Real-world Effectiveness of Intravenous Ketamine for Suicidal Ideation in Treatment-Resistant Depression

By

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Abstract

Suicidal ideation is a significant symptom associated with mood disorders. Clinical trials have demonstrated rapid reduction in suicidal ideation following ketamine infusions, however, clinical trial results are not always generalizable to real world practice. A real-world effectiveness analysis of 96 adult outpatients with treatment-resistant depression (TRD) that received ketamine infusions in a community clinic in Toronto, Ontario was conducted. Suicidality and depressive symptom outcomes were assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) (self-report version) and the Quick Inventory for Depressive Symptomatology Self-Report 16-Item respectively. Mean C-SSRS score significantly decreased following a single ketamine infusion and was indicative of a reduction in suicidality from active to passive suicidal ideation on a group level. Results of the mediation analysis indicated that the antisuicidal effects of ketamine are partially independent of its antidepressant effects. This study suggests that ketamine is effective in reducing suicidal ideation in a real-world setting with benefits comparable to clinical trials.

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Contributions

- David Chen-Li was responsible for assessing participant eligibility, conducting study visits, collecting and entering data for KET-BD and KET-BD-SUSTAIN, data curation, formal analysis, investigation, methodology, visualization, original draft preparation, and writing of this thesis
- Dr. Joshua Rosenblat was involved in all aspects of this thesis and the studies described
- Dr. Rodrigo Mansur provided guidance and assistance for the statistical analysis of this thesis as well as mentorship and knowledge, as well as assessing participant eligibility
- Dr. Tony George provided guidance, mentorship and knowledge as the Chair of my Program Advisory Committee
- Dr. Cristian Llach-Lopez and Dr. Jeffrey Wieskopf were responsible for assessing participant eligibility
- Lee Phan was responsible for trial oversight, including ensuring quality and integrity of study protocols, SOPs, and training
- Sipan Haikazian, Danica Johnson, Erica Kazcmarek, Noah Chisamore, Sebastian Badulescu, Sabrina Wong, Gia Han Le, Aniqa Tabassaum were responsible for assessing participant eligibility, conducting study visits, collecting and entering data for KET-BD and KET-BD-SUSTAIN
- Drs. Neilish Soneji, Anuj Bhatia, Kayvan Karkouti, and Alexander Huang were responsible for providing on-site anesthesia care for KET-BD and KET-BD-SUSTAIN
- Deep Grewal, Victoria Barkley, Simryn Selby, Rachel LaFramboise were responsible for ensuring compliance with UHN and Health Canada policies for KET-BD and KET-BD-SUSTAIN

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ACT	Acceptance and commitment therapy
ADHD	Attention deficit hyperactivity disorder
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BA	Behavioural activation
BD	Bipolar disorder
BD-I	Bipolar I disorder
BD-II	Bipolar II disorder
BDNF	Brain-derived neurotrophic factor
BPD	Borderline personality disorder
BSI	Beck Scale for Suicide Ideation
C-SSRS	Columbia Suicide Severity Rating Scale
CAD	Canadian Dollar
CANMAT	Canadian Network for Mood and Anxiety Treatments
CBSAP	Cognitive behavioural analysis system of psychotherapy
CBT	Cognitive behavioural therapy
CHRT-SR	Concise Health Risk Tracking Self-Report
CONSORT	Consolidated Standards of Reporting Trials
CRTCE	Canadian Rapid Treatment Centre of Excellence
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EPDS	Edinburgh Postnatal Depression Scale
FDA	Food and Drug Administration
FFT	Family-focused therapy
GEE	Generalized estimating equations
HALY	Health-adjusted life years
IN	Intranasal
IPSRT	Interpersonal social-rhythm therapy
IV	Intravenous
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	Monoamine oxidase inhibitors

MBCT	Mindfulness-based cognitive therapy
MCT	Metacognitive therapy
MDD	Major depressive disorder
MDE	Major depressive episode
MDPU	Mood Disorders Psychopharmacology Unit
MI	Motivational interviewing
mTORC1	Mechanistic target of rapamycin complex 1
NCT	National Clinical Trial
NDRI	Norepinephrine-dopamine reuptake inhibitor
NMDA	N-Methyl-D-Aspartate
NRI	Norepinephrine reuptake inhibitor
OS	Ontario Shores Centre for Mental Health Sciences
PDT	Psychodynamic therapy
PHQ-2	2-item Patient Health Questionnaire
PHQ-9	Patient Health Questionnaire
PST	Problem-solving therapy
QIDS-SR16	16-Item Quick Inventory of Depressive Symptomatology Self Report
QoL	Quality of Life
RCT	Randomized controlled trial
RIMA	Reversible inhibitors of monoamine oxidase A
RR	Relative risk
SDM	Shared decision making
SMD	Standard mean difference
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSI	Scale for Suicide Ideation
SSRI	Selective serotonin reuptake inhibitor
STPP	Short-term psychodynamic psychotherapy
SUD	Substance use disorder
TCA	Tricyclic antidepressant
TRBD	Treatment-resistant bipolar depression
TRD	Treatment-resistant depression

TrkB	Tropomyosin receptor kinase B
UHN	University Health Network
USD	United States Dollar
USPSTF	United States Preventive Services Task Force
WHO	World Health Organization

Chapter 1: Introduction

1.1 Depression

1.1.1 History of Depression

Depression has been recognized as early as the time of Hippocrates in the form of a "melancholic affection," a distinct disease caused by a "fright or despondency [that] lasts for a long time" as detailed by Hippocrates in his Aphorisms (*Hippocrates, Aphorismi, SECTION VI, Part 23*, n.d.). Over time, academics, physicians and psychiatrists such as Emil Kraepelin, Jean-Pierre Falret, Jules Baillarger, Sigmund Freud, and Karl Abraham have contributed theories that have laid the foundation for our modern understanding and definition of depression (Paykel, 2008). In particular, Kraepelin regarded psychiatric disorders as diseases with a neurological basis possessing distinct etiology and pathology (Paykel, 2008), and his work revolved around classifying psychiatric disorders into two main categories: dementia præcox and manic-depressive insanity (Decker, 2007; Teodoro & Durval, 2022). Concurrently, Freud and Abraham proposed a psychoanalytical perspective of depression as the result of an actual or symbolic loss of a love object, insinuating the origin of depression to be psychogenic in nature (Paykel, 2008). Kraepelin's focus on the syndromic nature of psychiatric disorders would lay the groundwork for the modern classification systems in use today, including the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (American Psychiatric Association, 2013; Paykel, 2008; Teodoro & Durval, 2022).

1.1.2 Prevalence and Disease Burden of Major Depressive Disorder

Major depressive disorder (MDD) is a common and debilitating mental disorder that affects approximately 280 million people worldwide (*Depression*, n.d.). The average lifetime prevalence of MDD is 12% (Bains & Abdijadid, 2023), with MDD being nearly twice as prevalent in

women as it is in men (Pedersen et al., 2014). In Canada, the annual prevalence of a major depressive episode (MDE) was 4.7%, while the annual and lifetime prevalence of MDD was 3.9% and 9.9% respectively (Patten et al., 2015).

Depression is ranked by the World Health Organization (WHO) as the largest contributor to global disability and accounts for 7.5% of all years lived with disability in 2015 (World Health Organization, 2017). In Ontario, MDD accounted for a greater burden of disease as measured by health-adjusted life years (HALYs) than breast, colorectal, lung, and prostate cancers combined (Ratnasingham et al., 2013). MDD has a significant occupational impact, and is associated with major productivity losses due to time away from work and productivity loss due to illness while at work (Lam et al., 2016). Productivity loss due to mental illness has significant economic implications as well, with mental illness contributing an estimated $51 billion CAD burden to the Canadian economy (Lim et al., 2008). While there are no specific measures of the burden of MDD in Canada, the economic burden of adults in the United States with MDD estimated at $326.2 billion USD in 2018 (Greenberg et al., 2021).

1.1.3 Clinical Diagnosis of MDD

MDD in the DSM-5 is characterized by a history of one or more MDEs, and no history of mania or hypomania (American Psychiatric Association, 2013). Practitioners must take extra precaution while screening for MDD to rule out the possibility that the depressive disorder is due to another primary cause, such as a different medical condition, substance/medication-induced depressive disorder, dysthymia, cyclothymia, bereavement, adjustment disorder with depressed mood, bipolar disorder, schizoaffective disorder, schizophrenia, anxiety disorders, or an eating disorder

(Bains & Abdijadid, 2023). The diagnostic criteria for a MDE in the DSM-5 are the following (American Psychiatric Association, 2022):

Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
    1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad, empty, hopeless) or observations made by others (eg, appears tearful).
    2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
    3. Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
    4. Insomnia or hypersomnia nearly every day.
    5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
    6. Fatigue or loss of energy nearly every day.
    7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by their subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the direct physiological effects of a substance or to another medical condition.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic or hypomanic episode.

The United States Preventive Services Task Force (USPSTF) recommends screening for MDD in adults aged 18 years and older (Siu et al., 2016). as well as in adolescents aged 12 to 18 years old (US Preventive Services Task Force et al., 2022). Common screening instruments for depression include the Patient Health Questionnaire (PHQ-9), the Geriatric Depression Scale, and the Edinburgh Postnatal Depression Scale (EPDS) in adults, older adults, and postpartum and pregnant women respectively (Siu et al., 2016). The 2-item Patient Health Questionnaire (PHQ-2) is composed of two questions from the PHQ-9 inquiring into depressive symptom severity as

well as anhedonia over the past two weeks, and is particularly useful due to the short duration of the questionnaire (Lam et al., 2024).

