Data Supplement for Williams et al., Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism. Am J Psychiatry (doi: 10.1176/appi.ajp.2018.18020138)

Supplemental Methods

Design

We also employed the Montgomery–Åsberg Depression Rating Scale (28) and the self-rated Beck Depression Inventory Version II (29) as secondary measures of depression at Days 1, 3, 5, 7, and 14.

Data analyses

A third set of analyses included all participants who received at least one infusion (n=14). For the latter analysis, only the first infusion was considered, and treatment condition for that first infusion (ketamine + placebo [n=9] versus ketamine + naltrexone [n=5]) was a between-subjects factor. The change in 17-item and 6-item Hamilton Depression Rating Scale from pre- to post-infusion was the dependent variable. Analyses of other clinical data included descriptive statistics on the Montgomery–Åsberg Depression Rating Scale and Beck Depression Inventory Version II.

On other measures of depression, including the Montgomery–Åsberg Depression Rating Scale and Beck Depression Inventory Version II, similar attenuations of the antidepressant response in the ketamine + naltrexone condition were observed. Data from these depression measures are shown in Figures S2A and S2B. Additional data, including a between-subjects analysis of Hamilton Depression Rating Scale scores from only the first infusion (including all participants who received at least one infusion, n=14), are provided in the supplement and shown in Figure S3. A fixed effects analysis of variance indicated that there was a significantly greater reduction from baseline in 17-item Hamilton Depression Rating Scale scores among those receiving ketamine + placebo as their first infusion versus reductions in the ketamine + naltrexone ($F=6.1$, $p=0.030$) as well as the 6-item scale ($F=7.7$ $p=0.017$) (Figure S4).

FIGURE S1. Flow Diagram of participants in a Study of Ketamine's Antidepressant Effect after Naltrexone Pretreatment

