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Long-term safety and tolerability of cariprazine as adjunctive therapy in major depressive disorder

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Lack of treatment response is a critical problem in major depressive disorder (MDD). Cariprazine is a D_3-preferring dopamine D_3/D_2 receptor partial agonist and 5-HT_{1A} partial agonist. This phase 3, multicenter, open-label, long-term (26-week), flexible-dose (1.5–4.5 mg/day) study assessed the long-term safety and tolerability of cariprazine used adjunctively with antidepressant therapy in adult patients with MDD who had either completed a lead-in study ($n = 311$) or had been newly recruited ($n = 131$). A higher percentage of continuing patients (66.2%) than new patients (35.9%) completed the study. The most common reason for discontinuation was adverse events (AEs; 13.9%); 79% of patients experienced a treatment-emergent AE [most common: akathisia (15.9%,) headache (11.6%)]. Serious AEs occurred in 2% of patients; two deaths occurred (one traffic accident, one completed suicide, both considered unrelated to treatment). The mean changes in clinical laboratory, cardiovascular, and ophthalmologic parameters were generally not clinically relevant. The mean (SD) changes from the open-label baseline in Montgomery–Åsberg Depression Rating Scale total score and Clinical Global Impression-Severity score at week 26 were −7.3 (9.5) and −1.0 (1.2), respectively. By week 26, 53.3% of patients were in remission (Montgomery–Åsberg Depression Rating Scale total score ≤ 10). The results suggest that cariprazine was generally safe and well tolerated as adjunctive therapy to treat MDD. *Int Clin Psychopharmacol* 34:76–83 Copyright © 2018 The Author (s). Published by Wolters Kluwer Health, Inc.

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Introduction

Major depressive disorder (MDD) is estimated to affect ~15.4 million adults aged 18 years and older in the USA each year (Greenberg *et al.*, 2015), leading to significant economic and societal burden (Ferrari *et al.*, 2013). Although pharmacological treatment is a mainstay for MDD, many patients show an inadequate response to antidepressant therapy (ADT). Roughly one-third of patients show remission of depressive symptoms after the first treatment with ADT (Trivedi *et al.*, 2006), and patients who have successive treatment failures may be less likely to respond to subsequent treatment or more likely to relapse if they do respond (Rush *et al.*, 2006). Current treatments for patients who fail to respond to ADT include switching to a different ADT (within or between pharmacological classes), combination therapy, adjunctive use of mood stabilizers or atypical antipsychotics, and nonpharmacological treatments (American Psychiatric Association, 2010; Davidson, 2010). Although atypical antipsychotics have shown efficacy as adjunctive therapy in various studies, their use may be limited by safety concerns, including cardiovascular and metabolic side effects such as weight gain, hyperglycemia, and dyslipidemia (Chen *et al.*, 2011; de Sousa *et al.*, 2015).

Cariprazine is a dopamine D_3/D_2 receptor partial agonist that is approved for the treatment of adults with schizophrenia (USA and Europe) or manic or mixed episodes associated with bipolar I disorder (USA); cariprazine is currently under investigation for use as adjunctive treatment in MDD and monotherapy in bipolar depression. Cariprazine binds with higher affinity to D_3 receptors than D_2 receptors (Kiss *et al.*, 2010; Girgis *et al.*, 2016), and recent preclinical and clinical data suggest that enhanced D_3 activity may play a role in neuroadaptive changes related to antidepressant activity (Leggio *et al.*, 2013). Low affinity for serotonin 5-HT_{2C}, histamine H_1, and adrenergic receptors may also contribute to reduced potential for adverse effects associated typically with antipsychotic treatment (Kiss *et al.*, 2010). In addition, cariprazine acts as a partial agonist at 5-HT_{1A} receptors and as an antagonist at 5-HT_{2B} receptors (Kiss *et al.*, 2010). Antidepressant and anxiolytic effects may be mediated through affinity for these receptors, which may enhance the effects of selective serotonin reuptake inhibitors (Celada *et al.*, 2004). Previous long-term studies of cariprazine in adult patients with schizophrenia or bipolar disorder have shown few metabolic and cardiovascular side effects (Durgam *et al.*, 2016b; Cutler *et al.*, 2018; Durgam *et al.*, 2017; Ketter *et al.*, 2017; Nasrallah *et al.*, 2017), which may make

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cariprazine an attractive option for patients who fail to respond to ADT.

Cariprazine was safe and efficacious in an 8-week study in adults with depressive episodes associated with bipolar depression (Durgam *et al.*, 2016c) and in a previous 8-week study as an adjunctive treatment to ADT in adults with MDD (Durgam *et al.*, 2016a). In an additional 8-week study of cariprazine as an adjunctive treatment to ADT in MDD (NCT01715805) (Earley *et al.*, 2018), cariprazine did not differ from placebo on the primary efficacy measure, the Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). To further evaluate the safety of cariprazine plus adjunctive ADT in patients with MDD, a long-term, open-label study (NCT01838876) was also carried out. In this study, the negative 8-week study (NCT01715805) served as a lead-in for some patients, whereas other patients had been newly enrolled and had no previous cariprazine exposure.

