The Effect of a Single Dose of Intravenous Ketamine on Suicidal Ideation: A Systematic Review and Individual Participant Data Meta-Analysis

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Objective: Suicide is a public health crisis with limited treatment options. The authors conducted a systematic review and individual participant data meta-analysis examining the effects of a single dose of ketamine on suicidal ideation.

Method: Individual participant data were obtained from 10 of 11 identified comparison intervention studies that used either saline or midazolam as a control treatment. The analysis included only participants who had suicidal ideation at baseline (N=167). A one-stage, individual participant data, meta-analytic procedure was employed using a mixed-effects, multilevel, general linear model. The primary outcome measures were the suicide items from clinician-administered (the Montgomery-Åsberg Depression Rating Scale [MADRS] or the Hamilton Depression Rating Scale [HAM-D]) and self-report scales (the Quick Inventory of Depressive Symptomatology–Self Report [QIDS-SR] or the Beck Depression Inventory [BDI]), obtained for up to 1 week after ketamine administration.

Results: Ketamine rapidly (within 1 day) reduced suicidal ideation significantly on both the clinician-administered and self-report outcome measures. Effect sizes were moderate to large (Cohen's d=0.48–0.85) at all time points after dosing. A sensitivity analysis demonstrated that compared with control treatments, ketamine had significant benefits on the individual suicide items of the MADRS, the HAM-D, and the QIDS-SR but not the BDI. Ketamine's effect on suicidal ideation remained significant after adjusting for concurrent changes in severity of depressive symptoms.

Conclusions: Ketamine rapidly reduced suicidal thoughts, within 1 day and for up to 1 week in depressed patients with suicidal ideation. Ketamine's effects on suicidal ideation were partially independent of its effects on mood, although subsequent trials in transdiagnostic samples are required to confirm that ketamine exerts a specific effect on suicidal ideation. Additional research on ketamine's long-term safety and its efficacy in reducing suicide risk is needed before clinical implementation.

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Suicide is a public health crisis and ranks among the top three causes of mortality worldwide for individuals ages 15–44 (1, 2). Unfortunately, the suicide rate has increased over the past two decades despite renewed efforts to address this crisis (3). Studies suggest that approximately 90% of individuals who commit suicide suffer from a treatable psychiatric disorder, most commonly a mood disorder (4). Nevertheless, current treatment options for patients at acute risk for suicide are limited and generally consist of hospitalization plus pharmacotherapy, psychotherapy, ECT, or a combination thereof. The National Action Alliance for Suicide Prevention has highlighted the importance of identifying fast-acting interventions for suicidal individuals as a critical research goal to reduce the suicide rate (5). Treatment with lithium and clozapine, as well as dialectical behavioral therapy and cognitive-behavioral therapy (CBT), have been shown to reduce suicide deaths (2, 6, 7) and rates of suicide attempts (8, 9). However, while these treatments and interventions function to reduce suicide risk long-term, they have not been shown to be effective in acute settings.

Since 2000, several small clinical trials have demonstrated that subanesthetic doses of ketamine have rapid-acting antidepressant properties (10–14) as well as potential antisuicidal properties (15–18) in patients with mood disorders (both major depressive disorder and bipolar depression). Given ketamine's rapid antidepressant effects, there is considerable interest regarding its potential ability to stabilize patients with mood

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disorders who are at imminent risk of suicide. Here, we report on a systematic review and meta-analysis using patient-level data of explicit measures of suicidal ideation to assess ketamine's potential antisuicidal effects.

METHOD

Study Identification and Selection

Two reviewers (S.T.W., E.D.B.) searched MEDLINE using the terms "ketamine," "NMDA receptor antagonist," "ketamine-like," or "rapid antidepressant" and "suicide," "suicidality," or "suicidal ideation" (filter: clinical trials) for articles published between Jan. 1, 2000, and Nov. 15, 2016. The identified systematic reviews and meta-analyses were searched for relevant published and unpublished research. Additional studies were identified through cross-reference or communication with investigators.

This meta-analysis investigated studies of single-dose intravenous ketamine for the treatment of any psychiatric disorder; only comparison intervention trials (using saline placebo or midazolam as a control) were included. Studies in which multiple ketamine doses were administered were excluded. The corresponding authors of identified publications were contacted and asked to provide individual subject data regarding how suicidal ideation was assessed in each potentially eligible trial. Authors also provided individual suicide assessment scores, individual depression severity scores, and baseline demographic and clinical information.

Statistical Analysis

Patient-level data were collected for several distinct variables, including 1) suicidal ideation, assessed via two clinician-administered and two self-report rating scales (item 10 on the Montgomery-Åsberg Depression Rating Scale [MADRS]; item 3 on the 17-item Hamilton Depression Rating Scale [HAM-D]; item 12 on the Quick Inventory of Depressive Symptomatology–Self Report [QIDS-SR]; and/or item 9 on the Beck Depression Inventory [BDI]); 2) overall severity of depressive symptoms, assessed via total score on the MADRS, HAM-D, QIDS-SR, and/or BDI; 3) treatment assignment (ketamine or control treatment); and 4) potential moderators of treatment effect (age, gender, race, inpatient versus outpatient status, use of concomitant medications). Whenever available, all data were collected from each investigator for baseline and postinfusion days 1, 2, 3, and 7. Our method for handling missing data is described in the data supplement that accompanies the online edition of this article. Table S1 in the data supplement lists which rating scales were used in each study.