1.1.4 Current Treatments for MDD

The principles of clinical management of MDD as detailed by the Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines (Lam et al., 2024):

- Conduct a thorough biopsychosocial assessment, using clinical scales.
- Obtain collateral information whenever possible.
- Formulate a diagnosis and differential diagnosis.
- Establish a therapeutic alliance.
- Support education and self-management.
- Engage the patient as a partner to determine treatment goals.
- Construct a comprehensive management plan, including safety, together with the patient and his or her family (or other supports) if possible.
- Deliver evidence-based treatments.
- Monitor outcomes with measurement-based care.

The establishment of a comprehensive assessment and management plan with particular attention to safety is a fundamental component of quality care for MDD. CANMAT guidelines also highlight a 2-phase model for treating MDD; an acute treatment phase lasting 8 to 12 weeks and a maintenance treatment phase lasting 6 to 24 months or longer (Lam et al., 2024). The goal of the acute treatment phase is symptom remission and restoration of functioning to levels

comparable to before the patient was ill (Lam et al., 2024). During this phase, the clinician should aim to establish a therapeutic alliance, educate the patient and support self-management, select and deliver evidence-based treatment(s), and monitor the patient's progress (Lam et al., 2024). Symptom remission is an important clinical target, as partial or non-remitters are at significantly higher risk of relapse than patients who have successfully achieved symptom remission (Conradi et al., 2012; Pintor et al., 2003). The goal of the maintenance treatment phase is the prevention of recurrence, and a return to full functioning and quality of life for the patient (Lam et al., 2024). Following a successful acute treatment phase, clinicians should aim to rehabilitate, treat comorbidities, monitor for recurrence of depressive symptoms, and evaluate whether the patient requires longer term care and the duration of treatment, especially if the patients have risk factors for recurrent depressive episodes, such as a greater number of previous episodes, a family history of psychiatric illness, poor social support, and stressful life events (Lam et al., 2024). A recent meta-analysis by Kato et al. concluded that patients with MDD who continued on antidepressants after achieving symptom remission were less likely to relapse compared to patients who did not continue on antidepressants, and highlighted the importance of flexibly-dosed maintenance therapy for at least 6 months following symptom remission (Kato et al., 2021).

1.1.4.1 Lifestyle Interventions for MDD

Lifestyle factors such as sleep, diet, and substance consumption have been implicated in the risk of developing MDD as well as contributing to worsening symptoms (Lam et al., 2024). Accordingly, certain lifestyle modifications such as exercise and light therapy have demonstrated benefits for improving symptom severity in MDD both in isolation and in conjunction with

pharmacological and psychological treatments. First-line lifestyle interventions recommended by the CANMAT guidelines include supervised exercise at a low to moderate intensity for 30-40 minutes at a time at a frequency of 3 to 4 times a week for a minimum of 9 weeks for MDE with mild severity, and light therapy with 10,000 lux fluorescent white light for 30 minutes daily for seasonal-pattern MDE (Lam et al., 2024). Second-line lifestyle interventions include light therapy as a monotherapy for mild, non-seasonal MDE, and adjunctive exercise and light therapy for moderate, non-seasonal MDE (Lam et al., 2024).

1.1.4.2 Psychological Treatments for MDD

The CANMAT guidelines highlight cognitive behavioural therapy (CBT), interpersonal therapy (IPT), and behavioural activation (BA) as first-line treatments for MDD based on currently available evidence (Lam et al., 2024). At the time of writing this thesis, CBT is the most established first-line psychological treatment for MDD, both in the acute and maintenance treatment phases (Parikh et al., 2016). Recommended second-line treatments include cognitive behavioural analysis system of psychotherapy (CBSAP), mindfulness-based cognitive therapy (MBCT), problem-solving therapy (PST), short-term psychodynamic psychotherapy (STPP), and transdiagnostic psychological treatment of disorders (Lam et al., 2024). Recommended third-line treatments include acceptance and commitment therapy (ACT), long-term psychodynamic psychotherapy (PDT), metacognitive therapy (MCT), and motivational interviewing (MI) (Lam et al., 2024).

1.1.4.3 Pharmacological Treatments for MDD

Table 1 (Lam et al., 2024) summarizes the recommended pharmacological treatments for MDD according to the CANMAT guidelines, which categorizes 31 antidepressants into first, second, and third-line treatment. 17 of these antidepressants are considered first-line therapies based on available evidence from placebo-controlled randomized controlled trials (RCTs) supporting their efficacy and safety (Lam et al., 2024). A decision on which pharmacotherapy to start is made by the clinician after taking into consideration efficacy, the potential for adverse effects, the clinical presentation of the patient as well as the patient's personal preferences, and cost (Lam et al., 2024). The majority of first-line pharmacotherapies consist of selective-serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) which target monoaminergic receptors in the synaptic cleft that inhibit reuptake of target neurotransmitters (Racagni & Popoli, 2010). The mechanism of action of SSRIs is through selectively inhibiting the 5-hydroxytryptamine (5-HT) receptors responsible for reuptake of serotonin from the synaptic cleft into the presynaptic neuron (Racagni & Popoli, 2010). SNRIs work through the inhibition of both serotonin and norepinephrine reuptake via the inhibition of their respective transporters (Racagni & Popoli, 2010).

1.1.4.4 Selecting Treatments

The decision regarding the initial treatment for MDD should be made collaboratively between the clinician and patient, following a shared decision making (SDM) model and taking into account the patient's preferences (Lam et al., 2024). While SDM may not significantly improve intervention adherence or symptom severity (Lam et al., 2024), recent meta-analyses have established that SDM can increase patient satisfaction and engagement in the decision making

process (Aoki et al., 2022; Samalin et al., 2018), and establishes a strong therapeutic alliance that is conducive to facilitating psychoeducation and improving patient knowledge (Lam et al., 2024). Additionally, involving patients in the discussion allows for the acknowledgement and consideration of local realities unique to the patient, such as cost and access, when determining a treatment, and allows for the opportunity to present alternative options that align best with the patient's values and needs (Lam et al., 2024). A diagnosis of treatment-resistant unipolar depression (TRD) is given when a patient has failed an adequate course of two or more first-line therapies (Hidalgo-Mazzei et al., 2019; US Food and Drug Administration, 2018).

1.1.5 Bipolar Disorder

Bipolar depression, or bipolar disorder (BD) is characterized by episodes of mania or hypomania that alternate with depressive episodes, and is chronically occuring (Jain & Mitra, 2023). The presence of manic episodes, which are periods of one-week or longer where an individual experiences a change in behaviour that significantly impacts their social or occupational functioning (Dailey & Saadabadi, 2023). Common characteristics of mania include increased talkativeness, rapid speech, a reduced need for sleep, and racing thoughts (Dailey & Saadabadi, 2023). The same defining characteristics of mania are also true for hypomania, with the key distinguishing feature between the two conditions being that social and occupational functioning are not impaired during a hypomanic episode (Dailey & Saadabadi, 2023). The diagnostic criteria for a manic or hypomanic episode is summarized from the DSM-5-TR below (American Psychiatric Association, 2022):

Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).

B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:

    1. Inflated self-esteem or grandiosity.
    2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
    3. More talkative than usual or pressure to keep talking.
    4. Flight of ideas or subjective experience that thoughts are racing.
    5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
    6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).
    7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition.

Hypomanic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day.

B. During the period of mood disturbance and increased energy and activity, three (or more) of the following symptoms have persisted (four if the mood is only irritable), represent a noticeable change from usual behavior, and have been present to a significant degree:

1. Inflated self-esteem or grandiosity.
2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.
7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.

D. The disturbance in mood and the change in functioning are observable by others.

E. The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.

F. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition.

1.1.6 Clinical Diagnosis of Bipolar Disorder

A diagnosis of BD can be specified as type I or II, depending on the presence of manic or hypomanic episodes alternating with depression (American Psychiatric Association, 2022). The DSM-5 criteria for a diagnosis of bipolar I disorder (BD-I) is the presence of recurring mood episodes, including manic, hypomanic, and depressive episodes, as well as the presence of at least one manic episode. While MDEs are common in BD-I, they are not necessary for a diagnosis of BD-I (American Psychiatric Association, 2022). The DSM-5 criteria for a diagnosis of bipolar II disorder (BD-II) includes the presence of at least one hypomanic episode and at least one major depressive episode that are not better explained by another disorder, and the absence of any manic episodes in the patient's history (American Psychiatric Association, 2022). Additionally, the symptoms of depression or the resulting symptoms from the alternation between hypomanic and depressive episodes must cause clinically significant impairment in social or occupational functioning (American Psychiatric Association, 2022). A misdiagnosis of MDD is the most common for individuals with BD, as patients are more likely to seek treatment

for depressive symptoms while also not recalling or not interpreting periods of hypomania or mania as pathological (Yatham et al., 2021). Conversely, there are symptoms of comorbid disorders such as borderline personality disorder (BPD), substance use disorder (SUD), and attention deficit hyperactivity disorder (ADHD) that strongly overlap with symptoms of hypomania or mania, leading to a potential misdiagnosis of BD instead (Yatham et al., 2021).

1.1.7 Current Treatments for Bipolar Disorder

The cyclical nature of BD necessitates a long-term approach to treatment and disease management, and patient health education and pharmacotherapy are the foundational steps for treatment for all patients (Yatham et al., 2018). Similar to treatment guidelines for MDD, treatment approaches for BD patients follow a two-phase model, with an acute phase aiming to reduce symptoms and restore functioning and a maintenance phase to prevent recurrence and restore quality of life to the patient.

