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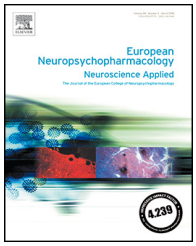

Efficacy of cariprazine across symptom domains in patients with acute exacerbation of schizophrenia: Pooled analyses from 3 phase II/III studies

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Abstract
Schizophrenia affects various symptom domains, including positive and negative symptoms, mood, and cognition. Cariprazine, a dopamine D_3/D_2 receptor partial agonist and serotonin 5-HT_{1A} receptor partial agonist, with preferential binding to D_3 receptors, is approved for the treatment of adult patients with schizophrenia (US, Europe) and mania associated with bipolar I disorder (US). For these investigations, data were pooled from 3 positive, 6-week, double-blind, placebo-controlled, phase II/III trials of cariprazine in patients with acute exacerbation of schizophrenia (NCT00694707, NCT01104766, NCT01104779); 2 trials were fixed-dose and 1 trial was flexible-dose. Post hoc analyses evaluated mean change from baseline to week 6 in Positive and Negative Syndrome Scale (PANSS) -derived symptom factors (positive symptoms, negative symptoms, disorganized thought, uncontrolled hostility/excitement, anxiety/depression) and PANSS single items for cariprazine (1.5–9.0 mg/d) versus placebo. *P* values were not adjusted for multiple comparisons. At week 6, statistically significant differences versus placebo were

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seen for cariprazine on all 5 PANSS factors ($P < 0.01$ all). Effects sizes ranged from 0.21 (anxiety/depression) to 0.47 (disorganized thought). Dose-response analysis from the fixed-dose studies found significant differences for all cariprazine doses (1.5, 3.0, 4.5, and 6.0 mg/d) versus placebo in PANSS total score, and in negative symptom and disorganized thought factor scores ($P < 0.001$). Differences between cariprazine and placebo were also statistically significant on 26 of 30 PANSS single items ($P < 0.05$). In these post hoc analyses, cariprazine was effective versus placebo in improving all 5 PANSS factor domains, suggesting that it may have broad-spectrum efficacy in patients with acute schizophrenia.

1. Introduction

Schizophrenia symptoms affect a variety of psychological domains, including behavior, mood, cognition, and perception (Nasrallah et al., 2011). In patients with acute schizophrenia, treatment is initially focused on alleviating positive symptoms such as hallucinations, delusions, and suspiciousness/persecution. However, negative (e.g., blunted affect, anhedonia, and avolition), cognitive, and mood symptoms (e.g., depression) also have significant effects on patient quality of life and can persist in clinically stable patients (Hunter and Barry, 2012; Rabinowitz et al., 2013a,2013b; Suttajit and Pilakanta, 2015). Negative and cognitive symptoms can lead to poor social and occupational functioning and have a profound impact on daily life (Hunter and Barry, 2012; Milev et al., 2005). Mood symptoms are associated with suicide, substance abuse, and relapse (Conley et al., 2007; Pallanti et al., 2004; Reine et al., 2003). Currently approved antipsychotics effectively treat the positive symptoms of schizophrenia, but they have limited efficacy in other symptom domains (Keefe et al., 2007; Nasrallah et al., 2011). Negative symptoms and cognitive deficits can greatly increase the burden of disease for patients with schizophrenia, and treatments are needed that improve outcomes across multiple symptom domains.

Determining the efficacy of antipsychotic treatment in the difficult-to-treat symptoms of schizophrenia is an important goal in clinical research. The 30-item Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was designed to assess the dimensions of schizophrenia symptoms. Although the original construction of the PANSS grouped the items into subscales for the positive symptoms, negative symptoms, and general psychopathology of the illness, several studies have subsequently shown that a 5-factor model better characterizes PANSS data in patients with schizophrenia (Lancon et al., 2000; Lindenmayer et al., 1994,2004; Marder et al., 1997). Factors use a smaller number of grouped items than the original PANSS subscales to characterize the critical negative and positive symptom dimensions of schizophrenia; additionally, factors for concepts related to disorganized thought, excitement, and depression are represented in most models (Wallwork et al., 2012). Although no single model has received consensus from investigators, and the items that compose each component factor vary somewhat from model to model, the differentiation of symptoms into these 5 factors consistently emerges in research, and empirically based investigation into these major symptom dimensions of schizophrenia can be conducted (Wallwork et al., 2012). Evaluation of drug effects utilizing these factor models can help characterize the effectiveness of individual antipsychotic treatments across different symptom domains. However, since some domains, such as cognitive impairment, negative symptoms, and depression, tend to be elevated in patients with acute psychosis and tend to improve as psychosis is treated, it can be difficult to determine whether the treatment under evaluation is directly modulating these symptom domains or whether effects are secondary to improvements in psychosis.

