Efficacy of adjunctive low-dose cariprazine in major depressive disorder: a randomized, double-blind, placebo-controlled trial

Maurizio Fava\textsuperscript{a}, Suresh Durgam\textsuperscript{b}, Willie Earley\textsuperscript{b}, Kaifeng Lu\textsuperscript{c}, Robert Hayes\textsuperscript{b}, István Laszlovszky\textsuperscript{d} and György Németh\textsuperscript{d}

This 19-week, double-blind, placebo-controlled, randomized phase 2 study evaluated the efficacy, safety, and tolerability of adjunctive cariprazine (0.1–0.3 and 1.0–2.0 mg/day) as an antidepressant treatment for adults with treatment-resistant major depressive disorder (MDD) (NCT00854100). The primary endpoint was change in the Montgomery–Åsberg Depression Rating Scale (MADRS) total score and the secondary was change in the Clinical Global Impression-Intensity score. Additional efficacy parameters were also assessed. A total of 231 patients were randomized. None of the predefined parameters reached significance for either cariprazine doses, but higher doses yielded numerically greater mean changes in MADRS and Clinical Global Impression-Intensity scores, and MADRS response and remission rates, compared with placebo. No differences were seen on any measures between cariprazine 0.1–0.3 mg/day and placebo. Cariprazine was relatively well tolerated, and common treatment-emergent adverse events (incidence ≥5% and twice the placebo group rate) in both dosage groups included headache, arthralgia, restlessness, fatigue, increased appetite, insomnia, dry mouth, and constipation. In conclusion, both cariprazine doses were relatively well tolerated; although differences were not statistically significant, patients treated with cariprazine 1.0–2.0 mg/day had greater mean decreases in measures of depression symptoms compared with placebo, which is consistent with another adjunctive cariprazine MDD study, and thus warrants further investigation. \textit{Int Clin Psychopharmacol} 33:312–321

Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.

\textit{International Clinical Psychopharmacology} 2018, 33:312–321

Keywords: adjunctive, antidepressant, antipsychotic, cariprazine, depression, major depressive disorder

\textsuperscript{a}Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts, \textsuperscript{b}Departments of Clinical Development, \textsuperscript{c}Biostatistics, Allergan Ptc, Giralda Farms, Madison, New Jersey, USA and \textsuperscript{d}Medical Division, Gedeon Richter Ptc, Budapest, Hungary

Correspondence to Maurizio Fava, MD, Department of Psychiatry, Massachusetts General Hospital, 55 Fruit Street, Bulfinch 351, Boston, MA 02114, USA
Tel: +1 617 724 0838; fax: +1 617 726 2688; e-mail: mfava@mgh.harvard.edu

Received 24 December 2017 Accepted 7 June 2018

Introduction

Major depressive disorder (MDD) is a chronic disease with a lifetime prevalence of 16.2% for adults in the USA (Kessler \textit{et al.}, 2003). MDD is associated with significant morbidity (Baldessarini \textit{et al.}, 2017), can lead to substantial disability, and has larger effects on disability and days out of role than most other medical conditions (Merikangas \textit{et al.}, 2007). Despite the availability of a wide range of antidepressant treatment (ADT) options with diverse molecular targets, insufficient treatment response remains a significant problem in MDD, and patients frequently experience inadequate response to one or more ADTs of adequate dose and duration (Fava, 2003). Half of all patients with MDD fail to achieve adequate response (i.e. ≥50% reduction in Quick Inventory of Depressive Symptomatology-Self-Report score) (Rush \textit{et al.}, 2003) to their initial ADT (Nemeroff, 2007). The STAR*D study found that only 37% of patients achieved remission [score of ≤7 on the 17-item Hamilton Depression Rating Scale (HAMD17)] (Hamilton, 1960) during initial treatment with citalopram, a selective serotonin reuptake inhibitor (SSRI), and patients who did not achieve remission began a second treatment step (switching to another ADT, augmentation of citalopram with an additional ADT or cognitive therapy, or cognitive therapy alone), and 31% of them achieved remission (Rush \textit{et al.}, 2006; Warden \textit{et al.}, 2007). In addition, patients with MDD are less likely to respond, and they more likely to suffer a relapse, as treatment steps are added (Warden \textit{et al.}, 2007).

Currently, treatment-resistant MDD is addressed by switching to another ADT medication from the same or different class (e.g. from an SSRI to a serotonin...
norepinephrine reuptake inhibitor) (Fava, 2000), combination strategy, which combines ADTs from different classes (Lam et al., 2002), and adjunctive treatment to augment ADT efficacy with another class of medication, for example, a mood stabilizer or atypical antipsychotic (Nelson and Papakostas, 2009; Wright et al., 2013). Some atypical antipsychotics can treat MDD effectively (Nelson and Papakostas, 2009; Wright et al., 2013), but only brexipiprazole (Otsuka America Pharmaceutical Inc., 2015), aripiprazole (Otsuka America Pharmaceutical Inc., 2014), and quetiapine extended release (AstraZeneca Pharmaceuticals LP, 2013) are the Food and Drug Administration (FDA)-approved for adjunctive treatment with ADTs.

Cariprazine is an orally active atypical antipsychotic that was approved by the FDA in 2015 for the treatment of acute exacerbation of schizophrenia and manic or mixed episodes in bipolar I disorder I in adults (Allergan, 2016). Cariprazine is a potent dopamine D3-preferring D3/D2 receptor partial agonist that exhibits high affinity and occupancy of both D3 and D2 receptors (Kiss et al., 2012; Silfstein et al., 2013). These characteristics make cariprazine a promising candidate for MDD treatment, because D3 receptors are highly expressed in brain regions involved in motivation and reward-related behavior (Carnicella et al., 2014), leading investigators to hypothesize that cariprazine may have positive effects on cognition (Marder et al., 2016) and mood (Gross and Drescher, 2012; Nakajima et al., 2013). Cariprazine is also a partial agonist of 5-HT1A receptors, which may enhance SSRIs effects (Hayes et al., 2011). In preclinical trials, cariprazine has exhibited antidepressant-like effects in various animal models of behavior (Duman et al., 2012), and, in mice, these effects were found to be at least partially mediated by the D3 receptor (Papp et al., 2014).

