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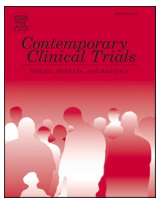

Ketamine treatment in youth for fast reduction of suicidality and engagement in psychotherapy: A randomized placebo-controlled trial protocol

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ABSTRACT

Background: Suicide is a leading cause of death in young persons. While ketamine has demonstrated rapid anti-suicidal effects, its safety and efficacy in youth has not been fully investigated. The Collaborative Assessment and Management of Suicidality (CAMS), a suicide-focused treatment shown to decrease suicidal ideation and symptom distress, has never been studied in combination with ketamine.
Objectives: This study investigates whether ketamine infusion, as compared to placebo, rapidly reduces severe suicidality in youth and young adults and enhances effectiveness of CAMS to decrease suicidality after acute treatment and at 3-month follow-up. We explore whether participants who receive ketamine, as compared to placebo, have decreased suicidality, suicide attempts, emergency department visits for suicidality, and psychiatric readmissions over 3-month follow-up.
Methods: This randomized controlled trial is enrolling 140 participants (ages 14–30) hospitalized with severe suicidal ideation or after attempted suicide. While hospitalized, participants are randomized to receive up to 6 treatments of either ketamine or placebo. Concurrently, participants engage in CAMS sessions, starting while inpatient and continuing post-discharge for up to 12 sessions via telehealth or until resolution of suicidality criteria are met. Monthly follow-up assessments are conducted for 3 months.
Discussion: Historically, hospital admissions have not decreased suicidal behavior following discharge. We hypothesize that ketamine, as compared to placebo, will lead to rapid improvement in suicidality and enhance engagement in CAMS, requiring significantly fewer sessions to resolve high-risk suicidality after discharge. We hypothesize that the ketamine group will have decreased suicidality, suicide attempts, and readmissions compared to the placebo group over 3-month follow-up.

1. Introduction

1.1. Background

Suicide is the most serious complication of any psychiatric disorder and is a major public health concern in the United States, with suicide remaining the second leading cause of death in youth and young adults ages 10–24 [1]. After a brief decline in overall US suicide rates in 2019 and 2020, rates in 2021 increased up to the peak levels of 2018, with 48,344 deaths by suicide [2]. Suicide rates among persons ages 10–24 years increased significantly during 2018–2021 among Black persons (from 8.2 to 11.2; a 36.6 % increase) [2]. From 2018 to 2021, there was also a 5 % increase overall among those ages 25–44, with particularly alarming increases among American Indian/Alaskan Native (33.7 %), Black (22.9 %) Hispanic (19.4 %) and non-Hispanic multi-racial (20.6 %) persons [2]. The Centers for Disease Control (CDC) recently reported increasing rates of suicidal ideation (thoughts about ending one's own life, ranging from fleeting thoughts to detailed planning) in youth, with

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22 % of high school students seriously contemplating suicide in 2021, and even higher rates of suicidal ideation in females (30 %) and in youth (45 %) who identify as lesbian, gay, bisexual, queer, questioning or plus, including other sexual orientations and gender identities (LGBQ+) [3]. In 2021, 18 % of high school students made a suicide plan and 10 % attempted suicide within the past year, with significantly higher rates in females (24 % plan; 13 % attempt) and in LGBQ+ youth (37 % plan; 22 % attempt) [3].

Youth and young adults admitted to an inpatient psychiatric unit secondary to suicidal ideation with intent or suicidal behavior are among the highest risk populations for suicide. Patients with previous suicide behaviors have an elevated risk for future suicide attempts [4], with the year following hospital discharge being a particularly risky timeframe [5,6]. Thus, there is an urgent need to improve care provided for young persons at risk for suicide, beginning with those hospitalized for a suicide attempt. While inpatient and partial hospitalization offer intensive multidisciplinary treatments and skilled observation and support, there is no empirical evidence that these interventions are effective in reducing rates of suicidal ideation, nonlethal attempts, or completed suicide among youth [7].

1.2. Ketamine

Ketamine, an *N*-methyl-D-aspartate (NDMA) receptor antagonist, is a short-acting anesthetic which has been shown to have rapid antidepressant effects in patients with major depressive disorder and treatment-resistant depression [8]. While decades of research support the use of electroconvulsive therapy (ECT) for treatment-resistant major depression, Anand and colleagues recently conducted an open-label, randomized noninferiority trial in 403 patients and found that ketamine was non-inferior to ECT in the treatment of non-psychotic treatment-resistant depression [9]. Ketamine has also been shown to have rapid and robust acute effects in reducing suicidal ideation in adults [10]. There is also growing enthusiasm for the use of ketamine in youth and adolescents with mood disorders and suicidality [11,12], but it has not yet been widely tested in this population.

