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Jenko KJ, Anzilotti JH. Subanesthetic IV ketamine reduces acute suicidal ideation in patients with mood disorders. JMU Scholarly Commons Physician Assistant Capstones.

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Subanesthetic IV ketamine reduces acute suicidal ideation in patients with mood disorders

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ABSTRACT

Background. Depression and suicide are common in the United States and present a significant problem in the healthcare landscape. Currently, there are few options that can rapidly reduce suicidal ideation in patients with depression. Ketamine, a glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist, has been shown to reduce acute suicidality in patients with depression. Previous studies have a reduction of suicidal ideation compared to saline placebo, but few studies have shown a significant effect compared to a similar psychoactive drug such as midazolam.

Method. A search of PubMed and PsychNET was performed in September 2018 using the terms “ketamine,” “suicide,” and “depression” with a filter for human clinical trials. Three randomized controlled trials were discovered that compared the effects of intravenous (IV) ketamine or midazolam on active, acute suicidal ideation in patients with a history of depression. Suicidal ideation and depression were measured using similar scales to allow for relative comparison between studies. Baseline measurements of suicidal ideation were assessed before IV administration of the randomized medications, and repeat assessments were obtained 24 hours after administration of the medication.

Results. All three studies evaluated showed a reduction in suicidal ideation in patients that received ketamine compared to those that received midazolam. Grunebaum et al. and Price et al. both saw statistically significant reductions in SI in patients who received ketamine and assessed with the Beck Scale for Suicidal Ideation (BSI) or the Scale for Suicidal Ideation (SSI). Murrough et al. observed a nonsignificant reduction in SI at 24 hours using the BSI, but did see a statistically significant reduction using the Montgomery-Asberg Depression Rating Scale (MADRS-SI). SI was reduced in the midazolam group in all studies, but none were significant, and none as extensive as the ketamine groups.

Conclusion. Ketamine administered at subanesthetic doses can provide acute relief of suicidal ideation in patients with depression within 24 hours.

INTRODUCTION

Few options exist to rapidly relieve suicidal ideation in patients with mental health disorders. The 2015 National Ambulatory and Medical Care Survey from 2015 indicated that approximately 10% of physician office visits are due to depression and as of 2016, suicide is the 10th leading cause of death in the United States, accounting for approximately 45,000 deaths per year.^{1,2} Behavioral health disorders including bipolar disorder, borderline personality disorder (BPD), and particularly major depressive disorder (MDD) are strongly associated with SI. Early intervention in depressed individuals using antidepressants is important to reduce the likelihood of suicidality. However, current treatment options for acute suicide (hospitalization, medications,

psychotherapy and electroconvulsive therapy are not ideal due to the prolonged delay of onset, lack of anti-suicidal properties, or significant adverse side effects.³ Some medications, such as selective serotonin reuptake inhibitors (SSRIs), have been shown to potentially increase the risk of self-harm within weeks of initial administration, and lithium has beneficial effects that can take weeks to manifest.⁴⁻⁶ The initial treatment of acute suicidality for hospitalized patients primarily involves protecting them by removing dangerous objects from their room with constant monitoring by a trained staff member. Therefore, a pharmacological treatment for rapid relief of suicidal ideation is an important and advantageous intervention for suffering patients.

The use of ketamine, a glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist, has garnered extreme interest in the past decade as a rapid-acting antidepressant. More recently, it is being investigated to specifically reduce suicidal ideation (SI). First approved in 1970 by the U.S. Food and Drug Administration (FDA) for anesthetic use, it shows potential for treatment resistant-major depressive disorder (TRD), bipolar depression (BD), post-traumatic stress disorder (PTSD), and SI.⁷ Despite its serious side effects at higher doses and potential for abuse, ketamine's other properties make it a potential agent for short-term therapy.

Ketamine is a drug that is in the early stages of investigation and use for suicidal, hospitalized patients who require safe management. Other medical therapies are guided towards long term reduction in suicide risk, leaving a gap in the acute management of patients with mood disorders. Our objective is to compare the efficacy of IV ketamine versus midazolam to reduce acute suicidality.

CASE

A 47-year-old woman with a history of treatment-resistant depression was admitted to the hospital after being found unconscious by her husband at home following a self-poisoning attempt using her prescribed bromazepam (1200mg).⁸ After full resolution of her delirium, she reported a history of suicidal plans for approximately 6 months.⁹ On being questioned, she had clear suicidal intent despite adhering to her prescribed risperidone and selegiline, reported that she would have preferred to die, and presented with full depressive symptoms including deep hopelessness, anhedonia, and feeling unsafe at home. During previous suicidal attempts, the patient remained suicidal despite sedation by diazepam and venlafaxine. We offered her the option of administering ketamine infusion. Can ketamine be used to treat the patient's acute SI?

