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**Intranasal ketamine for alleviation of acute suicidal ideation. An emergency department, trans-diagnostic approach: randomised, double-blind, placebo-controlled, proof-of-concept trial.**

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## **Abstract**

**Background:** suicidal patients are often presented to the Emergency Department, where specific treatment is lacking. Ketamine, a rapidly acting antidepressant with anti-suicidal properties might offer relief. **Methods:** thirty eligible participants who suffered acute suicidal ideation and required hospitalization were randomized to intranasal ketamine 40mg or placebo, between August 2016 to April 2018. Safety and efficacy evaluations were scheduled for two and four hours, on days 1, 3, 7, and 21 post administration. Primary outcome was suicidal ideation four hours post administration. Randomisation was carried out by the pharmacist while the rest of the study group was blinded. **Outcomes:** fifteen subjects were randomised for ketamine and fifteen for control, 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, was 1.267 (95% confident interval 0.1-2.43,  $P<0.05$ ) favoring the ketamine group, with suicidal ideation remission rates of 80% of the ketamine group compares with 33% of 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 the ketamine group. The treatment was safe and well-tolerated. **Interpretation:** Intranasal ketamine alleviated suicidal ideation, and improved depressive symptoms four hours post ketamine administration. We present an innovative paradigm for the management of suicidal individuals in emergency setting. Future larger-scale studies

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are warranted to establish treatment recommendation. Founding: This study was supported by the American Foundation of Suicide Prevention.

ClinicalTrials.gov Identifier: NCT02183272, Keywords: suicide, intranasal, ketamine, acute suicide ideation.

## **Introduction:**

Suicide is the 10<sup>th</sup> leading cause of death in the U.S (1). and the suicide rates are alarmingly increasing (2). Suicide is highly related to depression, however, it has been suggested (3) that suicide is mediated by a general psychopathology dimension. In accordance, we suggest that suicide should be studied as a distinct entity, using a "trans-diagnostic approach". this argument is supported by the DSM5 proposed criteria of "Suicidal behavior disorder"(4), by the discovery of blood biomarkers for suicide (5), and by recent description of neural presentation of suicide (6).

Ketamine, a glutamatergic modulator, has demonstrated action as a rapidly acting antidepressant (7). ketamine's large and consistent anti-depressant effect is rapid, yet transient, and lasted up to 7 days (8, 9). Moreover, ketamine has been shown to rapidly reduce Suicidal Ideation (SI) in patients with depression (10, 11). In addition, Esketamine, the S enantiomer of racemic ketamine was studied for the rapid reduction of acute SI for depressed subjects who suffered imminent suicide risk (12). The authors reported that participants in the Esketamine group had greater improvement in score on the MADRS suicidal thoughts item compared with those in the placebo group 4 hours after first dose ( $p=0.002$ ; effect size=0.67) but not 24 hours after the first dose.

In accordance with the trans-diagnostic approach, it was suggested that ketamine's anti-suicidal properties are not entirely driven by improvement in depressive symptoms

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and that ketamine's anti-suicidal properties may be independent of the severity or type of psychiatric diagnosis (9, 13) and independent of its antidepressant effect.

Acute Suicidal patients are often presented to the Emergency Department (ED). Those patients, represent more than half a million annually admissions to emergency departments in the US(14). The ED is required to rapidly manage these patients, sometimes prior to establishing a thorough diagnosis. In such cases a trans-diagnostic approach is particularly useful.

Currently, most suicidal patients are hospitalized for brief stabilization, and are often discharged before psychopharmacological treatments show efficacy. No strong evidence base exists to demonstrate that brief inpatient hospitalizations are associated with significant reduction in suicidal potential. Further, SI can quickly and unexpectedly progress to suicidal behavior or to death by suicide. Thus, there is an urgent and compelling need to study treatment options for acute SI especially in the ED setting. Ketamine, a rapid acting antidepressant with potentially anti suicidal properties, was evaluated in the ED setting in two small controlled trials (15, 16) with promising results. The objective of the current study was to test the feasibility, tolerability and efficacy of a single ED intervention of low dose intranasal ketamine in reducing SI in extremely suicidal patients in the ED setting independently of their diagnosis.

## **Methods:**

### **a. Participants:**

Thirty subjects suffering acute SI, in need for hospitalization, were presented to the ED of the University of Cincinnati Medical Center (UCMC) between August 2016 to April 2018. Subjects were included if they required psychiatric hospitalization due to suicidal risk and suffered SI with a cutoff score of at least three on the first 5 items on the Beck Scale for Suicidal Ideation (BSS) (17) meaning at least a death wish; and a score higher than 2 on the Columbia Scale for Suicide Severity Rating (C-SSRS) (18), meaning at least active suicidal thoughts. All participants had been evaluated by the primary clinical team prior to contact by study personal, and admission criteria had been determined by a treating (non-study) clinician. Participants were age 18 to 65 and included all genders, racial and ethnic groups. Participants had no inclusion nor exclusion requirements for past psychiatric diagnosis, apart from safety concerns that led us to exclude schizophrenia spectrum disorders, or any of the other following conditions: dissociative disorder, pervasive developmental disorder or cognitive disorder. We excluded acute intoxication or withdrawal from alcohol or any substance of abuse, as determined by clinical interview and urine drug screen. Use of hallucinogen (except cannabis), one month prior to study enrolment was also excluded, and 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 effect to ketamine and subjects who suffered any clinically

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significant medication or condition that would preclude the use of ketamine including respiratory illness requiring the regular use of oxygen.

## **b. 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. Those meeting all inclusion and no exclusion criteria were randomized (1:1) to racemic ketamine 100mg/ml 40 mg (0.4 ml) or matched inactive placebo (normal saline). The dose of 40 mg was derived from the well-known dose of 0.5mg/kg, being used in other ketamine studies(7, 11, 19, 20). The drug was administered 4 times during 10 minutes through an intranasal mucosal atomization device, under the supervision of a study physician. Prior to subjects' consent, the pharmacist, who was the only non-blinded member of the study group prepared active drug and placebo in similar 10 ml syringes following a randomization schedule. Subjects' vital signs were monitored for 4 hours post administration. At the completion of post-treatment observation period, the participant was admitted to the Psychiatry Units at the UCMC. The time of discharge from hospital 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 and follow-up by the treating (non-study) psychiatrist. The treating



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physicians could make any changes in treatment they deemed warranted by the patient's condition.

**c. Assessments:**

The primary outcome measure was the change in SI four hours post administration. Secondary outcomes were change of depressive symptoms, remission from SI, days of admission, and safety assessments. Study assessments were performed at baseline prior to treatment and at 2 and 4 hours, and on days 1, 3, 7, and 21 post administration. Additional registered data was diagnostic information, though not as an inclusion/exclusion criteria.

Suicide Scales: Baseline SI, intensity of ideation, and suicidal behaviors were assessed using the Columbia Suicide Severity Rating Scale (C-SSRS, Baseline and Versions) (18). The C-SSRS is a widely used and valid scale used to assess both recent and lifetime suicide-related thoughts and behaviors.

We evaluated change in SI with two different scales: The first scale was the suicidal thoughts item on the Montgomery Åsberg Depression Rating Scale (MADRS)- (MADRS-SI). The MADRS is valid, widely used, questionnaire for depression (see below) and the MADRS-SI -suicidal thoughts- (graded 0-6) is an overall valid estimation of SI, represents clinical global rater-based impression of SI, and particularly useful in rapid acting antidepressants, include ketamine (21). The second scale was the Beck Scale for Suicidal ideation (BSS) (17). The Scale for Suicidal Ideation (SSI). and the SSI version for patient self-administration, the Beck Scale for Suicidal Ideation (BSS) have been designed to assess severity of SI and have been shown to be prospectively associated with suicidal behavior including death by suicide. (For further discussion on

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suicidal scores please refer to additional data). SI remission was defined by a score of 0 on the MADRS-SI item (indicating no suicidal thoughts).

Depression scale: The MADRS (22) 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 (23, 24) The MADRS has been modified to reflect the period since last assessment.

Length of hospitalization reflects a broad clinical assessments and risk evaluation. This outcome has an economical significance and an effect on patient's satisfaction. Discharge was decided by a non-study physician, who was blinded to randomization.

Additional participant's data: **Diagnostic:** The Mini International Neuropsychiatric Interview (MINI) was the primary instrument for diagnostic ascertainment. The MINI is a semi-structured psychiatric diagnostic interview. The MINI has excellent reliability and validity and is preferable in the ED setting because of its relative brevity.

Safety, tolerability, and adverse effects:

We have developed Ketamine Side Effects Scale (KSES) to assess for known side effects of ketamine. In this scale we evaluated vital sign abnormalities, agitation, sedation, dizziness, nausea, psychosis and dissociation, in a concise manner such that these symptoms could be assessed rapidly (scales of 0-5). In addition, we evaluated

**Psychosis and mania:** using symptoms from 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.

**d. 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).

**e. 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 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. Baseline demographic characteristics such as age, gender, were compared using chi-square or t-test. Comparison of the two groups for SI and depressive symptoms four hours post administration was calculated using t-test, or Mann -Whitney, confidence interval (CI) is reported at 95%. Remission rates were calculated using Chi square. When appropriate missing values were handled with Last Observation carried Forward (LOCF). Days of admission were evaluated descriptively median is reported with 25<sup>th</sup> and 75<sup>th</sup> percentiles. And statistics calculations were used using Mann Whitney U- test. Tolerability and safety were evaluated descriptively 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, BSS full assessment and first 5 items of 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 the primary and secondary outcomes. There were no differences between groups at baseline in any of the demographic or assessment scale. The main outcome measure was change in SI four hours post administration, as measured by the MADRS-SI. Additional outcomes were change in SI as measured by the BSS full scale and first 5 items, SI remission as indicated by MADRS-SI=0, total days of admission, and a change in depression as measured by the MADRS.

### **Efficacy Results:**

Evaluating suicidal symptoms, we found ketamine to reduce SI, four hours post administration, the mean difference in SI measured by the MADRS-SI (scale of 0-6), was 1.267 (95% Confidence Interval 0.1-2.43,  $P < 0.05$ ). Similarly, there was a reduction of  $17.4 \pm 9.4$  points in the full BSS in the ketamine group compared to a reduction of  $10.5 \pm 8.21$  in the placebo group. There was a trend towards the positive effect of ketamine ( $p = 0.086$ ). When considering the first five questions of the BSS, which reflect current desire for suicide, and thus are more sensitive to rapid change, the ketamine's subjects experienced a reduction from  $7.53 \pm 2.20$  to  $1.83 \pm 2.33$  compared with  $7.61 \pm 1.80$  to  $3.69 \pm 3.07$  for the controls 4 hours post administration. At other time points, no statistically significant difference from control was noticed, however, the improvement in SI was numerically greater in the ketamine group at all time points during the 21 days of

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the study. Unexpectedly the suicidal score of the ketamine group remained low for the entire study trial following single ketamine administration. See figure 1 and figure 4 (complementary data) for change in suicidal score across time

Secondary outcomes:

Remission: Remission from SI as defined by a score of 0 on the MADRS-SI item (indicating no suicidal thoughts), four hours post infusion. Twelve of 15 subjects of the ketamine group achieved remission (80%) compare to 5 of 15 (33%) in the placebo group ( $p < 0.01$ ). missing values was handled with LOCF.