Because this study sought to determine the effects of ketamine on suicidal ideation, patients who had no suicidal ideation at baseline were excluded from the analysis. We included active or passive suicidal ideation, which was operationalized a priori as a score ≥2 on MADRS item 10 ("weary of life/fleeting suicidal ideation") or a score ≥1 on the HAM-D suicidal ideation item ("feels life is not worth living") for the clinician-administered scales; for the self-report scales, suicidal ideation was defined as a score ≥1 on QIDS-SR item 12 ("I feel that life is empty or wonder if it's worth living") or a score ≥1 on BDI item 9 ("I have thoughts of killing myself, but I would not carry them out").

We used a standard one-stage hierarchical modeling approach (19), with participants nested within studies. A general linear mixed model was used; the dependent variable was suicidal ideation. The specific hypothesis tested using this model was that ketamine would resolve suicidal ideation more rapidly than the control treatment. The following independent variables were used in the first model: baseline suicidal ideation (held constant over time), group, time, and a group-by-time interaction. The following covariates were included in an additional model: age, gender, race, treatment setting (inpatient versus outpatient), diagnosis, and whether the patient was taking concomitant psychotropic medications. In a final model, we dropped terms that had no main effect and adjusted for changes in severity of depressive symptoms over time in an attempt to assess whether ketamine's effects on suicidal ideation were independent of its effects on other depressive symptoms; in these analyses, the suicide items were removed from the composite depression score.

Dichotomous outcomes (being free of suicidal ideation) among those with some level of baseline suicidal ideation were also analyzed in two separate models (using self-report and clinician-administered rating scales; see the online data supplement).

Effect sizes (Cohen's d) were calculated using mean differences between baseline and each time point (postinfusion days 1, 2, 3, and 7). For all analyses, the significance threshold was set at 0.05, two-tailed. Because several trials showed evidence of carryover effects associated with ketamine treatment, we analyzed only data from the first treatment (ketamine or control treatment) in crossover trials.

The online data supplement describes how data from different scales were combined.

Correlations between change in suicidal ideation and overall severity of depressive symptoms were calculated using Pearson correlation coefficients. Changes were calculated between baseline and postinfusion days 1, 2, 3, and 7; for this analysis, suicide items were removed from the overall composite depression score.

RESULTS

Included Studies

Eleven eligible trials were identified from 153 citations (Figure 1). Corresponding authors provided individual subject data for 10 of these 11 potentially eligible citations (10–14, 17, 20–23). Correspondence with authors of the remaining study (24) indicated that none of the participants had baseline suicidal ideation and would thus not have been eligible for inclusion in the present analysis. Three of the studies were conducted at the National Institutes of Health (11–13) under a single protocol and were included in a review of ketamine's ability to reduce suicidal ideation (15). Because these three studies were done under a single protocol, for the purposes of

FIGURE 1. Flowchart Depicting the Procedure for Selecting Eligible Trials for a Meta-Analysis of Ketamine's Effect on Suicidal Ideation