Cariprazine, a potent dopamine D_3/D_2 receptor partial agonist and serotonin 5-HT_{1A} receptor partial agonist, with preferential binding to the D_3 receptors, is approved by the FDA in the United States for the treatment of adult patients with schizophrenia (1.5–6.0 mg/d) and acute manic or mixed episodes associated with bipolar I disorder (3.0–6.0 mg/d) and by the European Medicines Agency (EMA) for the treatment of adults with schizophrenia (1.5–6.0 mg/d). The efficacy of cariprazine in acute exacerbation of schizophrenia was demonstrated in 3 positive, randomized, international, placebo-controlled, Phase II/III clinical trials (Durgam et al., 2015,2014; Kane et al., 2015); 2 of the trials included active-comparator arms to evaluate assay sensitivity. On the primary efficacy parameter, change from baseline to week 6 in PANSS total score, differences were statistically significant in favor of cariprazine versus placebo for all 3 studies (Durgam et al., 2015,2014; Kane et al., 2015). To better characterize the effects of cariprazine across the multiple symptom domains of schizophrenia, we conducted post hoc analyses using pooled data from the 3 Phase II/III trials of cariprazine in acutely exacerbated patients. In our analyses, we used a PANSS-derived model consisting of factors for positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression to evaluate the efficacy of cariprazine (Marder et al., 1997).

2. Experimental procedures

2.1. Study design

Data were pooled from 3 similarly designed, positive, 6-week, double-blind, placebo-controlled, Phase II/III trials of cariprazine in patients with acute exacerbation of schizophrenia: RGH-MD-16 (NCT00694707) (Durgam et al., 2014), RGH-MD-04 (NCT01104766) (Durgam et al., 2015),

and RGH-MD-05 (NCT01104779) (Kane et al., 2015). Detailed methods of the individual studies have been previously published. The trials each consisted of a 1-week washout period, 6 weeks of double-blind treatment, and 2 weeks of safety follow-up. In RGH-MD-16 and RGH-MD-04, patients were randomized equally to placebo, fixed doses of cariprazine, or an active comparator, included for assay sensitivity; studies were not powered for head-to-head comparisons between cariprazine and the active comparator. The treatment groups included in RGH-MD-16 were placebo, cariprazine 1.5, 3.0 or 4.5 mg/d, and risperidone 4.0 mg/d; the treatment groups in RGH-MD-04 were placebo, cariprazine 3.0 or 6.0 mg/d, and aripiprazole 10 mg/d. RGH-MD-05 used a fixed/flexible-dose design in which patients were randomized 1:1:1 to placebo, or cariprazine 3.0–6.0 or 6.0–9.0 mg/d.

2.2. Patients

The individual studies included male and female patients aged 18–60 years, inclusive, with a diagnosis of schizophrenia (paranoid, disorganized, catatonic, and/or undifferentiated types) per *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) (APA, 2000) criteria for a minimum of 1 year, and a current acute episode < 2 weeks in duration. Clinical inclusion criteria for all studies included a Clinical Global Impressions-Severity of Illness (CGI-S) (Guy, 1976) score ≥ 4, PANSS total score ≥ 80 and ≤ 120, and a score ≥ 4 on at least 2 of the PANSS positive symptoms of delusions, hallucinatory behavior, conceptual disorganization, or suspiciousness/persecution. Typical exclusion criteria for schizophrenia studies were applied, including patients meeting DSM-IV-TR criteria for certain other psychiatric disorders (e.g., schizoaffective disorder, bipolar I and II disorder, severe axis II disorders) and patients with a first episode of psychosis, treatment resistance, substance abuse within 3 months of the study, or suicide risk. Treatment with psychotropic drugs was prohibited, except for lorazepam, oxazepam or diazepam (for agitation, irritability, hostility, and restlessness), eszopiclone, zolpidem, zolpidem extended release, chloral hydrate, or zaleplon (for insomnia), and diphenhydramine, benztropine or equivalent, or propranolol (for extrapyramidal symptoms [EPS]).

2.3. Post hoc analyses

To assess the efficacy of cariprazine across the multiple symptom domains of schizophrenia, post hoc analyses evaluated changes in previously validated PANSS factors (Marder et al., 1997) (Table 1) and individual PANSS items. Efficacy on the PANSS factors and individual items was evaluated in pooled data in the intent-to-treat (ITT) population (patients who had received at least 1 dose of study medication and had ≥ 1 postbaseline PANSS total score assessment) from the 3 component studies; to accommodate the fixed- and flexible-dose designs of the constituent studies, all cariprazine doses (1.5–9.0 mg/d) were combined for analysis. To investigate the effects of cariprazine by dose, efficacy on the PANSS factors was also evaluated using data from the ITT population of the 2 fixed-dose component studies (RGH-MD-16, RGH-MD-04); data were pooled into placebo and cariprazine 1.5-, 3.0-, 4.5-, and 6.0-mg/d dose groups. Least squares (LS) mean change from baseline to week 6 and the LS mean difference (LSMD) for the active treatment arms versus placebo on the PANSS-derived factors and individual PANSS items were determined.

