Psych Congress | MasterClass

# Aiming Higher in MDD:
## Practical Strategies and Novel Monotherapies to Improve Outcomes

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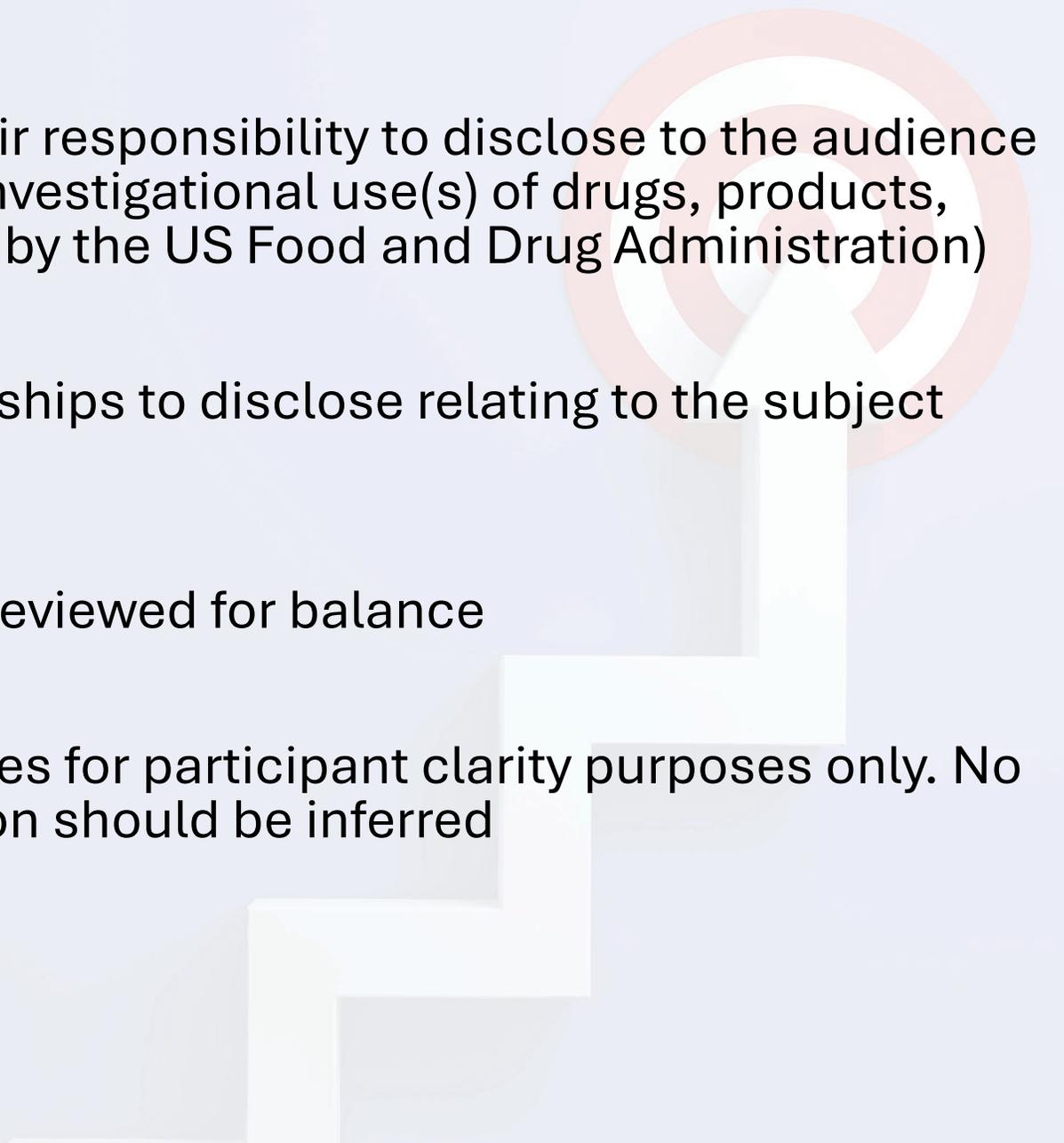
# Learning Objectives

- Describe the challenges and suboptimal outcomes associated with conventional antidepressants for MDD

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

- Evaluate the MOAs and latest clinical evidence associated with novel/investigational monotherapies for MDD and their potential to improve patient outcomes
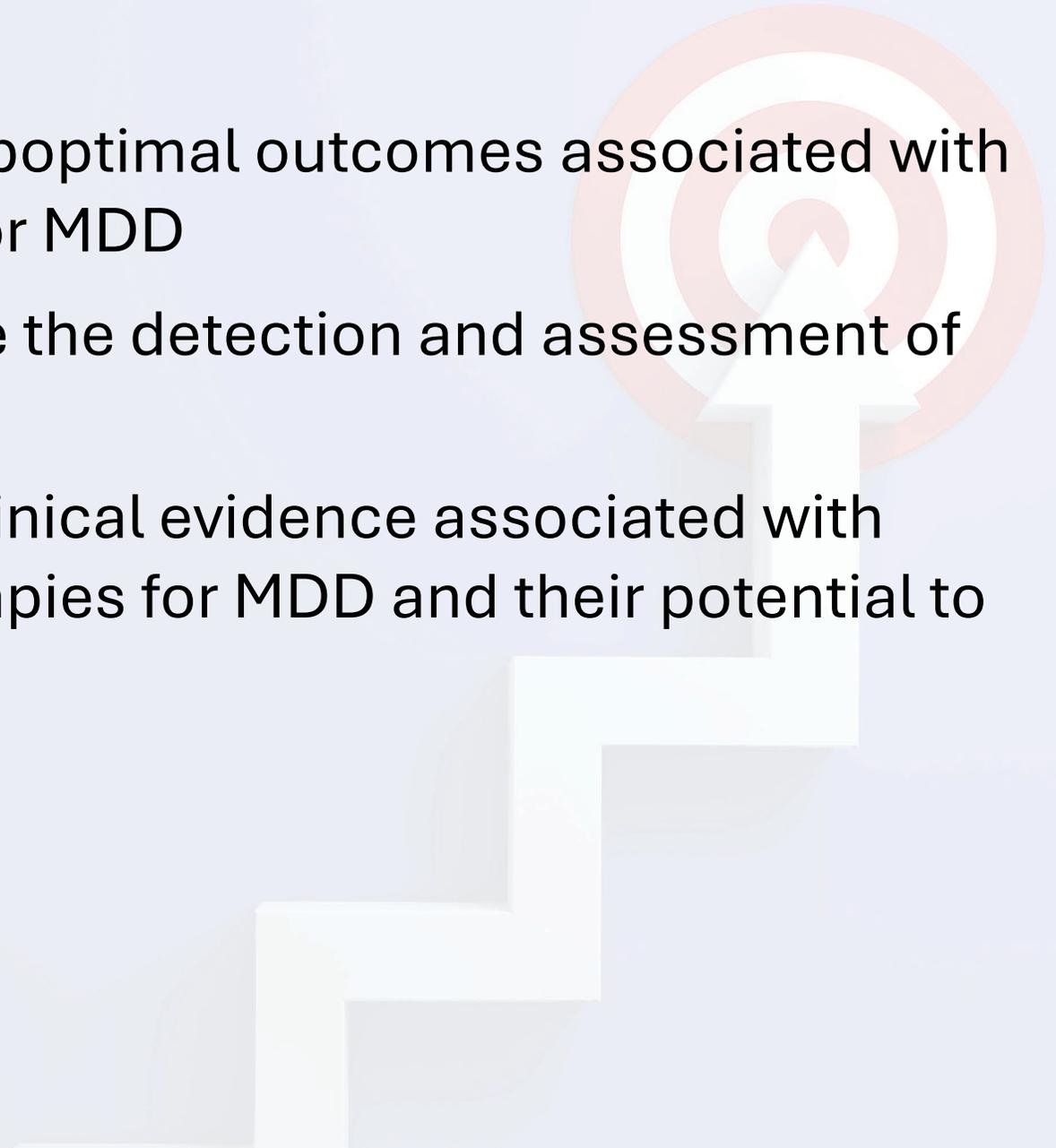
# Overview

Current State of the Knowledge Regarding MDD Epidemiology and Treatment Gaps

# Depressive Disorders Are the #2 Cause of Disability In the World



>**21** million
**US adults are affected every year**

## MDD Poses a Substantial Burden

**75**% of people with MDD have **comorbidities**
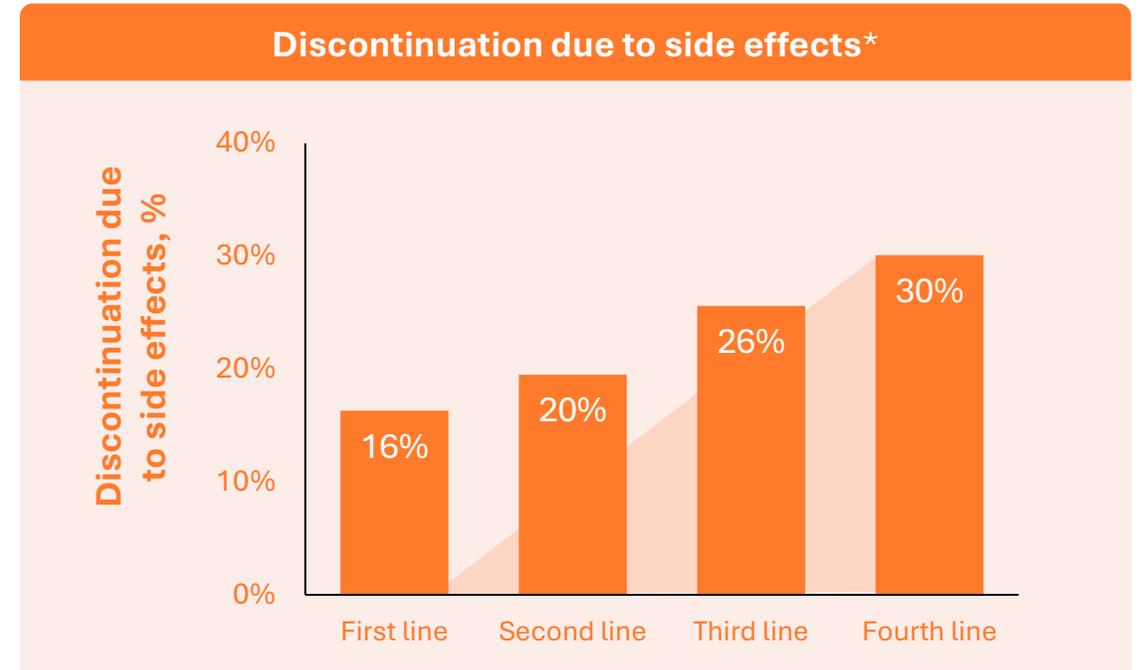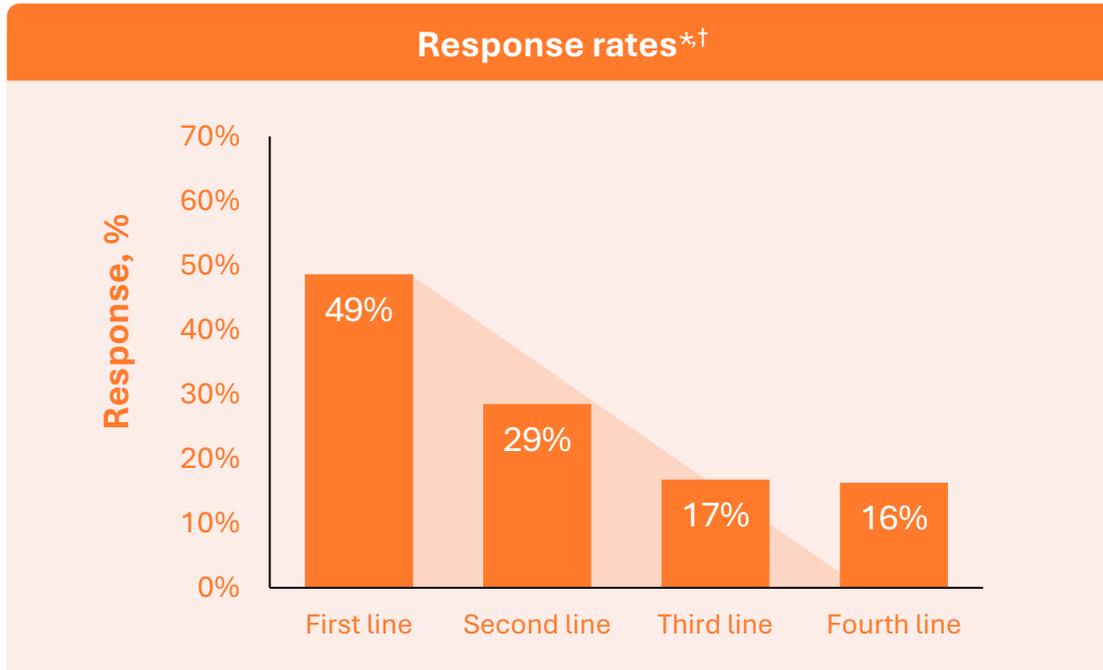
**~50**% of adults go **untreated**

**20**× higher **suicide** risk than the general population

MDD = major depressive disorder.

GBD 2021 Diseases and Injuries Collaborators. *Lancet*. 2024;403(10440):2133-2161. Bhatia R. Anxiety and Depression Association of America. November 2, 2020. Updated August 21, 2025. Accessed February 7, 2025. https://adaa.org/understanding-anxiety/depression/facts-statistics. Hasin DS, et al. *JAMA Psychiatry*. 2018;75(4):336-346. Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917. Chesney E, et al. *World Psychiatry*. 2014;13(2):153-160.

# Monoaminergic Antidepressants Have Not Been a Successful Strategy for Many Patients

## And "Flipping" Is Not a Successful Strategy

### Response rates*,†

Response, %

| | |
|---|---|
| First line | 49% |
| Second line | 29% |
| Third line | 17% |
| Fourth line | 16% |

### Discontinuation due to side effects*

Discontinuation due to side effects, %

| | |
|---|---|
| First line | 16% |
| Second line | 20% |
| Third line | 26% |
| Fourth line | 30% |

# Inadequately Treated MDD (Especially Anhedonia) Puts Patients at Increased Risk

## Even mild residual symptoms negatively impact patients' mental and physical health

**Increased risk of relapse**

**Reduced time to next depressive episode**

**Higher rates of heart attack and stroke**

**Increased risk for death by suicide**

**Impaired psychosocial functioning**

Habert J, et al. *Prim Care Companion CNS Disord*. 2016;18(5). Israel JA. *Pharmaceuticals (Basel)*. 2010;3(8):2426-2440.

# Challenges of Treating Anhedonia with Monoaminergic Antidepressants

Monoaminergic antidepressants may not only fail to alleviate anhedonia but can also produce reductions in emotional experience.
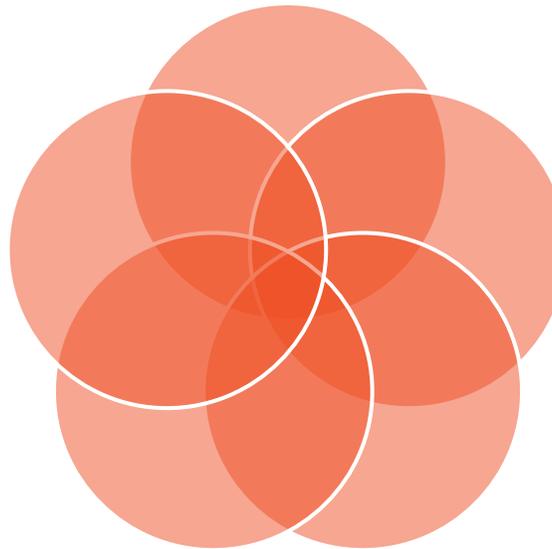
## How do we know if it is residual anhedonia vs side effect of emotional blunting (EB)?

**Prevalence**

- 40%-65% of patients with MDD on SSRIs/SNRIs experience EB

**Psychological effects**

- >75% of MDD patients taking SSRIs experienced psychological AE: "narrowed range of affect" (46%), "not feeling like self" (33%), "loss of creativity" (24%), "inability to cry" (21%), "apathy" (19%), "loss of empathy" (14%)

**Treatment discontinuation**

- Psychological side effects cited as frequently as physical side effects and more often than insufficient efficacy as reasons for discontinuing treatment

**Patient perception**

- Among patients taking an antidepressant and reporting EB within the past 6 weeks, 56% attributed this change to MDD while 45% attributed it to the medication

EB = emotional blunting; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; AE = adverse event.
Ma H, et al. *Frontiers in Psychiatry*. 2021;12:792960. Christensen MC, et al. *Annals of General Psychiatry*. 2022;21(1):1-8. Goodwin GM, et al. *J Affect Disord*. 2017;221:31-35. Read J, et al. *Psychiatry Res*. 2014;216:67-73. Cartwright C, et al. *Patient Prefer Adherence*. 2016;10:1401-1407. Bolling MY, et al. *Psychother Psychosomatics*. 2004;73(6):380-385.

