Long-Term Remission With Cariprazine Treatment in Patients With Schizophrenia:
A Post Hoc Analysis of a Randomized, Double-Blind, Placebo-Controlled, Relapse Prevention Trial

Christoph U. Correll, MDa,b,c,∗; Steven G. Potkin, MDd; Yan Zhong, PhDe;
Judith Harsányi, MDe; Balázs Szatmári, MDe; and Willie Earley, MDe

ABSTRACT

Background: Long-term remission is an important treatment goal in schizophrenia. Cariprazine, a dopamine D3/D2 receptor and serotonin 5-HT1A receptor partial agonist, is approved in the United States and Europe to treat adults with schizophrenia.

Methods: Post hoc analyses of data from a long-term cariprazine relapse prevention study (NCT01412060; September 27, 2011–September 3, 2014) investigated the efficacy of cariprazine for maintaining remission in clinically stable patients with DSM-IV-TR–defined schizophrenia. Patients were stabilized with open-label cariprazine (20 weeks), then randomized 1:1 to cariprazine (3, 6, or 9 mg/d) or placebo for double-blind treatment (up to 72 weeks). Symptomatic remission was defined as scores ≤3 on 8 items from the General, Positive, and Negative Symptoms subscales of the Positive and Negative Syndrome Scale (PANSS). Sustained remission included meeting remission criteria at the current and all prior double-blind visits or for ≥6 consecutive months.

Results: At randomization, 169/200 patients (84.5%) met symptomatic remission criteria. During double-blind treatment, time to loss of sustained remission was significantly longer (P = .0020) for cariprazine versus placebo (hazard ratio = 0.31). 60.5% of cariprazine-treated and 34.9% of placebo-treated patients sustained remission through the final visit (odds ratio [OR] = 2.85; P = .0012; number needed to treat [NNT] = 4). Almost twice as many cariprazine-treated (39.6%) as placebo-treated (21.2%) patients met symptomatic remission criteria at all visits ≥6 consecutive months immediately before/including the final double-blind visit (OR = 2.44; P = .0057; NNT = 6). More cariprazine-treated (41.6%) than placebo-treated (27.3%) patients sustained remission for any ≥6 consecutive month period (OR = 1.90, P = .0379; NNT = 7).

Conclusions: Cariprazine was associated with significantly longer sustained remission, higher remission rates, and increased likelihood of sustaining remission for ≥6 consecutive months versus placebo.

Trial Registration: ClinicalTrials.gov identifier: NCT01412060

J Clin Psychiatry 2019;80(2):18m12495


To share: https://doi.org/10.4088/JCP.18m12495
© Copyright 2019 Physicians Postgraduate Press, Inc.

Schizophrenia, a chronic and complex neuropsychiatric syndrome, is characterized by multiple episodes of relapse over the course of the illness.1 Frequently associated with treatment nonadherence,2 relapse promotes disease progression through slower and less complete recovery, difficulty regaining the previous level of function, increased rates of hospitalization, and the potential for treatment resistance.2,3 Using a long-term treatment strategy to prevent relapse may allow a patient to achieve remission, with the goal of functional recovery.2 Sustained remission, or the long-term alleviation of symptoms to levels that do not significantly influence behavior,4 is associated with improved outcomes, including social functioning.5,6 Given the importance of maintaining remission in people with schizophrenia, there is a need for treatments that have long-term efficacy and tolerability to minimize the risks of treatment nonadherence and relapse.

The Remission in Schizophrenia Working Group (RSWG) developed a consensus definition and operational criteria for symptomatic remission based on 3 dimensions of schizophrenia psychopathology: psychoticism, disorganization, and negative symptoms.4 The criteria to define remission consist of a symptomatic component and a time component. The symptomatic component requires that patients have scores corresponding to a severity level of mild or better (<3) on 8 individual items of the Positive and Negative Syndrome Scale (PANSS)2 chosen to map the 3 dimensions of psychopathology and the 5 criteria for schizophrenia specified in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)8 (ie, delusions, unusual thought content, hallucinatory behavior, conceptual disorganization, mannerisms/posturing, blunted affect, social withdrawal, and lack of spontaneity). The time component requires that symptomatic criteria be met for ≥6 consecutive months. Meeting both the symptomatic and time...
Schizophrenia is a chronic illness that requires effective long-term treatment to improve patient well-being and functional recovery.

