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Ketamine vs Midazolam: Mood Improvement Reduces Suicidal Ideation in Depression

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DCOI

Drs. Mann and Burke receives royalties for the commercial use of the Columbia Suicide Severity Rating Scale. The other authors (Grunebaum, Madden, Keilp and Hochschild) report no financial or other relationships pertinent to the subject of this article.

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Conflict of Interest

Drs. Mann and Burke receive royalties for the commercial use of the Columbia Suicide Severity Rating Scale which was not part of this analysis. The other authors report no financial or other relationships pertinent to the subject of this article.

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Abstract

Objective: Studies demonstrate rapid antidepressant and anti-suicidal ideation effects of subanesthetic ketamine. The specific subcomponents of depression that are most closely tied to reduction of suicidal ideation with ketamine treatment are less explored.

Methods: Exploratory, post hoc analysis of data from a randomized clinical trial of ketamine vs midazolam in patients with major depressive disorder (MDD) and clinically significant suicidal ideation examined changes in factor analysis-derived symptom clusters from standard measures of depression (Hamilton Depression Rating Scale, HDRS; Beck Depression Inventory, BDI) and mood disturbance (Profile of Mood States, POMS), and their relationship to severity of suicidal ideation (Beck Scale for Suicidal Ideation; SSI). Ratings obtained before and one day after blinded intravenous infusion were decomposed into component factors or published subscales. Treatment effects on factors/subscales were compared between drugs, correlations with changes in suicidal ideation were tested, and stepwise regression was used to derive predictors of change in SSI.

Results: Factor scores for HDRS Psychic Depression, HDRS Anxiety, BDI Subjective Depression, POMS Depression and POMS Fatigue improved more with ketamine than midazolam. Stepwise regression showed across both drugs that improvement in HDRS Psychic Depression, POMS Depression, and HDRS Anxiety predicted 51.6% of the variance in reduction of suicidal ideation.

Limitations: Secondary analysis of clinical trial data.

Conclusions: Ketamine's rapid effects on suicidal ideation appear to be mostly a function of its effects on core mood and anxiety symptoms of MDD, with comparatively little contribution from neurovegetative symptoms with the potential exception of vigor/fatigue.

Trial Registration: Data used in this secondary analysis came from [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01700829) identifier: [NCT01700829](https://clinicaltrials.gov/ct2/show/study/NCT01700829).

Introduction

U.S. age-adjusted suicide rates have increased 33% in the past twenty years (Hedegaard et al., 2020) — a period of declining deaths due to other causes including ischemic heart disease, neoplasms and motor vehicle accidents (Woolf and Schoomaker, 2019). Declining US life expectancy has been linked partly to increased suicide rates (Case and Deaton, 2020). Ninety percent of deaths by suicide are associated with psychiatric illness with depressive disorders implicated in 60% of these (Mann, 2003; Mann et al., 2005), suggesting that effective treatment of depression may reduce suicide risk.

Suicidal behavior is typically preceded by suicidal thoughts, and treatment with traditional, monoaminergic antidepressants reduces suicidal ideation in part via reduction in overall depression severity (Gibbons et al., 2012; Grunebaum et al., 2013). Suicidal crises require urgent action (Fu et al., 2020; Ionescu et al., 2019; Ionescu et al., 2016; Mallick and McCullumsmith, 2016) but standard antidepressant agents typically require several weeks of treatment before significantly relieving symptoms (Schatzberg and DeBattista, 2015). Ketamine is a rapidly acting antidepressant and anti-suicidal ideation agent capable of relieving suicidal ideation within hours rather than weeks (Al Jurdi et al., 2015; Ballard

et al., 2017; Bartoli et al., 2017; Grunebaum et al., 2018; Zarate et al., 2012). As such, it has the potential to transform treatment of patients presenting with acute suicidal ideation (Bartoli et al., 2017; Reinstatler and Youssef, 2015; Sanacora et al., 2017).

In our previous trial (Grunebaum et al., 2018), ketamine's effects on suicidal ideation were stronger than the midazolam comparator. Ketamine was superior to midazolam in reduction of Profile of Mood States (POMS) Depression score but fell short of significance on the Hamilton Depression Rating Scale (HDRS-17). This raised the question of which depressive symptom components ketamine affected most and how these changes might be related to its rapid reduction of suicidal thoughts.

Depression is a heterogenous entity, and we had previously found that mood components of depression—and not neurovegetative symptoms—are related to suicidal thinking cross-sectionally (Keilp et al., 2012). We further observed improvement in mood components of depression are most strongly related to reductions in suicidal ideation during pharmacologic treatment (Keilp et al, 2018a), and that the effectiveness of a particular treatment is related to its efficacy in reducing these core mood symptoms (Grunebaum et al., 2013). We sought to investigate whether ketamine may act similarly, and more rapidly.

