NEW DRUGS

Cariprazine hydrochloride

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Approved indication: schizophrenia

Reagila (Gedeon Richter)
1.5 mg, 3 mg, 4.5 mg and 6 mg capsules

Antipsychotic drugs are part of the multifaceted management of schizophrenia. Since the emergence of the 'second generation' antipsychotics, these drugs, such as aripiprazole and risperidone, have become first-line therapy. Cariprazine hydrochloride adds to the available options.

The effect of cariprazine is thought to be due to its action on dopamine and serotonin (5-HT) receptors. It is a partial agonist at dopamine D_2 and D_3 and $5HT_{1A}$ receptors, with preferential binding to the D_3 receptor. Cariprazine is an antagonist at 5-HT_2 and histamine H_1 receptors.

Treatment begins with a dose of 1.5 mg once daily. This can be increased gradually to 6 mg daily depending on the patient's response. Doses are well absorbed and, apart from grapefruit juice, cariprazine can be given with or without food. The drug is extensively metabolised. This metabolism involves cytochrome P450 3A4 and co-administration of enzyme inhibitors, such as diltiazem, erythromycin and ketoconazole, or inducers, such as St John's wort and rifampicin, is contraindicated. Cariprazine is also not recommended for patients with severe hepatic or renal impairment. Most of the metabolites are excreted in the faeces. While the effective half-life of cariprazine is about two days, one of its active metabolites has a half-life of eight days. When cariprazine treatment ends it can take up to a month for all the drug and its metabolites to be excreted. Women planning a pregnancy should be advised to avoid conception for at least 10 weeks after stopping treatment. (Cariprazine has had adverse effects in studies of pregnant animals.) The long half-life also means that there may be a delayed response to changes in the dose of cariprazine.

A proof-of-concept trial was carried out in adults with acute exacerbations of previously diagnosed schizophrenia. In this six-week trial 392 patients were randomised to receive daily doses of cariprazine 1.5–4.5 mg (128), 6–12 mg (134) or a placebo (130). Efficacy was assessed with the Positive and Negative Syndrome Scale (PANSS). At the start of the study the average PANSS score was approximately 95. This reduced by 9.74 points with placebo, 14.53 points with lower dose cariprazine and 12.62 points with higher dose cariprazine. Only the lower dose range was statistically superior to placebo.[1]

Most of the phase III trials used the lower doses of cariprazine. A pooled analysis of three trials in acute exacerbations of schizophrenia included 1024 patients who took cariprazine and 442 who took placebo. Their mean baseline PANSS score was approximately 97. After six weeks this was reduced by 16.8 points with a daily dose of cariprazine 1.5 mg and by 19.5 points with a 6 mg dose. The mean reduction in the placebo groups was 10.3 points.[2] One trial used aripiprazole and another used risperidone as active controls. These drugs had effects on the PANSS score that were similar to those of cariprazine.

While the biggest effect of cariprazine was on positive symptoms, such as delusions, it also reduced negative symptoms, such as a blunted affect. A phase III trial therefore specifically studied the effect of cariprazine in 460 adults with predominantly negative symptoms. These patients had had schizophrenia for an average of 12–13 years. On a rating scale for negative symptoms (PANSS–FSNS) they had an average score of approximately 27.5. The patients were randomly switched from their usual treatment to either cariprazine or risperidone. Over 26 weeks, both drugs reduced the PANSS score and the 230 patients who took cariprazine had a bigger reduction on the scale of negative symptoms (8.9 vs 7.44 points). The mean daily doses used were cariprazine 4.2 mg and risperidone 3.8 mg.[3]

As schizophrenia is a long-term illness, cariprazine has been studied for the prevention of relapse. Patients were stabilised on open-label cariprazine for 12 weeks then randomly allocated to take cariprazine or a placebo. This double-blind phase was for 26–72 weeks with the mean duration of treatment being 257 days in the 101 patients who took cariprazine. A relapse occurred in 24.8% of these patients compared with 47.5% of the 99 patients in the placebo group. The median time to relapse was 296 days in the placebo group, but could not be calculated for the cariprazine group.[4]

The adverse effects of cariprazine resemble those of other antipsychotic drugs. They include akathisia, extrapyramidal symptoms and tremor. Compared to placebo more patients taking cariprazine experience insomnia, restlessness and weight gain. Cariprazine can affect blood pressure, but appears to have little effect on the QT interval of the ECG. Caution is advised in patients at risk of stroke. Measurement of lipids and liver function is recommended, but cariprazine does not appear to cause hyperprolactinaemia. In animal studies, cariprazine has been associated with cataracts and changes in the retina. It is unknown if the same effects will be seen in humans.

Cariprazine may have a higher affinity for D_3 receptors than D_2 receptors, but it is unclear if this has any clinically relevant effects. While cariprazine has

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improved the negative symptoms of schizophrenia, the difference between cariprazine and risperidone on the PANSS–FSNS scale was 1.46 points. This was statistically significant, but may not be a clinically significant advantage.[3] In the short-term trials the effect of cariprazine seemed similar to the effects of aripiprazole and risperidone. When deciding which drug to prescribe for controlling acute schizophrenia, it may be a consideration that cariprazine takes five days to reach 90% of its steady-state concentration. Patients with schizophrenia may move from the oral form of an antipsychotic drug to its depot formulation, however there is no long-acting injectable depot formulation of cariprazine.

T T manufacturer provided additional useful information

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.