UPDATES IN DRUG THERAPY

mhc MENTAL HEALTH CLINICIAN

LITERATURE REVIEW Open Access

Review of cariprazine in management of psychiatric illness

Rebecca H. Campbell, PharmD[1]; Michael Diduch, PharmD[2]; Kristen N. Gardner, PharmD, BCPP[3]; Christopher Thomas, PharmD, BCPS, BCPP[4]

How to cite: Campbell RH, Diduch M, Gardner KN, Thomas C. Review of cariprazine in management of psychiatric illness. Ment Health Clin [Internet]. 2017;7(5):221-9. DOI: 10.9740/mhc.2017.09.221.

Abstract

Schizophrenia and bipolar disorder are severe and debilitating psychiatric disorders. Despite the availability of numerous antipsychotic drugs, many patients still experience poor outcomes and treatment-limiting adverse side effects. Cariprazine is a novel antipsychotic with unique pharmacodynamic and pharmacokinetic properties. It is both a dopamine type 2 and dopamine type 3 partial agonist with 2 equipotent metabolites, desmethyl cariprazine and didesmethyl cariprazine, of which didesmethyl cariprazine has a half-life of 1 to 3 weeks. The objective of this article is to review the literature regarding efficacy and tolerability of cariprazine in the management of psychiatric disorders to determine its current place in therapy.

Keywords: partial dopamine agonist, schizophrenia, bipolar disorder, pharmacotherapy

[1] PGY2 General Pharmacy Practice Resident, Chillicothe VA Medical Center, Chillicothe, Ohio, ORCID: http://orcid.org/0000-0003-3339-0693; [2] PGY2 General Pharmacy Practice Resident, Chillicothe VA Medical Center, Chillicothe, Ohio, ORCID: http://orcid.org/0000-0002-9272-6647; [3] (Corresponding author) Clinical Pharmacy Specialist – Behavioral Health, Kaiser Permanente Colorado, Highline Behavioral Health Clinic, Denver, Colorado, gardner.750@gmail.com, ORCID: http://orcid.org/0000-0003-4016-4731; [4] Director, PGY-1 and PGY-2 Residency Programs, Clinical Pharmacy Specialist in Psychiatry, Chillicothe VA Medical Center, Chillicothe, Ohio, and Clinical Associate Professor of Pharmacology, Heritage College of Osteopathic Medicine, Athens, Ohio, ORCID: http://orcid.org/0000-0003-1146-8891

Disclosures: No disclosures to report.

Introduction

Cariprazine (Vraylar®) is a new antipsychotic manufactured by Forest Laboratories (New York, NY) that was approved by the Food and Drug Administration in September 2015.[1] Originally, the new drug application was submitted in 2012; however, the Food and Drug Administration[2] required additional studies primarily to identify optimal dosing recommendations given the drug's unique pharmacokinetics and dose-related adverse effects. Cariprazine is indicated for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar 1 disorder as monotherapy only.[1] Cariprazine is only contraindicated in people with hypersensitivity reaction to the drug. The package insert includes a standard antipsychotic black box warning for increased risk of mortality in elderly patients with dementia-related psychosis. Target dose recommendations vary according to indication (Table 1). Cariprazine is pharmacodynamically and pharmacokinetically distinct from other oral antipsychotics.

Regarding pharmacodynamics, cariprazine is similar to other atypical antipsychotics in exhibiting antagonistic activity at serotonin type 2A receptors.[1] It carries further similarities to aripiprazole and brexpiprazole in exhibiting partial agonist activity at dopamine type 2 (D_2), dopamine type 3 (D_3), and serotonin type 1A receptors. However, unlike aripiprazole and brexpiprazole, cariprazine exhibits higher affinity for the D_3 versus the D_2 receptor. While this unique property continues to be highlighted throughout the literature, the clinical significance of this remains unknown. Other receptor properties include moderate histamine antagonism (same as aripiprazole and brexpiprazole), low α-1a antagonism (aripiprazole exhibits moderate affinity; brexpiprazole exhibits high affinity), and no appreciable affinity for muscarinic cholinergic receptors (same as aripiprazole; brexpiprazole exhibits low

TABLE 1: Dosing guidelines per indication[1]

Indication	Starting Dose[a]	Titration	Target Dose	Maximum Dose
Schizophrenia	1.5 mg/d	Day 2: May increase to 3 mg Further adjustments of 1.5 to 3 mg/d are permitted	1.5 to 6 mg/d	6 mg/d
Bipolar 1 disorder acute manic or mixed episodes	1.5 mg/d	Day 2: Increase to 3 mg to reach target dose Further adjustments of 1.5 to 3 mg/d are permitted	3 to 6 mg/d	6 mg/d

[a]Dosage forms: 1.5 mg, 3 mg, 4.5 mg, and 6 mg capsules.

affinity).[3] A comprehensive receptor binding profile can be found in Table 2.

Regarding pharmacokinetics, cariprazine is distinct from all other oral antipsychotics in that there are 3 equipotent contributors (cariprazine and 2 active metabolites) to its efficacy and tolerability for which the main determinants changes over time.[1] The parent drug and desmethyl cariprazine (DCAR) metabolite is responsible for early efficacy and tolerability.[1-2] Conversely, the didesmethyl cariprazine (DDCAR) metabolite is primarily responsible for later efficacy and tolerability. In fact, after 12 weeks, the mean concentrations of DDCAR and DCAR are 400% and 30%, respectively, relative to cariprazine concentrations. Comprehensive pharmacokinetic drug information can be found in Table 3.

