Archives of Suicide Research

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/usui20

Single, Fixed-Dose Intranasal Ketamine for Alleviation of Acute Suicidal Ideation. An Emergency Department, Trans-Diagnostic Approach: A Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept Trial

Yoav Domany & Cheryl B. McCullumsmith

To cite this article: Yoav Domany & Cheryl B. McCullumsmith (2021): Single, Fixed-Dose Intranasal Ketamine for Alleviation of Acute Suicidal Ideation. An Emergency Department, Trans-Diagnostic Approach: A Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept Trial, Archives of Suicide Research, DOI: 10.1080/13811118.2021.1878078

To link to this article: https://doi.org/10.1080/13811118.2021.1878078

Published online: 14 Feb 2021.

ARCHIVES OF SUICIDE RESEARCH
https://doi.org/10.1080/13811118.2021.1878078

Routledge
Taylor & Francis Group

Single, Fixed-Dose Intranasal Ketamine for Alleviation of Acute Suicidal Ideation. An Emergency Department, Trans-Diagnostic Approach: A Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept Trial

Yoav Domany and Cheryl B. McCullumsmith

ABSTRACT

Background: Suicidal patients often present to the emergency department, where specific anti-suicidal treatment is lacking. Ketamine, a Glutamate modulator and a rapidly acting antidepressant with anti-suicidal properties, might offer relief.

Aims: Evaluation of single, fixed-dosed intranasal ketamine for acute suicidal ideation in the emergency department.

Methods: Between August 2016 and April 2018, 30 eligible suicidal subjects, scheduled for psychiatric hospitalization, independently of their psychiatric diagnosis, were randomized to intranasal ketamine 40 mg or saline placebo. Safety and efficacy evaluations were scheduled for 30, 60, 120 and 240 min post administration and on days 1, 2, 3, 4, 5, 7, 21 and 28. Primary outcome was suicidal ideation.

Results: Fifteen subjects were randomized for each study group. All were analyzed for primary and secondary outcomes. Four hours post administration, the mean difference in suicidal symptoms between the groups, measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) item of suicidal thoughts (MADRS-SI), was 1.267 (95% confident interval 0.1–2.43, $p < 0.05$) favoring treatment. Remission from suicidal ideation was evident in 80% for the ketamine group compared with 33% for the controls ($p < 0.05$). The mean difference in depressive symptoms, measured by MADRS, at the same time was 9.75 (95% confident interval 0.72–18.79, $p < 0.05$) favoring ketamine. Treatment was safe and well-tolerated. Conclusions: Single, fixed-dose, intranasal ketamine alleviated suicidal ideation and improved depressive symptoms four hours post administration. We present here an innovative paradigm for emergency department management of suicidal individuals. Future larger-scale studies are warranted. ClinicalTrials.gov Identifier: NCT02183272

KEYWORDS
Ketamine; intra-nasal; suicidal ideation; emergency department

INTRODUCTION

Acute suicidal patients represent more than half a million annual admissions to emergency departments in the U.S (Ting et al., 2012). In the absence of specific treatment for acute suicidal ideation, these patients are often hospitalized for brief stabilization and later discharged before psychopharmacological treatments can show efficacy. Although suicide is frequently associated with depression, it may be mediated by a general psychopathology dimension (Hoertel et al., 2015), and can be considered as a

distinct, "trans-diagnostic" entity, independent of other psychiatric diagnosis. Trans-diagnostic approach can be useful in the emergency department, where suicidal patients need to be rapidly managed, sometimes prior to establishing a thorough diagnosis.

Ketamine: A glutamatergic modulator, has been shown to rapidly improve depressive symptoms in unipolar (Mallick & McCullumsmith, 2016; Singh et al., 2016; Zarate et al., 2006), and bipolar depression (Diazgranados et al., 2010), and Esketamine the S-enantiomer of ketamine, was recently approved by the FDA as a treatment for resistant depression (Daly et al., 2018; Kim et al., 2019). The rapid antidepressant effect of ketamine makes it a promising treatment option for *suicidal ideation* both in unipolar (Grunebaum et al., 2018; Price et al., 2009), and bipolar depression (Grunebaum et al., 2017). A recent meta-analysis (Witt et al., 2020) found it to reduce suicidal ideation up to 72 hours post infusion. Esketamine was also studied for the rapid reduction of suicidal ideation for depressed subjects with imminent suicide risk (Canuso et al., 2018; Fu et al., 2020) with mixed results.

Furthermore, the rapid anti-suicidal effect of ketamine makes it a promising treatment option for *emergency department interventions*. This was studied by Kashani et al., in a small open trial (Kashani et al., 2014),who reported a significant reduction in suicidal ideation but failed to reach their preset goal of a Scale for Suicidal Ideation (SSI)<4. Another small ($n=10$) controlled study, (Burger et al., 2016), found a significant reduction of suicidal ideation four hours post infusion, and concluded that ketamine may be an effective means of acutely improving suicidal ideation and depression. In our previous pilot study (Domany et al., 2020), subjects with depression and acute suicidal ideation who presented to the emergency department, were randomized to *intravenous* ketamine or control. Our preliminary results showed a reduction in suicidal ideation two hours post ketamine infusion.

Additionally, in accordance with the trans-diagnostic approach, it was suggested that ketamine's anti-suicidal properties may not be entirely driven by improvement in depressive symptoms (Ballard et al., 2014; Wilkinson et al., 2018).