METHODS

A search of PubMed and PsychNET was performed in September 2018 using the terms "ketamine," "suicide," and "depression" with a filter for human clinical trials and yielded a total of 20 non-duplicated articles. Inclusion criteria included randomized control trials published within the last 5 years. Individual studies were screened. Those that were excluded did not use midazolam as the control or suicidal ideation as the treatment outcome. Others were excluded because they were not randomized clinical trials or the treatment was given intranasally instead

of IV. One study was removed due to it being a proof of concept study. Three studies were appropriate and selected for review. Figure 1 demonstrates the article selection process.

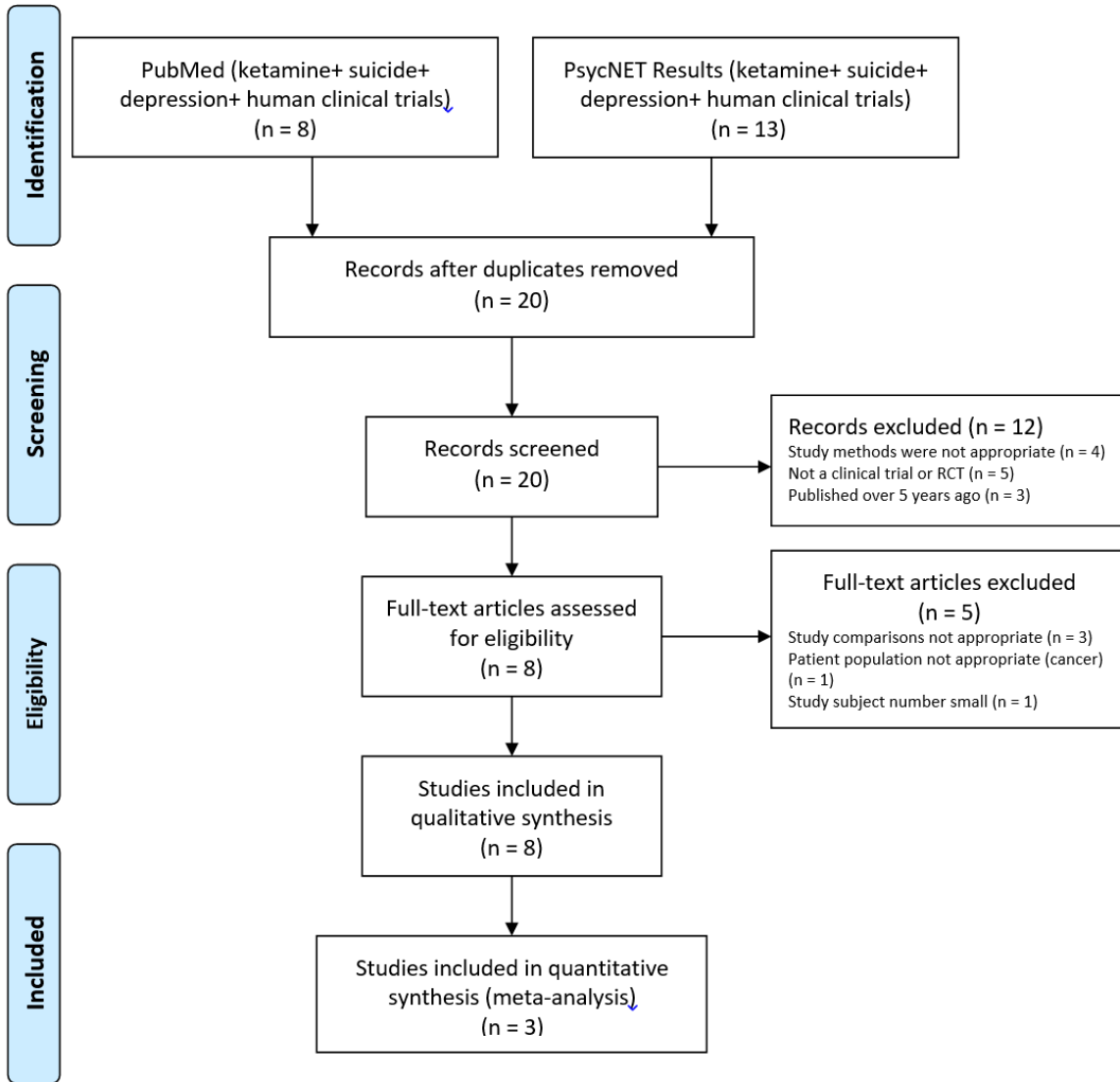


Figure 1. Flowchart depicting the methods for selecting eligible studies for review