In this post-hoc analysis: we decomposed depression severity ratings from the HDRS and BDI into factor analysis-derived symptom clusters (Grunebaum et al., 2005); generated subscores from an additional mood rating (POMS); and examined changes in these more specific symptom measures one day following a single blinded infusion with either ketamine or midazolam. Our goal was to determine which symptom factor scores or subscales were most strongly affected by ketamine, and to determine if changes in these symptoms were related to reductions in suicidal ideation at day one. Data from our published, midazolam-controlled clinical trial of ketamine for MDD with clinically significant suicidal ideation (Grunebaum et al., 2018) was used for this analysis. We hypothesized, as in our prior work (Grunebaum et al., 2013, Keilp et al, 2018a), that reduction in the core mood dimensions of these rating scales would be most associated with ketamine effects, and that reductions in these would most strongly correlate with reduction in suicidal ideation.

Methods

Participants

Trial methods and primary results have been reported (Grunebaum et al., 2018). Briefly, we conducted a randomized clinical trial ($N=80$) testing adjunctive sub-anesthetic intravenous ketamine (0.5 mg/kg) versus midazolam (0.02 mg/kg) in patients with MDD and clinically-significant suicidal ideation, defined as a score of ≥ 4 on the clinician-rated SSI (Brown et al., 2000; Price et al., 2014). Primary outcome was change in SSI score at 24-hours post-infusion. Main eligibility criteria were: age 18-64 years old; DSM-IV MDD (First, 1994) with score ≥ 16 on the 17-item HDRS (Hamilton, 1960); SSI ≥ 4 ; and voluntary admission to an inpatient research unit. Exclusions included: unstable medical or neurological illness; significant EKG abnormality; pregnancy or lactation; current psychosis; history of ketamine abuse or dependence; drug or alcohol dependence within six months of study enrollment; suicidal ideation due to binge substance abuse or withdrawal; previous inadequate response

to ketamine; prior adverse reaction to ketamine or midazolam; daily opiate medication (equivalent to >20mg oxycodone) over the three days prior to infusion; a score of <25 on the Mini Mental State Exam for those over 60 years old (Folstein et al., 1975); lack of capacity or inadequate English comprehension for informed consent. The study was approved by the New York State Psychiatric Institute's Institutional Review Board. Written informed consent was obtained from all participants, and the study was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (identifier: [NCT01700829](https://clinicaltrials.gov/ct2/show/study/NCT01700829)).

Patients were randomized to ketamine or midazolam infused in 100mL normal saline over 40 minutes. Participants and study staff were blind to treatment. Baseline characteristics between treatment groups differed only in frequency of borderline personality disorder, which was not found to affect the primary outcome — summarized in Table 1 (for additional information see Grunebaum et al., 2018).

Outcome Measures

SI was assessed via the SSI, one day prior and one day after infusion. Depressive symptoms were assessed using the clinician-rated HDRS (Hamilton, 1960), the self-rated BDI (Beck et al., 1961) and self-rated POMS (McNair, 1981). Factor analyses of the HDRS and BDI have been described previously (Grunebaum et al., 2005), and derived factors have been studied in prior publications (Grunebaum et al., 2005; Grunebaum et al., 2013; Keilp et al., 2018a; Keilp et al., 2012; Keilp et al., 2018b; Milak et al., 2010; Milak et al., 2005). The HDRS was decomposed into five factors assessing: Psychic Depression; Loss of Motivation; Disturbed Thinking; Anxiety; and, Sleep Disturbance. For example, the Psychic Depression factor includes items such as depressed mood, worthlessness and hopelessness. The BDI was decomposed into three factors: Subjective Depression; Self-Blame; and Somatic Complaints. For instance, the Subjective Depression factor comprises items including sadness and pessimism. The POMS is comprised of six standard subscales assessing: Depression; Tension/Anxiety; Anger; Confusion; Fatigue; and, Vigor. Further details regarding scale items comprising each factor or subscale score are presented in Supplemental Tables s1 - s3. The suicidal ideation item on the HDRS, which loads on the Psychic Depression factor (Grunebaum et al., 2005), was removed in the calculation of this factor score for analyses, given its redundancy with items on the SSI (see Keilp et al., 2012) as in our previous analyses of treatment effects with this scale (Keilp et al., 2018). The suicidal ideation item of the BDI does not load on any one factor for the BDI (Keilp et al., 2012), and thus is not included in factor score computations for the BDI. There are no items on the POMS that ask directly about suicidal ideation.

