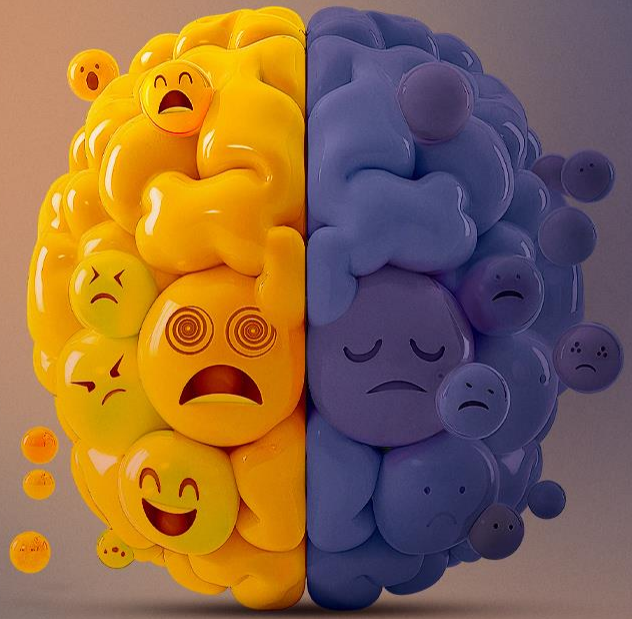
IMS04

EFFECTIVE IN AFFECTIVE

THE TREATMENT OF COMORBID **MOOD DISORDERS** IN SCHIZOPHRENIA



37th ECNP Congress,
21 September 2024, Milan, Italy

The role of serotonin & dopamine in affective symptoms of schizophrenia

Depression and mania are might be caused by the complex interplay of various neurotransmitter systems, including serotonin, dopamine and norepinephrine.[1,2]

Affective symptoms worsened by:

- DA-2 antagonism

Affective symptoms improved by:

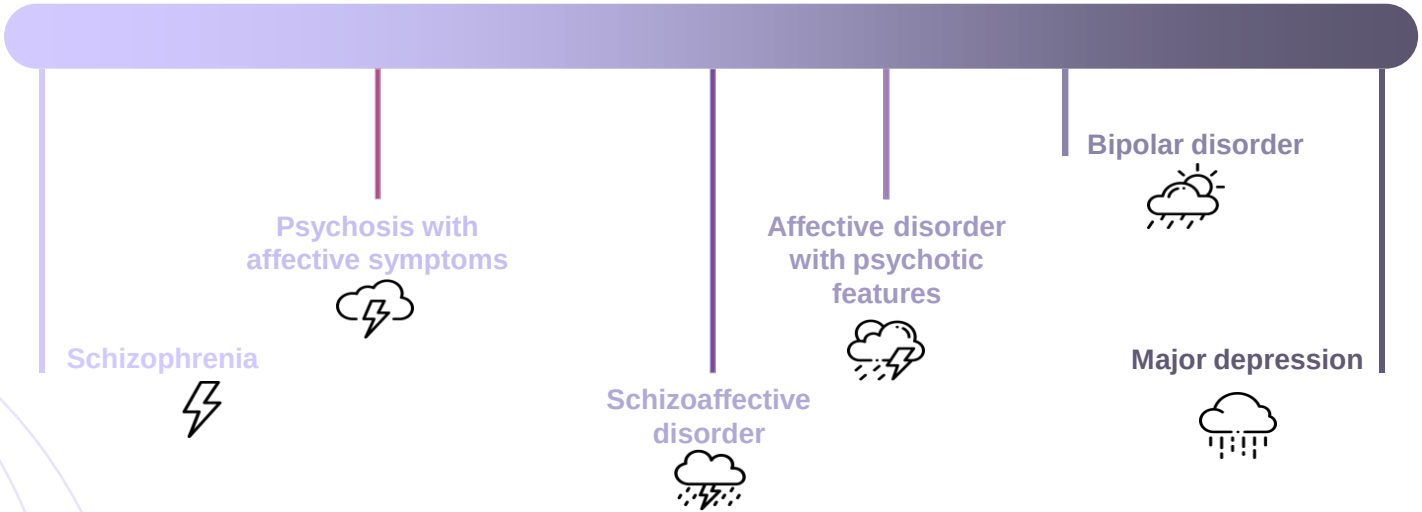
- DA-2 partial agonism
- DA-3 partial agonism
- 5HT1A modulation
- 5HT2A inverse agonism

