Cariprazine (Reagila®)
for the treatment of Negative Symptoms in Adults with Schizophrenia

Schizophrenia

Schizophrenia is a complex, chronic and heterogenous disorder with an estimated global prevalence of 1%.[1] Key features of schizophrenia include positive, negative, and cognitive symptoms.[2] Positive symptoms include hallucinations and delusions. Negative symptoms include deficits in motivation (avolition), pleasure seeking (anhedonia), social interaction (asociality), verbal communication (alogia) and emotional expression (blunted affect and poverty of speech).[3]

Burden and Course of Negative Symptoms

Negative symptoms are present throughout the course of schizophrenia. They can occur early, increase in severity and persist over time.(Fig 1)[4,5] It is thought that up to 60% of patients with negative symptoms meet clinical treatment thresholds.[4] Despite this statistic, negative symptoms continue to be associated with poor health outcomes and significant social burden.[2,5] The CLAMORS study showed that 58% of stable outpatients with schizophrenia who received antipsychotic treatment had at least one negative symptom of moderate severity or worse on the Positive and Negative Syndrome Scale (PANSS) scale and the most common negative symptoms included social withdrawal (48%), emotional withdrawal (46%) and poor rapport (36%).[6]

Neurobiology of Negative Symptoms

The neurobiology of negative symptoms is distinct from that of positive symptoms, which involve the dopamine and glutamate networks and are mediated in the mesolimbic pathways. Negative symptoms are mediated via the fronto-cortical temporal and cortico-striatal pathways.[5] Confused

Fig. 1: Course of Negative Symptoms in Schizophrenia (adapted from Correll & Schooler et al., 2020)[5]

