

New developments in the management of schizophrenia and bipolar disorder: potential use of cariprazine

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Abstract: Cariprazine is a recently developed antipsychotic drug with a partial agonism for the D₂ and D₃ receptors. It shows a tenfold greater affinity for the D₃ receptor. In clinical trials, its therapeutic effect has been tested in patients with an acute exacerbation of schizophrenia and in patients with acute mania in bipolar disorder. Like risperidone, cariprazine improves positive and negative schizophrenic symptoms, and ameliorates cognitive functions. Cariprazine induces extrapyramidal symptoms less often than risperidone and can cause acute akathisia. It is a prolactin-sparing antipsychotic drug and has a favorable metabolic profile. In acute mania in bipolar disorder, it treats manic symptoms significantly better than placebo. As a consequence of its improved adverse effects, cariprazine improves patients' quality of life to a greater extent than other second-generation antipsychotic drugs. Cariprazine is a promising antipsychotic drug in the treatment of schizophrenia, acute mania in bipolar disorder, and in schizophrenia with mania. In these patients, its long-term therapeutic effect and its action in comparison with other second-generation antipsychotic drugs, above all aripiprazole, remain to be tested in clinical trials.

Keywords: cariprazine, second-generation antipsychotic drug, schizophrenia, acute mania, D₂ receptor, D₃ receptor, partial agonism, akathisia, metabolic parameters, cognitive function

Introduction to developments in the management of schizophrenia and bipolar disorder

Psychotic disorders can be divided into schizophrenia and affective disorders. Schizophrenia is a chronic disabling disorder, which manifests as an acute psychosis with positive symptoms such as hallucinations, paranoia, and illusions. Second-generation antipsychotic drugs are the preferred drugs in the treatment of schizophrenia because they improve positive and negative schizophrenic symptoms, however, in most cases after the remission of the acute psychotic symptoms, negative symptoms such as autism, social withdrawal, and cognitive symptoms remain. Permanent medication is necessary in order to prevent a recurrence of psychotic symptoms.¹ A milestone in the antipsychotic treatment of schizophrenic patients was the introduction of typical neuroleptics, such as haloperidol, a D₂ antagonist. Haloperidol, above all, improves positive schizophrenic symptoms, but often causes extrapyramidal side effects, weight gain, and increased prolactin levels.² Schizophrenia is undoubtedly an inheritable disease with genetically encoded neurotransmitter alterations. The enzymes catalyzing dopamine breakdown have a reduced activity. Moreover, GABAergic and glutaminergic neurons, which have a presynaptic inhibitory action, have a decreased function in the brain regions involved in schizophrenia.³ In the mesolimbic system,

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hippocampus, and prefrontal cortex both dopamine and serotonin hyperactivity can be found in schizophrenia, whereas a stimulation of D_2 and serotonin ($5-HT_{2A}$) receptors enhances psychotic symptoms.⁴⁻⁶ Among the second-generation antipsychotic drugs, combined D_2 and $5-HT_{2A}$ antagonists, the most commonly used antipsychotic drugs are risperidone, olanzapine, and quetiapine.⁴ The affective disorder with manifestations of depressive and manic symptoms is bipolar disorder.¹ In depressive patients, hypoactivity of monoamines in the brainstem and hippocampus occurs. Antidepressant drugs, which block the reuptake of serotonin and/or noradrenaline, fail to improve the lack of energy, interest, and pleasure. Only antidepressant drugs, which block the reuptake of noradrenaline and dopamine or triple reuptake inhibitors, can improve the decreased effects, ie, the loss of energy, pleasure, and interest.⁷ In manic patients, hippocampal dopaminergic neurons show alternating hypo- and hyperactivity with transient normal activity via D_2 receptors that can be improved by administering cariprazine.⁸ The alterations in monoamines are due to polymorphisms of the monoamine transporter genes.⁹ Depressive symptoms are treated by monoamine reuptake inhibitors, for example, selective serotonin reuptake inhibitors or serotonin and noradrenaline reuptake inhibitors. Patients with bipolar disorder are treated with mood-stabilizing drugs such as lithium, carbamazepine, or valproic acid.¹⁰ One-third of patients treated with lithium show no recurrence of depressive or manic symptoms.¹⁰ Bipolar patients can also be treated with new mood-stabilizing drugs such as topiramate or lamotrigine or second-generation antipsychotic drugs such as quetiapine.¹¹