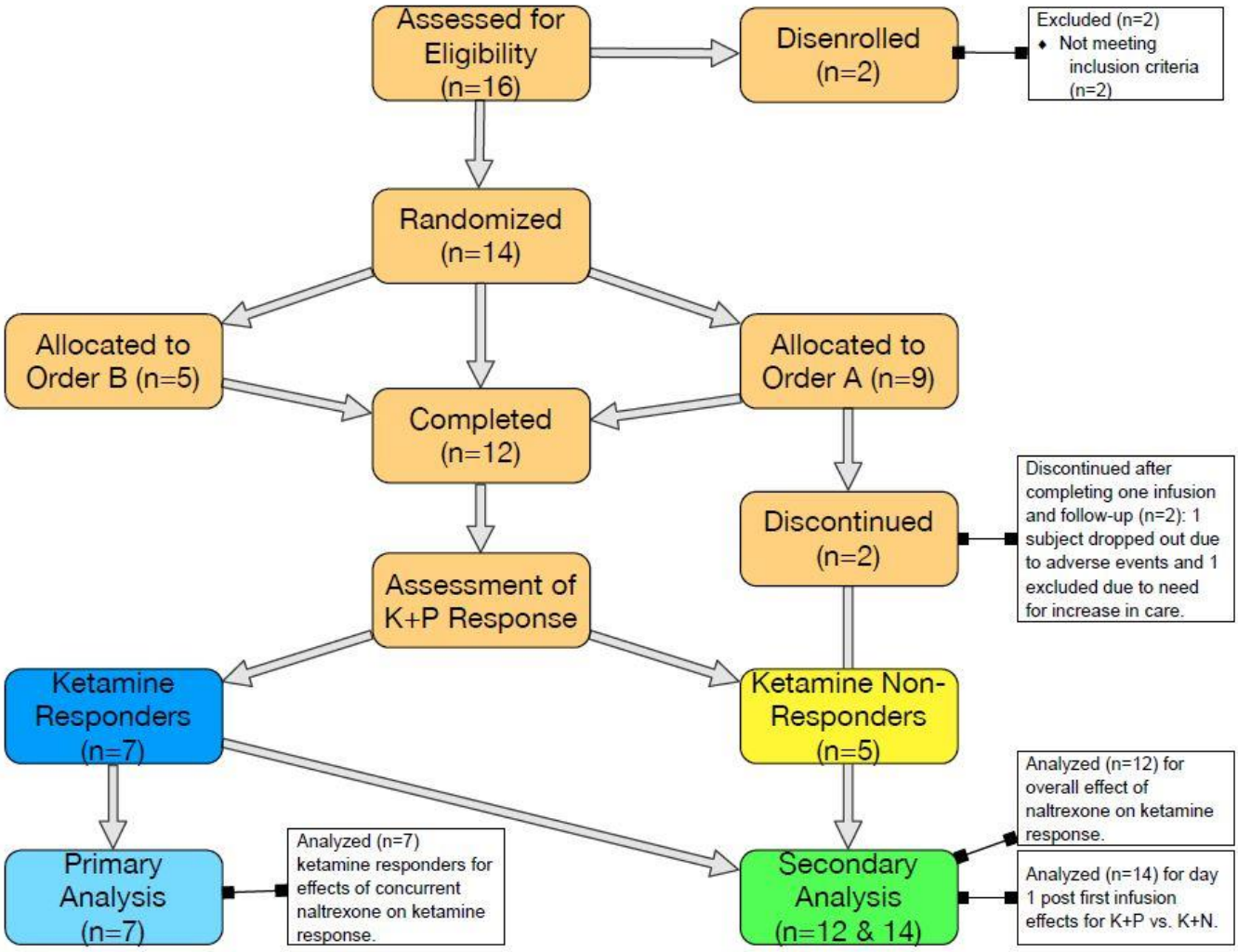

FIGURE S2. Naltrexone blocks ketamine's antidepressant effect on multiple rating scales. Time-course of ancillary outcome measures (mean ± SD) for ketamine-responsive TRD patients (n=7) in two crossed over conditions, ketamine + naltrexone (K+N) and ketamine + placebo (K+P). Treatments delivered on Day 0 following first questionnaire. K+N group scores were significantly higher than K+P group scores on Day 1 post infusion for both MADRS (**A**), BDI-2 (**B**).