Methods

A review of the literature was conducted for the use of cariprazine in schizophrenia, bipolar disorder, and major depressive disorder. A PubMed advanced search was performed until October 2016, using the keywords "cariprazine" AND "schizophrenia," "cariprazine" AND "bipolar disorder," and "cariprazine" AND "major depressive disorder," filtered by clinical trials. The search yielded 10 total published phase II, phase III, and longitudinal trials across all indications. A search of ClinicalTrials.gov, also completed in October 2016, produced 22 trials, of which 3 were ongoing.

TABLE 2: Receptor profile and binding affinities[1]

Receptor	Binding Profile	Affinity Category
Dopamine type 3	Partial agonist	High
Dopamine type 2L	Partial agonist	High
Serotonin type 2B	Antagonist	High
Dopamine type 2S	Partial agonist	High
Serotonin type 1A	Partial agonist	High
Serotonin type 2A	Antagonist	Moderate
Histamine type 1	Antagonist	Moderate
Serotonin type 7	Antagonist	Low
Serotonin type 2C	Antagonist	Low
Alpha type 1A	Antagonist	Low
Muscarinic	Antagonist	No appreciable affinity

Results

Schizophrenia

A phase II, randomized, fixed-dose, international clinical trial conducted by Durgam et al[4] evaluated the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia. Average total baseline Positive and Negative Syndrome Scale (PANSS) scores indicated that patients were markedly ill. A total of 732 patients ranging in age from 18 to 60 years were randomized (1:1:1:1:1) to receive placebo, cariparazine 1.5 mg/d, cariprazine 3.0 mg/d, cariprazine 4.5 mg/d, or risperidone 4.0 mg/d for a 6-week, double-blind phase and a 2-week safety follow-up. Hospitalization occurred for screening and a minimum of 4 weeks of double-blind treatment. The risperidone active comparator arm was included for assay sensitivity purposes and was not designed to assess inferiority or superiority of treatment arms. The primary endpoint was the change in total PANSS score from baseline to week 6. A statistically significant reduction in scores was found across all cariprazine treatment groups versus the placebo group ($P < .001$). The active treatment groups separated from the placebo group beginning at week 1 for risperidone and cariprazine $\geq$3 mg/d groups and at week 2 for the cariprazine 1.5 mg/d group. The most common treatment-emergent adverse events (TEAEs) in the cariprazine group included insomnia, extrapyramidal disorder, akathisia, sedation, nausea, dizziness, and constipation. More patients in the cariprazine and risperidone groups had extrapyramidal symptoms (EPSs) and akathisia versus the placebo group (Table 4). Metabolic parameter changes did not differ significantly across the placebo and cariprazine treatment groups. A relationship between tolerability and dose was not observed.[14]

A phase III, fixed-flexible dosage study conducted internationally by Kane et al[5] evaluated the efficacy and

TABLE 3: Pharmacokinetic drug information[1-3]

Pharmacokinetic Parameters	Drug Information		
Absorption	Food requirements = none; may take with or without food	Tmax = 3 to 6 h	Cariprazine half-life = 2 to 4 d, steady-state concentrations reached in 1 to 2 wk DCAR half-life = 3 to 7 d, steady-state concentrations reached in 1 to 2 wk DDCAR half-life = 1 to 3 wk, steady-state concentrations reached in 4 to 8 wk (up to 12 weeks in some patients)
Distribution	Protein bound = 91% to 97%		
Metabolism	CYP3A4 major substrate[a] CYP2D6 minor substrate[b] Metabolized to 2 active and equipotent metabolites: DCAR and DDCAR		
Elimination	Elimination kinetics allow faster removal from body than otherwise expected based on accumulation kinetics After the last dose, it took between 1 and 7 d to achieve a 50% decrease in mean plasma levels (1 d for cariprazine and DCAR; 7 d for DDCAR) and between 1 and 4 wk to achieve a 90% decrease in mean plasma levels (1 wk for cariprazine and DCAR; 4 wk for DDCAR)		Use in mild to moderate hepatic impairment cautioned[c] Use in severe renal (<30 mL/min) or hepatic impairment is not recommended as it has not been studied No dose adjustments for mild to moderate renal impairment given minimal urinary excretion

DCAR = desmethyl cariprazine; DDCAR = didesmethyl cariprazine.

[a]CYP3A4 strong inhibitors (eg, nefazodone, ritonavir, indinavir, nelfinavir, saquinavir, itraconazole, ketoconazole) do clinically impact cariprazine pharmacokinetics; thus, a 50% cariprazine dose reduction OR an every other day dosing schedule should be used when coadministering a strong CYP3A4 inhibitor. Unfortunately, pharmacokinetics using CYP3A4 moderate inhibitors (eg, verapamil, diltiazem, fluconazole, grapefruit juice) or CYP3A4 inducers (eg, carbamazepine, oxcarbazapine, modafinil, phenytoin, phenobarbital, rifamycins, St John's Wort) have not been studied.

[b]CYP2D6 poor metabolizers did not clinically impact cariprazine pharmacokinetics. As such, CYP2D6 strong inhibitors (eg, bupropion, paroxetine, fluoxetine) are not expected to clinically affect cariprazine kinetics.

