OXFORD

International Journal of Neuropsychopharmacology (2022) 25(10): 827–838

https://doi.org/10.1093/ijnp/pyac055
Advance Access Publication: August 22, 2022
Regular Research Article

REGULAR RESEARCH ARTICLE

A Participant-Level Integrative Data Analysis of Differential Placebo Response for Suicidal Ideation and Nonsuicidal Depressive Symptoms in Clinical Trials of Intravenous Racemic Ketamine

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Abstract

Background: Clinical trials of intravenous (IV) racemic (*R*,*S*)-ketamine (hereafter referred to as *IV ketamine*) have consistently reported rapid and substantial reductions in overall depressive symptoms compared with saline (inactive placebo) or midazolam (active placebo). The evidence for IV ketamine's specific effects on suicidal ideation is less clear, however. This study sought to examine whether differential placebo (saline or midazolam) response to overall depressive symptoms vs suicidal ideation may help explain these divergent findings.
Methods: Data for this participant-level integrative data analysis were drawn from 151 participants across 10 studies, and linear regression was used to examine the relationship between placebo response for suicidal ideation vs other depressive symptoms indexed from standard rating scales—specifically, depressed mood, anhedonia, anxiety, and guilt—over time.
Results: For participants receiving saline placebo (n = 46), greater placebo response was observed for suicidal ideation compared with other symptoms indexed from standard depression rating scales, except for anxiety. For those receiving midazolam placebo (n = 105), greater placebo response was observed for suicidal ideation compared with depressed mood or anhedonia, and no significant differences were observed when comparing suicidal ideation with anxiety or guilt.

Received: March 3, 2022; **Revised:** June 3, 2022; **Accepted:** August 22, 2022

Significance Statement

Clinical trials of intravenous (IV) ketamine have consistently reported improvement in overall depressive symptoms, but studies of ketamine's specific effects on suicidal thoughts have reported conflicting results. This study sought to investigate whether, on average, individuals who receive placebo—either inactive saline or active midazolam (a medication that can cause sedation)—have a greater improvement in suicidal thoughts than other depressive symptoms, such as low mood, loss of ability to experience pleasure, and feelings of guilt or worthlessness. Greater improvements in suicidal thoughts caused by placebo may make it more difficult to detect improvements in suicidal thoughts from potential treatments such as ketamine. This study found preliminary evidence that placebo may improve suicidal thoughts more than other depressive symptoms in individuals participating in clinical trials of single-dose IV ketamine. Future work is needed to replicate the findings and to investigate how other key aspects of clinical trial design affect placebo response.

Conclusions: Taken together, the results provide preliminary evidence of a differential placebo response for suicidal ideation vs other depressive symptoms, while anxiety and suicidal ideation appear to produce similar placebo response profiles. These findings may help explain the more modest findings in clinical IV ketamine trials for suicidal ideation than overall depression.

Keywords: Suicidal ideation, placebo, midazolam, ketamine, clinical trials

INTRODUCTION

Clinical trials of intravenous racemic (*R*,*S*)-ketamine (hereafter referred to as *IV ketamine*) have consistently reported rapid and substantial reductions in overall depressive symptoms compared with placebo (Zarate et al., 2006; Murrough et al., 2013; Han et al., 2016). Evidence of IV ketamine's specific effect on suicidal ideation is less clear, however. A previous meta-analysis of 10 randomized controlled trials found that IV ketamine rapidly reduced suicidal ideation within 24 hours after infusion and that this effect was sustained up to 1 week after infusion (Wilkinson et al., 2018). Conflicting findings have also been noted, however, in trials of IV ketamine (Murrough et al., 2013; Grunebaum et al., 2017; Grunebaum et al., 2018; Ionescu et al., 2019). Although not the subject of this analysis, the related compound esketamine (the intranasally delivered [*S*]-enantiomer of ketamine) has also produced conflicting findings with regard to suicidal ideation (Canuso et al., 2018; Fu et al., 2020; Ionescu et al., 2021), and the emergence of suicidal ideation has been shown to be more common in those receiving esketamine than in those receiving venlafaxine (Gastaldon et al., 2021). Several possible reasons exist for these divergent findings, including route of delivery (IV vs intranasal), trial phase, and trial setting (early clinical trials in well-controlled settings vs later-stage trials in real-world environments), among other factors.

One comparatively underexplored possibility is that differential placebo response to overall depressive symptoms vs suicidal ideation may affect results. Clinical trials in psychiatry, particularly studies of depression, have long been plagued by high placebo response rates (Fava et al., 2003). Here, placebo *response* is defined as any change in the outcome of interest resulting from placebo being provided, including all contextual effects (eg, investigator-participant interaction, natural course of the disease, and regression to the mean). In contrast, placebo *effect* refers more narrowly to the neurophysiologic changes associated with placebo being provided (Haflidadóttir et al., 2021). In this manner, placebo response is the aggregate of placebo effects and additional contextual effects. The higher the rate of placebo response, the lower the likelihood of detecting a therapeutic effect (Iovieno and Papakostas, 2012). Previous studies identified several study design-based factors and patient-centered factors that moderate relatively high placebo response, including low baseline severity of symptoms, unbalanced randomization, and more recent publication year for the trial (Weimer et al., 2015). The degree to which placebo response rates differ between various symptom domains has rarely been studied, however. Even less is known about placebo response in studies of suicidal ideation.

Studies examining data drawn from IV ketamine trials have investigated individual differences in placebo response to depressive symptoms and to suicidal ideation by type of placebo—specifically, saline (inactive placebo) vs midazolam (active placebo). Midazolam was initially used in IV ketamine trials because of concerns that IV ketamine's psychotomimetic side effects might lead to functional unblinding when compared with saline (Murrough et al., 2013); midazolam, a benzodiazepine with anxiolytic effects and a similar pharmacokinetic profile to IV ketamine, may mask nonspecific behavioral effects, thus reducing the likelihood of unblinding. A previous meta-analysis of IV ketamine studies suggested that midazolam might be more strongly associated with a differential drug-control reduction in depressive symptoms than saline (Wilkinson and Farmer, 2019), although no direct comparison between saline and midazolam has been investigated in a clinical trial. In addition, the effect size of IV ketamine vs midazolam on suicidal ideation was found to be more modest than that for IV ketamine vs saline (Wilkinson et al., 2018; Wilkinson and Farmer, 2019), but this result did not reach statistical significance, possibly because of the small sample size (Wilkinson et al., 2018). No research to date on placebo response has directly compared symptom domains such as suicidal ideation and nonsuicidal depressive symptoms.