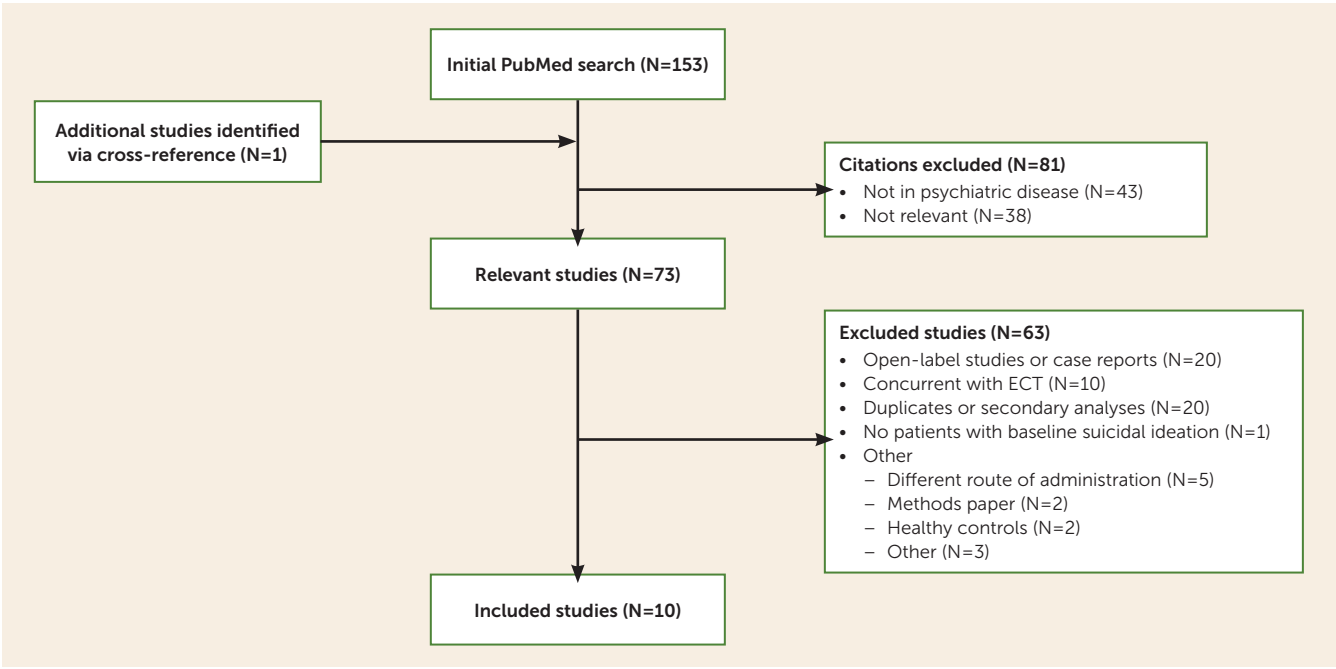


TABLE 1. Characteristics of Studies Included in a Meta-Analysis of Ketamine's Effect on Suicidal Ideation

Authors (Reference Number)	Total N	Included N	Setting	Control Treatment	Diagnosis	Concomitant Medications[a] N	Concomitant Medications[a] %
Berman et al. (10)	8	5	Outpatient	Saline	Major depression	0	0
Valentine et al. (23)	11	4	Outpatient	Saline	Major depression	0	0
Sos et al. (22)	27	9	Inpatient	Saline	Major depression	9	100
Murrough et al. (14)	73	35	Inpatient/ outpatient[b]	Midazolam	Major depression	0	0
Feder et al. (20)	41	5	Inpatient/ outpatient[b]	Midazolam	Posttraumatic stress disorder	0	0
Ballard et al.[c] (15)	87	59	Inpatient	Saline	Major depression or bipolar disorder	26	44
Hu et al. (21)	27	26	Outpatient	Saline	Major depression	26	100
Murrough et al. (17)	24	24	Inpatient/ outpatient	Midazolam	Mixed[d]	19	79
Total	298	167				80	48

[a] Concomitant medications included antidepressants, antipsychotics, or mood stabilizers
[b] Patients were admitted as inpatients for ketamine infusion and then discharged as outpatients 24 hours after infusion.
[c] This was a review and secondary analysis of ketamine data from a research protocol evaluating the effects of ketamine on depressive symptoms (NCT00088699); publications from these results include references 11–13.
[d] The inclusion criterion for this investigation was suicidal ideation, not a specific DSM diagnosis. The most common diagnoses were major depressive disorder, bipolar disorder, and posttraumatic stress disorder.

statistical modeling we considered this a single study (hence, k=8). In addition to participants from these published trials, 36 additional participants analyzed in the earlier review (15) were included in this analysis.

Characteristics of the Included Sample

Individual patient-level data were obtained for 298 patients who participated in the 10 included ketamine trials; 167 patients met criteria for baseline suicidal ideation. Study characteristics are summarized in Table 1, and patient demographic characteristics in Table S2 in the online data supplement. Patients who were included for analysis did not differ significantly from those who were excluded in mean age (t=0.105, p=0.917) or in gender distribution (χ^2=0.27, p=0.604). Overall, included patients had more severe depressive symptoms at baseline than excluded patients as measured by the MADRS (mean score, 33.4 compared with 25.9; t=9.08, p<0.001), the HAM-D (mean score, 20.5 compared with 16.3; t=4.8, p<0.001), the QIDS-SR (mean score, 17.7 compared with 14.2; t=4.81, p≤0.001), and the BDI (mean score, 29.2 compared with 21.1; t=5.62, p<0.001). Included patients were also more likely than excluded patients to

be receiving concomitant psychotropic medications (47.9% compared with 27.5%; χ^2=12.9, p≤0.001).

Among the included patients, those who received ketamine did not differ significantly from those who received a control treatment in mean age (t=−0.27, p=0.788), gender distribution (χ^2=1.01, p=0.314), diagnoses (χ^2=0.40, p=0.527), inpatient versus outpatient status at time of drug exposure (χ^2=0.52, p=0.470), proportion receiving concomitant psychotropic medications (χ^2=1.23, p=0.268), or baseline MADRS score (t=0.867, p=0.388).

