Impact of midazolam vs. saline on effect size estimates in controlled trials of ketamine as a rapid-acting antidepressant

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Methodological Question

Is midazolam superior to saline at maintaining the integrity of the blind in clinical studies of ketamine in depression?

Introduction

- Ketamine has emerged as the prototypical rapid-acting antidepressant [1], yet several challenges remain in both clinical and research domains
- The integrity of the blind when ketamine is evaluated in clinical trials is one such challenge
- There is strong argument that functional unblinding occurs at a high rate due to the psychoactive effects of ketamine
- Midazolam has been used as an "active placebo" control condition because of similar pharmacokinetic properties and for its non-specific behavioral effects [2]
- Yet it is unknown whether this improves the blind compared to saline
- Most clinical trials do not formally evaluate the integrity of the blind, hence it is difficult to formally assess midazolam in this respect
- We undertook to examine the effectiveness of midazolam as a comparator through investigation of effect sizes and dissociative effects

Methods

Studies

- We compiled participant-level data from 9 studies (N=367) where ketamine was compared to saline or midazolam [2-13]
- Studies from the National Institutes of Health were conducted under a single protocol and are therefore coded as one study
- All participants had Major Depressive Disorder or Bipolar Disorder

Measures Used

- Hamilton Depression Rating Scale (HAM-D)
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Clinician Administered Dissociative State Scale (CADSS)
- Baseline and 24-hour post-infusion

Data Analysis

- For comparability to parallel-arm studies, data from only the first period of crossover studies were used (k=4, N=151)
- Subjects categorized into four groups:

1. Ketamine (midaz) – ketamine in midazolam-controlled studies
2. Ketamine (sal) – ketamine in saline-controlled studies
3. Midazolam
4. Saline

- We compared change in MADRS at 24 hours using a linear mixed-model with random effect of study
- Fixed effects of treatment, time, and their interaction were included, with Satterthwaite correction to the denominator degrees of freedom
- differences between treatment groups were evaluated with between-group contrasts of change from baseline to Day 1
- To conform to distributional assumptions, CADSS scores were natural-log transformed (after adding a constant of 1)
- Cohen's d was calculated using the least-square mean estimated differences, standard errors, and DF of a given test
- All analyses were performed using SAS/STAT Version 9.3

