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Study Title: CAP-Ketamine for Antidepressant Resistant PTSD (NCT02655692)

Brief Statistical Analysis Plan:

Briefly, the PCL-5 was considered the primary outcome, while CAPS-5 and MADRS were considered secondary measures. The primary analysis used mixed effects models, with group, time, and group-by-time effects. The secondary analyses examined the rapid and sustained effects of ketamine compared to placebo, at 24 hours post-first and post-last infusion, respectively, by focused contrasts in the mixed models. Sustainability of the effects of ketamine on PTSD symptoms was assessed with similar mixed models for PCL-5 and CAPS-5 during the follow-up period; considering that this analysis included only the responders (non-responders received open label ketamine), we covaried for pretreatment symptom severity. However, there was no difference in pretreatment severity and the results are similar without covarying for severity. The dissociative and psychotomimetic effects were examined using comparable mixed models for CADSS and PANSS, while adding interval (30 minutes vs. 120 minutes) and appropriate interactions to the models.

Supplemental

Mixed models were constructed to evaluate the effects of posttraumatic stress disorder (PTSD) treatment on the PTSD Checklist for *DSM-5* (PCL-5), Clinician-Administered PTSD Scale for *DSM-5*, Montgomery-Åsberg Depression Rating Scale (MADRS), Clinician-Administered Dissociative State Scale (CADSS), and Positive and Negative Syndrome Scale (PANSS) based on all available observations within individual patients. Treatment group (Standard, Low, Placebo), time (pre each infusion, 24 hours post-first and post-last infusions for PCL-5 and MADRS, baseline and post-last infusion for CAPS-5, during each session for CADSS and PANSS), site and all possible interactions were fit as fixed effects. Alcohol use disorder (AUD) diagnosis was included as a covariate. The CADSS and PANSS models also included interval (30 and 120 minutes) and the interaction between interval and treatment. Subject was the clustering factor. The best-fitting variance-covariance structure in each model was selected based on Bayesian information criterion. Residuals were assessed, and CADSS was log-transformed to correct for positive skewness of this outcome. In the final models, nonsignificant interactions not involving treatment were dropped for parsimony. Focused least square mean comparisons of change from baseline to 24 hours post-first infusion and from baseline to 24 hours post-last infusion within treatment group, and for pairwise differences in change from baseline between treatment groups, were evaluated regardless of the significance of the interactions and main effects. Follow-up data on the PCL-5 and CAPS-5 also were analyzed using mixed models covarying for baseline severity. Individuals with open label treatment were excluded from these analyses. Responder status was calculated as at least 25% improvement from pretreatment on the PCL-5. Missing data were treated as failure (i.e., nonresponder). The primary analyses for the binary outcomes were logistic regressions with treatment, site, and AUD as predictors, and missing treated as failure. The treatment by site interactions were nonsignificant and were dropped for parsimony in the final models.
For the PCL-5 self-assessments, 1.6% of assessments specified incorrect index trauma event referenced for symptom scoring, and 23.6% of assessments were completed without specifying the index trauma. A sensitivity analysis determined that mixed methods ANOVA results were essentially unchanged with or without their inclusion.