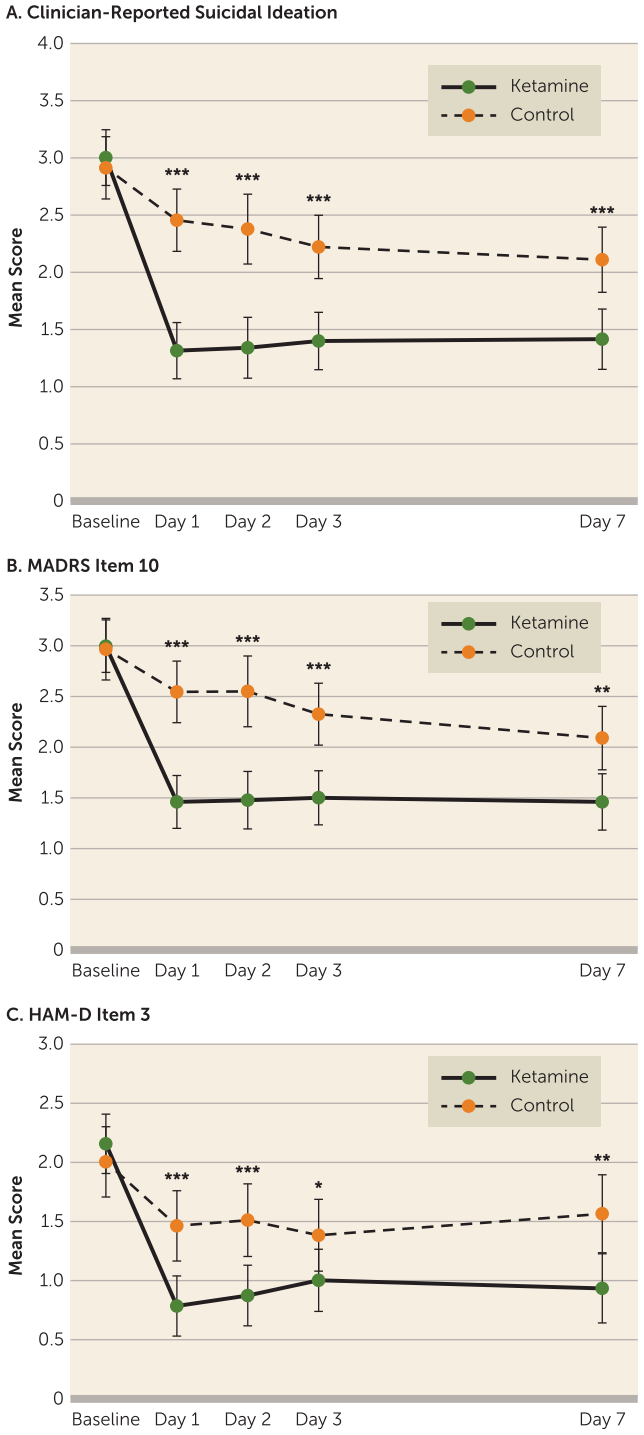
The Effects of Ketamine on Clinician-Administered Suicidal Ideation Item Scores

As assessed via clinician-administered rating scales, ketamine reduced suicidal ideation more rapidly than was observed with the control treatments on the MADRS and the HAM-D, with significant benefits appearing as early as day 1 after treatment and extending up to day 7 (total N=167, k=8; group-by-time interaction, χ^2=50.6, p<0.001) (Figure 2A). The benefits of ketamine compared with control treatments remained significant after baseline covariates (age, gender, race, use of concomitant psychotropic medications, outpatient versus inpatient status, diagnosis) were adjusted for in the model (group-by-time interaction, χ^2=50.5, p<0.001). None of the baseline variables significantly moderated ketamine's effects on suicidal ideation.

The mean MADRS scores for the group exposed to ketamine were 33.8 (SD=6.8) at baseline, 19.5 (SD=12.3) at day 1, 19.4 (SD=12.1) at day 2, 20.1 (SD=12.2) at day 3, and 22.0 (SD=11.5) at day 7. The mean MADRS scores for the group exposed to control treatments were 32.9 (SD=6.5) at baseline, 29.2 (SD=9.3) at day 1, 29.1 (SD=10.5) at day 2, 27.3 (SD=9.8) at day 3, and 27.5 (SD=10.0) at day 7.

