TRD in MDD

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Disclosures: Dr. Roger McIntyre

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Unmet Need in Psychiatry, Especially for Difficult to Treat Psychiatric Disorders

Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions

Roger S. McIntyre, Mohammad Alsuwaidan Bernhard T. Baune, Michael Berk, Koen Demyttenaere, Joseph F. Goldberg, Philip Gorwood, Roger Ho Siegfried Kasper Sidney Kennedy, Josefina Ly-Uson, Rodrigo B. Mansur, Hamish McAllister-Williams James W. Murrough, Charles Nemeroff, Andrew Nierenberg Joshua D. Rosenblat, Gerard Sanacora, Alan Schatzberg, Richard Shelton, Steve Stahl Madhukar Trivedi, Eduard Vieta, Maj Vinberg Nolan Williams Allan Young Mario Maj

McIntyre RS, et al. World Psychiatry 2023;22:1–19

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Factors Influencing Response to Antidepressants

Many factors have been identified as being associated with reduced antidepressant response, but relatively few are established as risk factors specifically for TRD

Risk factors may include:

Sociodemographic factors[1]

- Older age
- Female sex
- Lower socioeconomic position

Adverse experiences and trauma[1]

- Childhood maltreatment
- Childhood emotional abuse
- Life stress events

Psychosocial factors[2]

- High disease burden
- Low HRQoL
- Reduced function and productivity

Clinical factors[1,3]

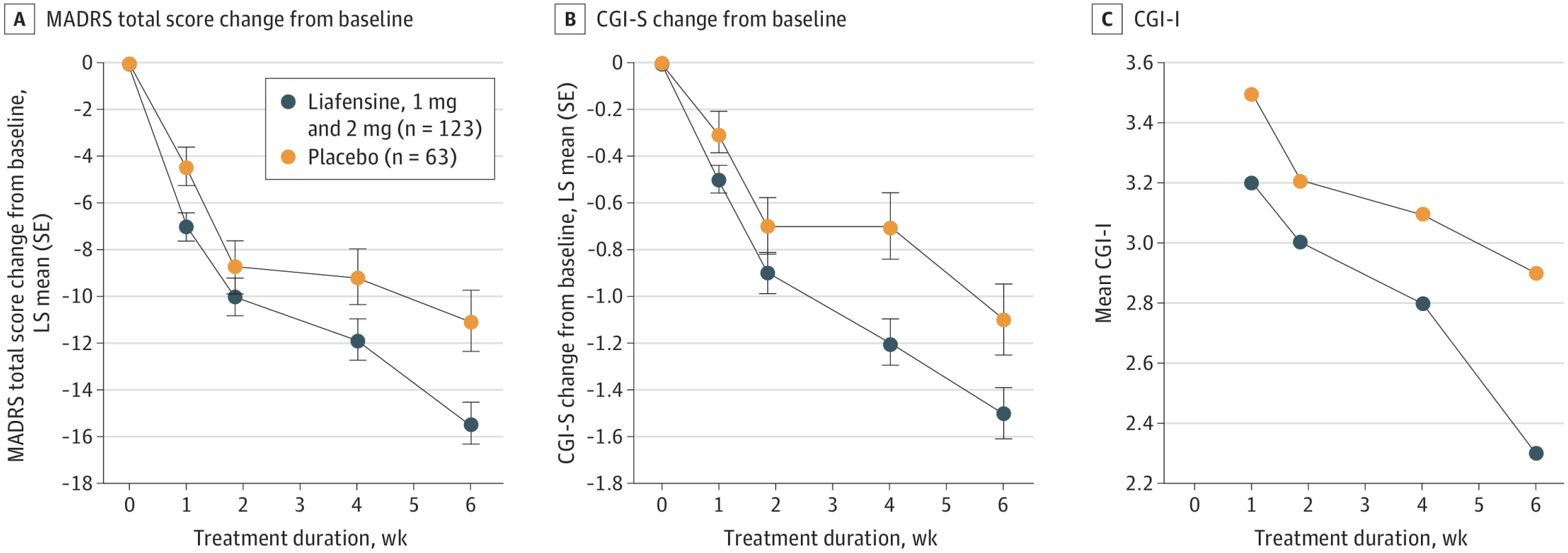
- Greater baseline severity
- Longer illness duration
- Psychotic symptoms, mixed features
- Anhedonia
- Cognitive deficits
- Anxiety
- Psychiatric comorbidities
- Physical comorbidities *(incl. cardiovascular disease, obesity, type 2 diabetes mellitus, osteoporosis and metabolic syndrome)*

TRD, treatment-resistant depression.

1. McIntyre RS, et al. World Psychiatry 2023;22:394–412;
2. Heerlein K, et al. J Affect Disord 2021;283:115–22;
3. Nigatu YT, et al. BMC Public Health 2015;15:1–8.

ANK3 as a Novel Genetic Biomarker for Liafensine in Treatment-Resistant Depression: The ENLIGHTEN Randomized Clinical Trial

Efficacy Results



Wang G., JAMA Psychiatry. 2025 Sep 10:e252416.

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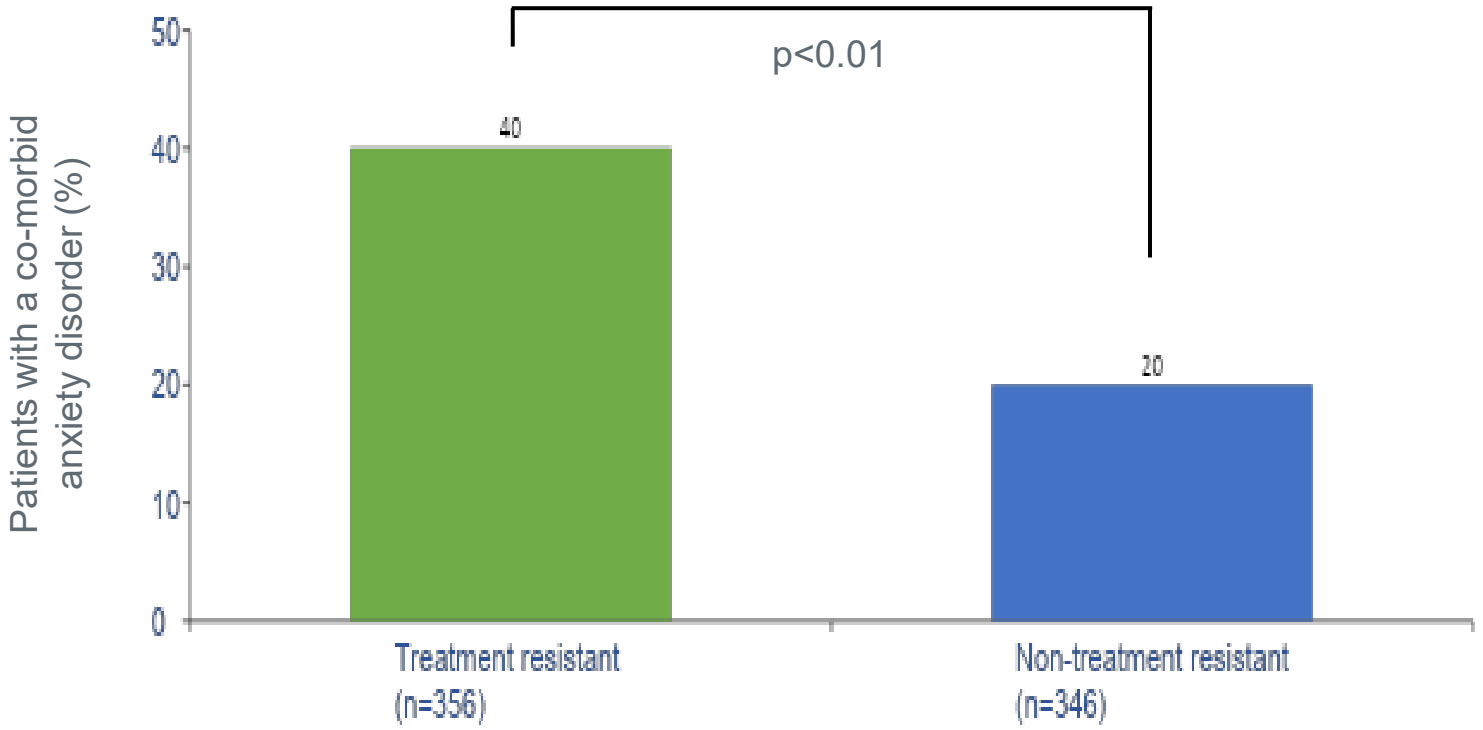
Co-morbid MDD and Anxiety is Associated with Increased Treatment Resistance

- Presence of a co-morbid anxiety disorder is associated with a **2.6-fold** increased risk of resistance[a] to antidepressants[b,1]



An increased number or severity of anxiety symptoms for patients with MDD can **increase the likelihood of non-response** to antidepressant treatment[2]

[a]Treatment resistance was defined as a lack of response following 2 courses of antidepressants; [b]antidepressants included fluoxetine, citalopram, sertraline, fluvoxamine, paroxetine, clomipramine, desipramine, nortriptyline, amitriptyline, imipramine, venlafaxine, reboxetine, moclobemide, phenelzine, mirtazapine, minanserin, milnacipran, trazodone and St John's wort
MDD, major depressive disorder

1. Souery D et al. J Clin Psychiatry 2007;68:1062-70; 2. Papakostas GI et al. Psychiatry Res 2008;161:116-20

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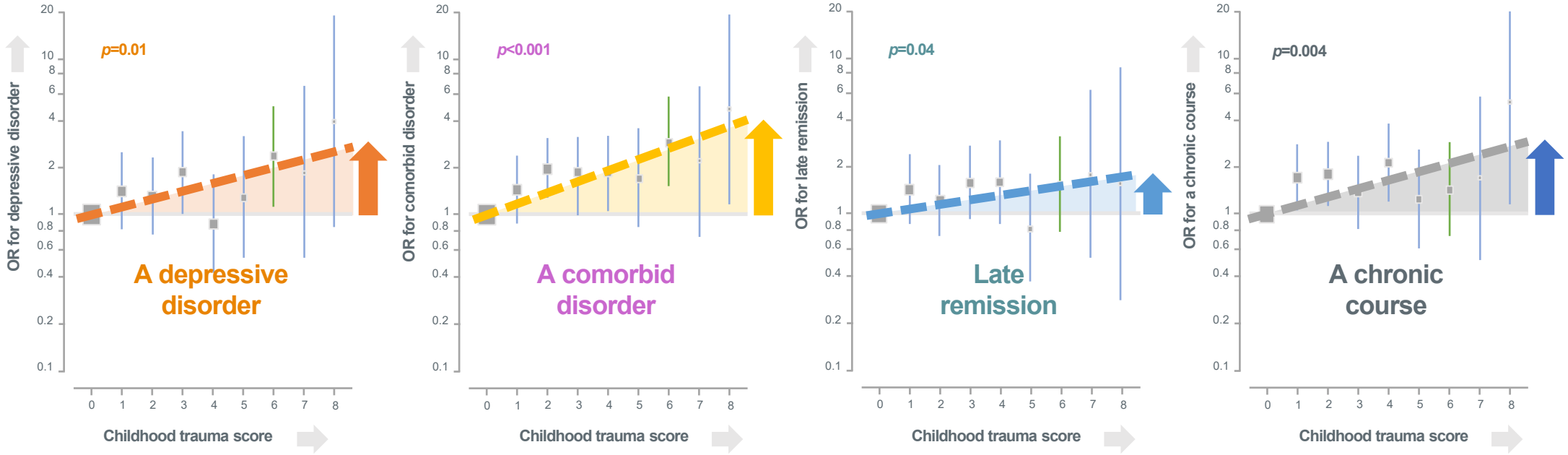
Childhood Trauma is Associated with An Increased Persistence of Comorbidity and Chronicity in Adults with Depressive Disorders and/or Anxiety

Odds ratios for the **2-year diagnosis** and course trajectory outcomes in patients with baseline diagnoses of depressive or anxiety disorders (N=1,209) according to childhood trauma level*

An increased score on the childhood trauma index corresponded with an increased chance of having:

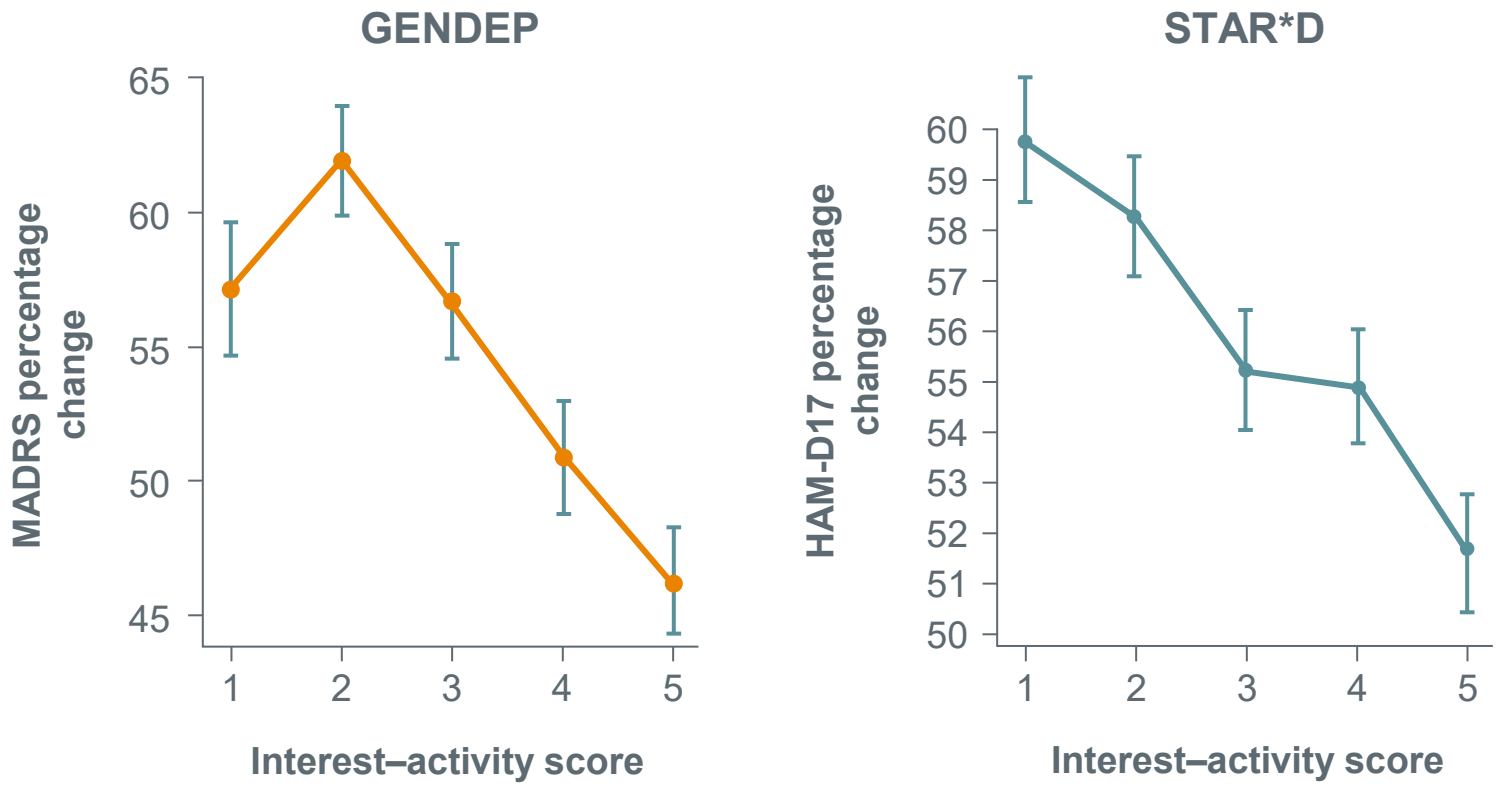


*Versus no childhood trauma as the reference category. Values adjusted for gender, age and education. The size of each square is proportional to the number of participants; vertical lines indicate 95% confidence intervals. *p*-values by multinomial logistic regression analysis. OR = odds ratio.

Hovens JGFM, et al. Acta Psychiatr Scand. 2012;126(3):198–207.

Anhedonia Strongly Predicts Poor Antidepressant Outcomes in Patients with MDD

Association between interest–activity score and percentage improvement over 12 weeks



Low interest–activity, reflecting reduced enjoyment in addition to interest and activity, strongly predicted poor antidepressant outcome, as assessed by MADRS and HAM-D17

GENDEP = Genome-based Therapeutic Drugs for Depression; HAM-D17 = 17-item Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = major depressive disorder; STAR*D = Sequenced Treatment Alternatives to Relieve Depression.

Uher R, et al. Psychol Med. 2012;42:967–980.

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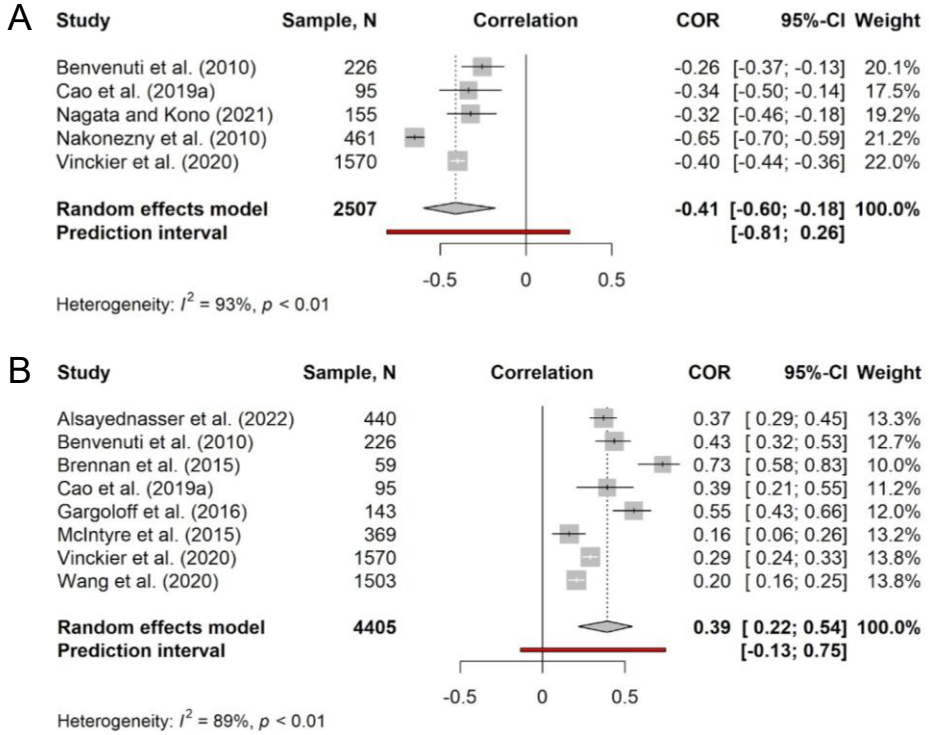
Anhedonia is Associated with Negative Patient-Reported Outcomes in Persons with MDD

Anhedonia had a **significant and negative correlation** with HRQoL (*r* = -0.41; 95% CI = [-0.60, -0.18]).

Anhedonia had a **significant and positive correlation** with functional deficits (r = 0.39; 95% CI = [0.39, 0.54].



Effect size between anhedonia and patient-reported outcomes. A. Correlation with HRQoL. B. Correlation with functional outcomes

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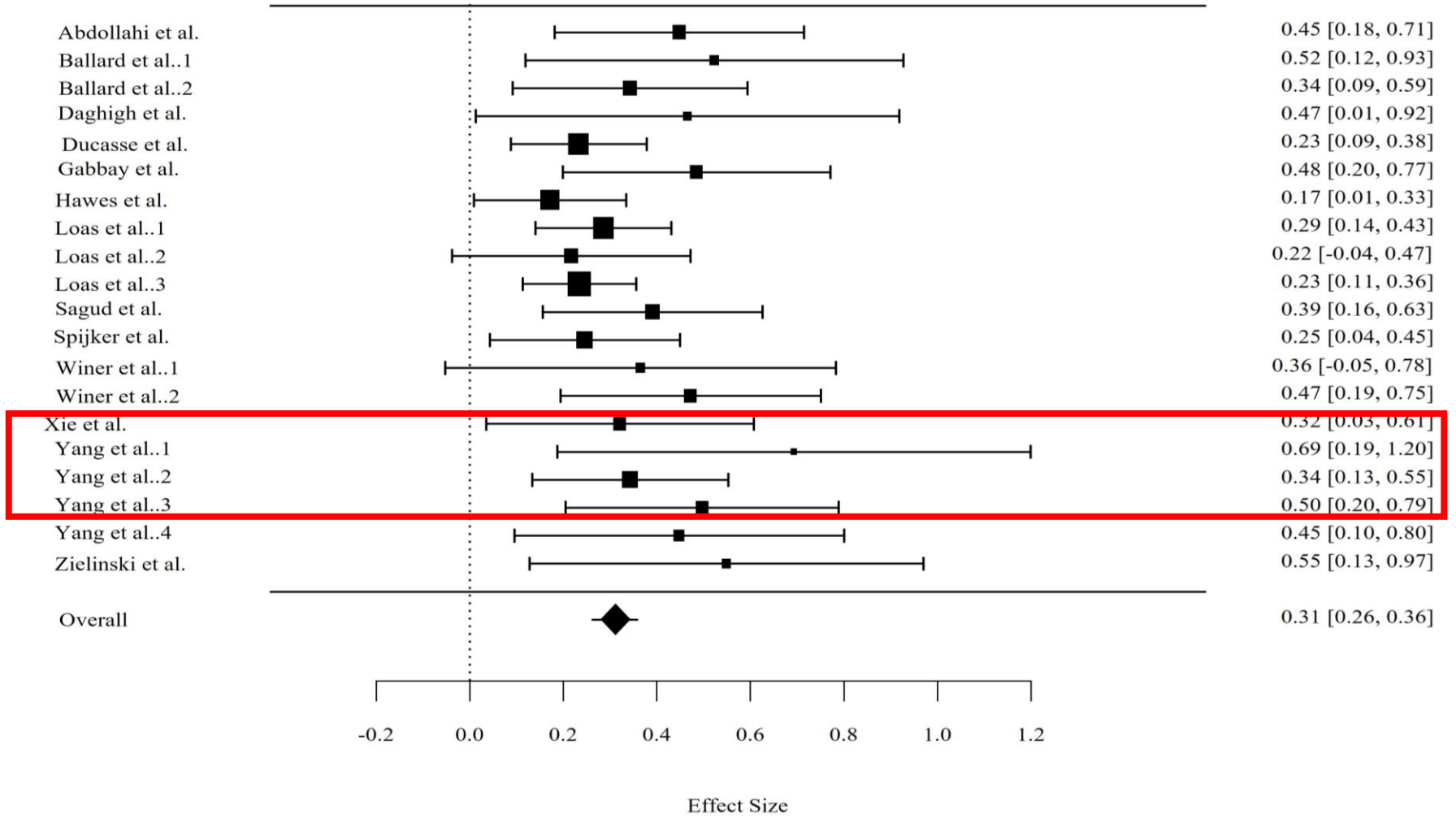
Wong S et al. J Affect Disord 2024

Evaluating Anhedonia as a Risk Factor in Suicidality: A Meta-Analysis



Anticipatory anhedonia (r = 0.40, 95% CI: 0.26 – 0.54, p < 0.001)

- Gillissie ES, et al. J Psychiatr Res. 2023.

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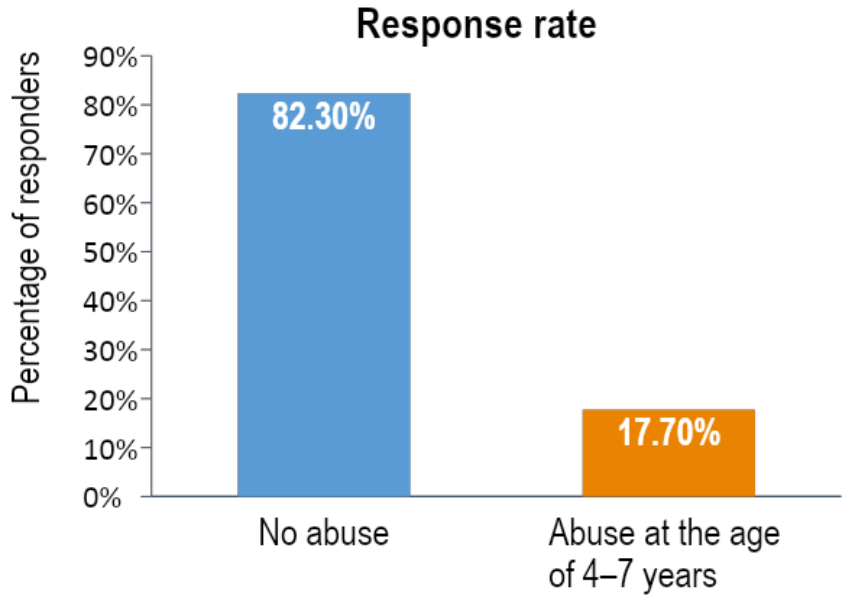
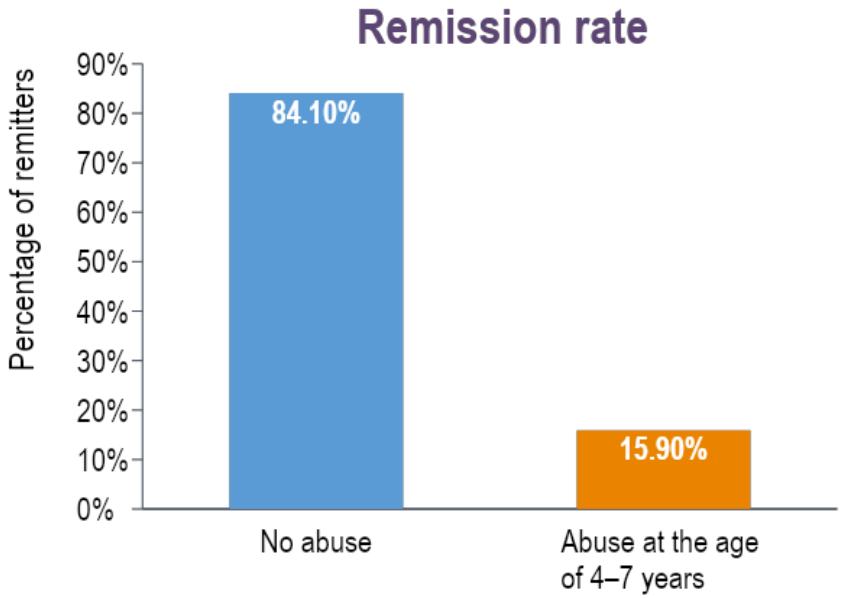
Childhood Trauma Can Lead to Poor Treatment Outcomes in Patients With MDD

Response and remission rates in MDD patients receiving SSRI/SNRIs with or without childhood trauma as measured by HAM-D (N=722)





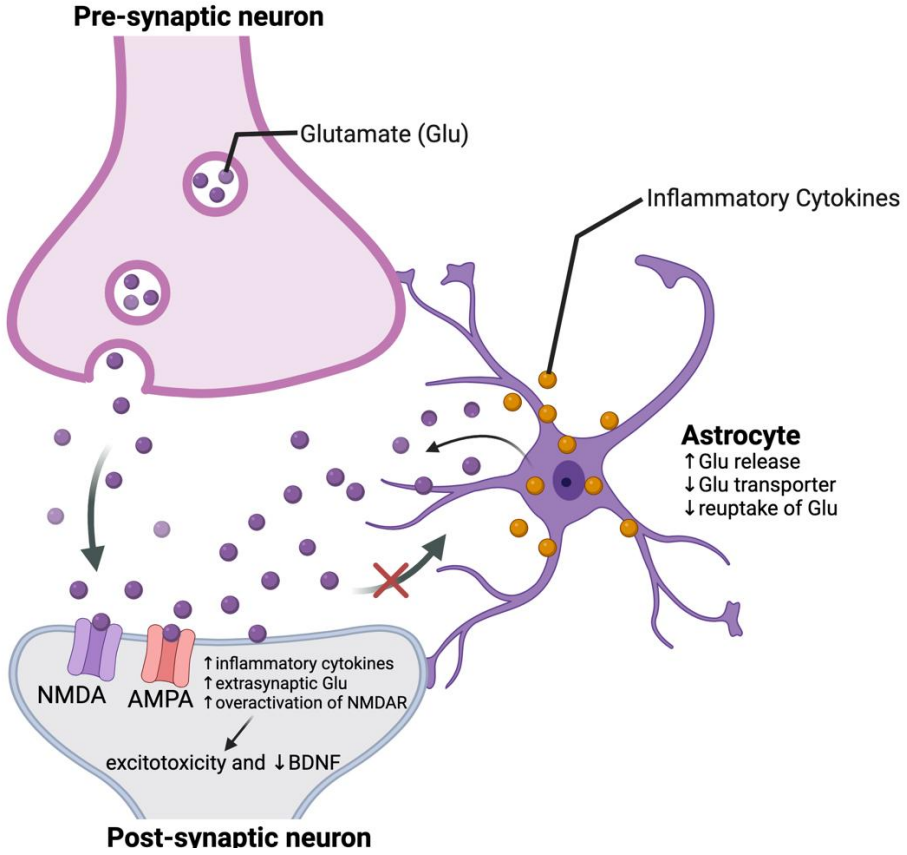
Patients with MDD were **1.6 times less likely** to achieve response or remission if exposed to abuse at the age of 4−7 years: OR=1.574 for response (p=0.034); OR=1.606 for remission (p=0.032)

HAM-D=Hamilton Depression Rating Scale
MDD=major depressive disorder
OR=odds ratio
SNRI=serotonin-norepinephrine reuptake inhibitor
SSRI=selective serotonin reuptake inhibitor

Williams LM et al. Transl Psychiatry 2016;6(5):e799.