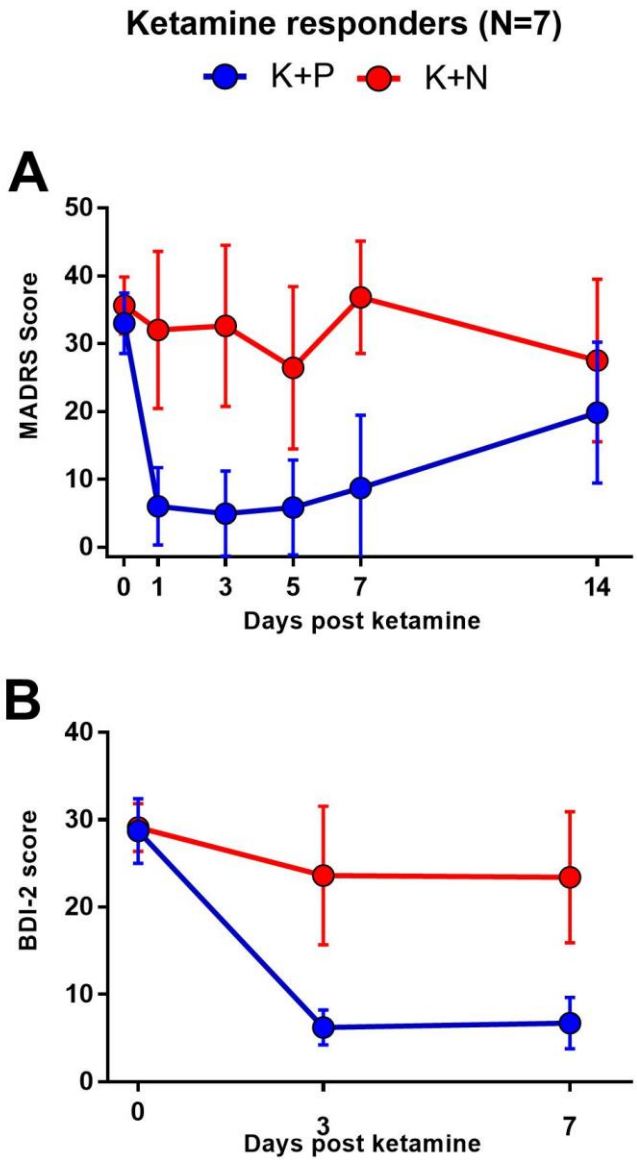

FIGURE S3. Naltrexone consistently blocks ketamine's antidepressant effect when removing the cross-over component of the trial. Time-course of primary outcome measures (mean ± SD) for all patients receiving at least one infusion (N=14), including 2 patients who withdrew from the study following the first infusion. This analysis differs from that shown in **Fig. 2** and **Fig. 3** in that only the first infusion is considered, eliminating confounds of cross-over design. On the first infusion, N=9 patients received K+P and N=5 patients received K+N. Treatments delivered on Day 0 following first questionnaire. **A.** HDRS6 time-course. Analysis of between-group HDRS6 differences on Day 1 shows that K+N group scores were significantly higher than K+P group scores, with the latter group demonstrating expected post-infusion HDRS6 score reduction. **B.** HDRS17 time-course, demonstrating qualitatively similar results as in **A.**

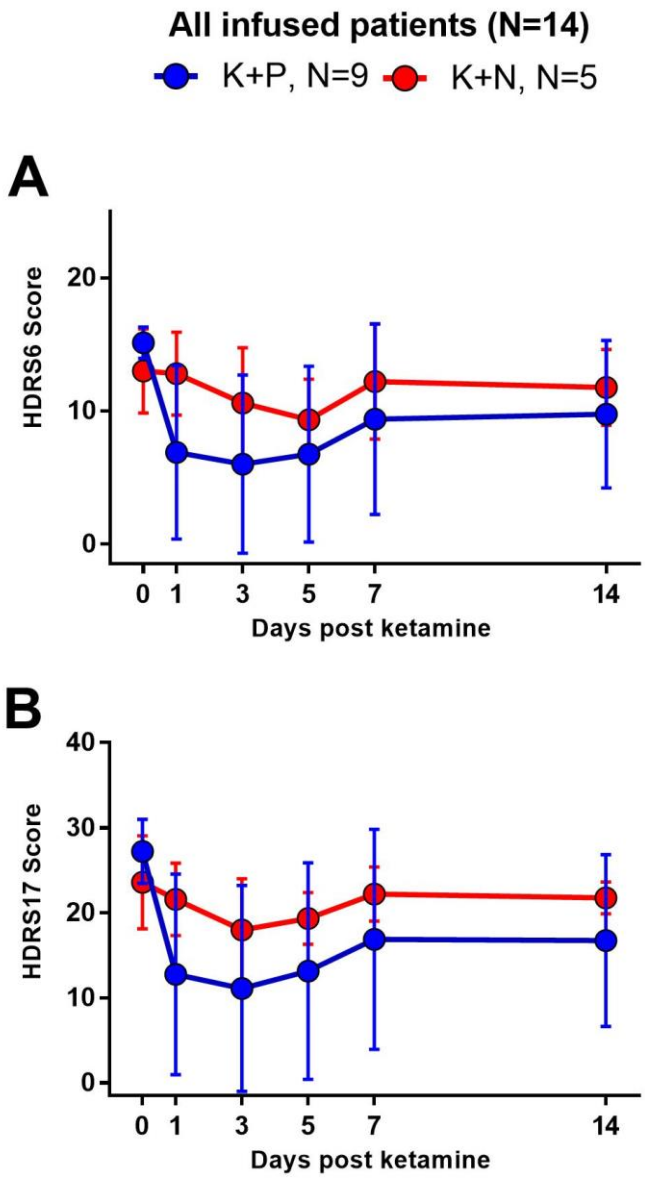

FIGURE S4. Visual Analog Scale (VAS) scores after naltrexone or placebo, but before ketamine infusion, do not differ between groups. Oral placebo (PBO) or naltrexone (NAL) was given 45 minutes to 1 hour before infusion. VAS scores for a variety of subjective effects were obtained 5 minutes prior to the initiation of infusion. Data is shown for all crossed-over patients (N=12, mean + SD). VAS scores do not differentiate which pretreatment a patient received.