Innovation in **mind**

AFFECTIVE SYMPTOM GUIDE

GEDEON RICHTER

Developed by Gedeon Richter Plc. Global Medical Division.

Please note that cariprazine is only indicated for the treatment of schizophrenia in Europe.

Affective symptoms

Affective symptoms are emotional disturbances or abnormalities that are observed in various psychiatric disorders, particularly mood disorders.[1] They can be classified broadly into depressive and manic categories which are defined by the Diagnostic and Statistical Manual 5th Edition (DSM-5) as the following:[2]

DEFINITION

Depressive symptoms

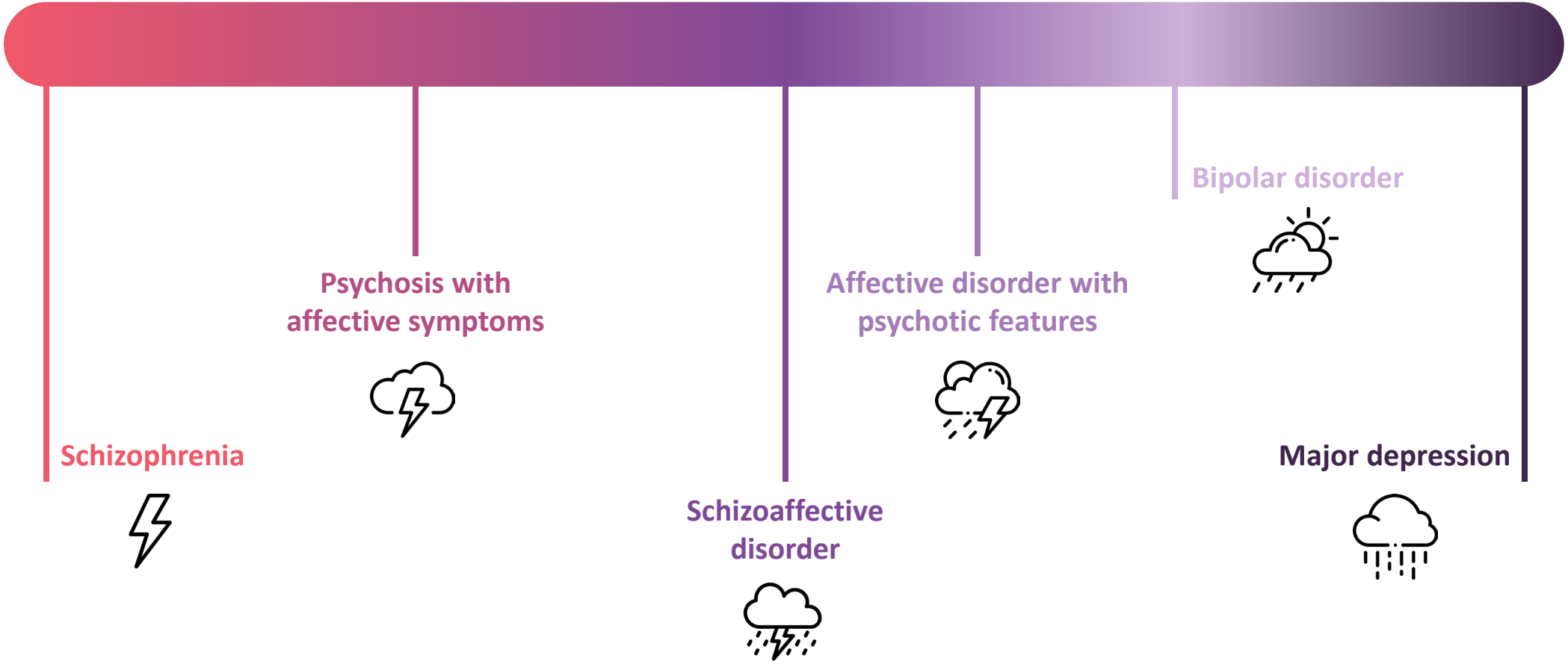
- Depressed mood
- Loss of interest or pleasure
- Weight loss or weight gain
- Insomnia or hypersomnia
- Fatigue
- Feelings of worthlessness/ guilt
- Inability to concentrate
- Thoughts of dying or attempting suicide
- Psychomotor retardation or agitation

