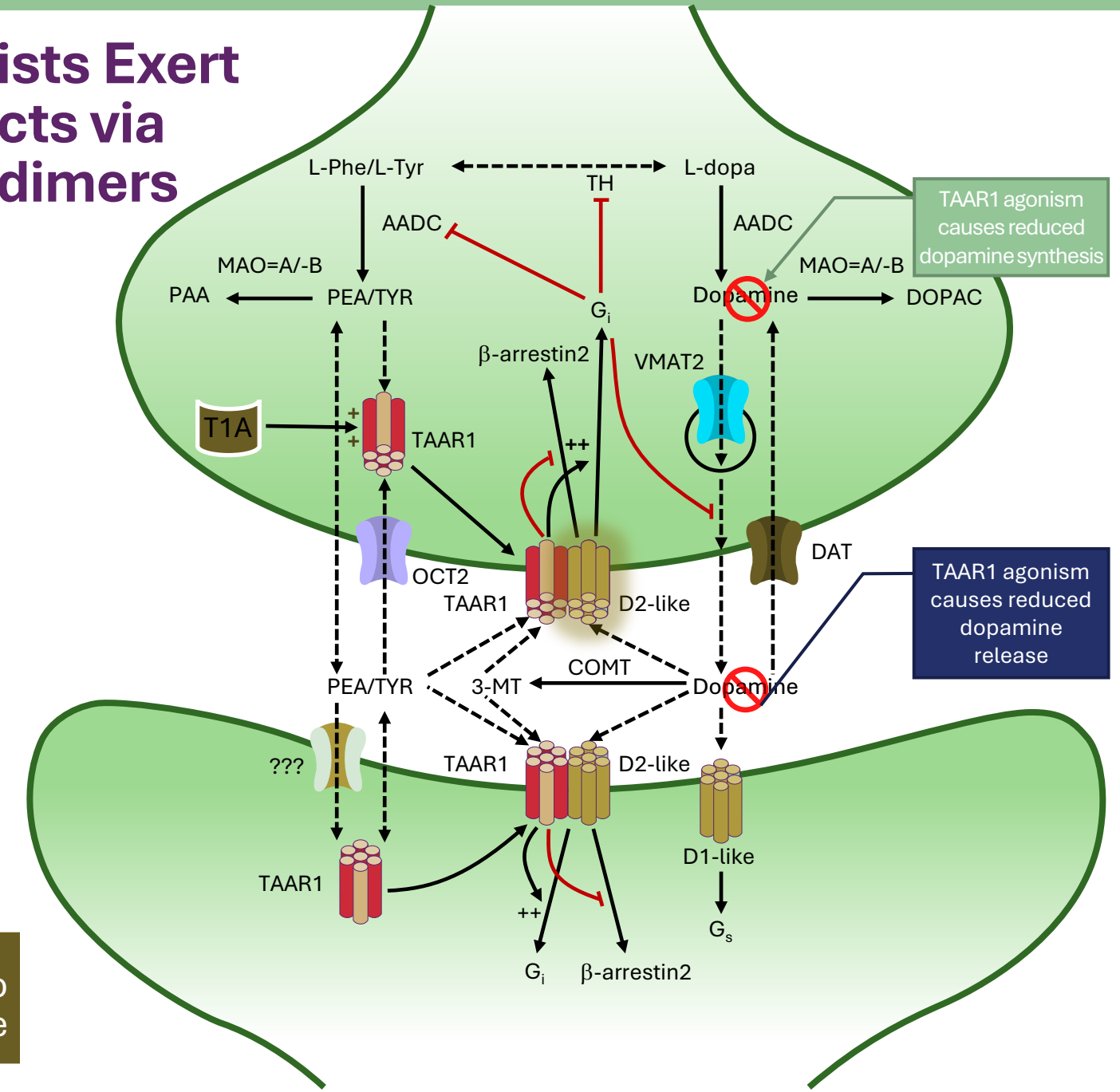
Berry MD, et al. *Pharmacol Ther*. 2017;180:161-180. Borowski B, et al. *Proc Natl Acad Sci USA*. 2001;98:8966-71. Bräunig J, et al. *Front Pharmacol*. 2018;9:222. Cisneros IE, Ghorpade A. *Neuropharmacology*. 2014; 85:499-507. Di Cara B, et al. *J Neurosci*. 2011;31:16928-40. Espinoza S, et al. *Mol Pharmacol*. 2011;80(3):416-425. Espinoza S, et al. *Neuropsychopharmacol*. 2015; 40:2217-2227. Revel FG, et al. *Proc Natl Acad Sci USA*. 2011;108(20):8485-8490. Revel FG, et al. *Mol Psychiatry*. 2013;18(5):543-556. Revel FG, et al. *Neuropharmacol*. 2019;371:1-14. Sukhanov I, et al. *Pharmacol. Res*. 2016; 103:206-214. Xie X, Miller GM. *J Pharmacol Exp Ther*. 2008;325:617-628. Zhang Y. et al. *Pharmacol Res*. 2021;167:105571. Alnefeesi Y, et al. Neurosci. Biobehav. Rev. 131 (2021): 192-210.

In Schizophrenia - TAAR1 Agonists Exert Presynaptic Antipsychotic Effects via Formation of D_2/TAAR1 Heterodimers

When stimulated by an agonist, TAAR1 forms a heterodimer with presynaptic D_2 receptors, increasing the sensitivity of the autoreceptor

When dopamine transmission is excessive, the more sensitive D_2/TAAR1 complex results in greater reduction in the synthesis and release of dopamine

Key Learning Point:
TAAR1 agonists act presynaptically to reduce dopamine synthesis and release



