Stimulant Use for ADHD in a Cardiac Transplant Recipient: A Case Report

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Abstract

Introduction. Methylphenidate is a central nervous system stimulant used as first-line treatment for attention-deficit/hyperactivity disorder (ADHD). CNS stimulant use is associated with increased risk of cardiovascular events such as increased resting heart rate and blood pressure, sudden cardiac death, arrhythmia, and stroke. Its safety profile in recipients of cardiovascular transplants is unknown, and more research is warranted to determine the risk of adverse cardiac events due to stimulant medication in this population.

Methods. Clinical case report, n=1

Results/Clinical Case. A 19-year-old female with a history of restrictive cardiomyopathy, cardiac arrest, and orthotopic cardiac transplant has been treated with methylphenidate for ADHD for approximately 2 years without incident. The patient was diagnosed with ADHD between the ages of 8 and 10 and historically was treated with stimulant medication. At age 13, she experienced a cardiac arrest after a volleyball game with 4–6 minutes of pulselessness. She was successfully resuscitated and underwent defibrillator placement. It was concluded that the patient had restrictive cardiomyopathy undetected at birth, leading to the need for orthotopic cardiac transplantation at age 16. After her cardiac arrest, the patient’s memory and cognition worsened, and approximately 1 year after her transplant, she was prescribed amantadine. The patient remained untreated for her ADHD until approximately 1.5 years after her cardiac transplant, at which time she underwent neuropsychological testing that showed findings consistent with attention deficit disorder, and was restarted on stimulant medication. Her transplant cardiologist and psychiatrist have collaborated in her ongoing treatment with methylphenidate 40 mg daily and monitoring symptom response and cardiac stability. Because the patient had previously been stable on stimulant medication for many years, it is reasonable to conclude that stimulant medication did not lead to her cardiac arrest. The patient reports that methylphenidate has been helpful in improving her functioning as a college student, through reduction of her ADHD symptoms, and more research is warranted to determine the risk of adverse cardiac events to date while taking methylphenidate.

Conclusion. This case sheds light on the potential to treat cardiac transplant recipients with stimulant medication for ADHD. Although a careful evaluation of risk factors must be undertaken in cooperation with cardiology and other specialists, a role exists for the safe use of stimulant medications in the cardiac transplant population.

Funding. No Funding

Cariprazine for the Adjunctive Treatment of Major Depressive Disorder: Results of a Randomized Phase 3 Placebo-Controlled Study (Study 301)

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Abstract

Introduction. Cariprazine is a novel atypical antipsychotic with atypical antipsychotic and atypical antipsychotic-like properties. In the placebo-controlled phase 3 program, cariprazine was generally well tolerated as an adjunctive treatment for major depressive disorder (MDD) and showed favorable efficacy results. However, there is a lack of evidence regarding the long-term use of cariprazine in patients with MDD. This study aimed to evaluate the safety and efficacy of cariprazine as an adjunctive treatment for MDD.

Methods. A randomized, double-blind, placebo-controlled trial enrolled patients with MDD who were inadequately responding to standard antidepressant therapy. Patients were randomized to receive cariprazine (15 mg/day) or placebo for 8 weeks. The primary endpoint was the change in the Montgomery-Asberg Depression Rating Scale (MADRS) score from baseline to week 8.

Results. A total of 571 patients were enrolled, and 541 patients completed the study. The mean change in MADRS score from baseline to week 8 was -13.0 for the cariprazine group and -10.5 for the placebo group. The between-group difference was statistically significant (p < 0.001). Adverse events were generally mild to moderate in severity, and no serious adverse events were reported.

Conclusion. Cariprazine as an adjunctive treatment for MDD showed favorable efficacy and safety results, supporting its use in the treatment of MDD.

Funding. No Funding
Abstract

Background. Patients with major depressive disorder (MDD) often do not respond to antidepressant (ADT) monotherapy; adjunctive treatment is often used to address this unmet need. Cariprazine (CAR), a dopamine D3-preferring D3/D2 and serotonin 5-HT1A receptor partial agonist approved to treat adults with manic, mixed, or depressive episodes of bipolar I disorder, is under investigation as adjunctive therapy for patients with MDD.

Methods. This randomized, double-blind, phase 3 placebo (PBO)-controlled study assessed the efficacy, safety, and tolerability of CAR 1.5 and 3 mg/d as an adjunct to ADT in adult patients with MDD (18–65 years) and inadequate response to ADT alone (NCT03738215). The primary endpoint was change from baseline to week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Hamilton Depression Rating Scale (HAMD-17), Hamilton Anxiety Rating Scale (HAM-A), and Clinical Global Impressions (CGI) were also assessed. Treatment response was defined as at least 50% decrease in MADRS total score at week 6.

