

Ketamine for Treatment of Suicidal Ideation and Reduction of Risk for Suicidal Behavior

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Abstract Ketamine, an NMDA receptor antagonist with efficacy as a rapid anti-depressant, has early evidence for action to reduce suicidal ideation. This review will explore several important questions that arise from these studies. First, how do we measure reductions in suicidal ideation that occur over minutes to hours? Second, are the reductions in suicidal ideation after ketamine treatment solely a result of its rapid anti-depressant effect? Third, is ketamine only effective in reducing suicidal ideation in patients with mood disorders? Fourth, could ketamine's action lead us to a greater understanding of the neurobiology of suicidal processes? Last, do the reductions in depression and suicidal ideation after ketamine treatment translate into decreased risk for suicidal behavior? Our review concludes that ketamine treatment can be seen as a double-edged sword, clinically to help provide treatment for acutely suicidal patients and experimentally to explore the neurobiological nature of suicidal ideation and suicidal behavior.

Keywords Ketamine · Suicidal Ideation · Depression · Mood disorders · Suicidal Ideation Assessment Scales · Suicidal attempt · RDoC domains

Introduction

Ketamine, a well-established anesthesia medication with a novel role as a rapidly acting anti-depressant treatment, is

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developing increasing evidence for a very unique property, efficacy to acutely decrease suicidal ideation [1, 2••]. Several excellent recent papers have reviewed the literature and neurobiological basis for ketamine's rapid action in decreasing depressive symptoms and suicidal ideation [3•, 4• 5••]. The discovery of ketamine's rapidly acting anti-depressant treatment with efficacy to reduce suicidal ideation brings up many questions about both our evaluation suicide risk and our treatment for those at risk. This review will explore several important questions that arise from ketamine treatment studies. First, how do we measure reductions in suicidal ideation that occur over the course of minutes to hours when the very diagnostic criteria for most psychiatric disorders require the presence of symptoms for weeks or longer. Because most psychiatric symptom measures are designed for longer time scales, the accurate and reproducible measurement of rapid changes in mood and suicidal ideation may well require a consideration of the appropriateness of current assessment tools. Second, are the reductions in suicidal ideation seen after acute ketamine treatment solely a result of its rapid anti-depressant effect? While suicidal thinking has often been thought of as the end result of severe mood disruption, other models strongly suggest that factors beyond depression may be critical to the development of suicidal ideation and behavior. Third, is ketamine only effective in reducing suicidal ideation in patients with mood disorders? Suicidal ideation and behavior occur in a broad range of diagnoses and situations. If ketamine has actions on suicidal ideation beyond its impact on depression, then ketamine might help reduce suicidal risk in non-mood disorder contexts. Fourth, could neurobiological functional systems of behavior such as those suggested by the NIMH Research Domain Criteria (RDoC) domains have measurable roles in the actions of ketamine to decrease suicidal ideation? Establishing defined neurobiological mechanisms of action for ketamine might lead us to a greater understanding of the

neurobiology of suicidal processes. Last, do the rapid reductions in depression and suicidal ideation seen after ketamine treatment translate into decreased risk for suicidal behavior? While short-term reductions in suicidal ideation may well prove sufficient to decrease suicidal behavior, this premise has not yet been adequately tested. Full examination of these questions will allow us to use ketamine treatment as a double-edged sword, clinically to help us to provide greatly needed help to acutely suicidal patients and experimentally to explore the nature of suicidal ideation and suicidal risk and their relation to psychiatric illness and neurobiological processes.

Evidence That Ketamine Reduces Suicidal Ideation

Anti-depressant therapies have traditionally taken weeks to months to demonstrate full efficacy [6, 7]. However, this paradigm changed dramatically with the demonstration that the NMDA receptor antagonist ketamine at a sub-anesthetic dose (0.5 mg/kg) produced anti-depressant effects within hours of administration [8]. This finding has since been confirmed by multiple other placebo-controlled studies for treatment-resistant depression and bipolar disorder, including in intranasal formulations of ketamine [9–16]. Ketamine treatment has also been demonstrated to be effective in reducing suicidal ideation in patients without clinically significant suicidal ideation but who were being treated for treatment-resistant depression and bipolar disorder. Recently, several studies have demonstrated reductions in suicidal ideation, including one small, open-label test of ketamine in actual emergency settings [1, 2•, 4, 8, 15, 17–19, 20, 21, 22, 23, 24••] (Table 1). Ketamine's anti-suicidal ideation effects start as early as 40 min after treatment and last up to 5 days. Our preliminary data demonstrates efficacy of low-dose ketamine for treatment of acute suicidal ideation to patients with diverse depressive disorders presenting to an emergency department for care (unpublished data). Ketamine has demonstrated safety and tolerability at these very low sub-therapeutic doses, with the most common side effects of transiently increased blood pressure, pulse, and transient dissociative effects, drowsiness, blurred vision, poor coordination, and dizziness [25••].