Route of administration

Ketamine was traditionally administered intravenously. Other routes of administrations (e.g., oral, subcutaneous, intramuscular, and intranasal) (Domany et al., 2018; Lapidus et al., 2014) have been less studied, and have been reported to be safer with less psychomimetic and cardiovascular side effects (36% compared with 72%) though of lesser efficacy (40% vs 60% response rate, at 24 h) (Short et al., 2018). Alternatively, a small trial reported (Loo et al., 2016) similar efficacy and side effects between IV, IM, and SC administration of ketamine. The bioavailability of nasal ketamine spray is reported to be approximately 45% (Peltoniemi et al., 2016) and is greater than sublingual, rectal, or oral administration. Esketamine, as mention earlier, was administered intranasally, (Daly et al., 2018) and a commercial device was announced (Bahr et al., 2019).

As a next step of our pilot study (Domany et al., 2020) we aimed to evaluate intranasal administration, which is a more practical route of administration and can be used as an emergency intervention. Furthermore, our patients were recruited based on

theirsuicidal ideation and intent independently of their psychiatric diagnosis meaning that, for example, no diagnosis of depression was required.

Objectives: Evaluation of the feasibility, tolerability, and efficacy of a single, fixed-dose *of intranasal* ketamine for alleviation of acute suicidal ideation in trans-diagnostic extremely suicidal patients in an emergency department setting, independent of their diagnosis.

METHODS

Participants

Forty-five subjects, with suicidal ideation in need of psychiatric hospitalization were evaluated in the Emergency Department of the University of Cincinnati Medical Center (UCMC) between August 2016 and April 2018 and were assessed for study eligibility. Fifteen subjects were ruled out due to medical or psychiatric exclusion criteria. Thirty subjects were allocated for randomization. Subjects were included if they required psychiatric hospitalization due to suicidal risk and suffered suicidal ideation with a cutoff score of at least three on the first five items on the Beck Scale for Suicidal Ideation (BSS) (Beck et al., 1988) meaning at least a death wish; and a score higher than 2 on the Columbia Scale for Suicide Severity Rating (C-SSRS) (since last visit, version 1/14/09) (Posner et al., 2011), meaning at least the presence of active suicidal plans. All participants were evaluated by the primary clinical team prior to contact by study personnel and admission criteria was determined by a treating (non-study) clinician. Participants were age 18–65, with no genders, racial nor ethnic exclusions. Participants were excluded if they were diagnosed with schizophrenia spectrum disorders, dissociative disorders, pervasive developmental disorder or cognitive disorder. Acute intoxication or withdrawal from alcohol or other substances, as determined by clinical interview and urine drug screen were also excluded. Homicidal risk as determined by clinical interview was excluded. Pregnant, lactating or post-partum women (within 2 months of delivery) were excluded; all women of reproductive potential had a negative urine pregnancy test. Subjects were excluded if they had any known hypersensitivity or history of a serious adverse reaction to ketamine and if they had suffered any clinically significant medical condition that would preclude the use of ketamine, including respiratory illness requiring the regular use of oxygen.

Procedure

This study was reviewed and approved by the University of Cincinnati Institutional Review Board and registered with clinicaltrials.gov (ClinicalTrials.gov Identifier**:** NCT02183272). Written informed consent was obtained from all participants after a thorough description of the study and prior to any study-specific procedure. Baseline assessments included physical examination, a full medical and psychiatric history, and urine obtained for drug screen and pregnancy test for women of reproductive potential. Prior to subjects' consent, the pharmacist, the only non-blinded member of the study group, prepared active drug and placebo in similar 10 ml syringes following a randomization schedule. Those meeting all inclusion and no exclusion criteria

were randomized (1:1) to racemic ketamine 100 mg/ml 40 mg (0.4 ml) or matched inactive placebo (normal saline).

Originally, we intended to administer weight-based ketamine intravenously with a dose of 0.2 mg/kg, as reported in clinicalTrials.gov. However, the first reports of intranasal administration (Lapidus et al., 2014) lead us to evaluate this more practical way of administration, and to simplify dosing we investigated fixed-dosing, considering a bioavailability of 45% (Peltoniemi et al., 2016), the calculated dose (based on average human weight of 80 kg) was 40 mg.

An intranasal mucosal atomization device was used to provide one intranasal application of solution (volume 0.1 ml) in each nostril and an additional squirt in each nostril separated by 10 minutes, (altogether 4 squirts). Each of the 4 ketamine squirts provided 10 mg of study drug, totaling 40 mg. Drug was applied by the study physician- a psychiatrist. Subjects' vital signs were monitored for 4 hours post administration. At the completion of the post-treatment observation period, the participant was admitted to the psychiatry units at the UCMC. The time of discharge was determined by a blinded, non-study physician who was not aware of the patient's status (randomization) in the study. All patients received standard psychiatric care by the treating (non-study) psychiatrist. The treating physicians could make any changes in treatment they deemed warranted by the patient's condition.

Assessments

The primary outcome was change in suicidal ideation over a 4-week period. As this was a proof-of-concept trial no a-priori timepoint was chosen as a specific primary outcome measure. Further we chose to observe both rater-based and patient-reported-scales; Beck Scale for Suicide ideation (BSS) and the suicidal thoughts item on the Montgomery Åsberg Depression Rating Scale (MADRS)-(MADRS-SI), respectively. Assessments were performed at baseline prior to treatment and at 30, 60, 120 and 240 min post-administration, and on days 1, 2, 3, 4, 5, 7, 14, 21 and 28 post-administration.