TAAR1-Mediated Modulation of Monoamines and Glutamate May Impact MDD and GAD

➢ **TAAR1** is found **in brain regions** implicated in **mood disorders**

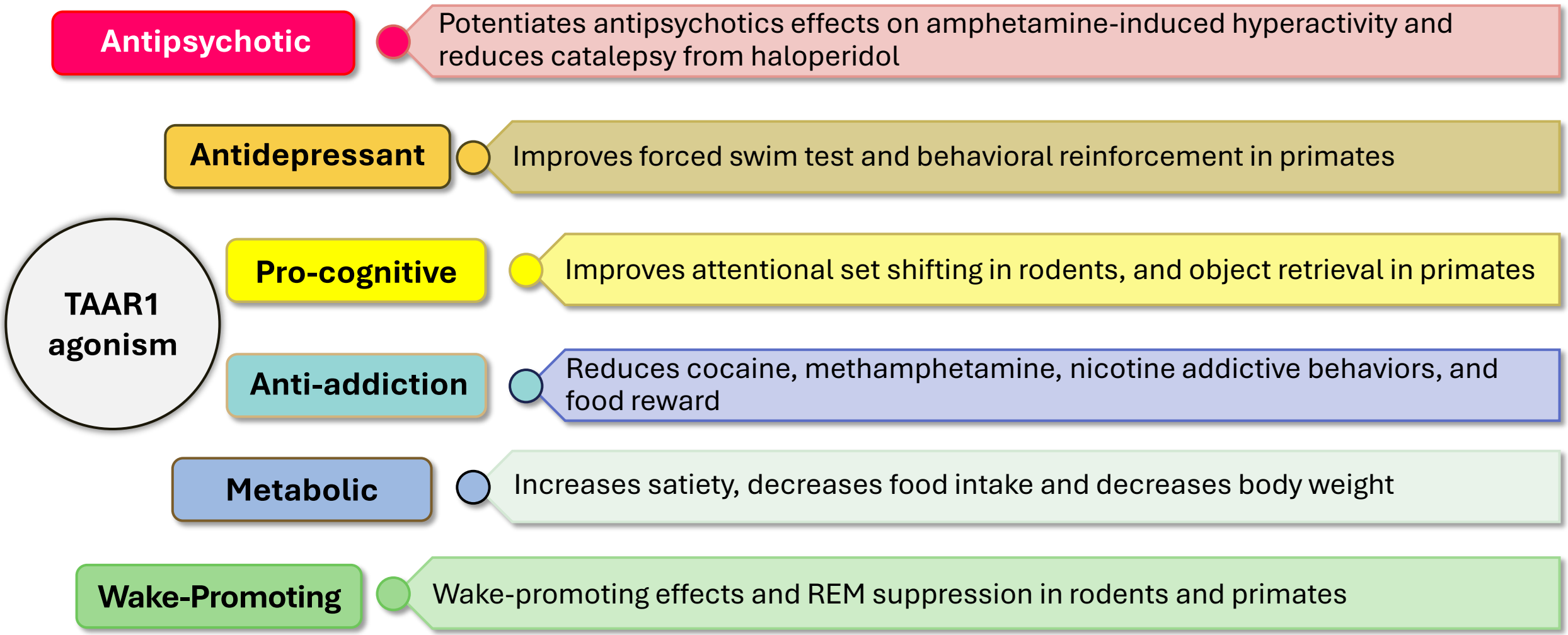
In a rodent **depression model**, there is **less TAAR1** expression in the **prefrontal cortex**

TAAR1 knockout mice have **impaired neuroplasticity,** which a TAAR1 partial agonist improved

TAAR1 agonists show **antidepressant-** and **anxiolytic-like effects** in multiple species (including nonhuman primates)

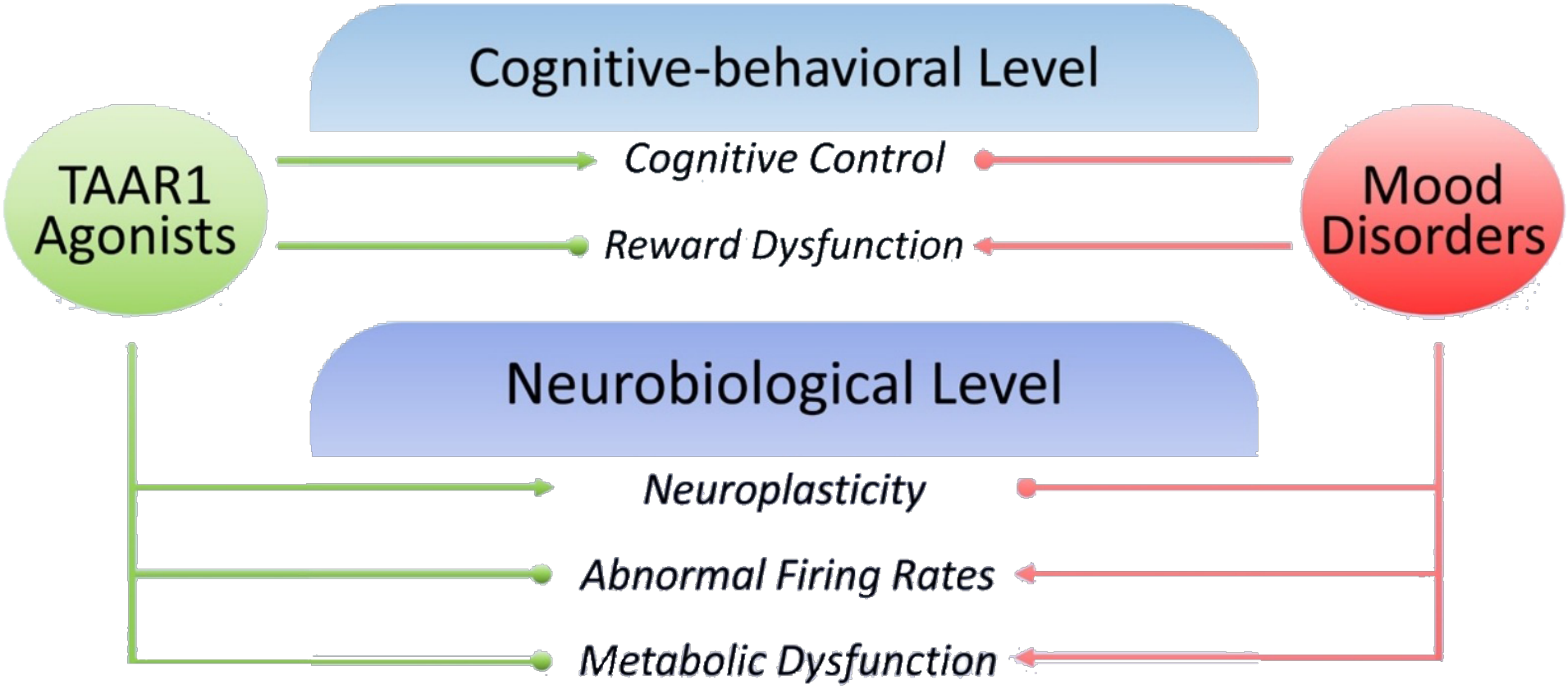
Ayub M, et al. *J Med Genet B Neuropsychiatr Genet*. 2013;162B(2):157-162. Berry MD, et al. *Pharmacol Ther*. 2017;180:161-180. Borowski B, et al. *Proc Natl Acad Sci USA*. 2001;98:8966-71. Chu TT, Li Y. *J Hum Genet*. 2012;55:282-295. Di Cara B, et al. *J Neurosci*. 2011;31:16928-40. Espinoza S, et al. *Neuropsychopharmacol*. 2015; 40:2217-2227. Li M et al. *World J Biol Psychiatry*. 2025;25(10):604-621. Lindeman L, et al. *J Pharmacol Exp Ther*. 2008;324:948-956. O'Donnell JM, et al. *Neurosci Biobehav Rev*. 2005;29: 785-798. Shemiakova TS, et al. *Biomedicines*. 2024;12(6):1263.