Should Glutamatergic Modulators Be Considered Preferential Treatments for Adults with Major Depressive Disorder and A Reported History of Trauma? Conceptual and Clinical Implications

Interaction Between Inflammatory Cytokines, Glutamatergic Dysregulation and Brain-Derived Neurotrophic Factor (BDNF)



NMDA = N-Methyl-D-Aspartate receptor
AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic receptor
GLU = glutamate
BDNF = Brain-derived neurotrophic factor

Teopiz KM, et al. CNS Spectr. 2025 May 26:1-19. Online ahead of print.

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The “4 As” Increase Suspicion of Mixed Features

Mixed episode

- Described in the DSM-IV-TR
- Requires an individual to simultaneously meet the criteria for a major depressive episode and a manic episode

Mixed features specifier

- Described in the DSM-5
- Can be applied to episodes of major depression, mania, and hypomania
- Requires the presence of at least 3 manic or hypomanic non-overlapping symptoms during a major depressive episode
- Requires the presence of at least 3 depressive non-overlapping symptoms during a hypomanic or manic episode

Healthcare professionals should be aware of the “4 As”:

- **A** nxiety
- **A** gitation
- **A** nger / irritability
- **A** ttentional disturbance-distractibility

These symptoms are highly suggestive of mixed features in individuals with mood disorders

McIntyre et al. Lancet. 2020;396:1841.

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Timely and Accurate Diagnosis of Bipolar Disorder Is Critical: Screening Using the Rapid Mood Screener

Item	Response	
1. Have there been at least 6 different periods of time (at least 2 weeks) when you felt deeply depressed?	Yes	No
2. Did you have problems with depression before the age of 18?	Yes	No
3. Have you ever had to stop or change your antidepressant because it made you highly irritable or hyper?	Yes	No
4. Have you ever had a period of at least 1 week during which you were more talkative than normal with thoughts racing in your head?	Yes	No
5. Have you ever had a period of at least 1 week during which you felt any of the following: unusually happy; unusually outgoing; or unusually energetic?	Yes	No
6. Have you ever had a period of at least 1 week during which you needed much less sleep than usual?	Yes	No

Highest estimated accuracy was observed with ≥ 4 "yes" responses

- RMS sensitivity was 0.88 and specificity was 0.80; concordance index 0.87
- MDQ sensitivity was 0.86 and specificity was 0.78; concordance index 0.82

1. McIntyre RS, et al. Curr Med Res Opin. 2021;37:135-44; 2. Thase ME, et al. Prim Care Companion CNS Disord. 2023;25(2):22m03322

Management of MDD with Insufficient response: World Psychiatry Association

Proven strategies in adults with ongoing insufficient response to **one antidepressant**[1,2]

Options:[1]
Extending antidepressant trial
Switching antidepressants
Combining antidepressants
Ketamine
Esketamine
SGAs
ECT
rTMS
Vagus nerve stimulation
Psychotherapies

Intravenous ketamine is not EMA or FDA-approved for depression.[3,4]

ECT, electroconvulsive therapy; EMA, European Medicines Agency; FDA, Food and Drug Administration; MDD, major depressive disorder; rTMS, repetitive transcranial magnetic stimulation; SGA, second-generation antipsychotic; TRD, treatment-resistant depression.

1. McIntyre RS, et al. World Psychiatry 2023;22:394–412; 2. Mohamed S, et al. JAMA 2017;318:132–145;

Dextromethorphan-Bupropion for MDD

Dextromethorphan (Dex; NMDA antagonist/sigma-1 agonist) + bupropion (Bup; dopamine and norepinephrine reuptake inhibitor that increases bioavailability of Dex)

ASCEND Study Summary

Design: 6-week, double-blind, randomized trial (dextromethorphan-bupropion vs. bupropion) in adults with moderate–severe MDD (N=80).

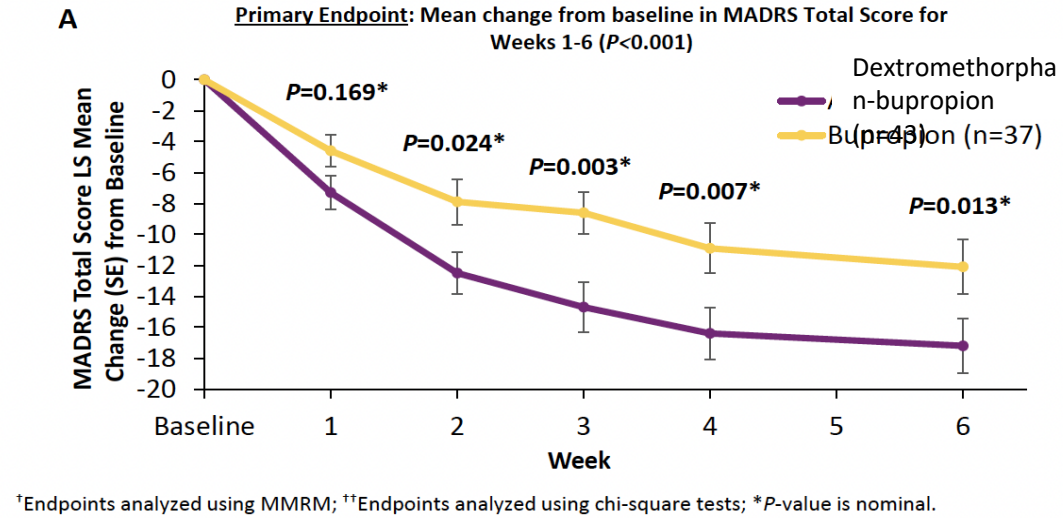
Results:

Greater improvement in **MADRS score** with **dextromethorphan-bupropion** vs bupropion (−13.7 vs −8.8; *P*<0.001).

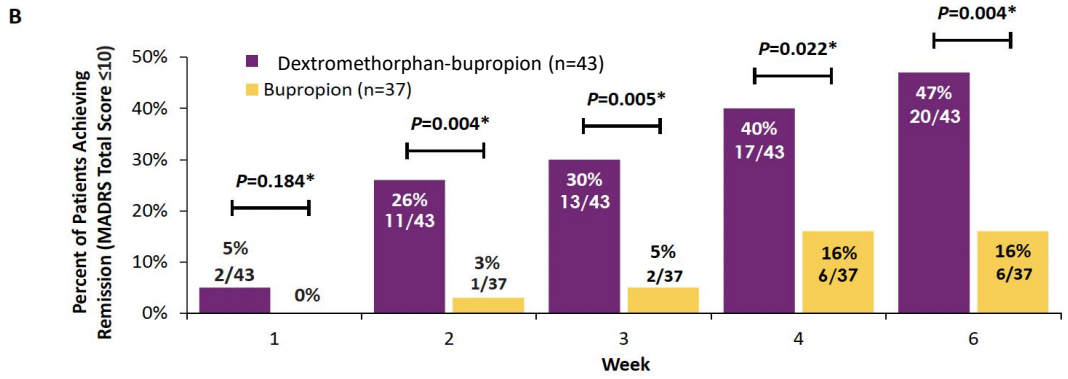
Efficacy onset: Significant from Week 2 onward.

Remission rates higher with dextromethorphan-bupropion (Weeks 2–6)

Figure 3. A. MADRS Total Scores†; B. Remission (MADRS Total Score ≤10)††



†Endpoints analyzed using MMRM; ††Endpoints analyzed using chi-square tests; **P*-value is nominal.



Iosifescu DV et al. Poster presented at Psych Congress; September 17–21, 2025; San Diego, California, USA.

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Distinct Pharmacology of Dopamine Partial Agonists

Cariprazine		Aripiprazole		Brexpiprazole	
0.49 nM	↔	D_2	0.34 nM	↔	0.30 nM
0.085 nM	↑~10x	D_3	0.8 nM	↔	1.1 nM
2.6 nM	↔	5-HT_{1A}	1.7 nM	↑ 14x	0.12 nM
18.8 nM	↓ 6x	5-HT_{2A}	3.4 nM	↑ 7x	0.47 nM
0.58 nM	↔	5-HT_{2B}	0.36 nM	↓ 5x	1.9 nM
111 nM	↓ 3x	5-HT_7	39 nM	↑ 11x	3.7 nM
155 nM	↓ 3x	α_{1A}	57 nM	↑ 15x	3.8 nM
-	-	α_{1B}	35 nM	↑ 205x	0.17 nM
-	-	α_{2A}	74 nM	↑ 5x	15 nM
-	-	α_{2B}	103 nM	↑ 6x	17 nM
-	-	α_{2C}	38 nM	↑ 65x	0.59 nM

Citrome L. *Int J Clin Pract*. 2015;69(11):1211-1220.

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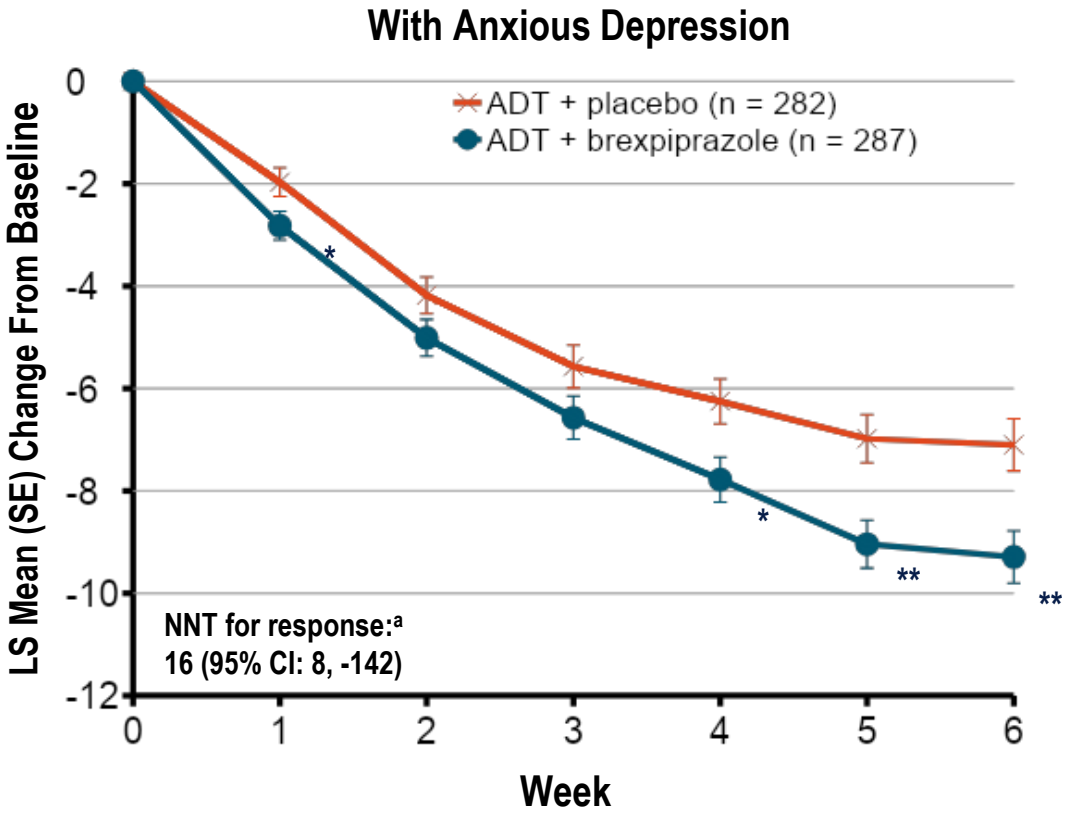
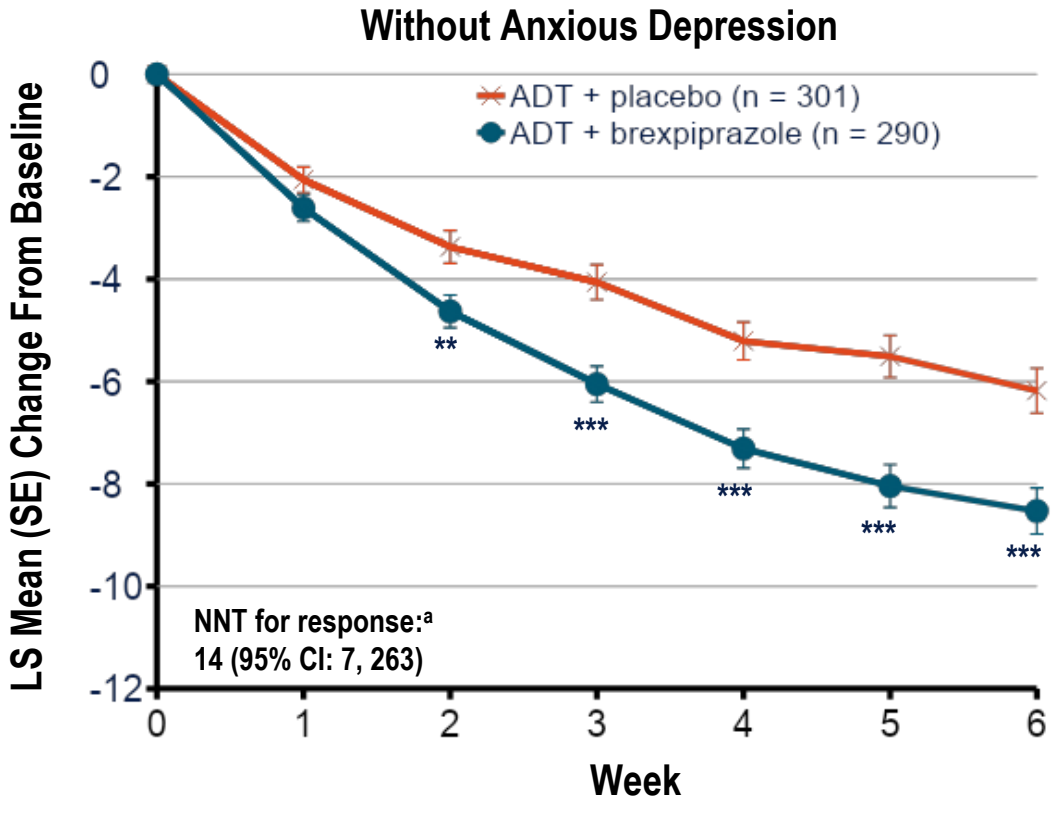
Adjunctive Therapy With Brexpiprazole

Patients With and Without Anxious Depression





- MADRS total baseline for patients with anxious depression: ADT + placebo, 28.6; ADT + brexpiprazole, 28.9.
- MADRS total baseline for patients without anxious depression: ADT + placebo, 24.8; ADT + brexpiprazole, 24.6.

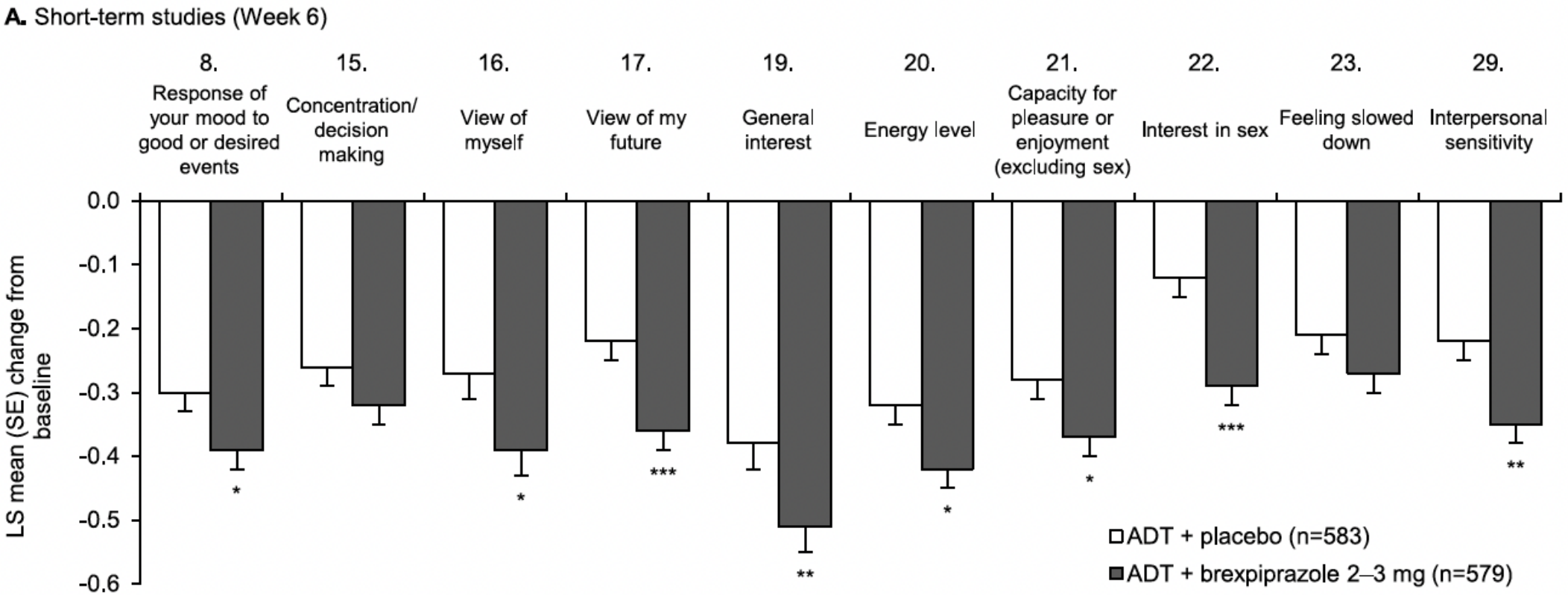
*P <.05. **P <.01. ***P <.001 vs placebo. MMRM. [a] Response defined as ≥50% reduction from baseline in MADRS total score. ADT: antidepressant; LS: least squares; MADRS: Montgomery-Åsberg Depression Rating Scale; MMRM: mixed effect model repeat measurement; NNT: number needed to treat; SE, standard error.

Thase ME et al. Neuropsychiatr Dis Treat 2018;15:37-45.

Brain and Cognition DISCOVERY FOUNDATION

Effects of Adjunctive Brexpiprazole on Patient Life Engagement in Major Depressive Disorder: *Post hoc* Analysis of Inventory of Depressive Symptomatology Self-Report data

Mean change from baseline in IDS-SR10 Life Engagement item scores in A. the short-term studies (MMRM)



McIntyre RS, et al. Journal of Psychiatric Research. 2023; 162:71-78

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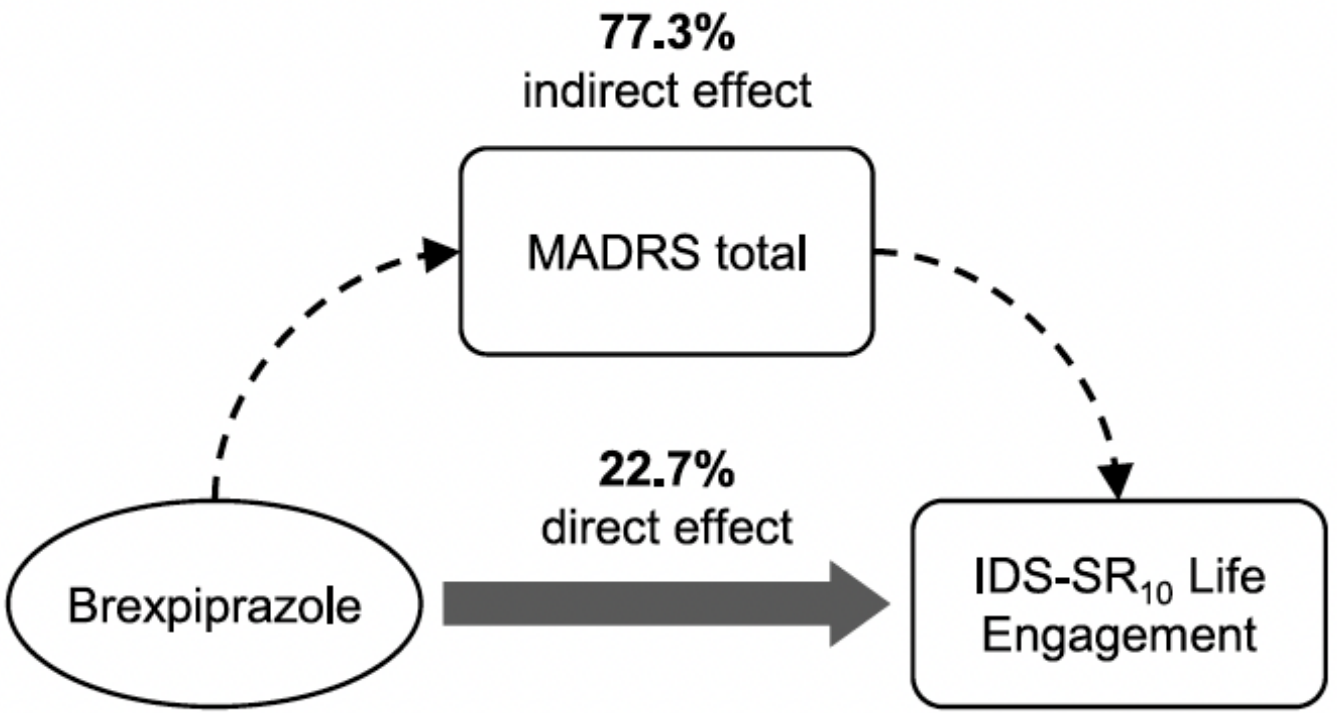
Effects of Adjunctive Brexpiprazole on Patient Life Engagement in Major Depressive Disorder: *Post hoc* Analysis of Inventory of Depressive Symptomatology Self-Report Data

Path analysis of change from baseline to Week 6 in IDS-SR10 Life Engagement subscale score in the short-term studies, with indirect effect mediated through improvement of MADRS total score (Case 1). IDS-SR, Inventory of Depressive Symptomatology Self-Report; MADRS, Montgomery–Åsberg Depression Rating Scale.



McIntyre RS, et al. Journal of Psychiatric Research. 2023; 162:71-78

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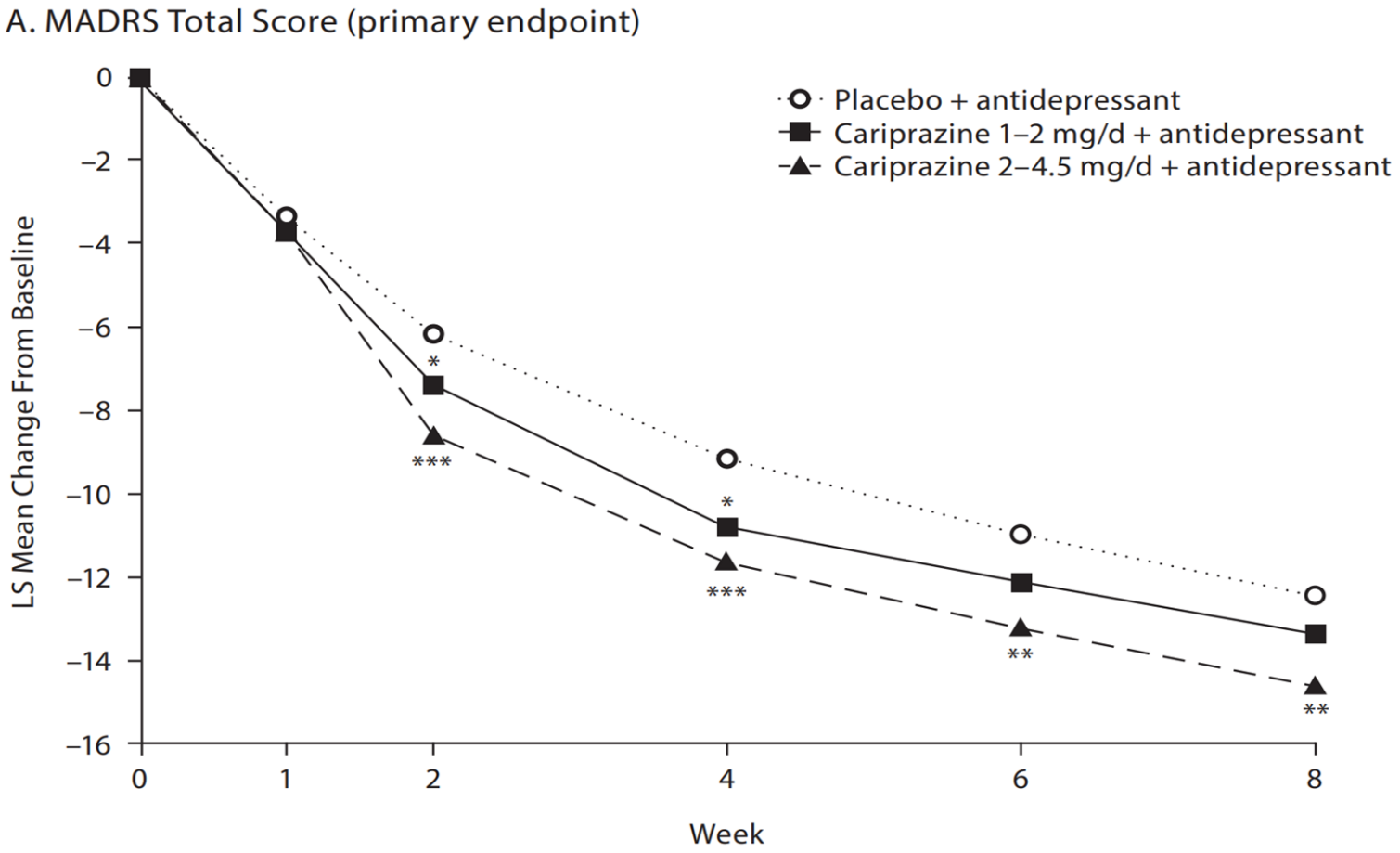
Adjunctive Cariprazine: Effective for MDD With Inadequate Antidepressant Response



Treatment-emergent adverse events (TEAEs) that occurred in ≥ 10% of patients in either cariprazine group and at incidence greater than placebo were akathisia, insomnia, and nausea

*P<.05. **P<.01. ***P<.001 versus placebo for pairwise comparisons; not adjusted for multiple comparisons

LS=least squares
MADRS = Montgomery-Åsberg Depression Rating Scale

Durgam S et al. J Clin Psychiatry 2016;77(3):371-8.

