Cariprazine for the Treatment of Schizophrenia: A Review of this Dopamine D3-Preferring D3/D2 Receptor Partial Agonist

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Abstract

Cariprazine is an antipsychotic medication and received approval by the U.S. Food and Drug Administration for the treatment of schizophrenia in September 2015. Cariprazine is a dopamine D3 and D2 receptor partial agonist, with a preference for the D3 receptor. Cariprazine is also a partial agonist at the serotonin 5-HT1A receptor and acts as an antagonist at 5-HT2B and 5-HT2A receptors. The recommended dose range of cariprazine for the treatment of schizophrenia is 1.5–6 mg/d; the starting dose of 1.5 mg/d is potentially therapeutic. Cariprazine is administered once daily and is primarily metabolized in the liver through the CYP3A4 enzyme system and, to a lesser extent, by CYP2D6. There are two active metabolites of note, desmethyl-cariprazine and didesmethyl-cariprazine; the latter's half-life is substantially longer than that for cariprazine and systemic exposure to didesmethyl-cariprazine is several times higher than that for cariprazine. Three positive, 6-week, Phase 2/3, randomized controlled trials in acute schizophrenia demonstrated superiority of cariprazine over placebo. Pooled responder rates were 31% for cariprazine 1.5–6 mg/d vs. 21% for placebo, resulting in a number needed to treat (NNT) of 10. In a 26–72 week, randomized withdrawal study, significantly fewer patients relapsed in the cariprazine group compared with placebo (24.8% vs. 47.5%), resulting in an NNT of 5. The most commonly encountered adverse events (incidence ≥5% and at least twice the rate of placebo) are extrapyramidal symptoms (number needed to harm [NNH] 15 for cariprazine 1.5–3 mg/d vs. placebo and NNH 10 for 4.5–6 mg/d vs. placebo) and akathisia (NNH 20 for 1.5–3 mg/d vs. placebo and NNH 12 for 4.5–6 mg/d vs. placebo). Short-term weight gain appears small (approximately 8% of patients receiving cariprazine 1.5–6 mg/d gained ≥7% body weight from baseline, compared with 5% for those randomized to placebo, resulting in an NNH of 34). Cariprazine is associated with no clinically meaningful alterations in metabolic variables, prolactin, or the ECG QT interval. Cariprazine is also approved for the acute treatment of manic or mixed episodes associated with bipolar I disorder. Clinical trials are ongoing in patients with acute bipolar I depression and as adjunctive treatment to antidepressant therapy in patients with major depressive disorder.

Key Words: Schizophrenia, Cariprazine, Antipsychotic, Dopamine, Psychopharmacology

Introduction

Cariprazine received approval by the U.S. Food and Drug Administration (FDA) in September 2015 for the treatment of schizophrenia and for the acute treatment of manic or mixed episodes associated with bipolar I disorder (1), based on a clinical development program well described in the Drug Approval Package available on the FDA's website (2). Cariprazine is the third dopamine receptor partial agonist antipsychotic to become available, joining aripiprazole and brexpiprazole; the former now available as a generic medication and the latter as a branded product approved in 2015 (3-5). In general, having additional choices for antipsychotic medications is beneficial, as the different agents vary in their tolerability profiles and finding interventions that are suitable for an individual patient can be challenging (6-8). This paper reviews the pharmacology of cariprazine and the evidence supporting its use in persons with schizophrenia. A literature search was conducted using the U.S.

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What are number needed to treat (NNT) and number needed to harm (NNH)?*

"P-values," even as low as p<0.00001, do not necessarily mean that a result is clinically relevant. In order to determine possible clinical relevance (i.e., clinical significance), effect size needs to be evaluated. Number needed to treat (NNT) and number needed to harm (NNH) are measures of effect size that are clinically intuitive. NNT answers the question: *"How many patients would you need to treat with Intervention A instead of Intervention B before you would expect to encounter one additional positive outcome of interest?"* NNH answers the question: *"How many patients would you need to treat with Intervention A instead of Intervention B before you would expect to encounter one additional outcome of interest that you would like to avoid?"*

NNT (used for desired outcomes) and NNH (used for undesired outcomes) are simple to calculate:

A=frequency of outcome for Intervention A
B=frequency of outcome for Intervention B
NNT or NNH=1/(A-B)

For example, if giving a test medication results in response 50% of the time and giving placebo results in response 25% of the time, NNT for response for the test medication vs. placebo is 1/(50%-25%)=1/(0.50-0.25)=1/(0.25)=4. Thus, for every 4 persons given the test medication instead of placebo, you would expect to encounter one additional responder.

Most psychotropic medications for most indications have NNT values between 3 and 9 for clinically relevant definitions of response. The *lower* the NNT the more often desired outcomes are encountered. On the other hand, *higher* NNH values are optimal, so that adverse outcomes are seldom encountered.

NNH values 10 or greater generally denote tolerability outcomes that are not excessively problematic; however, there are always exceptions if the adverse effect is serious and/or persistent—in that case desirable NNH values could be much higher. On the other hand, a single-digit NNH (i.e., <10) may be acceptable if the adverse event is mild or moderate, does not lead to discontinuation, is temporary or causes little distress, and does not pose a serious health risk, or if a treatment has good (single-digit NNT) efficacy and there is a compelling need for efficacy that mitigates the low NNH tolerability limitation.

