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BRIEF REPORT

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# A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department

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**Abstract**

We examined the preliminary feasibility, tolerability and efficacy of single-dose, intravenous (i.v.) ketamine in depressed emergency department (ED) patients with suicide ideation (SI). Fourteen depressed ED patients with SI received a single i.v. bolus of ketamine (0.2 mg/kg) over 1–2 min. Patients were monitored for 4 h, then re-contacted daily for 10 d. Treatment response and time to remission were evaluated using the Montgomery–Asberg Depression Rating Scale (MADRS) and Kaplan–Meier survival analysis, respectively. Mean MADRS scores fell significantly from 40.4 (S.E.M. = 1.8) at baseline to 11.5 (S.E.M. = 2.2) at 240 min. Median time to MADRS score $\leqslant$10 was 80 min (interquartile range 0.67–24 h). SI scores (MADRS item 10) decreased significantly from 3.9 (S.E.M. = 0.4) at baseline to 0.6 (S.E.M. = 0.2) after 40 min post-administration; SI improvements were sustained over 10 d. These data provide preliminary, open-label support for the feasibility and efficacy of ketamine as a rapid-onset antidepressant in the ED.

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**Key words**: Depression, emergency department, ketamine, MADRS, suicide ideation.

## Introduction

There are no validated approaches to the pharmacotherapy of depression or suicidality in the emergency department (ED) setting. Available antidepressant drugs have slow onset of action, and inherent short-term liabilities (Nestler & Carlezon, 2006). Indeed, many suicidal patients are admitted to hospital for safety reasons alone, despite the disruptive and costly nature of this disposition. (Frueh *et al.* 2000). However, recent studies suggest that ketamine, an *N*-methyl-D-aspartic acid (NMDA) glutamate receptor antagonist, may exert a rapid antidepressant effect in research subjects with treatment-resistant depression (TRD), bipolar disorder and suicide ideation (SI) (aan het Rot *et al.* 2010; Berman *et al.* 2000; Diaz Granados *et al.* 2010; Mathew *et al.* 2009; Phelps *et al.* 2009; Price *et al.* 2009; Zarate *et al.* 2006). In these studies a slow sub-anaesthetic infusion of intravenous (i.v.) ketamine rapidly reduced depressive symptoms within several hours of drug infusion, with this response maintained in some patients for up to 7 d (aan het Rot *et al.* 2010; Berman *et al.* 2000; Diaz Granados *et al.* 2010; Mathew *et al.* 2009; Phelps *et al.* 2009; Price *et al.* 2009; Zarate *et al.* 2006). Recent studies also suggest an anti-suicidal effect of ketamine (Price *et al.* 2009). Thus, there is a possibility that rapidly acting antidepressant medications might play a role in alleviating distress, reducing SI, and mitigating hospitalization in some subsets of ED patients. To explore this hypothesis, this study evaluated the effects of a low-dose i.v. ketamine bolus on depression and suicidality in ED patients.

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## Methods and materials

The study was approved by the Human Investigations Committee (HIC) of the Yale University School of Medicine–Yale New Haven Hospital (Protocol No. 0909005766) and signed informed consent was obtained from all patients prior to their participation, according to the principles outlined in the Declaration of Helsinki.

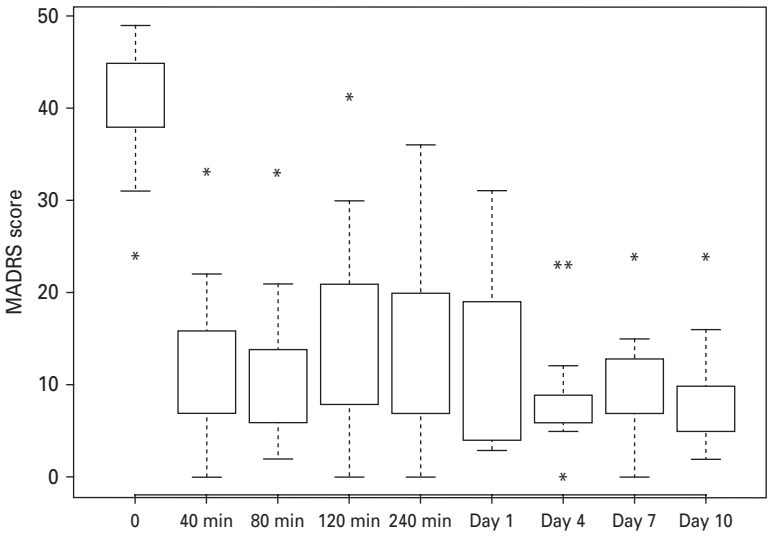


**Fig. 1.** Course of mood, measured by Montgomery–Asberg Depression Rating Scale (MADRS), over 10 d in 14 patients who received ketamine.