1.1.7.1 Psychosocial Interventions for Bipolar Disorder

Psychosocial interventions can be adjunctively administered to aid in treating acute depressive episodes, helping to prevent relapse of symptoms in BD, and to improve and restore quality of life to the patient and their family (Reinares et al., 2014). During treatment for a depressive episode, CBT and family-focused therapy (FFT) are recommended second-line adjunctive therapies, with interpersonal social-rhythm therapy (IPSRT) recommended as a third-line adjunctive therapy (Yatham et al., 2018). During the maintenance phase, psychoeducation is recommended as a first-line adjunctive psychological treatment for BD (Yatham et al., 2018).

CBT and FFT are recommended second-line treatments, while IPSRT and peer support are recommended third-line treatments (Yatham et al., 2018).

1.1.7.2 Pharmacological Interventions for BD

Both monotherapy and combination therapy are available options for pharmacological interventions for BD, with the decision being made depending on the speed of therapeutic effect required (i.e. if the patient requires a more rapid response to treatment), whether the patient had a previous history of partial response to monotherapy, a history of mania, and tolerability concerns with combination therapy (Yatham et al., 2018). Roughly 50% of patients with mania will respond to monotherapy, and experience a significant reduction in manic symptoms within 3-4 weeks (Ketter, 2008). Medications such as lithium, quetiapine, divalproex, asenapine, aripiprazole, paliperidone, risperidone, and cariprazine are recommended as first-line monotherapies for BD based not only on their capacity to treat acute manic and depressive episodes, but also their ability to prevent the recurrence of additional mood episodes (Yatham et al., 2018). Concurrently, preference is given to combination therapy as available evidence suggests that 20% more patients will respond to combination therapy compared to monotherapy (Ketter, 2008; Lin et al., 2006). Combination therapy is typically recommended as a combination of atypical antipsychotics such as quetiapine, aripiprazole, risperidone, or asenapine in conjunction with lithium or divalproex. First-line treatments for bipolar depression include quetiapine, lithium, lamotrigine, and lurasidone as monotherapies (Yatham et al., 2018). Second-line therapies include divalproex monotherapy or adjunctive antidepressant therapy with SSRIs in conjunction with atypical antipsychotics or lithium/divalproex (Yatham et al., 2018). Therapeutic response is expected within 1 to 2 weeks for both mania and depression with

aforementioned medications, and clinicians are advised to consider switching or adding therapies if no response is observed in that time frame (Yatham et al., 2018). A diagnosis of treatment-resistant bipolar depression (TRBD) is given when a patient has failed an adequate course of two or more first-line therapies (Hidalgo-Mazzei et al., 2019; US Food and Drug Administration, 2018).

1.2 Suicidality

Suicidality is defined by the American Psychological Association as " the risk of suicide, usually indicated by suicidal ideation or intent, especially as evident in the presence of a well-elaborated suicidal plan (American Psychological Association, n.d.)," and is a significant societal and healthcare problem (Bachmann, 2018), with more than 700,000 deaths globally attributed to suicide each year (*Suicide,* n.d.). Psychiatric disorders are strongly correlated with suicidality, with depression being one of the most relevant risk factors for completed suicide (Bachmann, 2018; Brådvik, 2018). In particular, MDD and hopelessness are some of the most common risk factors for suicide (Ribeiro et al., 2018). Intentional self-harm or suicide was ranked as the 13th leading cause of death in Canada in 2022 (Government Of Canada & Canada, 2023).

1.2.1 Stress-Diathesis Model of Suicidal Behaviour

The currently available clinical predictors of suicide are limited, and there is an absence of established biomarkers to aid clinicians in predicting and treating suicide (van Heeringen & Mann, 2014). Stress-diathesis models of suicide have been proposed, and in general describe suicide as the result of an interaction between exposure to stressors (e.g. financial problems, exacerbation of psychiatric disorders, emotional pain, etc.) and a constitutional vulnerability or

genetic disposition (diathesis) to suicidal behaviour (van Heeringen, 2012; van Heeringen & Mann, 2014). The investigation of biomarkers related to the diathesis may help clinicians in assessing suicide risk and tailoring treatment options for the prevention of suicide (van Heeringen & Mann, 2014).

Mann et al. (1999) put forward a clinical stress-diathesis model of suicidal behaviour based on findings from a large clinical study of patients admitted to a university psychiatry hospital. The investigators found that patients who had previously attempted suicide scored higher on assessments for subjective depression and suicidal ideation compared to patients who had not previously attempted suicide (Mann et al., 1999). Additionally, patients who had previously attempted suicide also demonstrated higher rates of aggression, impulsivity, and comorbid borderline personality disorder, which may result from contributing genetic components or early life experiences (e.g. history physical or sexual abuse) (Mann et al., 1999; van Heeringen, 2012). Consequently, Mann et al. (1999) proposed that the risk for suicidal acts is determined not only by the presence of a psychiatric illness but also by a disposition to aggression and impulsivity (Mann et al., 1999).

A cognitive stress-diathesis model of suicidal behaviour has also been proposed, suggesting that suicidal behaviour is the resulting response to life stressors in individuals who have dispositional vulnerability factors that make them more susceptible to acting in response to these life stressors (Wenzel & Beck, 2008). Wenzel and Beck (2008) have stratified these dispositional vulnerability factors into five categories: impulsivity and related constructs, problem solving deficits, an overgeneral memory style, a trait-like maladaptive cognitive style, and personality (Wenzel &

Beck, 2008). These variables are hypothesized to increase the likelihood that an individual may engage in suicidal behaviour by potentially creating life stress, exacerbating psychiatric conditions, or reducing adaptive cognitive processing (Wenzel & Beck, 2008). However, they are not regarded as risk factors as they are not established in empirical studies to precede suicidal behaviour (Wenzel & Beck, 2008).

There has been increasing evidence in support of a stress-diathesis model of suicidality, and further understanding of diatheses implicated in increased susceptibility for suicidal behaviour may aid in identifying potential therapeutic targets.

1.2.2 Suicidal ideation in MDD and BD

Suicidality is one of the nine symptoms of a MDE as defined by the DSM-5 (American Psychiatric Association, 2013). Individuals with MDD are at higher risk of suicidal ideation (Cai et al., 2021), with a lifetime odds ratio of 2.88 [95% confidence interval (CI) = 0.30–27.22, p = 0.36] compared to non-MDD controls (Cai et al., 2021). Treatment-resistant depression specifically has a greater association with suicidality than non-treatment resistant cases (McIntyre et al., 2023). In particular, MDD and symptoms of hopelessness are some of the most common risk factors for suicide (Ribeiro et al., 2018). Concurrently, suicide is one of the leading causes of death in patients with BD, accounting for 6-7% of all deaths in patients identified with BD (Schaffer et al., 2015; Webb et al., 2014). Approximately 43% of patients with BD report suicidal ideation in the past year, while 21% report having a plan and 16% report attempting suicide (Merikangas et al., 2011).

1.2.3 Assessment of Suicidal Risk

The CANMAT guidelines advise prioritizing assessing suicide risk and developing nad implementing a safety plan in both MDD and BD patients (Lam et al., 2024; Yatham et al., 2018). Several validated assessment tools for assessing suicide risk are available, including clinician-administered assessments such as the Columbia Suicide Severity Rating Scale (C-SSRS) and the Scale for Suicide Ideation (SSI), as well as self-administered assessments such as the Beck Scale for Suicide Ideation (BSI) and the Concise Health Risk Tracking Self-Report (CHRT-SR). The most commonly used scales by researchers and healthcare professionals are the C-SSRS and the BSI (Andreotti et al., 2020), with the FDA recommending the C-SSRS for use in clinical trial settings to prospectively assess for the occurrence of suicidal ideation and behaviour (Center for Drug Evaluation & Research, 2022). In particular, five levels of suicidal ideation and suicidal behaviour (summarized below) are identified as important to assess and capture in a clinical trial setting (Center for Drug Evaluation & Research, 2022).

Suicidal Ideation	**Suicidal Behaviour**
1. Passive 2. Active: Non-specific (no method, intent, or plan) 3. Active: Method, but no intent or plan 4. Active: Method and intent, but no plan 5. Active: Method, intent, and plan	1. Completed suicide 2. Suicide attempt 3. Interrupted attempt 4. Aborted attempt 5. Preparatory actions toward imminent suicidal behaviours

Additionally, it is also recommended to assess and capture self-injurious behaviour with no suicidal intent, as the distinction should be made from actions with suicidal intent to ensure that a suicide attempt is correctly identified (Center for Drug Evaluation & Research, 2022). While the C-SSRS is widely acknowledged and accepted as the "gold standard" for assessing suicidality, there remains no standardized measures used to assess individual characteristics of suicidal ideation (Reeves et al., 2022). It is also important to note that suicidal ideation is not a reliable measure for assessing risk of completed suicide, as suicidal ideation has limited sensitivity for predicting suicide attempts and death from suicide (McHugh et al., 2019).

1.3 Ketamine

1.3.1 Ketamine in medical use

Ketamine was first synthesized in 1962 by Calvin Stevens, a consultant and organic chemist aiming to develop an analog of phencyclidine (PCP) that maintained the anesthetic properties of PCP while minimizing the prolonged delirium that PCP would induce (Domino, 1980; Li & Vlisides, 2016). Ketamine is a structural analog of PCP and is far less potent, making it suitable for human trials, with the first trial conducted by Drs. Edward Domino and Guenter Corssen in 1964 (Li & Vlisides, 2016). Over the next few years, Drs. Domino and Corssen established the analgesic properties of ketamine that make it particularly suitable for surgical procedures. Ketamine was found to have a limited duration of effect, allowing it to be safely administered repeatedly, and it lacked severe side effects compared to PCP (Corssen & Domino, 1966; Domino et al., 1965). These promising results led to the approval of the first formulation of ketamine, Ketalar, by the FDA for human use (U.S. Food and Drug Administration, Center for Drug Evaluation and Research, 1970).

