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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