when the lower dose range of CAR is used, a more favorable NNH regarding discontinuation because of an AE.
Importance. The benefit-risk profile of CAR is favorable for adjunctive treatment of MDD.
Funding. AbbVie

Effect of Adjunctive Cariprazine on Symptoms of Anhedonia in Patients with Major Depressive Disorder

Roger S. McIntyre[1], Vladimir Maletic[2], Prakash Masand[3], Andrea C. Wilson[4], Jun Yu[4], Kenneth Kramer[4], Julie L. Adams[4] and Majid Kerolous[4]

[1]University of Toronto; [2]University of South Carolina; [3]Duke-NUS and [4]AbbVie (Madison, NJ)

Purpose. Anhedonia, a multidimensional domain including the reduced ability to experience pleasure, is a core diagnostic symptom of major depressive disorder (MDD) and a common residual symptom. In patients with MDD, anhedonia has been associated with poor treatment outcomes, suicide and reduced functioning and quality of life. This post-hoc analysis of data from a phase 3 trial (NCT03738215) evaluated the efficacy of adjunctive cariprazine (CAR) treatment on anhedonia symptoms in patients with MDD.
Methods. Patients with MDD and inadequate response to ongoing antidepressant therapy (ADT) were randomized to CAR 1.5 mg/d + ADT, CAR 3 mg/d + ADT, or placebo + ADT for 6 weeks of double-blind treatment. Post hoc analyses evaluated the change from baseline to Week 6 in Montgomery–Åsberg Depression Rating Scale (MADRS) total score, MADRS anhedonia subscale score (items: 1 [apparent sadness], 2 [reported sadness], 6 [concentration difficulties], 7 [lassitude], and 8 [inability to feel]), and MADRS anhedonia item 8 in the overall modified intent-to-treat (mITT) population and in subgroups of patients with baseline MADRS anhedonia item 8 score of ≥4 or baseline anhedonia subscale score of ≥18. Least square (LS) mean change from baseline to Week 6 was analyzed using a mixed-effects model for repeated measures.
Results. There were 751 patients in the mITT population (CAR + ADT: 1.5 mg/d=250, 3 mg/d=252; placebo + ADT=249). At baseline, 508 (67.6%) patients had MADRS anhedonia item 8 scores ≥4, and 584 (77.8%) had MADRS anhedonia subscale scores ≥18. In the overall mITT population, LS mean change from baseline to Week 6 in anhedonia subscale score was significantly greater for CAR 1.5 mg/d + ADT (-8.4) and CAR 3 mg/d + ADT (-7.9) than for placebo + ADT (-6.8; both $P<.05$). The LS mean change from baseline in MADRS individual item 8 was also significantly greater for CAR 1.5 mg/d + ADT (-1.7) vs placebo + ADT (-1.3; $P=.0085$). In both subgroups of patients with baseline anhedonia, CAR 1.5 mg/d + ADT was associated with significantly greater reduction in MADRS total score, MADRS anhedonia subscale score, and MADRS item 8 score compared with placebo + ADT (all $P<.05$). In the CAR 3 mg/d + ADT group, significantly greater reductions vs placebo + ADT were observed for MADRS total score and MADRS anhedonia subscale score in the subgroup of patients with baseline anhedonia subscale scores ≥18 (both $P<.05$).
Importance. Adjunctive treatment with CAR was associated with a reduction in symptoms of anhedonia relative to adjunctive placebo in patients with MDD and inadequate response to ADT alone. In subgroups of patients with moderate-to-severe anhedonia at baseline, CAR + ADT demonstrated greater improvements than placebo + ADT in overall depressive symptoms and symptoms of anhedonia. These results suggest that adjunctive CAR treatment may be effective for improving symptoms of anhedonia in patients with MDD who have symptoms of anhedonia.
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Incidence and Characteristics of Akathisia with Adjunctive Cariprazine Treatment in Patients with Major Depressive Disorder