Suicide scales

Baseline suicidal ideation, intensity of ideation, and suicidal behaviors were assessed using the Columbia Suicide Severity Rating Scale (C-SSRS), (Since last visit, version 1/14/09) (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. Additional evaluation of baseline suicidal ideation was performed using the Beck Scale for Suicidal ideation (BSS) (Beck et al., 1988). This scale is the self-reported version of the more prevelent Scale for Suicide Ideation (SSI) and has been shown to be prospectively associated with suicidal behavior including death by suicide. (Horon et al., 2013), and the suicidal thoughts item on the Montgomery Åsberg Depression Rating Scale (MADRS)-(MADRS-SI). The MADRS is a valid, widely used, questionnaire for depression (see below) and the MADRS-SI-suicidal thoughts-(graded 0–6) is an overall clinician-rated global impression of suicidal thoughts and actions.

Change in suicidal ideation was evaluated using the BSS scale. This scale, however, has some limitations with interpretation of the changes over time. Most notably because

the structure of the scale dictates that the scale changes depending on the patient's responses to the first five questions; if the answers to questions 4 and 5 are zero (which assess approach toward death), the other 14 questions are not asked. This changes the possible total score of the scale significantly. Further issues with the BSS are that it conflates trait and state factors, with many questions not able to change imminently or at all. The second scale for change in suicidal ideation was the suicidal thoughts item on the (MADRS)- The (MADRS-SI). This question has been used in many studies of treatment effects on suicidal behavior, including rapidly acting anti-suicidal treatments (Canuso et al., 2018), and has been validated for those trials (Ballard et al., 2015).

Secondary outcomes

Secondary outcomes were changes in depressive symptoms, remission from suicidal ideation, days of admission, and harms.

Depression scale

The MADRS (Montgomery & Asberg, 1979) was the measure of change in depression. The MADRS is a commonly used and reliable clinician-rated assessment of depression severity that is sensitive to treatment effects. It has been used successfully in prior ketamine studies (Ionescu et al., 2015; Murrough et al., 2015) The MADRS has been modified to reflect the period since last assessment.

Remission from suicidal ideation was defined by a score of 0 on the MADRS-SI item (indicating no suicidal thoughts).

Length of hospitalization

This outcome reflects a broad clinical evaluation, risk assessments, and especially, suicidality evaluation. Additionally, this outcome holds public health significance, with economic implications. Time of discharge (which determined this outcome) was decided by a non-study physician, who was blinded to the randomization.

Safety, tolerability, and adverse effects

Currently the assessments of side effects in ketamine trials for depression is inadequate (Short et al., 2018). Therefore, we have developed a Ketamine Side Effects Scale (KSES), a similar version of the recently published, Ketamine Side Effect Tool (KSET) (Short et al., 2020), to assess for ketamine side effects. In this scale, we evaluated vital sign abnormalities, agitation, sedation, dizziness, nausea, psychosis and dissociation in a concise manner (scales of 0–5).

Data collection and management

To ensure the quality of Electronic Data Capture (EDC) and management, the data management team used the REDCap EDC system. 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).

Statistical analysis

All outcomes were summarized descriptively (e.g., frequencies, summary statistics) and assessed for normality prior to analysis using normal probability plots and Kolmogorov Smirnov tests. 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 ($n = 60$). However, because the primary investigator has left the institution, we had to prematurely end study recruitment. Baseline demographic characteristics such as age and gender were compared using chi-square or *t*-test. Comparison of the two groups for suicidal ideation and depressive symptoms at several intervals post-administration was calculated using linear mixed models. In addition, data at four hours post-administration was analyzed using *t*-tests for independent samples. Remission rates were calculated using Chi square. Median length of hospitalization was reported with 25th and 75th percentiles, and statistics calculations used the Mann Whitney *U*-test. Tolerability and safety were evaluated descriptively and separately for each treatment group and compared using chi-square or *t*-test.

RESULTS

Demographic characteristics and mean baseline scores on the MADRS, MADRS-SI, and the BSS of recruited subjects are presented in Table 1. Fifteen subjects were randomized to the ketamine group and 15 to the placebo group. All were analyzed for primary and secondary outcomes. There were no differences between groups at baseline in any of the demographic or assessment scales. The main outcome measure was change in suicidal ideation, as measured by the self-reported BSS and rater-based MADRS-SI. Additional outcomes were remission from suicidal ideation as indicated by MADRS-SI = 0, total days of admission, and a change in depression as measured by the MADRS. This trial was prematurely ended because the primary investigator has left the institution.

TABLE 1. Baseline demographics and outcome measures.

Variables	Total ($n = 30$)	Placebo ($n = 15$)	Ketamine ($n = 15$)	X^2 or *t* value	Sig
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		36.17 (±5.92)	40.23 (±5.29)	1.8	.85
MADRS SI		4.93 (±1.27)	5.14 (±0.95)	0.51	.65
BSS total Score		23.81 (±4.83)	25.61 (±5.22)	−.875	.358

Abbreviations: MADRS: Montgomery–Åsberg Depression Rating Scale; MADRS SI: Montgomery–Åsberg Depression Rating Scale item of suicidal thoughts; BSS: Beck Suicidality Scale; $^*p < 0.05$.

Efficacy results

Four hours post drug administration; we found a reduction in suicidal ideation. The mean difference in suicidal symptoms between the groups, measured by the MADRS-SI (scale of 0–6), was 1.267 (Reduction of 4.89 ± 0.4 compares with 3.35 ± 0.5) (95% confident interval 0.1–2.43, $p < 0.05$) favoring treatment. In the self-reported BSS scale (full version), we observed a reduction of 17.4 ± 9.4 points in the ketamine group compared to a reduction of 10.5 ± 8.21 in the placebo group. This reduction, however, did not reach a statistically significant level ($p = 0.086$). Furthermore, linear mixed model did not show significance for the group by time interaction. Unexpectedly, the suicidal ideation score for the ketamine group remained low for the entire study trial following a single ketamine administration. See Figure 1 for mean suicidal score across time. Figure 1A: self *reported* BSS, and Figure 1B. *rater based* MADRS-SI.