Measurement of Rapidly Changing Suicidal Ideation and Risk

Designing studies to assess this rapid efficacy of ketamine to reduce suicidal ideation is complicated by the lack of appropriate tools to accurately capture these rapid changes and to determine their clinical meaning. Current suicide assessment tools are not designed to measure changes in suicidal ideation that occur in the context of minutes to hours [26••]. Ketamine

studies examining reductions in suicidal ideation have used questions from well-validated depression assessment tools such as the Hamilton Depression Rating Scale (HAM-D) [27, 28], the Montgomery-Asberg Depression Rating Scale (MADRS) [2••, 29, 30], and the Beck Depression Inventory (BDI) [31, 32], as well as stand-alone suicide assessment tools such as the Scale for Suicidal Ideation (SSI) or patient-administered version, the Beck Scale for Suicidal Ideation (BSI). These tools are generally hampered for use in studies demonstrating rapid effects because they were designed to assess a patient's state over several days to weeks, and full suicide assessment tools often contain unchanging risk factors for suicide. Full interpretation of the data on ketamine's effect on suicidal ideation and behavior depends on an understanding of the assessment tools used. For example, assessment of suicidal ideation is not the same as assessment of suicide attempts. Several factors are critical to consider in evaluation of the appropriate scales to use for evaluation of ketamine's effects. First, scales must be validated and sensitive to assess changes for a rapid time frame. Second, scales should be quantitative, with changes in scores having both logical consistency and clinical meaning. Third, scales should separate demographic non-changing factors from dynamic treatment amenable suicide-related thoughts and behaviors. Fourth, an ideal scale would delineate and separate different dimensions of suicidal ideation and behavior. The development of rapidly acting anti-depressant and anti-suicide agents necessitates the use of measurements that can validly and sensitively measure clinically meaningful changes in suicidal ideation and behavior over short time scales.

Many studies demonstrating efficacy of ketamine on suicidal ideation use a single suicide question from well-validated depression measures such as the MADRS, HAM-D, or the BDI [1, 2••, 4•, 8, 15, 18, 19, 20, 33, 34•]. However, the MADRS and HAM-D suicide questions have several difficulties when used as the sole outcome measure in suicide research. First, they combine passive suicidal ideation, active suicidal ideation, and plans into one question, making it impossible to study these aspects of suicidal behavior separately. Second, both rating scales are weighted toward passive suicidal thoughts and have anchors that combine aspects of passive and active suicidal thoughts. Third, both scales contain elements of static risk factors such as the presence of suicide plans (MADRS) and a suicide attempt in the past week (HAM-D), neither of which is likely to change acutely after a ketamine treatment. The BDI is much more specific, solely asking about active suicidal ideation, desire, and intent. While this clarifies the issue of conflation of multiple behaviors present for other single questions, the BDI question does not specifically measure passive suicidal ideation or any aspects of suicidal behavior (plans and attempts).

The SSI and its patient self-administration version, the Beck Scale for Suicidal Ideation (BSS or BSI), have been

Table 1 Studies demonstrating an effect of ketamine treatment on suicidal ideation