# Anhedonia

A Deeper Dive

# First Things First – Defining Anhedonia

Patients with anhedonia have a reduced ability to experience pleasure or interest in things previously enjoyable

"without"

**An**hedonia

"pleasure"

**Anhedonia has both consummatory and anticipatory elements**

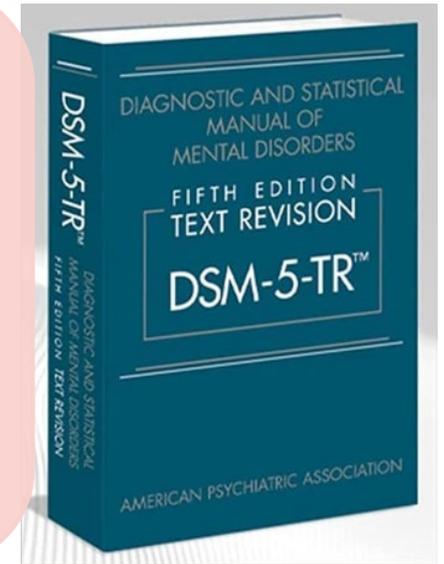| Consummatory | Anticipatory |
|---|---|
| **Inability to feel pleasure during current events**<br><br>**Reduced joy or interest in interpersonal or social interactions and natural rewards, including eating and sexual behaviour** | **Inability to predict future experience of pleasure**<br><br>↓<br><br>**Lower reward responsiveness and reduced motivation to act towards future pleasure** |

Gillissie ES, et al. *J Psychiatr Res*. 2023;158:209-215.

# Anhedonia in DSM-5

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

**How anhedonia is featured in the DSM-5:**

- **Major Depressive Disorder**: Key symptom; defined as a significant loss of interest or pleasure in all or almost all activities
- **Schizophrenia and Other Psychotic Disorders**: Part of negative symptoms, indicating reduced pleasure from daily activities
- **Substance Use Disorders**: Can occur due to alterations in the brain's reward system from prolonged drug use

American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. APA Publishing; 2013.

# Consequences of Anhedonia

# *(oh so, many, many....)*

# One Way to Think About Anhedonia – It Is the Fountainhead For a Lot of Huge Challenges for MDD Patients
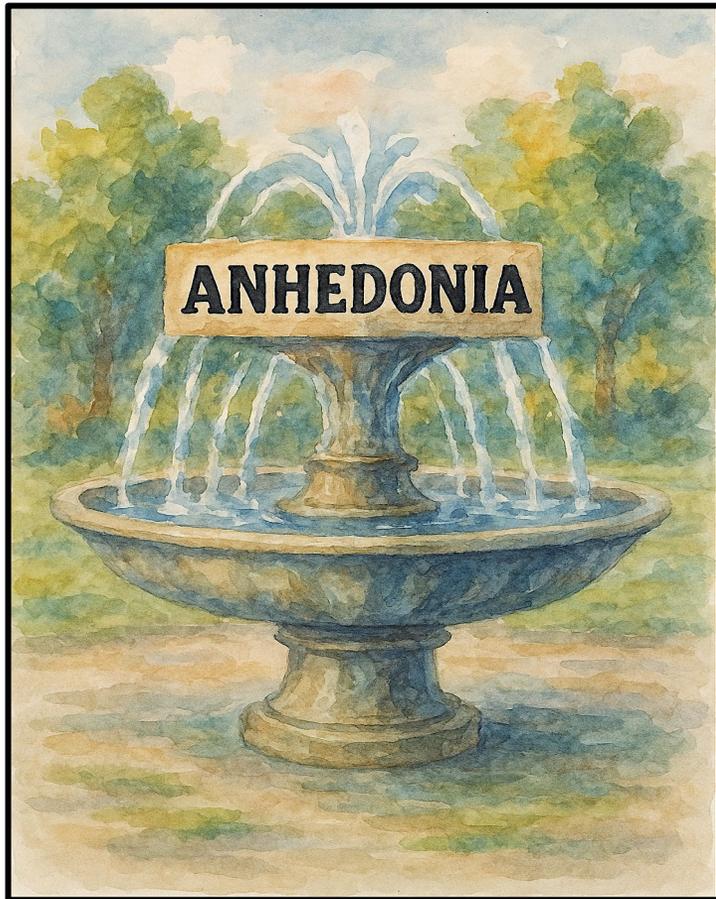


**A short list of "Who's Who" in the World of MDD Consequences of Prominent Anhedonia Symptoms**

- Greater depressive symptoms
- Greater resistance to monoaminergic antidepressants
- Greater suicidal ideations
- Greater impairment in psychosocial functioning
- And, alas, more ….

McMakin DL, et al. *J Am Acad Child Adolesc Psychiatry*. 2012;51(4):404-411.

# Anhedonia Is Associated with Depression Severity, Episode Duration, and Suicidality

Anhedonia is associated with: (A) overall depression severity (CDRS-R minus the anhedonia question), (B) suicidality (Beck Scale for Suicidal Ideation), and (C) episode duration (months) in a sample of 90 depressed adolescents.
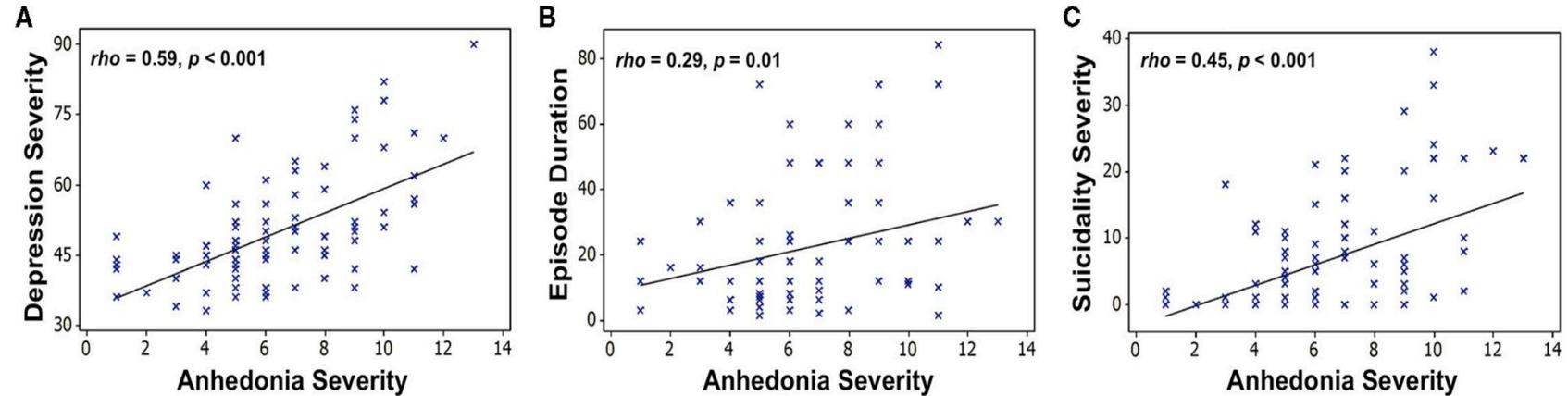
Anhedonia severity predicts future (A) depression severity, (B) anhedonia severity, and (C) suicidality, assessed after ~24 months in a sample of 29 adolescents with mood and anxiety symptoms (triangles) and 14 healthy adolescent controls (circles)



CDRS-R = Children's Depression Rating Scale – Revised.
Ely BA, et al. *Frontiers in Psychiatry*. 2021;12(678709).
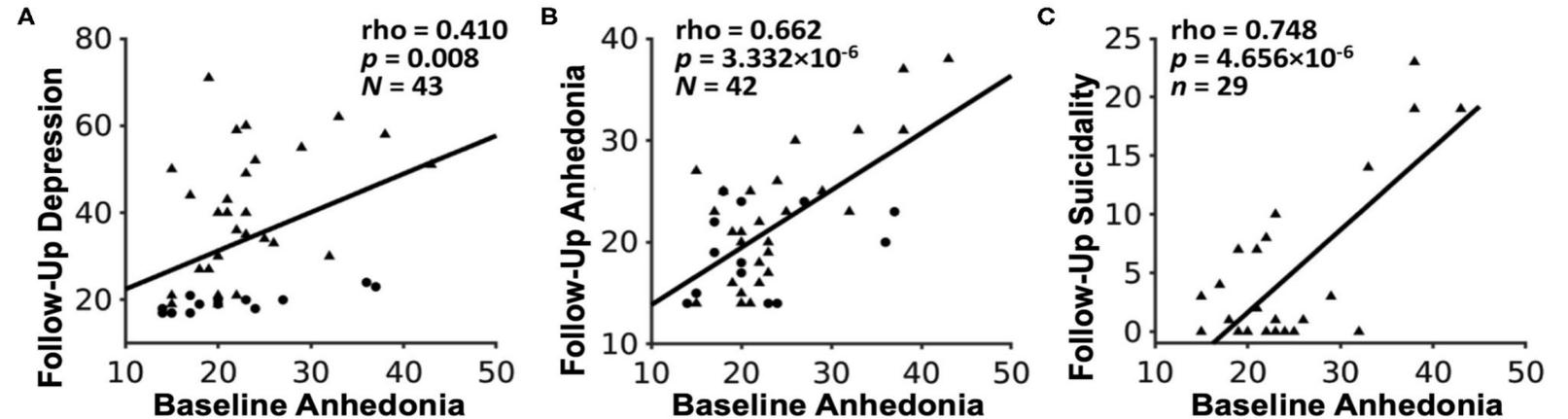
# Anhedonia Negatively Predicts Time to Remission with SSRI

In a trial of adolescents with MDD, anhedonia was the only unique negative predictor of both **time to remission** with an SSRI and the **number of depression-free days** over the 24-week period

| Depression-free days | Univariate model[a] | | Multivariate model[b] | |
|---|---|---|---|---|
| | B (SE) | Partial correlation | B (SE) | Partial correlation |
| Depressed mood | -2.63 (0.65)*** | -0.23 | -1.19 (-0.83) | -0.09 |
| Anhedonia | -5.21 (1.01)*** | -0.29 | -4.355 (1.18)*** | -0.23 |
| Somatic symptoms | -1.92 (0.67)** | -0.17 | -0.89 (0.71) | -0.08 |
| Morbid thoughts | -2.04 (0.74)** | -0.16 | -1.414 (0.84) | -0.11 |
| Observed depression | -2.08 (0.94)* | -0.13 | -0.84 (0.96) | -0.05 |

**Anhedonia predicts a longer time to remission (HR 0.91; 95% CI 0.84, 0.99)[b] and is an important treatment target, as well as a marker of disease severity**

Data from a multivariate analysis of a trial of adolescents with MDD with treatment resistance to SSRIs (n=334) who were randomised to switch medication or switch and receive CBT.

Prior to entry into the study, participants had undergone **8 weeks of an SSRI regimen, during the last 4 weeks of which they received fluoxetine ≥40 mg/day or its equivalent** (eg, paroxetine 40 mg, citalopram 40 mg, escitalopram 20 mg, or sertraline 150 mg).

*$P<0.05$; **$P<0.01$; ***$P<0.001$; [a]models are adjusted for age, sex, and race (coded as Caucasian vs non-Caucasian); [b]includes all CDRS-R dimensions simultaneously and is adjusted for adolescent age, sex, and race.
SE = standard error; HR = hazard ratio; CI = confidence interval; CBT = cognitive behavioral therapy.
McMakin DL, et al. *J Am Acad Child Adolesc Psychiatry*. 2012;51(4):404-411.

# Anhedonia Is Associated with Increased Anxiety And Compromised Cognitive Control

Anhedonia is an important treatment target in affective disorders, and there is a strong connection between anhedonia and cognitive control in individuals with MDD on a behavioral and brain structural level. Brain structural overlap of anhedonia and cognitive control, taken together with the already proposed major cortical nodes of the salience network (ie, dorsolateral anterior cingulate cortex, anterior insula, mediodorsal thalamus), puts a stronger focus on emotional regulation within the salience network.

**MDD is heterogeneous.**
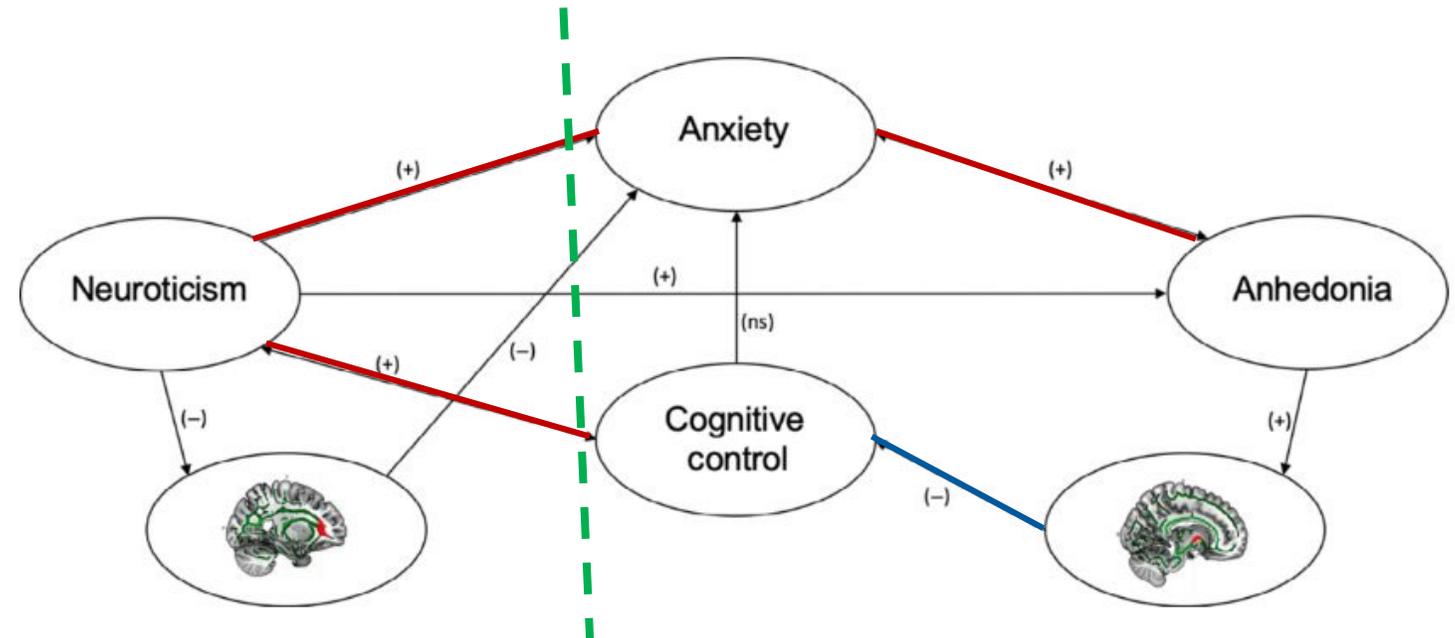


Brain structural correlates found in our DTI (diffusion tensor imaging) analyses showed two autonomous connectivity paths, one representing the impact of a personality trait on brain structure and one representing the impact of a main symptom representation on brain structure in an MDD sample. Both, however, had an effect on cognitive control independently of each other.

# Anhedonia as a Risk Factor for Suicide: Meta-Analysis



| Study | Effect Size [95% CI] |
|---|---|
| Abdollahi et al. | 0.45 [0.18, 0.71] |
| Ballard et al..1 | 0.52 [0.12, 0.93] |
| Ballard et al..2 | 0.34 [0.09, 0.59] |
| Daghigh et al. | 0.47 [0.01, 0.92] |
| Ducasse et al. | 0.23 [0.09, 0.38] |
| Gabbay et al. | 0.48 [0.20, 0.77] |
| Hawes et al. | 0.17 [0.01, 0.33] |
| Loas et al..1 | 0.29 [0.14, 0.43] |
| Loas et al..2 | 0.22 [-0.04, 0.47] |
| Loas et al..3 | 0.23 [0.11, 0.36] |
| Sagud et al. | 0.39 [0.16, 0.63] |
| Spijker et al. | 0.25 [0.04, 0.45] |
| Winer et al..1 | 0.36 [-0.05, 0.78] |
| Winer et al..2 | 0.47 [0.19, 0.75] |
| Xie et al. | 0.32 [0.03, 0.61] |
| Yang et al..1 | 0.69 [0.19, 1.20] |
| Yang et al..2 | 0.34 [0.13, 0.55] |
| Yang et al..3 | 0.50 [0.20, 0.79] |
| Yang et al..4 | 0.45 [0.10, 0.80] |
| Zielinski et al. | 0.55 [0.13, 0.97] |
| Overall | 0.31 [0.26, 0.36] |

Effect Size

Anticipatory anhedonia was the highest risk factor ($r = 0.40$; $P<0.001$), with a moderate to large effect size

Gillissie ES, et al. *J Psychiatr Res*. 2023;158:209-215. CDC. March 26, 2025. Accessed August 2025. https://www.cdc.gov/suicide/facts/data.html.

# 3 Crucial Points to Remember Regarding Anhedonia

- Anhedonia, as defined by DSM-5, is NOT a COMPLETE loss of pleasure …. But just a very significant presence

- Most patients with Anhedonia do retain 1-2 areas of life where they still derive pleasure

- Some patients with significant Anhedonia may even derive EXCESSIVE pleasure from problematic behaviors (eg, overeating carbohydrates, pornography, gambling, substance misuse, internet addiction, etc.)