RESULTS

Overall study design

The three articles selected had comparable patient demographics, methodologies, and outcome measurements (Table 1). Inclusion and exclusion criteria for the three studies were relatively similar. These studies used several rating scales to measure SI; therefore, descriptions of these scales can be found in the supplementary material. We compared the findings of clinically relevant SI scores and effect sizes between treatment groups.

Table 1: Inclusion and Exclusion Criteria

	INCLUSION	EXCLUSION
Grunebaum et al.	DSM-IV Major Depressive Disorder (≥ 16 on HAM-D and ≥ 4 on SSI) Voluntary admission to inpatient unit	Unstable medical condition or neurological illness Significant EKG abnormality Pregnancy/lactation Current psychosis History of ketamine abuse/dependence Other drug/alcohol dependence within 6 months Suicidal ideation due to substance use or withdrawal Prior ineffective trial of or adverse reaction to ketamine or midazolam Daily opioid use >20 mg oxycodone or equivalent Score <25 on MMSE for persons >60 years old Lack of capability to consent Inadequate understand of English
Murrough et al.	Clinically significant suicidal ideation (≥ 4 on MADRS-SI)	Lifetime history of schizophrenia or other primary psychotic disorder Current psychotic or manic symptoms Substance abuse disorder within 1 month of screening Positive urine toxicology at screening Any lifetime abuse of ketamine or phencyclidine Any unstable medical illness If outpatient, experienced current intent to make a suicide attempt Pregnant
Price et al.	TRD MDD	Individuals at imminent risk Psychotropic medication free for ≥ 1 week (4 weeks for fluoxetine)

Study 1. Grunebaum et al. Ketamine for rapid reduction of suicidal thoughts in major depression: a midazolam-controlled randomized control trial.¹⁰

Study Objective

To test the acute effect of adjunctive subanesthetic intravenous ketamine on clinically significant suicidal ideation in patients with major depressive disorder (MDD).

Study Design

Participants: 80 adults 18-65 years old with MDD were enrolled in a randomized, blocked design, clinical trial. Further population information is shown in Table 2. Patients with a DSM-IV diagnosis of MDD, defined by a score of ≥ 16 on the 17-item Hamilton Depression Rating Scale (HAMD-RS) and a score of ≥ 4 on the Scale for Suicidal Ideation (SSI), were included. Exclusion criteria are further described in Table 1.

Table 2. Study Population Information

	Grunebaum et al.	Murrough et al.	Price et al.
Study style	RCT	RCT	Two Site double blind RCT
Patient (N)	80	24	57
Gender	Midazolam: M = 14, F = 26 Ketamine: M = 18, F = 22	Midazolam: M = 4; F = 8 Ketamine: M = 4; F = 8	Midazolam: M = 11; F = 10 Ketamine: M = 16; F = 20
Mean age (years)	Midazolam: 40.7 Ketamine: 38.4	Midazolam: 39.1 Ketamine: 45.8	Midazolam: 43.8 Ketamine: 48.6
Ketamine dose (mg/kg)	0.5	0.5	0.5
Midazolam dose (mg/kg)	0.02	0.045	0.045

RCT: randomized control trial; M: male; F: female

Intervention: Participants were randomly assigned to receive IV racemic ketamine hydrochloride at 0.5 mg/kg or midazolam at 0.02 mg/kg infused over 40 min. Patient response was assessed at 24 hours (day 1) after infusion. Patients were allowed to stay on their current dosage of antidepressant medication.

Outcome measures: Raters were doctoral or master's level psychologists. The clinician rated SSI assessed current severity of suicidal ideation with 19 items scaled from 0 (least severe) to 2 (most severe). The SSI assessment was administered at screening, baseline within 24 hours before infusion, at 230 min after infusion, at 24 hours after infusion (day 1), and at weeks 1-6 of follow-up.

Randomization and Blinding: Patients and study personnel were blind to treatment. Patients and raters were asked on day 1 whether they thought the infusion was midazolam or ketamine or if they had "no idea." Treatment response was defined as a day 1 SSI score \geq 50% below baseline.