Author and title	Sample size/design	Diagnosis	Treatment	Scales showing reduction in suicidal ideation	Results
Berman RM et al. 2000 [8]	n = 8/randomized, controlled (saline placebo)	MDD	0.5 mg/kg i.v. ketamine over 40 min	HDRS	Significant decreases in mean score of depressed mood, suicidality, helplessness, and worthlessness on HDRS at 72 hrs post infusion
Price RB et al. 2009 [17]	n = 26/open study	TRD	0.5 mg/kg i.v. ketamine over 40 min Nine patients got infusions three times a week for 12 days	MADRS	Mean scores of suicidal ideation on MADRS and IAT were reduced significantly within 24 hours and for those with repeated doses, MADRS reductions were sustained for 12 days
DiazGranados N et al. 2010 [1]	n = 33/open study	MDD	0.5 mg/kg i.v. ketamine over 40 min	SSI, MADRS, HDRS, BDI	Mean scores on all scales were significantly decreased between 40 min and 4 h
Larkin GL and Beutrais AL 2011 [18]	n = 14/open study	SI patients in ER	0.2 mg/kg i.v. ketamine over 1–2 min	MADRS	Mean scores dropped significantly within 40 min and sustained up to 10 days post-infusion
Thakurta et al. 2012 [23]	n = 27 open label	TRD	0.5 mg/kg i.v. ketamine	SSI, HDRS	Mean scores decreased from 40 up to 230 min
Zarate CA, Jr. et al. 2012 [15]	n = 15/randomized, controlled, crossover	Bipolar 1 or 2 with current depressive episode	0.5 mg/kg i.v. ketamine over 40 min	MADRS, HDRS, BDI	Mean SI scores were statistically different at these time points: MADRS: between 40 min and day 3. HDRS: between 40-80 min and day 2. BDI : between 40 min, day 2 and 10
Rasmussen et al. 2013 [202]	n = 10 open label	TRD	0.5 mg i.v. ketamine given two times a week for up to four doses	SSI, Suicide Status Form (SSF) [203]	Mean SSI and SSF scores were statistically significantly different at 4-weeks endpoint than at baseline
Zigman D and Blier P 2013 [22]	n = 1/case report	TRD	0.5 mg/kg i.v. ketamine over 40 min	Clinical Interview	SI self-rating decreased from 9/10 to 0/10 and the effect lasted 8 days
Harihar C, Dasari P, and Srinivas JS 2013 [19]	n = 2/case report	Depression	0.5 mg/kg ketamine intramuscularly	HDRS	In both cases the score decreased
Diamond et al. 2014 [204]	n = 28 open label	TRD unipolar or bipolar depression patients getting ECT TRD with previous suicide attempts	0.5 mg/kg i.v. ketamine Three or six infusions over 3 weeks	HDRS	61 % pts had decreased HDRS suicide question score which persisted for 21 days in responders
De Gioannis A and De Leo D 2014 [20]	n = 2/case reports	TRD	0.5-mg/kg oral suspension	MADRS	Mean scores of MADRS and MADRS-SI decreased significantly after 24 hrs
Price RB et al. 2014 [34•]	n = 57/double-blind, randomized, controlled midazolam	TRD	0.5 mg/kg i.v. ketamine over 40 min	BSS, MADRS, QIDS-SR, IAT	Composite scores of SI were significantly lowered after 24 hr with ketamine vs midazolam IAT scores had no difference
Murrough JW et al. 2015 [2••]	n = 24/randomized, controlled midazolam	Depression and anxiety spectrum with significant SI	0.5 mg/kg i.v. ketamine over 40 min	BSI and MADRS-SI	BSI score was not different at 24 h, but was significantly lower at 48 h MADRS-SI score was lower in ketamine vs midazolam groups at 24 h
Ballard Elizabeth D et al. 2015 [26••]	n = 60/randomized, crossover, control (saline)	MDD and BD	0.5 mg/kg i.v. ketamine over 40 min	HAM-D, MADRS, BDI items, and SSI	Mean significant difference in MADRS-SI, BDI suicide item and SSI-5 at each time point between ketamine and placebo

prospectively associated with suicidal behavior including death by suicide, albeit with low positive predictive value and sensitivity [35–37]. The SSI and BSS scales change in parallel with changes in depression and hopelessness in clinical trials, addressing suicide risk over weeks' to months' time duration [38–41] as well as in a few studies examining decreased risk over the time frame of hours present in the use of rapidly acting anti-depressants such as ketamine [1, 2••]. Perhaps because of the significant number of static risk factors present in the SSI and BSS, acute BSS scores in the emergency psychiatry setting did not correlate with physician determination of imminent risk in a psychiatric emergency room setting [42]. Some significant issues exist with interpretation of quantitative changes in the BSS and SSI scales, because the structure of the scale changes depending on the patient's responses to the first five questions. If the answers to questions 4 and 5 are zero (these questions assess will to live vs will to die), the remaining 14 questions are not asked. This changes the possible total score of the scale significantly and skews scores much lower for those who do not answer positively to questions 4 or 5. While this might be useful clinically, to help separate out those at higher risk from those at lower risk, this dichotomization of the scales limits the use of these scales for quantitative assessment of changes in suicidal ideation and intent. In our unpublished work, we administered the BSS to 200 consecutive patients in an emergency room referred for psychiatric consultation and found a bimodal distribution of BSS scores, rather than the normal distribution that might be expected for a linear measure of increasing suicidal ideation. This quantitative concern may well be why Ballard et al. found significant differences between the usefulness of the full SSI scale and the first five questions in ability to change rapidly after ketamine treatment and why several ketamine studies did not show differences in the full SSI/BSS score after ketamine treatment [26••, 33].

Work is ongoing by several groups to either use existing depression and suicide assessment tools in different ways or to develop novel suicide assessment tools that can more accurately measure changes in suicidal ideation and behavior in the acute setting [43–45].