[c]Studies in mild to moderate hepatic impairment found 25% higher exposure for cariprazine and 45% lower exposure for metabolites after cariprazine 0.5 mg and 1 mg doses.

safety of cariprazine in 446 patients ranging in age from 18 to 60 years with acute exacerbation of schizophrenia.[5] The mean baseline total PANSS score indicated moderate-severe schizophrenia. Patients were randomized to receive placebo, cariprazine 3 to 6 mg/d (mean dose = 5.2 mg/d), or cariprazine 6 to 9 mg/d (mean dose = 7.7 mg/d) for a 6-week, double-blind treatment phase. Hospitalization occurred for washout/screening and a minimum of 4 weeks of double-blind treatment. The primary endpoint was the change in total PANSS score from baseline to week 6, which showed a statistically significant reduction with cariprazine-treated patients versus placebo-treated patients (3 to 6 mg/d, $P = .003$; 6 to 9 mg/d, $P < .001$). Improvements in total PANSS scores relative to the placebo group began at week 1 and 2 for cariprazine 6 to 9 mg/d and 3 to 6 mg/d groups, respectively. Common TEAEs in the active treatment groups included akathisia, extrapyramidal disorder, and tremor; most incidents were reported as mild or moderate in severity (Table 4). More patients treated with cariprazine versus placebo had EPSs and akathisia-related TEAEs. Patients treated with cariprazine 6 to 9 mg/d had higher total scores on the Simpson Angus Scale compared with those receiving placebo; otherwise, mean changes in other EPS scales were similar between groups. One patient in the cariprazine 6 to 9 mg/d group discontinued treatment due to akathisia. Cariprazine-treated patients did not demonstrate a clinically significant increase in metabolic parameters, vital signs, sedation, prolactin, or QTc interval across all treatment groups. Serious adverse events that occurred in the active treatment arms mainly included worsening psychosis not considered to be drug-related; however, 1 patient in the cariprazine 6 to 9 mg/d group experienced hepatitis that was considered to be drug related. Alanine aminotransferase and aspartate aminotransferase had a slightly greater mean increase in the cariprazine groups versus the placebo group; however, levels meeting the Hy law criteria were rare and did not differ among all treatment groups.[5]

A phase III, multinational, randomized, double-blind, fixed-dose, placebo- and active-controlled study conducted by Durgam et al[6] enrolled 617 patients aged 18 to 60 years with acute exacerbation of schizophrenia. Most patients were considered markedly ill based on their mean total baseline PANSS scores. Patients were randomized to

TABLE 4: Extrapyramidal symptoms and akathisia incidence across clinical studies

Study	Population	Study Duration, wk	Treatment Group	Extrapyramidal Symptoms vs Extrapyramidal Disorder, n (%)	Akathisia, n (%)
Schizophrenia					
Durgam et al[4] (2014)	Acute exacerbation of schizophrenia	9	Placebo	7 (4.6)	12 (7.9)
			Cariprazine 1.5 mg/d	15 (10.3)	16 (11.0)
			Cariprazine 3 mg/d	12 (8.2)	22 (15.1)
			Cariprazine 4.5 mg/d	12 (8.2)	19 (12.9)
			Risperidone 4 mg/d	14 (10.0)	14 (10.0)
Kane et al[5] (2015)	Acute exacerbation of schizophrenia	9	Placebo	3 (2.0)	5 (3.4)
			Cariprazine 3 to 6 mg/d	8 (5.3)	24 (15.9)
			Cariprazine 6 to 9 mg/d	15 (10.1)	25 (16.9)
Durgam et al[6] (2015)	Acute exacerbation of schizophrenia	9	Placebo	. . .	7 (4.6)
			Cariprazine 3 mg/d	. . .	11 (7.1)
			Cariprazine 6 mg/d	. . .	23 (14.6)
			Aripiprazole 10 mg/d	. . .	11 (7.2)
Durgam et al[7] (2016)	Acute exacerbation of schizophrenia	6	Placebo	6 (4.7)	1 (0.8)
			Cariprazine 1.5 to 4.5 mg/d	8 (6.3)	13 (10.2)
			Cariprazine 6 to 12 mg/d	13 (9.8)	12 (9.0)
Durgam et al[8] (2016)	Relapse prevention in patients with schizophrenia	97	Open-label phase: cariprazine 3 to 9 mg/d	56 (7.3)	147 (19.2)
			Double-blind phase: placebo	3 (3.0)	3 (3.0)
			Double-blind phase: cariprazine 3 to 9 mg/d	6 (5.9)	5 (5.0)
Bipolar I disorder					
Durgam et al[9] (2015)	Acute manic or mixed episodes associated with bipolar I disorder	9	Placebo	11 (9.3)	7 (5.9)
			Cariprazine 3 to 12 mg/d	29 (24.9)	22 (18.6)
Sachs et al[10] (2015)	Acute manic or mixed episodes associated with bipolar I disorder	6	Placebo	3 (1.9)	7 (4.5)
			Cariprazine 3 to 12 mg/d	24 (15.2)	35 (22.2)
Calabrese et al[11] (2015)	Acute manic or mixed episodes associated with bipolar I disorder	6	Placebo	8 (5.0)	6 (3.7)
			Cariprazine 3 to 6 mg/d	16 (9.6)	29 (17.4)
			Cariprazine 6 to 12 mg/d	11 (6.5)	37 (21.9)
Durgam et al[12] (2016)	Bipolar I depression	8	Placebo	. . .	2 (1.4)
			Cariprazine 0.75 mg/d	. . .	4 (2.8)
			Cariprazine 1.5 mg/d	. . .	7 (4.8)
			Cariprazine 3.0 mg/d	. . .	21 (14.4)
Major depressive disorder					
Durgam et al[13] (2016)	Major depressive disorder	8	Placebo	8 (3)	6 (2.3)
			Cariprazine 1 to 2 mg/d	17 (6.2)	18 (6.6)
			Cariprazine 2 to 4.5 mg/d	30 (11)	61 (22.3)