This study examined differential placebo response to suicidal ideation compared with nonsuicidal depressive symptoms indexed from standard depression rating scales—specifically, depressed mood, anhedonia, anxiety, and guilt—in IV ketamine trials using a saline or midazolam comparator. These symptoms were chosen for 2 reasons. First, like suicidal ideation, these symptoms may exhibit greater variability over the short term than other depressive symptoms, such as sleep or appetite, which may be less responsive to treatment in the short term. Second, like suicidal ideation, these symptoms are traditionally represented by a single item on clinical measures of depression

in clinical trials (Luckenbaugh et al., 2015). In addition, depressed mood may provide an overall summary of a participant's depression. The study hypotheses were that (1) placebo response would be larger for suicidal ideation than for depressed mood, anhedonia, or guilt regardless of whether saline or midazolam was used as a comparator, and (2) suicidal ideation and anxiety would show similar response profiles when saline was used as a comparator because of the expected high reactivity and variability of both symptom types but, because of midazolam's anxiolytic effects, response would be larger for anxiety than for suicidal ideation when midazolam placebo was used.

MATERIALS AND METHODS

Participants

Data were initially drawn from two systematic reviews (Wilkinson et al., 2018; Wilkinson and Farmer, 2019) that included 13 randomized controlled trials examining the antidepressant effects of IV ketamine vs placebo (either saline or midazolam) and 2 additional midazolam-controlled studies evaluating IV ketamine for treatment-resistant depression (N = 495) (Fava et al., 2020; Phillips et al., 2020). Of those 15 trials, 2 studies (Sos et al., 2013; Hu et al., 2016) were excluded from the final data set because additional participant-level data required for our analysis were no longer available (personal communication with authors). Three additional studies (Berman et al., 2000; Valentine et al., 2011; Feder et al., 2014) were excluded because no study participant met criteria for inclusion in our final data set, which required suicidal ideation, anhedonia, anxiety, and feelings of guilt at baseline (Montgomery-Åsberg Depression Rating Scale [MADRS] item score ≥2 or Hamilton Depression Rating Scale [HAM-D]) item score ≥1 on all 4 items), and receipt of placebo. Two studies were combined for this analysis because they were conducted under the same research protocol (Diazgranados et al., 2010; Zarate et al., 2012). Our final sample thus consisted of 151 participants (46 of whom received saline and 105 of whom received midazolam) drawn from 10 studies (Zarate et al., 2006; Diazgranados et al., 2010; Zarate et al., 2012; Murrough et al., 2013; Murrough et al., 2015; Grunebaum et al., 2017; Grunebaum et al., 2018; Nugent et al., 2019; Fava et al., 2020; Phillips et al., 2020). All studies that used saline as a placebo and employed a cross-over design, while all but 1 study (Phillips et al., 2020) that used midazolam as a placebo employed a parallel design. Two studies were conducted in an outpatient setting, both of which used midazolam as placebo (N = 42). Additional details for all the included studies can be found in Table 1. All patients gave written informed consent when entering the original studies.

Measures

The primary outcome measures were MADRS and HAM-D scores; each scale contains single-item questions relating to depressed mood (MADRS item 2 and HAM-D item 1), anhedonia (MADRS item 8 and HAM-D item 7), anxiety (MADRS item 3 and HAM-D item 10), guilt (MADRS item 9 and HAM-D item 2), and suicidal ideation (MADRS item 10 and HAM-D item 3). The MADRS items are rated on a 6-point scale, while the HAM-D items are rated on a 4-point scale. Four of the 10 studies included in our data set used the MADRS, 3 used the HAM-D, and 2 used both scales (Table 1).

To enable comparison across studies and scales, item scores were recorded on a scale of 0 to 3, with the following scores: none (score of 0), mild (score of 1), moderate (score of 2), or severe (score of 3) (see Table 2). The timing of assessments varied by study and included assessments at baseline and at days 1, 2, 3, 5, and 7 after infusion; the studies conducted baseline, day 1, and day 7 assessments, except for 1 midazolam study that did not include a day 1 assessment and 2 midazolam studies that did not include a day 7 assessment (see Table 1). Additional participant-level data included age, sex, diagnosis, use of concomitant medications, and setting (inpatient or outpatient).

Statistical Analysis

Summary statistics were calculated for demographic and clinical characteristics by study and placebo type. Linear mixed models were used to examine the relationship between placebo response for suicidal ideation vs each additional comparator depressive symptom (depressed mood, anhedonia, anxiety, and guilt) over time. Each model was structured as a repeated-measures model, with 2 outcomes per person: (1) suicidal ideation item score and 2) comparator depressive symptom item score. The predictor variables were symptom domain (an independent variable to indicate either suicidal ideation or the comparator depressive symptom), time (treated as a categorical variable, with the following levels: baseline, day 1 after infusion, and day 7 after infusion), and a symptom domain indicator by time interaction. The symptom domain by time interaction was the main test of our hypothesis of a differential placebo response for suicidal ideation vs the comparator depressive symptom over time. Study and a symptom domain by study interaction were included as fixed effects in all models to allow baseline suicidal ideation and comparator depressive symptom scores to vary by study. The model included a random intercept for each participant, with an exchangeable within-participant correlation structure estimated separately for each symptom domain (suicidal ideation or comparator depressive symptom). All models were run with and without adjustment for covariates, including sex, age, diagnosis, and use of concomitant medications. To allow for model convergence, age was dichotomized (<45 or ≥ 45 years) in adjusted models. Because placebo type (saline or midazolam) was collinear with study, separate models were run for saline and midazolam.

We conducted several sensitivity analyses to test for robustness. First, to address missing data, we ran complete case analyses for each model. Second, each model was run with the original uncombined scales (MADRS or HAM-D) as the outcome variables to ensure that recoding into a combined variable did not substantially affect the results. Third, we reran the models after having removed participants who received placebo second in a cross-over study to evaluate the effect of differing placebo expectancy. All analyses were conducted using Stata, version 16, statistical software (StataCorp, College Station, TX, USA).

RESULTS

Of the 151 participants analyzed (drawn from 10 studies), 46 participants (drawn from 4 studies) received saline, and 105 participants (drawn from 6 studies) received midazolam (Table 1). The mean (SD) age of the participants who received saline was 42.3 (12.4) years, 25 (54.4%) were female, 30 (65.2%) had a diagnosis of major depressive disorder (MDD), and 16 (34.8%) were taking concomitant psychotropic medications during the study period. The mean (SD) age of the participants who received midazolam was 41.1 (11.9) years, 62 (59.6%) were female, 91 (86.6%) had a diagnosis of MDD, and 70 (66.7%) were taking concomitant psychotropic medications during the study period. Severity of