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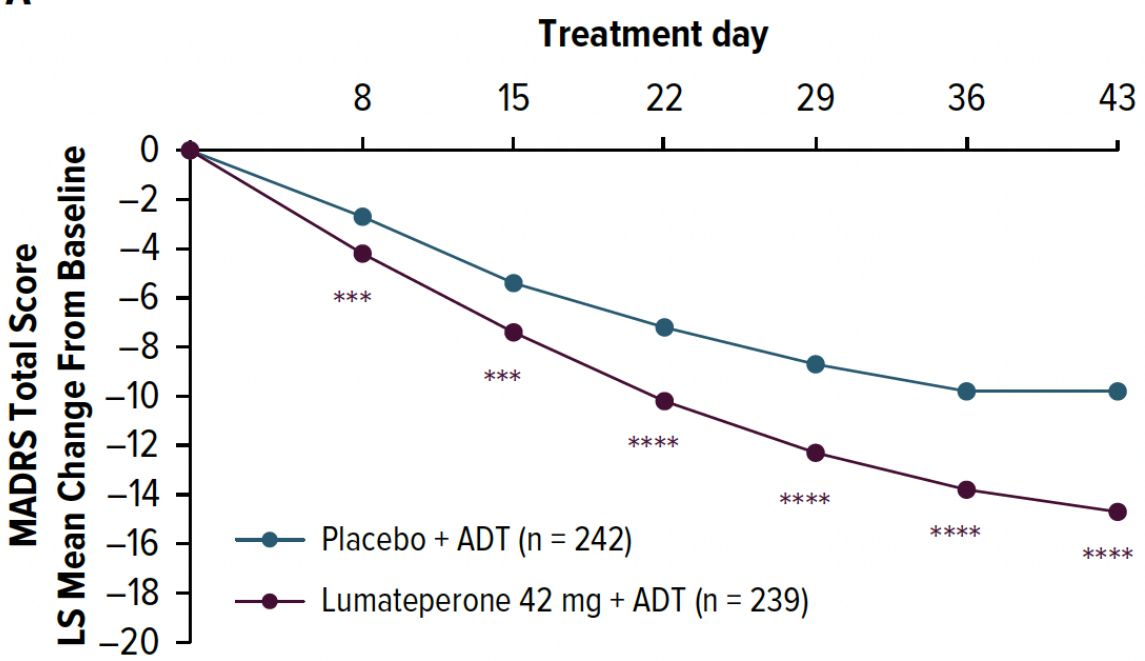
Phase 3 Adjunctive Lumateperone for MDD With Inadequate Antidepressant Response

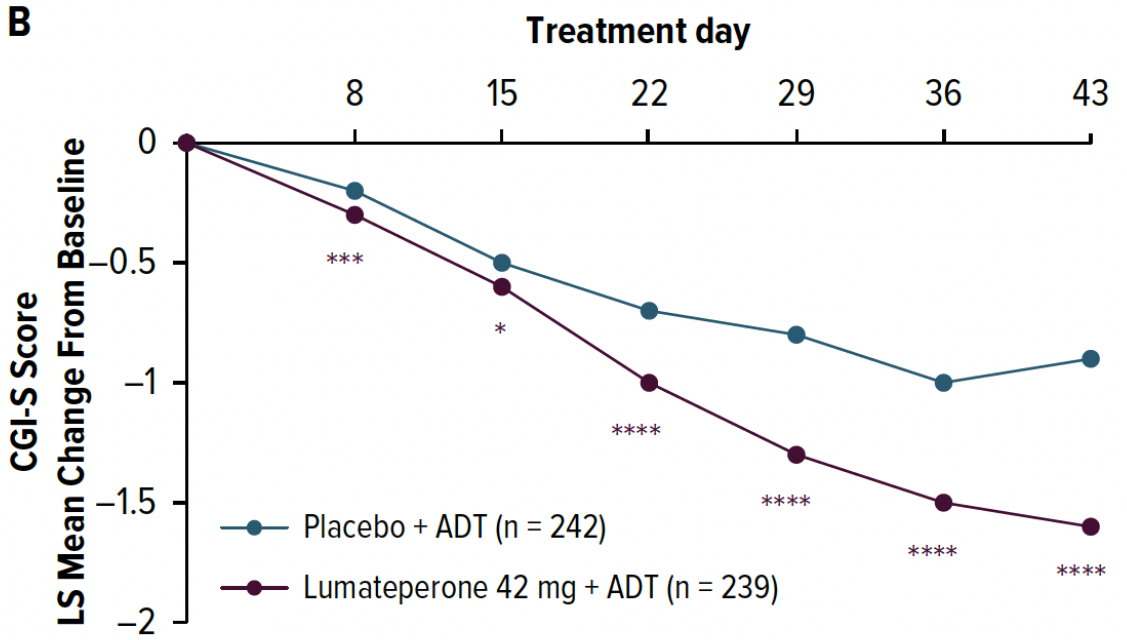
Study Design
- 485 adults with **MDD + inadequate response to 1–2 ADTs**
- Randomized: Lumateperone 42 mg + ADT vs Placebo + ADT
- 6 weeks, double-blind, multicenter trial

A



MADRS Total score — placebo vs lumateperone → significant improvement by Day 8, sustained through Day 43 (LSMD –4.9, ES –0.61, *P* < .0001)

B



CGI-S score → significant improvement (LSMD –0.7, ES –0.67, *P* < .0001)

Durgam S, Earley WR, Kozauer SG, et al. J Clin Psychiatry. 2025;86(4):25m15848.

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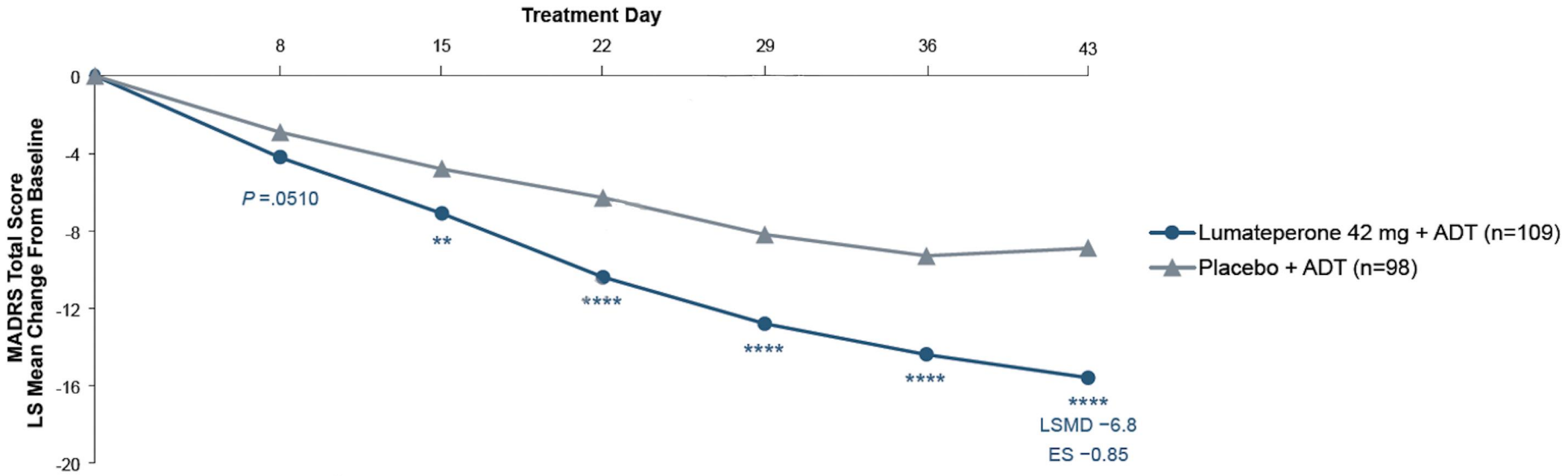
Lumateperone as Adjunctive Therapy in Patients with MDD and Anxious Distress

LS Mean Change From Baseline in MADRS Total Score in Patients With Anxious Distress (mITT Population)



**P<.01 ***P<.0001. LSMD vs Placebo. MMRM in mITT population.
ADT, antidepressant therapy; ES, effect size; LS, least squares; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat; MMRM, mixed-effects model for repeated measures.

Lumateperone 42 mg + ADT significantly improved MADRS Total score change from baseline at Day 43 compared with placebo + ADT in patients with anxious distress

Durgam S et al., Lumateperone as Adjunctive Therapy in Patients With Major Depressive Disorder and Anxious Distress. Presented at the Psych Congress Annual Meeting, September 17-21, 2025, San Diego, CA

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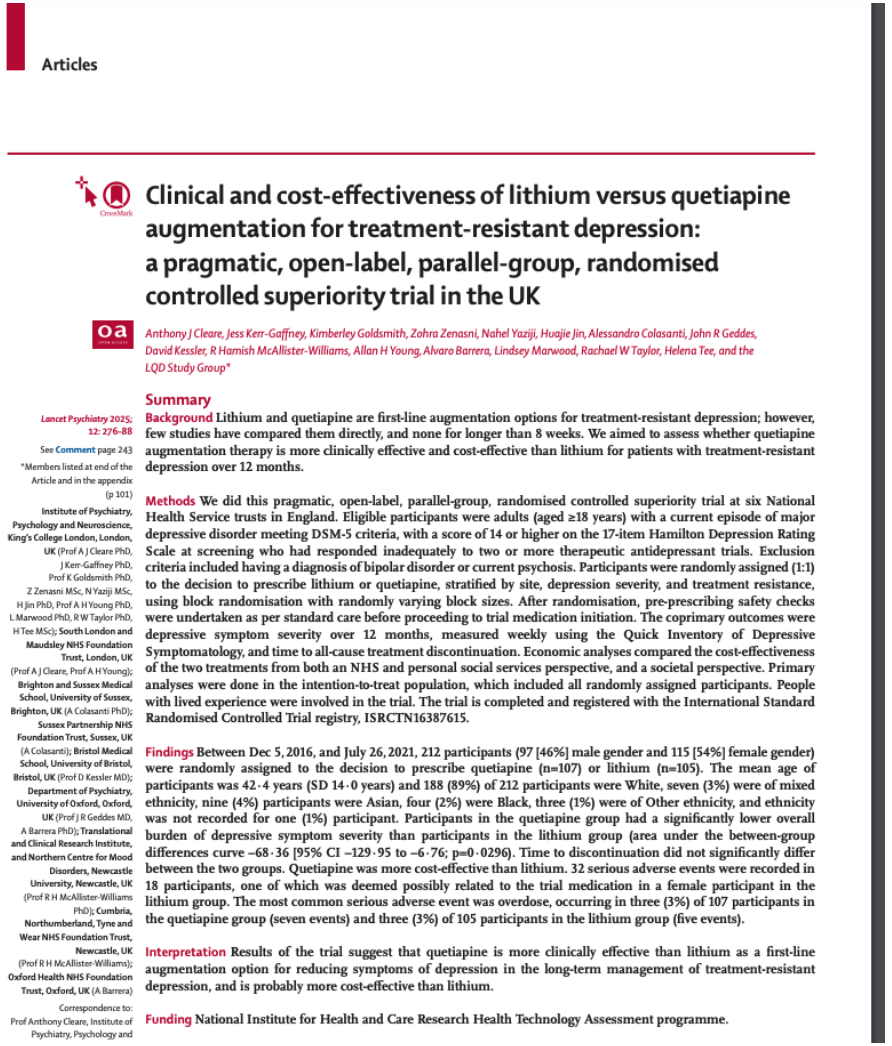
Psychotropic Drug-Related Weight Gain

Risk of Weight Gain*	Antidepressants	Antipsychotics	Lithium and Anticonvulsants
High	Amitriptyline, citalopram, clomipramine, fluvoxamine, mirtazapine, nortriptyline, paroxetine, phenelzine	Clozapine, olanzapine	Valproate (valproic acid)
Moderate	Desipramine, duloxetine, escitalopram, sertraline, venlafaxine	Chlorpromazine, olanzapine/samidorphan, paliperidone, quetiapine, risperidone	Lithium
Low	Agomelatine, desvenlafaxine, gepirone, levomilnacipran, moclobemide, selegiline, tranylcypromine, vilazodone, vortioxetine	Amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, haloperidol, iloperidone, ziprasidone	Carbamazepine, gabapentin, oxcarbazepine, pregbalin
Neutral or weight loss	Bupropion, dextromethorphan-bupropion, esketamine, fluoxetine, zuranolone	Lumateperone, lurasidone	Lamotrigine, topiramate

*Risk categorization based on primary reports, meta-analytic evidence, product monographs, and expert opinion.

McIntyre RS et al. Am J Psychiatry. 2024;181:1

Lithium vs. Quetiapine for Treatment-Resistant Depression



Articles

Clinical and cost-effectiveness of lithium versus quetiapine augmentation for treatment-resistant depression: a pragmatic, open-label, parallel-group, randomised controlled superiority trial in the UK

Anthony J Cleare, Jess Kerr-Gaffney, Kimberley Goldsmith, Zohra Zenasni, Nahel Yaziji, Huajie Jin, Alessandro Colasanti, John R Geddes, David Kessler, R Hamish McAllister-Williams, Allan H Young, Alvaro Barrera, Lindsey Marwood, Rachael W Taylor, Helena Tee, and the LQD Study Group*

Lancet Psychiatry 2025; 12: 276-88

See Comment page 243

*Members listed at end of the Article and in the appendix (p 101)

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Correspondence to: Prof Anthony Cleare, Institute of Psychiatry, Psychology and

Summary

Background Lithium and quetiapine are first-line augmentation options for treatment-resistant depression; however, few studies have compared them directly, and none for longer than 8 weeks. We aimed to assess whether quetiapine augmentation therapy is more clinically effective and cost-effective than lithium for patients with treatment-resistant depression over 12 months.

Methods We did this pragmatic, open-label, parallel-group, randomised controlled superiority trial at six National Health Service trusts in England. Eligible participants were adults (aged ≥18 years) with a current episode of major depressive disorder meeting DSM-5 criteria, with a score of 14 or higher on the 17-item Hamilton Depression Rating Scale at screening who had responded inadequately to two or more therapeutic antidepressant trials. Exclusion criteria included having a diagnosis of bipolar disorder or current psychosis. Participants were randomly assigned (1:1) to the decision to prescribe lithium or quetiapine, stratified by site, depression severity, and treatment resistance, using block randomisation with randomly varying block sizes. After randomisation, pre-prescribing safety checks were undertaken as per standard care before proceeding to trial medication initiation. The coprimary outcomes were depressive symptom severity over 12 months, measured weekly using the Quick Inventory of Depressive Symptomatology, and time to all-cause treatment discontinuation. Economic analyses compared the cost-effectiveness of the two treatments from both an NHS and personal social services perspective, and a societal perspective. Primary analyses were done in the intention-to-treat population, which included all randomly assigned participants. People with lived experience were involved in the trial. The trial is completed and registered with the International Standard Randomised Controlled Trial registry, ISRCTN16387615.

Findings Between Dec 5, 2016, and July 26, 2021, 212 participants (97 [46%] male gender and 115 [54%] female gender) were randomly assigned to the decision to prescribe quetiapine (n=107) or lithium (n=105). The mean age of participants was 42·4 years (SD 14·0 years) and 188 (89%) of 212 participants were White, seven (3%) were of mixed ethnicity, nine (4%) participants were Asian, four (2%) were Black, three (1%) were of Other ethnicity, and ethnicity was not recorded for one (1%) participant. Participants in the quetiapine group had a significantly lower overall burden of depressive symptom severity than participants in the lithium group (area under the between-group differences curve −68·36 [95% CI −129·95 to −6·76; p=0·0296). Time to discontinuation did not significantly differ between the two groups. Quetiapine was more cost-effective than lithium. 32 serious adverse events were recorded in 18 participants, one of which was deemed possibly related to the trial medication in a female participant in the lithium group. The most common serious adverse event was overdose, occurring in three (3%) of 107 participants in the quetiapine group (seven events) and three (3%) of 105 participants in the lithium group (five events).

Interpretation Results of the trial suggest that quetiapine is more clinically effective than lithium as a first-line augmentation option for reducing symptoms of depression in the long-term management of treatment-resistant depression, and is probably more cost-effective than lithium.

Funding National Institute for Health and Care Research Health Technology Assessment programme.

Study Design:

- Pragmatic, open-label, parallel-group RCT at 6 NHS Trusts in England
- **212 adults** with treatment-resistant major depressive disorder (TRD)
- Randomized 1:1 to **quetiapine** (n=107) or **lithium** (n=105) augmentation

Primary Outcomes:

- Depressive symptom severity over 12 months (QIDS-SR)
- Time to all-cause treatment discontinuation

Cleare AJ et al. Lancet Psychiatry 2025;12(4):276–88.

Brain and Cognition DISCOVERY FOUNDATION

Lithium vs. Quetiapine for Treatment-Resistant Depression

Clinical Effectiveness:

- **Quetiapine** led to **greater reduction in depressive symptoms** (AUC: –68.36; *p*=0.0296)
- No significant difference in time to discontinuation (*p*=0.12)
- Improved clinician-rated depression and functional impairment at 52 weeks

Cost-Effectiveness:

- **Quetiapine** was **more cost-effective** than lithium:
  - Lower healthcare/social care costs
  - Greater QALY (Quality-Adjusted Life Year) gains (0.540 vs. 0.468)
  - 99% probability of cost-effectiveness at NICE threshold (£20,000/QALY)

Safety:

- Serious adverse events similar across groups

Implications:

- **Quetiapine may be preferred as first-line augmentation** in TRD due to better long-term symptom relief and economic benefit
- Highlights need for personalized treatment approaches and improved access to augmentation therapies

Cleare AJ et al. Lancet Psychiatry 2025;12(4):276–88.

Brain and Cognition
DISCOVERY FOUNDATION

International Guidance on the Evidence and Implementation of Ketamine and Esketamine

Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation

Roger S. McIntyre, M.D., Joshua D. Rosenblat, M.D., M.Sc., Charles B. Nemeroff, M.D., Ph.D., Gerard Sanacora, M.D., Ph.D., James W. Murrough, M.D., Ph.D., Michael Berk, Ph.D., M.B.B.Ch., Elisa Brietzke, M.D., Ph.D., Seetal Dodd, Ph.D., Philip Gorwood, M.D., Ph.D., Roger Ho, M.D., M.B.B.S., Dan V. Iosifescu, M.D., Carlos Lopez Jaramillo, M.D., Ph.D., Siegfried Kasper, M.D., Kevin Kratiuk, B.Pharm., Jung Goo Lee, M.D., Ph.D., Yena Lee, H.B.Sc., Leanna M.W. Lui, Rodrigo B. Mansur, M.D., Ph.D., George I. Papakostas, M.D., Mehala Subramaniapillai, M.Sc., Michael Thase, M.D., Eduard Vieta, M.D., Ph.D., Allan H. Young, M.Phil., M.B.Ch.B., Carlos A. Zarate, Jr., M.D., Stephen Stahl, M.D., Ph.D.

Replicated international studies have underscored the human and societal costs associated with major depressive disorder. Despite the proven efficacy of monoamine-based antidepressants in major depression, the majority of treated individuals fail to achieve full syndromal and functional recovery with the index and subsequent pharmacological treatments. Ketamine and esketamine represent pharmacologically novel treatment avenues for adults with treatment-resistant depression. In addition to providing hope to affected persons, these agents represent the first non-monoaminergic agents with proven rapid-onset efficacy in major depressive disorder. Nevertheless, concerns remain about the safety and tolerability of ketamine and esketamine in mood disorders. Moreover, there is uncertainty about the appropriate position of these agents in treatment algorithms, their comparative effectiveness, and the appropriate setting, infrastructure, and personnel required for its competent and safe implementation. In this article, an international group of mood disorder experts provides a synthesis of the literature with respect to the efficacy, safety, and tolerability of ketamine and esketamine in adults with treatment-resistant depression. The authors also provide guidance for the implementation of these agents in clinical practice, with particular attention to practice parameters at point of care. Areas of consensus and future research vistas are discussed.

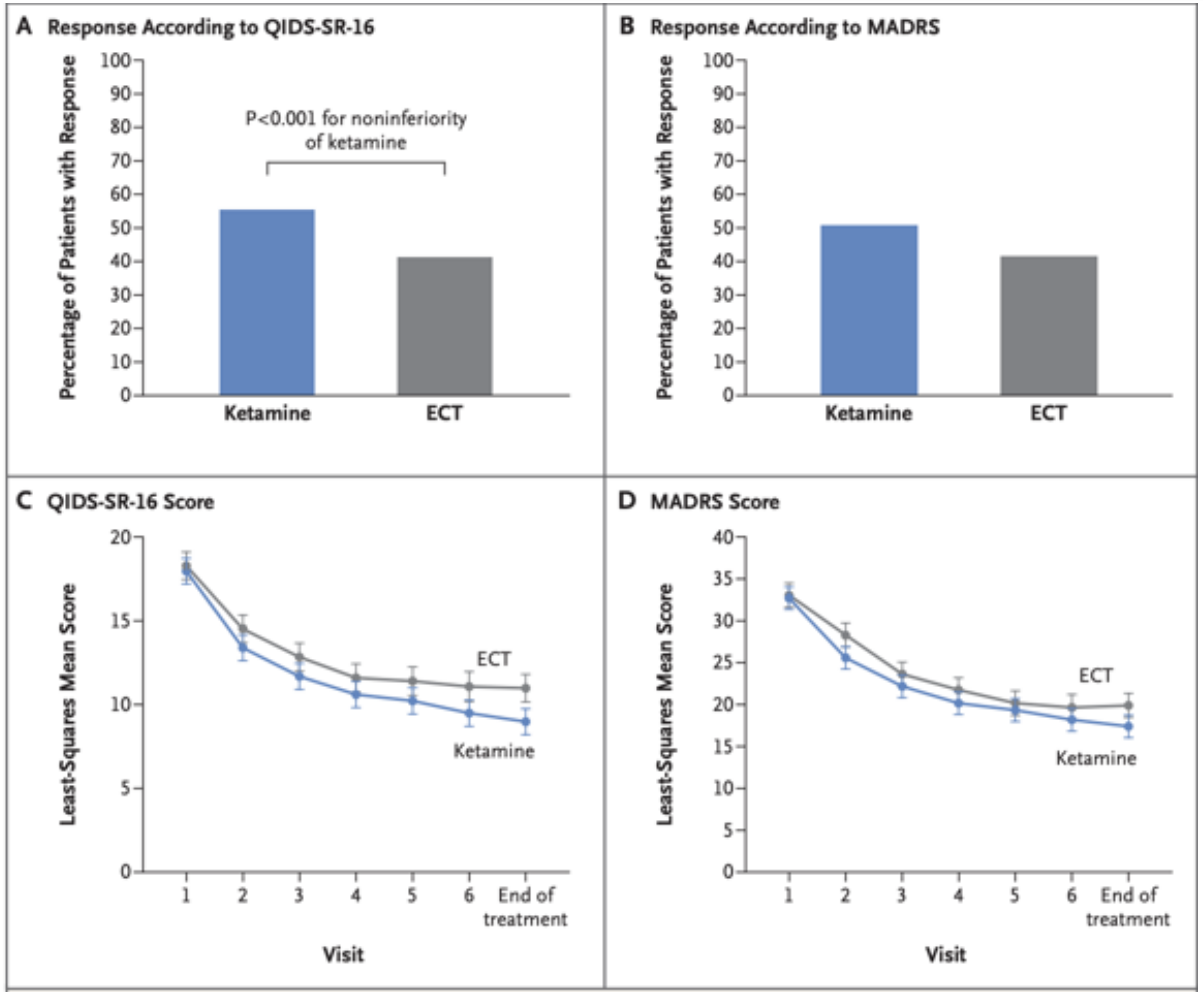
Am J Psychiatry 2021; 00:1–17; doi: 10.1176/appi.ajp.2020.20081251

McIntyre RS. et al., Am J Psychiatry. 2021 May 1;178(5):383-399.

Brain and Cognition DISCOVERY FOUNDATION

Ketamine Not Inferior to ECT in Outpatients with Nonpsychotic Treatment-Resistant Major Depression

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



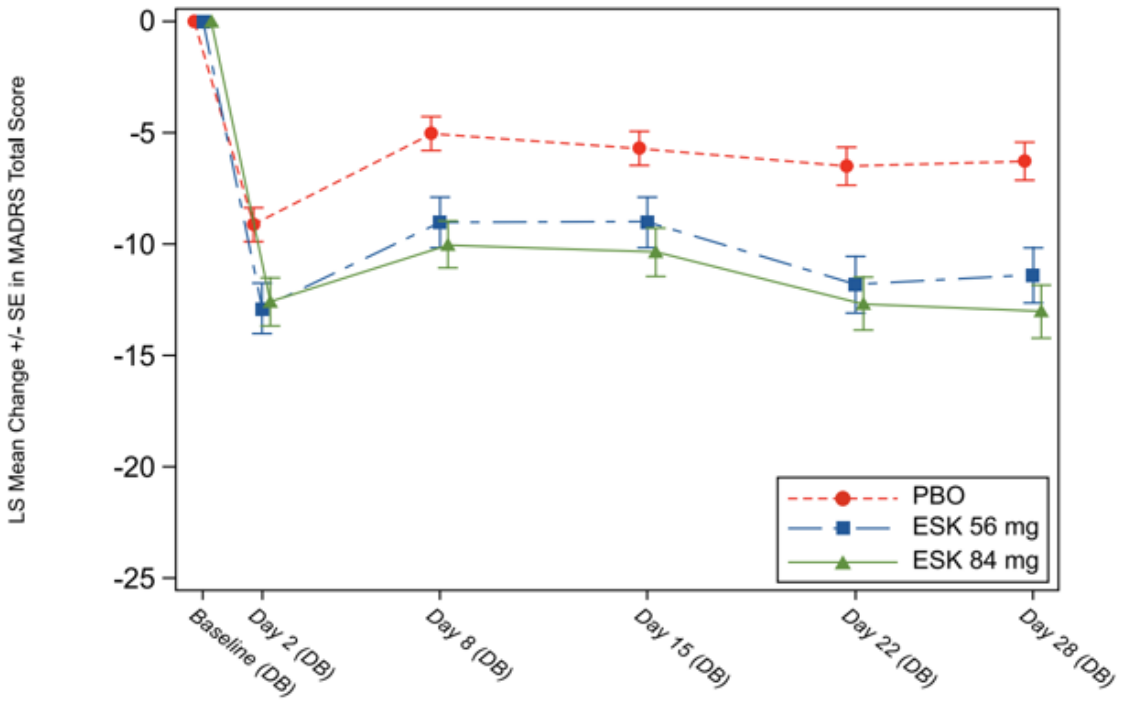
Shown are the percentages of patients who had a response to ketamine or electroconvulsive therapy (ECT) according to the scores on the Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16, Panel A) and the Montgomery–Åsberg Depression Rating Scale (MADRS, Panel B) at the end-of-treatment visit, as well as the leastsquares mean QIDS-SR-16 scores (Panel C) and the mean MADRS scores (Panel D) at the assessment visits during the initial 3-week treatment phase.

Anand A, et al. N Engl J Med. 2023 May 24. Online ahead of print.

Brain and Cognition DISCOVERY FOUNDATION

Efficacy and Safety of Esketamine Nasal Spray as Monotherapy in Adults with Treatment-Resistant Depression: A Randomized, Double-Blind, Placebo-Controlled Study

MADRS total score: LS mean change (± SE) over time in the DB phase - MMRM observed case (full efficacy analysis set)



No. of Participants

PBO	197	195	190	189	187	185
ESK 56 mg	86	84	84	84	81	82
ESK 84 mg	95	93	89	89	87	89

Effect sizes (Day 28): ESK 56 mg vs PBO, 0.48; ESK 84 mg vs PBO, 0.63

DB, double-blind; ESK, esketamine; LS, least squares; MADRS, Montgomery-Asberg Depression Rating Scale; MMRM, mixed model for repeated measures; PBO, placebo; SE, standard error.

