

# The effects of ketamine on suicidality across various formulations and study settings

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## Abstract

**Introduction:** Suicidality and self-injurious behavior afflict patients with a wide variety of psychiatric illnesses. Currently, there are few pharmacologic treatments for suicidality and self-injurious behavior and none that treat these conditions emergently. Recently, ketamine has demonstrated efficacy in treating both depression and acute suicidal ideation. An increasing usage of ketamine, of a variety of formulations, has been studied for these indications. This article reviews the evidence for use of ketamine in self-injurious behavior and suicidality.

**Methods:** A review of the MEDLINE database for articles relating to ketamine, self-injurious behavior, suicidality, and self-harm was conducted. Additional articles were assessed via cross-reference.

**Results:** A total of 24 articles that included clinical trials, meta-analyses, case series, and case reports were analyzed. The majority of studies of ketamine for suicidal ideation include the intravenous route using a dose of 0.5 mg/kg over 40 minutes. These studies suggest that intravenous ketamine may be effective at reducing suicidal ideation acutely. Data on use of ketamine in the intramuscular, intranasal, and oral forms are limited and of poorer quality. Studies on these formulations contain greater variability of positive and negative results of ketamine for reducing suicidality and self-injurious behavior. The durability of the antisuicidal effects across all formulations is limited.

**Discussion:** Ketamine may be an effective option for the treatment of suicidal ideation in patients across inpatient, outpatient, or emergent settings. At this time, more research is needed on the efficacy of ketamine across all formulations being used in clinical practice.

**Keywords:** ketamine, suicidal, self-injurious behavior, self-harm

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## Introduction

Self-injurious behavior (SIB), including both nonsuicidal self-harm and suicidal behavior, affects millions of patients annually.<sup>1</sup> An estimated 800 000 people die by suicide each year, and nonfatal self-harm occurs 20 times more frequently.<sup>2</sup> Each episode of self-harm increases the likelihood of a future suicide or SIB.<sup>3</sup> Although these behaviors are commonly associated with major depressive disorder (MDD), patients with schizophrenia, personality disorders, autism, bipolar disorder, and substance use disorders may also exhibit these characteristics.<sup>4</sup>

In addition to the detriment to the patient and those close to the patient, SIB contributes to numerous hospitalizations each year, which, in turn, result in significant cost to patients, communities, and health systems.<sup>5</sup>

Despite the prevalence of SIB across several psychiatric conditions, advances in the treatment options for these behaviors have been limited. Currently, the management options for patients with depression are limited by pharmacologic modality and inability to treat acute suicidal behaviors in a targeted manner. Additionally, first-line antidepressants may take several weeks for therapeutic effect and about two thirds of patients will require either augmentation or a trial of an alternate pharmacotherapy for their depressive symptoms.<sup>6</sup> The black box warning of antidepressants for suicidality among children and adolescents may also present as barriers for using these agents. Furthermore, most clinical trials of antidepressants exclude suicidal patients, which limits generalizability of the results of efficacy trials for patients who display behaviors of self-harm.<sup>7</sup> Nonantidepressants, such as lithium or clozapine, have demonstrated benefit in reducing suicidal behaviors; however, these outcomes were not demonstrated in the emergent setting.<sup>8</sup> Electroconvulsive therapy may provide the most rapid response for reducing acute suicidality, but access to this treatment modality may be limited and may not be considered a favorable option for patients. Additionally, several sessions of treatment are usually necessary for full remission.<sup>8</sup>

Ketamine is an NMDA (N-methyl-D-aspartate) antagonist that has received attention as a novel pharmacologic option for major depression and, more importantly, for reducing acute suicidality.<sup>9</sup> Since development, ketamine has predominantly been viewed as an anesthetic as well as an illicit drug of abuse; however, ketamine (as well as the *s*-enantiomer esketamine) has demonstrated benefit in rapidly reducing symptoms of depression in refractory patients at subanesthetic doses.<sup>10</sup> Numerous investigations have been reported; albeit sample sizes remain relatively low and vary in formulation and treatment settings. The reports are flawed with other study design issues, such as inclusion of comorbid conditions, number of administrations, and duration of treatment, just to name a few.<sup>10</sup> Despite these limitations, the discussion of how ketamine may be used to treat the consequences of so many psychiatric illnesses remains important. Most of these studies have demonstrated a benefit in improving symptoms of depression using validated measures, such as the Montgomery-Asberg Depression Rating Scale (MADRS)<sup>11</sup> or Hamilton Depression Rating Scale for Depression (HAM-D)<sup>12</sup>; however, several studies have also shown ketamine's benefit in specifically reducing suicidal symptoms acutely.<sup>13</sup> In this review, we summarize published reports describing the use of ketamine (intravenous [IV], intramuscular [IM], intranasal [IN], sublingual) and esketamine (IN) for SIB.

