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Intramuscular ketamine vs. midazolam for rapid risk-reduction in suicidal, depressed emergency patients: Clinical trial design and rationale

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Abstract

Emergency department (ED) visits for suicidal ideation or behavior have been increasing in all age groups, particularly younger adults. A rapid-acting treatment to reduce suicidal thinking, adapted for ED use, is needed. Previous studies have shown a single dose of ketamine can improve depression and suicidal ideation within hours. However, most studies used 40 min intravenous infusions which can be impractical in a psychiatric ED. The ER-Ketamine study we describe here is a randomized midazolam-controlled clinical trial (RCT; NCT04640636) testing intramuscular (IM) ketamine's feasibility, safety, and effectiveness to rapidly reduce suicidal ideation and depression in a psychiatric ED. A pre-injection phase involves screening, informed consent, eligibility confirmation, and baseline assessment of suicidal ideation, depression, and comorbidities. The randomized double-blind IM injection is administered in the ED under research staff supervision, vital sign monitoring, pharmacokinetic blood sampling, and clinical assessments. The post-injection phase occurs on a psychiatric inpatient unit with follow-up research assessments through four weeks post-discharge. Outcome measures are feasibility, safety, and effects on suicidal ideation and depression at 24 h post-injection, and through follow-up.

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Declaration of Competing Interest

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The target sample is $N = 90$ adults in a major depressive episode, assessed by ED clinicians as warranting hospitalization for suicide risk. Here we report design, rationale, and preliminary feasibility and safety for this ongoing study. Demographics of the 53 participants (ages 18 to 65 years) randomized to date suggest a diverse sample tending towards younger adults.

Keywords

Ketamine; Emergency department; Intramuscular; Suicide; Clinical trial design

1. Introduction and background

Suicide, a global public health problem, is the fourth leading cause of death worldwide among adolescents and young adults (World Health Organization, 2021). In the U.S., suicide rates rose more than 30 % across all age groups from 2000 to 2019 (CDC, 2021). In addition to personal tragedy, this costs an estimated $100 billion annually (Shepard et al., 2016). Compared to Asian countries, Western countries have greater suicide mortality rates related to major depressive episodes (MDEs) (Bachmann, 2018; Bertolote and Fleischmann, 2002). Emergency department (ED) visits for suicidal ideation or behavior increased in all age groups from 2008 to 2017 (Owens et al., 2020). From 2011 to 2020, suicide-related ED visits increased among young adults (20–24yrs) at an average annual rate of 22 % (Bommersbach et al., 2023). The COVID-19 pandemic has exacerbated rates of suicide ideation and nonfatal suicide attempts (Dube et al., 2021). Pandemic ED visits for suicide-related reasons increased most dramatically in adolescents (Overhage et al., 2023; Yard et al., 2021). COVID-19-related stress, economic recession, and political issues may have heightened the risk of suicide and violent acts (Pandi-Perumal et al., 2022).

Research suggests individuals who visit an ED for self-harm or suicidal thoughts have suicide rates within a year that are greater than age-, sex-, and race/ethnicity-adjusted general population groups (Olfson et al., 2021). Thus the ED is a key setting for interventions to reduce suicide risk.

Antidepressant medications and psychotherapy are evidence-based treatments for suicidal ideation and depression, but usually take weeks to months to show substantial effects. Up to 50 % of MDEs may be resistant to medications (Trivedi et al., 2006).

A safe, easy-to-use, scalable, and rapid-acting intervention for high-risk, suicidal individuals would give busy ED clinicians a useful tool to advance public health. Clinical trials show relief of suicidal thoughts within hours of subanesthetic intravenous (IV) ketamine treatment. Previous randomized clinical trials (RCT) in bipolar (Grunebaum et al., 2017) and unipolar (Grunebaum et al., 2018) suicidal depressed patients found that ketamine reduced suicidal thoughts within hours and improvement lasted up to six weeks with optimized, standard pharmacotherapy. Ketamine has also been found to have anti-anhedonic effects in individuals with MDD, contributing to its antidepressant properties (Zheng et al., 2023). Some research finds that repeated infusions of ketamine may be more effective in younger adults with depression than older adults (Zheng et al., 2023).