Patients and methods

The primary objective of this open-label study was to assess the long-term safety and tolerability of cariprazine 1.5–4.5 mg/day as adjunctive therapy to ADT. The study protocol was approved by an institutional review board at each of 61 study centers; the study was carried out in accordance with the Declaration of Helsinki, ICH Guidance on General Considerations for Clinical Trials, and ICH Good Clinical Practices. All patients provided written, informed consent or other appropriate documentation according to local regulatory requirements.

Study design and participants

This phase 3, multicenter, flexible-dose, open-label study included a 2-week screening period, where patients continued their previously prescribed ADT, but did not receive cariprazine (i.e. cariprazine washout period for rollover patients), a 26-week open-label cariprazine plus ADT period, and a 2-week safety follow-up period. Patients entering from the 8-week lead-in study (NCT01715805; rollover patients) continued ADT at their lead-in study dose; new patients continued their protocol-allowed ADT [citalopram, escitalopram, fluoxetine, sertraline, paroxetine (CR), vilazodone, venlafaxine (XR/IR/ER), desvenlafaxine, duloxetine, or bupropion (XL)]. On day 1, cariprazine was initiated at 0.5 mg/day; the dosage was increased by 0.5 mg/day until the target dose of 3.0 mg/day was received on days 6 and 7. Dosages could be decreased to 1.5 mg/day for tolerability reasons at any time beginning at week 1 or increased to 4.5 mg/day for inadequate response between weeks 2 and 10.

The study included adult patients (18–65 years of age, inclusive) who fulfilled *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision (DSM-IV-TR) (American Psychiatric Association, 2000) criteria for MDD on the basis of the Structured Clinical Interview, with a current major depressive episode of at least 8 weeks' duration and inadequate response (< 50% improvement in the current episode as established by the Antidepressant Treatment Response Questionnaire) to ADT of adequate dose and duration. Rollover patients who responded (as determined by the clinical rating scale criteria) to placebo plus ADT during a single-blind, open-label phase in the lead-in study continued ADT plus single-blind placebo for the duration of the lead-in study. Rollover patients who did not respond during the single-blind open-label phase in the lead-in study completed the 8-week randomized, double-blind treatment phase (cariprazine or placebo plus continued ADT) before entering the screening period of the current study with continued ADT. New patients were included if they showed an ongoing inadequate response to one or two protocol-allowed ADT trials of adequate dose and duration. Patients were required to have normal findings on physical examination, clinical laboratory test results, and ECG results or abnormal findings that were judged not to be clinically significant by the investigator.

Patients were excluded if they had a DSM-IV-TR axis I diagnosis other than MDD within 6 months of the study or an axis II disorder of sufficient severity to interfere with participation. Lifetime history of certain psychiatric disorders (e.g. schizophrenia, psychotic disorders, bipolar I/II disorder, pervasive developmental disorder, cognitive disorders) was exclusionary, as was alcohol or substance abuse/dependence within 6 months of the study. Patients at significant risk of suicide [investigator judgment, suicide attempt within the last year, or MADRS Item 10 (suicidal thoughts) score ≥ 5 at visit 1 or 2] or injuring themselves or others (investigator judgment) were excluded. Psychotropic medications were not allowed, except for short-term use of zolpidem, zolpidem extended release, zaleplon, eszopiclone, zopiclone, and chloral hydrate for insomnia; benztropine, diphenhydramine, and propranolol for extrapyramidal symptoms (EPS) or akathisia; and lorazepam as a rescue medication.

Assessments

Safety assessments included adverse events [AEs, all visits (screening, weeks 0, 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26)], clinical laboratory parameters and ECGs (screening, weeks 1, 8, 16, 26), vital signs (all visits), and ophthalmologic examinations (screening, weeks 9 and 26). Suicidality as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner *et al.*, 2011) was assessed at all visits. EPS were assessed using the Barnes Akathisia Rating Scale (Barnes, 1989), the Simpson-Angus Scale (Simpson and Angus, 1970), and the Abnormal Involuntary Movement Scale (Guy, 1976) (screening, weeks 0, 4, 8, 12, 18, 26).

As the primary objective of this study was long-term safety and tolerability, efficacy assessments were collected, but not grouped into primary, secondary, or additional categories. Assessments included change from baseline in the MADRS total score and Clinical Global Impressions-Severity (CGI-S) score. MADRS response (≥50% reduction from baseline in MADRS total score) and remission (MADRS total score ≤ 10) rates were determined.