## Methods

We conducted a search of the MEDLINE database for studies published between January 1, 1960, and May 31, 2018, using the following keywords: ketamine, suicid\*, self-injur\*, esketamine, and self-harm. We included studies published in the English language that were conducted with human subjects. From this initial search, the primary author (D.D.) gathered additional literature from cross-references. Studies that were already included in meta-analyses, studies that did not assess suicidality or SIB, or those that were post hoc analyses of included studies were excluded from this manuscript. We have summarized the studies by the formulation of ketamine studied and by strength of study design (systematic review/meta-analyses, individual randomized controlled trials, open-label trials, case series, and case reports) using the Center for Evidence-Based Medicine Levels of Evidence for Therapeutic Studies.<sup>14</sup>

## Results

We identified 24 studies that included 2 meta-analyses, 9 clinical trials, 12 case series/reports, and 1 retrospective chart review. We excluded trials that were included in the included meta-analyses as well as those that were post hoc analyses of previously published data.

## Intravenous

A recent meta-analysis conducted by Wilkinson and colleagues<sup>13</sup> described ketamine trials for patients with major depression, bipolar depression, or post-traumatic stress disorder for suicidal ideation (SI; Table). The authors identified 10 ketamine trials for psychiatric disorders that met the study inclusion criteria of single-dose trials, had a comparator group (placebo or midazolam), and utilized the IV route. The study authors assessed the effect of ketamine to resolve SI as compared with a control using a general linear mixed model with covariates including age, sex, race, treatment setting, diagnosis, and concomitant psychotropic medications.

In total, data were obtained for 298 patients from the selected trials. Of those, 167 were included due to baseline SI. Patients included in the analysis had more severe depressive symptoms at baseline as measured by the MADRS (33.4 vs 25.9,  $P < .001$ ), HAM-D (20.5 vs 16.3,  $P < .001$ ), Quick Inventory of Depressive Symptomatology – Self-Report<sup>15</sup> (17.7 vs 14.2,  $P < .001$ ), and Beck Depression Inventory<sup>16</sup> scales (29.2 vs 21.1,  $P < .001$ ). Of the included patients, those who received ketamine did not differ significantly from control groups with regard to age, sex, diagnoses, inpatient status, or proportion receiving concomitant psychotropic medications. The

**TABLE:** Summary of published reports for ketamine and self-injurious behavior

Study, y	Study Characteristics	Intervention	Results/Comment
Intravenous			
Wilkinson et al <sup>13</sup> (2018)	<i>Study Design, Duration:</i> Meta-analysis, 10 studies 7 d <i>Setting:</i> IP, OP <i>Patient Population, Sample Size:</i> n = 167 MDD, posttraumatic stress disorder, bipolar depression <i>Inclusion criteria:</i> Single-dose, IV ketamine, comparator group, any psychiatric disorder with SI at baseline <i>Exclusion criteria:</i> open-label, case reports, secondary analyses, no baseline SI	Single-dose, IV, 0.5 to 0.54 mg/ kg over 40 min 7 studies used saline control, 3 studies used midazolam IV 0.045 mg/kg as control	Patients who received ketamine had lower scores on clinician- rated scores of suicidality on days 1 and 7 using HAM-D or MADRS (group-by-time interaction, chi-square = 50.6, $P < .001$ ) Data collected from the selected trials included SI as assessed by item 10 of the MADRS, item 3 on the HAM-D, item 12 on the QIDS-SR, and/or item 9 on the Beck Depression Inventory
Bartoli et al <sup>17</sup> (2017)	<i>Study Design, Duration:</i> Meta-analysis, 5 studies 4 h <i>Setting:</i> IP, OP, ED <i>Patient Population, Sample Size:</i> n = 99 Subjects with suicidal ideation <i>Inclusion criteria:</i> single IV dose of ketamine for SI, assess change in SI with appropriate rating scale within 4 h <i>Exclusion criteria:</i> treatment-resistant depression, bipolar depression, no baseline SI metric, SI changes beyond 4 h	63 patients treated with 0.2 mg/kg bolus (over 1 min) 36 patients treated with 0.5 mg/kg infusion (over 40 to 45 min) No comparators	Ketamine decreased SI (standardized mean difference = $-0.92$ , 95% confidence interval $-1.4$ to $-0.44$ , $P < .001$ ) Nonsignificant higher effect with ketamine bolus vs infusion
Grunebaum et al <sup>19</sup> (2018)	<i>Study Design, Duration:</i> Randomized controlled, double-blind, single center Assessments at 24 h, follow-up of 6 wk <i>Setting:</i> IP <i>Patient Population, Sample Size:</i> n = 80 (40 per group) MDD, significant SI (score of 4 or greater on SSI) <i>Inclusion criteria:</i> voluntary admission to inpatient research unit, diagnosis of MDD, score of 16 or greater on HAM-D, score of 4 or greater on SSI <i>Exclusion criteria:</i> unstable medical or neurological illness, current psychosis, history of ketamine abuse or dependence, history of other substance or alcohol dependence, SI related to substance use	IV infusion Ketamine: 0.5 mg/kg over 40 min Midazolam: 0.045 mg/kg	Ketamine: SSI was reduced 4.96 points greater than comparator ( $P < .001$ ) Proportion of responders on the SSI was 55% for ketamine group vs 30% in midazolam group ( $P = .024$ )