Statistical Analysis: The study was powered assuming a two-sided test of the group effect at an alpha level of 0.05. A sample size of 70, 1:1 each treatment, provided \geq 80% power to detect a 25% reduction in SSI score over 24 hours in the ketamine group and no reduction in the midazolam group.

Study Results

Primary Outcome Measure: Day 1 Suicidal Ideation: The average SSI score at day 1 post-infusion was lower than baseline in both ketamine and midazolam treatments (14.2 vs 5.8 and 15.8 vs 11.8, respectively), but the average SSI score at day 1 was 4.96 points lower in the ketamine group compared with the midazolam group (95% CI = 2.33-7.59; $t = 3.75$; $df = 77$, $p < 0.001$). The comparison in reduction between the two groups yielded a Cohen's d score of 0.75. Baseline borderline personality disorder diagnosis as a covariate had little effect on the results. Of note, SSI is considered to have a greater than 90% correlation with the Beck scale for Suicidal Ideation (BSI) scoring system. Summaries of results are found in Table 3 and Figure 2.

Table 3. Mean SI scores

	Grunebaum et al.		Murrough et al.				Price et al.					
	SSI		BSI		MADR-SI		BSI		MADR-SI		SI _{comp}	
	BL	Day 1	BL	Day 1	BL	Day 1	BL	Day 1	BL	Day 1	BL	Day 1
Ketamine	14.2	5.8*	17.5	10.8	3.8	1.8*	6.11	1.13*	1.61	0.72	0.15	-2.23
Midazolam	15.8	11.8	18	14	3.9	3.3	6.19	3.95	1.48	1.24	-0.21	-0.91

SSI: Scale for Suicidal Ideation; BSI: Beck Scale for Suicidal Ideation; MADRS-SI: Montgomery-Asberg Depression Rating Scale- Suicidal Ideation;

SI_{comp}: summing z-scores on the BSS, MADRS-SI, and Quick Inventory of Depressive Symptomatology-Self Report. *p <0.05

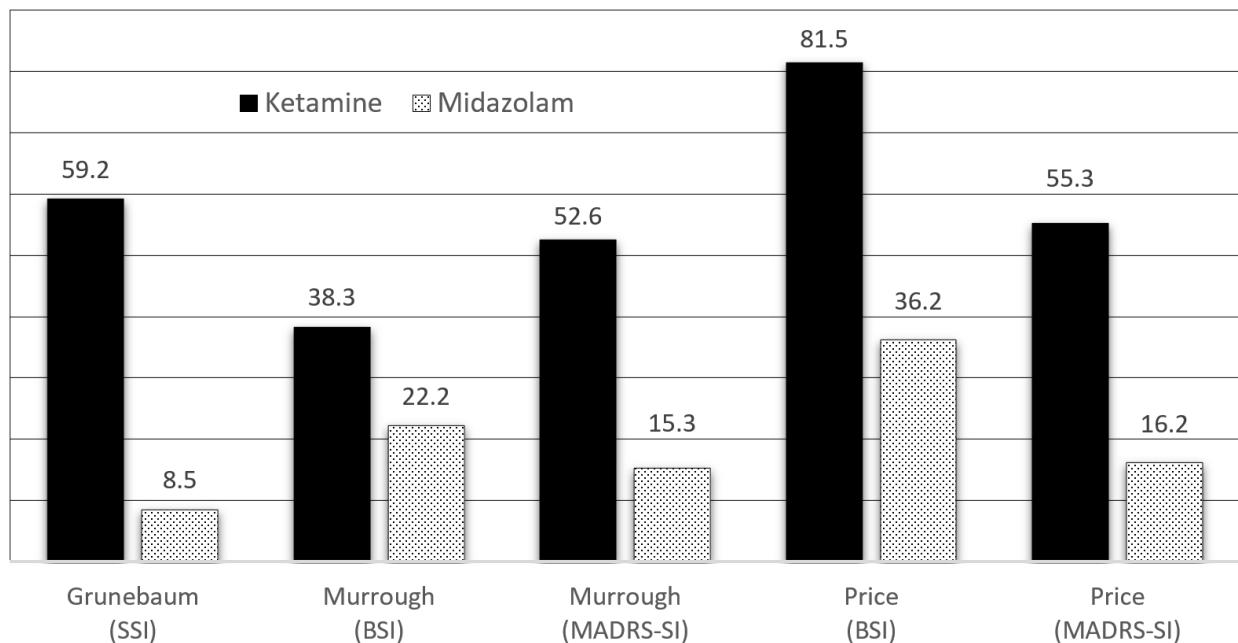


Figure 2. Percent reduction of mean SI score at baseline and day 1.