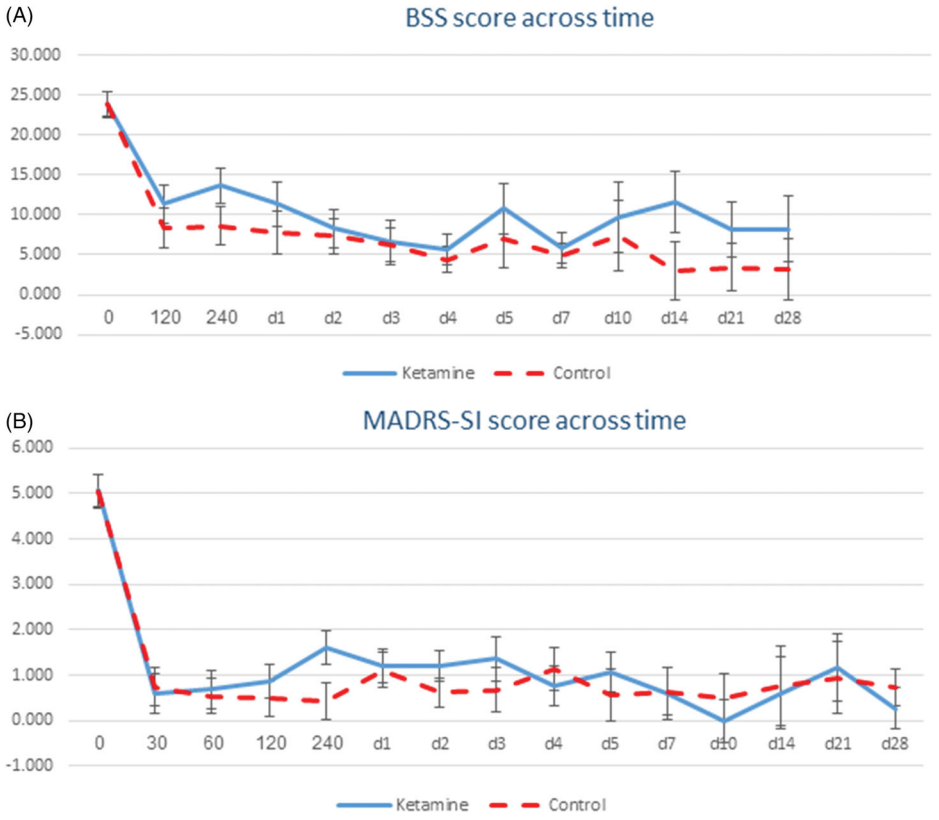

FIGURE 1. Change in suicidal symptoms across time using linear mixed model with standard errors (SE): (A) As evident in the self-reported Back Scale for Suicide ideation (BSS). (B) As evident in the rater based MADRS 10th question (MADRS-SI)—score of 0–6. Illustration of the mean MADRS-SI score. 30, 60, 120, 240 stands for number of minutes, d1–d28 stands for number of days. BSS: Back Scale of Suicide ideation; MADRS: Montgomery-Åsberg Depression Rating Scale, MADRS-SI Montgomery-Åsberg Depression Rating Scale, item for suicidal thoughts.

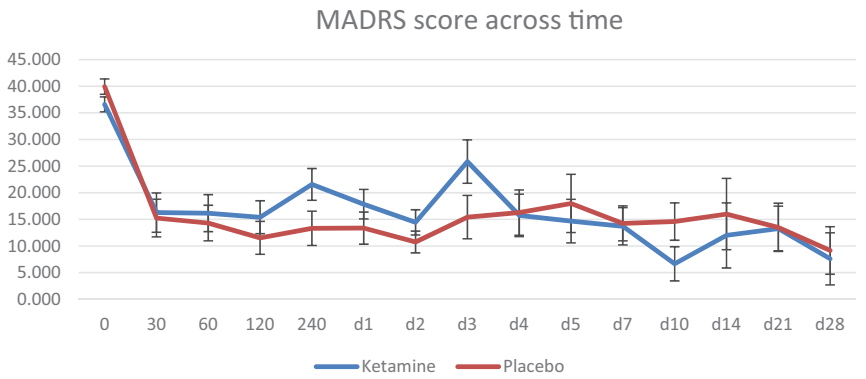

FIGURE 2. Change in depressive symptoms across time as evident in the MADRS. Illustration of the mean MADRS score, using linear mixed model with standard errors (SE). MADRS: Montgomery-Åsberg Depression Rating Scale. 30, 60, 120, 240 stands for number of minutes, d1–d28 stands for number of days.

Secondary outcomes

Remission from suicidal ideation was defined by a score of 0 on the MADRS-SI item (indicating no suicidal thoughts). Four hours post-administration, twelve of 15 subjects in the ketamine group achieved remission (80%) compared to 5 of 15 (33%) in the placebo group ($p < 0.01$). *Depression*: The mean difference in depressive symptoms, measured by MADRS, at 4 hours was 9.75 (95% Confidence Interval 0.72–18.79, $p < 0.05$) favoring the ketamine group. See Figure 2 for the change in depressive symptoms across time as apparent from the MADRS. *Length of hospitalization:* The ketamine group had median hospitalization length of 5 days (4–8.5) compared with 9 days (5.5–10.5) for the control (median is reported with 25th and 75th percentiles). There was a trend toward the effect of ketamine on the reduction of admission length ($p = 0.089$). See Figure 3.