TAAR1 Agonists Have Wide-Ranging Effects in Preclinical Models



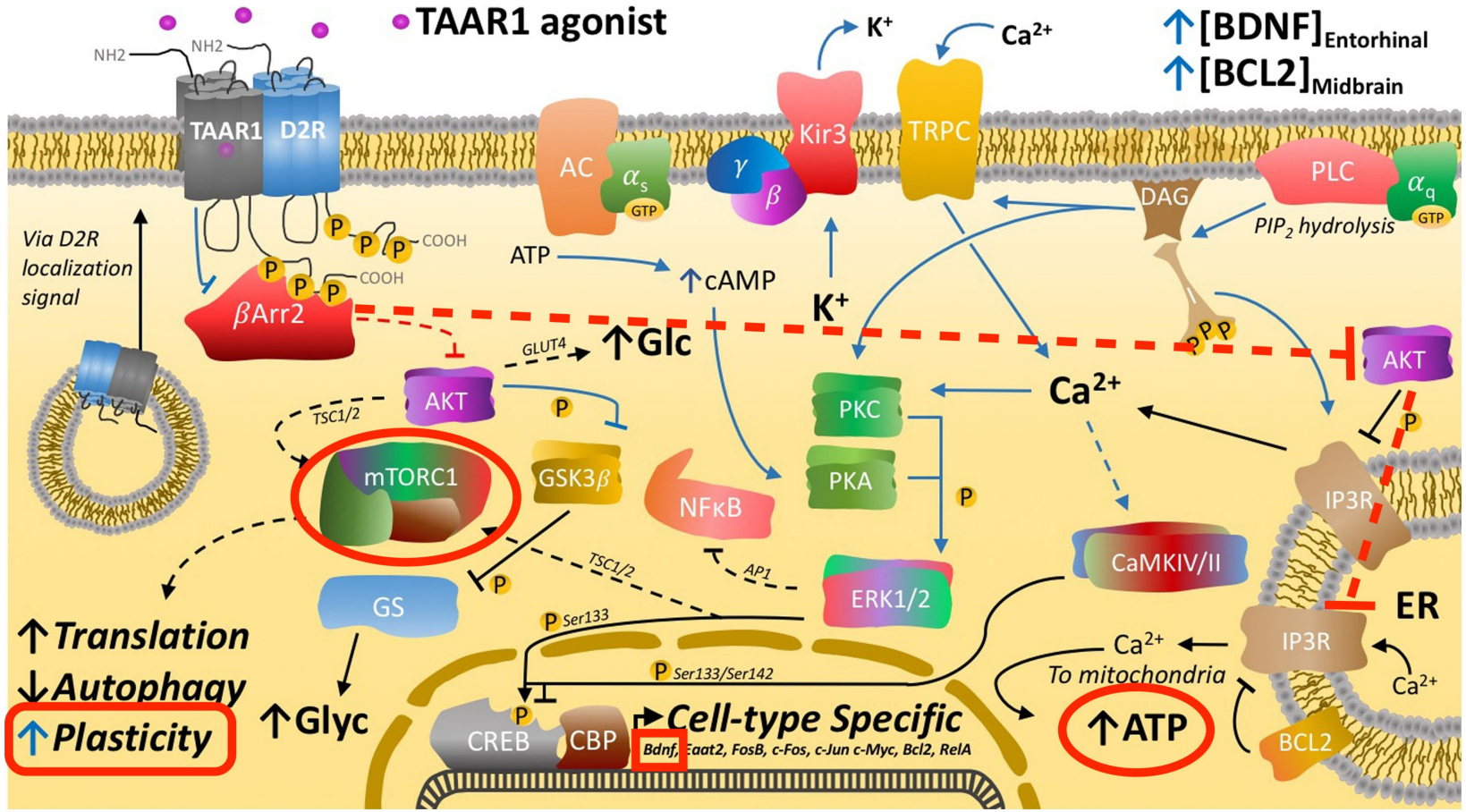
Revel FG, et al. *Mol Psychiatry*. 2013;18(5):543-556. Rutigliano G, et al. *Cell Mol Neurobiol*. 2020;40(2):239-255. Dedic N, et al. J Pharm Exp Ther. 2019;371:1-14. Dedic N, et al. *J Pharm Exp Ther*. 2019;371(Suppl):1-38.

Exciting News! There is Evidence of TAAR1 MOA in MDD



Alnefeesi, Y, et al. *Neuroscience & Biobehavioral Reviews*. 2021;131:192-210.