Presented at American Society of Clinical Psychopharmacology (ASCP) Annual Meeting; May 28-31, 2024; Miami, FL, USA

Number Needed to Treat (NNT) for Ketamine and Esketamine in Adults with Treatment-Resistant Depression: A Systematic Review and Meta-Analysis

NNT Per Study and Pooled Results for Racemic Ketamine and Esketamine Treatments

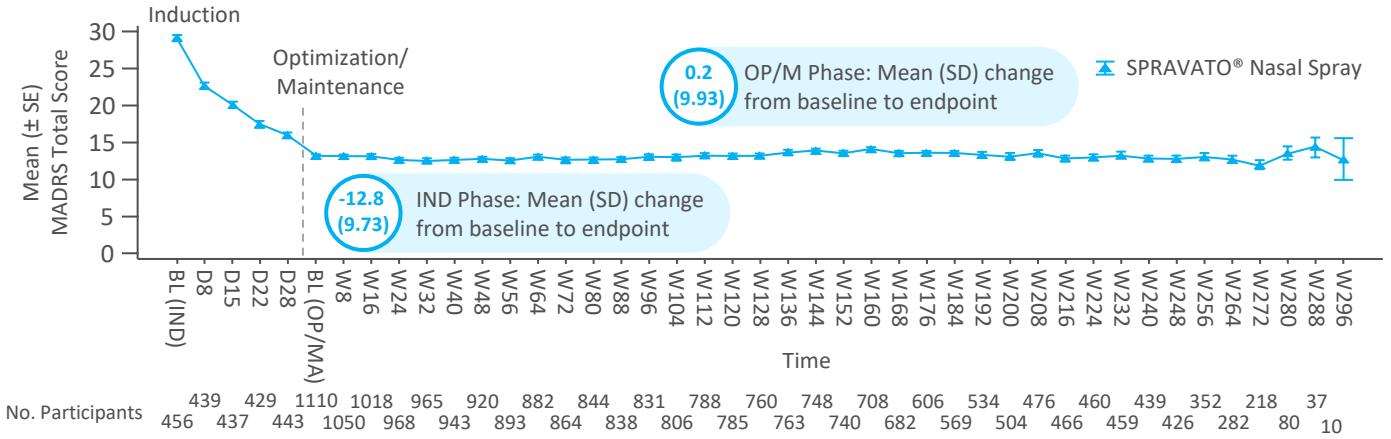
Author	Ketamine Treatment	Response at 4 h		Response at 1 to 3 days		Response at 1 to 2 weeks		Response at 4 weeks	
		NNT	95 % CI	NNT	95 % CI	NNT	95 % CI	NNT	95 % CI
Zarate 2006 (Zarate et al., 2006)	Racemic	–	–	2	[2: 2]	–	–	–	–
Murrough 2013 (Murrough et al., 2013)	Racemic	–	–	3	[3: 5]	–	–	–	–
Lapidus 2014 (Lapidus et al., 2014)	Racemic	–	–	3	[2: 4]	–	–	–	–
Singh 2016a (Singh et al., 2016a)	Racemic	–	–	–	–	3	[2: 4]	–	–
Singh 2016b (Singh et al., 2016b)	Esketamine	–	–	2	[2: 2]	–	–	–	–
Li 2016 (Li et al., 2016)	Racemic	8	[−∞: −414, 4: ∞]	–	–	–	–	–	–
Su 2017 (Su et al., 2017)	Racemic	–	–	4	[3: 5]	–	–	–	–
Chen 2018 (Chen et al., 2018)	Racemic	6	[4: 12]	4	[3: 6]	–	–	–	–
Fava 2020 (Fava et al., 2020)	Racemic	–	–	4	[3: 5]	–	–	–	–
Ionescu 2019 (Ionescu et al., 2019)	Racemic	–	–	–	–	–	–	-13	[−∞: −4, 11: ∞]
Fedgchin 2019 (Fedgchin et al., 2019)	Esketamine	–	–	–	–	–	–	9	[6: 17]
Popova 2019 (Popova et al., 2019)	Esketamine	–	–	–	–	–	–	8	[5: 15]
Ochs-Ross 2020 (Ochs-Ross et al., 2020)	Esketamine	–	–	–	–	–	–	9	[6: 21]
Phillips 2019 (Phillips et al., 2019)	Racemic	–	–	4	[3: 6]	–	–	–	–
Tiger 2020 (Tiger et al., 2020)	Racemic	7	[−∞: −65, 4: ∞]	–	–	–	–	–	–
Shiroma 2020 (Shiroma et al., 2020)	Racemic	–	–	–	–	3	[3: 5]	–	–
Takahashi 2021 (Takahashi et al., 2021)	Esketamine	–	–	–	–	–	–	148	[−∞: −20, 31: ∞]
Loo 2023 (Loo et al., 2023)	Racemic	–	–	–	–	–	–	7	[5: 10]
Su 2023 (Su et al., 2023)	Racemic	–	–	5	[4: 7]	–	–	–	–
Pooled ketamine		7	[5: 16]	3	[3: 4]	3	[3: 4]	9	[6: 14]
Pooled esketamine		–	–	2	[2: 2]	–	–	11	[8: 16]

The symbol — indicates no data was available at that time point. By convention, NNT values were rounded up to the next whole number. The presence of ∞ and − ∞ in the 95 % CI (Confidence interval) indicates the confidence interval passes through the possibility of no treatment effect (a number approaching ∞ patients could be treated and there would still not be one expected additional responder in the treatment group). Negative NNT values, sometimes reported as NNTH (number needed to treat (harm)), indicate greater event probabilities in the placebo group.

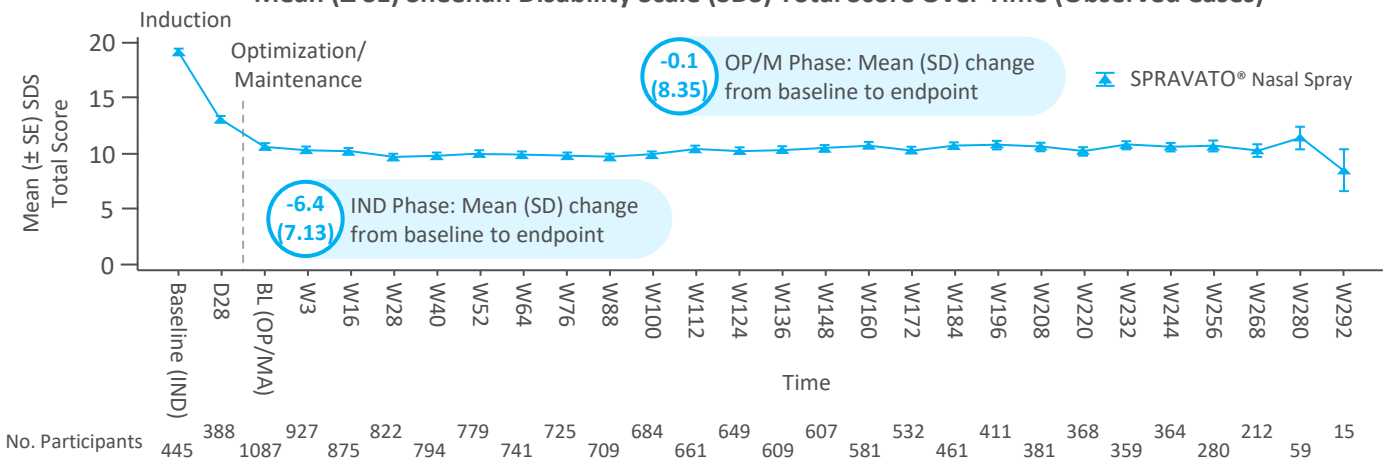
Calder CN, et al. J Affect Disord. 2024 Apr 16:S0165-0327(24)00640-2. Online ahead of print.

SUSTaIN-3 Results: Esketamine Safe, Well-Tolerated with Multiple Years of Exposur

Mean (± SE) Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score Over Time (Observed Cases)



Mean (± SE) Sheehan Disability Scale (SDS) Total Score Over Time (Observed Cases)



Reductions from baseline in mean MADRS and SDS total scores during the IND phase appeared to be maintained throughout the OP/M phase

Proportion of Patients Who Attained Response or Remission Status

	IND phase end point, n/N (%)	OP/M phase last assessment, n/N (%)
MADRS		
Response: ≥50% improvement from baseline	**224/455** (49.2)	-
Remission: Total score ≤12	(35.6)	(50.0)
SDS		
Response: Total score ≤12, ≤4 for each item	**174/388** (44.8)	**593/1084** (54.7)
Remission: Total score ≤6, ≤2 for each item	**89/388** (22.9)	**401/1084** (37.0)

• 1. Zaki N, et al. Poster presented at: Psych Congress 2023; September 6-10, 2023; Nashville, Tennessee

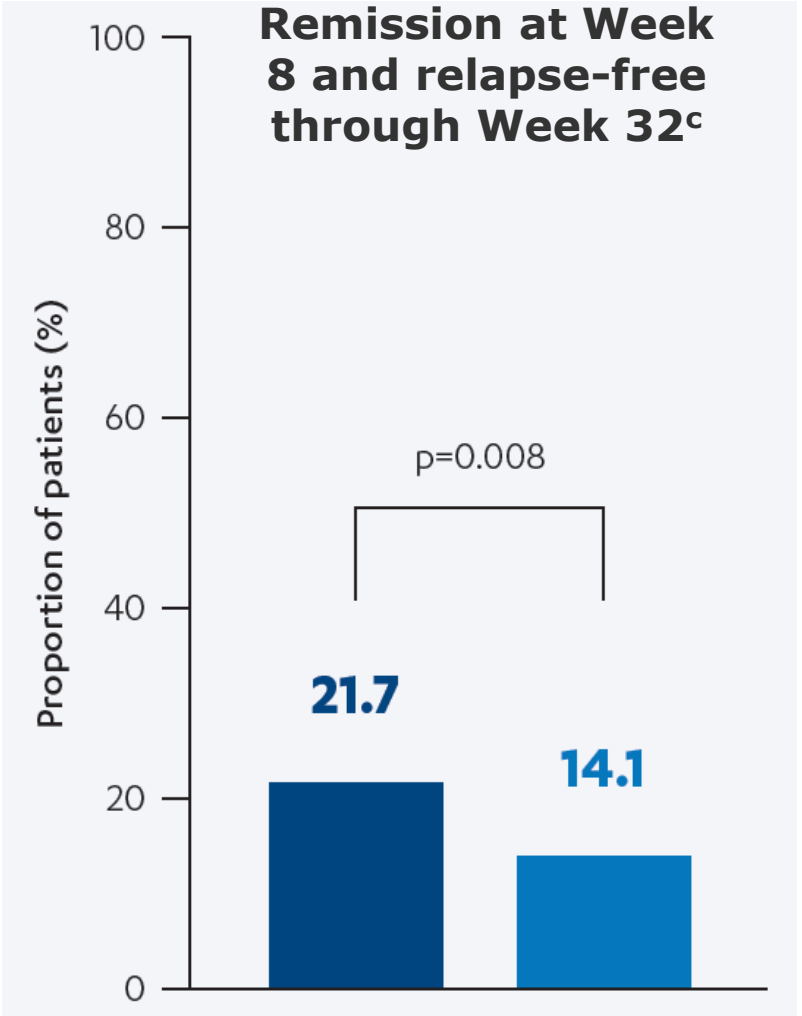
Brain and Cognition DISCOVERY FOUNDATION

Esketamine Superior to Quetiapine in TRD

Key secondary endpoint: proportion of participants achieving **remission at Week 8 without subsequent relapse through Week 32**

Key secondary endpoint	ESK[a] (n=336)	QUE XR[a] (n=340)
Both in remission at Week 8 and relapse-free through Week 32,[c] n (%)	73 (21.7)	48 (14.1)
Difference in percentage (95% CI) Adjusted OR[b] (95% CI) Adjusted p-value[b]	7.61 (1.85, 13.37) 1.72 (1.15, 2.57) 0.008	
Relapse, n (%) Hospitalized for worsening depression or suicide MADRS total score ≥22	8 (2.4) 2 (0.6) 6 (1.8)	6 (1.8) 3 (0.9) 3 (0.9)
Without relapse and discontinued after being in remission at Week 8, n (%)	10 (3.0)	6 (1.8)

Full analysis set; MADRS, Montgomery-Asberg Depression Rating Scale
[a]ESK and QUE XR were both flexibly dosed and taken in addition to an ongoing SSRI/SNRI
[b]Treatment groups were compared using a Cochran-Mantel-Haenszel chi-square test, adjusted for age group (18–64 years; 65 to <75 years) and total number of treatment failures
[c]Patients who discontinued treatment were input as non-responders, LOCF was used for patients with missing MADRS assessment at Week 8 but remained in the study



Reif A. N Engl J Med 2023;389(14):1298-309. doi: 10.1056/NEJMoa2304145.

Brain and Cognition DISCOVERY FOUNDATION

The Effects of Ketamine and Esketamine on Functional Outcomes in Major Depressive Disorder and Treatment-Resistant Depression: A Systematic Review

Journal of Psychiatric Research 192 (2026) 280–288

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

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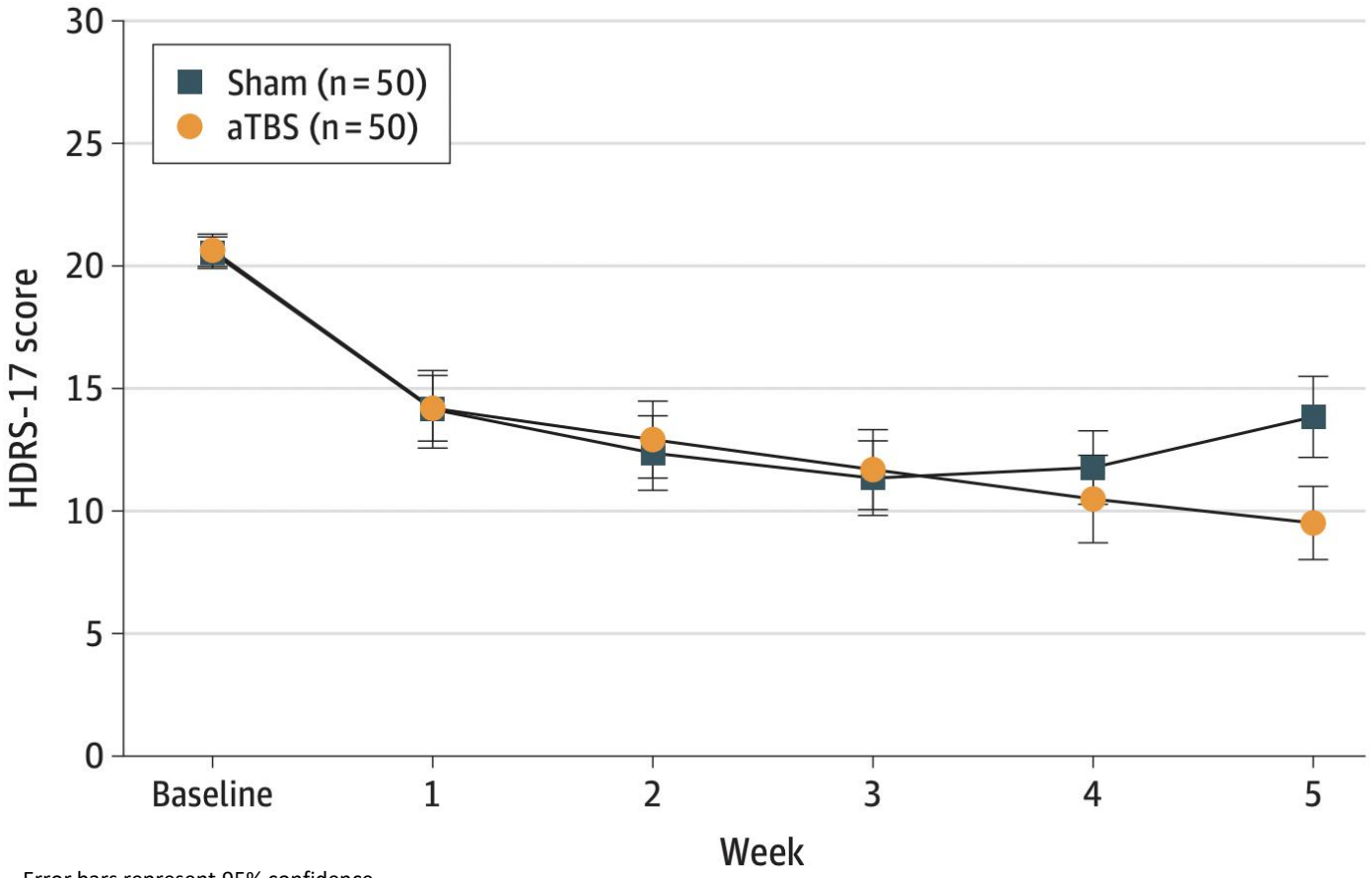
The effects of ketamine and esketamine on functional outcomes in major depressive disorder and treatment-resistant depression: A systematic review

Isabella S. Ji [a,b], Morgan C.H. Cheng [a,c], Kayla M. Teopiz [a,d], Christine E. Dri [a], Sabrina Wong [a,k,l], Gia Han Le [a,d,l], Taeho Greg Rhee [f,g], Hernan F. Guillen-Burgos [h,i,j], Heidi K.Y. Lo [m], Yang Jing Zheng [a,d], Roger S. McIntyre [e,*]

Accelerated Theta-Burst Stimulation for Treatment-Resistant Depression A Randomized Clinical Trial

Change in 17-Item Hamilton Depression Rating Scale (HDRS-17) Score in the Randomized, Sham-Controlled Phase of the Study



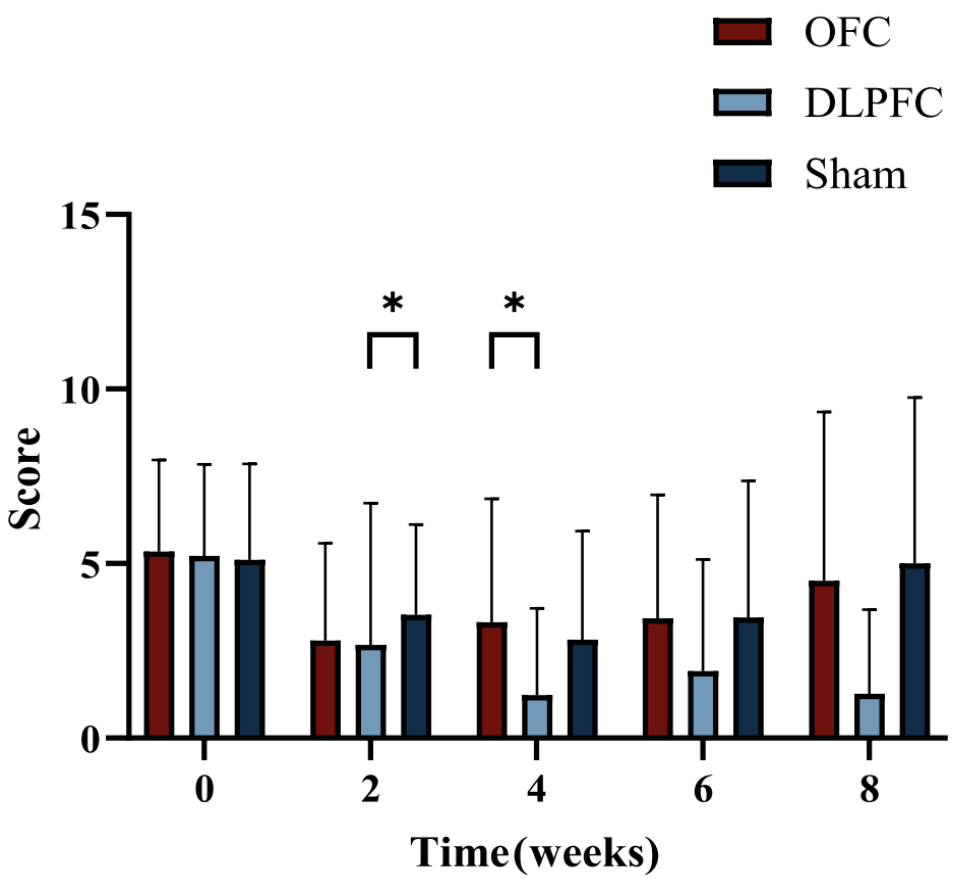
Error bars represent 95% confidence intervals. aTBS indicates accelerated theta-burst stimulation

Ramos M.R.F. et al JAMA Psychiatry. 2025 Mar 5:e250013

Brain and Cognition
DISCOVERY FOUNDATION

tDCS to the DLPFC May Improve Anhedonia

- Transcranial Direct Current Stimulation (tDCS) decreases SHAPS score from baseline to 8 weeks of treatment with tDCS to the left dorsolateral prefrontal cortex (DLPFC)



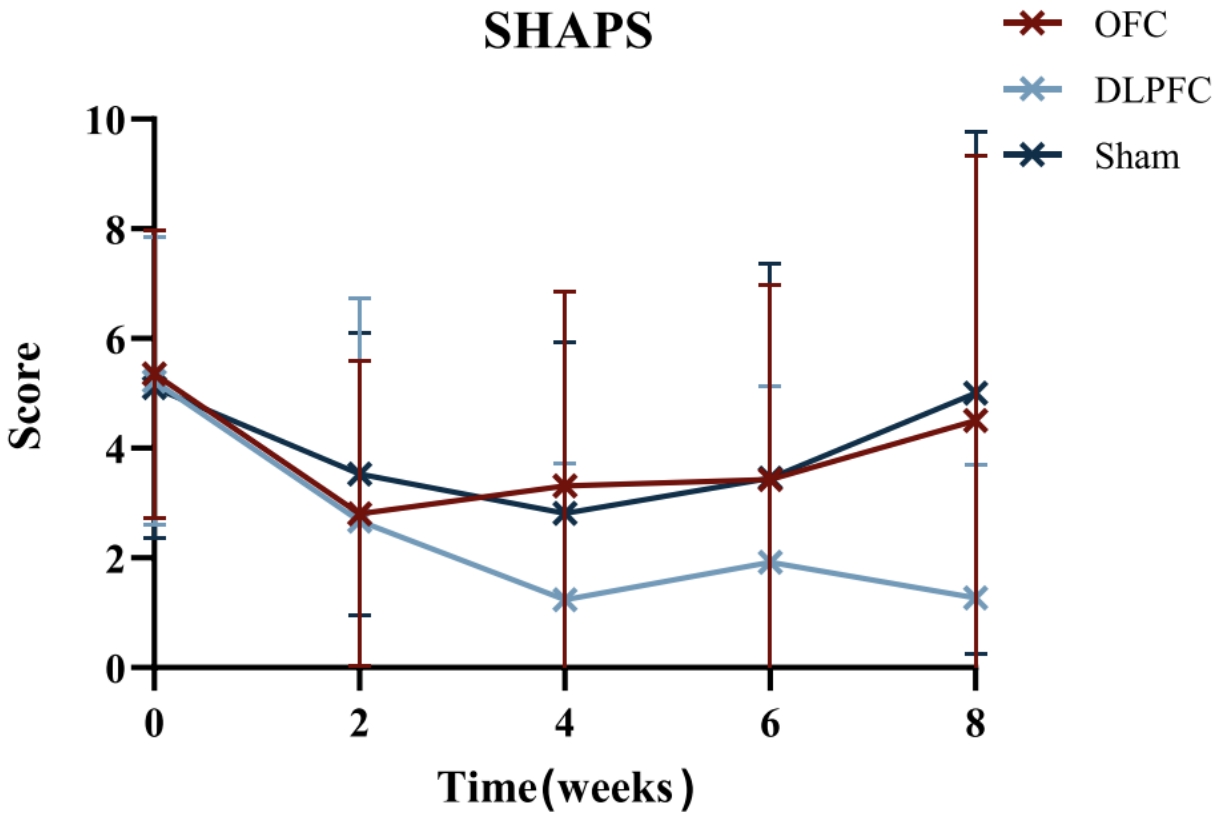


Fig. 4. SHAPS scale scores in the study groups over time.

Rezaei M et al. J Affect Disord 2023;339:756-62; Kong S et al. J Affect Disord 2024;350:264-73.

Brain and Cognition DISCOVERY FOUNDATION

ASCERTAIN-TRD Trial

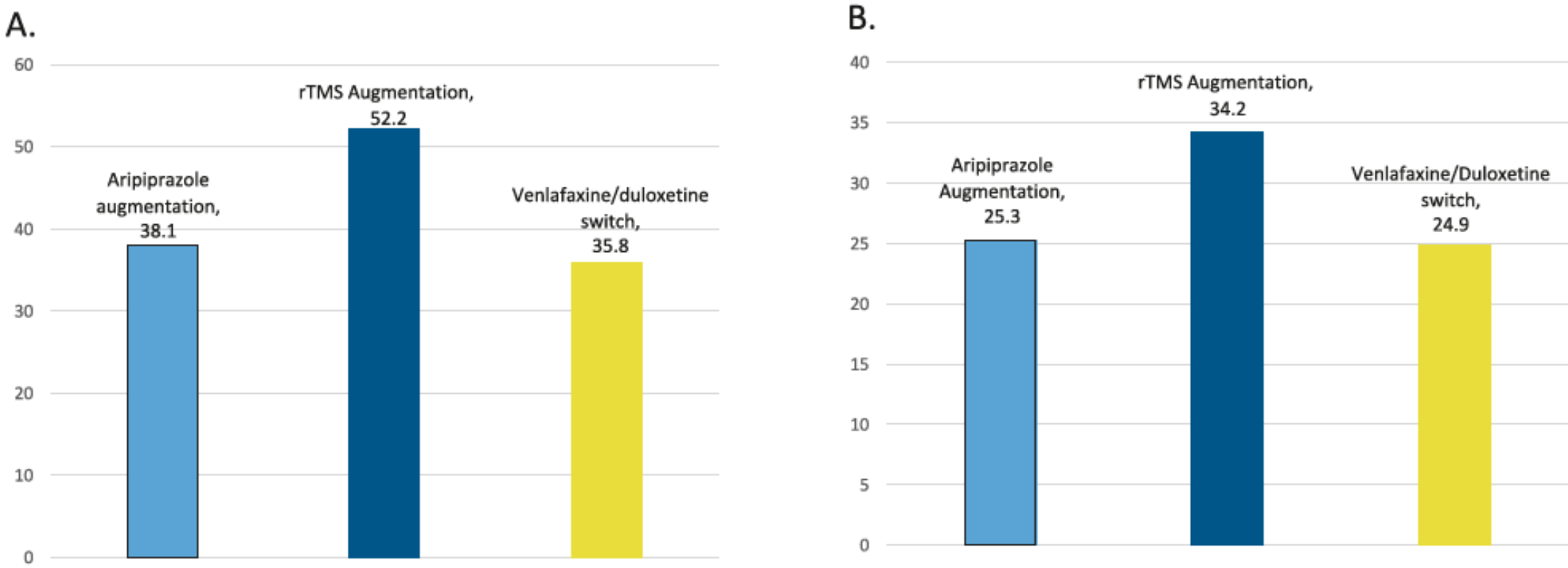


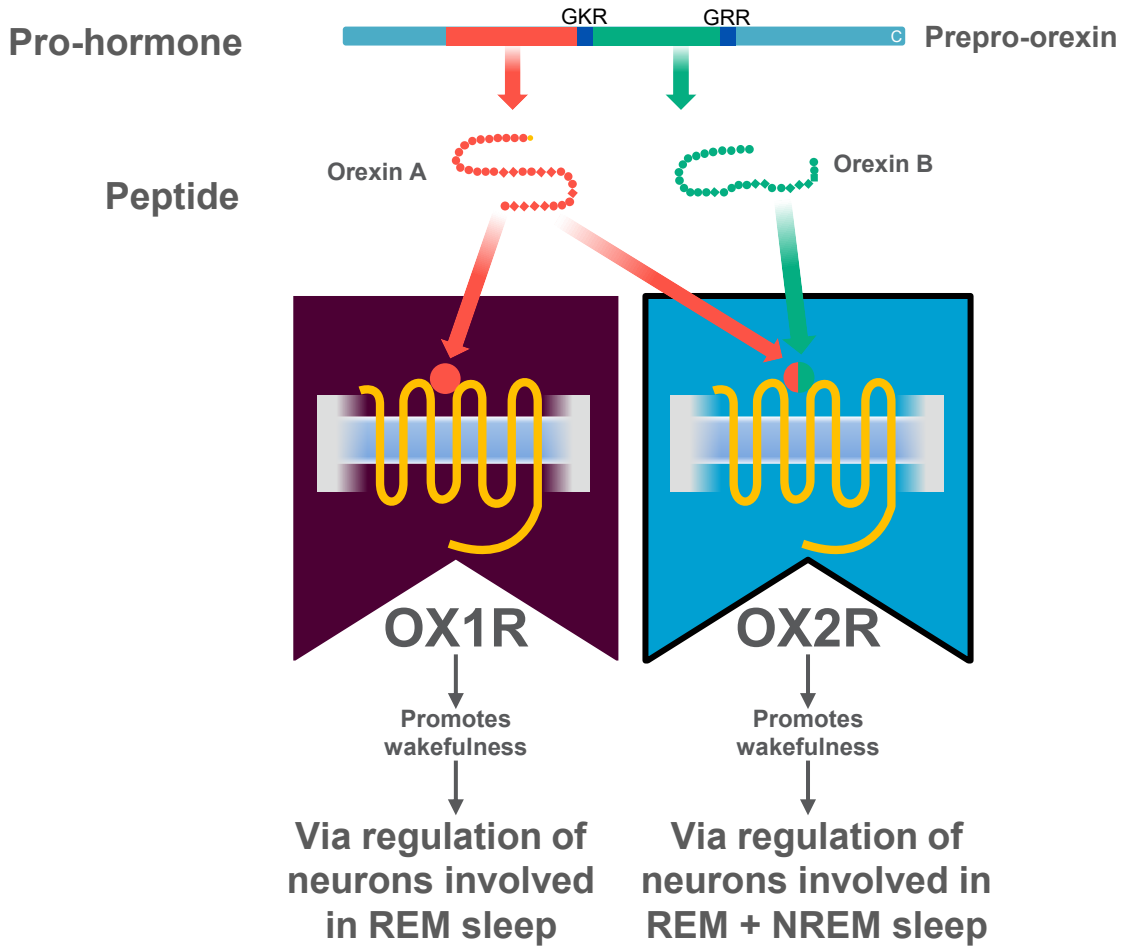
Fig. 4 MADRS response and remission rates comparing different study arms. A MADRS response rates (%); **B** MADRS remission rates (%). MADRS Montgomery-Asberg Depression Rating Scale (MADRS), rTMS Repetitive Transcranial Magnetic Stimulation; y-axis = % response/remission, x-axis = study arms.