References: 1. Ordway GA, et al. Neurocircuitry of mood disorders: Neuropsychopharmacology: the 5th Generation of Progress. American College of Neuropsychopharmacology, 2002:1051-1064; 2. Stahl, SM. (2013). Stahl's Essential Psychopharmacology: Neuroscientific Basis and practical applications (4th ed.). Cambridge University Press

Affective disorders

Affective (mood) disorders are psychiatric conditions primarily characterised by disturbances in mood and emotion.[1] The most common affective disorders are **major depression and bipolar disorder**, however, affective symptoms can be present in other disorders, creating a spectrum.

2

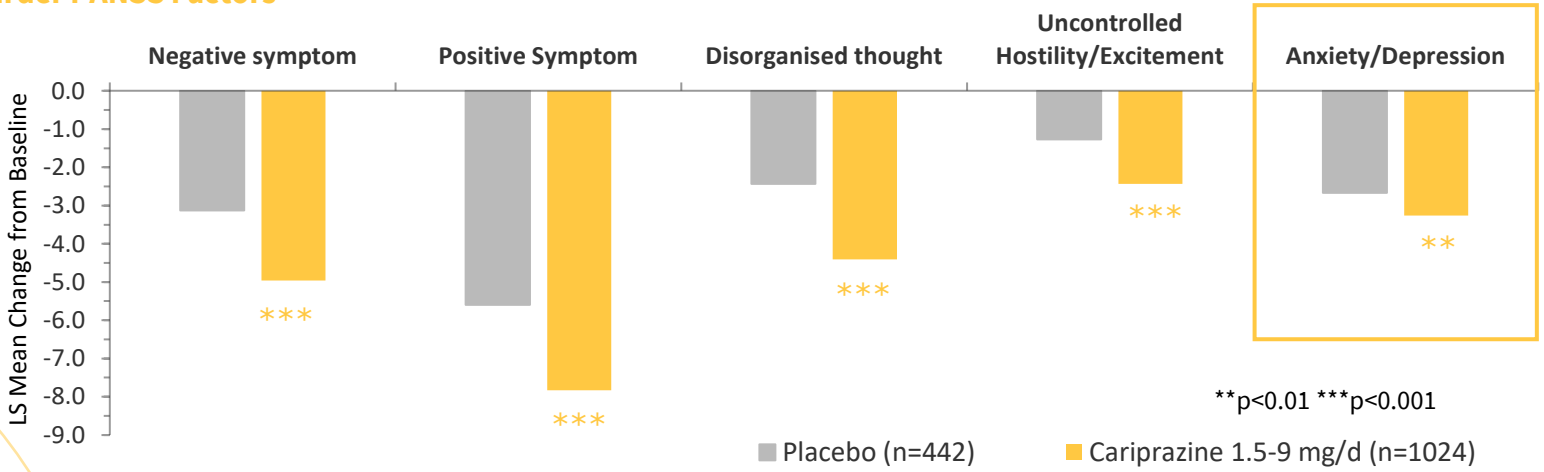


References: 1. https://www.isad.org.uk/aboutus/affective-disorders.asp#:~:text=Function%3A%20noun,%2D%2D%20called%20also%20affective%20disorder ;
2. Morrissette, D. A. & Stahl, S. S. Drug Discov. Today Ther. Strateg. 2011;8(1–2):3-9

Cariprazine in schizophrenia with affective symptoms

Cariprazine proved to be effective in the treatment of schizophrenia as shown in **3 short-term, randomised clinical trials**. Sub-analyses of the **schizophrenia population** concerning **affective symptoms** showed significant efficacy on this symptom domain within the acute patient population.