Safety results

We evaluated the harms throughout the study period. Side effects were most prominent one-hour post administration and the results of the KSES at one hour are presented in Table 2. The ketamine group reported a higher prevalence of side effects; however, no statistically significant difference was noted. Two hours post administration; no evidence of side effects were found. No subject suffered psychotic symptoms. This observation may be, in part, due to the relatively low bioavailability of intranasal administration (45%) (Peltoniemi et al., 2016). One subject, who had baseline dissociative symptoms, reported worsening of those symptoms; however overall, this subject reported a good experience, and his suicidal scales improved.

DISCUSSION

We found single, fixed-dose intranasal ketamine to alleviate acute suicidal ideation and improve depressive symptoms four hours post administration in a trans-diagnostic, extremely suicidal cohort presenting to the emergency department. Further, we found ketamine to induce remission of suicidal ideation in 80% of our study subjects, and we report a trend toward the effect of ketamine in shortening the length of hospitalization.

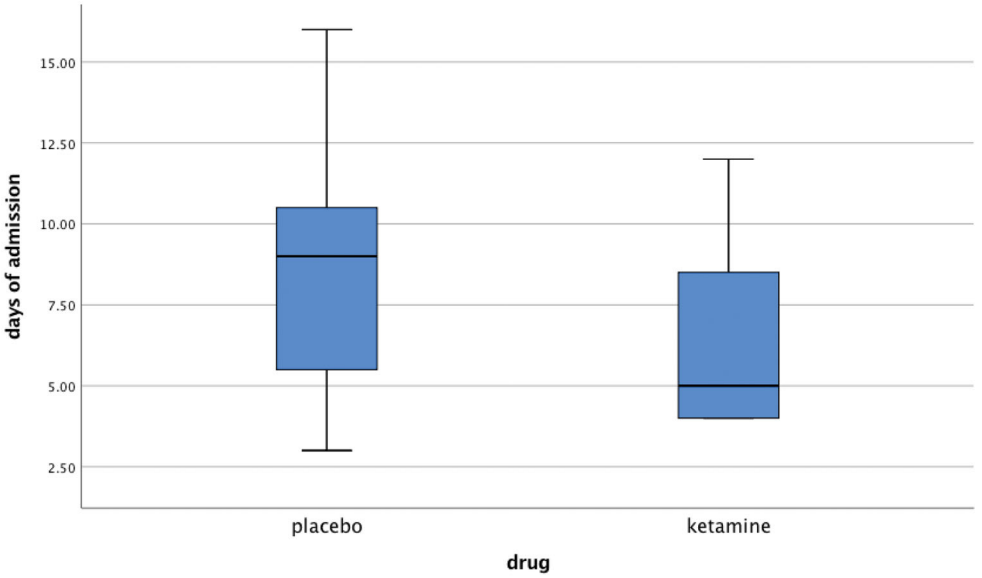

FIGURE 3. Comparison of days of admission between the ketamine and placebo groups, presented as a box plot. As can be seen in the figure, the median days of admission for the ketamine group was 5 (4–8.5) compares with 9 (5.5–10.5). Percentiles 25 and 75 are additionally reported.

TABLE 2. Safety results.

	Ketamine	SD	Placebo	SD	*p*
Increase in Systolic BP	0.64	1.03	0.29	0.49	0.35
Increase in Pulse	0.36	0.81	0.78	1.09	0.36
Sedation	0.33	0.65	0.78	0.83	0.20
Agitation	0.25	0.62	0.22	0.44	0.91
Vertigo	0.33	0.89	0	0	0.22
Dizziness while sitting	0.33	0.49	0.1	0.32	0.19
Nausea	0.33	0.65	0	0	0.15
Nystagmus	0	0	0	0	Non-applicable
Unusual thought content	0	0	0.1	0.32	0.34
Paranoia	0	0	0	0	Non-applicable
Hallucinations	0	0	0	0	Non-applicable
Visual illusions	0	0	0.1	0.32	0.34
Experience where time was altered	0.17	0.39	0	0	0.17
Experience where space was altered	0.17	0.39	0.2	0.63	0.89
Experience incapable of being expressed in words	0.33	0.78	0.4	1.26	0.89
Experience of leaving my body	0	0	0.2	0.632	0.34

Side effects 1 h post administration
Evaluation was conducted on the Ketamine side effect scale
For each side effect there is a 0–5 scale
0-None, 1-mild, 2-moderate, 3-marked, 4-severe, 5-very severe discontinue and consider intervention.
For increase in systolic blood pressure the scale for was: 1-<10 mmHg, 2-10–20 mmHg
3-20–30 mmHg, 4 – 40–50 mmHg, 5->50 mmHg
For increase in pulse the scale was: 1-<5bpm, 2- 5–10 bpm, 3-10–15 bpm, 4-15–20 bpm, 5->20 bpm.

Comparison to other studies

Our study replicated the results of emergency department settings of Burger et al. (Burger et al., 2016), and of our pilot study (Domany et al., 2020) in a larger cohort. Further, our findings are consistent with others who demonstrated the anti-suicidal

effect in a non-emergency context in treatment resistant depression (Grunebaum et al., 2018; Price et al., 2014), bipolar depression (Diazgranados et al., 2010) and on a wider diagnostic cohort (Murrough et al., 2015). In our previous study (Domany et al., 2020), we demonstrated the anti-suicidal effect of a single intravenous infusion of ketamine; here, we administered ketamine intranasally; which potentially can be safer and more practical. Our study is similar in design to the study of Canuso et al. (2018) with two main differences. The first is that they studied Esketamine, and the second is our trans-diagnostic approach. The similar results, however, emphasis the replicability of the data and strengthen both studies. Fixed 100 mg dose intranasal administration of ketamine for treatment resistant depression was evaluated by Galvez et al (Galvez et al., 2018) but they had to suspend their trial due to tolerability problems. Our study was designed to assess ketamine for suicidal ideation, and we used lower doses (40 mg compared to 100 mg). Both of the studies used fixed-dose and not the traditional weight-based dose (usually 0.5 mg/kg). Compared to Galvez et al (Galvez et al., 2018), all of our subjects tolerated this route of administration well, we found it to be pragmatic and applicable for clinical settings.