Statistical Analyses

Total scores on the SSI, HDRS, BDI and POMS were compared across treatment and time using repeated measures Analysis of Variance (ANOVA), with **Drug** (2 levels, ketamine vs. midazolam) and **Time** (2 levels, baseline one day prior to infusion and one day after) as factors, to illustrate global treatment effects.

Depression factors and POMS subscales were compared hierarchically as follows: for each of the three rating scales, a repeated-measures General Linear Model was applied with

Factor Score (5 levels for HDRS, 3 for BDI, and 6 for POMS), **Drug** (2 levels), and **Time** (2 levels, baseline and 24-hours post-infusion) as factors. A significant Drug x Time, or Factor Score x Drug x Time effect led to examination of specific factor scores in a repeated measures Analysis of Variance with Drug and Time as factors.

Pearson correlations were computed between changes in each factor/subscale and change in SSI, between baseline and one day post-infusion. These change scores were examined in all participants, and in those treated with ketamine alone.

A stepwise linear regression was then run in all participants with factor/subscales showing any significant effect of time or drug x time) as potential predictors of reduction in SSI. This regression was then repeated in the ketamine treated participants alone, with factor/subscales that showed a differential effect for ketamine. In our initial approach to this analysis in ketamine-treated participants, we included marginal effects ($p < .055$) in order to insure including potentially relevant predictors. We then repeated these analyses including only those measures that clearly met significance criteria ($p < .05$) in hierarchical analyses, which allow for exploration of omnibus effects without adjustment for multiple comparisons (versus if these analyses had been strictly univariate). Analyses were run in SPSS version 26 (IBM Corp, Armonk, New York).

Results

Total Score Analyses

Compared with midazolam, ketamine was associated with greater reduction in SSI score (Drug x Time interaction $F[1, 78]=7.41, p=0.008$). The Drug x Time interaction on the HDRS total score, however, was not significant (Drug x Time interaction $F[1, 78]=2.53, p=0.116$). This effect was marginal for BDI and POMS total scores (Drug x Time interaction for BDI: $F[1, 72]=3.86, p=.053$; Drug x Time interaction for POMS: $F[1, 78]=3.86, p=0.053$).

Depression Factor Score Analyses

In the omnibus analysis of the five HDRS factors, there was a significant Factor Score x Drug x Time interaction ($F[2, 144]=3.89, p=.023$). Changes across treatment are illustrated in Figure 1. In univariate comparisons, the Drug x Time effect, illustrating a superiority for ketamine, was significant for the HDRS Psychic Depression factor score ($F[1, 78]=4.99, p=.028$), and marginal for the HDRS Anxiety factor score ($F[1, 78]=3.88, p=.052$), but none of the other three factor scores were statistically significant (Table 2.; Figure 1).

In the omnibus analysis of the three BDI factor scores, there was a significant Factor Score x Drug x Time interaction ($F[4, 312]=4.42, p=.002$). Changes in these scores across treatment are illustrated in Figure 2. In univariate comparisons, the Drug x Time effect, showing superiority for ketamine, was significant for the BDI Subjective Depression factor score ($F[1, 72]=4.44, p=.039$), but not the other factors (Table 2.; Figure 2.).

In the omnibus analysis of the six POMS subscales, there was a marginally significant Drug x Time interaction across all subscale scores ($F[1, 78]=3.51, p=.051$), with a non-significant

Factor Score x Drug x Time interaction ($F[5, 390]=1.62, p=.153$), indicating a trend toward a global effect across all subscales. Changes in these subscales across treatment are illustrated in Figure 3. In univariate comparisons, a Drug x Time effect, illustrating a superiority for ketamine, was significant for the POMS Depression subscale ($F[1, 78]=4.10, p=.046$) and the POMS Fatigue subscale ($F[1, 78]=4.24, p=.043$) (Table 2.; Figure 3).

Correlations with Change in Suicidal Ideation

Across all participants, irrespective of drug group, change in SSI was significantly correlated with change in all depression factor/subscales except for HDRS Disturbed thinking ($p = .90$). Effect sizes were largest for HDRS Psychic Depression ($r = .62, p < .001$), BDI Subjective Depression ($r = .61, p < .001$), and POMS Depression ($r = .61, p < .001$).