Statistical analysis

Baseline for safety parameters for rollover patients who completed the double-blind treatment was the lead-in double-blind baseline; for new patients and rollover patients who received continued open-label ADT, the safety baseline was last nonmissing safety assessment before the first dose of open-label cariprazine. Demographic and baseline characteristics and safety parameters were summarized using descriptive statistics for the safety population (all patients who received at least one dose of cariprazine). Demographic and other baseline characteristics were measured at lead-in study screening for rollover patients and at open-label screening for new patients.

The efficacy baseline was the lead-in baseline for rollover patients and the last available efficacy assessment before the first dose of open-label cariprazine for new patients. Efficacy parameters were summarized using descriptive statistics for the intent-to-treat population (patients from the safety population who had at least one efficacy assessment after visit 2); no inferential statistical analyses were carried out for efficacy parameters.

Results

Patient population

Of the 442 patients enrolled in the study, 345 fulfilled the inclusion criteria, received the open-label study drug, and were included in the safety population; 336 patients were included in the intent-to-treat population. A total of 311 patients had continued from the lead-in study and 131 were new patients (Fig. 1). Of those continuing from the lead-in study, 109 had received double-blind placebo plus ADT, 108 had received double-blind cariprazine plus ADT, and 94 had received single-blind placebo plus ADT. Approximately 61% of the patients completed the study; a higher percentage of new patients (64.1%) discontinued versus patients who completed the lead-in study (double-blind treatment, 33.3%; single-blind treatment, 34.9%). The most common reasons for discontinuation overall were AEs (13.9%), protocol violation (9.3%), and withdrawal of consent (7.5%). A higher percentage of new patients (20.3%) and patients who received placebo (13.8%) versus cariprazine (9.8%) during the lead-in study discontinued because of an AE. Akathisia (2.9%), restlessness (2.0%), anxiety (1.7%), and fatigue (1.2%) were the most common AEs leading to discontinuation.

Patient characteristics were generally similar between groups (Table 1); however, new patients had a longer duration of current depressive episode compared with patients continuing from the lead-in study. In addition, baseline MADRS scores were the lowest in patients who received placebo plus ADT in the lead-in study, which may be a result of this subgroup including patients who responded to placebo plus ADT before randomization in the lead-in study.

Extent of exposure

The mean (SD) duration of treatment was 134.7 (65.1) days for cariprazine and 135.8 (64.1) days for ADT. Approximately 50% of patients received the target cariprazine dose (3 mg/day) as their modal [i.e. most frequently taken dose; 52.8% (182/345)] and final [50.4% (174/345)] daily dose. The modal daily dose was 1.5 mg/day for 99 (28.7%) patients and 4.5 mg/day for 59 (17.1%) patients. Lorazepam was the most commonly used concomitant psychotropic medication (15.7% of patients overall).

Adverse events and extrapyramidal symptoms

Approximately three-quarters of patients [79.4% (274/345)] experienced a treatment-emergent adverse event (TEAE) (Table 2). Most TEAEs (97.1%) were considered mild or moderate; 64.1% of patients had TEAEs that were considered to be related to treatment. TEAEs occurring in at least 10% of patients overall were akathisia (15.9%) and headache (11.6%). Serious adverse events (SAEs) occurred in 2.0% of patients overall; no individual SAE occurred in more than one patient. During the open-label treatment, two (0.6%) deaths occurred [one road traffic accident (new patient); one completed suicide (lead-in cariprazine 1.5–4.5 mg/day)]. The patient who completed suicide had no reported depression-related TEAEs and no history of C-SSRS-documented suicidal ideation or behavior (lifetime history or during open-label treatment); no information on the reason was available. Neither death was considered by investigators to be related to treatment.

