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## Does Ketamine Have Anti-Suicidal Properties? Current Status and Future Directions

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### Abstract

Ketamine, a widely used anesthetic agent, is currently being investigated as a novel therapeutic for depression and suicidality. Ketamine has garnered substantial attention from researchers, clinicians, media outlets, and patients alike, but numerous questions remain. One of the compelling features of ketamine is the rapidity of its antidepressant effects, which peak just 24 hours after infusion, setting it apart from other existing treatments. Ketamine's rapid time course has inspired research efforts to explore its potential as a life-saving therapy for patients at imminent risk of suicide. In this article, we review current evidence supporting ketamine's rapid effects on suicidal ideation in the context of unipolar and bipolar depression. We then discuss several future directions that are necessary before ketamine can be considered as a viable treatment option for suicidality in clinical settings. These include: testing for a specific anti-suicidal effect—separate from overall antidepressant effects—to ascertain whether ketamine might hold promise for a broader class of suicidal patients; ensuring that acute benefits of ketamine can be prolonged over a clinically meaningful timeframe; and developing a better understanding of the mechanisms by which ketamine might reduce suicide risk. Such efforts will enable the field to more accurately assess ketamine's potential, as well as its limitations, allowing for appropriate placement within the context of comprehensive clinical care for suicide prevention.

### 1. Introduction

Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist that has shown promise as a novel therapeutic for unipolar and bipolar depression [1, 2]. The rapidity of ketamine's antidepressant effects, together with its efficacy in patients failing to respond to conventional antidepressant treatment [e.g., 3, 4], has sparked interest in its potential as an anti-suicide treatment. Depressive symptom reductions are typically observed within 2 hours of ketamine infusion, and peak by 24 hours post-infusion, making ketamine a theoretically attractive candidate for securing the safety of patients who are at imminent risk of death by suicide. Given that suicide is a leading cause of death and disease

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burden in the US and worldwide, with approximately one million annual deaths, the prospect of saving lives via rapid reduction in *suicidality* [a term which we use to encompass both thoughts of suicide (“suicidal ideation”; SI) and overt suicidal behaviors [5].

Suicide rates have continued to rise in recent decades despite ongoing clinical and research efforts [5, 6]. Existing treatment options for those at imminent suicide risk include conventional antidepressants, electroconvulsive therapy (ECT), psychotherapy (e.g., cognitive therapy for suicidal patients; dialectical behavior therapy), lithium, and clozapine. Although each of these options has some degree of established efficacy for reducing markers of suicide risk [7], only clozapine has a U.S. Food and Drug Administration (FDA) approved indication for suicidal behavior (in the context of psychotic disorders only), and a controversial FDA black box warning alerts prescribers to the possibility of increased suicidality in depressed youth treated with selective serotonin reuptake inhibitors, further complicating treatment decisions. Furthermore, a substantial portion of patients (e.g., 50–70%) will prove resistant to any one existing approach [8], and algorithms for efficient patient-treatment matching have proven elusive.

An additional limitation of each of these options—compounded by the problem of treatment resistance—is the relative sluggishness of therapeutic onset, leaving a window of danger during which suicidal acts may be pursued. For instance, it is well established that conventional antidepressants take weeks to improve depression symptoms including SI. Alternatives such as ECT are considered more rapid, but in a sample of patients at high acute suicide risk, 6 ECT sessions (conducted over a 2 week period) were needed before clinician-rated suicidality was eradicated in at least half of patients [9]. Finally, while treatments for acute suicidality are frequently offered in the context of inpatient hospitalization to promote immediate patient safety, hospitalization is costly to the healthcare system and viewed as largely undesirable by both patients and clinicians. Furthermore, death by suicide occurs even within the inpatient context [10] and is particularly likely in the period immediately post-discharge [11]. A safe, feasible, cost-effective, and less stigmatizing means to efficiently reduce suicide risk in clinical settings would therefore be highly desirable.