Table 1 PANSS factors and component items (Marder et al., 1997).

PANSS factor	Items
Negative symptom	Blunted affect (N1)
	Emotional withdrawal (N2)
	Poor rapport (N3)
	Passive social withdrawal (N4)
	Lack of spontaneity (N6)
	Motor retardation (G7)
	Active social avoidance (G16)
Positive symptom	Delusions (P1)
	Hallucinatory behavior (P3)
	Grandiosity (P5)
	Suspiciousness (P6)
	Stereotyped thinking (N7)
	Somatic concern (G1)
	Unusual thought content (G9)
	Lack of judgment and insight (G12)
Disorganized thought	Difficulty in abstract thinking (N5)
	Mannerisms and posturing (G5)
	Disorientation (G10)
	Poor attention (G11)
	Disturbance of volition (G13)
	Preoccupation (G15)
	Conceptual disorganization (P2)
Uncontrolled hostility/ excitement	Poor impulse control (G14)
	Excitement (P4)
	Hostility (P7)
	Uncooperativeness (G8)
Anxiety/depression	Anxiety (G2)
	Guilt feelings (G3)
	Tension (G4)
	Depression (G6)

Data were analyzed using a mixed-effects model for repeated measures (MMRM) approach with treatment, visit, and study as fixed factors, baseline as covariate, and treatment-by-visit and baseline-by-visit as interactions; an unstructured covariance matrix was used to model the covariance of within-patient scores. Effect sizes (ES) for the change from baseline to week 6 in PANSS factors and PANSS items were calculated using Cohen's *d* based on the MMRM model. All tests were 2-sided at the 5% significance level; *P* values were not adjusted for multiple comparisons.

3. Results

In the pooled population, 1466 patients received baseline and postbaseline PANSS assessments and were included in the analysis. Baseline patient demographics,

Table 2 Patient demographics and baseline characteristics (pooled ITT population).

	Placebo ($n = 442$)	Cariprazine 1.5-9.0 mg/d ($n = 1024$)
Demographics		
Age, mean (SD), years	37.0 (11.2)	36.9 (10.2)
Sex, men, *n* (%)	301 (68.1)	713 (69.6)
Race/ethnicity, *n* (%)		
White	198 (44.8)	476 (46.5)
Black/African-American	124 (28.1)	269 (26.3)
Asian	89 (20.1)	219 (21.4)
Other	19 (4.3)	28 (2.7)
Schizophrenia characteristics		
Duration of illness, mean (SD), years	11.7 (9.7)	11.2 (9.1)
Age at onset of diagnosis, mean (SD), years	25.4 (9.0)	25.7 (8.4)
Number of prior psychiatric hospitalizations, mean (SD)	5.5 (7.0)	6.1 (7.1)
Duration of current episode, n (%)		
≤7 days	123 (27.8)	320 (31.3)
8-14 days	313 (70.8)	691 (67.5)
15 to 21 days	4 (0.9)	6 (0.6)
>21 days	1 (0.2)	6 (0.6)
Baseline efficacy scores, mean (SD)		
PANSS total score	96.8 (9.2)	96.5 (9.0)
Negative symptom factor	23.7 (4.4)	23.0 (4.5)
Positive symptom factor	29.2 (4.2)	29.4 (4.0)
Disorganized thought factor	22.4 (3.9)	22.5 (3.6)
Uncontrolled hostility/excitement factor	10.3 (3.2)	10.4 (3.2)
Anxiety/depression factor	11.2 (3.2)	11.2 (3.1)
CGI-S total score	4.8 (0.6)	4.8 (0.6)

CGI-S, Clinical Global Impressions-Severity; ITT, intent-to-treat; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.

disease characteristics, CGI-S total score, and scores for all 5 PANSS factors were similar between the pooled placebo- and cariprazine-treatment groups (Table 2). Baseline PANSS and CGI-S total scores in both treatment groups were indicative of patients who were markedly ill (Leucht et al., 2005).

In the pooled analyses at week 6, the difference in mean change from baseline was statistically significant in favor of cariprazine (1.5-9.0 mg/d) versus placebo on all 5 PANSS factors (Fig. 1). The largest treatment effect was observed in the disorganized thought factor (ES = 0.47, $P < 0.0001$). Treatment effects were similar among the negative symptom (ES = 0.39, $P < 0.0001$), positive symptom (ES = 0.37, $P < 0.0001$), and uncontrolled hostility/excitement (ES = 0.34, $P < 0.0001$) factors. Small but significant improvement was also observed on the anxiety/depression factor (ES = 0.21, $P < 0.01$).