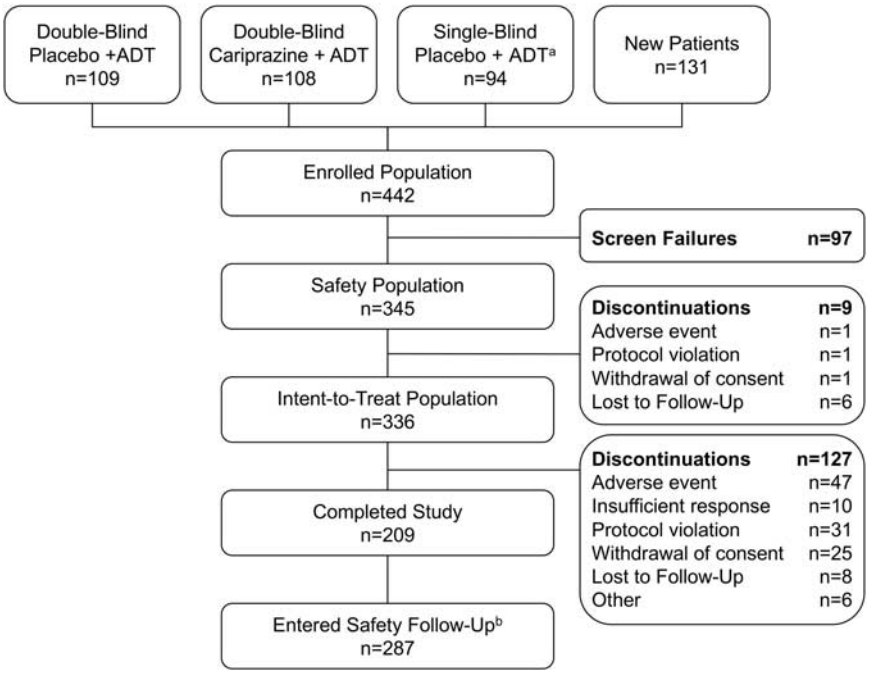
On the basis of EPS rating scales, treatment-emergent akathisia (Barnes Akathisia Rating Scale baseline ≤ 2 and postbaseline > 2) and parkinsonism (Simpson–Angus Scale baseline ≤ 3 and postbaseline > 3) occurred in 18.5 and 1.8%, respectively, of patients overall (Table 3). Although EPS-related TEAEs were reported in 98 (28.4%) patients, only 17 (4.9%) discontinued because of EPS-related AEs. The majority of EPS-related TEAEs were considered mild or moderate in severity [96.9% (95/98)]. Approximately 21% of patients used rescue medication, and anti-Parkinson medication was used by 4.9% of patients overall.

Suicidality

During the open-label treatment, three (0.9%) patients experienced a TEAE of suicidal ideation (two patients discontinued treatment; one event considered treatment-related). Two patients experienced suicidality-related SAEs [one patient (attempted suicide, discontinued) and one patient died (death because of completed suicide)]; neither event was considered to be treatment-related.

C-SSRS-assessed suicidal ideation was reported by 37/345 (10.7%) patients during open-label treatment and 13/287 (4.5%) patients during safety follow-up. The majority of reported suicidal ideations in the open-label [27/37 (73.0%)] and safety follow-up [10/13 (76.9%)] periods were in the least severe category (wish to be

Fig. 1



Patient disposition in the long-term safety and tolerability study of cariprazine as adjunctive therapy in major depressive disorder. [a]Patients who responded to treatment during the prospective ADT period of the lead-in study and therefore remained on placebo plus ADT during the double-blind treatment period of the lead-in study. [b]Includes patients who completed the study and patients who discontinued participation in the study prematurely. ADT, antidepressant therapy.

Table 1 Patient demographics and baseline characteristics (safety population)

Characteristics	Lead-in placebo + ADT ($n = 189$)	Lead-in cariprazine + ADT ($n = 92$)	New patients ($n = 64$)	Total ($N = 345$)
Demographics				
Age [mean (SD)] (years)	47.0 (10.3)	46.5 (10.7)	45.8 (11.1)	46.7 (10.5)
Male [*n* (%)]	50 (26.5)	28 (30.4)	18 (28.1)	96 (27.8)
Race [*n* (%)]				
Caucasian	151 (79.9)	74 (80.4)	55 (85.9)	280 (81.2)
Black or African American	31 (16.4)	17 (18.5)	6 (9.4)	54 (15.7)
All other races	7 (3.7)	1 (1.1)	3 (4.7)	11 (3.2)
Weight [mean (SD)] (kg)	83.2 (18.7)	84.7 (18.8)	84.0 (18.1)	83.8 (18.6)
BMI [mean (SD)] (kg/m^2)	29.7 (5.5)	30.0 (5.9)	29.8 (5.5)	29.8 (5.6)
Psychiatric history				
Major depression [*n* (%)]				
Recurrent	183 (96.8)	91 (98.9)	61 (95.3)	335 (97.1)
Single episode	6 (3.2)	1 (1.1)	3 (4.7)	10 (2.9)
Age at onset [mean (SD)] (years)	33.3 (12.5)	33.0 (12.2)	28.8 (11.9)	32.4 (12.4)
Duration of current episode [mean (SD)] (weeks)	27.2 (11.5)	29.5 (11.7)	46.8 (45.8)	31.4 (23.4)
Baseline efficacy values[a] (ITT population[b]) [mean (SD)]				
MADRS total score	18.9 (9.1)[c]	25.8 (5.2)	30.9 (5.4)	22.8 (9.0)
CGI-S score	3.4 (1.1)[c]	4.2 (0.6)	4.2 (0.5)	3.8 (1.0)