Manic symptoms

- Increased self-esteem or grandiosity
- Decreased need for sleep
- Increased talking
- Increased flight of ideas or racing thoughts
- Increased distractibility
- Increased goal-directed activity
- Excessive involvement in pleasurable activities with potentially negative consequences

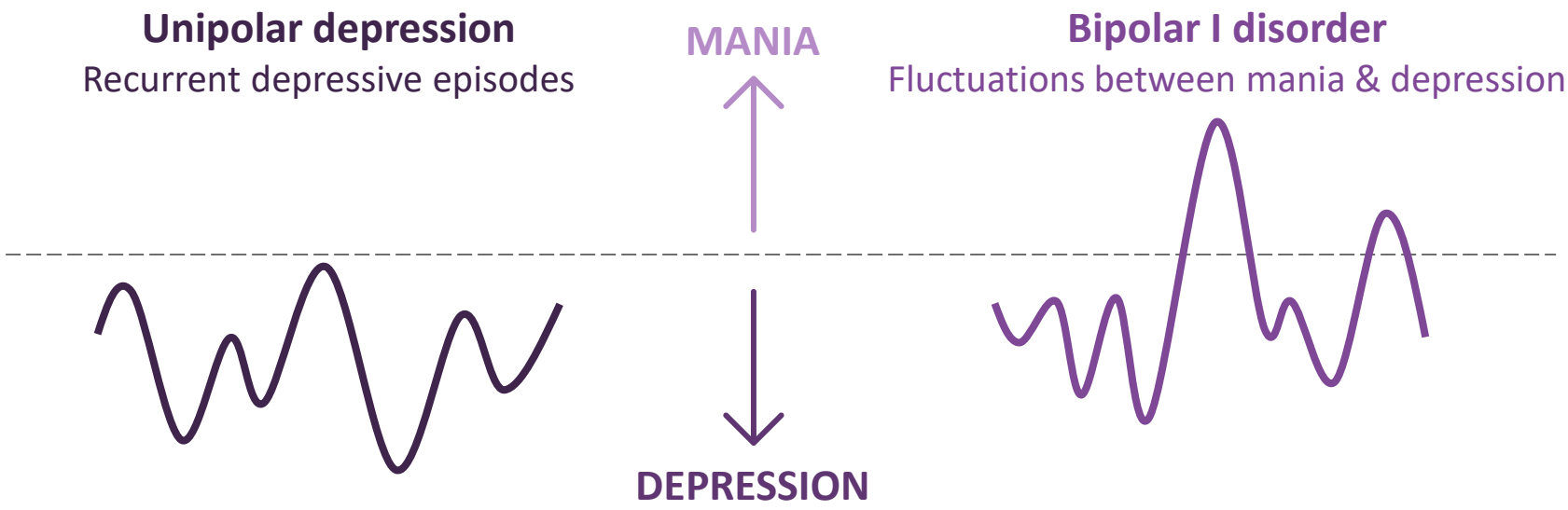
Affective disorders

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, hence creating a spectrum.



Major depression & Bipolar disorders

Major depressive disorder (MDD) or unipolar depression is a serious psychiatric illness, negatively impacting on feeling, behaviour and thinking.[3] Bipolar I and bipolar II disorders are characterised by different mood states: depression and mania/hypomania. [2, 4]



Two types of bipolar disorders are distinguished: **bipolar I** and **bipolar II disorders**.