Cariprazine 2.0–4.5 mg/day demonstrated efficacy and was relatively well tolerated as an adjunctive treatment to ADT in adult patients with treatment-resistant MDD in a previously published phase 2 study (Durgam et al., 2016a). In addition, treatment with cariprazine 1.5 mg/day monotherapy in adults with bipolar depression significantly improved symptoms and was relatively well tolerated (Durgam et al., 2016b). The present phase 2 study evaluated the efficacy, safety, and tolerability of two dosage ranges (0.1–0.3 and 1.0–2.0 mg/day) of adjunctive cariprazine with ADT.

**Patients and methods**

**Study design**

This was a 19-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of adjunctive cariprazine 0.1–0.3 and 1.0–2.0 mg/day in outpatients with MDD who had failed to respond to one or two previous ADTs given at adequate dose and titration (protocol MD-71; NCT00854100). The study was conducted from 2009 to 2010; patients were enrolled at 41 sites in the USA, and the protocol was approved by the Institutional Review Boards at each study center. ICH-E6 Good Clinical Practice guidelines were followed, and all participants provided written informed consent before study initiation.

The study period comprised a 1-week no-drug screening period followed by an 8-week prospective open-label ADT treatment phase (ADTs included citalopram, duloxetine, escitalopram, sertraline, or venlafaxine ER), an 8-week open-label ADT plus randomized double-blind adjunctive treatment (1 : 1 : 1 placebo, cariprazine 0.1–0.3 or 1–2 mg/day) phase, and a 2-week safety follow-up period. Adjustments to ADT dosage were permitted through week 4 of the open-label period, and ADT nonresponders at week 8 were randomized (Supplementary Fig., Supplemental digital content 1, http://links.lww.com/ICP/A45). ADT responders [i.e. those who achieved ≥50% improvement in HAMD17 total score, HAMD17 total score ≤14, or Clinical Global Impressions-Improvement (CGI-I) score <3] (Guy, 1976) continued their respective open-label ADT and single-blind placebo adjunct treatment for 8 weeks.

Treatment allocation randomization codes were generated by Statistical Programming. Each drug package label had a randomization number, and each study center was provided drug supplies corresponding to a sequence of patient randomization numbers for the double-blind phase. ADT nonresponders were assigned drug supplies corresponding to the randomization sequence, as they entered the double-blind phase. Investigational product was provided as 2-week blister packs at each visit; placebo and active cariprazine capsules were identical in appearance, taste, and packaging. All patients, investigators, and study staff remained blinded to double-blind treatment allocation (while only patients were blinded during the single-blind period) for the full duration of the study, until database lock.

In the first week of the double-blind period, the cariprazine 1.0–2.0 mg/day group received 0.5 mg/day cariprazine, and was titrated to 1.0 mg/day in the second week. The cariprazine 0.1–0.3 mg/day group were treated with 0.1 mg/day cariprazine from randomization to week 12. After 4 weeks of treatment, doses could be increased to 0.3 or 2.0 mg/day for patients in the 0.1–0.3 and 1.0–2.0 mg/day groups, respectively, if inadequate response [<40% Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) improvement and MADRS score >10] and no significant tolerability problems occurred. If tolerability issues developed after a dose increase, reduction to starting dose was allowed between weeks 12 and 14. No dose adjustments were allowed during the first 4 or final 2 weeks of double-blind treatment. Randomized patients’ ADT dose was the same as that of the open-label period.

To select the maximum dose of cariprazine for this first study on adjunctive cariprazine for MDD, phase 1 results
available before study initiation, which indicated a maximum tolerated dose of 1.0 mg/day in healthy individuals and 12.5 mg/day in patients with schizophrenia, were considered. Cariprazine 2.0 mg/day was hypothesized as the highest tolerated dose for patients with MDD, a previously untested population, and chosen for this study. The cariprazine 0.1–0.3 mg/day was selected on the basis of efficacy at low doses in preclinical studies (Papp et al., 2014) and tolerability concerns for outpatient participants.

**Patients**

Male or female outpatients (18–65 years) who met the Diagnostic and Statistical Manual of Mental Disorders, fourth ed., Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000) criteria for moderate to severe MDD without psychiatric features, on the basis of the Mini-International Neuropsychiatric Interview were eligible for inclusion (Sheehan et al., 1997). Patients had a current major depressive episode of at least 8 weeks in which they failed to respond to one or two adequate trials of ADT (<50% reduction in depressive symptoms using the Antidepressant Treatment Response Questionnaire) (Fava, 2003). At screening and baseline, patients had a 17-item HAMD17 score of at least 18 and 24-item HAMD (HAMD24) score of at least 2 on item 1.

Exclusion criteria included the following: a principal axis I disorder or any axis I disorder other than MDD that was the primary focus of treatment within 6 months; history of depressive episodes with psychotic features; meeting the DSM-IV-TR criteria for any manic or hypomanic episode, obsessive compulsive, psychotic, borderline, or antisocial disorders; anorexia nervosa or bulimia; and dementia or other cognitive disorder. Patients with alcohol or substance abuse or dependence in the past 6 months, risk of injuring others or self, or suicide risk [attempt within the past year, investigator’s judgement, Columbia-Suicide Severity Rating Scale (Posner et al., 2011) survey, or MADRS item 10 score ≥5] were also excluded. Patients had a BMI (kg/m²) of at least 18 to 40 or less, normal physical, laboratory, and ECG results, and no concurrent medical condition that would have interfered with the study. Patients were not permitted to have taken any antipsychotic, anticonvulsant, mood stabilizer, anxiolytic, sedative/hypnotic medication, or ADT for longer than 1 week or 5 half-lives of the medication before baseline. Electroconvulsive therapy, adjunctive antipsychotic treatment, vagus nerve or transcranial magnetic stimulation, or any experimental CNS treatment within the previous 6 months or in the current episode, or previous inadequate response to electroconvulsive therapy, monoamine oxidase inhibitor, or adjunctive antipsychotic treatment, or any depot antipsychotic use was prohibited.