Table 1. Demographic, Clinical, and Study Design Characteristics by Study

Study	No.	Age (SD), y	Female, No. (%)	Diagnosis (%)	Concomitant Medications, No. (%)	Setting, No. (%)	Study Days	Outcome Measure
Saline placebo[a]								
Zarate et al., 2006	12	45.0 (12.4)	8 (66.7)	MDD	0	Inpatient	0, 1, 2, 3, 7	HAM-D
Diazgranados et al., 2010; Zarate et al., 2012	16	48.8 (9.5)	8 (50.0)	Bipolar	16 (100)	Inpatient	0, 1, 2, 3, 7	MADRS/ HAM-D
Nugent et al., 2019	18	34.8 (11.2)	9 (50.0)	MDD	0	Inpatient	0, 1, 2, 3, 7	MADRS/ HAM-D
Total	46	42.3 (12.4)	25 (54.4)	MDD: 30 (65.2), Bipolar: 16 (34.8)	16 (34.8)	–	–	–
Midazolam placebo[b]								
Murrough et al., 2013	10	41.2 (9.1)	2 (20.0)	MDD	0	Inpatient/outpatient[c]	0, 1, 2, 3, 7	MADRS
Murrough et al., 2015	11	38.9 (11.1)	8 (72.7)	MDD: 6 (54.5) Bipolar: 2 (18.2) PTSD: 2 (18.2) Borderline: 1 (9.1)	9 (81.8)	Inpatient: 8 (66.7)	0, 1, 2, 3, 7	MADRS
Grunebaum et al., 2017	9	42.9 (14.0)	7 (77.8)	Bipolar	9 (100)	Inpatient	0, 1	HAM-D
Grunebaum et al., 2018	33	40.1 (12.7)	20 (62.5)	MDD	23 (69.7)	Inpatient	0, 1	HAM-D
Fava et al., 2020	13	44.0 (14.5)	8 (61.5)	MDD	0 (0)	Outpatient	0, 3, 5, 7	MADRS
Phillips et al., 2020	29	40.2 (10.7)	17 (58.6)	MDD	29 (100)	Outpatient	0, 1, 7	MADRS
Total	105	41.1 (11.9)	62 (59.6)	MDD: 91 (86.6) Bipolar: 11 (10.5) PTSD: 2 (1.9) Borderline: 1 (1.0)	70 (66.7)	–	–	–

Abbreviations: HAM-D: Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; PTSD, posttraumatic stress disorder.

[a]All saline placebo studies employed a cross-over design.

[b]All midazolam placebo studies employed a parallel design, except for Phillips et al. (2020), which employed a cross-over design.

[c]Participants were admitted to an inpatient research unit for infusion and discharged 24 hours after infusion.

Table 2. Categorization of MADRS and HAM-D Depressed Mood and Suicidal Ideation Scores

Outcome	HAM-D	MADRS
Depressed mood	Item 1 (Depressed Mood)	Item 2 (Reported Sadness)
None (0)	(0) "Absent."	(0 or 1) "Occasional sadness in keeping with the circumstances."
Mild (1)	(1) "These feeling states indicated only on questioning."	(2 or 3) "Sad or low but brightens up without difficulty."
	(2) "These feeling states spontaneously reported verbally."	–
Moderate (2)	(3) "Communicates feeling states non verbally, i.e. through facial expression, posture, voice and tendency to weep."	(4 or 5) "Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances."
Severe (3)	(4) "Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication."	(6) "Continuous or unvarying sadness, misery or despondency."
Suicidal ideation	Item 3 (Suicide)	Item 10 (Suicidal Thoughts)
None (0)	(0) "Absent."	(0 or 1) "Enjoys life or takes it as it comes."
Mild (1)	(1) "Feels life is not worth living."	(2 or 3) "Weary of life. Only fleeting suicidal thoughts."
Moderate (2)	(2) "Wishes he/she were dead or any thoughts of possible death to self."	(4 or 5) "Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention."
Severe (3)	(3) "Ideas or gestures of suicide." (4) "Attempts at suicide."	(6) "Explicit plans for suicide when there is an opportunity. Active preparations for suicide."
Anhedonia	Item 7 (Work and Activities)	Item 8 (Inability to Feel)
None (0)	(0) "No difficulty."	(0 or 1) "Normal interest in the surroundings and in other people."
Mild (1)	(1) "Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies."	(2 or 3) "Reduced ability to enjoy usual interests."
Moderate (2)	(2) "Loss of interest in activity, hobbies or work – either directly reported by the patient or indirect in listlessness, indecision and vacillation."	(4 or 5) "Loss of interest in the surroundings. Loss of feelings for friends and acquaintances."
	(3) "Decrease in actual time spent in activities or decrease in productivity."	–
Severe (3)	(4) "Stopped working because of present illness."	(6) "The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends."
Anxiety	Item 10 (Anxiety Psychic)	Item 3 (Inner Tension)
None (0)	(0) "No difficulty."	(0 or 1) "Placid. Only fleeting inner tension."
Mild (1)	(1) "Subjective tension and irritability."	(2 or 3) "Occasional feelings of edginess and ill-defined discomfort."
	(2) "Worrying about minor matters."	–
Moderate (2)	(3) "Apprehensive attitude apparent in face or speech."	(4 or 5) "Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty."
Severe (3)	(4) "Fears expressed without questioning."	(6) "Unrelenting dread or anguish. Overwhelming panic."
Guilt	Item 2 (Feelings of Guilt)	Item 9 (Pessimistic Thoughts)
None (0)	(0) "Absent."	(0 or 1) "No pessimistic thoughts."
Mild (1)	(1) "Self reproach, feels he/she has let people down."	(2 or 3) "Fluctuating ideas of failure, self-reproach or self-depreciation"
Moderate (2)	(2) "Ideas of guilt or rumination over past errors or sinful deeds."	(4 or 5) "Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future."
Severe (3)	(3) "Present illness is a punishment. Delusions of guilt." (4) "Hears accusatory or denunciatory voices and/or experiences threatening VH."	(6) "Delusions of ruin, remorse and irredeemable sin. Self-accusations which are absurd and unshakable."

Abbreviations: HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; VH, visual hallucinations.

depressive symptom scores varied by study and placebo type; specifically, severity of suicidal ideation was higher at baseline in studies that used midazolam as a placebo than in those that used saline, while severity of anxiety and guilt were higher in those who used saline (Table 3).

For simplicity, results are reported only for the primary models; fixed effects of study, which were included in every model, are not shown (for results of the full models, see supplementary Tables S1- S4). A similar pattern of results was observed in sensitivity analyses with complete cases (see supplementary Tables S5 and S6), with the original uncombined scales (MADRS or HAM-D) as the outcomes (see supplementary Tables S7 and S8), and after removing participants who received placebo second in a cross-over study (see supplementary Tables S9 and S10).