Sustained remission is a critical concept of treatment response that emphasizes symptom stability over prolonged periods of time for patients with schizophrenia.

These post hoc analyses suggest that cariprazine may be an effective treatment for sustaining stable, prolonged remission in patients with schizophrenia who have previously tolerated and responded to cariprazine.

criteria is referred to as sustained remission. Importantly, this definition of remission uses an absolute threshold of symptom severity, not degree of improvement from a baseline score, suggesting that it can be used throughout the course of the disease and may permit between-trial comparisons of different antipsychotics and their efficacy in promoting remission.5

Cariprazine is a potent, orally active, dopamine D1-preferring D2/D3 receptor partial agonist and serotonin 5-HT1A receptor partial agonist approved for the treatment of adults with schizophrenia (United States and Europe) and acute manic or mixed episodes associated with bipolar I disorder (United States). Cariprazine has 2 active metabolites, desmethyl cariprazine and didesmethyl cariprazine. The combined half-life for all 3 active moieties is 1 week,9 which is relatively longer than that of other oral atypical antipsychotics.10,11 This longer half-life may be associated with sustained blood cariprazine levels and some continued effect after antipsychotic treatment interruption or discontinuation, which may have the potential to lessen relapse events in cases of intermittent or partial treatment noncompliance and increase the likelihood of sustained remission. Cariprazine has demonstrated efficacy in several short-term, placebo- and active-controlled trials in patients with acute schizophrenia.12–14 In a long-term, double-blind, placebo-controlled trial to assess the effectiveness of cariprazine in relapse prevention,15 time to relapse, the primary efficacy endpoint, was significantly longer for cariprazine versus placebo (P = .001). The hazard of relapse for cariprazine-treated patients was less than half that of placebo-treated patients (hazard ratio; HR [95% CI] = 0.45 [0.28 to 0.73]). During double-blind treatment, 24.8% of cariprazine- and 47.5% of placebo-treated patients met relapse criteria, with a number needed to treat (NNT) of 5.

To investigate the ability of cariprazine to sustain remission in stable patients with schizophrenia, we conducted post hoc analyses of data from this relapse prevention study applying the RSWG remission criteria.4

METHODS
Study Design
Post hoc analyses were performed using data from the long-term (up to 92 weeks), multinational, randomized, double-blind, placebo-controlled relapse prevention study of cariprazine in patients with schizophrenia (NCT01412060, September 27, 2011–September 3, 2014). Detailed methods and results, including a CONSORT diagram and safety outcomes, have been previously published.15 Briefly, patients were initially stabilized with flexible-dose cariprazine (3–9 mg/d) during a 20-week, open-label phase. Patients who met stabilization criteria (PANSS total score ≤ 60; ≥ 20% decrease in PANSS total score from baseline; Clinical Global Impressions-Severity of Illness [CGI-S]16 score ≤ 4; score ≤ 4 on 7 PANSS items [delusions, conceptual disorganization, hallucinatory behavior, suspiciousness/persecution, hostility, uncooperativeness, and poor impulse control]) were randomized 1:1 to fixed-dose cariprazine (3, 6, or 9 mg/d [same dose as in the stabilization phase]) or placebo for up to 72 weeks of double-blind treatment. The study was administratively terminated for all active patients when the last randomized patient completed 26 weeks of treatment. This study was approved by an institutional review board (US study centers) or independent ethics committee (non-US study centers) and was conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent.