**TABLE:** Summary of published reports for ketamine and self-injurious behavior (continued)

Study, y	Study Characteristics	Intervention	Results/Comment
Fan et al <sup>20</sup> (2017)	<i>Study Design, Duration:</i> Randomized controlled 7 d <i>Setting:</i> IP <i>Patient Population, Sample Size:</i> n = 37 (20 in intervention) Newly diagnosed cancer patients with symptoms of depression and suicidality <i>Inclusion criteria:</i> diagnosed with cancer within 3 mo of study <i>Exclusion criteria:</i> cardiorespiratory disease, history of substance use disorder, neuropsychiatric or cognitive diseases, suicide attempts or ideation before cancer diagnosis, family history of psychiatric disorder	IV infusion Ketamine: 0.5 mg/kg over 40 min Midazolam: 0.05 mg/kg	BSSI and MADRS-SI reduced in ketamine vs midazolam groups 9.5 vs 16.8 and 1.7 vs 3.4; $P < .05$ , respectively
Kudoh et al <sup>21</sup> (2002)	<i>Study Design, Duration:</i> Randomized controlled 5 d: 2 d preoperative, 3 d postoperative follow-up <i>Setting:</i> IP <i>Patient Population, Sample Size:</i> N = 95 (35 in intervention, 35 in comparator, 25 in control) MDD treated with antidepressant, undergoing orthopedic surgery <i>Inclusion criteria:</i> MDD diagnosis and received antidepressant for more than a year, undergoing orthopedic surgery with general anesthesia <i>Exclusion criteria:</i> anemia, immune dysfunction, cardiovascular, respiratory, or endocrine disorder	IV Ketamine: 1 mg/kg (part of anesthesia regimen as below) Coadministered with 1.5 mg/kg propofol + 2 mcg/kg fentanyl Comparator group: MDD diagnosis and received fentanyl and propofol but no ketamine Control group: received propofol, ketamine, and fentanyl but without MDD	HAM-D reduced in ketamine depressed group vs no ketamine group Suicide item on HAM-D decreased from 1.3 to 0.3 in ketamine group vs 1.1 to 1.1 in comparator ( $P < .001$ )
Price et al <sup>22</sup> (2014)	<i>Study Design, Duration:</i> Randomized controlled 24 h <i>Setting:</i> OP <i>Patient Population, Sample Size:</i> n = 57 (intervention = 36) MDD, treatment-resistant <i>Inclusion criteria:</i> moderate to severe depression, free from psychotropic medications for 1 wk or more prior to infusion (4 wk for fluoxetine) <i>Exclusion criteria:</i> patients deemed unsafe for study participation due to serious and imminent suicidality	IV infusion Ketamine: 0.5 mg/kg over 40 min Midazolam: 0.05 mg/kg	53% of ketamine patients scored 0 on all 3 explicit suicide measures (BSSI, MADRS, QIDS) compared to 24% in midazolam group

**TABLE:** Summary of published reports for ketamine and self-injurious behavior (continued)

Study, y	Study Characteristics	Intervention	Results/Comment
Grunebaum et al <sup>23</sup> (2017)	<p><i>Study Design, Duration:</i> Randomized controlled 24 h <i>Setting:</i> OP <i>Patient Population, Sample Size:</i> N = 16 Bipolar depression, SSI score 4 or greater Inclusion criteria: Current depressive episode scoring <math>\geq 16</math> on the HAM-D and score <math>\geq 4</math> on the SSI Exclusion criteria: unstable medical or neurological illness, current psychosis, past history of ketamine abuse/dependence, other drug/alcohol dependence in previous 6 mo or suicidality due to binge substance use, prior ineffective trial, or adverse reaction to ketamine or midazolam</p>	<p>IV infusion Ketamine: 0.5 mg/kg over 40 min Midazolam 0.02 mg/kg</p>	<p>Mean reduction of SSI was 5.84 points greater in ketamine group as compared with midazolam group</p>
Price et al <sup>24</sup> (2009)	<p><i>Study Design, Duration:</i> Prospective single arm 24 h <i>Setting:</i> IP <i>Patient Population, Sample Size:</i> n = 26 MDD, treatment-resistant, moderate to severe depression Inclusion criteria: Moderate to severe depression, psychotropic medication free for 2 wk prior to infusion (4 wk for fluoxetine), free of substance abuse/dependence for 6 months or greater, no lifetime use of ketamine and phencyclidine, no history of psychotic disorder or mania, no clinically unstable medical or neurological conditions Exclusion criteria: patients deemed unsafe for study due to highly active suicidality</p>	<p>IV infusion Ketamine: 0.5 mg/kg over 40 min No comparator</p>	<p>MADRS-SI reduced average of 2.08 points (6-point scale), 81% of patients achieved a 0 or 1 rating 24 h postinfusion</p>
Thakurta et al <sup>25</sup> (2012)	<p><i>Study Design, Duration:</i> Prospective, open-label, single center 4 wk for washout, 2 d postinfusion <i>Setting:</i> IP <i>Patient Population, Sample Size:</i> n = 27 MDD, treatment-resistant Inclusion criteria: 2 or more failed antidepressant trials; psychotropic medication free for 2 wk prior to infusion; 4 wk for fluoxetine; free of substance use for 6 mo; denied lifetime use of ketamine or phencyclidine; no previous psychotic disorder, mania, or hypomania; no unstable medical conditions Exclusion criteria: none noted</p>	<p>IV Ketamine: 0.5 mg/kg over 40 min No comparator</p>	<p>Mean decrease in SSI score from 5 to 1 maintained from minute 40 to 230 (<math>P &lt; .01</math>), returned to baseline by day 2 HDRS-SI score from 1.4 to 0.4 (<math>P &lt; .01</math>) after 40-min infusion and returning to baseline by day 2</p>