ADT, antidepressant therapy; CGI-S, Clinical Global Impression-Severity; MADRS, Montgomery–Åsberg Depression Rating Scale.
[a]For patients from the lead-in study who were randomized to and completed double-blind treatment, the lead-in study efficacy baseline was used as the baseline for this study.
[b]Intent-to-treat population ($N = 336$).
[c]Patients who responded to treatment during the prospective ADT period of the lead-in study and were maintained on single-blind placebo and patients who were inadequate responders who were randomized to placebo during the double-blind period.

dead). In addition to the patient who completed suicide, one patient who had received single-blind placebo in the lead-in study had suicidal behavior (actual attempt), which was considered moderate in intensity, not related to treatment, and resulted in study discontinuation. The patient had no C-SSRS lifetime history of suicidal ideation

Table 2 Summary of adverse events (safety population)

Adverse events	Lead-in placebo + ADT ($n = 189$) [n (%)]	Lead-in cariprazine + ADT ($n = 92$) [n (%)]	New patients ($n = 64$) [n (%)]	Total ($N = 345$) [n (%)]
Patients with any TEAE	149 (78.8)	75 (81.5)	50 (78.1)	274 (79.4)
Patients with SAEs	4 (2.1)	1 (1.1)	2 (3.1)	7 (2.0)
Patients with AEs leading to discontinuation	26 (13.8)	9 (9.8)	13 (20.3)	48 (13.9)
AEs leading to discontinuations in at least 2% of patients in any group				
Akathisia	8 (4.2)	1 (1.1)	1 (1.6)	10 (2.9)
Restlessness	4 (2.1)	3 (3.3)	0	7 (2.0)
Anxiety	2 (1.1)	2 (2.2)	2 (3.1)	6 (1.7)
Fatigue	1 (0.5)	1 (1.1)	2 (3.1)	4 (1.2)
Weight increased	0	0	2 (3.1)	2 (0.6)
Deaths	0	1 (1.1)	1 (1.6)	2 (0.6)
TEAEs in at least 5% of patients in any group, preferred term				
Akathisia	29 (15.3)	14 (15.2)	12 (18.8)	55 (15.9)
Headache	26 (13.8)	11 (12.0)	3 (4.7)	40 (11.6)
Anxiety	20 (10.6)	7 (7.6)	7 (10.9)	34 (9.9)
Insomnia	19 (10.1)	7 (7.6)	8 (12.5)	34 (9.9)
Restlessness	18 (9.5)	7 (7.6)	9 (14.1)	34 (9.9)
Weight increased	22 (11.6)	4 (4.3)	8 (12.5)	34 (9.9)
Fatigue	17 (9.0)	10 (10.9)	3 (4.7)	30 (8.7)
Nasopharyngitis	13 (6.9)	12 (13.0)	5 (7.8)	30 (8.7)
Nausea	14 (7.4)	5 (5.4)	2 (3.1)	21 (6.1)
Dizziness	12 (6.3)	6 (6.5)	2 (3.1)	20 (5.8)
Sedation	15 (7.9)	2 (2.2)	2 (3.1)	19 (5.5)
Upper respiratory tract infection	8 (4.2)	5 (5.4)	2 (3.1)	15 (4.3)

For patients who did not participate in the safety follow-up period, AEs that occurred within 30 days after the last dose of open-label treatment were included.
ADT, antidepressant therapy; AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Table 3 Summary of extrapyramidal symptoms (safety population)[a]

Extrapyramidal symptoms	Lead-in placebo + ADT ($n = 189$)	Lead-in cariprazine + ADT ($n = 92$)	New patients ($n = 64$)	Total ($N = 345$)
Patients with treatment-emergent EPS [$n/N1$ (%)][b]				
Akathisia (BARS baseline ≤ 2 and postbaseline > 2)	33/187 (17.6)	17/91 (18.7)	12/58 (20.7)	62/336 (18.5)
Parkinsonism (SAS baseline ≤ 3 and postbaseline > 3)	3/187 (1.6)	3/91 (3.3)	0 (0.0)	6/336 (1.8)
Patients with EPS-related TEAEs [n (%)]				
At least one EPS-related TEAE	55 (29.1)	22 (23.9)	21 (32.8)	98 (28.4)
EPS-related TEAE (excluding akathisia/restlessness)	16 (8.5)	4 (4.3)	3 (4.7)	23 (6.7)
Akathisia/restlessness	46 (24.3)	20 (21.7)	20 (31.3)	86 (24.9)
Patients with EPS-related AE resulting in discontinuation	12 (6.3)	4 (4.3)	1 (1.6)	17 (4.9)

ADT, antidepressant therapy; AE, adverse event; BARS, Barnes Akathisia Rating Scale; EPS, extrapyramidal symptoms; SAS, Simpson–Angus Scale; TEAE, treatment-emergent AE.
[a]For patients who did not participate in the safety follow-up period, AEs that occurred within 30 days after the last dose of open-label treatment were included in the summary.
[b]$N1$ is the number of patients who had a baseline and at least one postbaseline assessment; n is the subset of patients from $N1$ who fulfilled the criteria.

or behavior. The last dose of cariprazine was taken on day 132 and the suicidal behavior was recorded on day 134.