For the participants who received saline placebo, suicidal ideation showed greater placebo response (reduction in item score from baseline) than depressed mood, anhedonia, or guilt after adjusting for covariates (Table 4). Specifically, suicidal ideation decreased by 0.50 points (95% confidence interval [CI]: −0.75 to −0.25) on the combined 0 to 3 scale from baseline to day 1, with a 1-point difference representing a change in clinical category (ie, severe to moderate or moderate to mild). From baseline to day 1, depressed mood decreased by 0.13 points (95% CI: −0.30 to 0.04), anhedonia decreased by 0.06 points (95% CI: −0.14 to 0.01), and guilt decreased by 0.25 points (95% CI: −0.42 to −0.08). A difference in day 1 change from baseline was found between suicidal ideation and depressed mood ($b = -0.37$ [95% CI: −0.66 to −0.07]) and anhedonia ($b = -0.43$ [95% CI: −0.7- to −0.16]). A difference in day 7 change from baseline was also observed for suicidal ideation vs anhedonia ($b = -0.31$ [95% CI: −0.61 to −0.001]) and guilt ($b = -0.39$ [95% CI: −0.72 to −0.05]). No significant differences were observed in day 1 or day 7 change from baseline between suicidal ideation and anxiety.

For the participants who received midazolam placebo, suicidal ideation showed greater placebo response (reduction in item score) than depressed mood and anhedonia after adjusting for covariates (Table 4). Suicidal ideation decreased by 0.48 points (95% CI: −0.68 to −0.29) from baseline to day 1 compared with a decrease of 0.29 points (95% CI: −0.42 to −0.17) for depressed mood and 0.18 points for anhedonia (95% CI: −0.34 to −0.02). A difference in day 1 change from baseline was found for suicidal ideation vs anhedonia ($b = -.30$ [95% CI: −0.52 to −0.08]). Although a difference in day 1 change from baseline was observed for suicidal ideation vs depressed mood in the unadjusted model ($b = -0.23$ [95% CI: −0.44 to −0.02]), this result was not statistically significant in the model adjusted for covariates (depressed mood: $b = -0.19$ [95% CI: −0.39 to 0.01]). A difference in day 7 change from baseline was also observed for suicidal ideation vs depressed mood (depressed mood: $b = -0.17$ [95% CI: −0.34 to −0.001]). No significant differences were observed in day 1 or day 7 change from baseline between suicidal ideation and anxiety or guilt.

DISCUSSION

This participant-level integrative data analysis of IV ketamine studies found a greater placebo response for suicidal ideation than depressed mood, anhedonia, or guilt in participants receiving saline placebo and a greater placebo response for suicidal ideation than depressed mood or anhedonia in participants receiving midazolam placebo. These results generally support our first hypothesis, although no difference in placebo response for suicidal ideation vs guilt was observed in participants receiving midazolam placebo. In addition, a similar placebo response was noted for both suicidal ideation and anxiety, regardless of the type of placebo used, contrary to our second hypothesis that midazolam placebo response would be greater for anxiety than for suicidal ideation. Overall, the results provide preliminary evidence of a differential placebo response for suicidal ideation vs other depressive symptoms but a similar placebo response for anxiety and suicidal ideation.

Several factors may underlie this finding of greater placebo response for suicidal ideation than for other depressive symptoms. First, research in different psychiatric populations, including those with depression, suggests that longitudinal trajectories of suicidal ideation may be highly variable for some patients (Kleiman et al., 2017; Madsen et al., 2019; Rizk et al., 2019; Bloomfield-Clagett et al., 2022). This variability suggests that suicidal ideation may be particularly reactive to a variety of influences, including psychological factors and environmental stimuli that participants in a clinical trial may experience more frequently (ie, interactions with treatment providers) (Kleiman and Riskind, 2013). In this context, isolating the influence of a pharmacologic treatment may be difficult in the presence of a potentially large placebo response because of these other nonpharmacologic influences. Second, it is possible that specific characteristics of the studies and analyses presented here—such as study population and outcome measures—are biasing the results. It should be noted, however, that although differences in baseline severity across symptoms may exist and different item scores may be differentially sensitive to change, the relative robustness of the results across symptom pair models, type of placebo, and sensitivity analyses is reassuring.

These findings differed from our hypotheses in some respects. With regard to the divergent findings for guilt between saline and midazolam placebo, the day 1 estimate for suicidal ideation was greater than that for guilt in participants receiving midazolam placebo, as expected; however, the result was not statistically significant, suggesting that our sample size may not have been large enough to detect a difference. As regards the finding that midazolam placebo response to anxiety and suicidal ideation did not differ, it is possible that no difference was observed 24 hours after infusion because of midazolam's relatively short half-life (Heizmann et al., 1983). In addition, findings from both pharmacologic and nonpharmacologic clinical trials suggest that improving anxiety measures may have subsequent antisuicidal effects (Ballard et al., 2014; Schmidt et al., 2017), and other research suggests that the relationship between anxiety and suicidal ideation may occur independent of depression (Sareen et al., 2005; Capron et al., 2012).

Several additional limitations to this analysis bear mention. First, this was an exploratory analysis, and the relevant findings should be interpreted with caution. Second, of the 6 midazolam studies included, 1 did not include an assessment at day 1, and 2 studies did not include an assessment at day 7. The complete case analysis conducted to address these missing data, however, obtained similar results (see supplementary Tables S5 and S6). Third, all studies included in this analysis were single-dose studies of IV ketamine; the effects of repeat-dose IV ketamine on depressive symptoms are currently being researched. Fourth, although the item scores used as outcomes in the analysis are ordinal in nature, for the purposes of this analysis they were treated as continuous because the differences between levels were clinically meaningful and the assumption of equal intervals between scores should not greatly distort the results. Treating the outcome measures as continuous also improves the interpretability of the results, and this approach has been used