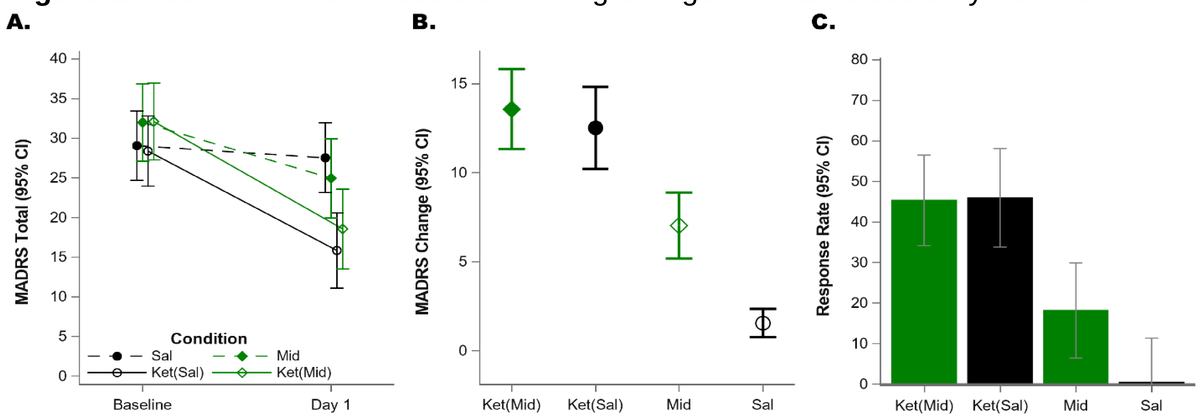
Results

Table 1. Demographic and clinical characteristics by study and treatment group

Reference	Total N	Age (SD)	Female, N (%)	White, N(%)	MDD Diagnosis, N (%)	Concomitant Medications, N (%)	Inpatient, N (%)	Assignment to Ketamine, N (%)	CADSS Data	Comparator
By Study										
Berman et al 2000 [3]*	8	37.6 (11.2)	4 (50)	7 (87.5)	8 (100)	0	0	4 (50)	Yes	Saline
Valentine et al 2011 [4]*	11	43.2 (12.4)	6 (54.5)	7 (63.6)	11 (100)	0	0	0	Yes	Saline
Sos et al 2013 [5]	27	43.8 (12.2)	11 (40.7)	27 (100)	27 (100)	27 (100)	27 (100)	9 (33.3)	No	Saline
Murrough et al 2013 [2]	73	45.5 (12.4)	38 (52.1)	61 (83.6)	73 (100)	0	73 (100)	48 (65.8)	Yes	Midazolam
NIH Studies [6-9]*	105	42.5 (11.8)	62 (59.1)	80 (76.2)	44 (41.9)	41 (39.1)	105 (100)	55 (52.4)	Yes	Saline
Hu et al., 2015 [10]	27	39 (12.6)	17 (63)	0 (0)	27 (100)	27 (100)	0	13 (48.2)	No	Saline
Murrough et al., 2015 [11]	20	42.4 (13.3)	13 (65)	17 (85)	11 (55)	15 (75)	11 (55)	11 (55)	Yes	Midazolam
Grunebaum et al., 2017 [12]*	16	41.3 (12.4)	10 (62.5)	14 (87.5)	0 (0)	15 (93.8)	16 (100)	7 (43.8)	Yes	Midazolam
Grunebaum et al., 2018 [13]*	80	39.6 (13.2)	48 (60)	74 (92.5)	80 (100)	50 (62.5)	80 (100)	40 (50)	Yes	Midazolam
By Treatment Group										
Saline	97	42.6 (11.7)	52 (53.6)	72 (75.0)	76 (78.4)	52 (53.6)	68 (70.1)	--	39 (40.2)	--
Midazolam	83	41.5 (12.5)	49 (59.0)	76 (91.6)	72 (86.8)	40 (48.2)	81 (97.6)	--	82 (98.8)	--
Ketamine (Sal)	81	41.4 (12.4)	48 (59.3)	49 (63.6)	58 (71.6)	43 (53.1)	64 (79.0)	--	43 (53.0)	--
Ketamine (Midaz)	106	43.2 (13.5)	59 (55.7)	88 (83.0)	97 (91.5)	40 (37.7)	99 (93.4)	--	103 (97.2)	--
TOTAL	**367**	**42.2 (12.5)**	**208 (56.7)**	**285 (77.7)**	**303 (82.6)**	**175 (47.7)**	**312 (82.3)**	**197 (53.7)**		--

*These studies used the 24-item HAMD rather than MADRS. A conversion of the HDRS score to MADRS equivalent was applied. This transformation also applied to one of the NIH studies (n=22)
Some statistically significant ($p<0.05$) differences were observed between groups at baseline. Race: Midazolam vs. Saline, p=.004; Midazolam vs. Ketamine (saline), p<.0001; Ketamine (midazolam) vs. Ketamine (saline), p=.003. MDD Diagnosis: Ketamine (midazolam) vs. Saline, p=.008; Ketamine (midazolam) vs. Ketamine (saline), p=.003; Ketamine (saline) vs. Midazolam, p=.017. Age and sex did not differ across treatment groups.

Figure 1. Results of mixed models evaluating change in MADRS score by treatment



Ket(Mid) = Ketamine (in midazolam-controlled studies, N=106); Ket(Sal) = Ketamine (in saline-controlled studies, N=81); Mid = Midazolam (N=83); Sal = Saline (N=97). Plotted values are model-estimated means from mixed models predicting MADRS (panel A and B) and predicted binary response (≥50% improvement in MADRS vs. <50% improvement) from treatment at 24 hours.

Figure 2. Model-estimated means predicting CADSS scores at 30-40 minutes

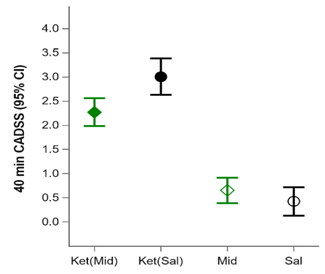


Table 2. Comparison of effect sizes between midazolam- and saline-controlled ketamine studies

Comparison	Effect Size (95% CI)	Effect size comparison	
		t_{276}	p value
Ket(Mid) v. Midazolam	0.7 (0.4-0.9)	2.32	0.02
Ket(Sal) v. Saline	1.8 (1.4-2.2)		

The effect size in midazolam-controlled studies was significantly smaller than the effect size in saline-controlled studies and this was driven by greater improvement in the midazolam arm compared to saline (Figure 1C).

Table 3. Participant blinding in select studies where integrity of blind was formally evaluated

Reference	Comparator	Sample Size	p value
Grunebaum et al., 2017	Midazolam	16	0.046
Grunebaum et al., 2018	Midazolam	80	0.37
Murrough et al., 2013	Midazolam	73	0.81

Three studies formally assessed the integrity of the blind by asking participants to guess to which treatment they were assigned. We selected guess data from the 24-hr point in each study and coded responses of "I don't know" or "not sure" as incorrect. In the two largest studies, the blinding remained intact.

Discussion

The goal of this study was to examine the effect of midazolam vs. saline on drug-comparator effect size as a proxy for preserving the blind in ketamine studies through analysis of efficacy and dissociative effects from previously published clinical trials. We found that the average antidepressant effect of ketamine was smaller when compared with midazolam than when compared with saline using both continuous (depression rating scales) and categorical outcomes (response rates). The difference in effect size was driven by greater improvement in the midazolam group compared to the saline group. One interpretation of the smaller effect size is that midazolam was superior to saline in preserving the integrity of the blind. While we were not able to assess this directly, we did find that neither saline nor midazolam produced appreciable dissociative side effects as measured by CADSS and there was no difference between these controls groups in this respect. Still, the available data indicated that patients were unable to distinguish between midazolam and ketamine. However, alternative explanations for the difference in effect size depending on comparator, such as the hypothesis that a single infusion of midazolam has antidepressant effects that extend for 24 hours, cannot be excluded. A three-arm study comparing ketamine, midazolam, and saline would be necessary to definitively answer this question.

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