Secondary Outcome Measures: Suicidal ideation: Patients who responded on the SSI at day 1 were 2.85 times more likely to be treated with ketamine than midazolam. Four patients required treatment with ketamine in order to have an SSI response (NNT = 4). While not statistically significant, an exploratory analysis showed the odds of an SSI score of 0 at day 1 were 2.8-fold greater for the ketamine group. At day 1, SSI worsening was observed in nine midazolam patients and two ketamine patients.

Study Critique

There is no established definition of a clinically meaningful reduction in score on a standard suicidal ideation scale. Despite utilizing midazolam as a more accurate control than saline, patients were able to correctly guess the blinded drugs in 42% of midazolam and 44% of ketamine cases ($\chi^2 = 0.02$, $df = 1$, $p = 0.895$). Patients guessed correctly 55% of the time with both drugs ($p = 1.000$). This is evidence that midazolam is still imperfect as a placebo. A lower dose of midazolam compared to other studies was used to reduce additive sedation. Another critique of this study is that it used mixed diagnoses, inpatient and outpatient settings, and a higher midazolam dose compared to other similar studies. This study used a clinician-reported

SSI whereas other previous studies used a self-reported SSI. While self-reported and clinician-rated versions correlate >0.90 , patients tend to report higher scores than clinicians. This study also allowed patients to continue their regular antidepressant medication while other studies employed a medication washout during the week before the trial began. Additionally, more patients treated with ketamine had borderline personality disorder than in the midazolam group (28% compared with 8%).

Study 2. Murrough et al. Ketamine for rapid reduction of suicidal ideation: a randomized controlled trial.¹¹

Study Objective

To assess the rapid antidepressant effects of ketamine in reducing suicidality in patients with a variety of psychiatric disorders.

Study Design

Participants: 24 participants, including males and females 18-80 years old, were enrolled in the study. Ten subjects were treated as inpatients and 14 as outpatients. Among the patients, there was a variety of mental health disorders (54% MDD, 29% BPD, 12.5% PTSD. 62.5% had history of suicide attempt). They were enrolled in a single-site randomized control trial from 2012-2014. Further population information is shown in Table 2. Patients who had clinically significant SI on the Montgomery-Asberg Depression Rating Scale (MADRS-SI score ≥ 4 ; range 0-6) were included. Patients were excluded if they had a current suicidal intent as indicated by a 4 or 5 on the Columbia Suicide Severity Scale (CSSS). Other exclusion criteria are described in Table 1. Patients were screened during study enrollment, and again the morning of the infusion. Written consent was obtained from all participants.

Intervention: Two groups either received 0.5 mg/kg racemic ketamine hydrochloride or 0.045 mg/kg midazolam over a 40 minute infusion in double-blind conditions. Patients were allowed to stay on their current dosage of antidepressant medication.

Outcome measure: Patients' suicidal intent was measured by the BSI scale at baseline and 24 hours (day 1). Secondary suicidal intent was measured by the MADRS-SI, Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR), and Concise Associated Symptoms Tracking scale scores. Scores were reassessed at 24, 48, 72 hours and again at 7 days post-infusion.

Randomization: Randomization into two groups was generated by the research pharmacy using permuted blocks of size six. All investigators, anesthesiologists, raters and patients were blinded to randomization.

Statistical Analysis: The intention-to-treat sample included all participants who were randomized and completed at least one post-treatment assessment. SI severity was compared between the two groups using separate analysis of covariance (ANCOVA) models, controlling for baseline SI levels. Sample size was based primarily on feasibility. Treatment effects are quantified as mean differences between groups, and associated effect sizes are based on standardized mean difference (Cohen's *d*). All statistical tests were two-sided with an alpha set at 0.05.

Study Results

Primary outcome: Day 1 Suicidal Ideation BSI: All participants completed the study, and all reported similar side effects of the medications, most commonly headache, dizziness and anxiety. At day 1, BSI score changes were reduced in both treatment groups compared to baseline; however, the reductions were similar between both the ketamine and midazolam groups (10.8 ± 8.5 , 14.0 ± 10.2), as seen in Table 3. The association between ketamine and midazolam groups resulted in a small Cohen's d score of 0.34.

Secondary Outcome: Day 1 Suicidal Ideation MADRS-SI: MADRS-SI scores were significantly lower in ketamine compared to midazolam (1.8 ± 1.9 and 3.3 ± 1.6 , respectively, $F_{1,21} = 4.3$, $p = 0.05$, Cohen's $d = 0.86$).

