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KETAMINE: A POTENTIAL RAPID-ACTING ANTISUICIDAL AGENT?

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Abstract

Ketamine has attracted widespread attention as a potential rapid-acting antidepressant. There is also considerable interest in its use for the rapid treatment of patients deemed at risk for suicide. Here, we review the available evidence (open-label and randomized controlled trials) that examine the effects of ketamine on suicidal ideation (SI). Overall, data suggest that ketamine has a rapid albeit transient effect in reducing SI, though some studies had mixed results at different time points or using different assessments. Weaknesses to the existing literature include the small sample sizes of the studies, the exclusion of patients with significant SI at baseline from many of the studies, and the potential functional unblinding when participants are randomized to saline as placebo. The evidence supporting the clinical use of ketamine for SI is very preliminary. Although ketamine appears to a promising therapeutic option in a context where there is a great unmet need (i.e., patients at imminent risk of suicide), further controlled trials are needed to allow for meaningful clinical recommendations.

Keywords

ketamine; suicidal ideation; suicide; depression; antidepressant

INTRODUCTION

Forty-two thousand seven hundred and seventy-three deaths by suicide were reported in the United States in 2014, making suicide the 10th leading cause of death of Americans of all ages.^[1] For individuals aged 15–44 years, suicide is among the top three causes of mortality worldwide.^[2,3] Beyond the devastating impact of suicide-related mortality on individuals and families, there are also tremendous economic and public health concerns associated with suicide attempts. More than 490,000 hospital visits related to suicide attempts or self-harm behavior were recorded in the United States for 2013, and the economic cost of suicide death, related mostly to loss of productivity in the United States, being estimated to be greater than \$44 billion annually.^[4] Already aware of the tremendous societal burden related to suicidal behavior, the US Surgeon General released a Call to Action to Prevent Suicide in 1999 calling for a renewed effort to identify and develop better treatments and suicide

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prevention methods.^[5] Unfortunately, despite these efforts, suicide rates have not decreased since the 1950s,^[6] but have paradoxically been increasing over the past 10 years.^[1]

Although not all suicides are associated with mental illness, it is estimated that approximately 90% of individuals who commit suicide suffer from a treatable psychiatric disorder,^[7,8] most commonly a mood disorder. Generally, the longer time spent in a depressive episode, the higher the chance of suicide.^[9] Evidence surrounding the efficacy of the currently available standard treatments for mood disorders in treating suicidal ideation (SI) presents a complex picture, with some evidence suggesting an overall benefit of the treatments^[10] and other studies suggesting an age-related acute worsening of SI with treatment initiation.^[11–13] However, in either case, it is clear that the currently available standard antidepressant treatments do not provide a robust and rapid relief of SI.

The existing treatment options for patients assessed to be at acute risk for suicide are limited. Current management of patients deemed at acute risk of suicide usually consists of hospitalization plus pharmacotherapy, psychotherapy, electroconvulsive therapy (ECT) or a combination thereof. Significant evidence supports a reduction in the long-term risk of suicide in mood disorders associated with lithium treatment,^[14] though it has not been shown to be effective in the acute setting.^[15] Clozapine has received an FDA-approved indication for “reducing the risk of recurrent suicidal behavior,” but this is primarily based on data from patients diagnosed with schizophrenia or schizoaffective disorder, and not patients with mood disorders, which constitute the largest portion of patients who commit suicide.^[16] Further, clozapine has not been shown to decrease SI in the acute setting. Even ECT, considered the most highly efficacious antidepressant treatment, may not provide a reduction in SI for 1–2 weeks.^[17] Moreover, hospitalization, which is designed to provide a safe environment for patients, is not completely effective in preventing suicide. Although uncommon, suicide among inpatients remains one of the most commonly reported sentinel events.^[18] These facts highlight the need for the development of more effective means of identifying those at risk for suicide and for the introduction of novel effective therapeutic approaches with more rapid rates of onset of antisuicidal action.^[19,20]

In 2000, Berman et al.^[21] first reported that ketamine, an *N*-methyl-D-aspartic acid antagonist, possesses rapid-acting antidepressant properties. Since then, several randomized placebo-controlled trials and case series have confirmed that the drug produces a rapid onset, transient antidepressant response in both treatment-resistant depression (TRD) unipolar and bipolar depression.^[22–26] Given the rapid-acting nature of ketamine and the reports of high rates of efficacy in TRD, the potential utility of the drug in the acute treatment of suicidal patients with mood and other disorders has gained great interest. Here, we review the evidence for ketamine’s effects on SI in patients with mood disorders. We first review evidence gleaned from open-label trials and case series, followed by evidence from randomized controlled trials examining ketamine’s general antidepressant properties. We later consider whether the effects of ketamine on suicide are independent of the drug’s effects on mood in general and review the limited evidence specifically attempting to address the antisuicidal effect of ketamine. The promise and limitations of this approach as a treatment of suicidal thinking and behavior are considered. Except where noted, all protocols reviewed utilize an intravenous infusion of 0.5 mg/kg ketamine over 40 min.