# Here Is How One Can Visualize Anhedonia in MDD



**Anhedonia Is a Drag –**

It's a Drag on All Outcomes that Patients and Their HCPs Desire with MDD

# Anhedonia Is Associated with Disturbances in Reward Circuit Pathways

- Anhedonia may involve disturbance of central dopaminergic, mesolimbic, and mesocortical reward circuit pathways

- These pathways are involved with hedonic drive, motivation, cognition, and perception



MSNs
GABAergic
Glutamatergic
Dopaminergic
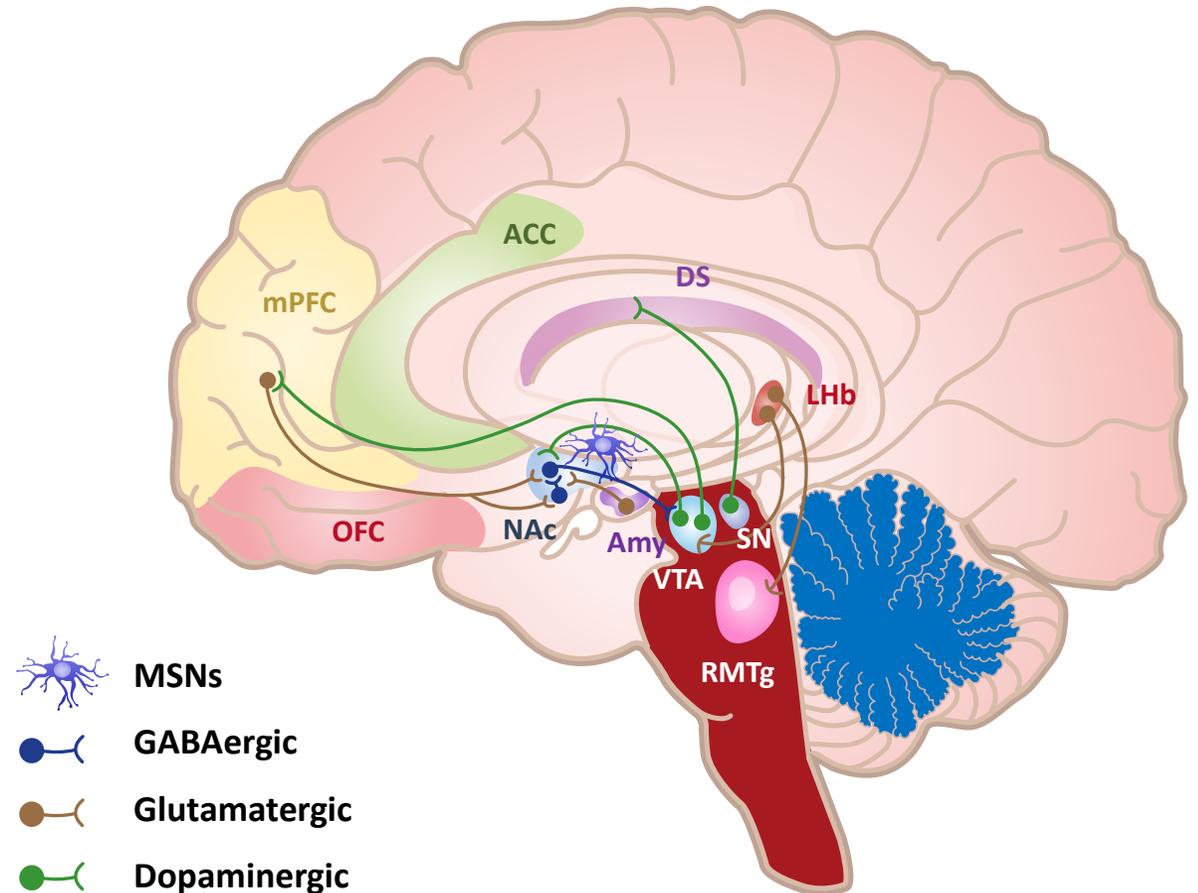
mPFC = medial prefrontal cortex; ACC = anterior cingulate cortex; DS = dorsal striatum; LHb = lateral habenula; OFC = orbitofrontal cortex; Nac = nucleus accumbens; Amy = amygdala; VTA = ventral tegmental area; SN = substantia nigra; RMTg = rostromedial tegmental nucleus; MSN = medium spiny neuron; GABA = gamma-aminobutyric acid.

Pan Z, et al. *Curr Pharm Des*. 2017;23(14):2065-2072. Su YA, Si T. *Gen Psychiatr*. 2022;35(1):e100724.

# Anhedonic Depression Is Associated with Abnormal Glutamatergic Metabolism
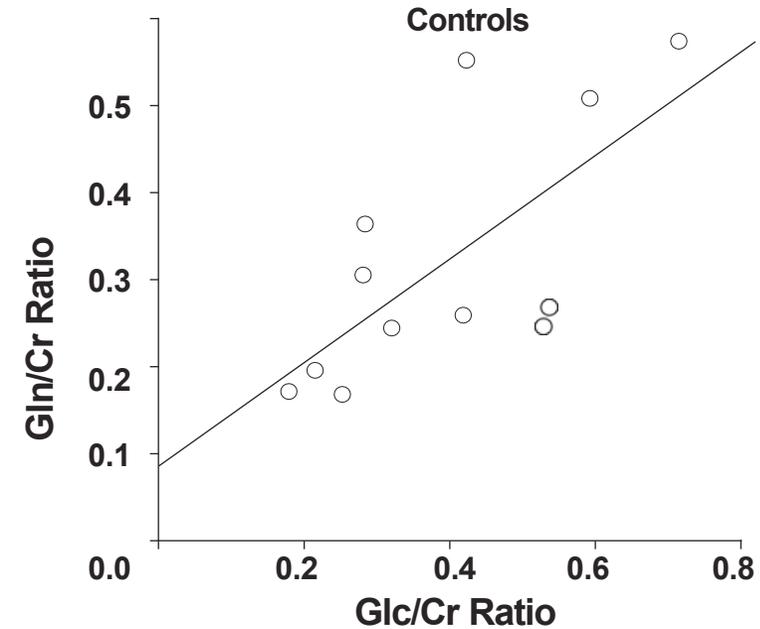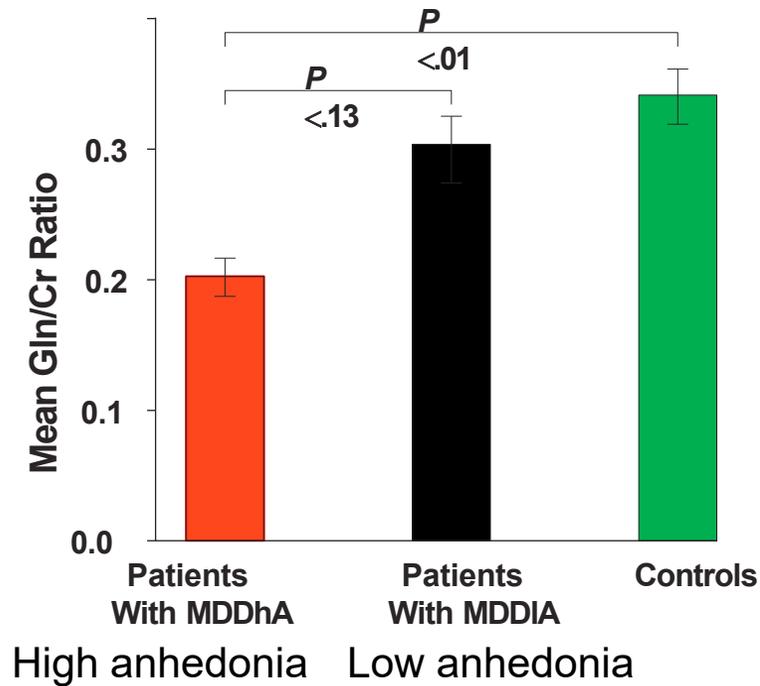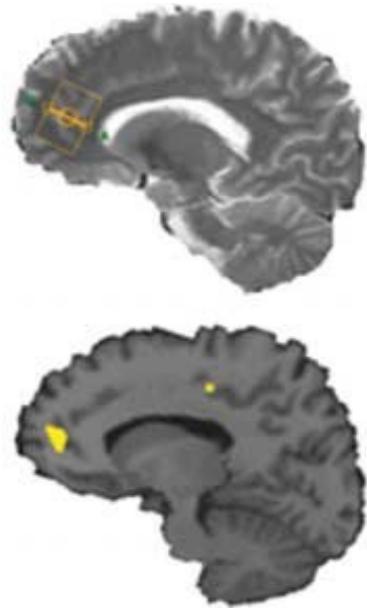


**Magnetic resonance spectroscopic voxel depicted in MDD patients with high anhedonia (MDDhA) (n=5) and low anhedonia (MDDlA) (n=5) and healthy controls (n=14).** Anhedonia measure was a 3-factor solution of the BDI with the factors anhedonia, somatic complaints, and negative self-focus.

Gln = glutamine; Glc = glucose; Cr = creatine; MDDhA = MDD high anhedonia; MDDlA = MDD low anhedonia; BDI = Beck Depression Inventory.
Walter M, et al. *Arch Gen Psychiatry*. 2009;66(5):478-486.

# How Do We Evaluate For Anhedonia?

# Dimensions of Anhedonia:
## 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 |

Serretti A. *Clin Psychopharmacol Neurosci*. 2023;21(3):401-409. Gillissie ES, et al. *J Psychiatr Res*. 2023;158:209-215.

# A GOOD WAY TO REMEMBER THE SUBTYPES OF ANHEDONIA:

Use the Mnemonic "AC/DC"

**Anticipatory**

**Consummatory**



**DC**

**Anhedonia Discontinues**

- *Pleasure*
- *Joy*
- *Meaning*
- *Etc.*

# MADRS Anhedonia Subscale Score



The MADRS anhedonia subscale includes five items from the MADRS

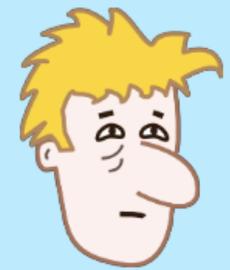Apparent sadness | Reported sadness | Concentration difficulties | Lassitude | Inability to feel

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.

# Validated Anhedonia Rating Scales

## SHAPS

| Question |
| --- |
| 1. I would enjoy my favorite television or radio program |
| 2. I would enjoy being with my family or close friends* |
| 3. I would find pleasure in my hobbies and pastimes |
| 4. I would be able to enjoy my favorite meal* |
| 5. I would enjoy a warm bath or refreshing shower* |
| 6. I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread |
| 7. I would enjoy seeing other people's smiling faces* |
| 8. I would enjoy looking smart when I have made an effort with my appearance |
| 9. I would enjoy reading a book, magazine, or newspaper* |
| 10. I would enjoy a cup of tea or coffee or my favorite drink |
| 11. I would find pleasure in small things, eg, bright sunny day, telephone call from a friend |
| 12. I would be able to enjoy a beautiful landscape or view |
| 13. I would get pleasure from helping others |
| 14. I would feel pleasure when I receive praise from other people |

14 item self-reported scale assessing consummatory anhedonia

A higher score indicates higher levels of anhedonia

**\*Reverse scored with answer choices: strongly agree, agree, disagree, strongly disagree**

## DARS

**List at least 2:**

A. List at least 2 of your favorite pastimes/hobbies that are NOT primarily social:

1. I would enjoy these activities
2. I would spend time doing these activities
3. I want to do these activities
4. These activities would interest me

B. List at least 2 of your favorite foods or drinks:

5. I would make an effort to get/make these foods/drinks
6. I would enjoy these foods/drinks
7. I want to have these foods/drinks
8. I would eat as much of these foods as I could

C. List at least 2 of your favorite social activities:

9. Spending time with doing these things would make me happy
10. I would be interested in doing things that involve other people
11. I would be the one to plan these activities
12. I would actively participate in these social activities

D. List at least 2 of your favorite sensory experiences

13. I would actively seek out these experiences
14. I get excited thinking about these experiences
15. If I were to have these experiences, I would savor every moment
16. I want to have these experiences
17. I would make an effort to spend time having these experiences

17 item self-reported scale assessing anticipatory and consummatory anhedonia in 4 domains

A higher score indicates higher levels of anhedonia

**SHAPS = Snaith-Hamilton Pleasure Scale; DARS = Dimensional Anhedonia Rating Scale.**
**Nakonezny PA, et al. *Int Clin Psychopharmacol*. 2010;25(6):328-333. Rizvi SJ, et al. *Psychiatry Res*. 2015;229(1-2):109-119.**

# Key Learning Points
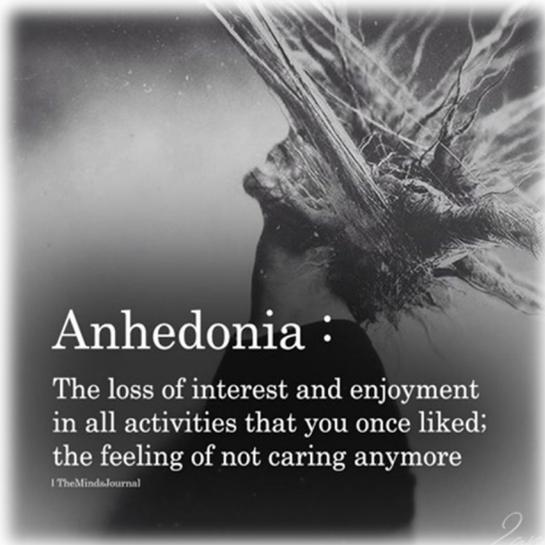


- Anhedonia is a core symptom of MDD, characterized by a significant reduction in interest or pleasure in activities once found rewarding

- It differs from apathy and emotional blunting, which may be worsened by antidepressant use

- Traditional monoaminergic antidepressants often fail to effectively address anhedonia and may even reduce positive emotions

- 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 :
The loss of interest and enjoyment in all activities that you once liked; the feeling of not caring anymore
| TheMindsJournal

# Why Is Anhedonia Underrecognized in Clinical Practice?

# Answer:

1. We Clinicians Don't Often Ask About It,

2. Don't Often Evaluate for It, and

3. Aren't Fully Aware of the Ethnographic Descriptions Offered by Patients

# Listen to Patients to Detect Anhedonia

## OARS: Four Core Skills of Motivational Interviewing

**Open questions** →
- Promote trust for enhanced communication
- For example, *"What concerns do you have ….?"*

**Affirmations** →
- Validate positive attributes, efforts, etc.
- For example, *"You've done a great job with…"*

**Reflections** →
- Demonstrate active listening and invite exploration
- For example, *"I see this upsets you…"*

**Summaries** →
- Bundle concluding reflections; invite elaboration
- For example, *"Let me summarize what I heard you say; please let me know if it's correct…"*

OARS = open questioning, affirmation, reflections, and summaries.
Cole S, et al. *Progress in Cardiovascular Diseases*. 2023;77:86-94.

# Dancing Around Anhedonia:

## How People with Lived Experience and Clinicians Talk About Anhedonia

An analysis of 60 recorded conversations from psychiatry and primary care outpatient visits with patients experiencing MDD revealed that anhedonia was brought up by healthcare providers in only 40% of cases when discussed.
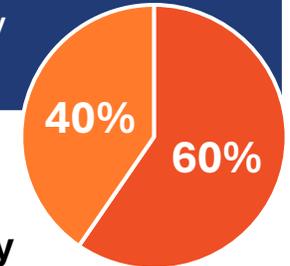
**Clinician-introduced**  **Patient-introduced**

40%  60%

**Four combined meanings used by patients to convey lack of volition for generic activity**

**(Negative    +    Volition)**

*Dis*interested // *Nothing* // *Nowhere* // don't *even* // don't *ever* // haven't // literally *can't* // *just* can't // *lost* // *lack* of // was *not* // *rather* than // just *not* there // *never* // *not* as interested // *not* wanting // *too* much // *un*motivated // *used* to

don't *want* // don't *feel like* // don't *like to* // not *interested* // can't get *into it* // there's no *enthusiasm* // don't *care* // *rather* be // no *interest* in // not *thrilled* // *interest* me // seemed *worthwhile* // [no] *reason* to

**+**

**(Generic    +    Activity)**

do *something* // do *anything* // do *things* // do *stuff* // do *nothing* // do *shit* // do *much* // go *anywhere* // get *stuff* done // be around *anybody*

*do* physical activity // *get* out of the house // *go* to work // *get up* and *do* anything // *go* anywhere // *get* going // *get* out of bed // *lay* around // *lay* on the couch // *get* around to // *sit* around // *stay* in bed // *go* outside // *keep* myself busy

Only 1 healthcare provider and no person with lived experience used the term anhedonia – more commonly they described a **"lack of volition for generic activity"**

Drissen T, et al. How Patients with Depression and Their Providers Navigate Anhedonia: An Ethnographic Evaluation of Discourse Dynamics of Psychiatrists and Primary Care Providers in Clinical Settings. Poster Presented at: Psych Congress Elevate; May 30-June 2, 2024; Las Vegas, NV.

# Activities and Experiences Impacted by Anhedonia



"it actually has **taken away from my focus on work** [...] I found myself [...] **daydreaming, not really focused** on [...] I would notice more errors [...] **where typically I'm, I'm very focused.**" (1002-F-55-4)

"I was the person that would get all our friends together [...] I wish I could go back to that person and I've tried, [...] it's just difficult, it's hard. And I'm sorry, I got a little emotional." (2002-F-50-4)

"it started **affected my relationship**. Um, like, **even intimate parts**, it affect – you know, it affected that. Like, **I had no desire**, um, well, yeah." (2002-F-50-4)

"**when my boyfriend wants to come over**, me knowing that I have to shower, I tell him that I, **I want to be alone**, 'cause **I don't want to get out of bed.**" (2002-F-50-4)

"going to **visit family**, going to the **supermarket**, sometimes, um, going to the **carwash**, yeah, it, err, it **affects a lot of things.**" (2002-F-50-4)

"**being in groups with my family**, that – you know, **holidays, birthdays**, things like that, was, um, **very difficult to go to.**" (1006-F-29-4)

"I had **lost interest in eating** [...] **I'm not, like, taking pleasure in food like I used to.**" (4007-M-54-4)

"Most impacted is [...] my physical body, [...] **all of my life from playing basketball, to softball** [...] **now just being in the house doing nothing**, like, not getting any exercise." (2002-F-50-4)

**Anhedonia impacts:** Work (n=9), Daily activities (n=11), Family (n=8), Food/drink (n=3), Hobbies (n=9), Romantic relationships (n=3), Sensory (n=10), Social (n=13)

# In Conclusion:

## A Successful Pathway to Assessment for Anhedonia

**Open-Ended Questions:**

Create a dialogue. For instance, "Tell me about what you like to do for fun? What are you looking forward to?"