Depression: The mean difference in depressive symptoms, measured by MADRS, at the same time 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 days of 5 days (4-8.5) compares with 9 days (5.5-10.5) for the control (median is reported with 25<sup>th</sup> and 75<sup>th</sup> percentiles). There was a trend toward the effect of ketamine on the reduction of days of admission. ( $p = 0.089$ ). See figure 3

Safety results:

We evaluated the harms throughout the study period. Thirty minutes post administration there were hardly no side effects. The peak of the side effects was one-hour post administration and the results of the KSES at one hour are presented in table 2. Although the ketamine group reported higher abundance of side effect it did not reach statistically significant level. Two hours post administration the acute effect of ketamine has faded. Therefore, it is safe to say that the side effects were transient. No subject

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had suffered psychotic symptoms. One subject, who had baseline dissociative symptoms, reported worsening of those symptoms, however that subject reported it as a good experience, and his suicidal scales has improved.

## **Discussion:**

We have found low dose intranasal ketamine to decreased acute SI and improve depressive symptoms 4 hours post administration in a trans-diagnostic, extremely suicidal cohort presenting to an ED for SI. Further, we found ketamine to induce SI remission in 80% of our study subjects. In addition, we report a trend towards the effect of ketamine in shortening length of hospitalization

### Comparison to other studies

Our findings are consistent with others who demonstrated the anti-suicidal effect of single dose Intravenous (IV) ketamine (9) in varied diagnosis; either TRD (25), bipolar depression (26) and on a wider diagnostic cohort (23).

In our previous study (27) we similarly demonstrated the anti-depressant effect of repeated oral administration of ketamine; the current study however is focused on single ED intervention of intranasal administration of ketamine and on suicidal ideation as main outcome measure.

Our study is also consistent with an intranasal administration of ketamine that demonstrated similar anti-depressive effect.(28). Recent studies evaluated intranasal Esketamine for depression with and without SI (12). In addition, the findings are similar to other studies conducted in ED settings (11, 15, 16). Our study is similar in design to

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the recently published study of Canuso et al (12). with two main differences, the first is that we have used racemic ketamine, the second is that we enrolled trans-diagnostic approach. The similar results however, emphasize the replicability of the data and strengthen both studies.

### Trans-diagnostic approach

Suicide is highly related to depression, and it is a grave endpoint of many different mental disorders or life adversities. Hoertel et al in a national prospective study (3) argued that suicide attempts are related to a general psychopathology dimension representing the shared effect across all mental disorders. This approach was strengthened by the DSM5 proposed criteria of “Suicidal behavior disorder”(4). Further, suicide, as a distinct entity, was supported by Niculescu(5) who discovered blood biomarkers for suicide, and by neural presentation of suicide which recently have been described (6). Ketamine’s rapid antidepressant and anti-suicidal effect brought new insights to suicide research; Ballard et al (13) described that the improvement in SI following ketamine infusion is related, but not completely driven, by improvement in depression and anxiety.

A trans-diagnostic approach to the management of SI is particularly useful in the ED setting, in which a potentially life-threatening condition needs an immediate reaction, sometimes prior to a comprehensive diagnosis, which, can be challenging considered the stressful situation of acute SI and ED setting. The trans-diagnostic approach can be compared to emergency treatment for myocardial infarction without the necessity to acquire a thorough history of the underlying condition, such as heart failure or identified

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risk factors. The results of the current study support a trans-diagnostic approach for SI care.

### Clinical applicability

Few treatment options for SI are available, such as lithium, clozapine, Electro-Convulsive Treatment (ECT), and psychotherapies such as Cognitive Behavioral Treatment (CBT) or Dialectical Behavioral Treatment (DBT). All of them lack rapid effect and decrease SI over periods of weeks to months (29). Since SI often occurs in the context of depression, another widely used approach is prescribing antidepressants. Antidepressants, however, are sub-optimal for acute SI. First, because of the time frame, similarly to the previously described options, there is a time lag of weeks to months until full efficacy. Second, about one third of patients fail to achieve remission, even with advanced treatment strategies (30), thus, leaving those suffering SI at suicide risk. Third, antidepressants can occasionally, paradoxically, enhance SI, especially in young adults and adolescents (31). Therefore, although antidepressants are widely used for treatment of depression, it is clearly suboptimal treatment to reduce SI, in the acute setting.

Acute presentation in the emergency setting represents an opportunity for rapidly effective interventions, which have a high likelihood of reducing morbidity, mortality, functional impact, cost savings. While many individuals with acute SI experience rapid resolution of these thoughts, SI unpredictably and rapidly might translate into suicide attempts and/or death by suicide in too many individuals, and the time frame to act is



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brief and critical. Therefore, there is a clear and compelling case for the development of rapidly effective interventions for suicidal patients in the ED.

Notwithstanding the limitations of concluding clinical guidelines from a proof-of-concept study, this study findings support the use of intranasal ketamine in the ED using a trans-diagnostic approach. According to our findings, ketamine alleviated suicidal thoughts and depressive symptoms four hours post administration, this might obtain precious time to the treatment team and might enable them to peruse a suicide prevention strategy. Furthermore, it can change the treatment setting from the stressful ED to ambulatory clinic. Given the safety, applicability, and efficacy of the treatment, the use of a single, low dose intranasal ketamine for suicidal individuals deserves serious consideration as a suicide prevention measure. Further steps are needed in order to embrace this treatment paradigm, such as establishment of ambulatory settings for the sub-acute period post ketamine effect.

Unexpectedly we found that that the SI did not relapse, the relatively extended follow-up of 21 days was designed to assess safety, however, we were surprised to learn that the rates of SI stayed low. While no statistically difference from the controlled group was established, this observation deserves serious consideration for future studies, including study design with power to evaluate this observation.

### Strength and importance

We suggest a novel paradigm to the management of acute SI in the ED settings, that includes diagnosis consideration- trans-diagnostic approach and treatment option- single dose intranasal ketamine. Although similar treatment option has been suggested

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(12) we demonstrate, for the first time, that ketamine is efficient anti-suicidal agent in a trans-diagnostic sample (3). The importance of such a paradigm, if replicated, validated and accepted, cannot be overestimated.

### Limitations

As this was a pilot, proof-of-concept study our sample size was small, and the ability to conduct conclusions from such a sample is restricted. Second, efficient masking is an inherent problem in all ketamine studies due to ketamine's rapid psychomimetic effect. An active placebo, such as midazolam (11) might have better secure the blindness; on the other hand, active placebo such as midazolam may offer some anxiety relief and thus cause a different bias (type 2 error) . Second obstacle for blindness might have been the cardiovascular effect, which can be apparent to raters and subjects alike. We, however, found no significant difference in side effect profile between the two groups, no difference in psychiatric side effects, and no difference in pulse or in blood pressure. Thus, we don't have a reason to assume impairment of blindness. Future studies should consider prescribing active placebo and using different efficacy and safety raters to maintain proper masking. Additional limitation is the lack of blood ketamine levels, such evaluation could determine whether subjects achieved appropriate levels and that administration of ketamine was successful. It would be appropriate for future studies to evaluate blood levels for other routes of administration of ketamine.

To conclude, intranasal ketamine was found to be a safe and feasible treatment option in the ED setting for trans-diagnostic cohort suffering acute SI, in need for hospitalization. We found it to alleviate SI four hours post administration and induce SI remission in 80% of the participants. Further, we observed a trend towards the effect of

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ketamine in shortening length of hospitalization. We present here a novel paradigm which include diagnostic consideration- trans-diagnostic approach, and treatment option- single dose intranasal ketamine, for acute SI in the ED setting. Future larger-scale studies are warranted based on this approach to establish treatment recommendation for acute SI in the ED.

Table 1: Demographics and Baseline Outcome Measures

Figure 1: change in suicidal symptoms across time as can be seen as MADRS 10<sup>th</sup> question, suicidal thoughts

Figure 2: change in depressive symptoms symptoms across time as can be seen as percentage of baseline symptoms of the first 5 question of BSS.

Figure 3: plot box comparison ketamine and control - days of admission

Table 2: safety results

Figure 4: (complementary data). change in suicidal symptoms across time as can be seen as percentage of baseline symptoms of the first 5 question of BSS.

Complementary data: Discussion of suicidal scales.

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Table 1: Baseline Demographics and Outcome Measures

Variables	Total (n=30)	Placebo (n=15)	Ketamine (n=15)	X <sup>2</sup> or t value	Sig
<b>DEMOGRAPHICS</b>					
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
<b>OUTCOME MEASURES</b>					
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)	-0.875	.358
BSS 5 questions Score		<b>7.62</b> <b>(±1.71)</b>	<b>7.53</b> <b>(±2.2)</b>	0.11	.913
Abbreviations: MADRS: Montgomery-Åsberg Depression Rating Scale, BSS: Beck Suicidality Scale, BHS: Beck Hopelessness Scale, BAI: Beck Anxiety Index, BIS: Barrett Impulsivity Scale * P < 0.05.					

Figure 1: change in suicidal thoughts across time as evident in the MADRS 10<sup>th</sup> question of suicidal thoughts. This single question, scale 0-6 is a rater based assessments of suicidal symptoms. Illustration of the mean 10<sup>th</sup> question of suicidal thoughts score, with standard errors (SE).

MADRS: Montgomery-Åsberg Depression Rating Scale

\*p<0.05

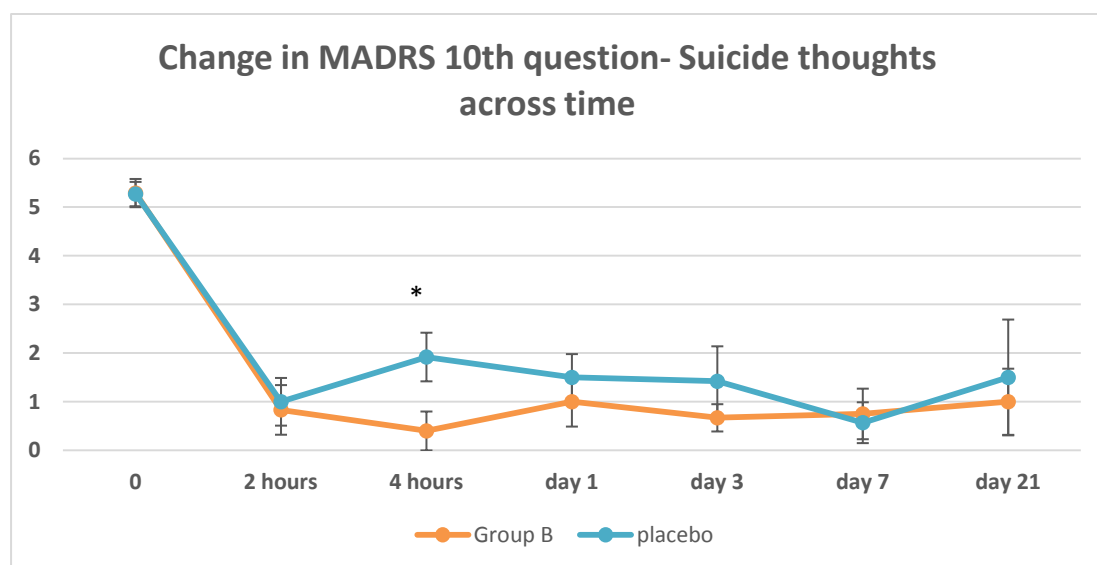


Figure 2: change in depressive symptoms, across time as evident in the MADRS. Illustration of the mean MADRS score, with standard errors (SE).

