

ANTI-ANHEDONIC EFFECTS OF CARIPRAZINE IN PRECLINICAL AND CLINICAL STUDIES: A SYSTEMATIC REVIEW

Jin Kiat Ang^{1*†}, Gilbert Madriaga^{2†}, Khamelia Malik³, Yee Ming Mok⁴, and Pornjira Pariwatcharakul⁵

¹Universiti Putra Malaysia, Malaysia ²Tanabe Pharma Singapore, Singapore ³Universitas Indonesia, Indonesia ⁴Institute of Mental Health, Singapore ⁵Mahidol University, Thailand

†These authors contributed equally to this work. *Correspondence: gilmadriaga@icloud.com

5 Studies met inclusion criteria

Systematic search across PubMed, Scopus, and Google Scholar up to June 2025

2 Preclinical chronic stress models

CUS mouse and CMS rat models assessed with sucrose consumption

3 Human studies across major depressive disorder (MDD), bipolar 1 depression (BP-1) and schizophrenia

Post-hoc RCT analyses and one open-label observational study

BACKGROUND & OBJECTIVE

Anhedonia is a functionally important symptom across psychiatric disorders, but targeted treatment options remain limited.

Cariprazine, a dopamine D3/D2 partial agonist with preferential affinity for D3 receptors, may have therapeutic relevance to reward dysfunction.

Objective

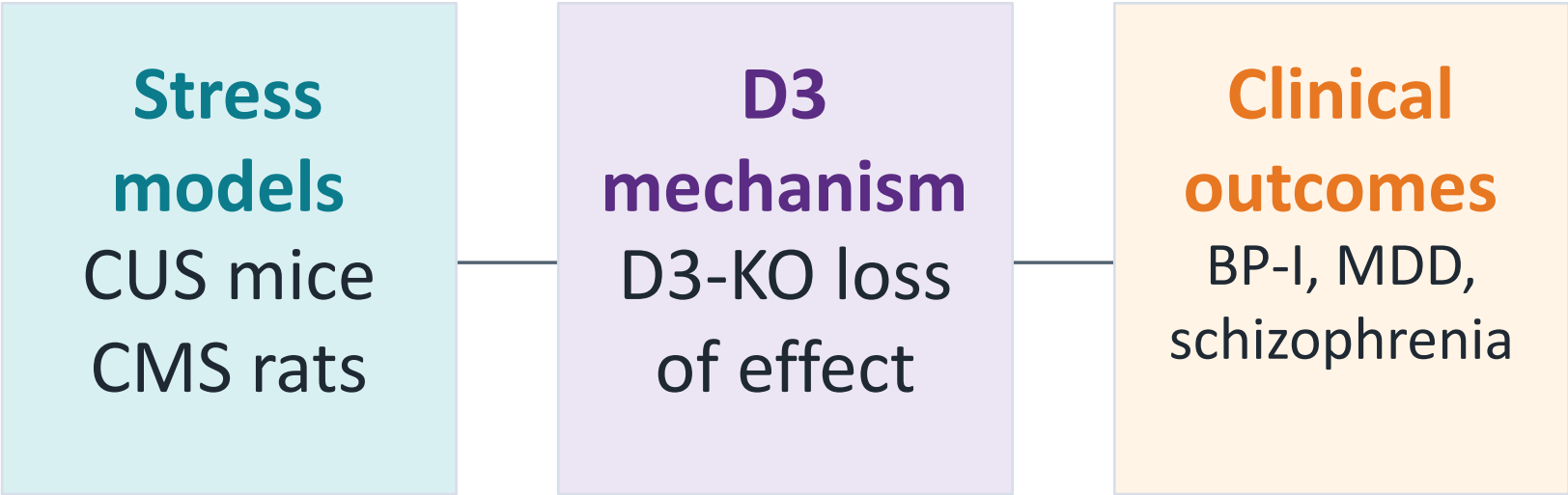
To synthesize preclinical and clinical evidence on the anti-anhedonic effects of cariprazine across psychiatric disorders.

METHODS

Search: PubMed, Scopus, Google Scholar
Population: animal models of anhedonia or psychiatric disorders with anhedonia outcome
Intervention: cariprazine monotherapy or adjunctive therapy
Primary outcome: change in anhedonia measures
Key concepts: cariprazine; anhedonia; dopamine D3 receptor
Quality tools: SYRCLE, ROB 2, NIH before-after tool
Data synthesis: narrative synthesis due to heterogeneity

Meta-analysis was planned but not performed due to heterogeneity in models, populations, and anhedonia measures.

RESULTS: TRANSLATIONAL SIGNAL



KEY FINDINGS

Preclinical
Cariprazine attenuated stress-induced reduction in sucrose consumption in CUS mice.
Cariprazine restored sucrose consumption in CMS rats.
D3-knockout experiment supported dopamine D3 receptor involvement.

Clinical
BP-I depression: 1.5 and 3 mg/day improved MADRS anhedonia factor score at Week 6.
MDD: adjunctive cariprazine improved MADRS anhedonia subscale scores versus adjunctive placebo.
Schizophrenia: SAND anhedonia item decreased from 3.2 to 2.1 by Week 16 or termination.

Overall pattern

A consistent narrative signal was observed from stress-induced anhedonia-like behavior in animals to anhedonia-related measures in clinical populations.

INTERPRETATION

The findings suggest possible therapeutic relevance of cariprazine for anhedonia in MDD, BP-I depression, and schizophrenia, with biologic plausibility related to D3-preferring pharmacology.

Possible mechanism

D3-preferring modulation may influence reward and motivational processes. Direct mechanistic evidence was limited to one preclinical D3-knockout study.