Within the ketamine-treated group, the strongest correlations of change in SSI were with (in descending order of effect size): POMS Vigor ($r = -.69, p < .001$; scale is reverse scored from others), POMS Confusion ($r = .63, p < .001$) and POMS Depression ($r = .62, p < .001$), BDI Subjective Depression ($r = .61, p < .001$), HDRS Loss of Motivation ($r = .55, p < .001$) and HDRS Psychic Depression ($r = .54, p < .001$). Correlations were significant with all factor/subscales except HDRS Disturbed Thinking ($p = .31$) and Sleep Disturbance ($p = .09$).

We explored two other possible contributions to the decline in suicidal ideation: concurrent medications and neuropsychological changes. Neither the presence/absence of concomitant medications, their number, nor specific class of coadministered medication (antidepressants, lithium, benzodiazepines, or antipsychotics) contributed additional variance to our prediction of SSI decline. Two neuropsychological tasks, Choice Reaction Time and Stroop Interference, (in the same sample, reported in (Keilp et al., 2021)) showed relative improvement in ketamine vs. midazolam treated participants. However, as additional factors in stepwise regression, neither contributed to prediction of SSI decline.

Stepwise Regression of Change in Suicidal Ideation

A stepwise regression model with all participants, including all significant factor/subscale scores and drug assignment, found three predictors accounting for 51.6% of the variance in reduction of SSI score after blinded infusion (final model: $F[3,76] = 26.99, p < .001$). These were change in HDRS Psychic Depression ($\beta = .34, t = 3.34, p = .001$), change in POMS Depression ($\beta = .41, t = 4.17, p < .001$) and change in HDRS Anxiety ($\beta = .20, t = 2.39, p = .019$).

In the ketamine group, a similar model was extracted (final model: $F[2,37] = 15.35, p < .001$) accounting for 45.4% of the variance in the reduction in suicidal ideation. This model included two variables, change in HDRS Psychic Depression ($\beta = .30, t = 2.10, p = .002$) and POMS Depression ($\beta = .47, t = 3.33, p = .002$). Change in HDRS Anxiety fell short of significance in this model ($t = 1.76, p = .087$).

Using the final model derived in both drug groups, including all participants in the study, predicted scores versus actual change in SSI was calculated and plotted in Figure 4. Separate regression lines were plotted to depict the relationship for each drug. Regression lines

overlap significantly, suggesting a common mechanism for reducing suicidal thinking across both drugs.

We repeated the regression analysis in the ketamine group using only those change scores that were clearly significant hierarchically i.e. HDRS Psychic Depression and BDI Subjective Depression (POMS scales would not be included because for the omnibus effect across all subscales $p = .051$). An equation including change in HDRS Psychic Depression ($\beta = .35$, $t = 2.49$, $p = .018$) and BDI Subjective Depression ($\beta = .41$, $t = 2.88$, $p = .007$) was significant (final model: $F[2,39] = 13.38$, $p < .001$) and predicted 42.0% of variance in the reduction of SSI score in the ketamine group.

Discussion

One day after treatment, ketamine exhibited superiority to midazolam for reduction of suicidal ideation primarily by its stronger impact on core mood disturbance (i.e. HDRS Psychic Depression, BDI Subjective Depression, and POMS Depression) with little apparent contribution of change in somatic symptoms except possibly for fatigue/vigor. Changes in core mood ratings across both drugs exhibited the strongest correlations to changes in suicidal thinking. A stepwise linear regression revealed that a linear combination of changes in HDRS Psychic Depression, POMS Depression, and HDRS Anxiety accounted for 51.6% of the variance in SSI change with treatment, regardless of drug assignment. A comparable result was observed in the ketamine group alone.

Consistent with our prior studies of other antidepressants, changes in mood and anxiety components of standard, multi-dimensional depression scales were most strongly related to decline in suicidal ideation. It is noteworthy that after considering these robust associations, there is an additional 50% of decline in suicidal thinking that is unexplained. This may partly be related to error variance within each scale (i.e. none is a “perfect” measure) or to idiosyncratic factors at the individual level that are difficult to capture in any set of rating scales.

Another domain which may help further elucidate the anti-SI effects of ketamine is its relation to anhedonia (Ballard et al., 2017). Nascent research suggests that reduction in SI following ketamine treatment may be independently associated with lessened anhedonia as reflected in specialized measures (Lally et al., 2015). Future work may capture additional symptomatology related to suicidal thinking by probing domains that standard depression scales do not target very well, such as: psychic pain; feelings of burdensomeness, entrapment; or rumination (Shneidman, 1993; De Beurs et al., 2019).