**TABLE:** Summary of published reports for ketamine and self-injurious behavior (continued)

Study, y	Study Characteristics	Intervention	Results/Comment
Vande Voort et al <sup>26</sup> (2016)	<i>Study Design, Duration:</i> Single arm, open-label 10 wk <i>Setting:</i> IP <i>Patient Population, Sample Size:</i> n = 12 MDD, treatment-resistant, hospitalized for SI Inclusion criteria: nonpsychotic, treatment-resistant MDD or bipolar disorder, failure to respond to 2 or more antidepressants or mood stabilizers Exclusion criteria: psychotic symptoms, duration of current depressive episode greater than 2 years, current alcohol or substance dependence, developmental delay or intellectual disorder	IV infusion Ketamine: 0.5 mg/kg over 100 min 3 times weekly for 2 wk (phase I) Patients who remitted in phase 1 proceeded to receive once weekly ketamine infusions for 4 wk Phase 2: 0.5 mg/kg over 100 min once weekly for 4 wk	41.7% of patients remitted (MADRS score $\leq 9$ ) 58.3% of patients responded (50% or greater reduction in MADRS) MADRS suicide item reduced from 2.9 at baseline to 1.7 after phase I
Aligeti et al <sup>27</sup> (2014)	<i>Study Design, Duration:</i> Case report 120 h <i>Setting:</i> IP <i>Patient Population, Sample Size:</i> n = 1 Presenting after highly lethal suicide attempt	IV infusion Ketamine: 0.5 mg/kg over 45 min	Baseline HAM-D and MADRS scores reduced from 15 and 34 to 1 and 4, respectively Postinfusion, suicidal cognition items on both tests were 0 (baseline value not reported), patient remained stable at 6 mo follow-up
Bartova et al <sup>28</sup> (2015)	<i>Study Design, Duration:</i> Case report Unknown duration <i>Setting:</i> IP <i>Patient Population, Sample Size:</i> n = 2 MDD, treatment-resistant, recurrent suicidal crises	IV Esketamine: 0.6 to 0.8 mg/kg	Subjective report of “good antisuicidal effects lasting approximately 1 day”
Gurnani and Khurshid <sup>29</sup> (2017)	<i>Study Design, Duration:</i> Case report 8 d <i>Setting:</i> IP <i>Patient Population, Sample Size:</i> n = 1 MDD, treatment-resistant, presenting after suicide attempt	IV infusion Ketamine: 0.5 mg/kg over 40 min $\times$ 4 treatments over 8 d Coinfused with midazolam 2 mg for sedation	50% reduction in MADRS score, suicidal thoughts item was among most improved in this case (specific score unreported)
López-Díaz et al <sup>30</sup> (2017)	<i>Study Design, Duration:</i> Case report 60 d <i>Setting:</i> IP <i>Patient Population, Sample Size:</i> n = 1 Bipolar depression, treatment-resistant, chronic suicidal thoughts	IV infusion Ketamine: 0.5 mg/kg over 40 min, 3 times weekly for 2 wk (6 sessions)	ISST decreased from 13 to 1, maintained at 1 for more than a month Readmitted to hospital 2 mo later following suicide attempt with ISST score of 18
Mischel et al <sup>31</sup> (2018)	<i>Study Design, Duration:</i> Case series Up to 3 mo <i>Setting:</i> IP <i>Patient Population, Sample Size:</i> n = 2 MDD and pain presenting after traumatic suicide attempt	IV infusion Ketamine 0.3 to 0.4 mg/kg/h	Subjective improvement in mood, affect, and SI