MADRS: Montgomery-Åsberg Depression Rating Scale

\*p<0.05

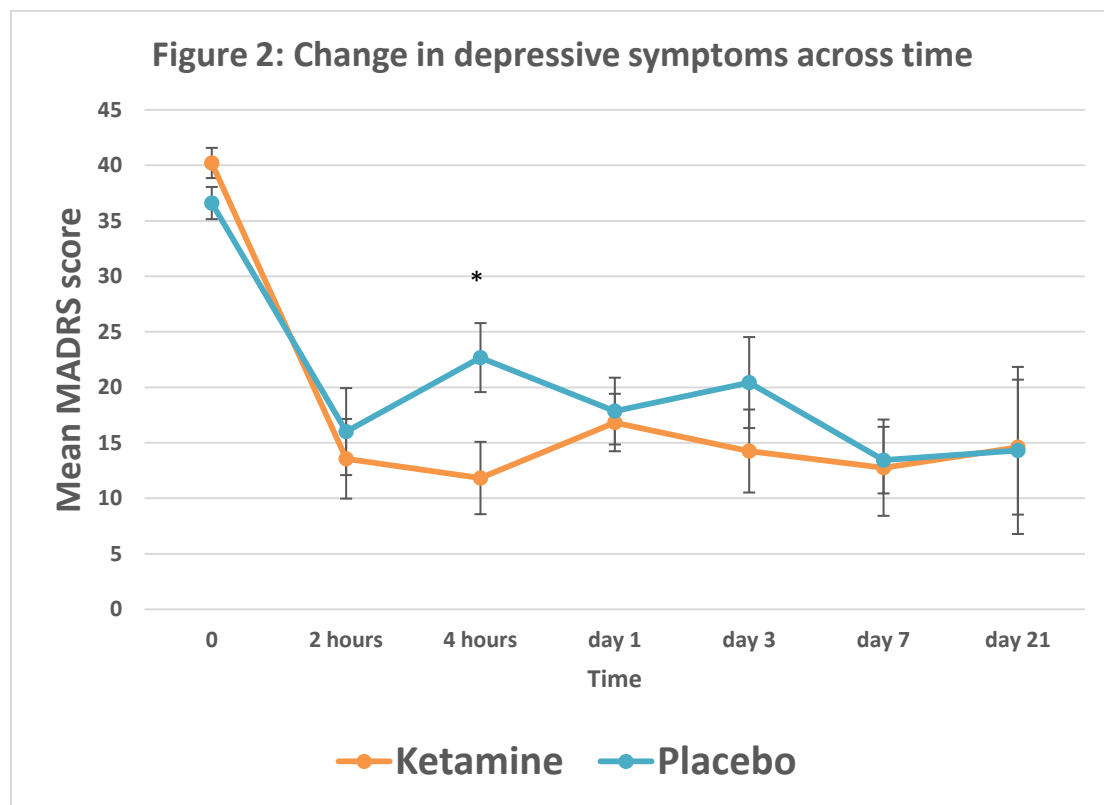




Figure 3: Comparison of days of admission between the ketamine and placebo groups, presented as a box plot. As can be seen in the figure, the median days of admission for the ketamine group was 5 (4-8.5) compares with 9 (5.5-10.5). Percentiles 25 and 75 are additionally reported. There was a trend toward the effect of ketamine on the reduction of days of admission. ( $p=0.089$ ).

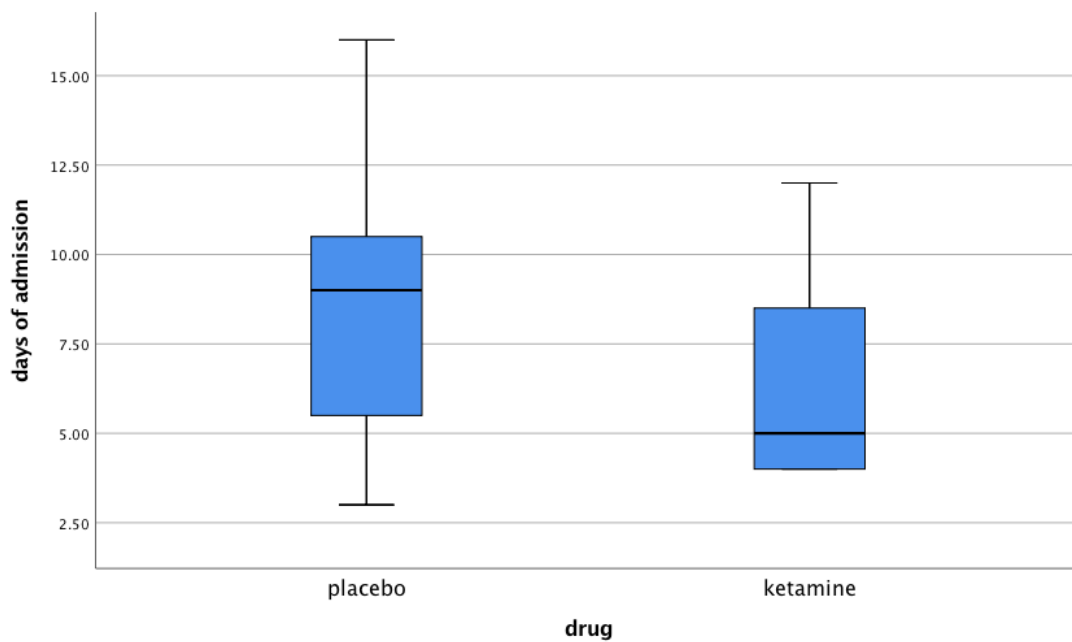


Table 2: safety results

Side effects 1 hour 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

	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

**Consort check list**

**[Click here to download Necessary Additional Data: CONSORT 2010 Checklist ketamine4SI.doc](#)**

**Figure 4: change in suicidal symptoms across time. Presented her**

**[Click here to download Necessary Additional Data: Figure 4 change in suicidal symptoms across time.docx](#)**



## MEDICAL IRB RESEARCH PROTOCOL

**Cheryl McCullumsmith, MD PhD**

### **“Ketamine as brief adjuvant treatment of acute suicidal ideation in nonpsychotic patients”**

- Specific Aims

The objective of the current program of research will be to test whether intranasal ketamine treatment is more effective than placebo in reducing suicidal ideation in suicidal patients presenting for acute treatment in hospital and emergency department settings. Secondary objectives will test biological mechanisms that are related to ketamine influence on suicidal ideation i.e. genotyping, Electro-Encephalo- Gram (EEG) and the correlation of speech patterns and facial movement patterns

**Specific Aim 1:** To assess the acute efficacy and durability of effect over a 3 week time period of single dose of 40 mg intranasal ketamine treatment on suicidal ideation and depression in individuals with acute suicidal ideation as measured by the Beck Scale for Suicidal Ideation (BSS) Montgomery-Asburg Depression Rating Scale (MADRS), and the Columbia Suicide Severity Rating Scale (C-SSRS) as compared to placebo.

Hypothesis 1a: Ketamine treatment will have a greater effects on suicidal ideation as measured by the BSS and depression as measured by the MADRS within 120 minute period compared to placebo treatment

Hypothesis 1b: Ketamine treatment will have a greater effects on suicidal ideation or depression over a four day time period compared to placebo treatment.

Hypothesis 1c: Patients who receive a single ketamine treatment will have no increase in suicidal ideation or behavior over from day 4 to week 3 after treatment compared to placebo treatment measured by the C-SSRS

**Specific Aim 2:** To compare the acute efficacy and 3 week durability of effect of 40 mg intranasal ketamine on RDoC negative valence domain measures related to suicidal ideation including anxiety (Beck Anxiety inventory (BAI)), anhedonia (Snaith-Hamilton Pleasure Scale (SHAPS)), hopelessness (Beck Hopelessness Scale(BHS)), rumination (Rumination Scale), hostility and aggression (Buss-Perry Aggression)in non-psychotic individuals with acute suicidal ideation compared to placebo

Hypothesis 2a: Ketamine treatment will have a greater effect on anxiety, anhedonia and hopelessness within 120 minutes and at days 1 through 4 compared to placebo treatment

Hypothesis 2b: Ketamine treatment will have a greater effects on rumination hostility and aggression measures within 120 minutes and at days 1 through 4 compared to placebo treatment

Hypothesis 2c: Patients who receive ketamine treatment will not have increased severity of negative valence measures from day 4 to week 3 after treatment compared to placebo

**Exploratory Aim 3:** To assess objective biomarkers as predictors of suicide risk and response to ketamine.

Hypothesis 3a: Genetic variants will predict response to ketamine

Hypothesis 3b: Linguistic patterns, voice and facial movements will alter similar to those found in suicidal and non-suicidal individuals after ketamine treatment compared to baseline

Hypothesis 3c: Ketamine treatment will change EEG patterns proportionally to subjective assessments of suicidal ideation compared to placebo

### **Background and Significance: –**

A sobering fact is that currently available antidepressants are not optimal in efficacy<sup>(1)</sup> and speed of onset.<sup>(2)</sup> This is nowhere more evident than in acutely depressed persons presenting in the emergency setting with suicidal ideation. Although many of these patients will be hospitalized, these stays are typically of short duration and may not be associated with significant reduction in depression or suicidal potential. In fact, the period of highest risk for suicide is the first two weeks post-discharge from hospital, representing about a third of all post-discharge suicides.<sup>(3, 4)</sup> This problem is amplified by the fact that there more than one half million admissions to emergency departments for depression in the US each year.<sup>(5)</sup> The range of outcomes for these patients includes hospitalization, intensive outpatient care, and subsequent suicide attempts, making depression associated with suicidal potential a huge public health problem. However, presentation in the emergency setting represents an opportunity for quickly effective interventions, which have a high likelihood of reducing morbidity, mortality, functional impact, and cost savings. There is therefore a clear and compelling case for the development of rapidly effective interventions for suicidal depressed patients in the emergency department.