A dose-response analysis was additionally performed using pooled data from the 2 fixed-dose studies (RGH-MD-04, RGH-MD-16). The difference in mean change from baseline in PANSS total score, negative symptom factor score, and disorganized thought factor score was statistically significant in favor of all doses of cariprazine (1.5, 3.0, 4.5, and 6.0 mg/d) versus placebo (Table 3); effect sizes ranged from 0.34 to 0.62. Slightly larger treatment effects were observed with cariprazine 4.5 and 6 mg/d than with cariprazine 1.5 and 3 mg/d on PANSS total, negative symptom, positive symptom, and disorganized thought factor scores. On the PANSS positive factor, the differences between the 3 highest doses of cariprazine and placebo were statistically significant, while all doses except cariprazine 4.5 mg/d were significantly different than placebo on the uncontrolled hostility/excitement factor. On the anxiety/depression factor, only cariprazine 6.0 mg/d was significantly different than placebo.

On the PANSS individual items, baseline scores for all 30 items were similar between the pooled cariprazine- and placebo-treatment groups (Table 4). High baseline scores (> 4), indicative of moderate to moderate/severe disease (Kay et al., 1987), were observed on the difficulty in abstract thinking, delusions, hallucinatory behavior, and suspiciousness/persecution PANSS items in both the treatment groups; other items had relatively lower baseline scores, reflecting minimal to mild severity. Differences in mean change from baseline were statistically significant for cariprazine versus placebo on 26 of 30 PANSS individual items (Table 4).

4. Discussion

In our post hoc analyses, we investigated the efficacy of cariprazine in a validated PANSS-derived 5-factor model to better characterize effects on positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hos-

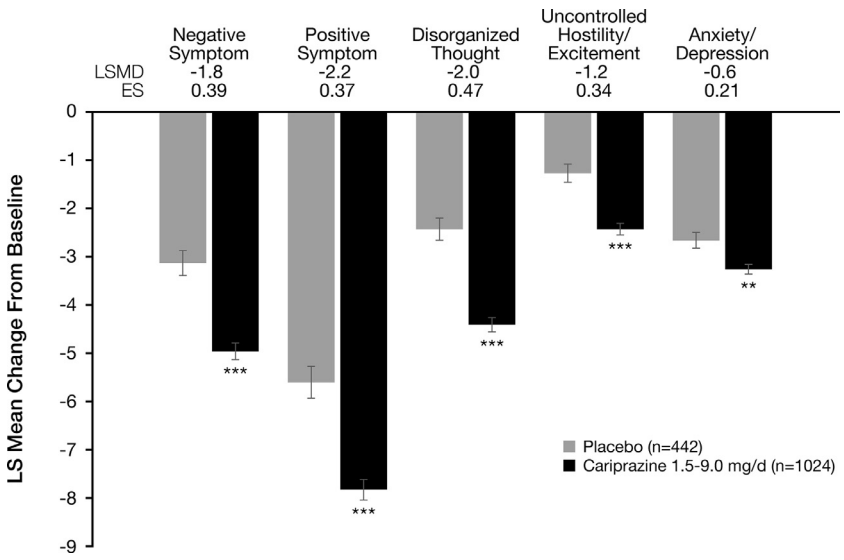

Figure 1 Mean change from baseline to week 6 in the PANSS factors (pooled ITT population). $^{**}P < 0.01$; $^{***}P < 0.001$. Error bars = standard error of the LS mean. ES, effect size; ITT, intent-to-treat; LS, least squares; LSMD, LS mean difference; PANSS, positive and negative syndrome scale.

tility/excitement, and anxiety/depression; changes in individual PANSS items were also evaluated. Differences in change from baseline to week 6 were statistically significant in favor of cariprazine versus placebo on all 5 PANSS factors. The largest cariprazine treatment effect was observed on the PANSS disorganized thought factor, with smaller and similar effect sizes noted for the negative, positive, and uncontrolled hostility/excitement factors. A minimal effect size was observed on the anxiety/depression factor, which may be related to low baseline scores on 2 of the 4 component items of the factor (i.e., guilt feelings and depression); mild severity on these items suggests that the potential for a cariprazine effect may have been tempered by a relative lack of symptoms in this population. Future studies on patient populations with higher anxiety/depression symptoms are warranted to support the clinical relevance of cariprazine in the treatment of these symptoms.

When analyses were performed on data from the 2 fixed-dose studies to assess the potential for dose-related response, slightly larger effect sizes were observed for cariprazine 4.5 mg/d and 6 mg/d than for lower doses in PANSS total score, positive symptom factor, negative symptom factor, and disorganized thought factor, suggesting a possible dose response in some symptom clusters. Also of note, since the flexible-dose study included some patients who received cariprazine doses of 9 mg/d, which falls outside of the FDA- and EMA-recommend dose range (1.5–6 mg/d), separate analysis of the 2 fixed-dose studies allowed us to evaluate doses exclusively within the recommended dose range. As such, we found that effect sizes for PANSS factors in patients receiving doses $\leq$ 6 mg/d were comparable to those in the overall cariprazine group. Collectively, our results support the hypothesis that the pharmacologic profile of cariprazine may confer benefits for managing the more difficult-to-treat symptoms in patients with acute exacerbation of schizophrenia and that cariprazine doses in the recommended dose range are effective for treating these symptoms.