Hypothesized MOA of TAAR1 Agonists in MDD Involves Multiple Intracellular Signal Transduction Cascades



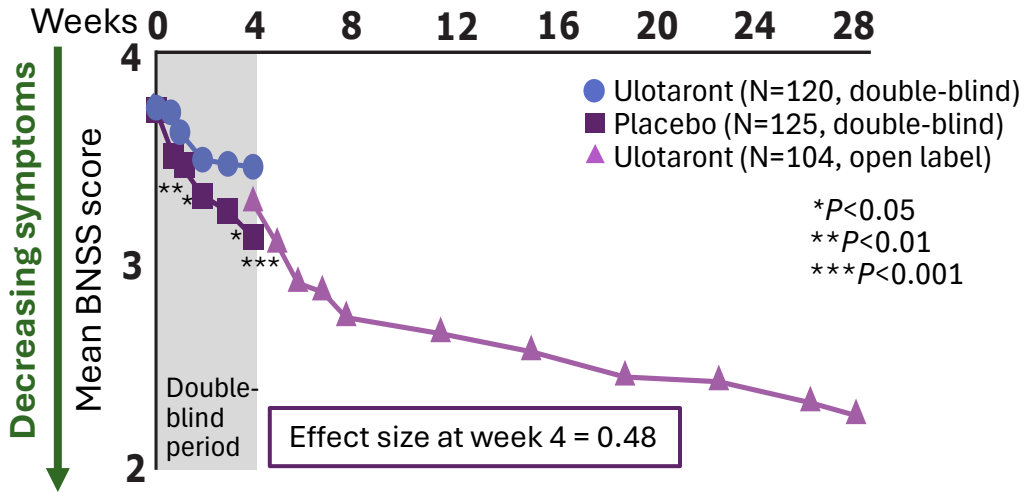
TAAR1 agonism may have downstream effects leading to increased neuroplasticity, which other treatments for MDD are believed to potentiate

Alnefeesi, Y, et al. *Neuroscience & Biobehavioral Reviews*. 2021;131:192-210.

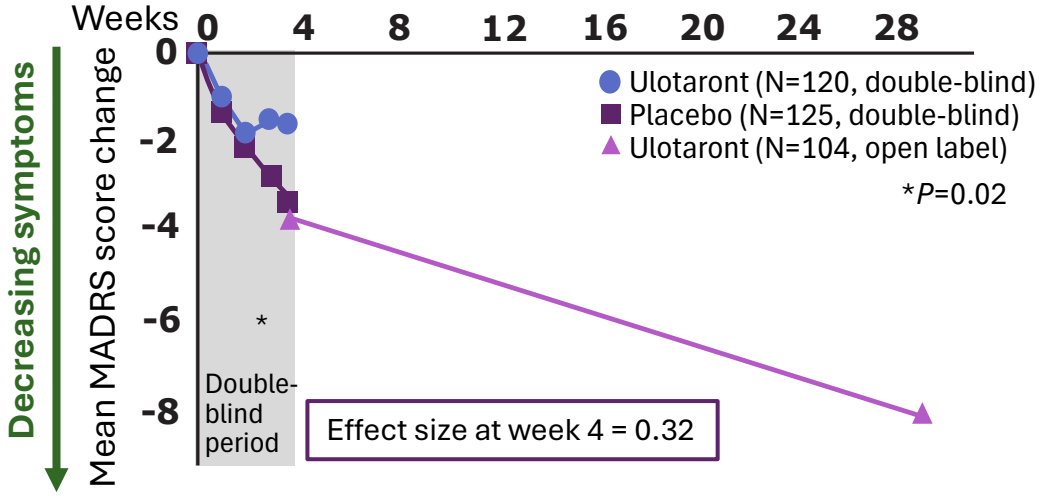
Let’s Now Turn Our Attention to The Therapeutic Potential of TAAR-1 Agonists…

Studies of TAAR1 Agonists in Schizophrenia Have Suggested Potential Benefits in Mood

Ulotaront is a **TAAR1 and 5-HT$_{1A}$ agonist** that was evaluated in a Successful Phase 2 trial in Acutely Exacerbated Schizophrenia



Ulotaront reduced **negative** and **affective** symptoms of schizophrenia



Ulotaront significantly reduced **depressive** symptoms in patients with schizophrenia

NB: *P* values are nominal as there was no adjustment for multiple measures on these secondary outcomes.

Corell CU, et al. Poster 204. Presented at American College of Neuropsychopharmacology; 2019. Dedic N, et al. *J Pharmacol Exp Ther*. 2019;371:1-14. Heffernan MLR, et al. *ACS Med Chem Lett*. 2021;13(1):92-98. Koblan, et al., *N Engl J Med*. 2020;382:1497-506. Revel FG, et al. *Proc Natl Acad Sci USA*. 2011;108(20):8485-8490. Revel FG, et al. *Mol Psychiatry*. 2013;18(5):543-556. Revel FG, et al. *Biol Psychiatry*. 2012;72:934–942. Saarinen M, et al. *Neuropsychopharmacol*. 2022;47:2319-2329. Zhang Y, et al. *Pharmacol Res*. 2021;167:105571. https://clinicaltrials.gov/study/NCT02970929.

Few Adverse Events Were Seen in Phase 2 Study and Open-Label Extension of Ulotaront in Schizophrenia

AEs During 4-Week Double-Blind Period		
Adverse event	Ulotaront N=120	Placebo N=125
Somnolence	7%	5%
Agitation	5%	5%
Nausea	5%	3%
Diarrhea	3%	1%
Dyspepsia	3%	0%
Extrapyramidal symptoms	3%	3%

AEs During Open-Label Period	
Adverse event in ≥5%	Ulotaront (N=156)
Schizophrenia	12%
Headache	12%
Insomnia	8%
Anxiety	5%
Somnolence	5%
Nasopharyngitis	5%

Other Measures in Double-Blind Period		
Weight gain	0.8 lb	-0.2 lb
Cholesterol (mg/dL)	-6.0	-0.4
Glucose (mg/dL)	+/-0.0	+1.8
Triglycerides (mg/dL)	-2.5	-8.0
Prolactin (ng/mL)	-2.15	-1.25

