



Dimensions of Schizophrenia – The role of cariprazine

Continuing the discussions around the dimensions of schizophrenia as part of our Schizophrenia Awareness Week series, in this article we are going to look at the role of cariprazine in addressing the different dimensions of schizophrenia from symptoms to stages.

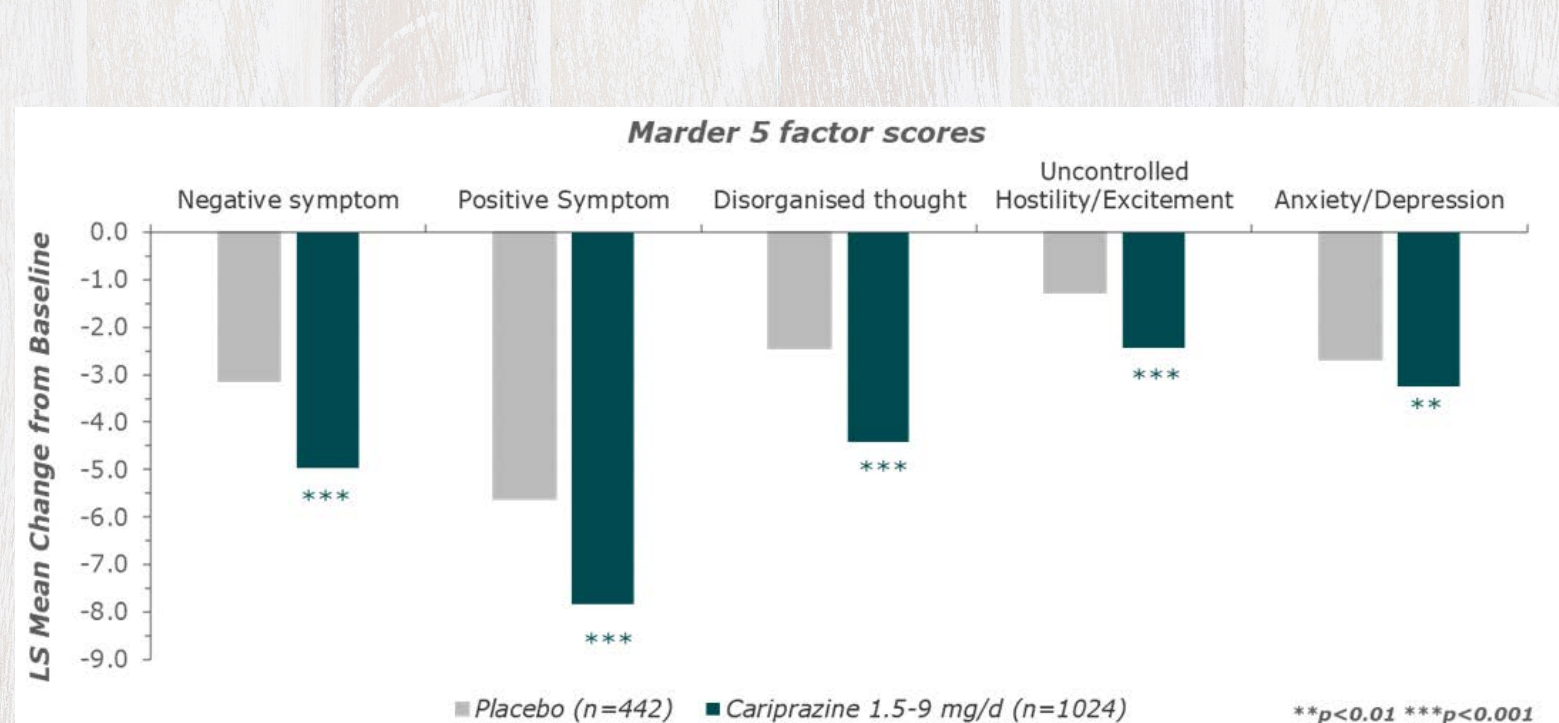
Symptom dimensions

Cariprazine is a dopamine D3/D2 and serotonin 5HT1A partial agonist and serotonin 5HT2A antagonist with preferential binding to the D3 receptors (1). Due to this mechanism of action, cariprazine is able to address a wide range of symptoms from positive to hostility.

