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Suicide (MS Goodman, Section Editor)

"Does Ketamine Have Rapid Anti-Suicidal Ideation Effects?"

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Introduction

Suicide is defined as an act of violence toward oneself with the intention to die. Suicide completion is a prominent cause of worldwide mortality, and its prevention poses a major challenge to the psychiatric and world health communities. The Centers for Disease Control and Prevention (CDC) reported that as of 2013, suicide was the tenth major cause of death—totaling 41,149 deaths in the USA (CDC) [1]. Despite a growing armamentarium of psychiatric medications to treat mood disorders, effective pharmacologic interventions for suicidality continue to elude us. Statistics demonstrate no meaningful decrease in the rate of suicide [2, 3]. In fact, within the USA, there has been an alarming 28.4 % increase in the age-adjusted suicide rates (from 13.7 to 17.6 per 100,000) for adults aged 35–64 years between 1999 and 2010 (CDC [4]), as well as a 2.4 % increase in the age-adjusted death rate due to suicide in 2012 compared to 2011 [5].

Suicide is a multifactorial phenomenon, and our current nosology addresses it within symptom components of other psychiatric conditions exclusively. Almost 90 % of suicide cases are associated with some form of psychiatric illness, chiefly major depressive disorder (MDD), psychotic disorders, or borderline personality disorder [2]. The new DSM-5 Task Force and work groups recognized an emerging need for the investigation of suicidality as an independent phenomenon. To stimulate thinking along these lines, a new category "suicidal behavior disorder" was added to the manual under

"Conditions for Further Study" [6]. Recent guidelines from the National Alliance for Suicide Prevention Research Task Force outline priority questions to guide current and future research on suicide. Paramount among this research agenda is defining the etiology of suicide with the aim of increasing detection and accurately predicting suicide risk to provide effective preventive services and interventions.

In this review, we will describe current treatment approaches to suicidality and summarize the existing literature on ketamine as a potential treatment candidate. We will consider clinical trial data concerning the rapid anti-depressant effects of ketamine in mood disorders, as well as the strength of evidence for ketamine's anti-suicidal effect beyond its anti-depressant actions. The neurobiology of suicide, including the role of glutamate, will be discussed.

Current approaches to the treatment of suicidality

In current practice, suicide prevention involves enhanced environmental safety as well as adequate treatment of any underlying psychiatric conditions and associated symptoms. Large prospective studies have suggested that depression is a major risk factor for suicide [7]. Despite the decrease in suicidal ideation (SI) with anti-depressant treatment, a meaningful effect on suicidal behavior has been more difficult to demonstrate [8]. Studies have shown a negative correlation between higher anti-depressant prescription rates and suicide completions. Yet, well-powered randomized controlled studies and meta-analyses have not detected an effect of anti-depressant treatment on suicide completion due in part to the low baseline prevalence of suicidal behavior [9].

Meta-analyses of clinical trials comparing lithium (Li) with placebo or active treatments provide evidence supporting the protective effect of Li on suicidal behavior in patients with MDD, bipolar disorder, and schizoaffective disorder. Compared to placebo, treatment with Li was associated with lower number of suicide attempts (odds ratio (OR) 0.13 with 95 % confidence interval (CI) of 0.03–0.66) and death from any cause (OR 0.38, 95 % CI 0.15–0.95) [10]. Some studies conducted in patient populations across the spectrum of affective disorders show fewer suicides even in patients with inadequate mood benefit [11–13]. The underlying mechanism of the observed anti-suicidal effect is largely unknown. Lithium's effect on aggression and impulsivity could be one factor related to the anti-suicidal effect [13]. In clinical practice, lithium's narrow therapeutic window and risk of overdose must be taken into account when prescribed to patients with elevated suicide risk. Retrospective studies have also shown that intentional overdoses are common earlier in the course of treatment and gradually decrease with an extended course of treatment [14].

Clozapine, the oldest second-generation anti-psychotic, is the only medication to demonstrate superiority in lowering suicide rates among high-risk patients with schizophrenia and schizoaffective disorder compared to the other anti-psychotic agents. Based on a large 2-year multicenter randomized controlled trial comparing clozapine to olanzapine, there were fewer suicide attempts among clozapine patients (hazard ratio 0.76, 95 % CI 0.58–0.97, p=0.03) [15]. Despite its potentially life-

threatening side effects, including agranulocytosis and myocarditis, epidemiologic studies have shown significant mortality reduction in clozapine patients. Yet, the required close monitoring has largely limited the utilization of this medication as a management strategy for suicide risk [16].