Table 3. Baseline Depressive Symptom Scores by Study

Outcome	Saline Placebo				Midazolam Placebo						
	Zarate et al., 2006	Diazgranados et al., 2010 and Zarate et al., 2012	Nugent et al., 2019	Total	Murrough et al., 2013	Murrough et al., 2015	Grunebaum et al., 2017	Grunebaum et al., 2018	Fava et al., 2018	Phillips et al., 2018	Total
Suicidal ideation, No. (%)											
Mild	8 (66.8)	6 (37.5)	9 (50.0)	23 (50.0)	9 (90.0)	2 (18.2)	0 (0)	4 (12.1)	12 (92.3)	16 (55.2)	43 (41.0)
Moderate	2 (16.6)	8 (50.0)	6 (33.3)	16 (34.8)	1 (10.0)	9 (81.8)	1 (11.1)	8 (24.2)	1 (7.7)	13 (44.8)	34 (31.4)
Severe	2 (16.6)	2 (12.5)	3 (16.7)	7 (15.2)	0 (0)	0 (0)	8 (88.9)	21 (63.7)	0 (0)	0 (0)	29 (27.6)
Depressed mood, No. (%)											
Mild	1 (8.3)	2 (12.5)	1 (5.6)	4 (8.7)	0 (0)	2 (18.2)	2 (22.2)	11 (33.3)	2 (15.4)	5 (17.2)	22 (21.0)
Moderate	10 (83.4)	13 (81.2)	14 (77.8)	37 (80.4)	10 (100)	9 (81.8)	5 (55.6)	20 (60.6)	9 (69.2)	24 (82.8)	77 (73.3)
Severe	1 (8.3)	1 (6.3)	3 (16.7)	5 (10.9)	0 (0)	0 (0)	2 (22.2)	2 (6.0)	2 (15.4)	0 (0)	6 (5.7)
Anhedonia, No. (%)											
Mild	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (45.4)	1 (11.1)	0 (0)	2 (15.4)	8 (27.6)	16 (15.3)
Moderate	11 (91.6)	16 (100.0)	17 (94.4)	44 (95.6)	9 (90.0)	6 (54.6)	5 (55.5)	24 (72.7)	10 (76.9)	21 (72.4)	75 (71.4)
Severe	1 (8.3)	0 (0)	1 (5.6)	2 (4.4)	1 (10.0)	0 (0)	3 (33.3)	9 (27.3)	1 (7.7)	0 (0)	14 (13.3)
Anxiety, No. (%)											
Mild	6 (50.0)	4 (25.0)	3 (16.7)	13 (28.3)	4 (40.0)	2 (18.2)	5 (55.6)	26 (78.8)	9 (69.2)	16 (55.2)	62 (59.0)
Moderate	6 (50.0)	12 (75.0)	10 (55.5)	28 (60.8)	6 (60.0)	9 (81.8)	4 (44.4)	7 (21.1)	3 (23.1)	13 (44.8)	42 (40.0)
Severe	0 (0)	0 (0)	5 (27.8)	5 (10.9)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7.7)	0 (0)	1 (1.0)
Guilt, No. (%)											
Mild	3 (25.0)	3 (18.7)	1 (5.6)	7 (15.2)	2 (20.0)	3 (27.3)	1 (11.1)	6 (18.2)	3 (23.1)	5 (17.2)	20 (19.0)
Moderate	9 (75.0)	9 (56.3)	13 (72.2)	31 (67.4)	8 (80.0)	8 (72.7)	5 (55.6)	21 (63.6)	10 (76.9)	24 (82.8)	76 (72.4)
Severe	0 (0)	4 (25.0)	4 (22.2)	8 (17.4)	0 (0)	0 (0)	3 (33.3)	6 (18.2)	0 (0)	0 (0)	9 (8.6)

Table 4. Coefficients of Predictors of Suicidal Ideation vs Depressed Mood, Anhedonia, Anxiety, and Guilt for Participants Receiving Saline (n = 46) and Midazolam Placebo (n = 105)[a]

	Depressed Mood						Anhedonia						Anxiety						Guilt					
	b	95% CI	*P* Value	Adj *b*[b]	95% CI	*P* Value	*b*	95% CI	*P* Value	Adj *b*[b]	95% CI	*P* Value	*b*	95% CI	*P* Value	Adj *b*[b]	95% CI	*P* Value	*b*	95% CI	*P* Value	Adj *b*[b]	95% CI	*P* Value
Saline (n = 46)																								
Fixed effects																								
SI symptom domain																								
Comparator symptom	[Reference]																							
Suicidal ideation	−0.47	−0.87 to −0.07	0.021	−0.47	−0.87 to −0.07	0.021	−0.48	−0.87, −0.09	0.016	−0.48	−0.87 to −0.09	0.016	−0.05	−0.40 to 0.30	0.774	−0.05	−0.40 to 0.30	0.771	−0.18	−0.57 to 0.21	0.361	−0.18	−0.57 to 0.21	0.360
Day																								
0 (baseline)	[Reference]																							
1	−0.13	−0.30 to 0.04	0.128	−0.13	−0.30 to 0.04	0.132	−0.07	−0.14 to 0.01	0.073	−0.07	−0.14 to 0.01	0.074	−0.33	−0.52 to −0.15	<.001	−0.33	−0.52 to −0.15	<.001	−0.25	−0.42 to −0.08	0.004	−0.25	−0.42 to −0.08	0.004
7	−0.21	−0.42 to 0.01	0.056	−0.21	−0.42 to 0.00	0.051	−0.01	−0.09 to 0.07	0.824	−0.01	−0.09 to 0.07	0.807	−0.25	−0.46 to −0.04	0.021	−0.25	−0.46 to −0.03	0.022	0.06	−0.15 to 0.27	0.560	0.06	−0.15 to 0.27	0.584
Symptom domain day																								
SI × day 1	−0.37	−0.66 to −0.07	0.015	−0.37	−0.66 to −0.07	0.015	−0.43	−0.70 to −0.16	0.002	−0.43	−0.70 to −0.16	0.002	−0.17	−0.47 to 0.13	0.276	−0.17	−0.46 to 0.13	0.280	−0.25	−0.55 to 0.05	0.107	−0.25	−0.55 to 0.05	0.108
SI × day 7	−0.11	−0.43 to 0.22	0.508	−0.11	−0.43 to 0.22	0.510	−0.31	−0.61 to 0.00	0.048	−0.31	−0.61 to 0.00	0.049	−0.07	−0.36 to 0.22	0.650	−0.07	−0.36 to 0.22	0.644	−0.39	−0.72 to −0.05	0.024	−0.39	−0.72 to −0.05	0.025
Random effects																								
Subject intercept	0.03	0.00-0.20	–	0.00	0.03-0.00	–	0.32	0.00-0.14	–	0.02	0.00-0.18	–	0.06	0.01-0.21	–	0.05	0.01-0.20	–	0.06	0.01-0.28	–	0.06	0.01-0.27	–
Residual var (Sx)	0.23	0.15-0.34	–	0.25	0.05-0.15	–	0.35	0.01-0.15	–	0.03	0.01-0.17	–	0.24	0.16-0.35	–	0.25	0.17-0.36	–	0.27	0.17-0.44	–	0.27	0.16-0.45	
Residual cov (Sx)	0.05	−0.05 to 0.14	–	0.07	0.05 to −0.04	–	0.15	−0.05 to 0.03	–	−0.01	−0.05 to 0.03	–	0.04	−0.05 to 0.12	–	0.05	−0.04 to 0.13	–	0.05	−0.05 to 0.16	–	0.05	−0.06 to 0.17	–
Residual var (SI)	0.62	0.47-0.82	–	0.60	0.09-0.46	–	0.81	0.49-0.81	–	0.63	0.49-0.81	–	0.57	0.44-0.75	–	0.56	0.43-0.73	–	0.59	0.46-0.74	–	0.59	0.46-0.76	–
Residual cov (SI)	0.26	0.08-0.45	–	0.24	0.10-0.07	–	0.45	0.09-0.46	–	0.28	0.09-0.46	–	0.21	0.05-0.38	–	0.20	0.04-0.36	–	0.23	0.08-0.38	–	0.24	0.07-0.40	–
Midazolam (n = 105)																								
Fixed effects																								
SI symptom domain																								
Comparator symptom	[Reference]																							
Suicidal ideation	−0.93	−1.18 to −0.68	<.001	−0.95	−1.20 to −0.70	<.001	−0.95	−1.17 to −0.73	<.001	−0.96	−1.18 to −0.75	<.001	−0.47	−0.72 to −0.23	<.001	−0.49	−0.73 to −0.24	<.001	−0.68	−0.88 to −0.49	<.001	−0.69	−0.89 to −0.50	<.001
Day																								
0 (baseline)	[Reference]																							
1	−0.28	−0.41 to −0.15	<.001	−0.29	−0.42 to −0.17	<.001	−0.18	−0.33 to −0.02	0.023	−0.18	−0.34 to −0.02	0.023	−0.31	−0.45 to −0.17	<.001	−0.31	−0.46 to −0.17	<.001	−0.36	−0.50 to −0.22	<.001	−0.35	−0.49 to −0.21	<.001
7	−0.19	−0.32 to −0.05	0.008	−0.19	−0.33 to −0.05	0.006	−0.25	−0.44 to −0.05	0.012	−0.25	−0.44 to −0.06	0.012	−0.34	−0.52 to −0.16	<.001	−0.34	−0.52 to −0.16	<.001	−0.40	−0.56 to −0.23	<.001	−0.39	−0.56 to −0.23	<.001
Symptom domain × day																								
SI × day 1	−0.23	−0.44 to −0.02	0.032	−0.19	−0.39 to 0.01	0.059	−0.33	−0.56 to −0.10	0.005	−0.30	−0.53 to −0.08	0.008	−0.20	−0.42 to 0.02	0.072	−0.17	−0.38 to 0.04	0.116	−0.15	−0.35 to 0.05	0.138	−0.13	−0.33 to 0.07	0.195

