4 panelists (1 psychiatrist, 2 neurologists/MDSs, and 1 APP) who tested the questions in clinical practice for revision and refinement. The same group also worked with the sponsor to develop 2 additional sections that could be used to elicit more information from patients. The panel recognized the need for a tool that could facilitate telehealth screening for TD, including audio-only interactions. Therefore, practices from speech-language pathologists (eg, diadochokinetics) were used to refine the questionnaire.
Results. Part 1 of the MIND-TD questionnaire includes a yes-or-no question for each of the 4 following topics: presence of extra or unwanted movements (Movement); feelings of embarrassment or self-consciousness (Impact); if anyone else has noticed the movements (Notice); and if movements interfere with everyday routines (Daily Activities). Part 1 can be administered by any trained medical staff, either in person or via telehealth (with video or audio-only). Routine administration is suggested in all patients who meet any of the following criteria: current or prior use of any first- or second-generation antipsychotic; use of an anticholinergic medication in conjunction with a current or past antipsychotic; or current diagnosis of TD. Part 2 of the MIND-TD questionnaire has 2 sections. The first (Thorough Interview) includes 9 items related to physical/functional difficulties (eg, eating, speaking, walking, and gripping objects) and 3 simple instructions for speech difficulties. The second section (Differentiate) includes checklists of characteristic movements for TD and drug-induced parkinsonism, along with an item related to akathisia and suggestions for observing abnormal or involuntary movements. Part 2 should be administered by the treating HCP in patients who have abnormal movements that may be related to TD. Part 2 requires visual observation of the patient, whether in-person or via video.
Conclusions. MIND-TD is a screening questionnaire that can facilitate a dialogue between HCPs and patients about the risks, symptoms, and impact of TD. The MIND questions can stand alone and be administered during in-person visits or telehealth visits (video or audio-only). The TD section can be used to gather more information about a patient's abnormal movements.
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Long-Term Effects of Once-Daily Valbenazine in Older and Younger Adults with Tardive Dyskinesia

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Abstract

Introduction. Older patients taking a dopamine receptor blocking agent (eg, first- or second-generation antipsychotic) have an increased risk for tardive dyskinesia (TD), a persistent and potentially disabling movement disorder. Valbenazine, a selective and potent vesicular monoamine transporter 2 inhibitor, is approved for once-daily treatment of TD with no dosing adjustments required for older patients. This analysis of valbenazine clinical trial data, which is the first to evaluate an approved TD medication in a population ≥65 years, was conducted to better understand treatment outcomes in older patients.
Methods. Data from two 48-week long-term studies (KINECT 3-extension, KINECT 4) were pooled and analyzed in older (≥65 years) and younger (<65 years) participants. Analyses based on the Abnormal Involuntary Movement Scale (AIMS) total score included: mean change from baseline (BL); clinically meaningful response (≥30% improvement from BL [AIMS-30%]); and protocol-defined response (≥50% improvement from BL [AIMS-50%]). Additional analyses included response thresholds for Clinical Global Improvement-Tardive Dyskinesia and Patient Global Impression of Change as follows: rating of "minimally improved" or better (score ≤3) at week 48 (CGI-TD≤3, PGIC≤3); rating of "much improved" or "very much improved" (score ≤2) at week 48 (CGI-TD≤2, PGIC≤2).
Results. AIMS outcomes in the older subgroup were generally comparable to (or better than) outcomes in the younger subgroup and overall study populations. In participants ≥65 years, pooled AIMS results indicated substantial improvements in TD movements with valbenazine 40 mg (n = 8) and 80 mg (n = 20): mean change from BL (−6.4 and −9.8 [for 40 and 80 mg, respectively]); AIMS-30% (75% and 95%); AIMS-50% (75% and 85%). CGI-TD and PGIC response rates indicated that clinician- and patient-reported global improvements were also substantial in the older subgroup: CGI-TD = 3 (88% and 100% [for 40 and 80 mg, respectively]); CGI-TD = 2 (88% and 95%); PGIC = 3 (88% and 100%); PGIC = 2 (75% and 90%).
Conclusions. These analyses, which are the first to evaluate long-term valbenazine effects in patients ≥65 years, indicate that older study participants had clinically meaningful and substantial improvements in TD that were comparable to (or better than) those in younger participants.
Funding. Neurocrine Biosciences, Inc.

Rhabdomyolysis in Young Adult Male Stabilized on Mirtazapine and with History of COVID-19 Infection

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Abstract

Study Objective. The purpose of this case study is to review the clinical presentation and medical workup of a young adult male presenting with rhabdomyolysis in the setting of suspected contributing factors, including treatment with mirtazapine and history of COVID-19 infection.
Method. This case study involves a 19-year-old male in a residential setting with a psychiatric history of major depressive disorder and post-traumatic stress disorder who had been stabilized on mirtazapine for 9 months. Then, the patient exhibited fever, sore throat, cough, nausea, diarrhea, and malaise and was

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diagnosed with COVID-19 infection; he did not require hospitalization, was treated with supportive care, and signs and symptoms resolved uneventfully. Approximately 2 months later, in the winter, the patient presented for clinical assessment due to hematuria and painful urination. History revealed that he had been exercising excessively exercising over the past 24 hours, completing hundreds of push-ups and sit-ups. The patient presented to a nearby community hospital and was found to have creatine kinase of over 500,000. He was transferred to a large Midwestern university hospital for further evaluation and management.