**Frequency and Duration:**

Follow up with specific questions about the frequency and duration of these symptoms. "How often do you feel this way?" and "How long has it been since you felt pleasure in [specific activities]?"

**Impact Assessment:**

Gauge how these symptoms affect the patient's daily life by asking, "How has your lack of interest or enjoyment affected your daily routine or responsibilities?"

**Behavioral Observations:**

Note any behavioral cues or body language that indicate lack of interest or enthusiasm during the conversation.

**Normalize the Discussion:**

Reassure the patient that their experiences are common and valid, which helps to reduce any stigma associated with their feelings.

**Additional Symptoms:**

Inquire about related symptoms that may accompany anhedonia, such as social withdrawal, fatigue, sleep disturbances, or changes in appetite.

# Evaluating Novel and Investigational Monotherapies for MDD

# Dextromethorphan-Bupropion (FDA-Approved)

# DXM-BUP:
## Exploring the Key Components



**Dextromethorphan**

**NMDA receptor antagonist**

**Sigma-1 receptor agonist**

**+**

**Bupropion**

**(Relatively) weak inhibitor of NE and DA reuptake**

**Increases and prolongs the plasma concentration of DXM**

1. **Increases glutamate release by decreasing presynaptic inhibition**
2. **Redirecting synaptic glutamate to AMPA**
3. **Removing inhibitory signal of extrasynaptic NMDA**

1. **Fine-tunes monoamine and glutamatergic signaling**
2. **Reduces neuroinflammation and promotes neuronal repair and regeneration**
3. **Helps degrade misfolded proteins and dampen glutamate excitotoxicity**

DXM-BUP = dextromethorphan/bupropion; NMDA = N-methyl-D-aspartate; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NE = norepinephrine; DA = dopamine.
Stahl SM. CNS Spectr. 2019;24(5):461-466.

# Pharmacokinetics of Dextromethorphan

**Absorption**
- Oral Administration:
  DXM peak serum levels in 2-3 hours after oral administration
- Bioavailability:
  Due to extensive first-pass metabolism, only 1%-2% reaches systemic circulation in extensive metabolizers. Poor metabolizers show higher DXM levels

**Clearance**
- Metabolism:
  Primarily by CYP2D6 to DXO; CYP3A4 also contributes minimally
- Excretion:
  Mostly excreted in urine as conjugated metabolites, 85% eliminated within 24 hours
- Half-life:
  DXM: 1.4-3.9 hours; DXO: 3.4-5.6 hours

DXM is rapidly metabolized in the liver by CYP2D6 to its active metabolite, dextrorphan.
**CYP2D6 Inhibitors** like fluoxetine, paroxetine, bupropion, and quinidine inhibit CYP2D6, slowing clearance and increasing the bioavailability of DXM.

Dextromethorphan Concentration-Time Profile

Plasma Concentration (ng/mL) vs Time (h)

- - ■ - - Dextromethorphan      — ● — Dextromethorphan + Bupropion

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

# Bupropion:
## A Strategic Choice



**Bupropion**

DAT

2D6

NET

nACh α4β4

A strong CYPD6 inhibitor, which increases the plasma levels of dextromethorphan

Bupropion is devoid of clinically significant serotonergic effects
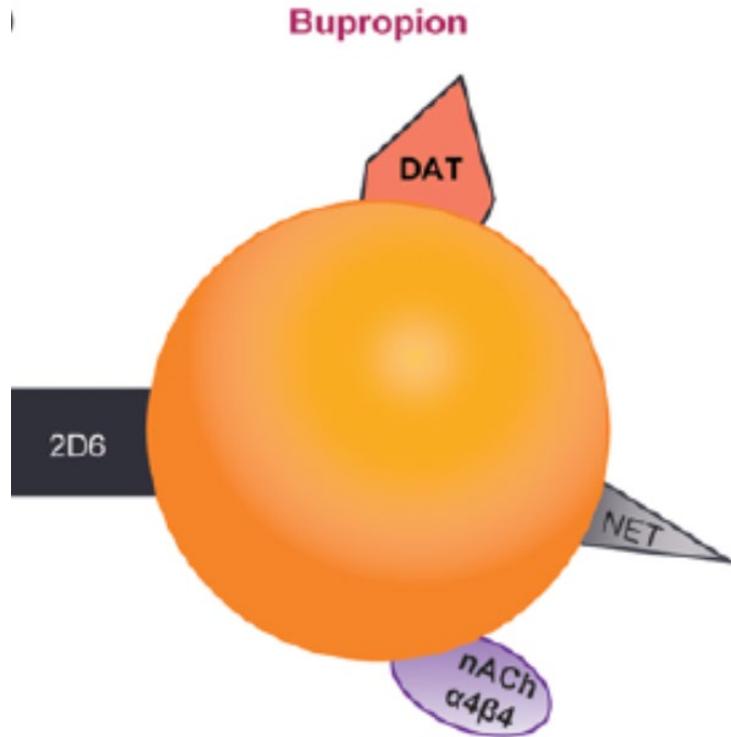
Other strong CYP2D6 inhibitors, like fluoxetine and paroxetine, can be associated with undesirable side effects such as weight gain and sexual side effects

# Determination of Optimal Dose Amounts

**Dextromethorphan Concentration Over Time**
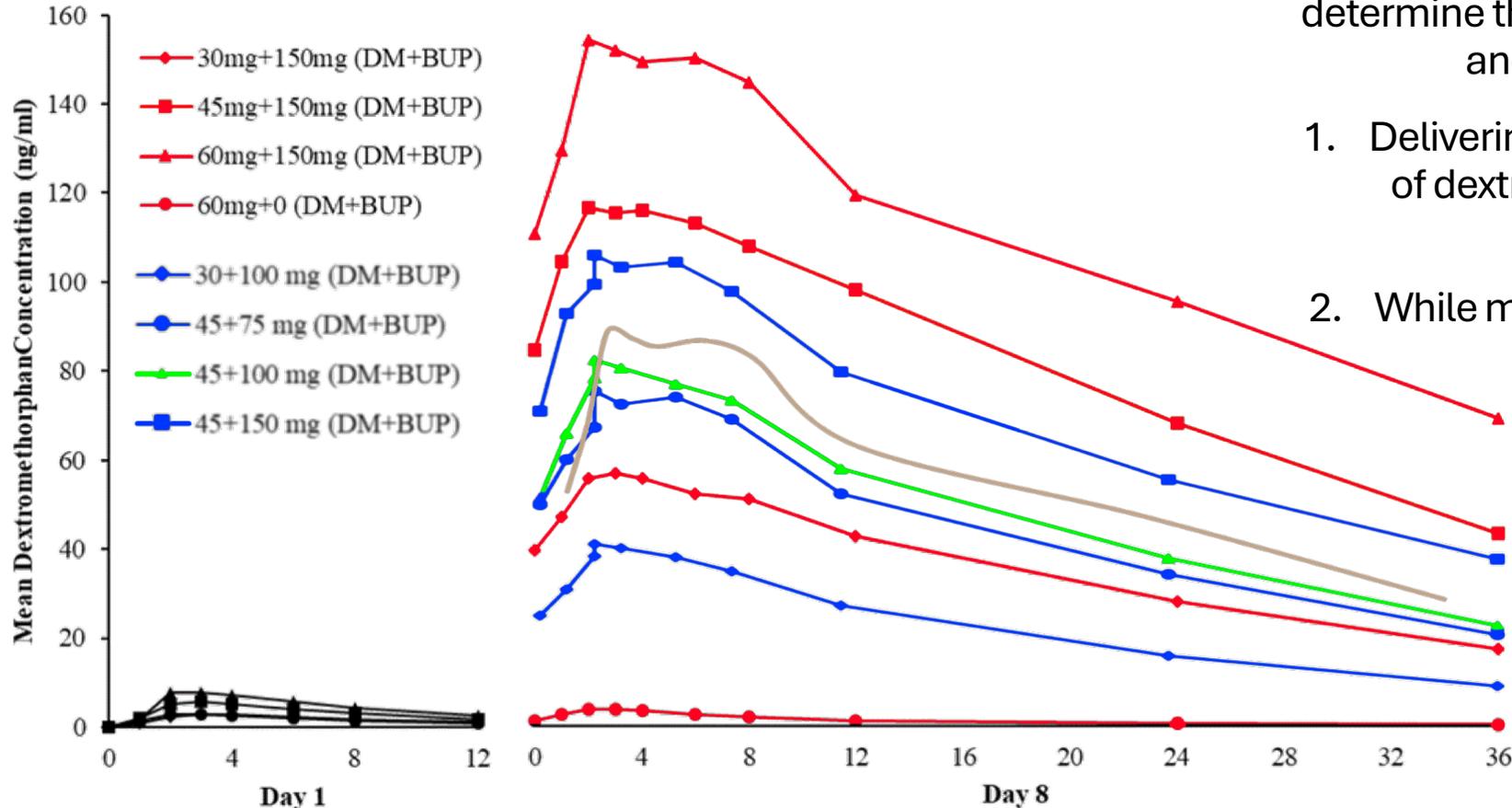


Multiple clinical trials and in silico pharmacokinetic simulations were conducted to determine the optimal doses of dextromethorphan and bupropion with the goals of:

1. Delivering the sustained plasma concentration of dextromethorphan believed necessary for antidepressant effects

2. While minimizing the potential adverse effects

**The precise combination of 45 mg dextromethorphan with 105 mg of bupropion SR twice daily was determined to be the optimal dose of each medication**

DM = 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.

# Leave Your DIY Projects at Home!

Generic bupropion SR can vary between as much as 80% less to 125% more than the reference medication—and pharmacies change generic manufacturers at any time.

The over-the-counter availability of dextromethorphan may lead patients to believe that it is safe to titrate the dose themselves as they see fit.

Patient self-titration outside FDA-approved doses may not give similar efficacy and could lead to:

> Dissociation, serotonin syndrome, and neurological side effects, including seizures (with self-titration of bupropion)

Dextromethorphan, when co-administered with Bupropion, displays nonlinear pharmacokinetics at steady state

Clinical studies comparing combination DXM-BUP to DXM and BUP given separately have not been conducted

The dosages of DXM and BUP in combination DXM-BUP are not commercially available

Attempts to approximate the individual components are not practical, with significant potential pill burden, risk of over- or under-dosage

Tabuteau H, et al. *Am J Psychiatry*. 2022;179(7):490-499. AUVELITY® (dextromethorphan hydrobromide and bupropion hydrochloride) Prescribing Information. Drugs@FDA: FDA-Approved Drugs. Accessed September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/215430s008lbl.pdf.

# DXM-BUP Safety and Tolerability

**AEs >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% |

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

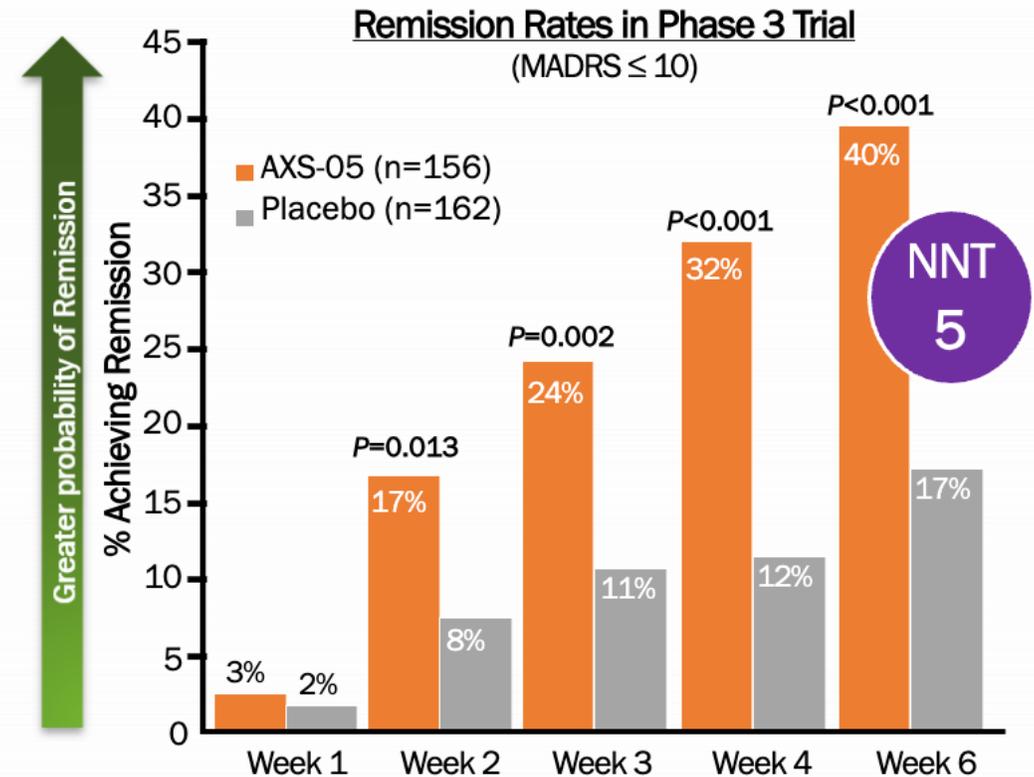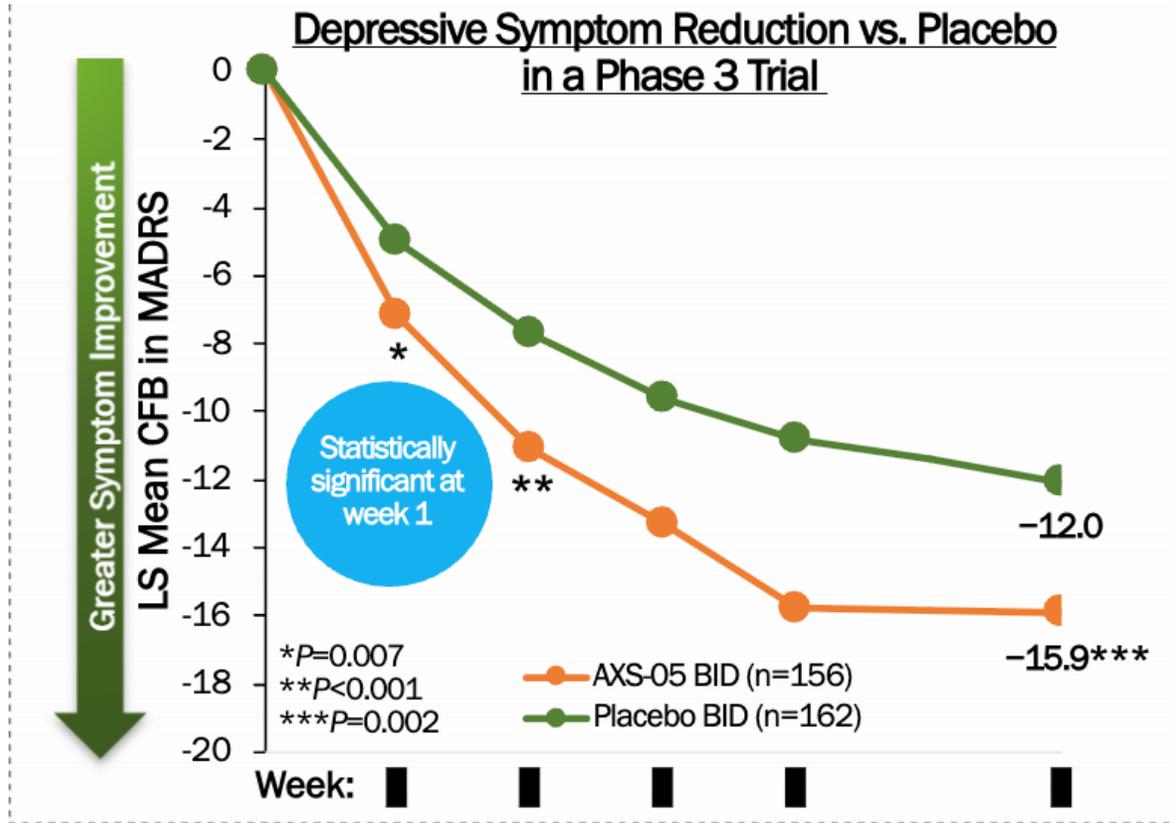**Weight Change**
-0.60 lbs AXS-05
+0.73 lbs Placebo

