Replication of Ketamine's Antidepressant Efficacy in Bipolar Depression: A Randomized Controlled Add-on Trial

Supplemental Information

Supplemental Results

The Influence of Mood Stabilizer on Response

In an attempt to explore any possible influence of mood stabilizer on response, the primary analysis was conducted with patients receiving lithium. The number of patients taking valproate was too small to compare the mood stabilizers directly. A linear mixed model with the Montgomery-Asberg Depression Rating Scale (MADRS) showed a significant drug by time interaction ($F_{10,156}$ = 7.11, p < .001). Post-hoc tests indicated significantly fewer depressive symptoms in those patients who received ketamine versus placebo from 40 minutes to 2 days post-infusion. The effect sizes were large at 40 minutes (d = 1.06, 95% C.I. = .75-1.36) through 230 minutes (d = .81, 95% C.I. = .51-1.12). At Day 1, the effect was moderate to large (d = .62, 95% C.I. = .31-.92).

Assessment of Anxiety, Manic, and Dissociative Symptoms

Anxiety symptoms were assessed with the Hamilton Anxiety Rating Scale (HAM-A) and Visual Analogue Scale (VAS)-Anxiety subscale. Significant drug by time interactions were noted for both measures (HAM-A: $F_{7,141}$ = 2.75, p = .01; VAS-Anxiety scale: $F_{10,166}$ = 2.12, p = .03). Post-hoc tests indicated significant drug differences; patients who received ketamine displayed fewer anxiety symptoms from 230 minutes through Day 2 using the HAM-A, and from 40 minutes through Day 7 using the VAS-Anxiety subscale. Drug responses also differed at Day 14 on the VAS-Anxiety scale.

Manic symptoms were measured using the Young Mania Rating Scale (YMRS). No significant main effect was noted for drug ($F_{1,117} = 2.71$, $p = .10$), nor for the interaction between drug and time ($F_{10,198} = .61$, $p = .81$) (Figure S1). Although not statistically significant, YMRS scores were generally lower in patients who received ketamine versus placebo; this suggests that ketamine infusion did not increase manic symptoms.

For the Clinician Administered Dissociative Scale (CADSS), a significant interaction was observed between drug and time ($F_{10,206} = 30.32$, $p < .001$). Patients who received ketamine had higher scores than those who received placebo at 40 minutes but not at any other point (Figure S1). No difference was noted for the positive symptom subscale of the Brief Psychiatric Rating Scale (drug: $F_{1,115} = .22$, $p = .64$; drug x time: $F_{10,200} = .82$, $p = .61$) (Figure S1). Spearman correlations were used to further investigate the relationship between change in dissociative and depressive symptoms. Given scores of zero at baseline for patients on the CADSS, absolute change was used for each measure, although using absolute or percent change in MADRS did not alter the results. No significant correlations were noted at either 40 minutes or Day 1.