Until recently, there were few options for rapid intervention in depression. However, this changed dramatically with a study by Berman et al.<sup>(6)</sup> demonstrating that intravenous treatment of the NMDA-receptor antagonist ketamine at a sub-anesthetic dose (0.5 mg/kg), produced antidepressant effects within hours of administration. This finding has since been confirmed by several other placebo controlled studies by Zarate *et al.*<sup>(7)</sup>, DiazGranados et al<sup>(8)</sup>, and Valentine et al<sup>(18)</sup>. Subsequent studies have shown benefit even in ECT-resistant patients.<sup>(9)</sup> Of significance to the current study, ketamine treatment has also been demonstrated to be effective in reducing suicidal ideation in patients with depression.<sup>(9, 10)</sup> Additional study<sup>(11)</sup> evaluated the effect of ketamine on suicidal ideation independently of the psychiatric diagnosis. In this study they evaluated inpatients as well as out patients. Notably, however, there has only been one small, open-label test of ketamine in actual emergency settings<sup>(12)</sup>. Intranasal ketamine has been used in several settings as a safe, effective alternative to intravenous ketamine. Several placebo-controlled studies of examining the use of 10-50 mg intranasal ketamine for the treatment of pain found only mild side effects after intranasal ketamine administration, reports of transient changes in taste, rhinorrhea, nasal passage irritation, and transient elevation in blood pressure and no reports of auditory or visual hallucinations 60 min and 24 h after intranasal ketamine administration.<sup>{Carr, 2004, Safety and efficacy of intranasal ketamine for the treatment of breakthrough pain in patients with chronic pain: a randomized, double-blind, placebo-controlled, crossover study; Carr, 2004, Safety and efficacy of intranasal ketamine in a mixed population with chronic pain}</sup>. Further, a prospective observational study of 40 patients 6 years and older were treated with 0.5-0.75 mg/kg intranasal ketamine in an emergency department setting for pain with side effects of transient dizziness, unreality, nausea, mood change, hearing changes and no changes in vital signs<sup>(13)</sup>. Finally, a recently published trial demonstrated efficacy and safety with use of intranasal ketamine at a dose of 50 mg for treatment of treatment resistant major depressive disorder with minimal dissociate effects and no clinically significant changes in hemodynamic parameters.<sup>(14)</sup>

The objective of the current program of research will be to test whether low dose intranasal ketamine is more effective than placebo in reducing both depression and suicidal ideation in suicidal patients presenting for acute treatment in emergency department and inpatient hospital settings. Secondary objectives will test the safety and tolerability of ketamine treatment, and the decreased length of stay in the emergency room setting and inpatient psychiatric hospitalization due to the rapid antidepressant effects

- Preliminary Studies –

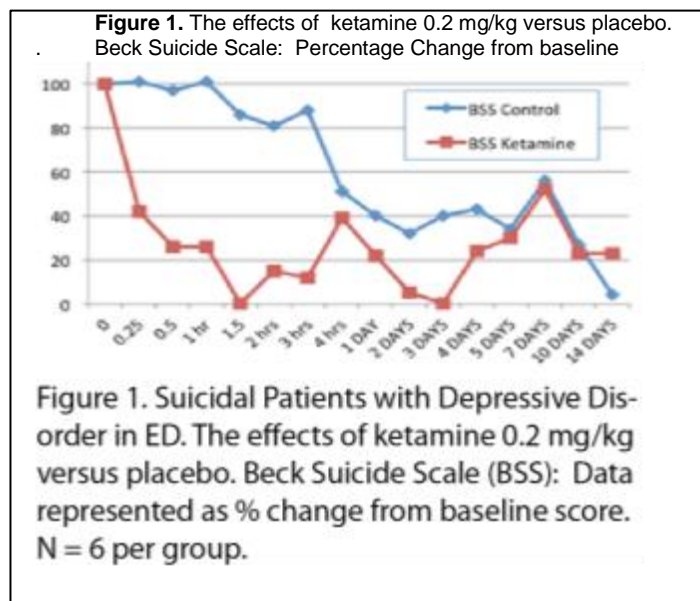
While at University of Alabama at Birmingham (UAB), the principal investigator had initiated a pilot randomized placebo-controlled study of the use of ketamine for patients with depressive disorders and suicidality presenting to the emergency department. Thus far, 10 patients have been enrolled: 5 have received placebo (IV saline) and 5 have received 0.2 mg/kg ketamine treatment. No significant side effects have been noted in these patients, except for one participant who experienced transient sedation. Patients who received ketamine had a rapid decrease in suicidality as measured by both the Beck Scale for Suicidal Ideation (Figure 1) and the MADRS suicide item (not shown) that occurred rapidly, within the first 15 minutes after treatment and persisted for over the full 14 days of follow-up. The suicidality of placebo-treated participants gradually declined over the 2 weeks, reflecting the changes in treatment they experienced in hospital. Over the first 7 days after ED presentation, patients who received placebo treatments had a steady but significant drop in suicide scores to about 40% of their initial presenting score, which accounted for a 5 fold increase in odds ratio of a 50% drop in the Beck suicide score by GEE logistic regression (Table 1).

**Table 1: Single Dose IV Ketamine Increases Likelihood of Treatment Response (50% Reduction in Beck Suicide Score) (GEE Logistic Regression)**

	<b>Odds Ratio Compared to Initial Value</b>	<b>Confidence</b>	<b>Interval</b>	<b>P value</b>
3 days	<b>7.6</b>	1.58	36.52	<b>0.0113</b>
4 days	<b>6.78</b>	1.37	33.48	<b>0.0188</b>
7 days	<b>5.93</b>	1.13	31.15	<b>0.0353</b>

Overall depression scores dropped consistently over the entire study time period for both controls and patients receiving ketamine, with the initial decrease in depression more rapid in the first four hours after treatment for those receiving ketamine. (Not shown). These data, while preliminary indicate that the project is feasible and safe, and support the study of ketamine for suicidal depression in the ED.





**Investigator Experience: -**

I am a collaborative and experienced manager of large clinical projects and my strong research background puts me in a unique position to run this large clinical trial. I have served as director of psychiatric emergency services at UAB for seven years, and now serve as associate director of psychiatric emergency services here at University of Cincinnati.

I have developed broad and deep research experience over the past five years with extensive collaborations and support. I collaborate with Karen Cropsey, PsyD on clinical research in a

community corrections population and with Scott Richards, PhD on a multisite study on depression in patients with spinal cord injury. I am working on clinical trials on depression and suicidality in conjunction with Richard Shelton, MD and Adrienne Lahti, MD. I am writing up the results of 2 clinical observational trials we have done in the ER setting : one on the transitional psychiatry clinic , \that has garnered a talk at my subspecialty national meeting and one on post traumatic stress disorder after tornados. I have independently developed 2 large clinical trials that are ongoing in the emergency room, in collaboration with Emergency Medicine faculty: Screening and Brief Intervention for Substance Use and a trial using intravenous ketamine as a rapid antidepressant in the ER setting.

**Experimental Design and Methods: -**

**SECTION III. RESEARCH METHODS.**

**Aims 1&2 reserch methods:**

**Overview:** The objective of this research is to provide the first placebo-controlled test of the efficacy, safety, and feasibility of the use of ketamine treatment for the treatment of acute suicidal ideation in a natural sample of patients with a range of underlying non-psychotic diagnoses. Based on prior preclinical and clinical data, and our own preliminary research, we anticipate that acute ketamine treatment will successfully reduce suicidal ideation, depression, Note that this study is adjunctive, in addition to the standard care treatment. Participation in this study will not delay or change standard treatment for these patients. Patients will receive a single acute intranasal treatment of ketamine at 40 mg or placebo (saline) in a double-blind manner. Study assessments including assessments of depression and suicidal ideation and negative valence domains such as anhedonia, hopelessness, aggression, rumination and hostility will be performed at baseline prior to treatment and at 30, 60, 120 and 240 minutes, and on days 1, 2, 3, 4, 7 (+/- 1 day) , 14 (+/- 1 day) , and 21 (+/- 1 day) , after ketamine treatment. Patients will be seen either in person or by phone per patient availability by a study psychiatrist on day 21. This study is an adjunct to usual care and patients will be placed immediately on their regular medical and psychotherapy treatment regimens and outpatient referrals on discharge from the hospital.

## EXPLORATORY AIM 3 RESEARCH METHODS:

For Exploratory aim 3 **only**, the inclusion criteria will include additional sub group of subjects that will be recruited as outpatients with some degree of suicidal ideation that is not sufficient for inpatient hospitalization, as deemed by both the patient's primary psychiatrist and the research team. For safety, those subjects will be evaluated by the study psychiatrist/ PI and if needed will be referred to the psychiatric emergency department before they will be recruited or at any time a necessity will arise. The evaluation of outpatients with mild to moderate suicidal ideation in a clinical trial using ketamine has been recently described (11)

A&B: A descriptive linguistic analysis will compare words, word count, stemming, par-of-speech, suicidal emotions and readability between the control and treatment group. linguistic, acoustic, facial expression and genetic information to produce a decision support index related to the likelihood of continued high suicidal ideation. Linguistic information, acoustic and facial expression information will be derived from interviews using the Columbia Suicide severity "Rating scale, linguistic Algorithmic Analysis (Cosine SVM classification) of transcribed answers to the Ubiquitous Questions.

C: We intend to record from up to 128 EEG electrodes during the resting state and both executive functions and emotional tasks before and after ketamine treatment.

1. Executive functions task: Nabck. During this task participants are presented with two conditions: 1) a minimal cognitive overload condition (0-back) 2) an overload condition (2-back). In each of the conditions numbers are presented on the screen. In the 0 back condition the participant is requested to push a button every time he/she sees the digit "0" on the screen. In the 2-back condition, the participant is required to push a button only if the number he/she sees on the screen appeared 2 digits beforehand.
2. Emotional task: facial recognition- in this task the participant is presented with a happy face, surprised face, neutral and a black circle. He/she is required to push one button for emotional expression (happy, surprised) and a different button for the non-emotional stimuli (black, neutral).

Reaction times and accuracy will be recorded for both tasks

We plan to analyze the data in the time frequency domain at both sensor and source spaces.

### D: Genotyping:

We propose to collect blood for whole-blood gene expression studies and to carry out fresh blood gene expression studies. We hypothesize that a series of markers will be identified that are induced in suicidal states (16-17). Those markers expression might change following ketamine treatment and resolution of suicidal state. We will collect blood before and after ketamine administration.

Genotyping will be done at the Indianapolis VA Medical Center and IU School of Medicine . We will collect blood for whole-blood gene expression studies which will be used for subsequent gene expression work. The blood will be collected in two RNA- stabilizing PAXgene tubes for each subject, aliquoted into 1cc cryovials pre-labeled with an anonymized ID number, and

stored at -80C in a locked freezer until the time of future processing. Whole blood (predominantly lymphocyte) RNA will be extracted for microarray gene expression studies from the PAXgene tubes blood.

**RNA extraction:** 2.5-5 ml of whole blood will be collected into each Paxgene tube by routine venipuncture. PaxGene tubes contain proprietary reagents for the stabilization of RNA. The cells from whole blood will be concentrated by centrifugation, the pellet washed, resuspended and incubated in buffers containing Proteinase K for protein digestion. A second centrifugation step will be done to remove residual cell debris. After the addition of ethanol for an optimal binding condition the lysate is applied to a silica-gel membrane/column. The RNA binds to the membrane as the column is centrifuged and contaminants are removed in three wash steps. The RNA is then eluted using DEPC-treated water.