An additional tutorial for the use of NNT and NNH that is free to access can be found at www.ncbi.nlm.nih.gov/pmc/articles/PMC4140623/

*Reprinted from McEvoy JP, Citrome L: Brexpiprazole for the treatment of schizophrenia: a review of this novel serotonin-dopamine activity modulator. Clinical Schizophrenia & Related Psychoses 2016;9(4):177-186.

National Library of Medicine's PubMed.gov resource, the Web of Science bibliographic resource, as well as querying the ClinicalTrials.gov and the EU Clinical Trials Register for completed Phase 2 or 3 studies of cariprazine for the treatment of schizophrenia. The use of data from posters presented at national and international congresses was limited to the principal findings of clinically relevant studies not otherwise published in full. Other sources of information included product labeling (1) and prior reviews published in the biomedical literature (9, 10). Effect sizes are described using the evidence-based medicine metrics of number needed to treat (NNT) and number needed to harm (NNH) (see Box).

Pharmacodynamics

Cariprazine is a dopamine D3 and D2 receptor partial agonist, with a preference for the D3 receptor (Ki for the latter 0.085 nM vs. 0.49 nM and 0.69 nM for the two types of D2 receptors assayed (1, 10, 11). Cariprazine is also a partial agonist at the serotonin 5-HT1A receptor (Ki value 2.6 nM). Cariprazine acts as an antagonist at 5-HT2B and 5-HT2A receptors, with high and moderate binding affinity (Ki values 0.58 nM and 18.8 nM, respectively). Moderate affinity is also observed at the histamine H1 receptor (Ki value 23.2 nM). Cariprazine has lower binding affinity to the serotonin 5-HT2C and α1A-adrenergic receptors (Ki values 134 nM and 155 nM, respectively) and has no appreciable affinity for cholinergic muscarinic receptors (IC50>1,000 nM). Whether targeting the dopamine D3 receptor over the dopamine D2 receptor is clinically advantageous remains unknown but, theoretically, dopamine D3 preferring agents may exert pro-cognitive effects, as evidenced in animal studies (12-14). The D3 receptor is an autoreceptor that controls the phasic, but not tonic, activity of dopamine neurons and mediates

behavioral abnormalities elicited by glutamate/N-Methyl-D-aspartate receptor blockade (15). Serotonin 5-HT1A partial agonism, a property cariprazine also shares with aripiprazole, brexpiprazole, and lurasidone, is also thought to possibly benefit negative symptoms and cognitive deficits as evidenced in preclinical studies (16, 17); however, human studies are required to establish this.

Pharmacokinetics and Dosing

Cariprazine is extensively metabolized by CYP3A4 and, to a lesser extent, by CYP2D6 to desmethyl-cariprazine (DCAR), which in turn is metabolized to didesmethyl-cariprazine (DDCAR) (1, 10). Of importance is that cariprazine activity is mediated not only by cariprazine but also by DCAR and DDCAR, which are pharmacologically equipotent to cariprazine (1, 10). Because of the substantially longer half-life of DDCAR compared to cariprazine and DCAR, the predominant circulating active moiety is DDCAR.

The pharmacokinetic profile of cariprazine and its metabolites was assessed in detail in a multicenter, randomized, open-label, parallel-group, fixed-dose (3, 6, or 9 mg/d) study of 28-week duration (≤4-week observation, 12-week open-label treatment, and 12-week follow-up) where once-daily cariprazine was administered to 38 adult patients with schizophrenia (18). Steady state was reached within 1–2 weeks for cariprazine and DCAR, 4 weeks for DDCAR, and 3 weeks for total active moieties. Cariprazine and DCAR levels decreased >90% within 1 week after the last dose, DDCAR decreased ~50% at 1 week, and total active moieties decreased ~90% within 4 weeks. The terminal half-lives of cariprazine, DCAR, and DDCAR ranged from 32–68, 30–38, and 314–446 hours (~2–3 weeks), respectively. The effective half-life (calculated from time to steady state) of total active moieties was approximately 1 week. Exposure was dose proportional over the range of 3–9 mg/d. The product label notes that mean concentrations of DCAR and DDCAR are approximately 30% and 400%, respectively, of cariprazine concentrations by the end of 12-week treatment (1). Time to peak concentration of cariprazine is 3–6 hours (1, 18). Administration of a single dose of 1.5 mg of cariprazine with a high-fat meal did not significantly affect the Cmax or area under the concentration curve of cariprazine or DCAR (1).

For patients with schizophrenia, the recommended dose range is 1.5 mg to 6 mg once daily (1). The starting dose is 1.5 mg, given once daily, with or without food, and can be increased to 3 mg on Day 2 (1). Further dose adjustments can be made in 1.5-mg or 3-mg increments depending upon clinical response and tolerability; however, because of the long half-life of cariprazine and its active metabolites, changes in dose will not be fully reflected in plasma for several weeks (1). The maximum recommended daily dose is 6 mg based on observations made during the short-term controlled trials where dosages above 6 mg daily did not confer increased effectiveness sufficient to outweigh dose-related adverse reactions (1).

Cariprazine and its major active metabolites are highly bound (91% to 97%) to plasma proteins (1).

