features, antisocial personality disorder, PTSD, and ASD, who was psychiatrically hospitalized for mania and psychosis at a large midwestern university hospital. At the time of evaluation in the emergency department, the patient endorsed suicidal ideation, religious/persecutory delusions, and auditory hallucinations of demons. Zyprexa Zydis was started and titrated to 20 mg every 12 hours, which did not sufficiently improve symptoms. Depakote EC/DR 1000 mg every 12 hours was then added for treatment of mania. Approximately 1 week later, the patient was observed to be somnolent and complained of malaise, nausea, and vomiting.

Results. Labs were collected which showed an elevated ammonia level of 336 umol/L and free valproic acid level of 13.3 mcg/ml. An EKG was performed which showed first-degree atrio-ventricular block with fusion complexes. The patient's baseline EKG displayed sinus bradycardia with no evidence of atrio-ventricular block. The patient's CMP was unremarkable except total bilirubin of 1.5 mg/dL and glucose of 104 mg/dL. His lactate was elevated at 1.95 mmol/L. The patient's troponin and CRP were unremarkable. The patient was medically transferred for management of hyperammonemia and EKG changes. Depakote was discontinued and lactulose 20 g TID was initiated. Patient was placed on telemetry and the first-degree atrio-ventricular block resolved within 24 hours after discontinuation of Depakote. Daily ammonia level, chem 7, and magnesium were collected. Ammonia decreased to 79 and 59 umol/L on consecutive days. Sodium was mildly elevated at 144 on day 2 of medical admission. Poison control was contacted and L-carnitine 990 TID was started for suspected carnitine deficiency. The patient medically recovered after several days and was readmitted to the psychiatric hospital for further psychiatric management.

Conclusions. The patient's presentation of hyperammonemia and first-degree atrio-ventricular block were likely due to valproic acid toxicity. We suspect that carnitine deficiency contributed to the patient's valproic acid toxicity at lower-than-expected blood levels. Although antipsychotics can cause prolonged QTc interval, conduction disorders are not typical abnormalities. Caution should be taken when prescribing Depakote to individuals at higher risk of developing toxicity, including those with potential nutritional deficiencies as well as those with limited self-advocacy abilities secondary to psychiatric illness. Rapid identification of side effects, such as valproic acid toxicity, remain crucial for favorable patient outcomes.

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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. The patient's blood pressure and heart rate remain within an acceptable range and she has not experienced any 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.

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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

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 D_3-preferring D_3/D_2 and serotonin 5-HT_{1A} 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 (-14.1 vs -11.5; adjusted *P*=.0050), but not for CAR 3 mg/d (-13.1; *P*=.0727). Differences for CAR 1.5 mg/d vs PBO were observed by week 2 (nominal *P*=.0453) and maintained at weeks 4 (nominal *P*<.0001) and 6 (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*=.0026) and 3 mg/d (nominal *P*=.0076) vs PBO. At week 6, improvement in HAMD-17 total score reached nominal significance for CAR 1.5 mg/d vs PBO (-13.1 vs -11.1; nominal *P*=.0017), but not for CAR 3 mg/day (-12.2; *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.
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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.

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