Ketamine May Affect Other Risk Factors for Suicidal Ideation and Behavior Besides Depression

While death by suicide is now the tenth leading cause of death in the USA overall, prediction of those most at risk for death by suicide or suicide attempts remains difficult. Because death by suicide is an uncommon and unpredictable event, proxy measures for suicide such as suicidal ideation, suicide attempts, self-harm events, or psychiatric hospitalization are often used as outcomes in suicide research [46–48]. While suicidal

ideation is very common in those with suicidal behavior, most patients with suicidal ideation never make a suicide attempt or die by suicide [49–51]. Indeed, epidemiological studies strongly suggest that suicidal ideation, suicidal attempts, and death by suicide have significantly different predictive risk factors [49, 52]. Similarly, not all “suicide risk factors” affect all aspects of suicidal ideation and behavior equally. For example, impulsivity is consistently associated with suicide attempts but not strongly associated with suicidal ideation [53–59]. Ideally, proxy measures are needed with strong positive predictive value to predict suicide attempts and death by suicide. Prevention of suicidal behavior among at risk individuals, who may or may not report suicidal ideation, may require the consideration of distinct risk factors that combine with suicidal ideation to lead to suicidal behavior. Identification of these precipitating risk factors might aid in identification of factors amenable to treatment therapy or medication.

From a review of the extensive literature on suicide risk factors, we have developed a simple model of progression from suicidal ideation to suicide attempt, where different factors may influence the development of suicidal ideation and subsequent progression to suicide attempt and death by suicide (Fig. 1) [49, 50, 52, 60–65]. Determination of how ketamine affects not just suicidal ideation and depression but factors that are thought to precipitate suicidal ideation will enable a more nuanced understanding of both the appropriate uses of ketamine and the neurobiology of suicidal ideation and behavior. Several studies have strongly suggested that the anti-suicidal ideation effect of ketamine is not due solely to the anti-depressant or anti-anxiety effects of ketamine [22, 24••]. Ketamine has been demonstrated to impact several factors associated with suicidal ideation, including hopelessness and depression, but has less evidence for impact on factors associated primarily with suicide attempt risk. A notable drawback to this epidemiological approach is that most of these factors are demographic risk factors and not amenable to change. Different approaches, namely, looking at different disease and risk factor models, will need to be taken to fully examine the effects of ketamine on suicidal risk.

Ketamine May Have Benefit for Reducing Suicidal Ideation in Disorders Other Than Mood Disorders

Suicide occurs in the context of a staggeringly diverse array of psychiatric diagnoses. In an examination of published studies on suicide deaths, nearly half of decedents had a mood disorder, but individuals with substance use disorders and personality disorders accounted for almost one third of the deaths [66]. Examining risks for suicidal ideation and attempts have shown staggeringly high relative risks for nearly all psychiatric diagnoses—particularly substance use disorders, anxiety disorders, impulse control disorders, and personality disorders

in addition to mood disorder diagnoses [49, 67–71]. While schizophrenia and psychotic states have been associated with increased risk of suicidal ideation and behavior, ketamine has not yet been examined in patients with a primary psychotic disorder due to the risk of increasing their psychosis [72, 73]. Future studies might re-examine the risk/benefit ratio of short-term ketamine treatment in patients with active psychosis. Ketamine has demonstrated efficacy in treatment of several conditions strongly associated with suicidal behavior, including substance use disorders, chronic pain conditions, anxiety disorders, and post-traumatic stress disorder and chronic medical illness.

Substance Use Disorders

Alcohol and substance use disorders carry extraordinarily high rates of suicidal ideation and behavior [55, 74].

Ketamine has been proposed as a treatment for drug and alcohol addictions, due in part to a significant role for the glutamatergic system in addiction [75–78]. Ketamine may reduce the need for opioids in opioid-dependent animals and individuals, but the impact of this effect on long-term opioid use is not clear [79–83]. Suggestions of the usefulness of ketamine for treatment of suicidal ideation in individuals with alcohol and other substance use disorders are suggested by several studies. First, family history of alcohol dependence predicted increased anti-depressant response to ketamine [84, 85]. Second, a small double-blinded study of patients with cocaine dependence demonstrated that a single sub-anesthetic dose of ketamine increased motivation to quit and reduced cue-induced craving for cocaine [86]. Ketamine has been used as a substance of abuse, and any increased risk for abuse in suicidal individuals with a history of substance use disorders is not yet known [87–91].