In light of these limitations in the clinical management of acute suicidality, ketamine’s potential to rapidly impact suicidality has been explored in several studies. However, numerous questions remain to be answered before this treatment can be considered a reasonable option in clinical settings. In this Current Opinion article, we review published studies on ketamine’s anti-suicidal properties. We then discuss several future directions for research, including studies necessary to a) establish a specific anti-suicidal effect of ketamine, b) ensure that acute effects of ketamine can be extended, and c) understand the mechanisms via which reductions in suicidality are achieved. Additional practical considerations, including dose optimization, infusion speed, and appropriate credentialing of medical professionals administering ketamine, are beyond the scope of the current review, but will be key factors to address prior to clinical adoption.

## 2. Studies of Ketamine's Anti-Suicidal Effects

### 2.1 Uncontrolled Studies

The first published report examining ketamine's effects on suicidality was an open-label trial of intravenous ketamine in a sample of 26 patients with treatment-resistant major depression (TRD)[12]. 24 hours after a single ketamine infusion (0.5 mg/kg over 40 minutes), large reductions (Cohen's  $d = 1.4$ ) in SI were observed on the clinician-rated suicide item of the Montgomery-Asberg Depression Rating Scale (MADRS; [13]), with 81% of patients rating 0 or 1 on the MADRS 6-point scale. To test whether these rapid effects could be sustained through repeated ketamine infusions, a subset of the patients (n=10) were recruited into a repeated-dose open-label trial. Nine out of 10 patients were classified as responders to a first infusion (based on a 50% reduction in overall MADRS score) and then received 5 additional infusions given thrice-weekly over the course of two weeks. In all nine patients, MADRS suicide item scores were reduced to 0 and remained at 0 or 1 throughout the two-week trial.

Similar results were obtained in a sample of 33 TRD patients following a single infusion at the same dose as in the Price et al report [14]. Significant reductions on the Scale for Suicide Ideation (SSI), as well as the suicide items from several depression inventories, were documented as early as 40 minutes after the start of the infusion (i.e., immediately after the infusion concluded), with gains maintained up to 230 minutes post-infusion (no data presented for later time points). Among patients who scored above a clinically significant cut-point on the SSI at baseline ( $> 4$ ), all fell below this cut-point by 80 minutes post-infusion, and 60% reached an SSI score of 0 within 80 minutes. These rapid and significant reductions at 40 and 230 minutes post-infusion were later replicated in 27 TRD patients receiving open-label ketamine (at the same dose) in India [15]; however, contrary to all other studies reporting on 24 hour outcomes, SI scores returned to baseline levels by 24 hours in this sample. Finally, a sample of 10 TRD patients were given serial doses of ketamine (0.5 mg/kg over 100min) twice weekly until either remission of general depression symptoms was obtained or the maximum of 4 doses was reached [16]. From baseline to 24-hours post final infusion, SI scores were significantly reduced on both self-report and clinician-rated measures.

Ketamine's anti-suicide effects have also been studied in routine clinical contexts. In a sample of 14 unipolar depression patients presenting to the psychiatric ER with SI, an intravenous bolus of ketamine 0.20 mg/kg delivered over 1–2 minutes (actual doses based on repeat weight assessment ranged from 0.16–0.26mg/kg) significantly reduced scores on the MADRS suicide item beginning 40min post-infusion, with gains maintained for 10 consecutive days post-infusion during ongoing, conventional treatment [17]. The efficacy of this bolus infusion suggests that additional studies are warranted to assess whether slow infusions of 0.5mg/kg, used in the vast majority of studies to date, are in fact necessary and optimal. In an ECT clinic, 28 TRD patients received either 3 doses (n=15) or 6 doses (n=13) of ketamine (0.5mg/kg over 40min) over 3 weeks, while continuing other psychotropic medications [18]. Scores on the suicide item of the Hamilton Rating Scale for Depression (HAM-D) were significantly reduced within 6 hours of the initial infusion and, in those

individuals who obtained a 50% decrease in total depression symptoms ( $n=8$ ), improvements in SI were sustained until the final assessment 4–7 days after the last infusion. Finally, two case reports have found marked beneficial effects of oral [19] and intravenous [20] ketamine when given to patients with intractable SI in clinical contexts.