LIMITATIONS

Small evidence base and heterogeneous study designs.
Clinical evidence mainly from post-hoc analyses
Anhedonia was not consistently assessed with dedicated validated instruments
Human studies did not report neurobiological correlates
Uncontrolled design in schizophrenia observational study

CONCLUSION

Cariprazine may be associated with improvement in anhedonia-related measures in MDD, BP-I depression, and schizophrenia. Larger prospective studies with prespecified anhedonia endpoints are needed.

TABLE 1. KEY ATTRIBUTES OF STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

Study	Design and population	Treatment /	Anhedonia	Key anhedonia findings
Study 1 Duric et al., 2017 [1]	Preclinical CUS mice; stress-induced anhedonia; WT / D3-KO mice; up to 26 days CUS.	Cariprazine 0.03-0.4 mg/kg vs vehicle; active comparators imipramine and aripiprazole.	Sucrose consumption	Cariprazine significantly attenuated stress-induced reduction in sucrose consumption vs CUS + vehicle. Effective doses: 0.2 mg/kg, p=0.018; 0.4 mg/kg, p=0.0002. In D3-KO mice, cariprazine did not reverse anhedonia-like behavior.
Study 2 Papp et al., 2014 [2]	Preclinical CMS rats; stress-induced anhedonia; male Wistar rats; 7-week CMS with 5 weeks of treatment.	Cariprazine 0.01-1.0 mg/kg vs vehicle; active comparators imipramine and aripiprazole.	Sucrose consumption	Cariprazine restored sucrose consumption. Effective doses: 0.03 mg/kg, 33%, p<.05; 0.065 mg/kg, 43%, p<.01 in Cohort 2 and 69%, p<.001 in Cohort 3; 0.25 mg/kg, 47%, p<.05.
Study 3 McIntyre, Llorca, et al., 2025 [3]	Post-hoc RCT analysis; BP-I depression; adults, n=1,383; 6 weeks.	Cariprazine 1.5 or 3 mg/day vs placebo.	MADRS anhedonia factor score	Pooled ITT Week 6: 1.5 mg/day LSMD -1.85, p<.001; 3 mg/day LSMD -1.57, p<.001. Higher anhedonia subgroup: 1.5 mg/day LSMD -1.97, p=.0009; 3 mg/day LSMD -2.07, p=.0006. Significant from Week 1 in pooled ITT.
Study 4 McIntyre, Maletic, et al., 2025 [4]	Post-hoc RCT analysis; MDD; adults, n=751 mITT; 6 weeks.	Cariprazine 1.5 or 3 mg/day + antidepressant therapy vs placebo + antidepressant therapy.	MADRS anhedonia subscale and MADRS item 8	Overall mITT Week 6: 1.5 mg/day LSMD -1.5, p=.0032; 3 mg/day LSMD -1.1, p=.0381. 1.5 mg/day showed significant effect from Week 2. More consistent findings at 1.5 mg/day.
Study 5 Rancans et al., 2021 [5]	Open-label observational study; schizophrenia; adults, n=116; 16 weeks.	Cariprazine 1.5-6 mg/day; no comparator.	SAND anhedonia item	SAND total score Week 16: mean change -7.3 points, p<.001; significant from Week 2. SAND negative symptom subscore: mean change -6.3, p<.001. Anhedonia item decreased 1.1 points, from 3.2 to 2.1.

Abbreviations: ADT, antidepressant therapy; BP-I, bipolar I disorder; CMS, chronic mild stress; CUS, chronic unpredictable stress; D3-KO, dopamine D3 receptor knockout; ITT, intention-to-treat; LSMD, least-squares mean difference; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; mITT, modified intention-to-treat; RCT, randomized controlled trial; SAND, Short Assessment of Negative Domains; WT, wild type.

REFERENCES

1. Duric, V.; Banasr, M.; Franklin, T.; Lepack, A.; Adham, N.; Kiss, B.; Gyertyán, I.; Duman, R.S. Cariprazine Exhibits Anxiolytic and Dopamine D3 Receptor-Dependent Antidepressant Effects in the Chronic Stress Model. *Int. J. Neuropsychopharmacol.* 2017, 20, 788–796.

2. Papp, M.; Gruca, P.; Lasoň-Tyburkiewicz, M.; Adham, N.; Kiss, B.; Gyertyán, I. Attenuation of Anhedonia by Cariprazine in the Chronic Mild Stress Model of Depression. *Behav. Pharmacol.* 2014, 25, 567–574.

3. McIntyre, R.S.; Llorca, P.-M.; Aronin, L.C.; Yu, J.; Nguyen, H.-B. Effect of Cariprazine on Anhedonia in Patients with Bipolar I Depression: Post Hoc Analysis of Three Randomized Placebo-Controlled Clinical Trials. *Adv. Ther.* 2025, 42, 246–260.

4. McIntyre, R.S.; Maletic, V.; Masand, P.; Wilson, A.C.; Yu, J.; Adams, J.L.; Kerolous, M. The Effect of Adjunctive Cariprazine on Symptoms of Anhedonia in Patients with Major Depressive Disorder. *J. Affect. Disord.* 2025, 385, 119366.

5. Rancans, E.; Dombi, Z.B.; Mátrai, P.; Barabáßy, Á.; Sebe, B.; Skrivele, I.; Németh, G. The Effectiveness and Safety of Cariprazine in Schizophrenia Patients with Negative Symptoms and Insufficient Effectiveness of Previous Antipsychotic Therapy: An Observational Study. *Int. Clin. Psychopharmacol.* 2021, 36, 154–161.