Letters to the Editor

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

TO THE EDITOR: A single intravenous dose of ketamine, an *N*-methyl-D-aspartate receptor (NMDAR) full antagonist, produces robust and rapid antiobsessional 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 antidepressant 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 minutes and at 230 minutes postinfusion and at 1 week postinfusion.

Method

We received approval from an institutional review board and recruited seven unmedicated outpatients with OCD (ages 18–55) between March 2014 and March 2015, and they provided written informed consent. Patients met criteria for OCD (as defined in both DSM-IV and DSM-5) with at least moderate symptoms (score ≥16 on the Yale-Brown Obsessive Compulsive Scale [YBOCS]) (7, 8). Exclusion criteria included severe depression (score >25 on the 17-item version of the Hamilton Depression Rating Scale [HAM-D]) (9), current cognitive-behavioral therapy (CBT), and other comorbid psychiatric or general medical conditions that made participation unsafe.

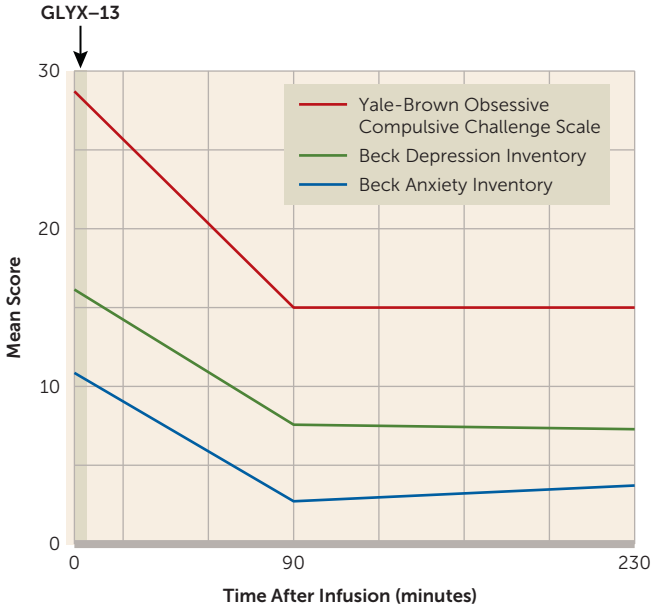
Patients (N=7) received a single 3- to 5-minute intravenous push of rapastinel (10 mg/kg). At baseline, 90 minutes postinfusion, and 230 minutes postinfusion, patients self-rated the severity of their obsessions and compulsions using the YBOC Challenge Scale (10), a 10-item self-report form that assesses 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. At the same time intervals, patients also self-rated the severity of their anxiety using the Beck Anxiety Inventory (BAI) (11) and the severity of their depression using the Beck Depression Inventory (BDI) (12). Side effects of dissociation (13), mania (14), and psychosis (15) were assessed at baseline, 90 minutes postinfusion, and 230 minutes postinfusion. At baseline and at 1 week postinfusion, an independent evaluator who was blind to study design evaluated patients using the YBOCS, which appraises obsessive and compulsive symptoms over the prior week, and patients self-rated anxiety and depression symptoms using the BAI and the BDI, respectively. Treatment response was defined a priori as a reduction of ≥35% in YBOCS scores (16). Outcomes were analyzed using a nonparametric Wilcoxon matched-pairs signed ranks test (alpha=0.05, 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: the mean YBOCS score at baseline was 28.9 (SD=4.4), with a mean duration of illness of 24.9 years (SD=10.6). The mean number of prior adequate serotonin reuptake inhibitor (SRI) trials was 3.4 (SD=2.8, median=3, 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 CBT 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 HAM-D scores of 11 (mild) and 14 (moderate). Compared with baseline, scores on the YBOC Challenge Scale, the BAI, and the BDI were significantly lower at 90 minutes and 230 minutes postinfusion (all $p<0.05$; Figure 1; see also Figure S1 in the data supplement that accompanies the online edition of this letter); the percentage decrease in YBOC Challenge Scale scores from baseline to 230 minutes postinfusion was 46.4%. OCD severity, as measured by the YBOCS, was not significantly decreased from baseline to 1 week postinfusion, and neither were scores on the BDI, although scores on the BAI were significantly decreased ($p=0.02$). No patient met the treatment response criterion (reduction of ≥35% in the YBOCS score) at 1 week postinfusion (the mean YBOCS score at baseline was 28.9 [SD=4.4] and was 26.0 [SD=5.4] at 1 week postinfusion). One individual with mild comorbid depression had a further reduction in HAM-D scores, from 11 (at baseline) to 1 (at 230 minutes), with a slight increase to 7 (by 1 week after infusion of rapastinel).

