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Safety and Tolerability of Cariprazine in Patients with Schizophrenia: A Pooled Analysis of Eight Phase II/III Studies

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Background: Long-term treatment with antipsychotic agents is indicated for patients with schizophrenia, but treatment is associated with adverse events (AEs) that contribute to medication discontinuation and nonadherence. Understanding drug safety profiles is critical to avoid unwanted side effects. Cariprazine is a potent dopamine D_3/D_2 receptor partial agonist that is approved for the treatment of adults with schizophrenia (EU, US) and acute manic/mixed and depressive episodes associated with bipolar I disorder (US).

Methods: Post hoc analyses were conducted to characterize the safety profile of cariprazine within the recommended 1.5–6 mg/d dose range for schizophrenia; data from 8 short- or long-term clinical trials were analyzed.

Results: In the pooled cariprazine-treated safety population (n=2048), the rate of study completion was 52.8%, with withdrawal of consent, insufficient response, and AEs the most common reasons for premature discontinuation. The most commonly reported AEs (>10%) in the overall cariprazine-treatment group were akathisia (14.6%), insomnia (14.0%), and headache (12.1%); most AEs were considered mild (71.0%) or moderate (26.5%). Most akathisia was mild/moderate (97.5%) and >93% of patients remained on treatment; akathisia events were managed by rescue medications (56.3%) or dose reduction (18.3%). The metabolic profile of cariprazine was neutral in patients with short- and long-term exposure; mean weight gain was 1 kg for overall cariprazine, with an AE of weight increased reported for 5.1%. Other AEs of special interest that occurred at >3% for overall cariprazine were extrapyramidal disorder (7.0%), sedation (3.7%), and somnolence (3.1%); prolactin elevation, cognition impairment, sexual dysfunction, suicidality, and QT prolongation occurred at ≤1%.

Conclusion: Akathisia, the most common cariprazine-related AE, was mild/moderate and resulted in few study discontinuations; symptoms were well managed and most patients remained on treatment. Results of this analysis indicated that cariprazine in the recommended dose range was safe and generally well tolerated in patients with schizophrenia.

Trial Registration: Studies registered with ClinicalTrials.gov (NCT00404573, NCT01104779, NCT00694707, NCT01104766, NCT01104792, NCT00839852, and NCT01412060) and EudraCT (2012–005485-36).

Keywords: cariprazine, atypical antipsychotic, schizophrenia, safety and tolerability, post hoc analysis

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Introduction

Long-term treatment with an antipsychotic agent is indicated for all patients with schizophrenia. Antipsychotic drugs can be of great benefit for a range of symptoms, but treatment may be associated with challenging side effects that contribute to

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discontinuation and adherence problems.[1] In schizophrenia, the rate of poor adherence to antipsychotic medication is around 50%, with an estimated range between 20% and 90%.[2–5] Nonadherence, which is one of the most common causes of relapse,[6] frequently occurs when a patient disagrees with the need for treatment, the dosing regimen is too complex (eg, multiple daily doses, complicated uptitration schedule, dependent on food or liquid intake), or when side effects are unacceptable.[4,6–9]

Antipsychotics have different receptor binding properties, which result in different side effect profiles.[10] Understanding the safety profile of a drug is critical to avoid unwanted side effects. While binding and blocking the D_2, D_3, and serotonin receptors are desired qualities of antipsychotic treatment, excess D_2 antagonism can result in motor side effects and blockade of H_1, M_1, and α1 receptors may be associated with other undesired outcomes, such as anticholinergic effects, cognitive deficits, weight gain, and sedation.[11–14] Akathisia is one of the most frequently occurring movement disorders associated with antipsychotic agents, although the propensity for its occurrence differs by pharmacologic profile and receptor-binding affinities; all antipsychotics may cause some degree of akathisia, with lower rates generally noted for second-generation agents versus first-generation agents.[15]

Cariprazine is a dopamine D_3/D_2 receptor partial agonist that is approved by the European Medicines Agency (EMA) and by the United States (US) Food and Drug Administration (FDA) for the treatment of schizophrenia (1.5–6 mg/d); it is additionally approved in the US for manic and mixed episodes associated with bipolar I disorder (3–6 mg/d), and for bipolar depression (1.5 or 3 mg/d).[16] Cariprazine differs from all other atypical antipsychotics in having a greater affinity for the D_3 receptor than does dopamine itself, thereby exhibiting a functional D_3 partial agonism in the human brain[17] that other antipsychotics, such as aripiprazole, risperidone, and olanzapine, fail to exhibit.[18–21] Since the D_3 receptor is thought to play a role in moderating negative and cognitive symptoms,[22] a compound that exhibits high affinity for D_3 receptors may confer benefits in treating these symptoms in schizophrenia.[23–27] In fact, in a large-scale, well-designed study, cariprazine was significantly more effective than risperidone in treating persistent, predominant negative symptoms of schizophrenia and improving associated psychosocial impairment.[28] Cariprazine also acts as an antagonist at serotonin 5-HT_{2B} receptors and as a partial agonist at 5-HT_{1A} receptors, with lower affinity for 5-HT_{2A}, 5-HT_{2C}, histamine H_1, and α_1 receptors and negligible affinity at other receptors.[29] This receptor binding profile may also have beneficial implications for cardiovascular,[30] metabolic,[31] sedative,[32] and hyperprolactinemia associated side effects.[33]

Although the safety and tolerability of cariprazine has been established in several clinical trials and post hoc analyses in patients with schizophrenia, some studies included doses that are outside the dose range that was subsequently established for cariprazine in schizophrenia.[28,34–42] To characterize the overall safety profile of cariprazine within the recommended 1.5–6 mg/d dose range for schizophrenia, we conducted additional post hoc analyses of safety data from 8 studies in patients with short- or long-term cariprazine exposure.

Methods

For all studies, the constituent study protocols were approved by a relevant ethics committee or institutional review board (US sites). ICH-E6 Good Clinical Practice guidelines were followed and written informed consent was obtained from all participants.