Clinical laboratory and safety parameters

The mean changes from baseline in clinical laboratory parameters were generally small and not clinically relevant (Table 4). Shifts from normal/borderline levels of total (< 240 mg/dl) or low-density lipoprotein (< 160 mg/dl) cholesterol at baseline to high levels (total: ≥ 240 mg/dl; low-density lipoprotein: ≥ 160 mg/dl) at the end of the open-label treatment occurred in 23/280 (8.2%) and 19/300 (6.3%) patients, respectively. Shifts from normal high-density lipoprotein cholesterol (≥ 40 mg/dl) to low levels (< 40 mg/dl) occurred in 19/313 (6.1%) patients. For fasting triglycerides, shifts from normal/borderline (< 200 mg/dl) to high levels (≥ 200 mg/dl) occurred in 30/283 (10.6%) patients. Among patients with normal fasting glucose (< 100 mg/dl) at baseline, 10/261 (3.8%) patients shifted to high levels (≥ 126 mg/dl). Less than one-third [98/341 (28.7%)] of patients developed an increase in fasting glucose of at least 10 mg/dl. Ophthalmologic testing showed no evidence for retinal toxicity or lenticular changes of clinical importance. Almost 20% of patients overall experienced a 7% increase or more from baseline in body weight during the open-label period; no remarkable pattern was observed when stratified by the baseline BMI category.

The mean changes from baseline in cardiovascular safety parameters were generally small and not clinically

Table 4 Change from baseline to the end of open-label treatment in clinical laboratory and cardiovascular parameters (safety population)

Parameters	Lead-in placebo + ADT ($n = 189$)	Lead-in cariprazine + ADT ($n = 92$)	New patients ($n = 64$)	Total ($N = 345$)
Metabolic parameters [mean change (SD)]				
Total cholesterol (mg/dl)	−2.7 (27.4)	−4.8 (37.9)	−7.4 (23.0)	−4.1 (29.9)
Total LDL (mg/dl)	−4.1 (25.0)	−3.1 (31.4)	−6.8 (20.4)	−4.3 (26.1)
Total HDL (mg/dl)	−1.5 (9.4)	−2.4 (11.5)	−3.8 (6.8)	−2.1 (9.6)
Fasting triglycerides (mg/dl)	13.8 (48.9)	0.2 (55.9)	20.0 (61.4)	11.2 (53.6)
Fasting glucose (mg/dl)	4.9 (20.5)	4.3 (20.3)	3.4 (17.4)	4.4 (19.8)
Prolactin (ng/ml)	2.5 (8.7)	1.0 (5.7)	3.7 (5.4)	2.3 (7.5)
Body weight (kg)	1.6 (4.0)	1.7 (4.5)	1.3 (3.7)	1.6 (4.1)
Waist circumference (cm)	0.6 (6.4)	1.3 (5.7)	1.0 (4.4)	0.8 (5.9)
Change (≥7%) in body weight [*n* (%)]				
≥ 7% increase from baseline	37 (19.6)	20 (21.7)	10 (15.6)	67 (19.4)
≥ 7% increase by baseline BMI categories (kg/m^2) [*n*/*N*1 (%)][a]				
< 18.5	0/0	0/1	0/1	0/2
≥ 18.5 and <25	14/46 (30.4)	6/27 (22.2)	2/13 (15.4)	22/86 (25.6)
≥ 25 and <30	9/52 (17.3)	9/23 (39.1)	1/18 (5.6)	19/93 (20.4)
≥ 30	14/91 (15.4)	5/41 (12.2)	7/32 (21.9)	26/164 (15.9)
≥ 7% decrease from baseline	10 (5.3)	6 (6.5)	2 (3.1)	18 (5.2)
Clinical laboratory parameters [mean change (SD)]				
CPK (U/l)	177.1 (2566.5)	−4.1 (149.8)	−65.8 (565.1)	83.4 (1914.9)
ALT (U/l)	1.1 (18.3)	1.5 (16.4)	24.3 (198.0)	5.5 (86.8)
AST (U/l)	2.1 (39.1)	−1.1 (9.9)	6.2 (67.3)	2.0 (41.2)
Total bilirubin (mg/dl)	0.0 (0.2)	0.0 (0.2)	0.0 (0.3)	0.0 (0.2)
Alkaline phosphatase (U/l)	0.6 (10.1)	1.1 (10.9)	0.6 (12.4)	0.7 (10.7)
Blood pressure and pulse [mean change (SD)]				
Systolic blood pressure (mmHg)	0.3 (10.6)	−1.5 (12.9)	−2.2 (12.1)	−0.7 (11.5)
Diastolic blood pressure (mmHg)	0.4 (7.5)	−0.4 (7.6)	0.1 (6.8)	0.1 (7.4)
Pulse (beats/min)	1.1 (10.5)	0.9 (10.5)	0.6 (11.8)	1.0 (10.7)
Orthostatic hypotension [*n* (%)][b]	38 (20.1)	21 (22.8)	16 (25.0)	75 (21.7)
ECG [mean change (SD)]				
Ventricular heart rate (beats/min)	2.4 (9.7)	2.3 (10.1)	6.0 (10.3)	3.0 (10.0)
PR interval (ms)	−1.0 (12.3)	−0.3 (12.0)	0.5 (12.5)	−0.5 (12.3)
QRS interval (ms)	−0.5 (8.0)	−0.7 (7.8)	−0.8 (7.1)	−0.6 (7.8)
QT interval (ms)	−7.9 (25.3)	−5.3 (25.5)	−13.4 (22.9)	−8.2 (25.0)
QTcB interval (ms)	−1.4 (19.4)	1.6 (18.0)	4.0 (19.1)	0.4 (19.0)
QTcF interval (ms)	−3.7 (17.2)	−0.8 (15.5)	−2.0 (14.6)	−2.6 (16.3)