1.3. Collaborative Assessment and Management of Suicide (CAMS)

The Collaborative Assessment and Management of Suicidality (CAMS) is an evidence-based, suicide-specific clinical treatment that has been shown to decrease suicidal ideation, overall symptom distress, and positively impact suicidal behaviors [13]. As one of only a few evidence-based treatment modalities shown to rapidly effectively treat suicidal risk, CAMS focuses on a strong and collaborative clinical alliance and actively engages patients in co-authoring their own treatment plan [14]. CAMS focuses on treating the difficulties and challenges that lead to suicidality, known as "drivers," and enhancing the patient's motivation to live. The Suicide Status Form-5 (SSF-5) assesses psychological pain, stress, agitation, hopelessness, self-hate, and overall risk of suicide over the entire course of care and engages the patient in conversation about suicidal risk [15]. The client and therapist collaboratively use SSF-5 based information to develop a suicide-specific stabilization plan, as well as a treatment plan to address the patient-defined suicidal drivers.

1.4. Combination of ketamine and CAMS for treatment of acute suicidality in adolescents and young adults

Research examining the combination of ketamine with empirically supported psychotherapeutic approaches to rapidly reduce suicidal risk in youth and young adults is in its earliest stages, with one prior published case series suggesting symptomatic and functional improvements, as well as high tolerability [16]. Ketamine has been shown to enhance neuroplasticity [17] and to have a synergistic effect with psychotherapies [18,19]. It has been hypothesized that ketamine can increase engagement and make patients more receptive to psychotherapy [20].

Here we describe the protocol for our ongoing National Institute of Mental Health funded study (PIs A. Anand and T. Falcone) testing a two-pronged intervention for the treatment of acute severe suicidality: ketamine which can rapidly reduce suicidal thoughts and CAMS which can actively engage patients in treatment focused on improving reasons for living. This combination has the potential to save many lives and prevent future readmissions for suicide attempts. Initial treatment with ketamine and rapid reversal of depression and suicidality will potentially increase patient engagement in CAMS, leading to better outcomes. As ketamine has also been shown to increase neuroplasticity, ketamine may also facilitate enhanced integration of the therapeutic concepts taught in CAMS. Our objectives are as follows:

Specific Aim 1: To investigate whether acute ketamine infusion is helpful in rapid reduction of severe suicidality in youth and young adults.

Hypothesis 1. Acute ketamine infusion, up to 6 treatments, will lead to rapid improvement in suicidality, as measured by Scale for Suicidal Ideation (SSI), compared to participants who receive placebo (saline), in psychiatry inpatients admitted with severe suicidality.

Specific Aim 2: To investigate whether acute ketamine infusion leads to better effectiveness of Collaborative Assessment and Management of Suicidality (CAMS) intervention to decrease suicidality immediately after acute treatment and over the course of 3-month follow-up.

Hypothesis 2. Ketamine infusion will significantly increase patient engagement in CAMS as measured with Working Alliance Inventory resulting in significantly reduced number of CAMS sessions required to achieve an enduring mental state with a decrease in suicidality after discharge.