receive placebo, cariprazine 3 mg/d, cariprazine 6 mg/d, or aripiprazole 10 mg/d for 6 weeks with a 2-week safety follow-up period. Hospitalization occurred for washout/screening and a minimum of 4 weeks of treatment. The aripiprazole active comparator arm was included for assay sensitivity purposes and was not designed to assess inferiority or superiority of treatment arms. The primary endpoint was the change in total PANSS score from

baseline to week 6, which showed a statistically significant reduction for the cariprazine groups versus the placebo group (3 mg/d, $P = .0078$; 6 mg/d, $P < .0001$). Active treatment groups separated from the placebo group beginning at week 1 for the cariprazine 6 mg/d and aripiprazole groups and at week 3 for the cariprazine 3 mg/d group. Common TEAEs were insomnia, akathisia, and headache. Akathisia incidence was significantly greater for the cariprazine 6 mg/d group versus the placebo group (14.6% vs 4.6%, $P = .0034$) and was likely treatment related (Table 4). Most cariprazine-related akathisia reports were considered mild to moderate in severity. Three patients in the cariprazine 3 mg/d group and 1 patient in the cariprazine 6 mg/d group discontinued due to akathisia/restlessness. The only serious adverse event that was possibly treatment related was 1 incidence of supraventricular tachycardia that resolved within 1 week of drug discontinuation. Incidences of body weight increases $\geq$7% were found in 6% of cariprazine 3 mg/d treated patients, 5% of cariprazine 6 mg/d treated patients, 3% of placebo-treated patients, and 6% of aripiprazole-treated patients. Otherwise, increases in metabolic parameters, sedation, prolactin, and QTc interval were not found to be clinically significant among the active treatment groups relative to the placebo group.[6]

A double-blind, placebo-controlled, flexible-dose, proof-of-concept study conducted by Durgam et al[7] aimed to evaluate the efficacy, safety, and tolerability of low- and high-dose cariprazine in patients with acute exacerbation of schizophrenia. Baseline total PANSS scores indicated that patients were moderately to severely ill. A total of 392 patients aged 18 to 65 years were randomized 1:1:1 to receive placebo, 1.5 to 4.5 mg/d (low dose; mean dose = 3.83 mg/d), or 6 to 12 mg/d (high dose; mean dose = 8.70 mg/d) for 6 weeks with a 4-week safety follow-up period. Hospitalization occurred during washout/screening and a minimum of 21 days after randomization. The primary efficacy endpoint focused on change in total PANSS score from baseline to week 6, which was found to not be statistically significant ($P = .100$). However, the pairwise comparison without multiplicity adjustment conducted between the low-dose cariprazine group and the placebo group had statistical significance ($P = .033$). Most EPS-related TEAEs were mild to moderate; akathisia was the most common EPS-related TEAE in both the low-dose and high-dose groups (Table 4). Other common TEAEs were restlessness (low-dose group), tremor (low-dose group), back pain (low-dose group), and extrapyramidal disorder (high-dose group). Across all groups, prolactin levels decreased. No changes in QT interval were noted. Possible dose-related adverse events included blood pressure increases, orthostatic hypotension, body weight increases, EPS, sedation, headache, and insomnia; however, statistical analysis was not performed.[7]

A long-term phase III study conducted by Durgam et al[8] evaluated the efficacy, safety, and tolerability of cariprazine for relapse prevention in patients with schizophrenia. The double-blind, placebo-controlled, parallel-group study with a duration of 97 weeks consisted of 5 phases: 1-week screening, 8-week flexible-dose open-label run-in (3 to 6 mg/d), 12-week fixed-dose open-label stabilization (cariprazine 3 mg/d, 6 mg/d, or 9 mg/d), 26- to 72-week fixed-dose double-blind treatment (placebo or cariprazine 3 mg/d, 6 mg/d, or 9 mg/d), and a 4-week safety follow-up. Hospitalization occurred during screening and for the first 2 weeks of the open-label run-in phase. Afterward, patients were either discharged or hospitalized for an additional 2 weeks; patients requiring hospitalization beyond 4 weeks were discontinued. A total of 200 patients aged 18 to 60 years were randomized 1:1 to fixed-dose cariprazine or placebo in the double-blind phase. Based on baseline PANSS scores, most patients were considered markedly ill upon entering the open-label phase. The primary efficacy endpoint was time to relapse, which was defined by worsening PANSS and Clinical Global Impression-Severity Scale scores, psychiatric hospitalization, aggressive/violent behavior, or suicidal/homicidal ideation. Time to relapse was significantly longer in the cariprazine treatment groups versus the placebo group ($P = .001$). Overall, 24.8% of the patients who received cariprazine and 47.5% of the patients who received placebo experienced relapse. Akathisia, insomnia, and headache occurred in >10% of patients during the open-label phases. Mild to moderate akathisia had a greater occurrence in the run-in (18.6%) phase as opposed to the stabilization phase (6%) and double-blind phase (placebo = 3%, cariprazine = 5%; Table 4). In the open-label phases, 1% of patients discontinued due to akathisia and other EPS adverse events. The TEAEs occurring in the double-blind phase were limited to tremor and back pain in patients who received cariprazine.[8]