### *Patients*

Patients were recruited from the Yale–New Haven Hospital ED. Participants were patients with a primary presenting complaint of depression with SI, who met DSM-IV criteria for major depressive disorder as assessed by the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan *et al.* 1998), and scored $\geqslant$24 on the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979), and $\geqslant$2 on the Scale for Suicide Ideation (SSI; Beck *et al.* 1988). Patients were excluded if they had acute medical problems or screening medical laboratory abnormalities that required clinical intervention, or if they had lifetime diagnoses of psychosis, mania or hypomania, or were receiving antipsychotic or NMDA antagonist medications.

### *Design*

Patients were administered a single sub-anaesthetic i.v. bolus of ketamine (0.2 mg/kg over 1–2 min) in the ED, with continuous monitoring of vital signs, adverse events and psychotomimetic side-effects for 4 h post-administration. Ratings included the 10-item MADRS and the 21-item SSI to assess depression and SI. Safety and tolerability were assessed with the 11-item Young Mania Rating Scale (YMRS; Young *et al.* 1978), and the 4-item Brief Psychiatric Rating Scale (BPRS+) items (Suspiciousness, Unusual thought content, Hallucinations, Conceptual disorganization) (Overall & Gorham, 1962). MADRS ratings were obtained at baseline, and at 40, 80, 120 and 240 min, in person, and

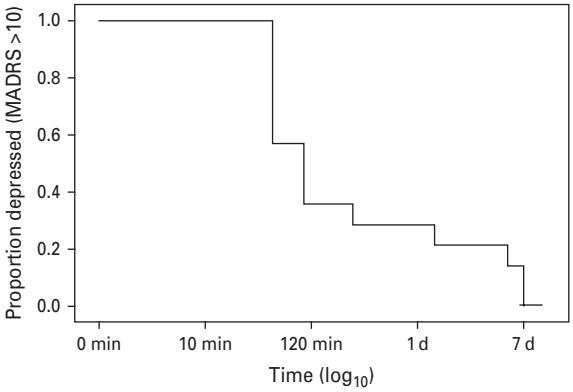


**Fig. 2.** Kaplan–Meier survival plot of time to remission of depression after bolus ketamine.

at 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 d post-administration. Daily follow-up interviews were conducted in person for those patients who were hospitalized, and by telephone once patients had been discharged. Throughout the study, all subjects continued to receive treatment as usual with both psychopharmacological and psychosocial interventions either in an outpatient or in-patient setting.

### *Statistical analysis*

Primary outcome measures were the MADRS for depression, and item 10 of the MADRS (MADRS-SI) for SI. Secondary measures included the YMRS and BPRS+. Changes from baseline in the MADRS, YMRS and BPRS+ were assessed using box-plot analysis and

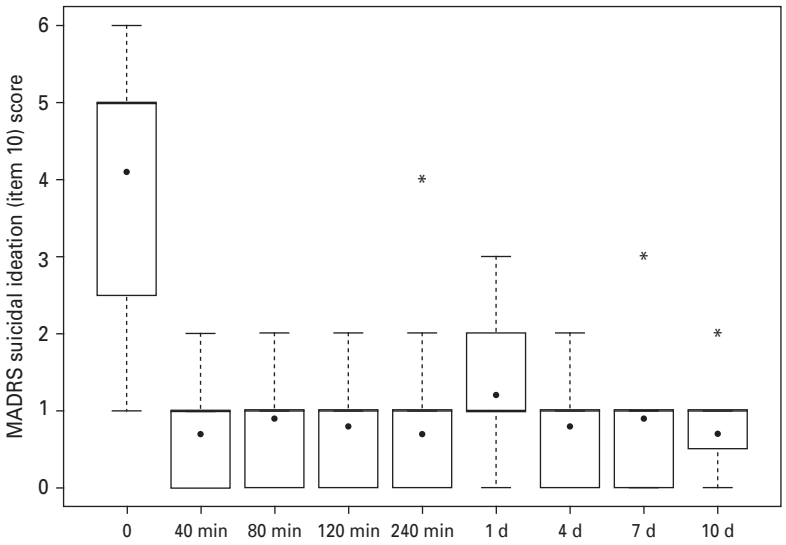


**Fig. 3.** Course of suicidal ideation, measured by Montgomery–Asberg Depression Rating Scale (MADRS) item 10, over 10 d in 14 patients who received ketamine.

repeated-measures ANOVA. Violations of sphericity were corrected by adjusting the degrees of freedom in the ANOVA using the Greenhouse–Geisser correction. Missing data were handled by carrying forward the subject's highest/worst scores. Time data were transformed using $\log_{10}$. Time to remission (defined as MADRS score $\leqslant 10$) was analysed using Kaplan–Meier survival analysis.

## Results

Fourteen patients (7 males) aged 18–53 yr [mean (S.E.M.) 31.1 (3.4) yr] participated in this study during March and April 2010. Their mean (S.E.M.) weight was 82.6 (5.7) kg, ranging from 60 to 123 kg. Repeat weight evaluation revealed that actual doses of ketamine given ranged from 0.16–.26 mg/kg. The median [interquartile range (IQR)] score of these 14 patients at baseline on the MADRS was 42 (IQR 38–47). The median (IQR) score on the SSI was 19 (IQR 12–28). Mean (S.E.M.) MADRS scores at baseline and 240 min post-administration were 40.4 (1.8) and 11.5 (2.2), respectively (repeated-measures ANOVA: $F = 23.7$, d.f. $= 95$, $p < 0.001$). These reductions were sustained at 7 d [mean MADRS score 8.4 (1.6)] for all patients, and for all 13 patients followed to 10 d [mean MADRS score 9.2 (1.7)]. (Fig. 1) One subject was lost to follow-up at day 8 and considered a non-responder. The cumulative proportion of patients reaching remission (MADRS score $\leqslant 10$) during the 10-d study is illustrated in Fig. 2 using Kaplan–Meier survival analysis. Mean time to remission was 240 min [95% confidence interval (CI) 70–720]; median time to remission was 80 min (95% CI 38–190). Of the 13 subjects followed for 10 d, 12 maintained response criterion ($>50\%$ reduction in MADRS scores compared to baseline) at 10 d post-administration.

Compared to a mean (S.E.M.) baseline MADRS-SI score of 3.9 (0.4), SI decreased significantly in all patients at 40, 80, 120, and 240 min after ketamine administration, yielding MADRS-SI scores of 0.6 (0.2), 0.6 (0.2), 0.7 (0.2) and 0.6 (0.1), respectively (Fig. 3). These data suggest that SI completely resolved in all patients by 40 min. Indeed, this resolution was sustained at 7 d in all patients, and in all 13 patients followed to day 10 [MADRS SI scores 0.8 (0.1) and 0.7 (0.2) at days 7 and 10, respectively]. Repeated-measures ANOVA reveals the 10-d SI trend to be significant ($F = 29.7$, df $= 97$, $p < 0.001$). For both the total MADRS and the MADRS-SI scores, all post-administration scores were significantly lower than baseline scores, and all scores at time-points beyond 40 min following ketamine administration were not significantly different from each other.

Ketamine elicited mild positive psychotomimetic symptoms in two patients, all of which resolved within 40 min. Mean (S.E.M.) BPRS+ scores were 0 (0) at each observation point of 40, 80, and 240 min. Two patients experienced unpleasant dissociative symptoms, as assessed by the YMRS, but these resolved within 30 min. Mean (S.E.M.) YMRS scores at 40, 80, and 240 min were 0.3 (0.2), 0.1 (0.5), and 0.1 (0.1), respectively.

## Discussion

This preliminary study suggests that administering ketamine to depressed patients in a busy ED setting is feasible, safe and potentially effective in inducing a rapid remission of depression and SI, as assessed by total MADRS, and MADRS-SI scores. These symptoms diminished rapidly and significantly within 40 min, with no evidence of recurrence during the 10 d follow-up (with ongoing, conventional treatment).

Our findings are consistent with recent research reporting ketamine's rapid response in unipolar, bipolar, and TRD (Diaz Granados *et al.* 2010; Mathew *et al.* 2009; Zarate *et al.* 2006), and in SI (aan het Rot *et al.* 2010). In several small studies slow infusions (over 40 min) of ketamine have been shown to rapidly reduce depressive symptoms in patients with refractory depression (aan het Rot *et al.* 2010; Berman *et al.* 2000; Mathew *et al.* 2009; Phelps *et al.* 2009; Price *et al.* 2009; Zarate *et al.* 2006), and bipolar disorder (Diaz Granados *et al.* 2010). While one study has shown a reduction in SI 24 h after a slow infusion of ketamine in TRD patients (Price *et al.* 2009), our study is the first to show this effect can be achieved with a rapid bolus, a more feasible mode of delivery for a busy ED setting.

The current preliminary data suggest that ketamine may reduce SI without a short-term risk of rebound of this symptom. Further controlled research will be needed to determine whether this protective effect is distinctive for ketamine relative to other antidepressant treatments. ECT, for example, may rapidly reduce SI in some patients (Sharma, 2001). Other than ECT, ketamine may be the first medication to produce evidence of a rapid and sustained reduction in SI. Anti-suicidal effects are reported with other pharmacologic treatments, such as lithium (Tondo & Baldessarini, 2009), and clozapine (Meltzer *et al.* 2003), but only during long-term therapy. The mechanism of ketamine's rapid antidepressant and anti-suicidal actions are unclear but appear to be related to glutamate neurotransmission (Li *et al.* 2010; Mathew *et al.* 2009; Zarate *et al.* 2006).

This study had several important limitations including the small number of patients, the open-label design, the lack of placebo or active comparators, short duration of follow-up, use of concomitant medications, and the use of a single item to assess SI. The small number of patients might obscure the likelihood of observing adverse events which may occur rarely. Despite small numbers, the antidepressant effects seen herein started within minutes. Indeed, our study is the first to show the feasibility and utility of ketamine as a rapidly acting antidepressant in a busy ED setting. However, this intervention is likely to be effective and appropriate for only some subgroups of the depressed and suicidal ED population. Until further research identifies those groups and elucidates the benefits and risks of ketamine used in this way, clinicians should be cautious about applying this intervention (Krystal, 2010).

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## Statement of Interest

None.

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