As noted, cariprazine and its metabolites are extensively metabolized by CYP3A4 (1, 10). Thus, a dose adjustment is recommended if a strong CYP3A4 inhibitor is co-administered with cariprazine. The product label recommends reduction of the cariprazine dose by half and, for patients taking 1.5 mg daily, the dosing regimen should be adjusted to every other day (1). Theoretically, dosing intervals can be prolonged given cariprazine's long-lived metabolite, DDCAR. Concomitant use of cariprazine and a CYP3A4 inducer has not been evaluated and is not recommended because the net effect on active drug and metabolites is unclear (1). Because metabolism via CYP2D6 plays a minor role, no dosage adjustment is required in the presence of CYP2D6 inhibitors or in persons who are CYP2D6 poor metabolizers (1).

For patients with mild to moderate hepatic or renal impairment, no dosage adjustment is required. However, because cariprazine has not been studied in patients with severe hepatic or renal impairment, it is not recommended for such patients (1).

No dosage adjustment for cariprazine is required on the basis of age, sex, race, or smoking status (1).

Efficacy of Cariprazine in Schizophrenia

Table 1 outlines the six Phase 2 and 3, double-blind, controlled clinical trials of cariprazine completed among patients with schizophrenia, as registered on ClinicalTrials.gov or the EU Clinical Trials Register. Three were positive, short-term, acute studies (19-21), one was a short-term study that although was negative on the primary outcome did show a signal for efficacy at the lower dose range (22), one trial was a long-term, randomized, withdrawal study testing efficacy for maintenance treatment (23), and one study was in patients with predominantly negative symptoms and was conducted entirely outside of the U.S. (24).

In the three six-week supportive pivotal trials in non-elderly adult patients with an acute exacerbation of schizophrenia, patients were hospitalized at screening and for at least 4 weeks of double-blind treatment (19-21). Mean age of the participants was 38 years, approximately 70% were male, and about 40% were Caucasian. Mean body mass index was 26 kg/m^2. A little more than 50% of subjects were located in the U.S. Study completion rates for the participants ranged

Table 1 Completed Randomized, Phase 2/3, Double-Blind, Controlled Clinical Trials of Cariprazine for Schizophrenia, as Registered at ClinicalTrials.gov or the EU Clinical Trials Register; All Placebo-Controlled Unless Otherwise Noted

ClinicalTrials.gov Identifier, Other Identifier(s)	Length* (weeks)	Phase	N	Cariprazine Dose (mg/d) (and dose of active control if applicable)	Comments, including Regarding Dose Titration
NCT00404573, RGH-MD-03	6	2	392	1.5–4.5, 6–12	Published as Durgam S, et al., 2016 (22). In this study of acute schizophrenia, 54% completed the study. Cariprazine dosing was initiated at 1.5 mg/d for all patients. Dose adjustments were based on investigator judgment of response and tolerability. In the low-dose group, cariprazine could be up titrated to 3 mg starting on Day 3, and to a maximum dose of 4.5 mg starting on Day 5. In the high-dose group, cariprazine dosage could be increased to 3 mg starting on Day 3, 6 mg starting on Day 5, 9 mg starting on Day 7, and to a maximum dose of 12 mg by Day 9. In patients with tolerability issues, reduction to a previous dose or a drug holiday of 1–2 days was allowed. There were no significant differences between the two doses ranges of cariprazine and placebo in PANSS total score change after multiplicity adjustment and, hence, this was not considered a positive study for regulatory purposes; however, cariprazine 1.5–4.5 mg/d vs. placebo showed significantly greater reductions in PANSS total score without multiplicity adjustment.
NCT00694707, RGH-MD-16	6	2	729	1.5, 3, 4.5 (dose of risperidone 4)	Published as Durgam S, et al., 2014 (19). In this study of acute schizophrenia, 64% completed the study. Cariprazine was initiated at 1.5 mg/d and increased by 1.5 mg until the target dose was reached (Day 2 or 3); risperidone was initiated at 2 mg/d and increased to 4 mg/d on Day 3. PANSS total score improvement at Week 6 was statistically significant vs. placebo for cariprazine 1.5 mg/d, 3 mg/d, and 4.5 mg/d and risperidone. This was considered a positive pivotal trial for regulatory purposes.
NCT01104766, RGH-MD-04	6	3	617	3, 6 (dose of aripiprazole 10)	Published as Durgam S, et al., 2015 (20). In this study of acute schizophrenia, 67% completed the study. Cariprazine was initiated at 1.5 mg/d; dosage was increased by 1.5 mg/d until the target dose was achieved (Day 2 and Day 4 for cariprazine 3 and 6 mg/d, respectively). Aripiprazole was initiated and maintained at 10 mg/d. PANSS total score improvement at Week 6 was statistically significant vs. placebo for cariprazine 3 mg/d, 6 mg/d, and aripiprazole 10 mg/d. This was considered a positive pivotal trial for regulatory purposes.
NCT01104779, RGH-MD-05	6	3	446	3–6, 6–9 (mean final daily doses were 5.2 and 7.7 mg/d, respectively)	Published as Kane JM, et al., 2015 (21). In this study of acute schizophrenia, 60.5% completed the study. Cariprazine was initiated at 1.5 mg on Day 1 and 3 mg on Days 2 and 3. The 3- to 6-mg/d group remained at 3 mg until the end of Week 2 of double-blind treatment; starting on Day 4, the 6- to 9-mg/d group received 6 mg until the end of Week 2 of double-blind treatment. In cases of inadequate response (<20% improvement from baseline on PANSS total score and a Clinical Global Impressions-Severity score ≥4), cariprazine dose was increased at the end of Week 2. In the 3- to 6-mg/d group, patients received 4.5 mg/d for Days 14 to 15 and 6 mg/d thereafter; in the 6- to 9-mg/d group, patients received 7.5 mg/d for Days 14 to 15 and to 9 mg/d thereafter. Patients who did not qualify as inadequate responders or had significant tolerability issues did not receive a dose increase. Dosage was fixed from the end of Week 3 to Week 6. PANSS total score improvement at Week 6 was statistically significant vs. placebo for cariprazine 3–6 mg/d and 6–9 mg/d. This was considered a positive pivotal trial for regulatory purposes.
NCT01412060, RGH-MD-06, 2011-002048-29	up to 72	3	200*	3, 6, 9	Presented as a poster by Durgam S, et al., 2015 (23). Dosing was established during the open-label phase. At randomization, 14 patients were taking cariprazine 3 mg/d, 37 patients were taking 6 mg/d, and 50 patients were taking 9 mg/d. See text.
EudraCT 2012-005485-36, RGH-188-005	26	3	461	Target 4.5 (dose of risperidone 4); no placebo control; dose can be adjusted within the range of 3–6 mg/d	Presented as a poster by Debelle M, et al., 2015 (24). See text.