Bipolar Disorder

A phase II trial conducted by Durgam et al[9] evaluated the efficacy, safety, and tolerability of cariprazine versus placebo in the treatment of acute mania or mixed episodes associated with bipolar I disorder. This multinational, randomized, double-blind, placebo-controlled, flexible-dose study included 238 patients aged 18 to 65 years with baseline scores on the Young Mania Rating Scale (YMRS) indicating moderate to severe mania. The study consisted of a 3-week double-blind treatment period where patients were randomized 1:1 to either flexibly dosed cariprazine 3 to 12 mg/d (mean dose = 8.8 mg/d) or placebo. Patients were hospitalized for a minimum of 14 days following the start of the double-

blind treatment. The majority of patients (66.1%) reached the maximum 12 mg/d dose. The primary efficacy endpoint was change from baseline to week 3 in YMRS scores; cariprazine-treated patients had statistically significant score reductions relative to placebo-treated patients ($P < .001$). Separation from the placebo group was observed at day 7, although assessments occurred at day 2 and day 5 as well. Similarly, a significantly greater percentage of cariprazine-treated patients compared with placebo-treated patients met criteria for YMRS response (48% versus 25%; $P < .001$) and remission (42% versus 23%; $P = .002$). Response was defined as $\geq$50% improvement in YMRS scores from baseline, and remission was defined as a YMRS score $\leq$12. Adverse events led to discontinuation of 10% of placebo-treated patients and 14% of cariprazine-treated patients. The most common TEAEs were extrapyramidal disorder, headache, akathisia, constipation, nausea, and dyspepsia. Specifically, cariprazine relative to placebo was associated with treatment-emergent akathisia and extrapyramidal disorder (Table 4). Changes in metabolic parameters were similar between groups, with the exception of fasting blood glucose. However, the percentage of patients shifting from clinically normal (<100 mg/dL) or prediabetic (100 to 126 mg/dL) glucose levels at baseline to high post-baseline levels (>126 mg/dL) was low and similar between groups.[9]

A phase III trial conducted by Sachs et al[10] evaluated the efficacy and tolerability of cariprazine in patients with acute manic or mixed episodes associated with bipolar I disorder. This randomized, double blind, placebo-controlled, flexible-dose study included 238 patients aged 18 to 65 years with baseline YMRS scores indicative of moderate to severe mania. Patients were randomized 1:1 to either flexibly dosed cariprazine 3 to 12 mg/d or placebo for 3 weeks with a 2-week safety follow-up period. Patients were hospitalized for a minimum of 14 days following the start of double-blind treatment. In the cariprazine group, 9%, 22%, 30%, and 39% of patients received a final daily dose of 3 mg/d, 6 mg/d, 9 mg/d, or 12 mg/d, respectively. The primary efficacy endpoint was the mean change in total YMRS score from baseline to week 3; there was a significantly greater reduction in patients receiving cariprazine 3 to 12 mg/d versus those receiving placebo ($P = .0004$). Significant differences in total mean change in YMRS score between groups were observed by day 4 and maintained throughout the double-blind treatment (all assessments $P < .01$). The most common cariprazine-related TEAEs were akathisia, extrapyramidal disorder, tremor, dyspepsia, and vomiting. Mean change in clinical laboratory values (liver function, cholesterol, fasting glucose, prolactin, vital signs) from baseline were generally small and similar between groups.[10]

A phase III trial conducted by Calabrese et al[11] evaluated the efficacy, safety, and tolerability of low- and high-dose cariprazine in patients with acute manic or mixed episodes associated with bipolar I disorder. This multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed/flexible-dose study included 497 patients aged 18 to 65 years with baseline YMRS scores indicating moderate to severe mania. Patients were randomly assigned on a 1:1:1 basis to placebo, cariprazine 3 to 6 mg/d (low dose group, mean dose = 4.8 mg/d), or cariprazine 6 to 12 mg/d (high dose group; mean dose = 9.1 mg/d) for 3 weeks with a 2-week safety follow-up period. All patients were hospitalized for a minimum of 12 days during double-blind treatment. The primary efficacy endpoint was mean change in YMRS total score from baseline to week 3, which was statistically significant for cariprazine groups versus the placebo group ($P < .001$) starting at day 5. More low- and high-dose cariprazine-treated patients relative to placebo-treated patients reached response (60.6% and 59.3% versus 37.5%; $P < .001$) and remission (44.8% and 44.3% versus 29.4%; $P < .001$). Both the low- and high-dose cariprazine groups yielded similar effect sizes and number needed to treat, suggesting no difference in efficacy between the low- and high-dose groups. More patients in the high-dose cariprazine group discontinued due to adverse events. The most common TEAEs for cariprazine were akathisia, nausea, constipation, and tremor (6 to 12 mg/d only). Mean changes in EPS rating scale scores, both Barnes Akathisia Rating Scale and Simpson Angus Scale, were significantly higher in the cariprazine groups ($P < .001$). Most EPS-related TEAEs were considered mild to moderate in intensity.[11]