**TABLE:** Summary of published reports for ketamine and self-injurious behavior (continued)

Study, y	Study Characteristics	Intervention	Results/Comment
Niciu et al <sup>32</sup> (2013)	<i>Study Design, Duration:</i> Case report 7 d <i>Setting:</i> IP <i>Patient Population, Sample Size:</i> n = 2 Obsessive-compulsive disorder with minimal depressive symptoms	IV infusion Ketamine: 0.5 mg/kg over 40 min	Reduced overall HAM-D scores 3 hours following infusion Observed subsequent worsening in HAM-D scores and SI Patients did not meet criteria for MDD
Vulser et al <sup>33</sup> (2018)	<i>Study Design, Duration:</i> Case report 20 d <i>Setting:</i> IP <i>Patient Population, Sample Size:</i> n = 1 MDD, anorexia, past substance use disorders, presenting with suicide attempt by overdose	IV infusion Ketamine: 0.5 mg/kg over 40 min, repeated in 2 d	No change in BSSI, or BHS after first infusion Within 1 week of second infusion, MADRS, BHS, and BSSI decreased to 3/60, 3/20, and 0/38, respectively (approximately 70% to 80% reductions from baseline)
Zigman and Blier <sup>34</sup> (2013)	<i>Study Design, Duration:</i> Case report 8 d <i>Setting:</i> IP <i>Patient Population, Sample Size:</i> n = 1 MDD	IV infusion Ketamine: 0.5 mg/kg over 40 min	SI reduced from 9/10 to 0/10
Intramuscular			
Bigman et al <sup>35</sup> (2017)	<i>Study Design, Duration:</i> Case report 30 d <i>Setting:</i> ED <i>Patient Population, Sample Size:</i> n = 1 Bipolar disorder, chronic pain, presents with SI	Intramuscular Ketamine: 30 mg (0.5 mg/kg)	Resolution of suicidality and subjective improvement in mood
Intranasal			
Canuso et al <sup>36</sup> (2018)	<i>Study Design, Duration:</i> Multicenter, randomized, double-blind controlled 25 d <i>Setting:</i> IP <i>Patient Population, Sample Size:</i> n = 68 MDD Inclusion criteria: MDD without psychotic features, requiring inpatient hospitalization due to imminent risk of suicide, score of 22 or greater on MADRS, subjects agreed to initiation or optimization of noninvestigational antidepressant Exclusion criteria: current diagnosis of bipolar disorder, moderate to severe substance use disorder, intellectual disability, antisocial personality disorder, borderline personality disorder, or current or past psychotic disorder	IN Esketamine: 84 mg + standard of care antidepressant ± augmentation Comparator group received standard of care (antidepressant ± augmentation)	Reduction in MADRS, MADRS-SI reduced at 4 h, but not remaining significant at 24 h or at day 25 No differences in clinical global judgment of suicide risk scores at any time

**TABLE:** Summary of published reports for ketamine and self-injurious behavior (continued)

Study, y	Study Characteristics	Intervention	Results/Comment
Papalos et al <sup>37</sup> (2018)	<i>Study Design, Duration:</i> Retrospective chart review of survey data 3 mo to 6.5 y <i>Setting:</i> OP <i>Patient Population, Sample Size:</i> n = 45 Fear of harm phenotype of pediatric bipolar disorder Inclusion criteria: treatment-resistant bipolar disorder with fear of harm phenotype Exclusion criteria: none noted	IN Ketamine: 5 to 20 mg per spray administered in alternating nostrils until minimum intolerable dose; repeated every 3 to 4 d Mean dosage of 165 mg IN every 2 to 5 d	Principal component analysis of Likert responses revealed SI/planning as high loading of principal component accounting for subject variability Ketamine demonstrated reduction in all component symptom categories
Schak et al <sup>38</sup> (2016)	<i>Study Design, Duration:</i> Case report Approximately 2 y <i>Setting:</i> IP <i>Patient Population, Sample Size:</i> n = 1 MDD, ketamine dependence	IN Ketamine: 75 to 150 mg 4 to 12 times per d	Patient enrolled in IV ketamine study and received IN ketamine from separate prescriber Began using more than prescribed, seeking out other providers when one stopped prescribing, and eventually attempted suicide 2 more times before dying of an automobile crash (potential suicide)
Oral/Sublingual			
De Giannis and De Leo <sup>39</sup> (2014)	<i>Study Design, Duration:</i> Case report 24 h, then monthly follow-up indefinitely <i>Setting:</i> OP <i>Patient Population, Sample Size:</i> n = 2 Bipolar depression, chronic suicidal ideation	Oral Ketamine: 1.5 to 3 mg/kg	Baseline MADRS score was 36 with 4/6 on the suicide item Patient 1: Following 24 h of treatment, scores reduced from 17 and 1 Patient 2: Following 24 h of treatment, MADRS reduced from 31 to 10; suicide item reduced from 4 to 2
Grande <sup>40</sup> (2017)	<i>Study Design, Duration:</i> Case report 1 to 6 mo <i>Setting:</i> OP <i>Patient Population, Sample Size:</i> n = 2 1 case of vague depressive symptoms with no formal diagnosis and suicidal thoughts Second case with bipolar I disorder with history of suicide attempts and ideation	Sublingual Ketamine: 16 to 128 mg daily	Subjective improvements in mood and suicidal thoughts 1 patient self-discontinued ketamine

BHS = Beck Hopelessness Scale; BSSI = Beck Scale for Suicidal Ideation; ED = emergency department; HAM-D = Hamilton Rating Scale for Depression; HDRS-SI = Hamilton Depression Rating Scale – Suicide Subscale; IN = intranasal; IP = inpatient; ISST = InterSePT Scale for Suicidal Thinking; IV = intravenous; MADRS = Montgomery-Asberg Depression Rating Scale; MADRS-SI = Montgomery-Asberg Depression Rating Scale – suicidal ideation; MDD = major depressive disorder; OP = outpatient; QIDS = Quick Inventory of Depressive Symptomatology; QIDS-SR = Quick Inventory of Depressive Symptomatology-Self Report; SI = suicidal ideation; SSI = Scale for Suicidal Ideation.

two groups did not differ in their baseline MADRS scores either (33.8 vs 32.9,  $P = .388$ ).