Electroconvulsive therapy (ECT) is currently the most rapid and efficacious treatment available for MDD [17], as well as a standard treatment for patients at risk for self-harm [18]. A multicenter study of the effect of ECT on depression and SI in unipolar depression showed a 61 % remission rate for SI after six ECT sessions [19]. Practical issues limiting ECT utilization exist, mainly its limited availability and the consent and medical clearance processes. Post-ECT treatment patients should be closely monitored for relapse of suicidal thinking, and ECT maintenance should be considered for high-risk patients [20].

The public health burden of suicide mandates the development of novel, efficacious, and reliable treatment strategies. Recent growing interest in the antidepressant effects of glutamatergic drugs has yielded lines of inquiry regarding their potential as anti-suicidal interventions.

Current evidence for anti-suicidal effects of ketamine

The discovery of the anti-depressant effect of ketamine, a well-known anesthetic, has sparked new momentum in the area of drug development for mood disorders and for suicidality. Ketamine is a high-affinity non-competitive antagonist at the glutamate N-methyl-D-aspartate (NMDA) receptor. The antidepressant effect of ketamine was first studied in clinical trials in unipolar depression [21, 22•, 23, 24] and later extended to bipolar depression [25, 26]. Rapid anti-depressant response and high response rate in patients with treatment-resistant depression (TRD) have suggested ketamine as a promising anti-depressant. Most recently, new research has provided preliminary evidence for the beneficial effect of ketamine on SI. Below is a summary of the available literature on the ketamine and suicidality. The data are largely from post hoc analyses of clinical trials of ketamine in patients with mood disorders. However, there has been one open-label prospective study and one randomized controlled trial (RCT) of ketamine for the treatment of SI. These studies are also summarized.

Berman et al. [21] conducted the first randomized, placebo-controlled, double-blind crossover study of intravenous (IV) ketamine (0.5 mg/kg) in seven medication-free MDD subjects who received two randomized infusions of ketamine or saline 1 week apart. The results showed a significant and rapid decrease in depression scores after ketamine compared to saline. On average, the ketamine group showed a 25-point decrease in the Hamilton Depression Rating Scale (HDRS) [27] scores (standard deviation (SD)=14) versus 0 point (SD=12) in the saline groups. When the individual items of HDRS were compared pre-infusion and post-infusion, decreased suicidality (p=0.02) was noted along with other reduced symptoms of depression [21]. The rapid anti-depressant effects of ketamine were subsequently replicated in a small study in patients with TRD using a similar crossover design [24].

The first report to specifically describe the effects of ketamine on SI included TRD patients from two separate small clinical trials designed to assess the anti-

depressant effects of ketamine [28]. One group of 26 patients with TRD received a single IV infusion of ketamine (0.5 mg/kg). While 65 % of the subjects showed at least 50 % decrease in their depressive symptoms as measured by the Montgomery-Asperg Depression Rating Scale (MADRS) [29, 23], post hoc analysis of suicidal ideation measured by the suicide item of the MADRS (MADRS-SI) showed 2.08 point decrease at 24-h post-infusion ($p<0.001$, Cohen's $d=1.37$, SI item range 0–6) [28]. Ten responders from the single-infusion trial continued to receive total of six infusions three times weekly as part of a separate repeated ketamine infusion study [30]. Nine out of the 10 participants continued to endorse reduction in SI during the 2-week ketamine treatment period ($p<0.001$, Cohen's $d=2.42$) [28].

A separate study reported the effect of single open-label ketamine infusion on 33 TRD-MDD patients [31]. As early as 40-min post-ketamine infusion (0.5 mg/kg), there was a significant decrease in SI consistently reported across different measures, including the Beck Scale for Suicidal Ideation (SSI) [32] ($F_{4,97}=7.03$, $p<0.001$), MADRS ($F_{4,110}=27.68$, $p<0.001$), HDRS ($F_{4,106}=17.25$, $p<0.001$), and the Beck Depression Inventory (BDI) [33] ($F_{4,103}$, $F=5.82$, $p<0.001$). While the effect size was very large at 40 min (Cohen's $d=1.05$, 95 % CI 0.65–1.45), it decreased to moderate at 230 min (Cohen's $d=0.45$, 95 % CI 0.12–0.77). Despite the open-label study design and the small number of the study subjects, the large effect size of the results in patients with refractory depression was encouraging [31]. Another group reported the results of a single open-label pilot study of ketamine (0.5 mg/kg) conducted in 27 medication-free patients with MDD. The results of this study also showed a rapid and significant decrease in suicidal thinking measured by the SSI [32] ($p<0.001$) and HDRS-SI (suicide subscale; $p<0.001$) after ketamine infusion. For both measures, the effect was significant from 40- to 230-min post-infusion, with maximum effect at 40 min and no significant effect past the first day [34].