## 2.2 Randomized Controlled Trials

A randomized controlled trial (RCT) examined ketamine's anti-suicidal properties in 15 patients with bipolar depression (BD) receiving ketamine (0.5 mg/kg over 40 min) or saline infusion in a double-blind, cross-over design [21]. Ketamine, but not saline, reduced scores on the MADRS suicide item beginning at 40 minutes post-infusion and continuing through the 72-hour assessment (with a large between-group effect size of  $d=2.09$  across all time points). SI levels no longer differed across arms when re-assessed at Day 7.

In a second RCT, ketamine was compared to midazolam, a psychoactive agent selected to mimic ketamine's sedative and anesthetic properties [22]. 57 TRD patients were randomized to ketamine or midazolam in a 2:1 ratio. 24-hours post-infusion, ketamine, but not midazolam, reduced scores on a composite index comprised of three measures (the Beck Suicide Scale and the suicide items of the MADRS and the Quick Inventory of Depressive Symptoms) with a large between-groups effect ( $d=.82$ ). Ketamine was associated with total eradication of SI across all three measures in 54% of the sample at 24-hours, compared to 24% of the midazolam group. As in this research group's previous open-label study, ketamine also reduced implicit suicide-related cognition (IAT "Escape=Me" associations); however, this implicit effect could not be definitively shown to be larger in the ketamine than the midazolam group.

In summary, results to date suggest a subanesthetic dose of ketamine shows initial promise in rapidly reducing SI (Table 1), but numerous questions remain for future research.

## 3. Future Directions

### 3.1 Establishing the Specificity and Generalizability of Anti-Suicidal Properties

Suicide risk is elevated in a wide range of diagnostic groups [23] and exhibits unique genetic variance that can be inherited separately from mood disorder risk [24]. It therefore may be most accurately viewed as a transdiagnostic dimension on which individuals with and without primary mood disorders vary. Although ketamine has shown initial promise in the treatment of suicidal ideation, conclusions from the extant literature are limited by the fact that suicidality has been examined exclusively in the context of (unipolar or bipolar) depression treatment trials which have generally excluded individuals at imminent risk for suicide. As a result, it remains unclear whether ketamine has suicide-specific properties that constitute more than simply a by-product or corollary of depression reduction. Studies to date have produced conflicting findings on this issue. In two studies of TRD patients by Price and colleagues [22, 12], SI reductions 24-hours post-infusion were statistically mediated by depression reductions (measured both at 24 hours and 4 hours post-infusion). In the context of these relatively small, chronically depressed samples, ketamine could therefore not be shown to have a unique effect on SI over and above depression alleviation, but produced SI reductions in concert with overall depression improvement.

By contrast, Ballard and colleagues pooled patient-level data across 4 previously published trials of ketamine in TRD and BD to examine the relationship between SI reduction and broader improvements in anxiety and depression [25]. In a subset of patients (n=57) who had significant SI at baseline and participated in placebo-controlled RCTs comparing ketamine and saline, ketamine infusion was related to decreased SI (assessed by the HAMD suicide item), lesser wish to die and greater wish to live (assessed by relevant individual items on the SSI) from 40min to 3 days post-infusion, even after controlling for depression and anxiety symptoms at each time point. Although formal statistical mediation analysis was not reported, the persistent association between ketamine and SI indices suggests reductions in anxiety and depression did not fully account for ketamine's anti-SI effects in these patients. The differing results may stem from the inclusion of BD in addition to TRD patients, a relatively large number of patients with significant SI at baseline, and/or multiple post-infusion timepoints, all of which may have allowed for a greater degree of depression-independent variance in SI to emerge.

It is important to note that studies to date have used measures of SI as indicators of decreased suicide risk following ketamine infusion. However, current SI is a relatively imprecise proxy for overt suicidal behaviors like suicide completion [26]. Inclusion of additional proxy measures as outcomes (e.g., psychic anxiety, anhedonia, impulsivity [27]) could help to extend SI findings. Suicidal behaviors themselves are comparatively rare and therefore more difficult to quantify in clinical trials research, particularly given that ketamine trials to date have often excluded patients deemed at imminent risk of suicide. Specifically recruiting high-risk samples (e.g., suicidal inpatients/ER visitors; suicide attempters) should increase statistical power to examine whether ketamine prevents suicidal behavior in addition to reducing ideation, although large sample sizes would still be required. Furthermore, recruiting a sample defined on the basis of suicide risk, as opposed to mood disorder diagnosis, affords the opportunity to ascertain whether ketamine's effects on suicidal indices might generalize to a wider range of patients, including those not meeting formal criteria for a mood disorder. Further research is clearly required to assess this possibility, and caution is warranted in patients who may be at increased risk due to ketamine's abuse potential. Several such trials in high-risk samples are recently concluded (ClinicalTrials.gov identifier: NCT01507181) or ongoing (NCT01892995; NCT01887990) and results should be forthcoming.