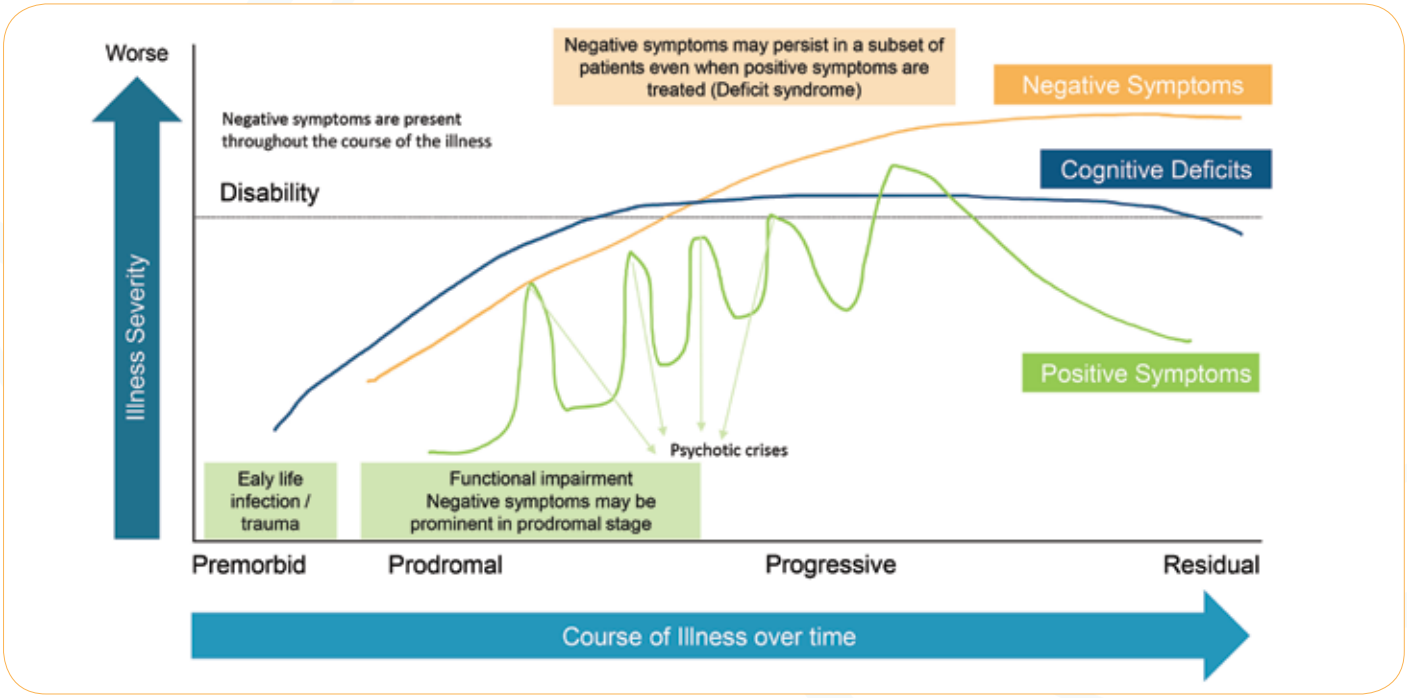
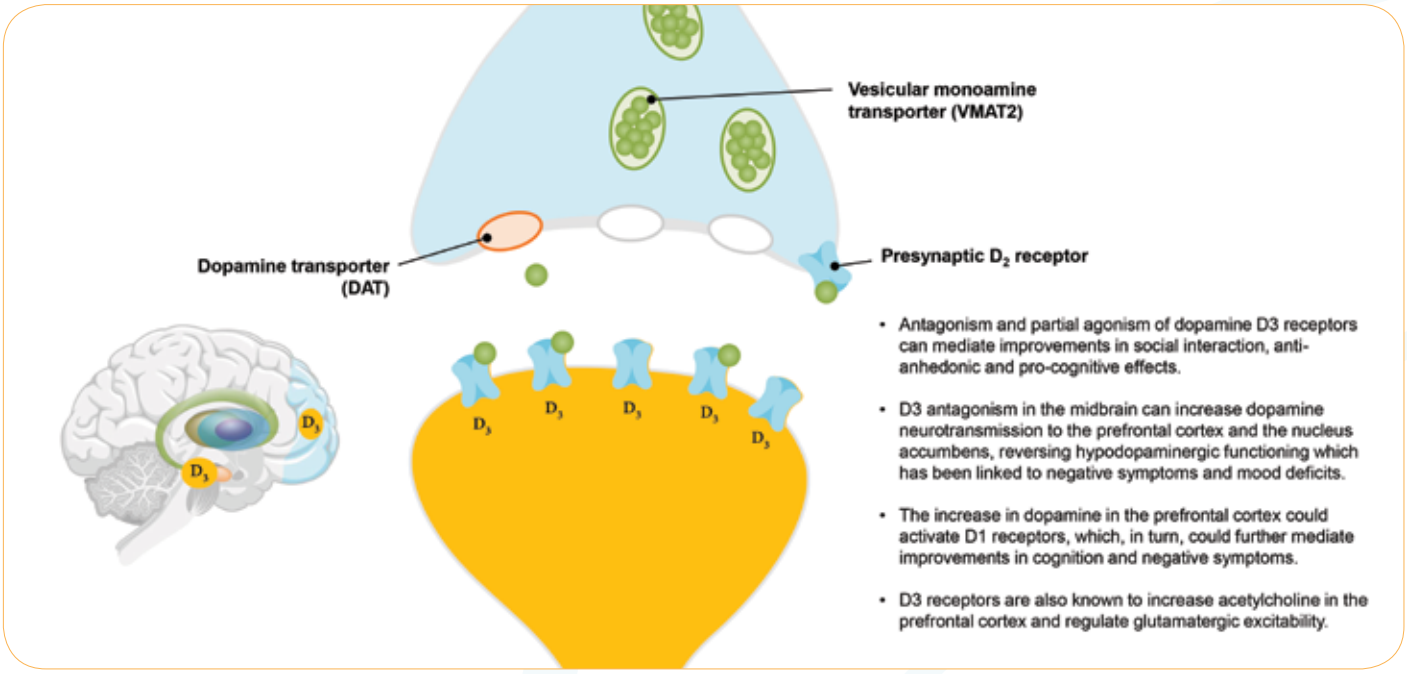


Fig. 2: Role of Dopamine (D3) receptors (adapted from Correll & Schooler et al. 2020).[5]



dopaminergic signalling is said to drive negative symptom states and deficits in anticipatory and consummatory pleasure are thought to be linked to cortico-striatal disruption. D3 receptors in the mesolimbic regions of the brain control reward, emotion and cognition.[4] D3 receptors possess a high affinity for DA (420 - fold higher than that of D2 receptors) and, unlike D2 receptors, small changes in their number or function may lead to dramatic effects on synaptic transmission.[7] (Fig. 2).