1.3.2 Formulations and metabolism of ketamine

Ketamine is an arylcycloalkylamine that exists in S(+) and R(-) isomers, and is typically prepared as a racemic mixture of the two (Li & Vlisides, 2016). Comparatively, the S(+) isomer has a greater binding affinity to the *N*-methyl-*D*-aspartate (NMDA) receptor and induces a much more potent anesthetic effect than the R(-) isomer (White et al., 1985). The converse has been shown to be true for the antidepressant effects of ketamine, with the R(-) isomer proving to be more potent (Zhang et al., 2014). Ketamine is able to be safely administered through several routes, including intravenous (IV), intramuscular (IM), intranasal (IN), oral, rectal, subcutaneous, and epidural routes (Li & Vlisides, 2016). The most ideal route of administration is IV, where ketamine is 100% bioavailable (Clements et al., 1982). Ketamine is highly lipid soluble and has relatively limited protein binding, allowing it to be rapidly taken up by the brain and redistributed, with a distribution half-life of 10-15 minutes (Domino et al., 1984; Wieber et al., 1975). After ketamine enters the body, it is metabolized by the liver into its metabolites, norketamine and dehydronorketamine (Clements et al., 1982), which is then renally excreted with an elimination half-life of two to three hours (Domino et al., 1984; Wieber et al., 1975).

1.3.3 Mechanisms of action of ketamine

Ketamine is a non-competitive NMDA receptor antagonist, and it is hypothesized that ketamine induces its antidepressant effects through several mechanisms (Zanos & Gould, 2018). Ketamine partially exerts its effects through the glutaminergic system (Moghaddam et al., 1997), in contrast to the monoaminergic targets (i.e. serotonin, dopamine, norepinephrine) of more traditional antidepressants such as SSRIs, SNRIs, and MAOIs, which likely contributes to

changes in synaptic plasticity and its subsequent antidepressant effects (Zanos & Gould, 2018). The disinhibition hypothesis proposes that ketamine disinhibits pyramidal neurons and enhances glutamatergic firing through selective inhibition of NMDA receptors expressed on GABAergic inhibitory interneurons (Moghaddam et al., 1997; Zanos & Gould, 2018). Glutamate released as a result subsequently binds to and activates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, resulting in an increased release of brain-derived neurotrophic factor (BDNF), activation of the tropomyosin receptor kinase B (TrkB) receptor, and the subsequent promotion of protein synthesis through the activation of the mechanistic target of rapamycin complex 1 (mTORC1) (Zanos & Gould, 2018). Another hypothesized mechanism of action for ketamine is through the inhibition of extrasynaptic NMDA receptors (Zanos & Gould, 2018). It is proposed that ketamine selectively blocks extrasynaptic GluN2B-containing NMDA receptors which disinhibits mTORC1 function, subsequently induces protein synthesis through mTOR signaling and promotes ketamine's antidepressant effects (Zanos & Gould, 2018).

1.3.4 Current evidence for ketamine for depression

Ketamine is a well established intervention for treatment-resistant unipolar and bipolar depression (Anand et al., 2023; McIntyre et al., 2021) with demonstrated rapid and robust antisuicidal effects (Auerbach et al., 2022; Witt et al., 2020; Xiong et al., 2020). Ketamine for use in depression is available in several formulations, including IV, IN, intramuscular, oral, sublingual, and intranasal formulations (McIntyre et al., 2021). As of writing this thesis, the majority of research on ketamine for depression is centered on IV and IN ketamine, with the IV formulation consisting of racemic ketamine while the IN formulation consists of just the S-enantiomer (esketamine) (McIntyre et al., 2021). A meta-analysis of 20 RCTs by Kryst et al.

determined that a single dose of IV ketamine produced its greatest effect in reducing depressive symptoms at 24 hours post-infusion (Standard Mean Difference (SMD) = -0.89, 95% CI: [-1.24, -.053], $p < 0.00001$) compared to controls (Kryst et al., 2020). In most cases, repeated doses of IV ketamine are required in order to maintain the therapeutic effect (Murrough et al., 2013), though the ideal frequency of repeated IV administration has not yet been established (McIntyre et al., 2021). The efficacy of IN esketamine as an augmentative treatment with conventional antidepressants has been investigated, with a meta-analysis of five randomized, double-blinded placebo-controlled clinical trials (n = 774) reporting a significant improvement in depressive symptomatology compared to placebo (SMD = 0.36, 95% CI: [0.24, 0.49], $p < 0.0001$), and pooled risk ratios for response and remission of 1.4 ($p < 0.0001$) and 1.45 ($p < 0.0001$) respectively (Papakostas et al., 2020). Ketamine-induced rapid and robust reductions in suicidality has also been observed and reported in clinical trials (Auerbach et al., 2022; Witt et al., 2020; Xiong et al., 2020). A systematic review conducted by Xiong et al. in 2020 evaluated the anti-suicidal effects of ketamine in MDD and BD patients after a single dose, and found the pooled effect size for anti-suicidal effects in nine RCTs was 1.035 (n = 6, 95% CI: 0.793, 1.277, $p < 0.001$) for IV ketamine (Xiong et al., 2020). IN and IV ketamine remain the most studied formulations of ketamine for TRD, and the rapid antidepressant effects of both formulations have been well established in randomized controlled trials (Kryst et al., 2020; McIntyre, Carvalho, et al., 2020; Papakostas et al., 2020; Wilkinson et al., 2018). While ketamine has demonstrated significant improvements in depressive symptomatology across different formulations, additional investigation is required into clinically significant parameters such as the dosing and frequency of administration required (McIntyre et al., 2021).

1.3.5 Antisuicidal effects of ketamine

Ketamine has demonstrated antisuicidal effects in clinical trial populations, with observed rapid reductions in suicidal ideation as soon as four hours post-infusion (Shen et al., 2024; Wilkinson et al., 2018; Witt et al., 2020). A systematic review and meta-analysis by Wilkinson et al. in 2018 evaluated the effect of a single ketamine infusion on suicidal ideation in comparison intervention studies (Wilkinson et al., 2018). Wilkinson et al. analyzed participant-level data for 298 patients who participated in the 10 clinical trials included in the analysis, and reported a rapid (i.e. within one day) ketamine-induced reduction in suicidal ideation as measured by both clinician-administered and self-report outcome measures that persisted up to one week (Wilkinson et al., 2018). A systematic review and meta-analysis by Witt et al. in 2020 assessed the short and long-term effectiveness of ketamine for suicidal ideation across 14 clinical trials that included 572 participants predominantly diagnosed with either unipolar or bipolar depression. (Witt et al., 2020). Ketamine was found to rapidly reduce suicidal ideation within four hours (SMD = -0.51, 95% CI: -1.00, -0.03), with similar ameliorative effects observed between 12 and 24 hours (SMD = -0.63, 95% CI: -0.99, -0.26) and 24 and 72 hours (SMD = -0.57, 95% CI: -0.99, -0.14), though it was noted that ketamine was no longer associated with significant antisuicidal effects beyond the 72 hour time point (Witt et al., 2020).

More recently, Shen et al. conducted a network meta-analysis encompassing 14 clinical trials and a total of 1380 participants and observed significant results in support of ketamine's antisuicidal properties (Shen et al., 2024). Shen et al. observed that ketamine was significantly more effective than placebo, esketamine, and midazolam at reducing suicidal ideation within the first day

following treatment, with a relative risk (RR) ratio of 10.01 (95% CI: 4.24 - 23.68) (Shen et al., 2024). Additionally, ketamine was more effective than placebo at three (RR = 2.89, 95% CI: 1.04 - 8.00) and 26 (RR = 4.29, 95% CI: 1.41 - 13.08) days post-treatment (Shen et al., 2024). There are several limitations to this study, most notably in the use of different continuous outcome measures across the included studies that were operationalized as a binary outcome for the purposes of comparison. However, the results of this analysis further establish the efficacy of ketamine in treating suicidal ideation under clinical trial settings.

Taken together, there is substantial evidence from clinical trials supporting the efficacy of ketamine for treating suicidal ideation, and the highly promising results of these meta-analyses of a single dose of ketamine provide a compelling basis for further investigation into the antisuicidal effects of ketamine. As clinical trial results often do not generalize into real-world settings, it is an important and logical next step to evaluate the effectiveness of ketamine in ameliorating suicidal ideation in a real-world setting. At present, there is a paucity of studies investigating the real-world effectiveness of ketamine under non-clinical trial settings, highlighting a need for further research into this topic.

Chapter 2: Rationale and Objectives

2.1 Study Rationale

As summarized in the earlier chapter, ketamine has been established as an effective antidepressant treatment for unipolar and bipolar depression, highlighting its potential for the treatment of comorbid symptomatology including suicidality. At the time of writing this thesis, only one study has been published evaluating the real-world effectiveness of repeated ketamine infusions for suicidality, highlighting a need for further investigation. If similar effects are observed in additional real-world patient populations, ketamine could be widely adopted as both an inpatient and outpatient treatment option.

2.2 Overview of Analyses

This thesis will present two analyses on the use of repeated ketamine infusions for suicidality in TRD and TRBD populations. The results of a retrospective chart review of real-world data from a community-based clinic will be presented. Additionally, the baseline results from two ongoing clinical trials evaluating IV ketamine for TRBD conducted at the Mood Disorders Psychopharmacology Unit (MDPU) at the University Health Network (UHN) will be presented. As both of these clinical trials are ongoing at the time of writing this thesis, an interim analysis was not conducted. The findings and results from these analyses will provide important insights into the potential clinical benefits of IV ketamine, specifically the anti-suicidal effects.