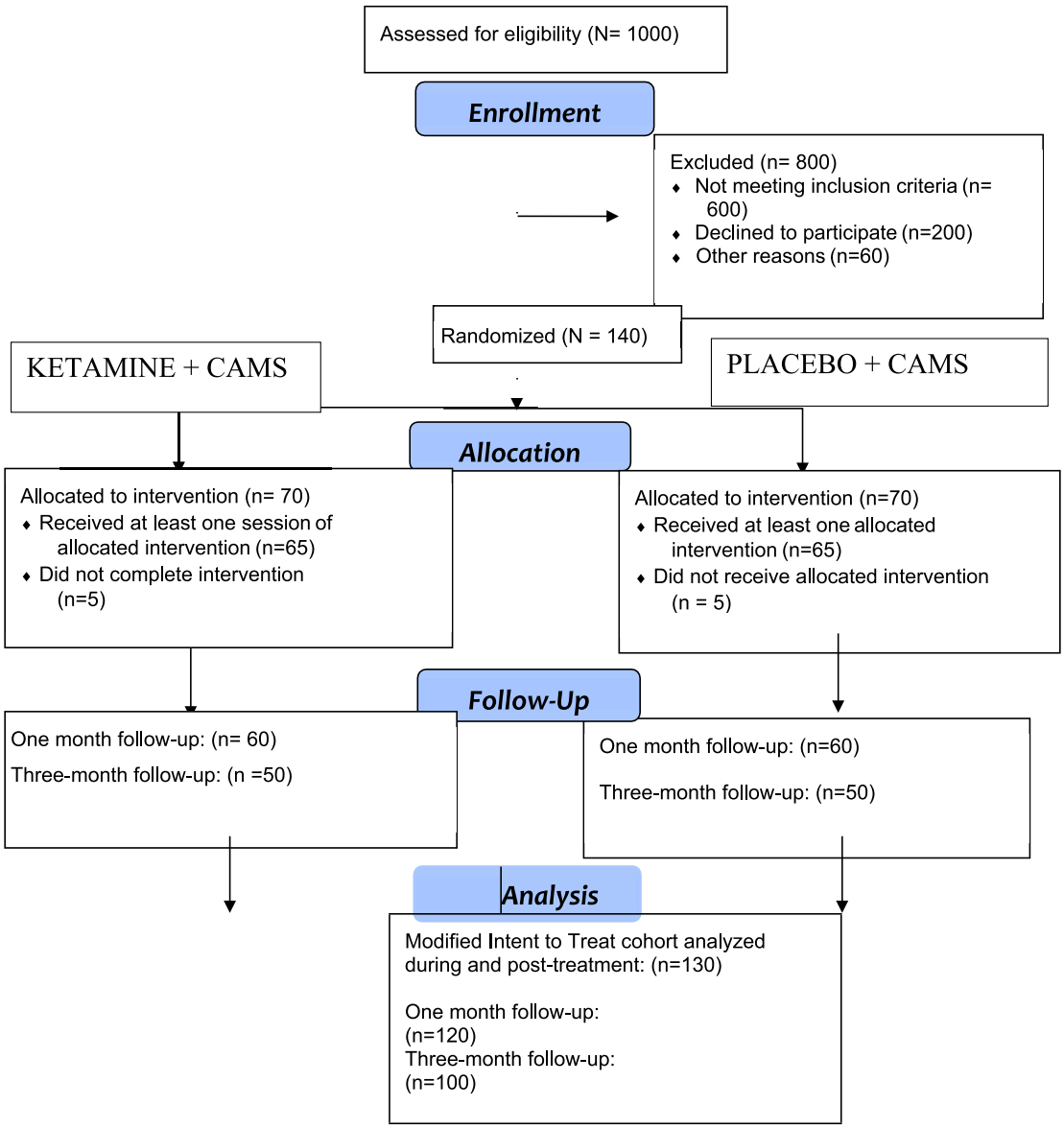
Exploratory Aim 3: To investigate whether participants who receive ketamine infusions compared to those who received placebo will have decreased suicidality over 3 month follow- up after acute treatment as evidenced by decrease on the Scale for Suicidal Ideation (SSI) score from visit 1 to month 1 visit, month 2 visit, and month 3 visit. Also, participants in the ketamine group compared to the placebo treatment group will have decreased number of suicide attempts, visits to the ED for suicidal ideation, and readmissions to psychiatry.

Hypothesis 3. The ketamine group will have a decrease in suicidality scores, decreased attempts, and decreased readmissions compared to placebo group over a 3-month follow-up period.

2. Methods

2.1. Study overview

This randomized controlled trial is enrolling 140 children and young adults (ages 14–30) admitted to inpatient psychiatric units at Cleveland Clinic (CC) or Massachusetts General Hospital (MGH) with severe suicidal ideation or after attempted suicide. Fig. 1 illustrates the study schema. Participants will be randomized to receive ketamine 0.5 mg/kg or normal saline over 40 min. While admitted on the inpatient unit, participants will receive at least one or up to 6 ketamine or placebo infusions (every other day Monday-Fridays excluding holidays) until they have a clinician rated Scale for Suicidal Ideation (SSI) [21] score of <4, >50 % decrease from baseline, and a clinical assessment of resolved suicidality, or until they have been discharged from the unit. Concurrently, participants will engage in weekly CAMS sessions, starting while inpatient and continuing post-discharge for up to 12 sessions via telehealth or until CAMS resolution of suicidality criteria are met for 3 consecutive sessions. Monthly follow up assessments for suicidal ideation, attempts, and readmissions are conducted for 3 months. Fig. 2 illustrates the study flow and procedures. The study is conducted under an Investigational New Drug Application (IND #155354) authorized from the Food and Drug Administration (FDA) and was approved by the



Abbreviations: CAMS: Collaborative Assessment and Management of Suicidality

Fig. 1. Study schema.
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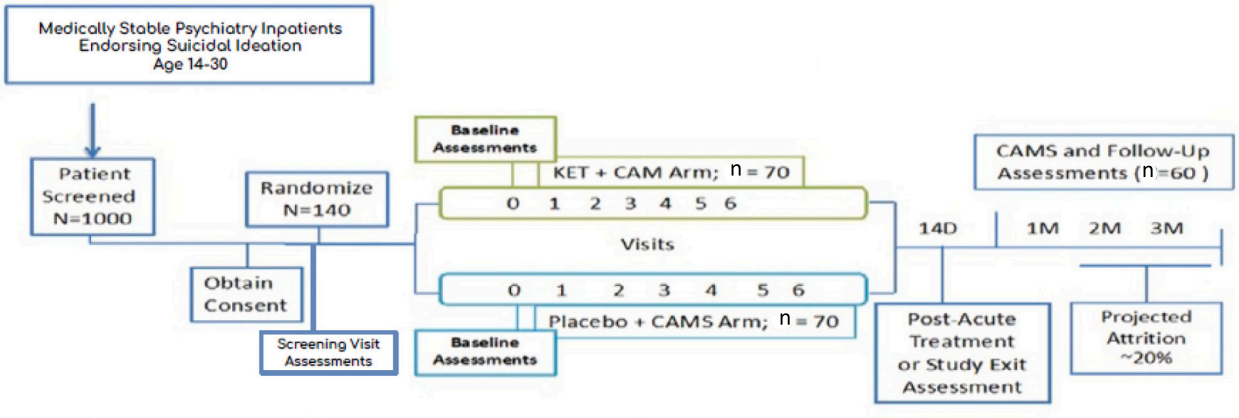