Papakostas GI et al. Mol Psychiatry 2024;29(13):2287–2295.

Brain and Cognition DISCOVERY FOUNDATION

Fundamental Role of Orexin in Sleep-Wake Regulation

- Orexin A and Orexin B are cleaved from prepro-orexin[1]
- Orexin A binds OX1R and OX2R[1]
- Orexin B binds OX2R[1] only
- Activation of OX1R/OX2R is responsible for the transition of respective sleep states to a state of wakefulness[1-3]



NREM=non-rapid eye movement; OX1R=orexin receptor type-1; OX2R=orexin receptor type-2; REM=rapid eye movement

1. Equihua AC et al. *Front Pharmacol.* 2013;4:163. **2.** Beuckmann CT et al. *J Pharm Mol Ther.* 2017;362(2):287-295. 3. Willie JT et al. *Neuron.* 2003;38(5):715-730

Brain and Cognition DISCOVERY FOUNDATION

Efficacy and Safety Profiles of FDA-approved Dual Orexin Receptor Antagonists in Depression: A Systematic Review of Pre-Clinical and Clinical Studies

Journal of Psychiatric Research 191 (2025) 752–769

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Efficacy and safety profiles of FDA-approved dual orexin receptor antagonists in depression: A systematic review of pre-clinical and clinical studies

Shreya Vasudeva [a,b], Sabrina Wong [a,c,d], Gia Han Le [a,d,e], Christine E. Dri [d], Kayla M. Teopiz [d,e], Roger Ho [g,h,i], Taeho Greg Rhee [j,k], Roger S. McIntyre [c,f,*]

Brain and Cognition DISCOVERY FOUNDATION

Pharmacological Treatments Under Investigation for Anhedonia

Monoaminergic

TREATMENT	*MOA*
Vortioxetine*	Various 5HT receptor modulation/SRI
Dextromethorphan-bupropion*	NMDA antag/SNDRI/ sigma-1 agonist
Bupropion*	NDRI
Agomelatine	MT1+MT2 agonist/5HT2C antag
Escitalopram*	SSRI
Sertraline*	SSRI
Fluoxetine*	SSRI
Vilazodone*	SSRI/5HT1A agonist
Venlafaxine ER*	SNRI
Levomilnacipran ER*	SNRI
Amitifadine	SNDRI
Moclobemide	MAOI-A
Clomipramine	TCA

Glutamatergic

TREATMENT	*MOA*
Ketamine	NMDA antagonist
Esketamine	NMDA antagonist
Riluzole	Glu reuptake enhancer

SDA-PAs, aka "Antipsychotics"

TREATMENT	*MOA*
Cariprazine*	D2+D3 partial agonist
Pramipexole	D2+D3 partial agonist
Aripiprazole*	D2 partial agonist
Lumateperone*	D2+5HT2A antag/D1 modulator/SRI

Opioid Agents

TREATMENT	*MOA*
Navacaprant	Kappa opioid antagonist

Psychedelics

TREATMENT	*MOA*
Psilocybin	5HT2A agonist

Anti-inflammatory Agents

TREATMENT	*MOA*
Infliximab	TNFα antag

Stimulants

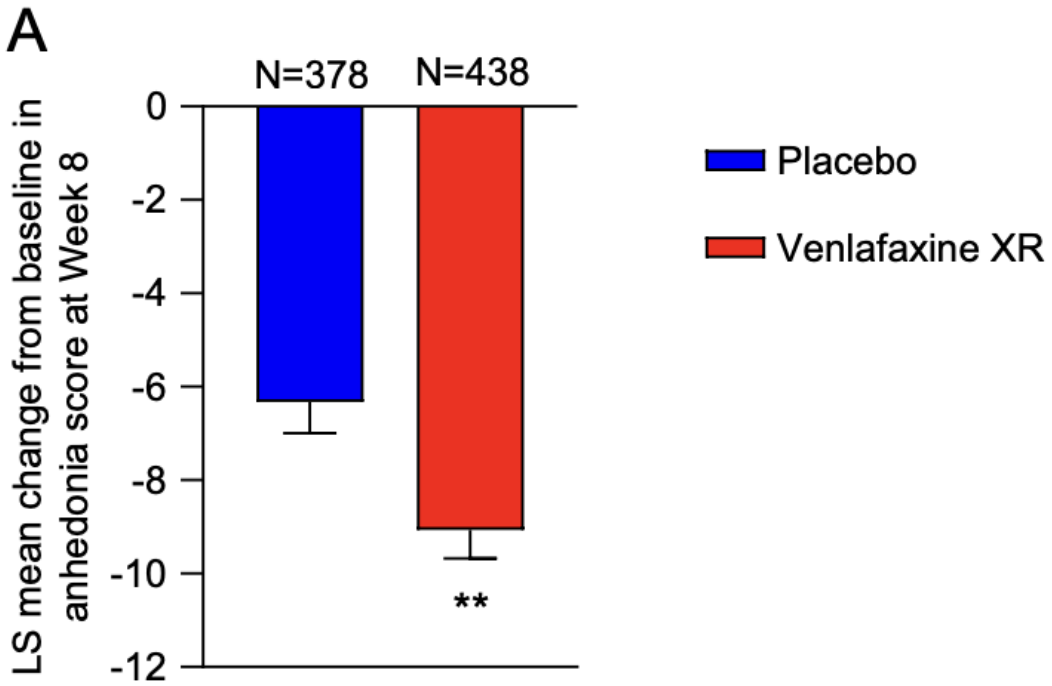
TREATMENT	MOA
Amphetamine	NDRI
Methylphenidate	NDRI

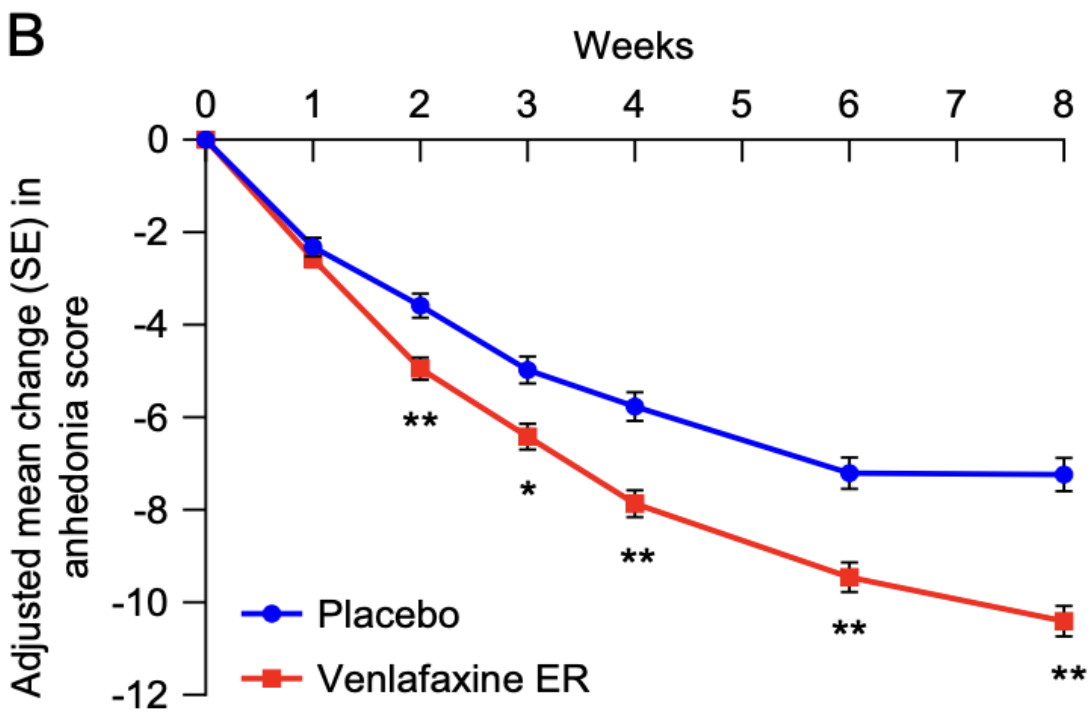
**FDA approved for depression*

Cao B et al. Prog Neuropsychopharmacol Biol Psychiatry 2019;92:109-17.

Venlafaxine XR Improves Anhedonia

- Compared MADRS score* from baseline to after 8 weeks of treatment with venlafaxine (75–225 mg/day; fixed or flexible dose; 5 clinical studies)





Between-group difference of -2.73 (95% CI: -3.63 to -1.82, p < 0.0001)

*MADRS anhedonia factors (items 1 [apparent sadness], 2 [reported sadness], 6 [concentration difficulties], 7 [lassitude], and 8 [inability to feel])

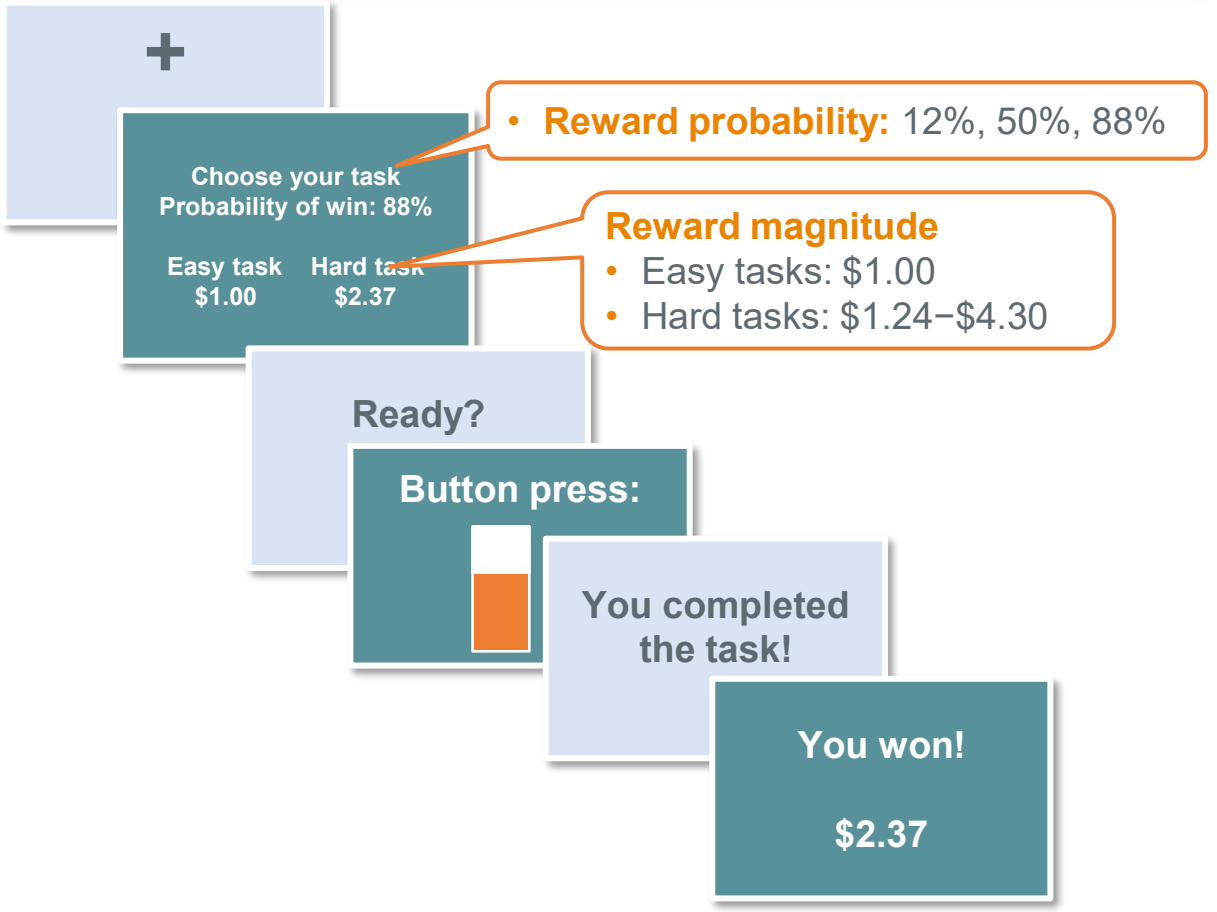
McIntyre RS et al. CNS Spectr 2024;29(3):206-14.

Brain and Cognition DISCOVERY FOUNDATION

Effort Expenditure for Rewards Task (EEfRT)

- **Anhedonia** is specifically associated with **decreased motivation for rewards**[1]
- **EEfRT:**
  - Measures participants' willingness to make efforts to obtain monetary reward under different conditions of **reward probability** and **magnitude**[1]
  - A multi-trial game in which participants are given an opportunity on each trial to choose between two different task difficulty levels in order to obtain rewards[1]
  - Can be used to examine differences in **motivation** in individuals experiencing **anhedonia**[2]

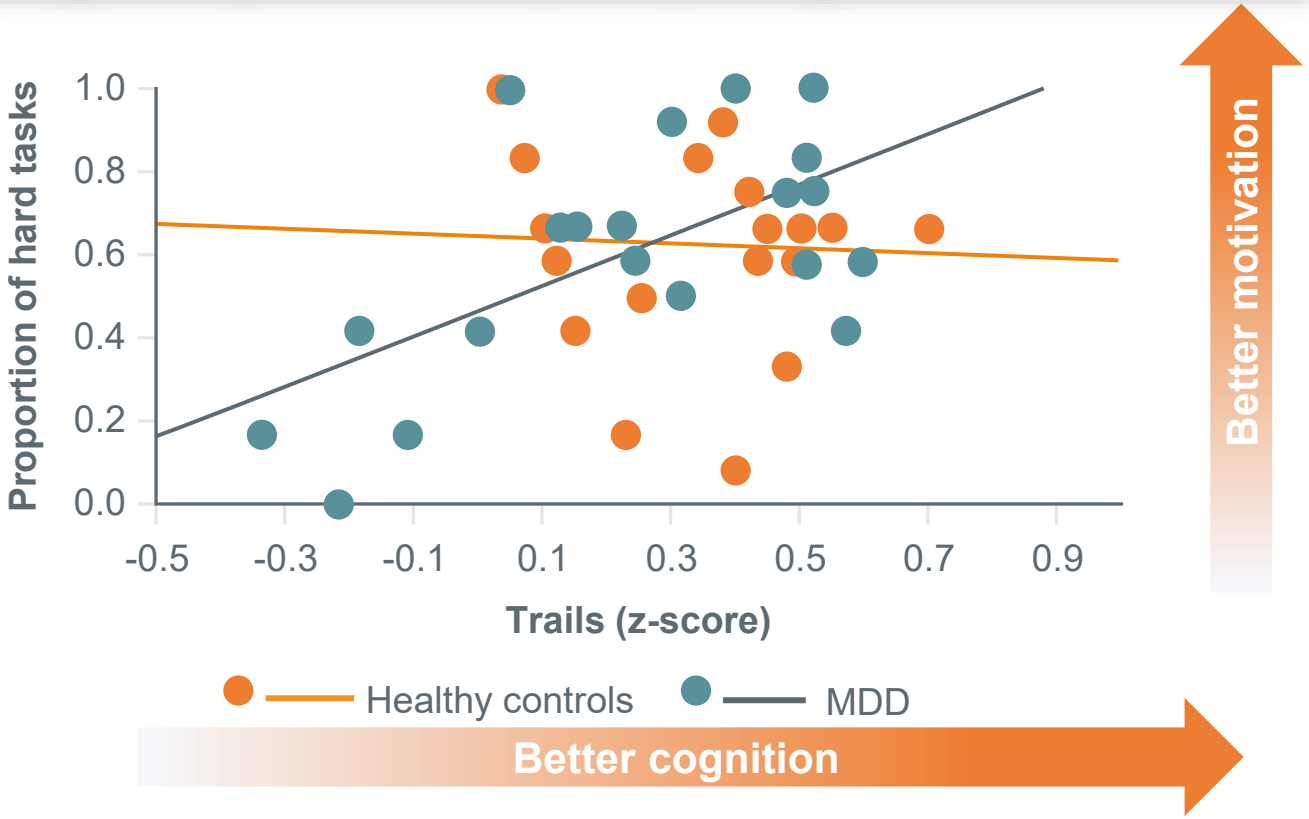
Schematic diagram of a single trial of the EEfRT[1]



EEfRT, Effort Expenditure for Rewards Task.
Adapted from 1. Treadway MT et al, PLoS One. 2009;4(8):e6598; 2. Bryant J et al. PLoS One. 2017;12(3):e0173439.

Improved performance in reward motivation was observed in patients with MDD treated with vortioxetine compared with healthy controls

Correlations between proportion of hard tasks and cognitive performance (Trails) in high reward conditions

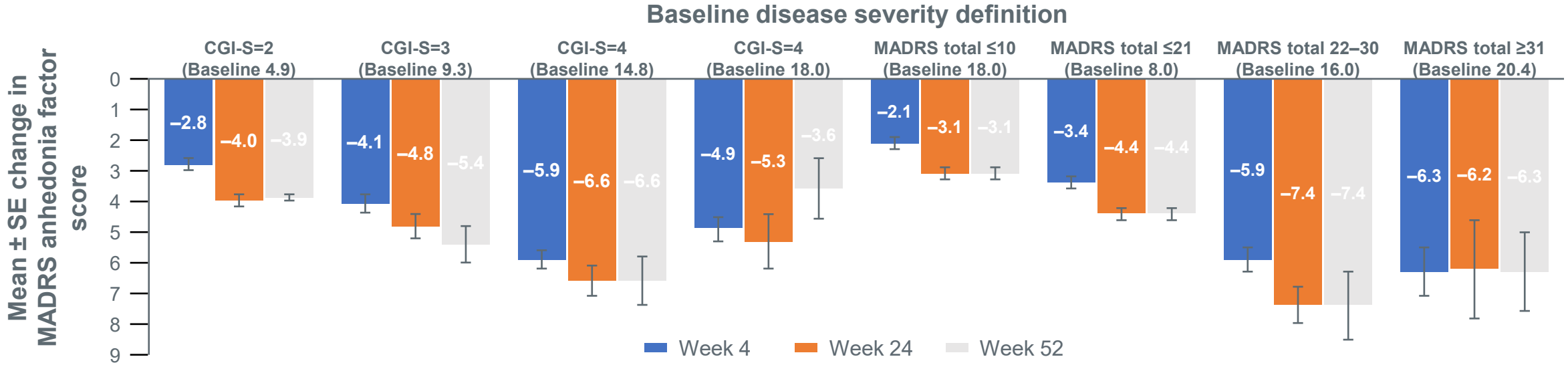


A positive association between Trails performance and more effort for high rewards in patients with MDD
(β=2.223, p=0.017)

MDD, Major depressive disorder.
Adapted from Subramaniapillai M et al. Compr Psychiatry. 2019;94:152113.

Effect of Vortioxetine on anhedonia: Implicates Glutamate and Dopmanine ?

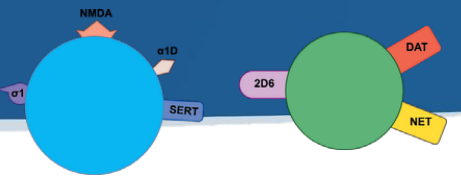
Change from baseline in MADRS anhedonia factor scores at weeks 4, 24 and 52 of vortioxetine maintenance treatment in patients with ≥1 level of improvement in CGI-S, categorised by baseline CGI-S and MADRS total scores

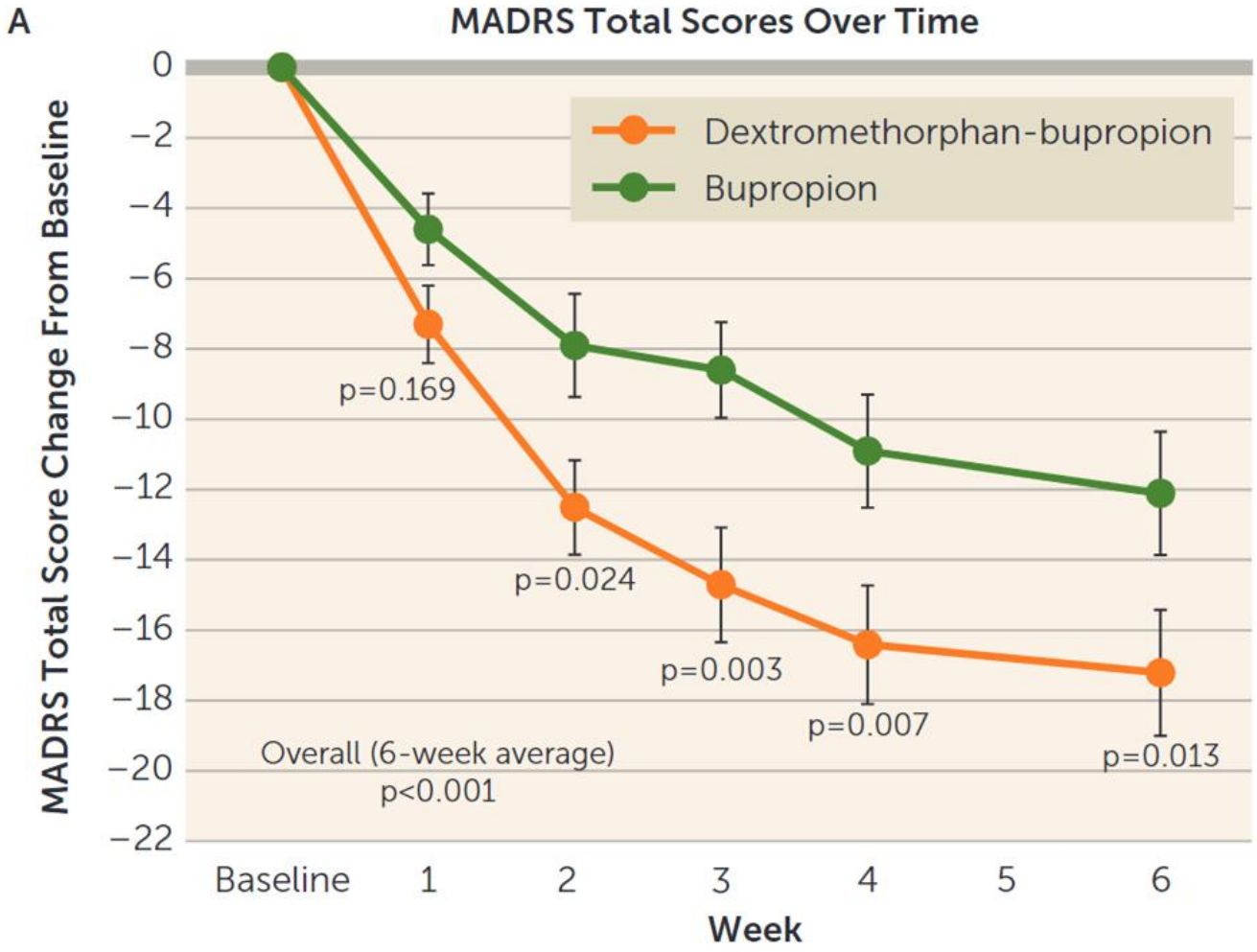


- Evaluation of the **MCIC anchored to at least 1 level of improvement in CGI-S** indicates a **relationship between baseline severity[b] and the magnitude of improvement in anhedonia scores deemed clinically meaningful by the clinician**
- **Worse baseline disease severity** was associated with a **higher MCIC for anhedonia**
- This suggests that patients with **more severe depression** may require **greater improvements in anhedonia** to experience a **clinically meaningful change**

McIntyre RS et al. J Affect Disord 2024;363:430-5

Dextromethorphan 90 mg/Bupropion 210 mg vs Bupropion 300 mg





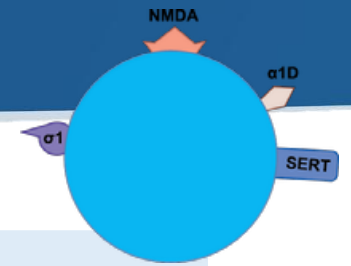
- AXS-05 (dextromethorphan-bupropion) is an oral NMDA receptor antagonist and sigma-1 receptor agonist, which utilizes inhibition of CYP2D6 to increase its bioavailability

- Week 1 CGI-I: separated; *P* = .045
- Week 6 MADRS remission: 47% vs 16%; *P* = .0004
- Cohen's d of 1.2 for the overall 6-week treatment effect on MADRS total scores

In patients with major depression, dextromethorphan-bupropion significantly improved depressive symptoms compared with bupropion, including anhedonia

Brain and Cognition
DISCOVERY FOUNDATION

Anti-Anhedonia Effects of Dextromethorphan: Driven by Sigma-1 Receptor Agonism



Dextromethorphan is the **first FDA-approved antidepressant** with explicit Sigma-1 Receptor (S1R) agonist action

Both preclinical and clinical studies support its antidepressant-like effects via S1R modulation

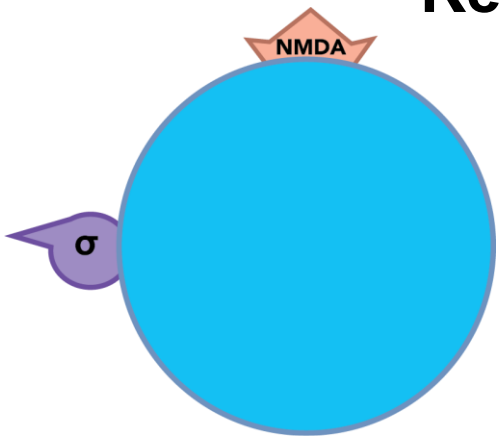
S1R agonism appears to be a promising avenue for addressing treatment-resistant depression, anhedonia, and neuroinflammation

Xiao N et al. Expert Opin Ther Targets 2025;29(6):345-59.