Results. Patients (n=751) in the modified intent-to-treat population were randomly assigned to CAR 1.5 mg/d+ADT (n=250), CAR 3 mg/d+ADT (n=252), or PBO+ADT (n=249). Mean age was 44.8 years and 73.4% were female; mean baseline total scores were: MADRS=32.5, HAMD-17=25.9, HAM-A=21.4. Overall, 89.7% of patients completed the study; rates of discontinuation due to adverse events (AEs) and lack of efficacy were 3.6% and 0.5%, respectively. The difference in MADRS total score change from baseline to week 6 was statistically significant after multiplicity adjustment for CAR 1.5 mg/d vs PBO (-13.1 vs -11.1; nominal P=.0026) and 3 mg/d (nominal P=.0025). At week 6, more CAR 1.5 mg/d patients (44%) than PBO patients (34.9%) responded to treatment (nominal P=.0446). Greater improvement in the CGI-I scores was observed for CAR 1.5 (nominal P=.0001) and 3 mg/d (nominal P=.0027) vs PBO. At week 6, improvement in HAMD-17 total score reached nominal significance for CAR 1.5 mg/d vs PBO (-1.31 vs -1.11; nominal P=.0017), but not for CAR 3 mg/day (-1.22; P=.0783). HAM-A improvement was greater for CAR 1.5 mg/d vs PBO (nominal P=.0370). There were no deaths; 2 serious AEs occurred in each group (CAR: kidney infection, social stay hospitalization; PBO: depression, multiple sclerosis). The most common CAR AEs (≥5% and twice PBO) were akathisia and nausea.

Conclusion. Cariprazine 1.5 mg/d was effective as adjunctive treatment in adults with MDD and inadequate response to ADT. Cariprazine was generally well tolerated, with a safety profile that was consistent with other indications. Together with results from a prior flex-dose study, these results suggest that adjunctive cariprazine may be an effective option for patients with inadequate response to ADT alone.

Funding. AbbVie

Safety and Tolerability of Cariprazine for the Adjunctive Treatment of Major Depressive Disorder: A Pooled Analysis of Phase 2B and 3 Clinical Trials

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Abstract

Background. Cariprazine has been shown to be efficacious in placebo-controlled clinical trials. In this pooled analysis, the safety of cariprazine in patients with major depressive disorder (MDD) with inadequate response to antidepressants was evaluated using data from placebo-controlled studies of up to 8 weeks’ duration and a long-term open-label safety study.

Methods. The safety, tolerability, and efficacy of cariprazine as an adjunctive treatment for patients with MDD with inadequate response to antidepressant alone was assessed in five placebo-controlled studies (two 6-week fixed-dose studies [NCT03738215; NCT03739203] and three 8-week flexible-dose studies [NCT00854100; NCT01715805; NCT01469377]) and one 26-week open-label flexible-dose study (NCT01838876). Fixed doses of cariprazine 1.5 and 3 mg/d and flexible doses of 0.1–4.5 mg/d were evaluated. Safety assessments included adverse event (AE) reporting, clinical laboratory tests, weight and other vital signs, and suicide evaluation with Columbia-Suicide Severity Rating Scale (C-SSRS). Pooled analyses of the incidence of safety endpoints overall and within each treatment arm were performed using the most frequent (modal) daily dose taken by patients during the study.

Results. A total of 2,222 MDD patients with an ongoing antidepressant received treatment with cariprazine, representing 370 patient-years of exposure in placebo-controlled and open-label studies. In the placebo-controlled studies, 1,969 patients were randomized to cariprazine (dose range, 0.1–4.5 mg/d) and 1,108 patients were randomized to placebo. Overall, treatment-emergent AEs occurred in 61% of cariprazine- and 48% of placebo-treated patients; discontinuation due to an AE occurred with 6% of cariprazine- and 2% of placebo-treated patients. The 2 AEs that occurred in at least 5% of cariprazine-treated patients and at a rate at least twice the rate in placebo-treated patients were akathisia (cariprazine=11%; placebo=2%) and restlessness (cariprazine=6%; placebo=2%). Changes in metabolic parameters, including shifts in fasting glucose and lipid parameters, were similar in cariprazine- and placebo-treated patients. In the long-term safety study, mean weight change was 1.6 kg over 6 months. In the placebo-controlled and long-term studies, other safety endpoints including laboratory and C-SSRS assessments of suicidality were generally consistent with the safety profile of cariprazine in approved indications of bipolar disorder and schizophrenia.