Patients
The relapse prevention study included male and female inpatients aged 18–60 years, with a DSM-IV-TR8 diagnosis of schizophrenia for a minimum of 1 year and a current psychotic episode of < 4 weeks’ duration. Clinical inclusion criteria included a PANSS total score ≥ 70 and ≤ 120 and a score ≥ 4 (moderately severe) on ≥2 of the following PANSS items: delusions, hallucinatory behavior, conceptual disorganization, and suspiciousness/persecution. Patients were excluded if they were experiencing their first psychotic episode or if they were diagnosed with another psychiatric disorder (eg, psychotic disorders, bipolar I or II disorder, substance abuse/dependence within 3 months of study); medical conditions (eg, clinically significant cardiovascular disease, seizure disorder, hypo- or hyperthyroidism) that could interfere with the conduct of the study were also exclusionary.

Post Hoc Analyses
Post hoc analyses were based on data from the double-blind intent-to-treat (ITT) population (patients who took ≥1 dose of study medication and had a baseline and ≥1 double-blind postbaseline PANSS total score or CGI-S assessment). Symptomatic remission based on RSWG criteria was defined as a score ≤ 3 (mild) on 8 PANSS items: mannerisms and posturing (G5), unusual thought content (G9), blunted affect (N1), social withdrawal (N4), lack of spontaneity (N6), delusions (P1), conceptual disorganization (P2), and hallucinatory behavior (P3).4

Outcomes
The efficacy of cariprazine was assessed using 4 definitions of sustained remission that were based on recommended
RESULTS

Open-label treatment was completed by 264 of 765 patients (34.5%); the most common reason for premature discontinuation was withdrawal of consent (~20%). The double-blind ITT population comprised 200 stable patients (cariprazine = 101, placebo = 99); of cariprazine-treated patients, 14 were taking 3 mg/d, 37 were taking 6 mg/d, and 50 were taking 9 mg/d. Significantly more placebo than cariprazine patients prematurely discontinued double-blind treatment for reasons other than relapse; the most common reason for discontinuation in both treatment groups was administrative termination per the study protocol. Baseline demographics and disease characteristics were generally similar between the randomized treatment groups (Table 1). At double-blind baseline, high and similar numbers of patients in both treatment groups (84%–85%) met symptomatic remission criteria for 6 consecutive months starting at baseline. For randomized patients, time to loss of sustained remission was estimated using Kaplan-Meier analysis; the difference between the treatment group curves was first evident at approximately 7 weeks after the start of double-blind treatment, and it was maintained until the end of the study.

Of patients in the double-blind ITT population, more cariprazine-treated (46.5%) than placebo-treated (29.3%) patients met sustained remission criteria 6 months after the double-blind baseline; the difference between the treatment groups was statistically significant in favor of cariprazine (OR [95% CI] = 2.1 [1.17 to 3.76]; P = .0136; NNT = 6) (Figure 2). Similarly, significantly more cariprazine-treated (41.6%) than placebo-treated (27.3%) patients had sustained remission at all visits for at least 6 consecutive months prior to the final visit (OR [95% CI] = 2.85 [1.52 to 5.32]; P = .0012; NNT = 4). This corresponds to a significantly longer time to loss of sustained remission with cariprazine than with placebo. The 25th percentile (95% CI) for time to loss of sustained remission, which signifies that 25% of patients lost sustained remission at or before that time, was 43 (22 to 71) days for placebo- and 58 (22 to 155) days for cariprazine-treated patients. For the 50th percentile, time to loss of sustained remission was 126 (85 to 184) days with placebo, and it could not be estimated for cariprazine because fewer than half of the patients lost sustained remission in this group (Table 2). Although there were too few patients to estimate the time to loss of sustained remission in the cariprazine group for the 50th percentile, based on the estimated lower limit of the 95% confidence interval, it would be greater than 240 days, more than double the time for the placebo group. Separation of the placebo- and cariprazine-treatment group curves was first evident at approximately 7 weeks after the start of double-blind treatment, and it was maintained until the end of the study.