Our earlier work indicates that suicidal ideation is most strongly correlated with the core mood components of depression (Keilp et al., 2012), and suicidal ideation is reduced in concert with clinical improvement produced by oral antidepressant medications in these symptoms (Grunebaum et al., 2005; Keilp et al., 2018a). Results here extend this association to ketamine treatment and reinforce the importance of improving mood as a means of reducing suicidal ideation, in the context of any antidepressant treatment. The speed with which ketamine acts to improve mood symptoms appears to be key to its rapid effects on

suicidal ideation. This contrasts with the actions of many antidepressant treatments which initially improve neurovegetative symptoms such as sleep, appetite, and energy (Machado-Vieira et al., 2010) while improving mood more slowly. Mood effects may only emerge weeks into treatment, even after the initiation of multiple treatments (Belmaker and Agam, 2008). In addition, whereas midazolam's mood effects appeared to wane after Day 1 post-infusion, ketamine's effects appeared to last longer (Grunebaum et al., 2018).

It is noteworthy that reduction in SSI score in the ketamine group was most strongly correlated with increase in POMS Vigor score, although change in this score did not differentiate between ketamine and midazolam. However, reduction in the POMS Fatigue score did differentiate between drugs, with ketamine superior. We have recently reported that Choice Reaction Time task performance improved to a greater degree in response to ketamine relative to midazolam (Keilp et al., 2021). Taken together, these findings suggest that improved energy is another feature of the ketamine response – a characteristic that should be studied further, particularly given the fatigue-inducing effects of antidepressant drugs for many patients.

Current antidepressant medications are thought to relieve depression via modulation of brain monoamines, but this mechanism of action may be less optimal for addressing acute suicidal states. Ketamine's rapid effects on glutamatergic and GABAergic systems may be more effective for this clinical need (Abdallah et al., 2015; Duman, 2014; Milak et al., 2020; Manji et al., 2001). Research into specific effects of ketamine and its metabolites including preferential localization to certain neural circuits is in its nascency (Abdallah et al., 2017; Mann et al., 2013). Investigation into regional neuroanatomical action of ketamine and induction of down-stream neurotransmission is a promising area for future research (Milak et al., 2016; Milak et al., 2020).

Our group has published other analyses using data from this trial relevant to in vivo ketamine metabolites and potential interactions of ketamine with opioid receptors (Grunebaum et al., 2019; Grunebaum et al., 2020), and a limitation of this study is its post-hoc approach. A medication washout was not required prior to the study intervention, which may have led to interactions with assigned treatments that may have altered treatment effects – however, there was no difference in frequencies of major classes of concomitant medications at baseline between the two groups (Grunebaum et al., 2018).

These results reinforce the connection between core mood disturbance and suicidal thinking, and the necessity to rapidly improve mood as a means of treating acutely suicidal patients. The findings suggest that ketamine's relative effectiveness in the treatment of acute suicidal states is due to its rapid effects on these mood-related components of depression, and perhaps should be considered a promising treatment for acute suicide risk. A new generation of mood and vigor enhancing antidepressant agents capitalizing on elucidation of ketamine's mechanism and improving on its roughly one-week duration of effect, would truly be a sea-change for depression patients.

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Highlights

Ketamine reduces SI in concert with MDD symptoms; primarily mood symptoms (73/85)

Improvements in mood correlate with improvements in SI in ketamine and midazolam (81/85)

Reduction in fatigue and improvement in vigor may be related to lessened SI (76/85)