**Outcome measures**

Primary and secondary efficacy parameters were MADRS total and CGI-I score changes from baseline (week 8) to end of the double-blind treatment (week 16) compared with placebo, respectively. Additional parameters included changes in CGI-Severity (CGI-S) (Guy, 1976), HAMD17 and HAMD24 total and subsection scores, and, at week 16, MADRS response (≥50% improvement from baseline) and remission rates (total score ≤10), HAMD17 remission rates (total score ≤7), and CGI-I response rates (score ≤2) versus placebo. The HAMD24, MADRS, and CGI-S assessments were conducted at each visit (weeks 1, 2, 4, 6, and 8 of the double-blind phase), except screening, from baseline to end of double-blind treatment, while HAMD24 was obtained at screening and each visit of the double-blind phase.

Safety assessments that occurred at every visit included adverse event (AE) reporting, and monitoring of vital signs and suicide risk. Laboratory tests, ECGs, and evaluations of extrapyramidal symptoms, using the Abnormal Involuntary Movement, Barnes Akathisia Rating (Barnes, 1989), and Simpson-Angus Scales (Simpson and Angus, 1970) were also recorded at least once during the double-blind period.

**Statistical analyses**

The double-blind safety population consisted of randomized patients who received at least one dose of double-blind study medication. The intent-to-treat population included all patients in the double-blind safety population with a baseline and at least one additional MADRS assessment during double-blind treatment. Analyses of MADRS, CGI-I, CGI-S, HAMD17, and HAMD24 score changes were analyzed using a mixed-effects model for repeated measures, with treatment group, study center, visit, and treatment group-by-visit interaction as fixed effects, and baseline values and baseline-by-visit interactions as covariates. An unstructured covariance matrix was used to model the covariance of within-patient scores. The analysis was performed on the basis of all postbaseline scores using only the observed cases without imputation of missing values.

For the study to be considered positive, at least one cariprazine dosage group had to show a statistically significant decrease in mean MADRS total score from baseline compared with placebo after multiplicity adjustment. A closed testing procedure was used for multiplicity adjustment across the two dose ranges and primary and secondary efficacy endpoints. The primary comparison between placebo and the average of the two dosage groups (0.0–0.3 or 1.0–2.0 mg/day) in MADRS total score was tested at the two-sided 5% significance level, and, if the primary comparison was positive, the pair-wise comparison between placebo and each of the two cariprazine flexible dosage groups was tested at the two-sided 5% significance level. Statistical hypothesis tests for all efficacy measures were two-sided at a 5% level of significance for main effects. Two-sided 95%
confidence intervals were also estimated for all applicable measures.

Analyses of response and remission rates were performed using a logistic regression model, with treatment group and the corresponding baseline values as the explanatory variables.

All safety parameters were summarized with descriptive statistics.

To determine sample size, it was estimated that 75 patients per treatment would provide ~85% power to detect a treatment effect difference of 3.8 points in MADRS score change between placebo and the mean of the two cariprazine dose groups at the two-sided significance level of 5%. This assumed a common SD of 8 for the primary efficacy parameters, a correlation coefficient of 0.5 for within-patient assessments, and a 30% patient drop-out rate.

Study raters performing MADRS assessments received training and certification in the rating scales used in this study by Concordant Rater Systems. To monitor and manage study raters, each patient completed a computerized MADRS assessment, and the data were compared against data from the study center rater assessment.

**Results**

**Patient characteristics and disposition**

Of 502 patients enrolled in the open-label period, 403 completed treatment (Fig. 1), and 172 (42.7%) were classified as responders. Of the 231 nonresponders who began double-blind treatment, 81, 76, and 74 were randomized to placebo, cariprazine 0.1–0.3 mg/day, and 1.0–2.0 mg/day, respectively. Of 230 safety and intent-to-treat patients, 205 (89.1%) completed treatment. Most premature discontinuations were due to protocol violations [nine (3.9%)], and causes of discontinuation were generally comparable among groups.

ADT responders (n = 172) continued ADT and adjunctive placebo, and two discontinued (one withdrew consent and one was lost to follow-up) before week 6 and were not included in this safety population. Data for responders were collected, but are not reported here.

Baseline demographics and disease history were generally similar among groups (Table 1).

**Efficacy**

MADRS changes (primary endpoint) were not statistically significant in either cariprazine group, but cariprazine 1.0–2.0 mg/day showed a nonsignificant greater reduction in depressive symptoms (MADRS least squares mean difference, −1.8; \( P = 0.227 \)) compared with placebo. No improvement was observed with cariprazine 0.1–0.3 mg/day treatment (Fig. 2a).

Although not statistically significant, cariprazine 1.0–2.0 mg/day exhibited a nonsignificant greater improvement in CGI-I scores relative to placebo (Table 2). No significant differences were observed in either group versus placebo in any additional efficacy parameters. MADRS response and remission rate differences were not statistically significant, but were nonsignificantly greater in both cariprazine dose groups relative to placebo (Fig. 2b). CGI-I response rates did not reach statistical significance, but were nonsignificantly greater with cariprazine 1.0–2.0 mg/day (Table 2).

**Safety**

**Exposure**

In the safety population, mean treatment duration days, were as follows: placebo, 53.8; cariprazine 0.1–0.3 mg/day, 53.4; and cariprazine 1.0–2.0 mg/day, 51.2. The mean daily cariprazine dose was 0.2 and 1.1 mg/day for cariprazine 0.1–0.3 and 1.0–2.0 mg/day treatment groups, respectively.

**Adverse events**

In the open-label period, 379 (75.5%) patients reported any treatment-emergent adverse event (TEAE). A summary of commonly occurring TEAEs during this phase is presented in Supplementary Table (Supplemental digital content 2, http://links.lww.com/ICP/A46). Nine patients reported serious AEs, five patients reported AEs that led to treatment discontinuation, and one death occurred (completed suicide by intentional overdose with zolpidem tartrate; patient had received duloxetine for 42 days and was not randomized).