Ketamine is novel in its rapid onset of benefit, and is effective in Treatment-Resistant Depression (TRD) (Serafini et al., 2014). Ketamine differs from other antidepressants in its more targeted effects on glutamate (Abdallah et al., 2018), a possible mechanism for its therapeutic action. Most ketamine RCTs have administered the inexpensive, generic, racemic form of the drug via 40 min IV infusion at a standard dose of 0.5 mg/kg. A previous trial randomized 18 depressed ED patients with acute suicidal ideation needing hospitalization to 5 min infusion of IV ketamine 0.2 mg/kg or saline placebo (Domany et al., 2020). Outcome assessments were done through day 14 post-treatment. Results showed an advantage for ketamine in reducing suicidal ideation at 90–180 min (Domany et al., 2020). These results are promising, but IV administration may be challenging for psychiatric EDs, which do not typically manage IV catheters or may not allow them. Also, a reduction in IV infusion time from the standard 40 to 5 min likely resulted in the administration of less than half the typical 0.5 mg/kg dose. Published RCT data in an outpatient sample with TRD showed doses below 0.5 mg/kg did not have consistent antidepressant effects ($N = 99$) (Fava et al., 2020).

Intramuscular (IM) injections are less labor-intensive than IV catheter insertion, take seconds to administer, are routine in psychiatric EDs, and can deliver the same effective 0.5 mg/kg dose as the 40 min IV infusions. Intranasal (IN) administration has advantages of quick administration, less training or specialized skill requirement, and elimination of IV procedure (An et al., 2021). However, IN administration has about 50 % bioavailability (Bahr et al., 2019; Morrison et al., 2018; Yanagihara et al., 2003). In contrast, IM ketamine has a 93 % bioavailability and plasma half-life similar to IV ketamine (Clements et al., 1982; Zanos et al., 2018). A study found that antidepressant efficacy and side effects of IV and IM ketamine were similar (Loo et al., 2016). It could be argued that psychiatric EDs should manage IV medications given the burden of medical illness in this population. Our psychiatric ED does not allow IV tubing because it poses a risk of suicide by hanging. For these reasons, we designed the Columbia ER-Ketamine RCT to utilize IM ketamine at the standard dose, and instead of saline placebo, a more robust, psychoactive midazolam control.

1.1. Aims and intervention

The study aims to test feasibility, safety, and efficacy of ketamine IM injection for rapid reduction of suicidal ideation in depressed patients needing hospitalization for suicide risk. The double-blind RCT is funded by an NIMH program targeted at safety and feasibility trials for rapid-acting interventions for severe suicide risk (NIMH, 2021). The clinicaltrials.gov identifier is NCT04640636. The study takes place in the Comprehensive Psychiatric Emergency Program (CPEP) of CUIMC in a diverse, underserved part of upper Manhattan, New York City. Participants who sign consent are randomly assigned, double-blind, to a single dose of IM ketamine (0.5 mg/kg) or midazolam (0.03 mg/kg) administered in the psychiatric ED. The study uses validated, structured instruments to assess diagnosis, clinical severity, response, frequency and severity of adverse effects acutely, during inpatient follow-up, and through four weeks after hospital discharge.

Several features make IM ketamine a promising potential ED treatment for acute suicidal ideation or behavior. Ketamine does not suppress respiratory drive as opiates do. A first-line military recommendation for battlefield anesthesia is ketamine 50–100 mg IM. This is similar to effective (0.5–1.0 mg/kg) IV doses used for depression and with similar, high bioavailability (Dickey et al., 2012; Fava et al., 2018; Shackelford et al., 2015; Wedmore and Butler, 2017). Onset of ketamine's clinical effects is about 1 min with IV and 5 min with IM administration (Dickey et al., 2012). The mean time to maximum plasma concentration of intranasal ketamine is 20–30 min (Yanagihara et al., 2003) versus only 5 min for IM ketamine (Mion and Villevieille, 2013). Thus, the rapidity of clinical effect and simpler logistics compared to IV infusion make low-cost, generic, racemic IM ketamine a promising potential intervention for busy ED clinicians to "jumpstart" treatment of high-risk, depressed, suicidal patients.