Positive symptoms

The efficacy of cariprazine in alleviating positive symptom such as hallucinations or delusions has been established in three short-term, double-blind, placebo-controlled clinical trials involving patients with acute exacerbation of schizophrenia (2–4). According to the individual as well as pooled results, cariprazine was significantly better than placebo in treating symptoms of schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS) total and positive factor scores as seen in Figure 1 (5).

Figure 1. Mean change from baseline to week 6 in the PANSS factors (pooled ITT population).



*cariprazine is approved in the dose range of 1.5 mg – 6.0 mg.

P < 0.01; *P < 0.001. Error bars = standard error of the LS mean. ES, effect size; ITT, intent-to-treat; LS, least squares; LSMD, LS mean difference; PANSS, positive and negative syndrome scale. Figure from: Marder S, Fleischhacker WW, Earley W, Lu K, Zhong Y, Németh G, et al. Efficacy of cariprazine across symptom domains in patients with acute exacerbation of schizophrenia: Pooled analyses from 3 phase II/III studies. *Eur Neuropsychopharmacol.* 2019;29:127–36.

Negative symptoms

As a core feature of schizophrenia, addressing negative symptoms is an important clinical goal for physicians (6). It is often described by the so-called 5As (anhedonia, asociality, amotivation, alogia and apathy) (6). Throughout the clinical development programme, cariprazine was found to be superior in treating this symptom dimension in patients with predominant negative symptoms compared to an active comparator, risperidone in a double-blind, randomized comparative trial (7). In Latvia, the results of this trial were repeated in a 16-week, open-label, flexible-dose observational study, indicating that indeed, cariprazine is a viable treatment option for patient suffering from the negative symptom dimension (8).

Cognitive symptoms

It is a well-known fact that cognitive symptoms play a major role in determining the quality of life and everyday functioning of patients (9), thus showing effectiveness in cognitive impairment associated with schizophrenia is key in achieving recovery. If looking back at Figure 1, it is clear that cariprazine was significantly better than placebo in addressing the PANSS disorganized thinking factor scores according to the pooled results of the short-term clinical trials (5). Furthermore, in a recent publication by Professor McIntyre and colleagues, cariprazine's efficacy in cognitive symptoms was evaluated post-hoc as measured by the Cognitive Drug Research (CDR) system attention battery. The authors concluded that greater improvement in cognitive symptoms was seen with cariprazine 3 mg/day than with placebo and thus cariprazine might have a potential in treating the cognitive dimension (10).

Mood symptoms

Mood symptoms such as depression or anxiety are not uncommon in schizophrenia. Again, pooled results of clinical trials signaled significant difference between cariprazine and placebo on the PANSS anxiety/depression factor scores (5). This is supported by a pre-clinical study as well where cariprazine significantly decreased chronic unpredictable stress-induced anhedonic-like behavior in wild-type mice (11).

Hostility

Hostile behaviour might be present in some schizophrenia patients, especially during psychotic episodes. In comparison with placebo, cariprazine was able to achieve significant improvement on the PANSS hostility item according to the results of the pooled data from 3 randomized controlled trials (12). Importantly, this effect increased with greater levels of baseline hostility (12).

Stages

Schizophrenia can also be viewed as a progressive disorder with distinct stages such as prodrome, first episode, remission and relapse and finally, chronic psychosis, as described in the white paper (13). In a post-hoc analysis by Falkai and colleagues, the effectiveness and safety of cariprazine was analysed in early (suffering from schizophrenia for less than 5 years) and late-stage (more than 15 years with schizophrenia) patients (14). In both patient groups, cariprazine was found to be statistically significantly better than placebo from baseline to week 6 in the PANSS total score (14). In terms of safety, early stage patients experienced similar amount of side effects as patients in the late stage (14). The results confirmed that patients from different stages can all benefit from cariprazine.