Tertiary Outcome: Day 2 Suicidal Ideation: At 48 hours, a difference emerged showing improvement in BSI scores in the ketamine group (8.8 ± 8.3) compared to midazolam (5.3 ± 10.9 ; $F_{1,21} = 1.04$, $p = 0.32$, Cohen's $d = 0.34$), but MADRS-SI was no longer significant (1.8 ± 1.9 and 3.2 ± 1.8 , respectively; $F_{1,21} = 3.56$, $p = 0.077$, Cohen's $d = 0.77$). After 72 hours, this difference was no longer apparent in either metric. The authors performed a linear correlation between BSI change and MADRS score and found non-significant positive associations at both 24 and 48 hours.

Study Critique

This study explored the effect of ketamine on patients with co-occurring psychiatric disorders with the intention of observing efficacy of ketamine across multiple high-risk groups. This is advantageous because suicide is often comorbid with multiple mental health disorders; however, it weakens the strength of results for each disorder. Data regarding individual patient results was not given for the primary and secondary outcome measurements, and there were no baseline measurements provided to compare results. Differences were calculated using linear graphs rather than quantitative data. This study had a small sample size ($n = 24$), which may impact findings.

Study 3. Price et al. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression.¹²

Study Objective

To evaluate the effects of ketamine as compared to a sedative in reducing suicidality in patients with treatment-resistant depression.

Study design

Participants: 57 patients with TRD were enrolled in a double-blind randomized controlled trial. Patients were diagnosed with MDD established by the SCID-I/P interview, and were determined to be treatment resistant if they failed at least three trials of antidepressant medication therapies. Prior to treatment, patients were assessed for depressive symptoms using the MADRS and QIDS-SR. Further inclusion and exclusion criteria are described in Table 1, and further population information is shown in Table 2. Patients were free of psychotropic medication for ≥ 1 week (four weeks for fluoxetine).

Intervention: Both groups were admitted overnight, and in the morning, were administered a single infusion of either 0.5 mg/kg of ketamine IV or 0.045 mg/kg of midazolam IV over 40 minutes. Patients remained inpatient the night after the infusion, and suicidal measurements were repeated at 24 hours post infusion.

Outcome Measures: Following infusion, all patients completed measures of explicit suicidal ideation. Explicit measurements used BSI with the clinician-rated SSI. To reduce Type 1 error and preserve power, a composite index score ($SI_{\text{composite}}$) was calculated by summing z-scores on the BSI, MADRS-SI, QIDS-SR.

Randomization and Blinding: The patients and researchers were blinded, and patients were randomly assigned to either the ketamine or midazolam group at a 2:1 ratio, resulting in 36 ketamine treatments and 21 midazolam treatments. Midazolam was used as placebo rather than saline in order to blind patients and providers to the sedative effects of ketamine by comparing it to a benzodiazepine.

Statistical Analysis: 24 hour scores were compared across groups using ANCOVA with baseline values as a covariate. A two-tailed P value was used for all analyses. Statistical trends at two-tailed $P < 0.1$ are reported along with significant effects ($P < 0.05$).

Study Results

Primary Outcomes: Day 1 Suicidal ideation: The $SI_{\text{composite}}$ was reduced in both treatment groups. $SI_{\text{composite}}$ scores and isolated BSI scores are shown in Table 3. The comparison in composite scores between ketamine and midazolam groups showed a Cohen's d score of 0.82.

Secondary Outcomes: Suicidal Ideation, Explicit and Implicit Measurements: BSI and MADRS-SI scores were reduced in both groups as seen in Table 3. The BSI scores from baseline to day 1 were significantly reduced in the ketamine group compared to the midazolam group (6.11 to 1.13, and 6.19 to 3.95, respectively; $p = 0.04$). MADRS-SI scores from baseline to day 1 showed a greater reduction in the ketamine group than the midazolam group (1.61 to 0.72 and 1.48 to 1.24, respectively; Cohen's $d = 0.86$).

Study Critique

Strengths of this study include the use of multiple explicit and implicit measurements of suicidality, and this study is the only one that evaluated implicit measurements. This is an important distinction because suicidal intent is often difficult to understand, and this study highlighted the differences in implicit and explicit measurements. A weakness of this study is the inability to measure patients that are imminently suicidal. The effect of studying suicidality in patients that are suicidal inclined versus suicide imminent has a major implication in the true effectiveness of the medication. Another weakness is the limited follow-up of only measuring at 24 hours post-infusion. The published paper itself did not specifically mention inclusion or exclusion criteria, although it appears to use the same criteria as Murrough et al.