OPEN-LABEL AND NATURALISTIC TRIALS

Several open-label and naturalistic studies examining either single-dose or repeated-dose administrations have attempted to gain insight into the potential anti-suicidal effects of ketamine (see Table 1). A study of 33 medication-free inpatients with Major Depressive Disorder (MDD, treatment-resistant) undergoing a single, open-label IV ketamine infusion, designed to assess antidepressant effects of ketamine, showed a reduction in SI in all scales employed in the study (Montgomery-Åsberg Depression Rating Scale [MADRS], Hamilton Depression Rating Scale [HDRS], Beck Depression Inventory [BDI], and Beck Scale for SI [SSI]).^[27] Pre-post effect sizes were largest at 40 min ($d = 1.05$), diminishing to moderate magnitude effect sizes at 230 min ($d = 0.45$). However, it should be noted that these effect sizes were much larger when considering only the 10 patients with high baseline SI (defined as SSI score >3) in the analysis: $d = 2.36$ at 40 min and $d = 1.27$ at 230 min. Notably, the participants in this study had stable SI as measured by the SSI for a mean period of 8 days prior to treatment. Thakurta et al.^[28] also reported on 27 inpatients with TRD (2 failures of antidepressants) who were given a single ketamine infusion after a 2-week washout of other antidepressant medications in India. SI was reported to be reduced in the immediate period following treatment (40–230 min) as assessed by the SSI and the HDRS, but this reduction was not sustained 24 hr following treatment. An additional open-label study of 26 medication-free patients with TRD undergoing a single intravenous ketamine infusion reported MADRS-SI scores¹ were significantly reduced 24 hr following treatment compared to baseline levels (pre-post effect size $d = 1.37$).^[29] Implicit measures (IAT²) of SI were also significantly reduced in a subset of 10 patients who completed the assessment in a pre-post comparison ($d = 1.36$). Notably, the decrease in SI was not shown to be independent of the overall reduction in depression symptoms in this study. A subset of 10 patients in the study who received six total infusions each, given three times per week, maintained a significant reduction in SI for the duration of the treatment. However, it should be noted that subjects with “highly active” SI were excluded from participation in this study. In another study of 24 TRD medication-free participants treated with six serial infusions of ketamine over 2 weeks, Murrough et al.^[30] noted a significant decrease in SI (MADRS-SI item) at 2 hr compared to baseline in both patients ultimately considered to be treatment responders and nonresponders (defined at 24 hr by 50% decrease in symptoms). Approximately 70% of responders had relapsed by 4 weeks following the final infusion; there is no mention of the duration of ketamine’s effects on SI. Rasmussen et al.^[31] reported on 10 TRD participants (both inpatients and outpatients) who were treated with ketamine IV 0.5 mg/kg over an extended 100 min infusion period in addition to treatment as usual (i.e., concomitant antidepressants). Participants continued to receive infusions until remission was achieved or four infusions (provided twice weekly) were given. Changes in explicit measures of SI were significant as assessed by the SSI and the SSF (Suicide Status Form) in a pre-post comparison; reduction in SI was correlated with reduction in overall depressive symptoms.

¹MADRS item 10: Suicidal Thoughts. Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and the preparations for suicide.

²IAT—Implicit Association Test, tests implicit cognitive associations between concepts such as “Death” and “Me” or “Escape” and “Me”. It has been shown to a good predictor of future behavior in certain socially stigmatized domains (i.e., prejudicial attitudes based on race).

There are two open-label, naturalistic studies exploring the use of ketamine treatments in emergency department (ED) settings. Larkin and Beautrais^[32] treated 14 patients with significant SI recruited from the ED with 0.2 mg/kg ketamine delivered IV over 1–2 min along with treatment as usual. They reported that SI decreased significantly in all patients at the 40-, 80-, 120-, and 240-min time points after ketamine administration using the MADRS-SI, and no evidence of recurrence was detected during the 10-day follow-up period. Another trial of 49 medication-free patients presenting to the ED of Imam Hossein hospital in Tehran for SI received a single dose of 0.2 mg/kg ketamine, delivered IV over 1 min along with treatment as usual.^[33] The investigators reported a significant decrease in SSI scores over the 2-hr period following ketamine dosing, and 94% of the patients reported no SI at day 10. Although these two studies provide some evidence to suggest the feasibility and potential benefits of using ketamine in the ED setting to treat SI, the value of these studies is markedly limited by shortcomings in the study designs, including small sample sizes, lack of diagnostic specificity, no comparison groups or historical subject comparisons, and the unique choice of dosing compared to other existing studies.