A study conducted by Durgam et al[12] evaluated the efficacy, safety, and tolerability of cariprazine monotherapy in 571 adult patients aged 18 to 65 years with acute bipolar I depression. This multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study randomly assigned (1:1:1:1) patients to receive placebo or cariprazine 0.75 mg/d, 1.5 mg/d, or 3.0 mg/d for 8 weeks with a 1-week safety follow-up period. Patients could be hospitalized during screening and for up to 2 weeks of double-blind treatment. Mean baseline Montgomery-Åsberg Depression Rating Scale (MADRS) total scores were indicative of moderate depression. The primary endpoint was change in total MADRS score from baseline to week 6. While all cariprazine treatment groups started to separate from the placebo group at week 1, effects persisted until week 8 only in cariprazine 1.5 mg/d and 3 mg/d groups. Furthermore, only the cariprazine 1.5 mg/d group showed significantly greater improvement on MADRS total score reductions compared with the placebo group when adjusted for multiple comparisons (adjusted $P = .003$). The most frequent reason for discontinuation was adverse

events, which were similar across groups. The most common TEAEs were akathisia (Table 4) and insomnia. Most cases of akathisia were considered mild to moderate. Weight gain was slightly higher with cariprazine-treated patients relative to placebo-treated patients.[12]

Major Depressive Disorder

Another study conducted by Durgam et al[13] investigated the use of adjunctive cariprazine in patients with major depressive disorder. This randomized, double-blind, placebo-controlled, flexible-dose study involved 3 phases: 1- to 2-week screening and washout, 8-week treatment period, and a 1-week safety follow-up. During the treatment period, patients continued antidepressant treatment and were randomized (1:1:1) to receive adjunctive cariprazine 1 to 2 mg/d (mean dose = 1.4 mg/d), cariprazine 2 to 4.5 mg/d (mean dose = 2.6 mg/d), or placebo. The study population was made up of 812 outpatient participants aged 18 to 65 years who had a current depressive episode (duration $\geq$8 weeks to $\leq$24 months) with inadequate response to antidepressant treatment for $\geq$6 weeks at recommended doses. Treatment refractory depression (inadequate response to $\geq$3 antidepressants at sufficient doses and duration) for the current episode was an exclusion criteria. The most commonly used antidepressants were sertraline (20.6%), citalopram (19.2%), escitalopram (18.2%), venlafaxine (11.8%), and duloxetine (10.8%). Mean baseline total MADRS scores were indicative of moderate depression. The primary efficacy parameter was change from baseline to week 8 in total MADRS score. Reduction in total MADRS score was significantly greater with adjunctive cariprazine 2 to 4.5 mg/d (adjusted $P = .0114$) but not with cariprazine 1 to 2 mg/d (adjusted $P = .2404$) compared with placebo. The TEAEs across both cariprazine groups were akathisia, insomnia, and nausea and were considered to be mild or moderate in intensity. Mean changes in metabolic parameters, prolactin, vital signs, and electrocardiogram parameters were low and similar between groups.[13]

Ongoing Clinical Trials

Three phase III clinical trials involving cariprazine are currently underway as determined by ClinicalTrials.gov. The first clinical trial[14] is investigating the efficacy and tolerability of cariprazine as adjunctive therapy for patients with major depressive disorder. Its final data collection was July 2016. The other 2 clinical trials[15,16] evaluating the efficacy and safety of fixed-dose cariprazine relative to placebo in bipolar depression I are still recruiting patients and are estimated to be completed in July 2018.

Discussion

Cariprazine is a novel second-generation antipsychotic approved as monotherapy for the management of schizophrenia and acute manic or mixed episodes associated with bipolar I disorder. It is currently being explored as an adjunctive therapy option for unipolar depression as well. Cariprazine is both pharmacodynamically and pharmacokinetically distinct given its preferential activity at the D_3 receptor and its 2 active, equipotent metabolites, DCAR and DDCAR, of which DDCAR has a half-life between 1 and 3 weeks.[1]

Across all studies[4–13] with the exception of 1 schizophrenia trial, the efficacy of cariprazine was found to be superior to placebo only as no active comparison trials have yet been conducted. Schizophrenia trials[4-8] using 1.5 to 9 mg/d dose regimens utilized changes in total PANSS scores from baseline to week 6 as the primary endpoint, with the exception of the long-term study[8] focusing on time to relapse. The acute manic and mixed bipolar I disorder trials[9-12] using 3 to 12 mg/d dose regimens measured efficacy using changes in total YMRS scores from baseline to week 3. The major depressive disorder trial[13] using 1 to 4.5 mg/d as adjunctive therapy utilized changes in total MADRS scores from baseline to week 8 to assess efficacy. Studies in patients with schizophrenia[4-7] suggest that cariprazine $\geq$3 mg/d may produce more rapid onset of effect by 1 to 2 weeks than lower doses (1.5 mg/d) with no difference in efficacy at week 6. This aligns with positron emission tomography data demonstrating that cariprazine at the intermediate dose of 3 mg/d given for 15 days results in 92% D_3 and 79% D_2 receptor occupancy, an occupancy percent that is expected to balance efficacy and EPS-related tolerability.[17] Similarly, the single study[13] of adjunctive cariprazine in major depressive disorder suggests dose-related efficacy as only cariprazine 2 to 4.5 mg/d, but not cariprazine 1 to 2 mg/d, significantly reduced total MADRS scores.