Overview of existing and emerging treatment options

Second-generation antipsychotic drugs are commonly administered in the treatment of schizophrenia because they improve positive and negative schizophrenic symptoms.¹ Typical neuroleptics or first-generation antipsychotic drugs such as haloperidol, a D_2 antagonist, often cause extrapyramidal symptoms, and although they treat positive schizophrenic symptoms adequately their effects on negative schizophrenic and cognitive symptoms are more reduced. Accordingly, second-generation antipsychotic drugs, which are mostly D_2 and $5-HT_{2A}$ antagonists, are preferred. While risperidone, which has greater affinity for the D_2 receptor, still often causes extrapyramidal symptoms, olanzapine has a better effect on negative schizophrenic symptoms than other second-generation antipsychotic drugs. Quetiapine, which shows greater affinity for the $5-HT_{2A}$ receptor, has clinical effects comparable to those

of other second-generation antipsychotic drugs. Currently, the injectable administration of aripiprazole, a partial D_2 agonist, $5-HT_{2A}$ antagonist and $5-HT_{1A}$ agonist, is recommended for the long-term treatment of schizophrenic patients because it is well tolerated and safe for the treatment of positive, negative, and cognitive schizophrenic symptoms.¹² The question that arises is whether a partial agonism at dopaminergic receptors, for example, the D_2 receptor, might enable better tolerability and a better quality of life, since it does not interfere with dopaminergic receptors of the extrapyramidal system very much.

The treatment of bipolar disorder, that is, psychosis with depressive and manic symptoms, consists of the administration of mood-stabilizing drugs. Among first-generation drugs, lithium is the most effective one because one-third of patients show full remission of their depressive and manic symptoms.¹⁰ Other first-generation mood-stabilizing drugs are carbamazepine and valproate, which also have a prophylactic effect. Among responders to lithium, risk genes have been examined. These genes are associated with the neurotransmitters dopamine, serotonin, and glutamate; with second messengers such as cyclic adenosine-monophosphate; with protein kinase C pathways, and with substances involved in neuroprotection.⁹ Among the second-generation mood-stabilizing drugs, the second-generation antipsychotic drugs risperidone and quetiapine, which block D_2 and $5-HT_{2A}$ receptors in the mesolimbic system and hippocampus, should be mentioned. Lamotrigine is a drug of second choice or an add-on therapy in the treatment of bipolar disorder. In this disorder, it stabilizes hippocampal dopaminergic neurons and blocks NMDA and AMPA receptors. The function of dopaminergic and glutaminergic neurons has been described in the nigrostriatum and hippocampus.^{10,13,14}

Review on the pharmacology, mode of action, and pharmacokinetics of cariprazine

Cariprazine is a second-generation antipsychotic drug whose mechanism of action differs from that of second-generation antipsychotic drugs such as risperidone, olanzapine, and quetiapine.¹ It exerts a partial agonism at D_2 and D_3 receptors, with a preferential binding for the D_3 receptor.^{12,15} Moreover, cariprazine exerts a $5-HT_{1A}$ agonistic effect. Cariprazine has a tenfold greater affinity for the D_3 receptor than for the D_2 receptor and hence has different mechanisms of action than other second-generation antipsychotic drugs. Cariprazine exerts a partial agonism at dopaminergic receptors and does not block serotonergic subreceptors. In animal experiments, it shows antipsychotic and antimanic effects. It suppresses the spontaneous activity of mesolimbic dopaminergic neurons,

but had no effect on nigrostriatal dopaminergic neurons.⁸ The partial agonism of cariprazine at D_2 and at D_3 receptors is achieved in the striatum and the prefrontal cortex. A sample of antipsychotic-naïve first-episode schizophrenia patients, who were treated with D_2/D_3 antagonist, showed normal sensory gating, that is, P50 gating and prepulse inhibition deficits.¹⁶ The data about pharmacokinetics of cariprazine can be summarized as follows. Cariprazine has a rapid absorption, and its mean half-time was 2–5 days.⁸ Cariprazine has two major metabolites, namely desmethyl cariprazine and didesmethyl cariprazine, which have pharmacological properties similar to those of cariprazine.¹⁷ Cariprazine can be administered with or without food and its plasma peak concentration is reached in 3–5 hours. It is mainly eliminated via hepatic metabolism, like other lipophilic antipsychotics. Steady state is reached by cariprazine and desmethyl cariprazine after 1 week and after 4 weeks by didesmethyl cariprazine.¹⁷ After dose withdrawal, a 50% reduction in plasma level is reached in about 1 week. No data are available in elderly patients or in patients suffering diseases of drug-eliminating organs.⁸ It is used for the treatment of schizophrenia and bipolar disorder.¹⁵ The most frequent adverse effects are as follows: insomnia, extrapyramidal disorder, akathisia, sedation, nausea, dizziness, and constipation. Mean changes in metabolic parameters are small and comparable to those observed in healthy volunteers.¹⁵