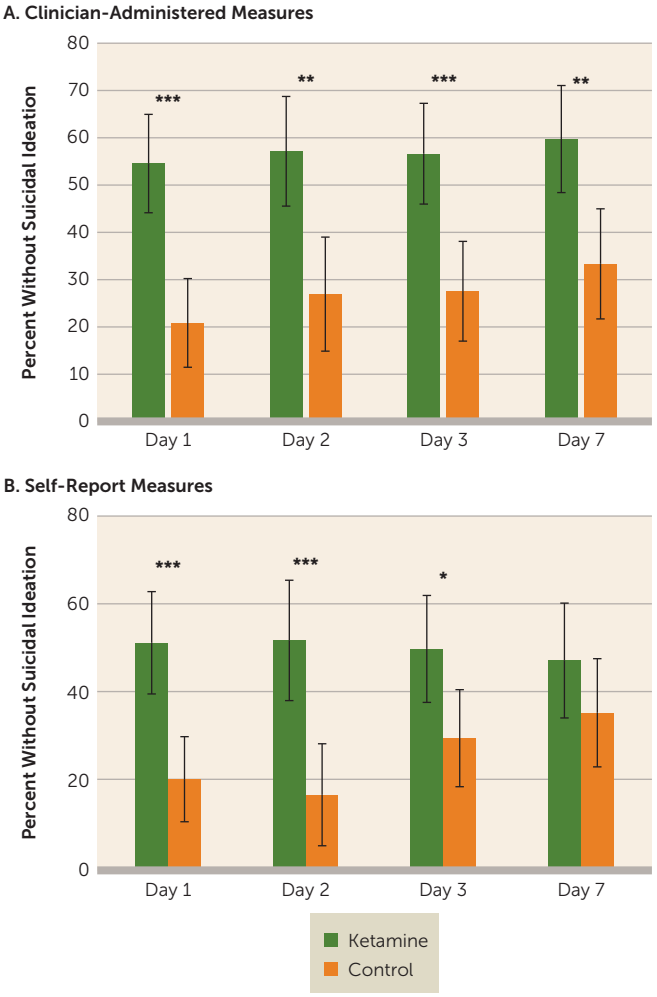
When each clinician-administered rating scale outcome was analyzed separately, ketamine continued to reduce suicidal ideation significantly more rapidly than control treatments on both the MADRS (group-by-time interaction, χ^2=35.0, p<0.001) (Figure 2B) and the HAM-D (group-by-time interaction, χ^2=19.4; p<0.001) (Figure 2C). Meta-analysis demonstrated little heterogeneity between studies (F=0.027, df=1, 791, p=0.87). Effect sizes (group difference divided by pooled standard deviation) for ketamine on change in suicidal ideation were moderate to large for the clinician-administered rating scales at all time points (at day 1, Cohen's d=0.85, 95% CI=0.53–1.17; at day 2, d=0.85, 95% CI=0.52–1.17; at day 3, d=0.67, 95% CI=0.35–0.99; at day 7, d=0.61, 95% CI=0.27–0.94). In addition, ketamine was associated with a significantly greater proportion of patients being free from suicidal ideation compared with control treatments, as assessed by clinician-administered ratings, at postinfusion days 1, 2, 3, and 7; over half of the participants reported no suicidal ideation across all postinfusion time points (all t values <−2.95, all p values <0.005) (Figure 3A). The number needed to treat for ketamine (compared with control treatment) for being free of suicidal ideation was in the range of 3.1–4.0 for all time points 1 to 7 days after ketamine infusion.

FIGURE 2. Effect of a Single Dose of Ketamine on Suicidal Ideation, as Indicated by Clinician-Administered Measures[a]



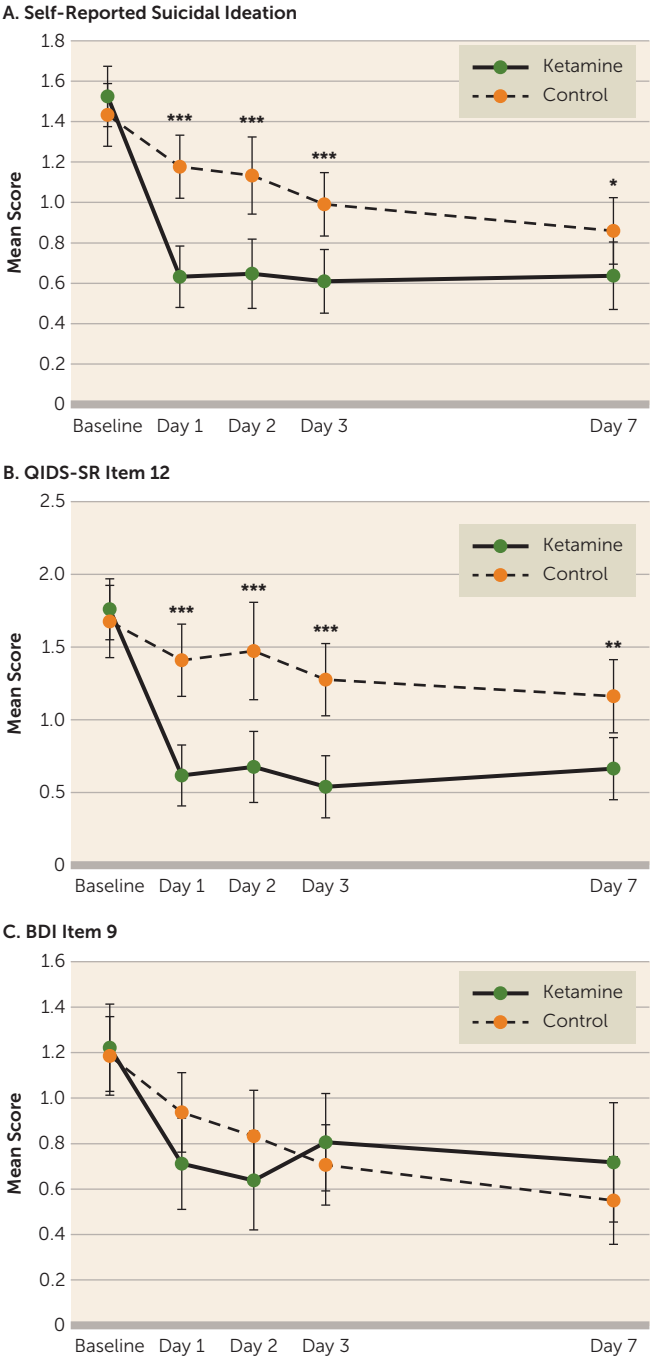
[a] Means are from a multilevel mixed-effects general linear model (subjects nested within studies) adjusting for baseline suicidal ideation and between-study effects. In panel A, the clinician-administered measures are combined and converted to Montgomery-Åsberg Depression Rating Scale (MADRS) units (N=167, k=8; χ^2=50.6, p<0.001 for overall time-by-treatment interaction). Panel B shows results for item 10 of the MADRS (N=140, k=6; χ^2=35.0, p<0.001 for overall time-by-treatment interaction), and panel C shows results for item 3 of the Hamilton Depression Rating Scale (HAM-D) (N=89, k=4; χ^2=19.4, p<0.001 for overall time-by-treatment interaction). Error bars indicate 95% confidence intervals.
*p<0.05. **p<0.01. ***p<0.001.