The main hypotheses are: (1) IM ketamine will be superior to IM midazolam for reduction of suicidal ideation at 24 h post-treatment; and (2) Neither drug group will experience clinically significant treatment emergent adverse effects at 24 h post-treatment. The study will explore potential moderators (biological sex, unipolar vs. bipolar depression) and secondary outcomes (cognitive control, ED/inpatient length of stay, suicidal ideation or behavior one month after hospital discharge, and pilot pharmacokinetic data). We will also measure the effect on depression severity and test that effect as a potential mediator of any reduction in suicidal ideation

1.2. Study procedures

The study has three phases: pre-injection, post-injection, and post-discharge. During the pre-injection phase, if ED clinical staff assess a patient as a potentially eligible candidate, they briefly describe the study and ask if the patient would like to learn more. If the patient is interested, the ED clinician contacts the study PI who reviews the electronic medical record of the patient's clinical ED evaluation, labs, and EKG. If eligibility seems likely, the PI meets with the patient in the ED to fully explain the study as part of an informed consent discussion. Individuals who choose to participate sign written informed consent as approved by the New York State Psychiatric Institute (NYSPI) and CUIMC Institutional Review Boards. Participants then undergo research diagnostic and clinical assessments to confirm eligibility. IRB-approved inclusion and exclusion criteria are summarized in Table 1. Standard medical tests for ED patients are: metabolic panel, CBC with platelets, hepatic function, urinalysis, TSH, ethanol assessment, drug screen, pregnancy test, and electrocardiogram (ECG). The study PI reviews labs and ECG prior to meeting with the patient to ensure participant safety and eligibility. Occasionally, the PI consults with the study anesthesiologist to discuss any concerns.

If eligibility is confirmed, the pharmacy is notified to randomize the new participant to a drug group. Simultaneously, participants complete baseline (pre-treatment) clinical research assessments with a range of validated instruments and a brief, repeatable computerized neuropsychological test battery (Table 2).

After baseline assessments, participants are set up in a private interview room in the ED, lying down, with a blood pressure (BP) cuff and pulse oximetry. After a time-out checklist

procedure to confirm that BP and other characteristics are stable, a psychiatric ED nurse administers the blinded study injection. For the next hour, the study PI and coordinator stay with the participant, monitoring clinical state, BP, and pulse oximetry every 10 min. During this time, they provide support and reassurance as needed. Participant responses range widely from calm or sleepy to talkative and from mild euphoria to anxiety or sadness. Brief clinical research assessments and blood sampling for pharmacokinetics are done at 30- and 60 min post-injection.

Participants are admitted, typically several hours after the injection, to one of two inpatient psychiatric units at our medical center campus of CUIMC/NYSPI for standard clinical inpatient treatment. Participants complete weekly clinical research measures throughout their inpatient stay. This study sets a precedent for inpatient unit involvement after ketamine treatment in the ED.

Study participation does not impact inpatient length of stay. The research team may act as a consultant, however the inpatient clinical team is in charge of participants' treatment, planning for discharge, and disposition for ongoing care. Participants are discharged from the inpatient unit when the clinical team determines they are safe for outpatient treatment and an appropriate aftercare plan is set. At hospital discharge, medications and disposition to individual versus group treatment (e.g. day program, partial hospital) are tracked in the database for future analysis. Follow-up research assessments are completed at the following post-injection timepoints – 30 min, 60 min, 4 h, 1 day, 3 days, and weekly through four weeks post-hospital discharge (Table 2). The time required to administer each assessment is noted in Table 2. At the 4 h timepoint usually in the evening, due to the challenge of staffing evening research ratings, participants complete web-based self-reports through a link accessed with a study iPad given to them by inpatient staff.

1.3. Major endpoints and research outcomes

The primary outcomes are feasibility, safety, and reduction of suicidal thoughts at 24 h post-injection. Secondary outcomes are effects on depression severity, length of stay, neurocognitive function, and suicidal thoughts and behavior during the month after hospital discharge, a high-risk period for suicide (Chung et al., 2019). Blood samples are drawn at 30- and 60 min post-injection for pharmacokinetic pilot data.

The clinician-rated Beck Scale for Suicide Ideation (SSI) (Beck et al., 1988) is the primary measure for severity of suicidal thoughts. The SSI is administered at screening, Day 1, Day 3, Weekly during inpatient stay through four weeks post-discharge. Other instruments include the Computerized Adaptive Test Suicide Scale (CAT-SS) and Depression Inventory (CAT-DI) (CAT-MH™, Adaptive Testing Technologies, Chicago, IL, www.adaptivetestingtechnologies.com). These are innovative, web-based self-report measures gathered for comparison with the traditional measures (Gibbons et al., 2017, 2012). A CAT-MH™ test is a computerized self-report that adjusts item administration to a given subject in real-time by learning that person's severity from prior item responses using a pre-calibrated item bank (Grunebaum et al., 2021), and can significantly shorten testing time. The Columbia Suicide Severity Rating Scale (C-SSRS) behavior subscale is used to

assess suicidal behavior during the weekly inpatient stay through one month post-discharge (Posner et al., 2011).