Among available antipsychotic agents, cariprazine has a unique pharmacology with almost 10-fold greater affinity for D_3 than D_2 receptors in vitro (Kiss et al., 2010) and high and balanced in vivo occupancy of both D_3 and D_2 receptors (Girgis et al., 2016; Kiss et al., 2012). While occupancy of the dopamine D_2 receptor appears to be necessary to treat the positive symptoms of schizophrenia and it is the common characteristic of all currently approved antipsychotic drugs (Nord and Farde, 2011), the dopamine D_3 receptor may be an important target for treating negative symptoms, as well as cognitive impairment and mood symptoms (Gyertyán et al., 2008; Joyce and Millan, 2005; Kiss et al., 2008; Laszy et al., 2005; Leggio et al., 2013). As such, efficacy in multiple schizophrenia symptom domains has been hypothesized for drugs that target both D_2 and D_3 receptors (Gyertyán et al., 2008; Joyce and Millan, 2005; Schwartz et al., 2000). In this vein, cariprazine has demonstrated efficacy in animal models of social interaction, cognitive impairment, and stress-induced anhedonia (Duric et al., 2017; Neill et al., 2016; Papp et al., 2014; Watson et al., 2016; Zimnisky et al., 2013); additionally, the procognitive and anti-anhedonic effects of cariprazine were shown to be mediated by the dopamine D_3 receptor (Duric et al., 2017; Zimnisky et al., 2013).

Results from the present post hoc analysis were in line with these preclinical findings, with the largest effects of cariprazine apparent on PANSS items related to cognitive and negative symptom domains. The potential for efficacy in treating negative symptoms of schizophrenia was further supported by a well-designed, prospective, Phase IIIb, risperidone-controlled clinical trial of cariprazine in stable patients with predominant negative symptoms (Nemeth et al., 2017). In this 26-week trial, differences in negative symptom improvement and patient functioning were statistically significant for cariprazine versus risperidone, with ef-

Table 3 Change from baseline to week 6 in the PANSS factors by dose group (pooled ITT population from the 2 fixed-dose studies).

PANSS factors	Placebo ($n=297$)	Cariprazine			
		1.5 mg/d ($n=140$)	3.0 mg/d ($n=291$)	4.5 mg/d ($n=145$)	6.0 mg/d ($n=154$)
PANSS total score					
Baseline score, mean (SD)	96.9 (9.1)	97.1 (9.1)	96.6 (8.7)	96.7 (9.0)	95.7 (9.4)
LS mean change (SE)	−10.3 (0.9)	−16.8 (1.4)	−17.6 (0.9)	−19.8 (1.4)	−19.5 (1.4)
LSMD (95% CI)	–	−6.5 (−9.8, −3.2)	−7.3 (−9.8, −4.8)	−9.5 (−12.7, −6.2)	−9.2 (−12.4, −6.0)
P value	–	0.0001	<0.0001	<0.0001	<0.0001
Effect size	–	0.37	0.38	0.53	0.45
Negative symptom					
Baseline score, mean (SD)	24.0 (4.4)	23.1 (4.3)	23.0 (4.6)	23.3 (4.8)	23.0 (4.5)
LS mean change (SE)	−3.4 (0.2)	−5.4 (0.4)	−4.9 (0.2)	−6.0 (0.4)	−5.6 (0.4)
LSMD (95% CI)	–	−1.9 (−2.8, −1.1)	−1.5 (−2.2, −0.8)	−2.5 (−3.4, −1.6)	−2.2 (−3.0, −1.3)
P value	–	<0.0001	<0.0001	<0.0001	<0.0001
Effect size	–	0.44	0.34	0.62	0.51
Positive symptom					
Baseline score, mean (SD)	19.6 (3.4)	19.5 (3.3)	19.9 (3.2)	19.9 (3.6)	19.2 (3.0)
LS mean change (SE)	−6.5 (0.3)	−7.2 (0.5)	−7.9 (0.3)	−8.7 (0.5)	−8.7 (0.4)
LSMD (95% CI)	–	−0.7 (−1.8, 0.4)	−1.4 (−2.2, −0.6)	−2.1 (−3.2, −1.1)	−2.2 (−3.3, −1.1)
P value	–	0.2365	0.0011	0.0001	<0.0001
Effect size	–	0.25	0.32	0.52	0.42
Disorganized thought					
Baseline score, mean (SD)	20.4 (3.7)	20.1 (3.2)	20.2 (3.3)	20.4 (3.2)	20.4 (3.4)
LS mean change (SE)	−2.7 (0.2)	−3.9 (0.3)	−3.8 (0.2)	−4.5 (0.3)	−4.4 (0.3)
LSMD (95% CI)	–	−1.2 (−2.0, −0.5)	−1.2 (−1.7, −0.6)	−1.8 (−2.5, −1.0)	−1.7 (−2.4, −1.0)
P value	–	0.0009	<0.0001	<0.0001	<0.0001
Effect size	–	0.40	0.38	0.60	0.49
Uncontrolled hostility/excitement					
Baseline score, mean (SD)	10.0 (3.1)	10.7 (3.4)	10.2 (3.2)	10.2 (3.2)	9.9 (3.1)
LS mean change (SE)	−1.7 (0.2)	−2.6 (0.3)	−2.4 (0.2)	−2.3 (0.3)	−2.8 (0.3)
LSMD (95% CI)	–	−0.9 (−1.6, −0.2)	−0.7 (−1.22, −0.2)	−0.6 (−1.2, 0.1)	−1.1 (−1.8, −0.5)
P value	–	0.0076	0.0057	0.0716	0.0007
Effect size	–	0.39	0.33	0.31	0.36
Anxiety/depression					
Baseline score, mean (S)	11.3 (2.9)	11.5 (2.8)	11.5 (2.7)	11.1 (2.7)	11.9 (3.0)
LS mean change (SE)	−3.1 (0.2)	−3.3 (0.3)	−3.2 (0.2)	−3.3 (0.2)	−4.0 (0.2)
LSMD (95% CI)	–	−0.2 (−0.8, 0.4)	−0.2 (−0.6, 0.3)	−0.2 (−0.8, 0.4)	−0.9 (−1.5, −0.3)
P value	–	0.4357	0.5166	0.4630	0.0032
Effect size	–	0.15	0.10	0.15	0.29

