



Volition Reignition: Achieving Patient Goals by **Detecting and Addressing Anhedonia in MDD**

MasterClass

Faculty

Brittany Albright MD

*Founder, Sweetgrass
Psychiatry, Mount
Pleasant, SC*

*Affiliate Assistant
Professor, Medical
University of South
Carolina*

Veronica Ridpath DO

*Founder & Medical
Director, Sweetgrass
Psychiatry Florence
Clinic, Florence, SC*

Katie Hahn

*Patient Advocate
Charleston, SC*

Faculty Disclosures

Brittany Albright, MD:

- Advisory Board- AbbVie, Bristol Myers Squibb, Compass Pathways, Definium Therapeutics, Eli Lilly, Johnson & Johnson, Neurocrine Biosciences, Vistagen.
- Consultant - AbbVie, Aidvance, Almatica, Axsome, Definium Therapeutics, Johnson & Johnson, Osmind, Precision Genetics.
- Speakers Bureau - AbbVie, Alkermes, Axsome, Bristol Myers Squibb, Johnson & Johnson, Tonix Medicines

Veronica Ridpath, DO:

- Advisory Board- AbbVie, Eli Lilly, Johnson & Johnson, Neurocrine Biosciences, Otsuka
- Consultant –Abbvie, Aidvance, Otsuka
- Speakers Bureau - AbbVie, Alkermes, Axsome, Neurocrine Biosciences, Johnson & Johnson, Teva

Katie Hahn:

- No disclosures

Disclosures

- 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.
- This CME activity includes brand names for participant clarity purposes only. No product promotion or recommendation should be inferred.
- Generative AI was used in the preparation of this presentation. Any AI-generated content was reviewed and verified by the presenter, who accepts full responsibility for the accuracy, completeness, and integrity of all content presented.

Learning Objectives



Describe patient-reported priorities in major depressive disorder (MDD) treatment, including the reduction of anhedonia and avoidance of emotional blunting, to ensure optimal antidepressant choices



Apply strategies to improve the detection and assessment of anhedonia in patients with MDD



Evaluate the mechanisms of action and latest clinical evidence associated with novel/investigational monotherapies for MDD and their potential to address anhedonia

A Patient First Approach to Major Depression

What Patients Really Care About: The Four Pillars of Life Engagement



1. Cognition

Restoration of executive function, mental processing speed, attention, and working memory capacity.

Addresses persistent cognitive deficits often unresolved by standard agents



2. Vitality

Rebuilding physical energy, mental stamina, alertness, and reversing underlying psychomotor retardation.

Combats residual fatigue to allow functional initiation of daily activities



3. Motivation

Reactivating goal-directed behavior, incentive processing, and willingness to expend effort for a reward.

Directly targets anticipatory (“wanting”) circuitry deficits



4. Pleasure

Restoring the capacity to experience joy, emotional consumption, and spontaneous hedonic responses.

Reverses consummatory (“liking”) anhedonia within positive valence systems

Anhedonia: The Help-Seeking Catalyst

It is one of the most common reasons patients seek depression treatment

Anhedonia is not just a symptom;
**it is one of the two foundational
diagnostic criteria for MDD in the
DSM-5.**

50–80% of individuals with MDD
experience anhedonia

Patients with anhedonia report
"hopelessness," the belief that
nothing will change.



Bridging the Patient-Clinician Goal Gap



Physician Priorities Clinical Stabilization

- Patient safety, resolved suicidal ideation
- Restoring social/occupational function
- Improved rating scale scores
- Treatment adherence

Patient Priorities Life Engagement

- Cognition, vitality, and motivation
- Ability to feel pleasure
- Improved anxiety and sleep
- Feeling connected to one's life

Restoring Joy as the Goal: While clinicians focus on "removing sadness," patients prioritize "restoring joy."



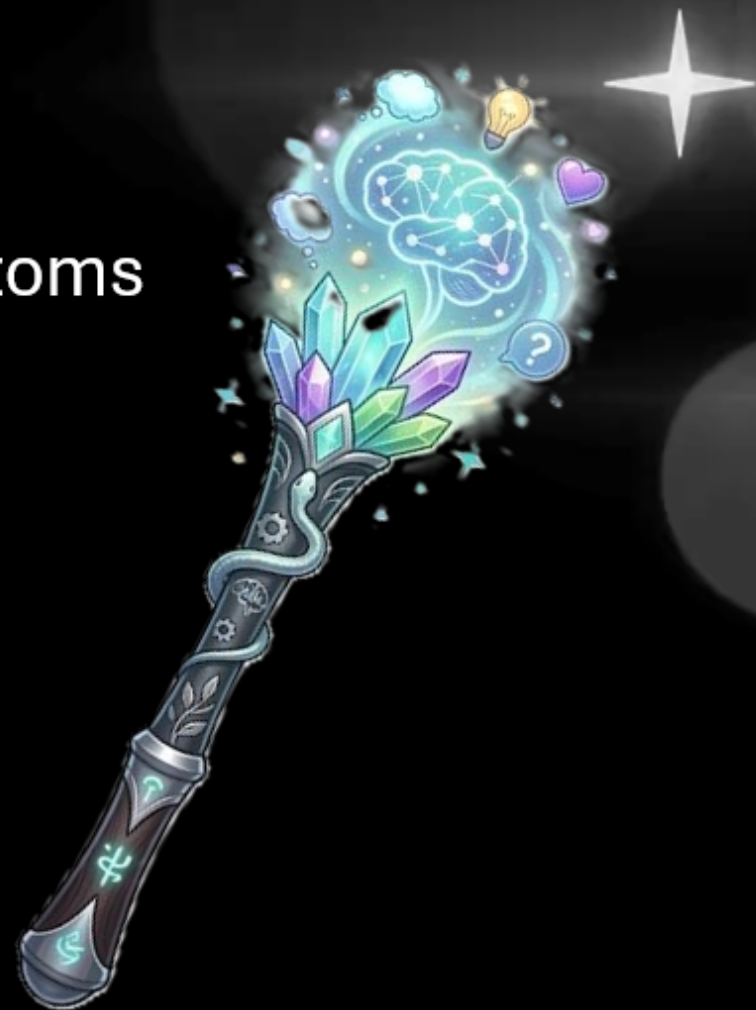
Transition from "What
is the matter with
you?" to

***"What matters
to you?"***

If You Could Wave a Magic Wand...

Imagining the Optimal Antidepressant

- Rapid onset of action
- Efficacy for full spectrum of depression symptoms
- Increased engagement in rewarding activities
- Improved functioning and cognition
- Minimal side effects
 - No weight gain
 - No sexual side effects
 - No emotional blunting / numbness



Drawbacks of Serotonergic Antidepressants

Why first-line response so often falls short of full recovery:

SSRIs

First-line
pharmacotherapy

Emotional Blunting & Anhedonia^{1,2}

Dulled positive affect and reward response; reported by ~40–60% of treated patients.

Incomplete Remission³

Only about 1 in 3 (33%) patients remit on a first-line SSRI trial (STAR*D Level 1).

Residual Symptoms^{4,5}

Anhedonia, fatigue and insomnia persist after response — early relapse 76% vs 25%..

Slow Path to Remission⁶

Drug effect begins week 1–2, but full remission typically takes 6–8 weeks.

Sexual Dysfunction⁷

Low libido, delayed or absent orgasm; 70–80% on citalopram, fluoxetine, paroxetine or sertraline

Somatic & Metabolic Burden^{8,9}

Weight gain, GI upset, hyponatremia, GI bleeding risk quadruples with NSAIDs (OR 4.25).

Early Activation & Sleep¹⁰

Jitteriness, insomnia, vivid dreams early on; reported rates vary widely (4–65%).

Discontinuation Syndrome⁶

Dizziness, paresthesias, flu-like symptoms; requires a slow taper.

Key Learning Points



Patients value life engagement and rewarding activity, not just symptom reduction; clinicians tend to focus on clinical stabilization



Anhedonia affects 50–80% of MDD patients and predicts treatment resistance



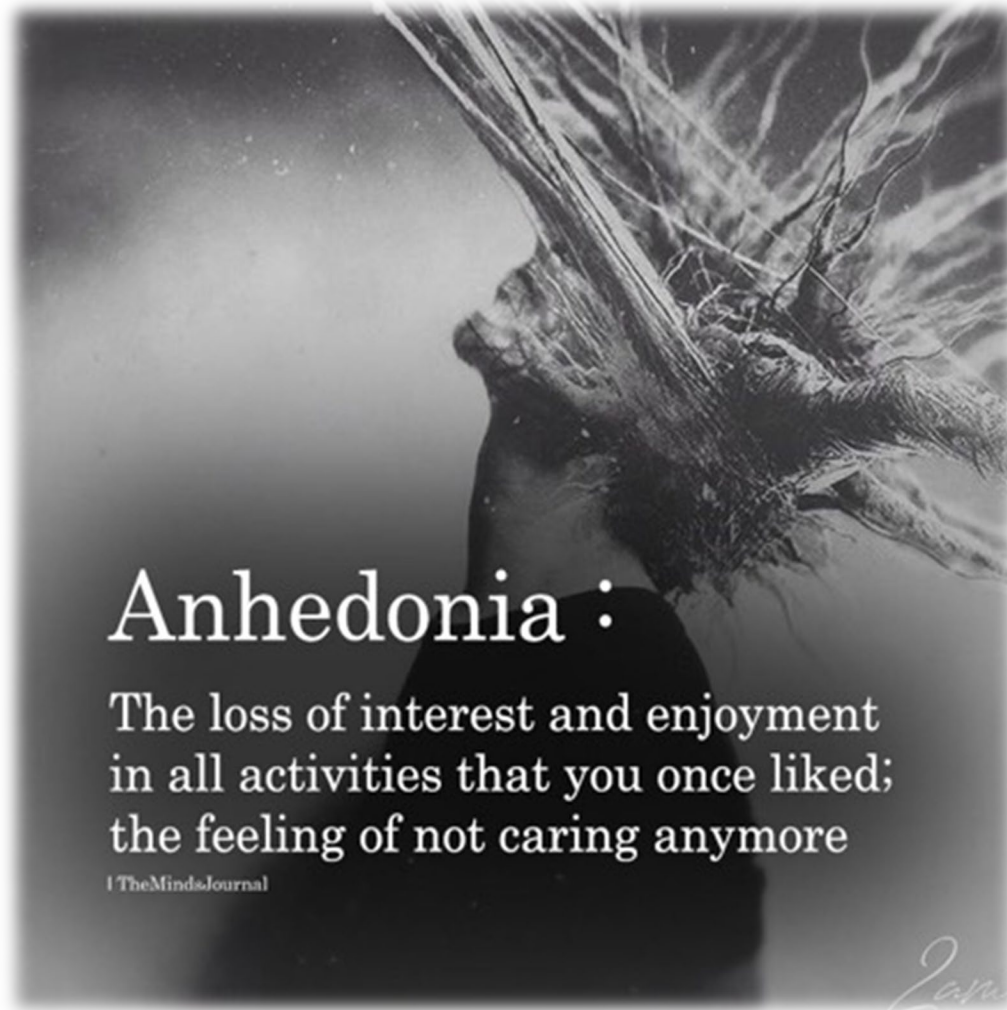
Standard serotonergic antidepressants may inadequately address anhedonia and can contribute to emotional blunting



The optimal antidepressant would target the full symptom spectrum, including reward processing

Understanding Anhedonia

What Exactly is Anhedonia?



An impaired capacity to experience or anticipate pleasure, present in majority of individuals with MDD

Characterized by a loss of interest and/or pleasure in previously enjoyable activities

Derived from the Greek words an (without) and hēdonē (pleasure)

Anhedonia is **transdiagnostic** and recognized in the DSM-V as a symptom

MDD = major depressive disorder.

Pan et al. *Curr Pharm Des.* 2017;23:2065; Pizzagalli DA. *Am J Psychiatry.* 2022;179:458-469; Rizvi SJ, Pizzagalli DA, Sproule BA, Kennedy SH. *Neurosci Biobehav Rev.* 2016;65:21-35; Wong S, Le GH, Phan L, et al. *J Affect Disord.* 2024;356:684-698.

The Evolution of Anhedonia Across DSM Editions

Definitional / Critical Changes (DSM-III)

Anhedonia is promoted from descriptive prose to a formal, co-equal gate criterion

Important Clarifications (DSM-5 and DSM-5-TR)

Defined as "markedly diminished interest or pleasure in all, or almost all, activities." The frequency qualifiers "most of the day, nearly every day"

Interest and pleasure were fused into a single item. That conflation persists to this day and blurs motivational (*wanting*) from consummatory (*liking*) deficits — a distinction central to current reward-circuitry models.

Criterion A required *dysphoric mood or loss of interest or pleasure in all or almost all usual activities and pastimes.*

Anhedonia became **sufficient on its own** — a patient could meet full MDE criteria without endorsing sad mood.

Anhedonia is **transdiagnostic** and recognized in the DSM-5 as a **symptom** (not a standalone diagnosis) associated with major depressive disorder and other mood disorders but can occur in anxiety disorders, substance use disorders, traumatic brain injury, neurocognitive disorders, stroke, and Parkinson's disease.

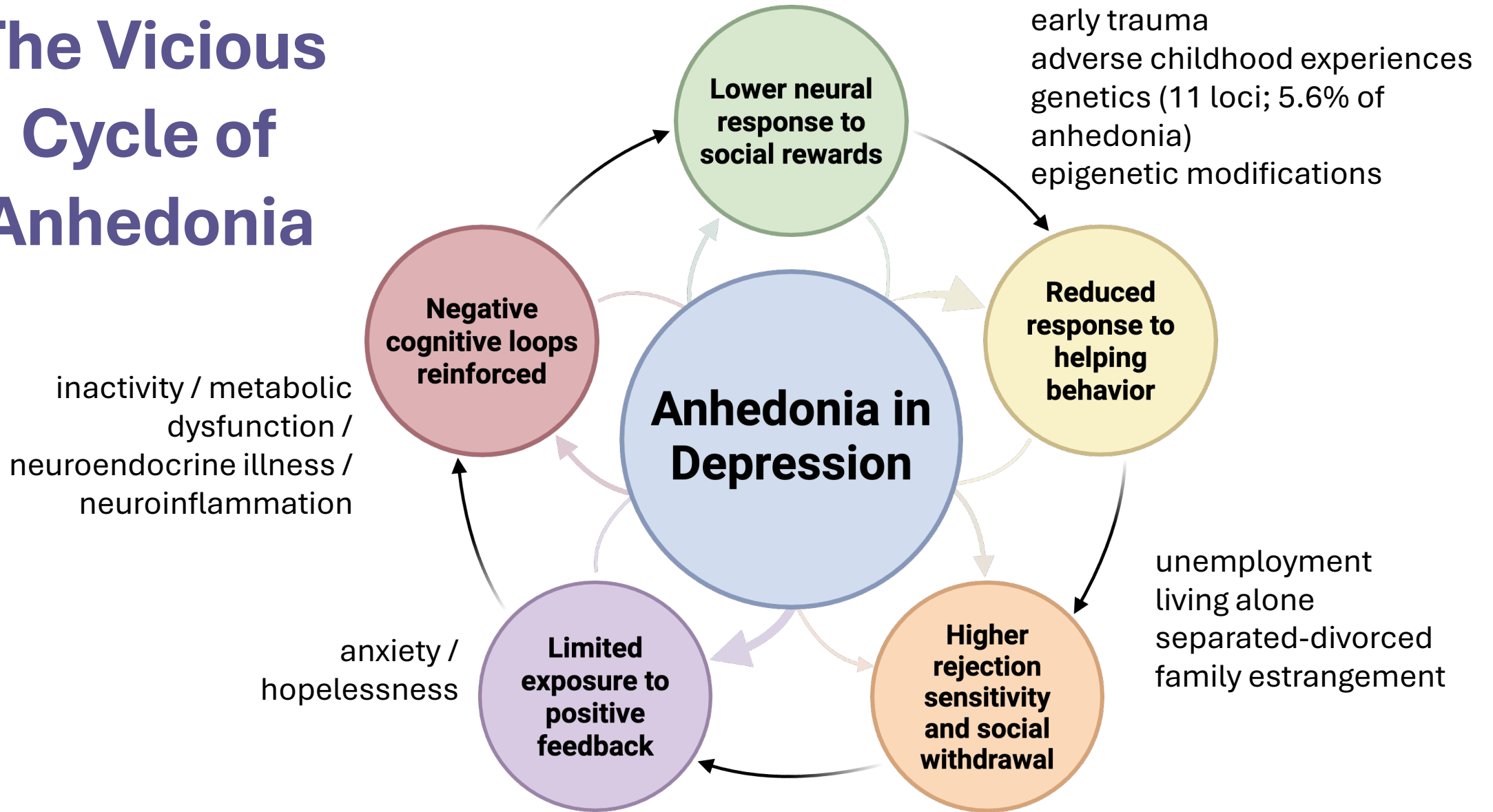
Why Do We Care About Anhedonia?