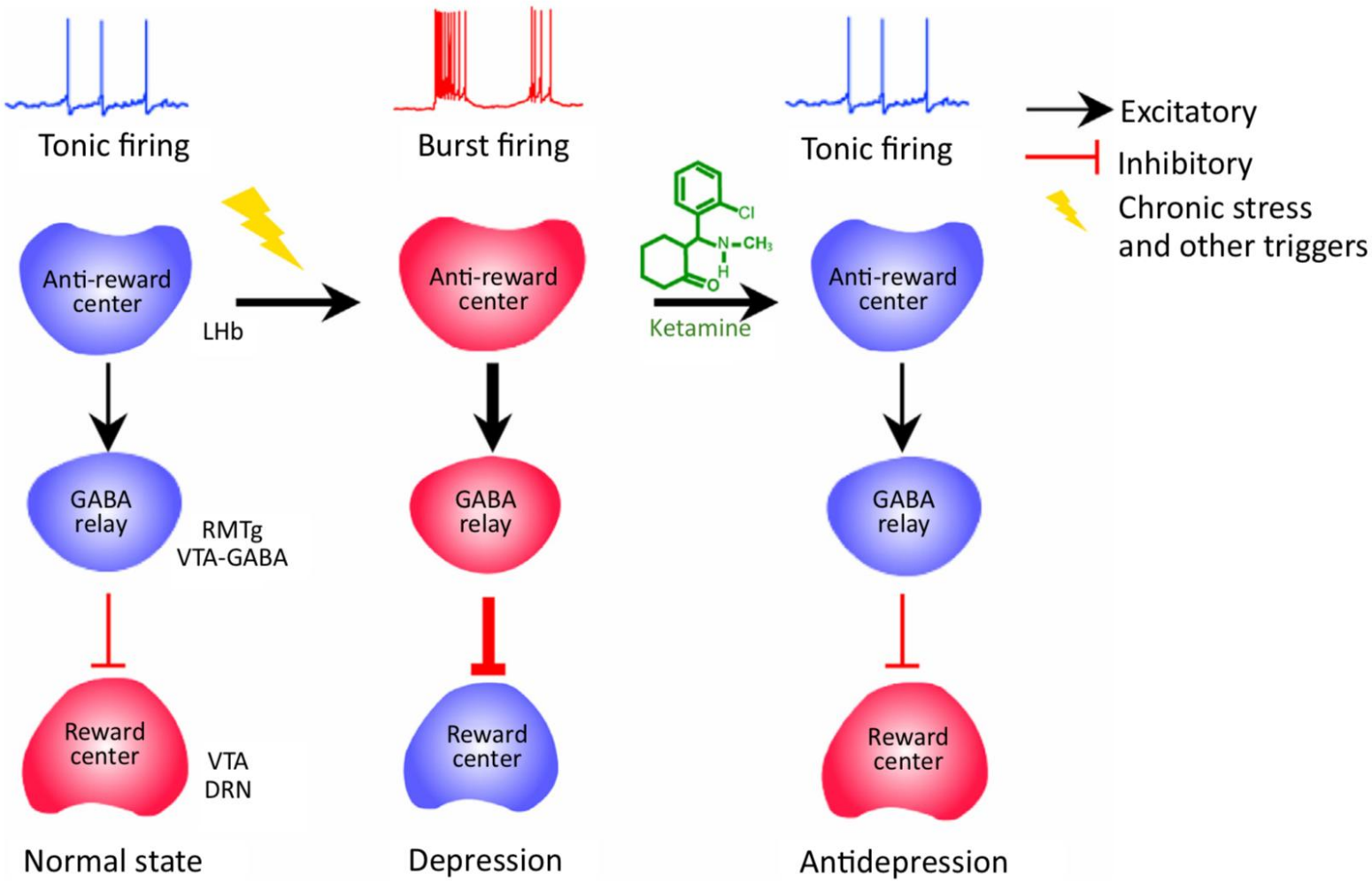
Brain and Cognition
DISCOVERY FOUNDATION

Circuit-Based Impact of Ketamine on Lateral Habenula Firing in MDD

Ketamine



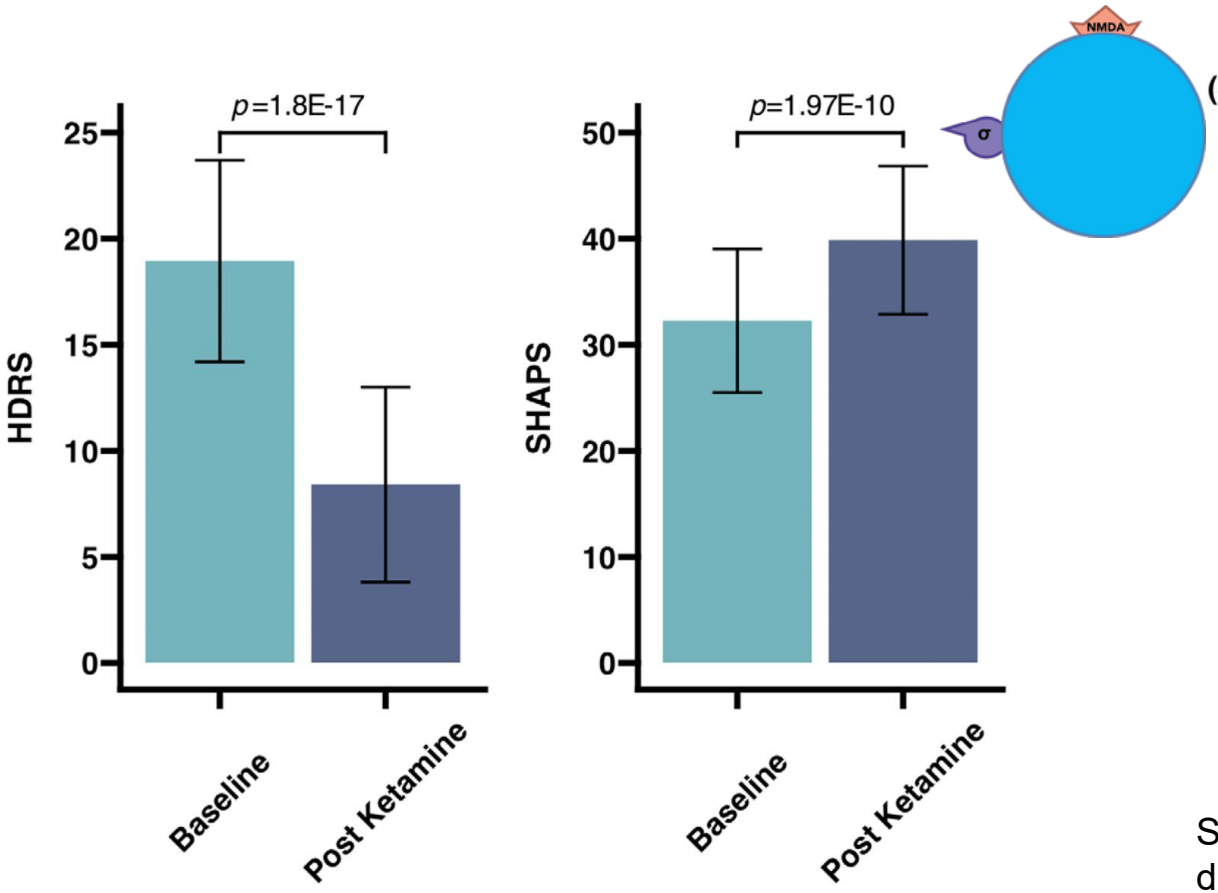
- NMDA receptor-mediated inhibition of inhibitory GABAergic interneurons in the PFC has been implicated in ketamine's antidepressant mechanism of action (Zanos P et al, 2018)



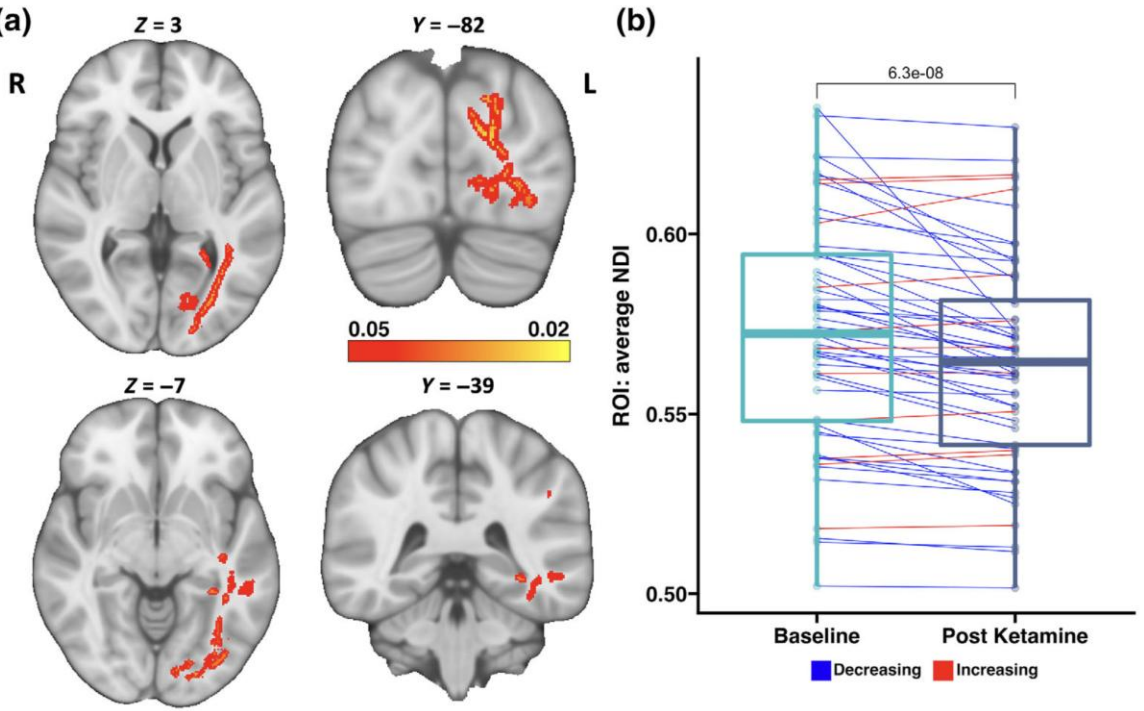
Cui Y, Hu S, Hu H. Trends Neurosci 2019;42(3):179-91.

Brain and Cognition DISCOVERY FOUNDATION

Serial Ketamine Infusions Improve Anhedonia, White Matter Changes, and Neuronal Density



TRD patients (N = 57, 49.12% female, mean age: 39.9) received four intravenous ketamine infusions (0.5 mg/kg) 2–3 days apart.

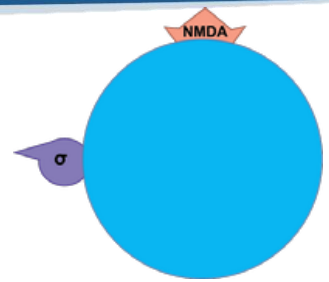


Significant changes in WM following Serial Ketamine Infusion. Significant decreases in the NDI were observed in tracts connecting temporal, occipital, and limbic regions, including the left posterior thalamic radiation, left inferior longitudinal fasciculus, and left retrolenticular region of the internal capsule. NDI, Neurite Density Index; ROI, region of interest; WM, white matter.

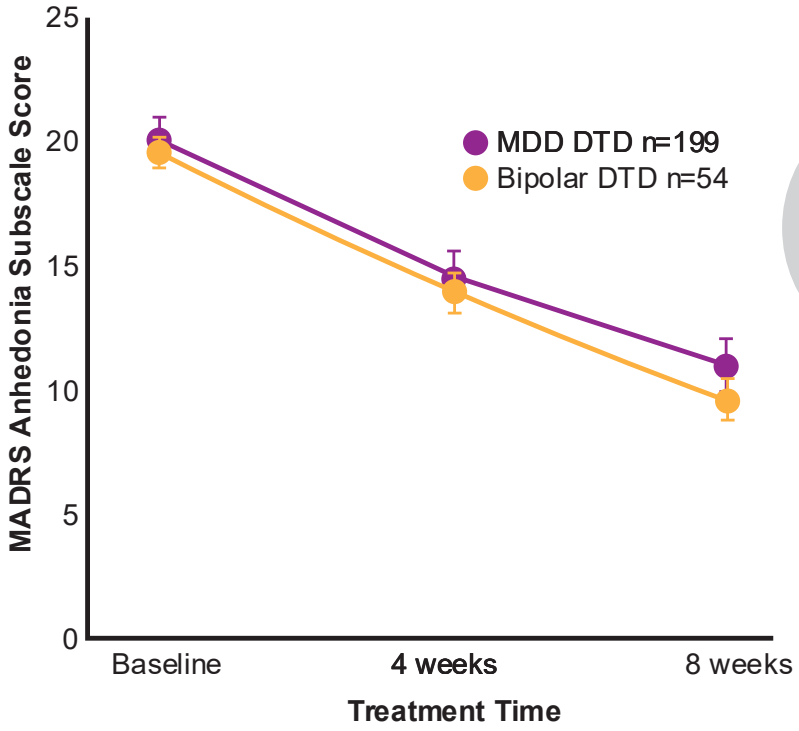
Taraku B et al. Hum Brain Mapp 2023;44:2395-406.

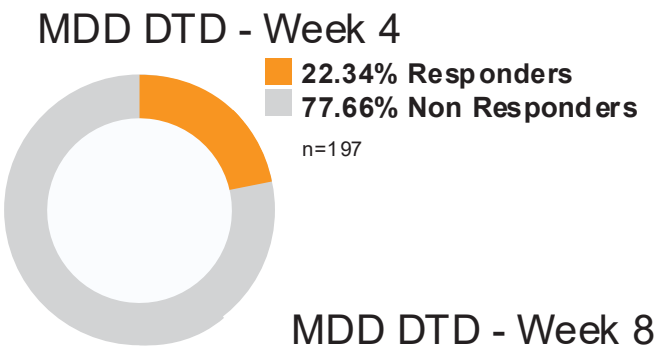
Brain and Cognition DISCOVERY FOUNDATION

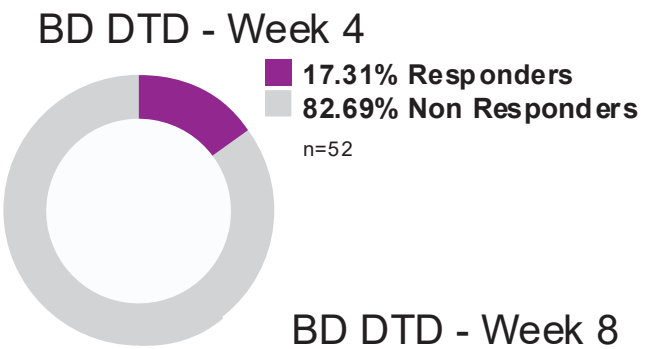
Adjunctive Esketamine Nasal Spray Reduces Anhedonia in Treatment-Resistant MD and BD

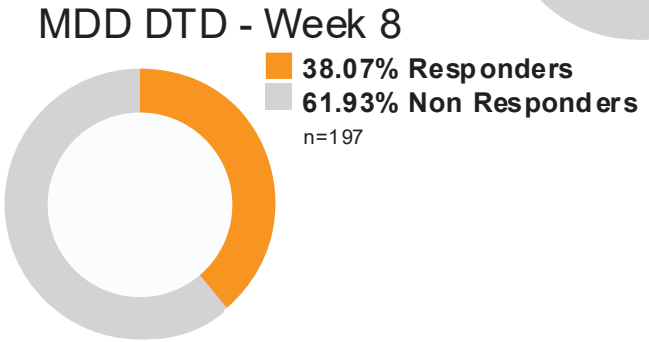


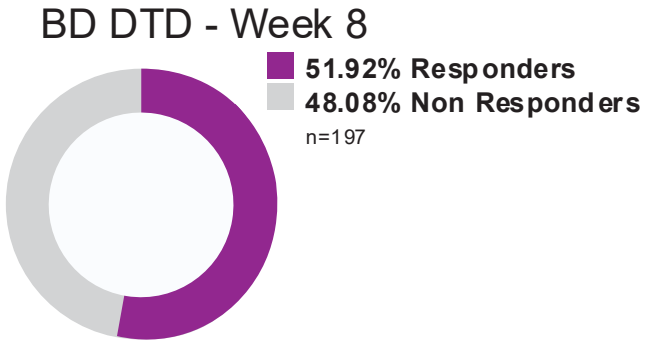
- Multicenter, observational, real-world study included 253 difficult-to-treat patients (199 with unipolar depression/DTD; 54 with bipolar depression/B-DTD)
- Participants received nasal esketamine adjunctive to their current medication regimen
    - Anhedonia was assessed using the MADRS anhedonia subscale
    - Response was defined as a ≥50% reduction in MADRS anhedonia subscale score from baseline











d'Andrea G et al. Psychiatry Res 2025;352:116655.

Brain and Cognition DISCOVERY FOUNDATION

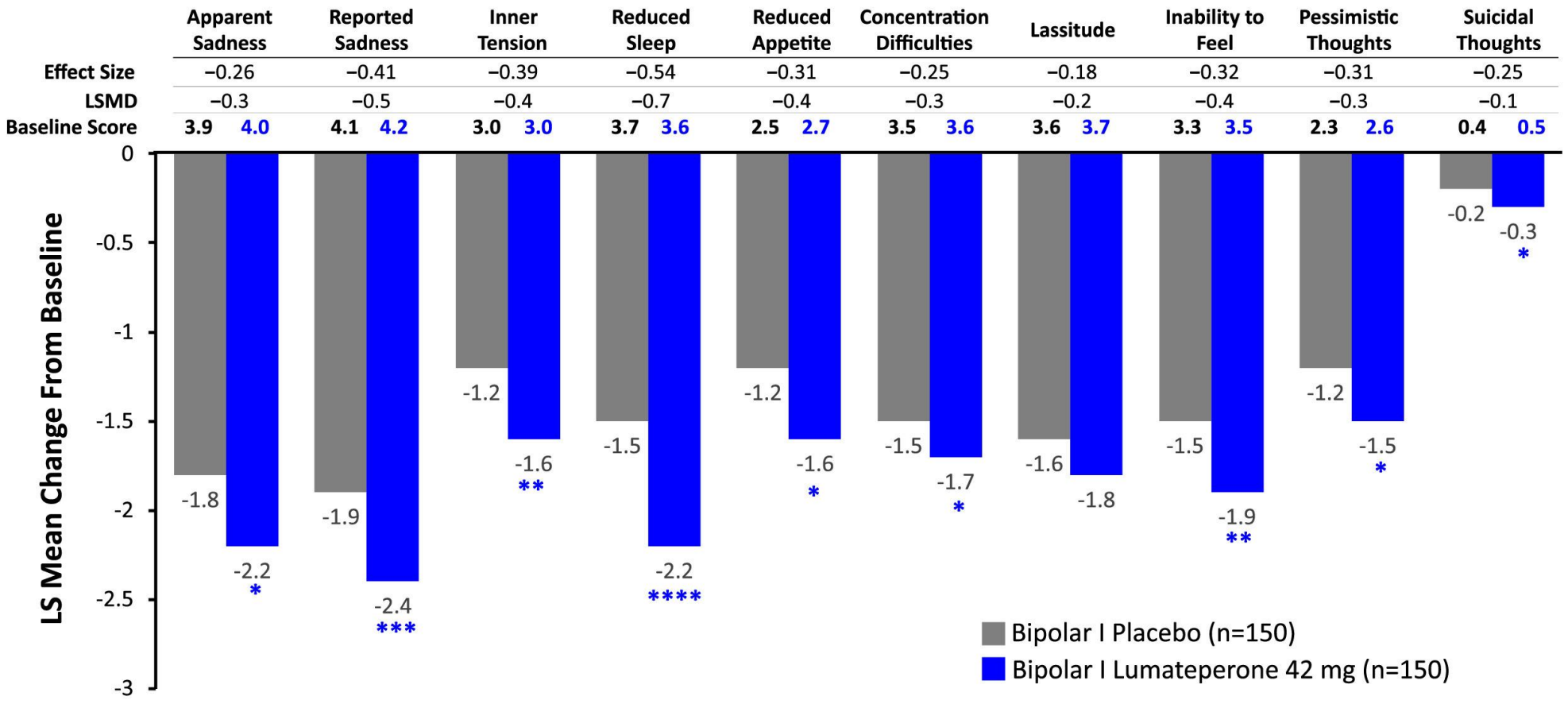
Lumateperone in Bipolar I and II Depression: Anhedonia Factor Post Hoc Analyses

Serotonin 5HT2A antagonist and dopamine D2 presynaptic partial antagonist/ postsynaptic antagonist

Actions also at D1, AMPA, NMDA, and SERT

Anhedonia items

Bipolar I Population



McIntyre RS et al. Eur Neuropsychopharmacol 2023;68:78-88.

Brain and Cognition DISCOVERY FOUNDATION

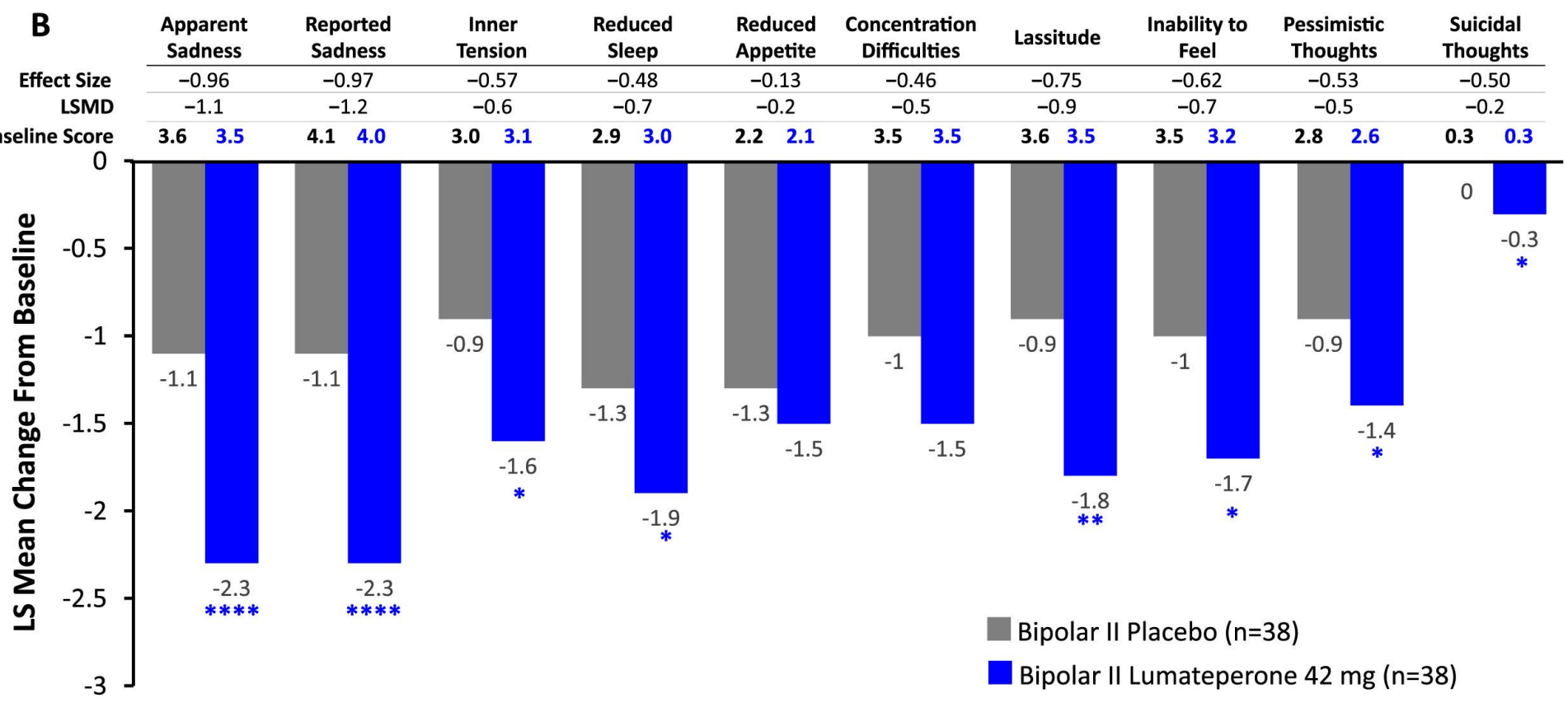
Lumateperone in Bipolar I and II Depression: Anhedonia Factor Post Hoc Analyses

Serotonin 5HT2A antagonist and dopamine D2 presynaptic partial antagonist/ postsynaptic antagonist

Actions also at D1, AMPA, NMDA, and SERT

Anhedonia items

Bipolar II Population



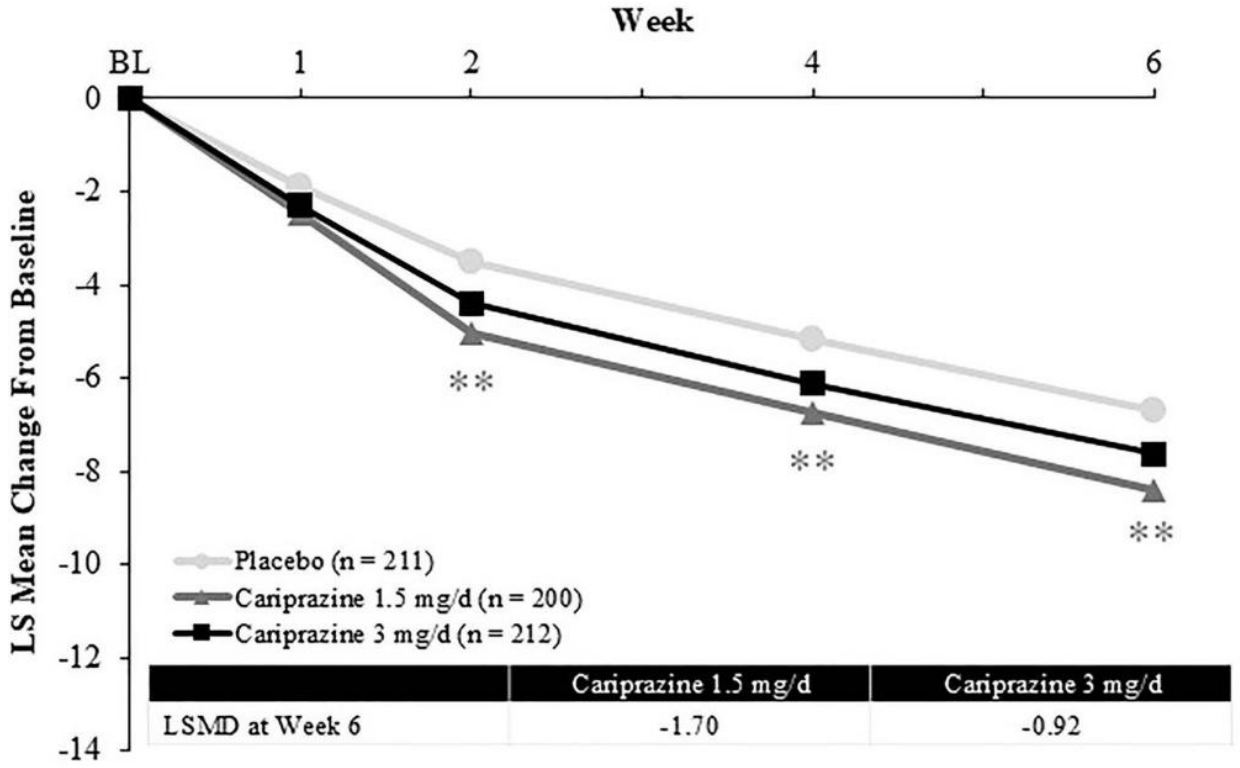
McIntyre RS et al. Eur Neuropsychopharmacol 2023;68:78-88.