Analysis based on fixed-dose studies RGH-MD-04, RGH-MD-16. CI, confidence interval; LS, least squares; LSMD, LS mean difference; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation; SE, standard error.

fect sizes for cariprazine of 0.31 for negative symptom and 0.48 for patient function. Since these effect sizes are considered clinically relevant for antipsychotic treatment compared with placebo (Correll et al., 2011), and cariprazine was being compared to an antipsychotic with proven efficacy in schizophrenia, the effect sizes in this case may suggest even greater clinical relevance.

Patients with schizophrenia have an increased risk for hostile and aggressive behavior, which in severe presentations may constitute a medical emergency (Citrome and Volavka, 2014; Volavka et al., 2011). Atypical antipsychotics are an important treatment option for patients with schizophrenia who exhibit hostile and/or aggressive behavior (Krakowski et al., 2006). Antihostility effects have been demonstrated for several atypical antipsychotics including asenapine, risperidone, quetiapine, olanzapine, and ziprasidone (Citrome et al., 2006,2001; Czobor et al., 1995; Pratts et al., 2014; Volavka et al., 2014,2011). Additionally, a previous post hoc analysis of the same 3 cariprazine studies demonstrated an antihostility effect of cariprazine via significant improvement versus placebo on the PANSS hostility item, with increasing efficacy seen with increasing levels of baseline hostility (Citrome et al., 2016). Significant improvement in favor of cariprazine versus placebo on the uncontrolled hostility/excitement factor in the present analysis support these previous results, which mutually suggest a beneficial effect in treating acutely exacerbated patients with hostile behavior.

It is generally recognized that the original positive and negative subscales of the PANSS do not adequately char-

Table 4 Change from baseline to week 6 in individual PANSS items (pooled ITT population).