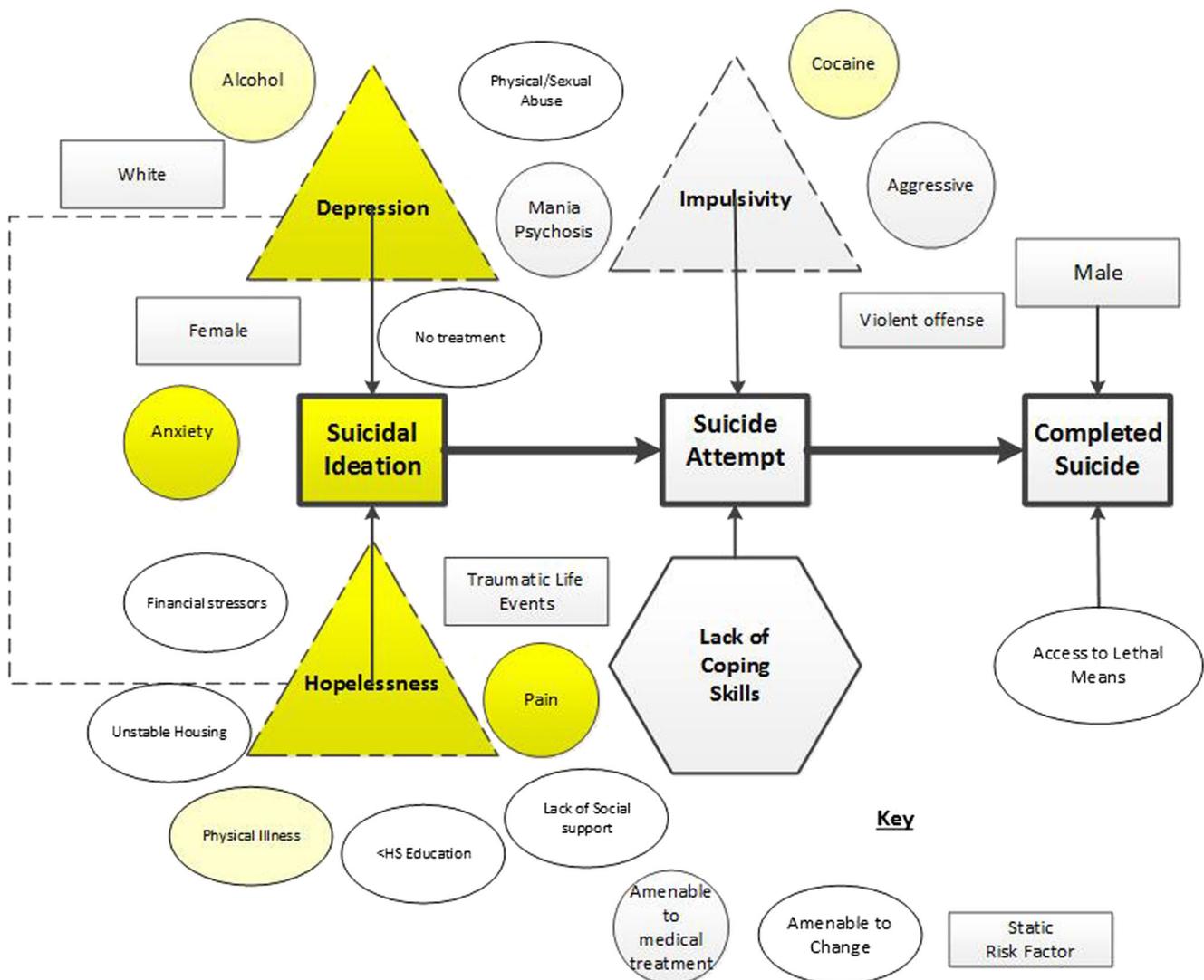


Fig. 1 Ketamine has demonstrated efficacy on multiple risk factors for suicidal ideation and behavior (shown in yellow). Ref: [49, 55, 68–70, 92–100, 102, 103, 127, 139–141, 143–146, 159, 160, 162]

Pain Disorders

Pain disorders are highly correlated with suicidal ideation and behavior [92–104]. Ketamine is an established, well-tolerated treatment for many chronic pain disorders (recently reviewed by Tawfic 2013) [105]. Ketamine treatment in individuals with pain conditions and depression might well prove a potent treatment to both treat symptoms and reduce suicide risk in these extraordinarily high-risk patients who often have ready access to suicidal means via opioid prescriptions.

Anxiety Disorders/Post-Traumatic Stress Disorder

All anxiety disorders and post-traumatic stress disorder (PTSD) have increased risks for suicidal ideation and behavior [106–110]. Ketamine has been demonstrated to reduce anxiety symptoms in patients and to work well in patients with anxious mood disorders [111, 112]. Ketamine has demonstrated to reduce PTSD symptom severity in randomized trials of patients with chronic PTSD disorder and in animal models of PTSD but might worsen acute stress disorder symptoms in patients immediately after a trauma [113–116]. Some studies have demonstrated rapid resolution of obsessive thoughts in patients with obsessive compulsive disorder (OCD) treated by ketamine, but other studies have not shown significant impact on OCD symptoms, especially compared to depressive symptom improvement [117–119]. However, there are case reports of increased anxiety and suicidal ideation in patients with OCD getting ketamine treatments [120]. Finally, one study on ketamine treatment of suicidal ideation demonstrated significant but not complete mediation of the anti-suicidal ideation effect of ketamine via reduction in anxiety [24••].

Chronic Medical Illness

Chronic medical illness is a significant risk factor for suicidal behavior [121, 122]. Ketamine treatments have been demonstrated to be safe in small open-label studies of critically ill patients and again in hospice patients to reduce depression and agitation while preventing respiratory depression [123, 124]. Finding rapidly acting treatments for depression and suicidal ideation for patients with significant medical illnesses would be a tremendous tool, especially in the acute hospital setting.