**Globin reduction:** To remove globin mRNA, total RNA from whole blood is mixed with a biotinylated Capture Oligo Mix that is specific for human globin mRNA. The mixture is then incubated for 15 min to allow the biotinylated oligonucleotides to hybridize with the globin mRNA. Streptavidin Magnetic Beads are then added, and the mixture is incubated for 30 min. During this incubation, streptavidin binds the biotinylated oligonucleotides, thereby capturing the globin mRNA on the magnetic beads. The Streptavidin Magnetic Beads are then pulled to the side of the tube with a magnet, and the RNA, depleted of the globin mRNA, is transferred to a fresh tube. The treated RNA is further purified using a rapid magnetic bead-based purification method. This consists of adding an RNA Binding Bead suspension to the samples, and using magnetic capture to wash and elute the GLOBINclear RNA.

**Sample Labeling:** Sample labeling is performed using the Ambion MessageAmp II-BiotinEnhanced aRNA amplification kit. The procedure is briefly outlined below and involves the following steps:

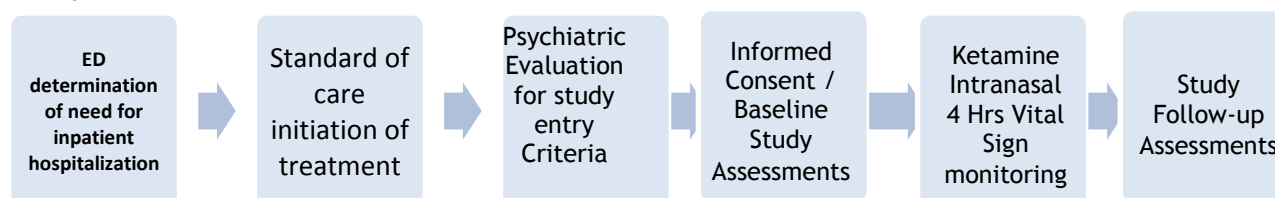
1. *Reverse Transcription to Synthesize First Strand cDNA* is primed with the T7 Oligo(dT) Primer to synthesize cDNA containing a T7 promoter sequence.
2. *Second Strand cDNA Synthesis* converts the single-stranded cDNA into a double-stranded DNA (dsDNA) template for transcription. The reaction employs DNA Polymerase and RNase H to simultaneously degrade the RNA and synthesize second strand cDNA.
3. *cDNA Purification* removes RNA, primers, enzymes, and salts that would inhibit in vitro transcription.
4. *In Vitro Transcription to Synthesize aRNA* with Biotin-NTP Mix generates multiple copies of biotin-modified aRNA from the double-stranded cDNA templates; this is the amplification step.
5. *aRNA Purification* removes unincorporated NTPs, salts, enzymes, and inorganic phosphate to improve the stability of the biotin-modified aRNA.

**Microarrays:** Biotin labeled aRNA are hybridized to Affymetrix HG-U133 Plus 2.0 GeneChips according to manufacturer's protocols

[http://www.affymetrix.com/support/technical/manual/expression\\_manual.affx](http://www.affymetrix.com/support/technical/manual/expression_manual.affx). All GAPDH 3'/5' ratios should be less than 2.0 and backgrounds under 50. Arrays are stained using standard Affymetrix protocols for antibody signal amplification and scanned on an Affymetrix GeneArray 2500 scanner with a target intensity set at 250. Present/Absent calls are determined using GCOS software with thresholds set at default values.

**Quantitative PCR:** Top genes of interest from the microarray findings will be verified by qPCR, using an Applied Biosystems 7300 Real-Time PCR system already present in the lab. Primers for the target genes will be purchased from ABI.

## Study Flow:



**Study design** 60 participants will enter a double-blind, placebo-controlled clinical trial to determine the utility of 40 mg dose of intranasal ketamine for treatment of suicidality. Participants will be randomized to receive either 40 mg dose ketamine or saline intranasal. Neither the patient nor the physician will know which study medicine (ketamine or placebo) the patient is receiving. If medically necessary, the medication information will be released to treating physicians can find out what medicine you were randomly assigned to.

The treatment participants will receive as part of the study will be in addition to their usual psychiatric care. The standard of care for patients presenting with suicidal ideation or attempts is hospitalization and the participants in this study are expected to be hospitalized. For example, lab work, ECGs, physical exams are part of the usual care, not research procedures. Participation in this study will not delay or change standard treatment for these patients, including initiation of standard antidepressant therapies, which can begin on the regular schedule, including the day of study drug treatment

Study subjects will receive the ketamine therapy under the supervision of physician on the research team with Advanced Cardiac Life Support (ACLS) certification, as well as the psychiatry research assistant. The patient will be in the psychiatric emergency room or inpatient unit where there is a crash cart, staff psychiatric nurses trained in ACLS as well as another staff psychiatrist. They will receive vital sign monitoring both during the treatment and for 2 hours following the treatment.

**a. Participants:** 60 persons presenting with clinically significant suicidal ideation for acute treatment to University of Cincinnati's emergency department, psychiatric emergency room or inpatient psychiatric hospital who have been evaluated by the primary clinical team and are deemed to require inpatient psychiatric hospitalization.

Inclusion criteria: 1. Males and females; 2. Ages 18-65; 3. All races and ethnicities; 4. Willing and able to provide informed consent; 5. A cutoff score of >3 on the Beck Scale for Suicidal Ideation; and >2 on the Columbia Scale for Suicide Severity Rating. 6. Meeting criteria for inpatient hospitalization or observation by primary clinical team.

Exclusion criteria: 1. Pregnancy or lactation; women of reproductive potential must have a negative urine pregnancy test; 2. Post-partum state (within 2 months of delivery); 3. Homicide risk as determined by clinical interview; 4. Any of the following DSM-IV diagnoses: a. Any current primary psychotic disorder; b. Acute intoxication or withdrawal from alcohol or any other substance of abuse, as determined by clinical interview and urine drug screen; except opioids c. use of any hallucinogen (except cannabis), in the last month; d. Any dissociative disorder; e. Pervasive developmental disorder; f. Cognitive disorder; g. Cluster A personality disorder; h. Anorexia nervosa. 5. Any known hypersensitivity or serious adverse effect with ketamine 6. Any clinically-significant medication or condition that would preclude the use of ketamine including respiratory illness requiring the regular use of oxygen.

**b. Site:** Dr. McCullumsmith serves as associate director of UC's Psychiatric Emergency Services,. All patients are medically cleared in the psychiatry emergency room prior to the decision to admit to inpatient psychiatry. Patients awaiting psychiatric hospitalization are bedded in the PES under the care of psychiatry.

**c. Assessments:** A schedule of assessments is presented in Table **below**. Note that reliability is carefully monitored in mandatory weekly meetings in our programs to maintain concordance. *A baseline medical evaluation and physical will be conducted to assess for the inclusion and exclusion criteria above.*

### **Assessment Tools**

Consent :

1. The UCSD Brief Assessment of Capacity to Consent (UBACC) is a validated tool to standardize assessment of patient understanding of information in the informed consent of a study

Diagnostic:

1. The **Mini International Neuropsychiatric Interview (MINI)** will serve as the primary instrument for diagnostic ascertainment for psychiatric exclusion criteria.
2. We will assess current suicidal ideation, plans, intent, and behaviors using the **Columbia Suicide Severity Rating Scale (C-SSRS)**.

Depression and Suicide Symptom measures:

1. **Montgomery-Åsberg Depression Rating Scale (MADRS)** is the primary measure of change in depression. The MADRS has been modified to reflect the period since last assessment (except for baseline, which will reflect the past week).
2. **Clinical Global Impression, Severity and Improvement Scales (CGI-I, CGI-S)**- physician rating of improvement of symptomatology
3. **Beck Suicide Scale (BSS)**- Self assessment scale for suicidal intent and ideation and risk
4. **Beck Hopelessness Scale (BHS)**- Self assessment tool for hopelessness, highly linked to suicide risk.
5. **VASSI – Visual Analog Scale for Suicidal Intention**
6. **SIBAT – Suicidal Ideation and Behavior Assessment Tool** may be used if available, this scale is in development
7. **Simplified Affective State Scale (SASS)** is an 11 item scale for measuring mood and anxiety, The SASS has a set of 11 visual analog scales (7 for mood, 4 for anxiety) that ends up providing a number ranging from 0 to 100 for mood state, and for anxiety state
  1. **Convergent Functional Information for Suicide (CFI-S)** is a new 22 item scale for suicide risk, which integrates, in a simple binary fashion (yes-1, no-0), similar to a polygenic risk score, information about known life events, mental health, physical health, stress, addictions and cultural factors that can influence suicide risk

RdoC : Negative Valence Domains

1. Acute Threat or Fear will be assessed with the **Beck Anxiety Inventory (BAI)**, a widely used, valid, and reliable self-report instruments for anxiety respectively.

2. Sustained Threat and Loss will be assessed by the **Snaith-Hamilton Pleasure Scale (SHAP)** is a validated scale to assess anhedonia
3. Hopelessness : **Beck Hopelessness Scale (BHS)**- well validated self-assessment tool )
4. Rumination : **Rumination Responses Scale**
5. Aggression : **Buss-Perry Aggression Scale** is a well-validated scale of aggression(69)

Drug Use History:

1. Alcohol and Drug Use Screen- assessment of alcohol and substance use in past 30 days
2. DAST- assessment of drug dependence and abuse
3. Audit- assessment of alcohol dependence and abuse

Psychiatric treatment history:

1. History of psychiatric treatment will be obtained using a modified version of the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ) adapted to cover all prior treatment (ATRQ-M).

Impulsivity:

1. Barrett Impulsivity Scale (BIS)- self assessment of impulsivity

Safety, tolerability, and adverse effects:

1. Psychosis: The presence of psychotic symptoms both pre- and post-treatment will be evaluated using symptoms from the Brief Psychiatric Rating Scale (BPRS) in the ketamine side effects scale
2. Behavioral Use Ketamine Side Effects Scale assesses known side effects in a concise manner such that these symptoms can be assessed rapidly at multiple time points : psychosis, dissociation, vital sign abnormalities, agitation, sedation,
3. Mania: The occurrence of mania will be queried using the Young Mania Rating Scale (YMRS), an 11-item, clinician-rated measure that queries symptoms of mania.
4. Drug Effects Questionnaire: 5 question assessment by visual analog scale of drug's effects and addiction potential: A visual analogue scale (VAS) measuring liking of drug, craving for drug and willingness to take the drug again will be administered at each time point in follow-up.
5. Pelvic Pain and Urinary Frequency Scale : (PUF) a standardized 8 question scale for bladder spasticity issues
6. Locator Information Form is used to find patients who might be lost to follow-up Releases to share information (location only) will be signed for all individuals that patients list as contacts on their locator information forms.