Patients who received ketamine had lower scores on clinician-rated scores of suicidality on days 1 and 7 using HAM-D or MADRS (group-by-time interaction, chi-square = 50.6,  $P < .001$ ). The number needed to treat for ketamine for being free of SI ranged from 3.1 to 4.0 for time points between days 1 and 7 after ketamine infusion. Changes associated with the individual SI item on these scales was significantly correlated with overall depressive symptoms ( $r^2 = .411$ ,  $t = 10.73$ ,  $P < .001$ ). When controlling for change in depressive symptoms, the effect on SI remained significant (time-by-treatment interaction, chi-square = 10.84,  $P = .028$ ).

This meta-analysis should be considered in the setting in which there were relatively few patients in the final analysis. In addition, the measurement of suicidal ideation in this patient population often involved a single item on either the MADRS or HAM-D. These measures are not as sensitive specific suicidal ideation assessments and were not originally validated to be used for this purpose. Other considerations include the relatively short follow-up of 7 days and the patients not being deemed as “imminent suicide risk.”

Another meta-analysis was conducted in 2017 by Bartoli and colleagues.<sup>17</sup> This meta-analysis assessed 5 single-arm trials of IV ketamine at reducing SI acutely (within 4 hours of infusion). This study utilized a different set of studies than the Wilkinson group<sup>13</sup> as they utilized single-arm studies. Bartoli et al<sup>17</sup> included 99 patients, 63 of which received IV bolus of ketamine 0.2 mg/kg (over 1 minute), and the remaining 36 received a ketamine 0.5 mg/kg infusion (over 40-45 minutes). A decrease in SI was noted by a standard mean difference of  $-0.92$  (95% confidence interval [CI]  $-1.4$  to  $-0.44$ ,  $P < .001$ ). The study found a nonsignificant reduction in SI in the ketamine bolus group as compared with the ketamine infusion group (standard mean difference:  $-2.11$  vs  $-0.86$ ,  $P = .27$ ).

The results of this study should be considered with several limitations. There was no comparator group in any of the 5 included ketamine trials, making it difficult to discern the absolute effect of ketamine on SI. In addition, the authors primarily considered the end point of 4 hours postinfusion. Although the acute management of SI is important, the degree of durability of this effect is also important to consider. Although the inclusion criteria for the meta-analysis were trials with specific and valid measurements of suicidality, outcomes for specific scales were not reported, nor were the differences in scales used among the trials. Finally, since publication, 1 of the trials<sup>18</sup> in the included analysis was retracted from publication due to inaccuracy in the reported data.

A randomized, midazolam-controlled trial<sup>19</sup> to assess SI in depressed patients was published recently. This study assessed suicidality using the Scale for Suicidal Ideation (SSI) 24 hours after infusion of ketamine or midazolam. They included patients with a score of 4 or greater on the SSI, which is considered a significant cutoff for SI. The scale consists of 19 items rated 0 to 2 for a maximum score of 38. Depression was also assessed utilizing HAM-D and Beck Depression Inventory.

The study<sup>19</sup> included 82 participants who were randomized to 1 of the treatment arms although 1 participant in each group dropped out prior to day 1 assessment; thus, 40 patients were analyzed in each group. The groups were similar at baseline with the exception of percentage of patients with borderline personality disorder (8% in midazolam group vs 28% in ketamine group,  $P = .03$ ). The baseline scores for the SSI in ketamine and midazolam groups were 14.3 and 15.7, respectively. The primary outcome was SSI score, which was reduced by 4.96 points in the ketamine group compared with the midazolam group (95% CI 2.33-7.59,  $P < .001$ ). Including borderline personality disorder as a covariate did not significantly alter the results (estimate = 4.76, 95% CI 1.89-7.63,  $P = .002$ ). Responders were defined as those with a 50% or greater reduction in the SSI score. Fifty-five percent of ketamine patients responded at day 1 post-infusion as compared with 30% of the midazolam group (odds ratio: 2.85, 95% CI 1.14-7.15,  $P = .024$ ). Although ketamine demonstrated a significantly greater response rate, it should be noted that the midazolam group, serving as an active placebo, demonstrated a stronger response than would be expected.

This trial was limited by the patient population, who were not necessarily treatment-resistant as in other ketamine trials, which may have contributed to the high response to midazolam treatment. In addition, there was a higher proportion of patients with borderline personality disorder in the ketamine group; however, subsequent analysis did not reveal a significant interaction with the results.