FIGURE 3. Proportion of Study Subjects Without Suicidal Ideation at Each Time Point After Ketamine Dosing[a]



[a] The clinician-administered outcome measures (panel A) are the Montgomery-Åsberg Depression Rating Scale and the Hamilton Depression Rating Scale. The self-report outcome measures (panel B) are the Quick Inventory of Depressive Symptomatology–Self-Report and the Beck Depressive Inventory. Error bars indicate 95% confidence intervals.
*p<0.05. **p<0.01. ***p<0.001.

FIGURE 4. Effect of a Single Dose of Ketamine on Suicidal Ideation, as Indicated by Self-Report Measures[a]



[a] Means are from a multilevel mixed-effects general linear model (subjects nested within studies), adjusting for baseline suicidal ideation and between-study effects. In panel A, scores for item 12 of the Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR) and item 9 of the Beck Depression Inventory (BDI) are combined (N=144, k=8; χ^2=45.5, p<0.001 for overall group-by-time interaction). Panel B shows results for item 12 of the QIDS-SR (N=77, k=4; χ^2=32.5, p<0.001 for overall group-by-time interaction), and panel C shows results for item 9 of the BDI (N=67, k=4; χ^2=8.34, p=0.080 for overall group-by-time interaction). Error bars indicate 95% confidence intervals.
*p<0.05. **p<0.01. ***p<0.001.

The Effects of Ketamine on Self-Reported Suicidal Ideation

Using self-report outcome measures, ketamine similarly reduced suicidal ideation significantly more rapidly than was observed with the control treatments, with significant benefits noted at each individual time point (N=144, k=8; group-by-time interaction, χ^2=45.5, p<0.001) (Figure 4A). The benefits of ketamine compared with control treatments remained significant after baseline covariates were adjusted for in the model. None of the baseline variables significantly moderated ketamine's effects on suicidal ideation. When each self-report measure was analyzed separately, ketamine reduced suicidal ideation significantly more rapidly than was observed with the control treatments on the QIDS-SR (group-by-time interaction, χ^2=32.5, p<0.001) (Figure 4B) but not on the BDI (group-by-time interaction, χ^2=8.34, p=0.08) (Figure 4C). Notably, these

analyses had smaller sample sizes (N=77 and N=67, respectively) because not all studies used each measure. Meta-analysis demonstrated little heterogeneity between studies (F=0.097, df=1, 671, p=0.76).

Effect sizes (group difference divided by pooled standard deviation) of ketamine on change in suicidal ideation were moderate to large on the self-report outcomes (at day 1, Cohen's d=0.73, 95% CI=0.38–1.07; at day 2, d=0.84, 95% CI=0.49–1.19; at day 3, d=0.63, 95% CI=0.28–0.98; at day 7, d=0.48, 95% CI=0.12–0.83). Ketamine was again associated with a significantly greater proportion of patients being free from suicidal ideation compared with the control treatments at postinfusion days 1, 2, and 3 (all t values <-2.30; all p values <0.05) but not at day 7 (t=−1.18, p=0.238) (Figure 3B). The number needed to treat for ketamine (compared with control treatments) for being free of suicidal ideation was in the range of 3.2–5.0 for days 1–3 after ketamine infusion, and 9.6 at day 7.

Correlation Between Suicidal Ideation and Severity of Depressive Symptoms

Changes in suicidal ideation and overall severity of depressive symptoms were strongly correlated at all time points. As measured using clinician-administered rating scales, change in suicidal ideation and change in severity of depressive symptoms were significantly correlated at day 1 (adjusted r^2=0.411, t=10.73, $p<0.001$), day 2 (adjusted r^2=0.460, t=11.66, $p<0.001$), day 3 (adjusted r^2=0.370, t=9.60, $p<0.001$), and day 7 (adjusted r^2=0.414, t=10.08, $p<0.001$). On the self-report measures, change in suicidal ideation and change in severity of depressive symptoms were significantly correlated at day 1 (adjusted r^2=0.405, t=9.75, $p<0.001$), day 2 (adjusted r^2=0.212, t=5.46, $p<0.001$), day 3 (adjusted r^2=0.208, t=5.95, $p<0.001$), and day 7 (adjusted r^2=0.103, t=3.83, $p<0.001$).

Independence of Improvement Measures for Suicidal Ideation and Change in Severity of Depressive Symptoms

After adjusting for change in severity of depressive symptoms over time, the time-by-treatment interaction remained significant regardless of whether clinician-administered (χ^2=10.84, p=0.028) or self-report (χ^2=13.19, p=0.010) outcome measures were used. Significant differences were observed between groups at all postinfusion time points on clinician-administered outcome measures (all t values <-2.30, all p values <0.05). On the self-report outcome measures, significant differences were noted at day 1 (t=−2.80, p=0.005), day 2 (t=−2.62, p=0.009), and day 3 (t=−1.99, p=0.047) but not day 7 (t=−0.36, p=0.720).