Assessment of Negative Symptoms

Negative symptoms can be detected using the PANSS considered the gold standard within clinical trials due to its high validity and sensitivity. The negative symptoms subscale, PANSS-factor score to negative symptoms (PANSS-FSNS) consists of N1 (blunted affect), N2 (emotional withdrawal), N3 (poor rapport), N4 (passive or apathetic social withdrawal), N6 (lack of spontaneity and flow of conversation), G7 (motor retardation), and G16 (active social avoidance), with a higher score indicating worse severity.[10] Additional evidence-based measures include the Scale for the Assessment of Negative Symptoms (SANS), the Brief Psychiatric Rating Scale (BPRS), and the Brief Negative Symptom Scale (BNSS) among others.[8] When assessing negative symptoms, it is important that clinicians also differentiate between primary symptoms (those intrinsic to schizophrenia) and those which are secondary (contributory).[5]

Table 1: Summary of results in study RGH-188-005 (MMRM analysis) [9, 10]

	REAGILA® LS mean	Risperidone LS mean	Estimated Treatment Difference	95% CI	p-value
PANSS-FSNS at Baseline	27.8	27.5	-	-	-
PANSS-FSNS at Week 26	18.5	19.6	-	-	-
PANSS-FSNS CfB to Week 26	-8.9	-7.4	-1.5	-2.4; - 0.5	0.002
Total PSP at Baseline	48.8	48.2	-	-	-
Total PSP at Week 26	64.0	59.7	-	-	-
Total PSP CfB to Week 26	14.3	9.7	4.6	2.7; 6.6	<0.001

PANSS-FSNS = PANSS factor score for negative symptoms CfB = change from baseline
PSP = Personal and Social Performance MMRM (mixed effects model for repeated measures)

Cariprazine

Cariprazine is a third generation antipsychotic found to be effective in the treatment of schizophrenia.[4] Its pharmacological profile and clinical applications make it an attractive first-line treatment option for management of negative symptoms.[2,4] In a recent primary efficacy analysis both cariprazine and risperidone-treated patient groups demonstrated statistically significant improvement in the change from baseline, in PANSS (p=0.002). From week 14 onward a statistically significant difference (p=0.008) was observed in favour of cariprazine over risperidone (Table 1).[9,10]

Other patients suitable for treatment with cariprazine include those with metabolic syndrome, weight gain or hyperprolactinaemia. [2]

Dosing

The Australian Reagila (cariprazine) PI states the following regarding Cariprazine dosing:[9]

- Taken once daily at the same time of the day with or without food
- The recommended starting dose is 1.5 mg once daily
- Thereafter the dose can be increased in 1.5 mg increments according to efficacy and tolerability to a maximum dose of 6 mg/day if needed
- The lowest effective dose should be maintained according to the clinical judgement of the treating physician

The optimal maintenance dose for patients with schizophrenia appears to be 4.5 mg/day, based on analysis of clinical data, but this depends on the severity of symptoms and the treatment setting, with higher doses being required for patients with more severe positive symptoms or agitation (fig.3).[2,11]