A recent study reported the effects of ketamine on SI in a larger group of patients with TRD. This study enrolled 72 participants in a two-site, parallel arm RCT of single-dose ketamine compared to active placebo, midazolam [35]. In the parent clinical trial, the investigators found that ketamine treatment, compared to the control, was associated with lower depression scores (7.95 point mean difference, 95 % CI 3.20–12.71) as measured by MADRS. Anti-depressant response rates were 64 and 28 % in the ketamine and midazolam groups, respectively [22•]. The secondary analysis of the SI in this cohort of patients showed that 24-h post-infusion, subjects treated with ketamine reported greater reduction in SI compared to the control group ($F_{1,54}=8.8$, $p=0.01$, Cohen's $d=0.82$). The authors used a composite score for SI combining three suicide measures (BSS [36], MADRS-SI, and QIDS [37] suicidality item (QIDS-SI)). Fifty-three percent of patients receiving ketamine compared to 24 % of those receiving midazolam scored zero on the composite suicide score [35].

The effect of repeated ketamine infusion on suicidality was further explored in two additional open-label studies. Rasmussen et al. studied the effect of a twice weekly slow infusion of add-on open-label ketamine (0.5 mg/kg over 100 min) in 10 depressed patients (MDD or bipolar II) [38]. The number of treatments was response-dependent; the study

continued until either symptom remission occured or after four infusions. Results showed that five of the 10 subjects achieved remission from depressive symptoms with an average MADRS score change from 33.3 (SD=6.5) at baseline to 16.7 (SD=13.2, p=0.0009). A reduction in suicidality paralleled improvement of the depressive symptoms, as measured both by the SSI [32] (t=3.04, p=0.007) and Suicide Status Form (SSF) [39] (t=2.25, p=0.026) [38].

Diamond et al. (2014) conducted another add-on repeated open-label study in a larger cohort in the United Kingdom with particular emphasis on memory function. Twenty-eight subjects with treatment-resistant MDD or bipolar depression were enrolled and received 0.5 mg/kg ketamine over 40 min during each treatment. Fifteen subjects received three infusions, and 13 subjects received six infusions over course of 3 weeks. Although the study showed a low initial response rate after the first treatment (11 %), 29 % of subjects eventually met the criteria for response at day 21. When measured by the suicide item of the HDRS, all subjects reported decreased SI. While responders continued to report improved SI up to day 21 (mean reduction 2.13 (SD=0.64)), this effect was not significant in the non-responder group. The effect of ketamine treatment on memory was assessed, and no memory impairments were detected in subjects after six treatments [40].

The effect of ketamine on treatment of depression and SI was also investigated in bipolar depression. Zarate et al. conducted a double-blind crossover study of IV ketamine (0.5 mg/kg) compared to placebo in 15 subjects diagnosed with bipolar I or II, currently depressed, who were on an adequate dose of mood stabilizer (i.e., Li or valproic acid). Similar to the unipolar depression trials, ketamine treatment was associated with a rapid (within 40 min) decrease in symptoms and SI (Cohen's d=0.89; 95 % CI=0.61–1.16 and 0.98, 95 % CI=0.64–1.33, respectively). On follow-up, the decreased suicidality remained significant for 3 days as measured by the MADRS-SI, 2 days as measured by the HDRS, and from 40 min to day 2 and at day 10 as measured by the BDI [25].

A recent post hoc analysis included pooled data from 133 patients with unipolar and bipolar depression from four studies of ketamine conducted at a single center. In this analysis, both double-blind and open-label studies were included in assessing the relationship between SI, depression, and anxiety symptoms. Results showed that at 230-min post-infusion, improvement of the depressive and anxiety symptoms only accounted for 19 % of the variance of SI change. These results suggest that ketamine exerts some direct benefits on suicidality, since the effect remained significant when controlling for depression and anxiety [41].

In contrast to the prior post hoc analysis studies, Larkin et al. reported on a prospective open-label ketamine study on 14 MDD patients who presented to the emergency room with SI. Ketamine was administered as a single bolus infusion at a lower dose compared to the prior studies (0.2 mg/kg), given over a period of 1 to 2 min. Subjects were monitored for 4 h after the infusion and subsequently discharged with daily telephone follow-up for 10 days. The study showed that at 240-min post-infusion, the mean MADRS scored dropped significantly from 40.4 (standard error of mean (SEM)=1.8) at baseline to 11.5 (SEM=2.2,

$p<0.001$). This improvement in SI persisted for 7 days in all subjects and in 13 subjects followed up on day 10 [42].