Table 4. Continued

	Depressed Mood				Anhedonia				Anxiety				Guilt			
	b	95% CI	*P* Value	Adj *b*[b]	*b*	95% CI	*P* Value	Adj *b*[b]	*b*	95% CI	*P* Value	Adj *b*[b]	*b*	95% CI	*P* Value	Adj *b*[b]
SI × day 7	−0.19	−0.36 to −0.01	0.033	−0.17	−0.12	−0.35 to 0.10	0.286	−0.11	−0.03	−0.21 to 0.15	0.751	−0.02	0.03	−0.15 to 0.20	0.762	0.04
Random effects																
Subject intercept	0.11	0.06-0.19	–	0.10	0.10	0.05-0.18	–	0.09	0.11	0.07-0.17	–	0.10	0.16	0.09-0.26	–	0.15
Residual var (Sx)	0.22	0.17-0.29	–	0.20	0.27	0.21-0.36	–	0.27	0.25	0.20-0.32	–	0.25	0.29	0.21-0.39	–	0.28
Residual cov (Sx)	0.03	−0.03 to 0.10	–	0.02	−0.03	−0.09 to 0.03	–	−0.04	−0.01	−0.07 to 0.05	–	−0.02	0.05	−0.04 to 0.14	–	0.05
Residual var (SI)	0.52	0.42-0.65	–	0.52	0.53	0.44-0.65	–	0.53	0.52	0.42-0.64	–	0.52	0.47	0.37-0.60	–	0.47
Residual cov (SI)	0.12	0.00-0.23	–	0.14	0.13	0.02-0.24	–	0.14	0.12	0.01-0.22	–	0.13	0.06	−0.05 to 0.17	–	0.08

	Depressed Mood				Anhedonia				Anxiety				Guilt			
	b	95% CI	*P* Value	Adj *b*[b]	*b*	95% CI	*P* Value	Adj *b*[b]	*b*	95% CI	*P* Value	Adj *b*[b]	*b*	95% CI	*P* Value	Adj *b*[b]
SI × day 7	−0.19	−0.36 to −0.01	0.033	−0.17	−0.12	−0.34 to 0.00	0.048	−0.11	−0.03	−0.21 to 0.15	0.333	−0.02	0.03	−0.15 to 0.20	0.859	0.04
Random effects																
Subject intercept	0.11	0.06-0.19	–	0.10	0.10	0.05-0.18	–	0.09	0.11	0.07-0.17	–	0.10	0.16	0.09-0.26	–	0.15
Residual var (Sx)	0.22	0.17-0.29	–	0.20	0.27	0.21-0.36	–	0.27	0.25	0.20-0.32	–	0.25	0.29	0.21-0.39	–	0.28
Residual cov (Sx)	0.03	−0.03 to 0.10	–	0.02	−0.03	−0.09 to 0.03	–	−0.04	−0.01	−0.07 to 0.05	–	−0.02	0.05	−0.04 to 0.14	–	0.05
Residual var (SI)	0.52	0.42-0.65	–	0.52	0.53	0.44-0.65	–	0.53	0.52	0.42-0.64	–	0.52	0.47	0.37-0.60	–	0.47
Residual cov (SI)	0.12	0.00-0.23	–	0.14	0.13	0.02-0.24	–	0.14	0.12	0.01-0.22	–	0.13	0.06	−0.05 to 0.17	–	0.08

	Depressed Mood				Anhedonia				Anxiety				Guilt			
	b	95% CI	*P* Value	Adj *b*[b]	*b*	95% CI	*P* Value	Adj *b*[b]	*b*	95% CI	*P* Value	Adj *b*[b]	*b*	95% CI	*P* Value	Adj *b*[b]
SI × day 7	−0.19	−0.36 to −0.01	0.033	−0.17	−0.12	−0.35 to 0.10	0.286	−0.11	−0.03	−0.34 to 0.11	0.333	−0.11	0.03	−0.19 to 0.16	0.859	−0.02
Random effects																
Subject intercept	0.11	0.06-0.19	–	0.10	0.10	0.05-0.18	–	0.09	0.11	0.07-0.17	–	0.10	0.16	0.09-0.26	–	0.15
Residual var (Sx)	0.22	0.17-0.29	–	0.20	0.27	0.21-0.36	–	0.27	0.25	0.20-0.32	–	0.25	0.29	0.21-0.39	–	0.28
Residual cov (Sx)	0.03	−0.03 to 0.10	–	0.02	−0.03	−0.09 to 0.03	–	−0.04	−0.01	−0.07 to 0.05	–	−0.02	0.05	−0.04 to 0.14	–	0.05
Residual var (SI)	0.52	0.42-0.65	–	0.52	0.53	0.44-0.65	–	0.53	0.52	0.42-0.64	–	0.52	0.47	0.37-0.60	–	0.47
Residual cov (SI)	0.12	0.00-0.23	–	0.14	0.13	0.02-0.24	–	0.14	0.12	0.01-0.22	–	0.13	0.06	−0.05 to 0.17	–	0.08

