Cariprazine

A third-generation antipsychotic with a twist

JUDITH D. HOPE MB BS(Hons), MPM, PhD, FRANZCP
NICHOLAS A. KEKS AM, MB BS, MPM, PhD, FRANZCP

Cariprazine is a new atypical antipsychotic medication with a similar side effect profile to aripiprazole and brexpiprazole. It has a low risk of weight gain and sedation, but akathisia can be troublesome. Cariprazine is effective in the treatment of schizophrenia and may be particularly beneficial for the negative symptoms of this disorder. It can also be useful in people with partial adherence because of its long half-life.

In Australia, schizophrenia and related disorders affect 0.3% of the population and are associated with functional disability, physical morbidity and increased mortality.[1] GPs have a key role in the treatment of patients with schizophrenia, particularly in managing physical health and monitoring and managing mental state.[2] Antipsychotic medication, although a cornerstone of treatment for schizophrenia, can cause serious adverse effects which need to be monitored and managed. In addition, psychosocial interventions are crucial for the goal of recovery from illness.[3]

MedicineToday 2022; 23(6): 55-57

Associate Professor Hope is Associate Professor of Psychiatry at the Eastern Health Clinical School, Monash University; a Consultant Psychiatrist at Eastern Health Mental Health Program; and Deputy Director of the Centre of Mental Health Education and Research at Delmont Private Hospital, Melbourne. Professor Keks is Professor of Psychiatry at Monash University; a Consultant Psychiatrist at Monash Medical Centre and in private practice; and Director of the Centre of Mental Health Education and Research at Delmont Private Hospital, Melbourne, Vic.

Although the underlying pathophysiology of schizophrenia and related disorders is not fully understood, all effective antipsychotic drugs block dopamine D_2 receptors in midbrain structures and thus regulate dopamine neurotransmission.[4] Older or 'typical' antipsychotic medications are prone to cause extrapyramidal side effects, such as dystonia, akathisia, pseudoparkinsonism and tardive dyskinesia. Newer or 'atypical' antipsychotics are characterised by lower propensity for extrapyramidal side effects but are associated with increased metabolic effects and physical consequences.[3]

The so-called 'third generation' of antipsychotic medications are the partial dopamine agonists (PDAs), the first of which were aripiprazole and brexpiprazole. These agents block dopamine D_2 receptors in high ambient dopamine states but become dopamine promoters when dopamine levels are low. PDAs possess antipsychotic efficacy through midbrain dopamine blockade but may also benefit the negative symptoms of schizophrenia, possibly because they compensate for dopamine deficiency in the forebrain. PDAs have a favourable tolerability profile, with a low risk of weight gain, sedation and hyperprolactinaemia.[4]

A third PDA, cariprazine, has now become available in Australia. It was listed on the PBS for the treatment of schizophrenia in September 2021. This article describes the features of cariprazine and its potential role in the treatment of patients with schizophrenia.

What are the properties of cariprazine?

Cariprazine is a high-affinity partial agonist at dopamine D_2 and particularly D_3 receptors, which may be an advantage for negative symptoms. It is also a partial agonist at serotonin $5HT_{1a}$ and $5HT_{2a}$ receptors, which predicts low extrapyramidal side effects. Cariprazine has lower D_2 affinity than aripiprazole, which predicts less activation (hyperactivity of thought and behaviour), insomnia and nausea; however, lower $5HT_{2a}$ affinity confers a greater risk of akathisia. Cariprazine has very low

TABLE. ADVERSE EFFECTS OF CARIPRAZINE

Adverse effect	Frequency[5]	Other measures[4]
Akathisia	14.6%	NNH 15
Extrapyramidal symptoms	7.0%	NNH 11
Nausea	6.9%	NNH 20
Weight gain	5.1%	NNH 34
Insomnia	14.0%	Similar to placebo
Sedation	3.7%	Risk ratio 1.12
Prolactin elevation	Low (may lower prolactin)	
QTc prolongation	Low	
Anticholinergic effects (dry mouth, blurred vision, constipation, urinary difficulties, tachycardia)	Very low to nil	

Abbreviation: NNH = number needed to harm.

affinity for histamine H_1 and alpha-1 adrenergic receptors, which predicts a low propensity for weight gain, sedation and postural hypotension. As cariprazine has no anticholinergic muscarinic effects, it is unlikely to cause dry mouth or constipation.

Cariprazine is rapidly absorbed from the gastrointestinal tract, is unaffected by food and achieves a peak plasma level in four to eight hours with high bioavailability. The half-life of cariprazine and its two active metabolites is seven to eight days, considerably longer than that of other antipsychotic compounds. It may take four to eight weeks to reach steady state, although 90% of the steady state level is reached in three weeks.[5]

Cariprazine and its metabolites are primarily metabolised in the liver by cytochrome P450 3A4 (CYP3A4). Inhibitors of CYP3A4 such as ketoconazole and grapefruit juice increase blood levels of cariprazine, and inducers of CYP3A4 such as carbamazepine, modafinil and St John's wort are expected to reduce blood levels. Age, sex, race, smoking status and renal impairment do not affect cariprazine pharmacokinetics, and hepatic impairment increases concentrations only modestly. Cariprazine is a P-glycoprotein inhibitor and may lower digoxin levels. It has no effect on oral contraceptive efficacy.[5]

What is the evidence?