In MDD, anhedonia is associated with:

- Poorer treatment outcomes
- Decreased quality of life
- Decreased psychosocial and occupational functioning
- Social withdrawal and social impairment
- Fewer depression-free days
- Higher severity of depression
- Prolonged time to response and lower rates of response to monoamine pharmacotherapy and psychotherapy
- Increased risk of suicide

Vinckier F, et al. *Eur Psychiatry*. 2017;44:1-8; Whitton AE, et al. *Mol Psychiatry*. 2023;28:5272-5281; McMakin DL, et al. *J Am Acad Child Adolesc Psychiatry*. 2012;51(4):404-411. Serretti. *Clin Psychopharmacol Neurosci*. 2023;21:401. Baune. *Neuropsychiatr Dis Treat*. 2021;17:2995. Rush. *Am J Psychiatry*. 2006;163:1905. 4. Wardenaar. *J Affect Disord*. 2012;136:1198.

The Vicious Cycle of Anhedonia



The Concept of Anhedonia in RDoC

Research Domain Criteria — a dimensional, mechanism-based framework for reward dysfunction

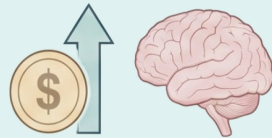
Anhedonia: Dimensional and Transdiagnostic Definition

- A continuum, not a present/absent symptom; reward function is measured from normal to severely impaired.
- **Transdiagnostic:** prominent in major depression, bipolar disorder, schizophrenia, PTSD, other anxiety disorders, autism spectrum disorders, substance use disorders, neurological disorders such as dementia, Parkinson's disease
- Related to impaired reward processing

Positive Valence System: Broken in Anhedonia

Positive valence system is responsible for responses to positive motivational situations or contexts, such as reward seeking, consummatory behavior, and reward/habit learning

Reward Responsiveness



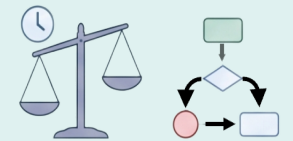
- anticipation
- initial response to reward
- satiation

Reward Learning



- probabilistic & reinforcement learning
- prediction error
- habit

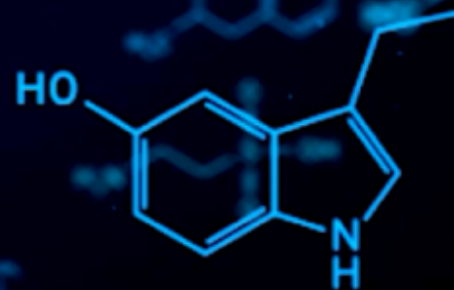
Reward Valuation



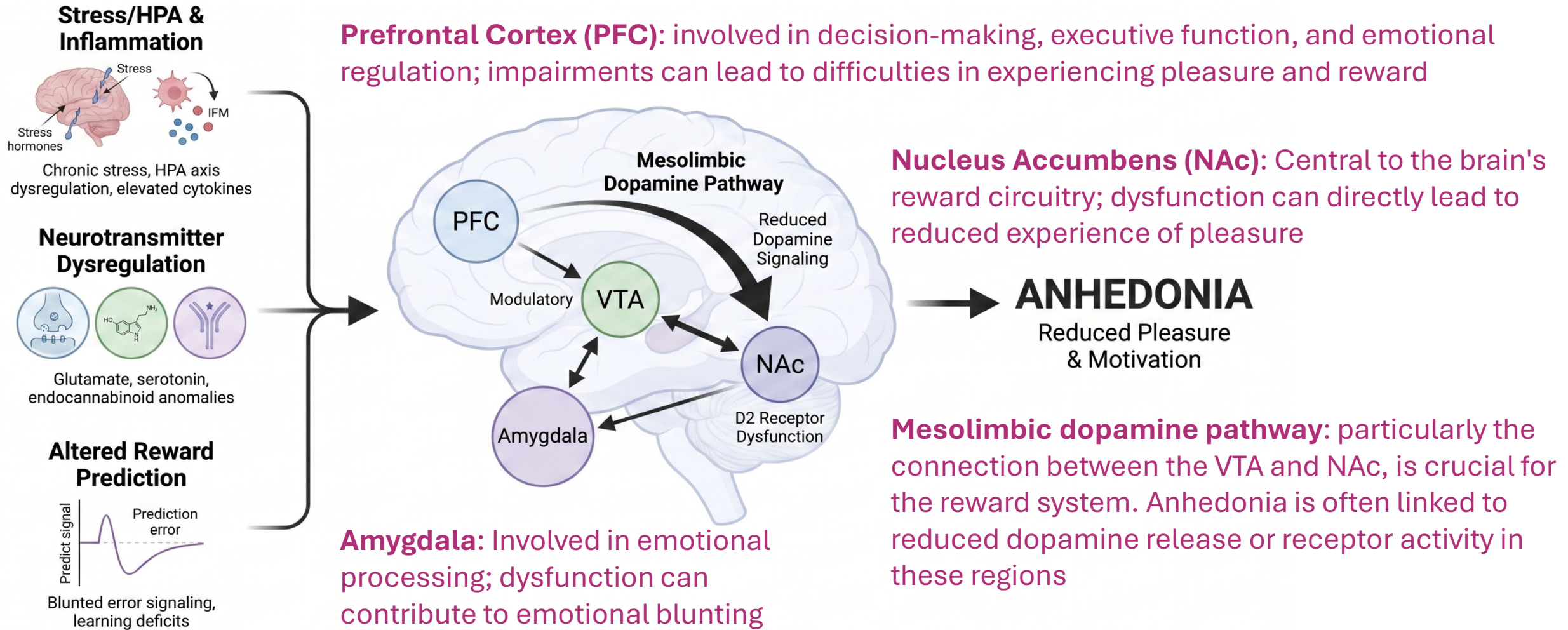
- ambiguity/risk
- delay
- effort

RDoc = Research Domain Criteria. PTSD = post traumatic stress disorder. Rizvi SJ, et al. Assessing anhedonia in depression: potentials and pitfalls. *Neurosci Biobehav Rev.* 2016;65:21-35. National Institute of Mental Health. Definitions of the RDoC Domains and Constructs. nimh.nih.gov/research/research-funded-by-nimh/rdoc/definitions-of-the-rdoc-domains-and-constructs. Image created in BioRender.com

In individuals with anhedonia, their ability to learn and make corrective changes in their life is lesioned at the neurophysiological level with alterations in reward processing.



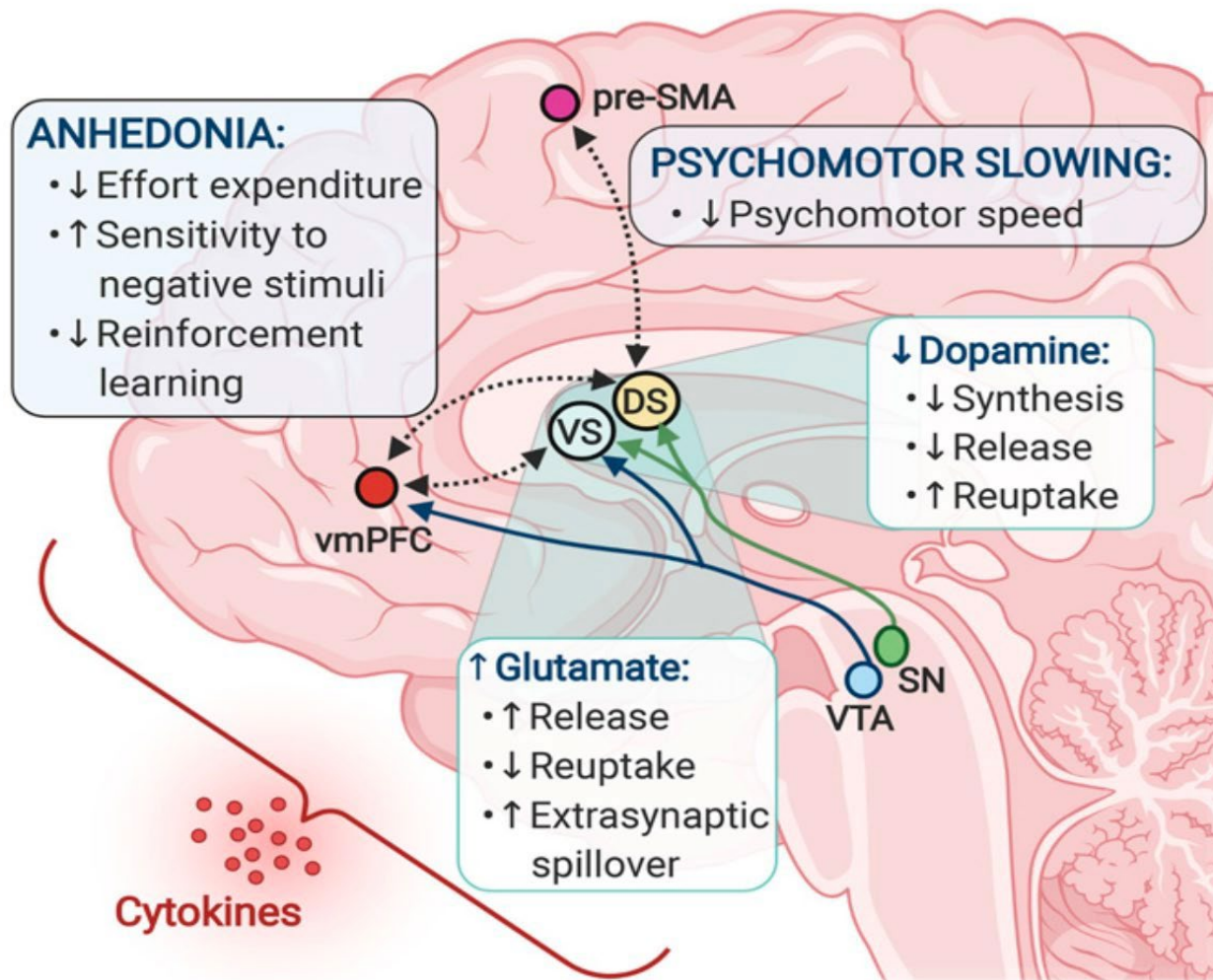
Pathophysiology of Anhedonia: Multiple Brain Regions



VTA = ventral tegmental area. Image created using BioRender.com

Der-Avakian. Trends Neurosci. 2012;35:68; Gorwood. Dialogues Clin Neurosci. 2008;10:291. Thomsen. Front Behav Neurosci. 2015;9:49.

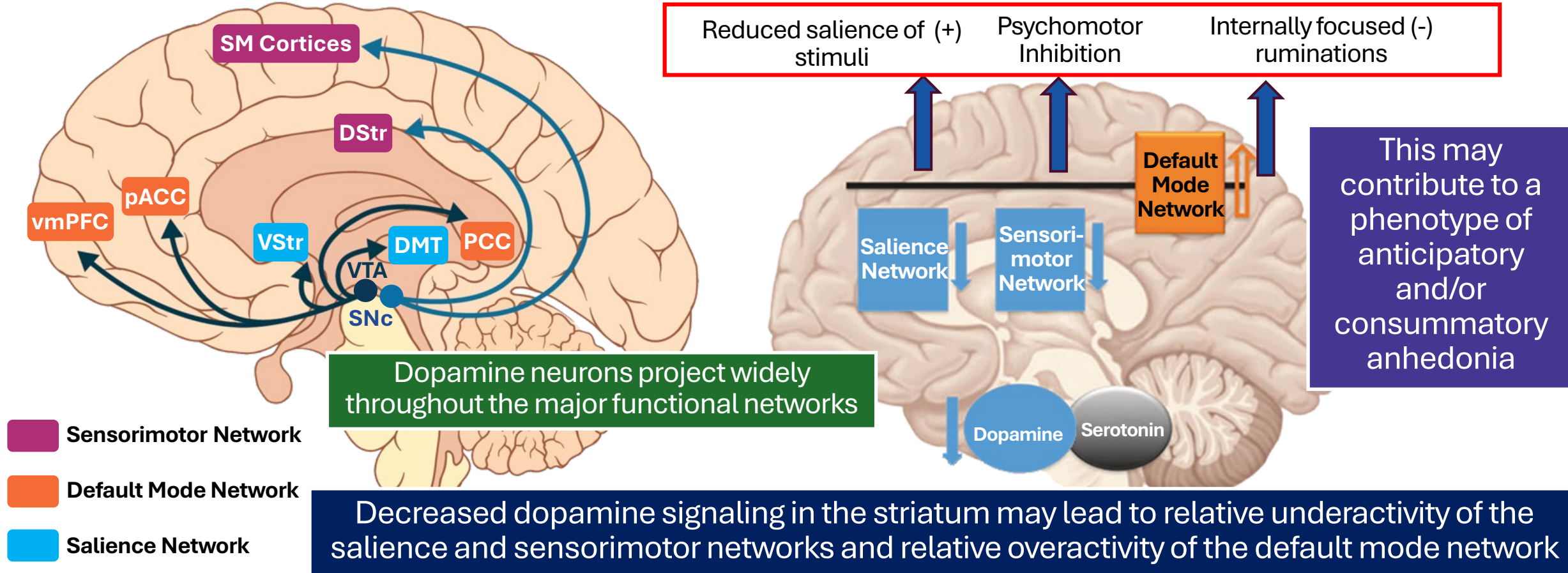
Pathophysiology of Anhedonia: Neurotransmitter Dysfunction



- **D2 receptors:** Dysregulation of D2 dopamine receptors in the striatum may contribute to anhedonia because these receptors are involved in the motivation and pleasure aspects of reward
- **Glutamatergic dysfunction:** Overactivity or underactivity of glutamatergic signaling, particularly in the PFC, can disrupt the integration of reward signals, contributing to the blunted experience of pleasure
- **Serotonergic dysfunction:** Serotonin plays a role in mood regulation and the processing of reward-related information. Dysregulation in serotonergic pathways, especially in the prefrontal cortex and limbic system, can contribute to anhedonia

vmPFC = ventromedial prefrontal cortex; sgACC = subgenual anterior cingulate cortex; SMA = supplementary motor area
Miller AH, Raison CL. Mol Psychiatry 2023;28(1):68-75; Lucido MJ et al. Pharmacol Rev 2021;73(3):1084-117.

Pathophysiology of Anhedonia: Striatal Dopamine Signaling Deficits → Network Dysfunction



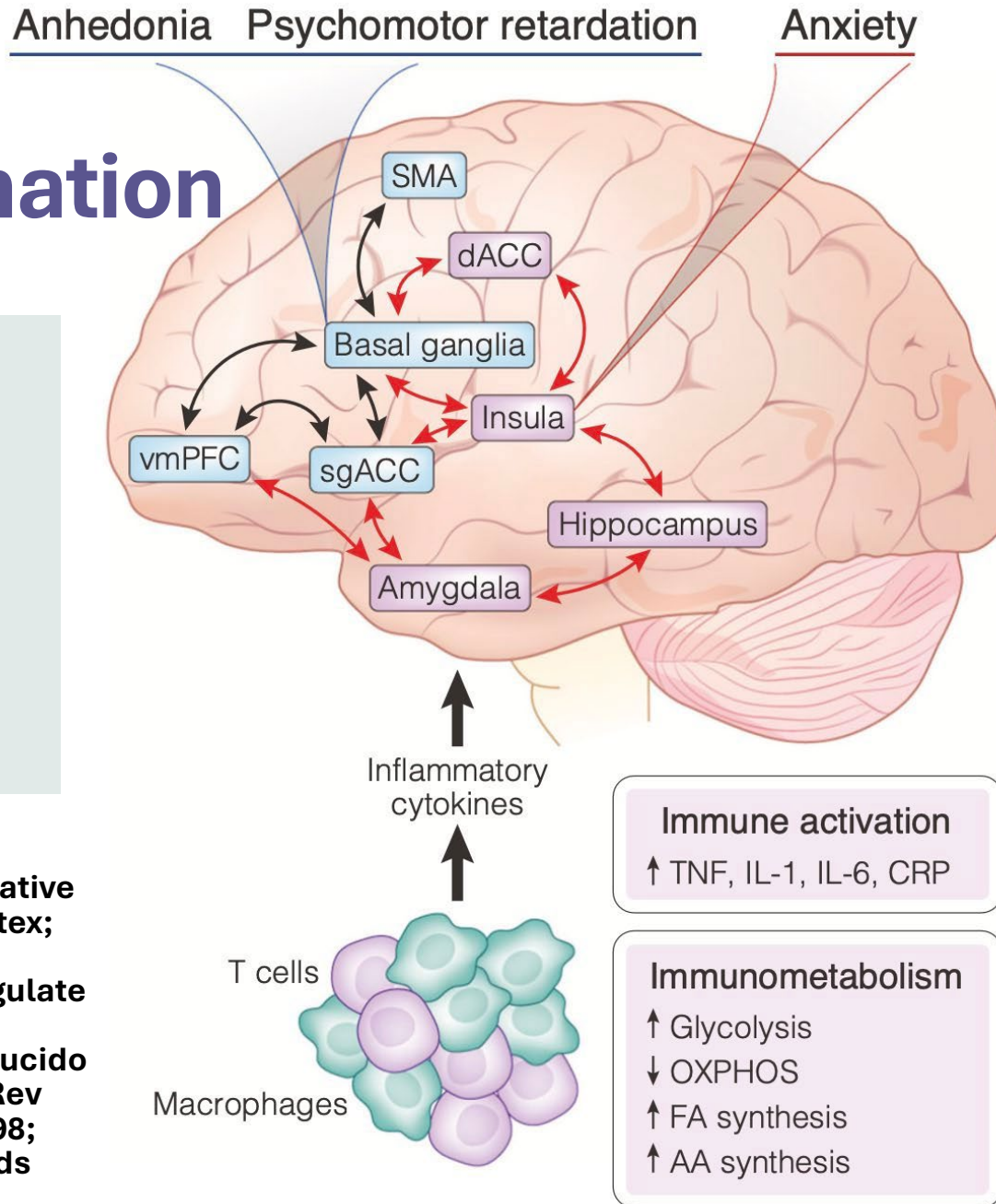
dACC=dorsal anterior cingulate cortex; DMN=default mode network; DMT=dorsomedial thalamus; DStr=dorsal striatum; pACC=perigenual anterior cingulate cortex; PCC=posterior cingulate cortex; SNc=substantia nigra pars compacta; vmPFC=ventromedial prefrontal cortex; VStr=ventral striatum; VTA=ventral tegmental area.
 Conio et al. Mol Psychiatry. 2020;25:82.