Serious AEs reported during double-blind treatment included unstable angina (placebo) and chronic obstructive pulmonary disease (1.0–2.0 mg/day group). Commonly occurring TEAEs (occurring in ≥5% of patients and with an incidence of at least twice the placebo rate) were headache and arthralgia with cariprazine 0.1–0.3 mg/day, and headache, restlessness, fatigue, increased appetite, insomnia, dry mouth, and constipation with cariprazine 1.0–2.0 mg/day (Table 3). Most TEAEs were mild to moderately severe (placebo, 95.1%; 0.1–0.3 mg/day, 94.7%, and 1.0–2.0 mg/day, 93.2%). Discontinuations due to AEs occurred in two (2.5%), one (1.3%), and one (2.7%) patients, respectively, in placebo, cariprazine 0.1–0.3, and 1.0–2.0 mg/day. No deaths occurred during the double-blind phase.

No newly emergent AEs were reported in more than 4% of patients in any group in the safety follow-up period.

**Extrapyramidal symptoms-related events**

Akathisia occurred more frequently with cariprazine 1.0–2.0 mg/day compared with placebo, but less frequently with cariprazine 0.1–0.3 mg/day (Table 3). Treatment-emergent parkinsonism (Simpson-Angus Scales score > 3) occurred in 2 patients in each treatment group. The incidence of treatment-emergent akathisia (Barnes Akathisia Rating score > 2), was highest with cariprazine 1.0–2.0 mg/day, followed by placebo and then cariprazine 0.1–0.3 mg/day (Table 3).
Laboratory parameters, vital signs, and ECG
Minimal mean changes from baseline were observed and generally comparable across treatment groups for vital signs, waist circumference, and BMI (Table 4). Fewer patients treated with cariprazine 1.0–2.0 mg/day had orthostatic hypotension (9.4%) relative to placebo (20%) or cariprazine 0.1–0.3 mg/day (15.1%). A greater number of patients had at least 7% increase in body weight with cariprazine 1.0–2.0 mg/day (15.1%) than in placebo (3.7%) or cariprazine 0.1–0.3 mg/day (1.3%).

Mean changes in laboratory parameters were generally comparable across treatments, except for insulin and prolactin levels, both of which had a greater mean increase with cariprazine 1.0–2.0 mg/day than with placebo (Table 4).

Suicidality
No suicidal behavior was reported during double-blind treatment, and the incidence of measured suicidal ideation was higher in patients treated with placebo than either cariprazine dose as measured with the Columbia-Suicide Severity Rating Scale (19.8%, placebo; 11.8%, cariprazine 0.1–0.3 mg/day; and 12.3%, cariprazine 1.0–2.0 mg/day).

Discussion
In this phase 2 study, cariprazine 0.1–0.3 and 1.0–2.0 mg/day did not show statistically significant superiority to placebo in any efficacy measures. Therefore, this was a negative study, but cariprazine 1.0–2.0 mg/day did show a nonsignificant greater reduction (i.e. improvement) in depressive symptoms compared with placebo. Both dosage ranges of cariprazine were well tolerated as an adjunctive to ADT in adult patients with MDD and previous inadequate ADT response. While cariprazine 0.1–0.3 mg/day did not separate from placebo in any predefined endpoints, cariprazine 1.0–2.0 mg/day led to a nonsignificantly higher reduction in depressive symptoms in nearly every parameter assessed compared with placebo. The MADRS treatment effect for cariprazine 1.0–2.0 mg/day was −1.8 points, which approaches the two-point threshold commonly considered clinically relevant (Montgomery and Moller, 2009). Previously, a
positive adjunctive trial of cariprazine 2.0–4.5 mg/day exhibited an MADRS treatment effect of –2.2 points (Durgam et al., 2016a); however, the cariprazine mean daily dose was 2.6 mg in that study compared with 1.1 mg in this trial. These findings indicate that cariprazine doses of more than 1.0–2.0 mg/day may increase the therapeutic response, and should therefore be investigated further.

Changes in laboratory parameters, vital signs, waist circumference, and BMI were generally small and comparable across treatment groups, while orthostatic hypotension

Table 1 Baseline characteristics of the double-blind safety population

| Cariprazine + ADT | Placebo + ADT (n = 81) |
|-------------------|------------------------|
| 0.1–0.3 mg/day (n = 76) | 1.0–2.0 mg/day (n = 73) |
| **Age** [mean (SD)] (years) | 45.2 (10.2) | 46.6 (11.7) |
| **Women [n (%)]** | 61 (75.3) | 52 (68.4) |
| **White [n (%)]** | 69 (85.2) | 57 (75.0) |
| **Black or African American [n (%)]** | 10 (12.3) | 15 (19.7) |
| **Asian [n (%)]** | 0 | 2 (2.6) |
| **Weight** [mean (SD)] (kg) | 84.3 (15.1) | 84.0 (17.8) |
| **BMI** [mean (SD)] (kg/m²) | 30.0 (5.0) | 29.5 (5.6) |
| **At MDD onset** [mean (SD)] (years) | 29.0 (12.2) | 30.6 (12.1) |
| **Recurrence MDD [n (%)]** | 69 (85.2) | 65 (85.5) |
| **Duration of current episode** [mean (SD)] (months) | 31.9 (82.1) | 25.0 (33.5) |
| **Baseline MADRS total score** [mean (SD)] | 26.4 (6.3) | 26.8 (7.0) |
| **Open-label ADT [n (%)]** | 7 (8.6) | 12 (15.8) |
| **Citalopram** | 22 (27.2) | 29 (37.8) |
| **Duloxetine** | 20 (24.7) | 18 (23.7) |
| **Sertraline** | 11 (13.6) | 10 (13.2) |
| **Venlafaxine ER** | 21 (25.9) | 16 (21.1) |

%: Proportion of patients; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; n, number of patients.

*Six patients were enrolled twice in the study; only data from the first enrollment phase are included. Baseline for the double-blind treatment phase is the last nonmissing assessment before the first dose of double-blind investigational product.
Six patients were enrolled twice in the study. Only data from the first enrollment phase are included.