Efficacy, safety, and tolerability issues

Clinical trials have been carried out about the use of cariprazine in patients with schizophrenia and mania, in bipolar disorder. A randomized, clinical study of cariprazine and risperidone in a phase II study addressing the treatment of acute exacerbation of schizophrenia has been reported.^{15,18} A total of 1,011 patients were enrolled in the study, and 732 patients were randomized to receive treatment. The Positive and Negative Syndrome Scale (PANSS) total score changed from baseline to week 6 in patients receiving cariprazine, that is, the improvement of positive and negative schizophrenic symptoms was greater than that of placebo.¹⁵ Cariprazine at a dosage of 3 or 4.5 mg/day was more efficient at improving the PANSS total score in comparison with the control group. The group receiving 1.5 mg/day showed improvements from week 2 to week 6.¹² Risperidone also afforded improvements in the PANSS total score as compared to the control group. The mean duration of treatment with the placebo was 30 days, 33 days for cariprazine, and 35 days for risperidone.¹⁵ Adverse effects occurred in 70% of the patients, in which insomnia, extrapyramidal disorder, akathisia, sedation, nausea, dizziness, and constipation were observed.

Serious side effects occurred in 19 patients, but there were no deaths. Weight gain was observed in a few patients receiving cariprazine, although it was more frequent in the group treated with risperidone. Patients receiving cariprazine had a slightly higher heart rate, and patients receiving risperidone had an elongation of the QT segment. Extrapyramidal symptoms such as parkinsonism and akathisia occurred more frequently in the group treated with risperidone.¹⁵

Haloperidol and second-generation antipsychotic drugs are also effective in the treatment of acute mania in bipolar disorder. Although these drugs have a safe therapeutic effect, adverse effects such as extrapyramidal symptoms, metabolic side effects, and weight gain are problems for the patients treated. The main question is whether cariprazine has a safe therapeutic effect for the treatment of acute mania in bipolar disorder.¹⁹ Altinbas et al performed a double-blind, randomized study with cariprazine, using doses from 3 to 12 mg/day, in 238 patients with acute mania in bipolar disorder.¹⁹ Cariprazine improved the manic symptoms in week 3 in comparison with the control group receiving placebo. The most frequent adverse effects were extrapyramidal symptoms, headache, akathisia, constipation, nausea, and dyspepsia, which can be explained in terms of the partial dopamine agonism. Adverse effects observed in the treatment with other second-generation antipsychotic drugs, such as weight gain, metabolic disturbances, increases in prolactin levels, or QT prolongation, were not reported. The study revealed that manic symptoms were very much improved in comparison with the patients receiving placebo.¹⁹ However, adverse treatment-emergent acute effects such as akathisia and tremor can occur. Cariprazine has a greater antagonistic effect on the D_2 receptor than aripiprazole and improves cognitive functions. Cariprazine has a therapeutic effect in acute mania in bipolar disorder like other second-generation antipsychotic drugs.¹⁹

Patient-focused perspectives such as quality of life, patient satisfaction/acceptability

First, the effect of cariprazine on patients' quality of life during the treatment of an acute exacerbation of schizophrenia is described.^{8,15} Cariprazine, a new second-generation antipsychotic drug with a different pharmacological profile, improves all significant parameters, that is, the positive PANSS total score and the negative PANSS total score in comparison to placebo.¹⁵ The doses in the treatment of acute schizophrenia are 1.5–4.5 mg/day (low dose) and 6–12.0 mg/day (high dose).²⁰ Higher doses of cariprazine had a greater effect; they improved the total PANSS score better, and safety and

tolerability were maintained.¹⁵ The therapeutic effect was comparable to that of risperidone, although the PANSS changes from baseline were greater on many parameters in the risperidone group. Patients receiving cariprazine underwent a smaller weight gain than patients receiving risperidone, and patients treated with cariprazine had no increases in prolactin levels, in contrast to the risperidone group. While second-generation antipsychotic drugs such as risperidone increase the risk of coronary artery heart disease, cariprazine does not increase cholesterol, triglycerides, or glucose levels.^{1,21} Cariprazine and risperidone caused extrapyramidal symptoms, and these occurred in a higher percentage in the risperidone group.¹⁵ Cariprazine has a greater affinity for the D₂ and D₃ receptors than aripiprazole and has a stronger antagonistic effect on the D₂ receptor.²² Clinical trials should explore whether cariprazine exerts therapeutic effects comparable to those of aripiprazole.²²