Tina Matthews-Hayes[1], Theresa Cerulli[2], Andrea C. Wilson[3], Jun Yu[4], Julie L. Adams[3] and Majid Kerolous[3]

[1]Seaside Behavioral Health, Virginia Beach, VA, USA; [2]Beth Israel Deaconess Medical Center, Boston, MA, USA; [3]AbbVie, Madison, NJ, USA and [4]AbbVie, North Chicago, IL, USA

Purpose. Akathisia is a common adverse effect associated with use of dopamine receptor blocking agents.[1,2] Symptoms of akathisia, in severe cases, may lead to discontinuation of treatment. Cariprazine is a dopamine D_3-preferring D_3/D_2 receptor partial agonist and serotonin 5-HT_{1A} receptor partial agonist approved to treat schizophrenia and acute manic, mixed, and depressive episodes of bipolar 1 disorder. Cariprazine is well tolerated in patients across its indications, but is associated with a higher incidence of akathisia compared with placebo.[3,4] This pooled post hoc analysis of data from phase 3 clinical trials of adjunctive cariprazine aimed to characterize the incidence, severity, and management of akathisia and other extrapyramidal symptoms (EPS) in adult patients with MDD.
Methods. Patients with MDD and inadequate response to ongoing antidepressant therapy (ADT) were randomized to cariprazine 1.5 mg/d + ADT, cariprazine 3 mg/d + ADT, or placebo + ADT for 6 weeks of double-blind treatment. Post hoc analysis evaluated incidence, severity, and time to resolution of akathisia, restlessness, and other EPS; use of rescue medications; and the rate of discontinuation due to these treatment-emergent adverse events (TEAEs).
Results. A total of 1508 patients (cariprazine + ADT: 1.5 mg/d, n=502, 3 mg/d, n=503; placebo + ADT, n=503) were included in these 2 studies. The incidence of akathisia was greater with cariprazine 3 mg/d + ADT (9.7%) than with cariprazine 1.5 mg/d + ADT (6.4%) and placebo + ADT (2.0%). Most patients treated with

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cariprazine + ADT (94%) experienced only mild or moderate akathisia. The incidence of restlessness was 3.8% for patients treated with cariprazine 3 mg/d + ADT, 3.6% for cariprazine 1.5 mg/d + ADT, and 1.8% for placebo + ADT. The incidence of EPS excluding akathisia and restlessness was 4.4% for patients treated with cariprazine 3 mg/d + ADT, 4.6% for cariprazine 1.5 mg/d + ADT, and 3.2% for placebo + ADT. For patients treated with cariprazine + ADT and placebo + ADT, respectively, EPS-related study discontinuations were 1.4% and 0.4% due to akathisia, 0.2% and 0.0% due to restlessness, and 0.1% and 0.4% due to EPS excluding akathisia and restlessness. Rescue medications were used to treat EPS-related TEAEs during the double-blind treatment period in 3% of cariprazine-treated patients and 0.4% of placebo-treated patients. The mean time to resolution of akathisia during treatment was slightly shorter in cariprazine-treated patients (15.6 days) versus placebo-treated patients (19.5 days).

Importance. Incidence of akathisia was higher for cariprazine than placebo, with a lower incidence observed for patients treated with cariprazine 1.5 + ADT than with cariprazine 3 mg/d + ADT, suggestive of a dose related effect. Most patients experienced mild or moderate akathisia. Rates of study discontinuation and rescue medication use due to akathisia were low, suggesting that akathisia was tolerated by most patients.