2.3 Study Objectives and Hypothesis

The primary objective of both analyses will be to determine in both a real-world and clinical trial population of TRD and TRBD the efficacy and effectiveness of IV ketamine for ameliorating suicidal ideation over a 14-day period. Based on the established effectiveness of ketamine for

suicidal ideation in MDD populations after a single dose, it is hypothesized that similar effects will be observed in both TRD and TRBD populations. Secondary objectives of both analyses will be to determine the mediational effect of overall depressive symptom severity on suicidal ideation.

Chapter 3: Methods

3.1 Braxia Health

3.1.1 Study description

The Canadian Rapid Treatment Centre of Excellence (CRTCE), now known as Braxia Health as of 2022, is an outpatient clinical and research facility located in Mississauga, Ontario, Canada that provides IV ketamine treatment for adults with TRD as part of MDD or BD. The CRTCE is the first Canadian clinic offering intranasal (IN) esketamine, racemic IV, and oral ketamine treatment to adults (age ≥ 18 years) with TRD and a primary diagnosis of MDD and BD. Patients with other primary diagnoses (i.e. post-traumatic stress disorder, obsessive compulsive disorder, etc) were considered on a case-by-case basis for potential investigational use of IV ketamine. This retrospective chart analysis is registered on ClinicalTrials.gov (NCT04209296).

3.1.2 Participants

The data presented in this analysis was obtained from patients referred to the CRTCE in Mississauga, Canada between May 03, 2021 and September 15, 2023. The eligibility criteria and treatment protocol for patients at CRTCE have previously been described (McIntyre, Rodrigues, et al., 2020). Briefly, patients referred to CRTCE were eligible for IV ketamine treatment if they had a primary diagnosis of MDD or BD, met the criteria for Stage 2 Resistance or higher as defined by Thase & Rush (i.e. insufficient response to two or more major antidepressant drug classes), had the ability to consent to IV ketamine which involves a full understanding of the risks, benefits, and alternatives to IV ketamine. Patients with suicidal ideation were not excluded from receiving treatment. Additionally, patients with dementing disorders, psychotic disorders, active substance use, alcohol use disorders, or who did not have a mood disorder as a primary diagnosis were excluded from receiving IV ketamine. Eligibility was confirmed by psychiatrists

and anesthesiologists, and informed consent was obtained prior to treatment. Participants were required to have a primary diagnosis of MDD or BD as defined by the DSM-5 and be currently experiencing a major depressive episode.

3.1.3 Assessments

Baseline demographic information was collected for each participant (Table 1). Depressive symptoms were assessed using the 16-Item Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR16). The QIDS-SR16 is a 16-item self-report questionnaire with a total score between 0 and 27 that converts the responses to the questionnaire into the nine symptom criteria domains of the DSM-V used to make a diagnosis of MDD (Rush et al., 2003; Weiss et al., 2023). The nine domains evaluated include sad mood, concentration, self-criticism, suicidal ideation, interest, energy/fatigue, sleep disturbance, decrease/increase in appetite/weight, and psychomotor agitation/retardation (Rush et al., 2003).

The clinician rated Columbia Suicide Severity Rating Scale (C-SSRS) is a Food and Drug Administration (FDA) designated instrument for evaluating suicidality (Center for Drug Evaluation & Research, 2022), and measures four constructs of suicidal ideation and behaviour across four subscales: severity of ideation, intensity of ideation, behaviour, and lethality (Posner et al., 2011). The current study measured severity of suicidal ideation based on self-report responses to yes or no responses to six questions regarding the past month or since the last visit (*Screener Recent Self-Report*, 2016). The self-report questions are summarized below:

C-SSRS Self-Report Questions
1. Have you wished you were dead or wished you could go to sleep and not wake up?

2. Have you actually had any thoughts of killing yourself?
3. Have you thought about how you might do this?
4. Have you had any intention of acting on these thoughts of killing yourself, as opposed to you have the thoughts but you would not act on them?
5. Have you started to work out, or actually worked out, the specific details of how to kill yourself and did you actually intend to carry out the details of your plan?
6. Have you ever done anything, started to do anything, or prepared to do anything to end your life?

The baseline/infusion 1 visit measured response to the 6-item C-SSRS with respect to the past month, and subsequent infusions investigated participant responses since the last visit.

3.1.4 Study Procedures

Participants received four infusions of ketamine hydrochloride diluted in 0.9% saline solution over a period of two weeks. Ketamine was administered intravenously over a 40-minute period under the supervision of a nurse and anesthesiologist. The treatment schedule was adjusted to accommodate individual patient availability, however participants typically received their second infusion three days after their first infusion (i.e., day 3), their third infusion four days thereafter (i.e., day 7), and their fourth infusion three days thereafter (i.e., day 10). All participants received a dose of 0.5 mg/kg during their first and second infusions. Patients who did not experience a clinically meaningful benefit (i.e. $\leq$ 20% reduction in the total QIDS-SR16 score) after the first two infusions but tolerated 0.5 mg/kg doses were eligible for a dose increase to 0.75mg/kg for the remaining two infusions. This flexible dosing intervention was employed as evidence

suggests that a dose increase may invoke an antidepressant response in individuals who did not respond to lower doses of ketamine (Cusin et al., 2017). The actual body weight for each participant was used to calculate their dose for the infusion. In the case of a participant's body mass index exceeding 35 kg/m^2, the Devine formulas were used to determine their dose, based on their ideal body weight: ideal body weight = 50 kg + [2.3 kg * (height in inches - 60 inches)] for males or 45.5 kg + [2.3 kg * (height in inches - 60 inches)] for females (Pai & Paloucek, 2000). All participants had their vital signs and oxygen saturation monitored for up to one hour post-infusion for safety.

3.2 KET-BD

3.2.1 Study description

KET-BD is a phase II, double-blinded, midazolam-controlled, two-week RCT evaluating the efficacy, safety and tolerability of four flexibly-dosed adjunctive ketamine infusions (0.5-0.75mg/kg infused over 40 minutes) for acute treatment of moderate to severe treatment-resistant bipolar disorder (TRBD) (type I & II). At the time of writing, this study is ongoing and being conducted at two sites: the Mood Disorder Psychopharmacology Unit (MDPU) located within the University Health Network (UHN) in Toronto, Ontario, Canada, and the Ontario Shores Centre for Mental Health Sciences (OS), located in Whitby, Ontario, Canada. This trial is registered on ClinicalTrials.gov with the National Clinical Trial (NCT) number NCT05004896.

3.2.2 Primary aim and hypothesis

The primary objective of this clinical trial is to evaluate the safety and efficacy of subanesthetic IV ketamine in patients with moderate to severe TRBD. Efficacy will be evaluated using the

Montgomery-Asberg Depression Rating Scale (MADRS). Response (defined as a MADRS decrease > 50%) and remission (defined as a MADRS score < 12) will be reported. It is hypothesized that IV ketamine will be associated with significant antidepressant effects in patients with TRBD from baseline to the primary week endpoint.

3.2.3 Secondary aim and hypotheses

There are multiple secondary objectives evaluated in this phase II clinical trial, including safety, tolerability, acceptability, the anti-suicidal effects of ketamine, and the impact of ketamine on quality-of-life improvements. Safety, tolerability and acceptability will be assessed through adverse event reporting and attrition, and there will be careful monitoring of treatment-emergent manic symptoms (i.e., manic-switch rate). It is hypothesized that IV ketamine and study participation will be generally well tolerated. The anti-suicidal effects of ketamine will be assessed through validated rating scales (e.g. C-SSRS), and it is hypothesized that IV ketamine will be associated with a significant reduction in suicidal ideation. Additionally, the impact of ketamine on quality of life (QoL) will be evaluated at baseline and endpoint. It is hypothesized that ketamine will be positively correlated with improvements in QoL and function. Finally, exploratory analyses will be conducted to evaluate clinical predictors of response.

3.2.4 Participants

A total of 100 participants will be recruited, with 50 participants randomized to the intervention (ketamine) arm and 50 participants randomized to the control (midazolam) arm. Patients were selected for participation if they were aged between 21 and 65, diagnosed with bipolar disorder

type I or II and currently experiencing a major depressive episode. Patients were eligible for participation based on the following criteria:

Inclusion Criteria
1. Provide written, voluntary informed consent prior to study enrollment 2. Male or female between the ages of 21 to 65, inclusive 3. Meets DSM-5 criteria for Bipolar I or II Disorder, currently experiencing a Major Depressive Episode without psychotic features 4. Patient must present with a moderate to severe depressive episode, as determined by a MADRS score greater than 21 5. Current depressive episode has inadequate response to two or more adequate first-line treatment trials (lithium, valproate, carbamazepine, lamotrigine, and/or any antipsychotic medication) for bipolar depression, as per the 2018 CANMAT Bipolar Disorder Guidelines 6. Patient must be receiving guideline-concordant pharmacotherapy without changes in the last month, including a therapeutic dose of a guideline-concordant mood stabilizer/antipsychotic.