ADT, antidepressant therapy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a]*N*1 is the number of patients with baseline BMI in the given category and ≥ 1 postbaseline weight measurement during open-label treatment; *n* is the subset of patients in *N*1 who fulfilled the criteria at least once during the open-label treatment period.

[b]Orthostatic hypotension was defined as a reduction of ≥ 20 mmHg in systolic blood pressure or a reduction of ≥ 10 mmHg in diastolic blood pressure while changing from the supine to the standing position.

relevant (Table 4). No patient had a QTcB or a QTcF interval more than 500 ms during open-label treatment. Two patients each had a QTcB and QTcF interval increase more than 60 ms during the open-label treatment.

Efficacy assessments

Using an observed cases (OC) method ($n = 210$), the mean (SD) changes from open-label baseline to week 26 in the MADRS total score and the CGI-S score were −7.3 (9.5) and −1.0 (1.2), respectively; using a last observation carried forward (LOCF) method ($n = 336$), the mean (SD) changes were −5.5 (10.3) and −0.7 (1.3), respectively. At week 26, the rate of remission was 53.3% (112/210) on the basis of an OC approach and 45.8% (154/336) on the basis of an LOCF approach. At week 26 using an OC approach, 43.3% (91/210) of patients were considered MADRS responders; using an LOCF approach, 37.2% (125/336) of patients were considered MADRS responders.

Discussion

In this phase 3, multicenter, open-label, long-term, flexible-dose safety study in adult patients with a primary diagnosis of MDD, cariprazine 1.5–4.5 mg/day was generally safe and well tolerated when used as long-term adjunctive therapy in the treatment of MDD. Just under two-third of patients completed the study, with 13.9% discontinuing because of AEs. In general, the mean changes in laboratory values, vital signs measurements, and ECG parameters were small and not clinically relevant.

Although the percentage of patients discontinuing because of AEs was comparable to the long-term studies of cariprazine monotherapy to treat schizophrenia (3–13%), the overall percentage of patients who completed this study (61%) was higher than what has been observed previously with long-term cariprazine monotherapy (35–50%) (Durgam *et al.*, 2016b; Cutler *et al.*, 2018; Durgam *et al.*, 2017). Further, the completion rate was only slightly lower than a previous 8-week study of adjunctive cariprazine for MDD (Durgam *et al.*, 2016a), which may be expected, given the increased length of the present study. Discontinuations because of AEs were lower in patients who had previously received cariprazine compared with new patients and patients who had received placebo during the lead-in study. As those who

had received cariprazine for the longest duration discontinued at a lower rate, this may suggest that some patients are able to acclimate to AEs that they initially consider troublesome or that some AEs may reduce over time.

The most common AE in all subgroups was akathisia, which is consistent with previous long-term cariprazine studies in patients with schizophrenia (Durgam *et al.*, 2016b; Cutler *et al.*, 2018; Durgam *et al.*, 2017) as well as a previous short-term study of cariprazine as adjunctive therapy to ADT in MDD (Durgam *et al.*, 2016a). The incidence of SAEs was low, with only 2.0% patients experiencing at least one SAE. Two patients died during the study; both deaths were determined by the investigator to be unrelated to treatment. In addition, EPS are commonly experienced with atypical antipsychotics. Although just over one-quarter of patients experienced at least one EPS-related TEAE (including akathisia/restlessness) in this study, relatively few patients discontinued as a result, suggesting that EPS were manageable for many patients. Rollover patients who had received cariprazine experienced fewer EPS-related TEAEs, suggesting that events may occur early in treatment and decrease over time. This finding is in line with previous results for cariprazine monotherapy in schizophrenia (Earley *et al.*, 2017b) and bipolar mania (Earley *et al.*, 2017a), which showed that akathisia typically occurred within the first few weeks of treatment and resolved quickly (within ~2 weeks).