*Randomized phase; PANSS=Positive and Negative Syndrome Scale.

from approximately 60% to 67%. Mean baseline Positive and Negative Syndrome Scale (PANSS) total scores ranged from approximately 96 to 98, depending on the study and study arm. All the tested doses of cariprazine—1.5, 3, 4.5, 6, 3–6, and 6–9 mg/d—were superior to placebo on reduction of the PANSS total score, the primary outcome measure for each of the trials (see Figure 1). The 95% confidence intervals for the PANSS placebo-subtracted change scores appear to overlap, suggesting the lack of a substantial dose response; however, statistically significant separation from placebo was observed as early as one week after randomization for the higher doses (3 and 4.5 mg/d in study [19], 6 mg/d in study [20], and 6–9 mg/d in study [21]) and the effect was maintained throughout the remainder of the study. Patients were also assessed using the Clinical Global Impressions (CGI) Scale severity score (CGI-S), which was the key secondary endpoint measure; cariprazine was consistently superior to placebo on this outcome as well. Of clinical relevance are the observed effect sizes for antipsychotic response, as defined by change from baseline ≥30% in PANSS total score (see Figure 2). Pooling together data for the approved dose range of cariprazine (1.5–6 mg/d), the NNT vs. placebo was 10 (95% CI 7–19); however, in one of the trials, the NNT vs. placebo for response was as robust as 6 (19).

Available as a poster are the results of a Phase 3 maintenance study that demonstrated the effectiveness of cariprazine in preventing exacerbation of psychotic symptoms/impending relapse in non-elderly adult patients with schizophrenia (23). Eligible patients were required to have a current psychotic episode <4 weeks' duration, PANSS total score ≥70 and ≤120, and a score ≥4 (moderate) on at least 2 PANSS positive symptoms (delusions, hallucinatory behavior, conceptual disorganization, suspiciousness/persecution). After screening, the study consisted of a 20-week, open-label, treatment phase (8-week run-in phase and a 12-week stabilization phase) where patients received cariprazine 3–9 mg/d (starting at 1.5 mg/d on Day 1), with the dose being fixed by the end of Week 6. Dosage decrease was allowed if there were significant tolerability issues as judged by the Investigator. Patients were hospitalized during screening and for at least the first 2 weeks of open-label treatment. In order to be randomized to either continue cariprazine or to receive placebo, patients were required to meet all the following criteria: no significant tolerability issues; PANSS total score ≤60; PANSS total score decrease from open-label baseline ≥20%; score ≤4 on these PANSS items: delusions, conceptual disorganization, hallucinatory behavior, suspicious/persecution, hostility, uncooperativeness, and poor impulse control; and, CGI-S score ≤4. Once randomized, the double-blind phase consisted of up to 72 weeks of fixed-dose treatment. Double-blind treatment ended for all active patients when the last randomized patient completed 26 weeks of double-blind treatment, or at early termination (including relapse). The primary efficacy outcome was the

Figure 1 **Placebo-Subtracted Differences in Least Squares Mean Change from Baseline and 95% Confidence Intervals on the Positive and Negative Syndrome Scale in the Pivotal Trials for Schizophrenia**