**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 |

AUVELITY® (dextromethorphan hydrobromide and bupropion hydrochloride) Prescribing Information. Drugs@FDA: FDA-Approved Drugs. Accessed September 2025. 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.
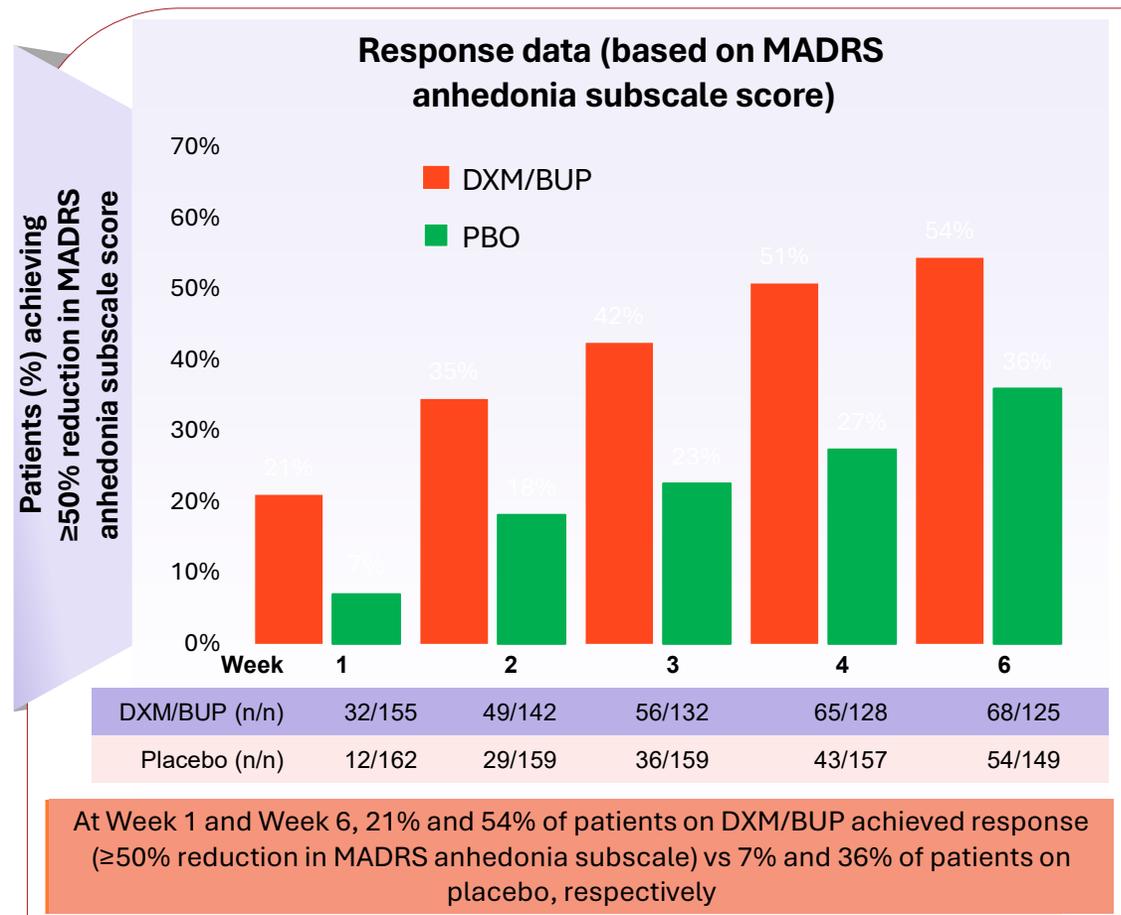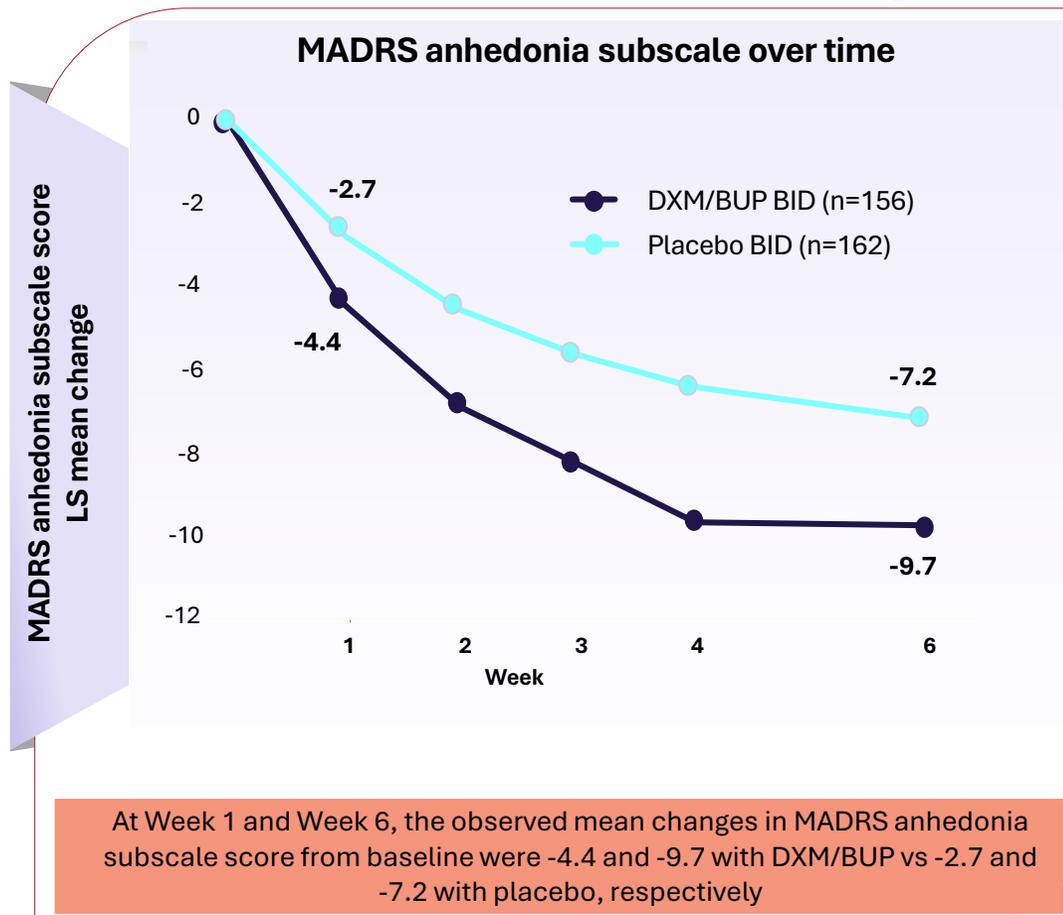
# DXM-BUP Efficacy



Depressive Symptom Reduction vs. Placebo in a Phase 3 Trial

Greater Symptom Improvement — LS Mean CFB in MADRS

Statistically significant at week 1

−12.0
−15.9***

*P=0.007
**P<0.001
***P=0.002

AXS-05 BID (n=156)
Placebo BID (n=162)

Week:

Remission Rates in Phase 3 Trial (MADRS ≤ 10)

Greater probability of Remission — % Achieving Remission

AXS-05 (n=156)
Placebo (n=162)

Week 1: 3% / 2%
Week 2: P=0.013, 17% / 8%
Week 3: P=0.002, 24% / 11%
Week 4: P<0.001, 32% / 12%
Week 6: P<0.001, 40% / 17%

NNT 5

LS = least squares; CFB = change from baseline.
Iosifescu DV, et al. *J Clin Psychiatry*. 2022;83(4):21m1434. Tabuteau H, et al. *Am J Psychiatry*. 2022;179(7):490-499.

# Post Hoc Analysis: Dextromethorphan/Bupropion (DXM/BUP) Demonstrated a Reduction in the MADRS Anhedonia Subscale Score and Increased Response Rates Over 6 Weeks



**MADRS anhedonia subscale over time**

- DXM/BUP BID (n=156)
- Placebo BID (n=162)

DXM/BUP: -4.4 (Week 1), -9.7 (Week 6)
Placebo: -2.7 (Week 1), -7.2 (Week 6)

At Week 1 and Week 6, the observed mean changes in MADRS anhedonia subscale score from baseline were -4.4 and -9.7 with DXM/BUP vs -2.7 and -7.2 with placebo, respectively



**Response data (based on MADRS anhedonia subscale score)**

- DXM/BUP
- PBO

DXM/BUP: 21% (Week 1), 35% (Week 2), 42% (Week 3), 51% (Week 4), 54% (Week 6)
PBO: 7% (Week 1), 18% (Week 2), 23% (Week 3), 27% (Week 4), 36% (Week 6)

| | Week 1 | Week 2 | Week 3 | Week 4 | Week 6 |
|---|---|---|---|---|---|
| DXM/BUP (n/n) | 32/155 | 49/142 | 56/132 | 65/128 | 68/125 |
| Placebo (n/n) | 12/162 | 29/159 | 36/159 | 43/157 | 54/149 |

At Week 1 and Week 6, 21% and 54% of patients on DXM/BUP achieved response (≥50% reduction in MADRS anhedonia subscale) vs 7% and 36% of patients on placebo, respectively

**Note:** statistical adjustments were not made for multiple comparisons, potentially inflating the type 1 error rate.

# Vortioxetine
# (FDA Approved)

# Vortioxetine Mechanism of Action

- **SSRIs** increase serotonergic signaling, down-regulating noradrenergic and dopaminergic signaling → **emotional blunting**

- **Vortioxetine** offers serotonin receptor activity modulation and SERT inhibition in one molecule, with preclinical research indicating activation of additional pathways:
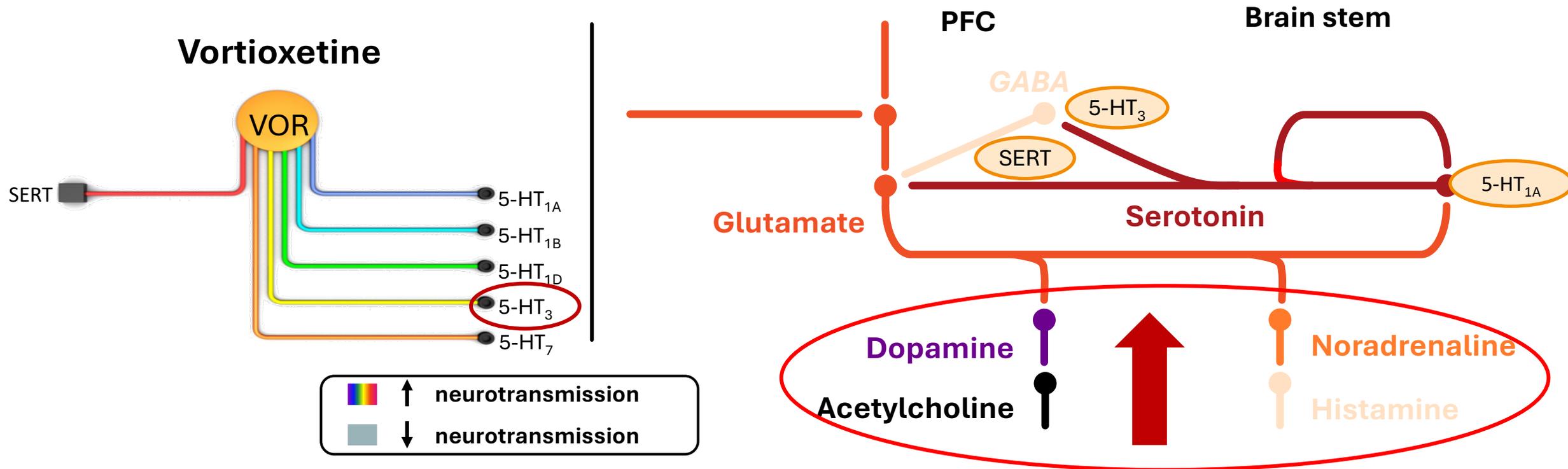


SERT = serotonin transporter; VOR = vortioxetine; PFC = prefrontal cortex.

Guilloux JP, et al. *Neuropharmacology*. 2013;73:147-159. Pehrson AL, et al. *Eur Neuropsychopharmacol*. 2013;23(2):133-145. Mørk A, et al. *Pharmacol Biochem Behav*. 2013;105:41-50. Pehrson AL, Sanchez C. *CNS Spectr*. 2014;19(2):121-133.

# Vortioxetine: "RELIEVES" Depression Burden in Real World Patients
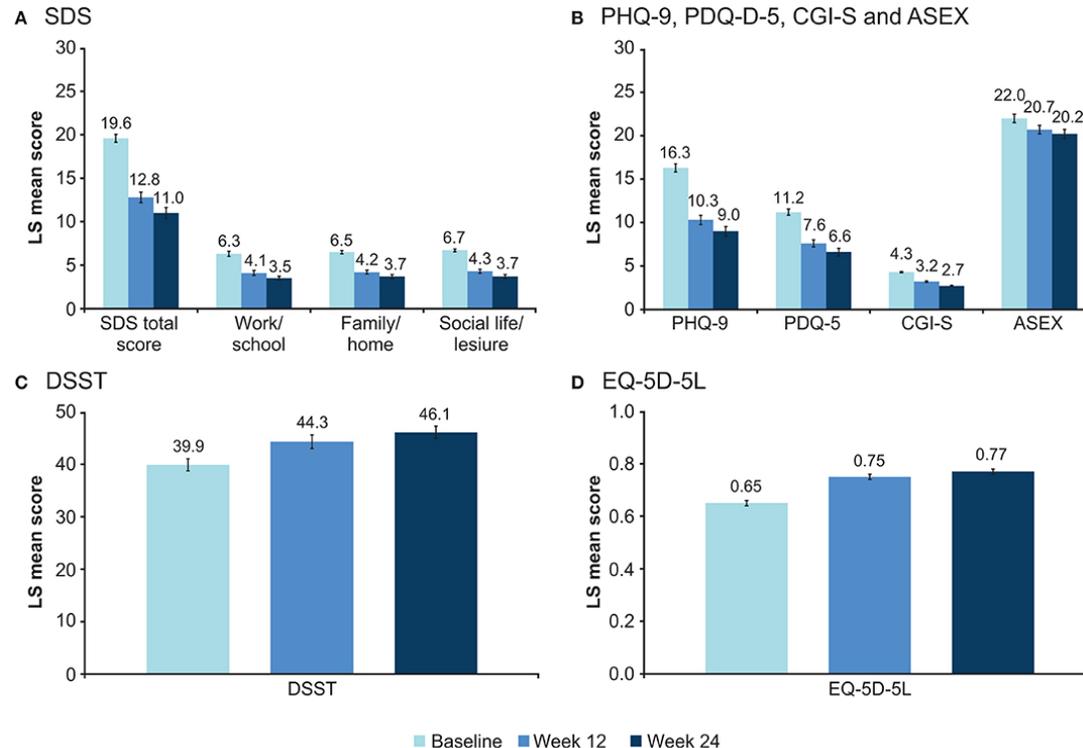


- The RELIEVE study was a 24-week multinational, observational, prospective cohort study of 737 outpatient adult patients with MDD who were initiated on Vortioxetine

- 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

- Results 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.

# Vortioxetine: Response + Remission



**Response Rates (Defined as ≥50% Decrease in MADRS) at Week 6/8 (FAS, LOCF)**
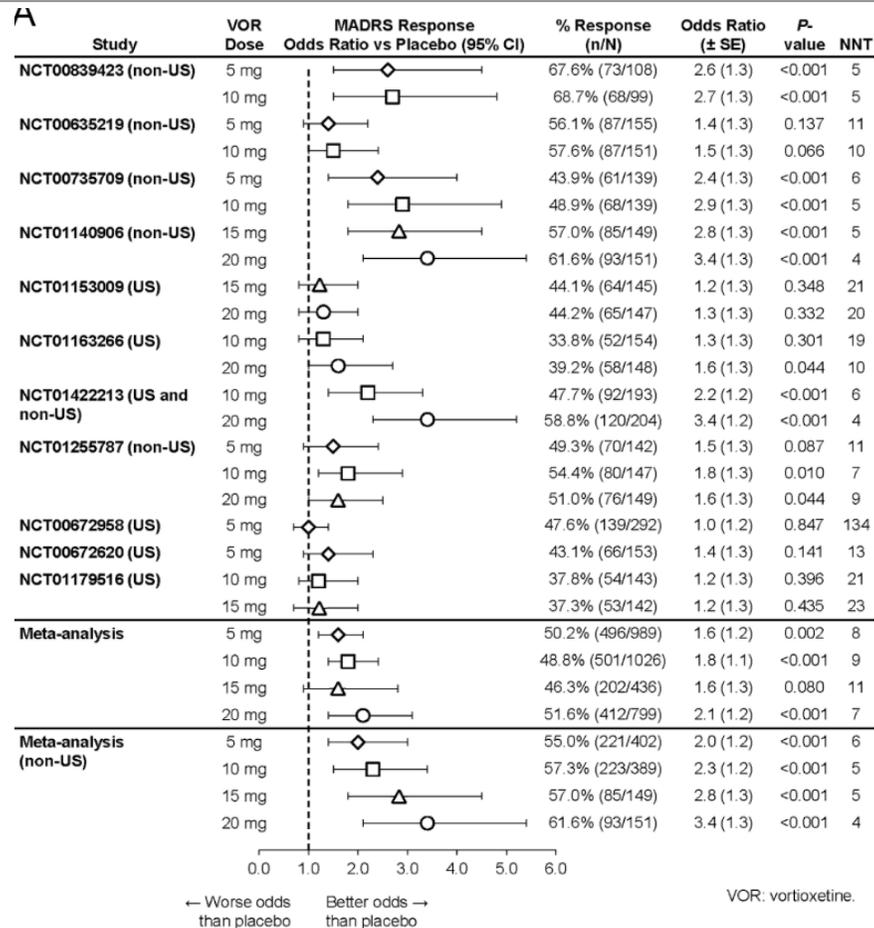
**Remission Rates (Defined as MADRS ≤10) at Week 6/8 (FAS, LOCF)**
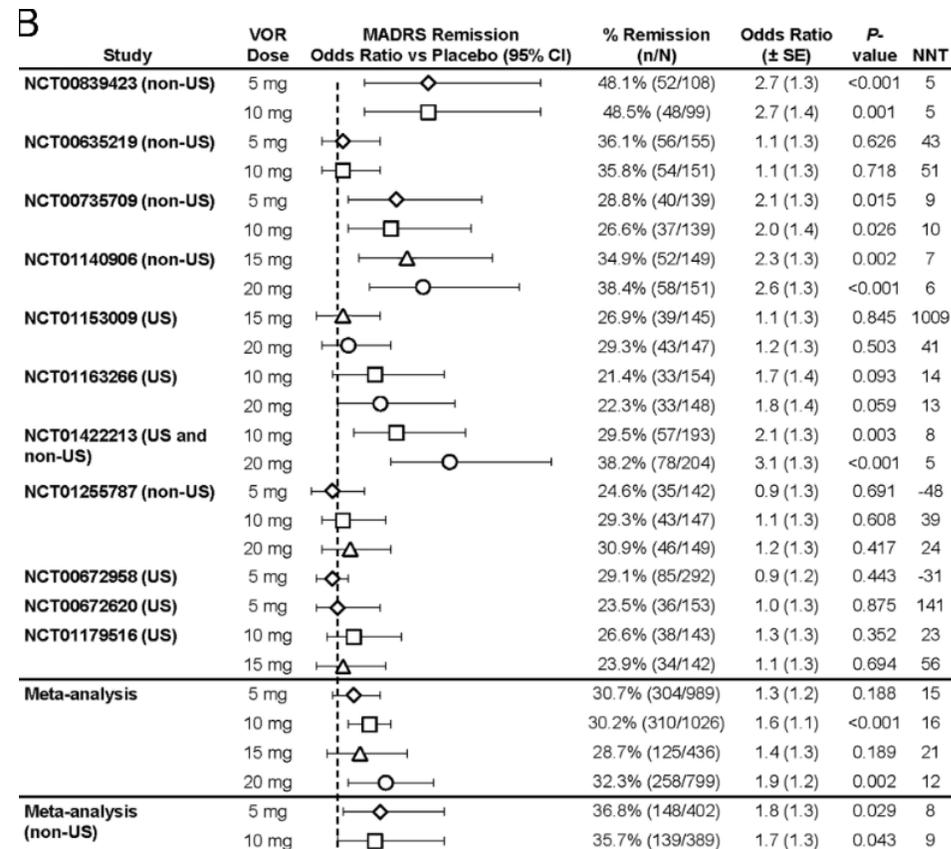
- Results from meta-analysis data from 11 randomized, double-blind, placebo-controlled trials of 6/8 weeks' treatment duration