Pathophysiology of Anhedonia: Inflammation

Inflammatory markers, such as cytokines, can interfere with neurotransmitter metabolism, neurogenesis, and brain plasticity, contributing to the development of anhedonia

TNF = tumor necrosis factor; IL-1 = interleukin-1; IL-6 = interleukin-6; CRP = C-reactive protein; OXPHOS = oxidative phosphorylation; vmPFC = ventromedial prefrontal cortex; sgACC = subgenual anterior cingulate cortex; SMA = supplementary motor area; dACC = dorsal anterior cingulate cortex.

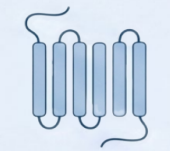
Miller AH, Raison CL. Mol Psychiatry 2023;28(1):68-75; Lucido MJ et al. Pharmacol Rev 2021;73(3):1084-117. Lutz. Nat Rev Neurosci. 2015;16:705. Mikulska. Brain Sci. 2021;11:1298; Felder. Neuroscience. 2013;246:199. Der-Avakian. Trends Neurosci. 2012;35:68.



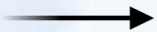
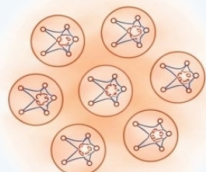
Pathophysiology of Anhedonia: Dopamine-Opioid Interactions in the Reward Circuit

The third neuromodulator: dopamine sets the pursuit, mu-opioid signaling generates the pleasure, kappa/dynorphin is the brake.

μ Mu Opioid — the “liking” system



Mu-opioid receptor (MOR)



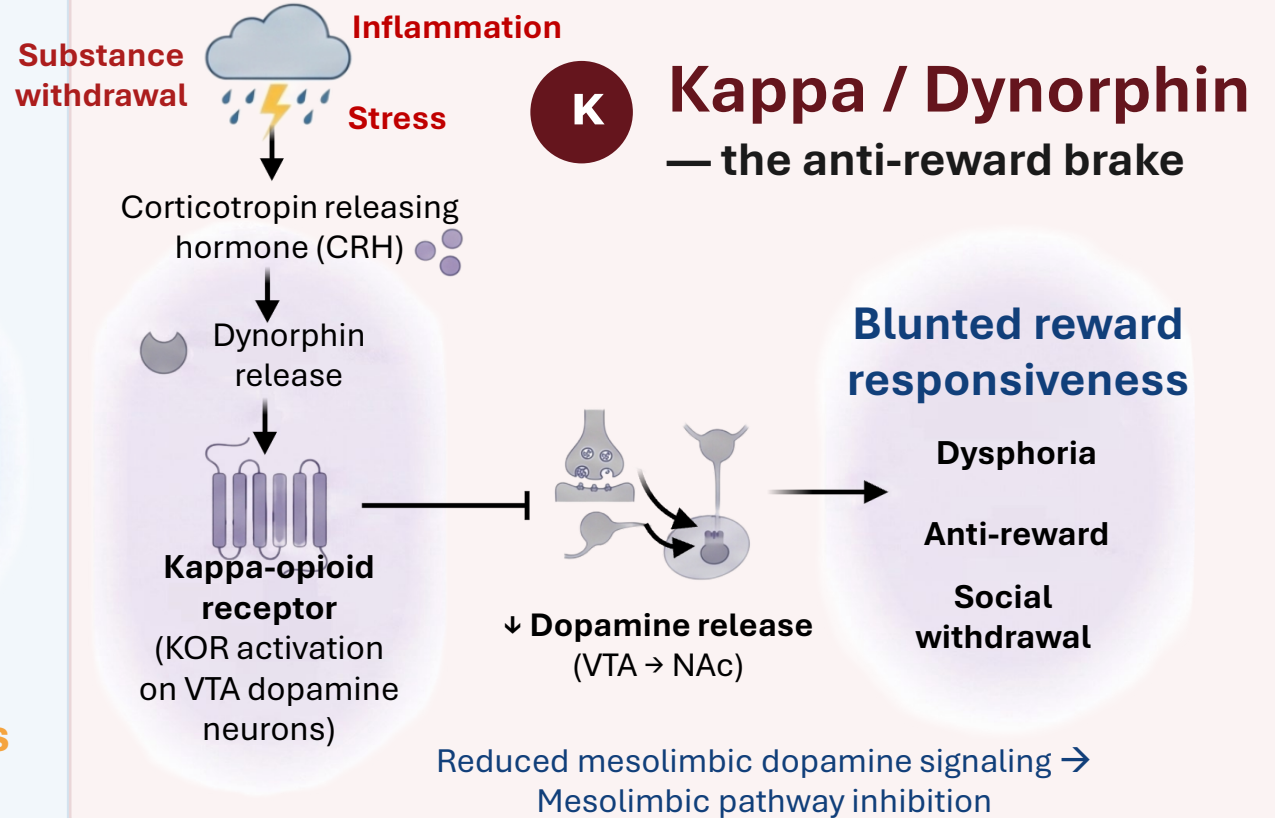
Hedonic hotspot
(e.g., Nucleus accumbens (NAc) shell, Ventral Pallidum)



Liking /
Consummatory
pleasure

Social warmth

**Enhanced
reward
responsiveness**



VTA = ventral tegmental area. Berridge KC, Kringelbach ML. Neuron. 2015;86(3):646-664. Smith KS, Berridge KC. J Neurosci. 2007;27(7):1594-1605. Kennedy SE, et al. Arch Gen Psychiatry. 2006;63(11):1199-1208. Land BB et al. Proc Natl Acad Sci U S A. 2009;106(45):19168-19173. Ehrich JM et al. J Neurosci. 2015;35(37):12917-12931. Krystal AD, Pizzagalli DA, et al. Nat Med. 2020;26(5):760-768. Schmidt ME et al. Neuropsychopharmacology. 2024;49(9):1437-1447.

Key Learning Points

- Anhedonia acts as a significant barrier to functional recovery in MDD and frequently persists even after other symptoms have improved.
- It is linked to worse outcomes in MDD, including more severe, longer depressive episodes and an increased risk of suicidality.
- Anhedonia has many potential etiologies, which may converge on functional network dysregulation involving multiple neurotransmitters, but crucially dopamine, glutamate, and opioid receptors.

Recognizing Anhedonia in MDD

Anticipatory vs. Consummatory Anhedonia

**Anticipatory
Pleasure:**
“wanting”



**Consummatory
Pleasure:**
“liking”

	Anticipatory Anhedonia	Consummatory Anhedonia
Definition	Reduced ability to experience pleasure in anticipation of rewarding events	Reduced ability to experience pleasure during enjoyable activities
Example	A person may no longer anticipate / look forward to activities previously enjoyed, such as playing a sport or going on a vacation	A person may not feel joy while doing something they typically find pleasurable, such as eating their favorite meal or watching a show
Consequences	reduced motivation, difficulty planning and initiating activities, lack of excitement about future events	reduced pleasure from social and recreational activities, reduced frequency engaging in pleasurable activities



So, how exactly do we recognize anhedonia in depression?

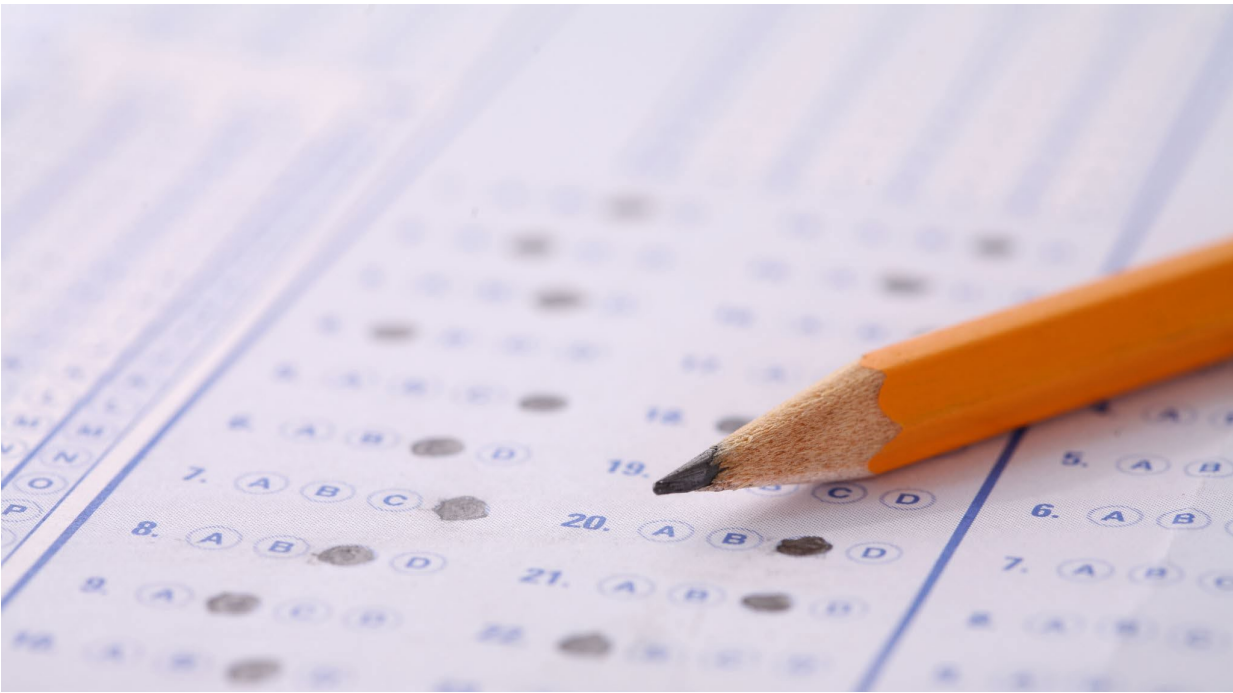
Patient Advocate: Katie Hahn

Lived Experience with Anhedonia

Screening Tools: Clinical Blind Spots

Standard mood scales frequently underestimate the depth of reward system impairment

Clinicians under-recognize nearly **50%** of patients who screen positive for anhedonia via SHAPS



Scale	Anhedonia Capture
PHQ-9	Only 1 item (Item 1)
HAM-D	Focus on general interest
SHAPS	14 items (Specific Reward)
TEPS	Anticipatory vs Consummatory

PHQ-9 = Patient Health Questionnaire-9; HAM-D = Hamilton Depression Scale; SHAPS = Snaith-Hamilton Pleasure Scale; TEPS = Temporal Experience of Pleasure Scale.
Mittmann G, et al. *Psychiatry Res.* Published online September 20, 2025. Kasahara-Kiritani, M. et al. *BMC Psychiatry* 25, 631 (2025).

MADRS Anhedonia Subscale Score

The **MADRS** is a 10-item clinician-administered questionnaire to measure the severity of depressive episodes in adults

*Image created by Dr. Albright & used without Dr. Jain's permission

MADRS = Montgomery-Åsberg Depression Rating Scale.
Montgomery SA, et al. Br J Psychiatry. 1979;134:382-389. Cao B, et al. Front Psychiatry. 2019;10:17.

Five items from the MADRS are often used to measure anhedonia:



How to Assess for Anhedonia



Name three things depression has stolen from you...

Anhedonia vs Emotional Blunting vs Apathy



	Anhedonia	Emotional Blunting	Apathy
Description	Inability to experience joy or pleasure in normally pleasurable acts	Diminished sensitivity and responsiveness to a broad range of emotions	State of indifference or emotional detachment, not secondary to mental health disorder
Experience of positive emotions	Decreased	Perception blunted	Decreased
Experience of negative emotions	Perception heightened	Perception blunted	Decreased
Motivation	Decreased	Neutral	Decreased
Prevalence in MDD	~75%	~45% taking SSRI/SNRI	~40%

Ma et al. Front Psychiatry. 2021;12:792960. Christensen MC, et al. Annals of General Psychiatry. 2022 Dec;21(1):1-8. Goodwin, GM. et al. Journal of affective disorders 221 (2017): 31-35. Husain, M and JP Roiser. Nature Reviews Neuroscience 19.8 (2018): 470-484.

Key Learning Points



- Anhedonia is multidimensional: anticipatory and consummatory components are neurobiologically and clinically dissociable
 - Clinicians underestimate anhedonia prevalence by approximately 50%
- Standard screening tools (PHQ-9) are insufficient to detect anhedonia; dedicated scales (SHAPS, DARS, TEPS) are needed
- Probe across domains (hobbies, food, social, sensory) and across reward phases (wanting, anticipating, enjoying)
- Differentiate disease-related anhedonia from medication-induced emotional blunting by assessing timing, dose relationship, and whether both positive and negative emotions are affected
 - **Negative emotions are often decreased in apathy and perceptually heightened in anhedonia**

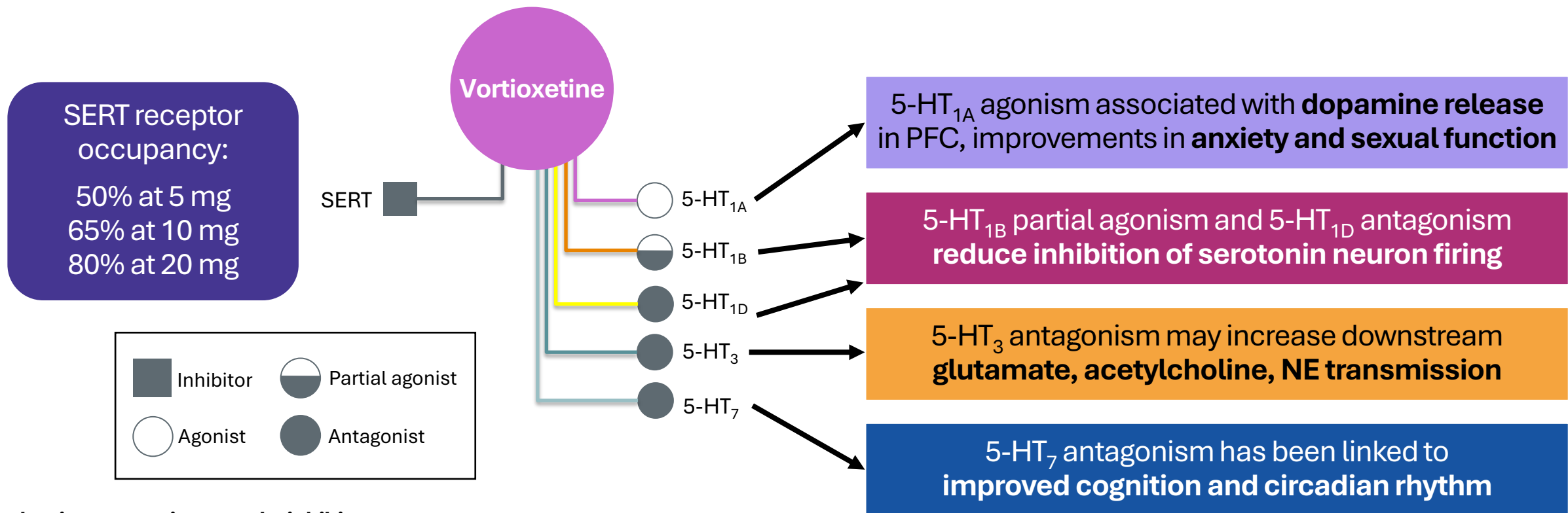
Antidepressant Monotherapies for Major Depression

That Have Evidence in Targeting Anhedonia

Vortioxetine

Vortioxetine's Multimodal Mechanism May Overcome SSRI Shortcomings

SSRIs **nonspecifically increase** serotonin, which has downstream effects of **downregulating NE and DA** signaling, and may lead to **emotional blunting** and other undesirable effects



SSRI=selective serotonin reuptake inhibitor

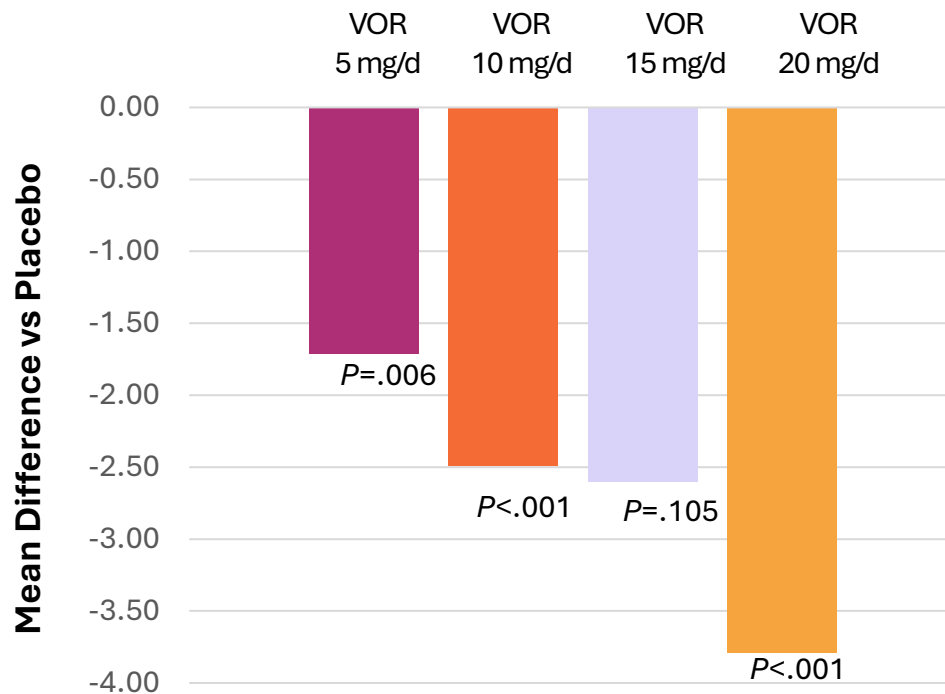
5-HT=5-hydroxytryptamine; DA=dopamine; NE=norepinephrine; SERT=serotonin reuptake transporter; PFC=Prefrontal Cortex

Bang-Andersen B, et al. *J Med Chem.* 2011;54:3206–21. Sanchez C, et al. *Pharmacol Ther.* 2015;145:43–57. Vortioxetine prescribing information. Drugs@FDA: FDA Approved Drugs. Accessed March 6, 2024. www.accessdata.fda.gov/scripts/cder/daf/.