Our group recently completed a prospective RCT comparing a single IV dose of ketamine to midazolam (functioning as an "active placebo") on SI as the primary outcome [43•]. Suicidality was measured by the Beck Scale for Suicidal Ideation (BSI, primary) [36] and by the MADRS-SI (secondary). Patients (n=24) were inpatient or outpatient and had a range of primary psychiatric diagnoses, including MDD, bipolar disorder, PTSD, and borderline personality disorder. This study specifically aimed to recruit patients with high levels of SI who are otherwise often excluded from the clinical trials in mood disorders. After a single infusion of ketamine or midazolam in addition to standard of care treatment, SI was measured at 24-h time point as well as at 48 and 72 h and 1 week after the infusions. Given the high risk of suicidality among these patients, the study implemented several safety measures including safety planning, reiteration of emergency contacts, and weekly phone follow-ups. The results showed that the treatment was well tolerated in this high-risk population. Although the primary outcome of the study (i.e., decrease in the 24-h post-infusion BSI) was not met, the results were promising for a number of secondary measures: there was a significant decrease in suicidality in the ketamine compared to the midazolam group measured by BSI at 48 h (BSI 8.8 (SD=8.3) and 15.3 (SD=10.9), respectively; $F_{1,21}$=4.45, p=0.047, Cohen's d=0.67) and by clinician-administered MADRS-SI at 24 h (MADRS-SI 1.8 (SD=1.9) and 3.3 (SD=1.6), respectively; $F_{1,21}$=4.3, p=0.05, Cohen's d=0.86). The treatment effect of ketamine was short-acting, and there was no significant difference in suicide measures at day 7. Despite the encouraging findings of the study, the results will need to be replicated and expanded in larger well-powered studies [43•].

In line with the objectives of the National Alliance for Suicide Prevention Research Task Force and as efforts to obtain a more objective and indirect measure of suicidality in ketamine trials, Price and colleagues utilized the Implicit Association Test (IAT) in two of the ketamine treatment trials [35]. The IAT is a computerized task measuring automatic associations of two concepts (e.g., "escape" vs. "stay") with an attribute (e.g., "me") [44]. The test was found to be reliable and predictive of future behavior [45]. In one open-label study summarized above [28], the authors measured the associations between "escape-me" before and after the infusion in subset of 12 patients. "Escape-me" was correlated with explicit SI (MADRS-SI) at baseline, and this association was decreased 24 h after treatment (p=0.006, Cohen's d=1.37), correlating with reduction MADRS-SI score at the trend level (r=0.57, p=0.09). This reactivity to the treatment highlighted the possible benefits of IAT as a tool to detect clinical response. When the IAT was utilized in a RCT of ketamine and midazolam [22•], "escape-me" again correlated with the explicit suicidal measure at baseline. There was a reduction in self- and escape-related word associations 24 h after ketamine (p=0.01, d=0.58) but not after midazolam [35].

In addition to the above open-label study and RCTs, there are several case reports of ketamine decreasing suicidality [46–48]. Haribar et al. (2013) reported a significant decrease in SI in two patients after

intramuscular (IM) injection of ketamine (0.5 mg/kg) [46]. A separate report described two cases of TRD with SI who achieved improvement in depression and remission of SI after receiving an oral liquid suspension of ketamine [47].

Potential mechanism underlying the observed effect of ketamine on suicide

The specific pathophysiology of suicide remains largely unknown. There are data suggesting that the vulnerability to or diathesis toward suicide may be, at least partly, independent of co-occurring psychiatric conditions. In particular, suggested mechanisms include dysregulation of the hypothalamic-pituitary-adrenal axis (HPA) and serotonin system [49•]. The evidence suggesting specific anti-suicidal effects of ketamine independent of its anti-depressive effect [41] is consistent with the growing body of research implicating the glutamate system in the neurobiology of suicide [49•].