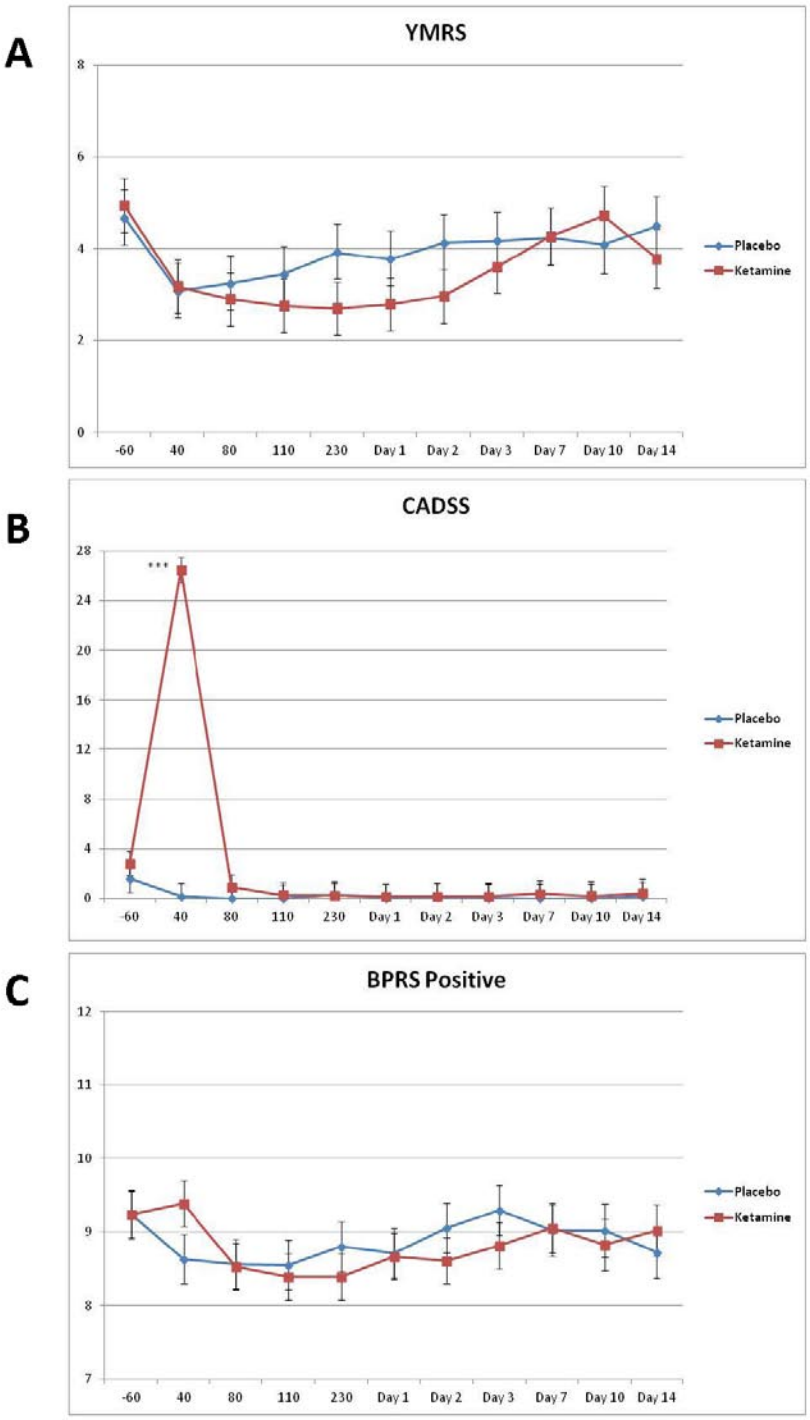

Figure S1. Change in Young Mania Rating Scale (YMRS), Brief Psychiatric Rating Scale (BPRS) positive, and Clinician Administered Dissociative Scale (CADSS) scores over two weeks. Values are expressed as generalized least square means and standard errors for the intent to treat analysis. *** $p < .001$.

Table S1. Number of patients experiencing moderate to severe increases in specific symptoms up to two weeks post-infusion.

	Ketamine		**Placebo**	
	+80 Minutes	+110 Minutes Thru Week 2	+80 Minutes	+110 Minutes Thru Week 2
Dry mouth	2	0	0	0
Headache	1	3	0	3
Breast pain/swelling	0	1	0	0
Leg cramping	0	1	0	0
Muscle/bone/joint pain	0	0	0	4
Decreased body temperature	1	1	0	0
Increased body temperature	0	0	0	1
Concentration difficulties	1	1	0	1
Drowsiness/sedation	0	3	0	2
Woozy/loopy	0	1	0	0
Early morning awakening	0	4	0	2
Difficulty falling asleep	0	3	0	3
Interrupted sleep	0	2	0	0
Vivid dreams	0	1	0	0
Tiredness/fatigue	0	1	0	0
Dizziness/faintness	0	2	0	1
Difficulty speaking	0	1	0	0
Tachycardia	0	1	0	0
Dermatologic/skin irritation/lesions	0	1	0	0
Flushed	0	1	0	0
Red blotching	0	1	0	0
Sweating	0	1	0	0
Noise sensitivity	0	1	0	0
Fearful	0	1	0	0
Irritability	0	1	0	2
Slowed	0	0	0	1
Coughing	0	1	0	0
Increased thirst	0	1	0	0
Flatulence	0	2	0	0
Stomach/abdominal discomfort	0	1	0	1
Diarrhea	0	1	0	0
Appetite decrease	0	1	0	0
Weight loss	0	1	0	0
Stool discoloration	0	1	0	0
Menstrual irregularity	0	1	0	0
Increased libido	0	1	0	0
Decreased libido	0	0	0	1
Tremor	0	1	0	0