Patients were ineligible for participation if they met one or more of the following criteria:

Exclusion Criteria
1. Currently exhibiting symptoms of mania, hypomania, or mixed state bipolar, as determined by a Young Mania Rating Scale (YMRS) score greater than 12

2. Current symptoms of psychosis or a substance use disorder within the past 3 months (history of psychotic features during a mood episode will not be excluded)
3. History of neurological disorders (including, but not limited to, uncontrolled seizure disorder, history of stroke within past 12 months, major head injuries, aneurysmal vascular disease [including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels], arteriovenous malformation, or intracerebral hemorrhage)
4. Lifetime history of a primary psychotic disorder (including, but not limited to, schizophrenia or schizoaffective disorder)
5. Lifetime history of ketamine use disorder
6. Presence of active suicidality, requiring involuntary inpatient treatment or recent suicide attempts within the past 3 months
7. Presence of a contraindication to ketamine or midazolam, including a drug allergy, uncontrolled hypertension (baseline systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg), low or labile blood pressure, myocardial infarction within past 12 months, cardiac arrhythmia, moderate to severe hepatic impairment (i.e., Child-Pugh score of B or C), moderate or severe renal impairment (glomerular filtration rate (GFR) < 45 milliliters/min), heart failure, or coronary artery disease
8. Pregnant or breastfeeding women or women who intend to get pregnant (patients who are sexually active must agree to use a highly effective contraceptive method)
9. Use of prohibited concomitant medications at specified time points, including other forms of ketamine or esketamine, benzodiazepines, stimulants, alcohol, and medical or recreational cannabis taken during the trial at a specific prohibited time

10. Use of ketamine in the 30 days leading up to the patient's entry in the trial
11. Use of monoamine oxidase inhibitors (MAOIs) at least two weeks prior to receiving study treatment.

From July 2022 to the time of writing this thesis, outpatients were referred to the MDPU at UHN or OS and assessed by a psychiatrist specializing in the management of mood disorders and bipolar disorder in particular. Outpatients that were interested in participating in the study were then contacted by research coordinators of the study for pre-screening via phone. If deemed eligible following pre-screening, the participant was invited to provide written informed consent before being enrolled in the study.

3.2.5 Assessments

The primary outcome measure of depressive symptomatology is measured by the Montgomery-Asberg Depression Rating Scale (MADRS). The MADRS is a clinician-rated scale consisting of 10 items, each scored from 0 (normal) to 6 (severe), for a total possible score of 60 (Montgomery & Asberg, 1979). Higher scores denote greater severity within the past two weeks (Montgomery & Asberg, 1979). The response criteria of $\geq 50\%$ reduction from baseline severity and remission criteria of < 10 have been validated and are commonly used (Hawley et al., 2002). The MADRS is administered by trained study personnel after they receive training to ensure that the assessment is being conducted consistently throughout the duration of the study. While several secondary outcomes are captured in KET-BD and its sister study KET-BD-SUSTAIN, the outcome measure of interest to this thesis is suicidality as measured by the clinician administered C-SSRS. While the self-report version is described earlier, the clinician-rated version is a semi-

structured interview designed to assess the severity and intensity of suicidal ideation, suicidal behavior, and non-suicidal self-injurious behavior over a specified time period. The measurement of suicidal ideation is based on 5 “yes” or “no” questions with accompanying descriptions arranged in order of increasing severity. If the patient answers “yes” to either questions 1 or 2, the intensity of ideation is assessed in 5 additional questions related to frequency, duration, controllability, deterrents, and reasons for the most severe suicidal ideation. Suicidal behavior is assessed by asking questions categorizing behaviors into actual, aborted, and interrupted attempts; preparatory behavior; and non-suicidal self-injurious behavior.

3.2.6 Study Procedures

The trial procedures for KET-BD cover a span of four weeks or 28 days, with the treatment period comprising the first two weeks and a follow-up and assessment period comprising the last two weeks. A baseline visit is conducted at day 0 after obtaining informed consent from the participant. The visit consists of bloodwork, mood, and cognitive assessments to screen for eligibility and to establish a baseline mood score. Additionally, a visit with a study psychiatrist is conducted to confirm eligibility. Once a participant is deemed eligible, they are randomly assigned to either the treatment or control group using the biased coin randomization method. The treatment group receives IV-ketamine starting at a dose of 0.5mg/kg, with an allowable dose increase up to 0.75mg/kg while the control group receives IV-midazolam at a dose of 0.02mg/kg with an allowable dose increase of up to 0.03mg/kg. The increases in dose for both groups will occur after the second infusion day, and will depend on response to treatment as determined by the MADRS and CGI, and at the discretion of study psychiatrists.

On the infusion day, pre-infusion assessments consisting of the MADRS, C-SSRS, and the MaRRRS-14 are conducted 1-hour before the infusion. Pre-infusion anthropometrics are also obtained, including heart rate, blood pressure, and body weight. Research coordinators ensure the participant has been fasting for at least 6 hours prior to the infusion, and that they have not consumed any liquids for at least 3 hours. Research coordinators will also ensure that the appropriate medications have been stopped by the participant since at least the previous night. Research coordinators are responsible for picking up the study medication dispensed by unblinded members of the pharmacy team at UHN in an opaque paper bag. The bag will contain the appropriate medication (either control or treatment) and a 100mL saline bag for the infusion. The participant is then brought to the infusion room, and situated comfortably in a stretcher. A delegated anesthesiologist or anesthesiologist assistant (AA) will be present to prepare the medication and administer the infusion. To ensure the blind is not broken, both the participant and the research coordinator are asked to be out of visual and hearing range of the AA during preparation of the medication, and an unblinded member of the study staff is present to ensure the correct dose is being prepared. The unblinded study staff are also responsible for ensuring any remaining medication is logged and properly disposed of. The AA subsequently prepares the IV line and ensures the appropriate vital sign monitors (electrocardiogram, oxygen sensor, respiration monitor, blood pressure cuff) are attached to the participant and recording at the appropriate time intervals. The medication is then administered intravenously over a period of 40-minutes, with vital signs recorded at 10-minute intervals. Participants are required to remain in the infusion room for an additional 1-hour post-infusion to monitor for any treatment-emergent adverse events and for the study staff to assess discharge criteria. During the post-infusion period, the research coordinator will administer post-infusion assessments monitoring

for dissociative, manic, and suicidal symptoms. If discharge criteria is met, the research coordinator will discharge the participant to a designated caregiver that will accompany them home.

Two follow-up visits are conducted virtually or over the phone after each infusion, occurring one and two-days post infusion. Study staff will administer mood questionnaires, and evaluate for and document any treatment-emergent adverse events. After two infusions, participants meet with a study psychiatrist to discuss their symptom progression and determine whether a dose increase is warranted or not. Participants are eligible for a dose increase if their MADRS scores do not decrease by more than 25% compared to baseline at day 7 of the study, and if they are tolerating the medication well. If eligible, the dose will be increased to 0.75mg/kg for ketamine and 0.03mg/kg for midazolam.

The primary and secondary endpoints of the study occur at day 14 and day 28 respectively. At the primary endpoint, mood and cognitive assessments are administered and compared to scores obtained at baseline to evaluate treatment response. The participant will also meet with the study psychiatrist to evaluate tolerability and safety. Five follow-up visits are conducted between the primary and secondary endpoints to continually monitor mood and adverse events. At the secondary endpoint, the same battery of mood and cognitive assessments are conducted to evaluate whether any treatment response or non-response experienced at the primary endpoint persisted following treatment cessation. Both participants and study staff will then be unblinded to the treatment administered. A more detailed summary of each visit day and the corresponding assessments is provided in Table 9.

3.3 KET-BD-SUSTAIN

3.3.1 Study description

KET-BD-SUSTAIN is a 12-week, single arm, open-label, two-site extension trial of KET-BD that will evaluate the effects of flexible dosed adjunctive ketamine infusions. This study is registered on ClinicalTrials.gov with the NCT number NCT05339074. At the time of writing, this study is being conducted at two sites: MDPU at UHN in Toronto, Ontario, Canada and OS in Whitby, Ontario, Canada. Patients will be recruited exclusively from the KET-BD trial, and are eligible to participate regardless of whether they were in the treatment (ketamine) arm or the control (midazolam) arm. Over the 12-week study, participants will be offered a maximum of 6 booster infusions.

3.3.2 Primary aim and hypothesis

The primary aim of KET-BD-SUSTAIN is to evaluate the effect of flexibly dosed adjunctive IV ketamine in maintaining antidepressant effects for patients who responded or remitted to ketamine following an acute course of four infusions. The primary outcome is the change in MADRS scores over the 12-week study, and it is hypothesized that repeated, flexibly dosed infusions of ketamine will maintain antidepressant effects over the 12-week period, with minimal change to MADRS scores over time.

3.3.3 Secondary aim and hypotheses

The secondary aims and hypotheses of KET-BD-SUSTAIN consist primarily of safety, tolerability, and acceptability of ketamine as a treatment for TRBD.

3.3.4 Participants

Patients diagnosed with BD-I or BD-II who had previously participated in the parent RCT (KET-BD) will be selected for inclusion in this trial. Only patients aged 21-65 will be considered for participation in this trial. A total of 60 participants will be recruited from the KET-BD study population. Patients were eligible for participation if they met the following inclusion criteria:

Inclusion Criteria

1. Provide written, voluntary informed consent prior to study enrollment. Substitute decision-makers will not be allowed to consent to study on a potential patient's behalf.
2. Male or female between the age of 21 to 65, inclusive.
3. Meets DSM-5 criteria for Bipolar I or II Disorder, currently experiencing a Major Depressive Episode without psychotic features. Diagnosis confirmed by study psychiatrist at the start of the parent KET-BD randomized controlled trial (RCT).
4. Patient in the KET-BD RCT
    a. Patients in the ketamine arm of the KET-BD RCT must have experienced an antidepressant response (i.e. change in MADRS score ≥ 50% at day 14 compared to baseline or Clinical Global Impression-Improvement (CGI-I) = 2 'much improved' or 1 'very much improved') or experienced clinical remission of symptoms (i.e., MADRS score < 12 on day 14)
    b. Patients in the midazolam arm of the KET-BD RCT must present as moderately to severely depressed (MADRS >21) on days 14 and 28 of the parent RCT and must be responders or remitters following four flexibly dosed infusions over 2 weeks.