- 3304 patients received vortioxetine

FAS = full analysis set; LOCF = last observation carried forward.
Thase ME, et al. *Eur Neuropsychopharmacol*. 2016;26(6):979-993.

# Vortioxetine: Safety and Tolerability

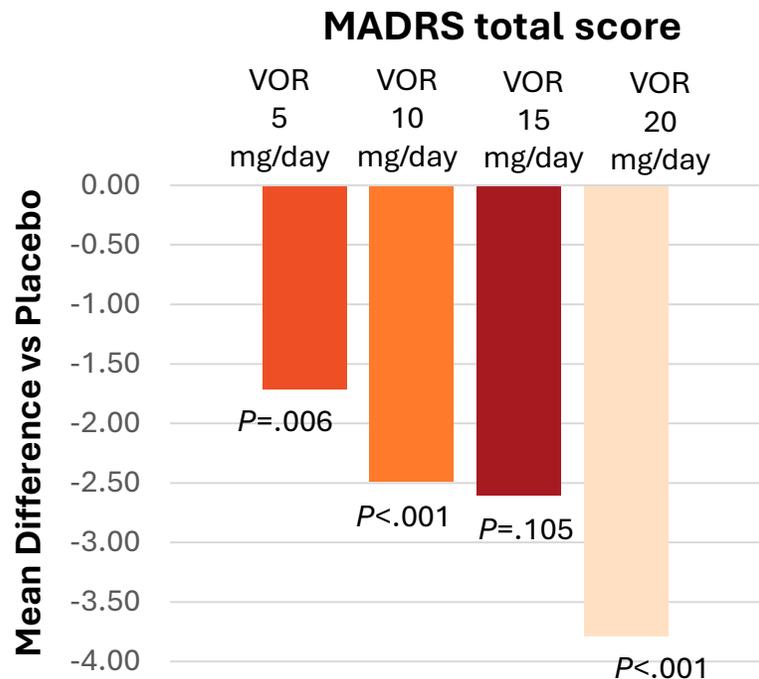| Adverse Reactions Occurring in >2% of Patients Treated with Any Vortioxetine Dose AND at least 2% Greater Than Incidence in Placebo-Treated Patients | | | | | |
|---|---|---|---|---|---|
| **Adverse Effect** | **VOR 5mg/d %** | **VOR 10mg/d %** | **VOR 15mg/d %** | **VOR 20mg/d %** | **Placebo %** |
| **Nausea** | 21 | 26 | 32 | 32 | 9 |
| **Diarrhea** | 7 | 7 | 10 | 7 | 6 |
| **Dry Mouth** | 7 | 7 | 6 | 8 | 6 |
| **Constipation** | 3 | 5 | 6 | 6 | 3 |
| **Vomiting** | 3 | 5 | 6 | 6 | 1 |
| **Flatulence** | 1 | 3 | 2 | 1 | 1 |
| **Dizziness** | 6 | 6 | 8 | 9 | 6 |
| **Abnormal dreams** | <1 | <1 | 2 | 3 | 1 |
| **Pruritus** | 1 | 2 | 3 | 3 | 1 |

| **Dose** | **Discontinuation Incidence** |
|---|---|
| 5mg/d | 5% |
| 10mg/d | 6% |
| 15mg/d | 8% |
| 20mg/d | 8% |
| Placebo | 4% |

*Nausea was the most common AE reported as a reason for discontinuation*

**Vortioxetine PI. Drugs@FDA: FDA-Approved Drugs. Accessed August 2025.**
**https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/204447s021s022lbl.pdf.**

# Vortioxetine Significantly Improved Depressive Symptoms, Anhedonia, and Functioning

## Pooled analysis of all 11 short-term, placebo-controlled studies



MADRS total score
MADRS anhedonia subscale score

- n=4988 patients with MDD and n=495 in the active-comparator study
- Improvements in functioning associated with vortioxetine were driven by the effect of treatment on MADRS anhedonia factors
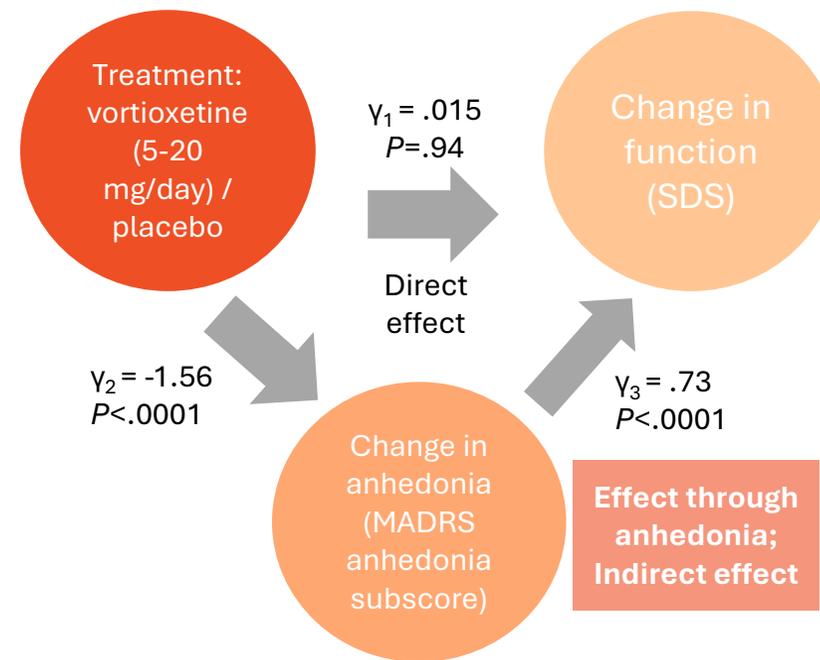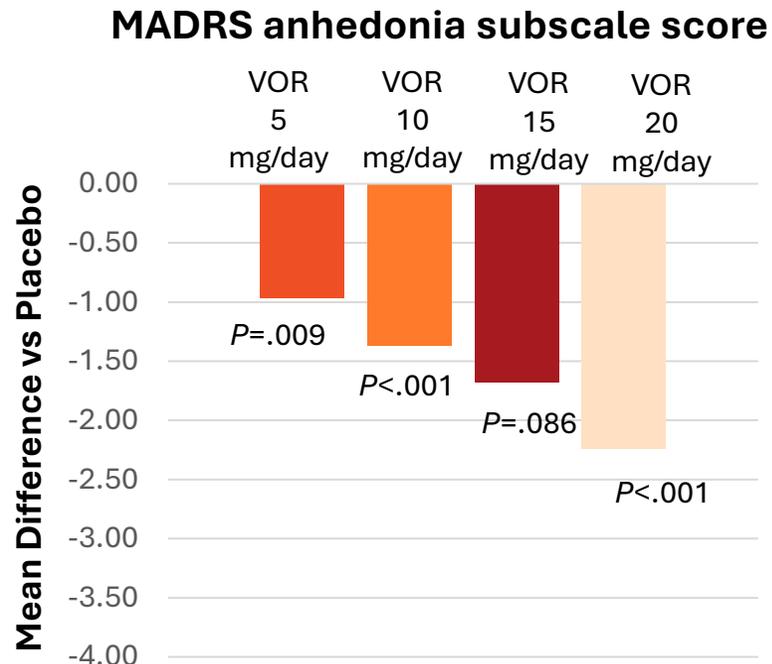
Vortioxetine-associated **improvements in functioning** appear to be **driven mostly by the effect** of vortioxetine **on anhedonia.**

**McIntyre RS, et al. *Neuropsychiatr Dis Treat*. 2021;17:575-585.**

# Vortioxetine Significantly Improved Anhedonia as Evidenced by Improvements in SHAPS Scores

## Change in SHAPS scores with treatment of vortioxetine



**Week 2**
ΔSHAPS
-1.0 (-1.7, -0.3), p=0.004

**Week 8**
ΔSHAPS
-2.9 (-3.7, -2.2), p<0.0001

*(y-axis: SHAPS score, 0 to 10)*

Baseline (n=95) — Week 2 (n=92) — Week 8 (n=79)
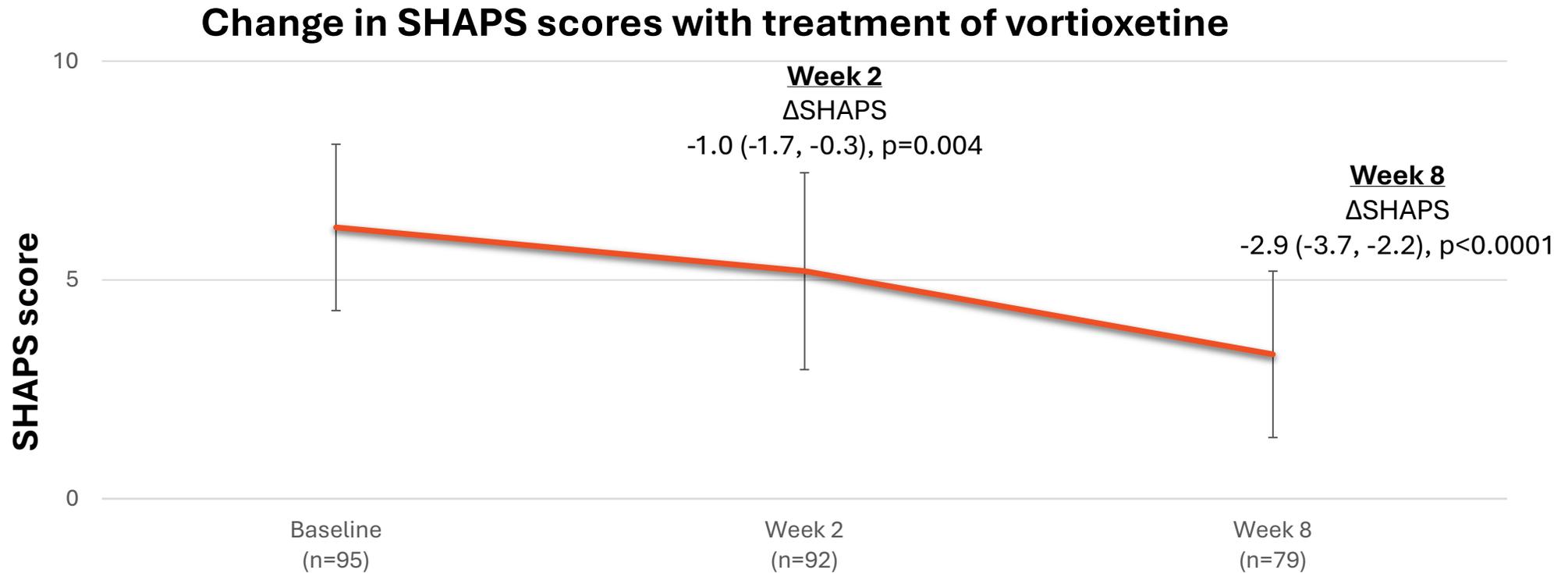
**Participants with MDD were dosed with vortioxetine (10-20 mg, flexibly dosed) daily for 8 weeks. All enrolled participants will receive vortioxetine 10 mg/day for the first 2 weeks. They also had the option of moving up to 20 mg.**

**SHAPS score is a pre-planned secondary outcome measure of the primary study as confirmed by study investigators.**

Cao B, et al. *Front Psychiatry*. 2019;10:17.

# Kappa Opioid Receptor Antagonists (Investigational)

# Primer on the Endogenous Opioid System
## *(Not All Opioids Are Bad!)*

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 **agonism?** | Reward benefit with **antagonism?** |
|---|---|---|---|
| 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

Selective KOR antagonism seems to strike a favorable balance of benefits and risks

KOR = kappa opioid receptor.
Lutz PE, Kieffer BL. *Trends Neurosci.* 2013;36(3):195-206.

# Dopamine-Opioid Interactions in the Reward Circuit

Stress

Substance withdrawal

Inflammation

Dynorphin release
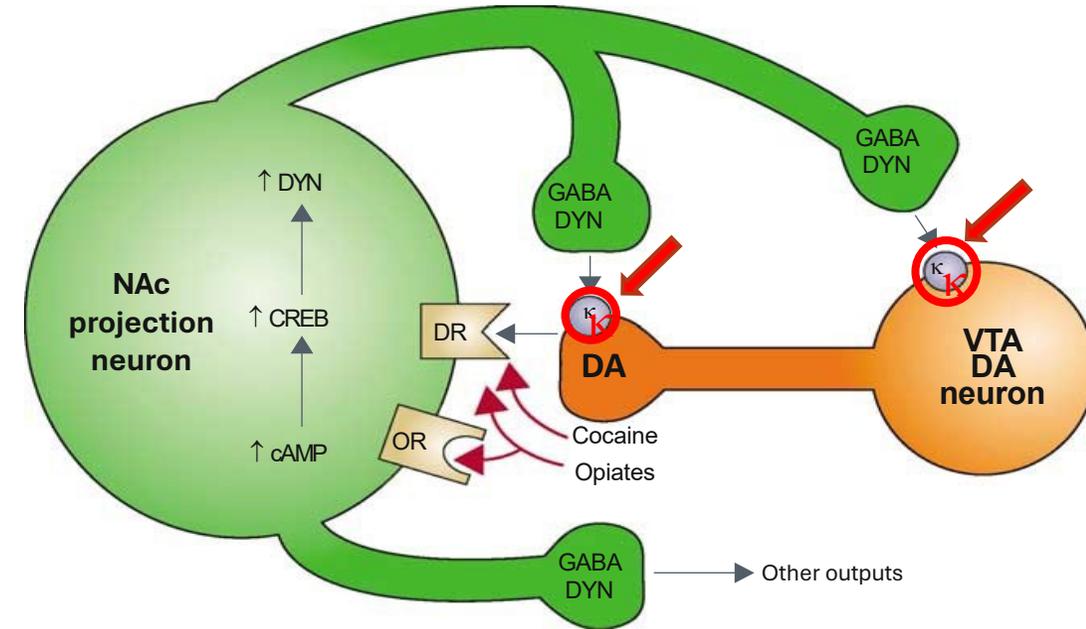
KOR activation

Anhedonia
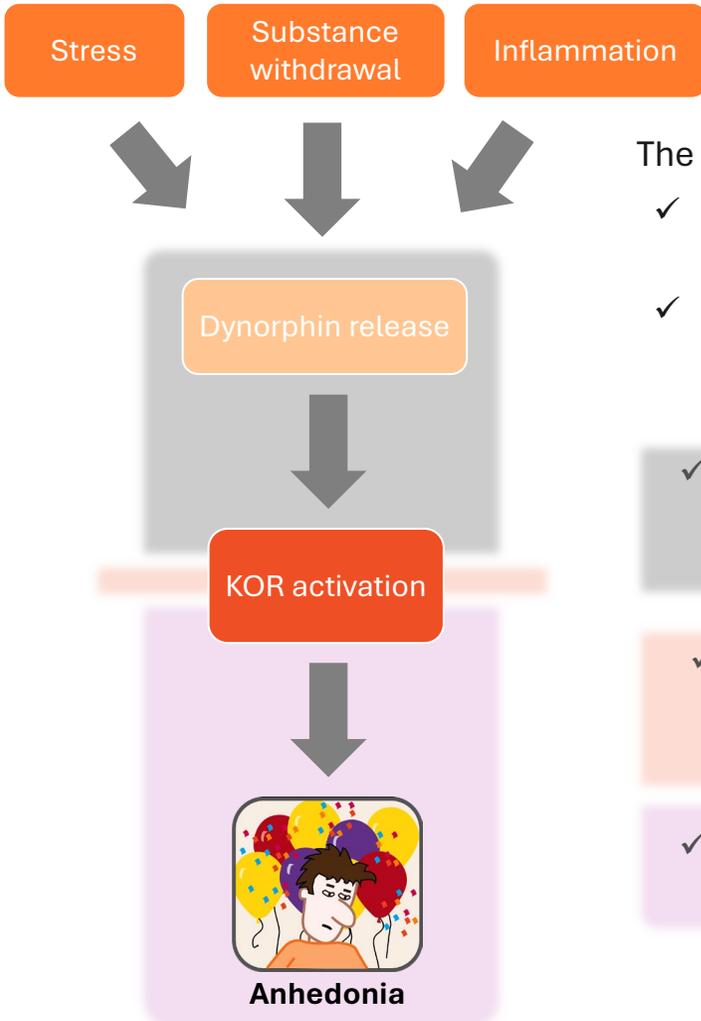
The endogenous opioid system comprises

