



Ketamine for Depression, 6: Effects on Suicidal Ideation and Possible Use as Crisis Intervention in Patients at Suicide Risk

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

A growing body of literature suggests that ketamine, administered in subanesthetic doses, has early-onset antidepressant action in patients with severe and even treatment-refractory depression. Many case reports, open-label studies, and randomized controlled trials (RCTs) suggest that ketamine may have dramatic antisuicidal effects, as well. This article examines the benefits of ketamine in patients with suicidal ideation with particular focus on the findings of recent RCTs and meta-analyses. Important findings are that a single dose of ketamine is associated with antisuicidal benefits that emerge within an hour of administration and persist for up to a week. The benefits are seen in patients with mild as well as clinically significant suicidal ideation. The benefits are observed in midazolam- as well as saline-controlled trials. Effect sizes are medium to large. The improvement in suicidal ideation is only partly explained by improvement in depression severity. It is concluded that there is consistent evidence that a single dose of ketamine has dramatic antisuicidal action that emerges almost immediately after dosing and persists for at least a week. The short- and intermediate-term safety and efficacy of ketamine as a crisis intervention treatment for suicidal patients merit study. Areas that need research are outlined.

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Previous articles in this column discussed the efficacy, adverse effects, and possible mechanism(s) of action of subanesthetic doses of ketamine in the treatment of depression¹; the indications and contexts for the use of ketamine as an off-label antidepressant²; the antidepressant benefits and adverse effects of ketamine and its enantiomers³; issues related to dosing, rate of administration, route of administration, duration of treatment, and frequency of sessions when ketamine is used to treat depression⁴; and potential pharmacokinetic and pharmacodynamic interactions when ketamine is used as an off-label treatment for depression.⁵ The present article examines the effects of ketamine on suicidal ideation and its possible use as a pharmacologic crisis intervention in patients at suicide risk.

The first randomized, double-blind, placebo-controlled (crossover) trial of subanesthetic dosing with ketamine in patients with major depressive illness found that, among other results, ketamine reduced the severity of suicidal ideation.⁶ Subsequently, many case reports,⁷⁻¹² uncontrolled and open-label trials, and randomized controlled trials (RCTs) confirmed this finding. Data from uncontrolled and controlled trials have been examined in meta-analyses.

Ketamine Reduces Suicidality Within 1–4 Hours in At-Risk Patients: Results of Meta-Analysis

In a systematic review and meta-analysis of uncontrolled and controlled (ketamine arms only) clinical trials of the immediate antisuicidal action of ketamine, Bartoli et al¹³ identified 5 studies (pooled N = 99) that assessed outcomes at or within 4 hours of a single dose of intravenous (IV) ketamine in inpatients or outpatients (3 studies) or emergency room patients (2 studies) with active suicidal ideation. Two studies administered ketamine as an IV bolus (0.2 mg/kg; pooled N = 63); the other 3 administered ketamine as an IV infusion (0.5 mg/kg; pooled N = 36).

In this meta-analysis,¹³ ketamine was associated with substantial pre- vs posttreatment decrease in suicidal ideation at the last posttreatment assessment point. The effect size was large (SMD = 0.92; 95% CI, 0.44–1.40) and heterogeneity was low. Large, statistically significant benefit was observed from as early as 40 minutes posttreatment.

Limitations of this meta-analysis¹³ were many: the authors included uncontrolled as well as controlled studies; the number of studies was small; the pooled sample size was small; only within-groups analysis was performed (these are sensitive to placebo effects and yield larger effect sizes than between-groups analysis); and one of the studies¹⁴ was recently retracted. Therefore, the findings of this meta-analysis are, at best, a pointer to the potential of ketamine to quickly reduce suicidal ideation.

Ketamine Reduces Suicidality in At-Risk Patients: 1 Day to 1 Week Results of Individual Patient Data Meta-Analysis

In a larger and more informative systematic review and meta-analysis, Wilkinson et al¹⁵ obtained individual patient data from single ketamine

Table 1. Summary of an Individual Patient Data Meta-Analysis of the Acute (1–7 Days Posttreatment) Antisuicidal Effects of Ketamine in Patients With Baseline Suicidal Ideation¹⁵