RANDOMIZED CONTROLLED TRIALS

In their original study of ketamine in medication-free outpatients with MDD, Berman et al.^[21] specifically noted significant decreases in SI HDRS-SI item (not adjusted for multiple comparisons) shortly following a single ketamine infusion in their original report on the drug's antidepressant efficacy (see Table 1). Since that report, there have been several other accounts of secondary analyses attempting to gain insight into the relationship between ketamine and SI using data from randomized controlled ketamine studies that were not originally designed to examine effects on SI. Ballard et al.^[34] examined the data from three placebo (saline)-controlled RCTs including participants with both MDD and bipolar disorder, and one open-label study conducted at the NIMH. In the total sample of 133 subjects, after controlling for both depression and anxiety symptom clusters in a regression model, ketamine exerted an effect on SI that was independent of its effects on depression and anxiety. Restricting the analysis to 57 subjects who participated in a randomized study and demonstrating the presence of some SI at baseline (HDRS SI item score >0), there was again evidence of an independent effect of ketamine on SI. Thus, this evidence suggests that ketamine exerted an independent effect on SI as opposed to this effect being mediated solely by an overall reduction in depressive or anxiety symptoms. Overall, this secondary analysis suggests that ketamine's effects on SI may in fact be independent of its effects on other depression or anxiety symptoms. Moreover, further analysis from the same datasets using a slightly broader definition of SI found ketamine to have significant effects on SI rating on all scales, with the exception of the total score of the SSI, but there were significant effects noted as measured by the abbreviated SSI5 scale.^[35] Consistent with the previous reports showing large effects of a single ketamine infusion on SI, a recent study randomizing 30 patients with MDD to ketamine infusion plus escitalopram or saline infusion plus escitalopram at Beijing Chao-Yang Hospital,^[36] found the subjects in the ketamine/escitalopram group had lower explicit measures of SI (as measured by Quick Inventory of Depressive Symptomatology [QIDS] SI item) compared to the placebo/escitalopram group from 1 to 72 hr following treatment, with Cohen's *d* ranging from 1.05 to 2.24 during this

time period. These participants were outpatients and, other than the concomitant initiation of escitalopram on the first treatment day, were free of other psychotropic medication.

Analyzing data from 57 outpatients with TRD assessed using *explicit measures* (a composite measure of SI scores from various scales) and *implicit measures* (derived from an IAT) of SI at baseline and 24 hr following a single infusion of ketamine or midazolam, Price et al.^[37] reported SI scores 24 hr postinfusion were reduced in those receiving ketamine compared to midazolam in explicit measures, but difference between groups at 24 hr using two variants of IAT measures, identified in the previous open-label study, did not reach statistical significance in omnibus analyses. Notably, subjects with “serious and imminent” SI were excluded from participation. Also, in this study the decrease in explicit measures of SI appeared to be explained by the overall decrease in depressive symptoms.

Murrough et al.^[38] recently completed the only randomized trial thus far designed specifically to assess the effect of ketamine on SI. A sample of 24 subjects with significant SI (13 with MDD, 7 with bipolar disorder, 3 with PTSD) recruited from both inpatient and outpatient settings were randomized to a single-dose infusion of intravenous ketamine or 0.045 mg/kg intravenous midazolam (active control) over 40 min, added on to their existing medication regimen. Although this likely underpowered study failed to show a significant effect of ketamine treatment on the primary outcome measure (group difference in SSI at 24 hr), the ketamine treatment group had lower SSI scores at 48 hr and the MADRS-SI item (secondary outcome) was significantly lower in the ketamine group at 24 hr but not at 48 hr.