Study Designs

Eight schizophrenia studies were included in these analyses; methods for each have been previously published.[28,34–39,41] There were 4 short-term, randomized, 6-week double-blind, placebo-controlled studies of similar design. The first study was a flexible-dose, proof-of-concept study in which patients were randomized to cariprazine 1.5–4.5 or 6–12 mg/d or placebo (NCT00404573).[38] The second study also had a flexible-dose design with patients randomized to cariprazine 3–6 mg or 6–9 mg/d or placebo (NCT01104779).[41] The third study was a fixed-dose study with patients randomized to cariprazine 1.5 mg/d, 3 mg/d, or 4.5 mg/d, risperidone 4 mg/d, or placebo (NCT00694707).[39] The fourth study also had a fixed-dose design, with patients randomized to cariprazine 3 mg/d or 6 mg/d, aripiprazole 10 mg/d, or placebo (NCT01104766).[35] In the fixed-dose studies, risperidone and aripiprazole were included for assay sensitivity.

In addition to the 4 short-term studies, the cariprazine clinical development program for schizophrenia comprised 4 long-term studies (≥6 months) that were included in these analyses. Two of the long-term studies were 48-week open-label, flexible-dose safety studies in which cariprazine doses of 3–9 mg/d (NCT01104792)[34] or cariprazine 1.5–4.5 mg/d (NCT00839852)[37] were administered. The third long-term

study evaluated relapse prevention using a randomized withdrawal design (NCT01412060).[36,43] This study had 5 phases (screening, open-label run-in, open-label stabilization, double-blind treatment [up to 72 weeks], safety follow-up) with a total duration of up to 92 weeks; patients received flexible or fixed doses of cariprazine 3, 6, or 9 mg/d (depending on which open-label phase they were in), followed by fixed-dose cariprazine or placebo in the double-blind phase. The fourth long-term study was a 26-week, double-blind, active-controlled, fixed-flexible dose study in patients with persistent, predominantly negative symptoms of schizophrenia (EudraCT 2012–005485-36).[28] Patients received a target dose of cariprazine 4.5 mg/d or risperidone 4 mg/d; the dose could be adjusted once during treatment in the dose range of 3–6 mg for both compounds.

Patient Populations

All patients included in these studies were adults (18 to 65 years) with a Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision (DSM-IV-TR)[44] diagnosis of schizophrenia; key inclusion and exclusion criteria are presented in Supplemental Table 1. In brief, patients in the short-term studies were required to have a current exacerbation of symptoms as shown by a Clinical Global Impressions-Severity (CGI-S)[45] score corresponding to moderately ill or worse and Positive and Negative Syndrome Scale (PANSS)[46] total and item scores indicating marked to severe levels of illness.[47]

The long-term, 48-week, open-label cariprazine safety studies served as extensions to the short-term studies, with patients first completing 6 weeks of double-blind treatment in a lead-in study; one long-term study additionally accepted newly enrolled patients. All patients who participated in the open-label studies were required to have stable symptoms, as determined by PANSS and CGI-S scores, and fulfil inclusion criteria that were consistent with the lead-in trials. In the relapse prevention trial, patients with acute schizophrenia and a current psychotic episode were included in the 20-week open-label lead-in stabilization phase. Patients who met stabilization criteria and had no significant investigator-judged tolerability issues at the end of open-label treatment were randomized to fixed-dose cariprazine at their established open-label dose or switched to placebo for double-blind treatment.

In the negative symptom trial, the included patients were stable for at least 6 months before screening (ie, no psychiatric hospital admissions, acute exacerbations, or imprisonments), had predominant negative symptoms for at least 6 months (medical records/investigator judgment), and met negative symptom criteria based on the PANSS Factor Score for Negative Symptoms (PANSS-FSNS)[48] and PANSS negative symptom items. Further, to ensure that improvements in negative symptoms were not secondary to improvements in other psychopathological domains (ie, pseudospecific), patients also had to have insignificant PANSS positive symptoms, minimal depressive symptoms as shown by the Calgary Depression Scale for Schizophrenia (CDSS),[49] and clinically inconsequential parkinsonism as assessed by the Simpson-Angus Scale (SAS).[50]

In all studies, exclusion criteria were typical of clinical studies in schizophrenia and included the presence of some other DSM-IV-TR diagnoses (eg, psychotic disorders, schizoaffective disorder, bipolar disorders), treatment-resistant schizophrenia, substance abuse, and active suicidal intent or past attempt (Supplemental Table 1). Concurrent medical conditions that could interfere with the conduct of the study, confound the interpretation of results, or endanger the patient's well-being were also exclusionary. Drugs with psychotropic activity were not allowed, except for lorazepam for agitation, hostility, and restlessness; eszopiclone, zolpidem, chloral hydrate, or zaleplon for insomnia; and diphenhydramine, benztropine, or propranolol for extrapyramidal symptoms (EPS). Of note, since analysis populations from clinical trials are highly selective due to strict protocol-specified inclusion and exclusion criteria, the patient sample used in our analysis may not be representative of a general population sample of patients with schizophrenia.

Safety Assessments

Safety was assessed by adverse event (AE) recordings, clinical laboratory tests, vital sign parameters, weight changes, and electrocardiograms (ECGs). Events of akathisia were assessed through reports of AEs and by the Barnes Akathisia Rating Scale (BARS).[51] The Columbia-Suicide Severity Rating Scale (C-SSRS)[52] was used to assess suicidality.

Statistical Evaluation

Safety analyses were performed in the pooled safety population, which consisted of patients who received at least 1 dose of cariprazine in an included clinical trial. In concert with prespecified statistical methods in the constituent study protocols, safety parameters in these analyses were estimated using descriptive statistics; no inferential

analyses were performed because of the numerous comparisons that were included. Since a placebo arm was not included in every study and statistically significant differences for cariprazine versus placebo were not determined, pooled placebo values are presented for reference, not as true comparators. Findings were summarized for placebo, overall cariprazine in the approved dose range (1.5–6 mg/d), and by cariprazine dose (1.5, 3, 4.5, 6 mg/d) to evaluate potential dose–response relationships. Dose response was assumed if the frequency of findings increased from the 1.5 mg/d dose to the 6 mg/d dose. To address the potential for a relationship between suicidality and akathisia, the incidence of C-SSRS suicidality or a suicidality TEAE was evaluated in the subset of patients with a TEAE of akathisia, restlessness, or treatment-emergent akathisia (BARS score ≤2 at baseline and >2 postbaseline).