1. When suicidal ideation items from clinician-administered instruments (MADRS, HDRS) were examined, ketamine was superior to control interventions for reduction in suicidal ideation at all time points between days 1 and 7 posttreatment; this finding remained true even after adjusting for age, gender, race, use of concomitant medications, inpatient vs outpatient status, and diagnosis. No baseline covariate significantly moderated the benefits of ketamine. There was little heterogeneity in the analyses. The findings remained significant when MADRS and HDRS outcomes were separately examined. Effect sizes were medium to large (0.61 to 0.85) across the week of assessment.
2. When MADRS and HDRS item data were examined, significantly more ketamine than control patients were free of suicidal ideation across the week of assessment (54%–60% vs 20%–33%, respectively). The NNTs, favoring ketamine, were in the 3–4 range.
3. When suicidal ideation items from self-report instruments (QIDS-SR, BDI) were examined, ketamine was superior to control interventions for reduction in suicidal ideation at all time points between days 1 and 7 posttreatment; this finding remained true even after adjusting for age, gender, race, use of concomitant medications, inpatient vs outpatient status, and diagnosis. No baseline covariate significantly moderated the benefits of ketamine. There was little heterogeneity in the analyses. The findings remained significant when QIDS-SR (but not BDI) outcomes were separately examined. Effect sizes were mostly medium to large (0.48 to 0.84) across the week of assessment.
4. When QIDS-SR and BDI data were examined, significantly more ketamine than control patients were free of suicidal ideation across the week of assessment (53%–55% vs 16%–35%, respectively). The NNTs, favoring ketamine, were in the 3–5 range.
5. The correlation between improvement in suicide scores and improvement in depression scores was in most instances strong, with 10%–46% of the variance in the relationship between these variables explained on different rating measures and at different points in time. Despite the high correlation, ketamine remained superior to control treatments on both clinician- and self-rated suicide assessment outcomes at nearly all time points even after controlling for improvement in depression scores.

Abbreviations: BDI = Beck Depression Inventory, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, NNT = number needed to treat, QIDS-SR = Quick Inventory of Depressive Symptoms-Self Report.

session, saline- or midazolam-controlled RCTs ($k = 10$) of patients with active suicidal ideation (pooled $N = 167$). One RCT recruited patients with posttraumatic stress disorder and another recruited patients with mixed diagnoses; the remainder included only patients with major depression. The patients with suicidal ideation who were included in the meta-analysis were more severely depressed than those who did not have suicidal ideation and who were excluded. Included patients did not differ significantly in ketamine (pooled $N = 93$) vs control (pooled $N = 74$) groups on sociodemographic and important clinical parameters such as baseline severity of depression.

The findings of this meta-analysis¹⁵ are summarized in Table 1. In short, on almost all outcomes at almost all time points between posttreatment days 1 and 7, ketamine was superior to control intervention. However, the advantage for ketamine was smaller in midazolam-controlled trials relative to saline-controlled trials; effect sizes were 0.34 to 0.69 for the former vs 0.69 to 0.90 for the latter. This suggests that

unmasking of the treatment blind may have boosted the placebo effect.

A limitation of this meta-analysis¹⁵ is that although there were 10 studies that contributed data, the pooled sample size was still small. The analyses examined single item scores in depression rating scales that assessed depression severity; there were no data based on specific suicide rating scales that assessed the frequency and severity of suicidal ideation, intent and planning, hopelessness, and other elements. No primary outcome was stated in the plan of analysis, and no correction for multiple hypothesis testing was applied. More importantly, patients in the RCTs were generally treatment-resistant and thereby enriched for a lesser likelihood of response to placebo; however, in clinical practice, patients who are acutely suicidal are not typically antidepressant-refractory and so may more readily respond to nonspecific aspects of whatever intervention is applied.¹⁶ Importantly, even patients with mild suicidal ideation were included in the analysis; worse still, many of the source studies specifically excluded patients at serious suicidal risk. In this context, what clinicians really want to know is the efficacy of ketamine as a crisis intervention in these very patients, that is, patients with the highest levels of suicidal ideation and intent. Many of these concerns were expressed in an editorial¹⁷ that discussed the meta-analysis.

Recent Randomized Controlled Trials of Ketamine in Patients With Clinically Significant Suicidal Ideation

At least 2 RCTs,^{18,19} not included in the meta-analyses discussed,^{13,15} have recently been published. Both RCTs recruited patients with clinically significant suicidal ideation, operationalized as a Scale for Suicidal Ideation (SSI) score of at least 4.

In the first RCT,¹⁸ 16 patients with bipolar depression and clinically significant suicidal ideation were randomized to receive IV ketamine (0.5 mg/kg) or midazolam (0.02 mg/kg); ongoing psychotropics, barring benzodiazepines, were continued unchanged during the study. One day after treatment, SSI scores attenuated substantially and near-significantly more with ketamine than with midazolam. The lack of statistical significance was not disappointing because the study was a pilot investigation and was underpowered.

In perhaps the largest and most important RCT to date, Grunebaum et al¹⁹ randomized 80 inpatients with moderately severe major depressive disorder and clinically significant suicidal ideation (mean SSI score of approximately 15) to receive a single infusion of either ketamine (0.5 mg/kg) or midazolam (0.02 mg/kg); ongoing antidepressant medications, if any, were continued unchanged, but benzodiazepine use was barred. Nearly half of the patients had a prior history of suicide attempt.