Ketamine May Cause Measurable Changes in Functional Systems of Behavior (RDoC Domains) Related to Suicide Risk

A novel way to conceptualize risk factors for suicidal ideation and behavior is to examine them within the framework of the neurobiological system-based research domains in the NIMH RDoC research strategy [125] (Table 2). RDoC criteria are

divided into domains, negative valence domains which are defined as “systems primarily responsible for responses to aversive situations or context” and positive valence domains where are defined as “systems primarily responsible for responses to positive motivational situations or contexts,” cognitive systems, systems for social processes, and arousal/regulatory systems. Items in all of these domains have been associated with risk for suicidal ideation and behavior (Fig. 2). The negative valence domains contain many neurobiological systems frequently associated with depression and commonly correlated with suicidal ideation and behavior. Negative valence domains commonly associated with suicidal ideation and behavior that also have been demonstrated or suggested to be altered by ketamine treatment include anhedonia, anxiety, hopelessness, rumination, hostility, and aggression. Determination of ketamine’s effect on these negative valence domains can be inferred by examination of ketamine’s effect on well-validated clinical assessment and research tools used to assess these negative valence domains. For example, acute threat or fear can be assessed by tools to assess anxiety such as the Beck Anxiety Inventory (BAI) or Hamilton Anxiety Rating Scale (HAM-A) [126]. Sustained threat and loss can be assessed by the Snaith-Hamilton Pleasure Scale (SHAPS), a validated scale to assess anhedonia [127]. Examination of these neurobiological domains is a novel perspective that may give additional insights into both ketamine’s unique actions and the neurobiological underpinnings of suicidal ideation and behavior.

Anhedonia

Anhedonia is a cardinal feature of depression and has demonstrated strong associations with suicidal ideation and death by suicide [128–131]. However, traditional anti-depressants may not adequately treat anhedonia and might make some forms of positive reward processing worse [132, 133]. Recently, mouse and some human trials strongly suggest that ketamine decreases anhedonia, in both treatment-resistant depression and in bipolar depression, and that these anti-anhedonic effects, measured by a specific anhedonia scale such as the SHAPS, may be independent of the more general anti-depressant effects [1, 134–137].

Anxiety

See section above on anxiety.

Hopelessness

Hopelessness has been independently and repeatedly associated with increased risk for suicidal ideation, suicide attempts, and death by suicide, both prospectively and retrospectively [1, 128, 138–147]. Ketamine has been shown to decrease

Table 2 Negative valence RDoC domains with potential roles in suicidal ideation and behavior

	Symptom	Scales that can measure this domain in humans	Evidence correlating with suicidal ideation or behavior	Evidence this parameter is impacted by ketamine
Negative valence				
Acute threat “fear”	Anxiety	Beck Anxiety Inventory (BAI) [125] Hamilton Anxiety Rating Scale (HAMA) [206]	[70]	[24••]
Sustained threat	Anhedonia	Snaith-Hamilton Pleasure Scale (SHAP) [126]	[127–130]	[1, 133–136]
Loss	Anhedonia	SHAP	[127–130]	[1, 133–136]
	Hopelessness	Beck Hopelessness Scale	[41, 47, 57, 127, 139, 145, 146, 207–216]	
	Rumination	Rumination Scale		
	Guilt			
Frustrative non-reward	Hostility	Buss-Durkee	[155–163]	
	Aggression	Buss-Perry	[155–163]	

hopelessness in patients with treatment-resistant MDD [1, 148]. Our preliminary data (unpublished communication) suggests that ketamine decreases anxiety and hopelessness in parallel with and for longer duration than reductions in suicidal ideation.

Rumination

Rumination has been associated with both suicidal ideation and attempts [149–153]. A role for ketamine in reduction of rumination is suggested by a recent functional MRI (fMRI) study in healthy subjects, demonstrating that ketamine decreased resting state functional connectivity between functional nodes of the default mode network (DMN) [154]. In patients with major depression, a failure to normally down-regulate activity in the DMN is associated with higher levels of maladaptive, depressive rumination and lower levels of adaptive, reflective rumination [155]. Therefore, ketamine might reduce depression and suicide risk by impact on rumination via improved down-regulation of the DMN.

Hostility and Aggression

Multiple studies have demonstrated a link between hostility and aggression with impulsivity in promotion of risk for suicide attempts and death by suicide [156–164]. Ketamine has reported efficacy as a tranquilizer at high doses in a limited number of case reports and to reduce aggression in animal models, but no studies have systematically examined low-dose ketamine’s effect on hostility and aggression in association with depression or suicidal ideation [165–168].