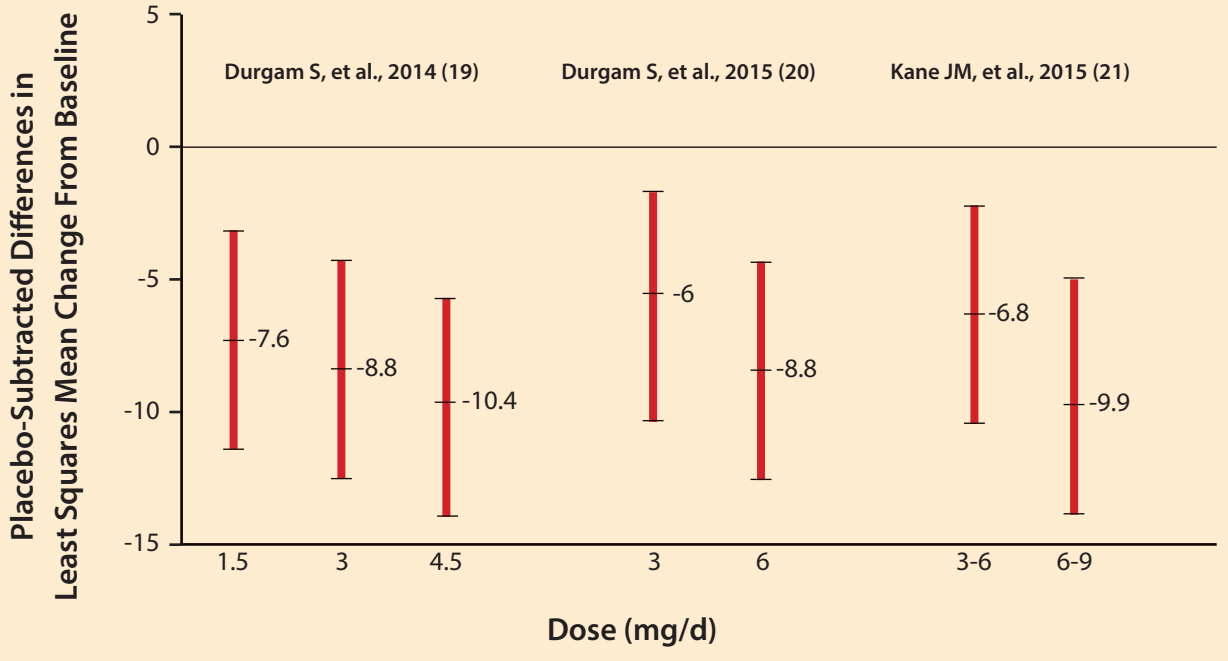
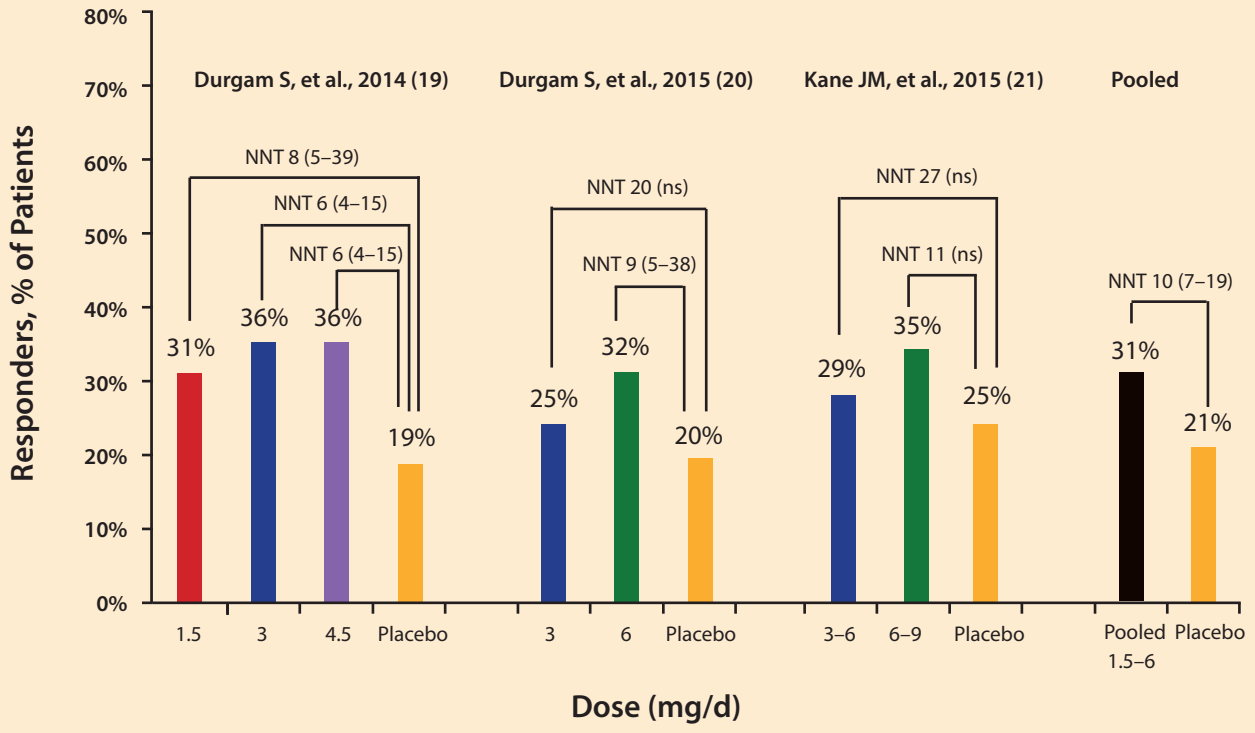


Figure 2 **Response, as Defined by ≥30% Decrease in the Positive and Negative Syndrome Scale Total Score, as Observed in the Pivotal Trials for Schizophrenia, and Pooled for Cariprazine Doses of 1.5–6 mg/d**



NNT=number needed to treat (with 95% confidence interval); ns=not significant.

time to first relapse during the double-blind phase; relapse was defined as meeting any one of the following: PANSS total score increase of ≥30% (for patients who scored ≥50 at randomization) or ≥10 points (for patients who scored <50 at randomization); score ≥4 on 1 or more of the following PANSS items: delusions, conceptual disorganization, hallucinatory behavior, suspicious/persecution, hostility, uncooperativeness, and poor impulse control; CGI-S increase ≥2 points since randomization; psychiatric hospitalization due to worsening of schizophrenia; deliberate self-injury or aggressive/violent behavior, or clinically significant suicidal or homicidal ideation as judged by the Investigator.