Abbreviations: Adj adjusted; CI, confidence interval; cov, covariance; SI, suicidal ideation; var, variance; Sx, comparator symptom.
[a]All models include study as a fixed effect as well as a study-by-symptom domain interaction. The reference group for SI symptom domain is the comparator depressive symptom domain. The reference group for day is day 0 (baseline).
[b]Adj *b*: For saline models, betas adjusted for age and sex (not adjusted for diagnosis or concomitant medications because these variables are collinear with study). For midazolam models, betas adjusted for age, sex, diagnosis, and concomitant medications.

in similar studies (Wilkinson et al., 2018; Wilkinson and Farmer, 2019). Fifth, although the models included baseline clinical and demographic variables to adjust for possible confounders, we could not test for moderation effects, which in our models would involve a 3-way interaction that our analysis was not powered to detect. Finally, saline and midazolam studies also differed in terms of their study design (parallel vs cross-over), so it cannot be definitively determined whether the observed findings were the result of placebo type or study design. Similar results were obtained, however, when restricting the data set to include only participants who received placebo in phase 1 of a cross-over design (and who, thus, were as likely to receive placebo as participants in a parallel-design study), suggesting that study design did not substantially affect the findings.

These findings suggest a greater placebo response for suicidal ideation than for nonsuicidal depressive symptoms that may contribute to more modest findings in clinical trials of IV ketamine for suicidal ideation. Further studies with larger sample sizes are needed to replicate the above findings and to examine how differential placebo response to different symptom domains and with different scales may affect results. It should be noted that our sample did not allow the investigation of whether other study factors—such as treatment setting (inpatient or outpatient) or stage (early clinical trials in well-controlled settings vs later-stage trials in real-world environments)—might have affected placebo response rates. Future research is warranted to investigate these factors.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

Funding and Conflict of Interest

This work was supported by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH; ZIAMH002857).

S.T.W. has received contract research funding from Janssen, Sage Therapeutics, and Oui Therapeutics for the conduct of clinical trials administered through Yale University and consulting fees from Janssen, Sage Therapeutics, Oui Therapeutics, Eleusis, and Biohaven Pharmaceuticals.

In the past 5 years, J.W.M. has provided consultation services and/or served on advisory boards for Allergan, Boehringer Ingelheim, Clexio Biosciences, Fortress Biotech, FSV7, Global Medical Education (GME), Otsuka, and Sage Therapeutics. J.W.M. is named on a patent pending for neuropeptide Y as a treatment for mood and anxiety disorders and on a patent pending for the use of ezogabine and other KCNQ channel openers to treat depression and related conditions. The Icahn School of Medicine (J.W.M.'s employer) is named on a patent and has entered into a licensing agreement and will receive payments related to the use of ketamine or esketamine for the treatment of depression. The Icahn School of Medicine is also named on a patent related to the use of ketamine for the treatment of PTSD. J.W.M. is not named on these patents and will not receive any payments.

S.J.M. is supported through the use of facilities and resources at the Michael E. Debakey VA Medical Center, Houston, Texas, and receives support from The Menninger Clinic. S.J.M. has served as a consultant to Alkermes, Allergan, Axsome Therapeutics, BioXcel Therapeutics, Clexio Biosciences, Eleusis, EMA Wellness, Engrail Therapeutics, Greenwich Biosciences, Intra-Cellular Therapies, Janssen, Levo Therapeutics, Neurocrine,

Perception Neuroscience, Praxis Precision Medicines, Relmada Therapeutics, Sage Therapeutics, Seelos Therapeutics, and Signant Health. He has received research support from Biohaven Pharmaceuticals, Merck, Sage, and VistaGen Therapeutics.