Depressive symptom severity is measured for short-term changes post-injection by the Profile of Mood States (POMS), a 65-item self-report designed for repeated administration over the short time intervals required for a rapid-acting treatment such as ketamine (McNair et al., 1981). For longer follow-up intervals, the 24-item Hamilton Depression Rating Scale (HDRS) is obtained at baseline, and weekly inpatient and post-discharge ratings. The 24-item HDRS is used as an established clinician-rated measure (Hamilton, 1960). The Single Question Anxiety Rating (SQAR: rated 0–4 “not at all” to “extremely”) is less burdensome and was found to be an adequate replacement for the longer State Trait Anxiety Inventory (STAI) (Davey et al., 2007) and is done at baseline, and post-injection at 30 min, 60 min, Day 1, and Day 3. Clinical state is also assessed using the Clinical Global Impressions (CGI) scale that captures clinical impression of symptom severity (Busner and Targum, 2007).

Adverse effects are assessed through spontaneously reported events and structured instruments. Using data on the most frequently positive items from our prior IV ketamine studies, we shortened the Clinician Administered Dissociative States Scale (CADSS) (Bremner et al., 1998) for this study by excluding items 4,8–10, and 12–14 to increase speed in the ED. The 4-item positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) is used to assess acute, injection-related psychotomimetic symptoms. These are administered at baseline, 30 min, 60 min, and Day 1. The Systematic Assessment for Treatment Emergent Events self-report (SAFTEE-SR) measures a range of side effects at the 4 h and 1 day timepoints (Levine and Schooler, 1986). At study completion, a short substance check questionnaire assesses substance use since hospital discharge.

Participants are surveyed about psychiatric history including suicidal ideation and behavior. Psychiatric diagnosis is made using the Mini International Neuropsychiatric Interview (MINI) computerized version for DSM5 (Sheehan et al., 1998). MINI modules are administered during eligibility screening to assess major depressive disorder and episode, bipolar disorder, psychotic disorders, and generalized anxiety disorder. Other modules are administered on Day 3 post-injection or after to assess comorbid diagnoses of alcohol or substance use, panic disorder, agoraphobia, social anxiety, obsessive-compulsive disorder, anorexia nervosa, bulimia nervosa, binge eating, antisocial and borderline personality disorders. Participants are also asked for demographics, previously prescribed psychiatric medication, and information on previous suicide attempts. Beck’s Suicide Intent Scale (SIS) (Beck et al., 1979) is completed for the most lethal and most recent suicide attempt.

A brief computerized neurocognitive battery that can be administered at bedside is used to assess neurocognitive changes related to treatment. It includes tests measuring deficits associated in published literature with depression and/or suicidal behavior (Keilp et al., 2013) and sensitive to effects of either ketamine or midazolam (Keilp et al., 2021; Murrough et al., 2013; Zavaliangos-Petropulu et al., 2023). The battery is done at Baseline, Day 1 and Week 1 and includes: Choice Reaction Time (reaction time), Stroop Task (cognitive control/interference processing), Flanker Task (cognitive control/interference processing), Acquired

Equivalence Task (“fish/face” associative learning/memory), and Implicit Associations Test (implicit suicidal preoccupation).

1.4. Safety measures and suicide risk mitigation

Given the higher risk population, the protocol includes several safety measures. At enrollment, participants are asked for an emergency contact and provider information. The study injection is administered in a psychiatric ED staffed with nurses, physicians, security personnel, and located adjacent to the medical ED. After the ED injection procedure, all participants are admitted to one of our inpatient psychiatric units and receive open, clinical treatment managed by the inpatient team, including standard pharmacotherapy, milieu therapy, and outpatient care planning. Electro-convulsive therapy (ECT) is offered, if necessary. The inpatient units do not currently offer transcranial magnetic stimulation (TMS) or ketamine treatment.