The safety baseline was the last non-missing value before the first dose of the study drug; the end of treatment was the last non-missing value during treatment. For cariprazine-treated patients continuing from a lead-in study to a long-term, open-label study, the lead-in study safety baseline was used as the baseline for all analyses; for new patients who were included in one of the open-label safety studies and patients who received placebo or a treatment other than cariprazine in a lead-in study, baseline was the last value before the first dose of open-label cariprazine.

Patients who were treated with cariprazine in a lead-in study and who continued into an open-label follow-up safety study were counted only once for the overall assessment of AEs; patients who were treated with placebo in a lead-in study and who continued into an open-label follow-up study where they then received cariprazine were counted for AEs twice (once in each study). The same was true in the relapse prevention study where patients who were stabilized on cariprazine in the open-label phase and who continued on cariprazine in the double-blind phase were counted once for AEs, while patients who were stabilized on open-label cariprazine but continued onto placebo treatment were counted twice (once while on cariprazine in the open-label phase and once while on placebo in the double-blind phase).

Data from the risperidone and aripiprazole active-comparator treatment arms and the active-control risperidone arm were not included in these pooled analyses because the observation periods for evaluated safety events were too dissimilar to allow for meaningful comparison with cariprazine. Comparative safety data from the original studies that included risperidone or aripiprazole as control treatment arms have been previously reported.[28,35,39]

Results

Patient Disposition and Baseline Demographic Characteristics

There were 2731 patients in the analyzed pooled safety population (total cariprazine=2048; placebo=683); although each study that included placebo randomized patients in a balanced manner, the open-label and negative symptom studies did not include a placebo arm, which accounts for the greater number of cariprazine patients in this analysis population. Of patients treated with cariprazine in the approved dose range (1.5–6 mg), 1114 patients participated in the short-term studies (6 weeks) and 1122 patients participated in the long-term open-label or double-blind studies (≥26 weeks) (Table 1). A total of 188 patients continued into a long-term open-label safety study from a lead-in study and were already counted once in the short-term study total; 343 of 531 patients in the long-term extension studies were new to cariprazine and were included in the overall long-term study count.

Demographic and baseline characteristics of the safety population are presented in Table 2.

The most frequent reason for discontinuation in any group was withdrawal of consent, followed by insufficient response and AEs (Table 3).

Safety Findings

Extent of Exposure

Overall exposure to cariprazine in the schizophrenia program over time is shown in Table 4. In the pooled schizophrenia studies, 2048 patients received at least one dose of cariprazine and the overall mean daily dose was 4.1 mg. Patient-years exposure (total amount of time exposed to cariprazine expressed in years) was 630.8 years.

Adverse Events

A total of 3 deaths were reported in cariprazine-treated patients who participated in the schizophrenia program. Two cariprazine-treated patients (cariprazine 6 mg/d for 21 days and cariprazine 4.5 mg/d for 322 days) completed suicide. One additional patient died of acute myocardial infarction and ischemic stroke after 37 days on cariprazine 6 mg/d. None of these events were considered by investigators to be related to cariprazine treatment.

A summary of AEs reported in the schizophrenia program is presented in Table 5; individual terms related to a more general AE were grouped and reported collectively as the broad AE for some events (see Supplemental Table 2 for grouped terms). The most frequent AEs (>10%) reported in

Table 1 Patient Populations

Study	Placebo (N)	Cariprazine (N)[a]				
		1.5 mg	3 mg	4.5 mg	6 mg	Total 1.5–6 mg/d
Schizophrenia Studies Total	683	180	619	549	794	2048[b]
Schizophrenia Short-Term Studies						
Placebo-controlled short-term	584	164	375	257	318	1114
Schizophrenia Long-Term Studies						
Overall	99	17	260	311	536	1122[b]
Open-label long-term	—	13	157	63	298	531[b]
Relapse prevention	99	4	103	18	238	361[c]
Negative symptom study	—	—	—	230	—	230

Notes: [a]For the fixed-dose studies, patients were counted to the dose level that they were randomized to; for the flexible-dose studies, modal daily doses were considered, meaning patients were counted to the dose level that they took for the most time; [b]To calculate the total number of patients treated with cariprazine, 188 patients receiving cariprazine in both the short-term studies and subsequent follow-up safety studies were counted only once; [c]Patients randomized to placebo in the relapse prevention study received cariprazine for 20 weeks in the open-label phase; 2 patients had different modal doses during the open-label and double-blind phases and they were counted 1 time for each respective dose group, but only once for the total.

Table 2 Baseline Demographic and Disease Characteristics

Characteristics	Placebo (N=683)	Cariprazine[a]				
		1.5 mg (N=180)	3 mg (N=619)	4.5 mg (N=549)	6 mg (N=794)	Total[b] 1.5–6 mg/d (N=2048)
Pooled Schizophrenia Studies						
Age, mean (SD), years	37.8 (10.9)	37.3 (9.5)	38.2 (10.6)	38.6 (10.8)	38.1 (10.6)	38.2 (10.6)
Sex, male n (%)	485 (71.0)	120 (66.7)	440 (71.1)	367 (66.8)	544 (68.5)	1409 (68.8)
Race, n (%)						
Caucasian	275 (40.3)	94 (52.2)	298 (48.1)	361 (65.8)	349 (44.0)	1039 (50.7)
Black/African American	245 (35.9)	48 (26.7)	194 (31.3)	111 (20.2)	273 (34.4)	611 (29.8)
Asian	126 (18.4)	36 (20.0)	85 (13.7)	63 (11.5)	129 (16.2)	301 (14.7)
Other	37 (5.4)	2 (1.1)	42 (6.8)	5 (0.9)	43 (5.4)	88 (4.3)
Weight, mean (SD), kg	77.5 (19.6)	73.7 (18.1)	77.4 (18.5)	78.7 (18.1)	77.2 (19.0)	77.5 (18.7)
BMI, mean (SD), kg/m2	26.4 (5.4)	25.4 (5.0)	26.2 (5.2)	26.4 (5.1)	26.4 (5.5)	26.3 (5.3)
Duration of schizophrenia (SD), years	12.6 (10.3)	11.9 (8.7)	12.1 (9.4)	13.3 (10.7)	12.1 (9.6)	12.4 (9.8)
Age at onset of original diagnosis of schizophrenia (SD), years	25.2 (8.9)	25.5 (8.4)	26.1 (8.6)	24.1 (8.3)	26.0 (9.0)	25.6 (8.7)