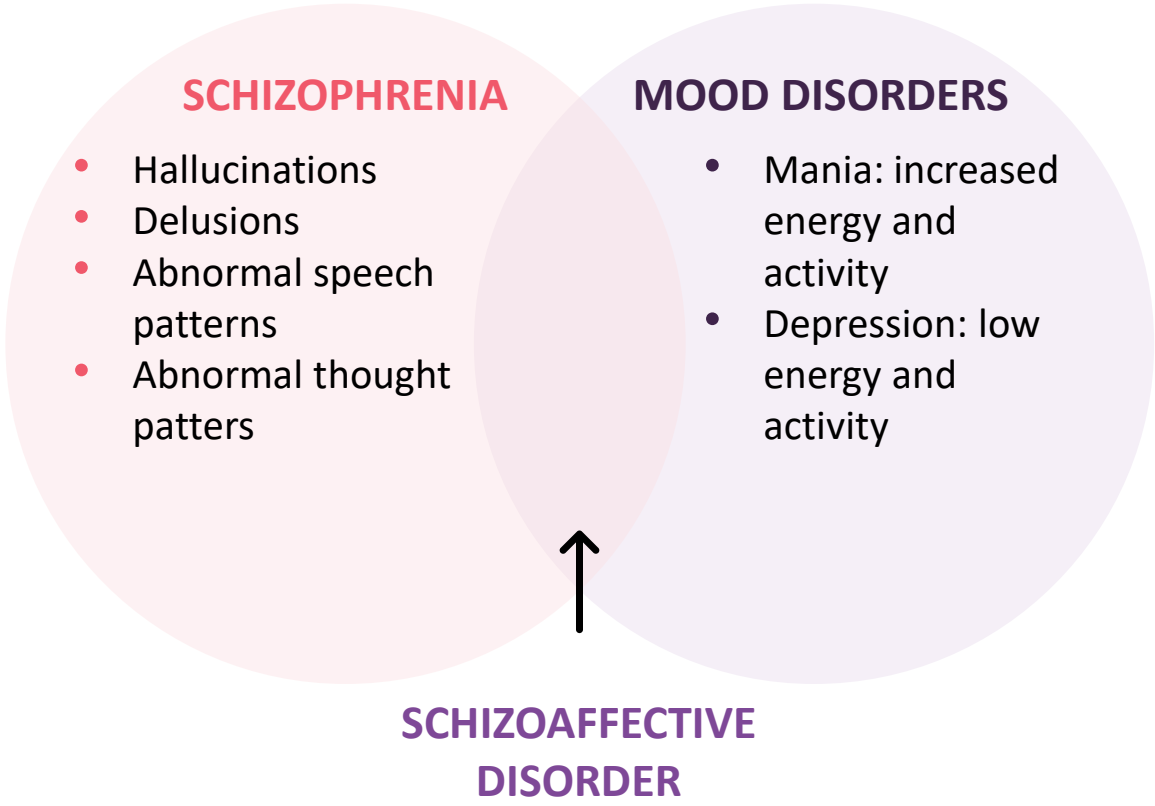
- Individual with **bipolar I** disorder have a history or presence of a manic episode. Patients also commonly experience depression and hypomania, but these mood states are not essential for diagnosis. Those with bipolar I disorder also experience euthymic periods, where mood is considered to be in the “normal” range; no elevated or depressed mood is present.[2]
- Individuals with **bipolar II** disorder experience at least one hypomanic episode (milder and shorter form of mania) and one major depressive episode.[2]

Schizoaffective disorder

Schizoaffective disorder is defined in the DSM-5 as a mental health condition that exhibits characteristics of **both schizophrenia** and **mood disorders**.[2*]

Criteria for meeting the diagnosis for schizoaffective disorder according to DSM-5 are the following:[2]

- Meeting the criteria for schizophrenia, with at least one of the symptoms being either hallucination or delusion.
- A major mood episode (either major depression or mania) that lasts for an uninterrupted period of time.
- Mood symptoms are present for the majority of the illness.
- Delusions or hallucinations for two or more consecutive weeks without mood symptoms sometime during the life of the illness.
- The symptoms are not caused by substance use.



**The International Classification of Disorders 11th edition has a similar definition for schizoaffective disorder.*

Schizophrenia with affective symptoms

Affective symptoms such as anxiety, guilt feelings, tension, and depression[5] are prevalent symptoms in schizophrenia. They have severe impact on the quality of life of patients, therefore making their diagnosis and treatment crucial.[6]

Several symptom domains characterise schizophrenia, including positive, negative, cognitive, **affective symptoms** and symptoms of aggression.[6]

There is **significant overlap between the various symptom domains**, making it especially challenging to differentiate negative symptoms from affective symptoms, including depression and anxiety.[6]

The coexistence of affective symptoms, particularly depression, can **severely impact the quality of life and longevity** of individuals with schizophrenia. Therefore, it is crucial to accurately diagnose and effectively treat affective symptoms.[6]

Neurobiological background of affective symptoms

Depression and mania are might be caused by the complex interplay of various neurotransmitter systems, including serotonin, dopamine and norepinephrine.[7,12]

Depression may be caused by altered levels of monoamines such as **serotonin**, **norepinephrine** and **dopamine**.[7]