Providing a connection between these negative valence domains and reduction of suicidal ideation in patients treated with ketamine will provide valuable insights into the neurobiological pathways responsible for ketamine’s efficacy and for the creation of suicidal ideation itself.

Work in the impact of ketamine on positive valence, social processes, cognition, and alertness domains remains exploratory but intriguing. Positive valence with associations with suicidal ideation and behavior that show promise to be altered by ketamine treatment include positive response to reward, ability to delay for a future positive reward (whose converse is impulsivity), willingness to work (or drive), expectancy/craving, and reward responsiveness [168–171]. Impaired reward processing including intolerance for delayed reward and abnormal processing of both positive and negative rewards have been strongly associated with suicidal behavior and verified by functional imaging [172–175]. A role for ketamine in affecting these reward processing domains is only suggested by a few animal behavioral and normal human subject fMRI studies [176–178]. Cognitive domains such as attention, performance monitoring, goal selection, and working memory have associations with suicidal ideation and behavior but have not yet been explored in any systematic approaches with ketamine treatment [179–181]. While acute ketamine treatment results in clear-cut alterations in memory that resolve within minutes to hours of treatment, the longer-term cognitive effects of low-dose ketamine treatment are less clear [14, 25••, 182–184]. In one study, a series of six ketamine treatments over 12 days in patients with treatment-resistant depression demonstrated significant improvements in their visual memory, simple working memory, and complex working memory; however, none of these changes were significant when the improvement in depression was taken into account [185]. However, a larger, placebo-controlled study showed no differential effect on neurocognitive function at 7 days after ketamine infusion compared to midazolam control [186]. The impact of ketamine treatment on cognitive domains is also suggested by data on the Implicit Association Test (IAT), a performance-based cognitive measure of implicit suicidal thoughts, demonstrated to predict suicide attempts in the 6 months after a psychiatric crisis of suicidal ideation