ADT, antidepressant therapy; CGI-I, Clinical Global Impressions-Improvement; CGI-S, Clinical Global Impressions-Severity; CI, confidence interval; HAMD17, Hamilton Depression Rating Scale, 17 item; HAMD24, Hamilton Depression Rating Scale, 24 item; ITT, intent-to-treat; LSMD, least squares mean difference; MADRS, Montgomery–Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures; n, number of patients.

*LS mean (SE), LSMD versus placebo, 95% CI, and P values are based on an MMRM model with treatment group, pooled study center, visit, and treatment group-by-visit interaction as fixed effects, and the baseline value and baseline-by-visit interaction as the covariates.

Analyses of response and remission rates were performed using a logistic regression model, with treatment group and the corresponding baseline values as the explanatory variables.

### Table 2  Efficacy end points

| Efficacy parameters at week 16                  | Placebo + ADT (n = 81) | 0.1–0.3 mg/day (n = 76) | 1.0–2.0 mg/day (n = 73) |
|------------------------------------------------|------------------------|----------------------------|----------------------------|
| **MADRS total score**                           | Baseline [mean (SD)]    | 26.4 (6.3)                 | 26.6 (7.0)                 | 26.3 (6.5)                 |
|                                                | LS change at week 16 [mean (SE)] | −8.0 (1.0)                  | −7.5 (1.1)                 | −9.8 (1.1)                 |
|                                                | LSMD (95% CI)           | −0.5 (−2.4 to 3.4)         | −1.8 (−4.8 to 1.1)         |
| **P value**                                     | −                      | 0.746                      | 0.227                      |
| **CGI score**                                   | Baseline [mean (SD)]    | 2.6 (0.1)                  | 2.5 (0.1)                  | 2.3 (0.1)                  |
|                                                | LS at week 16 [mean (SE)] | 2.5 (0.1)                  | 2.5 (0.1)                  | 2.3 (0.1)                  |
|                                                | LSMD (95% CI)           | 0.0 (−0.3 to 0.3)          | −0.2 (−0.6 to 0.1)         |
| **P value**                                     | −                      | 0.918                      | 0.167                      |
| **CGI-I response (score ≥ 2)**                  | Responders             | 49.4                       | 474                        | 58.9                       |
| **Odds ratio vs. placebo (95% CI)**             |                         | 0.9 (0.5–1.7)              | 1.5 (0.8–2.8)              | 1.2 (0.7–2.0)              |
| **P value**                                     | −                      | 0.805                      | 0.229                      |
| **CGI-S score**                                 | Baseline [mean (SD)]    | 4.0 (0.5)                  | 4.1 (0.6)                  | 4.2 (0.7)                  |
|                                                | LS change at week 16 [mean (SE)] | −0.9 (0.1)                 | −0.9 (0.1)                 | −1.3 (0.1)                 |
|                                                | LSMD (95% CI)           | −0.1 (−0.2 to 0.4)         | −0.3 (−0.7 to 0.0)         |
| **P value**                                     | −                      | 0.569                      | 0.058                      |
| **HAMD24 total score**                          | Baseline [mean (SD)]    | 19.7 (3.9)                 | 20.3 (4.4)                 | 20.2 (4.3)                 |
|                                                | LS change at week 16 [mean (SE)] | −5.9 (0.8)                 | −6.1 (0.8)                 | −7.4 (0.8)                 |
|                                                | LSMD (95% CI)           | −0.2 (−2.3 to 1.9)         | −1.5 (−3.7 to 0.6)         |
| **P value**                                     | −                      | 0.829                      | 0.166                      |
| **HAMD32 total score**                          | Baseline [mean (SD)]    | 24.5 (5.9)                 | 25.7 (6.6)                 | 24.9 (6.1)                 |
|                                                | LS mean change at week 16 [mean (SE)] | −7.6 (1.0)                 | −7.9 (1.0)                 | −9.5 (1.1)                 |
|                                                | LSMD (95% CI)           | −0.3 (−3.0 to 2.5)         | −1.9 (−4.7 to 0.9)         |
| **P value**                                     | −                      | 0.847                      | 0.184                      |

and suicidal thoughts/behaviors were lower with cariprazine 1.0–2.0 mg/day compared with placebo. In this study, the incidence of TEAEs was lower than that reported in previously published cariprazine MDD (Durgam et al., 2016a) and monotherapy bipolar manic trials (Durgam et al., 2015; Sachs et al., 2015). A notable AE in this population, akathisia, had a generally lower occurrence (5.5%) than that observed in other adjunctive antipsychotic MDD trials: aripiprazole (25%) (Otsuka America Pharmaceutical Inc., 2014), brexpiprazole (4–14%) (Otsuka America Pharmaceutical Inc., 2015), and cariprazine (2.0–4.5 mg/day, 22.3%) (Durgam et al., 2016a), but was higher than that reported for quetiapine fumarate (2%) (AstraZeneca Pharmaceuticals LP, 2013). The tolerability of cariprazine 1.0–2.0 mg/day provides additional support for assessing higher doses in future trials.

While not significant, the difference in MADRS response rates between cariprazine 1.0–2.0 mg/day and placebo was greater than the 10% threshold generally considered clinically significant (Montgomery and Moller, 2009). The mean difference in cariprazine and placebo responders (12.5%) was greater than the difference in the previous cariprazine 2.0–4.5 mg/day aydose group in the positive trial (11.1%) (Durgam et al., 2016a), and similar to SSRIs-serotonin norepinephrine reuptake inhibitors response rates (compared with placebo) in the study data submitted to the FDA (mean: 16%; range: 3.3–49.6%; Melander et al., 2008).

The lack of statistical significance may be partially explained by the small sample size of ~70 patients per group for a three-way comparison of two dosage groups and placebo. The overall population (N=230), when compared with the patient population in other adjunctive antipsychotic trials, was more than 30% smaller than that of the trials of aripiprazole, and approximately half that of the trials of quetiapine fumarate and brexpiprazole (all pivotal trials), and cariprazine 2.0–4.5 mg/day (Durgam et al., 2016a).