Notes: [a]For the fixed-dose studies, patients were counted to the dose level that they were randomized to; for the flexible-dose studies, modal daily doses were considered, meaning patients were counted to the dose level that they took for most of the time; [b]To calculate total number of patients treated with cariprazine, patients participating in the short-term and subsequent follow-up safety study were counted only once.

the total cariprazine group were akathisia, insomnia, and headache; the only AEs that occurred in >5% of the overall cariprazine group and twice the rate of placebo were akathisia, extrapyramidal disorder, and weight increased. Most AEs were mild (71.0%) or moderate (26.5%) in intensity and 57.3% of AEs were considered related to treatment. In addition to akathisia and insomnia (Table 5), there was a suggestion of dose response across cariprazine 1.5 mg, 3 mg, 4.5 mg, and 6 mg doses, respectively, for blurred vision (0.6%, 1.6%, 1.1%, 2.0%), creatine phosphokinase (CPK) elevation (1.7%, 2.3%, 1.5%, 3.7%), restlessness (3.9%, 6.3%, 4.2%, 7.3%), and anxiety (4.4%, 7.1%, 5.5%, 7.9%). Serious AEs (SAEs) and discontinuations due to AEs were balanced between cariprazine doses, with no clear dose-

Table 3 Disposition and Reasons for Discontinuation

Disposition Events	Placebo (N=683) n (%)	Cariprazine[a]				
		1.5 mg (N=180) n (%)	3 mg (N=619) n (%)	4.5 mg (N=549) n (%)	6 mg (N=794) n (%)	Total[b] 1.5–6 mg/d (N=2048) n (%)
Pooled Schizophrenia Studies[c]						
Completed study	350 (51.2)	97 (53.9)	284 (45.9)	367 (66.8)	334 (42.1)	1082 (52.8)
Prematurely discontinued	333 (48.8)	84 (46.7)	351 (56.7)	198 (36.1)	520 (65.5)	1153 (56.3)
Reason for Discontinuation						
Did not meet inclusion/exclusion criteria	2 (0.3)	1 (0.6)	—	—	1 (0.1)	2 (0.1)
Relapse event[d]	47 (6.9)	—	9 (1.5)	—	26 (3.3)	35 (1.7)
Adverse event	76 (11.1)	28 (15.6)	73 (11.8)	53 (9.7)	97 (12.2)	251 (12.3)
Insufficient therapeutic response	100 (14.6)	18 (10.0)	47 (7.6)	45 (8.2)	52 (6.5)	162 (7.9)
Protocol violation	9 (1.3)	3 (1.7)	24 (3.9)	16 (2.9)	36 (4.5)	79 (3.9)
Withdrawal of consent	74 (10.8)	30 (16.7)	148 (23.9)	62 (11.3)	193 (24.3)	433 (21.1)
Lost to follow-up	12 (1.8)	1 (0.6)	20 (3.2)	13 (2.4)	39 (4.9)	73 (3.6)
Other reasons	13 (1.9)	3 (1.7)	30 (4.8)	9 (1.6)	76 (9.6)	118 (5.8)

Notes: [a]For the fixed-dose studies, patients were counted to the dose level that they were randomized to; for the flexible-dose studies, modal daily doses were considered, meaning patients were counted to the dose level that they took for most of the time; [b]Total=the number of patients from the short-term studies (n=1114) plus the overall number of patients from the long-term studies (n=1122) minus the number of patients continuing from a lead-in study to an open-label extension (n=188); [c]Completion and discontinuation values may not sum to 100% because patients who completed a lead-in study and discontinued in an extension study were counted twice (once for completed and once for discontinuation); [d]Restricted to relapse prevention study only.

Table 4 Extent of Exposure to Cariprazine in the Approved Dose Range (1.5–6 mg/d) in Pooled Schizophrenia Studies

Treatment Duration	Number of Patients (%)				
	Short-Term Studies	Long-Term, Open-Label Studies	Relapse Prevention Study	Negative Symptom Study	Total
Enrolled (screened)	3052	851	1149	533	5118
≥ 1 day	1114 (100.0)	531 (100.0)	361 (100.0)	230 (100.0)	2048 (100.0)
≥ 3 weeks	820 (73.6)	456 (85.9)	242 (67.0)	220 (95.7)	1570 (76.7)
≥ 6 weeks	565 (50.7)	398 (75.0)	206 (57.1)	213 (92.6)	1255 (61.3)
≥ 12 weeks (3 month)	—	349 (65.7)	163 (45.2)	188 (81.7)	716 (35.0)
≥ 24 weeks (6 month)	—	281 (52.9)	44 (12.2)	140 (60.9)	508 (24.8)
≥ 48 weeks (12 month)	—	179 (33.7)	27 (7.5)	—	225 (11.0)

dependency observed. Rates of other AEs that are of interest in relation to antipsychotic treatment are included in Table 5.

Akathisia

Akathisia was the most common adverse effect in cariprazine-treated patients (Table 5). Most events were judged to be mild or moderate in intensity (cariprazine=97.5%, placebo=95.8%) and most patients remained on treatment despite symptoms (>93%). Treatment-emergent akathisia, defined as a BARS score ≤2 at baseline and >2 at any visit during the treatment period, was noted in 362/2048 (17.7%) cariprazine-treated patients and 43/683 (6.3%) placebo-treated patients. Symptom management included anti-EPS medication and slight down-titration of treatment (Table 6). The medications used for akathisia during active treatment and safety follow-up

Table 5 Treatment-Emergent Adverse Events (Pooled Schizophrenia Safety Population)