A total of 264 patients out of 765 (34.5%) completed the open-label phase and 200 patients were randomized (55 patients were not randomized because of a randomization cap). Demographic and baseline characteristics of the participants entering the open-label phase were similar to that for the acute short-term trials described above, save for a somewhat lower baseline PANSS total score of 91. Baseline PANSS at the start of the double-blind phase was 51. Based on the Kaplan-Meier analysis, the time to relapse was significantly longer for patients who continued on cariprazine than for patients randomized to placebo, with a hazard ratio of 0.45 (95% CI 0.28–0.73). Observed relapse rates were 24.8% for cariprazine vs. 47.5% for placebo, for an NNT of 5 (95% CI 3–11).

Presented as a poster is a 26-week, double-blind, randomized study comparing cariprazine 4.5 mg/d with risperidone 4 mg/d in non-elderly adult patients with schizophrenia, and predominant negative symptoms for at least 6 months (24). Participants were required to have a PANSS Negative Factor Score (NFS) ≥24. The PANSS-NFS is composed of the sum of the following PANSS items: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, lack of spontaneity and flow of conversation, motor retardation, and active social avoidance (25). Subjects were also required to score ≥4 on at least two of the following PANSS items: blunted affect, passive/apathetic social withdrawal, and lack of spontaneity and flow of conversation. Subjects were not eligible if they had a hospital admission for, or history of, acute exacerbation of schizophrenia within the last six months prior to the study, a PANSS Positive Factor Score >19, significant positive or negative symptom fluctuations (i.e., instability) during the prospective lead-in period, treatment with clozapine in the 12 months prior to the study, moderate to severe depressive

Table 2 Potentially Relevant Adverse Events Associated with the Use of Cariprazine for Doses up to 6 mg/d (Incidence of ≥2% and Cariprazine Incidence Greater than Placebo by ≥2%) as Observed in the Pivotal Trials for Schizophrenia, Percentage of Subjects, and Number Needed To Harm vs. Placebo and 95% Confidence Intervals*

	Placebo	Cariprazine			
	(N=584)	1.5–3 mg/d (N=539)		4.5–6 mg/d (N=575)	
Adverse Event	%	%	NNH (95% CI)	%	NNH (95% CI)
Extrapyramidal symptoms	8	15	15 (10–31)	19	10 (7–15)
Akathisia	4	9	20 (13–48)	13	12 (9–18)
Insomnia	11	12	100 (ns)	13	50 (ns)
Restlessness	3	4	100 (ns)	6	34 (19–163)
Anxiety	4	6	50 (ns)	5	100 (ns)
Somnolence (includes sedation)	5	5	ND	8	34 (18–610)
Constipation	5	6	100 (ns)	7	50 (ns)
Nausea	5	5	ND	7	50 (ns)
Vomiting	3	4	100 (ns)	5	50 (ns)
Dizziness	2	3	100 (ns)	5	34 (20–113)
Fatigue	1	1	ND	3	50 (28–258)
Weight increased	1	3	50 (28–287)	2	100 (ns)
Hypertension	1	2	100 (ns)	3	50 (28–258)

*The adverse events and percentages are taken from product labeling (1). CI=confidence interval; ND=no difference; NNH=number needed to harm; ns=not significant at the p<0.05 threshold and, thus, the 95% CI is not shown.

symptoms, clinically relevant parkinson symptoms, or treatment with antidepressant medications and/or anticholinergic medications used to treat abnormal movements. After randomization, patients were up-titrated in two weeks to the target dose of cariprazine 4.5 mg/d, or risperidone 4 mg/d. At the end of Week 3 and at every subsequent visit, the dose of the double-blind study medication could be decreased to 3 mg/d in case of poor tolerability. In case of impending psychotic deterioration, the dose could be increased to 6 mg/d. The primary outcome measure was change from baseline in the PANSS-NFS and the key secondary outcome measure was change from baseline on the Personal and Social Performance (PSP) score. Overall, 77% of patients completed the double-blind treatment period and more than 77% of the patients were kept on the same dose during the whole study treatment period, at similar rates for the two treatment groups. Mean age was 40 years, and 57% of patients were male. Cariprazine was superior to risperidone on both the primary and the key secondary outcome. Specifically, the risperidone-subtracted difference in least squares mean change from baseline and 95% confidence interval on the PANSS-NFS was -1.5 (95% CI -2.4, -0.5). The pairwise difference on the PSP was 4.6 (95% CI 2.7, 6.6).

Side Effects, Safety and Tolerability in Patients with Schizophrenia

Safety and tolerability data collected during the four 6-week acute trials in schizophrenia (19-22) included the incidence of spontaneously reported adverse events, assessments of body weight, laboratory measurements, vital signs, electrocardiograms, and movement disorder scales. For cariprazine doses of 1.5–6 mg/d, the rates of discontinuation because of an adverse event were overall lower for patients receiving cariprazine vs. placebo (9% vs. 12%) (3). As per the product label, there was no single adverse reaction leading to discontinuation that occurred at a rate of ≥2% in cariprazine-treated patients and at least twice the rate of placebo (1). Table 2 provides a list of the spontaneously reported adverse events associated with the use of cariprazine 1.5–6 mg/d (incidence of ≥2% and cariprazine inci-

dence greater than placebo by ≥2%) as observed in the four 6-week acute trials in schizophrenia and reported in product labeling (1), together with their respective values for NNH vs. placebo. The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) for patients with schizophrenia were extrapyramidal symptoms and akathisia. NNH values vs. placebo were as strong as 10 (95% CI 7–15) for extrapyramidal symptoms and 12 (95% 9–18) for akathisia at the higher dose range of 4.5–6 mg/d. The product label notes that adverse events may first appear several weeks after the initiation of treatment, probably because plasma levels of cariprazine and its major metabolites accumulate over time (1).