Results. The patient's serum creatine kinase level was found to be 510,000 U/L. Patient's ALT, AST, and alkaline phosphatase were 283, 79, and 76 IU/L, respectively, while creatinine was 0.92. Patient received vigorous hydration, supportive care, and further evaluation. Treatment with mirtazapine was discontinued. The following week he developed severe nausea and vomiting; creatine kinase had decreased to 920, while hepatic function tests remained mildly elevated. Evaluation for hepatitis, cytomegalovirus, and Epstein-Barr virus were negative, as was Wilson's disease and hemochromatosis. Further medical workup for other potential causes of rhabdomyolysis was negative. The patient recovered and is asymptomatic with return to normal lab values. He remains in psychiatric follow-up.

Conclusions. The patient's presentation of rhabdomyolysis may have been attributable to multiple factors. Independently, sustained excessive physical activity, COVID-19 infection, and treatment with mirtazapine have all been implicated in the development of rhabdomyolysis. Caution should be taken when prescribing mirtazapine in individuals at higher risk of developing rhabdomyolysis, including those engaged in excessive exercise or who have had COVID-19 infection.

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A Phase 2a Double-Blind Randomized Trial of REL-1017 (Esmethadone) in Patients with MDD: Analysis of Subscales from the Symptoms of Depression Questionnaire

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Abstract

Background. Major depressive disorder (MDD) is the second leading cause of disability and chronic disease burden in the United States. The importance of improving functional outcomes in MDD is increasingly recognized. The Symptoms of Depression Questionnaire (SDQ), a patient-reported measure, was developed to capture the heterogeneity of symptoms of MDD. REL-1017 (esmethadone HCl; D-methadone), is a novel *N*-methyl-D-aspartate receptor (NMDAR) channel blocker and potential rapid antidepressant currently in Phase 3 development. In a Phase 2a trial, REL-1017 showed robust, rapid, and sustained antidepressant efficacy as adjunctive treatment in patients with MDD. The objective of this study was to assess the effects of REL-1017 on SDQ subscales to better characterize the functional implications of its therapeutic effects.

Methods. A double-blind, placebo-controlled, inpatient, two-doses, 25 and 50 mg, three-arm, 1:1:1, randomized, phase 2a trial of REL-1017 was conducted at 10 centers in the United States. Least square (LS) mean scores and Cohen's effect sizes of the total score of a 44-item of SDQ and its 5 subscales: lassitude, mood, cognitive/social functioning (SDQ-1); anxiety, agitation, anger, and irritability (SDQ-2); desire to be dead (SDQ-3); disruptions in sleep quality (SDQ-4); changes in appetite and weight (SDQ-5) were compared between REL-1017 and placebo.

Results. A total of 62 adult male and female patients (18-65 years of age) diagnosed with MDD participated in the trial. On day 14, the last day of efficacy measurement, the difference from placebo of the LS mean (90% CI) for REL-1017 25 mg and REL-1017 50 mg groups, respectively, showed improvement for both tested doses on SDQ total score (−23.2; $P = .0066$ [effect size: 0.9]; −26.8 $P = .0014$ [effect size: 1.1]). Additionally, for SDQ subscales, REL-1017 25 mg and REL-1017 50 mg groups, respectively, showed significant improvement as compared with placebo: SDQ-1 (−13.9; $P = .0025$ [effect size: 1.0]; −15.0; $P = .0009$ [effect size: 1.1]), SDQ-2 (−4.6; $P = .0398$ [effect size: 0.7]; −7.2; $P = .0012$ [effect size: 1.1]) and SDQ-4 (−2.7; $P = .0055$ [effect size: 1.0]; −2.8; $P = .0029$ [effect size: 1.0]). No significant differences were observed between the treated groups and placebo in the SDQ-3 and SDQ-5 subscales.

Conclusions. In patients with MDD, aside from improving the overall CFB compared to placebo in SDQ total score, REL-1017 resulted in clinically meaningful and statistically significant improvements in cognitive/motivational, anxiety/irritability, and sleep-specific domains. The robust, rapid, and sustained efficacy of REL-1017 for MDD is not limited to improving mood, but potentially extends to cognitive, motivational, sleep, and social functions, with potentially meaningful therapeutic and socioeconomic implications. These results may signal disease-modifying effects of esmethadone for MDD that may offer potential advantages over symptomatic treatment with standard antidepressants.

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