Diagnostic considerations

Suicide is highly related to depression; however, it might also be a devastating result of many different mental disorders or life adversities. Ballard et al. (2014) described that the improvement in suicidal ideation following ketamine infusion, is related, but not completely driven by improvement in depression and anxiety. Hoertel et al in a national prospective study (Hoertel et al., 2015) argued that suicide attempts are related to a general psychopathology dimension. This approach was strengthened by the DSM5 proposed criteria of "Suicidal behavior disorder" (Oquendo & Baca-Garcia, 2014). Further, suicide, as a distinct entity, was supported by Niculescu et al (Le-Niculescu et al., 2013) who reported specific blood biomarkers for suicidality, and additional study (Just et al., 2017) reported a neural presentation of suicide. A trans-diagnostic approach to the management of suicidal ideation is particularly useful in the emergency department settings, in which a potentially life-threatening condition requires an immediate reaction, sometimes prior to a comprehensive diagnosis.

Novelty and importance

Few treatment options for suicide ideation are available, including lithium, clozapine, electro-convulsive treatment (ECT), and psychotherapies such as cognitive behavioral treatment (CBT) or dialectical behavioral treatment (DBT). Those treatment options lack the desired rapid effect. (Griffiths et al., 2014). Since suicidal ideation often occurs in the context of depression, another widely used approach is prescribing antidepressants. which are sub-optimal for the management of acute suicidal ideation, because of the time lag until full efficacy, and that substantial portion of the patients which will fail to achieve remission (Rush et al., 2006). Further, antidepressants can paradoxically, enhance suicidal thoughts, especially in young adults and adolescents (Brent, 2016). Therefore, there is an urgent need for rapidly effective strategies to reduce suicidal

ideation. The importance of this study is the proposal of a novel paradigm to the management of acute suicidal ideation in the emergency department settings, one that includes diagnostic considerations- a trans-diagnostic approach, and treatment option- a single, fixed-dose intranasal ketamine.

Clinical implications

We found that ketamine alleviated suicidal thoughts, and depressive symptoms four hours post administration. Although promising, our observation is inconclusive, and the linear mixed statistical model did not show significance for the random group by time interaction. Suicidal ideation can be brief and transient, thus even temporary relief, as was seen by the reduction in suicidal ideation 4 hours post-treatment in our study, can have a crucial effect on morbidity and mortality. Another potential outcome of this might be a reduction in patient load in emergency departments; instead, some of the patients in question might be referred for treatment in an ambulatory clinic given the reduction in the severity of their suicidal symptoms. In order to fully assess the clinical advantages, one should consider two additional questions; the first is remission from suicidal ideation. This binary measure is important in order to evaluate the management of suicidal patients, meaning hospitalization or discharge. We defined remission as a score of 0 on the MADRS-SI item (indicating no suicidal thoughts). We found that four hours post infusion, 80% of the subjects in the ketamine group achieved remission compared to 33% in the placebo group ($p < 0.01$). which could potentially lead to fewer hospitalizations. The other relevant measure is the length of hospitalization. An intervention that can shorten the length of hospitalization, may improve satisfaction and quality of life for patients and will have great clinical and economical value. We showed a trend toward shortening the length of hospitalization. The ketamine group had a median four days of hospitalization fewer than the control group; 5 days (4–8.5) compared with 9 days (5.5–10.5), (Percentiles 25 and 75 are additionally reported, $p = 0.089$). See Figure 3. To conclude; the clinical implication of our observation - a temporary relief of suicidal ideation is yet to be determained, and further studies, with longer follow-up and outcome-oriented measures are warranted to establish well-grounded evidence on the anti-suicidal effect of ketamine, and in any case further steps are needed in order to embrace this treatment paradigm, such as establishment of ambulatory settings for the sub-acute period following the treatment effect.

Unexpectedly, we found that suicidal ideation did not relapse. The relatively extended follow-up of 28 days was designed to assess safety; however, we were surprised to learn that the rates of suicidal ideation stayed low. While no statistically significant group by time interaction was noted, this observation, which was similarly reported by Grunebaum et al. (2018), can be partly explained by the safety and support provided in inpatient units, and deserves consideration for future studies; including a study design with the power to evaluate this unexpected observation.

We found this treatment safe; however, this study is underpowered to draw safety results conclusively. Given the lack of acute treatment for suicide ideation and the lack of serious adverse events, the use of ketamine for acutely suicidal individuals deserves serious considerations.

While the large placebo effect, described here and in other ketamine studies, can disguise of the anti-suicidal effect of ketamine, it's important to consider that the placebo effect in our study should be viewed as treatment-as-usual, which encompassed admission to a psychiatric ward including biological and psychological treatments as well as social interventions. In addition, the placebo effect is an example of the *observer effect* (the mere observation of a phenomenon inevitably changes the phenomenon). In this case, measurement of suicidal ideation, can have empathic virtue which can reduce suicidal thoughts.