Follow-up study ratings are administered weekly during the inpatient stay through four weeks post-discharge. Psychologists administering study assessments for SI and depression communicate with the study PI if they feel a participant is at imminent risk and the study PI shares this information with the inpatient clinical team. If participants have a very high suicide risk score in the CAT-SS, the computerized system automatically emails an alert to the study PI and coordinator. If either situation occurs post-discharge, the study PI reaches out to the participant to evaluate risk and initiate safety measures as indicated. These may include calling an emergency contact, the participant’s current provider, referral to mobile crisis team, or calling emergency services as a last resort. Additional suicide risk management safeguards include 24 h on-call psychiatrist emergency phone coverage in our research clinic.

1.5. Concurrent treatments

To prevent potential excessive sedation, a regular daily benzodiazepine dose greater than 3 mg lorazepam or equivalent is an exclusion at screening. Similarly, benzodiazepine and non-benzodiazepine sleeping medications are prohibited for 6 h before the study treatment procedure. Otherwise, participants are allowed to continue current medications unless there is a specific contraindication.

1.6. Study participants

Relatively broad inclusion and limited exclusion criteria (Table 1) were chosen to recruit a sample representative of the ED population with nonpsychotic depression and suicidal ideation severe enough to warrant hospitalization. The goal is to obtain results generalizable to ED patients for whom an evidence-based, rapid-acting, anti-suicidal intervention would be helpful for rapid risk-reduction. Main exclusions are found in Table 1. Co-occurring substance use disorder (other than opioids, ketamine, and PCP) not requiring specialized treatment is included to increase ecological validity due to the common comorbidity of substance use disorders (SUD) in suicidal patients (Onaemo et al., 2022).

Participant agreement to voluntary inpatient admission is part of inclusion criteria based on the rationale that it would be premature in this pilot study to discharge from the ED a

recently suicidal patient who responded positively to the study intervention without greater confidence that this was not a placebo or very transient effect. Ketamine's antidepressant and anti-suicidal ideation effects are known to diminish after approximately a week (Wilkinson et al., 2018; Newport et al., 2015). High-risk participants need initiation of clinical treatment and engagement in as comprehensive an outpatient care plan as possible within the limits of resources and health insurance.

1.7. Enrollment, randomization, and blinding

The pharmacy uses a statistician-generated computerized randomization scheme based on stratified blocked randomization obtained using the R library "blockrand" (R Core Team, 2018) to assign participants to the ketamine or midazolam group in a 2:1 ratio. Randomization is stratified by baseline SSI score with a lower (<8) and a higher ideation group (8 or above) (SSI score ranges 0–38). A permuted block design is used, with block size randomized between 2, 4 and 6 with equal probability for each. Participants, study psychiatrist, and assessors are blind to drug assignment. An un-blinded pharmacist who is not part of the research team prepares the blinded syringe for IM injection. After research ratings on Day 1 post-injection, participants and raters complete a blind adequacy assessment asking their best guess as to which medication they received. After study completion, participants are offered a letter indicating which study drug they received. In this case, the pharmacy provides a tamper resistant letter which is mailed directly to the participant. Participants are also sent a letter thanking them for their participation and a pre-paid debit card with their study compensation. Participants receive $25 for each set of ratings with a maximum compensation of $300.

1.8. Data collection and management

All assessments are collected electronically using HIPAA compliant web-based platforms involving deidentification. Most measures utilize a Research Electronic Data Capture (REDCap) database built for the study and hosted at NYSPI/CUIMC. REDCap is a secure, web-based software platform designed to support data capture for research studies with an intuitive interface well-suited for clinical trials, audit trails, and export functions for statistical analysis (Harris et al., 2019, 2009). Study measures not collected using REDCap are the neurocognitive battery, the MINI 7.0.2 for DSM-5 diagnosis (Sheehan et al., 1998) electronic version (Proem Behavioral Health, Atlanta, GA), and the Computerized Adaptive Tests for suicidality and depression (CAT-SS, CAT-DI) (Gibbons et al., 2017, 2012) (Adaptive Testing Technologies, Chicago, IL).

An innovation of this study is the use of CAT for head-to-head comparison with traditional scales of suicidal ideation and depressive symptoms. There is a shift toward empirically derived and "interview independent tools" (Bolton et al., 2015). Advances in CAT (Gibbons et al., 2016, 2012) have improved the ability to precisely measure mental health constructs such as depression (Gibbons et al., 2012) and suicidality (Gibbons et al., 2017). As an example, it was shown that the information contained in a 389-item bank of depressive symptoms could be adaptively measured using a mean of 12 items in an average of two minutes, with a correlation of $r = 0.95$ with the item bank total score (Gibbons et al., 2012). We piloted CAT measurements of depression and suicidality in our prior ketamine trials and

found lower coefficients of variation for baseline measurements compared with traditional scales, indicating a better signal-to-noise ratio (Grunebaum et al., 2021).