Patients with MDD commonly show suicidal ideations and behavior (Isometsa, 2014). Studies have found that the absolute lifetime risk of suicide in patients with MDD is between 4 and 7%, and illness-related factors, such as severe or recurrent depression or failure to achieve remission, further exacerbate risk (Isometsa, 2014). History of suicide attempt is 30–40% of all patients with MDD, and having a current depressive episode represents a high-risk state for suicidal ideation and behavior (Isometsa, 2014). As this study required patients to have a current episode of at least 8 weeks, these patients already represent a higher-risk category for suicidal behavior even though risk of suicide was an exclusion criterion. Adjunctive treatment with cariprazine did not appear to increase the risk of suicidal behavior or ideation, nor were any clear trends in suicidality noted among patients who had or had not previously been exposed to cariprazine. In addition to one patient who completed suicide, which was considered unrelated to treatment, there was only one report of suicidal behavior and the incidence of suicidal ideation was 11%.

Metabolic side effects may limit the use of atypical antipsychotics in the treatment of MDD. It is noteworthy that weight gain is common with some atypical antipsychotics used as monotherapy (e.g. quetiapine) or adjunctive therapy (e.g. olanzapine/fluoxetine combination) for MDD (Chen *et al.*, 2011). The mean weight gain with cariprazine in this trial (+1.6 kg) was similar to previously reported trials with risperidone and aripiprazole (+2.0 kg, each) (Chen *et al.*, 2011), suggesting weight gain that was comparable to atypical antipsychotics that are on the lower end of the weight gain spectrum. The mean weight gain in this study was higher than that in short-term bipolar mania and schizophrenia studies using monotherapy cariprazine (Earley *et al.*, 2017a, 2017b); however, polypharmacy with adjunctive cariprazine may act to compound the weight gain typically observed with ADTs (Fava, 2000). Weight increase of at least 7% were observed in just under 20% of patients, which was less than that in previous long-term studies with cariprazine monotherapy (range: 26–33%) (Durgam *et al.*, 2016b, 2017; Cutler *et al.*, 2018; Nasrallah *et al.*, 2017). In this study, changes in cardiovascular and hematology parameters were generally small, and none were considered clinically relevant. Further, no clear trends were noted among patients who had previously received cariprazine and patients who were new to cariprazine treatment.

In terms of efficacy assessments, the open-label trial design is a limitation, but may provide some descriptive measures of drug effectiveness (Vieta *et al.*, 2017). MADRS and CGI-S scores decreased during open-label treatment, suggesting that long-term treatment was not associated with worsening of MADRS scores. Furthermore, using an OC approach, almost half of the patients responded to treatment and over half of the patients achieved remission. This is an interesting finding as inclusion criteria required patients to have inadequate response to previous treatments. However, it is not possible to draw efficacy conclusions as this was an open-label study and it was not designed to assess efficacy.

The limitations of the study include the open-label study design, and the absence of a placebo-comparator or an active-comparator group. Although the flexible-dose regimen more closely mimics real-world clinical practice, it limits the ability to draw conclusions on dose–response relationships for safety parameters. The inclusion of both rollover and new patients further limits interpretation of the data and may have biased safety outcomes. Namely, the subset of patients with previous exposure to cariprazine might be considered an enriched sample with a higher probability to remain well in comparison with newly enrolled patients. Further, new patients had higher baseline symptom severity than rollover patients, which allowed for greater decreases in rating scale scores during open-label treatment for these patients than for patients who had been treated with cariprazine in the lead-in study. In addition, since cariprazine was being used as adjunctive therapy, it is difficult to make direct safety comparisons between this trial and previously published trials with cariprazine monotherapy. Although the wide range of allowed ADTs presents a realistic scenario of real-world clinical practice, it is likely that some AEs, such as weight gain, or other safety parameters might have been related to a specific ADT and not cariprazine; without a placebo group, it is not possible to fully assess this likelihood.

Conclusion

In patients with MDD, cariprazine was generally safe and well tolerated when used as adjunctive treatment to ADT. The safety profile was generally consistent with that observed in patients with MDD after short-term use in the previous adjunctive cariprazine study and was consistent with the known pharmacological properties of cariprazine. No unexpected AEs emerged that appear to be related to long-term exposure or combined treatment with ADT, and no clinically relevant changes in the majority of safety parameters were observed.

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Conflicts of interest

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