5. Current depressive episode has inadequate response to two or more adequate first-line treatment trials for bipolar depression, as per the 2018 CANMAT Bipolar Disorder Guidelines. First-line treatment trials include the use of lithium, valproate, carbamazepine, lamotrigine and/or any antipsychotic medication. Adequate medications confirmed at the start of the parent KET-BD RCT.
6. Patient must be receiving guideline-concordant pharmacotherapy without changes in the last month, including a therapeutic dose of a mood stabilizer.

Patients were ineligible for participation if they met the following exclusion criteria:

Exclusion Criteria

1. Currently exhibiting symptoms of mania, hypomania, or mixed state bipolar, as determined by the Young Mania Rating Scale (YMRS) score greater than 12.
2. Current symptoms of psychosis or a substance use disorder within the past 3 months. History of psychotic features during a mood episode will not be excluded.
3. History of neurological disorders (including, but not limited to, uncontrolled seizure disorder, history of stroke within past 12 months, major head injuries, aneurysmal vascular disease [including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels], arteriovenous malformation, or intracerebral hemorrhage)
4. Lifetime history of a primary psychotic disorder (including, but not limited to, schizophrenia or schizoaffective disorder)
5. Lifetime history of ketamine use disorder
6. Presence of active suicidality, requiring involuntary inpatient treatment or recent

suicide attempts within the past 3 months.

7. Presence of a contraindication to ketamine, including a drug allergy, uncontrolled hypertension (baseline systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg), low or labile blood pressure, myocardial infarction within past 12 months, cardiac arrhythmia, moderate to severe hepatic impairment (i.e., Child-Pugh score of B or C), moderate or severe renal impairment (glomerular filtration rate (GFR) < 45 milliliters/min), heart failure, or coronary artery disease
8. Pregnant or breastfeeding women or women who intend to get pregnant. Patients who are sexually active must agree to use a highly effective contraceptive method (as outlined in section 5.9).
9. Use of prohibited concomitant medications, including other forms of ketamine or esketamine, benzodiazepines, monoamine oxidase inhibitors, stimulants, medical or recreational cannabis of any form.
10. Patients in the ketamine-arm of the parent RCT, that did not reasonably tolerate 4 infusions of flexibly-dosed ketamine, as determined by the investigator and/or patient.

An important criteria for inclusion is that participants in the ketamine arm must have shown response or remission at the primary endpoint of KET-BD (Day 14) while participants in the midazolam arm must not have shown response or remission (i.e. remained moderately to severely depressed as measured by the MADRS). Additionally, participants in the ketamine arm must have tolerated ketamine well as determined by the study psychiatrist.

3.3.5 Study Procedures

The procedures for KET-BD-SUSTAIN will differ depending on which arm (ketamine, midazolam) of KET-BD the participant was a part of. Broadly, if the participant was in the ketamine arm of KET-BD and responded or remitted, they will begin KET-BD-SUSTAIN in the maintenance phase, and will be administered a maintenance ketamine infusion within one week of day 28 of KET-BD. Maintenance ketamine infusions will begin at a frequency of one infusion every two weeks, and can be reduced to once every four weeks. Ketamine infusions are also flexibly dosed up to a maximum of 1.0mg/kg, and participants will be offered a maximum of 6 booster infusions over the 12-week period.

The infusion day protocol is identical to the infusion protocol of KET-BD, with the only difference being that a blinded member of the research staff is no longer needed to facilitate disposal of the medication as this is an open-label study. Follow-up assessments (mood, adverse events) are also identical to KET-BD, and will be conducted on a weekly basis. The frequency and dose of the infusion may be adjusted depending on the MADRS score or at the discretion of the study psychiatrist. If MADRS score does not increase by more than two points between infusions, the frequency will be reduced to once every three weeks instead of two. If there is no evidence of relapse between boosters for two infusions in a row, the frequency will be further reduced to every four weeks. If MADRS score increases by more than two points between booster infusions, the frequency will be maintained or increased to a maximum of once every two weeks. If MADRS scores continue to increase (i.e. relapse is observed), the dose of ketamine will be increased up to a maximum of 1.0mg/kg.

If the participant was in the midazolam arm and did not respond or remit, they will begin with the an acute course of ketamine over two weeks, following the same trial procedures as KET-BD. If response or remission is observed in the two days following the last acute infusion, the participant will remain eligible for booster infusions and will follow the same procedures outlined above.

3.4 Statistical Analysis

3.4.1 Braxia Health

The primary clinical outcome was baseline to endpoint SI as measured by mean change in the C-SSRS. Secondary outcomes were depressive symptom severity as measured by the QIDS-SR16. Only participants that receieved four doses of IV ketamine were included in the analysis. Data was collected and stored on the Research Electronic Data Capture (REDCap) and analyzed using Python (v3.9.13) and Statistical Product and Service Solutions (SPSS v28.0.1.1 (14)). Generalized estimating equations (GEE) with a Poisson distribution and logarithmic link function model and an autoregressive covariance structure were used to assess mean change in suicidal ideation outcomes while controlling for age, sex, and baseline depression severity. These parameters were chosen due to account for the statistical requirements of assessing the outcome measures over a period of time. Additionally, the mediator effect of overall depressive symptom severity on suicidal ideation was evaluted (i.e. QIDS-SR16). A simple mediation analysis using ordinary least squares path analyses was conducted to evaluate whether ketamine exerts a beneficial effect on suicidal ideation independent of its effect on overall depressive symptom severity. A p-value of 0.05 was used to delineate statistical significance. The mediation analysis was conducted using the PROCESS macro for SPSS (Hayes, 2021).

3.4.2 KET-BD and SUSTAIN

As both studies are ongoing at the time of writing this thesis, an interim analysis was not conducted. An overview of the trial will be presented, including a Consolidated Standards of Reporting Trials (CONSORT) diagram for both KET-BD and KET-BD-SUSTAIN and baseline demographic data.

Chapter 4: Results

4.1 Braxia Health

4.1.1 Baseline demographics

Suicidal ideation data was available for 96 patients with baseline SI as defined by a C-SSRS score of 2 or greater. All patients included in this analysis received IV ketamine at the CRTCE. Baseline clinical and demographic characteristics are summarized in Table 1.

4.1.2 Mean change in CSSRS Score

The most significant decrease in estimated mean C-SSRS scores occurred from infusion 1 to infusion 2 (Figure 1). Estimated mean C-SSRS scores were 3.320 (95% CI: 3.098, 3.558) , 1.793 (95% CI: 1.508, 2.133), 1.454 (95% CI: 1.187, 1.781), and 1.452 (95% CI: 1.185, 1.779) at infusions one, two, three, and four respectively (Table 2). Estimated mean C-SSRS scores after controlling for age, sex, and change in depressive symptomatology from baseline was 2.628 (95% CI: 2.384, 2.896), 1.650 (95% CI: 1.397, 1.949), 1.535 (95% CI: 1.284, 1.834), and 1.551 (95% CI: 1.266, 1.899) from infusions one to four respectively (Table 3). Estimated mean scores after controlling for age, sex, and depressive symptom severity was 2.770 (95% CI: 2.505, 3.064), 1.681 (95% CI: 1.431, 1.976), 1.512 (95% CI: 1.264, 1.810), and 1.531 (95% CI: 1.274, 1.839) (Table 4). The mean C-SSRS score was significantly lower at each infusion compared to baseline. The pairwise differences between each infusion is reported in Table 5. The mean C-SSRS score differences at infusions two, three, and four were significant ($P < 0.001$) compared to baseline, with the greatest difference observed at infusion three compared to baseline with a mean difference of -1.093 (95% CI: -1.384, -0.802), which coincides with the time point of the optional dose increase. The mean differences between consecutive infusions (i.e. between infusion two and three, infusion three and four) were not significant.

4.1.3 Depression severity mediates IV ketamine induced reduction in SI

The direct effect of IV ketamine infusions on SI was significant ($\beta = -0.4685$ ($p < 0.0001$), Figure 2), and the indirect effect of IV ketamine infusions on SI as moderated by depressive symptom severity was significant ($\beta = -0.1830$ (SE = 0.027), Figure 2). The direct effect of IV ketamine has a greater magnitude on the reduction of SI compared to the indirect effect as mediated by depressive symptom severity, suggesting that the anti-suicidal effects of IV ketamine may act partially independently of its anti-depressive effects.

4.2 KET-BD and KET-BD SUSTAIN

A summary of preliminary baseline demographic information is presented in Table 11.