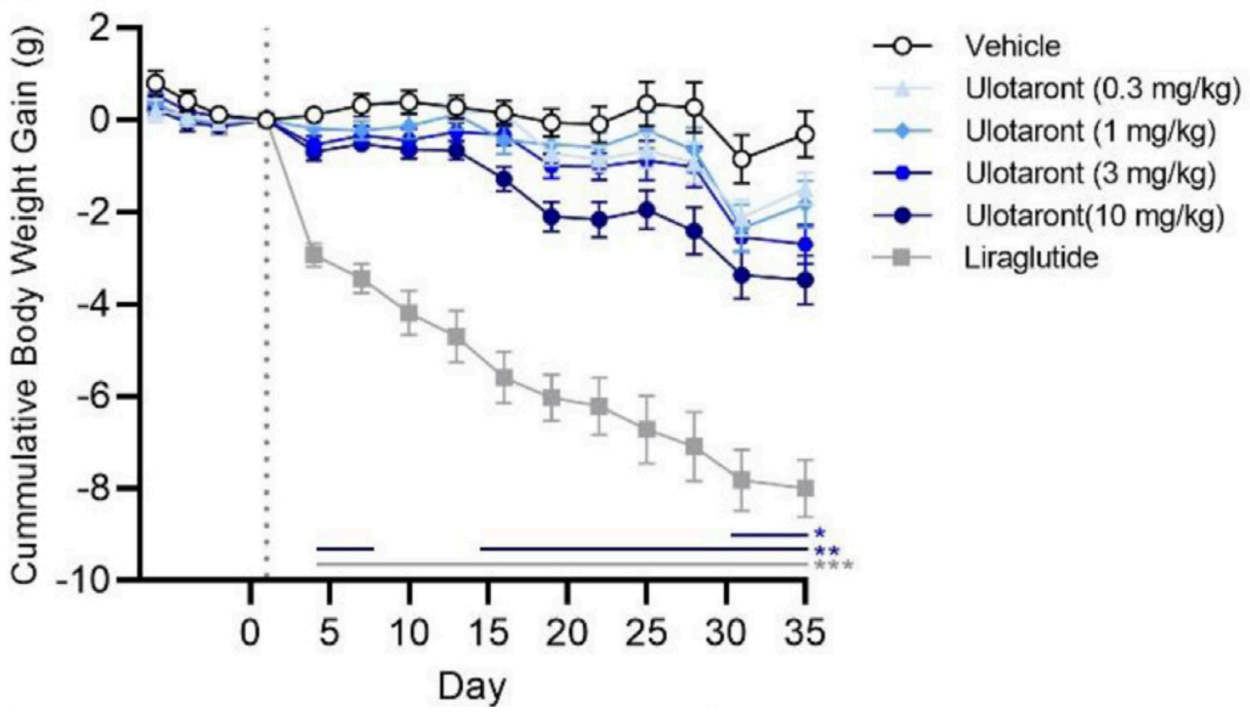
Other Measures in Open-Label Period	
Weight change	-0.3 lb
Total cholesterol (mg/dL)	-6.0
Glucose (ng/mL)	-2.15
HbA1c % change	0.0
Prolactin (ng/mL)	-2.7

Corell CU, et al. Poster 204. Presented at American College of Neuropsychopharmacology; 2019. Koblan KS, et al. *New Engl J Med*. 382(16):1497-1506.

GLP-1 Receptor Agonist-Like Effects of TAAR1 Activators and Agonists, Including Ulotaront

- **TAAR1 activation improved metabolic parameters** in mouse models of diabetes and obesity
  - **Normalized glucose fluctuations**
  - Improved insulin sensitivity, plasma triglyceride levels, and liver triglyceride content

- **TAAR1 agonists may have similar effects**
  - **Prevent olanzapine-induced weight gain** in rats
  - **Decrease body weight** in lean rodents
  - **Reduce food intake and excess body weight** in a mouse model of diet-induced obesity
  - **Attenuate binge-like eating** in rats



Dedic N, et al. *Mol Metab*. 2024;80:101883. Moore CF, et al. *Front Pharmacol*. 2018;9(FEB):1–7. Revel FG, et al. *Mol Psychiatry*. 2012;18(January):1–14.

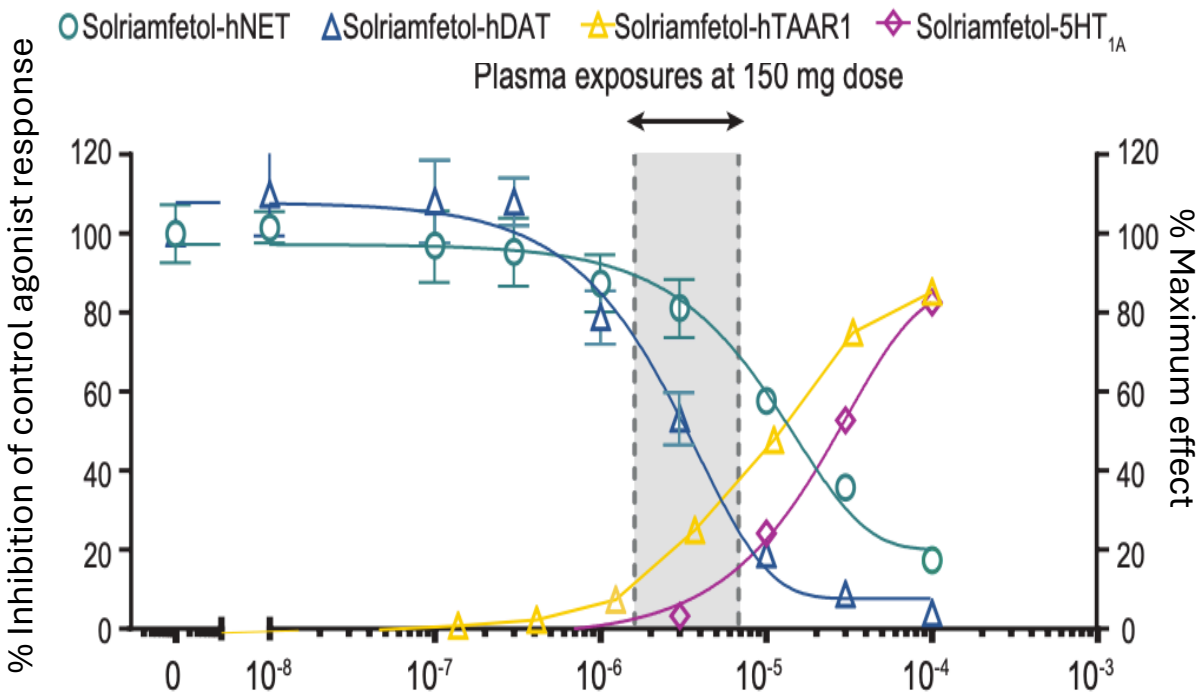
Solriamfetol, Approved for Excessive Daytime Sleepiness in Narcolepsy or OSA, Has TAAR-1 Agonist Properties

Solriamfetol is dopamine-norepinephrine reuptake inhibitor indicated for treatment of EDS in OSA or narcolepsy

Solriamfetol is not classified as a stimulant.