Mechanism of action

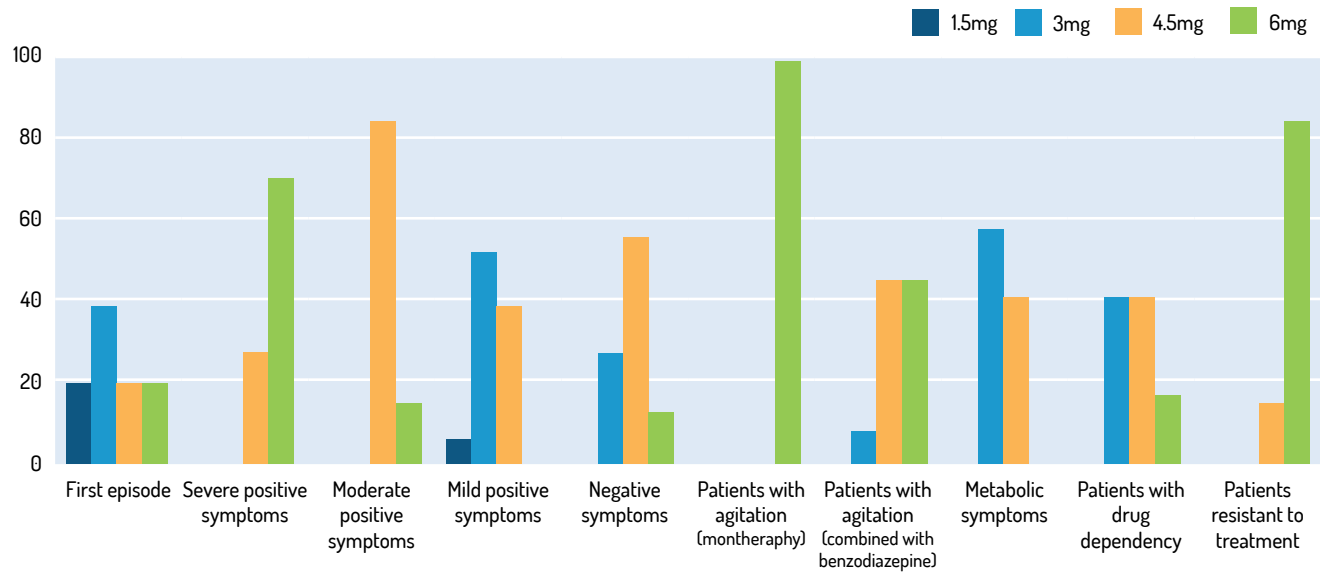
Cariprazine's mechanism of action is hypothesised to be mediated through the partial agonism of dopamine D2 / D3 receptors, serotonin 5-HT1A receptors, and antagonism of serotonin 5-HT2A receptors. Cariprazine also shows a low affinity for alpha-type 1A receptors, where it acts as an antagonist. Cariprazine is reported to have no appreciable affinity for muscarinic receptors.

There are two isoforms of the D2 receptor, each with different functions.[12] The D2S is dominant in the cell bodies and projection axons of the dopaminergic cells in the mesencephalon (midbrain). D2S auto-receptors (on dendrites and soma) are known to inhibit cell firing and activate DA reuptake while inhibiting DA synthesis.[12] Cariprazine has a higher affinity for D3 receptors than D2 receptors.[4] The affinity of cariprazine is functionally higher than the affinity of dopamine itself for the D3 receptor which differentiates it from other currently available atypical antipsychotics.[4,7]

Pharmacokinetics

Cariprazine has a half-life of 2 to 4 days and reaches peak plasma concentration within 3 to 6 hours. Cariprazine has two main metabolites, desmethyl cariprazine (DCAR) and di-desmethyl cariprazine (DDCAR), and both metabolites have receptor binding profiles similar to cariprazine.[4] The active metabolite has a half-life of 1–3 weeks, the longest of any atypical antipsychotic and the estimated time to reach steady state is approximately 3 weeks.[9] Cariprazine is extensively metabolised in the liver by CYP3A4 and to a smaller degree by CYP2D6 via hydroxylation and demethylation.[9] The Australian Product information states that Reagila® (cariprazine) is contraindicated with moderate and strong inhibitors or inducers of CYP3A4.[9]

Fig. 3: Cariprazine dosages given by expert panel (%) to treat schizophrenia (Fagiolini et al., 2020) [2]



Based on Real World Experience

Safety and tolerability

Cariprazine is well-tolerated with a low risk of metabolic syndrome and weight gain.[2] 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. Patients should therefore be monitored for adverse reactions and treatment response for several weeks after starting cariprazine and after each dosage change. No dose adjustment is needed in mild/moderate renal or hepatic impairment.[9]

Conclusion

Cariprazine is a partial agonist at dopamine D3/D2 and 5HT1A receptors with preferential affinity for the D3 receptor.[4,7] It is administered orally as a once daily dose and appears to be well tolerated. The pharmacokinetic and pharmacodynamic properties of cariprazine make it a useful therapeutic option for treating negative symptoms in patients with schizophrenia.

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