RSWG symptomatic and time criteria: (1) meeting symptomatic remission criteria at the visit in question and all previous double-blind visits, (2) meeting symptomatic remission criteria for 6 consecutive months starting at double-blind baseline, (3) meeting symptomatic remission criteria at each visit for 6 consecutive months prior to a patient’s last visit in remission during the double-blind period, and (4) meeting symptomatic remission criteria for 6 consecutive months preceding a patient’s final study visit.

Time to loss of sustained remission, duration of sustained remission, and percentage of patients achieving remission criteria were compared between placebo and pooled cariprazine (3–9 mg/d) treatment groups.

Statistical Analyses

Patients who completed open-label treatment and met stabilization criteria were randomized to double-blind treatment; randomization was considered the double-blind baseline. For randomized patients, time to loss of sustained remission (equivalent to duration of sustained remission) was defined as no longer meeting symptomatic criteria for remission, or as having discontinued due to relapse, using a last-observation-carried-forward (LOCF) approach. Time to loss of sustained remission was estimated using Kaplan-Meier analysis; P values were based on the log-rank test. The HR and 95% CI were based on the Cox proportional hazards regression model, with treatment group as an explanatory variable. The percentage of patients meeting 6-month remission criteria as well as the corresponding odds ratios (ORs) and 95% CIs were calculated using an observed cases approach for each definition of sustained remission; P values were based on the Fisher exact test. The NNT was calculated by dividing 1 by the risk difference and rounding up to the next integer. Treatment compliance (measured by site investigators) was defined as the number of capsules actually taken by a patient during a period divided by the number of capsules prescribed for the same period multiplied by 100; results were presented by descriptive statistics.

### Table 1. Baseline Demographic and Disease Characteristics (Double-Blind ITT Population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Placebo (n = 99)</th>
<th>Cariprazine 3–9 mg/d (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>38.4 (10.5)</td>
<td>37.7 (10.1)</td>
<td>39.2 (10.9)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>132 (66.0)</td>
<td>70 (70.7)</td>
<td>62 (61.4)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>83 (41.5)</td>
<td>38 (38.4)</td>
<td>45 (44.6)</td>
</tr>
<tr>
<td>White</td>
<td>61 (30.5)</td>
<td>30 (30.3)</td>
<td>31 (30.7)</td>
</tr>
<tr>
<td>Other</td>
<td>56 (28.0)</td>
<td>31 (31.3)</td>
<td>25 (24.8)</td>
</tr>
<tr>
<td>Duration of schizophrenia, mean (SD), y</td>
<td>11.2 (10.0)</td>
<td>10.5 (9.5)</td>
<td>11.9 (10.4)</td>
</tr>
<tr>
<td>PANSS total score at DB baseline, mean (SD)</td>
<td>50.9 (6.7)</td>
<td>50.5 (6.1)</td>
<td>51.3 (7.2)</td>
</tr>
<tr>
<td>CGI-S total score at DB baseline, mean (SD)</td>
<td>2.7 (0.6)</td>
<td>2.6 (0.6)</td>
<td>2.8 (0.6)</td>
</tr>
<tr>
<td>Met symptomatic remission criteria at DB baseline, n (%)</td>
<td>169 (84.5)</td>
<td>83 (83.8)</td>
<td>86 (85.1)</td>
</tr>
</tbody>
</table>

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness, DB = double-blind, ITT = intent-to-treat, PANSS = Positive and Negative Syndrome Scale, SD = standard deviation.
Table 2. Survival Analysis Summary of Time to Loss of Sustained Remission During the Double-Blind Treatment Period (LOCF)*

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 99)</th>
<th>Cariprazine 3–9 mg/d (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients meeting remission criteria at randomization, n (%)</td>
<td>83 (83.8)</td>
<td>86 (85.1)</td>
</tr>
<tr>
<td>Patients with sustained remission, n (%)</td>
<td>29 (34.9)</td>
<td>52 (60.5)</td>
</tr>
<tr>
<td>Duration of sustained remission, days (95% CI)**</td>
<td>... (189 to ...)</td>
<td>... (... to ...)</td>
</tr>
<tr>
<td>75th Percentile</td>
<td>126 (85 to 184)</td>
<td>(240 to ...)</td>
</tr>
<tr>
<td>50th Percentile (median)</td>
<td>43 (22 to 71)</td>
<td>58 (22 to 155)</td>
</tr>
<tr>
<td>P value†</td>
<td>.0020</td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.51 (0.33 to 0.79)</td>
<td></td>
</tr>
</tbody>
</table>