Overall, data from RCTs suggest that ketamine has a rapid effect in reducing SI, though some studies had mixed results at different time points or using different assessments. However, it should be noted that there are several major weaknesses regarding the quality of data available evaluating the antisuicidal effect of ketamine generated from these studies. One weakness of this literature is that, with the exception of Murrough et al.,^[38] these RCTs were designed primarily to test ketamine’s antidepressant effects and, in many cases, patients with clinically meaningful SI, or thought to be at imminent risk of suicide, were excluded from participation. Further, it should be emphasized that most studies measured SI only as a secondary outcome, and some measured SI by a single scale item that is part of a general depression scale, rather than a scale designed to measure SI (the SSI). Among patients receiving ketamine, the individual SI items of the MADRS, HDRS, and BDI have been shown to correlate with the abbreviated five-item SSI, but not with the full scale.^[35]

Another weakness of these studies is that most are generally of small sample size, limiting their power to detect group differences. Nonetheless, despite this limitation, there is converging evidence that ketamine may rapidly reduce SI. A third significant limitation is the potential functional unblinding that may occur due to the dissociative properties of ketamine. It is quite probable that most subjects become functionally unblinded; evidence for this is seen in the extremely low placebo response rates seen where saline infusion is used as the control. More recently, some trials have used midazolam as an active comparator to reduce the amount of functional unblinding. Although it is unclear whether using midazolam as the active comparator completely resolves the problem of unblinding, these

trials generally have higher placebo response rates and, hence, lower between-group effect sizes, but still appear to show meaningful differences with ketamine treatment.

DISCUSSION

The collective existing data provide intriguing preliminary evidence suggesting that ketamine may produce uniquely rapid effects on SI. However, both the openlabel and placebo-controlled trials have many limitations that restrain our ability to draw firm conclusions at this point in time. Fortunately, the results of several clinical trials evaluating the efficacy of ketamine or esketamine (S-enantiomer) to stabilize patients in need of hospitalization due to risk of suicide (clinical trials identifier: ,) or outpatients with significant SI (;) should provide more reliable data related to ketamine's antisuicidal effects in the relatively near future.

Although, as discussed in the introduction, there is a great unmet need for more robust and rapidly acting antisuicidal treatments, the evidence to date supporting the clinical use of ketamine for this purpose is extremely preliminary. Any consideration of the clinical use of ketamine should weigh heavily the known risks of the treatment approach (can we reference another paper in this issue?), the limited evidence of efficacy, and any possible delays it may cause in receiving established treatments for reducing the risks of SI and behavior, such as ECT, lithium, or clozapine. Moreover, there remains little data of strategies for maintaining the antisuicidal properties of ketamine, and concerns exist regarding the repeated administration of ketamine.^[39] Finally, all studies reviewed examined the effects of ketamine on suicidal *ideation*, not on suicidal *behavior*; whether ketamine's effects on SI translate into effects on suicidal behavior has not been studied.

There is also significant interest in the question of whether ketamine's effect on SI is independent of its general antidepressant effects (i.e., pseudospecificity). The issue of pseudospecificity could impact the path to FDA approval of ketamine or related medications for use in the treatment of SI or behavior. The FDA has considered claims for drug effects in psychiatric illnesses to be pseudospecific if it is found to be artificially narrow (i.e., focusing on a particular aspect or symptom of an illness) in the absence of any empirical evidence to support such a restricted focus.^[40] For example, to evaluate the claims of pseudospecificity with regard to negative symptoms in schizophrenia, the FDA asked the following questions: (1) Are negative symptoms phenomenologically distinct from other symptoms of schizophrenia?; and (2) do they have a course that is distinct from other symptoms?^[41] It could be assumed that the agency will take a similar view on claims of antisuicidal effects of ketamine or related compounds in mood disorders. To date, the literature on whether ketamine has a specific effect on SI or whether reductions in SI are mediated by an overall reduction in general depression symptoms is inconclusive. Although some data suggest the antisuicidal effect to be present across different diagnostic groups, it is limited by the relatively small sample sizes and the fact that the participants enrolled in the studies had minimal or no baseline SI. Larger controlled studies are clearly needed to more definitively address this question.

In sum, ketamine (at least at 0.5 mg/kg i.v. infused over 40 min) appears to represent a promising treatment for patients with SI. However, more data are clearly needed, especially in patients with elevated baseline levels of SI, prior to making any meaningful clinical recommendations on the utility of the treatment. Although there are some interesting data suggesting the effects of ketamine may reduce SI independently of its more general effects on mood and anxiety, this will need to be examined in greater detail in future studies in order to address the issue of pseudospecificity. Future studies will also need to determine if ketamine-induced effects on SI and behavior will be generalizable to patients who do not suffer primarily from a mood disorder (i.e., PTSD, obsessive-compulsive disorder, alcohol abuse). Other drugs with putative rapid-acting antidepressant effects also in development will be subjected to similar concerns, and will require studies designed to specifically address the unique aspects of SI and behavior to establish efficacy and possible FDA approvals. As with all treatments, the risks of ketamine must be weighed against potential benefits in considering future development of the treatment strategy in the clinical setting.

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TABLE 1.