	Placebo (N=683) n (%)	Cariprazine[a]				
		1.5 mg (N=180) n (%)	3 mg (N=619) n (%)	4.5 mg (N=549) n (%)	6 mg (N=794) n (%)	Total 1.5–6 mg/d (N=2048) n (%)
Death	0	0	0	1 (0.0)	2 (0.0)	0
SAE	21 (3.1)	4 (2.2)	10 (1.6)	17 (3.1)	24 (3.0)	55 (2.7)
AE related to study drop out	54 (7.9)	18 (10.0)	49 (7.9)	42 (7.7)	64 (8.1)	173 (8.4)
TEAE	431 (63.1)	118 (65.6)	445 (71.9)	370 (67.4)	632 (79.6)	1520 (74.2)
TEAEs >10% in the Total Cariprazine Group						
Akathisia[b]	23 (3.4)	14 (7.8)	97 (15.7)	50 (9.1)	143 (18.0)	299 (14.6)
Insomnia[b]	69 (10.1)	19 (10.6)	79 (12.8)	68 (12.4)	122 (15.4)	287 (14.0)
Headache	81 (11.9)	20 (11.1)	63 (10.2)	47 (8.6)	118 (14.9)	247 (12.1)
Other AEs of Interest Associated with Antipsychotic Treatment						
Extrapyramidal disorder	22 (3.2)	15 (8.3)	41 (6.6)	33 (6.0)	56 (7.1)	143 (7.0)
Sedation	21 (3.1)	7 (3.9)	21 (3.4)	26 (4.7)	22 (2.8)	75 (3.7)
Somnolence	13 (1.9)	3 (1.7)	20 (3.2)	18 (3.3)	23 (2.9)	63 (3.1)
Prolactin elevation[c]	1 (0.1)	0	0	0	0	0
Cognition impairment[c]	2 (0.3)	2 (1.1)	1 (0.2)	3 (0.5)	5 (0.6)	11 (0.5)
Sexual dysfunction[c]	2 (0.3)	1 (0.6)	3 (0.5)	6 (1.1)	10 (1.3)	20 (1.0)
Suicidality[c]	1 (0.1)	0	6 (1.0)	3 (0.5)	9 (1.1)	18 (0.9)
QT prolongation[c]	1 (0.1)	1 (0.6)	7 (1.1)	1 (0.2)	6 (0.8)	15 (0.7)
Weight increased	10 (1.5)	6 (3.3)	40 (6.5)	9 (1.6)	50 (6.3)	104 (5.1)
Treatment-Emergent Metabolic AEs						
Hyperlipidemia-related[c]	5 (0.7)	2 (1.1)	13 (2.1)	9 (1.6)	19 (2.4)	43 (2.1)
Hyperglycemia/diabetes mellitus-related[c]	7 (1.0)	1 (0.6)	12 (1.9)	4 (0.7)	8 (1.0)	25 (1.2)

Notes: [a]For the fixed-dose studies, patients were counted to the dose level that they were randomized to; for the flexible-dose studies, modal daily doses were considered, meaning patients were counted to the dose level that they took for most of the time; [b]Dose-dependency observed; [c]Includes grouped terms organized under broader AE (Supplemental Table 2).

Abbreviations: AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

(patient % [dose range]) were propranolol (47.9% [10–360 mg/d]), trihexyphenidyl (20.1% [2–18 mg/d]), benzatropine (19.5% [0.5–4 mg/d]), diphenhydramine (5.3% [25–50 mg/d]) biperiden (4.7% [1–6 mg/d]), lorazepam (1.2% [1–2 mg/d]), hydroxyzine (0.6% [25 mg/d]), and oxazepam (0.6% [20 mg/d]).

No relationship between suicidal tendency and akathisia/restlessness TEAEs or BARS-defined akathisia was observed in the cariprazine schizophrenia program (Table 7). In the overall pooled schizophrenia studies, rates of any suicidality in patients with akathisia/restlessness were comparable between placebo and cariprazine; rates of suicidal ideation in patients with akathisia/restlessness were slightly higher for both placebo and cariprazine, with most instances categorized in the least severe category ("wish to be dead").

Metabolic Parameters

In the overall cariprazine dose group, levels of total cholesterol, high-density lipoprotein cholesterol, and fasting triglycerides decreased from baseline; no dose response was noted for any parameter (Table 8). Increases in fasting glucose were small and similar to placebo for each cariprazine dose group and overall. A higher percentage of placebo-treated patients (9.3%) than total cariprazine-treated patients (8.4%) had shifts in total cholesterol from normal to high levels (<6.2 to >6.2 mmol/L). The percentage of patients with shifts from normal to high levels of triglycerides (<1.7 to >2.2 mmol/L) was the same for the placebo- (9.7%) and total cariprazine- (9.4%) treatment groups. Slightly more total cariprazine-treated patients (3.4%) than placebo-treated patients (2.0%) shifted from normal to high levels

Table 6 Incidence and Management of Akathisia (Pooled Schizophrenia Safety Population)

Incidence of Akathisia TEAEs	Placebo N=683	Cariprazine 1.5–6 mg N=2048
Patients with akathisia, n (%)	23 (3.4)	299 (14.6)
Akathisia events, n[a]	23	334
Mild, n (%)	14 (60.8)	180 (53.9)
Moderate, n (%)	8 (34.8)	145 (43.5)
Severe, n (%)	1 (4.4)	9 (2.6)
Akathisia Treated with Anti-EPS Medication		
Akathisia events treated with anti-EPS medication, n (%)	12 (52.1)	188 (56.3)
Median time of anti-EPS medication administration, days, n	7	18
Median time to resolution of akathisia with anti-EPS medication, days, n	16	17
Unresolved events after anti-EPS treatment, n (%)	7 (58.3)	28 (14.9)
Akathisia Treated With Study Drug Down-Titration		
Akathisia events resulting in study drug down-titration, n (%)[b]	–	61 (18.3)
Median time to resolution of akathisia in patients with study drug down-titration, days, n	–	15
Unresolved events in patients with study drug down-titration, n (%)	–	4 (6.6)
Discontinuation		
Akathisia events resulting in discontinuation, n (%)	1/23 (4.4)	21/334 (6.3)

Notes: [a]A patient might have experienced more than one akathisia event; events were counted separately if there were 3 or more days between them; [b]Depending on the timing of the event, down-titration may not have been allowed in the fixed-dose studies.
Abbreviations: EPS, extrapyramidal symptoms; TEAEs, treatment-emergent adverse events.