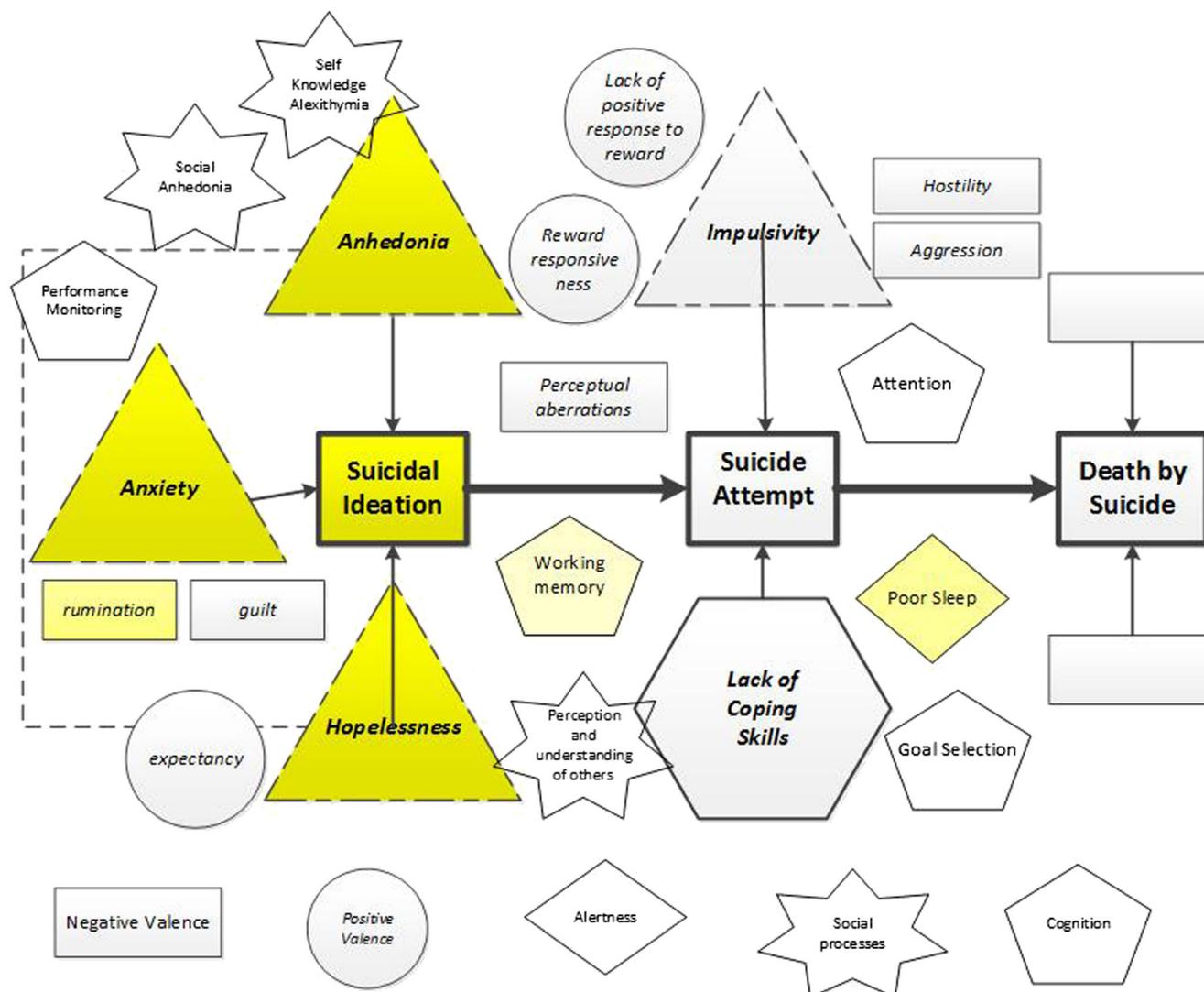


Fig. 2 Ketamine has demonstrated effects on multiple RDoC domains associated with suicidal ideation and behavior (shown in yellow). Ref: [49, 55, 67, 106–109, 121, 127–131, 137–139, 143–147, 149–152, 159, 160, 172, 173, 179, 180, 191, 193, 196, 68–70]

[187–190]. Ketamine treatment in patients with treatment-resistant depression resulted in rapid and significant responses in the suicidal version of the IAT, correlating to the rapid decrease in subjective suicidal ideation although not universally statistically significant [17, 21]. Social processes such as self-knowledge, perception, and understanding of others and social anhedonia are fruitful areas of future work in the treatment of suicidal ideation and behavior. Alertness domains such as sleep quality, sleep amount, and nightmares have shown dramatic abilities to predict future suicidal behavior. Poor sleep quality, insomnia, and especially nightmares have been strongly and prospectively associated with suicidal behavior, even predicting suicide attempts over a span of 20 years in a large Norwegian sample [191–197]. Recent pre-clinical and human studies indicate a beneficial effect of single-ketamine infusions on sleep, with increased brain-derived neurotrophic factor (BDNF) and increased slow wave

activity sleep [198–200]. These findings of the effects of ketamine on sleep raise intriguing concepts about both the mechanism of action of ketamine and its possible effect on suicidal behavior over longer time periods after acute treatment.

Conclusion: Future Work Will Need to Determine if Acute Ketamine Treatments Will Result in Decreased Risk for Suicidal Behavior

The data for the effectiveness of ketamine for long-term prevention of suicidal behavior is not yet available. In the meantime, the arguments for the use of short-term ketamine treatment as an adjunctive agent to specifically treat acute suicidal ideation are compelling. While we do not truly know who among those with suicidal ideation is at imminent risk of

suicide, the consequences of not treating the person at risk are grave and very time critical. While suicide is the main source of fatality for psychiatric illness, currently available psychiatric treatments take too long to take effect to address the immediacy of the crisis of acute suicidal ideation [6]. Even psychiatric hospitalization stays are typically shorter than the time for psychiatric medications to take full efficacy. While many acutely suicidal patients will be hospitalized, these stays are typically of short duration and may not be associated with significant reduction in depression or suicidal potential. In fact, the period of highest risk for suicide is the first 2 weeks post-discharge from hospital, representing about a third of all post-discharge suicides [201, 202].

Consider the analogy that an individual with untreated psychiatric illness and suicidal ideation is like a car that has stopped running. Acute adjunctive ketamine treatment would be analogous to jump-starting the car to enable it to be driven to the garage to get the needed full repairs (analogous to treating the underlying psychiatric disorder). Just as the car does not need jump-started every day, the patient may not need more than a single treatment of ketamine to reduce acute risk for suicide and to engage in treatment. Similarly, the jump-start (and the ketamine) may not be the ultimate treatment but enables the provision of needed treatment. Treating acute suicidal ideation has myriad implications for patient care. Someone who is acutely suicidal has days of psychological agony (psychache) that could be avoided [8]. Someone who is acutely suicidal cannot fully engage in treatment. Someone who is acutely suicidal may die by suicide before their treatment for their underlying disorder has a chance to take effect. Adjunctive treatment acutely with ketamine may allow clinicians to bridge patients more safely during the tenuous early days of initiation of treatment for the underlying psychiatric condition and allow for more effective engagement of patients in their care during this time. Further, the use of ketamine treatment can be seen as a double-edged sword, clinically to help us to provide greatly needed help to acutely suicidal patients and experimentally to explore the nature of suicidal ideation and suicidal risk and their relation to psychiatric illness and neurobiological processes.

Compliance with Ethical Standards

Conflict of Interest Faryal Mallick declares no conflict of interest.

Cheryl B. McCullumsmith served as a consultant and on the advisory board for Janssen for the development of a clinical trial for use of esketamine for the treatment of treatment-resistant depression and acute suicidal ideation.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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