Between 4 and 24 hours after intervention, the fall in SSI scores was 4–5 points greater with ketamine than with midazolam; the effect size at 24 hours was 0.75, which is medium to large. Reduction in mean SSI scores by > 50% was observed in 55% vs 30% of ketamine vs midazolam patients, respectively (number needed to treat = 4). Improvement in

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the Profile of Mood States depression subscale mediated only 34% of the effect on ketamine on the SSI score. The mean SSI score in the ketamine group, which fell to about 5 a day after the infusion, remained in the 5–6 point range during a 6-week follow-up period in which treatments were optimized to individual needs.

This study¹⁹ is important because of the large sample size, the use of midazolam as a biologically active control, and the assessment of suicidal ideation using the SSI. Another strength is that patients were not limited to those who were antidepressant-refractory; this makes the sample more representative of depressed and suicidal patients in clinical practice. The study is limited by the absence of the assessment of the effects of ketamine in a double-blind, controlled fashion beyond 1 day.

Other Relevant Studies

In a small pilot study conducted in a military emergency department setting, Burger et al²⁰ randomized depressed and suicidal patients who met criteria for inpatient care to receive IV ketamine (0.2 mg/kg) or saline placebo. Two of 3 ketamine patients had dramatic reductions in suicidality and hopelessness within 40 minutes; no such improvements were observed in any of 7 saline controls. In a small, 3-week, open-label study,²¹ repeated ketamine administration (0.50–0.75 mg/kg, IV) was shown to attenuate mild but chronic suicidal ideation in 14 patients with major depressive disorder.

In a poorly described study,²² a single dose of ketamine (0.5 mg/kg IV) was associated with greater reduction in suicidal ideation than control treatment (midazolam) in patients (N=42) with newly diagnosed cancer who were acutely depressed and suicidal. The benefits, however, were significant only at days 1 and 3 and not at day 7 posttreatment. This study provides preliminary support for the early antisuicidal action of ketamine in acutely depressed and suicidal patients who do not have major depression.

Comments

Patients who are suicidal are usually managed as inpatients because suicide completion is less likely in an inpatient setting than in the community; psychotherapy, pharmacotherapy, and/or electroconvulsive therapy (ECT) are then initiated, as appropriate. However, none of these interventions is associated with dramatic antidepressant and antisuicidal benefits, as appears possible with ketamine. Therefore, if unanswered questions (Table 2) can be resolved

Table 2. Unanswered or Inconclusively Answered Questions About the Benefits of Ketamine, Relative to Control Interventions, for Reduction in Suicide Risk

Is ketamine effective when suicide risk is assessed using suicide rating scales rather than with single items in depression rating scales?
Is ketamine effective against suicide risk in diagnoses other than major depressive disorder, such as bipolar depression and posttraumatic stress disorder?
Is ketamine effective in patients who are at the highest risk of suicide, that is, when crisis intervention is indicated for a psychiatric emergency? In such patients, is crisis intervention with ketamine superior to crisis intervention by other means, including simple hospitalization and supportive psychotherapy?
Is ketamine effective in patients who are not treatment-resistant?
What is the influence of dose, route of administration, and number and frequency of ketamine sessions on outcomes in suicidal patients?
Besides reduction in suicidal ideation, is suicidal behavior (exemplified by conceiving plans, making preparations, or actually attempting self-harm) also reduced by ketamine?
What are long-term outcomes in suicidal patients who receive ketamine as crisis intervention?

in favor of ketamine, subanesthetic dosing with ketamine may become an important crisis intervention strategy to buy time while other treatments are instituted and take effect.²³

As discussed in earlier articles in this series,^{1,2,4} respiratory risks with ketamine are low, even in anesthetic doses, and the drug is relatively safe, even in untrained hands, such as when used in military medical emergencies. An important possibility, then, is that ketamine may be a potential pharmacologic crisis intervention for the suicidal patient even in low-resource, primary care settings in developing countries, where facilities for psychiatric admission, psychotherapy, and ECT are unavailable. In this context, there is need to explore whether oral or subcutaneous ketamine is also effective with appropriate dose adjustments to compensate for poor bioavailability and other pharmacokinetics matters.⁴ Given that elaborate monitoring facilities are unlikely to be available in low-resource settings, the risk-benefit profile of ketamine in such settings requires study, and minimum standards of care require to be set. There are already reports in the literature of the safe and effective domiciliary self-administration of sublingual ketamine, as required, in patients with suicidal ideation.¹¹

Subanesthetic dosing with ketamine has the potential to enter emergency medicine and mainstream psychiatry as a crisis intervention treatment for suicidal patients.²³

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