Several other randomized controlled trials of ketamine's antisuicidal properties have been conducted<sup>20-23</sup> and have demonstrated reduction in SI. One of these studies,<sup>20</sup> interestingly, occurred in patients with a recent cancer diagnosis but no past psychiatric history. The study demonstrated a significant reduction in SI as measured by both the Beck Scale for Suicidal Ideation as well as the MADRS-SI question as compared with a midazolam-controlled group. Kudoh and colleagues<sup>21</sup> assessed patients with MDD who were undergoing orthopedic surgery. This study utilized ketamine as part of an anesthetic regimen and, thus, utilized higher initial doses of ketamine, 1 mg/kg. The study compared patients with MDD who did not receive ketamine as part of their

general anesthesia to those who did receive ketamine. The study found that depressed patients who received ketamine had a significantly improved HAM-D score overall and a significantly reduced score on the individual SI item of the HAM-D than patients who did not receive ketamine in their general anesthesia. In a cohort of treatment-resistant MDD patients,<sup>22</sup> 53% scored 0 on 3 explicit suicide measures after treatment with IV ketamine at a dose of 0.5 mg/kg over 40 minutes. A proof-of-concept study<sup>23</sup> also demonstrated a greater reduction in SSI score in patients with bipolar disorder treated with 0.5 mg/kg of ketamine over 40 minutes as compared with those treated with a midazolam control.

Intravenous ketamine has also been studied and demonstrated benefit in patients with treatment-resistant depression and SI in 3 open-label, single-arm studies.<sup>24-26</sup> Two of these studies<sup>24,26</sup> demonstrated that depressed patients scored significantly lower on the MADRS-SI item (averaging a 1- to 2-point reduction) after receiving a parenteral infusion of ketamine. Thakurta and colleagues<sup>25</sup> showed a reduction in SI utilizing a validated scale for SI; however, the demonstrated benefit seemed shorter than in other studies with benefit lasting approximately 1 day.

Finally, 8 publications<sup>27-34</sup> of case reports/series report both subjective and objective improvements in SI following IV infusion of ketamine (typically at 0.5 mg/kg over 40 minutes) although 1 study<sup>27</sup> utilized esketamine at a dose of 0.6 to 0.8 mg/kg. Even though the generalizability of these cases is low and warrants caution with application of the results, it is important to note that some of these cases represent patients who have presented to the hospital immediately following a highly lethal suicide attempt.<sup>27,29,31</sup> In another case series, Niciu et al<sup>32</sup> describes an initial improvement in depressive symptoms in 2 patients with comorbid obsessive-compulsive disorder several hours after ketamine infusion. However, after approximately 1 day, these patients had worsening of depressive symptoms, including subjective reports of SI without plan or intent despite negative suicidality upon hospitalization.

### **Intramuscular**

One case report<sup>35</sup> of IM ketamine has been reported to have subjective benefit in a patient with bipolar disorder and SI in the emergency department setting (Table). This patient received a ketamine 0.5 mg/kg IM injection with subjective improvement in SI. Of note, this patient also had a co-occurring pain disorder that the authors hypothesized would also improve with IM ketamine. The patient was discharged from the hospital in 3 days and had no SI at the follow-up appointment 30 days later.

### **Intranasal**

A recent multicenter, double-blind, randomized, placebo-controlled trial<sup>36</sup> of IN esketamine found a reduction in SI as measured by the MADRS-SI item, 4 hours after the dose (Table). This effect was not significant at 24 hours postdose. Besides the formulation, this trial differs from other trials in that it utilized a fixed dose of esketamine for each patient. In addition, the patients included had a baseline suicidality that warranted inpatient admission. Although the MADRS-SI item demonstrated benefit at 4 hours, the clinician global judgment of suicide risk rating never differentiated from placebo at any time point.

Another study<sup>37</sup> that assessed the utility of IN ketamine reported results of a retrospective review of survey data. This study documented the experience from an outpatient provider in treating primarily pediatric and adolescent patients (mean age = 15 years) with bipolar disorder with the fear of harm phenotype. The fear of harm phenotype is characterized by treatment-resistant bipolar disorder that often presents with physical aggression and separation anxiety. Patients in this study were treated with IN ketamine for an average of  $1.71 \pm 1.36$  years. During dose titration, patients were assessed clinically twice weekly. A principal component analysis of the survey data showed that SI improvement was among the most impactful measures assessed in patients who were treated with IN ketamine with a mean dosage of 165 mg every 2 to 5 days.

Finally, a case report<sup>38</sup> of a patient who was previously enrolled in an IV ketamine study but continued treatment with IN ketamine was published in 2016. This case report documents a patient with a significant past history of substance abuse and multiple suicide attempts. The prescribed dose of IN ketamine in this case is much higher than other reported IN ketamine doses. The patient did not significantly improve on ketamine or other treatment modalities and eventually died due to presumed suicide involving a motor vehicle accident.

### **Oral/Sublingual**

Several case reports<sup>39,40</sup> have been published documenting the use of oral ketamine in patients with bipolar depression or depressive symptoms (Table). These reports use weight-based dosing of ketamine ranging from 1.5 to 3 mg/kg as well as fixed doses ranging from 16 to 128 mg/d. Although these reports have documented improvement in the MADRS-SI item and subjective improvement in SI, these cases should be carefully considered in the setting of great variability of dosing.