Fig. 2. Study Flow.

Institutional Review Boards of CC and MGH.

2.2. Eligibility criteria

Participants must be 14 to 30 years of age and admitted to the inpatient unit following a suicide attempt (any intentional, non-fatal self-injury regardless of medical lethality, if intent to die was indicated) with continued suicidal ideation or endorsing ongoing suicidal ideation with risk of self-harm. All participants must have a clinician rated Scale for Suicidal Ideation (SSI) score ≥ 6 and be able to understand and sign a written informed consent document. Patients with a history of autism spectrum disorder, moderate to severe intellectual disability, schizophrenia, or history of any type of psychosis are excluded. Patients with urine toxicology positive for phencyclidine, cocaine, or amphetamines (except amphetamines prescribed for ADHD) in the past 6 months or moderate or severe substance or alcohol use in the past 6 months are also excluded. Any medical contraindications to ketamine, allergic reactions to ketamine, currently pregnant or breast feeding, previous recreational ketamine use or therapeutic ketamine use that exceeds maximum cumulative lifetime exposure of 480 mg. (per FDA IND requirement), uncontrolled hypertension, history of myocardial infarction, congestive heart failure ($\geq$ stage 2), angina, or QTcF of at least 450 msec. are also criteria for exclusion. Table 1 summarizes the full inclusion and exclusion criteria.

2.3. Assessments

Table 2 provides an overview of the outcome measures and scales used in the study from screening, through active treatment and follow-up.

Table 1
Inclusion and exclusion criteria.

Subject eligibility	Patients admitted to Cleveland Clinic (CC) or Massachusetts General Hospital (MGH) expressing ongoing suicidal ideation are eligible candidates for the study.
Inclusion criteria	1. 14 to 30 years of age 2. Admitted to CC or MGH inpatient psychiatric units after a suicide attempt with continued suicidal ideation or endorsing ongoing suicidal ideation and unable to contract for safety placing them at an increased risk to attempt suicide. Subjects will need a clinical rated Scale for Suicidal Ideation (SSI) score ≥ 6. 3. Ability to understand and sign a written informed consent.
Exclusion criteria	1. Known history of autistic spectrum disorder; non-verbal patients. 2. Moderate or severe intellectual disability 3. Schizophrenia or history of any type of psychosis including mood disorder related psychosis and brief reactive psychosis 4. Within 6 months before initial screening, urine toxicology positive for phencyclidine, cocaine, or amphetamines (subjects prescribed amphetamines for Attention Deficit Hyperactivity Disorder will not be excluded) 5. Moderate or severe substance or alcohol use per DSM-5 criteria in the past 6 months. 6. Any medical contraindication to or allergic reaction to ketamine 7. Currently pregnant and/or breast feeding. 8. Previous recreational ketamine use. Previous therapeutic Ketamine use that exceeds the maximum cumulative lifetime exposure of 480 mg. 9. Uncontrolled hypertension, history of myocardial infarction, congestive heart failure of stage 2 or higher, angina, or QTcF* of at least 450 msec. 10. In custody of Children's Services.

Abbreviations: DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; QTcF: QT interval corrected for heart rate by Fridericia's cube root formula.

Table 2
Measures.