Marder PANSS Factors

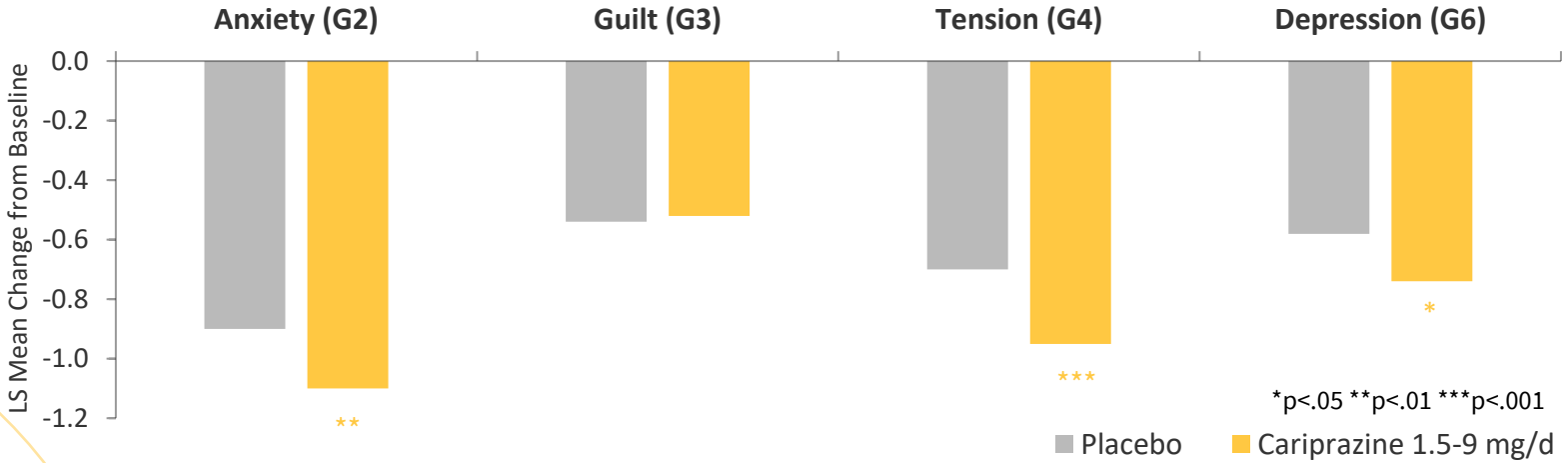


Reference: Marder, S. et al. Eur. Neuropsychopharmacol. 29, 127–136 (2019).

Cariprazine in schizophrenia with affective symptoms

Cariprazine significantly improved **overall affective (anxiety/depressive) symptoms**.
Additionally, cariprazine improved 3 of 4 subdomains, including **anxiety**, **tension** and **depression**.