Short-term mean weight changes with cariprazine were observed to be small (0.8 kg with 1.5–3 mg/d, and 1 kg with 4.6–6 mg/d, vs. 0.3 kg with placebo). Moreover, approximately 8% of patients receiving cariprazine 1.5–3 mg/d or 4.5–6 mg/d gained ≥7% body weight from baseline, compared with 5% for those randomized to placebo (1), resulting in an NNH of 34 (95% CI 19–162) (3). In long-term, uncontrolled trials with cariprazine in schizophrenia, the mean changes from baseline in weight at 12, 24, and 48 weeks were 1.2 kg, 1.7 kg, and 2.5 kg, respectively (1).

In the four 6-week acute trials in schizophrenia, the proportion of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) and borderline (≥100 and <126 mg/dL) to high, as well as shifts in fasting total cholesterol, LDL, HDL and triglycerides, was similar in patients treated with cariprazine and placebo. In the long-term, open-label schizophrenia studies, 4% of patients with normal hemoglobin A1c baseline values developed elevated levels (≥6.5%) (1).

Cariprazine does not appear to increase prolactin and, in general, decreases in prolactin are observed, consistent with cariprazine acting as a dopamine D2 receptor partial agonist (19-22). Cariprazine does not appear to lengthen the ECG QTc interval (1, 19-22).

The development of cataracts was observed in animal studies (1) and, thus, ophthalmological examinations were required during the clinical trials. The mean changes in ophthalmologic parameters were similar between groups in the randomized, 6-week, acute trials in schizophrenia where this was reported (20-22). In a 48-week, uncontrolled schizophrenia trial, the incidence of cataracts was 0.1% (1).

There were no clinically meaningful differences between cariprazine-treated patients and placebo-treated patients in mean change from baseline to endpoint in supine blood pressure parameters except for an increase in supine diastolic blood pressure for patients with schizophrenia receiving cariprazine 9–12 mg/d (1), a dose range that exceeds the recommendations contained in product labeling.

In the randomized-withdrawal maintenance study (23), during open-label treatment, 147 (19%) and 71 (9%) patients had adverse events of akathisia and restlessness, respectively; insomnia was reported in 110 (14%). During double-blind treatment, akathisia was reported in 3 (3%) and 5 (5%) of placebo- and cariprazine-treated patients, respectively, and 2 (2%) patients in each group had an adverse event of restlessness; insomnia was reported in 8 (8%) in each group.

In the 26-week study comparing cariprazine with risperidone (24), the most common adverse event for cariprazine was akathisia (8.3%), which was also observed for 5.2% of persons randomized to risperidone.

An integrated summary of safety and tolerability data from two 48-week studies of open-label, flexible-dose cariprazine in adult patients with schizophrenia is available in poster form (26). Data were pooled. In the first study (NCT01104792), new patients and patients who completed double-blind treatment in one of two lead-in studies (20, 21) received cariprazine 3–9 mg/d (initiated at 1.5 mg/d and could be increased to a maximum of 9 mg/d by Day 8). In the second study (NCT00839852), patients who completed a double-blind, lead-in trial (19) received cariprazine 1.5–4.5 mg/d (initiated at 1.5 mg/d and could be increased to a maximum of 4.5 mg/d by Day 3). In both studies, dosage was increased only if response was inadequate and there were no tolerability issues; dosage could be decreased due to tolerability issues at any time. Of 679 patients (444 from a lead-in study and 235 new patients), 40% completed open-label treatment, with a mean duration of treatment of 188 days. Among patients who prematurely discontinued the study, the most common reason for discontinuation was withdrawal of consent (25%); discontinuations due to adverse events occurred in 12% of patients, with "schizophrenia" the only adverse event that resulted in premature discontinuation in ≥2% of patients. The most common adverse events were akathisia (15%, with 97% of these mild or moderate in severity), insomnia (13%), headache (13%), and weight increase (10%). Incidences of parkinsonism and akathisia as determined by rating scales were 11% and 18%, respectively. Mean increase in body weight was 2.5 kg and no clinically significant mean changes in laboratory values (including metabolic parameters), blood pressure, or ECGs were noted. Mean prolactin levels decreased from baseline to the end of study. Ophthalmologic testing revealed no clinically meaningful changes.

The product label for cariprazine includes class-level warnings for increased mortality in elderly patients with dementia-related psychosis; this bolded boxed warning is in the product labels of all antipsychotics. There are no contraindications to cariprazine other than known hypersensitivity to the product. Other warnings and precautions include

cerebrovascular adverse reactions including stroke in elderly patients with dementia-related psychosis, neuroleptic malignant syndrome, tardive dyskinesia, leukopenia/neutropenia/agranulocytosis, orthostatic hypotension/syncope, seizures, body temperature dysregulation, dysphagia and potential for cognitive and motor impairment; these warnings and precautions are found in all antipsychotic drug labels (27), as is standard language regarding caution for women who are pregnant or nursing. Warnings about metabolic changes are also present, as for all second-generation antipsychotic medication labels, and details regarding the profile of cariprazine are as previously described above.

