

### Effects of Rapastinel (Formerly GLYX-13) on Serum Brain-Derived Neurotrophic Factor in Obsessive-Compulsive Disorder

**To the Editor:** Serum brain-derived neurotrophic factor (BDNF) may be a treatment efficacy marker in depression<sup>1,2</sup> and may be altered in obsessive-compulsive disorder (OCD) and anxiety disorders.<sup>3,4</sup> Rapastinel is an *N*-methyl-D-aspartate glutamate receptor modulator shown to affect BDNF levels in vitro.<sup>5</sup> It exerts acute therapeutic effects on OCD symptoms without ketamine-like side effects.<sup>6</sup> We analyzed exploratory data regarding serum BDNF samples collected from OCD patients before and after rapastinel infusion. Our goal was to determine whether (1) rapastinel alters serum BDNF levels in the interval from 0 to 230 minutes postinfusion and (2) whether changes in BDNF levels correlated with changes in OCD symptoms during this period.

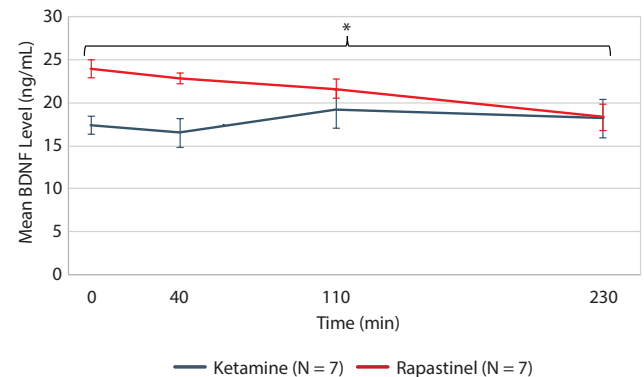
**Methods.** We received approval from an institutional review board and recruited 7 unmedicated outpatients with OCD (ages 18–55 years) between March 2014 to March 2015, and the patients provided written informed consent. Eligible patients met criteria for OCD (both *DSM-IV*<sup>7</sup> and *DSM-5*<sup>8</sup>) and were at least moderately symptomatic (Yale-Brown Obsessive Compulsive Scale<sup>9,10</sup> score  $\geq 16$ ).<sup>11</sup> Three (43%) of the 7 OCD subjects had no other psychiatric comorbidity. Two subjects (29%) met criteria for comorbid generalized anxiety disorder. Two others (29%) met criteria for comorbid major depression, with baseline 17-item Hamilton Depression Rating Scale (HDRS-17)<sup>12</sup> scores of 11 (mild) and 14 (moderate), respectively. The median HDRS-17 score at baseline was 4 (normal), with a range of 1–14.

All participants (N = 7) received a single 3- to 5-minute intravenous infusion of rapastinel (10 mg/kg). Blood was drawn in the morning (after an overnight fast) at baseline and 40, 110, and 230 minutes postinfusion. Serum BDNF levels were determined using a Millipore ChemiKine Sandwich ELISA Kit.<sup>13</sup> OCD severity was assessed at baseline and 230 minutes using the YBOCS Challenge Scale,<sup>14</sup> a 10-item self-report form assessing obsessions and compulsions over the previous hour. Depression severity was assessed at identical time points using the HDRS-17.<sup>12</sup>

We assessed BDNF level changes over time using the nonparametric Wilcoxon signed rank test. A mixed-effects regression model assessed BDNF levels' time trend. Spearman correlation tested whether changes in serum BDNF levels from baseline to 230 minutes postinfusion correlated with OCD symptom severity change. As a negative control, we compared BDNF levels of the current patient sample to those of an independent cohort of 7 OCD patients who received a ketamine infusion,<sup>15</sup> with BDNF serum levels determined in identical intervals, at the same time of day (morning), after an overnight fast, per recommended protocols.<sup>13</sup> Both sample sets were stored, processed, and analyzed concurrently using the same ELISA kit and identical methods.