Anxiety / Depression factor items

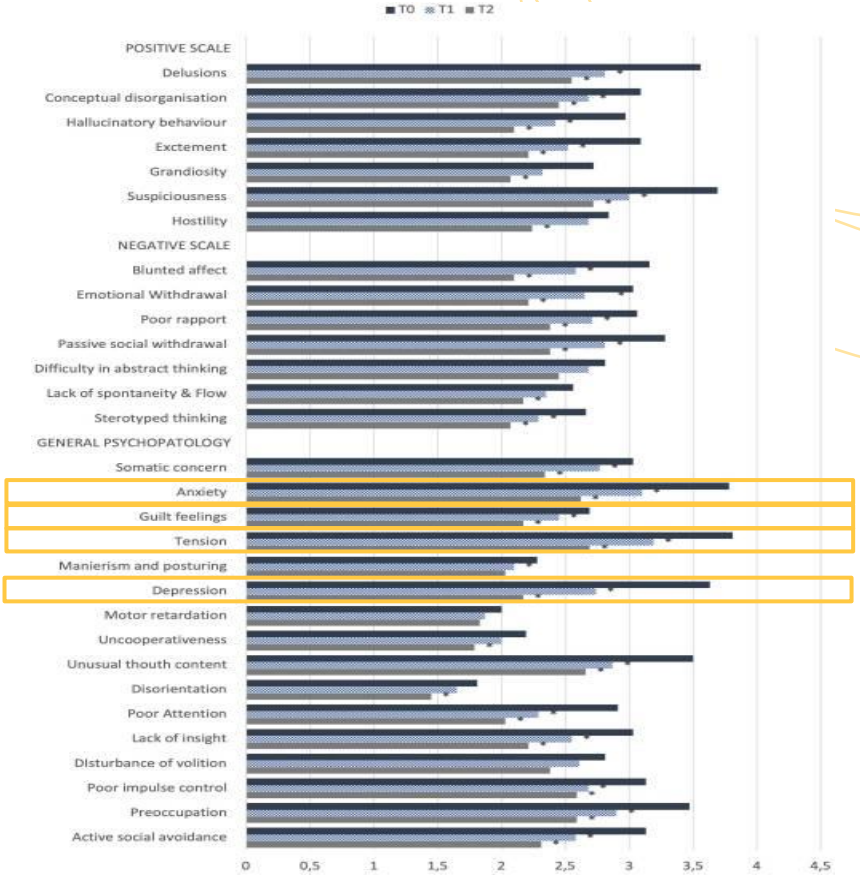


Reference: Marder, S. et al. Eur. Neuropsychopharmacol. 29, 127–136 (2019).

Naturalistic follow-up of cariprazine in schizophrenia

TABLE 2 PANSS scale scores' comparison between T0 (baseline) and T1 (6-month follow-up) in the total sample (N=31) and between T0 and T2 (12-month follow-up) in the total sample (N=29).

PANSS scores		Total sample mean ± SD	p	PANSS scores	Total sample mean ± SD	p
Positive scale	T0	21.7 ± 5.7	.001	T0	21.7 ± 5.9	<.001
	T1	18.42 ± 5.9		T2	16.4 ± 5.9	
Negative scale	T0	20.8 ± 7.8	.002	T0	19.9 ± 7.5	<.001
	T1	18.0 ± 7.8		T2	15.7 ± 6.5	
General psychopatology scale	T0	47.3 ± 10.5	<.001	T0	47.4 ± 10.8	<.001
	T1	40.3 ± 11.4		T2	35.8 ± 9.5	
Total score	T0	89.7 ± 19.0	<.001	T0	89.2 ± 19.4	<.001
	T1	76.8 ± 22.2		T2	67.9 ± 19.0	
Marder PANSS' positive symptoms factor	T0	25.1 ± 6.4	<001	T0	25.1 ± 6.7	<.001
	T1	21 ± 6.5		T2	18.7 ± 5.7	
Marder PANSS' negative symptoms factor	T0	20.2 ± 6.9	.001	T0	19.7 ± 6.6	<.001
	T1	17.5 ± 7.1		T2	15.3 ± 5.7	
Marder PANSS' disorganized though factor	T0	19.1 ± 5.6	.001	T0	18.8 ± 5.7	<.001
	T1	16.9 ± 5.9		T2	15.3 ± 5.7	
Marder PANSS' uncontrolled hostility/excitement factor	T0	11.2 ± 3.5	.015	T0	11.4 ± 3.7	<.001
	T1	9.9 ± 3		T2	8.8 ± 3.9	
Marder PANSS' anxiety/depression factor	T0	13.9 ± 3.7	<.001	T0	13.9 ± 3.8	<.001
	T1	11.5 ± 3.8		T2	9.6 ± 3.4	



Reference: Carmassi, C. et. al. Front Psychiatry. 2024 May 21:15:1382013.

Cariprazine in schizoaffective disorder

Cariprazine showed to be effective in the treatment of **schizoaffective disorder** as demonstrated by various **cases in real-life settings**. Randomised clinical trials, to date, are not available.

EVIDENCE	DIAGNOSIS	MEDICATION(S)	PRESENTING PROBLEM	OUTCOME
Case report[1-3]	Schizoaffective disorder, depressive type	CAR+CLOZ	Negative symptoms	• No adverse events • Better engagement and fuller affect (6 months) • 73% reduction in SANS score (from 88 to 24) • Some persistent positive symptoms remained
	Treatment-resistant schizoaffective disorder	CAR+CLOZ+VAL	Negative and cognitive symptoms	• No side-effects • Gradual improvement in negative and cognitive symptoms and functionality • Significant improvement in illness-severity (CGI-S)
	Schizoaffective disorder, depressive type	CAR	Psychotic, depressive, and anxiety symptoms	• Response and remission after 4 weeks • Reduction in psychotic and depressive symptoms • After 16 weeks of treatment, twice weekly administration with continued efficacy and sustained remission
Pilot study[4]	Schizoaffective disorder	CAR+CLOZ	Treatment-resistance and negative symptoms	• Dizziness with higher CAR dose • Improvement in PANSS Positive (35%), Negative (88%) and Total (47%) scores
	Schizoaffective disorder	CAR+CLOZ	Metabolic side-effects and negative symptoms	• Good tolerability • Marked improvement in PANSS Positive (100%), Negative (100%) and Total (67%) scores
	Schizoaffective disorder	CAR+CLOZ	Treatment-resistance	• Discontinuation after 6 weeks due to poor response