- ✓ Ligands: endorphins, enkephalins, and **dynorphins**
- ✓ Receptors: mu (MOR), delta (DOR), and **kappa (KOR)**

- ✓ Dynorphin activates KORs on ventral tegmental area dopamine neurons, reducing dopamine release

- ✓ KOR are expressed in neural circuits associated with reward learning, depressive & anxiety disorders

- ✓ KOR agonists produce dysphoria and anhedonia (negative affect)

NAc projection neuron

↑ DYN

↑ CREB

↑ cAMP

GABA DYN

GABA DYN

DR

OR

DA

Cocaine

Opiates

VTA DA neuron

GABA DYN

Other outputs

Feedback between the NAc and VTA via CREB activation. Cocaine and amphetamine have been shown to activate prodynorphin gene expression in the nucleus accumbens (NAc) and dorsal striatum via D1 dopamine receptor stimulation.
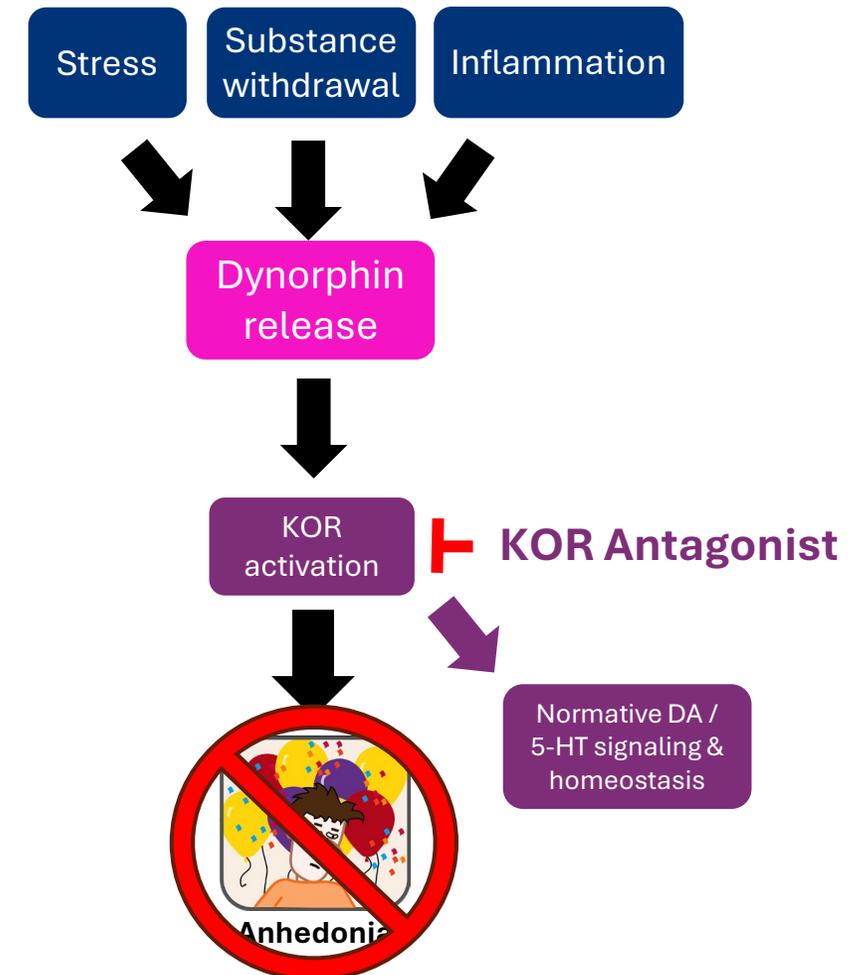
MOR = mu opioid receptor; DOR = delta opioid receptor; KOR = kappa opioid receptor; NAc = nucleus accumbens; VTA = ventral tegmental area; CREB = cAMP response element binding protein; DYN = dynorphine.

Knoll AT, Carlezon WA Jr. *Brain Res*. 2010;1314:56-73. Carlezon WA Jr, Thomas MJ. *Neuropharmacology*. 2009;56(Suppl 1):122-132. Carlezon WA Jr, et al. *Pharmacol Ther*. 2009;123(3):334-343. McClung CA, Nestler EJ. *Neuropsychopharmacology*. 2008;33(1):3-17.

# Kappa Opioid Receptor (KOR) Antagonism

- The endogenous opioid system plays an important role in the regulation of **mood, cognition, reward, and behavior**

- Kappa opioid receptors (KORs) are localized to brain regions involved in reward & aversion

  - Exposure to stress leads to elevated expression of the KOR ligand dynorphin, resulting in depressive & anxiety-related symptoms

  - Blocking this action via KOR antagonists has antidepressant- & anxiolytic-like effects
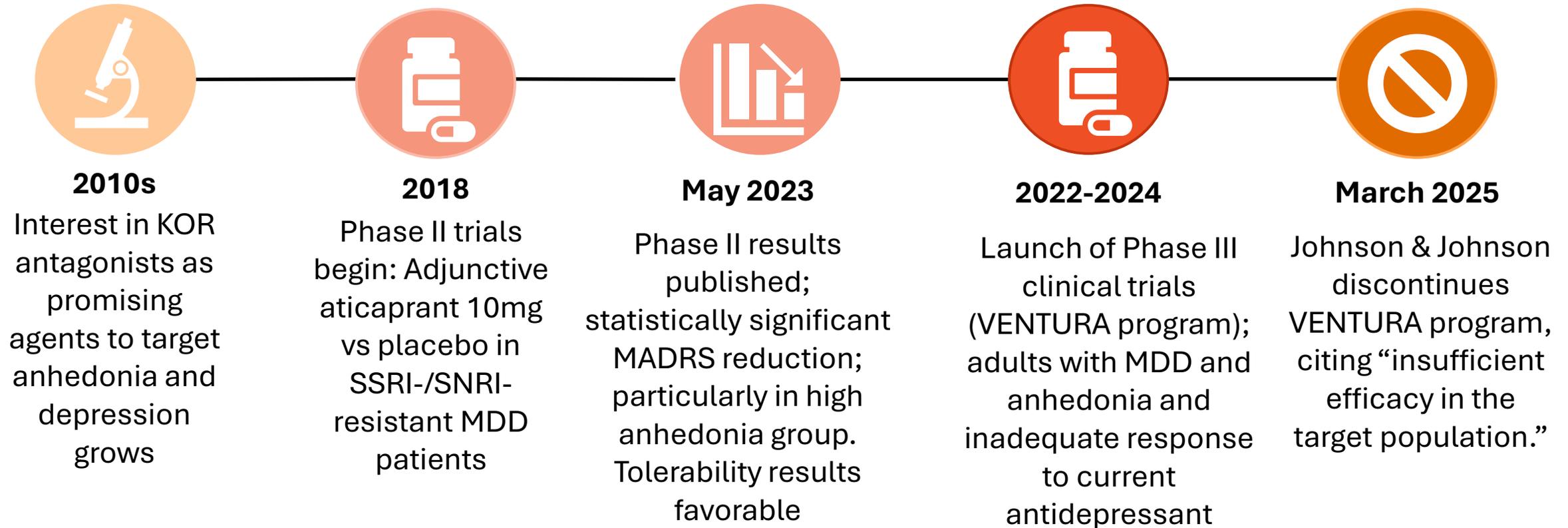
**KOR Antagonism in Major Depressive Disorder & Mood Disorders**

Stress → Substance withdrawal → Inflammation → Dynorphin release → KOR activation ⊢ **KOR Antagonist** → Normative DA / 5-HT signaling & homeostasis

Anhedonia

Ehrich E, et al. *Neuropsychopharmacology*. 2015;40:1448-1455. Cahill CM, et al. *Front Pharmacol*. 2014;5:253. Carlezon WA, Krystal AD. *Depress Anxiety*. 2016;33(10):895-906. Thomas CS, et al. *Neuropsychopharmacology*. 2022;47(3):728-740. Van't Veer A, Carlezon Jr WA. *Psychopharmacology (Berl)*. 2013;229(3):435-452. Muschamp JW, Carlezon Jr WA. *Cold Spring Harbor Perspect Med*. 2013;3:a012005. Knoll AT, Carlezon WA. *Brain Res*. 2010;1314:56-73. Limoges A, et al. *Front Syst Neurosci*. 2022;16:963691.
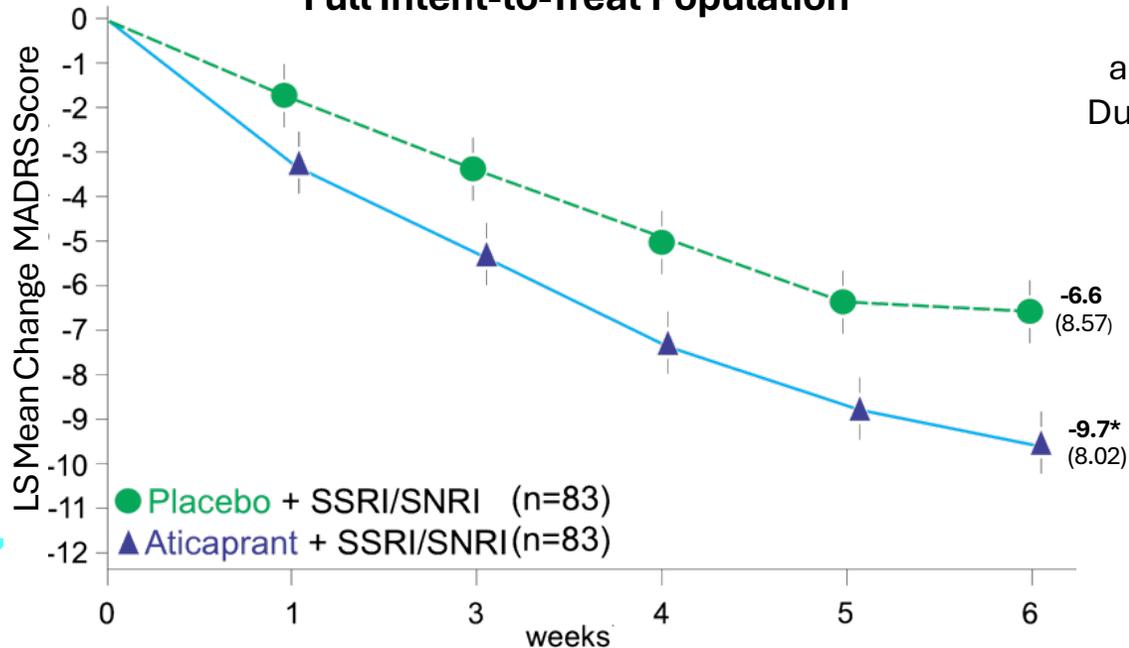
# Aticaprant:

## Clinical Program Timeline



**2010s**
Interest in KOR antagonists as promising agents to target anhedonia and depression grows

**2018**
Phase II trials begin: Adjunctive aticaprant 10mg vs placebo in SSRI-/SNRI-resistant MDD patients

**May 2023**
Phase II results published; statistically significant MADRS reduction; particularly in high anhedonia group. Tolerability results favorable

**2022-2024**
Launch of Phase III clinical trials (VENTURA program); adults with MDD and anhedonia and inadequate response to current antidepressant

**March 2025**
Johnson & Johnson discontinues VENTURA program, citing "insufficient efficacy in the target population."

Schmidt ME, et al. *Neuropsychopharmacology*. 2024;49(9):1437-1447. NIH. Updated May 25, 2025. Accessed August 2025. https://clinicaltrials.gov/study/NCT05550532.

# Aticaprant Phase II:
## Glimmers of Hope

**Depressive Symptom Reduction in Phase 2a Study Full Intent-to-Treat Population**

LS Mean Change MADRS Score

Reduced Depression

-6.6 (8.57)

-9.7* (8.02)

● Placebo + SSRI/SNRI   (n=83)
▲ Aticaprant + SSRI/SNRI (n=83)

weeks

**Key Finding:** Aticaprant added to ongoing current antidepressant achieved statistically significant greater reduction in overall depression severity compared to continuing the current antidepressant plus placebo. Durability of effect with greatest difference seen at week 6

47% Greater improvement vs placebo at wk 6

Tx Difference: -3.1 (1.05)
Effect size=0.36

| Adverse Events ≥ 5% in any arm | Aticaprant + SSRI/SNRI | Placebo + SSRI/SNRI |
|---|---|---|
| Headache | 10 (11.8%) | 6 (7.1%) |
| Diarrhea | 7 (8.2%) | 2 (2.4%) |
| Nasopharyngitis | 5 (5.9%) | 2 (2.4%) |
| Pruritis | 5 (5.9%) | 0 |
| D/C due to AE | 1 (1.2%) | 1 (1.2%) |
| No weight/metabolic changes or sexual AEs | | |