	Responsible Personnel RC: Research Coordinator MD : study physician	Study Entry Criteria	Initial Evaluation	Post Treatment Times: 30 min 60 min 120 min 240 min	Follow-up Days 1,2,3,4,7, ,14,21 Assessment window of 2 days +/-
<u>AIM 1</u>					
<u>Informed consent</u>	RC	X			
	RC	X			
<u>Diagnostic</u>					
• MINI	RC	X			
• C-SSRS	RC/MD	X (RC verified by MD)			Days 7, 14,21 (MD)
• BSS	RC		X	120,240	X
<u>Depression</u>					
• MADRS	RC		X	120,240	X
• SASS	RC		X	120,240	X
<u>Suicidality</u>					
BSS as above					
• VASSI	RC	x	X	X	X
• SIBAT	MD		X	240 min	Days 7,21
• CFI-S		x		120,240	
<u>Drug Use</u>					
Survey of use	RC		X		Days 7,21
• Audit	RC		X		
• DAST	RC		X		
<u>Psychiatric Treatment History</u>					

• ATRQ	RC		X		X (update)
•					
<u>Impulsivity</u>					
• BIS	RC		X		Days 7,14,21
<u>Side Effects/Tolerability</u>					
• CGS	RC		X		X
• CGI					X
• Ketamine Side Effects Scale	RC		X	X	X
• YMRS	RC		X		Days 7,21
• Pain	RC		X	240 min	days 1,4,7,21
• Drug Effect	RC			X	X
• Side effect review	RC		X	X	X
• PUF	RC		X		days 1,4,7,21
• Locator Information Form	RC	X			
<u>Medical tests</u>					
• Vital Signs	Reviewed by study physician	X	X	X	
• Clinical labs		reviewed			
• Physical exam		reviewed			
• Urine drug		reviewed			
<u>Prescription of</u>	Study Physician				
<u>Study Drug Treatment</u>	Study physician or designee	X			



AIM 2	Negative Valence RDoC Measures				
BAI	RC		X	240 min	X
<u>BHS</u>	RC		X	240 min	days 1,4,7,21
<u>SHAP</u>	RC		X	240 min	Days 1,4,7,21
<u>Rumination</u>	RC		X	240 min	days 1,4,7,21
<u>Buss-Perry</u>	RC		X	240 min	days 1,4,7,21
<u>Exploratory Aim 3</u>					
<u>Informed consent</u> <u>For Aim 3</u>	RC	X			
Ubiquitous Questions			X	240 min	Day 1 and 3 (if possible) Weeks 4
Videotaping of interview			X	240 min	Day 1 and 3 (if possible) Weeks 4
EEG	RC		X		Day 1
genotyping	RC		x	240 min	Day 1, day 3

**b.1. Psychiatric Assessments.** Diagnostic: The Mini International Neuropsychiatric Interview (MINI) will serve as the primary instrument for diagnostic ascertainment. The MINI is a semi-structured 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 ED setting because of its relative brevity.

Suicide: We will assess current suicidal ideation, plans, intent, and behaviors using the Columbia Suicide Severity Rating Scale (C-SSRS, Baseline and Versions). The C-SSRS is a widely used and valid scale used to assess both recent and lifetime suicide-related thoughts and behaviors. Our groups have extensive experience using this scale. The effects of treatment on suicidal potential will be assessed using the Beck Scale for Suicidal Ideation (BSS). The

BSS is a 21-item, 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 interrater reliability and has been shown definitively to be sensitive to change in clinical trials, including ketamine studies. The Convergent Functional Information for Suicide (CFI-S) Scale is a new 22 item scale for suicide risk, which integrates, in a simple binary fashion (yes-1, no-0), similar to a polygenic risk score, information about known life events, mental health, physical health, stress, addictions and cultural factors that can influence suicide risk (16). Depression and Anxiety Symptom measures: The Montgomery-Åsberg Depression Rating Scale (MADRS) will serve as the primary 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.(8-11) The MADRS has been modified to reflect the period since last assessment. We will use the Simplified Affective State Scale (SASS) to capture current mood and anxiety symptoms. The SASS is an 11 item scale for measuring mood and anxiety, The SASS has a set of 11 visual analog scales (7 for mood, 4 for anxiety) that ends up providing a number ranging from 0 to 100 for mood state, and for anxiety state

Pain Measures: The Brief Pain Inventory (BPI) allows patients to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function and has been used in hundreds of research studies.

Psychiatric treatment history: History of psychiatric treatment will be obtained using a modified version of the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire<sup>49</sup> adapted to cover all prior treatment (ATRQ-M).

Substance Use History and Severity: AUDIT and DAST

**b.2.Safety, tolerability, and adverse effects:** Psychosis: and Dissociative symptoms: experienced during ketamine treatment will be assessed the ketamine side effects scale which incorporates relevant questions from the Brief Psychiatric Rating Scale (BPRS) and the Clinician Administered Dissociative States Scale .. Mania: The occurrence of mania will be queried using the Young Mania Rating Scale (YMRS), an 11-item, clinician-rated measure that queries symptoms of mania.<sup>90</sup> Addiction potential: A visual analogue scale (VAS) measuring liking of drug, craving for drug and willingness to take the drug again will be administered at each time point in follow-up. Bladder spasticity: the Pelvic Pain and urinary frequency (PUF) scale is a validated scale to assess bladder spasticity issues (15) Other Safety and Tolerability Data: Spontaneously reported adverse events will also be recorded.

**b.3.Relapse:** A major concern that could limit the viability of this approach in EDs is the risk for relapse following initial response. We will determine the number of relapses in the drug and placebo initial responders. For the purposes of relapse estimation, initial response will be defined as at least a 50% reduction in baseline BSS scores. Relapse will then be defined as a return to greater than or equal to 80% of the baseline BSS score. Relapse rates will be reported to Data Safety Monitoring Board (DSMB) for quarterly evaluations.

**b.4. Data Safety Monitoring Board (DSMB):** A DSMB will be established to review both assessments and adverse outcomes. This DSMB will meet quarterly and on an ad hoc basis.

### **c. Procedures :**

Participants who present in psychiatric crisis to UC's psychiatric emergency services, inpatient hospital or ED will be selected based on the presence of sufficient suicidal ideation to warrant hospitalization or observation.

Potential participants will be approached by a study physician or research coordinator who will describe the study and elicit consent. Written informed consent will be obtained from all

participants after a thorough description of the study. Baseline assessments and a full medical and psychiatric history will be obtained, and urine obtained for drug screen and pregnancy test for women of reproductive potential. Those meeting all inclusion and exclusion criteria will qualify for participation and will be randomized (1:1) to IN ketamine 40 mg or matched placebo (normal saline), randomized 1:1. Study drug may be given in the PES, the main ED, the main UC hospital or the inpatient psychiatric hospital unit. The research pharmacies at UC will prepare ketamine and placebo for IN treatment and will maintain the randomization schedule. Study medication will be drawn up into a one ml syringe and transported to the patient bedside. At bedside, an intranasal mucosal atomization device will be placed onto the syringe via the luer lock connector. The patient will be placed in a reclining position and  $\frac{1}{4}$  the dose will be administered into the right nostril, then  $\frac{1}{4}$  of the dose will be administered into the left nostril. The patient will be instructed not to blow the nose but to sniff a few times. After 10 minutes, the second dose ( $\frac{1}{4}$  the syringe dose per nostril), will be administered. The treatment may be stopped by the participant at any point. Vital signs including pulse, blood pressure, respiratory rate, and oxygen saturation measurements will be recorded for two hours after treatment. Note that ACLS certified study physicians will be available throughout the period of observation. Ratings and other assessments will be given according to the schedule outlined in Table 1, notably at 30, 60, 120 and 240 minutes after treatment. At the completion of post-treatment observation period the participant will be hospitalized in the Psychiatry Units at the UC Hospital. The time of discharge from hospital will be determined by a physician who is not involved in the study. All patients will then receive standard of care by the treating (non-study) psychiatrist, which will not be delayed or changed by participation in the study. Study assessments will be performed at baseline prior to treatment and at 30, 60, 120 and 240 minutes, and on days 1, 2, 3, 4, 7, 14, and 21, after ketamine treatment. The weekly assessments are given a window of 2 days for completion. Patients will be assessed by a study psychiatrist on day 21, either in person or by phone depending on patient availability. Patients will receive standard psychiatric care for their underlying condition and will receive standard psychiatric follow-up. Study participation will be complete and the participant will be referred for follow-up treatment.

**d. Data Collection and Management:** To ensure the quality of Electronic Data Capture (EDC) and management, the data management team will use the REDCap EDC system.<sup>93</sup> 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).

**e. Statistical Analysis:**

**Aim 1 and 2**

**i. General Strategy:** All outcomes will be summarized descriptively and assessed for normality prior to analysis using normal probability plots and Kolmogorov test statistics. Transformations or nonparametric analyses will be performed as necessary. All tests will be two-sided and considered statistically significant at  $\alpha=.05$ . Post-hoc comparisons will be performed as appropriate and significance levels will be adjusted for multiple tests using the Bonferroni correction. All analyses will be performed using SPSS. Linear mixed models will be used to compare acute changes in suicidal ideation as measured by the BSS (Aim 1), between treatment groups. In these models group (placebo vs. ketamine) will be included as a between-subjects factor and time (pre- vs. 120 min post-treatment) will represent a within-subjects factor. A significant group by time interaction explained by reduced BSS (or MADRS) scores following ketamine treatment compared to placebo will be supportive of our hypothesis. The durability of

ketamine effects on suicidal ideation, pain and depression will be analyzed using the same models above except time will extend to two weeks. Similar mixed models described above will be employed to evaluate secondary outcomes (e.g., PANSS, CADSS). And baseline characteristics such as age, gender, and psychiatric treatment history (ATRQ) will be considered as potential covariates. Tolerability and safety will be evaluated descriptively (e.g., frequencies, summary statistics) separately for each treatment group and compared using simple test statistics (e.g., chi-square, t-test) as appropriate. **ii. Power Analysis:** We will recruit 60 subjects and randomly assign  $n=30$  to either ketamine or placebo bolus. In terms of acute reductions in BSS and MADRS scores (Aims 1), with  $n=30$  per group, we will have 80% power to detect medium to large effects ( $d>0.81$ ), previously observed by DiazGranados (8), Price (10), and Larkin (12) related to ketamine's ability to acutely reduce suicide ideation and depression (all  $d>1.1$ ), assuming a between subjects test and a two-sided  $\alpha=0.05$  (Cohen, 1988). This compares well to the effect sizes in our own pilot data from UAB comparing 5 control with 4 subjects administered ketamine in the ER, at 150 minutes post-treatment, ketamine showed robust reductions in MADRS-Suicide with a Cohen's  $d=2.4$ , we will have power to detect clinically meaningful effects in each of the proposed Aims.

#### **EXPLORATORY AIM 3A:**

Sample size calculations: for sample size calculations for our microarray validations based on a 2-group Student t-test strategy using the program PS, version 2.1.31 (2004). We assume that gene expression levels have a normal distribution with mean 100 and standard deviation 100. Although these choices were informed by our real data we should emphasize that the mean and variance will vary significantly across the individual genes in any given signature or profile. We chose a false positive rate (alpha error) = 0.0001. At this level, 50 samples have about 90% power to detect a fold change of 2, and only 25 samples have about 90% power to detect a fold change of 2.5. Pathway analyses: Ingenuity Pathway Analysis 7.0 (Ingenuity Systems, Redwood City, CA) will be used to analyze the biological roles categories of the top candidate genes resulting from our CFG analysis.

