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

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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

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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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adults. Dissociation is a well-known side effect to treatment and can be measured using the CADSS (Clinician Administered Dissociative States Scale). To date, patient specific factors that may contribute to the severity of dissociation have not been described.
Methods. This case series describes two patients receiving treatment with 84-mg esketamine nasal spray twice weekly in an outpatient clinic for TRD who experienced an episode of significant dissociation several months into their treatments. History obtained prior to esketamine treatment included an assessment for any recent stressors. CADSS score was assessed posttreatment.
Results. Case 1 was a 55-year-old female who had been receiving esketamine for over two months who presented to the clinic complaining of recent sleep-deprivation while caring for her newborn grandchild. Patient experienced extreme dissociation following administration of esketamine, verbalizing that she felt "very big" and began twitching, grimacing, moaning, and repeating nonsensical statements. CADSS score after treatment was 27. Case 2 involves a 59-year-old female with a remote history of sexual trauma who was four months into esketamine treatments when she presented to the clinic feeling sad after listening to another sexual assault victim's testimony on social media prior to treatment. Shortly after receiving esketamine, she began experiencing a flashback to previous trauma and screaming loudly. CADSS score after treatment was 21. Although both patients reported a history of dissociation with esketamine treatments in the past, they both reported that the level of dissociation they experienced during the above sessions was far more severe.
Conclusions. Severe episodes of dissociation during treatment with esketamine in patients with TRD may be associated with patient specific factors. Assessing patients for the presence of recent stressors or changes to their routine prior to each treatment session may help healthcare professionals predict the risk of severe dissociation and allow providers to better prepare to support patients during these experiences.
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Drug-Drug Interactions with Vesicular Monoamine Transporter 2 Inhibitors: Population Estimate of Patients With Tardive Dyskinesia at Risk in Real-World Clinical Practice

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Introduction. Valbenazine and deutetrabenazine (vesicular monoamine transporter 2 inhibitors) are approved for tardive dyskinesia (TD) treatment in adults. To prevent potential drug-drug interactions (DDIs), valbenazine labeling recommends doses 40 mg/day when taking strong CYP3A4 or CYP2D6 inhibitors and avoidance of strong CYP3A4 inducers and monoamine oxidase inhibitors (MAOIs). Deutetrabenazine labeling recommends doses ≤36-mg/day when taking strong CYP2D6 inhibitors and avoidance of MAOIs. This study estimated proportions of patients with TD at risk of DDIs with valbenazine/deutetrabenazine in real-world practice.
Methods. Patients aged ≥18 years with TD and ≥1 antipsychotic claim(s) and no valbenazine/ deutetrabenazine claims ≥3 months prior and ≥12 months after diagnosis were identified in the Symphony Health Sciences database (US-based medical, hospital, and pharmacy claims database). Proportions of patients meeting valbenazine/deutetrabenazine concomitant medication labeling restrictions were summarized descriptively.
Results. 14,264/66,046 patients with TD met inclusion criteria. Proportions of patients at potential risk of DDIs were lower with deutetrabenazine ≤36 mg/day (0.2%) and >36 mg/day (21%) versus valbenazine 40 mg/day (4.4%; 22-times difference) and >40 mg/day (28%; 1.3-times difference). Across age groups, underlying conditions (major depressive, mood, and bipolar disorders; schizophrenia), and payer types, proportions of patients at potential risk of DDIs were lower with deutetrabenazine ≤36 mg/day (0.0%– 0.5%) and >36 mg/day (14%– 30%) versus valbenazine 40 mg/day (3%– 5%; 8.0- to >40.0times difference) and >40 mg/day (22%– 35%; 1.2- to >1.5-times difference).
Conclusions. Estimated proportions of patients with TD at potential risk of DDIs was lower with deutetrabenazine versus valbenazine overall and across age, underlying conditions, and payer types.
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Real-World Antipsychotic and Vesicular Monoamine Transporter Type 2 Inhibitor Treatment Patterns in Patients Newly Diagnosed with Tardive Dyskinesia

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