It is schedule IV, but showed no evidence of tolerance, withdrawal, or dependence, in trials

At 8x maximum recommended dose, the abuse potential was similar to or lower than phentermine

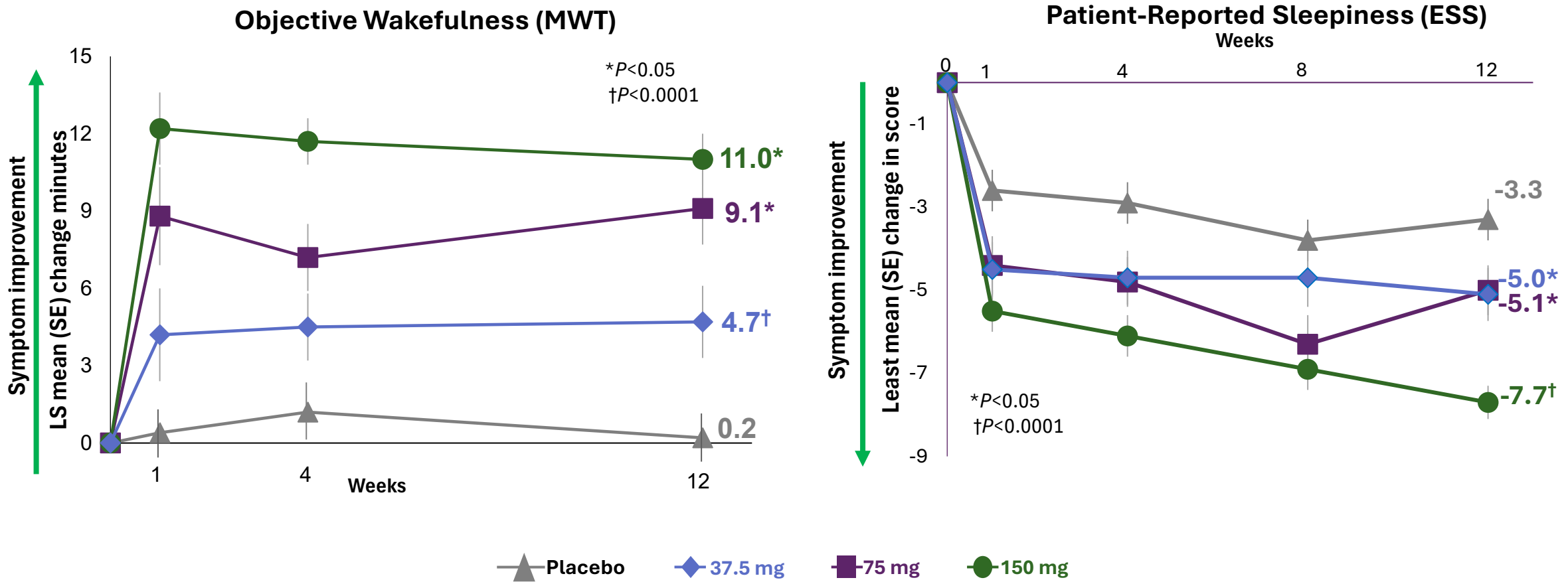


Subsequent pharmacologic characterization showed agonist activity at TAAR1 and 5-HT$_{1A}$

CYP = cytochrome P; EDS = excessive daytime sleepiness; OSA = obstructive sleep apnea; WPA = wake promoting agent.

Solriamfetol [prescribing Information]. Jazz Pharmaceuticals; 2021. Carter LP, et al. *J Psychopharmacol*. 2018;32(12): 1351-1361. Gurashani H, et al. Poster presented at 2022 SLEEP meeting.

Solriamfetol Improves Wakefulness and Reduces Sleepiness

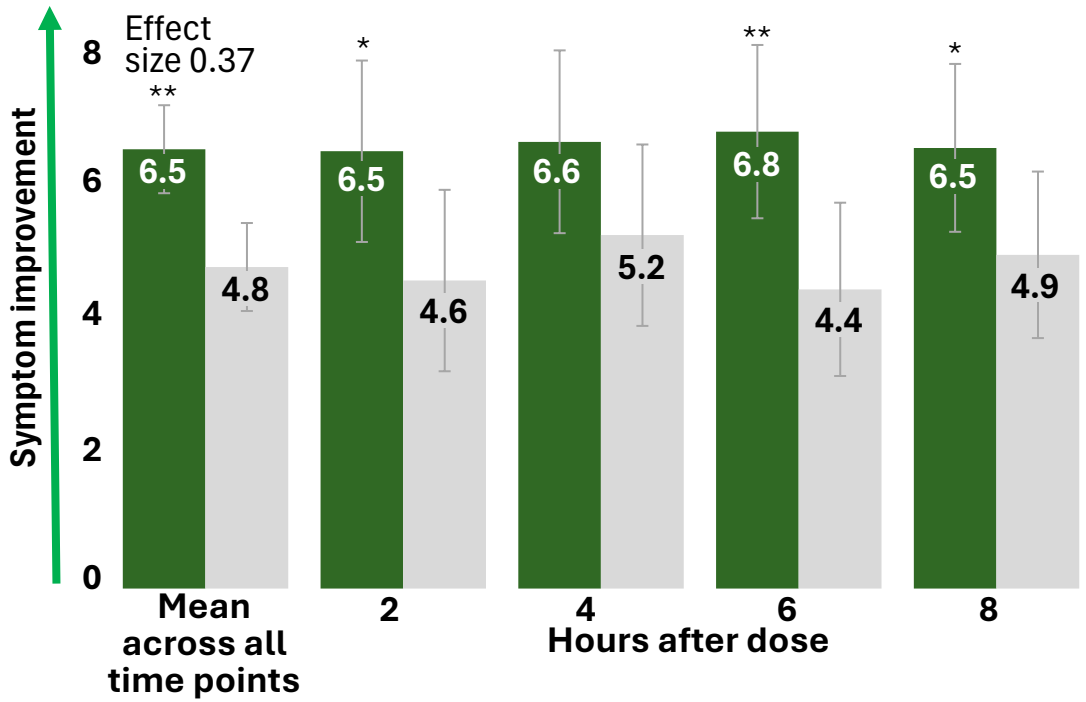


MWT = maintenance of wakefulness; ESS = Epworth Sleepiness Scale; LS = least squares; OSA = obstructive sleep apnea; SE=standard error.