Cariprazine was found to be an effective antipsychotic in patients with acute schizophrenia in both short- and longer-term placebo-controlled studies. In short-term studies of patients with acute psychosis, cariprazine was superior to placebo and equivalent to aripiprazole but was marginally outperformed by risperidone.[6-8] Longer-term (18-month) studies showed that stable patients with schizophrenia were less likely to relapse when taking cariprazine compared with a placebo, had a longer time to relapse and were more likely to have preserved function.[9]

The effect of cariprazine on negative symptoms of schizophrenia was examined in a 26-week head-to-head study with risperidone, which showed a clinically small but statistically significant advantage for cariprazine on negative symptoms after 10 to 14 weeks.[10] No head-to-head trials have compared negative symptoms with cariprazine versus other PDAs, amisulpride or clozapine (the latter is the treatment of choice for patients with prominent negative syndrome of schizophrenia). It is possible that cariprazine will have a role in augmenting clozapine treatment of negative syndrome.

Although cariprazine is not PBS approved for bipolar disorder, it was shown to be effective in patients with mania, mixed states and bipolar depression.[11,12]

What are the adverse effects of cariprazine?

The adverse effects of cariprazine are shown in the Table.[4,5] As predicted, cariprazine has a low propensity for weight gain, causes little sedation and can lower the prolactin level. The risks of extrapyramidal symptoms and QTc prolongation are low. Like other PDAs, cariprazine can cause akathisia, insomnia and gastrointestinal disturbance. The risks of neuroleptic malignant syndrome and tardive dyskinesia are very low but important to keep in mind.

Compared with aripiprazole, cariprazine is less prone to cause activation, insomnia, nausea, sedation and weight gain. However, cariprazine has a higher risk of causing akathisia and pseudoparkinsonism than aripiprazole and brexpiprazole, The frequency of akathisia in pivotal studies was 9 to 14%, with a number needed to harm (NNH) of 15.[4]

How is cariprazine prescribed?

Cariprazine is available at doses of 1.5 mg, 3 mg, 4.5 mg and 6 mg in hard gelatine capsules. Most patients require a dose of 3 to 6 mg (average 4.5 mg) for the treatment of schizophrenia. The maximum recommended dose according to the product information is 6 mg daily, although safety data are available to 9 mg. There are no safety data for pregnancy or breastfeeding.[5]

Cariprazine is usually prescribed once daily in the morning to avoid insomnia. It is usual to start treatment at a dose of 1.5 mg and to increase the dose slowly. If there is no clinical urgency, the dose can be increased in increments of 1.5 mg every two weeks to minimise emergent adverse

effects. In patients with acute psychosis, the dose can be increased as often as every two to three days, although adverse effects may become evident over the following three to four weeks.

Although cariprazine should be taken daily, the long half-life means that clinical efficacy may be retained when it is taken only two or three times weekly. Similarly, when cariprazine is ceased, the average time to relapse can be long (up to nine months for 50% of patients to relapse).[9] The lengthy half-life should be kept in mind when stopping or switching cariprazine.

GPs can prescribe cariprazine and monitor its use, although many clinical situations warrant specialist input.

Conclusion

Cariprazine is an important new option for the treatment of schizophrenia. Its inclusion on the PBS widens the 'metabolically friendly' compounds available to treat schizophrenia in Australia. Cariprazine has a long half-life and partial agonism at dopamine D_2 and D_3 receptors. It is generally well tolerated and carries a low risk of weight gain, insomnia, sedation, nausea, elevation of prolactin or QTc prolongation. Compared with aripiprazole and brexpiprazole, it may cause more akathisia and extrapyramidal symptoms. Cariprazine may be considered in patients with prominent negative syndrome or erratic oral adherence. MT

References

1. Morgan VA, McGrath JJ, Jablensky A, et al. Psychosis prevalence and physical, metabolic and cognitive co-morbidity: data from the second Australian national survey of psychosis. Psych Med 2014; 44: 2163-2176.
2. Hope J, Keks N. Chronic schizophrenia and the role of the general practitioner. Aust Fam Physician 2015; 44: 802-808.
3. Galletly C, Castle D, Dark F, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. Aust N Z J Psychiatry 2016; 50: 410-472.
4. Keks N, Hope J, Schwartz D, McLennan H, Copolov D, Meadows G. Comparative tolerability of dopamine D2/3 receptor partial agonists for schizophrenia. CNS Drugs 2020; 34: 473-507.
5. Gedeon Richter Australia. Australian product information – Reagila (cariprazine) hard capsules. Sydney: Gedeon Richter Australia; 2022.
6. Kane JM, Zukin S, Wang Y, 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: 367-373.
7. Durgam S, Earley W, Lipschitz A, et al. An 8-week randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in patients with bipolar I depression. Am J Psychiatry 2016; 173: 271-281.
8. Durgam S, Starace A, Li D, et al. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: a phase II, randomized clinical trial. Schizophr Res 2014; 152: 450-457.
9. Durgam S, Earley W, Li R, et al. Long-term cariprazine treatment for the prevention of relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled trial. Schizophr Res 2016; 176: 264-271.
10. Németh G, Laszlovszky I, Czobor P, 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: 1103-1113.
11. Calabrese JR, Keck PE Jr, Starace A, et al. Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. J Clin Psychiatry 2015; 76: 284-292.
12. Earley W, Burgess M, Rekeda L, et al. Cariprazine treatment of bipolar depression: a randomized double-blind placebo-controlled phase 3 study. Am J Psychiatry 2019; 176: 439-448.

COMPETING INTERESTS: Associate Professor Hope has received an honorarium from Lundbeck. Professor Keks: None.

Acknowledgement: The Centre of Mental Health Education and Research at Delmont Hospital receives support from the Pratt Foundation.