Table 7 Incidence of Suicidality Among Patients with TEAEs of Akathisia, Restlessness, or Akathisia According to the Barnes Akathisia Rating Scale (Pooled Schizophrenia Safety Population)

Group	Suicidality TEAE	Suicidal Ideation (C-SSRS)	Suicidal Behavior (C-SSRS)	Any Suicidality
Placebo	0/56[a] (0.0)	2/56 (3.6)	0/56 (0.0)	2/56 (3.6)
Cariprazine 1.5–6 mg	7/503[a] (1.4)	19/503 (3.8)	4/503 (0.8)	26/503 (5.2)

Note: [a]Suicidality in patients with reports of akathisia or restlessness TEAEs, or akathisia according to the Barnes Akathisia Rating Scale.
Abbreviations: C-SSRS, Columbia–Suicide Severity Rating Scale; TEAE, treatment-emergent adverse event.

of fasting glucose (<5.6 to >7 mmol/L), although levels for cariprazine patients remained stable over time.

Low rates of treatment-emergent metabolic AEs occurred in cariprazine-treated patients (Table 5). The incidence of hyperlipidemia-related AEs was low in all groups, but the rate was slightly higher in overall cariprazine-treated patients (2.1%) than in placebo-treated patients (0.7%); the rate was highest in the cariprazine 3 mg/d group (2.4%), but no true dose response was observed. The incidence of hyperglycemia/diabetes mellitus-related AEs was low and similar in all treatment groups. The mean increase in weight from baseline was 1 kg for overall cariprazine (Table 8); the AE of weight increased was greater in cariprazine-treated patients than in placebo, with no observed dose–response relationship for cariprazine (Table 5).

Other Key Clinical Laboratory Values

Small increases in alanine aminotransferase and aspartate aminotransferase levels relative to placebo were noted with cariprazine; there were no mean increases in bilirubin levels with cariprazine or placebo, and alkaline phosphatase levels decreased slightly in both groups (Table 8). Prolactin levels decreased from baseline in all cariprazine dose groups. Modest increases in creatine kinase levels were observed in cariprazine- versus placebo-treated patients. No TEAEs of prolactin elevation (blood prolactin increase and hyperprolactinemia) were noted in the pooled schizophrenia safety

Table 8 Mean Change from Baseline in Laboratory Parameters and Other Safety Findings

	Placebo	Cariprazine[a]				
		1.5 mg	3 mg	4.5 mg	6 mg	Total 1.5–6 mg/d
Metabolic Parameters, mean (SD)						
Cholesterol, mmol/L	0.1 (0.8)	−0.0 (0.8)	−0.2 (4.2)	−0.1 (0.9)	−0.3 (3.7)	−0.1 (2.4)
HDL cholesterol, mmol/L	−0.0 (0.3)	−0.0 (0.3)	−0.0 (0.3)	−0.1 (0.6)	−0.0 (0.3)	−0.0 (0.4)
Fasting triglycerides, mmol/L	0.0 (0.8)	0.0 (1.1)	−0.1 (1.1)	−0.1 (1.0)	−0.1 (1.0)	−0.0 (1.0)
Fasting glucose, mmol/L	0.3 (2.7)	0.1 (1.0)	0.2 (1.1)	0.3 (1.4)	0.2 (1.2)	0.3 (1.2)
Body weight increase, kg	0.2 (3.1)	0.9 (2.9)	1.3 (3.8)	0.6 (3.4)	0.8 (4.1)	1.0 (3.8)
Clinical Laboratory Parameters, mean (SD)						
Prolactin, ng/mL	−7.8 (28.2)	−14.7 (33.6)	−12.9 (32.0)	−11.3 (26.1)	−14.3 (38.2)	−13.0 (33.8)
Alanine aminotransferase, U/L	0.5 (17.6)	4.6 (44.3)	4.8 (29.9)	2.2 (19.9)	4.4 (31.2)	4.4 (29.0)
Aspartate aminotransferase, U/L	0.2 (10.8)	1.6 (17.9)	1.8 (16.4)	0.6 (12.3)	2.6 (25.5)	2.0 (20.2)
Alkaline phosphatase, U/L	−1.3 (26.3)	−3.1 (20.4)	0.0 (14.8)	−2.2 (20.8)	−2.2 (22.9)	−1.3 (20.3)
Total bilirubin, umol/L	0.6 (4.4)	0.4 (4.4)	0.5 (4.2)	0.7 (4.7)	0.4 (4.7)	0.5 (4.5)
Creatine phosphokinase, U/L	27.0 (373.8)	54.9 (373.4)	38.5 (346.6)	25.2 (301.8)	153.8 (2790)	87.8 (1802)
Gamma glutamyl transferase, U/L	−0.4 (35.6)	1.0 (20.5)	1.9 (18.9)	−1.3 (22.1)	0.5 (27.8)	0.4 (23.6)
Cardiovascular Parameters, mean (SD)						
Supine systolic blood pressure, mmHg	0.5 (10.4)	0.3 (10.1)	0.7 (10.5)	0.3 (10.9)	1.5 (10.6)	1.1 (10.7)
Supine diastolic blood pressure, mmHg	0.2 (8.0)	0.1 (7.3)	0.4 (8.0)	0.7 (8.5)	0.8 (8.5)	0.8 (8.3)
Supine pulse rate, bpm	0.1 (12.5)	0.2 (10.7)	−0.6 (11.2)	0.3 (11.3)	−0.3 (11.6)	0.1 (11.3)
Electrocardiographic Findings, mean (SD)						
Heart rate, bpm	0.7 (15.1)	−0.2 (14.9)	0.3 (14.9)	2.0 (14.8)	2.3 (15.2)	2.0 (14.9)
QRS interval, msec	0.6 (7.4)	0.6 (7.4)	0.6 (7.4)	−0.1 (6.9)	0.6 (7.5)	0.6 (7.3)
PR interval, msec	−0.3 (14.0)	−1.2 (14.2)	−0.3 (14.7)	−1.0 (13.8)	−1.2 (14.5)	−0.7 (14.4)
QT interval, msec	−2.2 (29.7)	−1.8 (28.3)	−1.7 (29.5)	−5.9 (30.3)	−5.5 (30.3)	−4.1 (30.0)
QTcB interval, msec	−0.8 (22.9)	−1.6 (21.7)	−1.3 (21.7)	−1.3 (20.2)	0.2 (22.0)	−0.0 (21.1)
QTcF interval, msec	−1.4 (17.8)	−1.5 (16.8)	−1.4 (17.3)	−2.9 (16.9)	−1.8 (17.2)	−1.6 (16.9)

Notes: Only patients with baseline and at least one postbaseline measurement are included; Roll-over patients in the extension studies who received treatment other than cariprazine in the lead-in study are counted twice in the respective treatment groups, with the lead-in end of study visit used as baseline for the extension study; patients receiving placebo in the relapse prevention study double-blind period are included in the placebo category; [a]For the fixed-dose studies, patients were counted to the dose level that they were randomized to; for the flexible-dose studies, modal daily doses were considered, meaning patients were counted to the dose level that they took for most of the time.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

population (Table 8). The rate of sexual dysfunction TEAEs was low across all cariprazine dose groups.