PANSS items		Placebo ($n = 442$)		Cariprazine 1.5-9.0 mg/d ($n = 1024$)		LSMD (95% CI)	*P* value	Effect size
		Baseline, mean (SD)	LS mean change (SE)	Baseline, mean (SD)	LS mean change (SE)			
G1	Somatic concern	2.37 (1.27)	−0.43 (0.05)	2.45 (1.28)	−0.55 (0.03)	−0.12 (−0.24, 0.00)	0.0595	0.13
G2	Anxiety	3.50 (1.10)	−0.90 (0.06)	3.50 (1.09)	−1.10 (0.04)	−0.20 (−0.35, −0.05)	0.0083	0.18
G3	Guilt feelings	1.96 (1.20)	−0.54 (0.04)	2.01 (1.18)	−0.52 (0.03)	0.01 (−0.09, 0.11)	0.8115	0.02
G4	Tension	3.10 (0.96)	−0.70 (0.06)	3.09 (0.97)	−0.95 (0.04)	−0.26 (−0.39, −0.12)	0.0002	0.26
G5	Mannerisms and posturing	2.40 (1.13)	−0.30 (0.05)	2.38 (1.05)	−0.42 (0.03)	−0.12 (−0.23, −0.01)	0.0286	0.15
G6	Depression	2.60 (1.25)	−0.58 (0.05)	2.58 (1.22)	−0.74 (0.03)	−0.15 (−0.28, −0.03)	0.0169	0.17
G7	Motor retardation	2.39 (1.06)	−0.44 (0.05)	2.35 (1.10)	−0.51 (0.03)	−0.07 (−0.18, 0.05)	0.2451	0.08
G8	Uncooperativeness	2.40 (1.03)	−0.18 (0.05)	2.38 (1.05)	−0.49 (0.03)	−0.32 (−0.44, −0.19)	<0.0001	0.34
G9	Unusual thought content	3.70 (1.10)	−0.71 (0.06)	3.75 (1.08)	−1.03 (0.04)	−0.32 (−0.46, −0.19)	<0.0001	0.32
G10	Disorientation	2.45 (1.02)	−0.34 (0.04)	2.44 (1.02)	−0.55 (0.03)	−0.21 (−0.31, −0.11)	<0.0001	0.27
G11	Poor attention	3.10 (0.90)	−0.32 (0.05)	3.17 (0.90)	−0.65 (0.03)	−0.33 (−0.45, −0.21)	<0.0001	0.36
G12	Lack of judgment and insight	3.69 (1.13)	−0.33 (0.05)	3.71 (1.04)	−0.61 (0.03)	−0.28 (−0.41, −0.16)	<0.0001	0.30
G13	Disturbance of volition	3.24 (0.92)	−0.36 (0.05)	3.22 (0.88)	−0.58 (0.03)	−0.22 (−0.34, −0.11)	0.0002	0.25
G14	Poor impulse control	2.52 (1.00)	−0.34 (0.05)	2.53 (1.01)	−0.56 (0.03)	−0.21 (−0.34, −0.09)	0.0008	0.23
G15	Preoccupation	3.49 (1.02)	−0.49 (0.06)	3.50 (0.96)	−0.78 (0.04)	−0.29 (−0.42, −0.16)	<0.0001	0.30
G16	Active social avoidance	3.72 (1.00)	−0.66 (0.06)	3.67 (0.94)	−1.03 (0.04)	−0.37 (−0.51, −0.24)	<0.0001	0.38
N1	Blunted affect	3.62 (1.01)	−0.39 (0.05)	3.54 (1.02)	−0.61 (0.03)	−0.22 (−0.34, −0.11)	0.0002	0.25
N2	Emotional withdrawal	3.79 (0.84)	−0.48 (0.05)	3.67 (0.84)	−0.79 (0.03)	−0.31 (−0.43, −0.20)	<0.0001	0.36
N3	Poor rapport	3.09 (0.97)	−0.40 (0.05)	3.00 (0.96)	−0.68 (0.03)	−0.29 (−0.41, −0.16)	<0.0001	0.31
N4	Passive/apathetic social withdrawal	3.85 (0.96)	−0.51 (0.05)	3.73 (1.01)	−0.86 (0.03)	−0.35 (−0.47, −0.22)	<0.0001	0.37
N5	Difficulty in abstract thinking	4.02 (1.05)	−0.35 (0.05)	4.00 (1.01)	−0.58 (0.03)	−0.22 (−0.34, −0.11)	0.0002	0.26
N6	Lack of spontaneity flow of conversation	3.23 (1.11)	−0.37 (0.05)	3.07 (1.09)	−0.62 (0.03)	−0.25 (−0.38, −0.13)	<0.0001	0.28
N7	Stereotyped thinking	3.16 (1.03)	−0.42 (0.05)	3.20 (0.97)	−0.62 (0.03)	−0.20 (−0.31, −0.08)	0.0007	0.23
P1	Delusions	4.68 (0.88)	−1.13 (0.07)	4.71 (0.83)	−1.51 (0.04)	−0.38 (−0.53, −0.22)	<0.0001	0.32
P2	Conceptual disorganization	3.72 (1.12)	−0.57 (0.05)	3.77 (1.04)	−0.99 (0.03)	−0.42 (−0.54, −0.29)	<0.0001	0.44
P3	Hallucinatory behavior	4.45 (1.15)	−1.39 (0.08)	4.41 (1.18)	−1.67 (0.05)	−0.27 (−0.45, −0.10)	0.0028	0.20
P4	Excitement	2.92 (1.09)	−0.58 (0.06)	2.97 (1.03)	−0.84 (0.04)	−0.26 (−0.40, −0.12)	0.0003	0.25
P5	Grandiosity	2.64 (1.50)	−0.53 (0.05)	2.60 (1.42)	−0.60 (0.03)	−0.07 (−0.19, 0.05)	0.2836	0.07
P6	Suspiciousness/persecution	4.50 (0.98)	−1.06 (0.07)	4.54 (0.92)	−1.50 (0.04)	−0.42 (−0.57, −0.26)	<0.0001	0.35
P7	Hostility	2.49 (1.06)	−0.39 (0.06)	2.53 (1.09)	−0.67 (0.04)	−0.28 (−0.41, −0.15)	<0.0001	0.28

CI, confidence interval; ITT, intent-to-treat; LS, least squares; LSMD, LS mean difference; PANSS, Positive and Negative Syndrome Scale; SE, standard error of the mean.