Another possible explanation for the lack of significance is the selection of a cariprazine dose too low to be effective, and delayed dose increases due to the fixed-flexible dose study design. By not allowing increases to the maximum dose until halfway through the
double-blind phase, patients may not have received potentially efficacious doses for sufficient durations to achieve clinically relevant responses. Finally, the negative results may be partly due to longer current depressive episode duration in study participants (mean: ~2.3 years), compared with that in the participants of the positive cariprazine trial (~7.5 months) (Durgam et al., 2016a) and positive aripiprazole trial (~18 months) (Berman et al., 2009), given that shorter current episodes appear to increase the likelihood of positive treatment outcomes (Habert et al., 2016).

The eight-point change in the MADRS score for placebo was numerically greater than those reported in the seven aripiprazole or brexipiprazole augmentation trials with similar study designs (Berman et al., 2007, 2009; Marcus et al., 2008; Kamijima et al., 2013; Lenze et al., 2015; Thase et al., 2015a, 2015b), and high placebo response can reduce signal detection, which may lead to negative results (Fava et al., 2003). The magnitude of placebo response may be partially attributed to rating errors (despite the use of Concordant Rater Systems), and to the study design; as the number of treatment arms or dosage groups increase, patients’ perception that they will benefit from treatment also increases (Papakostas and Fava, 2009). Another potential contributor to the placebo response was the requirement that patients take additional capsules when increasing their dose (Alphs et al., 2012).

Limitations of the current study included lack of an active comparator, which prevented determination of the assay sensitivity, and low fractional doses of cariprazine, which were selected on the basis of preclinical studies that showed efficacy at low doses (Papp et al., 2014) and concerns about tolerability in outpatients. However, in

### Table 3 Summary of adverse events (double-blind safety population)

| Adverse event summary | Placebo + ADT (n=81) [n (%)] | Cariprazine + ADT 0.1–0.3 mg/day (n=76) [n (%)] | Cariprazine + ADT 1.0–2.0 mg/day (n=73) [n (%)] |
|-----------------------|-------------------------------|-----------------------------------------------|-----------------------------------------------|
| Any TEAE              | 47 (58.0)                    | 42 (55.3)                                     | 48 (65.8)                                     |
| Serious AEs           | 1 (1.2)                      | 0                                             | 1 (1.4)                                       |
| Discontinuations due to AEs | 2 (2.5)                     | 1 (1.3)                                       | 2 (2.7)                                       |

Common TEAEs (reported by ≥5% of patients in any treatment group):

- Headache
- Restlessness
- Dizziness
- Fatigue
- Increased appetite
- Insomnia
- Nasopharyngitis
- Nausea
- Dry mouth
- Constipation
- Akathisia
- Diarrhea
- Arthralgia

Six patients were enrolled twice in the study. Only data from the first enrollment phase are included.

Version 13.0 of MedDRA was used to code adverse events.

% Proportion of patients with TEAE; ADT, antidepressant therapy; n, number of patients with TEAE; TEAE, treatment-emergent adverse events.

*Patients were counted only once within each preferred term. If a patient had more than one occurrence in the same event category, only the most related occurrence was counted.

### Table 4 Additional safety outcomes

| Measures                      | Placebo | Cariprazine 0.1–0.3 mg/day | Cariprazine 1.0–2.0 mg/day |
|-------------------------------|---------|----------------------------|---------------------------|
| n                             | Mean change (SD) | n | Mean change (SD) | n | Mean change (SD) |
| Vital signs                   |         |                            |                           |                           |
| Systolic blood pressure (mmHg) | 29 (9.6) | 1.1 (10.8) | -0.8 (10.5) |
| Diastolic blood pressure (mmHg) | 2.5 (8.7) | 0.7 (7.6) | 1.0 (7.8) |
| Heart rate (bpm)              |         |                            |                           |                           |
| Body weight (kg)              | 0.6 (2.6) | 0.1 (2.6) | 1.4 (3.6) |
| Waist circumference (cm)      |         | -0.2 (4.5) | 0.2 (4.7) |
| BMI (kg/m²)                   | 0.2 (0.9) | 0.0 (0.9) | 0.5 (1.3) |
| Laboratory tests              |         |                            |                           |                           |
| Glucose (fasting) (mmol/l)    | 68      | 0.0 (0.6) | -0.1 (0.8) |
| Insulin (nmol/l)              | 78      | 17.7 (107.3) | 15.5 (126.3) |
| Prolactin (ng/ml)             | 78      | 0.8 (3.6) | 1.7 (3.8) |
| Creatine kinase (U/l)         | 78      | 10.5 (47.7) | 5.2 (54.7) |
| Lipids                        | 78      | 75 | 67 |
| Total cholesterol (mmol/l)    | -0.2 (0.8) | 0.0 (0.8) | -0.1 (1.1) |
| HDL (nmol/l)                  | 0.0 (0.2) | 0.0 (0.2) | 0.0 (0.2) |
| LDL (nmol/l)                  | 0.0 (0.7) | 0.0 (0.7) | -0.1 (0.8) |
| Liver function                | 78      | 75 | 67 |
| Alanine aminotransferase (U/l) | 2.2 (11.0) | 1.7 (18.7) | 4.4 (20.9) |
| Alkaline phosphatase (U/l)    | -0.8 (12.4) | -0.4 (13.2) | -1.5 (13.8) |
| Aspartate aminotransferase (U/l) | 1.8 (8.3) | -0.5 (8.9) | 1.9 (10.2) |
| Total bilirubin (µmol/l)       | -1.0 (2.8) | -0.7 (4.6) | -1.3 (3.3) |

Six patients were enrolled twice in the study. Only data from the first enrollment period are included.