### 3.2 Prolonging Relief from Suicidality

As reviewed above, in a single uncontrolled study, repeated ketamine infusions have been shown to continuously eradicate SI over a period of two weeks [12]. However, the long-term effects of repeated ketamine infusions, both desirable (e.g., protracted protection from suicide) and undesirable (e.g., neurocognitive impairments, increasing abuse liability), remain inadequately studied and poorly understood. A critical, unanswered question is whether ketamine might eventually find a role within a larger, comprehensive treatment strategy designed to effect change in a lasting way, without necessitating repeated infusions in perpetuity. Anecdotal reports suggest the possibility for prolonged improvements in depression and SI lasting 1–3 months after ketamine treatment [28, 20, 29], consistent with enduring antidepressant-like effects observed in rats following repeated administrations

[30]. However, such responses are not normative in trials to date, and without a proven strategy to reliably extend ketamine's short-term benefits, there is a serious risk of rebound in suicidality that could prove dangerous without appropriate monitoring.

An improved understanding of the mechanisms of ketamine's anti-suicidal effects would facilitate efforts to extend ketamine's acute effects, either through development of alternative, less invasive treatments that target the same mechanisms, or through synergistic treatment combinations. For instance, the hypothesis that response to an initial infusion with ketamine could be prolonged by prescribing a similar glutamatergic agent in pill form (riluzole) was tested in TRD samples; however, riluzole showed no efficacy in these trials [31, 32]. Alternative synergistic combinations are certainly possible using a wide range of existing treatments that may be more durable, but slower to act (e.g., cognitive-behavioral therapies, conventional antidepressants, ECT), and/or through novel therapeutics targeting key mechanisms. Several candidate mechanisms, which could help foster such clinical trial hypotheses, are discussed below.

### 3.3 Delineating the Mechanisms of Ketamine's Effects on Suicidality

**3.3.1 Neuroinflammatory Pathways**—Neurobiological mechanisms of ketamine's antidepressant effects are the focus of substantial ongoing research efforts. Hypothesized mechanisms have been reviewed elsewhere [33], and include alterations in glutamatergic and dopaminergic function and neuroplasticity (e.g., brain-derived neurotrophic factor). As noted above, ketamine's effects on suicidality may be part and parcel of its overall antidepressant benefit, meaning that the neurobiological mechanisms may be highly overlapping. Methodologies including genetics, neuroimaging, and sleep architecture studies will likely continue to inform our understanding of both antidepressant and anti-suicide mechanisms [34].

One particularly noteworthy line of research points to a neuroinflammatory pathway that may be both uniquely altered in suicidal patients and relevant to ketamine's pharmacology, suggesting a potential suicide-specific mechanism of action. The amino acid tryptophan is a precursor for numerous neurochemicals, with the majority of tryptophan being metabolized to kynurenine, particularly during states of inflammation [35]. Kynurenine is, in turn, metabolized through two separate pathways to become either quinolinic acid, an NMDA receptor *agonist*, or kynurenic acid, an NMDA receptor *antagonist*. In a sample of recent suicide attempters, the total amount of quinolinic acid in the cerebrospinal fluid, as well as the ratio of quinolinic to kynurenic acid, was found to be elevated in comparison to healthy controls, suggesting a tip in the balance towards NMDA receptor stimulation [36]. Quinolinic acid was particularly elevated in participants with high scores on the Suicide Intent Scale and those who had attempted using violent means. A subset of participants returned for reassessment approximately 6 months after the attempt and showed decreased quinolinic acid levels that were comparable to healthy controls.