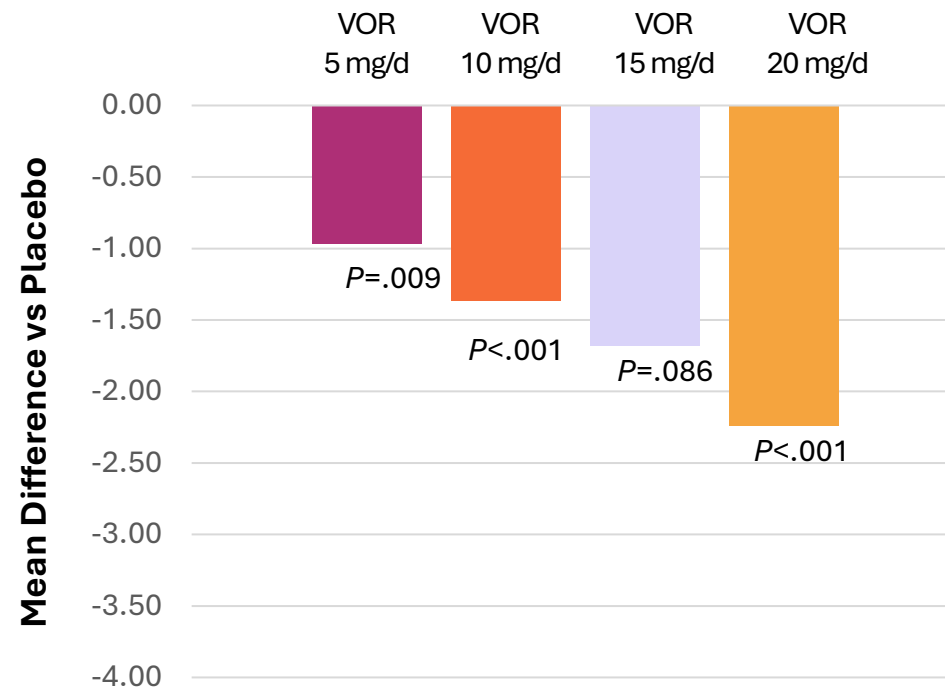
Vortioxetine Improves Depressive Symptoms, Anhedonia, and Functioning

Pooled analysis of all 11 short-term, placebo-controlled studies (n=4988)

MADRS total score



MADRS anhedonia subscale score



MADRS=Montgomery-Åsberg Depression Rating Scale; MDD=major depressive disorder; SDS=Sheehan Disability Scale; VOR=vortioxetine. McIntyre RS, et al. *Neuropsychiatr Dis Treat*. 2021;17:575-585.

Vortioxetine: Response, Remission, and Tolerability

In a meta-analysis of 20 RCTs (N=8,547 adults with MDD), vortioxetine showed:

vs Placebo
(16 RCTs; N=6,755)

↑ Response Rate (RR 1.35)*

↑ Remission Rate (RR 1.33)*

↑ Cognitive function† (SMD 0.34)**

vs SNRIs/SSRIs
(8 RCTs; N=3,159)/(2 RCTs; N=126)

- No difference in response rate nor remission rate (similar overall efficacy)
- Better tolerability vs SNRIs

Adverse Events Reported by ≥5%

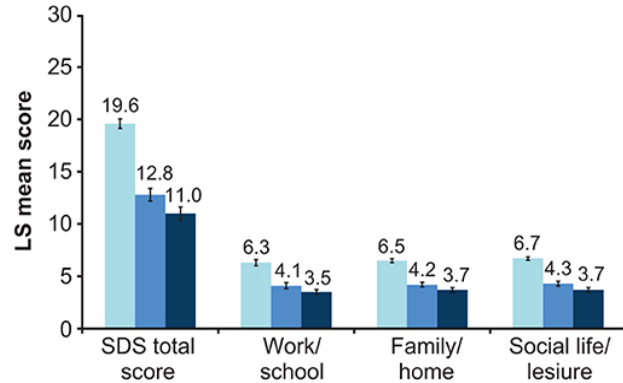
	Placebo N=1621	VTX 5 mg N=1013	VTX 10 mg N=699	VTX 20 mg N=455
Nausea	9%	21%	26%	32%
Diarrhea	6%	7%	7%	7%
Dry Mouth	6%	7%	7%	8%
Dizziness	6%	6%	6%	9%
Constipation	3%	3%	5%	6%
Vomiting	1%	3%	5%	6%
Discontinuation due to AEs	4%	5%	6%	8%

Vortioxetine had no significant effect on body weight as measured by the mean change from baseline in the 6 to 8-week placebo-controlled studies or a 6 month, double-blind, placebo-controlled phase of a long-term extension study.

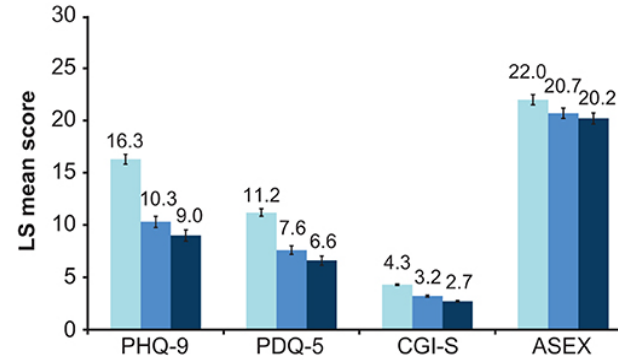
* $P<0.001$; ** $P=0.0003$; †measured with the Digit Symbol Substitution Test
RR = Risk Ratio; SMD = standardized mean difference; AE=adverse event; VTX=vortioxetine, SNRI = serotonin norepinephrine reuptake inhibitor.
Vortioxetine prescribing information. Drugs@FDA: FDA Approved Drugs. Accessed March 6, 2024. www.accessdata.fda.gov/scripts/cder/daf/;
Zhang X, et al. *Front Psychiatry*. 2022;13:922648.

Vortioxetine: “RELIEVES” Depression Burden in Real World Patients

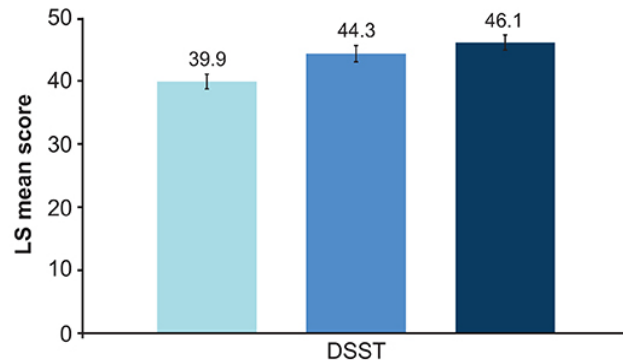
A SDS



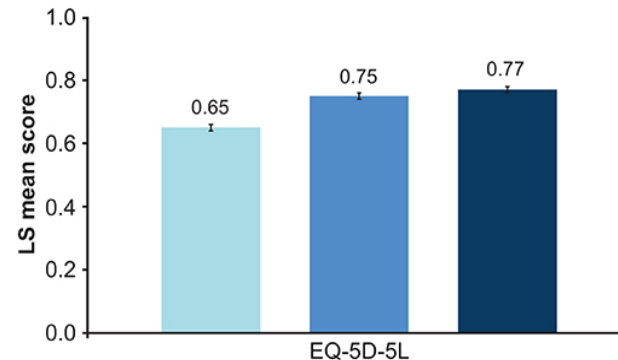
B PHQ-9, PDQ-D-5, CGI-S and ASEX



C DSST



D EQ-5D-5L



■ Baseline ■ Week 12 ■ Week 24

The RELIEVE study was a 24-week multinational, observational, prospective cohort study of 737 outpatient adults with MDD who were initiated on Vortioxetine

Primary outcome: Patient functioning measured by Sheehan Disability Scale (SDS)

Secondary outcomes: Depression severity via PHQ-9 and CGI, cognitive symptoms via PDQ-D-5, cognitive performance via DSST

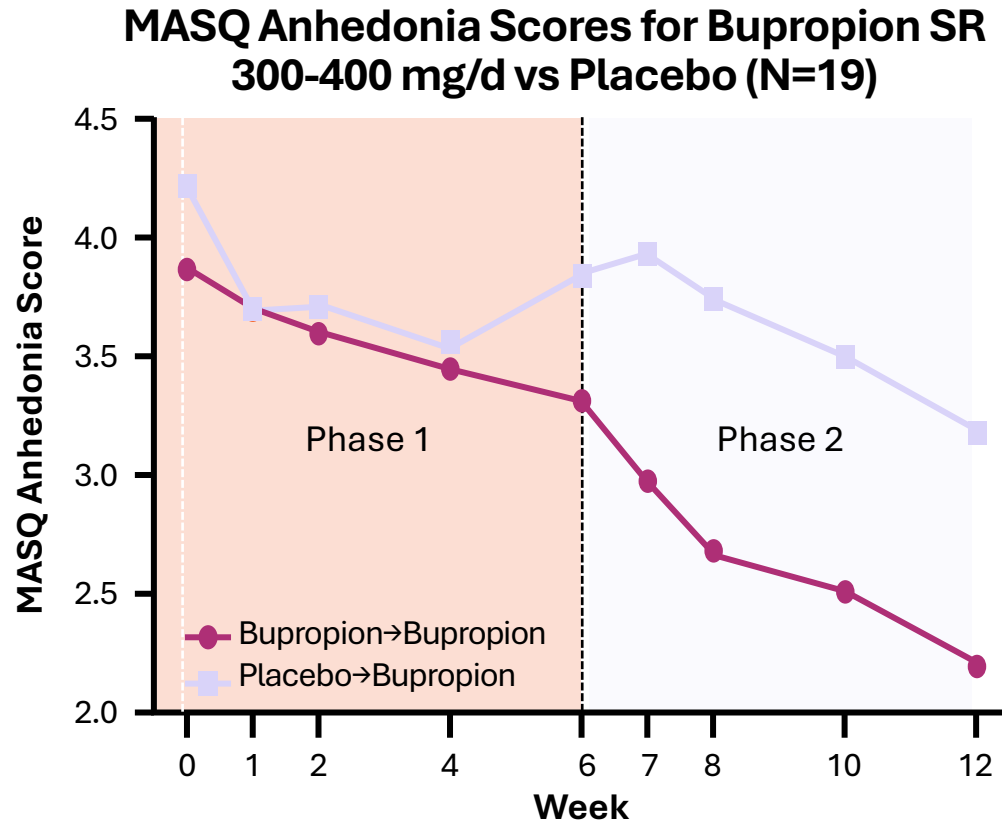
The study demonstrated that vortioxetine is effective for the treatment of MDD in a large and heterogeneous patient population

SDS = Sheehan Disability Scale; PHQ = Patient Health Questionnaire; PDQ-D = Perceived Deficits Questionnaire Depression; CGI = Clinical Global Impression; CGI-S = CGI-Severity; ASEX = Arizona Sexual Experience Scale; DSST = Digit Symbol Substitution Test; EQ-5D-5L = EuroQoL 5 Dimensions 5 Levels questionnaire.

Mattingly GW, et al. *Front Psychiatry*. 2022;13:824831. Thase ME, et al. *Eur Neuropsychopharmacol*. 2016;26(6):979-993.

Bupropion

Bupropion for Anhedonia: Strong Rationale, Thin Evidence



THE TOMARKEN TRIAL (2004)

- n = 19 crossover: MASQ anhedonia improved on bupropion SR, and the placebo arm improved only after crossover at week 6.
- Small, single-site and underpowered.

EXPERIMENTAL MEDICINE

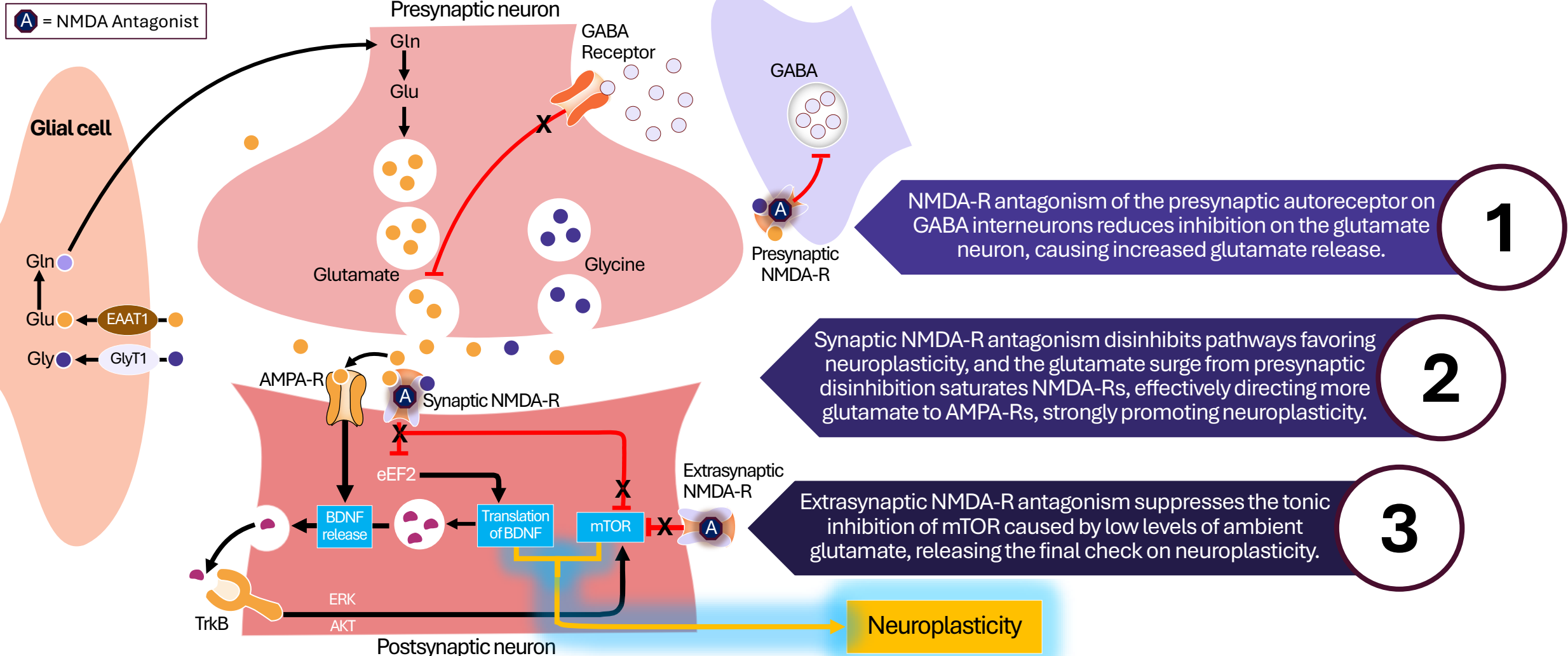
- **Healthy volunteers (n = 40):** no gain in reward learning; fewer high-probability win choices and higher SHAPS vs placebo.
- **Depressed patients (n = 46, 6 wks):** reward bias worsened at week 2, then normalized by week 6 — anhedonia may dip before it improves.

Widely used off-label for anhedonia — with no RCT that made anhedonia a primary endpoint.

MASQ = Mood and Anxiety Symptom Questionnaire; SHAPS = Snaith-Hamilton Pleasure Scale. Tomarken AJ, et al. J Affect Disord. 2004;78(3):235-241. Walsh AEL, et al. Front Psychiatry. 2018;9:482. Walsh AEL, et al. Philos Trans R Soc Lond B Biol Sci. 2018;373:20170030. Iosifescu DV, et al. AXS-05 MADRS anhedonia subscale post hoc analysis, ASCP 2022. Trivedi MH, et al. N Engl J Med. 2006;354:1243-1252 (STAR*D). Mohamed S, et al. JAMA. 2017;318:132-145 (VAST-D).