DISCUSSION

Overall, patients treated with IV ketamine exhibited rapid, clinically relevant reductions in SI, which were significantly greater than reductions observed in midazolam-treated patients. For Gruenbaugh et al., the average SSI score at day 1 post-infusion was lower than baseline using both treatments, but the average score was significantly lower in ketamine-treated patients than midazolam-treated patients ($p < 0.001$, Cohen's $d = 0.75$). In Murrough et al., BSI scores were similarly reduced for ketamine and midazolam-treated patients while MADRS-SI scores were significantly lower for ketamine-treated patients ($p = 0.5$, Cohen's $d = 0.86$). For Price et al., the BSI score was significantly reduced in ketamine-treated patients compared to midazolam ($p = 0.04$). Ketamine-treated patients showed a large effect size difference compared to midazolam when measured on the MADRS-SI and $SI_{\text{composite}}$ scores in Price et al. (Cohen's $d = 0.86$ and 0.82 , respectively). No studies showed a significant SI reduction when treated with midazolam. These studies showed that using most scales, ketamine significantly reduced suicidal ideation with moderate to large effect sizes. Ketamine can be used to treat acute suicidal ideation in patients with MDD or TRD, but more research is needed to make similar conclusions in patients with other co-occurring psychiatric disorders.

Despite there being no established definition of a clinically meaningful reduction in score on a suicidal ideation scale, studies suggest that patients who reported 50% reduction in SI symptoms at 24 hours had one-third the risk of later self-harm events over 24 days, compared with those whose SI remained over 50%.¹³ The United Kingdom's National Institute for Health and Care Excellence considered a Cohen's d value ≥ 0.5 to be clinically significant. Therefore, the three reviewed studies suggest that the reduction in SI at day 1 after ketamine infusion is clinically meaningful (Figure 2). Of note, Murrough et al. observed conflicting results between two different suicidal ideation scales at day 1: SI measured using the BSI was reduced in both the treatment and placebo trial, but not significantly. However, the MADRS-SI score was significantly lower in patients treated with ketamine compared to midazolam. Despite this, when taken together, these studies add to the body of evidence that ketamine can reduce suicidal ideation in patients suffering from an acute suicidal episode.

The studies have several limitations. First, each of the three studies evaluated suicidal ideation slightly differently, but the Beck Scale for Suicidal Ideation was incorporated into all three results. Grunebaum et al. used the SSI, which has greater than 90% correlation with BSI. Murrough et al. was the only researcher who used the BSI as the primary outcome, but Price et al. used BSI as part of a composite score. There is no universally accepted suicidal ideation scale, but BSI (or a strongly correlated scale) was used in all three studies and makes for a useful comparison in all three studies. Secondary measurements for Murrough et al. and Price et al. both included the MADRS-SI scale as well. Future studies should attempt coherence in patient recruitment and rating scales.

A second limitation is the differences in the criteria for patient inclusion. Murrough et al.'s research targeted patients across a range of mood and anxiety disorders including MDD, bipolar

disorder, PTSD, borderline personality disorder, social anxiety disorder, obsessive compulsive disorder, and others. Price et al. enrolled only suicidal patients with treatment-resistant depression. Grunebaum et al. enrolled suicidal patients with major depressive disorder, but some patients also had diagnoses of borderline personality disorder. The array of psychiatric disorders Murrough et al. included may have contributed to the differing results. However, a diverse patient population is important to include due to the multifactorial sources of SI.

There was already strong evidence that subanesthetic ketamine administered to patients with MDD and/or suicidal ideation have rapid-acting anti-suicidal effects when compared with a placebo.¹⁴⁻¹⁶ However, a limitation of these initial studies is the lack of an ideal control. When using saline as a placebo, patients have the possibility to become unblinded from their study group given the psychoactive properties of ketamine compared to saline. The studies we reviewed use midazolam as the control because its sedative effects make it more difficult for patients to discern which type of therapy they receive, thus further strengthening the evidence that ketamine is efficacious in reliving suicidal ideation.¹⁷ Ongoing studies of ketamine currently use a psychoactive control based on these findings. Despite midazolam being an improved control, limitations still exist. Grunebaum et al. noted that raters correctly guessed the drug they were administered in 42% of midazolam and 44% of ketamine cases ($p = 0.895$), while the other authors make no mention of blinding results after administration.

