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Effect of a Novel NMDA Receptor Modulator, Rapastinel (formerly GLYX-13) in OCD: Proof-of-Concept

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LETTER TO THE EDITOR

A single intravenous dose of ketamine, a N-methlyl D-aspartate receptor (NMDAR) full antagonist, produces robust and rapid anti-obsessional effects in obsessive-compulsive disorder (OCD),[1, 2] but ketamine's side effects, including dissociation and nausea, may limit clinical use.[1, 3–5] Rapastinel (formerly GLYX-13), a putative NMDAR functional glycine-site partial agonist, has shown rapid anti-depressant activity without ketamine-like side effects,[6] and may be a new therapeutic strategy for OCD. We conducted the first test of the tolerability and potential efficacy of rapastinel administration in OCD. Specifically, we explored the drug's acute effects on obsessive-compulsive symptoms, depression and anxiety at 90 and 230 minutes post-infusion and at one week post-infusion.

Methods

With IRB approval, seven unmedicated OCD outpatients (aged 18–55) were recruited (March, 2014 – March, 2015) and provided written informed consent. Patients met criteria for OCD (both DSM-IV and DSM-5) with at least moderate symptoms (Yale-Brown

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Obsessive-Compulsive Scale [Y-BOCS[7, 8]] score ≥16). Exclusion criteria included severe depression (Hamilton Depression Rating Scale [17 item version] >25),[9] current cognitive behavioral therapy, and other comorbid psychiatric or medical conditions that made participation unsafe.

Patients (n=7) received a single 3–5 minute IV push of rapastinel (dose=10 mg/kg). At baseline, 90, and 230 minutes post-infusion, patients self-rated the severity of their obsessions and compulsions (*Y-BOCS Challenge Scale* [*YBOCCS*],[10] a 10 item self-report form that assesses OCD symptoms [i.e., time spent, degree of control, severity] [total score range 0–40] over the previous *60 minutes*, facilitating symptom evaluation over shorter time intervals), anxiety (Beck Anxiety Inventory [BAI][11]), and depression (Beck Depression Inventory [BDI][12]). Side effects of dissociation,[13] mania,[14] and psychosis[15] were assessed at baseline, 90, and 230 minutes post-infusion. At baseline and one week post-infusion, an independent evaluator, blind to study design, evaluated patients using the Y-BOCS, which appraises obsessive and compulsive symptoms over the prior week, and patients self-rated anxiety (BAI) and depression (BDI). Treatment response was defined *a priori* as ≥35% Y-BOCS reduction.[16] Outcomes were analyzed using a non-parametric Wilcoxon signed-rank matched-pairs test ($\alpha = .05$, two-tailed) without adjustment for multiple comparisons given the exploratory nature of this study.

Results

All seven patients who received rapastinel completed the infusion. Patients had severe OCD symptoms: mean Y-BOCS score at baseline was 28.9 (SD = 4.4), with mean duration of illness of 24.9 years (SD = 10.6 years). The mean number of prior adequate serotonin reuptake inhibitor (SRI) trials was 3.4 (SD = 2.8, median = 3, with range 0–7). In our sample, 86% received at least one adequate trial of an SRI, 29% failed at least one prior adequate trial of antipsychotic augmentation, and 57% failed at least one prior adequate trial of cognitive behavior therapy with exposure and response prevention. Three of the seven OCD subjects (43%) had no other psychiatric comorbidity. Two subjects (29%) met criteria for comorbid generalized anxiety disorder. Two (29%) met criteria for comorbid major depression, with baseline HDRS scores of 11 (mild) and 14 (moderate). Compared to baseline, *YBOCCS*, BAI, and BDI scores were significantly lower at 90 and 230 minutes post-infusion (all p values < .05; Figure 1 and Supplementary Figure 1; the percentage decrease in *YBOCCS* from baseline to 230 minutes post infusion was 46.4%). OCD severity, as measured by the Y-BOCS, was not significantly decreased ($p = .20$) from baseline to one week post-infusion, nor was BDI ($p = .20$), although BAI was significantly decreased ($p = .02$). No patient met the treatment response criterion (≥35% Y-BOCS reduction) at one week post-infusion (mean Y-BOCS score was 28.9 [SD = 4.4] at baseline and 26.0 [SD = 5.4] at one week post infusion). One individual with mild comorbid depression had further reduction in HDRS score from 11 (at baseline) to 1 (at 230 min), with a slight increase to 7 (by one week post rapastinel infusion).

Rapstinel was well tolerated. Of note, in contrast to participant reports in a prior study of IV ketamine in OCD,[1] participants did not report adverse events (e.g., dizziness, nausea,

vomiting, or headache). Assessments of dissociation, mania, and psychosis were not significantly changed from baseline.

Conclusions/Discussion

The findings suggest that rapastinel is well tolerated in unmedicated OCD patients, as it is in patients with depression.[6] Specifically, rapastinel did not increase psychotomimetic effects following dosing in this sample of OCD patients, unlike ketamine in prior studies.[1, 3–5] In this small open-label sample, rapastinel had acute effects on obsessions and compulsions, anxiety and depression. However, rapastinel did not have significant effects on OCD symptoms one week post-infusion. To have clinical utility, glutamate modulators should refine molecular targets for rapid and sustained action while minimizing side effects. Mechanistic preclinical data suggests drugs like rapastinel[17] and ketamine's metabolite hydroxynorketamine[1,8] that act on AMPA receptor modulation pathways may be promising therapeutic strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Dr. Rodriguez received rapastinel for the present study at no cost, and she was reimbursed for travel and time to present findings to Allergan after the letter was submitted for publication; she reports no additional financial relationships relevant to the subject of this letter. Dr. Simpson received royalties from Cambridge University Press and UpToDate, Inc. Dr. Moskal was founder and owned stock in Naurex and Dr. Burch was an employee at Naurex when rapastinel was donated for the current study.

