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Research paper

The safety and tolerability of cariprazine in patients with manic or mixed episodes associated with bipolar I disorder: A 16-week open-label study

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ABSTRACT

Background: We evaluated the safety/tolerability of longer-term open-label treatment with cariprazine in patients who had responded to cariprazine for acute bipolar mania.

Methods: In this multinational, multicenter study, open-label, flexible-dose, cariprazine 3–12 mg/d was administered for up to 16 weeks to patients (18–65 years) with bipolar mania. Safety evaluations included adverse events (AEs), laboratory values, vital signs, and extrapyramidal symptom (EPS) scales. Symptom change was evaluated by Young Mania Rating Scale (YMRS) total score change from baseline using the last observation carried forward approach.

Results: Of the 402 patients taking cariprazine, 33% completed the trial; the most frequent reasons for discontinuation were withdrawal of consent (20%), AEs (16%), and protocol violation (14%). Most common AEs leading to discontinuation were akathisia (4.7%) and depression (1.5%). Mean treatment duration was 57.7 days; mean cariprazine dose was 6.2 mg/d. The incidence of serious AEs was 7.5% (most common: mania [2.2%], depression [1.2%]); 83.3% had treatment-emergent AEs, including akathisia (32.6%), headache (16.7%), constipation (10.7%), and nausea (10.4%). Mean body weight increased < 1 kg; 9.3% had ≥7% weight gain; 5.7% had sedation; 3% had somnolence. Mean changes in laboratory values, vital signs, ECGs, and ophthalmology parameters were not clinically significant. Mean YMRS total score decreased by −15.2 at week 16.

Limitations: Uncontrolled, open-label design.

Conclusions: Open-label cariprazine 3–12 (mean 6.2) mg/d for up to 16 weeks was generally well tolerated, with low (< 10%) rates of sedation and ≥7% weight gain. Although akathisia occurred in 33%, it yielded discontinuation in < 5%.

1. Introduction

Bipolar I disorder is a complex psychiatric disorder with a highly variable course. The distinguishing diagnostic feature is the occurrence of at least one manic or mixed episode, which commonly entails psychosis and/or psychiatric hospitalization. In addition to abnormally elevated mood, patients with bipolar I disorder also commonly experience frequent depressive episodes, cognitive impairment, functional impairment, sleep disturbance, psychotic symptoms, anxiety, substance use, and medical disorders (Judd et al., 2002; Osby et al., 2001; Sachs et al., 2011). While classically considered to be episodic and remitting, bipolar disorder is currently conceptualized as a disease with a more chronic presentation in which residual symptoms, emotional lability, and greater risk for psychiatric and medical comorbidities occur between acute mood episodes (Leboyer and Kupfer, 2010).

Long-term treatment is usually required to manage bipolar disorder (Yatham et al., 2013); initial treatment produces symptomatic recovery and stabilization of the acute mood episode, while maintenance treatment is necessary for recurrence prevention, reduction of subthreshold symptoms, and enhanced functioning (Geddes and Miklowitz, 2013).

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; CGI-S, Clinical Global Impressions-Severity; C-SSRS, Columbia-Suicide Severity Rating Scale; EPS, extrapyramidal symptoms; ITT, intent-to-treat; LOCF, last observation carried forward; MADRS, Montgomery-Åsberg Depression Rating Scale; OC, observed cases; SCID, Structured Clinical Interview; SAS, Simpson-Angus Scale; YMRS, Young Mania Rating Scale

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Atypical antipsychotic monotherapy is among the recommended first-line treatment options for bipolar mania (Yatham et al., 2013). Although atypical antipsychotics are categorized as a drug class, they differ in pharmacology, safety, tolerability, and efficacy (Liauw and McIntyre, 2010). Despite decreased risks of extrapyramidal symptoms (EPS) and tardive dyskinesia compared with first-generation antipsychotics, second-generation antipsychotics are commonly associated with other problematic adverse effects including clinically significant weight gain, sedation and somnolence (particularly with older agents), and akathisia (particularly with newer agents) (Cha and McIntyre, 2012). The efficacy of pharmacotherapy depends on patient treatment adherence. As such, a medication's safety and tolerability profile is important since treatment adherence is positively associated with higher medication satisfaction and negatively associated with side effects, negative attitudes toward medications, changes in appearance, and interference with life goals (Yatham et al., 2013).

Cariprazine, a dopamine D_3 and D_2 receptor partial agonist that preferentially binds to D_3 receptors (Kiss et al., 2010), is FDA-approved for the treatment of adult patients with schizophrenia (1.5–6 mg/d) or manic or mixed episodes associated with bipolar I disorder (3–6 mg/d). The short-term efficacy and safety/tolerability of cariprazine in adult patients with acute manic or mixed episodes associated with bipolar I disorder was demonstrated in three 3-week, phase 2 or phase 3 double-blind, placebo-controlled studies (Calabrese et al., 2015; Durgam et al., 2015; Sachs et al., 2015). Flexible-dose cariprazine 3–12 mg/d was used in 2 studies, and a fixed/flexible dose scheme (3–6 mg/d or 6–12 mg/d) was used in the third. In each trial, improvement from baseline to week 3 in Young Mania Rating Scale (YMRS) total score (Young et al., 1978) (primary efficacy measure) and Clinical Global Impressions-Severity (CGI-S) (Guy, 1976a) (secondary efficacy measure) was significantly greater for cariprazine versus placebo, and cariprazine was safe and generally well tolerated; akathisia was a more common adverse event than sedation/somnolence or weight gain.

This longer-term, open-label study was conducted to further characterize the safety and tolerability of cariprazine in patients with bipolar mania. The target population was patients previously diagnosed with bipolar I disorder who were currently untreated or not adequately responding to or tolerating their current treatment as judged by the investigator and symptom rating scale criteria at study entry (YMRS $\geq$18; Montgomery-Åsberg Depression Rating Scale [MADRS] $<$ 18) (Montgomery and Asberg, 1979).

2. Methods

This study was conducted from February 2010 to February 2012 in 39 centers in the United States, Germany, Hungary, Poland, and Spain in full compliance with guidelines for good clinical practice and the Declaration of Helsinki; all participants provided written informed consent. Since this was an open-label study, there was no blinding to treatment, and no control group was included.

2.1. Study design

This 20-week multicenter, phase 3, open-label, flexible-dose study of cariprazine 3–12 mg/d (NCT01059539) was conducted in patients with manic or mixed episodes associated with bipolar I disorder. The study consisted of a 4- to 7-day wash-out period, followed by 16 weeks of open-label treatment and a 3-week safety follow-up period. All patients received 1.5 mg of cariprazine on day 0 and 3 mg on days 1 and 2; starting on day 3, dosage could be increased in 3-mg increments if response was inadequate and there were no tolerability issues. Patients could receive a maximum dose of 6 mg on days 3 and 4; on days 5 and 6, the maximum dose was 9 mg. On day 7 and after, the maximum dose was 12 mg. In the case of a dose-limiting adverse event (AE), the dose could be decreased to the previous level at any time during the study.

All patients were hospitalized during screening and for the first 2–3 weeks of open-label treatment. By the end of week 3, all patients were discharged and followed-up as outpatients, or discontinued from the study in cases of clinical instability. Patients who were discontinued entered the 3-week safety follow-up period during which they were cross-titrated and stabilized on an appropriate medication as deemed necessary by the investigator. Patients with insufficient therapeutic response could be discontinued from the study at any time; insufficient response was defined as a YMRS or MADRS total score increase $\geq$30% from baseline to the end of week 2 or thereafter, or inadequate response based on investigator judgment, tolerability issues, or worsening of symptoms.

2.2. Patients

Patients with documented inadequate response or intolerance to their current treatment or patients not currently receiving any treatment were eligible to participate in this longer-term study. Male or female adults, aged 18–65 years (inclusive) had to meet *Diagnostic and Statistical Manual for Mental Disorders* (DSM-IV-TR) criteria (APA, 2000) for bipolar I disorder, confirmed by the Structured Clinical Interview (SCID) (First et al., 2007). Patients were required to have had a manic or mixed episode (with or without psychotic symptoms) that required treatment within 12 months of the study. To be included, clinical criteria required that patients currently had a YMRS total score $\geq$18 and a MADRS score $<$ 18. This YMRS score is consistent with requiring that patients have substantive current mood elevation symptoms; although patients with DSM-IV-TR mixed episodes were permitted, a MADRS score $<$ 18 taken together with a YMRS score $\geq$18 is consistent with patients having more severe mood elevation than depression.

Patients were excluded from the study if they had a principal axis I diagnosis other than bipolar I, severe personality disorder, rapid cycling (defined as $>$ 4 major depressive, manic, mixed, or hypomanic episodes in the prior 12 months), cognitive or psychotic disorders, alcohol or substance dependence/abuse (prior 3 months), or pregnancy. Patients experiencing their first manic episode were not eligible to participate. Suicide risk, defined as suicide attempt in the past year, score $\geq$5 on item 10 of the MADRS, and/or significant risk determined by investigator judgment or Columbia-Suicide Severity Rating Scale (C-SSRS) assessment (Posner et al., 2011), was exclusionary. Additionally, any concurrent medical condition that might interfere with the conduct of the study, confound the interpretation of study results, or endanger patient well-being was exclusionary. Psychotropic medications other than cariprazine were not allowed except for lorazepam for agitation (after day 8, maximum = 2 mg/d); eszopiclone (maximum = 3 mg/d), zolpidem (maximum = 10 mg/d), zolpidem extended release (maximum = 12.5 mg/d), chloral hydrate (maximum = 2000 mg/d acutely with approval), or zaleplon (maximum = 20 mg/d) for insomnia; or diphenhydramine (50 mg/d), benztropine (up to 4 mg/day [or 2 mg/day if given parenterally]), or propranolol (heart rate and blood pressure dependent dosing) for EPS.

2.3. Safety and efficacy evaluations

Safety assessments included AE reports, clinical laboratory parameters, vital signs, electrocardiograms (ECGs), ophthalmologic exams, and C-SSRS assessment. AE reports and findings from EPS/movement disorder rating scales were used to assess treatment-emergent EPS; EPS/movement disorder scales comprised the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976b), the Barnes Akathisia Rating Scale (BARS) (Barnes, 1989), and the Simpson-Angus Scale (SAS) (Simpson and Angus, 1970). Efficacy assessments were collected, but in view of the open, uncontrolled design, they were not categorized as primary or secondary; outcomes included change from baseline in MADRS and YMRS total score, and YMRS response ($\geq$50% reduction from baseline) and remission (YMRS $\leq$12) rates.