Only patients with available baseline and at least one postbaseline value in the double-blind treatment phase are included in the analyses. Mean change is mean change from baseline to end of treatment. Baseline was defined as the last available assessment in the double-blind treatment period. HDL, high-density lipoprotein; LDL, low-density lipoprotein; n, number of patients.
this study, patients tolerated cariprazine 1.0–2.0 mg/day reasonably well, and, in a study initiated subsequently, no significant tolerability issues with doses up to 4.5 mg/day were reported (Durgam et al., 2016a). Another limitation of the study was the fixed-flexible dose study design, which may be more representative of real-world practice, but it prevented analysis of specific dosages. As with all studies, patient characteristics and differences across treatment groups at baseline have the potential to confound results. For example, the proportion of placebo patients with MDD duration of more than 5 years was higher than in the two cariprazine groups, which might have influenced the findings (Perlis, 2013). Finally, the exclusion of patients with other primary axis I disorders may prevent generalization of these results to all patients with MDD.

The numerically greater, but not statistically significant, reduction (improvement) in depressive symptoms from baseline, compared with placebo, of cariprazine 1.0–2.0 mg/day that is reported, is consistent with the results of adjunctive cariprazine 2.0–4.5 mg/day from another placebo-controlled trial (Durgam et al., 2016a). Alternatively, in that previous trial, patients with MDD who received higher doses of adjunctive cariprazine had significantly greater improvements in MADRS total score compared with placebo by week 2 that were maintained to the end of the study. CGI-I and CGI-S score improvements were also significantly greater with cariprazine 2.0–4.5 mg/day treatment than with placebo in that trial (Durgam et al., 2016a), and significantly greater rates of MADRS response occurred with both cariprazine 1.0–2.0 and 2.0–4.5 mg/day treatment. Significant differences in response rates from placebo were detected at weeks 3 and 2 for the cariprazine 1.0 and 2.0–4.5 mg/day groups, respectively (Durgam et al., 2016a) It is likely that the cariprazine 1.0–2.0 mg/day used in the present study was too low to reach therapeutic significance, warranting future studies to characterize the optimal therapeutic dose of cariprazine, and its efficacy, safety, and tolerability as an adjunctive treatment for adults with MDD.

**Acknowledgements**

Writing assistance and editorial support for preparation of this manuscript was provided by Cherisse Loucks, PhD, of Allergan, Madison, New Jersey.

This study was supported by funding from Allergan (Madison, New Jersey, USA) and Gedeon Richter Plc. (Budapest, Hungary).

Allergan and Gedeon Richter Plc. were involved in the study design, collection (by contracted clinical investigator sites), analysis and interpretation of data, and decision to present these results.

**Conflicts of interest**

Drs. Durgam, Earley, Lu, and Hayes acknowledge a potential conflict of interest as employees of Allergan. Dr. Durgam is a stock shareholder of Allergan. Drs. Laszlovszky and Németh acknowledge a potential conflict of interest as employees of Gedeon Richter Plc. Drs. Laszlovszky and Németh are patent owners of the investigational medicinal product used in this study. Dr. Fava’s disclosure statement can be viewed online at http://mghcme.org/faculty/faculty-detail/maurizio_fava.

**References**

Allergan Plc (2016). VRAYLAR (cariprazine). Irvine, CA: Allergan Plc.

Alphs L, Benedetti F, Fleischhacker WW, Kane JM (2012). Placebo-related effects in clinical trials in schizophrenia: what is driving this phenomenon and what can be done to minimize it? Int J Neuropsychopharmacol 15:1003–1014.

American Psychiatric Association (2000). Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision. Washington, DC: American Psychiatric Association.

Baldessarini RJ, Forte A, Bolle V, Sim K, Tondo L, Undurraga J, Vazquez GH (2017). Morbidity in depressive disorders. Psychother Psychosom 86:65–72.

Barnes TR (1989). A rating scale for drug-induced akathisia. Br J Psychiatry 154:672–676.

Berman RM, Marcus RN, Swannik R, McQuade R, Carson W, Corey-Lisle P, Khan A (2007). The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry 68:843–853.

Berman RM, Fava M, Thase ME, Trivedi M, Swannik R, McQuade R, et al. (2009). Aripiprazole augmentation in major depressive disorder: a double-blind placebo-controlled study in patients with inadequate response to antidepressants. CNS Spectr 14:197–206.

Carnicella S, Dru G, Boulet S, Cercenac G, Favier M, Duran T, Savasta M (2014). Implication of dopamine D3 receptor activation in the reversion of Parkinson’s disease-related motivational deficits. Transl Psychiatry 4:e401.

Duman RS, Duric V, Bansar M, Adham N, Kiss B, Gyertyan I (2012). Cariprazine exhibits dopamine D3 receptor-dependent antidepressant-like activity in the chronic unpredictable stress model of anhedonia. 51st Annual Meeting of the American College of Neuropsychopharmacology, 2–6 December 2012; Hollywood, Florida: ACNP.

Durgam S, Earley W, Guo H, Li D, Nemeth G, Laszlovszky I, et al. (2016a). Efficacy and safety of adjunctive cariprazine in inadequate responders to antidepressants: a randomized, double-blind, placebo-controlled study in adult patients with major depressive disorder. J Clin Psychiatry 77:371–378.

Durgam S, Earley W, Lipschitz A, Guo H, Laszlovszky I, Nemeth G, et al. (2016b). An 8-Week randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in patients with bipolar I depression. Am J Psychiatry 173:271–281.

Durgam S, Starace A, Li D, Migliore R, Ruth A, Nemeth G, Laszlovszky I (2015). The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: a phase II trial. Bipolar Disord 17:63–75.

Fava M (2000). Management of nonresponse and intolerance: switching strategies. J Clin Psychiatry 61:10–12.

Fava M (2003). Diagnosis and definition of treatment-resistant depression. Biol Psychiatry 53:649–659.

Fava M, Evans AE, Dorer DJ, Schoenfeld DA (2003). The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. Psychother Psychosom 72:115–127.

Gross G, Drescher K (2012). The role of dopamine D3 receptors in antipsychotic activity and cognitive functions. Handb Exp Pharmacol 167:210–210.

Guy W (1976). ECDEU Assessment Manual for Psychopharmacology US Dept Health, Education, and Welfare Publication (ADM) 76-339. Rockville, MD: National Institute of Mental Health. pp. 218–222.

Habert J, Katzman MA, Oluboka OJ, McIntyre RS, McIntosh D, Macqueen GM, et al. (2016). Functional recovery in major depressive disorder: focus on early optimized treatment. Prim Care Companion CNS Disord 18:1–11.