Durability of Effect

Among the group of patients who achieved a resolution of suicidal ideation (as measured by clinician-administered measures) by 24 hours after infusion, the effect of ketamine on reduced suicidal ideation persisted for up to 1 week in 86.0% of patients, compared with 52.9% of patients who received control treatments (χ^2=7.98, p=0.005). Using self-report outcomes, the effect of ketamine on reduced suicidal ideation persisted for up to 1 week in 89.2% of patients in the ketamine group, compared with 42.9% who received control treatments (χ^2=12.1, $p<0.001$).

Midazolam Versus Saline as Control Treatment

To assess the differences between midazolam and saline as control treatments, we calculated effect sizes (group difference divided by pooled standard deviation) separately for saline and midazolam as control condition. The outcome measure was the change in suicidal ideation from baseline on clinician-administered outcome measures at each postinfusion time point. When only saline was used as a comparator (N=50 for the saline group, N=93 for the ketamine group), the effect sizes were as follows: at day 1, d=0.90, 95% CI=0.54–1.26; at day 2, d=0.90, 95% CI=0.53–1.26; at day 3, d=0.82, 95% CI=0.45–1.19; at day 7, d=0.69, 95% CI=0.31–1.07. When only midazolam was used as a comparator (N=24 for the midazolam group, N=93 for the ketamine group), the effect sizes were more modest: at day 1, d=0.62, 95% CI=0.16–1.08; at day 2, d=0.69, 95% CI=0.22–1.15; at day 3, d=0.34, 95% CI=−0.12–0.80; at day 7, d=0.41, 95% CI=−0.06–0.88. Comparing the effect of midazolam (N=24) versus saline (N=50) on suicidal ideation in the linear mixed model showed no group-by-time interaction nor a main effect of group.

DISCUSSION

This study is, to our knowledge, the first meta-analysis to use individual participant-level data to examine the effects of ketamine on suicidal ideation specifically in participants with some level of baseline suicidal ideation. We found that ketamine significantly reduced suicidal ideation, with moderate to large effect sizes observed within 1 day that extended 1 week after ketamine administration. We also found that patients treated with ketamine were significantly more likely to be free of suicidal ideation at all postinfusion time points (except day 7 as assessed by self-report outcome measures). Change in severity of depressive symptoms was strongly correlated with change in suicidal ideation and accounted for 10%−46% of the variance in change in suicidal ideation. Notably, after controlling for improvement in severity of depressive symptoms, ketamine's effects on suicidal ideation remained significant. This suggests that ketamine has a specific effect on suicidal ideation that depends only partly on change in overall severity of depressive symptoms. The study extends the literature by using an analytic sample comprising exclusively participants with some level of suicidal ideation—at an individual participant level—from all single-dose comparison intervention trials of intravenous ketamine.

Taken together, these results suggest that ketamine's salutary effects on suicidal ideation hold considerable promise, particularly given the lack of treatment options for patients who may be at risk of suicide. Indeed, in the present study, 54.9% of

patients were free of suicidal ideation 24 hours after a single ketamine infusion, and 60.0% were free of suicidal ideation at 1 week postinfusion. In comparison, in an open-label ECT study, 38.2% of 131 patients reporting significant suicidal ideation were free of suicidal ideation after three treatments (1 week), 61.1% after six treatments (2 weeks), and 80.9% at the end of the acute course (mean=7.5 treatments, SD=3.2) (25). To put this difference into context, it should be noted that ECT is standard care for patients who have a mood disorder and active suicidal ideation and generally leads to sustained resolution of suicidal ideation, while the effects of ketamine on suicidal ideation beyond 1 week have not yet been thoroughly investigated. Furthermore, clinical studies of ketamine may draw their subjects from a different patient population than clinical ECT studies.

Pseudospecificity

There is considerable interest regarding whether ketamine's antisuicidal properties occur independently of its general antidepressant effects (pseudospecificity), particularly because this may have an impact on the path toward U.S. Food and Drug Administration (FDA) approval for ketamine or related compounds in treating suicidal ideation or behavior (26). A related example of pseudospecificity is vortioxetine, which underwent the FDA New Drug Application process for potential approval for cognitive dysfunction in major depressive disorder. The application was submitted based on the consideration that cognitive dysfunction may be phenomenologically distinct from other symptoms of depression and that its course may be distinct from those of other depressive symptoms (27–29). Ultimately, the FDA did not grant approval for this pseudospecific indication for vortioxetine. However, vortioxetine did receive approval from the European Medicines Agency for a type II variation (a process similar to that of the FDA for pseudospecificity) for the treatment of cognitive dysfunction in major depressive disorder.