Cardiovascular Parameters and Electrocardiographic Findings

Mean changes from baseline in supine diastolic and systolic blood pressure were small and similar among all treatment groups (Table 8). Mean changes in heart rate and other electrocardiographic findings were also generally small and not clinically meaningful; a small dose-related increase in heart rate was noted for cariprazine. There were very few incidences of QT prolongations with cariprazine, with 3 (0.4%) patients reporting QTcB >500 msec (Bazett formula), one of whom also had QTcF >500 msec (Fridericia formula). QT prolongation TEAEs occurred in <1% of patients treated with placebo or cariprazine overall (Table 5).

Discussion

This post hoc analysis evaluated the safety and tolerability of cariprazine in the recommended dose range (1.5–6 mg/d) for patients with schizophrenia. Combined data from 8 studies in the clinical development program for schizophrenia (4 short-term, placebo-controlled clinical trials, 2 long-term, open-label safety studies, 1 relapse prevention trial, and 1 active-controlled trial in

patients with prominent and persistent negative symptoms) showed that cariprazine was generally well tolerated, with a good safety profile. The most common reasons for discontinuation from a study were withdrawal of consent, insufficient response, and AEs. A higher rate of TEAEs was noted in the total cariprazine group (77%) than in the placebo group (68%), with a higher percentage of events observed for cariprazine 6 mg/d compared with lower doses. Only akathisia, insomnia, and headache were reported by ≥10% of patients in the total cariprazine group.

In addition to the incidence, severity, and risks for discontinuation of various AEs, the safety profile of an antipsychotic is further informed by dose–response relationships. The presence or absence of dose–dependent effects with antipsychotics varies in accordance with the type of AE, with hyperprolactinemia and weight increase considered dose-related events, while akathisia, sexual dysfunction, QT interval prolongation, and somnolence are considered at least somewhat dose-related.[53] For cariprazine in general, an apparent dose–response relationship based on the observation of an increased incidence of events at higher doses is suggested for certain TEAEs, but not for SAEs or discontinuations due to AEs. The suggestion of dose response was noted for akathisia and insomnia, which were the most frequently occurring AEs, as well as for some less common events (eg, blurred vision, CPK elevation, restlessness, anxiety). No evidence of dose response was seen for any metabolic parameter, and although weight increase was highest in the 6 mg dose group, no true dose response was noted. Awareness of dose response encourages optimal antipsychotic dosing, with the goal of achieving good outcomes by avoiding lack of efficacy, which can occur if an inadequate dose is used, and excess side effect burden, which is more likely with higher dose levels.[54]

Although evidence suggests that second-generation antipsychotics have enhanced safety and tolerability characteristics compared with first-generation agents,[55] akathisia remains a commonly noted treatment-related event with second-generation agents. In a review of drug-induced akathisia, all second-generation antipsychotics were associated with treatment-emergent events, although the incidence was lower with second-generation agents than with first-generation agents.[56] In our safety analysis, akathisia was the most commonly reported AE for patients treated with cariprazine in the recommended dose range, with the highest incidence reported in the 6 mg/d group (18%). The rate of akathisia-related discontinuations was relatively low (6%) and the majority of events were considered mild or moderate; severe akathisia was only reported in 3% of cariprazine-treated patients. Events of akathisia appeared to be well managed with anti-EPS medication or cariprazine down-titration. The median time to resolution of akathisia treated with anti-EPS medication was 17 days, with 85% of events resolving. The median time to resolution of akathisia managed with down-titration was 15 days and over 90% of events resolved. Beyond its physical manifestations, akathisia has also been associated with adverse outcomes such as exacerbation of psychiatric symptoms and, in severe cases, aggression, violence, or suicide.[57] In our evaluation, rates of akathisia-related suicidality were comparable between cariprazine- and placebo-treated patients, suggesting no treatment-related increase associated with cariprazine. Of particular note with regard to cariprazine and akathisia in patients with schizophrenia, there is evidence beyond down-titration that lower doses may be associated with a lower incidence of akathisia. Namely, in the negative symptom study that found efficacy in favor of cariprazine over risperidone, the target dose of cariprazine was 4.5 mg/d and a slow titration schedule was applied.[28] Rates of cariprazine-related akathisia in this study were 8%, which is considerably lower than the rate that was observed with the 6 mg/d dose in our post hoc analysis, supporting a hypothesis that lower doses and slow titration of cariprazine may be a reasonable strategy to manage akathisia in patients with schizophrenia.

Second-generation antipsychotic medications are additionally associated with metabolic risks, with different agents having different propensities for causing metabolic side effects.[58] Metabolic consequences are cited as the most concerning aspect of treatment with psychotropic medication, contributing to perceived morbidity, quality-of-life reduction, and reduced satisfaction with care.[59] Evidence suggests that most individuals with schizophrenia are affected by at least 1 aspect of metabolic syndrome.[60] In an online survey that included over 1000 patients with schizophrenia, 36% of respondents identified weight gain as the most common treatment-related AE, with 42% additionally indicating that weight gain had contributed to other health problems including hypertension, diabetes, and hypercholesterolemia.[59] As such, it is important to note that in this pooled analysis of short- and long-term clinical studies, cariprazine in the approved dose range was metabolically neutral, with treatment-related

changes in weight gain, hyperlipidemia, hyperglycemia, and diabetes mellitus only slightly greater or comparable to placebo. Changes from baseline to the end of treatment in cholesterol, triglycerides, and fasting glucose were also small and similar to placebo. Additionally, since schizophrenia generally requires treatment over the course of the disease, it is noteworthy that decreases from baseline in lipid levels, with no dose–response relationship, were observed for metabolic parameters in the open-label, long-term cariprazine studies, further supporting the good metabolic profile of cariprazine.[42] The overall long-term mean change from baseline in weight was small (1.58 kg) and only slightly greater than the weight change observed in the 6-week controlled studies (~1 kg).[40]

In addition to weight gain, somnolence or insomnia (32%), concentration difficulties (21%), memory loss (18%), and disordered thoughts (16%) have been identified among the most common medication-related AEs in schizophrenia.[59] In our analyses, these and other AEs of special interest, including sedation, cognitive dysfunction, QT prolongation, and prolactin elevation, occurred at low rates that were similar to placebo in patients treated with cariprazine. Additionally, low rates of sexual dysfunction and a decrease in prolactin levels over the course of treatment with cariprazine are harmonious findings, since antipsychotic-induced prolactin elevation may be related to distressing adverse effects including menstrual disturbances, changes in libido, and erectile dysfunction.[61] Our collective findings suggest that cariprazine is generally well tolerated, with low rates of many challenging AEs that may be associated with antipsychotic treatment.