Hamilton M (1960). A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62.

Hayes R, Bose A, Lu K, AI E (2011). A double-blind, placebo-controlled study of cariprazine as adjunctive therapy in major depressive disorder. Presented at the Autumn Conference of the International Society for CNS Clinical Trials and Methodology, 3–4 October 2011; Amelia Island, Florida: ISCTM.

Kamijima K, Higuchi T, Ishigooka J, Ohnori T, Ozaki N, Kanba S, et al. (2013). Aripiprazole augmentation to antidepressant therapy in Japanese patients with major depressive disorder: a randomized, double-blind, placebo-controlled study (ADMIRE study). J Affect Disord 151:899–905.
Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Rush A, et al. (2003). The epidemiology of major depression disorder: results from the national comorbidity survey replication (NCS-R). JAMA 289:3095–3105.

Kiss B, Horti F, Bobok A (2012). Cariprazine, a D3/D2 dopamine receptor partial agonist antipsychotic, displays greater D3 receptor occupancy in vivo compared with other antipsychotics. Schizophr Res 136:S190.

Lam RW, Wan DDC, Cohen NL, Kennedy SH (2002). Combining anti-Kiss B, Horti F, Bobok A (2012). Cariprazine, a D3/D2 dopamine receptor partial agonist antipsychotic, displays greater D3 receptor occupancy in vivo compared with other antipsychotics. Schizophr Res 136:S190.

Lenze EJ, Mulsant BH, Blumberger DM, Karp JF, Newcomer JW, Anderson SJ, et al. (2015). Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomised, double-blind, placebo-controlled trial. The Lancet 386:2404–2412.

Marcus RN, McQuade RD, Carson WH, Henrickson D, Fava F, Simon J, et al. (2008). The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder a second multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol 28:156–165.

Marder S, Laszlovzky I, Szalai E, Szatmári B, Harsányi J, Barabássy A, et al. (2016). Efficacy of cariprazine on predominant negative symptoms of patients with schizophrenia: post hoc analysis of PANSS data, Marder factors, and cognition. Eur Neuropsychopharmacol 26:S550.

Melander H, Salomonson T, Abadie E, Van Zwieten-Boot B (2008). A regulatory Apologia: a review of placebo-controlled studies in regulatory submissions of new-generation antidepressants. Eur Neuropsychopharmacol 18:623–627.

Merikangas KR, Ames M, Cui L, Stang PE, Ustun B, Von Korff M, Kessler RC (1997). The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. Eur Psychiatry 12:232–241.

Nelson JC, Papakostas GI (2009). Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. Am J Psychiatry 166:980–991.

Nemeroff CB (2007). Prevalence and management of treatment-resistant depression. J Clin Psych 68:17–25.

Otsuka America Pharmaceutical Inc. (2014). Ability (aripiprazole). Rockville, MD: Otsuka America Pharmaceutical, Inc.

Otsuka America Pharmaceutical Inc. (2015). Rexulti (brexpiprazole). Rockville, MD: Otsuka America Pharmaceutical, Inc.

Papakostas GI, Fava M (2009). Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. Eur Neuropsychopharmacol 19:34–40.

Papp M, Grucha P, Lason-Tybirkiewicz M, Adham N, Kiss B, Gyertyán I (2014). Attenuation of anhedonia by cariprazine in the chronic mild stress model of depression. Behav Pharmacol 25:567–574.

Perlis RH (2013). A clinical risk stratification tool for predicting treatment resistance in major depressive disorder. Biol Psychiatry 74:7–14.

Posner K, Brown GK, Stanley B, Brent DA, Yershova K, Oquendo M, et al. (2011). The Columbia–Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 168:1266–1277.

Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, et al. (2003). The 16-item Quick Inventory Of Depressive Symptomatology (QIDS), Clinician Rating (QIDS-C), and Self-Report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry 54:573–583.

Simpson GM, Angus JW (1970). A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 212:11–19.

Thase ME, Youakim JM, Skuban A, Hobart M, Augustine C, Zhang P, et al. (2016a). Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants. J Clin Psychiatry 76:1224–1231.

Wright BM, Eland EH, Lorenz R (2013). Augmentation with atypical antipsychotics for depression: a review of evidence-based support from the medical literature. Pharmacotherapy 33:344–359.

Sachs GS, Greenberg WM, Starace A, Lu K, Rush A, Laszlovzky I, et al. (2015). Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, Phase III trial. J Affect Disord 174:296–302.

AstraZeneca Pharmaceuticals LP (2013). Seroquel XR (quetiapine fumarate extended-release). Wilmington, DE: AstraZeneca Pharmaceuticals LP.

Sheehan DV, Lecrubier Y, Janavs J, Weiller E, Keskiner A, et al. (1997). The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. Eur Psychiatry 12:232–241.

Silfstein M, Abi-Dargham A, D’Souza DC, Carson RE, Laszlovzky I, Durgam S, et al. (2013). Cariprazine demonstrates high dopamine D3 and D2 receptor occupancy in patients with schizophrenia: a clinical PET study with [11C]-(+)-PHNO. Neuropsychopharmacology 38:S520.

Simpson GM, Angus JW (1970). A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 212:11–19.

Thase ME, Youakim JM, Skuban A, Hobart M, Augustine C, Zhang P, et al. (2016a). Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants. J Clin Psychiatry 76:1224–1231.

Thase ME, Youakim JM, Skuban A, Hobart M, Zhang P, McQuade RD, et al. (2015). Adjunctive brexpiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants: a phase 3, randomized, double-blind study. J Clin Psychiatry 76:1232–1240.

Warden D, Rush AJ, Trivedi MH, Fava M, Wisniewski SR (2007). The STAR*D Project results: a comprehensive review of findings. Curr Psychiatry Rep 9:449–459.

Wright BM, Eland EH, Lorenz R (2013). Augmentation with atypical antipsychotics for depression: a review of evidence-based support from the medical literature. Pharmacotherapy 33:344–359.

Cariprazine as adjunctive therapy in MDD Fava et al. 321