*SI: Suicidal Ideation; MDD: Major Depressive Disorder

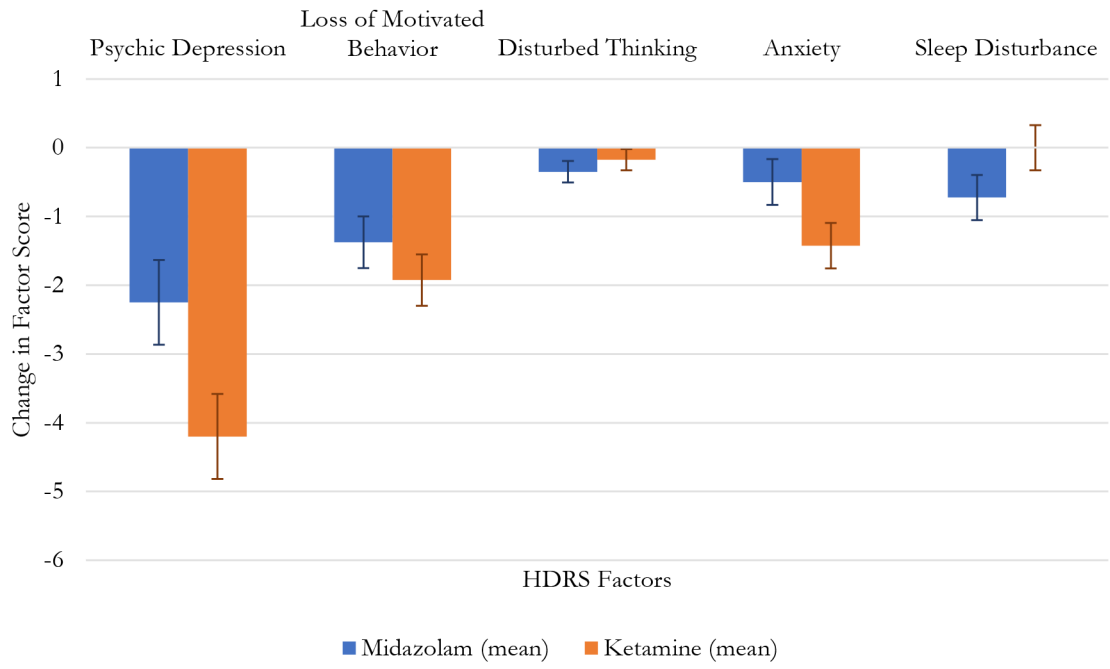


Fig. 1. Change in Hamilton Depression Rating Scale Factor Scores

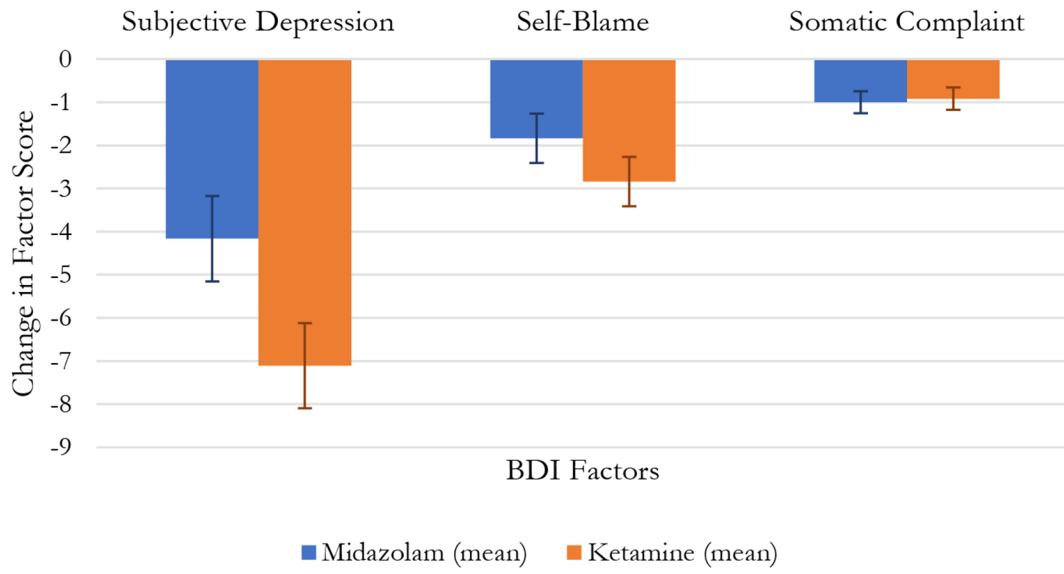


Fig. 2.
Change in Beck Depression Index Factors

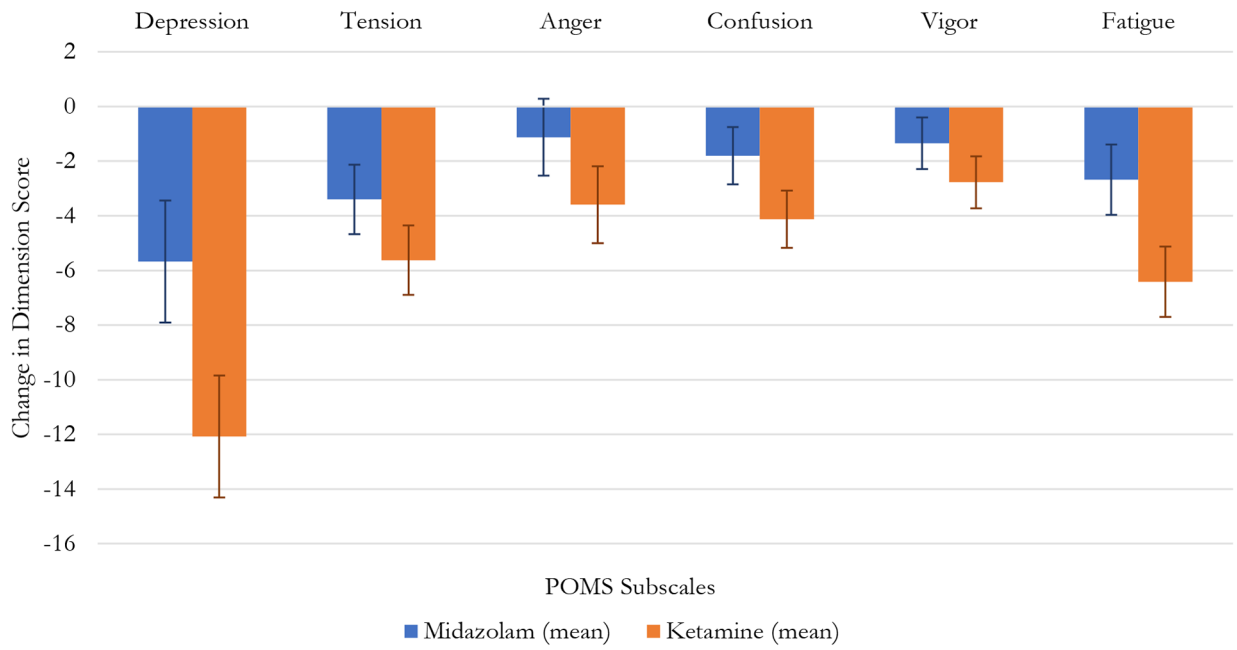


Fig. 3.