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Effect of Adjunctive Cariprazine Treatment on Anxiety and Somatization Symptoms in Patients with Major Depressive Disorder: A Post Hoc Analysis

Maurizio Fava[1], Vladimir Maletic[2], Jun Yu[3], Simranpreet Waraich[3], Julie L. Adams[3], Ken Kramer[3] and Majid Kerolous[3]

[1]Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA; [2]University of South Carolina School of Medicine, Columbia, SC, USA and [3]AbbVie, Madison, NJ, USA

Introduction. Patients with major depressive disorder (MDD) commonly experience comorbid anxiety and somatization, which can complicate treatment. Adjunctive therapy with atypical antipsychotics can be an effective treatment option for patients with MDD who had inadequate responses to antidepressant therapy (ADT) alone. Cariprazine is a dopamine D_3-preferring D_3/D_2 and serotonin 5-HT_{1A} receptor partial agonist that is approved as an adjunctive treatment for MDD. This post hoc analysis examined the effect of adjunctive cariprazine therapy on anxiety and somatization symptoms in patients with MDD.

Methods. A post hoc analysis was conducted using data from a phase 3, double-blind, placebo-controlled, fixed-dose study of patients with MDD who had inadequate responses to ADT alone. Patients were randomized (1:1:1) to receive ADT plus cariprazine 1.5 mg/d, 3 mg/d, or placebo for 6 weeks. The least squares (LS) mean change from baseline to week 6 in Hamilton Rating Scale for Depression (HAM-D) Anxiety/Somatization subscale was measured. The Anxiety/Somatization subscale includes six HAM-D items: anxiety-psychic, anxiety-somatic, gastrointestinal somatic symptoms, general somatic symptoms, hypochondriasis, and insight. The modified intent to treat population included 751 patients (placebo=249; cariprazine 1.5 mg/d=250; cariprazine 3 mg/d=252).

Results. The LS mean change from baseline in HAM-D Anxiety/Somatization subscale at week 6 was significantly greater than placebo + ADT for both cariprazine + ADT dose groups (placebo: -3.22; cariprazine 1.5 mg/d: -4.00, $P<.001$; 3 mg/d: -3.75, $P<.05$). LS mean change from baseline in the cariprazine 1.5 mg/d + ADT group was also significantly greater than placebo + ADT on the anxiety-psychic (placebo: -0.88; cariprazine 1.5 mg/d: -1.08, $P<.01$) and anxiety-somatic (placebo: -0.78; cariprazine 1.5 mg/d: -0.96, $P<.05$) items. In patients treated with cariprazine 3 mg/d + ADT, LS mean changes from baseline on anxiety-psychic and anxiety-somatic items were numerically larger than placebo + ADT but not statistically significant. Both cariprazine + ADT dose groups had significantly larger LS mean changes compared with placebo + ADT on the gastrointestinal somatic symptoms item (placebo: -0.51; cariprazine 1.5 mg/d: -0.66, $P<.01$; cariprazine 3 mg/d: -0.68, $P<.01$). General somatic symptoms, hypochondriasis, and insight items showed no significant difference between placebo + ADT and cariprazine + ADT groups.

Conclusions. Patients treated with adjunctive cariprazine demonstrated greater improvements than patients treated with adjunctive placebo on HAM-D Anxiety/Somatization subscale scores, as shown by reduced scores on anxiety-psychic, anxiety-somatic, and gastrointestinal items. These findings suggest adjunctive cariprazine therapy may be effective in reducing anxiety and somatization symptoms in patients with MDD.

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Role of External Factors in the Severity of Dissociation Experienced by Treatment-Resistant Depression Patients Following Esketamine Administration

Maria M. Vento-Correa, PharmD, BCPP, CPh[1], Vidhya Meyyappa, MD, PGY4[2], Alberto Augsten, PharmD, MS, BCPP, DABAT[1], Samantha Sotelo, PharmD, BCPP[1] and Gil Abramovici, MD[1]

[1]Memorial Healthcare System, Hollywood, Florida and [2]Psychiatry Residency Program, Memorial Healthcare System, Hollywood, Florida

Introduction. Esketamine nasal spray is an NMDA receptor antagonist which is FDA approved, in conjunction with an oral antidepressant, for treatment- resistant depression (TRD) in

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