M.F. reports the following lifetime disclosures. He has received research support from Abbott Laboratories; Acadia Pharmaceuticals; Alkermes, Inc; American Cyanamid; Aspect Medical Systems; AstraZeneca; Avanir Pharmaceuticals; AXSOME Therapeutics; BioClinica, Inc; Biohaven; BioResearch; BrainCells Inc; Bristol-Myers Squibb; CeNeRx BioPharma; Centrexion Therapeutics Corporation; Cephalon; Cerecor; Clarus Funds; Clexio Biosciences; Clintara, LLC; Covance; Covidien; Eli Lilly and Company; EnVivo Pharmaceuticals, Inc; Euthymics Bioscience, Inc; Forest Pharmaceuticals, Inc; FORUM Pharmaceuticals; Ganeden Biotech, Inc; Gentelon, LLC; GlaxoSmithKline; Harvard Clinical Research Institute; Hoffman-LaRoche; Icon Clinical Research; Indivior; i3 Innovus/Ingenix; Janssen R&D, LLC; Jed Foundation; Johnson & Johnson Pharmaceutical Research & Development; Lichtwer Pharma GmbH; Lorex Pharmaceuticals; Lundbeck Inc; Marinus Pharmaceuticals; MedAvante; Methylation Sciences Inc; National Alliance for Research on Schizophrenia & Depression (NARSAD); National Center for Complementary and Alternative Medicine (NCCAM); National Coordinating Center for Integrated Medicine (NiiCM); National Institute of Drug Abuse (NIDA); National Institutes of Health; National Institute of Mental Health (NIMH); Neuralstem, Inc; NeuroRx; Novartis AG; Novaremed; Organon Pharmaceuticals; Otsuka Pharmaceutical Development, Inc; PamLab, LLC; Pfizer Inc; Pharmacia-Upjohn; Pharmaceutical Research Associates., Inc; Pharmavite LLC; PharmoRx Therapeutics; Photothera; Praxis Precision Medicines; Premiere Research International; Protagenic Therapeutics, Inc; Reckitt Benckiser; Relmada Therapeutics Inc; Roche Pharmaceuticals; RCT Logic, LLC (formerly Clinical Trials Solutions, LLC); Sanofi-Aventis US LLC; Shenox Pharmaceuticals, LLC; Shire; Solvay Pharmaceuticals, Inc; Stanley Medical Research Institute (SMRI); Synthelabo; Taisho Pharmaceuticals; Takeda Pharmaceuticals; Tal Medical; VistaGen; WinSanTor, Inc; and Wyeth-Ayerst Laboratories. He has served on the advisory board or been a consultant for the following: Abbott Laboratories; Acadia; Aditum Bio Management Company, LLC; Affectis Pharmaceuticals AG; Alfasigma USA, Inc; Alkermes, Inc; Altimate Health Corporation; Amarin Pharma Inc; Amorsa Therapeutics, Inc; Ancora Bio, Inc; Angelini S.p.A; Aptinyx Inc; Arbor Pharmaceuticals, LLC; Aspect Medical Systems; Astella Pharma Global Development, Inc; AstraZeneca; Auspex Pharmaceuticals; Avanir Pharmaceuticals; AXSOME Therapeutics; Bayer AG; Best Practice Project Management, Inc; Biogen; BioMarin Pharmaceuticals, Inc; BioXcel Therapeutics; Biovail Corporation; Boehringer Ingelheim; Boston Pharmaceuticals; BrainCells Inc; Bristol-Myers Squibb; Cambridge Science Corporation; CeNeRx BioPharma; Cephalon, Inc; Cerecor; Clexio Biosciences; Click Therapeutics, Inc; CNS Response, Inc; Compellis Pharmaceuticals; Cybin Corporation; Cypress Pharmaceutical, Inc; DiagnoSearch Life Sciences (P) Ltd; Dainippon Sumitomo Pharma Co Inc; Dr Katz, Inc; Dov Pharmaceuticals, Inc; Edgemont Pharmaceuticals, Inc; Eisai Inc; Eli Lilly and Company; ElMindA; EnVivo Pharmaceuticals, Inc; Enzymotec LTD; ePharmaSolutions; EPIX Pharmaceuticals, Inc; Esthismos Research, Inc; Euthymics Bioscience, Inc; Evecxia Therapeutics, Inc; ExpertConnect, LLC; FAAH Research Inc; Fabre-Kramer Pharmaceuticals, Inc; Forest Pharmaceuticals, Inc; Forum Pharmaceuticals; Gate Neurosciences, Inc; GenetikaPlus Ltd; GenOmind, LLC; GlaxoSmithKline; Grunenthal GmbH; Happify; H. Lundbeck A/S; Indivior; i3 Innovus/Ingenis; Intracellular; Janssen Pharmaceutica; Jazz Pharmaceuticals, Inc; JDS Therapeutics, LLC; Johnson & Johnson Pharmaceutical Research & Development, LLC; Knoll Pharmaceuticals Corp; Labopharm Inc; Lorex Pharmaceuticals; Lundbeck Inc; Marinus Pharmaceuticals; MedAvante, Inc; Merck & Co., Inc; Mind Medicine Inc; MSI Methylation Sciences, Inc; Naurex, Inc; Navitor Pharmaceuticals, Inc; Nestle Health Sciences; Neuralstem, Inc; Neurocrine Biosciences, Inc; Neuronetics, Inc; NextWave Pharmaceuticals; Niraxx Light Therapeutics, Inc; Northwestern University; Novartis AG; Nutrition 21; Opiant Pharmaceuticals; Orexigen Therapeutics, Inc; Organon Pharmaceuticals; Osmotica; Otsuka Pharmaceuticals; Ovid Therapeutics, Inc; Pamlab, LLC; Perception Neuroscience; Pfizer Inc; PharmaStar; PharmaTher Inc; Pharmavite LLC; PharmoRx Therapeutics; Polaris Partners; Praxis Precision Medicines; Precision Human Biolaboratory; Prexa Pharmaceuticals, Inc; Protagenic Therapeutics, Inc; PPD; PThera, LLC; Purdue Pharma; Puretech Ventures; Pure Tech LYT, Inc; PsychoGenics; Psylin Neurosciences, Inc; RCT Logic, LLC (formerly Clinical Trials Solutions, LLC); Relmada Therapeutics, Inc; Rexahn Pharmaceuticals, Inc; Ridge Diagnostics, Inc; Roche; Sanofi-Aventis US LLC; Sensorium Therapeutics; Sentier Therapeutics; Sepracor Inc; Servier Laboratories; Schering-Plough Corporation; Shenox Pharmaceuticals, LLC; Solvay Pharmaceuticals, Inc; Somaxon Pharmaceuticals, Inc; Somerset Pharmaceuticals, Inc; Sonde Health; Sunovion Pharmaceuticals; Supernus Pharmaceuticals, Inc; Synthelabo; Taisho Pharmaceuticals; Takeda Pharmaceutical Company Limited; Tal Medical, Inc; Tetragenex; Teva Pharmaceuticals; TransForm Pharmaceuticals, Inc; Transcept Pharmaceuticals, Inc; University of Michigan, Department of Psychiatry; Usona Institute, Inc; Vanda Pharmaceuticals, Inc; Versant Venture Management, LLC; VistaGen; and Xenon Pharmaceuticals Inc. He has equity holdings in Compellis, Psy Therapeutics, and Sensorium Therapeutics. He holds a patent for Sequential Parallel Comparison Design (SPCD), licensed by MGH to Pharmaceutical Product Development, LLC (PPD) (US_7840419, US_7647235, US_7983936, US_8145504, US_8145505) and has submitted a patent application for a combination of ketamine plus scopolamine in major depressive disorder (MDD), licensed by MGH to Biohaven, as well as patents for pharmacogenomics of depression treatment with folate (US_9546401, US_9540691). He holds copyrights for the MGH Cognitive & Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs & Symptoms (DESS), Symptoms of Depression Questionnaire (SDQ), and SAFER; Lippincott, Williams & Wilkins; Wolkers Kluwer; World Scientific Publishing Co. Pte Ltd.

In the past 12 months, G.S. has provided consulting services to Allergan, Axsome Therapeutics, Biohaven Pharmaceuticals, Bristol-Myers Squibb, Denovo, EMA Wellness, Gilgamesh, Intra-Cellular Therapies, Janssen Pharmaceuticals, Lundbeck, Merck, Navitor Pharmaceuticals, Neurocrine, Novartis, Noven Pharmaceuticals, Perception Neuroscience, Praxis, Sage Pharmaceuticals, Seelos Pharmaceuticals, and XW Labs. He has received funds for contracted research from Janssen Pharmaceuticals, Merck, and Usona Institute. He holds equity in Biohaven Pharmaceuticals and has received royalties from Yale University paid from patent licenses with Biohaven Pharmaceuticals. His employer, Yale University, has a financial relationship with Janssen Pharmaceuticals and may receive financial benefits from this relationship.

C.A.Z. is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation; as a co-inventor

on a patent for the use of (2*R*,6*R*)-hydroxynorketamine, (*S*)-dehydronorketamine, and other stereoisomeric dehydroxylated and hydroxylated metabolites of (*R*,*S*)-ketamine metabolites in the treatment of depression and neuropathic pain, and as a co-inventor on a patent application for the use of (2*R*,6*R*)-hydroxynorketamine and (2*S*,6*S*)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and posttraumatic stress disorders. He has assigned his patent rights to the US government but will share a percentage of any royalties that may be received by the government.

B.B-C, E.D.B., D.K.G., M.F.G., and J.L.P. have no conflict of interest to disclose, financial or otherwise.

Acknowledgments

The authors thank the 7SE research unit and staff for their support. Ioline Henter (NIMH) provided invaluable editorial assistance; the authors are entirely responsible for the scientific content of the paper.

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