Conversely, studies in patients with acute mania or mixed episodes of bipolar disorder do not suggest dose-related efficacy; however, most studies used flexible dose regimens, which limits definitive conclusions.[9-11]

Regarding the tolerability and safety of cariprazine, the majority of studies employing a fixed-dose regimen suggest dose-related side effects based on magnitude differences of incidence rates; however, statistical analysis was not performed in most studies (Table 4). This influenced the maximum dose recommendation of cariprazine 6 mg/d despite the fact that higher doses were studied. Common side effects across all studies were akathisia, EPS, insomnia, headache, dizziness, tremor, and gastrointestinal disturbances. Akathisia, the most common TEAE, was generally regarded as mild to moderate,

but akathisia did lead to treatment discontinuation in several patients.[4-13] Similarly, a recent meta-analysis[18] found that cariprazine was associated with higher risks of EPS-related side effects versus placebo, including akathisia (relative risk [RR] 3.92, 95% confidence interval [CI] 2.83-5.43), restlessness (RR 2.17, 95% CI 1.38-3.40), and tremor (RR 2.41, 95% CI 1.53-3.79). Akathisia as a side effect should not be easily disregarded as it may lead to medication nonadherence; exacerbation of psychiatric symptoms; and sometimes violence, aggression, and suicide.[19] Furthermore, akathisia and EPS-related side effects are cited as a barrier to prescribing first-generation antipsychotics, which are more affordable alternatives if clinically appropriate.[20] Comparatively, cariprazine does not appear to adversely impact prolactin given its partial D_2 agonistic activity. Cariprazine also has minimal impact on metabolic parameters. Generally, second-generation antipsychotics are associated with metabolic side effects. As a result, metabolic syndrome can occur, which can lead to complications that can increase mortality, such as cardiovascular disease, hypertension, hyperlipidemia, prediabetes, and type II diabetes mellitus.[5] Aside from elevated fasting blood glucose levels in 2 studies conducted in bipolar I disorder, changes in body weight, waist circumference, and metabolic parameters were minimal and similar between cariprazine and placebo. Although a recent meta-analysis of cariprazine use in schizophrenia, bipolar disorder, and unipolar depression found clinically significant weight gain versus placebo (RR 1.68, 95% CI 1.12-2.52), this may be related to the heterogeneous patient population and differences in other risk factors for weight gain.[18] Additionally, QTc prolongation, vital sign abnormalities, and significant liver enzymes elevation (although there was 1 report of suspected drug-induced hepatitis with a cariprazine 12 mg/d regimen) did not occur more frequently in cariprazine-treated patients compared with placebo-treated patients.[4-13]

Limitations of the current trials include lack of an active comparator to test for superiority or inferiority to other antipsychotics, mood stabilizers, or combination regimens; mostly short-term trial durations (<6 to 10 weeks) given that the DDCAR metabolite may take up to 12 weeks to reach steady state and is responsible for late efficacy and tolerability; and lack of comparison to combination regimens, including valproate derivatives and lithium, which may result in additive EPS-related adverse events.[1,4-13] Fortunately, the elimination kinetics of cariprazine are much faster than expected based on accumulation kinetics, such that if an adverse event or drug reaction occurs, 50% to 90% of cariprazine is eliminated within 1 to 4 weeks. Nonetheless, since the total active cariprazine exposure continues to increase over several weeks as DDCAR approaches steady state, studies examining multiple lower doses as maintenance therapy relative to doses utilized in acute symptom control would provide insight into designing regimens that may yield a better balance in achieving efficacy and tolerability. Additionally, because total active drug exposure will increase as DDCAR reaches steady state, cariprazine may produce late-onset adverse effects.[1] In the only longitudinal study[8] conducted to date in patients with schizophrenia, attrition occurred prior to the double-blind phase, causing difficulty in characterizing the long-term effects of cariprazine and its active metabolites on tolerability over time.

Overall, cariprazine expands the antipsychotic armamentarium for management of acute schizophrenia exacerbations and acute manic and mixed bipolar disorder episodes. It is still under investigation for use in bipolar and unipolar depression. Advantages to its use include minimal anticholinergic, adrenergic, histaminergic, metabolic, and prolactin-related side effects; once daily dosing; absence of prolonged titration periods; and absence of CYP2D6 drug-drug interactions. Disadvantages include EPS-related side effects, especially akathisia; the high cost; clinically significant CYP3A4 drug-drug interactions; and lack of data for severe renal and hepatic impairment. Continued postmarketing studies with active comparators, longer trial durations, varied cariprazine dose regimens, and combination regimens with other mood stabilizers are critical to better establish the benefit versus risk ratio of cariprazine in the management of psychiatric illnesses.

Acknowledgments

This material is the result of work supported with resources and the use of facilities at the Chillicothe Veterans Affairs Medical Center in Chillicothe, Ohio. The content of this article does not represent the views of the US Department of Veterans Affairs or the US government.