MEASURE	NAME	DESCRIPTION
DIAGNOSTIC INTERVIEW		
MINI-PLUS 7.0.2	Mini Neuropsychiatric Interview-Plus and for adolescents MINI-KID	Psychiatric diagnostic interview used by interviewer to generate DSM-5 diagnosis
PATIENT RATED SCALES		
PHQ-9	Patient Health Questionnaire-9	Brief self-report tool using 9 items to assess the presence and severity of depressive symptoms
WAI-SR	Working Alliance Inventory (short form revised) Scale to measure alliance between client and therapist working relationship.	Scale to measure alliance between therapist and client working relationship on 12 items of client-therapist collaborative alliance on a visual analogue scale.
PRISE	Patient Rated Inventory of Side Effects	Self-report of adverse events specific to nine organ or function systems used in the STAR*D study
CRAFFT 2.1	CRAFFT Self-Administered Questionnaire	An efficient and effective self-report screening tool designed to identify substance use, substance-related riding/driving risk, and substance use disorder.
CLINICIAN RATED SCALES		
MADRS	Montgomery Asberg Depression Rating Scale	Commonly used clinician rated 10-item scale designed to measure severity of depression which sensitive to effects of antidepressant treatments
*CDRS-R	Children Depression Rating scale revised	Clinician rated scale to measure the severity of depression in adolescents
Beck SSI PRIMARY MEASURE	Beck Scale for Suicidal Ideation	Clinician rated suicidal ideation and intent rating scale
SSF-5	Suicide Status Form	Clinician rated suicide intensity scale–administered during CAMS
YMRS	Young Mania Rating Scale	11-item scale to measure symptoms of mania to record any emergence of mania
BPRS 4 items for psychosis	Brief Psychiatric Rating Scale 4 items	4-item scale to measure positive symptoms of psychosis; used extensively in ketamine studies
CGI-S and CGI-I	Clinical Global Impression Scale for Severity and Improvement	Scales to record global clinical impression by a clinician regarding improvement and severity of psychiatric condition

Abbreviations: DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; STAR*D: Sequenced Treatment Alternatives to Relieve Depression; CAMS: Collaborative Assessment and Management of Suicidality.
* CDRS assessment scale only used with adolescent participants in this study ages 14–17.

2.3.1. Diagnostic

The Mini-International Neuropsychiatric Interview-Plus (M.I.N.I.) 7.0 is a psychiatric diagnostic tool [22] that is used to generate DSM-V diagnoses in adult participants. The M.I.N.I.-KID [23], a version for children and adolescents, is used to assess participants ages 14–17.

2.3.2. Clinician rated

The primary outcome measure is the Beck Scale for Suicidal Ideation (SSI) [20] which assesses both active and passive suicidal ideation and intent, as well as reasons for living/dying and plans and preparations related to potential suicide attempts. The Montgomery Asberg Depression Rating Scale (MADRS) [24] is used to assess severity of depressive symptoms and is known to be sensitive to the effects of antidepressant

treatments. The Children's Depression Rating Scale – Revised (CDRS-R) [25] is used to assess the severity of depressive symptoms in our adolescent participants. The Young Mania Rating Scale (YMRS) [26] assesses for the emergence of manic symptoms and the Brief Psychiatric Rating Scale (BPRS) [27] utilizes 4 items (conceptual disorganization, unusual thought content, hallucinations and suspiciousness) to assess for the emergence of dissociation and positive symptoms of psychosis. The Clinical Global Impression Scale for Severity and Improvement (CGI—S, CGI—I) [28] are clinician administered assessments of global impressions related to overall severity and improvement. The Suicide Status Form-5 (SSF-5) [15] is used at each CAMS session to assess risk of suicide and related risk factors such as psychological pain, stress, agitation, hopelessness and self-hatred.

2.3.3. Self-report

Participant rated scales include the Patient Health Questionnaire-9 (PHQ-9) [29] to assess the presence and severity of depressive symptoms, the Patient Rated Inventory of Side Effects (PRISE) [30,31] to assess adverse events specific to nine organ/function systems, and the CRAFFT 2.1 [32] to assess substance use, substance-related riding/driving risk, and substance use disorder. Patients also complete the Working Alliance Inventory (short form revised) (WAI-SR) [33] to assess the alliance and working relationship between the therapist and client.

2.3.4. Schedule of events

Tables 3 and 4 illustrate the schedule of events and assessments during inpatient and outpatient treatment, as well as over the 3 month follow up period.

2.4. Measures to minimize bias: randomization and blinding

randomization

Participants are randomized in a 1:1 ratio to one of the study arms: Study Drug: Ketamine hydrochloride or Study Placebo: Saline (sodium chloride 0.9 %) via stratified randomization using REDCap Cloud. Participants will only receive the randomized treatment (up to 6 infusions) over the course of the study.

2.4.1. Blinding

After randomization and at each visit, Investigational Drug Services (IDS) access the randomization database to assign the appropriate study treatment to be used. IDS blinds the treatment bags which are administered by the designated clinical study team member who is blinded to the treatment.

2.4.2. Unblinding

During the 2-h post-infusion monitoring window, vital signs, cardiac function, and assessment of behavioral and psychiatric symptoms are continuously monitored by the clinical study team member who is blinded. Observation of the participant in the inpatient unit continues for up to 1-day post-infusion or until the participant is discharged from the inpatient unit. Any unblinding is done only in an emergency that requires the investigational product to be identified for the medical management of the patient.

2.5. Study treatments

2.5.1. Ketamine or placebo (Saline)

Ketamine is given as an intravenous infusion using a standard

Table 3
Inpatient Schedule of Events.