Rapastinel was well tolerated. Of note, in contrast to participant reports in a prior study of intravenous 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.

FIGURE 1. Obsessive-Compulsive, Depression, and Anxiety Severity Mean Scores at Baseline, 90 Minutes, and 230 Minutes After a Single Infusion of Rapastinel (N=7)[a]



[a] At baseline, 90 minutes postinfusion, and 230 minutes postinfusion (rapastinel at 10 mg/kg), patients self-rated the severity of their obsessions and compulsions using the Yale-Brown Obsessive Compulsive Challenge Scale (range=0–40), the severity of their anxiety using the Beck Anxiety Inventory (range=0–63), and the severity of their depression using the Beck Depression Inventory (range=0–63). For the 90-minute and 230-minute assessments, patients were instructed to rate their symptoms over the past 60 minutes for all three measures. Mean scores are plotted for each assessment measure.

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 and on symptoms of anxiety and depression. However, rapastinel did not have significant effects on OCD symptoms 1 week postinfusion. To have clinical utility, glutamate modulators should refine molecular targets for rapid and sustained action while minimizing side effects. Mechanistic preclinical data suggest drugs like rapastinel (17) and ketamine's metabolite hydroxynorketamine (1, 18) that act on AMPA receptor modulation pathways may be promising therapeutic strategies.

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The study drug, rapastinel (formerly GLYX-13), was supplied by Naurex (since drug donation, Naurex has been acquired by Allergan). 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 has received royalties from Cambridge University Press and UpToDate. Dr. Moskal was founder and owned stock in Naurex. Dr. Burch was an employee at Naurex when rapastinel was donated for this study. The other authors report no financial relationships with commercial interests.

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D-Cycloserine, an NMDA Glutamate Receptor Glycine Site Partial Agonist, Induces Acute Increases in Brain Glutamate Plus Glutamine and GABA Comparable to Ketamine

TO THE EDITOR: Ketamine, an *N*-methyl-D-aspartate glutamate receptor (NMDAR) antagonist, is effective acutely for major depression (1), but development of alternative NMDAR antagonists is limited by incomplete understanding of mechanism and optimal dosage. Based on preclinical and clinical studies (1, 2), we hypothesize that NMDAR antagonism will produce an acute increase in GABA and glutamate plus glutamine (Glx) as an early event in antidepressant action. Using proton magnetic resonance spectroscopy (^{1}H MRS), we found acute ketamine treatment in depressed patients produced rapid, transient elevations (approximately 40%) of both Glx and GABA levels in the medial prefrontal cortex (1), suggesting that this is an initial step in the antidepressant action cascade for NMDAR antagonists. We used the same methods (1) to assess the effects of high-dose D-cycloserine (1000 mg), an NMDAR glycine site partial agonist, on brain GABA and Glx in healthy subjects. Compared with ketamine, D-cycloserine has a slower (onset within 2–4 weeks) but comparable antidepressant effect (3). D-cycloserine has a dose-dependent biphasic effect on the NMDAR, potentiating function at low dosages (<100 mg), but functioning as a net antagonist at dosages >500 mg (4).

After baseline ^{1}H MRS scans, six healthy subjects (age=33 years, SD=4 years; four males and two females) were administered 1000 mg of oral D-cycloserine, followed by serial ^{1}H MRS scans for up to 90 minutes to measure Glx and GABA levels. Areas under the curve computed using the trapezoidal rule yielded large effect sizes for both Glx (69%, SD=48%, d=1.44) and GABA (39%, SD=31%, d=1.26) without inducing overt psychosis (Figure 1, next page). There was an overall main effect on Glx ($F_{5,22.8}$=2.9, p=0.034), with an initial peak at approximately 35 minutes postdose (increase of 23%, SD=5%) and a second peak 75–90 minutes postdose (increase of 20%, SD=7%). For GABA, there was a comparable, trend-level main effect ($F_{5,23.3}$=2.5, p=0.058; increase of 16%, SD=5%).

D-cycloserine increased both neurotransmitter levels comparably to ketamine, and this may be the initial step in the antidepressant cascade of NMDAR antagonism. Future studies should examine the relationship of these neurotransmitters to the degree of the antidepressant effect of D-cycloserine. Targeting the NMDAR and AMPA receptors may have specific advantages in treatment-resistant depression. The more rapid clinical improvement seen with ketamine may be due to other pharmacological effects that distinguish it from D-cycloserine, and these need to be identified to facilitate development of more rapidly acting antidepressants.

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