acterize the complexity of schizophrenia psychopathology. As such, several 5-factor structural models of PANSS data similar to the one we used in our analysis have been used to investigate atypical antipsychotic efficacy (Wallwork et al., 2012). In pooled post hoc analyses evaluating change from baseline in PANSS-derived 5-factor models, differences were statistically significant versus placebo for aripiprazole, lurasidone, and iloperidone on all 5 factors (Citrome et al., 2011; Janicak et al., 2009; Loebel et al., 2015), while olanzapine was significantly different from placebo on all factors except for anxiety/depression (Davis and Chen, 2001). In the lurasidone analysis, effect sizes for the pooled-dose group at week 6 were largest for the positive symptom factor (0.43) and the disorganized thought factor (0.42), with smaller and similar effects seen for the negative symptom (0.33), the hostility/excitement (0.31), and the depression/anxiety (0.31) factors (Loebel et al., 2015); effect sizes were not reported for aripiprazole or iloperidone. To put the results of the cariprazine analysis in context, the largest treatment effect for cariprazine was observed on the disorganized thought factor (0.47), with smaller and similar effects observed on the negative symptom (0.39), positive symptom (0.37), and uncontrolled hostility/excitement (0.34) factors; a small but significant effect was also observed on the anxiety/depression factor (0.21). Although it is not possible to directly compare results across studies, it is interesting to note that the effect of cariprazine was similar on the positive and negative symptom factors, while the effect of lurasidone was greater on the positive symptom factor than on the negative symptom factor. Similar effects for cariprazine on positive and negative symptom factors support its efficacy in both positive and negative symptom domains, which may distinguish it from antipsychotics that only have proven efficacy in positive symptoms.

Although our PANSS single item analysis should be considered exploratory and lack of adjustment for multiple comparisons should be noted, investigating the efficacy of cariprazine across the symptoms of schizophrenia remains of interest given the heterogeneous nature of the illness. Understanding the specific symptom domains that are most responsive to cariprazine treatment may be an important factor for clinicians making individualized treatment decisions for their patients. In the single item analyses, the difference in change from baseline to week 6 was statistically significant in favor of cariprazine over placebo on 26/30 individual items, suggesting broad spectrum efficacy across symptoms. Since antipsychotic efficacy is generally more robust in positive symptoms of schizophrenia than in other symptom domains, it is of note that when the items were clustered into 5 factors, cariprazine was more effective than placebo on 6/8 positive symptom items, 6/7 negative symptom items, 7/7 disorganized thought items, 4/4 hostility/excitement items, and 3/4 anxiety/depression items. The largest individual item effect sizes were observed on items related to disorganized thought and negative symptoms (i.e., conceptual disorganization, active social avoidance, passive social withdrawal, emotional withdrawal, and poor attention), further supporting the hypothesis that cariprazine may be beneficial in treating these symptom dimensions.

This study was subject to several limitations. Patients included in the component studies were experiencing an acute exacerbation of schizophrenia; as such, we cannot eliminate the possibility that improvement on some symptom domains may have been secondary effects resulting from improvements in psychosis. The short duration of the component studies is another limitation, since 6 weeks may not be long enough to fully evaluate the effects of cariprazine on some of the more difficult-to-treat domains, such as negative, cognitive, and mood symptoms in schizophrenia. These findings may not be generalizable to other patient populations because of the stringent inclusion/exclusion criteria in the primary studies, including the requirement that patients be experiencing an acute exacerbation of schizophrenia. In addition, it should be noted that while the 5 factors used in this analysis allow for evaluation of distinct symptom domains, they may not adequately characterize the full complexity of schizophrenia psychopathology. These results should also be interpreted with caution given the post hoc nature of the analyses and the generally modest changes observed in the pooled factor analysis.

Researchers are actively investigating clinical and pathophysiological markers in schizophrenia to identify heterogeneous diagnostic categories that can be divided into more objectively classified symptom subgroups (Dickinson et al., 2017). Analysis of the symptom dimensions identified by PANSS-derived factors helps to accomplish this goal, with the potential of choosing treatments that are most relevant to a patient's predominant symptoms. In post hoc analysis of pooled data from patients with acute schizophrenia, cariprazine 1.5–9.0 mg/d demonstrated efficacy across the full range of symptoms covered by 5 PANSS factors. In addition to proven efficacy in treating patients with an exacerbation of schizophrenia, these post hoc findings suggest that cariprazine may have clinical benefits for patients with symptoms that commonly occur in addition to the frank psychosis observed during times of acute illness.

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Contributors

W. Earley, G. Németh, I. Laszlovszky, E.Szalai, and S. Durgam were involved with study design, analysis, and interpretation of data. S. Marder and W. W. Fleischhacker contributed to the analysis and interpretation of the data. K. Lu and Y. Zhong performed statistical analyses. All authors contributed to the development and revision of the manuscript, and approved the final manuscript.

Conflict of interest

Stephen Marder reports personal fees from Allergan, personal fees from Lundbeck, personal fees from Takeda, per-

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