- The **serotonin hypothesis** is coming from the observation that hypertensive patients became depressed after taking reserpine, an anti-hypertensive agent that also depletes **serotonin** in the brain.[8]
- Treatments that target **monoamines** have been widely accepted & approved for use in MDD.[9,10]
- Manic symptoms are a result of altered functioning at **dopamine** (decreased dopamine signalling)[11] and **serotonin** receptors (may help offset decreased dopamine signalling).[12]

Key receptor targets

Among monoamine receptors, various types contribute to the emergence of depressive and manic symptoms, including serotonin 5HT1A, 5HT2C and 5HT2A; dopamine D2 and D3; and alpha-adrenergic receptors.[12-16]

NEUROTRANSMITTER	RECEPTOR	SYMPTOMS	DESIRED EFFECT[12]	SIDE EFFECT[12]
Serotonin	$5HT_{1A}$	Anxiety & depressive symptoms[13,14]	Anxiolytic effect	Headache, nausea & weight gain
	$5HT_{2A}$	Manic symptoms[12,15]	EPS decrease, mild sedation	More non-REM sleep
	$5HT_{2C}$	Depressive symptoms[13,14]	Improvement of depressive symptoms	Weight increase & increase of cardio-metabolic risk (diabetes)
Dopamine	D_2	Manic symptoms[12,15]	Antipsychotic effect	EPS & prolactin increase (sexual dysfunction)
	D_3	Cognitive and mood symptoms, amotivation[15]	Improvement of negative symptoms, cognition, mood	
Norepinephrine	α-Adrenergic	Depression[16]	Sedation	Sedation, orthostatic hypotension, dizziness, reflex tachycardia, ejaculation problems & stuffed nose

Impact of affective symptoms in schizophrenia

Depressive symptoms in schizophrenia can lead to severe outcomes, increasing patient and caregiver burden, healthcare utilisation and workplace costs.

IMPACT

Patient burden[17]

- Heightened risk of psychotic relapse and hospitalisation[6]
- Diminished social functioning[6]
- Lower quality of life[6]
- Increased risk of suicide with 64% of schizophrenia patients who commit suicide doing so during depressive episodes and with suicide attempts being more frequent in those with schizoaffective disorder than in individuals with either schizophrenia or a mood disorder alone[6]
- Increased risk for developing comorbid conditions[18]
- Impaired quality of life[19]

Health care utilisation[17]

- Increased in-and outpatient visits
- Treatment costs of comorbid conditions
- Brain stimulation therapies

Workplace costs[17]

- Increased absenteeism (missed time from work)
- Presenteeism (reduced productivity while at work)

Treatment of affective symptoms

Treatment of schizoaffective disorder as well as schizophrenia with affective symptoms always happens first with antipsychotics, ideally with an antipsychotic that is approved for mood disorders or with a D2/D3 partial agonist. [20,6]

Treatment of schizoaffective disorder[20]

- The mainstay of treatment should include **an antipsychotic**.
- A study that reported obtained data on treatment regimens for schizoaffective showed that **93% of patients received an antipsychotic**, 20% a mood-stabilizer in addition to an antipsychotic, and 19% received an antidepressant along with an antipsychotic.[20]
- There are **no specific guidelines available (e.g., NICE, APA, DGPPN)** to address the treatment of schizoaffective disorder. Overall schizoaffective disorder treatment **is generally handled in the framework of schizophrenia treatment** once again underlining that schizophrenia is the primary disorder.

Treatment of affective symptoms in schizophrenia[6]

