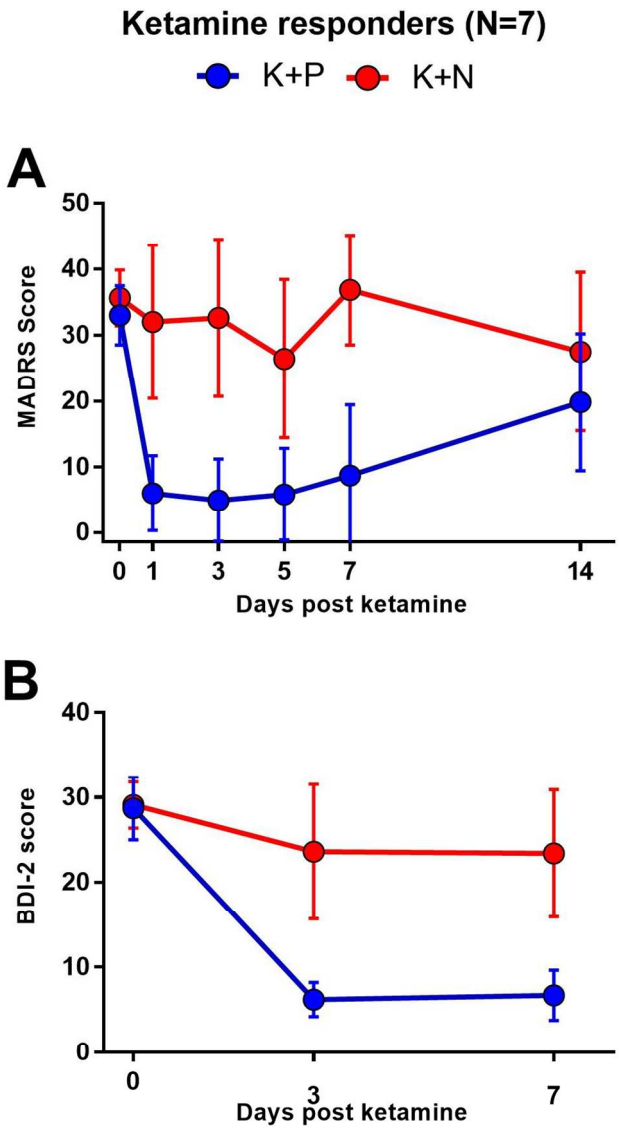
Supplementary Figure 1. Naltrexone blocks ketamine's antidepressant effect on multiple rating scales. Time-course of ancillary outcome measures (mean ± SD) for ketamine-responsive TRD patients (n=7) in two crossed over conditions, ketamine + naltrexone (K+N) and ketamine + placebo (K+P). Treatments delivered 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**).

Supplementary Figure 2. 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.**

Supplementary Figure 3. 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.



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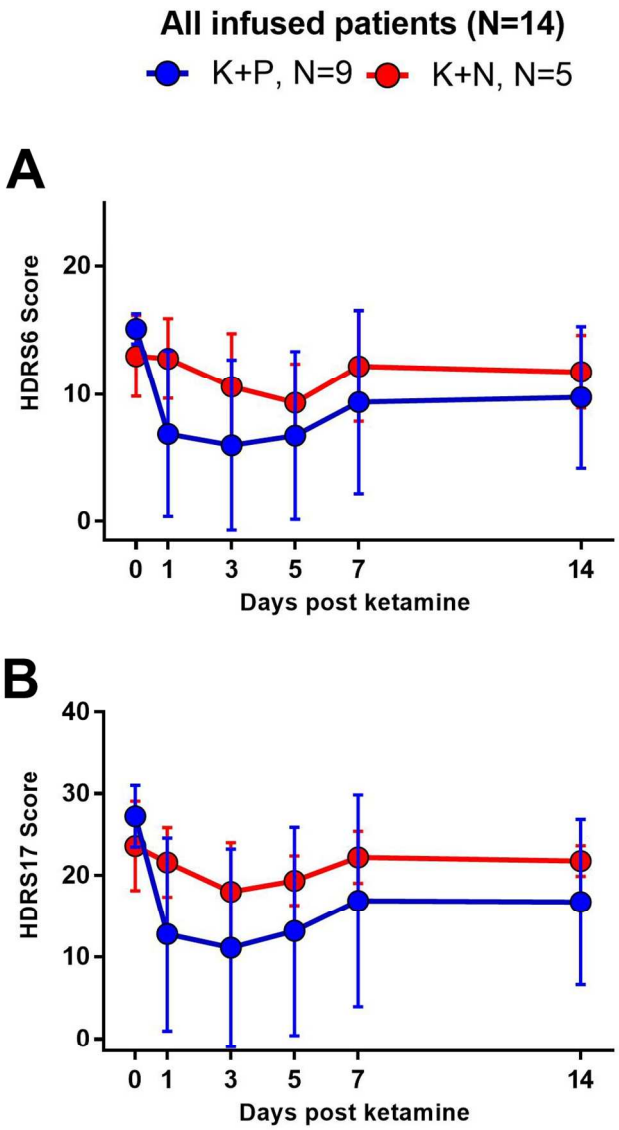

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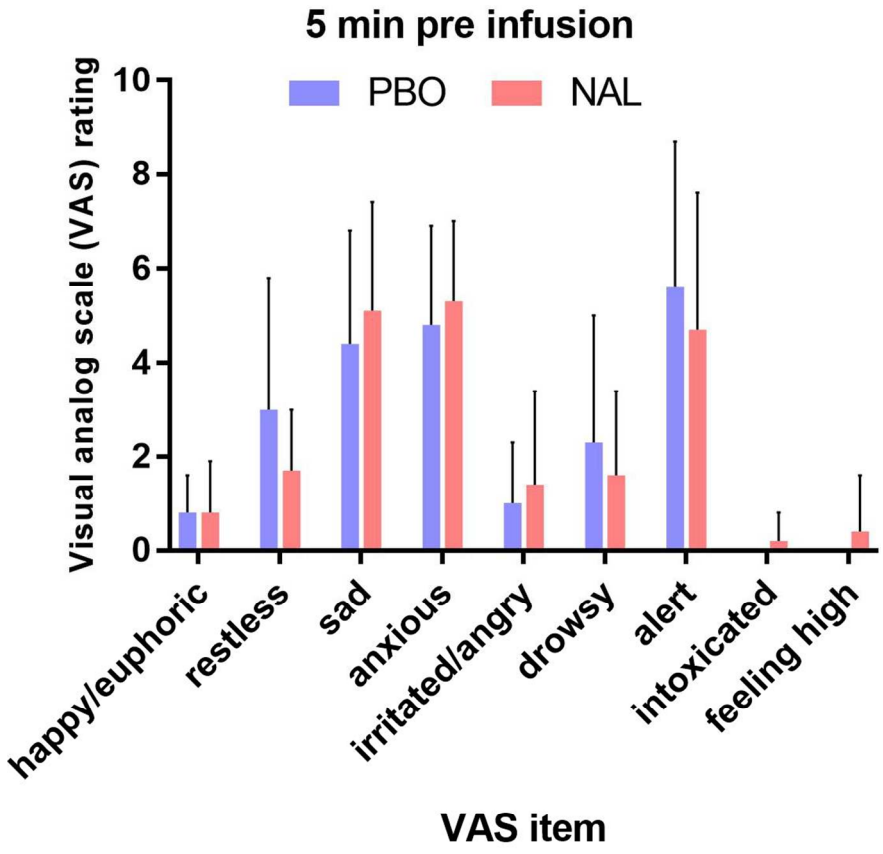

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