The research discussed may be affected by several biases. Researches on Grunebaum et al. have royalties for use of the Columbia Suicide Severity Rating scale and have stock in Bristol-Myers Squibb. Dr. Murrough et al. serves on boards for Janssen Research and Development and Genentech, is a consultant for clinical research and other pharmaceutical companies, has patents pending for ketamine use in mood and anxiety disorders and SI. Other authors of Murrough et al. and Price et al. have received consulting fees from pharmaceutical companies, academic institutions, biotech firms, and others. They also have licensing agreements for the use of ketamine as therapy for TRD, and have patents pending for ketamine treatment for PTSD, among others. Many authors may benefit financially if ketamine gains approval for the treatment of various psychiatric disorders.

Overall, the conclusions of these studies indicate that (1) ketamine is a promising therapy for acute SI treatment, and (2) the NMDA receptor is one of the pathological mechanisms implicated in suicidal ideation. These findings open the door to further development of treatments for suicidality that target similar mechanisms of action. Extensive research into the NMDA receptor shows that glutaminergic neurotransmission and NMDA dysregulation contribute to the pathology of MDD, a disorder that puts patients at significant risk for suicide.¹⁸⁻²⁰ It is uncertain whether suicidal ideation and depressive symptoms are of two separate mechanisms, but the results of the studies reviewed here indicate that the NMDA receptor is one of the pathological mechanisms implicated in suicidal ideation. In conclusion, ketamine can be used to reduce suicidal ideation.

PATIENT APPLICATION

Two of the three studies produced clinically relevant reductions in SI within one day, and a third study reduced SI within 48 hours. If the patient received ketamine, 0.5 mg/kg IV over 40 minutes, her acute SI can be relived in one day. Rather than ketamine, she may have been admitted to a psychiatric unit and treated with electroconvulsive therapy, both of which are expensive and stigmatizing. She can be managed and transferred to other units if her other conditions require management. Also, her medications can be reassessed and managed with less risk of immediate suicide. We recommend ketamine as treatment for acute SI.

CONCLUSION

Infusion of ketamine reduces suicidal ideation in patients with depression. Suicide is still a poorly understood process, and further investigation into its etiology could potentially yield more advantageous treatment interventions. However, with evidence of NMDA receptor's involvement in MDD, further research into ketamine-like drugs should be pursued. Future studies should also attempt to expand the therapeutic capabilities of ketamine as an anti-suicidal drug, particularly in patients that are actively suicidal. In addition to acute SI, ketamine shows promise in long-term reduction of symptoms for patients with MDD, PTSD, bipolar disorder, and other mood disorders.^{16,21-23} Some research is being conducted into intranasal administration of ketamine, which would allow for more attainable outpatient therapy.²⁴ The benefits of ketamine are significant because by reducing suicidal ideations, lives can be saved. Ketamine as anti-suicidal drug can be risky because its advantageous short-term effects could potentially be misinterpreted as long-term effects as well. Ketamine is best used as a short-term therapy to reduce suicidal ideations until a more effective anti-depressive drug regimen can be initiated.

Acknowledgements

We thank Dr. Abby Massey for her research and writing guidance, and are grateful for Dr. Erika Kancler's biostatistical instruction. Thank you to the James Madison University Library and University Writing Center for their research and writing assistance.

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SUPPLEMENTARY MATERIAL

Beck Scale for Suicidal Ideation (BSI)

Goal: Assess suicidal ideation

Scoring: 21 item

Interpretation: High scores indicate more severe suicidality

Columbia Suicide Severity Scale

Goal: Measure suicidal ideation and intensity of ideation

Scoring: 38 item checklist

Interpretation: higher scores indicate more severe suicidality

Hamilton Depression Rating Scale (HAMD-RS)

Goal: measure a patient's level of depression

Scoring: 21 items, first 17 are scored either 0-4 or 0-2

Interpretation: >7 indicates depression

Montgomery-Asberg Depression Rating Scale (MADRS-SI)

Goal: Diagnosing depression

Scoring: 10 item, scored 0-6

Interpretation: ≥ 4 considered significant suicidality

Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR)

Goal: Measure depression symptoms

Scoring: 16 item, with a single suicidality item scored 0-3

Interpretation: High scores indicate more severe depression

SCID-I/P interview

Goal: Establish diagnosis of major depressive disorder

Scoring: Clinical Interview

Interpretation: Per interviewer

Scale for Suicidal Ideation (SSI)

Goal: quantify and assess current suicidal ideation

Scoring: 19 item, scored 0-2

Interpretation: Higher scores indicate more severe suicidal ideation