Glutamatergic Modulators

NMDA-Receptor Antagonists May Promote Neuroplasticity in MDD



NMDA = N-methyl-D-aspartate; AMPA = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF = Brain-Derived Neurotrophic Factor; eEF2 = eukaryotic elongation factor 2; ERK = extracellular signal-regulated kinase; AKT = Protein kinase B; mTOR = mechanistic Target of Rapamycin; TrkB = Tropomyosin receptor kinase B.

Kadriu B, et al. *Int. J. Pharm.* 2019;22(2) 119-135. Murrough J, et al. *Nat Rev Drug Discovery*. 2017;16:472. Nicu, MJ. *Pharmacology Biochemistry and Behavior*. 2012;100(4): 656-664.

Dextromethorphan- Bupropion

NMDA-Receptor Antagonism and Sigma-1 Agonism:
A Marriage Made in Depression Remission?

Sigma-1 Receptor Agonism in Depression

σ 1R

What it is: Not a neurotransmitter receptor. It is a **ligand-operated chaperone protein** sitting at the mitochondria-associated ER membrane (MAM), the contact zone where ER and mitochondria physically touch.

1 Neuroplasticity

the synaptogenesis branch

↑ BDNF and TrkB signaling via ERK1/2 and mTOR.

More dendritic branching, higher spine density, ↑ PSD-95 — shown in prefrontal cortex and hippocampus.

2 Monoamines

why the onset looks fast

Rapidly raises tonic firing of raphe serotonin neurons.

σ 1R–5-HT1A receptor complexes let it amplify existing serotonergic tone rather than build a new one.

3 Resilience

stress physiology, undone

Chronic stress drives ER stress and mitochondrial failure.

σ 1R agonism quiets the unfolded protein response, supports mitophagy and bioenergetics.

4 Neuroinflammation

the glial branch

Shifts microglia toward a homeostatic phenotype and calms reactive astrogliosis.

Where the Evidence Actually Stands:

No selective σ 1 agonist is approved anywhere. Only via multimodal drugs: dextromethorphan–bupropion, fluvoxamine.

The causal anchor is preclinical. Dextromethorphan's antidepressant-like effect is abolished by a σ 1 antagonist.

Anhedonia specificity is unsettled. Whether σ 1 uniquely targets reward deficits still awaits determination.

5-HT1A = serotonin 1A receptor; BDNF = brain-derived neurotrophic factor; ER = endoplasmic reticulum; ERK1/2 = extracellular signal-regulated kinase 1/2; MAM = mitochondria-associated ER membrane; mTOR = mechanistic target of rapamycin; NF- κ B = nuclear factor kappa B; NLRP3 = NLR family pyrin domain protein 3; PSD-95 = postsynaptic density protein 95; TrkB = tropomyosin receptor kinase B; σ 1R = sigma-1 receptor. Hayashi & Su. Cell. 2007;131:596. Nguyen L, et al. PLoS One. 2014;9:e89985. Wang Y, et al. Glia. 2020;68:2415. Ren P, et al. Neurochem Int. 2025;184:105937. Xiao N, et al. Expert Opin Ther Targets. 2025;29:345.

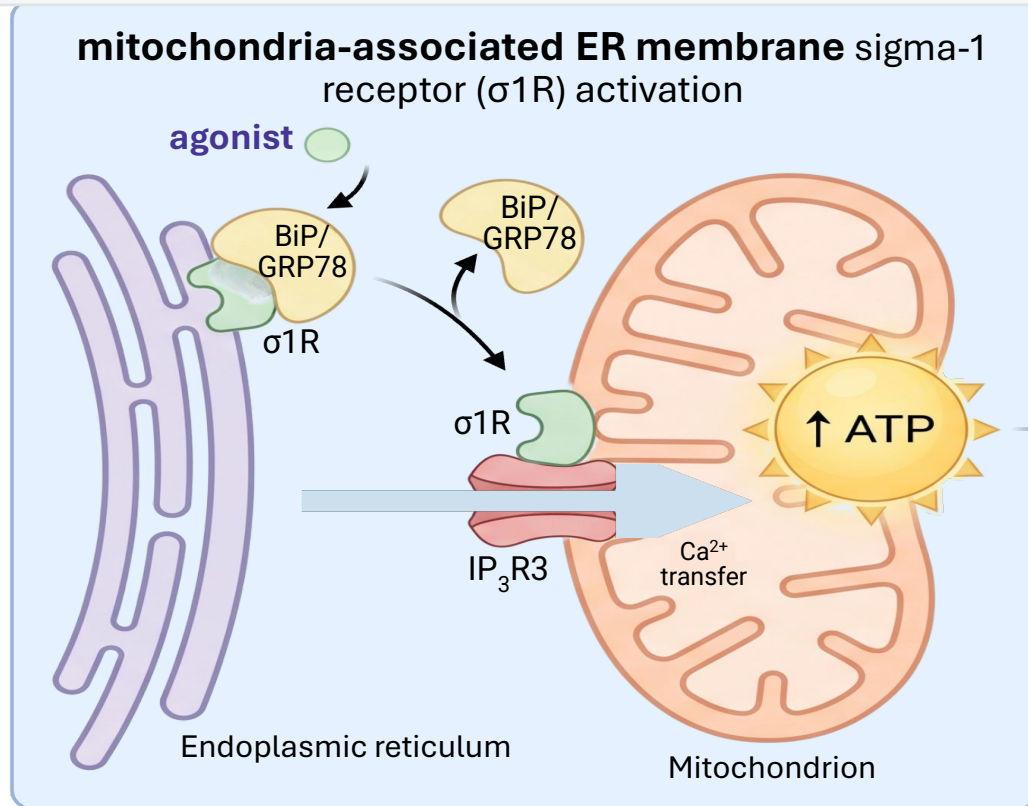
Sigma-1 Receptor Agonism in Depression

Agonist binds $\sigma 1R$

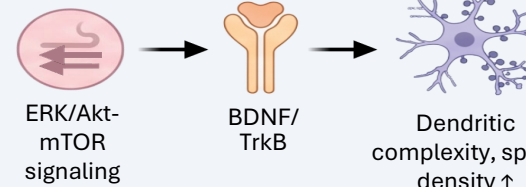
$\sigma 1R$ releases its partner
chaperone binding
immunoglobulin protein (BiP)

Freed $\sigma 1R$ stabilizes the IP_3
receptor

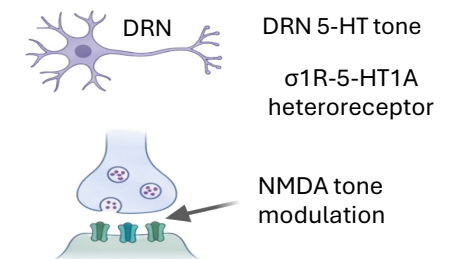
Sustained Ca^{2+} flows ER $\rightarrow$
mitochondria, $\uparrow$ ATP



Synaptic plasticity

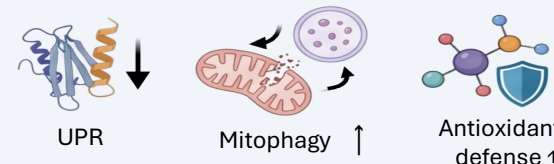


Monoaminergic modulation

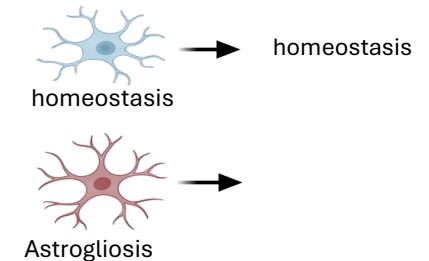


Improved neuronal resilience

Cellular stress resilience



Anti-inflammatory effects



5-HT/5-HT1A = serotonin/serotonin 1A receptor; Akt = protein kinase B; ATP = adenosine triphosphate; BDNF = brain-derived neurotrophic factor; DRN = dorsal raphe nucleus; ERK = extracellular signal-regulated kinase; IP_3R3 = inositol trisphosphate receptor 3; mTOR = mechanistic target of rapamycin; NMDA = N-methyl-D-aspartate; TrkB = tropomyosin receptor kinase B; UPR = unfolded protein response

Hayashi & Su. Cell. 2007;131:596 Nguyen L, et al. PLoS One. 2014;9:e89985 Wang Y, et al. Glia. 2020;68:2415. Ren P, et al. Neurochem Int. 2025;184:105937 .Xiao N, et al. Expert Opin Ther Targets. 2025;29:345. Image created in BioRender.com

Dextromethorphan Has All the Right Qualities for An Antidepressant

DEXTROMETHORPHAN



Has multimodal antidepressant pharmacology

- Glutamatergic modulation (NMDA antagonism)
- Sigma-1 receptor agonism
- Monoaminergic activity (SERT/NET inhibition)
- Cholinergic activity (nAChR antagonism)
- **No** significant opioid receptor activity



Rapid-acting antidepressant potential



Demonstrates neuroplasticity-related signaling

But...

Very rapid CYP2D6 metabolism alters the pharmacologic balance



...and shifts away from the intended therapeutic profile

DEXTRORPHAN



Has more potent NMDA receptor antagonism



DISSOCIATIVE

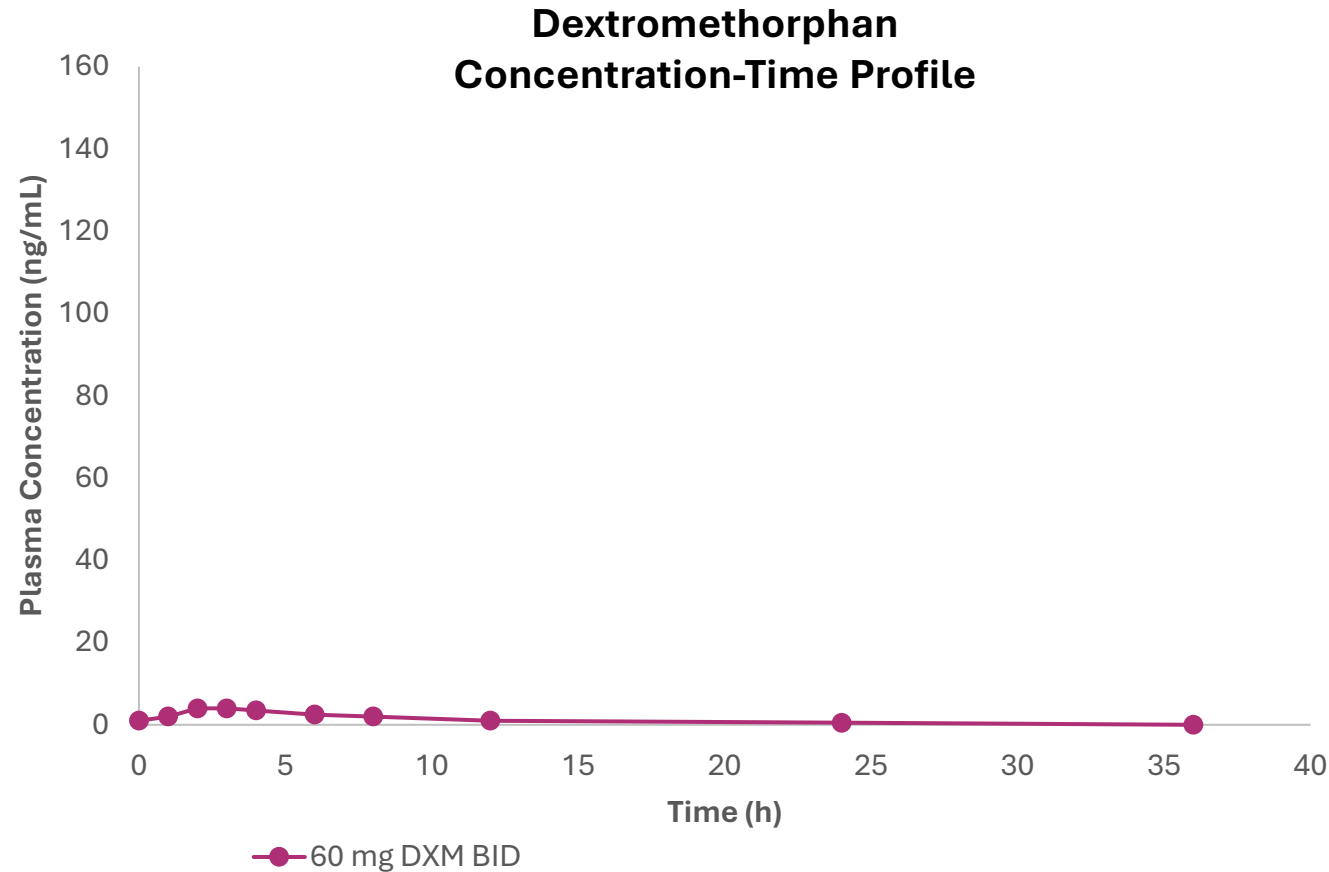


Reduced multimodal pharmacologic balance (less 5-HT activity)

Therapeutic interest in dextromethorphan focuses on preserving its antidepressant qualities, while improving its pharmacokinetic profile

Better Together:

The Sad Pharmacokinetics of DXM Alone



DXM has low bioavailability

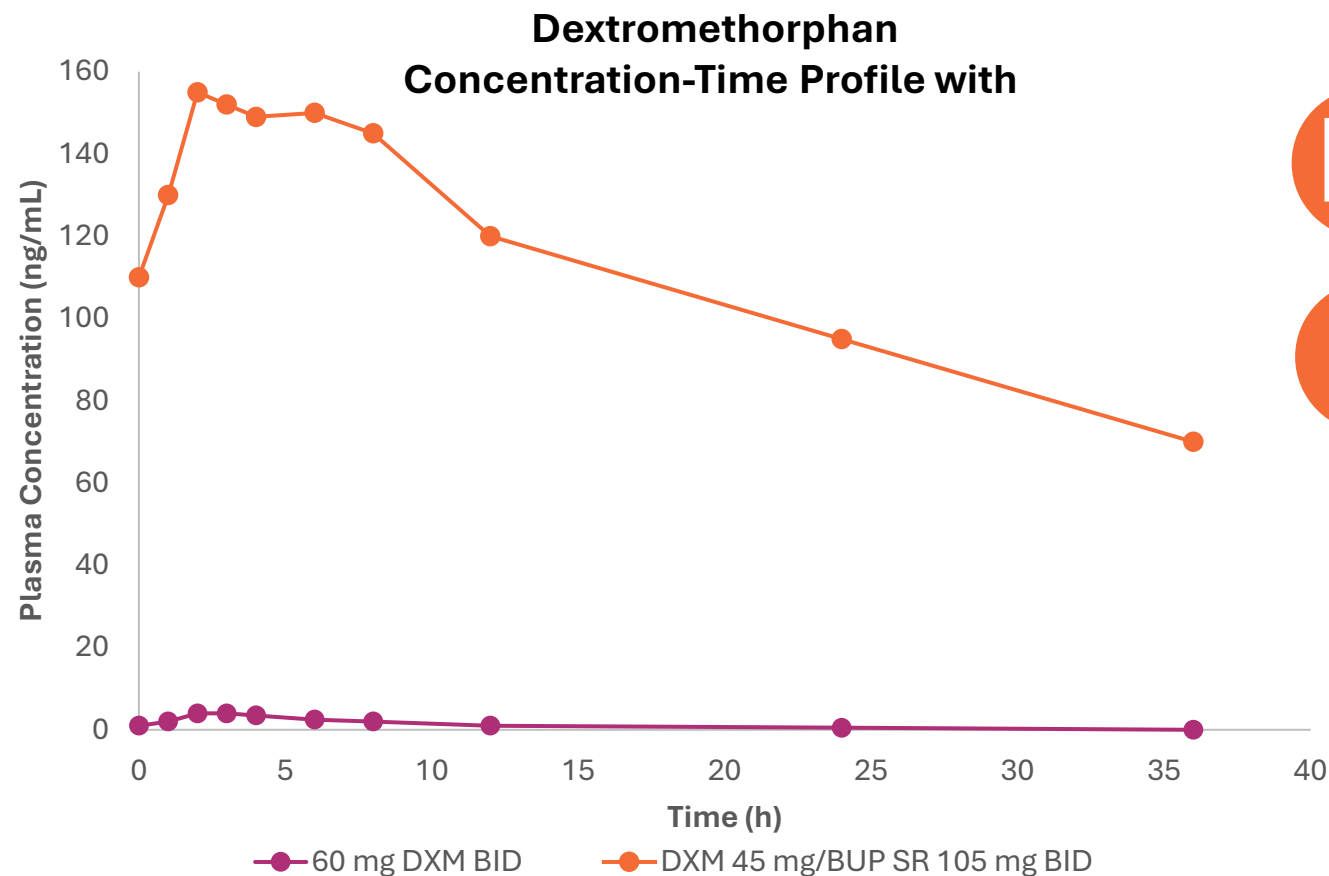
Rapid metabolism by CYP2D6 →
insufficient sustained exposure

The pharmacodynamics and
pharmacokinetics of DXM are
fundamentally **unequal!**

DXM = dextromethorphan

Silva AR, Dinis-Oliveira RJ. *Drug Metab Rev.* 2020;52(2):258-282.