	Screening Visit	Baseline/Infusion Visit 1	CAMS Visit	Infusion Visit 2	Infusion Visit 3	Infusion Visit 4	Infusion Visit 5	Infusion Visit 6
Obtain Informed Consent	X							
Review Inclusion/ Exclusion Criteria	X							
Medical History	X	X		X	X	X	X	X
Physical Exam	X							
Urine Pregnancy Test	X							
Urine Drug Screen	X							
EKG	X							
Ketamine or Saline Treatment		X		X	X	X	X	X
CAMS Treatment			X					
Evaluation for AEs/SAEs		X	X	X	X	X	X	X
MINI-PLUS 7.0.2 or MINI-KID	X							
Patient Rated Scales								
PHQ-9		X		X	X	X	X	X
WAI-SR				X	X		X	X
PRISE		X		X	X	X	X	X
CRAFFT 2.1	X							
Clinician Rated Scales								
BECK SSI **PRIMARY MEASURE**	X	X	X	X	X	X	X	X
MADRS		X		X	X	X	X	X
CDRS-R (for ages 14–18)	X							
SSF-5			X					
CAMS Therapeutic Worksheet			X					
YMRS		X		X	X	X	X	X
BPRS 4 items for psychosis		X		X	X	X	X	X
CGI-S		X		X	X	X	X	X
CGI-I				X	X	X	X	X

Abbreviations: CAMS: Collaborative Assessment and Management of Suicidality; AE: Adverse Event; SAE: Serious Adverse Event; MINI-PLUS 7.0.2/MINI-KID: Mini Neuropsychiatric Interview-Plus and for adolescents; PHQ-9: Patient Health Questionnaire-9; WAI-SR: Working Alliance Inventory (short form revised); PRISE: Patient Rated Inventory of Side Effects; CRAFFT 2.1:Self-report measure of substance use/risk; Beck SSI: Scale for Suicidal Ideation; MADRS: Montgomery Asberg Depression Rating Scale; CDRS-R: Children Depression Rating scale revised; SSF-5; Suicide Status Form; YMRS: Young Mania Rating Scale; BPRS: Brief Psychiatric Rating Scale; CGI-S/CGI-I: Clinical Global Impression Scale for Severity and Improvement.

Table 4
Outpatient Schedule of Events- Follow-Up Visits.

	Outpatient Visit #1	OP Visit #2	OP Visit #3	OP Visit #4/ Month 1 Follow up	OP Visit #5	OP Visit #6	OP Visit #7	OP Visit #8 / Month 2 Follow up	OP Visit #9	OP Visit #10	OP Visit #11	OP Visit #12 / Month 3 Follow up
Visit Window	7 days post discharge (±3 days)	7 days after visit 1 (±3 days)	7 days after visit 2 (±3 days)	Month 1 = 30 days post-discharge (+/− 1 week)	7 days after visit 4 (±3 days)	7 days after visit 5 (±3 days)	7 days after visit 6 (±3 days)	Month 2 = 30 days after Month 1 (+/− 1 week)	7 days after visit 8 (±3 days)	7 days after visit 9 (±3 days)	7 days after visit 10 (±3 days)	Month 3 = 30 days after Month 2 (+/− 1 week)
Medical History	X	X	X	X	X	X	X	X	X	X	X	X
Psychiatry Evaluation				X				X				X
Treatment (CAMS therapy)	X	X	X	X	X	X	X	X	X	X	X	X
Evaluation for AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X
Random Urine Drug Screens	O	O	O	O	O	O	O	O	O	O	O	O
Patient Rated Scales												
PHQ-9				X				X				X
WAI-SR				X				X				X
PRISE				X				X				X
CRAFFT 2.1		X										
Clinician Rated Scales												
Beck SSI **PRIMARY MEASURE**	X	X	X	X	X	X	X	X	X	X	X	X
MADRS				X				X				X
CDRS-R (for ages 14–18)				X				X				X
SSF-5	X	X	X	X	X	X	X	X	X	X	X	X
CAMS Therapeutic Worksheet	X	X	X	X	X	X	X	X	X	X	X	X
YMRS				X				X				X
BPRS 4 items for psychosis				X				X				X
CGI-S				X				X				X
CGI-I				X				X				X

O = Possibility for urine drug screen at any visit over the course of outpatient follow-up.
Abbreviations: CAMS: Collaborative Assessment and Management of Suicidality; AE: Adverse Event; SAE: Serious Adverse Event; MINI-PLUS 7.0.2/MINI-KID: Mini Neuropsychiatric Interview-Plus and for adolescents; PHQ-9: Patient Health Questionnaire-9; WAI-SR: Working Alliance Inventory (short form revised); PRISE: Patient Rated Inventory of Side Effects; CRAFFT 2.1:Self-report measure of substance use/risk; Beck SSI: Scale for Suicidal Ideation; MADRS: Montgomery Asberg Depression Rating Scale; CDRS-R: Children Depression Rating scale revised; SSF-5; Suicide Status Form; YMRS: Young Mania Rating Scale; BPRS: Brief Psychiatric Rating Scale; CGI-S/CGI-I: Clinical Global Impression Scale for Severity and Improvement.