1.9. Quality of life and functioning

Participants' quality of life and functioning are measured as "indirect costs" of suicidal depression. The Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form (Q-LES-Q) measures domains of health, work, and relationships (Endicott et al., 1993). The Work and Social Adjustment Scale (WSAS) is another self-report measuring effects of mental health on level of function in work, home, leisure, and relationships (Mundt et al., 2002). The Q-LES-Q and WSAS were used to measure change with treatment in the STAR*D depression trial (Rush et al., 2004) and are administered at baseline, weekly inpatient, and post-discharge ratings.

1.10. Anticipated statistical approach

Group differences in suicidal ideation change 24 h after the study injection (Day 1) is the primary efficacy outcome. Pre- to post-injection changes in the two groups will be compared by performing ANOVA in the modified intent-to-treat sample (Day 1 data obtained), with the baseline score, age and biological sex as covariates, followed by longitudinal analysis of both scores using mixed effect regression in the full sample, with randomization group and timepoint, and their interaction, as predictors, age and sex as covariates, with subject-specific random intercept and an AR(1) within-subject correlation structure. The coefficient of interest will be the one for group in the first model, and the group by time interaction in the longitudinal model. As in our inpatient trial (Grunebaum et al., 2018) we will calculate effect sizes including Cohen's d (difference in mean group change divided by the standard deviation of baseline values for the whole sample) and Number Needed to Treat (NNT) (proportion of responders on the SSI at day 1 in the treatment groups). The randomization group's interactions with sex will be explored in both models, although this study is not powered to test moderators.

Safety outcomes are adverse effects measured on several scales: modified CADSS for dissociative effects, BPRS positive symptom subscale for psychotomimetic effects, and the SAFTEE for a range of common physical side effects. These will be summarized and reported separately, by group with means and standard deviations for quantitative scales and median and Inter Quartile Range (IQR) for count data. Single-sample *t*-tests can be used to compare group means to pre-set cutoffs for "clinically significant" adverse effects, however, these cutoffs can be ambiguous and hard to identify, thus a descriptive approach will be preferred.

1.11. Sample size, power, and effect size

The effect size for suicidal ideation change at Day 1 is 0.75, based on the previous IV ketamine trial in MDD with clinically significant suicidal ideation (Grunebaum et al., 2018). With 90 subjects randomized 2:1 to IM ketamine or midazolam we would have 91 % power and we will have sufficient power for the primary outcome measure with $N = 66$ completers. Based on our prior IV ketamine trial, drop-out is expected to be less than 3 % for the 24 h post-treatment outcome (24 h completer sample size 58:29), and less than 15 % for the

longer-term outcome (up to four weeks post-hospital discharge). In the mixed effect models, all subjects with data for at least some timepoints will be used. Thus, we will assume a longitudinal sample of similar size to the completer sample.

1.12. Data monitoring and safety

Given the higher risk suicidal depressed sample, the study has a data and safety monitoring board (DSMB) that meets every six months via videoconference to discuss study progress, including recruitment, review of pooled Baseline and Day 1 data for key outcomes, Protocol Violations (PV), Serious Adverse Events (SAE), and other adverse effect frequencies (AE). During the inpatient phase, events such as restraint/seclusion and falls are documented as adverse events, and if they meet criteria for a Serious Adverse Event (SAE), are reported to the Institutional Review Board (IRB). The DSMB is made up of two psychiatrists and one biostatistician from outside our institution, all experienced with clinical research in mood disorders and controlled trials. The DSMB has met six times and has not requested unblinded data.

1.13. Trial progress

The study was funded in September 2020. After staffing, start-up, and database construction, recruitment began in February 2021 during the COVID pandemic. The study has so far largely met recruitment targets. The first year was notable for protocol amendments to improve efficiency and speed of procedures to be compatible with the rapid pace required in our busy, inner city psychiatric ED. Other protocol modifications were made to enhance recruitment and safety. The most significant of these was liberalizing the substance use exclusion to only exclude acute intoxication, need for specialized treatment, or frequent ketamine/PCP/opioid use. This shortened ED study procedures by moving MINI comorbidity modules into the inpatient phase and also enhances recruitment and ecological validity of the sample.