#### **EXPLORATORY AIM 3B**

A descriptive linguistic analysis will compare words, word count, stemming, part-of-speech, suicidal emotions and readability between the control and treatment group. Linguistic, acoustic, facial expression and genetic information to produce a decision support index related to the likelihood of continued high suicidal ideation. Linguistic information, acoustic and facial expression information will be derived from interviews using the Columbia Suicide severity "Rating scale, linguistic Algorithmic Analysis (Cosine SVM classification) of transcribed answers to the Ubiquitous Questions.

#### **Exploratory Aim 3c:**

All outcomes will be summarized descriptively and assessed for normality prior to analysis using normal probability plots and Kolmogorov test statistics. Transformations or nonparametric analyses will be performed as necessary. All tests will be two-sided and considered statistically significant at  $\alpha=0.05$ . Post-hoc comparisons will be performed as appropriate and significance levels will be adjusted for multiple tests using the Bonferroni correction. All analyses will be performed using SPSS.

Human Subjects - Describe the characteristics of the research population:

## **Protection of Human Subjects**

### **I. Risks to the Subjects**

#### **a. Human Subjects Involvement and Characteristics:**

**Participants:** 60 persons presenting with clinically significant suicidal ideation for acute treatment to University of Cincinnati's emergency department, psychiatric emergency room or inpatient psychiatric hospital who have been evaluated by the primary clinical team and are deemed to require inpatient psychiatric hospitalization.

Inclusion criteria: 1. Males and females; 2. Ages 18-65; 3. All races and ethnicities; 4. Willing and able to provide informed consent; 5. A cutoff score of >3 on the Beck Scale for Suicidal Ideation; and >2 on the Columbia Scale for Suicide Severity Rating.

Exclusion criteria: 1. Pregnancy or lactation; women of reproductive potential must have a negative urine pregnancy test; 2. Post-partum state (within 2 months of delivery); 3. Homicide risk as determined by clinical interview; 4. Any of the following DSM-IV diagnoses: a. Any current primary psychotic disorder; b. Acute intoxication or withdrawal from alcohol or any other substance of abuse, as determined by clinical interview and urine drug screen; except opioids c. use of any hallucinogen (except cannabis), in the last month; d. Any dissociative disorder; e. Pervasive developmental disorder; f. Cognitive disorder; g. Cluster A personality disorder; h. Anorexia nervosa. 5. Any known hypersensitivity or serious adverse effect with ketamine 6.. Any clinically-significant medication or condition that would preclude the use of ketamine including respiratory illness requiring the regular use of oxygen.

**b. Sources of materials:** Research data acquired will include assessments obtained by interview and by self-report as noted below. Laboratories will include urine pregnancy tests for fertile females and urine drug screen for all participants.

Assessments: *Diagnostic:* The Mini International Neuropsychiatric Interview (MINI) will serve as the primary instrument for diagnostic ascertainment.

*Depression and Anxiety Symptom measures:* The primary measure of change in depression will be the Montgomery-Åsberg Depression Rating Scale (MADRS). The MADRS has been modified to reflect the period since last assessment (except for baseline will be reflect the past week). Beck Anxiety Inventory (BAI) will be used for self-report of anxiety.

*Suicide:* We will assess current suicidal ideation, plans, intent, and behaviors using the Columbia Suicide Severity Rating Scale (C-SSRS, Baseline and Versions). The effects of treatment on suicidal potential will be assessed using the Beck Scale for Suicidal Ideation (BSS). Previous studies have identified a cutoff score > 3 as indicating significant suicidal ideation on the BSS. Therefore, a score of >3 on the BSS will be required for inclusion.

*Psychiatric treatment history:* History of psychiatric treatment will be obtained using a modified version of the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ) adapted to cover all prior treatment (ATRQ-M).

Safety, tolerability, and adverse effects: Psychosis: and Dissociative symptoms: experienced during ketamine treatment will be assessed the ketamine side effects scale which incorporates relevant questions from the Brief Psychiatric Rating Scale and the Clinician Administered Dissociative States Scale .. Mania: The occurrence of mania will be queried using the Young Mania Rating Scale (YMRS), an 11-item, clinician-rated measure that queries symptoms of mania. Addiction potential: A visual analogue scale (VAS) measuring liking of drug, craving for drug and willingness to take the drug again will be administered at each time point in follow-up. Bladder spasticity: the Pelvic Pain and urinary frequency (PUF) scale is a validated scale to

assess bladder spasticity issues (15) Other Safety and Tolerability Data: Spontaneously reported adverse events will also be recorded.

Psychosis: The presence of psychotic symptoms both pre- and post-treatment will be evaluated using questions from 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. Dissociative symptoms: Dissociative symptoms experienced during ketamine treatment will be assessed by selected questions from the Clinician-Administered Dissociative States Scale (CADSS), in the ketamine side effects scale.

*Mania*: The occurrence of mania will be queried using the Young Mania Rating Scale (YMRS), an 11-item, clinician-rated measure that queries symptoms of mania, and using questions from the Brief Psychiatric Rating Scale (BPRS).

Psychiatric treatment history: History of psychiatric treatment will be obtained using a modified version of the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ) adapted to cover all prior treatment (ATRQ-M).

Drug Use History: Alcohol and Drug Use Screen- assessment of alcohol and substance use in past 30 days, DAST- assessment of drug dependence and abuse, Audit- assessment of alcohol dependence and abuse

Bladder spasticity: the Pelvic Pain and urinary frequency (PUF) scale is a validated scale to assess bladder spasticity issues. {Parsons, 2002, Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynecologic cases identified using a new symptom questionnaire and intravesical potassium sensitivity}

*Other Safety and Tolerability Data*: Patients will be administered a visual analog scale measure of cravings for and desire to obtain ketamine.

**c. Potential risks:** There are several main sources of risk for participants in this study. First, there is the risk of the underlying condition, suicidal ideation. Persons who present to an emergency department for suicidal ideation are at elevated risk of completing suicide. Note that the active treatment in the study, ketamine, has not been shown to increase this risk in any way, including prior studies in suicidal patients. Nonetheless, there is always a possibility that the treatment with ketamine could increase suicidal ideation in some vulnerable participants. The second source of risk is that of ketamine treatment, which may lead to either mild psychotic symptoms (e.g., paranoid ideation) or dissociative symptoms (e.g., dissociation, depersonalization, or derealization); while these symptoms are very transient, they can be distressing to participants. A third source of risk is associated with being interviewed and answering detailed questionnaires. Personal questions, such as queries about early life trauma, may be distressing. Participation in the study may be inconvenient for some. A fourth area of risk is from side effects from ketamine which include sedation, increase heart rate and increased blood pressure. These symptoms are transient and the patient will be on vital sign monitoring for 2 hours after the treatment. Finally, there is a risk of loss of confidentiality. Confidentiality of all subjects will be protected per institutional federal requirements, and as described in greater detail below.

## **II. Adequacy of protection against risks**

**a. Recruitment and informed consent:** All materials used to recruit subjects for this protocol will be reviewed and approved by the IRB at the University of Cincinnati prior to their use. All subjects will receive the consent form for the study as well as the Human Subject's Bill of Rights. These documents will be read by the patients and also reviewed by the patient with a

clinician on the research staff prior to participating in the study. A study clinician prior to the patient signing consent will clarify any questions, concerns, or ambiguities. Patients will sign informed consent and only then will begin participation in the study.

**b. Protection against risk:** In reviewing the risk management plan for this study, it is important to keep in mind that the condition under study poses a significant risk to participants. *Any* study of a novel intervention that is intended to reduce depression and suicidal potential will pose some unavoidable risks related to the condition, much like treatment studies in cancer entail risks. *Any* intervention could, theoretically, increase risk, although there is absolutely no evidence of increased risk of suicide with ketamine. In fact, the reduction in depression associated with ketamine treatment would be expected to substantially reduce risk at least temporarily. The purpose of this initial study is limited by intent: Our objective is to test the efficacy, safety, and tolerability of ketamine treatment for suicidal ideation over a short time scale of 4 weeks. While we will ensure that all participants will have adequate treatment that extends beyond the study observation period, continuation treatment will not be done in this study. Testing methods of sustaining the benefits of ketamine treatment beyond the initial week would be premature prior to establishing an initial effect. Therefore, the purpose of this study is to test the *acute* effect of ketamine in the emergency setting.

A significant area of risk is on learning unfavorable information from the genetic typing to be done. Patients will be counseled as to the results of their genetic testing. No disease states can be predicted from this data and will not be elaborated to patients in a predictive manner.

In addition to the formal safety monitoring plan described, below, the procedures to protect against or minimize potential risks include the following. Emergency department personnel who will offer participation in the study will identify potential participants. Study participants will be people meeting all inclusion and exclusion criteria for the study and who have agreed to a voluntary admission to the Psychiatry Inpatient Units at UC Hospital. Study personnel will fully explain the project prior to obtaining written informed consent. Persons who provide written consent and who meet all inclusion and exclusion criteria will receive either intranasal ketamine or intranasal normal saline over 10 minutes. Study drug may be given in the PES, the main ED, the main UC hospital or the inpatient psychiatric hospital unit. Study participants will be on vital sign monitoring both during study drug treatment and for 2 hours after the treatment. Ratings will be done at baseline prior to treatment and at 30, 60, 120 and 240 minutes. The inpatient treating physician will be fully informed of the patient's participation in this study and the patient's initial diagnostic impression and presentation. They will be informed that there are no specific restrictions or limitations on the study participants' treatment. The inpatient physician will have full control over the treatment and time of discharge.

**Post\_ketamine Phase:** All participants will receive study assessments on days 1, 2, 3, 4, 7, 14, and 21, after ketamine treatment and will be assessed by a study psychiatrist on day , 21, and as needed. Participants will be followed for 3 weeks overall, then referred to standard community treatment., and inpatient physicians will be encouraged to change, augment, or start a new treatment for the patient's depression based on their best clinical judgment.

*Considering the question Won't participants who have received ketamine be at risk when the effect wears off?* Preliminary studies including our own preliminary data indicate that the antisuicide effect of ketamine eventually tapers off after about 5-7 days. However, many patients find that improvement in feelings of hopelessness and suicidal ideation persists beyond this period. In addition, all participants will have new treatments started or changed, which are

likely to improve the underlying state of depression. It should be noted that the typical length of stay of suicidal patients on inpatient units is 4-5 days, after which they are discharged into the community. Follow-up with a community clinician is often delayed for 2 weeks or more. Participation in the current study confers an extra measure of safety for participants since all will be assessed over 3 weeks. We also will ensure that all participants have appropriate aftercare.