Change in Profile of Mood States Subscale Scores.

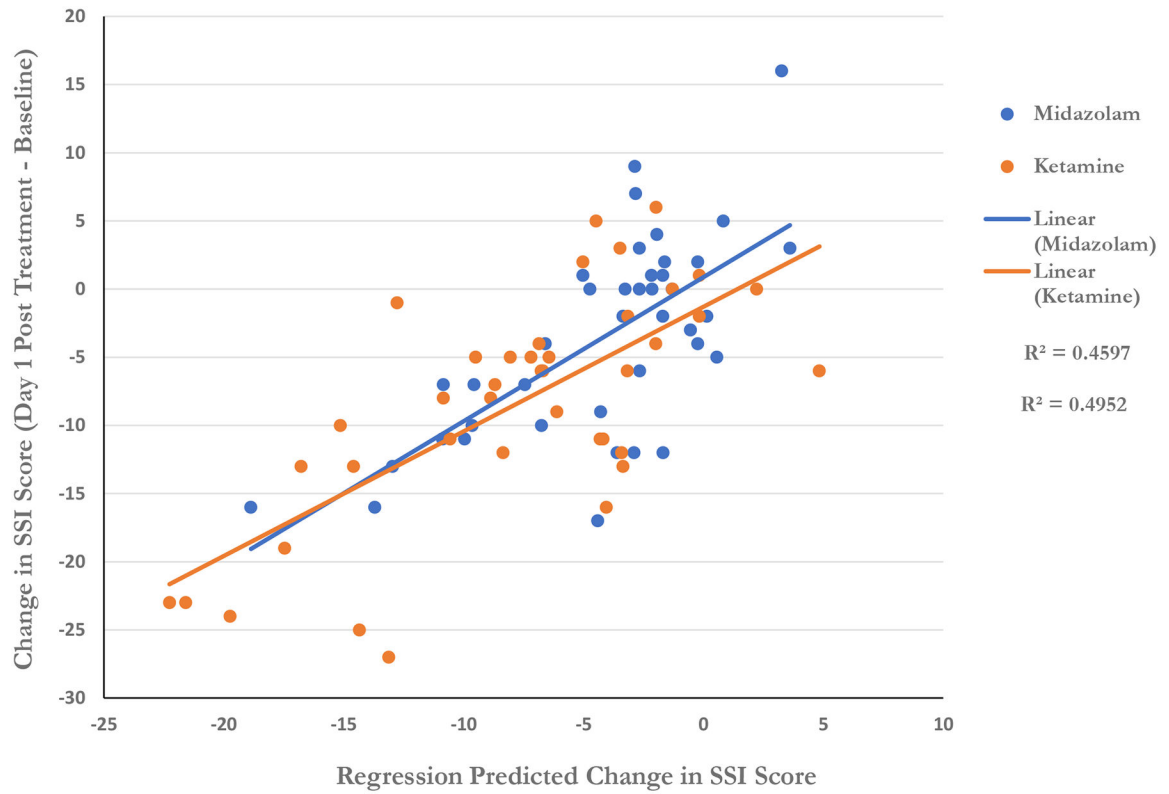


Fig. 4.
Regression Prediction of Change in Suicidal Ideation
Regression prediction based on linear combination of change in HDRS Psychic Depression, HDRS Anxiety, and POMS Depression scores (see text for details).