Brain and Cognition DISCOVERY FOUNDATION

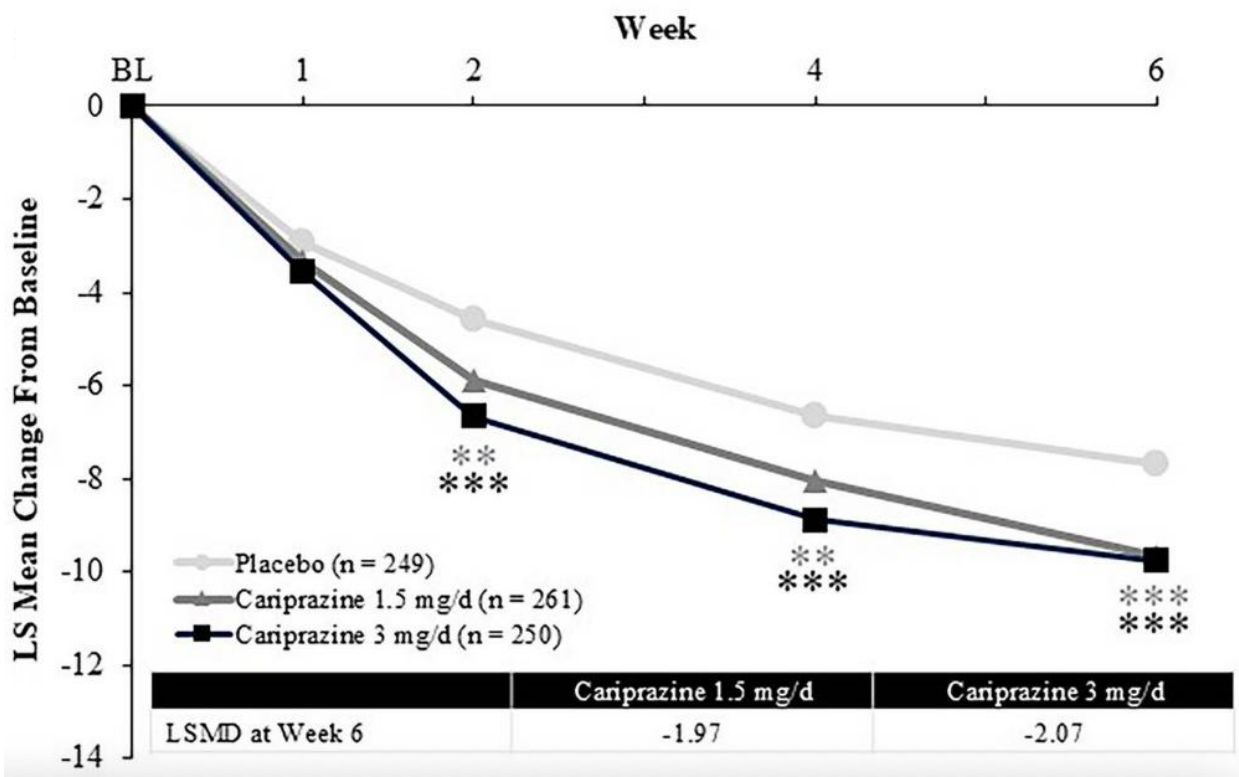
Adjunctive Cariprazine for Anhedonia in BP1: Key Findings and Implications

1383 adults from **three pooled clinical trials** (NCT01396447, NCT02670538, NCT02670551)

Lower anhedonia subgroup (score < 19; n=623), Higher anhedonia subgroup (score ≥ 19; n=760)



	Cariprazine 1.5 mg/d	Cariprazine 3 mg/d
LSMD at Week 6	-1.70	-0.92



	Cariprazine 1.5 mg/d	Cariprazine 3 mg/d
LSMD at Week 6	-1.97	-2.07

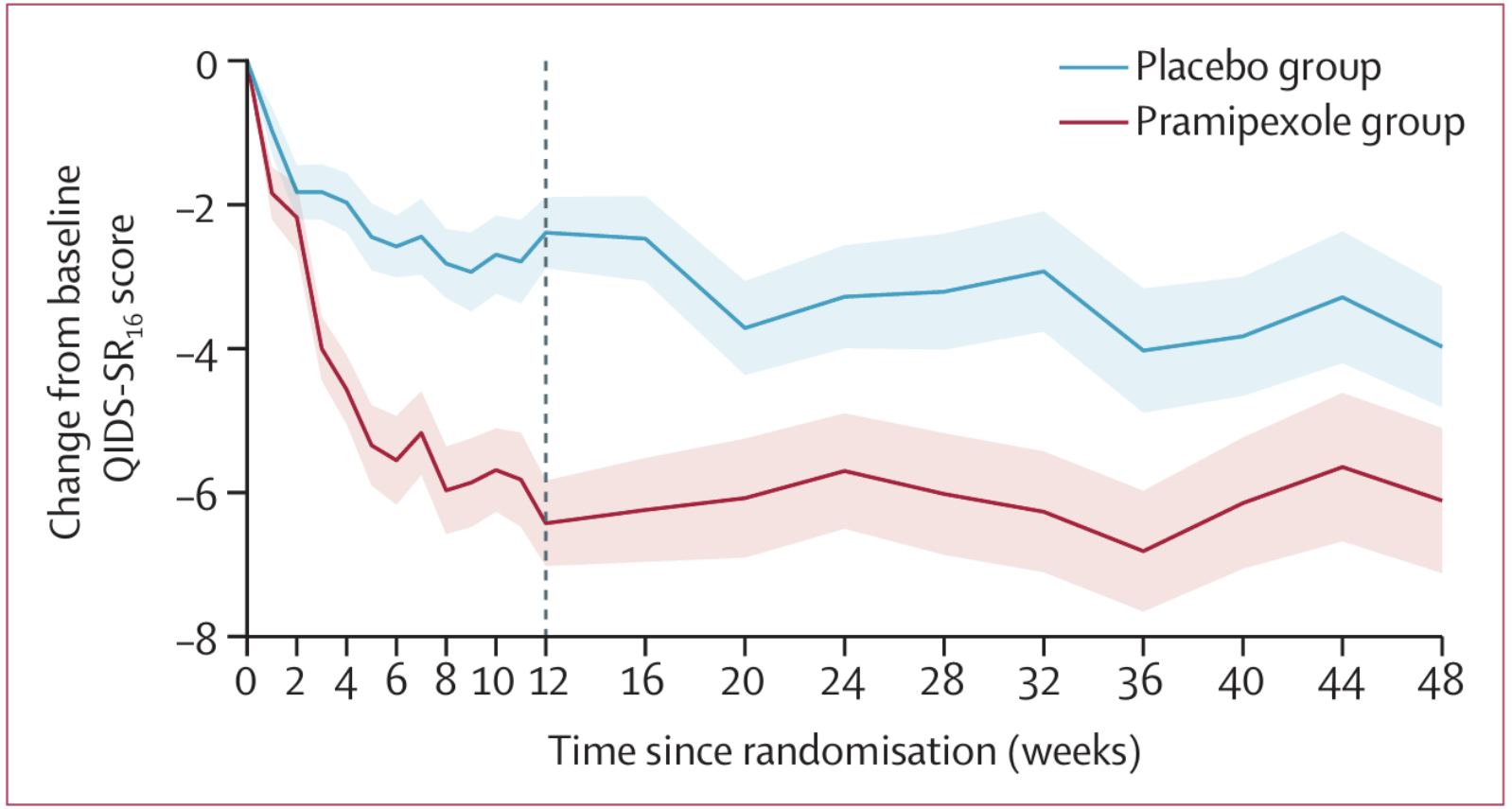
Cariprazine demonstrated anti-anhedonic effects regardless of baseline anhedonia symptoms in patients with BP-I depression

McIntyre RS et al. Adv Ther 2025;42:246-60.

Brain and Cognition DISCOVERY FOUNDATION

Pramipexole Augmentation for the Acute Phase of Treatment-Resistant, Unipolar Depression: A Placebo Controlled, Double-Blind, Randomised Trial in the UK

Primary efficacy assessment of change from baseline in QIDS-SR16 total score at week 12



Browning M., et al. Lancet Psychiatry. 2025 Aug;12(8):579-589.

Brain and Cognition DISCOVERY FOUNDATION

Pramipexole Augmentation for the Acute Phase of Treatment-Resistant, Unipolar Depression: A Placebo Controlled, Double-Blind, Randomised Trial in the UK

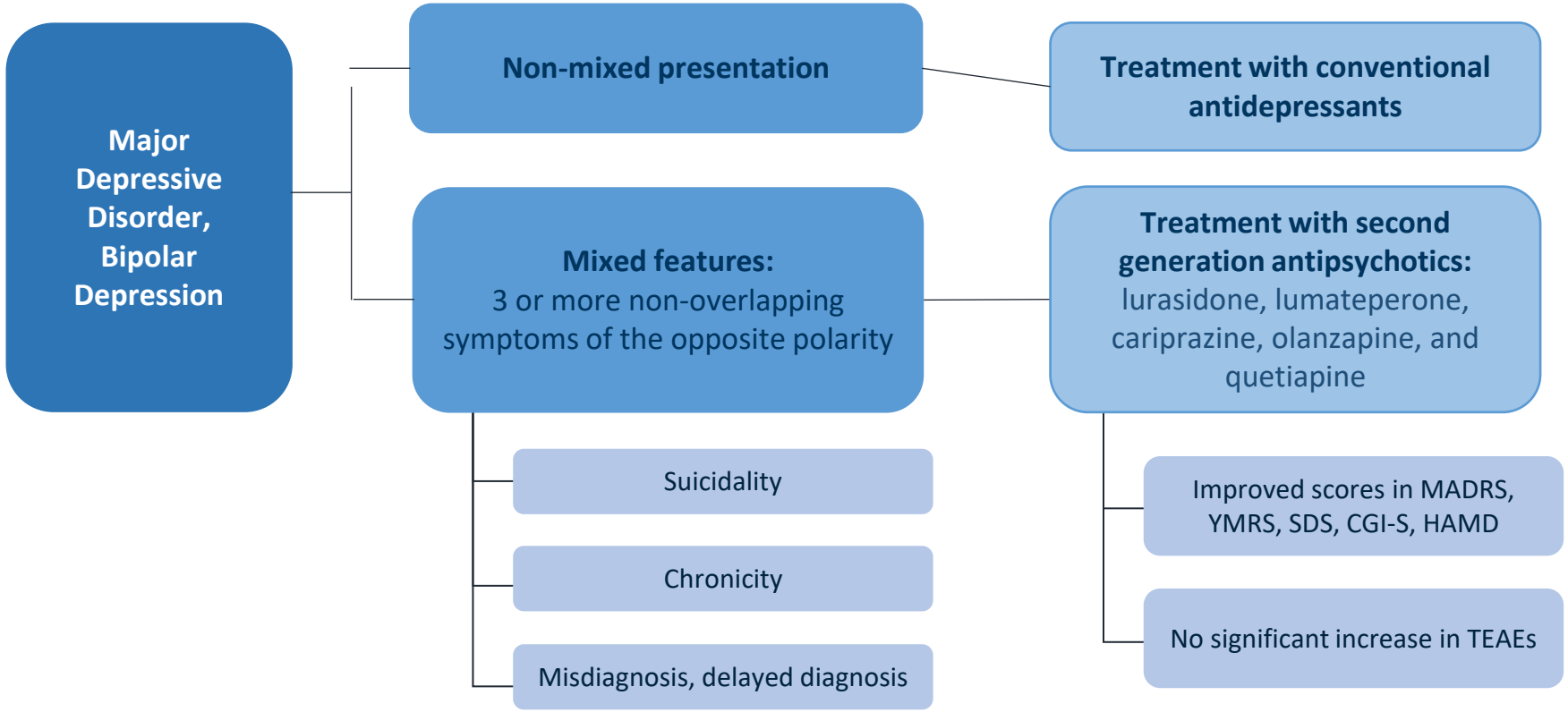
Primary efficacy assessment of change from baseline in QIDS-SR16 total score at week 12

	Pramipexole group (n=75)	Placebo group (n=75)	Treatment effect (95% CI)	Standardised mean difference (95% CI)	p value
Outcomes at week 12					
Primary efficacy endpoint					
Change from baseline to week 12 in QIDS-SR_{16} total score (mean [SD])	−6·4 (4·9)	−2·4 (4·0)	−3·91 (−5·37 to −2·45)*	−0·87 (−1·20 to −0·55)	<0·0001
Secondary efficacy endpoint					
QIDS-SR_{16} response rate at week 12†	30/68 (44%)	11/67 (16%)	2·72 (1·49 to 4·95)‡	0·62 (0·28 to 0·96)	0·0011
QIDS-SR_{16} remission rate at week 12§	19/68 (28%)	5/67 (8%)	3·94 (1·61 to 9·64)‡	0·56 (0·22 to 0·90)	0·0026
Change from baseline to week 12 in QIDS-C total score (mean [SD])	−6·1 (4·5)	−3·0 (4·9)	−3·26 (−4·67 to −1·86)*	−0·70 (−1·00 to −0·40)	<0·0001
Change from baseline to week 12 in SHAPS total score (mean [SD])	−3·8 (4·0)	−1·5 (3·6)	−2·20 (−3·41 to −1·00)*	−0·58 (−0·89 to −0·26)	0·0003
Change from baseline to week 12 in GAD-7 total score (mean [SD])	−4·1 (5·5)	−1·5 (4·7)	−2·51 (−3·97 to −1·06)*	−0·49 (−0·78 to −0·21)	0·0007
Outcomes at week 48					
Number of patients in study by week 48	40	39	..	..	..
Change from baseline to week 48 in QIDS-SR_{16} total score (mean [SD])	−6·1 (6·0)	−4·0 (5·1)	−2·02 (−3·73 to −0·31)*	−0·36 (−0·67 to −0·06)	0·021
Change from baseline to week 48 in WSAS total score (mean [SD])	−6·8 (11·4)	−3·3 (6·9)	−3·23 (−6·18 to −0·27)*	−0·34 (−0·66 to −0·03)	0·03

Browning M., et al. Lancet Psychiatry. 2025 Aug;12(8):579-589.

Brain and Cognition DISCOVERY FOUNDATION

Pharmacological Interventions in the Treatment of Major Depressive Disorder and Bipolar Depression With Mixed Features



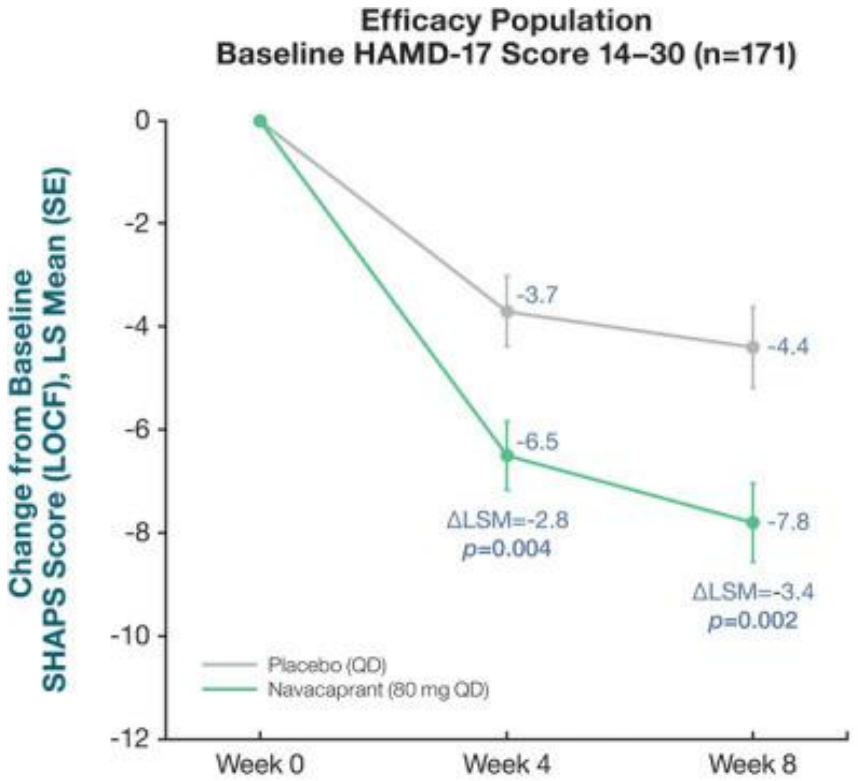
- MADRS, Montgomery–Åsberg Depression Rating Scale; YMRS, Young Mania Rating Scale; SDS, Sheehan Disability Scale; CGI-S, Clinical Global Impression – Severity of Illness; HAMD, Hamilton Depression Rating Scale; TEAE, Treatment-Emergent Adverse Event

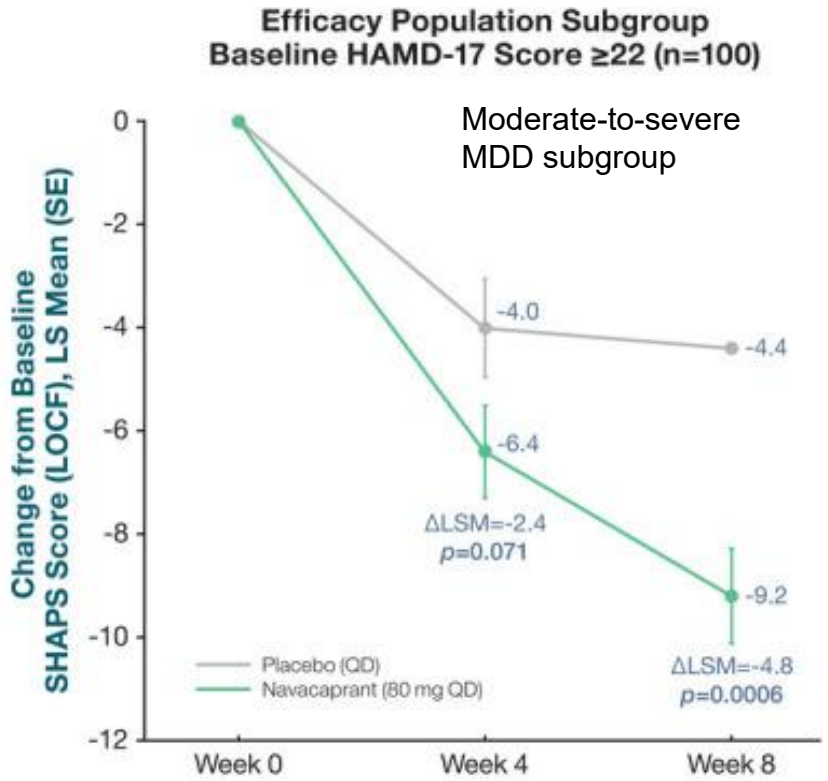
- Xiao N, et al. Bipolar Disorders 2025.

Brain and Cognition DISCOVERY FOUNDATION

Navacaprant, Kappa Opioid Receptor Antagonist, Reduces Anhedonia in MDD

- Phase 2a randomized, double-blind, placebo-controlled, 8-week trial assessed the efficacy and safety of navacaprant in adults with major depressive disorder (MDD)





While overall depression wasn't reduced in the efficacy population, there were **statistically significant improvements on anhedonia (SHAPS)**

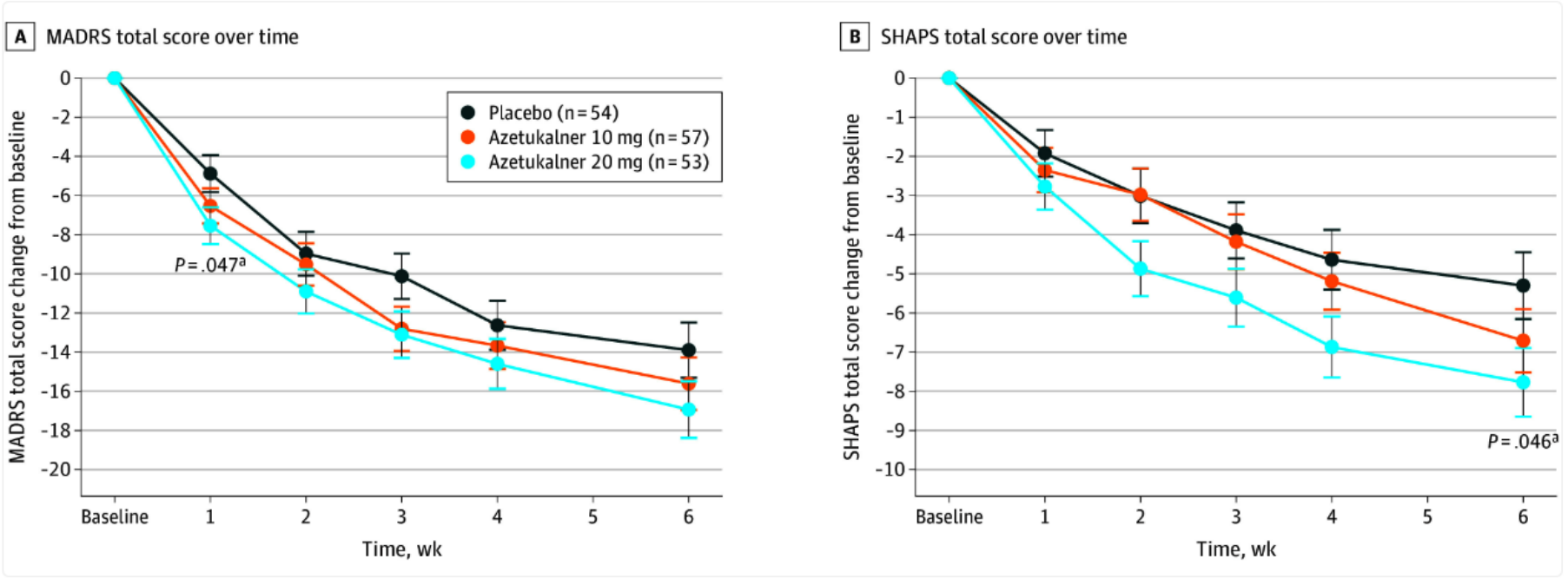
LOCF, Last Observation Carried Forward

Mathew SJ et al. J Clin Psychopharmacol 2025;45(3):267-76.

Brain and Cognition DISCOVERY FOUNDATION

Azetukalner, a Novel KV7 Potassium Channel Opener, in Adults With MDD

- Phase 2, multicenter, randomized, double-blind, placebo-controlled trial
- N=168 adults with moderate to severe MDD and anhedonia
- 6-week treatment, 10 mg or 20 mg daily
- **Significant improvements in anhedonia** (SHAPS and HAM-D17 scores) at week 6 but **not in total MADRS score**



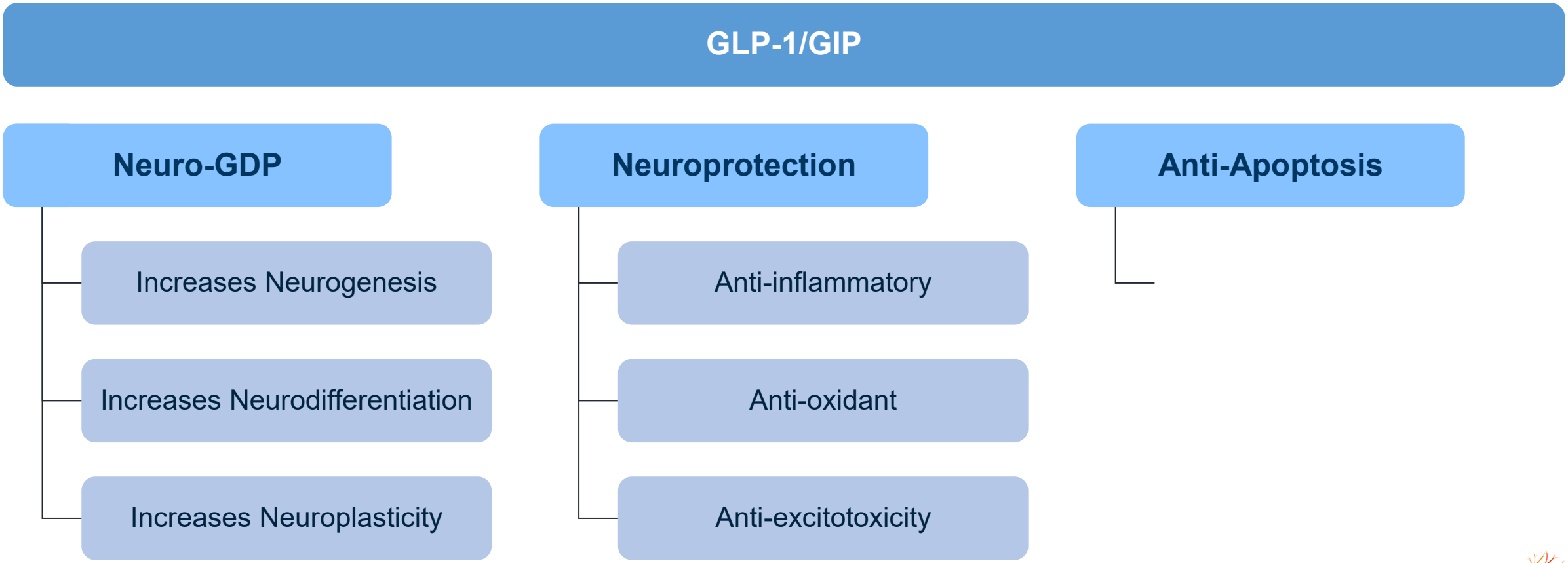
Azetukalner shows promise as a **first-in-class KV7 potassium channel opener** for anhedonia, with **rapid onset and favorable tolerability**

Butterfield NN et al. JAMA Netw Open 2025;8(5):e2514278.

Brain and Cognition DISCOVERY FOUNDATION

Risk factors for TRD: obesity and type 2 diabetes mellitus

GLP-1 expression is altered in depression, obesity and diabetes, and affects neurodynamics



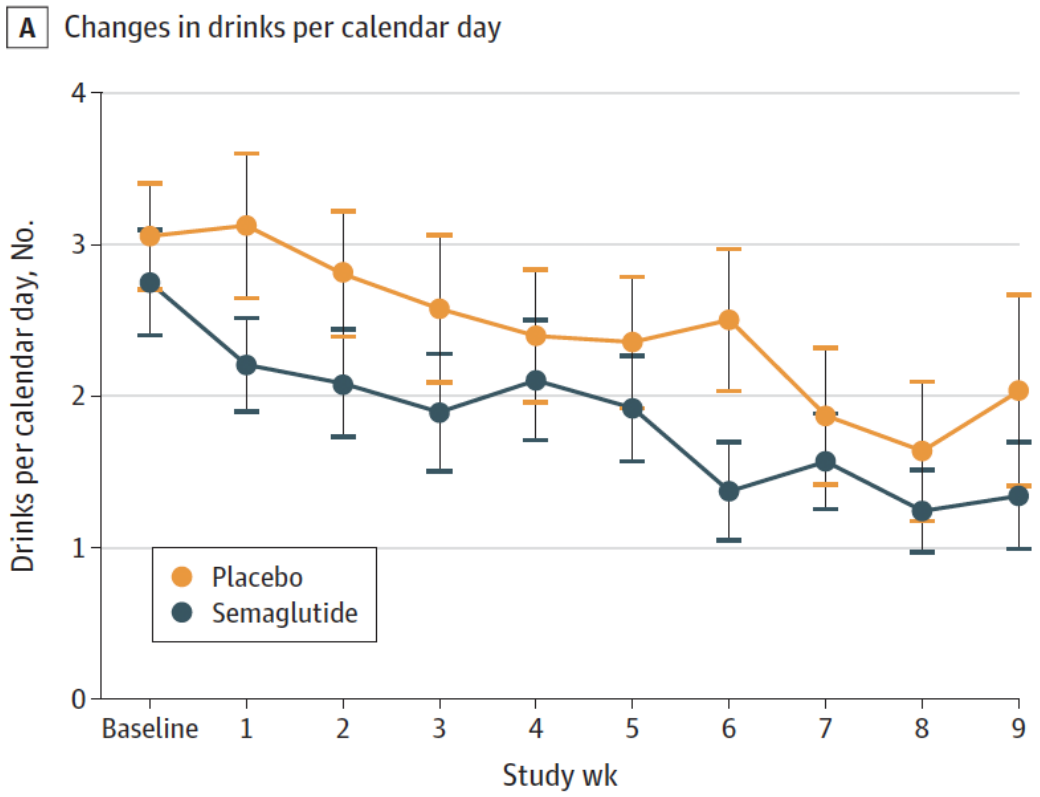
- BAX, BCL-2-associated X protein; BCL-2, B-cell lymphoma 2; GIP, glucose dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; Neuro-GDP, neuro-genesis, -differentiation, -plasticity; NMDA, N-methyl-D-aspartate; TRD, treatment-resistant depression.