How Does Cariprazine Compare With Other Antipsychotics?

Despite the availability of many antipsychotics for the treatment of schizophrenia, this disorder is complex and often difficult to treat. Antipsychotics vary in terms of tolerability and safety concerns (6), and patients themselves differ in terms of pre-existing risk factors and comorbidities that make drug selection challenging (7, 28). Table 3 contains a summary of NNH values vs. placebo for weight gain ≥7% from baseline, the incidence of somnolence as an adverse event, and the incidence of akathisia as an adverse event for approved first-line oral second-generation antipsychotics in adults with schizophrenia. With the exception of akathisia, cariprazine appears to have favorable (i.e., higher) NNH values than some of the other agents and, of particular interest, are the NNH values for somnolence where cariprazine appears best in class. When contrasting the three available dopamine receptor partial agonists, the rank order for propensity for weight gain appears to be brexpiprazole>aripiprazole>cariprazine, the propensity for somnolence aripiprazole>brexpiprazole>cariprazine, and the propensity for akathisia cariprazine>aripiprazole>brexpiprazole; these indirect comparisons will need to be confirmed by appropriately designed head-to-head clinical trials (3).

Despite the absence of sedation, cariprazine appears to have a significant antihostility effect, as evidenced in a post hoc analysis of pooled data (n=1,466) from the three positive studies of acute schizophrenia (29). Measured was mean change from baseline to Week 6 on the PANSS hostility item with adjustment for certain PANSS positive symptoms and sedation covariates. The least squares mean difference in change from baseline to Week 6 was statistically significant on all PANSS hostility item analyses in favor of cariprazine versus placebo and the magnitude of change for cariprazine increased with greater baseline hostility.

Table 3 Number Needed to Harm vs. Placebo for Approved, First-Line, Oral, Second-Generation Antipsychotics in Adults for Weight Gain, Somnolence, and Akathisia as Observed in Acute Short-Term Studies for Schizophrenia as Calculated from Product Labeling*

Antipsychotic	NNH for Weight Gain ≥7%	NNH for Somnolence Adverse Events	NNH for Akathisia Adverse Events
Cariprazine (to 6 mg/d)	34	100‡	15
Brexpiprazole	17	50‡	112
Aripiprazole	21	20†	25
Risperidone (to 8 mg/d)	18†	13	15
Olanzapine	6†	7†	25
Quetiapine Immediate Release	6	10†	ND
Quetiapine Extended Release	22	7	188
Ziprasidone	16	15	100
Paliperidone	35	42	39
Iloperidone	10	16	ND
Asenapine	35	17	34
Lurasidone	67	11	10

*Adapted from (3, 4); †Reported in product labeling for schizophrenia and bipolar mania pooled together; ‡Somnolence, sedation, hypersomnia. ND=no difference or rate with medication is lower than rate with placebo; NNH=number needed to harm.

Other Indications and Formulations

Cariprazine is also approved for the acute treatment of manic or mixed episodes associated with bipolar I disorder (1), as supported by three 3-week, Phase 2/3, randomized clinical trials (30-32). The recommended dosage for cariprazine for this indication differs from that for schizophrenia: recommended dose range is 3 mg to 6 mg once daily, with a starting dose of 1.5 mg on Day 1 and an increase to 3 mg on Day 2 (1).

Cariprazine is also being tested for the treatment of depression. Published is a report of a Phase 2, 8-week, randomized, placebo-controlled trial in patients with acute bipolar I depression (33). Registered on ClinicalTrials.gov are additional trials for this indication (NCT00852202, NCT02670551, NCT02670538), as well as trials for the use of cariprazine as adjunctive treatment to antidepressant therapy in patients with major depressive disorder (NCT01469377, NCT00854100, NCT01838876, NCT01715805).

In Phase 1 of clinical development is a new formulation of cariprazine, a prolonged release tablet(s) (NCT02165098).

Summary

Cariprazine is a new antipsychotic medication approved for the treatment of schizophrenia and for the acute treatment of manic or mixed episodes associated with bipolar I disorder. Although cariprazine is a dopamine D2 partial agonist, it differs from both aripiprazole and brexpiprazole in terms of having more potent receptor binding affinity at the dopamine D3 receptor. In addition, one of the active metabolites of cariprazine, DDCAR, has a terminal half-life of two to three weeks and systemic exposure to DDCAR is several times higher than that for cariprazine. Controlled randomized clinical trials support the efficacy of cariprazine at the recommended dose range of 1.5–6 mg/d for the treatment of schizophrenia. Overall tolerability is promising, with the rate of discontinuation due to adverse events lower than that observed for placebo in the four published 6-week, Phase 2/3 acute trials for schizophrenia. With the exception of akathisia, cariprazine appears to have favorable (i.e., higher) NNH values than some of the other agents and of particular interest are the NNH values for somnolence where cariprazine appears best in class. Short- and long-term weight gain appears minimal and no clinically relevant effects on glucose or lipids were apparent. Elevations in prolactin were not observed and no clinically relevant effects on the ECG QTc interval were evident.

Further characterization of the comparative effectiveness of cariprazine with other antipsychotics for the treatment of schizophrenia awaits the conduct of appropriately designed clinical trials.

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