Solriamfetol [prescribing Information]. Jazz Pharmaceuticals; 2021. Schweitzer PK, et al. *Am J Respir Crit Care Med*. 2019;199(11):1421-1431.

Solriamfetol May Provide Cognitive Benefits for Those with Cognitive Impairment Associated with EDS in OSA

A phase 4 randomized, double-blind, placebo-controlled, crossover trial



Solriamfetol (N=58)

Placebo (N=58)

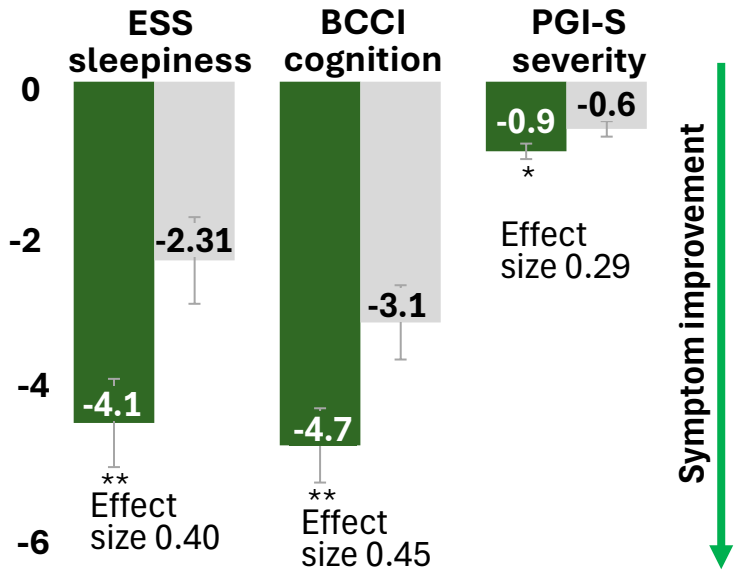
*$P \leq 0.05$

**$P \leq 0.01$

Adverse events with solriamfetol vs placebo in ≥2% of participants

Any	19% vs 10%
Nausea	7% vs 3%
Anxiety	3% vs 0%

None were serious



DSST RBANS score improved overall and throughout the day with solriamfetol vs placebo

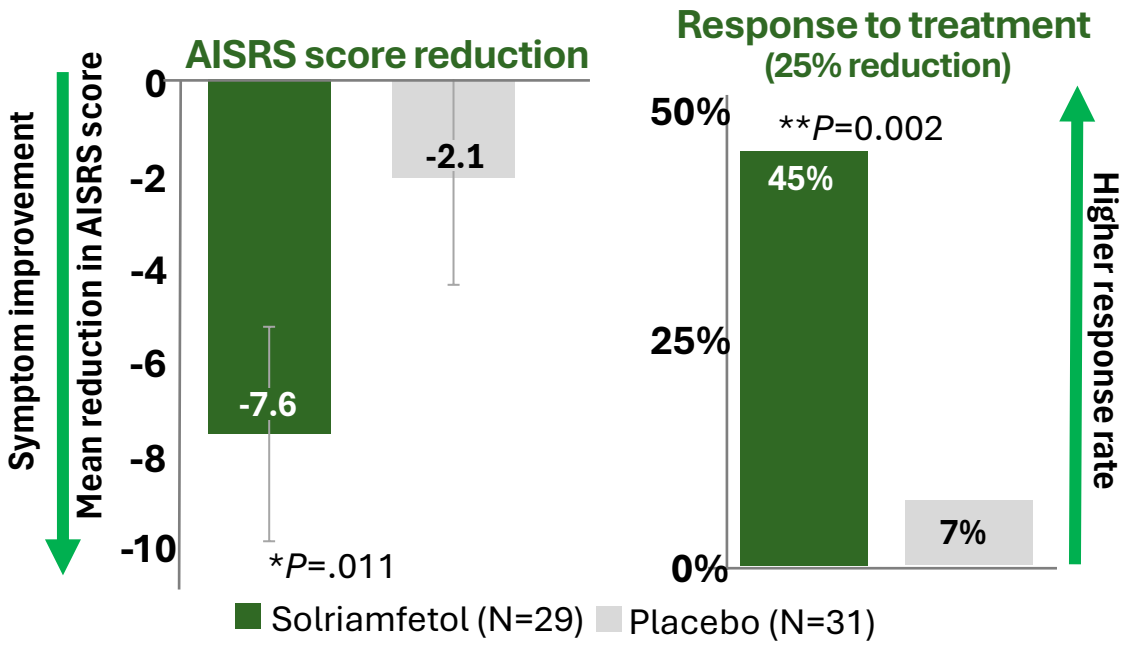
Solriamfetol vs placebo also significantly improved secondary outcomes

BCI = British Columbia Cognitive Complaints Inventory; DSST = Digit Symbol Substitution Test; PGI-S = Patient Global Impression of Change-Severity.

Van Dongen HPA, et al. *Chest*. 2025;167(3):863-875.

Solriamfetol Is Also Being Evaluated for Potential Treatment of ADHD

Investigator-Initiated 6-week, Double-Blind, Placebo-Controlled Trial of Adults with ADHD



Solriamfetol 150 mg reduced ADHD symptoms and increased response rates significantly more than placebo in adults with ADHD

AEs in solriamfetol group ≥5% and ≥2x Placebo		
AE	Solriamfetol	Placebo
Cardiovascular	17%	3%
Nausea/Vomiting/Diarrhea	24%	6%
Sedation	10%	3%
Increased Energy	14%	3%
Agitated/irritable	10%	5%
Decreased Appetite	17%	6%
Neurological	14%	3%

Solriamfetol also showed efficacy in a phase 3 trial of 516 adults with ADHD

AISRS reduced by 17.7 points for solriamfetol 150 mg and 14.3 points for placebo (p=0.039)

AEs were consistent with the established safety profile of solriamfetol

AISRS = Adult ADHD Investigator Symptom Rating Scale.