The present analysis provides evidence drawn from the largest sample to date that ketamine reduces suicidal ideation partially independently of mood symptoms. However, the specificity of this effect requires further exploration. While we purposefully included patients across a range of psychiatric diagnoses, most of the patients had major depressive disorder or bipolar depression and had treatment-resistant illness per inclusion criteria. For ketamine to have a future as a potential antisuicidal therapeutic in patients with a range of mood and anxiety disorders, studies specifically recruiting diverse populations must be conducted. Future studies should also consider whether ketamine may be a potential therapeutic for suicidal ideation in patients of varying levels of treatment resistance. This is particularly important because in the emergency settings where antisuicidal interventions might be most useful, clinical decisions must often be made quickly in the face of potential ambiguity of both diagnosis and treatment history. In one of the included studies, Murrough and colleagues (17) recruited a population considered at risk for suicide across diagnoses in an attempt to specifically measure ketamine's effect on suicidal ideation; this differed from other trials included in the meta-analysis, which recruited patients with specific diagnoses and excluded participants deemed at imminent risk of suicide. Notably, patients with diagnoses such as substance use disorder and schizophrenia/schizoaffective disorder were uniformly excluded in these studies. Given ketamine's abuse liability (30) and concern for exacerbation of psychotic symptoms (31), additional research is clearly required before ketamine can be considered a treatment option for these patient populations.

Limitations

Despite the robust findings described above, several limitations require comment. First, the relatively small sample sizes of the included studies limited sensitivity analyses of the individual scales, which may account for our mixed findings in the BDI analysis; nevertheless, three of the four scales (both clinician-administered and self-report instruments) yielded consistent findings. Second, all of the studies included in this meta-analysis examined the effects of ketamine on suicidal ideation; whether ketamine's effects on suicidal ideation translate to effects on suicidal behavior has not been studied. Third, with one exception (17), the included studies did not specifically recruit patients deemed at imminent risk for suicide. Thus, the assessment of suicidal ideation used in this analysis is limited to a single item from each scale. This limitation, however, is mitigated by our exclusion of patients who had no suicidal ideation at baseline. Fourth, while our finding that ketamine exerts significant effects on suicidal ideation even when the severity of depressive symptoms was controlled for was replicated in a similar analysis of open-label ketamine (32), the bulk of the current ketamine studies have been conducted in patients with active mood disorders. Fifth, the short follow-up of the studies precludes this analysis from providing further guidance on any sustained effects beyond 7 days after treatment. Finally, given the psychoactive properties of ketamine, a limitation of many, although not all, of the included studies is the possibility of functional unblinding of trials using saline as the comparator.

Future Work

Despite robust findings here and elsewhere indicating that ketamine has significant antisuicidal effects, a number of questions must be answered before ketamine can be regularly used in clinical settings to treat patients at risk of suicide. While ketamine's antisuicidal effects appeared to be maintained over 1 week, the possibility of rebound suicidal ideation remains, with potential negative outcomes within the weeks or months following exposure to ketamine (33). In addition, to date no study has demonstrated that ketamine specifically reduces the risk of suicidal behavior, only of suicidal ideation. Results from several ongoing clinical trials evaluating the efficacy of ketamine or esketamine (ketamine's *S*-enantiomer) to stabilize outpatients who have significant suicidal ideation (NCT02094898, NCT01700829) or patients who are

hospitalized because of acute suicide risk (NCT02133001, NCT02299440) should provide longer-term follow-up data as well as protocols for repeated dosing. Future studies should also explore the effects of combining ketamine with established somatic/pharmacologic (i.e., ECT, lithium [NCT01880593]) or psychotherapeutic (i.e., dialectical behavioral therapy or CBT) modalities to extend beneficial response. One preliminary study of ketamine combined with CBT reported improved longer-term outcomes in mood disorders (34), although we know of no such protocols examining similar combinations specifically for the treatment of suicidal ideation. Future clinical studies should also assess details of suicidal ideation, including frequency, intensity, duration, and past suicidal behaviors. Differentiation between acute and chronic factors in the emergence of suicidal ideation may also help establish expectations regarding treatment outcomes. While using midazolam as a control may attenuate the effect size of ketamine because of improved integrity of blinding, our study did not find a significant difference between the two control conditions, which may have been due to the relatively small number of patients who received midazolam. Also, no study has directly compared the effects of saline and midazolam on suicidal ideation.

CONCLUSIONS

This study used individual participant-level data from a sample comprising exclusively patients with some level of active or passive suicidal ideation drawn from all single-dose, comparison intervention trials of intravenous ketamine. We found that across 10 controlled trials, a single ketamine infusion rapidly reduced the severity of suicidal thinking, within 24 hours in more than half the patients, and with benefits observed up to 1 week.

These results suggest that ketamine holds considerable promise as a potential rapid-acting treatment for patients at risk of suicide. Further research examining ketamine and similar compounds for the treatment of suicidal patients is urgently needed. In particular, questions remain regarding optimal patient selection, dosing frequency, clinical monitoring, and follow-up assessment. Although a great unmet need exists for novel and rapid-acting therapeutics for patients at risk of suicide, the evidence for using ketamine in this context remains preliminary. Any consideration of the clinical use of ketamine should balance the known risks of this treatment approach (31), the still limited evidence of its efficacy (35), and any possible delays it may cause in receiving more established therapies for reducing the risk of suicidal ideation, such as ECT or lithium (26).

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