*Remission probability with placebo or cariprazine treatment in the intent-to-treat population. Loss of remission is defined as patients who no longer met remission criteria or who discontinued due to relapse.

**For patients meeting remission criteria at randomization, the duration of sustained remission (equivalent to time to loss of remission) was defined as the number of days during double-blind treatment before the first assessment at which remission criteria were no longer met or a patient discontinued due to relapse.

†Estimated from Kaplan-Meier model.

‡Based on the log rank test.

Abbreviation: LOCF = last observation carried forward.

Symbol: ... = value cannot be estimated from the data available.

to their last study visit in remission (OR [95% CI] = 1.90 [1.05 to 3.44]; P = .0379; NNT = 7). Almost twice as many cariprazine-treated (39.6%) as placebo-treated (21.2%) patients met symptomatic remission criteria at all visits for ≥ 6 consecutive months prior to the patient’s final visit in the double-blind period (OR [95% CI] = 2.44 [1.30 to 4.55]; P = .0057; NNT = 6).

DISCUSSION

In this post hoc analysis of data from a long-term, placebo-controlled, relapse prevention study, cariprazine was associated with a statistically significant and clinically meaningful longer time to loss of sustained remission than placebo. Significantly more cariprazine- than placebo-treated patients met sustained remission criteria using multiple time component criteria, with medium-to-large effect sizes (NNT = 6 to 7) that were clinically meaningful. These findings suggest that cariprazine was effective in maintaining remission in stable patients with schizophrenia.

Achieving sustained remission is an important step toward well-being and recovery for patients with schizophrenia. The lifetime nature of schizophrenia necessitates ongoing pharmacologic treatment to prevent relapse in most patients; as such, identifying treatments...
that can produce symptom stability over a long period of time is an important component of comprehensive clinical management. Patients who are able to maintain stability for long durations may be less likely to lose remission status or relapse, even when they are partially or intermittently nonadherent to their medication. Treatment nonadherence is frequently associated with failure to maintain remission in patients with schizophrenia, and approximately 50%–75% of patients with schizophrenia are only partially adherent. The results of our post hoc analyses suggest that cariprazine has the ability to sustain remission for at least 6 months, a timeframe that was selected by the RSWG based on that cariprazine has the ability to sustain remission for at least 6 months after an open-label relapse prevention study of quetiapine extended-release in patients with schizophrenia. After an open-label stabilization period, almost all placebo-treated (94/102 [92.2%]) and quetiapine-treated (86/93 [92.5%]) patients were in symptomatic remission at randomization; after 6 months, approximately 50%–75% of patients with schizophrenia are only partially adherent. The results of our post hoc analyses suggest that cariprazine has the ability to sustain remission for at least 6 months, a timeframe that was selected by the RSWG based on that cariprazine has the ability to sustain remission for at least 6 months after an open-label relapse prevention study of quetiapine extended-release in patients with schizophrenia.