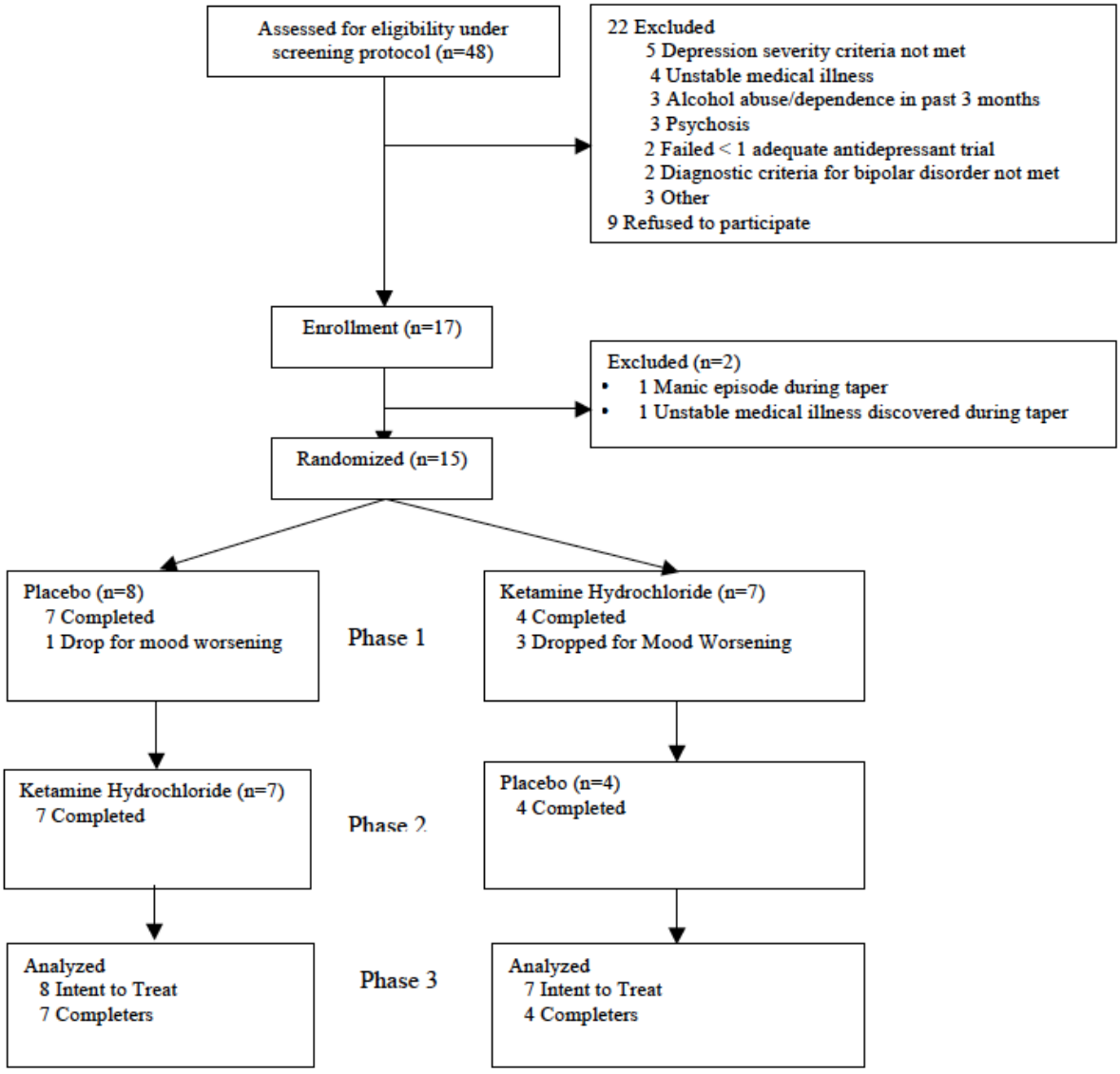

Figure S2. CONSORT 2010 Flow Diagram

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-6
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	8-9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	6-7
	4b	Settings and locations where the data were collected	6-7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	7
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6, 8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	9
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9-10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9-10

Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10-11
	13b	For each group, losses and exclusions after randomisation, together with reasons	10-11
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6-7
	14b	Why the trial ended or was stopped	7
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	25
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	10-11
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10-14
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	10-14
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	10-14
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	14-15
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	18
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	15-18
Other information			
Registration	23	Registration number and name of trial registry	1, 2
Protocol	24	Where the full trial protocol can be accessed, if available	2
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	19

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.