References

1. Kiss B, Horvath A, Nemethy Z, Schmidt A, Laszlovszky I, Bugovics G, et al. Cariprazine (RGH-188), a dopamine D3 receptor-neurochemical, D 3/D2 dopamine receptor antagonist partial agonist antipsychotic candidate: In vitro and neurochemical profile. *J Pharmacol Exp Ther.* 2010;333(1):328–40.
2. Durgam S, Starace A, Li D, Migliore R, Ruth A, Németh G, et al. An efficacy and safety study of cariprazine in patients with acute exacerbation of schizophrenia: A phase II, randomized clinical trial. *Schizophr Res.* 2014;152(2–3):450–7.
3. Durgam S, Cutler AJ, Lu K, Migliore R, Ruth A, Laszlovszky I, et al. Cariprazine in acute exacerbation of schizophrenia: A fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. *J Clin Psychiatry.* 2015;76(12):e1574–82.
4. Kane JM, Zukin S, Wang Y, Lu K, Ruth A, Nagy K, et al. Efficacy and Safety of Cariprazine in Acute Exacerbation of Schizophrenia: Results from an International, Phase III Clinical Trial. *J Clin Psychopharmacol.* 2015;35(4):367–73.
5. Marder S, Fleischhacker WW, Earley W, Lu K, Zhong Y, Németh G, et al. Efficacy of cariprazine across symptom domains in patients with acute exacerbation of schizophrenia: Pooled analyses from 3 phase II/III studies. *Eur Neuropsychopharmacol.* 2019;29:127–36.
6. Galderisi S, Mucci A, Buchanan RW, Arango C. Negative symptoms of schizophrenia: new developments and unanswered research questions. *The Lancet Psychiatry.* 2018;5(8):664–77.
7. Németh G, Laszlovszky I, Czobor P, Szalai E, Szatmári B, Harsányi J, et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. *Lancet.* 2017;389(10074):1103–13.
8. Rancans E, Dombi ZB, Mátrai P, Barabaissy A, Sebe B, Skrivele I, et al. 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;
9. Savilla K, Kettler L, Galletly C. Relationships between cognitive deficits, symptoms and quality of life in schizophrenia. *Aust N Z J Psychiatry.* 2008;42(6).
10. McIntyre RS, Daniel DG, Vieta E, Laszlovszky I, Goetghebeur PJ, Earley WR, et al. The Efficacy of Cariprazine on Cognition: A Post Hoc Analysis from Phase II/III Clinical Trials in Bipolar Mania, Bipolar Depression, and Schizophrenia. *CNS Spectr.* 2022;1–30.
11. Duric V, Banar M, Franklin T, Lepack A, Adham N, Kiss B, et al. Cariprazine exhibits anxiolytic and dopamine D3 receptor-dependent antidepressant effects in the chronic stress model. *Int J Neuropsychopharmacol.* 2017;20(10):788–96.
12. Citrome L, Durgam S, Lu K, Ferguson P, Laszlovszky I. The effect of Cariprazine on hostility associated with schizophrenia: Post hoc analyses from 3 randomized controlled trials. *J Clin Psychiatry.* 2016;77(1):109–15.
13. Dombi ZB, Barabaissy A, Sebe B, Laszlovszky I, Németh G. Clinical Staging in Schizophrenia Spectrum Disorders. In: Kenjiro F, editor. *Psychosis - Phenomenology, Psychopathology and Pathophysiology.* IntechOpen; 2021.
14. Falkai P, Dombi ZB, Acsai K, Barabácssy Á, Schmitt A, Németh G. The efficacy and safety of cariprazine in the early and late stage of schizophrenia: A post hoc analysis of three randomized, placebo-controlled trials. *CNS Spectr.* 2021;Dec:1–8.