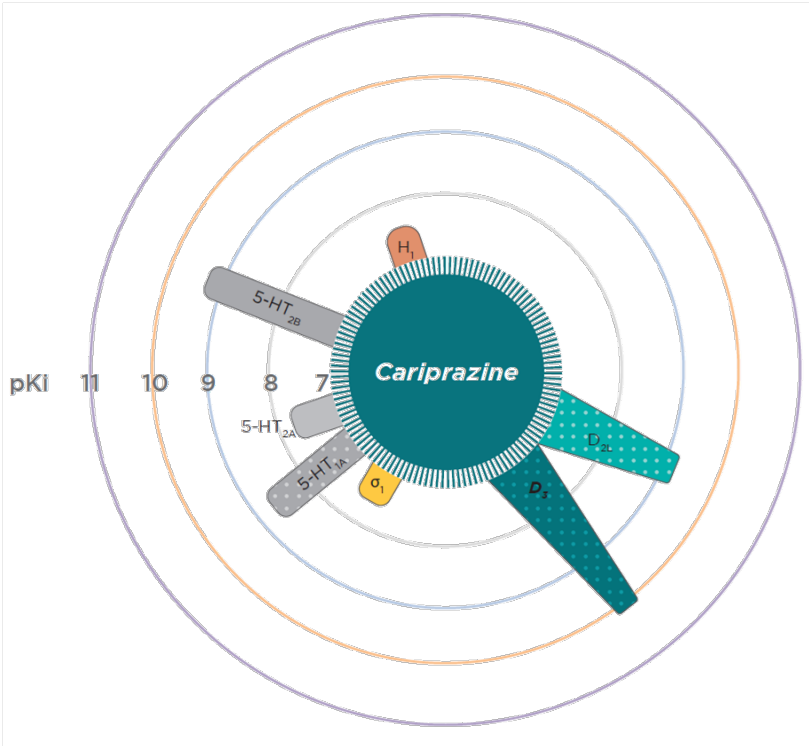
- It has been suggested that depression is associated with reduced **dopamine neurotransmission**, leading to insufficient tonic activity at dopamine D3 receptors and inadequate phasic activity at dopamine D2 receptors.
- **Partial agonists of D2/D3 receptors** may restore these tonic and phasic dopamine activities, producing antidepressant effects.
- Moreover, the actions of D2/D3 partial agonists might also provide **antipsychotic and antimanic benefits** due to their net antagonist effects on overstimulated D2/D3 receptors.

NICE: National Institute for Health and Care Excellence; APA: American Psychiatric Association; DGPPN: German Association for Psychiatry, Psychotherapy and Psychosomatics

Brain receptors and Cariprazine

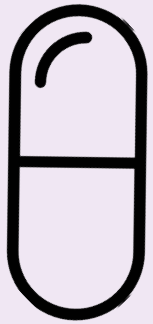
Cariprazine is a D3-preferring D2/D3 partial agonist with additional activity on serotonin receptors. Overall, cariprazine treatment results in the below described desired and undesired effects. [21-24]

RECEPTOR		DESIRED EFFECT	SIDE EFFECT
Dopamine	D2 Partial agonism	Antipsychotic effect (positive symptoms)	EPS No prolactin increase due to partial agonism
	D3 Partial agonism	Improvement of negative symptoms, cognition, mood	-
Serotonin	5-HT1A Partial agonism	Anxiolytic effect	Headache, nausea & weight gain
	5-HT2A Antagonism	Mild sedation	More non-REM sleep
	5-HT2B Antagonism	-	
Histamine	H1	-	Weight gain & sedation
Sigma	σ1	Improvement of depressive symptoms, schizophrenia, OCD & AD	



Cariprazine in affective disorders

Cariprazine has a unique receptor profile that may be able to address affective symptoms in several major psychiatric disorders including **major depressive disorder as add-on treatment**, **bipolar depression and mania**, **schizoaffective disorder**, and **schizophrenia with affective symptoms**.



- **major depressive disorder as add-on treatment**
- **bipolar depression**
- **bipolar mania**
- **schizoaffective disorder**
- **schizophrenia with affective symptoms**

Cariprazine in major depression and bipolar disorder

Cariprazine proved to be effective in the dose range of 1.5-3.0 mg/day for the treatment of major depressive disorder as add-on and 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.[25]

TREATMENT

major depressive disorder as add-on treatment				
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.		

manic/mixed episodes associated with bipolar I disorder			depressive episodes associated with bipolar I disorder			
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 3-6mg/day and the 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 the 3 mg/day dose groups showed statistically significant separation from placebo

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.