Limitations

The main limitation of this study is the small sample size, caused by early termination of recruitment (as described in the methods section). Second, effective masking is an inherent problem in all ketamine studies due to ketamine's rapid psychomimetic effects. An active placebo, such as midazolam (Grunebaum et al., 2017, 2018) might have better preserved the blindness. On the other hand, active placebo may offer relief from anxiety and might cause a different bias (type 2 error). Another obstacle for blindness might have been the cardiovascular effect, (i.e., elevation of blood pressure and/or pulse rate) which can be apparent to raters and subjects alike. Future studies should consider prescribing active placebo and using different efficacy and safety raters to maintain proper masking. An additional limitation was the lack of blood ketamine levels. The bioavailability of Intranasal administration of ketamine is approximately 45% (Peltoniemi et al., 2016). This could account for the low side-effects rate and the inconclusiveness of the efficacy results. Blood ketamine levels could determine whether subjects achieved appropriate dosing and that administration of ketamine was successful. Following the study intervention, we did not evaluate additional psychotropic medications or other interventions. Although, those interventions can be controlled using randomization it would have been preferable to record and report any difference between the groups.

CONCLUSIONS

Single fixed-dose intranasal ketamine was found to be a safe and feasible treatment option in the emergency department settings for a trans-diagnostic cohort with acute suicidal thoughts, in need of hospitalization. We found it to alleviate suicidal ideation four hours post administration, induce remission, and found a trend toward shortening the length of hospitalization. However, our results are inconclusive, and a linear mixed model failed to detect significance for the group by time interaction. We present here a novel paradigm including diagnostic considerations: a trans-diagnostic approach, and a treatment option- a single, fixed-dose of intranasal ketamine. Future larger-scale studies are warranted based on this approach to establish treatment recommendations for the acute management of suicidal patients.

ACKNOWLEDGEMENTS

First of all, we would like to acknowledge our participants and their families, we would like to thank AFSP for their support. Special gratitude to Caleb Adler, Eric Nelson, Jadienne Lord, Shaul

Schrieber, Mark Wieser, Rebeca J. Ackerman-Raphael, Ricardo Tarrasch, and Keren Armoni-Domany for their help and support.

FUNDING

This study was supported by the American Foundation for Suicide Prevention (AFSP), 2015 Standard Research Innovation Grant for Chery B. Mccullumsmith.

AUTHOR NOTES

Yoav Domany, Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, Cincinnati, OH, USA; Department of Psychiatry, Sheba Medical Center, Ramat Gan, Israel; Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel.
Cheryl B. McCullumsmith Department of Psychiatry, College of Medicine & Life Sciences, University of Toledo, Toledo, OH, USA

Correspondence concerning this author should be addressed to Yoav Domany, MD, Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, Cincinnati, OH, USA; Department of Psychiatry, Sheba Medical Center, Ramat Gan, Israel; Sackler School of Medicine, Tel Aviv University, Tel Aviv, 69978 Israel. Email: yoavdomany@gmail.com

ORCID

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

References

Bahr, R., Lopez, A., & Rey, J. A. (2019). Intranasal esketamine (Spravato(TM)) for use in treatment-resistant depression in conjunction with an oral antidepressant. *P T*, *44*(6), 340–375.

Ballard, E. D., Ionescu, D. F., Vande Voort, J. L., Niciu, M. J., Richards, E. M., Luckenbaugh, D. A., … Zarate, C. A. Jr. (2014). Improvement in suicidal ideation after ketamine infusion: Relationship to reductions in depression and anxiety. *Journal of Psychiatric Research*, *58*, 161–166. doi:10.1016/j.jpsychires.2014.07.027

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. doi:10.1016/j.jpsychires.2015.06.003

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. doi:10.1002/1097-4679(198807)44:4<499::AID-JCLP2270440404>3.0.CO;2-6

Brent, D. A. (2016). Antidepressants and Suicidality. *The Psychiatric Clinics of North America*, *39*(3), 503–512. doi:10.1016/j.psc.2016.04.002. 27514302

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. doi:10.7205/MILMED-D-15-00431

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*(7), 620–630. doi:10.1176/appi.ajp.2018.17060720

Daly, E. J., Singh, J. B., Fedgchin, M., Cooper, K., Lim, P., Shelton, R. C., … Drevets, W. C. (2018). Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy

in treatment-resistant depression: A randomized clinical trial. *JAMA Psychiatry*, *75*(2), 139–148. doi:10.1001/jamapsychiatry.2017.3739

Diazgranados, N., Ibrahim, L., Brutsche, N. E., Newberg, A., Kronstein, P., Khalife, S., … Zarate, C. A. Jr. (2010). A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Archives of General Psychiatry*, *67*(8), 793–802. doi:10.1001/archgenpsychiatry.2010.90

Domany, Y., Bleich-Cohen, M., Tarrasch, R., Meidan, R., Litvak-Lazar, O., Stoppleman, N., … Sharon, H. (2018). Repeated oral ketamine for out-patient treatment of resistant depression: Randomised, double-blind, placebo-controlled, proof-of-concept study. *British Journal of Psychiatry*, *214*(1), 20–27. doi:10.1192/bjp.2018.196

Domany, Y., Shelton, R. C., & McCullumsmith, C. B. (2020). Ketamine for acute suicidal ideation. An emergency department intervention: A randomized, double-blind, placebo-controlled, proof-of-concept trial. *Depression and Anxiety*, *37*(3), 224–233. doi:10.1002/da.22975

Fu, D. J., Ionescu, D. F., Li, X., Lane, R., Lim, P., Sanacora, G., … Canuso, C. M. (2020). Esketamine nasal spray for rapid reduction of major depressive disorder symptoms in patients who have active suicidal ideation with intent: Double-blind, randomized study (ASPIRE I). *The Journal of Clinical Psychiatry*, *81*(3), 19m13191. doi:10.4088/JCP.19m13191