In this post hoc analysis, 29/99 (29.3%) and 47/101 (46.5%) of placebo- and cariprazine-treated patients, respectively, met sustained remission criteria at 6 months after the double-blind baseline using RSWG remission criteria. These results need to be interpreted in the context of other studies that also used RSWG remission criteria. For example, a post hoc analysis estimated time to loss of remission for quetiapine and placebo in the previously summarized post hoc analysis occurred approximately 2–3 weeks after randomization. Interestingly, a similar delay until separation of the curves for cariprazine versus placebo was also apparent in the cariprazine relapse prevention study; although different criteria were used to estimate relapse than sustained remission, separation of the cariprazine and placebo curves for cumulative rate of relapse also occurred at approximately 6–7 weeks. Of note, other relapse prevention studies of similar design conducted using atypical antipsychotics have estimated comparatively shorter times to separation of the treatment- and placebo-group curves for incidence of relapse than what was observed for cariprazine and placebo, with separation occurring at approximately 1 week for asenapine, 2–3 weeks for lurasidone, and 4 weeks for brexpiprazole. The longer time to separation of the curves for cariprazine and placebo may be related to the relatively longer half-life of cariprazine compared with other antipsychotics and may suggest some persistent drug effect for patients switched to placebo at randomization. A delayed antipsychotic-placebo separation in placebo-controlled discontinuation trials has also been clearly described comparing the placebo substitution arms after stabilization with oral paliperidone, once-monthly paliperidone, or once-every-3-months paliperidone. This effect of a longer maintenance of efficacy even after drug
Correll et al

It is illegal to post this copyrighted PDF on any website.

You are prohibited from making this PDF publicly available.

Submitted: July 31, 2018; accepted November 5, 2018.

Published online: January 8, 2019.

Author contributions: Drs Correll, Potkin, Harsányi, Szatmári, and Earley were involved with the study design, analysis, and interpretation of data. Dr Zhong performed statistical analyses. All authors met ICMJE (International Committee of Medical Journal Editors) authorship criteria and contributed to and approved the final manuscript; they are accountable for all aspects of the work and the ability to identify the contributions of each coauthor and ensure the integrity of their contributions. Neither honoraria nor payments were made for authorship.

Potential conflicts of interest: Dr Correll has been a consultant and/or advisor to or has received honoraria from Alkermes, Allergan, Angelini, Gerson Lehrman Group, Intracellular Therapies, Janssen/Johnson & Johnson, LB Pharma, Lundbeck, Medavante, Medscape, Merck, Neurocrine, Otsuka, Pfizer, ROVI, Servier, Sunovion, Takeda, and Teva; provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka; served on data safety monitoring boards for Lundbeck, ROVI, and Teva; received royalties from UpToDate and grant support from Janssen and Takeda; and is a shareholder of LB Pharma. Dr Potkin has received grant support, funding, or honoraria from or served as a consultant for the following companies: that conducted scientific or medical research and/or marketed medications related to psychiatric and neurodegenerative disorders: Alkermes, Allergan, Baylor University, Eisai, Eli Lilly, Forest, FORUM Pharmaceuticals, Lundbeck, Merck, National Institutes of Health, Novartis, Otsuka, Roche/Genentech, Sunovion, Takeda, Teva, Toymama, University of Southern California, University of California San Diego, University of California San Francisco, Vanda, and the Gerson Lehrman Group. Drs Zhong and Earley are employees of Allergan. Drs Harsányi and Szatmári are employees of Gedeon Richter.

Funding/support: This analysis and manuscript were sponsored by Allergan plc and Gedeon Richter plc.

Role of the sponsor: Forest Research Institute, Inc, an Allergan affiliate, and Gedeon Richter plc participated in the study design, study conduct, and interpretation of the data, and they reviewed and approved the manuscript for publication.


Acknowledgments: Writing and editorial assistance were provided by Jennifer Fetting, PhD, of Prescott Medical Communications Group (Chicago, Illinois), a contractor of Allergan.

REFERENCES

10. Frankel JS, Schwartz TL. Brexpiprazole and cariprazine: distinguishing two new atypical antipsychotics from the original dopamine...
Long-Term Remission With Cariprazine in Schizophrenia

It is illegal to post this copyrighted PDF on any website.

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. © 2019 Copyright Physicians Postgraduate Press, Inc.

J Clin Psychiatry 80:2, March/April 2019


20. Kane JM, Crandall DT, Marcus RN, et al. Symptomatic remission in schizophrenia patients treated with aripiprazole or haloperidol for up to 52 weeks. Schizophr Res. 2007;95(1–3):143–150.