Thus far, 76 participants have been screened and 57 participants have enrolled in the study. Of those, 53 were randomized and provided complete primary outcome data. The blind is intact, thus between-group differences have not been studied.

Participant sociodemographic data show a diverse, younger adult sample: 28.3 % biologically male, 71.7 % biologically female, 22.6 % transgender or non-binary, 49.1 % Hispanic, 71.7 % non-White, with a mean age of 29.9 years (median = 26.5y). The relatively low average age is consistent with research that suggests an increased number of young adults who visit the ED for suicide ideation and nonfatal suicide attempts (Bommersbach et al., 2023; Overhage et al., 2023; Yard et al., 2021).

The ED study intervention has been associated with expected mild to moderate psychoactive effects and changes in blood pressure largely resolving within one hour of IM injection. These have been similar in frequency and severity to effects observed in our previous IV studies (Grunebaum et al., 2017, 2018). So far, 10 serious adverse events related to suicidal ideation and/or behavior have occurred, none resulting in serious medical injury. All have been reported to the IRB, DSMB, and NIMH, and have not resulted in major protocol modifications.

2. Discussion

Alarming suicide rates and increasing suicide-related ED visits in the US stress a need for rapid-acting treatment options for emergency settings. The psychiatric ED is a key setting for rapid interventions to reduce suicide risk in vulnerable individuals. While not the first study of IM administration (Loo et al., 2016) or psychiatric ketamine use in the ED (Domany et al., 2020), the Columbia-ER Ketamine trial combines these innovations with added design strengths: a psychoactive midazolam comparator and a sample powered for the primary outcome of rapid suicidal ideation reduction for severely suicidal ED patients.

A limitation of our study design is that all participants are admitted for inpatient treatment after the research ketamine vs midazolam procedure. Thus, the study is not designed to assess ketamine's potential for decreasing need for hospitalization. The current design was chosen since this is an initial safety and feasibility study and little is known about the safety of discharging suicidal, depressed patients from an ED soon after ketamine treatment. Another limitation is the inpatient team's awareness that a patient participated in the trial, which may result in extra attention that could affect outcomes, although we believe it would bias any medication group difference toward the null. While a reliable diagnosis in the ED is difficult (Baca-Garcia et al., 2007), the enrolled participant meets with various clinicians throughout the study including in the ED, with study staff, and on the inpatient unit. When a participant completes the study, the research team performs a consensus diagnosis process to review all clinical and research data and come up with the most accurate diagnosis possible at that point. Another limitation is not including an SSI assessment at the 4 h post-injection timepoint due evening rater staffing logistics.

The diversity and median age of our study sample are of public health importance since recent data show between 2018 and 2021 age-adjusted suicide rates increased significantly among American Indian/Alaska Native, non-Hispanic Black, and Hispanic persons, particularly youth and younger adults (Stone et al., 2023). The study is ongoing, however pooled data so far suggest preliminary signals of feasibility and safety in a diverse, younger adult sample of public health importance.

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Table 1

Study inclusion and exclusion criteria.

CRITERION		METHOD OF ASCERTAINMENT
Inclusion	1. 18–65 years old	Interview
	2. DSM5[1] unipolar or bipolar (I, II, or Unspecified) major depressive episode	MINI[2] diagnostic interview
	3. Assessed by psychiatric ED staff as needing inpatient treatment due to suicide risk	ED clinical assessment
	4. Subject agrees to voluntary inpatient admission	Interview
	5. Beck Scale for Suicidal Ideation (SSI) score of 4 or higher	SSI scale
	6. Subjects 60–65 years old must score 25 or higher on the Mini Mental Status Exam (MMSE) at screening	MMSE
Exclusion	1. Co-occurring substance excluded if: acute intoxication or withdrawal; more than rare recreational use of opioids/ ketamine/PCP (e.g. >once in past year); needs specialized addiction treatment/detox and cannot be handled on study units; primary alcohol/substance disorder with secondary depression	Assessed case by case in collaboration with ED team based on labs, clinical assessment, and study screening
	2. Current psychosis or mania	Clinical and MINI[2] assessments
	3. Intellectual disability	Clinical assessment
	4. Inadequate understanding of English and/or lack of capacity for informed consent.	Clinical assessment
	5. Pregnancy or lactation	Urine or blood pregnancy test
	6. Any medical contraindication to ketamine or midazolam; Total current dose of lorazepam or benzodiazepine equivalent greater than 3 mg daily is excluded.	Medical history
	7. Unstable medical or neurological illness such as uncontrolled hypertension, significant cardiac arrhythmia, unstable cerebrovascular disease. Chronic, stable medical conditions such as controlled hypertension or diabetes are not excluded.	Medical history, labs, and ECG

[1]DSM5 = Diagnostic and Statistical Manual of Mental Disorders Fifth Edition.