Galvez, V., Li, A., Huggins, C., Glue, P., Martin, D., Somogyi, A. A., … Loo, C. K. (2018). Repeated intranasal ketamine for treatment-resistant depression - the way to go? Results from a pilot randomised controlled trial. *Journal of Psychopharmacology*, *32*(4), 397–407. doi:10.1177/0269881118760660

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. doi:10.1016/j.amepre.2014.06.012

Grunebaum, M. F., Ellis, S. P., Keilp, J. G., Moitra, V. K., Cooper, T. B., Marver, J. E., … Mann, J. J. (2017). Ketamine versus midazolam in bipolar depression with suicidal thoughts: A pilot midazolam-controlled randomized clinical trial. *Bipolar Disorders*, *19*(3), 176–183. doi:10.1111/bdi.12487

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. *The American Journal of Psychiatry*, *175*(4), 327–335. doi:10.1176/appi.ajp.2017.17060647

Hoertel, N., Franco, S., Wall, M. M., Oquendo, M. A., Kerridge, B. T., Limosin, F., & Blanco, C. (2015). Mental disorders and risk of suicide attempt: A national prospective study. *Molecular Psychiatry*, *20*(6), 718–726. doi:10.1038/mp.2015.19

Horon, R., McManus, T., Schmollinger, J., Barr, T., & Jimenez, M. (2013). A study of the use and interpretation of standardized suicide risk assessment: Measures within a psychiatrically hospitalized correctional population. *Suicide & Life-Threatening Behavior*, *43*(1), 17–38. doi:10.1111/j.1943-278X.2012.00124.x

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. doi:10.1111/bdi.12277

Just, M. A., Pan, L., Cherkassky, V. L., McMakin, D., Cha, C., Nock, M. K., & Brent, D. (2017). Machine learning of neural representations of suicide and emotion concepts identifies suicidal youth. *Nature Human Behaviour*, *1*, 911–919. doi:10.1038/s41562-017-0234-y

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. *Emerg (Tehran)*, *2*(1), 36–39.

Kim, J., Farchione, T., Potter, A., Chen, Q., & Temple, R. (2019). Esketamine for treatment-resistant depression - first FDA-approved antidepressant in a new class. *The New England Journal of Medicine*, *381*(1), 1–4. doi:10.1056/NEJMp1903305

Lapidus, K. A., Levitch, C. F., Perez, A. M., Brallier, J. W., Parides, M. K., Soleimani, L., … Murrough, J. W. (2014). A randomized controlled trial of intranasal ketamine in major depressive disorder. *Biological Psychiatry*, *76*(12), 970–976. doi:10.1016/j.biopsych.2014.03.026

Le-Niculescu, H., Levey, D. F., Ayalew, M., Palmer, L., Gavrin, L. M., Jain, N., (2013). Discovery and validation of blood biomarkers for suicidality. *Molecular Psychiatry*, *18*(12), 1249–1264. doi:10.1038/mp.2013.95

Loo, C. K., Gálvez, V., O'Keefe, E., Mitchell, P. B., Hadzi-Pavlovic, D., Leyden, J., … Glue, P. (2016). Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression. *Acta Psychiatrica Scandinavica*, *134*(1), 48–56. doi:10.1111/acps.12572

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. . 10.1007/s11920-016-0680-7 [pii] doi:10.1007/s11920-016-0680-7

Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry: The Journal of Mental Science*, *134*, 382–389. doi:10.1192/bjp.134.4.382

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. doi:10.1017/S0033291715001506

Oquendo, M. A., & Baca-Garcia, E. (2014). Suicidal behavior disorder as a diagnostic entity in the DSM-5 classification system: Advantages outweigh limitations. *World Psychiatry : Official Journal of the World Psychiatric Association (WPA))*, *13*(2), 128–130. doi:10.1002/wps.20116

Peltoniemi, M. A., Hagelberg, N. M., Olkkola, K. T., & Saari, T. I. (2016). Ketamine: A review of clinical pharmacokinetics and pharmacodynamics in anesthesia and pain therapy. *Clinical Pharmacokinetics*, *55*(9), 1059–1077. doi:10.1007/s40262-016-0383-6

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. *The American Journal of Psychiatry*, *168*(12), 1266–1277. doi: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. doi: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. doi:10.1016/j.biopsych.2009.04.029

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. doi:10.1176/ajp.2006.163.11.1905

Short, B., Dong, V., Galvez, V., Vulovic, V., Martin, D., Bayes, A., … Loo, C. (2020). Development of the Ketamine Side Effect Tool (KSET). *Journal of Affective Disorders*, *266*, 615–620. doi:10.1016/j.jad.2020.01.120

Short, B., Fong, J., Galvez, V., Shelker, W., & Loo, C. K. (2018). Side-effects associated with ketamine use in depression: A systematic review. *The Lancet. Psychiatry*, *5*(1), 65–78. doi:10.1016/S2215-0366(17)30272-9

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. *The American Journal of Psychiatry*, *173*(8), 816–826. doi:10.1176/appi.ajp.2016.16010037

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. doi:10.1016/j.genhosppsych.2012.03.020

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. *The American Journal of Psychiatry*, *175*(2), 150–158. doi:10.1176/appi.ajp.2017.17040472

Witt, K., Potts, J., Hubers, A., Grunebaum, M. F., Murrough, J. W., Loo, C., … Hawton, K. (2020). Ketamine for suicidal ideation in adults with psychiatric disorders: A systematic review and meta-analysis of treatment trials. *The Australian and New Zealand Journal of Psychiatry*, *54*(1), 29–45. doi:10.1177/0004867419883341

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. doi:10.1001/archpsyc.63.8.856