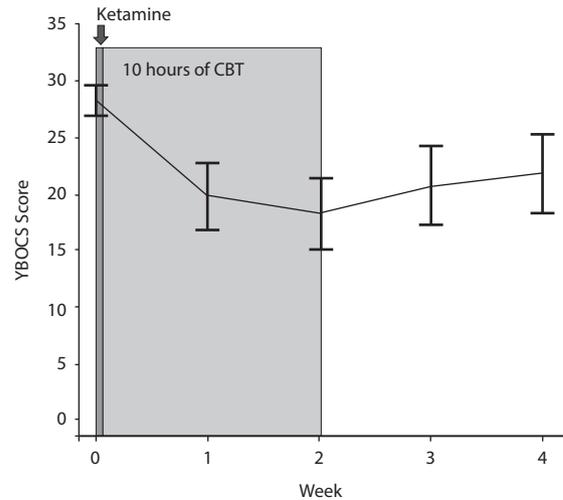


Figure 1. Obsessive-Compulsive Disorder Severity Over 4 Weeks (N = 8)^a



^aAfter a single 40-minute infusion of ketamine 0.5 mg/kg, 10 hours of exposure sessions were delivered over 2 weeks. Estimated means from mixed-effects regression are plotted with standard error. Patients had a mean illness duration of 20.5 years (standard deviation [SD] = 10.2 years). The mean number of adequate serotonin reuptake inhibitor (SRI) trials was 1.8 (SD = 1.4); 80% received at least 1 prior adequate trial of an SRI, 10% failed at least 1 prior adequate trial of antipsychotic augmentation, and 60% had failed at least 1 prior adequate trial of exposure and response prevention. Observed mean Yale-Brown Obsessive Compulsive Scale scores were as follows: baseline, 28.8 (SD = 4.6); week 2, 18.3 (SD = 8.9); week 4, 21.9 (SD = 9.8). Abbreviation: CBT = cognitive-behavioral therapy.

Can Exposure-Based CBT Extend the Effects of Intravenous Ketamine in Obsessive-Compulsive Disorder? An Open-Label Trial

To the Editor: A single subanesthetic intravenous (IV) dose of ketamine leads to rapid antiobsessional effects in obsessive-compulsive disorder (OCD) patients with near-constant intrusive obsessions,¹ but these effects usually do not persist.¹⁻³ We tested whether a brief course of exposure-based cognitive-behavioral therapy (CBT) could extend ketamine’s effects in a 2-week pilot open trial and if this effect was maintained (without additional treatment) 2 weeks later. Our rationale was (1) ketamine is reported to enhance plasticity and extinction learning in rodents,⁴⁻⁶ and (2) enhanced extinction learning may facilitate CBT gains, as reported in trials that combined CBT with medication thought to facilitate extinction learning (eg, D-cycloserine).^{7,8} Mimicking those trials, our study design included CBT that was abbreviated (ie, 10 one-hour exposure sessions) but delivered during the putative time interval when ketamine facilitates extinction learning (within 14 days).⁴

Methods. With institutional review board approval, 10 unmedicated OCD outpatients (ages 18–55 years) with near-constant intrusive obsessions (> 8 hours/d) were recruited (March 2014–March 2015). They provided written informed consent. Participants met *DSM-IV* and *DSM-5* criteria for OCD with at least moderate symptoms (Yale-Brown Obsessive Compulsive Scale [YBOCS]^{9,10} score ≥ 16). Exclusion criteria included severe depression (Hamilton Depression Rating Scale [HDRS]¹¹ > 25), current CBT, and comorbid psychiatric or medical conditions that made participation unsafe.

In an open-label design, participants received a single 40-minute IV infusion of ketamine (dose = 0.5 mg/kg), followed by 10 one-hour exposure sessions delivered over 2 weeks. The CBT treatment was planned in a 90-minute session the day before the ketamine

infusion. All CBT sessions were administered by the same therapist (M.W.) and followed standard procedures.¹²

At baseline, during the infusion, and at 20, 90, 110, and 230 minutes postinfusion, patients rated their obsessional severity using the OCD Visual Analog Scale (OCD-VAS).^{1,13-15} We focused on obsessions because the patients were supine and connected to stationary monitoring equipment during the infusion. At baseline and weekly for 4 weeks postketamine, an independent evaluator, blind to study design, evaluated patients using the YBOCS (primary outcome measure), which appraises obsessive and compulsive symptoms over the prior week. Treatment response was defined a priori as ≥ 35% YBOCS reduction at week 2.¹⁶ YBOCS outcomes were analyzed using mixed-effects regression to model symptoms as a function of time.

Results. Of the 10 patients who started ketamine, 9 completed the infusion. Eight reported a rapid reduction in obsessive severity as measured by the OCD-VAS, which persisted up to 230 minutes post-infusion in 7 patients; all 8 completed the 10 hours of exposure and the 2-week follow-up and were included in the YBOCS analyses. From baseline to 4 weeks postinfusion, OCD severity, as measured by the YBOCS, was significantly decreased over time ($F_{4,28} = 14.36$, $P < .0001$; Figure 1). Compared to baseline, the mean estimated YBOCS score was significantly lower at week 2 (difference = -10.75 points, SE = 1.44, $P < .0001$) and at week 4 (difference = -6.88, SE = 2.61, $P = .01$); there was a trend-level increase between weeks 2 and 4 (difference = 3.63, SE = 1.97, $P = .07$). At the end of CBT (week 2), 63% of patients demonstrated treatment response (≥ 35% YBOCS reduction). Importantly, individuals varied in their response, with 1 subject having no benefit, the majority benefitting for up to 2 weeks, and 1 no longer meeting criteria for OCD (ie, achieving minimal symptoms postinfusion that persisted throughout the CBT and up to 6 months in naturalistic follow-up).

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Discussion. These results corroborate prior findings¹⁻⁵ that IV ketamine can rapidly reduce obsessions in unmedicated OCD patients and advance the growing literature on enhancing CBT with agents that facilitate extinction learning.^{7,8,17} Limitations typical of an open-label trial include lack of randomization to a comparison group, which may lead to allocation and ascertainment (response) bias. The data suggest that a brief course of CBT may help some individuals maintain the improvement they experienced from ketamine; however, this needs to be formally tested in a randomized controlled trial to determine whether the improvement seen after 2 weeks of CBT is due to the addition of CBT, or whether the effects of ketamine persist longer in some than previously described.

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