Bupropion Serves to Match DXM's Pharmacokinetics to Its Favorable Pharmacodynamics



A strong CYP2D6 inhibitor, which increases the plasma levels of dextromethorphan



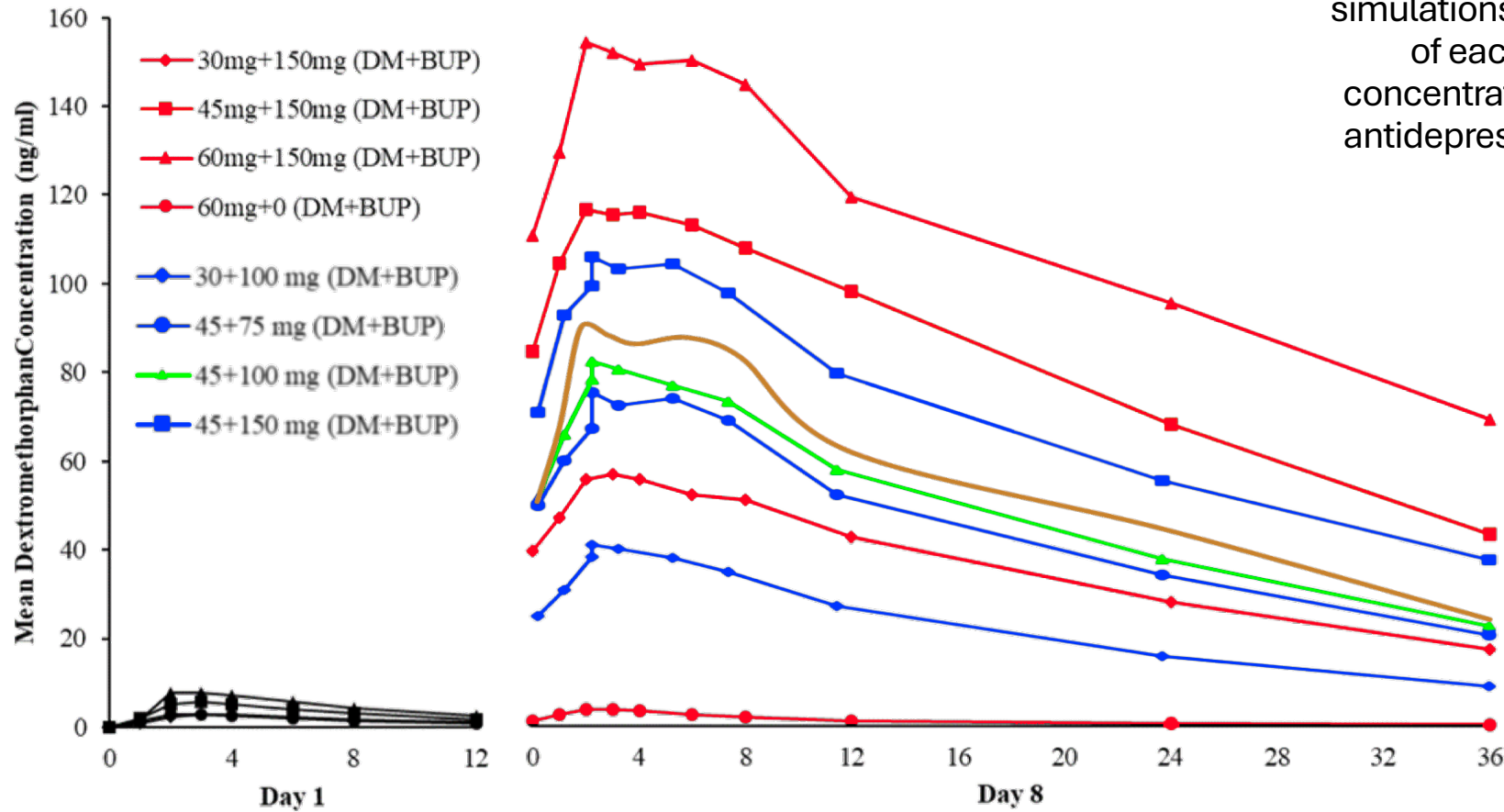
Generally well-tolerated at low doses, compared to other strong CYP2D6 inhibitors

DXM = dextromethorphan; BUP = bupropion.

Silva AR, Dinis-Oliveira RJ. *Drug Metab Rev.* 2020;52(2):258-282; Stahl SM. *CNS Spectr.* 2019;24(5):461-466

The 45 mg/105 mg Combination Was Precisely Scientifically Derived

Dextromethorphan Concentration Over Time



Multiple clinical trials and in silico pharmacokinetic simulations were conducted to determine the optimal doses of each medication to achieve a sustained plasma concentration of dextromethorphan believed necessary for antidepressant effects while minimizing **potential adverse effects**.

This precise combination of 45 mg DXM with 105 mg BUP SR twice daily is the only one proven to give the clinical results of the FDA-approved



Attempts to approximate the individual components are not practical. Generic bupropion SR can vary between as much as **80% less to 125% more** than the reference medication

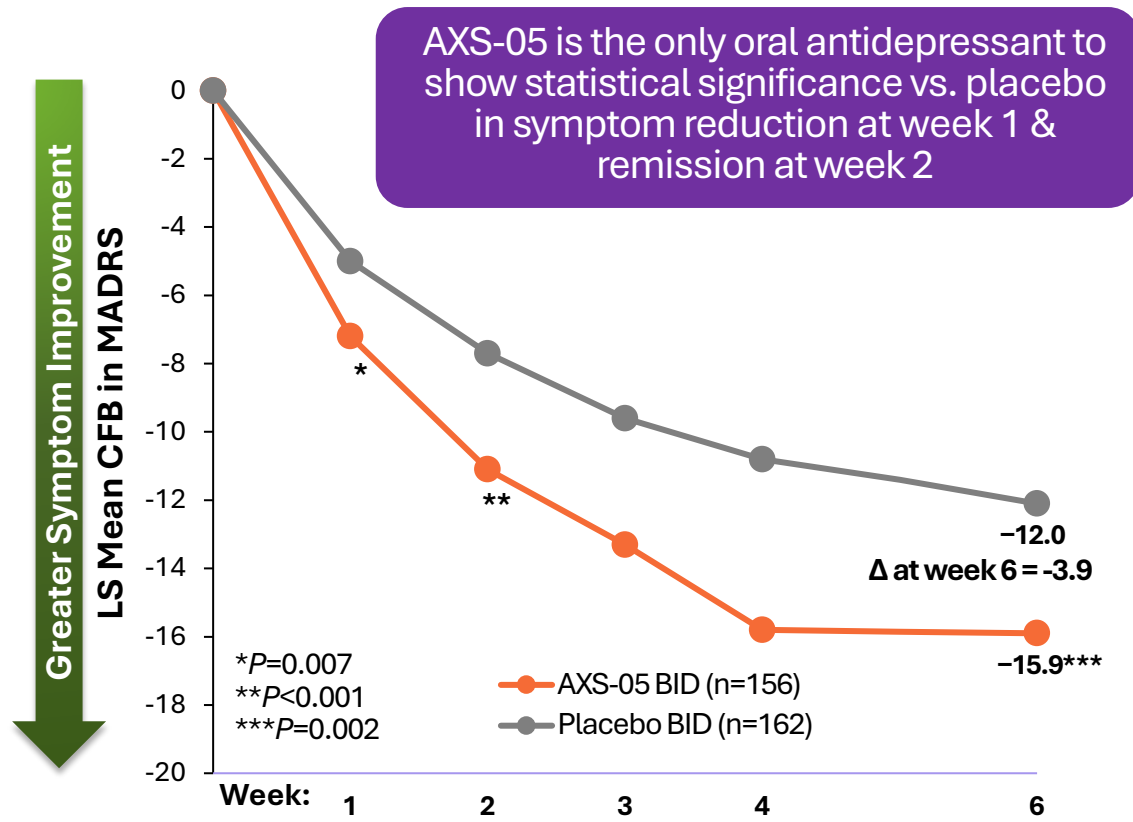
DM or DXM = dextromethorphan; BUP = bupropion; SR = sustained release.

Center for Drug Evaluation and Research. NDA/BLA Multidisciplinary Review and Evaluation. NDA 215430. July 7, 2019. Accessed August 2025. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/215430Orig1s000MultidisciplineR.pdf.

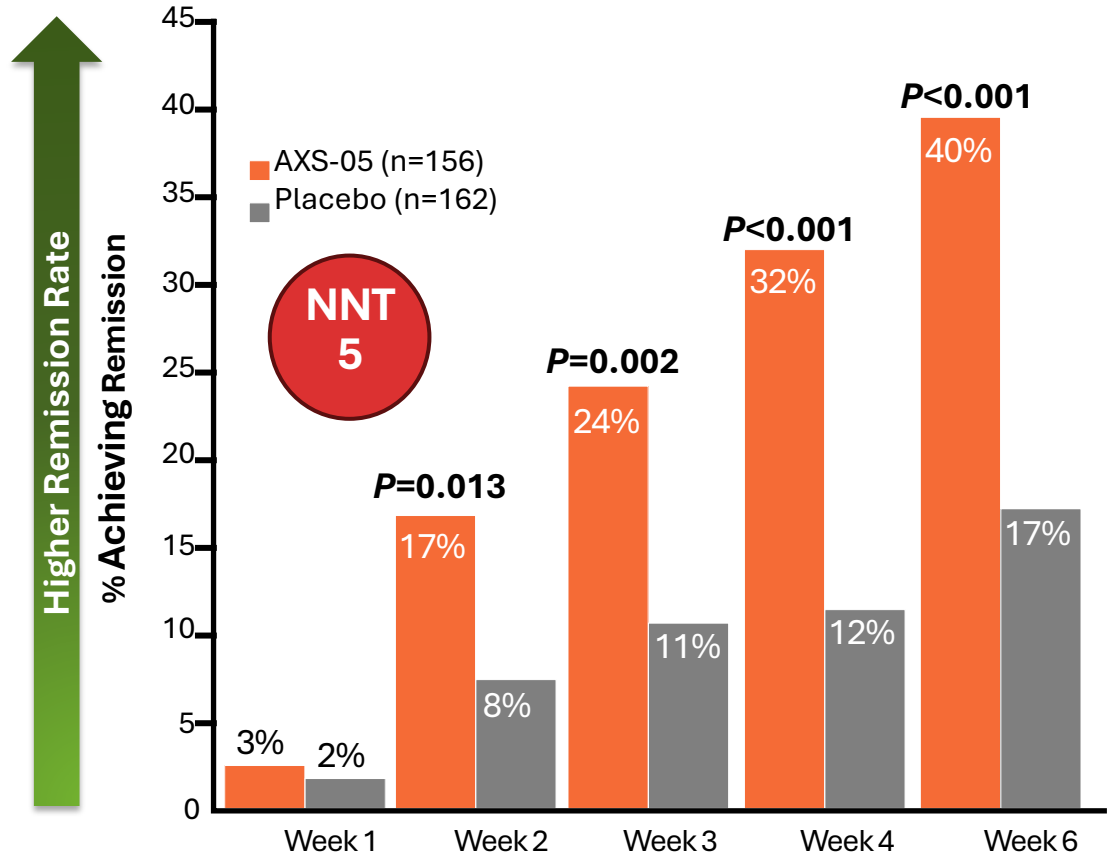


AXS-05 Rapidly and Substantially Reduced Depressive Symptoms and Improved Remission Rates in a Ph 3 Trial

Depressive Symptom Reduction



Remission Rates (MADRS ≤ 10)



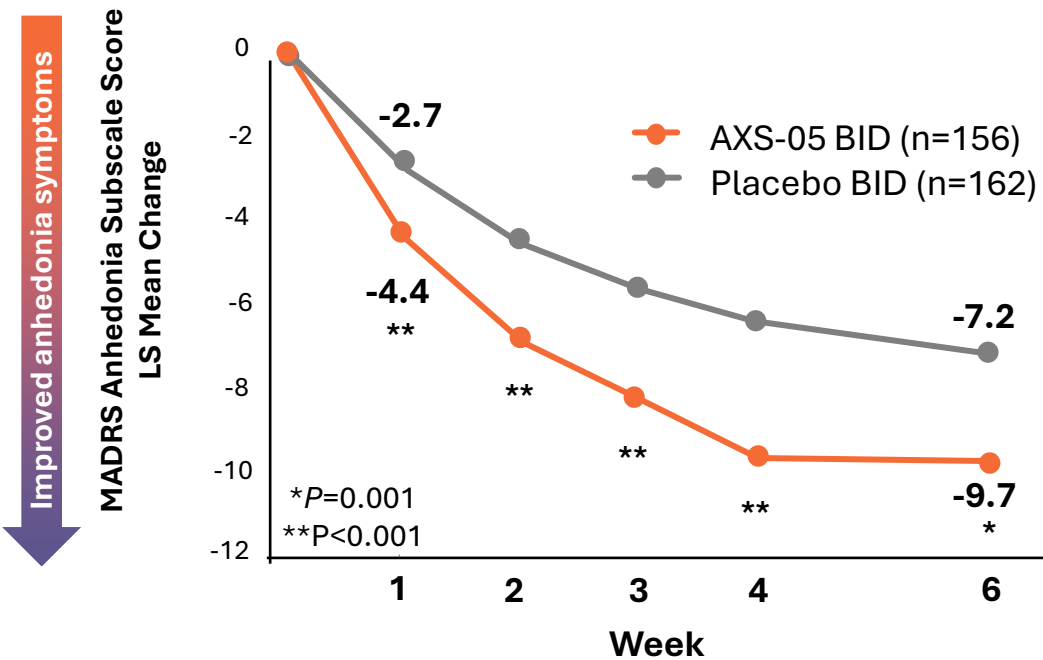
BID = twice daily; D/C = discontinuation; AE = Adverse Event.

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

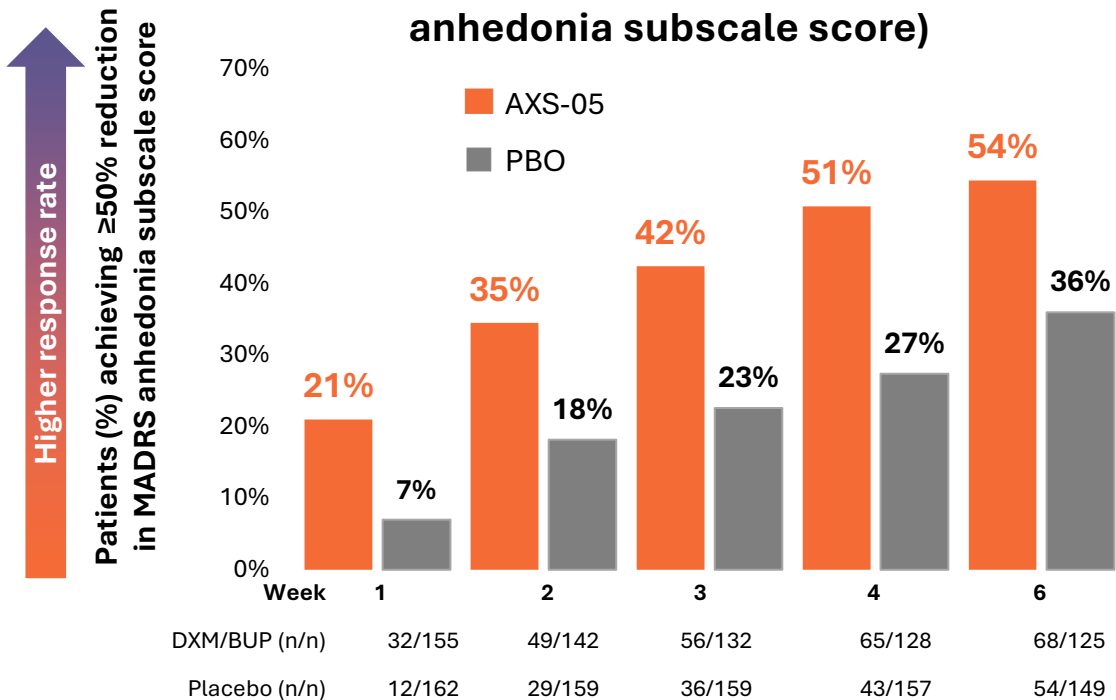
AXS-05 Rapidly Reduced Anhedonia Symptoms in a Post-Hoc Analysis of the Pivotal Trial



MADRS Anhedonia Subscale Over 6 Weeks



Response data (based on MADRS anhedonia subscale score)



While statistical adjustments were not made for multiple comparisons, these results suggest AXS-05 may have a benefit for anhedonia

AXS-05 Safety and Tolerability

AEs $\geq 5\%$ and $>2x$ the Rate of Placebo

	AXS-05	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%



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

Discontinuation due to AEs



4% AXS-05
0% Placebo

Weight Change



-0.60 lbs AXS-05
+0.73 lbs Placebo

AUVELITY® (dextromethorphan hydrobromide and bupropion hydrochloride) Prescribing Information. Drugs@FDA: FDA-Approved Drugs. Accessed May 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/215430s008lbl.pdf. 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.