**Results.** In the rapastinel group, baseline median serum BDNF level was 22.3 ng/mL (range, 16.8–34.9 ng/mL). At 230 minutes, median BDNF level was 17.55 ng/mL (range, 12.6–26 ng/mL) and decreased in 6 out of 7 participants. This reduction was statistically significant ( $P = .03$ ; Figure 1). BDNF levels exhibited a significant time-trend, decreasing from baseline to 230 minutes ( $\beta = -0.02$ ,  $P = .00003$ ). The median YBOCS Challenge Scale score at baseline was 28 (range, 24–39) and decreased in all participants (N = 7) at 230 minutes (median = 15; range, 3–20). From baseline to 230

**Figure 1. Serum BDNF Levels at Baseline and 40, 110, and 230 Minutes After a Single Infusion of Rapastinel or Ketamine<sup>a</sup>**



<sup>a</sup>Mean distribution of serum BDNF levels as a function of time. Error bars represent 1 standard error from the mean.<sup>16</sup>

\* $P < .05$ .

Abbreviation: BDNF = brain-derived neurotrophic factor.

minutes, changes in serum BDNF levels were highly correlated with changes in YBOCS Challenge Scale scores ( $r = 0.86$ ,  $P = .01$ ).

In contrast, in the ketamine group, the infusion did not significantly decrease serum BDNF levels over time. Baseline BDNF levels did not differ between the rapastinel and the ketamine OCD groups ( $P = .16$ ).

In this small sample, rapastinel reduced OCD patients' serum BDNF levels from baseline to 230 minutes, and these changes correlated with changes in OCD symptom severity. In a control sample, ketamine reduced OCD symptom severity but did not change serum BDNF levels.

In major depression, serum BDNF may be a biomarker of successful treatment,<sup>1,2</sup> with reports of serum BDNF increasing with depression symptom reduction. In contrast, we found changes in the opposite direction: serum BDNF decreased with OCD symptom reduction. Increases in BDNF are consistent with the neurotrophic hypothesis of depression, in which antidepressants mediate therapeutic benefit by up-regulating brain BDNF, reversing stress-related decreases in brain BDNF, and reversing neuronal atrophy.<sup>17,18</sup> The decreases in serum BDNF we observed with OCD symptom improvement suggest that BDNF may play a different role in OCD and stress-related mood disorders.

Limitations include small sample size and differences that may exist in typical community patients with comorbid depressive symptoms. In addition, peripheral BDNF levels have been studied as a readily accessible biomarker, under the assumption that serum levels reflect brain levels, given that BDNF has been reported to cross the blood-brain barrier.<sup>19</sup> However, peripheral changes in BDNF cannot be exclusively attributed to changes in brain BDNF since the exact source and function of peripheral serum BDNF are still being elucidated. Platelets bind, store, and release upon agonist stimulation; megakaryocytes, platelet progenitors, also can release BDNF proteins into serum.<sup>20</sup> Finally, we are unable to compare serum BDNF levels at baseline to those reported in OCD<sup>4</sup> and other disorders<sup>3</sup> due to the variety of sample collection and BDNF analysis methods used; indeed, when 6 different BDNF commercial assays were compared, interassay variation ranged from 5% to

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20%.<sup>18</sup> To avoid this problem, we used identical optimized sample collection (morning, under fasting conditions), storage, processing, and analysis methods to compare rapastinel samples with the control ketamine samples.

In sum, while both rapastinel and ketamine acutely relieved OCD symptoms, they acted differently on serum BDNF levels. Elucidating their mechanisms of action<sup>21</sup> requires further investigation.

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**Supplementary material:** See accompanying pages.

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Supplementary material follows this letter.



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## **Supplementary Material**

**Letter Title:** Effects of Rapastinel (Formerly GLYX-13) on Serum Brain-Derived Neurotrophic Factor in Obsessive-Compulsive Disorder

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### **List of Supplementary Material for the letter**

1. [eFigure 1](#) Serum BDNF Levels at Baseline, 40, 110, and 230 Minutes After a Single Infusion of Rapastinel in Seven Participants

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Supplementary eFigure 1. Serum BDNF levels at baseline, 40, 110, and 230 minutes after a single infusion of rapastinel in seven participants