Disclaimer: please note that cariprazine is only indicated for the treatment of schizophrenia in the EU and for the treatment of schizophrenia; depressive and manic/mixed episodes associated with bipolar I disorder; and for the adjunctive treatment of major depressive disorder in the US.

References:: 1. Oloyede E, et al. Ther Adv Psychopharmacol. 2022;12: 1–9.; 2. Bogren M et al. Front. Psychiatry. 2022;13:887547; 3. Dyrmishi E et al. Front. Psychiatry. 2022;13:876003.; 4. Pappa S et al. Ther Adv in Psychopharmacol. 2022;12.

Cariprazine in bipolar disorder

Cariprazine was examined in **7 randomised clinical trials** in patients with **bipolar disorder** (3 studies in bipolar mania and 4 studies in bipolar depression). Cariprazine proved to be effective in the dose range of **1.5-3.0 mg/day** for the treatment of **depressive episodes** associated with bipolar I disorder **and 3.0-6.0 mg/day** for the treatment of **manic/mixed episodes** associated with bipolar I disorder.

MANIA			DEPRESSION			
RGH-MD-31 Phase II	**RGH-MD-32** Phase III	**RGH-MD-33** Phase III	**RGH-MD-52** Phase II	**RGH-MD-56** Phase IIb	**RGH-MD-53** Phase III	**RGH-MD-54** Phase III
3 weeks			8 weeks		6 weeks	
YMRS Total Score			MADRS Total Score			
The 3-12 mg/day dose group showed statistically significant separation from placebo	The 3-12 mg/day dose group showed statistically significant separation from placebo	Both the 3-6 mg/day and 6-12 mg/day dose groups showed statistically significant separation from placebo	No statistically significant difference was observed between the cariprazine group and placebo group	The 1.5 mg/day dose group showed statistically significant separation from placebo	The 1.5 mg/day dose group showed statistically significant separation from placebo	Both the 1.5mg/day and 3 mg/day dose groups showed statistically significant separation from placebo

Disclaimer: please note that cariprazine is only indicated for the treatment of schizophrenia in the EU and for the treatment of schizophrenia; depressive and manic/mixed episodes associated with bipolar I disorder; and for the adjunctive treatment of major depressive disorder in the US.

Reference: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/204370s009lbl.pdf

Adjunctive cariprazine in MDD

Cariprazine was examined in **5 randomised clinical trials** in patients with **major depressive disorder as add-on treatment**. Cariprazine proved to be effective in the dose range of **1.5-3.0 mg/day** for the treatment of major depressive disorder.

PIVOTAL STUDIES		SUPPORTIVE STUDIES		
RGH-MD-75 Phase IIb	**3111-301-001** Phase III	**RGH-MD-71** Phase II	**RGH-MD-72** Phase III	**3111-302-001** Phase III
8 weeks	6 weeks	8 weeks	8 weeks	6 weeks
MADRS Total Score		MADRS Total Score		
The 2-4.5 mg/d + ADT dose group showed statistically significant separation from placebo	The 1.5 mg/day + ADT dose group showed statistically significant separation from placebo	Safety data is in line with the overall safety profile of cariprazine.		

Disclaimer: please note that cariprazine is only indicated for the treatment of schizophrenia in the EU and for the treatment of schizophrenia; depressive and manic/mixed episodes associated with bipolar I disorder; and for the adjunctive treatment of major depressive disorder in the US.

Reference: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/204370s009lbl.pdf