Table 1:Baseline demographic and clinical characteristics by treatment group (*N*=80)

	Midazolam (N=40), mean (SD)	Ketamine (N=40), mean (SD)
Age	40.7 (13.1)	38.4 (13.2)
Female, no. (%)	26 (65%)	22 (55%)
SSI	15.7 (6.9)	14.3 (6.3)
No of Past MDD ep, median (range)	3 (1 to "too many to count")	4.5 (1 to "too many to count")
Hx of Past Suicide Attempt at Randomization, no. (%)	22 (55)	17 (42.5)
Baseline HDRS-24	30.25 (6)	29.35 (6.2)
Baseline BDI	33.9 (8.1)	31.8 (8.1)
Baseline POMS	101.7 (35.2)	95.92 (37.4)

SSI = Beck Scale for Suicidal Ideation; MDD = Major Depressive Disorder; HDRS-24 = 24 item Hamilton Depression Rating Scale; BDI = Beck Depression inventory; POMS = Profile of Mood States

Table 2:

Factor Scores Across Treatment Conditions and Assessment Time Points

	Pre Midazolam (SD)	Post Midazolam (SD)	Pre Ketamine (SD)	Post Ketamine (SD)	Significance: Time Effect	Significance: Drug Effect	Significance: Time Effect x Drug Effect
Total Scores							
SSI	16.9 (5.8)	13.3 (8.4)	15.55 (6.2)	7.2 (6.4)	<0.001	0.004	0.008
HDRS-24	30.3 (6.0)	24.0 (8.8)	29.4 (6.2)	20.0 (9.7)	<0.001	0.091	0.116
BDI	33.1 (9.2)	25.0 (12.2)	31.7 (8.0)	18.8 (10.7)	<0.001	0.065	0.053
POMS	101.7 (35.2)	85.5 (46.2)	95.9 (37.4)	61.3 (45.5)	<0.001	0.064	0.053
HDRS Factors							
HDRS: Psychic Depression	11.1 (2.7)	8.8 (4.0)	11.5 (2.7)	7.3 (3.9)	<0.001	0.0378	0.028
HDRS: Loss of Motivated Behavior	6.1 (1.5)	4.7 (2.1)	5.8 (1.9)	3.8 (2.7)	<0.001	0.100	0.303
HDRS: Disturbed Thinking	0.8 (1.3)	0.4 (0.7)	0.5 (1.2)	0.4 (0.8)	0.019	0.504	0.427
HDRS: Anxiety	4.3 (2.4)	3.8 (2.0)	4.1 (1.8)	2.7 (1.7)	<0.001	0.119	0.052
HDRS: Sleep Disturbance	3.1 (1.8)	2.3 (1.8)	2.5 (1.8)	2.5 (1.7)	0.122	0.617	0.122
BDI Factors							
BDI: Subjective Depression	17.3 (4.9)	13.1 (6.1)	17.5 (4.2)	10.4 (6.8)	<0.001	0.246	0.039
BDI: Self-Blame	8.4 (3.5)	6.5 (4.0)	7.6 (3.2)	4.7 (3.2)	<0.001	0.073	0.220
BDI: Somatic Complaint	2.7 (2.1)	1.7 (1.9)	2.4 (1.8)	1.5 (1.6)	<0.001	0.517	0.825
POMS Subscales							
POMS: Depression	39.5 (12.8)	33.9 (17.7)	35.6 (14.6)	23.6 (16.1)	<0.001	0.023	0.046
POMS: Tension	20.2 (9.4)	16.8 (10.5)	19.2 (8.7)	13.6 (9.4)	<0.001	0.273	0.219
POMS: Anger	10.3 (9.9)	9.1 (11.5)	10.1 (9.7)	6.5 (8.6)	0.020	0.482	0.219
POMS: Confusion	15.7 (5.5)	13.9 (6.4)	15.4 (5.3)	11.3 (7.2)	<0.001	0.216	0.122
POMS: Vigor	3.5 (3.4)	27.2 (5.6)	2.9 (2.5)	26.3 (6.0)	0.003	0.836	0.290
POMS: Fatigue	19.4 (6.3)	16.7 (8.2)	18.5 (6.5)	12.1 (7.6)	<0.001	0.048	0.043

SSI = Beck Scale for Suicidal Ideation; MDD = Major Depressive Disorder; HDRS-24 = 24 item Hamilton Depression Rating Scale; BDI = Beck Depression inventory; POMS = Profile of Mood Stat