Together with a larger literature suggesting elevated pro-inflammatory and inflammatory cytokines in individuals at risk of suicide [37], these abnormalities within the kynurenine pathway suggest a state of immune activation and NMDA receptor stimulation that is posited to confer suicide risk. One compelling hypothesis is that ketamine, an NMDA

receptor antagonist, may help to remedy this imbalance by decreasing NMDA throughput, resulting in a less suicide-prone state. This hypothesis has yet to be tested in suicidal patients receiving ketamine.

**3.3.2 Cognitive and Behavioral Mechanisms**—In addition to its numerous neurobiological effects, ketamine also exerts a dramatic influence on patients at the level of conscious experience, thought, and behavior by rapidly relieving depressive symptoms that may have proven intractable for decades (e.g., average duration of current episode >12 years; [31, 4]). It is possible that even a transient experience of this sort could affect a patient's orientation and level of engagement with treatment in a manner that is protective against suicide, as discussed below. However, given that depression is a placebo-responsive illness [38], it is also likely that patient's expectancies amplify any genuine therapeutic effect of ketamine, particularly given that the majority of studies to date have been uncontrolled. Additional placebo-controlled trials with adequate blinding, at both the patient and clinician level, are necessary to test whether ketamine's effects are indeed superior to placebo, both statistically and clinically speaking.

Hopelessness is a key factor in cognitive models of suicide and one of the few variables that reliably and prospectively predicts suicidal behaviors themselves [39, 26]. Hopelessness was found to be acutely reduced by ketamine in two TRD studies [14, 22], which could reflect that hope is naturally instilled by experiencing long-sought therapeutic benefit. In a RCT comparing ketamine and midazolam [22], there was a trend towards greater reduction in hopelessness following ketamine compared to midazolam, and hopelessness decreases were strongly related to decreased SI. Although these results are suggestive, full statistical mediation requirements were not satisfied, which could reflect insufficient power due to the study design (i.e. recruitment of a TRD sample with heterogeneous levels of SI).

This study also found a trend towards statistical mediation of SI improvements by euphoria, which was assessed at the conclusion of the infusion when ketamine's transient mood-lifting effects were still evident. Ketamine-treated patients who reported the largest acute increases in euphoria were more likely to report substantial SI decreases at the 24-hour assessment (long after euphoria had subsided). This pattern could reflect either increased efficacy of glutamatergic target engagement during the infusion—resulting in both a larger acute “high” and greater therapeutic benefit—and/or a downstream cognitive effect whereby a transient euphoric experience helps to alleviate the desire to die up to 24 hours later. By contrast, dissociative symptoms during the infusion, another side effect of ketamine's glutamatergic mechanisms, were not significantly related to SI decreases. Notably, dissociative symptoms have been reported to correlate with ketamine's antidepressant effects [40], suggesting a possible dichotomy between antidepressant and anti-suicide mechanisms. These findings highlight the need to further explore the role of ketamine's acute euphoric, dissociative, and other cognitive (e.g., mystical; [41]) effects in producing both antidepressant and anti-suicidal effects, particularly given that other agents with transient mood elevating properties (e.g., stimulants, opiates) have had limited clinical impact and are generally proscribed due to abuse liability [42].

Anhedonia is a behavioral dimension of depression that has been previously linked to proximal risk of suicide completion [27]. In a recent report, anhedonia levels in a sample of 36 BD patients were reduced for up to 14 days following a single infusion of ketamine (but not saline), even after controlling for total depression at each timepoint [43]. This pattern suggests a specific benefit of ketamine on anhedonia, over and above its effect on other depression symptoms, which could potentially contribute to decreased immediate suicide risk, particularly if a state of decreased anhedonia allows for greater engagement with protective factors in the environment (e.g., increased social engagement). Decreased anhedonia was further linked to a pattern of increased glucose metabolism in reward-processing regions of the brain (dorsal anterior cingulate; putamen). The role of these motivation-related mechanisms in ketamine's anti-suicidal effects clearly warrants further study.