TREATMENT

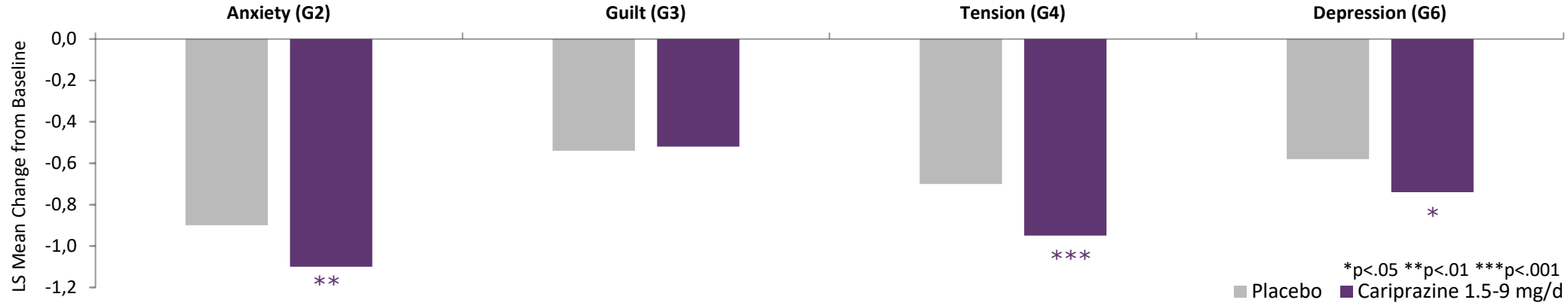
EVIDENCE	DIAGNOSIS	MEDICATION(S)	PRESENTING PROBLEM	OUTCOME
Case report[26-28]	Schizoaffective disorder, depressive type	CAR+CLOZ	Negative symptoms	• No adverse events • Better engagement and fuller affect (6 months) • 73% reduction in SANS score (from 88 to 24) • Some persistent positive symptoms remained
	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[29]	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

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.[5]

Marder PANSS Factors

Anxiety / Depression factor items



TREATMENT

Key take-aways

SUMMARY

1. Affective, or mood, disorders, are psychiatric conditions primarily characterised by disturbances in mood and emotion, negatively impacting patients' well-being and functioning
2. Affective symptoms, mainly depression and mania, might be caused by the complex interplay of various neurotransmitter systems, including serotonin, dopamine and norepinephrine
3. Treatment of schizoaffective disorder as well as schizophrenia with affective symptoms always happens first with antipsychotics, ideally with an antipsychotic that is approved for mood disorders or with a D2/D3 partial agonist
4. Cariprazine might be a good treatment option for MDD, bipolar disorders, schizoaffective disorders and schizophrenia with affective symptoms, as suggested by randomised clinical trials and real-world evidence
5. Cariprazine has a unique pharmacology concerning the D3/D2 receptor profile, which might be responsible for its broad-spectrum efficacy.

Abbreviated Summary of Product Characteristics

Cariprazine is available in 1.5 mg; 3 mg; 4.5 mg; 6 mg hard capsule for the treatment of schizophrenia in Europe.

SMPC

Name of the medicinal product
Reagila (cariprazine) 1.5 mg; 3 mg; 4.5 mg; 6 mg hard capsule, ATC code: N05AX15.

Therapeutic indications
Reagila is indicated for the treatment of schizophrenia in adult patients.

Posology
The recommended starting dose of cariprazine is 1.5 mg once daily. Thereafter the dose can be increased slowly in 1.5 mg increments to a maximum dose of 6 mg/day, if needed. Because of the long half-life of cariprazine and its active metabolites, changes in dose will not be fully reflected in plasma for several weeks.

Contraindications
Hypersensitivity to the active substance or to any of the excipients, concomitant administration of strong or moderate CY- P3A4 inhibitors or inducers.

Special warnings
Precautions for use: in case of suicidal thoughts or behaviour; in those who are prone to or already exhibit symptoms of akathisia; in patients with Parkinson disease; in patients with risk factors for stroke; in patients with medical history of seizure, cardiovascular disease (blood pressure changes, QT prolongation, risk for venous thromboembolism), diabetes mellitus. If signs and symptoms of tardive dyskinesia appear discontinuation should be considered. Drug discontinuation is recommended if signs and symptoms of neuroleptic malignant syndrome develops. Patients who would develop symptoms potentially related to cataract should be advised to ophthalmologic examination. Weight should be monitored regularly. Not recommended to treat elderly patients with dementia. Capsules of 3 mg, 4.5 mg and 6 mg contain Allura red AC which can cause allergic reactions.

Most common adverse reactions
Akathisia, extrapyramidal symptoms, body weight increase, increased or decreased appetite, dyslipidaemia, sleep disorders, anxiety, sedation, dizziness, blurred vision, tachyarrhythmia, hypertension, nausea, constipation, vomiting, increased liver enzymes and creatinine phosphokinase in blood, fatigue. Not recommended during pregnancy or for fertile women not using reliable contraception. The medicinal product has minor or moderate influence on the ability to drive and use machines.

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