Studies reporting effect of ketamine on SI

Reference	Design	Placebo	Intervention	Setting	Sample size	Diagnosis	SI measure	Result
Randomized controlled trials								
Berman et al. 2000	Crossover, single dose	Saline	0.5 mg/kg over 40 min	Outpatients	7	MDD, BP	HDRS	Significant decrease in HDRS-SI item compared to placebo ($P = .02$)
Price et al. 2014	Parallel, single dose	Midazolam	0.5 mg/kg over 40 min	Outpatients	57	MDD, TRD	Implicit: IATE Explicit: MADRS, QIDS, SSI	At 24 hr, ketamine resulted in significantly lower explicit measures ($d = 0.82$, $P = .01$); differences between groups using IAT did not reach statistical significance. The decrease in SI was explained by overall reduction in depression symptoms.
Hu et al. 2015	Parallel, single dose	Saline	0.5 mg/kg over 40 min	Outpatient	30	MDD	QIDS	Significantly lower SI measures from 2 to 72 hr following treatment in group receiving ketamine (d ranging from 1.05 to 2.24; all $P < .05$)
Murrough et al. 2015	Parallel, single dose	Midazolam	0.5 mg/kg over 40 min	Inpatients & outpatients	24	Various	SSI, MADRS	SSI: lower in ketamine group at 48 hr ($d = 0.67$, $P = .047$) but not at 24 hr ($P = .32$) MADRS-SI: lower in ketamine at 24 hr ($d = 0.86$, $P = .05$), but not at 48 hr ($P = .077$)
Open-label/case series								
Price et al. 2009	Open label, single dose	NA	0.5 mg/kg over 40 min	Inpatient for first 28 hr	26	MDD, TRD	MADRS ($n = 26$), IAT ($n = 10$)	Lower MADRS-SI scores 24 hr posttreatment ($d = 1.37$; $P < .001$) In subset, IAT reduced at 24 hr ($d = 1.36$; $P = .003$)
Diazgranados 2010	Open label, single infusion	NA	0.5 mg/kg over 40 min	Inpatients	33	MDD, TRD	MADRS, HDRS, BDI, SSI	Reduction in SI using all scales ($P < .001$) with largest effects at 40 min, $d = 1.05$; at 230 min, $d = 0.45$ Subanalysis among those with high baseline SI yielded higher effect sizes ($d = 2.36$ at 40 min and $d = 1.27$ at 230 min)
Larkin and Beatrais 2011	Open label/case series	NA	0.2 mg/kg over 2 min	Emergency department	14	MDD	MADRS, SSI	Significant reduction in SI (MADRS) for up to 10 days following infusion ($P < .001$)
Thakurta et al. 2012	Open label, single infusion	NA	0.5 mg/kg over 40 min	Inpatient	27	MDD, TRD	SSI, HDRS	Significant reduction in SSI/ HDRS-SI scores from 40 min through 230 min ($P < .01$).

Reference	Design	Placebo	Intervention	Setting	Sample size	Diagnosis	SI measure	Result
Murrough et al. 2013	Open label, six infusions (3x/week)	NA	0.5 mg/kg over 40 min	Inpatient for first treatment	24	MDD, TRD	MADRS	Change was not significant from day 1 onward. Both responders and nonresponders showed significant reduction at 2 hr in SI ($P < .05$)
Rasmussen et al. 2013	Open label, up to four infusions (2x/week)	NA	0.5 mg/kg over 100 min	Inpatients & outpatients	10	MDD/BPII, SSI, SSF TRD		Significant reduction in SI at study end were achieved in the SSI ($P = .007$) and SSF ($P = .026$)
Kashani et al. 2014	Open label, single infusion	NA	0.2 mg/kg over 1 min	Emergency department	49	Not reported	SSI	Significant decrease in SSI scores over time, with 44 of 49 patients reporting no SI at 10 days
Mixed								
Ballard et al. 2014/5	Secondary Analysis from three RCTs, one open-label	Saline	0.5 mg/kg over 40 min	Inpatients	60	MDD/BP, TRD	SSI, BDI, HDRS, MADRS	In patients with some baseline SI, all scales (except SSI) showed significant effect of ketamine on SI ($P < .01$). Effect of ketamine on SI was independent of reduction in overall depression and anxiety measures.

BDI, Beck depression inventory; BP, bipolar disorder; HDRS, Hamilton depression rating scale; IAT, implicit association test; MADRS, Montgomery-Asberg depression rating scale; MDD, major depressive disorder; QIDS, quick inventory of depressive symptomatology (self-report); SSF, suicide status form; SSI, Beck scale for SI; TRD, treatment-resistant depression.