At any point in the follow-up period, if a patient is deemed to pose a significant risk to themselves or others, hospitalization is immediately available. If a person is re-hospitalized, subsequent assessments will be conducted in the hospital setting for the full 3 weeks. Participants will be assessed on the schedule above in the hospital or in the community. Note that the level of observation in this study is far above what people experience in the usual clinical setting. They will be assessed 6 times after the day of treatment in person or by phone over 3 weeks, including assessments by the study psychiatrist on day 21, and as needed. A study physician will be available by phone 24 hours per day and may be contacted by participants, emergency department personnel, or study staff if needed. If a participant is found to be significantly suicidal following discharge, or if they are found to have another high-risk state (e.g., psychosis or homicidal ideation), they will be assessed and treated accordingly. Policies and procedures are in place in both settings to ensure participant safety. The participant and, if available, an accompanying adult will be instructed on how to contact the emergency mental health services of the Department of Psychiatry at UC Medical Center, which provide emergent psychiatry care on a 24 hour/day basis. Inpatient care is available at UC if needed. If a participant is found to have a high-risk state, a study physician will be contacted and will do a face-to-face or, if needed, phone evaluation to determine the appropriate level of care. If the participant is in a clinic they can be walked if needed to the Emergency Department and can be accompanied by security personnel if absolutely required. We will refrain from changing the other treatments that the participants may be receiving during participation. However, note that the study physicians may change other medications or the outside treating clinicians as needed to ensure patient safety. Note that after the 3 weeks of participation, the study physician will provide a summary of information to the treating clinician.

*Psychiatric assessments and scales:* A trained and experienced senior research assistant or research nurse will conduct all assessments. Participants will have the right to decline to participate in any portion of the study. They will be asked regularly regarding any distress and will be given the opportunity to take breaks if needed. In addition, Drs. McCullumsmith (or, in their absence, another research physician) will be available to debrief the participant. For study visits after hospital discharge, all subjects will be asked about any residual distress prior to leaving the clinic. Our respective programs have conducted interviews with thousands of research participants without serious problems.

*Loss of confidentiality:* Participant confidentiality will be maintained throughout. All project personnel, including those involved in data entry, have completed an on-line course in human subjects protection for patient-related research and annual recertification. Each participant will be assigned a unique ID number that will be used in all data files and on all measures in place of personal identifiers. Data entry forms will be developed using the REDcap database system developed at the Vanderbilt Institute for Clinical and Translational Research (CTSA). REDCap (Research Electronic Data Capture) is an Oracle-based, secure, password-protected, HIPAA-compliant, web-based application designed to support data capture for research studies. All data will be entered real-time at the site of collection. This system allows electronic data capture at each performance site. REDCap provides: 1) an intuitive interface for data entry (with intrinsic data validation); 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages



(SPSS, SAS, Stata, R); 4) procedures for importing data from external sources; 5) Real-time data cleaning and validation; 6) Automatic field computation; 7) Data dropdowns for choice lists (including condition selections based on earlier responses); 8) Data entry warnings for out of range or missing values; and 9) Electronic scheduling. Data entry can be performed anywhere using the internet and provides 128-bit SSL security. All electronic and hard entry forms will include unique patient identifiers to maintain patient confidentiality and will not relate to the patient in any way. Any protected personal health information will be encrypted and stored separately. The only link between identifying information (e.g., name, contact information) and project data will be in a key stored on a password-protected computer accessible only to the PI's and to the project coordinators, who will be making appointments and assigning research personnel to meet with the participant. Paper forms will be stored in locked file cabinets accessible on to study personnel.

*Venipuncture:* Only well-trained personnel using strict sterile technique will perform Venipuncture.

### **III. Potential Benefits**

**a. Benefits to the Patient:** the study may provide relief of depressive symptoms and suicidal ideation for some patients who participate. Even though the ongoing primary treatment for depression that participants will receive will not be changed as part of this study, we will review the treatment they are receiving and make recommendations for continued treatment after participation is completed. This is likely to improve the care received by at least some participants. Further, patients in this study will receive 6 assessments for 3 weeks after initial presentation and will be assessed by a study psychiatrist on days 21, and as needed.

**b. Benefits to Others:** This will be the first study of its scope assessing the potential utility of intranasal ketamine treatment to treat suicidal ideation in those with acute presentation in the psychiatric emergency setting. If ketamine proves to be safe and effective, it may benefit other people with suicidality; it may provide a means for rapidly treating depression in the acute setting thereby avoiding hospitalization as well as potentially decreasing emergency department lengths of stay and crowding..

### **IV. Importance of the Knowledge to be gained**

There are currently no treatments available that are known to rapidly improve suicidality in the acute treatment setting. In typical practice, patients who present with suicidal ideation do not improve rapidly and are often discharged from the ED or inpatient setting with continued suicide risk. Current treatment for suicidal ideation takes weeks to become effective leading to poor compliance with treatment and weeks of lost time for the patients. The identification of a safe and tolerable drug treatment with rapid antidepressant efficacy could help to improve treatment and treatment adherence for these patients.

### **V. Data and Safety Monitoring**

For this study of a marketed drug, monitoring of safety will be performed by the members of the study steering committee, and reviewed during the steering committee conference calls. Any serious or unexpected adverse events, or any other unanticipated problems involving risks to subjects or others, will be formally reported as below. In addition to the steering committee, we also appoint a Data and Safety Monitoring Board (DSMB) that will monitor our sites and serve as a reporting body to the IRB.

**Data and Safety Monitoring:** A Data and Safety Monitoring Board (DSMB) will be created as an independent body charged with ensuring that the safety of study subjects is protected. To support this purpose, the DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analyses of safety and tolerability. The DSMB will also ensure subject privacy and research data confidentiality.

**Membership of the DSMB:** To fulfill its mission of ensuring the safety and integrity of the study, it is necessary that the DSMB be comprised of members who possess a high degree of competence and experience, as well as the ability to function independently of all other parties involved in the study. The DSMB members should function free of any career and financial interests of its members. The DSMB will consist of three members with experience in conducting clinical trials for psychiatric or neurobehavioral disorders, experience in clinical pharmacology and toxicology, and a thorough knowledge of clinical trial ethics and human subject protection issues. At least one of these committee members will be a biostatistician.

**Functional Organization of the DSMB:** One individual will serve as chairperson of the DSMB and will communicate by e-mail and telephone conference with the other members. Communications among the DSMB members pertaining to the review of serious adverse events (SAEs) will occur within a week of receiving a new SAE report. Reporting and communication regarding other matters will occur on a regular, quarterly basis, for the duration of the study. Decisions of the DSMB will be made based on a majority vote of the members.

**Monitoring of Safety Data by the DSMB: a. Un-blinded Reporting:** Safety information for this study will be reported to the DSMB in an un-blinded manner. A statistical penalty will not be assessed for the ongoing un-blinded review of safety by the DSMB. Un-blinded data will not be released to the investigators unless necessary for safety reasons.

**b. Range of Safety Reporting to the DSMB –** It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but other data that may reflect differences in safety between treatment groups. This includes treatment retention rates, and reasons for drop-out, and laboratory values reflecting potential toxicity.

**c. Serious Adverse Events –** Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs). A serious adverse event is one that meets any of the following criteria: a) fatal or life threatening, b) requires prolonged inpatient hospitalization, c) results in persistent or significant disability, d) congenital anomaly, e) results in an important medical event that may jeopardize the patient or require intervention to prevent a serious outcome, f) cancer, g) overdose, or h) results in the development of drug dependency or abuse. For purposes of this study, all SAEs will be required to be reported to the DSMB, regardless of any judgment of their relatedness to the study drug. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, dosing history of all study drugs, concomitant medications, the subject's medical history and current conditions, and all relevant laboratory data. Notification by e-mail, and FAX transmittal of all related study forms shall be made to the DSMB within 24 hours of the occurrence of any SAE, followed by a full report within 10 working days. Information will be reviewed and a determination made of whether there was any possible relevance to the study drug.

**d. Non-Serious Adverse Events** – At periodic intervals (quarterly during the course of the study and then again at its completion), the DSMB will be provided with un-blinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.

**e. Other Safety-Related Reports** – At quarterly intervals throughout the course of the study, the DSMB will also receive un-blinded summary reports of treatment retention and reasons for drop-out, by treatment arm and study phase.

**f. Study Stopping Rules** – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

**g. Monitoring of Data Quality-** The DSMB will receive a report on data quality and completeness on an annual basis. At a minimum, this will include an overview of the progress of patient intake and retention; summary reports describing patient compliance with visits, evaluations, and dosing as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize patients, their dosing, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

**h. Adverse Events Reporting:** All treatment-emergent serious adverse events (SAEs) will be documented and reported immediately to the Human Research Committee at UC, to the study steering committee, the DSMB, and to the food and drug administration (FDA) (as appropriate). Specifically, a report by email, fax, or phone will be filed with both IRBs within 24 hours of the event, followed by a full report within 10 working days. An event that is serious must be recorded on the case record and requires expeditious handling to comply with regulatory requirements. In the event that a patient becomes ill or injured as a direct result of participation in the research study, necessary medical care will be made available. The NIMH Project Officer will be informed of any actions taken by the either IRB as a result of such adverse events. Non-serious adverse events will be recorded with the use of the SAFTEE scale.

**i. Outcomes Monitoring:** Outcomes will be carefully documented so that at the completion of the study, recommendations can be made for further treatment.

**j. Vulnerable populations:** This study will not be screening based on employment status. We would not be aware that individuals were employees or students at UC. All normal confidentiality considerations will be taken with this population

**k. Recruitment:** No advertising recruitment will be done. All patients will be recruited from the psychiatric emergency room after presentation for care. For exploratory Aim 3 only, sub group of subjects will be recruited as outpatient presenting for care in our outpatient clinics.

Describe the procedures for screening potential participants.

Patients seen in the Psychiatric Emergency Room with complaints of suicidal ideation will receive a standard of care clinical evaluation. If they do not meet any exclusion criteria, they will be informed of the study by the treating psychiatrist or psychiatric nurse. For patients in aim

3recruited as out patients, we will consult the treating physician. If they are interested, informed consent will be performed by someone on the research team. During the consent process the purpose of the study, its risks and benefits, the rights of the participants, and what will be required of participants will be discussed. The participants will be given time to ask questions and have their questions answered by trained research staff. After the consent has been signed, participants will then be administered the Mini International Neuropsychiatric Interview (MINI) and the Scale for Suicidal Ideation to determine eligibility.

Payment to patients

- **Screen Fail Patients : \$20**
- **Treatment day assessment and treatment: \$75;**
- **Genotyping : \$50**
- **Videotaping : \$50**
- **EEG: 50\$**
- **Follow-up : \$30 per visit ( 5 visits) including travel expenses**
- **Final Visit : \$75**
- **Total per completed study: \$ 450 (if participates in genetics, EEG and video component)**
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- Subject Costs – none: Patients will already have agreed to voluntary hospitalization.
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- Consent Form - The CONSENT FORMS are TO BE SEPARATE DOCUMENTs. There will be separate patient consent forms for the main study of ketamine therapy and for genotyping. It is important that this form follows the IRB prescribed format and includes all the required elements and certain other elements when appropriate.

- Literature Cited - The references should be limited to relevant and current literature pertinent to the proposed research.

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