regimen given in most studies conducted to date: 0.5 mg/kg over 40 min. Participants randomized to placebo are administered a saline drip for 40 min. A maximum allowed cumulative dose should not exceed 60 mg per administration and should not exceed a lifetime total of 480 mg (per FDA IND requirement for the current study). Ketamine or placebo infusions are given every other day (Monday - Friday with the exception of holidays) until, for 3 consecutive ratings, they have a clinician rated Scale for Suicidal Ideation (SSI) score of <4, $>$ 50 % decrease from baseline, and clinical assessment of patient not being suicidal, or a maximum of six infusions have been given over the course of 2 weeks, or they are discharged from the inpatient unit. During ketamine/placebo infusion and for 2 h post-infusion, participants are monitored for any change in behavior or psychiatric symptoms by a clinician who will be present alongside the patient during this time. Side effects, such as transient hypertension, are carefully monitored and reported by our medical team. Any adverse or serious adverse events will be reported. Participants are rated on the Clinician Rated SSI before each infusion, 2 h post-infusion, and again within 24 h post infusion or sooner if ready for discharge. In order to promote a quiet and non-stimulating environment, tools such as music and/or eye masks are offered to all participants during the infusion.

2.5.2. Psychological intervention CAMS

CAMS weekly sessions are also started immediately as an inpatient after the first infusion and conducted minimally on a weekly basis (or more if clinically indicated via PI review) while receiving ketamine or saline. CAMS is continued weekly after the participant is discharged and followed up as an outpatient. Weekly CAMS sessions are terminated after the participant, as an outpatient, has three consecutive outpatient CAMS sessions with an overall risk of suicide <3 (on the SSF-5 Core Assessment) along with no suicidal behavior in the past week and an ability to effectively manage suicidal thoughts/feelings. Up to 12 sessions of CAMS may be provided, with the expectation that 6–8 sessions is the average number needed for the effectiveness of CAMS. Participants

will be asked to provide consent for communication and release of information to outpatient providers, to facilitate safe and effective transfer back to routine care. The CAMS intervention is provided according to the CAMS manual [14] by trained clinicians and the CAMS Rating Scale (CRS) assesses for engagement and adherence to the treatment [34,35]. As CAMS usually has an effect only after at least 6 treatments, the use of CAMS is not expected to impact the measurement of acute effects of ketamine versus placebo. In order to provide CAMS care in a continuous context, the initial session of CAMS while on the inpatient unit is conducted virtually, with all follow-up CAMS sessions conducted virtually, unless requested otherwise by the participant. In order to ensure adherence to the CAMS delivery model, Dr. David Jobes (the creator of CAMS) and senior members of his lab access and view videos of CAMS virtual sessions (stored on a secured Microsoft O365 Office account), rate the providers using the CRS, and then give clinicians feedback based on their CRS. The CRS forms relating to the viewed videos are stored on the Microsoft O365 Office account, along with de-identified patient CAMS therapeutic case report forms, Suicide Status Form-5 (SSF-5). Dr. Jobes and his team maintain study CRS forms in the Microsoft O365 Office account and handle the training, adherence checks, and analysis of de-identified data on the SSF-5 forms. Dr. Jobes and his team meet weekly with providers for case conferences and share feedback to ensure adherence. Sessions of each clinician are reviewed until they achieve 3 total adherent sessions (3 sessions total across participants). Following this benchmark, the CAMS team will proceed with reviewing each participant's initial CAMS session and 2 randomly chosen reviews of interim sessions on various participants.

2.6. Statistical analysis plan and power

2.6.1. Data analysis

For Aim 1, the primary outcome measure is remission of suicidal symptoms at the end of treatment with ketamine or placebo. Remission of suicidal symptoms will be defined by a 50 % or greater reduction in the clinician-rated baseline SSI score, and SSI score less than the score of 4. The primary analysis will be performed on the modified intent to treat (mITT) population defined as a randomized patient having at least one treatment and one post-baseline SSI rating during the acute treatment phase. Participants' baseline characteristics will be summarized with descriptive statistics and will be compared between the two groups using the *t*-test, rank-sum test, Fisher's exact test or the Chi-square test as appropriate.

The primary outcome of the remission rate will be compared between the two groups using the Chi-square test. Statistical significance will be achieved at a two-tailed alpha of 0.05. A multivariable logistic regression model will be constructed to account for potential heterogeneity of treatment effect caused by confounding variables such as medication effects and unbalanced patient characteristics if there are any. As an exploratory analysis, a linear mixed-effects model will be conducted to compare the longitudinal SSI data, including group, time and their interaction as fixed effects and a subject-level random intercept, which will allow for comparison at each time point. Confounder variables will be included in the logistic and mixed-effects models if they are distributed unequally between groups.