Evidence suggesting a role of glutamate in suicide comes in part from post-mortem gene expression studies of suicide victims compared to controls. These studies are limited by small sample size and medication exposure in the victims, as well as absence of matched psychiatric controls [50]. These studies have reported alteration in glutamate pathway components including downregulation of metabotropic glutamatergic-3 (GRM3) and ionotropic AMPA-3 (GRIA3) receptors, as well as decreased glutamine recycling as evidenced by decreased expression of glutamate-ammonia ligase (GLUL) (also known as glutamine synthetase) genes in suicide completers [51, 52]. A recent post-mortem study comparing three groups of subjects (MDD suicide, MDD non-suicide, and subjects with no prior psychiatric disorders) showed a higher expression level of glutamate receptor (GluR) genes in the frontal cortex of MDD patients. Compared to the non-MDD non-suicide subjects, suicide completers expressed higher levels of the NR2B components of the NMDAR (GRIN2B) [53].

There are emerging data linking suicide vulnerability to alterations in neurotrophic signaling pathways and inflammatory processes, both of which are influenced by the glutamatergic pathway and impacted by ketamine [54, 55]. Post-mortem immune-histochemistry studies have reported increased microglia density, a potential indicator of CNS pro-inflammatory responses, in the dorso-lateral prefrontal cortex (DLPFC) in suicide victims [56]. Serum and cerebrospinal fluid (CSF) measurements in suicide attempters show higher cytokine interleukin 6 (IL-6) levels compared to non-attempters [57]. Inflammation may relate to deficiency of serotonin via consumption of tryptophan, the serotonin precursor [58]. One hypothesis is that inflammatory stimuli lead to consumption of tryptophan through the induction of the kynurenine pathway with an attendent increase the relevant metabolites. These metabolites include quinolinic acid (QUIN) and kynurenic acid (KYNA) and act as agonist and antagonist at the NMDA receptor, respectively [59].

Recently, increased levels of QUIN were shown in the blood [60] and CSF of patients with suicidal ideation [59]. Ketamine's anti-suicidal effect may be partly mediated by an indirect anti-inflammation process through modulating the NMDA receptor and the KYNA pathway.

Conclusions and future directions

The effects of ketamine and related glutamatergic agents on depression and suicidality continue to be a vigorous line of research inquiry. As per a US clinical trial registry (clinicaltrial.gov), there are currently nine studies investigating the therapeutic effect of ketamine on suicidal ideation. Literature has demonstrated that ketamine treatment is well-tolerated and provides rapid relief from SI in parallel to anti-depressant effects. Some caution is warranted, however, when considering a wider clinical use of ketamine for suicidality in light of the current evidence base. Ketamine carries some risk for abuse, and NMDA receptor antagonists may be associated with toxicity at high doses or following long exposure durations. Additional larger, well-powered, prospective studies are needed to confirm the efficacy and safety of ketamine for the treatment of suicidality and depression. Most studies of ketamine in mood disorder populations have involved a very short duration of ketamine exposure. It is essential to study longer-term outcomes of treatment on suicidal ideation, suicide attempts, and overall clinical response. It is important to note that studies to date have not rigorously investigated the effects of ketamine on suicidal behavior. Studies have focused exclusively on SI as a proxy for suicide risk reduction, and it will be important for future studies to examine the effects of ketamine on suicidal behavior and attempts specifically. Efficacy and safety of repeated ketamine infusions or ketamine combination treatments should be explored as a possible maintenance strategy for suicidality. One study of ketamine for SI [43•] included diagnoses beyond depression, but larger studies are required to establish an anti-suicidal effect of ketamine beyond its anti-depressant effects. Aside from ketamine's clinical application as a potential treatment agent, its observed anti-suicidal effect opens a new avenue for further study of the pathophysiology of suicide and for the identification of novel, urgently needed targets for drug development.

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Compliance with ethical standards

Conflict of interest

In the past 3 years, Dr. Murrough has served on advisory boards for Janssen Research and Development and Genentech; has provided consultation services for ProPhase, LLC, and Impel Neuropharma; and has received research support from Janssen and Avanir Pharmaceuticals; he is named on a patent pending for neuropeptide Y as a treatment for mood and anxiety disorders, on a patent pending for the combination of ketamine and lithium to maintain the anti-depressant response to ketamine, and on a patent pending for the combination of ketamine and lithium for the treatment of suicidal ideation. Dr. Dennis Charney (Dean of Icahn School of Medicine at Mount Sinai) and Icahn School of Medicine at Mount Sinai have been named on a use patent on ketamine for the treatment of depression. The Icahn School of Medicine has entered into a licensing agreement for the use of ketamine as therapy for treatment-resistant depression. Dr. Charney and Icahn School of Medicine at Mount Sinai could potentially benefit if ketamine was to gain approval for the treatment of depression. All other authors declare no interests.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by the authors.

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