Finally, implicit suicide-related cognition, assessed behaviorally using a performance-based measure, was reduced following ketamine infusion in two studies [22, 12]. Specifically, associations between escape- and self-related words on the Implicit Association Test (IAT) were reduced, with the degree of change on IAT performance tracking changes in explicit SI. Implicit suicide-related cognition, assessed by the IAT, is also a strong prospective predictor of future suicide attempts, outperforming a variety of demographic and clinical indicators [44]. Reductions in implicit associations could therefore represent a hypothetical pathway to protracted protection against suicide following ketamine, particularly if such changes can be shown to be stable over a clinically meaningful period of time. A similar model has recently been proposed for the serotonergic antidepressants, wherein acute drug effects on performance-based measures of implicit cognitive-affective processing are posited to explain downstream therapeutic benefits [45]. Additional studies incorporating long-term follow-up and repeated IAT assessment would be needed to further explore this possibility.

#### 4. Conclusions

Studies to date suggest intravenous ketamine produces substantial reductions in SI in patients with unipolar and bipolar depression, in both uncontrolled and randomized controlled trials (Table 1). Large reductions have been observed as early as 40 minutes post-infusion, with improvements maintained for variable amounts of time ranging from 230 minutes up to 10 days post-infusion (with ongoing conventional care). However, research published to date leaves numerous critical and clinically relevant questions unanswered, suggesting clinical adoption is not yet warranted. Further studies are indicated to explore the specificity, generalizability, durability, and mechanisms of ketamine's anti-suicidal effects. The promise of this line of work is that suicidal patients in need of life-saving measures will one day have access to rapid, durable, safe, and effective relief.

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**Key Points**

- Ketamine has shown initial promise as a rapid reducer of suicidal ideation in treatment-resistant unipolar and bipolar depression.
- More research is needed to: (a) explore whether ketamine has suicide-specific effects that generalize beyond depressed patients with low to moderate suicide risk; (b) test whether acute benefits can be prolonged; and (c) understand the mechanisms of ketamine's anti-suicidal properties.

Table 1

## Summary of Published Reports Examining Ketamine Effects on Suicidal Ideation

Case Reports	n	Study population	Protocol	Timepoints (post-infusion interval) with significant SI reduction	Maximum effect size (Cohen's <i>d</i> )
Zigman 2013 [20]	1	TRD	Single infusion (0.5mg/kg) + Li 600mg	40min, sustained over 1 month	--
De Gioannis 2014 [19]	2	BD	1.5–3mg/kg by mouth every 2–4 weeks	24 hours, sustained while receiving repeated doses	--
<b>Uncontrolled Trials</b>					
Price 2009 [12]	26	TRD	Single infusion (0.5mg/kg)	24 hours	<i>d</i> =1.4
Price 2009 [12]	9	TRD	6 repeated infusions (0.5mg/kg) thrice-weekly	Sustained over 2 weeks	<i>d</i> =2.4
DiazGranados 2010 [14]	33	TRD	Single infusion (0.5mg/kg)	40min through 230min	<i>d</i> =1.1
Larkin 2011 [17]	14	MDD w/SI	Single infusion (0.2mg/kg* bolus over 1–2min) delivered in ER setting	40min through 10 days	<i>d</i> =3.0
Thakurta 2012 [15]	27	TRD	Single infusion (0.5mg/kg)	40min through 230min	<i>d</i> =1.0
Rasmussen 2013 [16]	10	TRD	Maximum of 4 serial infusions (0.5mg/kg over 100min) twice weekly until remission reached	24 hours after last infusion	<i>d</i> =1.2
Diamond 2014 [18]	28	TRD	3 (n=15) or 6 (n=13) repeated infusions (0.5mg/kg) over 3 weeks	6 hours after first infusion; 21 days in responders	<i>d</i> =1.3
<b>RCTs</b>					
Zarate 2012 [21]	15	BD	Single infusion of ketamine (0.5mg/kg) vs. saline	40min through 72 hours	<i>d</i> =2.1
Price 2014 [22]	57	TRD	Single infusion of ketamine (0.5mg/kg) vs. midazolam (0.045mg/kg)	24 hours	<i>d</i> =0.8

Note: Infusions given over 40 minutes unless otherwise noted. TRD=treatment-resistant depression; BD=bipolar depression; Li=lithium; MDD=major depressive disorder; RCT=randomized controlled trial; SI=suicidal ideation

\* Intended dosing per protocol; actual dosing based on repeat weight assessment ranged from 0.16–0.26mg/kg