For Aim 2, the number of CAMS sessions needed to achieve enduring mental state will be summarized as mean, median, and inter-quartile range by each group. The Wilcoxon rank sum test will be used to compare the number of sessions between the two groups. A Poisson regression model will be used to adjust the results for other covariates as for Aim 1.

For Aim 3, continuous outcomes such as change of SSI score and other rating scales will be analyzed using the linear mixed-effects models to account for repeated measurements from the same patient over time. Appropriate contrasts for these models will be used to compare the score or rating changes from baseline to month 3 between the two groups. Binary outcomes such as readmissions to psychiatry or emergency department visits will be compared using the Chi-square test, and count variables such as the number of suicide attempts and the number of emergency department visits will be analyzed using the Poisson regression models.

2.6.2. Sample size and power analyses

The sample size justification is for the primary outcome measure specified in Study Hypothesis 1, namely that acute ketamine infusion, up to 6 treatments, will lead to rapid improvement in suicidality, compared to patients who receive placebo (saline), in psychiatric inpatients admitted with severe suicidality. For ketamine acute effects to decrease suicidality, previous studies suggest 86 % remission rates for ketamine [36]. With 62 patients in each group, the study will have 80 % power to detect a difference of 28 % between ketamine and placebo with 20 % attrition (two-sided alpha of 0.05). To account for a potential 10 % dropout rate, a total of 140 patients are planned to be randomized. The difference between ketamine and placebo is actually expected to be much greater. As recruitment is ongoing, we will periodically reassess sample size calculations and power analyses.

3. Discussion

This is the first study to examine the potentially synergistic effects of combining ketamine with CAMS, a suicide focused therapy, in a high-risk population of adolescents and young adults admitted to an inpatient psychiatric unit with severe suicidal ideation. This two-pronged approach attempts to address the alarming and escalating rates of suicide in these age groups and to provide robust care during the course of inpatient hospitalization. This study also continues the provision of CAMS throughout the hazardous post-discharge period, a time known to be at vastly heightened risk for suicidal behavior. It is hypothesized that ketamine's rapid antidepressant effects and capacity to enhance neuroplasticity will facilitate even greater engagement in CAMS, a psychotherapeutic framework empirically shown to increase hopefulness and reduce suicidal ideation. Clinicians providing CAMS collaboratively partner with patients to directly address the "drivers" of suicidal ideation and facilitate safety planning and means restriction, ideally safeguarding the post-discharge environment. This includes specific discussions around limiting access to lethal means, such as disposing of excess medications, self-restricting access to firearms and enlisting the support of trusted friends and family members. As the CAMS intervention is time limited, communication with outpatient providers will also be done if possible, as the participant transitions back to care as usual.

Challenges to recruitment include misperceptions or fears around the safety, tolerability, and addiction potential of ketamine, particularly due to recent high profile media coverage related to ketamine misuse. The investigational team will provide education and clarification of safety protocols with potential participants and their families and address risks and benefits in the informed consent process. Of note, patients with current or recent moderate to severe substance abuse, as well as any patients with a history of recreational ketamine use, are excluded. As recruitment is underway at academic medical centers, there is competition with other research programs for eligible participants, necessitating collaborative communication and equitable methods for approaching potential participants. As our current study is focused on investigating youth and young adults ages 14–30, our potential pool of participants is narrowed due to these criteria. Furthermore, inpatient hospital stays are also frequently brief in length and our research teams must work expeditiously to approach, consent and screen potential participants within a short timeframe, ensuring adequate time for infusion(s) and CAMS session(s) prior to discharge. It is expected that a significant number of participants included in the study will be from ethnic minority groups and LGBQ+ youth considering the recent escalation of suicide rates in these populations [2,3].

The design of the current study limits the administration of ketamine and placebo infusions to be delivered only throughout the course of

inpatient hospitalization. Depending on the results of the current study, it may be of interest in future studies to extend access to ketamine post-discharge and to examine its potential benefits on ongoing therapeutic engagement and reduction of suicidal risk.

4. Conclusions

The increase of suicidality among youth and young adults necessitates the delivery of increasingly powerful methods to rapidly and effectively address suicidal risk. The synergistic combination of ketamine and CAMS has the potential to meaningfully decrease suffering thereby saving lives and preventing future readmissions for suicide attempts.

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CRediT authorship contribution statement

Noreen A. Reilly-Harrington: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation. **Tatiana Falcone:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **David A. Jobes:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Christina Deisz:** Writing – review & editing, Project administration. **Claire Flannery:** Project administration. **Amber Wolf:** Writing – review & editing, Project administration, Conceptualization. **Bo Hu:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Amit Anand:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

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Data availability

No data was used for the research described in the article.

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