[2]MINI = Mini International Neuropsychiatric Interview.

Table 2

Time-points and frequency of study assessments.

Schedule of Research Measures		Pre-Injection				Post-Injection				Post-Hospital Discharge			
		Psychiatric ED				Inpatient Unit				Outpatient			
	Domain	Screening	Baseline	30 min	60 min	4 h	Day 1	Day 3	Week 1 (Repeats weekly)	Week 1	Week 2	Week 3	Week 4
Diagnosis	MINI[6] eligibility modules (depression, psychosis, mania) (30 min) (R[2]) MINI[6] comorbidity modules (substance, anxiety, eating, personality) (30–60 min) (R[2])	X						X					
Demographic	Screen Demographics (5 min) (C[4])	X											
	Demographics/Clinical History (45 min)(R[2])							X					
Clinical State	HDRS[7] (10–15 min) (R[2])		X						X	X	X	X	X
	POMS[8] (10 min) (Pt)		X			X	X	X	X				
	Anxiety (SQAR [20]) (5 min) (R[2])		X				X	X					
	CGI[9] (MD[3])		X				X	X	X				
	CAT-DI[10] (2 min) (Pt[1])	X	X*		X	X	X	X	X	X	X	X	X
Suicidal Ideation and behavior	Suicide History, Lethality Rating, SIS[13] (45 min) (R[2])†							X					
	SSI[12] (10 min) (R[2])	X	X*				X	X	X	X	X	X	X
	CAT-SS (2 min) (Pt[1])	X	X*		X	X	X	X	X	X	X	X	X
	CSSRS[14] (10 min) (R[2])							X	X	X	X	X	X
Medication and Adverse Effects	mCADSS[15] (10 min) (R[2])		X	X	X		X						
	BPRS[16] (5 min) (R[2])		X	X	X		X						
	SAFTEE-SR[17] (5 min) (Pt[1]) Substance check (5 min) (R[2])					X	X						X
Mechanistic	Neurocognition (30 min) (R[2])		X				X		X (Week 1 only)				
	Ketamine blood sample (C[4])			X	X								

Schedule of Research Measures		Pre-Injection				Post-Injection				Post-Hospital Discharge			
		Psychiatric ED				Inpatient Unit				Outpatient			
	Domain	Screening	Baseline	30 min	60 min	4 h	Day 1	Day 3	Week 1 (Repeats weekly)	Week 1	Week 2	Week 3	Week 4
Quality of Life and Functioning	Q-LES-Q-SF[18] (15 min) (Pt[1])		X						X	X	X	X	X
	WSAS[19] (15 min) (Pt[1])		X						X	X	X	X	X

[1] Pt= Administered by Participant/self.

[2] *R*= Administered by Rater.

[3] MD= Administered by Physician.

[4] C= Administered by Coordinator

[5] N= Administered by Neuropsychologist.

[6] MINI= Mini-International Neuropsychiatric Interview.

[7] HDRS= Hamilton Depression Rating Scale.

[8] POMS= Profile of Mood States.

[9] CGI= Clinical Global Impression.

[10] CAT-DI= Computerized Adaptive Test-Depression Interview.

[11] CAT-SS= Computerized Adaptive Test-Suicide Scale.

[12] SSI= Scale for Suicidal Ideation.

[13] SIS= Suicide Intent Scale, rated for past suicide attempts.

[14] CSSRS= Columbia Suicide Severity Rating Scale, behavior section.

[15] mCADSS= Modified Clinician Administered Dissociative States Scale.

[16] BPRS = Brief Psychiatric Rating Scale.

[17] SAFTEE-SR = Systematic Assessment for Treatment Emergent Events self-report.

[18] Q-LES-Q-SF= Quality of Life Enjoyment and Satisfaction Questionnaire short form.

[19] WSAS = Work and Social Adjustment Scale.

[20] SQUAR= Single Question Anxiety Rating.

[*] If ≥24 h since screen.

[†] Only done for past suicide attempts.