Esketamine

NMDA Receptor Antagonist FDA Approved for Treatment Resistant Depression

Esketamine: The Approved Glutamatergic Option

Indications in adults

- Treatment-resistant depression, as monotherapy or with an oral antidepressant
- Depressive symptoms in MDD with acute suicidal ideation or behavior, with an oral antidepressant

Safety guardrails

- Observe at least 2 hours in office; recheck BP & O2 saturation near 40 minutes
- Contraindicated in aneurysmal vascular disease, AV malformation, or prior intracerebral hemorrhage
- No driving until the next day after restful sleep



Dosing and course

- 56 mg or 84 mg intranasally; 28 mg per device
- Twice weekly for 4 weeks, then weekly, then weekly or every 2 weeks
- Reassess benefit after the 4-week induction

BOXED WARNINGS

Risk for sedation, dissociation, and respiratory depression

Abuse and misuse: Schedule III controlled substance

Suicidal thoughts and behaviors in young adults and adolescents: monitor closely; it is not shown to prevent suicide

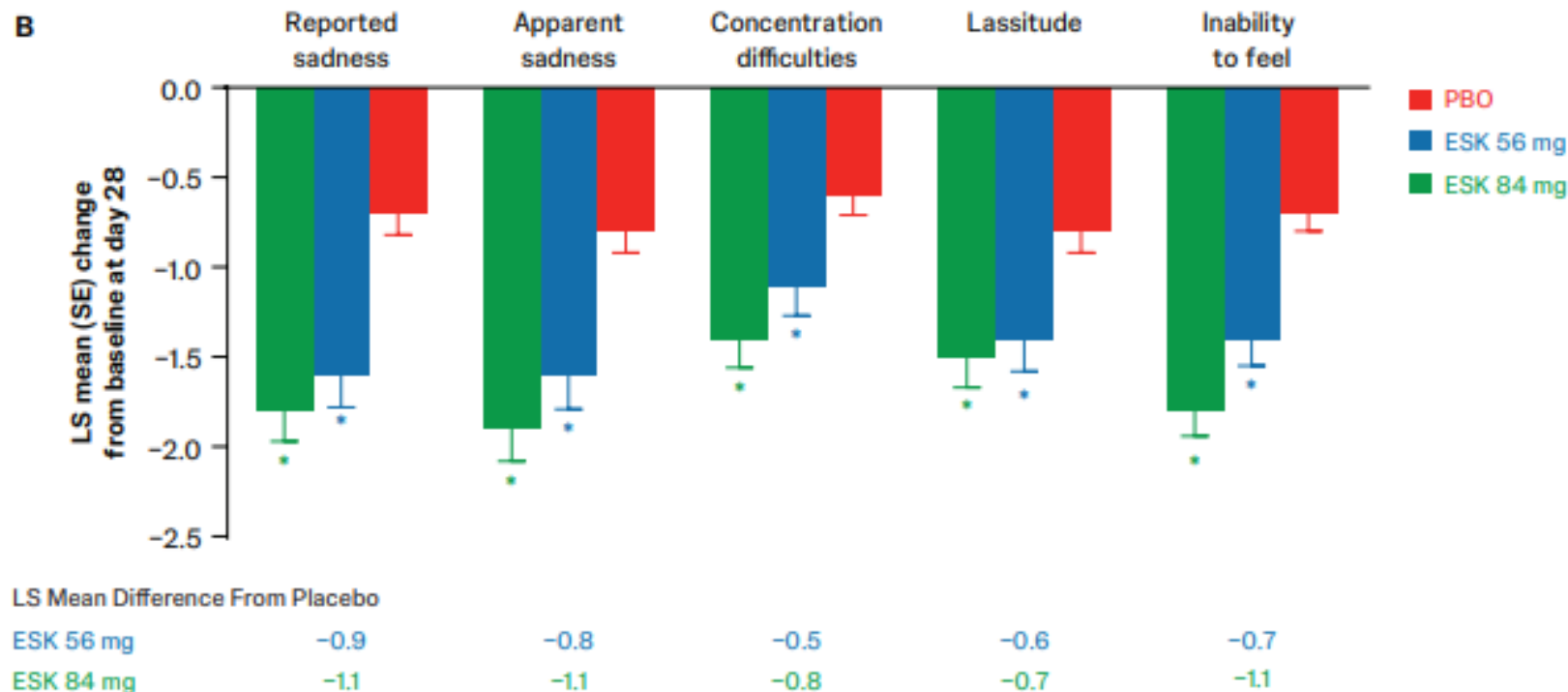
Because of these risks it is available only through a restricted REMS program.

Esketamine and Anhedonia: Phase 3 Evidence

What the Data Show:

- **Design:** post hoc analyses of placebo-controlled phase 3 trials; MADRS anhedonia factor (5 items).
- **Day 28 vs placebo:** LS mean difference -3.4 (56 mg) and -4.8 (84 mg) on monotherapy.
- **Rapid:** separation from placebo by 24 hours, held through day 28.
- **Every item improved:** both doses beat placebo on all five items ($P < .05$).
- **Caveat:** post hoc, no multiplicity adjustment.

LS mean change from baseline in individual MADRS items, day 28



BOTTOM LINE: the only approved monotherapy for TRD with rapid, replicated improvement in anhedonia items — but the anhedonia signal is post hoc, and delivery is limited to REMS-certified settings.

ESK = esketamine; LS = least squares; MADRS = Montgomery-Åsberg Depression Rating Scale; OAD = oral antidepressant. Analyses are post hoc and not adjusted for multiplicity. Sources: Chepke C, et al. Psych Congress, Sept 2025 (monotherapy; 56 mg n=86, 84 mg n=95, placebo n=197). Fu D-J, et al. TRANSFORM-2 post hoc (esketamine+OAD n=114, placebo+OAD n=109). Summarized at J&J Medical Connect, Effect of SPRAVATO on Anhedonia, 10 Feb 2026.

Investigational & Emerging Treatments for Depression

That Are Being Studied in Anhedonia

Kappa Opioid Receptor Antagonists

Primer on the Endogenous Opioid System

Effects from each receptor are distinct, and each may have pros or cons in agonism or antagonism

Receptor	Selected effects of receptor agonism	Reward benefit with <u>agonism</u> ?	Reward benefit with <u>antagonism</u> ?
Mu	+Reward; induces analgesia and dependence	✓	✗
Delta	Antidepressant and anti-anxiety-like behavior	✓	✗
Kappa	Anti-reward, pro-depression, causes dysphoria	✗	✓

Selective KOR antagonism is associated with antidepressant and pro-reward effects, without abuse potential

KOR antagonism may disinhibit (i.e., increase) dopamine release in the reward pathways of the brain that are believed to be impaired in anhedonia.

KOR = kappa opioid receptor.

Lutz PE, Kieffer BL. *Trends Neurosci.* 2013;36(3):195-206.

Kappa Opioid Antagonists: Not Great News

WHERE THE PROGRAMS STAND, SEPT 2026:

- **Navacaprant:** two phase 3 trials missed both the primary and the key secondary endpoints.
- **Aticaprant:** Johnson & Johnson stopped the VENTURA program in 2025, citing insufficient efficacy in depression with anhedonia.

EVERY EXPLANATION FOR THE FAILURES HAS BEEN TESTED



Placebo response

Sites cut, central monitoring added, professional subjects screened out. Difference from placebo: zero.



Too little anhedonia

VENTURA-1 enrolled anhedonic patients on purpose, as add-on therapy. $p = 0.467$.



Alone was too hard

Aticaprant was added to an antidepressant. Navacaprant went alone. Both failed.



Stress applies the
brake



The brake mutes
reward



Blockers lifted the
brake

The mechanism was right. The engagement was real. The drugs still did not work.

Reward-circuit effect size from the Fast-Fail trial in mood and anxiety disorders ($n = 89$). Sources: Krystal 2020 Neuron; Schmidt 2024 Neuropsychopharmacology; Wong 2024 Journal of Affective Disorders; VENTURA-1 and KOASTAL-1/-2/-3 registry postings.

Some Hope Left? Icalcaprant: KOR Antagonist in Development for MDD and Bipolar Depression

Icalcaprant is a selective kappa opioid receptor antagonist with ~31-fold selectivity over mu opioid receptor.

Current Development Status (as of August 2026)

MDD — Phase 2 (NCT07276997)

6-week RCT as **monotherapy** of MDD;
primary completion estimated Sep 2027

Bipolar Depression — Phase 2 (NCT06696755)

6-week RCT **adjunctive** to mood stabilizers in bipolar **I or II**;
primary completion estimated Nov 2027

Icalcaprant is the only remaining late-stage KOR antagonist program in major mood disorders; no Phase 3 program announced to date

MDD=Major Depressive Disorder; KOR=Kappa Opioid Receptor; MOR=Mu Opioid Receptor; RCT=Randomized Controlled Trial
https://www.probechem.com/products_icalcaprant.html. Accessed May 31, 2026. <https://clinicaltrials.gov/study/NCT05138653>. Accessed May 31, 2026.
<https://clinicaltrials.gov/study/NCT07276997>. Accessed May 31, 2026. <https://clinicaltrials.gov/study/NCT06696755>. Accessed May 31, 2026. Abbvie Pipeline Update, April 2026. <https://investors.abbvie.com/static-files/5bb173b5-053e-4e6e-b028-c82cf2ee96a0>. Accessed May 31, 2026.

Investigational Psychedelics

Psilocybin & Anhedonia

Psilocybin: Promising Data for Anhedonia

Kaczmarek 2026 — secondary analysis of a waitlist-controlled trial¹

n = 30 • Treatment Resistant Depression • Single 25 mg dose

A single 25 mg dose with psychotherapy reduced SHAPS anhedonia scores at 2 weeks (P = .001), with clinically meaningful improvement held at 3 and 6 months.

Caveat: secondary analysis, small sample, no active placebo control.

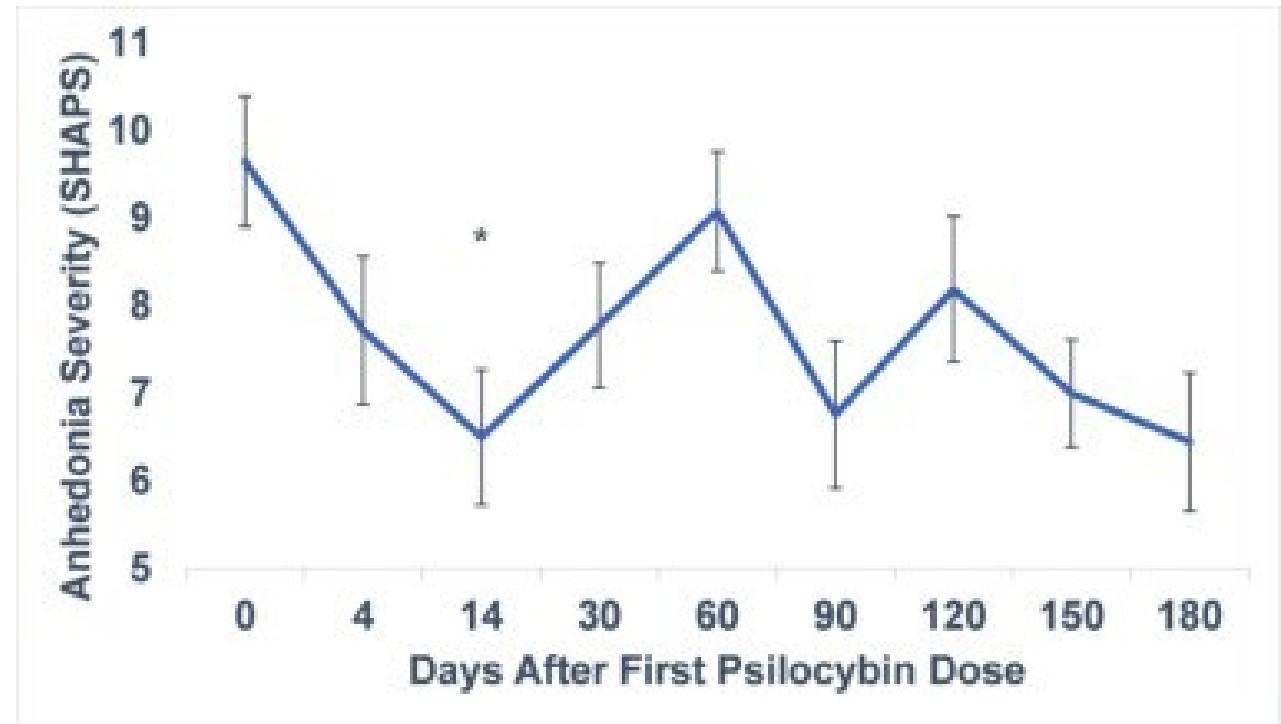
Psilocybin vs. escitalopram — phase 2 trial²

Superior on mood & anhedonia domains

Psilocybin outperformed escitalopram on mood and anhedonia domains and on every secondary outcome, including functioning and well-being, despite comparable primary depression outcomes at 6 weeks.

No emotional blunting of the kind commonly seen with SSRIs.

Open-label mean (± SE) SHAPS score (n = 29)



*Anhedonia was a secondary endpoint in both trials.

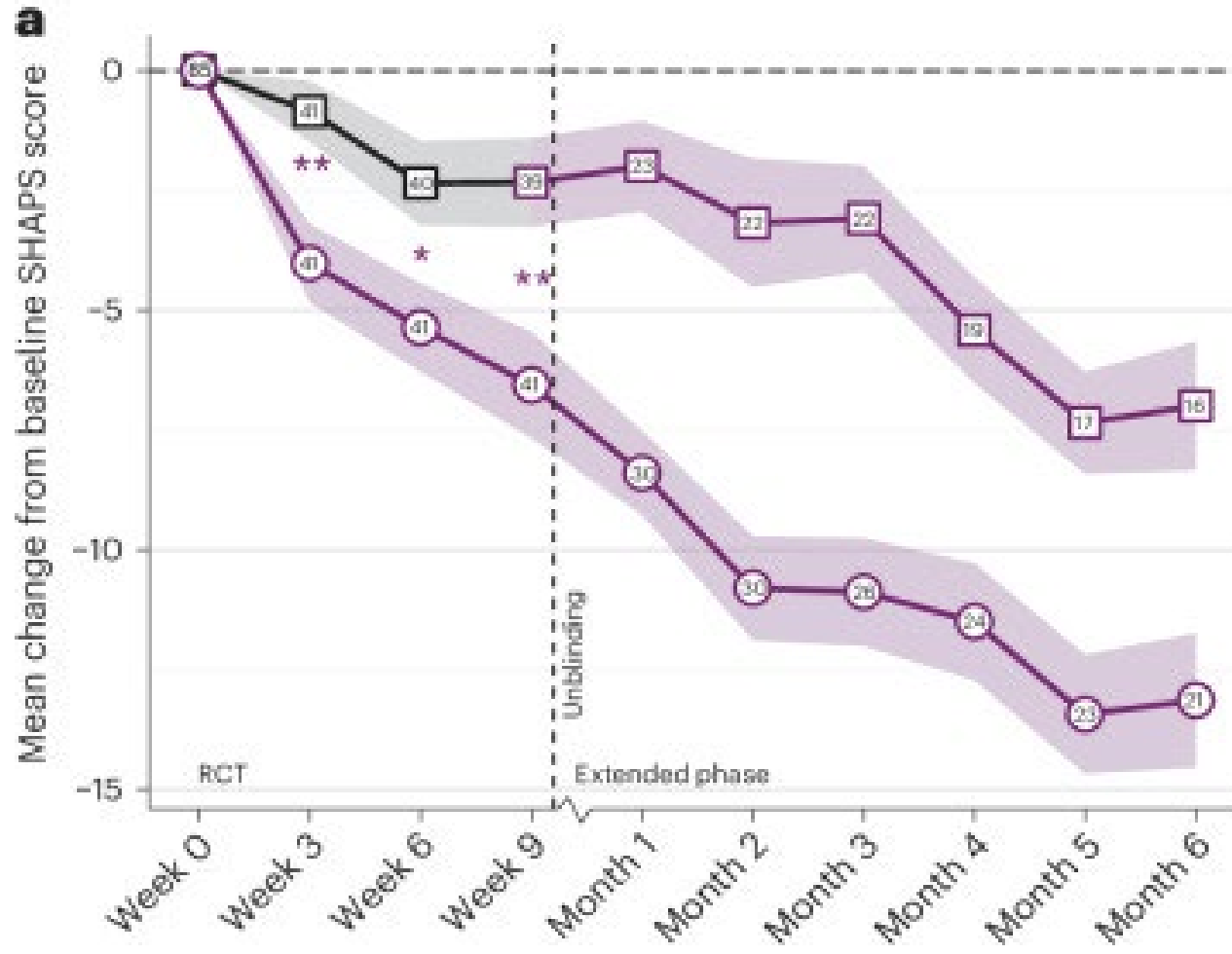
SE = standard error; SHAPS = Snaith-Hamilton Pleasure Scale; SSRI = selective serotonin reuptake inhibitor.