**Tx = treatment; D/C = discontinue.**
**Schmidt ME, et al.** *Neuropsychopharmacology*. **2024;49(9):1437-1447.**

# Aticaprant Phase II:
## Glimmers of Hope



MADRS Total Score: LS Mean Change Over Time by Baseline – Analysis of Each ANH Subset – Subjects with Baseline MADRS ≥25
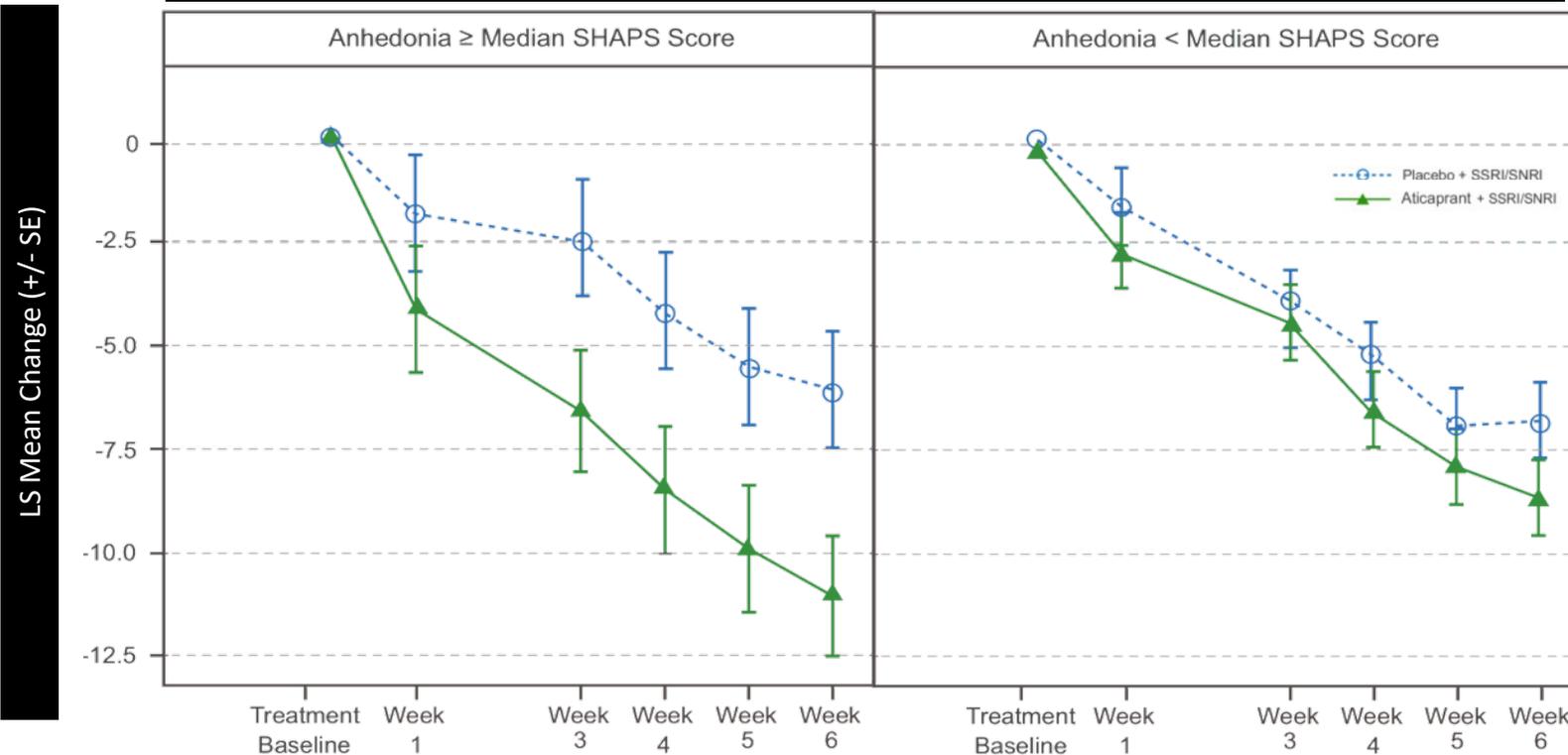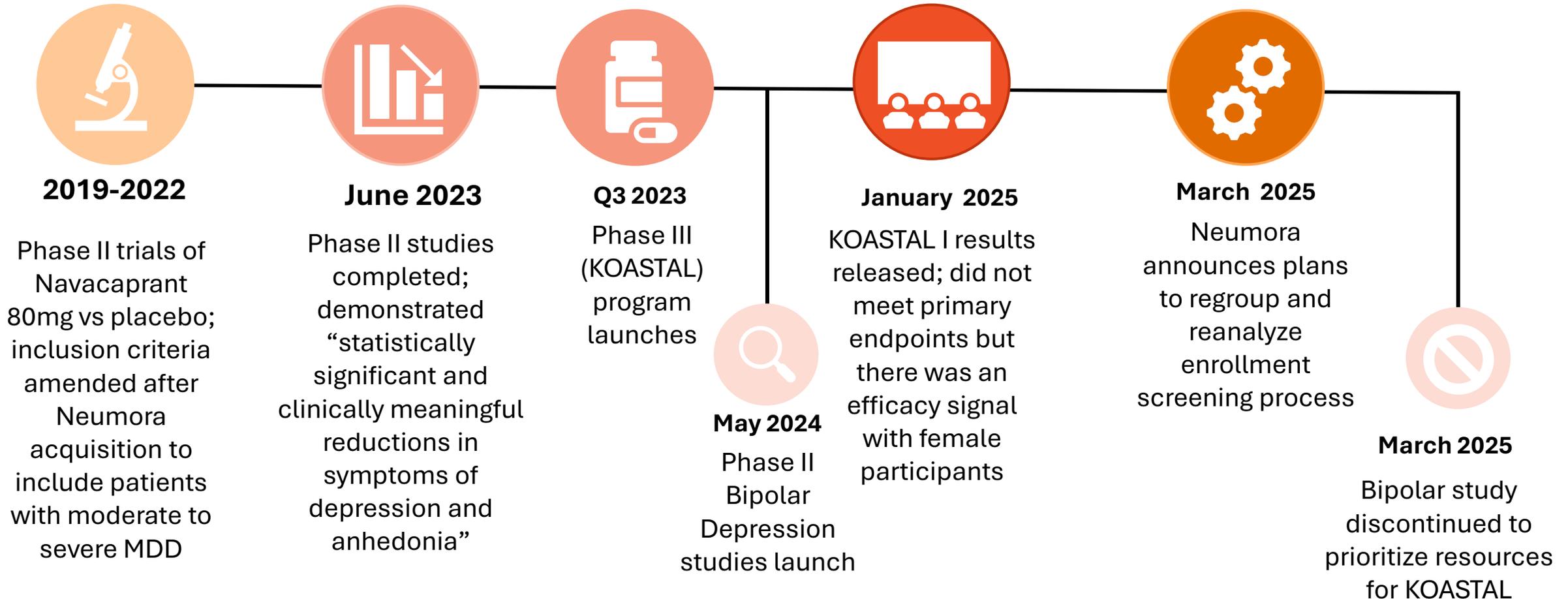
**Key Finding:**
Aticaprant had greater treatment effect in participants with higher levels of anhedonia

ANH = anhedonia; B/L = baseline.
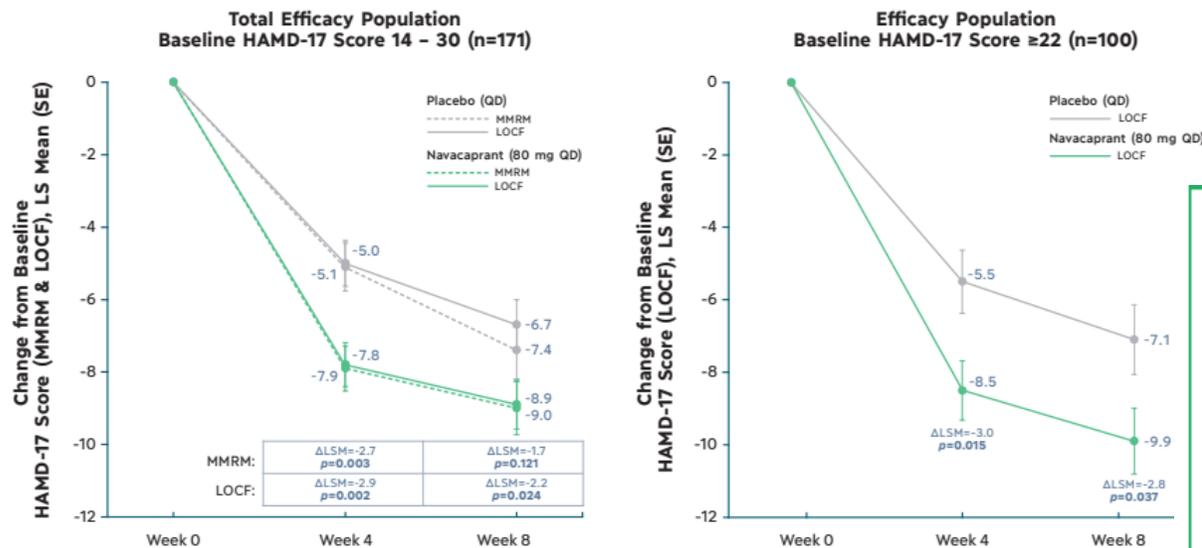Schmidt ME, et al. *Neuropsychopharmacology*. 2024;49(9):1437-1447.

# Navacaprant:

## Clinical Trial Timeline

**2019-2022**

Phase II trials of Navacaprant 80mg vs placebo; inclusion criteria amended after Neumora acquisition to include patients with moderate to severe MDD

**June 2023**

Phase II studies completed; demonstrated "statistically significant and clinically meaningful reductions in symptoms of depression and anhedonia"

**Q3 2023**

Phase III (KOASTAL) program launches

**May 2024**

Phase II Bipolar Depression studies launch

**January 2025**

KOASTAL I results released; did not meet primary endpoints but there was an efficacy signal with female participants

**March 2025**

Neumora announces plans to regroup and reanalyze enrollment screening process

**March 2025**

Bipolar study discontinued to prioritize resources for KOASTAL

# Navcaprant:

## Promising Signals from Phase 2
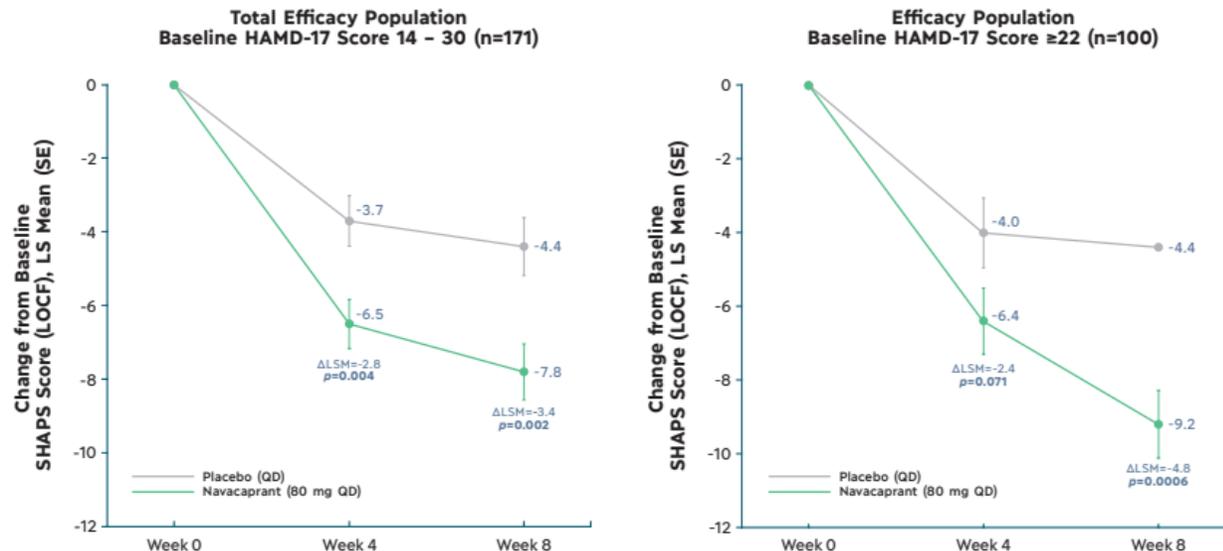
Initial inclusion criteria focused on mild-to-moderate patients (baseline HAMD-17 of 14-22)

Trial was amended to include moderate-to-severe patients (baseline HAMD-17 of 22-30)
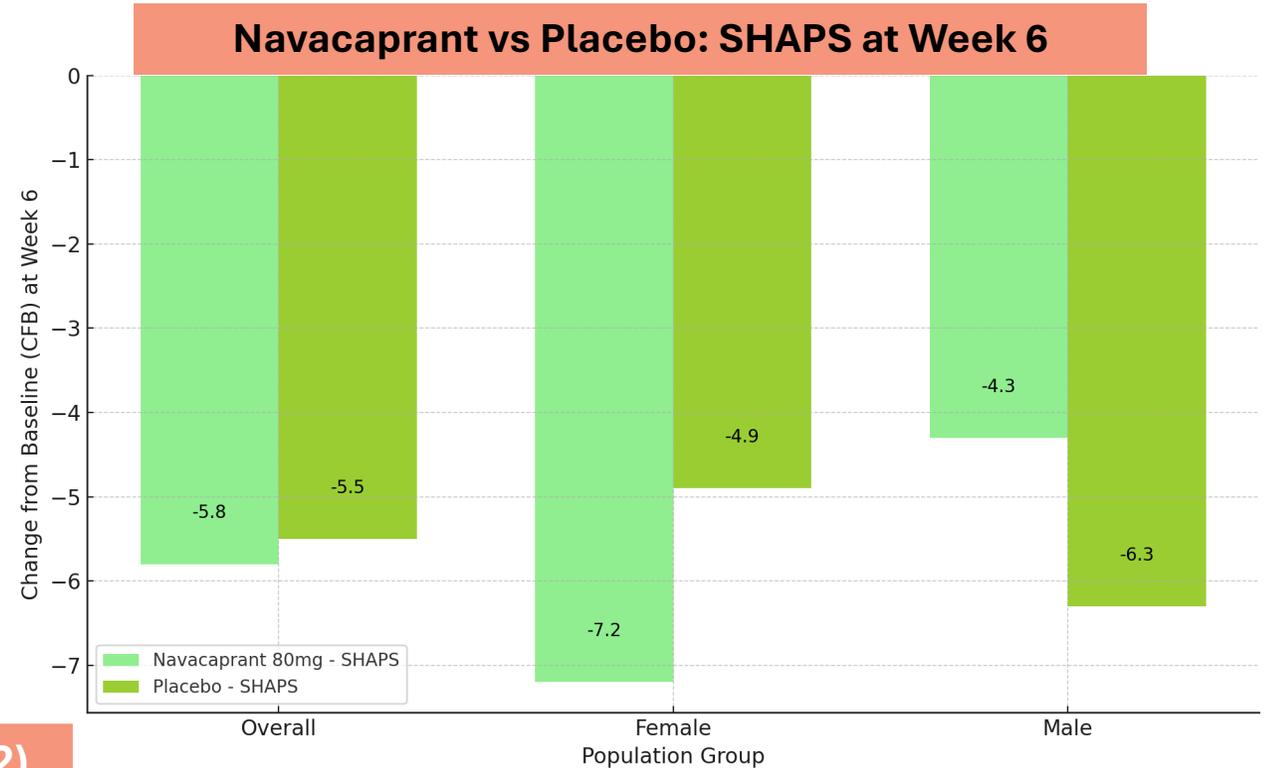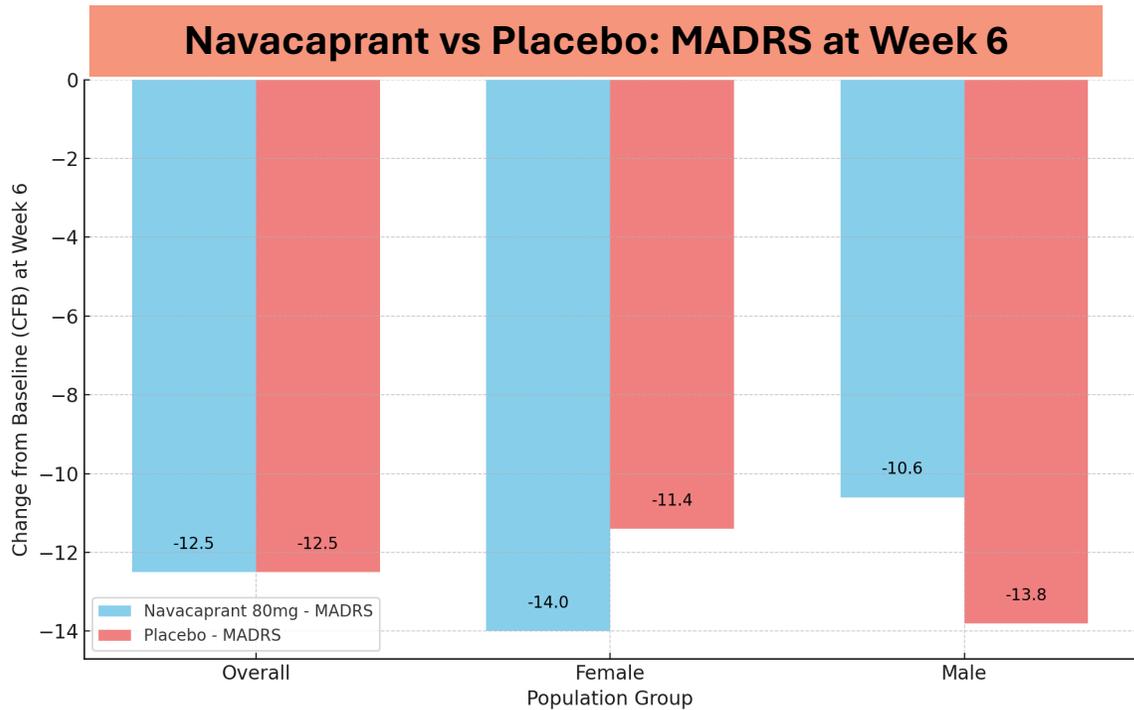
### Change from Baseline on HAMD-17



### Change from Baseline on SHAPS Score



- Incidence of TEAEs: 35.3% for navacaprant, 44.1% for placebo; no severe TEAEs for navacaprant
- Navacaprant not associated with weight gain or sexual dysfunction
- No evidence of suicidal behavior was identified as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS)

HAM-D = Hamilton Depression Rating Scale; TEAE = treatment-emergent adverse event; LSM = least squares mean.
Mathew SJ, et al. *J Clin Psychopharmacol*. 2025;45(3):267-276.

# Phase 3...Paused? But Not Forgotten



**Navacaprant vs Placebo: MADRS at Week 6**

Change from Baseline (CFB) at Week 6

- Navacaprant 80mg - MADRS
- Placebo - MADRS

| Population Group | Overall | Female | Male |
| --- | --- | --- | --- |
| Navacaprant 80mg | -12.5 | -14.0 | -10.6 |
| Placebo | -12.5 | -11.4 | -13.8 |

**Navacaprant vs Placebo: SHAPS at Week 6**

Change from Baseline (CFB) at Week 6

- Navacaprant 80mg - SHAPS
- Placebo - SHAPS

| Population Group | Overall | Female | Male |
| --- | --- | --- | --- |
| Navacaprant 80mg | -5.8 | -7.2 | -4.3 |
| Placebo | -5.5 | -4.9 | -6.3 |

| TEAES (<5%) | Navacaprant 80mg (n=191) | Placebo (n=192) |
| --- | --- | --- |
| Headache | 13 (6.8%) | 14 (7.3%) |
| Diarrhea | 10 (5.2%) | 4 (2.1%) |

# Key Learning Points

- **Dextromethorphan** is an **NMDA receptor antagonist and sigma-1 receptor agonist**. When co-administered with Bupropion, it displays nonlinear pharmacokinetics at steady state.

- **Vortioxetine** offers serotonin receptor activity modulation and **SERT inhibition in one molecule**, with preclinical research indicating activation of additional pathways.

- Kappa opioid receptor antagonist (such as **Navacaprant**) target **kappa opioid receptors (KORs)**, which are are localized to brain regions involved in reward & aversion.

**References**

# Panel Discussion

Four Important Topics

# How to Detect and Discuss Anhedonia with Patients with MDD

# Patient Advocate Experience With Conventional vs Novel MDD Monotherapies

# Faculty Recommendations Regarding Novel MDD Monotherapies

# Importance of Shared Decision-Making And Personalized Treatment Planning

# Practical Takeaways

- Anhedonia is a core symptom of MDD, characterized by a significant reduction in interest or pleasure in activities once found rewarding

- Traditional monoaminergic antidepressants often fail to effectively address anhedonia and may even reduce positive emotions

- Glutamate is an important consideration in the treatment of Anhedonia

- Selecting appropriate treatment for patients with prominent anhedonia symptoms is crucial in order to achieve optimum outcomes

Q&A