Role of the Sponsor: NARSAD, NYP-YAC, NIMH, and NYSPI had no role in the design, analysis, interpretation or publication of this study. Naurex supplied study materials (rapastinel at no cost) and Naurex staff participated in the outline of the study but had no role in study selection or interpretation of the data. Although staff at Allergan reviewed the manuscript, final approval for the decision to submit the manuscript was the sole decision of the authors.

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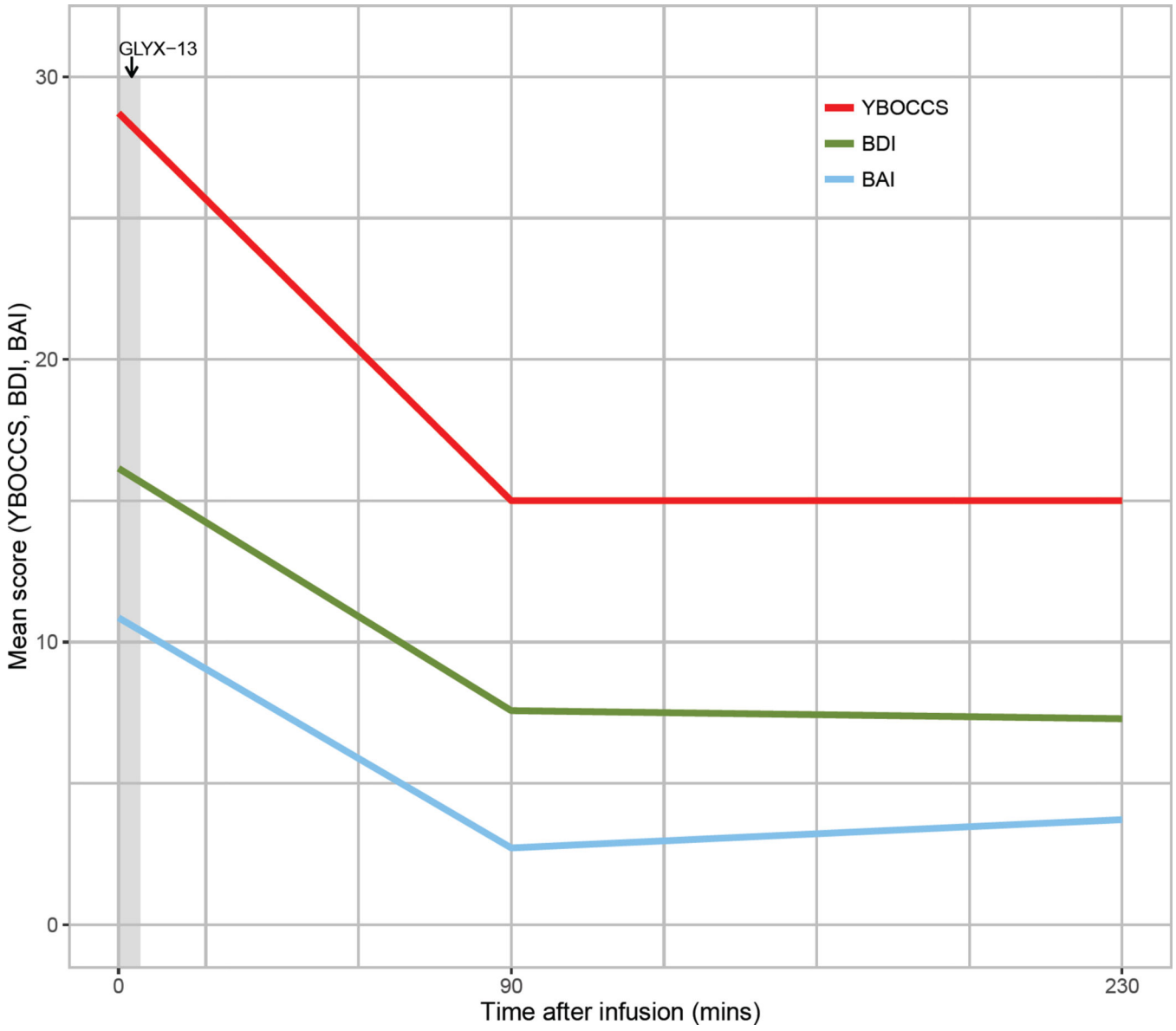

Figure 1. Obsessive-compulsive, Depression, and Anxiety Severity Mean Scores at baseline, 90, and 230 minutes after a Single Infusion of Rapastinel (N=7)

At baseline, 90, and 230 minutes post infusion (rapastinel 10mg/kg), patients self-rated the severity of their obsessions and compulsions (*YBOCCS* [range 0–40]), anxiety (BAI [range 0–63]), and depression (BDI [range 0–63]). For the 90 and 230 minute assessments, patients were instructed to rate their symptoms over the past 60 minutes for all three measures. Means scores are plotted for each assessment measure.

Abbreviation: *YBOCCS* = Yale-Brown Obsessive Compulsive Challenge Scale; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory.