Received: 17 October 2018 | Revised: 23 September 2019 | Accepted: 4 October 2019

DOI: 10.1002/da.22975

ANXIETY AND DEPRESSION ASSOCIATION OF AMERICA

WILEY

RESEARCH ARTICLE

Ketamine for acute suicidal ideation. An emergency department intervention: A randomized, double-blind, placebo-controlled, proof-of-concept trial

Yoav Domany[1,2,3] | Richard C. Shelton[4] | Cheryl B. McCullumsmith[5]

[1]Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, Cincinnati, Ohio

[2]Department of Psychiatry, Tel Aviv Sourasky Medical Centre, Tel-Aviv, Israel

[3]Sackler School of Medicine, Tel Aviv University, Tel-Aviv, Israel

[4]Department of Psychiatry and Behavioral Neurobiology, University of Alabama, Birmingham, Alabama

[5]Department of Psychiatry, College of Medicine and Life Sciences, University of Toledo, Toledo, Ohio

Correspondence
Yoav Domany, Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, 260 Stetson Street Suite 3200 Cincinnati, OH 45219.
Email: yoav.domany@uc.edu; yoavdomany@gmail.com

Abstract

Background: Depressed patients presenting to emergency departments with acute suicidal ideation are a major public health concern. Ketamine, a rapidly acting antidepressant with antisuicidal properties, might offer relief.

Methods: In a randomized, double-blind, placebo-controlled, proof-of-concept trial, 18 depressed subjects with acute suicidal ideation, who required hospitalization, were randomized to either an intravenous ketamine 0.2 mg/kg group or a saline placebo group. Safety and efficacy evaluations were scheduled for 15, 30, 60, 90, 120, 180, and 240 min, and on Days 1, 2, 3, 7, and 14 after infusion. The main outcome measure was suicidal ideation with secondary measures of depression.

Results: Nine subjects were randomized to each group. There were no differences between groups at baseline in any demographic or assessment scales. A reduction in suicidal ideation was noted at 90–180 min ($p < .05$). Ninety minutes after infusion, 88% of the ketamine group had achieved remission of suicidal ideation compared with 33% in the placebo group ($p < .05$). No serious adverse events were noted.

Conclusions: Ketamine was safe and effective for rapid reduction in suicidal ideation in depressed, highly suicidal subjects presenting to the emergency department. Our results support further study of ketamine for acute suicidal ideation.

KEYWORDS

acute suicidal ideation, anxiety, depression, hopelessness, ketamine, suicide

1 | INTRODUCTION

Suicide is the 10th leading cause of death in the United States (Heron, 2016), and the suicide rates are rising alarmingly (Rossen, Hedegaard, Khan, & Warner, 2018). Depressed patients often present to the emergency department with complaints of suicidal thoughts, which accounts for more than half a million admissions annually to the emergency department in the United States (Ting, Sullivan, Boudreaux, Miller, & Camargo, 2012). In the absence of specific treatments for acute suicidal ideation, most suicidal patients are hospitalized for brief stabilization and are often discharged before psychopharmacological treatments can show efficacy. No strong evidence base exists to demonstrate that brief inpatient hospitalizations are associated with a significant reduction in suicidal potential. Thus, there is an urgent need to pursue treatment options for suicidal ideation, especially in emergency department settings.

Ketamine, a glutamatergic modulator and a rapidly acting antidepressant (aan het Rot et al., 2010; Berman et al., 2000; Domany et al., 2018; Murrough et al., 2013; Singh et al., 2016; Zarate et al., 2006), has been shown to rapidly reduce suicidal ideation (Grunebaum et al., 2018; Ibrahim et al., 2011; Price, Nock, Charney, & Mathew, 2009). In addition, esketamine, the *S* enantiomer of racemic ketamine, has shown similar results (Canuso et al., 2018). Ketamine's antisuicidal properties raised interest in the emergency department settings, where it was evaluated in open-label trials (Larkin &

Beautrais, 2011). Kashani et al. (2014), in a small, open trial, reported a reduction in suicidal ideation which was significant, yet failed to reach their preset goal of scale for suicidal ideation (SSI) < 4. Therefore, they argued against ketamine for a fast reduction in suicidal ideation. Burger et al. (2016), in a controlled study, encountered methodological difficulties, which limited their analyzable data to 10 subjects. They reported a significant reduction in suicidal ideation 4 hr after infusion and concluded that ketamine may be an effective means of acutely improving suicidal ideation and depression.

We have previously suggested (Mallick & McCullumsmith, 2016) a novel way to conceptualize risk factors for suicidal ideation using the Research Domain Criteria (RDoC; Insel, 2014). And a recent meta-analysis (Glenn et al., 2018) pointed out some of the domains that are suicide related, such as hopelessness, anxiety, and impulsivity. Further, some of these RDoC constructs have been modified by ketamine (DiazGranados et al., 2010). Examination of these neurobiological domains is a novel perspective that may offer additional insights into both ketamine's unique actions and the neurobiological underpinnings of suicidal ideation.

The main objective of the current project was to randomly assess the safety, feasibility, tolerability, and efficacy of a single- and low-dose ketamine in reducing suicidal ideation. Second, we hypothesized that a novel RDoC-based model for suicide research would be preferable for the study of suicide neurobiology and the effect of ketamine on its different constructs. Thus, our secondary objectives were to test the effect of ketamine on symptoms of depression, anxiety, impulsivity, and hopelessness and to evaluate ketamine's subjective addictive properties. This study is important in two aspects; first, it suggests a treatment option for suicidal ideation in the emergency department settings. Second, it illustrates a novel paradigm for suicide research.

2 | MATERIALS AND METHODS

2.1 | Participants

Eighteen subjects, aged 18–65, presenting for acute treatment to the University of Alabama at Birmingham's (UAB) emergency department were enrolled. Subjects were included if they met DSM-IV-TR criteria (American Psychiatric Association, 2000) for major depression, bipolar depression, depression NOS (not otherwise specified), or dysthymia, as confirmed by the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). Subjects were included if they suffered clinically significant suicidal ideation, which warranted psychiatric hospitalization. Specifically, the inclusion criteria for suicidal ideation were defined as a score of at least 3 on the first five items on the Beck Scale for Suicidal Ideation (BSS)—meaning at least a death wish—and at least 3 on the Columbia Scale for Suicide Severity Rating (C-SSRS; Posner et al., 2011)—meaning at least active suicidal thoughts. All participants had been evaluated by the primary clinical team before being contacted by the study personnel, and the admission criteria had been determined by a treating (nonstudy) clinician. No inclusion requirements for past psychiatric treatment or depression severity were applied. Racial, gender, or ethnic groups were not excluded.

Potential participants were excluded if they had a current primary psychotic disorder (i.e., schizophrenia, schizoaffective disorders etc.), dissociative disorder, pervasive developmental disorder, cognitive disorder, or anorexia nervosa. In addition, acute intoxication or withdrawal from alcohol or any substance of abuse, as determined by a clinical interview and urine drug screening were excluded, including the use of any hallucinogens (except cannabis), 1 month before study enrollment; homicidal risk was excluded. Pregnant, lactating, or post-partum women (within 2 months of delivery) were excluded; women of reproductive potential had to have a negative urine pregnancy test. Subjects were excluded if their current treatment included any medication known to affect the *N*-methyl-D-aspartate receptor system (e.g., lamotrigine, acamprosate, memantine, riluzole, or lithium), or if they had any known hypersensitivity or history of a serious adverse reaction to ketamine. Subjects were excluded if they suffered any clinically significant medical condition that would preclude the use of ketamine, such as respiratory illness requiring regular use of oxygen, uncontrolled hypertension, or prolonged QTc.

2.2 | Study design

This study was reviewed and approved by the University of Alabama at Birmingham Institutional Review Board and registered with clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT01887990). Written informed consent was obtained from all participants after a thorough description of the study and before any study-specific procedure. Baseline assessments included physical examination, a full medical and psychiatric history, urine obtained for drug screening, and pregnancy test for women of reproductive potential. Those meeting all inclusion, but no exclusion, criteria were randomized (1:1) into an intravenous (IV) ketamine 0.2 mg/kg group or a matched placebo (normal saline) group. This low ketamine dose has been previously reported to alleviate suicidal ideation (Larkin & Beautrais, 2011). Furthermore, this relatively lower dose enabled us to administer the drug intravenously over 5 min, under the supervision of a board-certified emergency department physician, but not a psychiatrist. This 5-min administration is preferable and more feasible in emergency department settings than previously reported (Zarate et al., 2006) 40-min infusion. The pharmacist, who was the only nonblinded member of the study group, prepared active and placebo agents in similar 10-ml syringes following a randomization schedule. Subjects received continuous vital sign monitoring for 4 hr after study drug infusion. Study assessments were performed at baseline before treatment and at 15, 30, 60, 90, 120, 180, and 240 min, and on Days 1, 2, 3, 7, and 14 after drug administration. At the completion of the post-treatment observation period, the participants were hospitalized in the psychiatry units at the UAB Hospital. All patients received standard psychiatric care for their underlying condition and standard psychiatric follow-up by the

treating (nonstudy) psychiatrist, who could make any changes in the treatment deemed warranted by the patient's condition.

2.3 | Diagnostic evaluations

The MINI (Sheehan et al., 1998) was the primary instrument for diagnostic ascertainment. The MINI is a semistructured psychiatric interview designed to yield judgments with respect to all five axes in the DSM-IV-TR. The MINI has excellent reliability and validity and is preferable in the emergency department settings because of its relative brevity (Pinninti, Madison, Musser, & Rissmiller, 2003).

2.3.1 | Suicide scales

Baseline suicidal ideation, the intensity of ideation, and behaviors were assessed using the C-SSRS (baseline and versions; Posner et al., 2011). The C-SSRS is a widely used and valid scale used to assess both recent and lifetime suicide-related thoughts and behaviors.

2.4 | Outcomes

The primary outcome was changed in suicidal ideation as assessed using both the full version of the BSS, and item 10 (suicidal thoughts) on the Montgomery–Åsberg Depression Rating Scale (MADRS).

The BSS (Beck, Steer, & Ranieri, 1988) is a 21-item, self-reported rating scale that measures the current intensity of specific attitudes, behaviors, and plans to commit suicide. The BSS has high internal consistency, concurrent validity, and inter-rater reliability and has been definitively shown to be sensitive to change in clinical trials (Healy, Barry, Blow, Welsh, & Milner, 2006), including ketamine studies (Murrough et al., 2015). The other suicide assessment scale was the MADRS's 10th question on suicidal ideation (MADRS-SI). The MADRS-SI is an overall valid estimation of suicidal ideation, represents the clinical global impression of suicide according to the rater, and is particularly useful in rapid-acting antidepressants, including ketamine (Ballard et al., 2015).

2.4.1 | Secondary outcomes

Secondary outcomes included a change in depressive symptoms and a change in suicide-related RDoC constructs: hopelessness, pessimistic thoughts, anxiety, and impulsivity, in addition to safety evaluations.

- Depression scale: The MADRS (Montgomery & Asberg, 1979) was the primary measure of depression. The MADRS is a commonly used and reliable clinician-rated assessment of depression severity that is sensitive to treatment effects (Heiligenstein, Tollefson, & Faries, 1993). It has been used successfully in prior ketamine studies (Ionescu, Luckenbaugh, Niciu, Richards, & Zarate, 2015; Larkin & Beautrais, 2011; Murrough et al., 2015).
- Suicide-related RDoC constructs:
  - *Hopelessness* was evaluated using the Beck Hopelessness Scale (BHS; Beck, Weissman, Lester, & Trexler, 1974). The BHS is a self-assessment tool for hopelessness. Hopelessness was strongly linked to suicide risk (Beck, 1986; P. Wilkinson, Kelvin, Roberts, Dubicka, & Goodyer, 2011; Stefansson, Nordström, & Jokinen, 2012).
  - *Pessimistic thoughts*, including perceived burdensomeness, failure, and guilt, were evaluated through the ninth question of the MADRS.
  - *Anxiety* was measured by the Beck Anxiety Index (BAI; Beck, Epstein, Brown, & Steer, 1988). The BAI is a brief measure of anxiety with a focus on somatic symptoms of anxiety that was developed as a measure adept at discriminating between anxiety and depression (Julian, 2011). An additional assessment of anxiety is the third question of the MADRS.
  - *Impulsivity* was assessed using the Barratt Impulsivity Scale (BIS). The BIS is a 30-item self-report instrument designed to assess the personality/behavioral constructs of impulsiveness.
- Safety, tolerability, and adverse effects:
  - *Psychosis and manic symptoms*: The presence of psychotic and manic symptoms both pre- and post-treatment were evaluated using the Brief Psychiatric Rating Scale (BPRS). The BPRS is a widely used and reliable assessment of psychotic symptoms, including both positive (e.g., hallucinations and delusions) and negative (blunted affect, withdrawal) symptoms of psychosis (Bell, Milstein, Beam-Goulet, Lysaker, & Cicchetti, 1992). The Young Mania Rating Scale (YMRS), is an 11-item, clinician-rated measure that queries symptoms of mania (Bauer et al., 1991).
  - *Dissociative symptoms*: Dissociative symptoms experienced during ketamine treatment were assessed by the Clinician-Administered Dissociative States Scale (CADSS; Bremner et al., 1998).
  - *Addiction potential*: Due to ketamine's popular misuse (Bokor & Anderson, 2014), we additionally evaluated psychological and physiological addictive properties. We evaluated ketamine's addiction potential by asking our subjects to rate their response to drug administration on seven addiction-related issues. We evaluated the "strength of effect," the "good effect," the "bad effect", "feeling high" in addition to measurement of "liking," "craving," and "willingness to take the drug again." All issues were measured on a Likert visual analogue scale (see Figure S7a).

2.5 | Data collection and management

To ensure the quality of electronic data capture (EDC) and management, the data management team used the REDCap EDC system (Harris et al., 2009). REDCap provides a process for building a database, an interface for collecting data, data validation, and automated export procedures for data downloads to statistical packages (SPSS).

2.6 | Statistical analysis

All outcomes were summarized descriptively and assessed for normality before analysis using normal probability plots and Kolmogorov test statistics. Transformations or nonparametric analyses were performed as necessary. All tests were two-sided and considered statistically significant at $\alpha = .05$. All analyses were performed using SPSS. This study was planned, built, and powered for a larger sample size ($n = 100$). However, because the primary investigator has left the institution, we had to prematurely end study recruitment. Linear mixed models were used to compare acute changes in suicidal ideation as measured by the BSS between treatment groups. In these models, a group (placebo vs. ketamine) was included as a between-subjects factor, and time (pretreatment vs. 120 min post-treatment) represented a within-subjects factor. Similar mixed models described above were employed to evaluate secondary outcomes (e.g., BPRS, CADSS). In addition, baseline characteristics such as age, gender, and psychiatric treatment history (Antidepressant Treatment History Questionnaire [ATRQ]) were considered as potential covariates. Tolerability and safety were evaluated descriptively (e.g., frequencies, summary statistics), separately for each treatment group and compared using χ^2 or t test.

3 | RESULTS

3.1 | Efficacy results

Demographic characteristics and mean baseline scores on the MADRS, BSS, BAI, BIS, and the BHS of the recruited subjects are presented in Table 1. There were no differences between groups at baseline in any demographic or assessment scale. Nine subjects were randomized to the ketamine group and nine to the placebo group. All were analyzed for primary and secondary outcomes.

3.2 | Suicidal ideation

The main outcome was changed in suicidal ideation. We found a reduction in both the BSS, a patient self-report scale (Figure 1), and the rater-based MADRS-SI (Figure S5). We found ketamine to alleviate suicidal ideation at 90, 120, and 180 min after infusion according to the BSS and at 120 min according to the MADRS-SI score. Remission from suicidal ideation was defined by a score of 2 or less on the MADRS-SI item (indicating fleeting suicidal thoughts or less). Ninety minutes after infusion, eight of nine subjects of the ketamine group had remission (88%) compared with three of nine (33%) in the placebo group ($p < .05$).

3.3 | Depression

The change in depression, a secondary outcome, is presented in Figure 2. The reduction in depression fell just short of a statistically significant difference. This reduction was rapid with the nadir effect 3 days after infusion.

3.4 | Suicide-related RDoC constructs

3.4.1 | Negative valence systems

(A) *Loss*: We assessed "loss" through evaluation of hopelessness and pessimistic thoughts:
   (a) Hopelessness was evaluated using the BHS. We found ketamine to alleviate hopelessness: 3 days after ketamine

TABLE 1 Baseline demographics and outcome measures

Variables	Total ($n = 18$)	Placebo ($n = 9$)	Ketamine ($n = 9$)	χ^2 or t value	Significance
Demographics					
Age	35.44 (9.01)	35.78 (9.86)	35.11 (8.67)	.152	.881
Sex (male)	8 (44.4%)	4 (44.4%)	4 (44.4%)	.000	1.000
Race					
Black/African American	7 (38.9%)	5 (57.1%)	2 (22.2%)	2.104	.147
White/Caucasian	11 (61.1%)	4 (44.4%)	7 (77.8%)		
Marital status					
Single/never married	6 (33.3%)	4 (44.4%)	2 (22.2%)	2.810	.422
Divorced/widowed	5 (27.8%)	2 (22.2%)	3 (33.3%)		
Married	7 (38.9%)	3 (33.3%)	4 (44.4%)		
Education (years)	12.72 (1.64)	12.11 (1.76)	13.33 (1.32)	0.00	1.00
Employed	6 (33.3%)	2 (22.2%)	4 (44.4%)	5.167	.160
Outcome measures					
MADRS total score	36.00 (11.18)	36.67 (14.81)	35.33 (6.73)	.246	.809
BSS total score	22.00 (7.37)	20.56 (7.25)	23.44 (7.63)	−0.823	.422
BHS total score	15.89 (4.79)	14.33 (5.59)	17.44 (3.47)	−1.419	.175
BAI total score	26.28 (12.04)	31.22 (12.89)	21.33 (9.31)	1.865	.081
BIS total score	74.67 (9.45)	75.44 (11.07)	73.89 (8.12)	.340	.738

Abbreviations: BAI, Beck Anxiety Index; BHS, Beck Hopelessness Scale; BIS, Barratt Impulsivity Scale; BSS, Beck Suicidality Scale; MADRS, Montgomery–Åsberg Depression Rating Scale.
*$p < .05$.

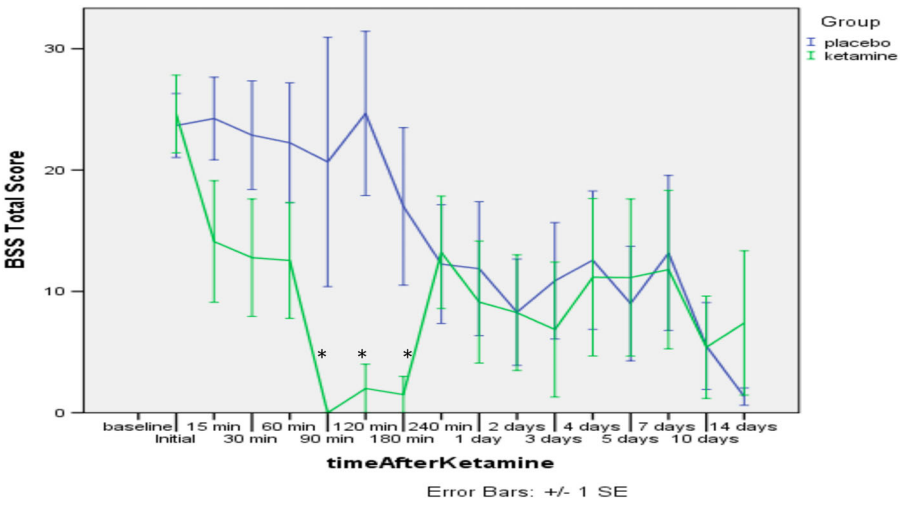

FIGURE 1 Change in BSS across time. *$p < .05$. BSS, Beck Suicidal Scale; *SE*, standard error of the mean

infusion, there was a reduction of 90.7% in the BHS compared with 17.5% in the control ($p < .05$; Figure 3a).

(b) Pessimistic thoughts were evaluated using the MADRS's ninth question. We found a reduction in pessimistic thoughts as evidenced by a rapid reduction in the ninth MADRS question at 15, 30, and 60 min as well as 3 days after ketamine infusion. In the first 3 days, the mean assessment of pessimism was lower than 2 (score of 0–6; Figure 3b).

(B) *Potential threat*: We assessed "potential threat" through evaluation of anxiety using BAI and MADRS's third question. Three days after infusion, there was a reduction of 82.4% of baseline BAI scores in the ketamine subjects compared with 47.3% in the controls ($p < .05$). MADRS's third question is presented in Figure 3c, and BAI is presented in Figure S6.

(C) *Cognitive systems*: We assessed "cognitive control" through evaluation of BIS. We found no effect of ketamine on impulsivity (Figure 3d).

3.5 | Safety results

Transient elevation of systolic blood pressure (higher than 140 mm/Hg) was noted in 22% of the subjects receiving ketamine compared with 11% of the subjects receiving a placebo. No other clinically significant cardiovascular effects were noted. There were no differences in psychiatric symptoms, as measured by the BPRS, between both groups (Figure 4a) or in dissociative symptoms (Figure 4b), at any of the time points. In addition, there were no differences in drug abuse evaluations (such as craving or willingness to take the drug again) between the ketamine and placebo at any of the time points (Figure S7 and S7a). No serious adverse events were noted.

4 | DISCUSSION

4.1 | Main findings

Single ketamine administration in the emergency department alleviated suicidal ideation over placebo at 90–180 min after

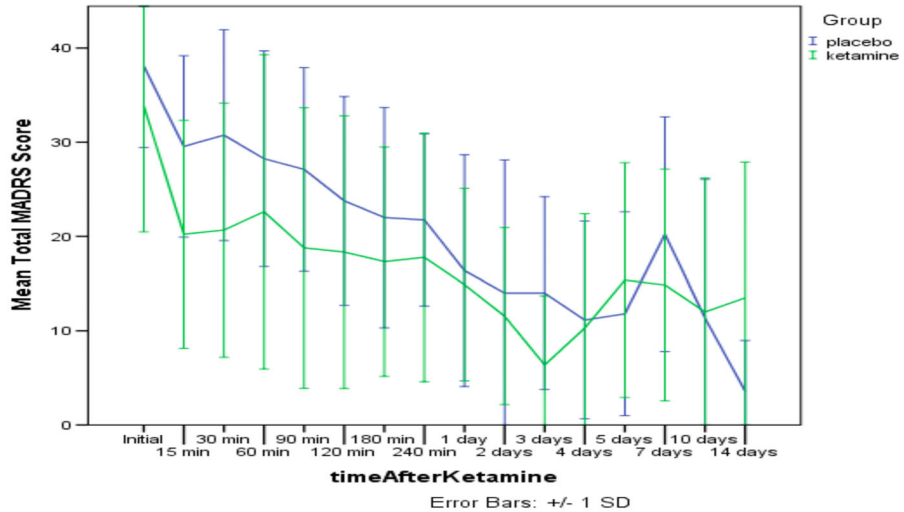

FIGURE 2 Change in MADRS scale across time. *SD*, standard deviation

MADRS: Montgomery-Åsberg Depression Rating Scale.

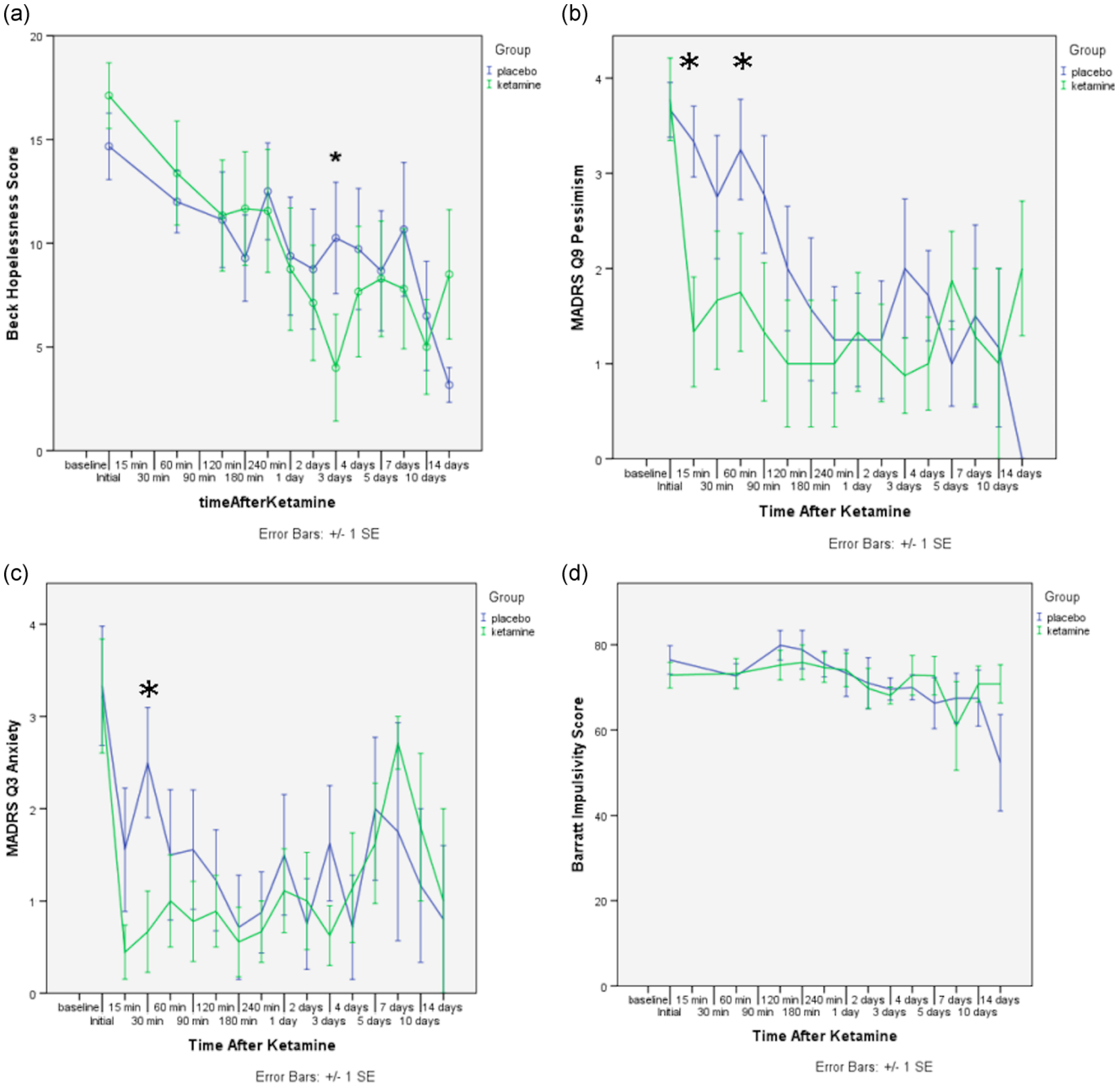

FIGURE 3 Change in suicide-related RDoC constructs across time. *$p < .05$. The two asterisks stands for two time points; 15 minutes and 60 minutes. MADRS, Montgomery–Åsberg Depression Rating Scale; RDoC, Research Domain Criteria; *SE*, standard error of the mean

administration in depressed patients presenting to the emergency department with suicidal ideation. Notably, 90 min after infusion, 88% of the ketamine-receiving subjects were no longer actively suicidal compared with 33% of the controls. Moreover, we found ketamine to improve negative and positive valence systems but not cognitive systems. Unexpectedly, our results did not establish a significant reduction in the depressive score.

4.2 | Comparison to other studies

Our findings are consistent with others who demonstrated the antisuicidal effect of ketamine (Grunebaum et al., 2018; S. T. Wilkinson et al., 2018). We, however, suggest here a more feasible way of administration, which is more appropriate for an emergency department settings (even before administration to psychiatric ward). Thus, this unique "5-min administration" technique using a relatively lower dose of 0.2 mg/kg may enable widespread emergency department usage. In addition, our findings are similar to other studies conducted in the emergency department (Burger et al., 2016; Grunebaum et al., 2018; Kashani et al., 2014; Larkin & Beautrais, 2011) and are similar to the results attained for esketamine (Canuso et al., 2018). The unexpected lack of a statistically significant reduction in the depressive score is similar to other studies that evaluated ketamine for suicidal ideation and considered depression

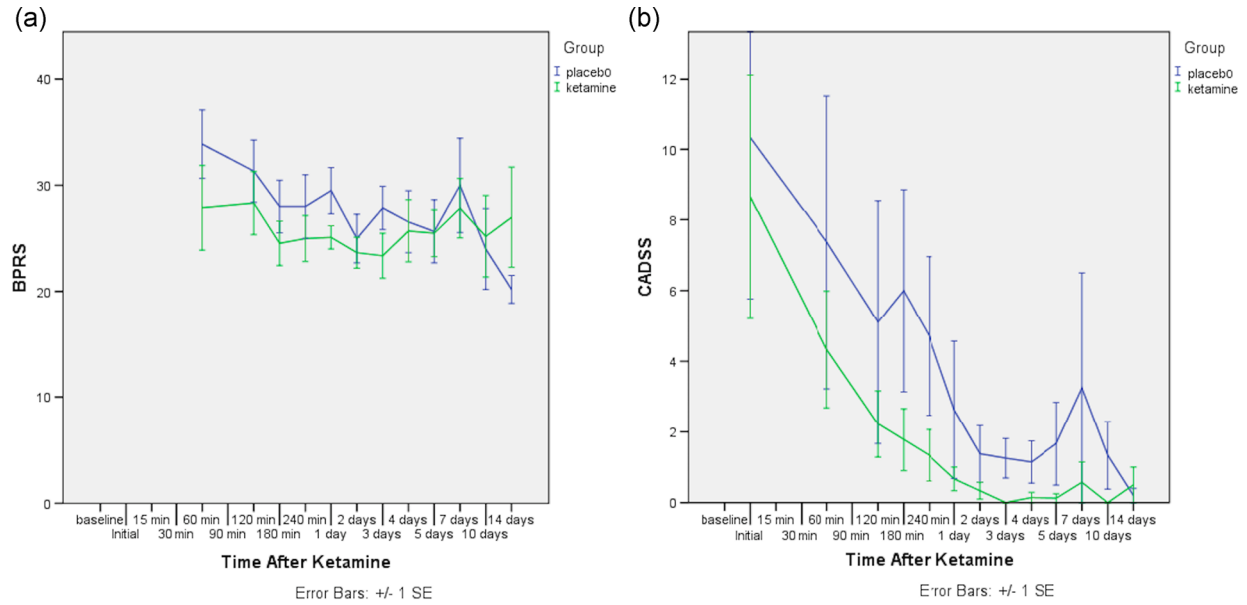

FIGURE 4 Side effects across time. BPRS, Brief Psychiatric Rating Scale; CADSS, Clinician-Administered Dissociative States Scale; *SE*, standard error of the mean

as a secondary outcome (Grunebaum et al., 2018; Murrough et al., 2015). This observation can be explained by the small sample size ($N = 18$). Alternatively, it can be explained by the relatively lower dose we used (0.2 mg/kg); this low dose, however, was based on a previous antisuicide study (Larkin & Beautrais, 2011). Most of the ketamine antidepressant studies used a higher dosage of 0.5–1 mg/kg, with preferable results (Fava et al., 2018). While such a dose may be preferable for treating depression, it might not be suitable for our "5-min technique."

4.3 | Novelty and importance

Specific treatments for depressed patients with suicidal ideation are scarce. Lithium, electroconvulsive treatment (ECT), and psychotherapies such as cognitive-behavioral therapy (CBT), and dialectical behavior therapy (DBT) have been suggested to alliviate suicidal ideation. These options, however, lack a rapid effect and may relieve suicidal ideation over weeks to months (Griffiths, Zarate, & Rasimas, 2014). The mainstay of managing depression with suicidal ideation is addressing the depression using monoamines antidepressants. This approach has some limitations. First, it is not specific for suicidal ideation. Second, there is a time lag of weeks to months until full efficacy (Nakajima, Suzuki, Watanabe, Kashima, & Uchida, 2010), Third, about one-third of patients fail to achieve remission even with advanced treatment strategies (Rush et al., 2006), thus, leaving those suffering acute suicidal ideation at high risk. Fourth, antidepressants can occasionally, paradoxically, enhance suicidal thoughts, especially in young adults and adolescents (Canadian Agency for Drugs and Technologies in Health Rapid Response Reports, 2015; Reeves & Ladner, 2010). Therefore, although antidepressants are widely used for the treatment of depression, it is clearly a suboptimal treatment to reduce suicidal ideation, especially in acute settings.

Acute presentation to the emergency department calls for rapidly effective strategies to reduce morbidity, mortality, functional impact, and promote cost savings. Our results may pave new avenues toward better management of this urgent challenge.

As our safety results indicate, given the lack of lasting side effects or cravings or even liking for drug—as evident in our addiction potential evaluation—the use of low-dose ketamine for suicidal individuals deserves serious consideration as a serious suicide-prevention intervention.

The strength and importance of this study, however, goes beyond a treatment option for suicide. This study presents a novel research paradigm for suicide research: evaluation of ketamine's effect on specific RDoC constructs. This approach, which was suggested in our previous work (Mallick & McCullumsmith, 2016) and by others (Burger et al., 2016; DiazGranados et al., 2010; Price et al., 2014), may lead to a better understanding of the neurobiological constructs of the suicide phenomena. Our results point out the beneficial effect of ketamine on positive and negative valence systems, but not on cognitive control. Further research is warranted on these specific domains and their response to different antisuicidal measures.

4.4 | Limitations

The main limitation of this study is the small sample size, resulting from the early termination of recruitment (as described in Section 2). Therefore, in spite of the statistically significant benefit, the ability to draw conclusions from such a sample is limited. Second, while subjects and study evaluators were blinded to randomization, there were subjective (dissociation, dizziness) and objective (pulse and blood pressure) effects that are diverse and may impair blindness. To that end, some studies have used midazolam as an active placebo. We, however, were concerned that the anxiolytic effect of midazolam

may influence suicidal ideation and other RDoC elements (i.e., anxiety) and might cause a different bias (type 2 error). Future studies should consider active and nonactive placebo. Third, follow-up was limited in time and not always complete, as patients were difficult to contact after discharge from the hospital. Fourth, we did not examine the length of hospital stay, an outcome that can reflect the clinical benefit of ketamine.

5 | CONCLUSION

A single infusion of ketamine, administered in the emergency department, is a safe and feasible treatment option for depressed, suicidal patients. We found it to alleviate suicidal ideation in the first hours after infusion. Furthermore, we present here an RDoC-based, novel paradigm, for suicide research. Future larger-scale studies should consider using a higher dose of ketamine (0.5 mg/kg) and addressing a transdiagnostic approach.

ACKNOWLEDGMENTS

We would like to thank our subjects and their families. In addition, we thank Keren Armoni-Domany and Jadienne Lord for their help and support.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

The authors choose not to share data.

ORCID

Yoav Domany http://orcid.org/0000-0002-7663-1584

REFERENCES

aan het Rot, M., Collins, K. A., Murrough, J. W., Perez, A. M., Reich, D. L., Charney, D. S., & Mathew, S. J. (2010). Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biological Psychiatry*, *67*(2), 139–145. https://doi.org/10.1016/j.biopsych.2009.08.038

American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders, fourth edition, text revision (DSM-IV-TR)*. Arlington, VA: Author.

Ballard, E. D., Luckenbaugh, D. A., Richards, E. M., Walls, T. L., Brutsche, N. E., Ameli, R., … Zarate, C. A., Jr. (2015). Assessing measures of suicidal ideation in clinical trials with a rapid-acting antidepressant. *Journal of Psychiatric Research*, *68*, 68–73. https://doi.org/10.1016/j.jpsychires.2015.06.003

Bauer, M. S., Crits-Christoph, P., Ball, W. A., Dewees, E., McAllister, T., Alahi, P., … Whybrow, P. C. (1991). Independent assessment of manic and depressive symptoms by self-rating: Scale characteristics and implications for the study of mania. *Archives of General Psychiatry*, *48*(9), 807–812.

Beck, A. T. (1986). Hopelessness as a predictor of eventual suicide. *Annals of the New York Academy of Sciences*, *487*, 90–96.

Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology*, *56*(6), 893–897.

Beck, A. T., Steer, R. A., & Ranieri, W. F. (1988). Scale for suicide ideation: Psychometric properties of a self-report version. *Journal of Clinical Psychology*, *44*(4), 499–505.

Beck, A. T., Weissman, A., Lester, D., & Trexler, L. (1974). The measurement of pessimism: The hopelessness scale. *Journal of Consulting and Clinical Psychology*, *42*(6), 861–865.

Bell, M., Milstein, R., Beam-Goulet, J., Lysaker, P., & Cicchetti, D. (1992). The Positive and Negative Syndrome Scale and the Brief Psychiatric Rating Scale: Reliability, comparability, and predictive validity. *The Journal of Nervous and Mental Disease*, *180*(11), 723–728.

Berman, R. M., Cappiello, A., Anand, A., Oren, D. A., Heninger, G. R., Charney, D. S., & Krystal, J. H. (2000). Antidepressant effects of ketamine in depressed patients. *Biological Psychiatry*, *47*(4), 351–354.

Bokor, G., & Anderson, P. D. (2014). Ketamine: An update on its abuse. *Journal of Pharmacy Practice*, *27*(6), 582–586. https://doi.org/10.1177/0897190014525754

Bremner, J. D., Krystal, J. H., Putnam, F. W., Southwick, S. M., Marmar, C., Charney, D. S., & Mazure, C. M. (1998). Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). *Journal of Traumatic Stress*, *11*(1), 125–136. https://doi.org/10.1023/a:1024465317902

Burger, J., Capobianco, M., Lovern, R., Boche, B., Ross, E., Darracq, M. A., & McLay, R. (2016). A double-blinded, randomized, placebo-controlled sub-dissociative dose ketamine pilot study in the treatment of acute depression and suicidality in a military emergency department setting. *Military Medicine*, *181*(10), 1195–1199. https://doi.org/10.7205/milmed-d-15-00431

Canadian Agency for Drugs and Technologies in Health (2015). *Second generation antidepressants for pediatric patients with major depressive disorder and anxiety disorder: A review of the clinical effectiveness and safety*. CADTH Rapid Response Reports. Ottawa, ON: Author.

Canuso, C. M., Singh, J. B., Fedgchin, M., Alphs, L., Lane, R., Lim, P., … Drevets, W. C. (2018). Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: Results of a double-blind, randomized, placebo-controlled study. *American Journal of Psychiatry*, *175*, 620–630. https://doi.org/10.1176/appi.ajp.2018.17060720

DiazGranados, N., Ibrahim, L. A., Brutsche, N. E., Ameli, R., Henter, I. D., Luckenbaugh, D. A., … Zarate, C. A., Jr. (2010). Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *Journal of Clinical Psychiatry*, *71*(12), 1605–1611. https://doi.org/10.4088/JCP.09m05327blu

Domany, Y., Bleich-Cohen, M., Tarrasch, R., Meidan, R., Litvak-Lazar, O., Stoppleman, N., … Sharon, H. (2018). Repeated oral ketamine for outpatient treatment of resistant depression: Randomised, double-blind, placebo-controlled, proof-of-concept study. *British Journal of Psychiatry*, *214*, 20–26. https://doi.org/10.1192/bjp.2018.196

Fava, M., Freeman, M. P., Flynn, M., Judge, H., Hoeppner, B. B., Cusin, C., … Papakostas, G. I. (2018). Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). *Molecular Psychiatry*, https://doi.org/10.1038/s41380-018-0256-5

Glenn, C. R., Kleiman, E. M., Cha, C. B., Deming, C. A., Franklin, J. C., & Nock, M. K. (2018). Understanding suicide risk within the Research Domain Criteria (RDoC) framework: A meta-analytic review. *Depression and Anxiety*, *35*(1), 65–88. https://doi.org/10.1002/da.22686

Griffiths, J. J., Zarate, C. A., Jr., & Rasimas, J. J. (2014). Existing and novel biological therapeutics in suicide prevention. *American Journal of Preventive Medicine*, *47*(3 Suppl 2), S195–S203. https://doi.org/10.1016/j.amepre.2014.06.012

Grunebaum, M. F., Galfalvy, H. C., Choo, T.-H., Keilp, J. G., Moitra, V. K., Parris, M. S., … Mann, J. J. (2018). Ketamine for rapid reduction of suicidal thoughts in major depression: A midazolam-controlled randomized clinical trial. *American Journal of Psychiatry*, *175*, 327–335. https://doi.org/10.1176/appi.ajp.2017.17060647

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap): A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*, *42*(2), 377–381. https://doi.org/10.1016/j.jbi.2008.08.010

Healy, D., Barry, K., Blow, F., Welsh, D., & Milner, K. (2006). Routine use of the Beck Scale for Suicide Ideation in a psychiatric emergency department. *General Hospital Psychiatry*, *28*(4), 323–329. https://doi.org/10.1016/j.genhosppsych.2006.04.003

Heiligenstein, J. H., Tollefson, G. D., & Faries, D. E. (1993). A double-blind trial of fluoxetine, 20 mg, and placebo in out-patients with DSM-III-R major depression and melancholia. *International Clinical Psychopharmacology*, *8*(4), 247–252.

Heron, M. (2016). Deaths: Leading causes for 2014. *National Vital Statistics Reports*, *65*(5), 1–96.

Ibrahim, L., Diazgranados, N., Luckenbaugh, D. A., Machado-Vieira, R., Baumann, J., Mallinger, A. G., & Zarate, C. A., Jr. (2011). Rapid decrease in depressive symptoms with an N-methyl-D-aspartate antagonist in ECT-resistant major depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *35*(4), 1155–1159. https://doi.org/10.1016/j.pnpbp.2011.03.019

Insel, T. R. (2014). The NIMH Research Domain Criteria (RDoC) project: Precision medicine for psychiatry. *American Journal of Psychiatry*, *171*(4), 395–397. https://doi.org/10.1176/appi.ajp.2014.14020138

Ionescu, D. F., Luckenbaugh, D. A., Niciu, M. J., Richards, E. M., & Zarate, C. A., Jr. (2015). A single infusion of ketamine improves depression scores in patients with anxious bipolar depression. *Bipolar Disorders*, *17*(4), 438–443. https://doi.org/10.1111/bdi.12277

Julian, L. J. (2011). Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). *Arthritis Care & Research*, *63*(Suppl 11), S467–S472. https://doi.org/10.1002/acr.20561

Kashani, P., Yousefian, S., Amini, A., Heidari, K., Younesian, S., & Hatamabadi, H. R. (2014). The effect of intravenous ketamine in suicidal ideation of emergency department patients. *Emergency*, *2*(1), 36–39.

Larkin, G. L., & Beautrais, A. L. (2011). A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. *International Journal of Neuropsychopharmacology*, *14*(8), 1127–1131. https://doi.org/10.1017/s1461145711000629

Mallick, F., & McCullumsmith, C. B. (2016). Ketamine for treatment of suicidal ideation and reduction of risk for suicidal behavior. *Current Psychiatry Reports*, *18*(6), 61. https://doi.org/10.1007/s11920-016-0680-7

Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry*, *134*, 382–389.

Murrough, J. W., Iosifescu, D. V., Chang, L. C., Al Jurdi, R. K., Green, C. E., Perez, A. M., … Mathew, S. J. (2013). Antidepressant efficacy of ketamine in treatment-resistant major depression: A two-site randomized controlled trial. *American Journal of Psychiatry*, *170*(10), 1134–1142. https://doi.org/10.1176/appi.ajp.2013.13030392

Murrough, J. W., Soleimani, L., DeWilde, K. E., Collins, K. A., Lapidus, K. A., Iacoviello, B. M., … Charney, D. S. (2015). Ketamine for rapid reduction of suicidal ideation: A randomized controlled trial. *Psychological Medicine*, *45*(16), 3571–3580. https://doi.org/10.1017/s0033291715001506

Nakajima, S., Suzuki, T., Watanabe, K., Kashima, H., & Uchida, H. (2010). Accelerating response to antidepressant treatment in depression: A review and clinical suggestions. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *34*(2), 259–264. https://doi.org/10.1016/j.pnpbp.2009.12.001

Pinninti, N. R., Madison, H., Musser, E., & Rissmiller, D. (2003). MINI International Neuropsychiatric Schedule: Clinical utility and patient acceptance. *European Psychiatry*, *18*(7), 361–364.

Posner, K., Brown, G. K., Stanley, B., Brent, D. A., Yershova, K. V., Oquendo, M. A., … Mann, J. J. (2011). The Columbia-Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. *American Journal of Psychiatry*, *168*(12), 1266–1277. https://doi.org/10.1176/appi.ajp.2011.10111704

Price, R. B., Iosifescu, D. V., Murrough, J. W., Chang, L. C., Al Jurdi, R. K., Iqbal, S. Z., … Mathew, S. J. (2014). Effects of ketamine on explicit and implicit suicidal cognition: A randomized controlled trial in treatment-resistant depression. *Depression and Anxiety*, *31*(4), 335–343. https://doi.org/10.1002/da.22253

Price, R. B., Nock, M. K., Charney, D. S., & Mathew, S. J. (2009). Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biological Psychiatry*, *66*(5), 522–526. https://doi.org/10.1016/j.biopsych.2009.04.029

Reeves, R. R., & Ladner, M. E. (2010). Antidepressant-induced suicidality: An update. *CNS Neuroscience & Therapeutics*, *16*(4), 227–234. https://doi.org/10.1111/j.1755-5949.2010.00160.x

Rossen, L. M., Hedegaard, H., Khan, D., & Warner, M. (2018). County-level trends in suicide rates in the U.S., 2005–2015. *American Journal of Preventive Medicine*, *55*(1), 72–79. https://doi.org/10.1016/j.amepre.2018.03.020

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., … Fava, M. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *American Journal of Psychiatry*, *163*(11), 1905–1917. https://doi.org/10.1176/ajp.2006.163.11.1905

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., … Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*, *59*(Suppl 20), 22–33. quiz 34–57.

Singh, J. B., Fedgchin, M., Daly, E. J., De Boer, P., Cooper, K., Lim, P., … Van Nueten, L. (2016). A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. *American Journal of Psychiatry*, *173*(8), 816–826. https://doi.org/10.1176/appi.ajp.2016.16010037

Stefansson, J., Nordström, P., & Jokinen, J. (2012). Suicide Intent Scale in the prediction of suicide. *Journal of Affective Disorders*, *136*(1–2), 167–171. https://doi.org/10.1016/j.jad.2010.11.016

Ting, S. A., Sullivan, A. F., Boudreaux, E. D., Miller, I., & Camargo, C. A., Jr. (2012). Trends in US emergency department visits for attempted suicide and self-inflicted injury, 1993–2008. *General Hospital Psychiatry*, *34*(5), 557–565. https://doi.org/10.1016/j.genhosppsych.2012.03.020

Wilkinson, P., Kelvin, R., Roberts, C., Dubicka, B., & Goodyer, I. (2011). Clinical and psychosocial predictors of suicide attempts and non-suicidal self-injury in the Adolescent Depression Antidepressants and Psychotherapy Trial (ADAPT). *American Journal of Psychiatry*, *168*(5), 495–501. https://doi.org/10.1176/appi.ajp.2010.10050718

Wilkinson, S. T., Ballard, E. D., Bloch, M. H., Mathew, S. J., Murrough, J. W., Feder, A., … Sanacora, G. (2018). The effect of a single dose of intravenous ketamine on suicidal ideation: A systematic review and individual participant data meta-analysis. *American Journal of Psychiatry*, *175*(2), 150–158. https://doi.org/10.1176/appi.ajp.2017.17040472

Zarate, C. A., Jr., Singh, J. B., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A., … Manji, H. K. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of General Psychiatry*, *63*(8), 856–864.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Domany Y, Shelton RC, McCullumsmith CB. Ketamine for acute suicidal ideation. An emergency department intervention: A randomized, double-blind, placebo-controlled, proof-of-concept trial. *Depress Anxiety*. 2019;1–10. https://doi.org/10.1002/da.22975