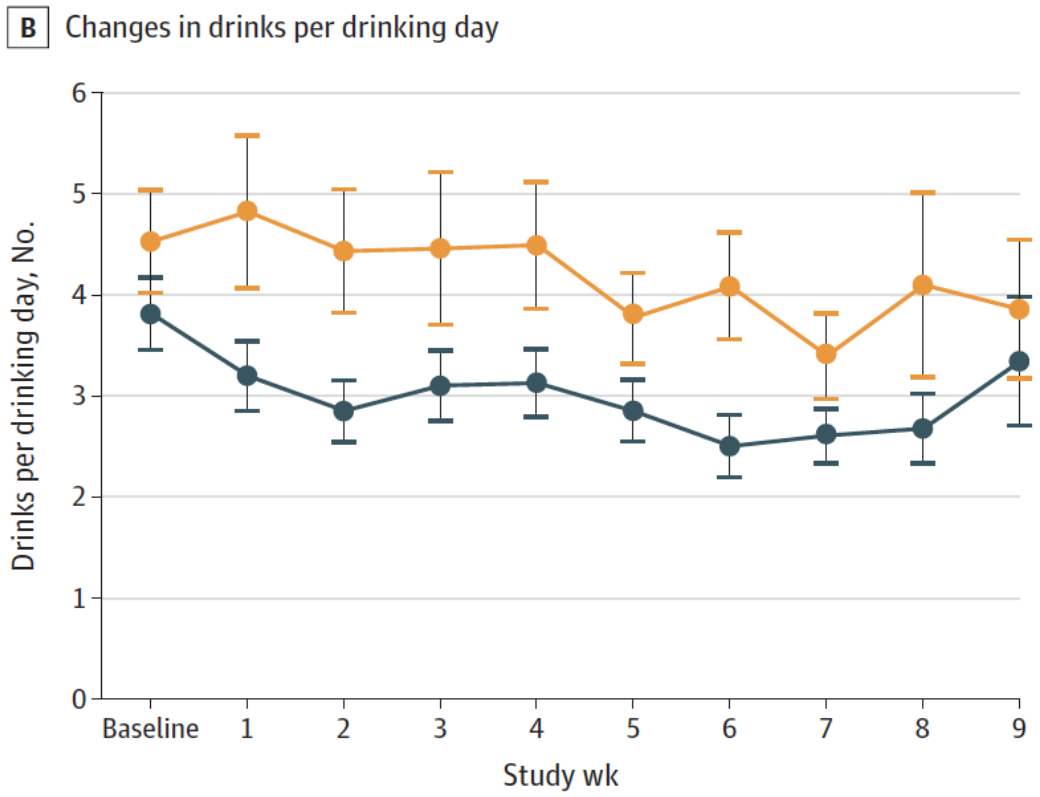
- McIntyre RS, et al. CNS Spectrums 2025:1–7.

Brain and Cognition DISCOVERY FOUNDATION

Once-Weekly Semaglutide in Adults With Alcohol Use Disorder: A Randomized Clinical Trial

Prospective Changes in Weekly Alcohol Outcomes





Hendershot. C.S. et al. JAMA Psychiatry. 2025 Feb 12.

Brain and Cognition DISCOVERY FOUNDATION

Psychedelics for the Treatment of Psychiatric Disorders: Interpreting and Translating Available Evidence and Guidance for Future Research

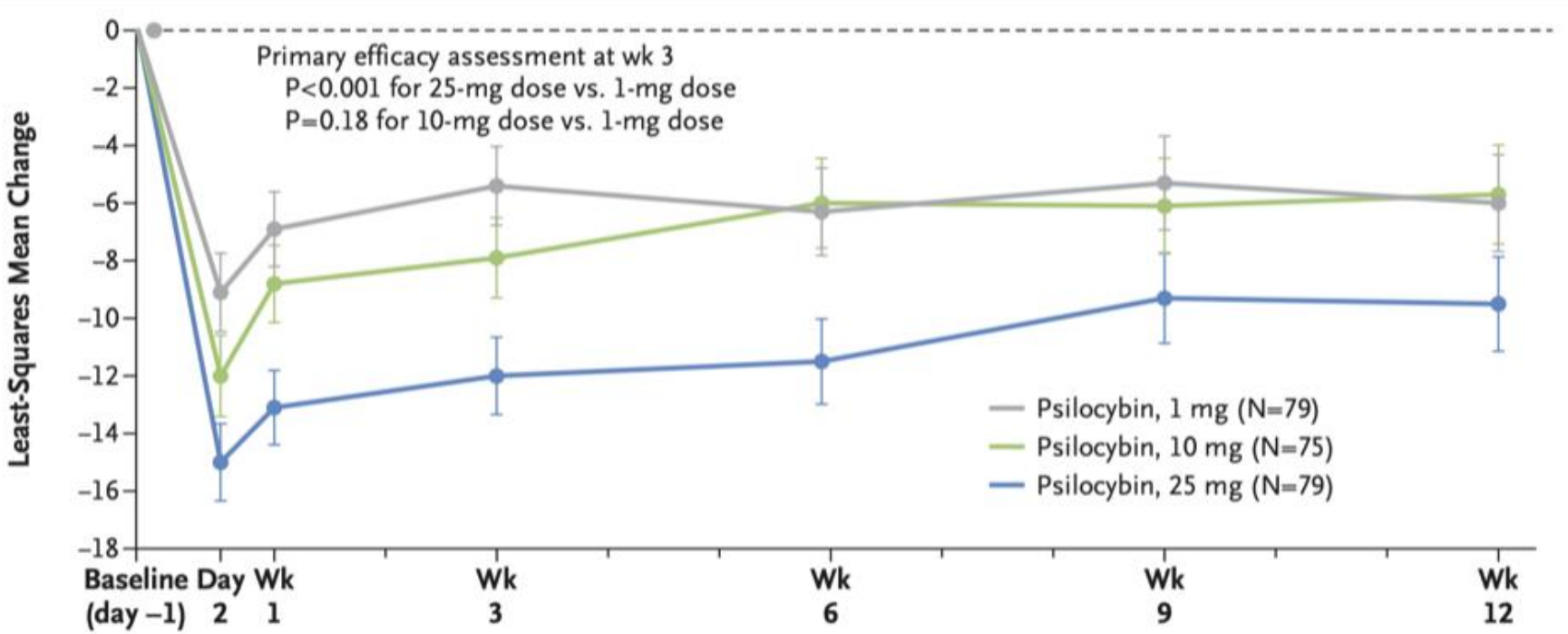
Roger S. McIntyre, M.D., F.R.C.P.C., Angela T. H. Kwan, M.Sc., Rodrigo B. Mansur, M.D., Ph.D., Albino J. Oliveira-Maia, M.D., Ph.D., Kayla M. Teopiz, H.B.Sc., Vladimir Maletic, M.D., Trisha Suppes, M.D., Ph.D., Stephen M. Stahl, M.D., Ph.D., Joshua D. Rosenblat, M.D., F.R.C.P.C.

McIntyre RS et al. Am J Psychiatry 182:1, January 2025.

Brain and Cognition
DISCOVERY FOUNDATION

Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression

Change from Baseline in MADRS Total Score (Modified Intention-to-Treat Population)

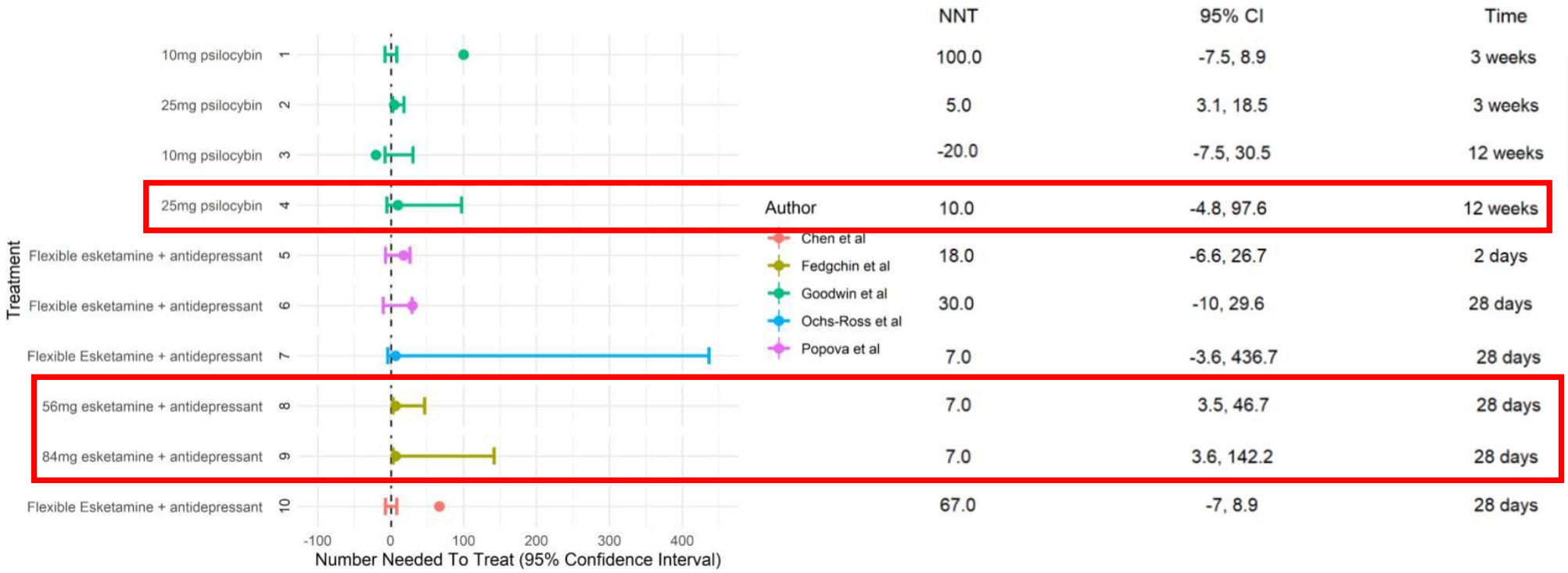


Goodwin GM, et al. N Engl J Med. 2022 Nov 3;387(18):1637-1648.

Brain and Cognition DISCOVERY FOUNDATION

Efficacy of Psilocybin vs Esketamine for Treatment-Resistant Depression

Forest plot of the calculated number needed to treat (NNT) for each treatment.



	NNT	95% CI	Time
10mg psilocybin	100.0	-7.5, 8.9	3 weeks
25mg psilocybin	5.0	3.1, 18.5	3 weeks
10mg psilocybin	-20.0	-7.5, 30.5	12 weeks
25mg psilocybin	10.0	-4.8, 97.6	12 weeks
Flexible esketamine + antidepressant	18.0	-6.6, 26.7	2 days
Flexible esketamine + antidepressant	30.0	-10, 29.6	28 days
Flexible Esketamine + antidepressant	7.0	-3.6, 436.7	28 days
56mg esketamine + antidepressant	7.0	3.5, 46.7	28 days
84mg esketamine + antidepressant	7.0	3.6, 142.2	28 days
Flexible Esketamine + antidepressant	67.0	-7, 8.9	28 days

25 mg psilocybin was clinically effective at 3 weeks post-dose

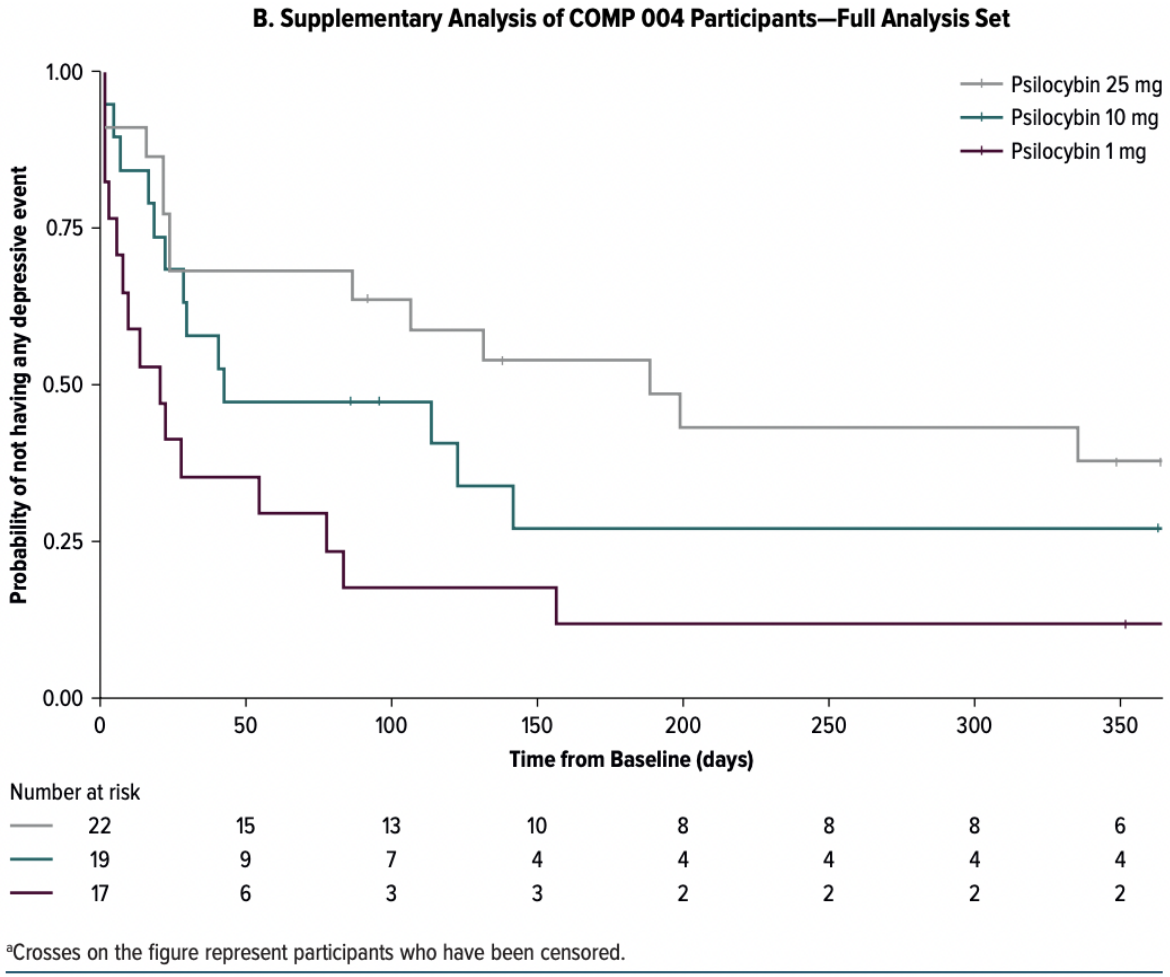
Fixed dose esketamine was clinically effective at 28 days post-dose

Wong S, et al. J Affect Disord. 2024 250; 698-705

Brain and Cognition DISCOVERY FOUNDATION

Results From A Long-Term Observational Follow-Up Study of a Single Dose of Psilocybin for a Treatment-Resistant Episode of Major Depressive Disorder

Kaplan-Meier Plots of Time to Any Depressive Event



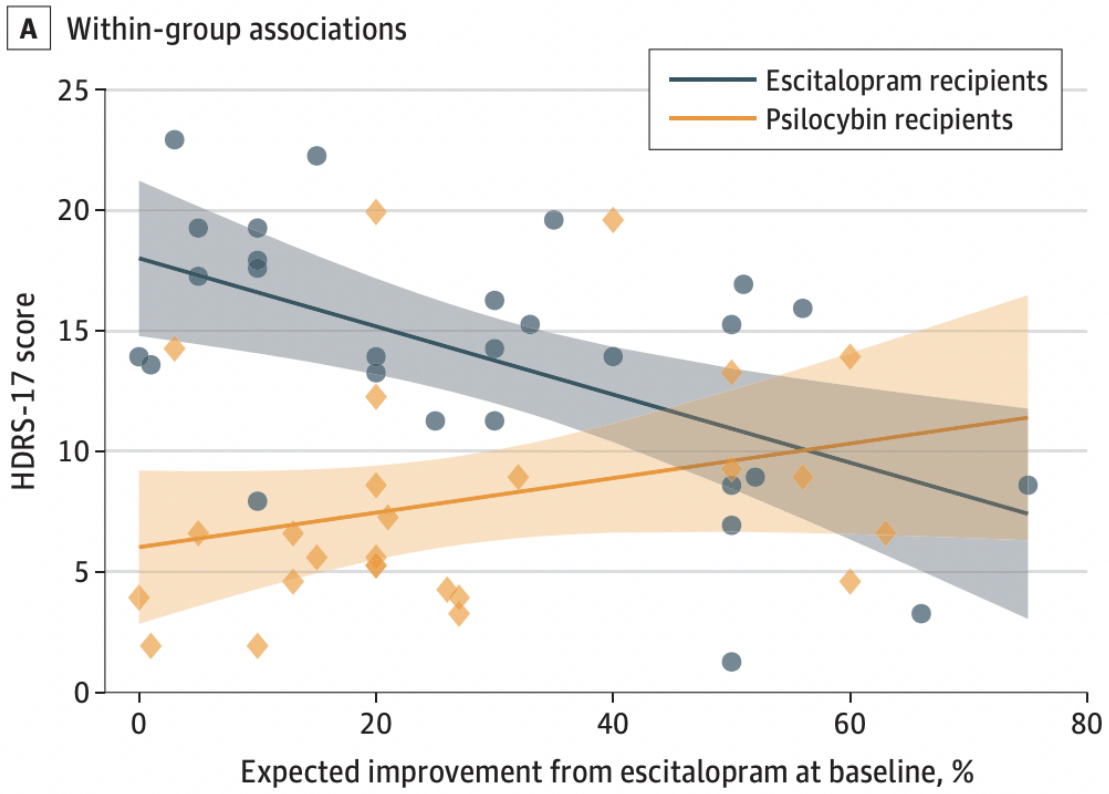
[a]Crosses on the figure represent participants who have been censored.

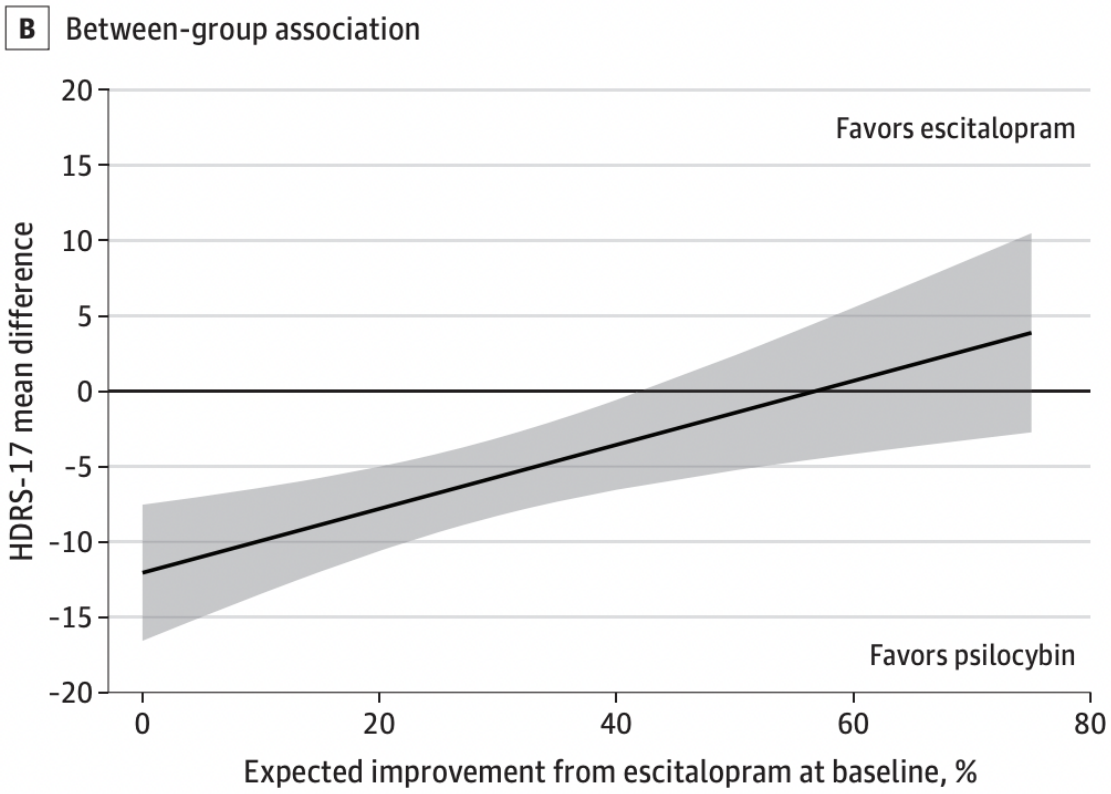
Goodwin G. M. et al. J. Clin. Psychiatry. 2025 Mar 3;86(1):24m15449.

Brain and Cognition DISCOVERY FOUNDATION

If You Believe That An SSRI Is Effective, No Treatment Difference with Psilocybin: If You Believe SSRI Not Particularly Effective Psilocybin Shows Advantage: The Power of Expectancy Bias

Association Between Escitalopram Expectancy and Treatment Outcome

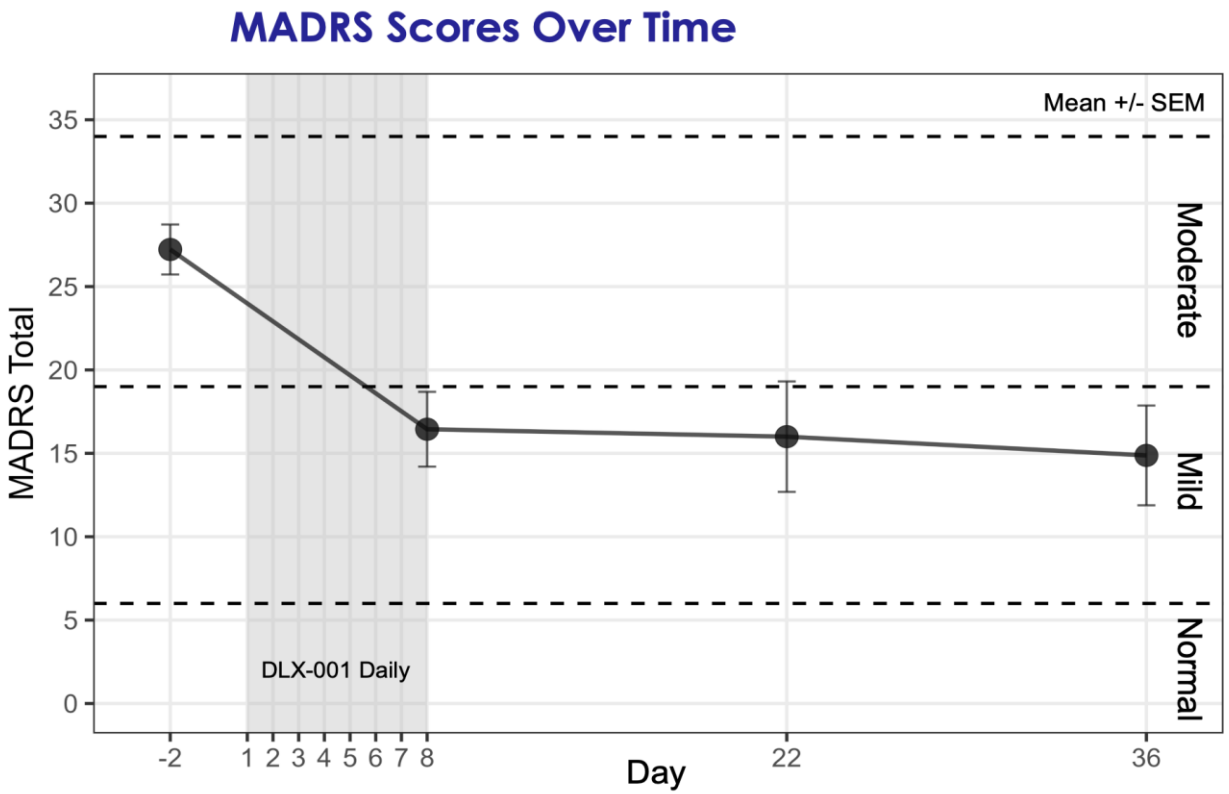


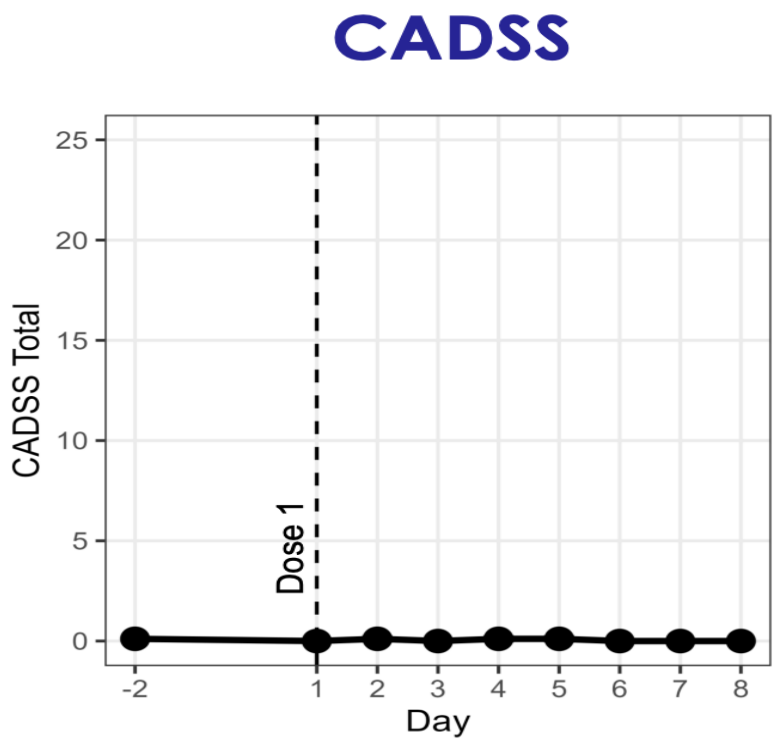


Krystal A.D & Dutcher E.G. JAMA Psychiatry. 2024 Dec. 9

Brain and Cognition DISCOVERY FOUNDATION

A Phase 1b Study to Evaluate Pharmacodynamics, Safety, and Tolerability of the Novel Neuroplastogen DLX-001 in Participants with Major Depressive Disorder: Interim Findings





Koenig et al. *Delix Therapeutics*. 2025, Poster Presentation

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TRD in MDD

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