1. Kaczmarek ES, Rodrigues NB, Chisamore N, et al. J Affect Disord. 2026;403:121385.

2. Erritzoe D, Barba T, Greenway KT, et al. EClinicalMedicine. 2024;76:102799.

Augmentation, Neuromodulation, & Wellness Strategies to Target Anhedonia in MDD

Adjunctive Pramipexole RCT for Anhedonia (2026)



Pramipexole: a D3/D2 Partial Agonist

Single-center, randomized, double-blind, placebo-controlled trial in adults with depression, dysthymia, or bipolar depression

Week 9 (MADRS-S) : pramipexole vs placebo

Response: 22% vs 17%

Remission: 15% vs 15%

Anhedonia (SHAPS) : pramipexole vs placebo

Response ($\geq 50\%$ reduction): 39% vs 31%

Remission: 22% vs 13%

6-month open label (n = 37)

Response: 51%

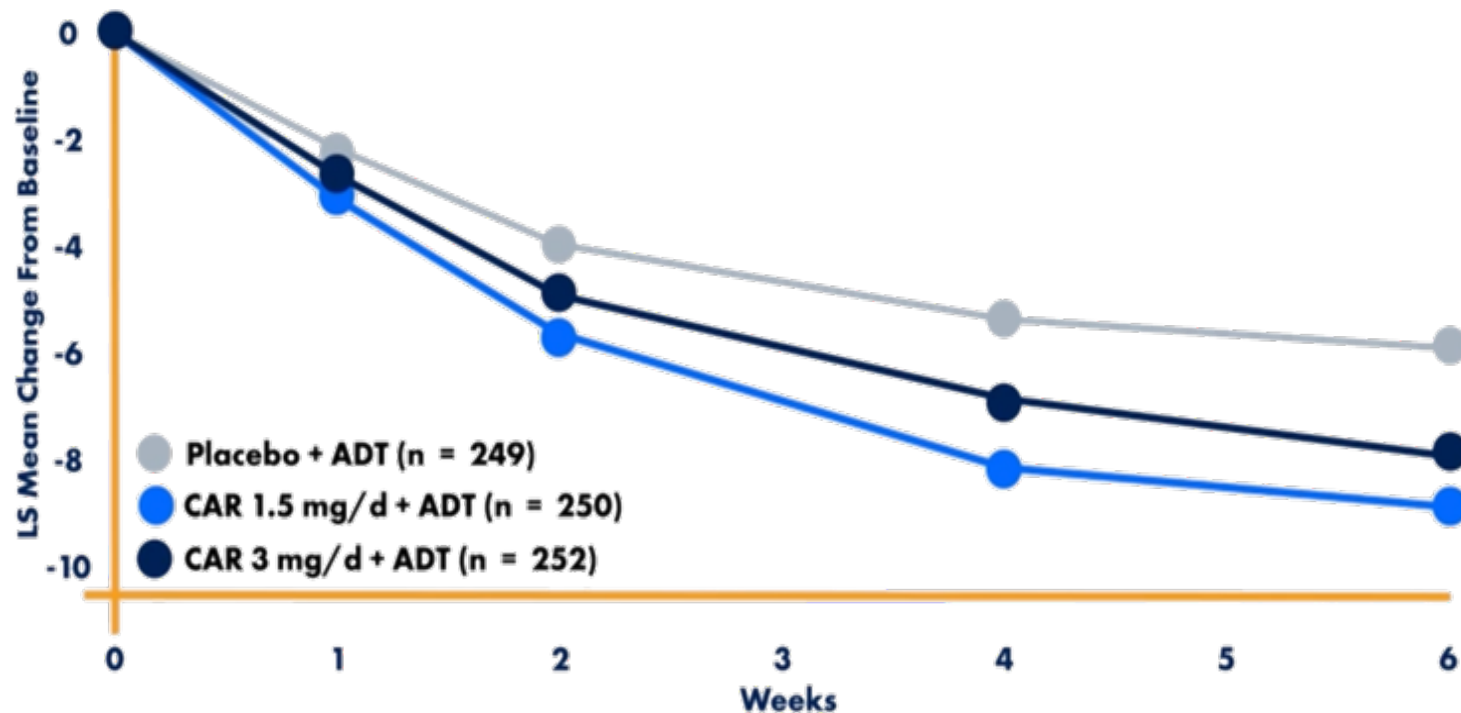
Remission: 41%

RCT = randomized controlled trial. SHAPS = Snaith–Hamilton Pleasure Scale.

Ventorp F, et al. Efficacy and target engagement of dopamine agonist pramipexole for anhedonic depression: a randomized placebo-controlled trial. Nat Med. 2026 Jul;32(7):2570-2578.

Adjunctive Cariprazine for Anhedonia

MADRS Anhedonia Subscale Score vs. Placebo



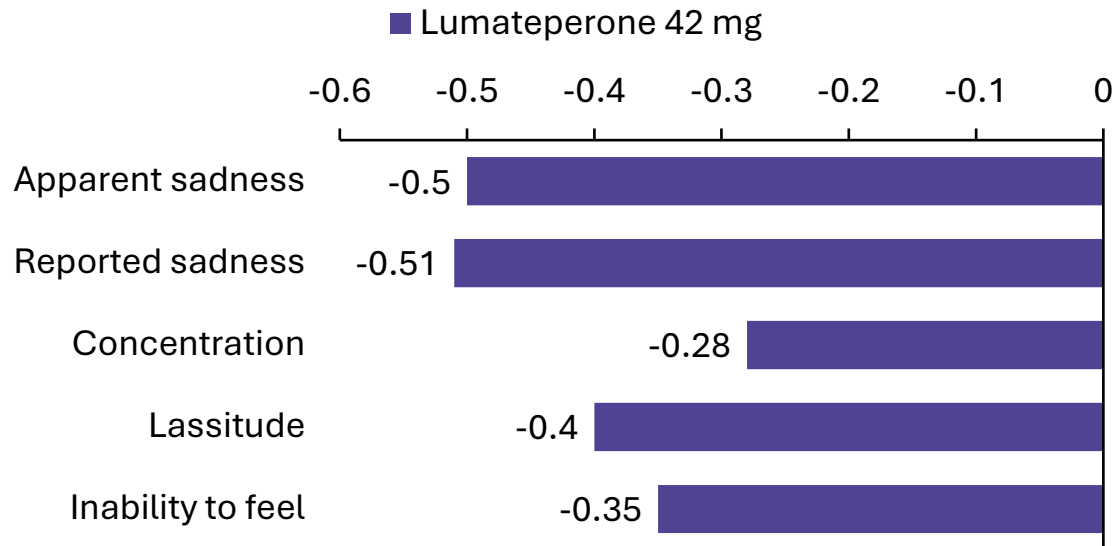
MECHANISM & MDD DATA

- **Mechanism:** dopamine D3-preferring D3/D2 partial agonist and serotonin 5-HT1A partial agonist.
- **Adjunctive MDD trial:** placebo + ADT (n = 249) vs cariprazine 1.5 mg/d (n = 250) and 3 mg/d (n = 252).
- **Result:** both doses separated from placebo on the MADRS anhedonia subscale by week 6.

BOTTOM LINE: cariprazine 1.5 mg/d is a reasonable adjunct for patients with MDD with residual anhedonia

Adjunctive Lumateperone for Anhedonia

Least squares mean difference (LSMD) vs. placebo of -2.8 (effect size [ES] = -0.55 , $P < 0.0001$) in anhedonia analyses, day 43



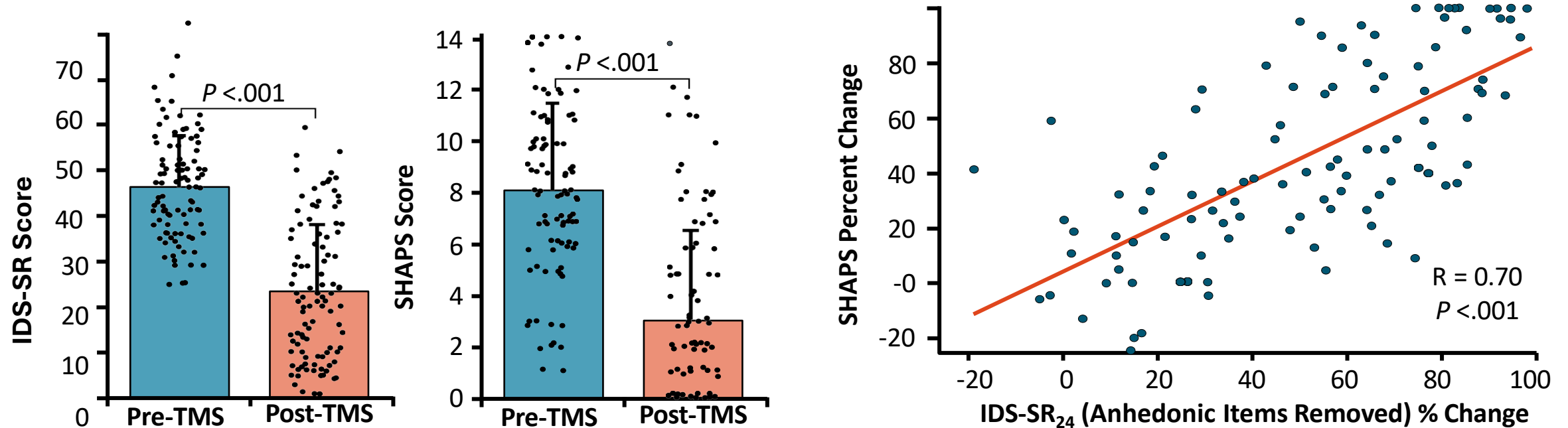
- **Mechanism:** serotonin 5-HT_{2A} antagonist and dopamine D₂ presynaptic partial agonist / postsynaptic antagonist, with actions at D₁, AMPA, NMDA and SERT.
- **Adjunctive MDD:** post hoc of a phase 3 trial (mITT, MMRM) — all five MADRS anhedonia factor items improved vs placebo by day 43.
- **Caveat:** all anhedonia findings are post hoc, and several are conference posters rather than peer-reviewed papers.
- **Enriched subgroup:** effects were larger in patients whose baseline anhedonia was above the median.

BOTTOM LINE: anti-anhedonic signal across unipolar depression — every item moves, but effect sizes are modest (0.4-0.6).

Thase ME, et al. Poster, 38th ECNP Congress, October 11-14, 2025, Amsterdam. McIntyre RS, et al. Eur Neuropsychopharmacol. 2023;68:78-88. Durgam S, et al. Poster, ACNP 2024. AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; LSMD = least-squares mean difference vs placebo; MADRS = Montgomery-Asberg Depression Rating Scale; mITT = modified intention-to-treat; MMRM = mixed model for repeated measures; NMDA = N-methyl-D-aspartate; SERT = serotonin transporter.

rTMS for Anhedonia

Improvement in anhedonia is strongly correlated with improvement in other depressive symptoms ($r = .55, P < .001$)



There was a significant improvement in depressive symptoms measured by IDS-SR scores from pre-TMS (46.36 ± 11.19) to post-TMS (25.40 ± 16.00), ($P < .001$, Cohen's $d = 1.49$) and a significant improvement in anhedonia symptoms reflected in a decrease in SHAPS scores from pre-TMS (8.10 ± 3.46) to post-TMS (3.06 ± 3.49), ($P < .001$, Cohen's $d = 1.45$). $N = 144$

rTMS = repetitive transcranial magnetic stimulation. SHAPS = Snaith–Hamilton Pleasure Scale. IDS-SR = Inventory of Depressive Symptomatology. Fukuda AM et al. Brain Behav 2021;11(9):e2329.

Evidence-Based Treatment Options for Anhedonia in MDD

Treatment	FDA status (US) for MDD/TRD	Evidence for Anhedonia
Pharmacological		
Vortioxetine	MDD	MADRS anhedonia factor and SHAPS improvement
Bupropion	MDD	Improvement in positive affect/anhedonia dimensions
Dextromethorphan–bupropion	MDD	Post-hoc MADRS anhedonia subscale improvement
Esketamine (IN)	TRD (monotherapy) or with oral AD	Factor-model analyses show anhedonia improvement
Ketamine (IV)	Off-label (ketamine is not FDA-approved for any psychiatric disorder)	Rapid anti-anhedonic effects; SHAPS improvement
Cariprazine (adjunct)	Adjunct MDD	Post-hoc improvement in anhedonia
Brexipiprazole (adjunct)	Adjunct MDD	Cluster analyses include anhedonia domains
Lumateperone (adjunct)	Adjunct MDD	Post-hoc MADRS anhedonia subscale improvement
Device-based		
Transcranial magnetic stimulation (TMS)	FDA-cleared for MDD after inadequate response to antidepressant(s)	Sham-controlled studies show anhedonia improvement
Electroconvulsive therapy (ECT)	Standard hospital-based treatment (not an FDA “drug indication”)	Reductions in anhedonia + reward-circuit changes
Transcranial direct current stimulation (tDCS)	FDA-cleared for moderate-to-severe MDD (at-home device, 2025)	Sham-controlled reduction in anhedonia
Behavioral		
Positive affect treatment (PAT)	n/a	RCT; improvement in positive affect and reduced negative affect
Behavioral activation (BATA) / MBCT	n/a	RCT; both show SHAPS improvement
Exercise (structured; often adjunct)	n/a	Improves positive valence symptoms

AD = antidepressant; SHAPS = Snaith-Hamilton Pleasure Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; ECT = electroconvulsive therapy; tDCS = transcranial direct current stimulation; PAT = positive affect treatment; BATA = behavioral activation treatment for anhedonia; MBCT = mindfulness-based cognitive therapy; RCT = randomized controlled trial. McIntyre RS, et al. *Neuropsychiatr Dis Treat.* 2021;17:575-585. Tomarken AJ, et al. *J Affect Disord.* 2004;78(3):235-241. Iosifescu DV, et al. *J Clin Psychiatry.* 2022;83(4):21m14345. Borentain S, et al. *Int J Methods Psychiatr Res.* 2022;31(4):e1927. Lally N, et al. *Transl Psychiatry.* 2014;4(10):e469. Kazemi R, et al. *Sci Rep.* 2025;15(1):899. Kong S, et al. *J Affect Disord.* 2024;350:264-273. McIntyre RS, et al. *J Affect Disord.* 2025;385:119366. Craske MG, et al. *J Consult Clin Psychol*;2019;87(5):457-471. Cernasov PM, et al. *Behav Res Ther.* 2024;182:104620. Touns M, et al. *J Affect Disord.* 2017;209:188-194.

Key Learning Points



- Novel antidepressants may address reward dysfunction and anhedonia through mechanisms beyond traditional monoaminergic pathways
- Vortioxetine, DXM-BUP, esketamine, ketamine, and several adjunctive agents have demonstrated benefits on anhedonia and functioning, with evidence of improvements in reward-related symptoms, cognition, and overall depressive outcomes, while maintaining generally favorable tolerability profiles
 - **In a pivotal Phase 3 trial, AXS-05 improved depressive symptoms at Week 2 and post-hoc analyses revealed a rapid reduction in anhedonic symptoms.**
- Emerging therapeutics such as KOR antagonists have shown potential for improving anhedonia, but mixed Phase 3 results highlight the need for further clinical validation. Psilocybin may be more promising.

Faculty and Patient Advocate Panel Discussion

Evaluating the Appropriateness of Novel Antidepressants for Individual Patients

Managing Side Effects of Novel Antidepressants (Dizziness, Nausea, etc.)

Non-Pharmacologic and Patient-Centered Strategies to Address Anhedonia

Patient Advocate: Advice for Clinicians

Prescription for Optimal Depression Treatment Outcomes

Rush AJ, Thase ME. Improving
Depression Outcome by
Patient-Centered Medical
Management. Focus (Am
Psychiatr Publ). 2020
Apr;18(2):244-254..

- Share decision making in the formulation of the treatment plan
- Clarify and prioritize patient's goals and treatment preferences
- Share and align expectations as to duration of treatment, critical decision points, and side effect management
- Provide education, information, and action plans for managing suicidal ideation, side effects, substance use, and concurrent general medical conditions
- Engage patient in monitoring symptoms, function, side effects, and healthy activities
- Anticipate and plan countermeasures to enhance adherence
- Define and counter obstacles to full recovery
- Develop relapse prevention/amelioration plan (e.g., prodrome, long-term side effects, dose management, risk reduction)

Summary

- Anhedonia is a transdiagnostic symptom that strongly predicts severity, poor antidepressant response, and suicidality
- Dysfunction of the dopamine-glutamate-opioid reward circuits underlies motivational and hedonic deficits
- Standard antidepressants often fail to resolve anhedonia
- Dopaminergic and multimodal agents (vortioxetine, cariprazine, lumateperone) show anti-anhedonic benefit
- Rapid-acting glutamatergic modulators (esketamine, dextromethorphan-bupropion) demonstrate robust improvement in reward-related symptoms
- Behavioral activation, rTMS, and exercise provide evidence-based non-pharmacological options that can be integrated into care

Practical Takeaways



Screen for anhedonia routinely in patients with depression, as it predicts poor treatment response, chronicity, and suicide risk, and often persists beyond mood improvement

- *Ask about motivation (“wanting”), pleasure (“liking”), and engagement in hobbies, social activities, food, and sensory experiences*



Use agents with evidence for anti-anhedonic effects, including dextromethorphan-bupropion, vortioxetine, esketamine, cariprazine or lumateperone, while monitoring functional as well as mood outcomes

- *Align treatment selection with patient goals, prioritizing life engagement and restoration of function*



Incorporate non-pharmacological strategies such as exercise, behavioral activation and neuromodulation (rTMS) to enhance reward processing and restore motivation

Questions?