References

1. DailyMed [Internet]. Bethesda (MD): National Library of Medicine (US) [rev. 2016 Mar; cited 2016 Jul 25]. Forest Laboratories, Ireland, Ltd. VRAYLAR (cariprazine) capsule, gelatin coated. 2015 [about 45 p]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4b5f7c65-aa2d-452a-b3db-bc85c06ff12f
2. Food and Drug Administration Center for Drug Evaluation and Research [Internet]. Silver Spring (MD): The Center. Mathis MV. Applicant number: 204370Orig1Orig2s000 Summary Review. 2015 Sept. Reference ID: 3820840. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/204370Orig1Orig2s000SumR.pdf
3. Citrome L. The ABC's of dopamine receptor partial agonists - aripiprazole, brexpiprazole and cariprazine: the 15-min challenge to sort these agents out. Int J Clin Pract. 2015;69(11):1211-20. DOI: 10.1111/ijcp.12752. PubMed PMID: 26477545.
4. Durgam S, Starace A, Li D, Migliore R, Ruth A, Németh G, 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(2-3):450-7. DOI: 10.1016/j.schres.2013.11.041. PubMed PMID: 24412468.
5. 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. DOI: 10.1097/JCP.0000000000000346. PubMed PMID: 26075487.
6. 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. DOI: 10.4088/JCP.15m09997. PubMed PMID: 26717533.
7. Durgam S, Litman RE, Papadakis K, Li D, Nemeth G, Laszlovszky I, et al. Cariprazine in the treatment of schizophrenia: a proof-of-concept trial. Int Clin Psychopharmacol. 2016;31(2):61-8. DOI: 10.109/YIC.0000000000000110. PubMed PMID: 26655732.
8. Durgam S, Earley W, Li R, Li D, Lu K, Laszlovszky I, 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(2-3):264-71. DOI: 10.1016/j.schres.2016.06.030. PubMed PMID: 27427558.
9. Durgam S, Starace A, Li D, Migliore R, Ruth A, Németh G, et al. The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: a phase II trial. Bipolar Disord. 2015;17(1):63-75. DOI: 10.1111/bdi.12238. PubMed PMID: 25056368.
10. Sachs GS, Greenberg WM, Starace A, Lu K, Ruth A, Laszlovszky I, et al. Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, phase III trial. J Affect Disord. 2015;174:296-302. DOI: 10.1016/j.jad.2014.11.018. PubMed PMID: 25532076.
11. Calabrese JR, Keck PE, Starace A, Lu K, Ruth A, Laszlovszky I, 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(3):284-92. DOI: 10.4088/JCP.14m09081. PubMed PMID: 25562205.
12. Durgam S, Earley W, Lipschitz A, Guo H, Laszlovszky I, Németh G, 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(3):271-81. DOI: 10.1176/appi.ajp.2015.15020164. PubMed PMID: 26541814.
13. Durgam S, Earley W, Guo H, Li D, Németh G, Laszlovszky I, et al. Efficacy and safety of adjunctive cariprazine in inadequate responders to antidepressants: a randomized, double-blind, placebo-controlled study in adult patients with major depressive disorder. J Clin Psychiatry. 2016;77(3):371-8. DOI: 10.4088/JCP.15m10070. PubMed PMID: 27046309.
14. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Forest Laboratories; Gedeon Richter Ltd. An efficacy, safety and tolerability of cariprazine as an adjunctive treatment to antidepressant therapy (ADT) in patients with major depressive disorder (MDD). 2000 [cited 2016 Aug 13]. Available from: https://clinicaltrials.gov/ct2/show/NCT01715805
15. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Forest Laboratories. Study on the efficacy, safety, and tolerability of cariprazine relative to placebo in patients with bipolar I depression. 2000 [cited 2016 Aug 13]. Available from: https://clinicaltrials.gov/ct2/show/NCT02670551
16. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Forest Laboratories. Study of the efficacy of a fixed-dose regimen of cariprazine compared to placebo for treatment of the depressive episode in patients with bipolar I disorder [cited 2016 Aug 13]. Available from: https://clinicaltrials.gov/ct2/show/NCT02670538
17. Girgis RR, Slifstein M, D'Souza D, Lee Y, Periclou A, Ghahramani P, et al. Preferential binding to dopamine D3 over D2 receptors by cariprazine in patients with schizophrenia using PET with the D3/D2 receptor ligand [(11)C]-(+)-PHNO. Psychopharmacol (Berl). 2016;233(19-20):3503-12. DOI: 10.1007/s00213-016-4382-y. PubMed PMID: 27525990.
18. Lao KSJ, He Y, Wong ICK, Besag FMC, Chan EW. Tolerability and safety profile of cariprazine in treating psychotic disorders, bipolar disorder and major depressive disorder: a systematic review with meta-analysis of randomized controlled trials. CNS Drugs. 2016;30(11):1043-54. DOI: 10.1007/s40263-016-0382-z. PubMed PMID: 27550371.
19. Lohr JB, Eidt CA, Abdulrazzaq Alfaraj A, Soliman MA. The clinical challenges of akathisia. CNS Spectr. 2015;20(suppl 1):1-14; quiz 15-6. DOI: 10.1017/S1092852915000838. PubMed PMID: 26683525.
20. Dibben CRM, Khandaker GM, Underwood BR, O'Loughlin C, Keep C, Mann L, et al. First-generation antipsychotics: not gone but forgotten. BJPsych Bull. 2016;40(2):93-6. DOI: 10.1192/pb.bp.115.050708. PubMed PMID: 27087995.