Second, the effect of cariprazine on patients' quality of life during the treatment of acute mania in bipolar disorder has been assessed.¹⁹ Cariprazine shows a good therapeutic effect and good safety and tolerability in the treatment of acute mania. Although second-generation antipsychotic drugs such as risperidone, olanzapine, and quetiapine elicit an increase in metabolic parameters, such as glucose, cholesterol, and triglycerides, and increase the risk of diabetes mellitus and coronary artery heart disease, cariprazine has a favorable metabolic profile because it binds only weakly to H₁ and 5-HT_{2C} receptors.²⁰ While risperidone is a prolactin-elevating antipsychotic drug, cariprazine is a prolactin-sparing drug.^{23,24} Cariprazine improves cognitive functions as a consequence of its high affinity for the D₃ receptor.²² This is an important aspect in comparison with other second-generation antipsychotic drugs. Although cariprazine causes extrapyramidal symptoms less often than risperidone, akathisia occurs more often in the treatment with cariprazine than in placebo groups.²⁵ All these results point to the good tolerability of cariprazine, although future clinical trials should be carried out in order to determine whether cariprazine improves patients' quality of life to a greater extent than other second-generation antipsychotic drugs.

Conclusion, place in therapy

Cariprazine is a recently developed second-generation antipsychotic drug with partial agonism at the D₂ and D₃ receptors: it has a tenfold greater affinity for the D₃ receptor than for the D₂ receptor, and it is recommended for the treatment of schizophrenia and acute mania in bipolar disorder. In the treatment of an acute exacerbation of schizophrenia,

cariprazine treats positive and negative schizophrenic symptoms better than placebo and exerts an effect comparable to that of risperidone. Through partial agonism at the D₃ receptor it improves cognitive functions. It causes extrapyramidal symptoms less often than risperidone, although acute akathisia and tremor can occur. In comparison with other second-generation antipsychotic drugs, it does not elicit changes in metabolic parameters that, if they did occur, could increase the risk for coronary artery heart disease or diabetes mellitus. Moreover, it does not raise prolactin levels, in contrast to risperidone. Low doses (1.5–4.5 mg/day) have the same therapeutic effect, safety, and tolerability as high doses (6–12 mg/day). However, one issue remains to be solved, that is, whether cariprazine has a safe therapeutic effect in the long-term treatment of schizophrenic patients.

In the treatment of acute mania in bipolar disorder, cariprazine improves the manic symptoms after 3 weeks as compared to the control group. The common adverse effects were extrapyramidal symptoms (acute akathisia and tremor can occur), constipation, nausea, and dyspepsia. Cariprazine shows a favorable metabolic profile. It elicits no weight gain in comparison with the control group and is a prolactin-sparing antipsychotic drug. Two important points should be noted here. First, cariprazine is a promising antipsychotic drug for the treatment of schizophrenia, acute mania in bipolar disorder, and of schizophrenia with mania. In this context, clinical trials for the treatment of schizophrenic patients with manic symptoms remain to be carried out. The tolerability and the profile of adverse effects are remarkable in comparison to other second-generation antipsychotic drugs such as risperidone, olanzapine, and quetiapine because cariprazine shows a favorable metabolic profile and it does not raise prolactin levels. It causes extrapyramidal symptoms less often than other second-generation antipsychotic drugs such as risperidone. Second, it is important to know whether cariprazine maintains its good therapeutic effect and tolerability during the long-term treatment of schizophrenic, manic, and schizophrenic patients with mania.

Cariprazine, a new antipsychotic drug with a partial agonism at D₂ and D₃ receptors and a 5-HT_{1A} agonism was examined in clinical trials for the treatment of schizophrenia and mania in bipolar disorder.^{8,15,19} In clinical trials, cariprazine shows superiority to placebo on improving manic and positive and negative schizophrenic symptoms. This drug has a favorable metabolic profile, is a prolactin-sparing drug and does not cause electrocardiogram (ECG) changes, however, it often causes akathisia.^{15,19} In comparison with risperidone, it shows similar antipsychotic properties.¹⁵ However,

the changes of psychotic symptoms from baseline, after administration of risperidone, were higher than those after administration of cariprazine. Clinical trials should be carried out to compare the effectiveness and safety of cariprazine with other second-generation antipsychotic drugs, above all aripiprazole. Moreover, long-term clinical trials should be undertaken in order to investigate the safety of cariprazine in the treatment of schizophrenia and bipolar disorder.⁸

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