A strength of these post hoc analyses is the characterization of the overall safety profile of cariprazine within the recommended 1.5–6 mg/d dose range for schizophrenia, which makes these findings clinically relevant in terms of acute and long-term management of patients with schizophrenia. To accommodate the heterogeneous dataset, caution was taken to ensure that safety events were accurately characterized to counterbalance the potential for confounding that could have arisen due to the inclusion of studies with different lengths and designs. Of note, 934 patients who were included in the overall long-term total were new to cariprazine (ie, not continuing from a lead-in study), with safety events counted from the first dose of cariprazine. The 188 patients who received cariprazine in both a short-term study and a subsequent long-term open-label study were only counted once in the total number of cariprazine-treated patients, while patients who were treated with placebo in a lead-in study and continued into a follow-up study where they then received open-label cariprazine were counted for AEs twice (once in each study). To further preserve accuracy and capture events in this disparate dataset, data from the relapse prevention study were handled differently depending on double-blind randomization, with patients who received cariprazine during both stabilization and double-blind treatment counted once, while patients who were stabilized on cariprazine and randomized to placebo were counted twice (once while on cariprazine in the open-label phase and once while on placebo in the double-blind phase).

These analyses are subject to several limitations including their post hoc nature and the inclusion of studies with different lengths and study designs. For example, although patients were counted to the dose level that they were randomized to in the fixed-dose studies, modal daily doses were considered in the flexible-dose studies, meaning that patients were counted to the dose level that they took for most of the time. Due to differences in study design and study length, meaningful comparisons between pooled cariprazine data and the active treatment arms could not be performed, though individual study results as well as prescribing information for these compounds suggest that the incidence of TEAEs with cariprazine was generally comparable with risperidone and aripiprazole. Safety outcomes were estimated using descriptive statistics; no inferential statistics were performed because of the numerous comparisons involved in these analyses. These analyses were based on data obtained from patients who participated in a clinical trial, where they were required to meet protocol-specified inclusion and exclusion criteria; as such, results may not be generalizable to all patients with schizophrenia. Although safety outcomes could not be delineated by duration in these analyses because data from the short- and long-term cariprazine studies were pooled, in previously published analyses of pooled data from the 4 short-term[40] and 2 long-term open-label cariprazine studies,[42] short-and long-term safety outcomes were similar and no new concerns were revealed with longer-term treatment.

Conclusion

In this pooled safety analysis using data from all the studies included in the clinical development program in schizophrenia, cariprazine was safe and generally well tolerated in patients with acute and long-term exposure in the recommended dose range. Akathisia was the most

common AE in cariprazine-treated patients. The majority of akathisia events were considered mild or moderate in severity and the majority of patients continued treatment despite symptoms; additionally, no relationship between TEAEs of akathisia or restlessness and suicidal tendency were found in the cariprazine schizophrenia program. Collectively, these findings suggest that akathisia in cariprazine-treated patients can be well managed with rescue medication and dose reduction. The metabolic profile of cariprazine was neutral in patients with short- and long-term exposure and weight gain was comparable to placebo. AEs of special interest, including sedation, prolactin elevation, sexual dysfunction, and cognitive dysfunction also occurred at rates that were similar to placebo, further substantiating good safety and tolerability for cariprazine. Results of these analyses suggest that cariprazine in the recommended dose range is a safe and well-tolerated treatment for patients with schizophrenia.

Abbreviations

AE, adverse event; BARS, Barnes Akathisia Rating Scale; C-SSRS, The Columbia-Suicide Severity Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; CGI-S, Clinical Global Impressions-Severity; CPK, creatine phosphokinase; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision; ECG, Electrocardiograms; EMA, European Medicines Agency; EPS, Extrapyramidal symptoms; FDA, Food and Drug Administration; HDL, High-density lipoprotein; LD, Low-density lipoprotein; PANSS, Positive and Negative Syndrome Scale; PANSS-FSNS, PANSS Factor Score for Negative Symptoms; SAS, Simpson-Angus Scale; SAE, Serious AE; TEAE, Treatment-emergent adverse event.

Data Sharing Statement

The datasets generated for this article are available on request to the corresponding author.

Ethics Approval and Consent to Participate

The constituent study protocols were approved by relevant ethics committees or an institutional review board (US sites). ICH-E6 Good Clinical Practice guidelines were followed and written informed consent was obtained from all participants.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

Ágota Barabássy, Barbara Sebe, Károly Acsai, István Laszlovszky, Balázs Szatmári and György Németh are employees of Gedeon Richter Plc. Barbara Sebe and Károly Acsai report personal fees from Gedeon Richter Plc., outside the submitted work. István Laszlovszky reports personal fees from Gedeon Richter Plc., during the conduct of the study; in addition, István Laszlovszky has a patent cariprazine issued. Balázs Szatmári reports personal fees from Gedeon Richter Plc., outside the submitted work; in addition, Balázs Szatmári has a patent cariprazine issued. Willie R. Earley reports being an employee of AbbVie, and share- or stock-holder of AbbVie, AstraZeneca and Eli Lilly; being a former employee of Allergan and Forest LP during the conduct of the study and outside the submitted work; and being previously employed with Forest LP, AstraZeneca, and Eli Lilly outside the submitted work. György Németh reports personal fees from Gedeon Richter Plc., outside the submitted work; in addition, Dr György Németh has a patent cariprazine issued. The authors report no other potential conflicts of interest for this work.

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