Surman CBH, et al. *J Clin Psychiatry.* 2023;84(6):23m14934. https://www.globenewswire.com/news-release/2025/03/25/3048592/33090/en/Axsome-Therapeutics-Announces-FOCUS-Phase-3-Trial-of-Solriamfetol-in-Adults-with-Attention-Deficit-Hyperactivity-Disorder-ADHD-Achieves-Primary-Endpoint.html Accessed 5-20-2025.

Solriamfetol is Also Under Investigation for MDD

In a 6-week, double-blind, placebo-controlled Phase 3 Proof of Concept Study:

No statistically significant difference in the overall population of 295 participants in MADRS scores vs placebo

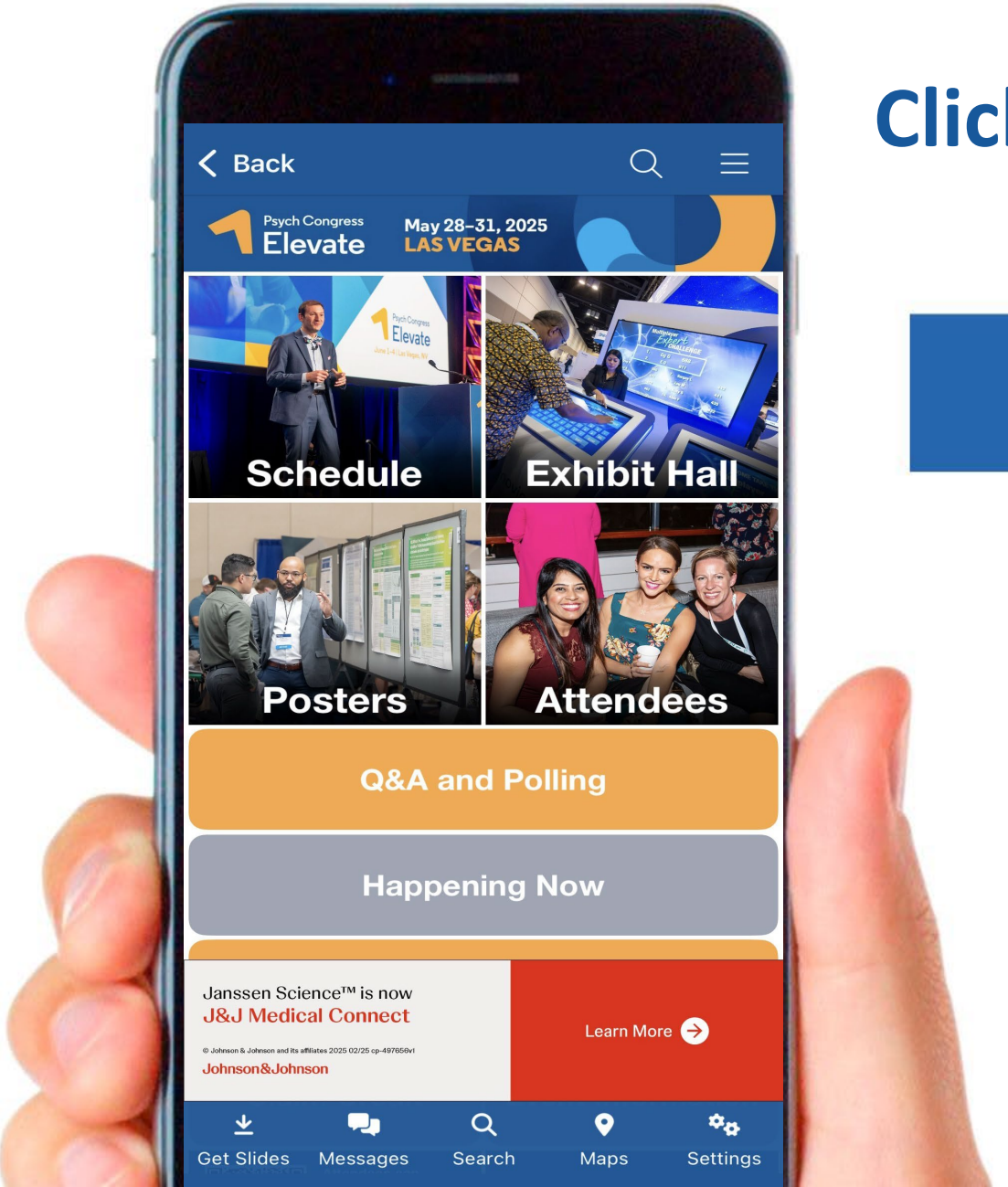
However, clinically meaningful improvements occurred with solriamfetol vs placebo among 51 participants with severe EDS (ESS score ≥16)

Future trials of solriamfetol for MDD with EDS are being planned

Axsome Therapeutics [press release]. April 1, 2025. Globe Newswire. Accessed May 7, 2025. https://www.globenewswire.com/news-release/2025/04/01/3053170/33090/en/Axsome-Therapeutics-Announces-Topline-Results-of-PARADIGM-Phase-3-Proof-of-Concept-Trial-of-Solriamfetol-in-Major-Depressive-Disorder-MDD-with-and-without-Excessive-Daytime-Sleepin.html

Key Learning Points

- ✓ **TAAR1** has both **intracellular** and **membrane-bound functions** with **strong evidence** that they **modulate monoamine** and **glutamate transmission**
- ✓ In preclinical studies, **TAAR1 agonists have been implicated** as having a role **in multiple psychiatric disorders** including **ADHD, GAD, MDD, schizophrenia**, and **sleep-wake disorders**
- ✓ **Medications with TAAR1 agonism** are **being investigated** in clinical trials **for** potential treatment of **MDD,GAD, ADHD**, and more…



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Panel Discussion

How to Keep Up With Emerging Information?

How to Talk About Novel Mechanisms of Action with Patients

How Can Personal Treatment Algorithms Be Updated to Incorporate Agents with Novel Mechanisms of Action?

Questions?