## Discussion

This review summarizes the available evidence on the effects of ketamine on SIB regardless of dosage formulation or study design. The available studies provide supporting evidence for the use of ketamine, primarily administered intravenously, to treat suicidality in patients with bipolar disorder or major depression. To date, few pharmacologic options exist for the treatment of suicidality. Clozapine is Food and Drug Administration-approved for recurrent suicidal behaviors in schizophrenia patients,<sup>41</sup> and lithium has demonstrated antisuicidal effects in patients with mood disorders.<sup>8</sup> However, few patients with MDD receive these agents due to Food and Drug Administration indication, declining use, adverse effects, and frequent monitoring.<sup>42,43</sup> In addition, traditional antidepressant medications were not commonly studied in patients with suicidal behaviors or those deemed to be at high risk for suicide; therefore, conclusions about their antisuicidal effects are limited and likely related to overall mood improvement.<sup>7</sup>

The evidence for the various formulations of ketamine should be carefully considered. The majority of studies report IV ketamine used at a dose of 0.5 mg/kg infused over 40 minutes. The antisuicidal effects have been demonstrated in meta-analyses, controlled trials, and case reports. Their antisuicidal effects have been measured by a variety of reliable and valid tools. In comparison, IM, IN, and PO/sublingual formulations have less data for use in SI or self-harming behaviors.

Although the antisuicidal response of ketamine in depressed patients occurs rapidly and profoundly in many of the patients reported, this effect can be short-lived. Typical duration of effects appears to be 1 week although several cases of effects lasting just a day have been reported. This also suggests that single-dose ketamine will not be sufficient in most patients because the suicidality can be persistent and recurrent.

At this time, there are limited data on repeated doses of ketamine for both safety and efficacy for SI. In this review, cases have been evaluated in which repeated dosing of ketamine did not provide additional benefit<sup>32,37</sup> as well as studies in which patients required multiple doses to achieve antisuicidal benefit.<sup>33</sup> Ketamine also demonstrated transient relief of suicidality in patients who have been admitted to the hospital following a suicide attempt or patients who have experienced chronic and severe suicidality. Although this data are limited to case reports, it represents a very high-risk population that has not been studied in other settings.

This is the first review article to report on the antisuicidal effects of multiple formulations of ketamine among

patients with various diagnoses and study designs. Although this analysis is a comprehensive review of the use of ketamine in this setting, there are several limitations that should be considered. First, the majority of reported studies utilized a single question item from a validated depression rating scale. Because the sensitivity and specificity of these single items were not specifically designed or validated for this purpose, it is difficult to make definitive conclusions. To that, several studies<sup>20,22</sup> did use specific scales that have been studied in patients with suicidality, such as the Beck Scale for Suicidal Ideation.

Several studies<sup>13,19</sup> presented herein described the antisuicidal effects of ketamine occurring distinctly from the overall antidepressant response. These findings appear to be unique to ketamine and may suggest the potential for future investigation in suicidal behavior or SIB in non-depression patient populations. In addition, long-term effects of ketamine are not well described in the literature despite an increasing number of providers of various formulations of ketamine.<sup>44</sup> Finally, the majority of these studies include parenteral ketamine and a smaller portion of patients who received PO or IN ketamine. Enteral formulations of ketamine are available; however, assumptions about its equivalent efficacy or safety cannot be made.

It is important to note that the exact mechanism of ketamine's antisuicidal effect is not currently known. Several hypotheses have been suggested related to AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, NMDA receptors, and enhanced neuroplasticity in certain brain regions.<sup>45</sup> This may have implications on different ketamine formulations as enteral ketamine has been shown to produce different proportions of ketamine and the active metabolite hydroxynorketamine (thought to be related to some antidepressant properties).<sup>46</sup> In addition, there have been published data<sup>47</sup> with regard to intolerability to certain forms of ketamine, making unsupervised use potentially dangerous.

Although ketamine has seen an increase in clinical usage and research, caution is still warranted with using ketamine in certain scenarios. For instance, certain side effects, such as affective switch,<sup>48</sup> have been reported as well as decompensation in mood symptoms and an increase in suicidality in patients with obsessive-compulsive disorder and no current depressive symptoms.<sup>32</sup> Access to providers who are experienced in evaluation of patients with SIB and administration of ketamine in a controlled environment may also be challenging for patients seeking care. Future studies in elucidating the mechanism of antisuicidal effect would help identify other uses for ketamine. Currently, it is uncertain whether other disorders with SIB, such as borderline personality disorder,

autism, or substance use disorders, may benefit from this type of therapy.

Overall, ketamine appears to be well-tolerated in patients. Immediately after dosing, patients are likely to experience altered sensorium, dissociative experiences, or hallucinations; however, these effects remit and are no different from midazolam controls at 240 minutes postdose.<sup>18</sup> In addition to these psychiatric symptoms, providers should note that ketamine has demonstrated an ability to cause increases in heart rate and blood pressure; however, these effects also appear to be transient and return to baseline states within 30 to 120 minutes from dosing.<sup>49</sup>

## Conclusion

Ketamine appears to be a promising option for self-harm and suicidal behaviors with good efficacy data and relatively low risk of safety concerns. Unanswered questions remain, such as the persistence of the antidepressant effects. Future studies are warranted to investigate whether the antisuicidal actions of ketamine are related to its antidepressant effects and whether there are other pharmacological targets involved in SIB.

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