Chapter 5: Discussion

5.1 IV ketamine is associated with rapid reductions in suicidality after a single dose

Mean baseline C-SSRS scores in this study were greater than 2, indicating a high level of suicidal ideation with a plan or intent to act. Mean C-SSRS scores were observed to fall below 2 following the first ketamine infusion, indicating a reduction in suicidal ideation severity from active to passive suicidality on a group level. Active suicidality reflects a present desire by an individual to end one's life with the expectation that their attempt could produce a fatal outcome (Harmer et al., 2024), whereas passive suicidality refers to a general wish to die without a specific plan or an intent to take one's own life (Harmer et al., 2024). Active and passive suicidality are better represented as distinct but related constructs that both contribute to increased suicide risk, with co-occurence potentially imparting a synergistic effect resulting in the greatest risk of suicide (Wastler et al., 2023). The reduction of mean C-SSRS scores to below two are indicative of a reduction of active suicidal ideation, and subsequently a significant reduction in suicide risk. This reduction was maintained throughout the entire study period, with mean C-SSRS scores remaining below 2 at each infusion. The mean difference from baseline was also significant at each infusion, though the mean difference between consecutive infusions was not significant. These results indicate that IV ketamine produces rapid and robust anti-suicidal effect following a single (likely the first) infusion, and that repeated infusions may contribute to maintaining the observed reduction in suicidality for a prolonged period of time. A possible floor effect could explain this observation, implying there may be more room for improvement at higher levels of SI. The results of this study support the efficacy of ketamine for acute suicidal ideation (Domany et al., 2020; Gaither et al., 2022). Given the current treatment protocol was over a two-week period, more investigation into the prolonged anti-suicidal effects of ketamine is warranted.

5.2 Anti-suicidal effects of ketamine act partially independently of anti-depressant effects

A mediational analysis of the data demonstrated that the effect of ketamine on reducing SI severity is partially mediated by a reduction in depressive symptomatology. These outcomes are in line with previous studies that suggest ketamine exerts a specific effect on suicidal ideation that depends only partially on changes in depressive symptoms (Abbar et al., 2022; Wilkinson et al., 2018; Xiong et al., 2020). It has been proposed that the anti-suicidal effects of ketamine could be mediated by an analgesic effect on psychological pain (Abbar et al., 2022). Psychological pain is defined as "an extreme and aversive emotionally based feeling, experienced as a lasting, unsustainable, and unpleasant condition resulting from negative appraisal or deficiency of the self" (Meerwijk & Weiss, 2014), and in recent studies has been implicated as a necessary but insufficient condition for suicidal ideation in depression (Jollant et al., 2020). Further research is required to elucidate the exact mechanism that ketamine acts through to induce its anti-suicidal effects, and to determine the degree to which the anti-depressant effects of ketamine contribute to its anti-suicidal properties. Moreover, mood-independent anti-suicidality effects open the door for further exploration of ketamine in non-mood disorders, such as personality disorders that may present with suicidality in the absence of depressive symptoms.

5.3 Limitations

Limitations of this study are that we did not enroll participants with a primary aim of exploring the association of IV ketamine with the variables explored herein. As ketamine was administered open-label, we cannot be certain of the extent to which the anti-suicidal effects observed can be explained by ketamine (versus placebo effects and expectancy bias). Moreover, the C-SSRS scores used in the analysis were scores obtained from the self-report version of the scale. It

would have been preferable to have scores from the clinician-rated C-SSRS to ensure inter-rater reliability and consistency in scoring, however, the self-report version was being used clinically due to greater convenience. Additionally, the windows of observation were different (i.e. the baseline measure of the C-SSRS considered suicidality in the past month [30-days] and the follow-up visits considered suicidality since the last visit [~3 days]). However, the observed sustained reduction in suicidality at all three follow-up timepoints support the robust anti-suicidal effects of ketamine. Long-term data was not available in this retrospective chart analysis due to variability in scheduling patients for maintenance infusions. Finally, while the results of this study are indicative of a reduction in suicidal ideation, care must be taken to not interpret it as a reduction in risk of completed suicide given the limited sensitivity of suicidal ideation for predicting suicide attempts and death from suicide (McHugh et al., 2019).

Tables

Line of Treatment	Antidepressant	Daily dose	Mechanism
First Line	Citalopram	20–40 mg	SSRI
	Escitalopram	10–20 mg	SSRI
	Fluoxetine	20–60 mg	SSRI
	Fluvoxamine	100–300 mg	SSRI
	Paroxetine	20–50 mg	SSRI
	Sertraline	50–200 mg	SSRI
	Desvenlafaxine	50–100 mg	SNRI
	Duloxetine	60–120 mg	SNRI
	Levomilnacipran*	40–120 mg	SNRI
	Venlafaxine-XR	75–225 mg	SNRI
	Bupropion	150–450 mg2	NDRI
	Mirtazapine	30–60 mg	α2 antagonist; 5-HT2 antagonist
	Vilazodone*	20–40 mg	SSRI; 5-HT1A agonist
	Vortioxetine	10–20 mg	SSRI; 5-HT1A, 5-HT1B agonist; 5-HT1D, 5-HT3A, 5-HT7 antagonist
	Agomelatine #	25–50 mg	MT1, MT2 agonist; 5-HT2 antagonist
	Mianserin #	30–90 mg	α2 antagonist; 5-HT2 antagonist
	Milnacipran #	50–200 mg	SNRI
Second line	Amitriptyline	75–300 mg	TCA

	Clomipramine	150–300 mg	TCA
	Desipramine	100–300 mg	TCA
	Doxepin	75–300 mg	TCA
	Imipramine	75–300 mg	TCA
	Nortriptyline	75–150 mg	TCA
	Protriptyline	30–60 mg	TCA
	Trimipramine	75–300 mg	TCA
	Moclobemide	150–450 mg3	RIMA
	Trazodone	150–400 mg	SRI; 5-HT2 antagonist
	Quetiapine	150–300 mg	DA, 5-HT, α1 & α2 antagonist; NRI
	Dextromethorphan-bupropion* #	45mg/105mg-90mg/210mg	NMDA antagonist; NDRI, sigma-1 agonist
	Nefazodone #	300–600 mg	SRI, 5-HT2 antagonist
	Selegiline transdermal #	6–12 mg	MAO-B inhibitor
Third line	Phenelzine	45–90 mg	MAO inhibitor
	Tranylcypromine	30–60 mg	MAO inhibitor
	Reboxetine #	8–12 mg	NRI

Table 1. Summary of CANMAT guideline-recommended antidepressants for MDD based on line of treatment.

Participant Characteristic	**Participants with baseline SI (CSSRS >=2)**
n	96
Age, mean years (SD)	41.196 (14.817)
Female	53
Male	43
Primary Diagnosis	
MDD	75
BD	12

PTSD	1
OCD	2
Other	3
Missing data	3
Total (n)	96
Baseline Clinical Measures	
Mean C-SSRS (SD)	3.358 (1.196)
Mean QIDS-SR16 (SD)	19.068 (3.768)

Table 2. Summary of participants' baseline characteristics

Infusion	Mean	Std. Error	95% Wald Confidence Interval	
			Lower	Upper
1	3.320	0.1171	3.098	3.558
2	1.793	0.1588	1.508	2.133
3	1.454	0.1505	1.187	1.781
4	1.452	0.1507	1.185	1.779
Covariates appearing in the model are fixed at the following values: Age =41.2820000969				

Table 3. Mean pre-infusion C-SSRS scores at each infusion controlling for age and sex.

Infusion	Mean	Std. Error	95% Wald Confidence Interval	
			Lower	Upper
1	2.628	0.1305	2.384	2.896
2	1.650	0.1402	1.397	1.949
3	1.535	0.1394	1.284	1.834
4	1.551	0.1602	1.266	1.899

Covariates appearing in the model are fixed at the following values: Age = 41.3339365778; QIDS-SR16 change from baseline = -2.307

Table 4. Mean pre-infusion C-SSRS scores at each infusion controlling for age, sex, and change in QIDS-SR16 from baseline.

			95% Wald Confidence Interval	
Infusion	Mean	Std. Error	Lower	Upper
1	2.770	0.1424	2.505	3.064
2	1.681	0.1385	1.431	1.976
3	1.512	0.1386	1.264	1.810
4	1.531	0.1432	1.274	1.839
Covariates appearing in the model are fixed at the following values: Age = 41.3339365778; QIDS-SR16 = 16.864				

Table 5. Mean pre-infusion C-SSRS scores at each infusion controlling for age, sex, and QIDS-SR16 score.

						95% Wald Confidence Interval for Difference	
(I) Infusion	(J) Infusion	Mean Difference (J-I)	Std. Error	df	Sig.	Lower	Upper
1	2	-.978[a]	0.1336	1	< 0.001	-1.240	-0.716
	3	-1.093[a]	0.1486	1	< 0.001	-1.384	-0.802
	4	-1.077[a]	0.1826	1	< 0.001	-1.435	-0.719

2	3	-0.115	0.1325	1	0.385	-0.375	0.145
3	4	0.016	0.1372	1	0.909	-0.253	0.285

Table 6. Mean C-SSRS score differences from infusion 1 at each time point and between each infusion accounting for the change in QIDS-SR16 from baseline

(I) Infusion	(J) Infusion	Mean Difference (J-I)	Std. Error	df	Sig.	95% Wald Confidence Interval for Difference	
						Lower	Upper
1	2	-1.089[a]	0.1357	1	< 0.001	-1.355	-0.823
	3	-1.258[a]	0.1525	1	< 0.001	-1.557	-0.959
	4	-1.240[a]	0.1753	1	< 0.001	-1.583	-0.896
2	3	-0.169	0.1305	1	0.196	-0.425	0.087
3	4	0.018	0.1325	1	0.891	-0.242	0.278

Table 7. Mean change in C-SSRS score from infusion 1 at each infusion and between each infusion accounting for the QIDS-SR16 score.

Assessment		**DAY**																	
		Screen/Baseline	1	2	3	5	6	7	9	10	11	12	13	14	16	19	21	24	28
Baseline																			
	Informed Consent	**X**																	
	Assess inclusion/ exclusion criteria	**X**																	
	Demographics	**X**																	
	Anthropometrics	**X**	**X**			**X**			**X**			**X**							
	Medication History	**X**																	
	Blood pressure and Heart Rate	**X**																	
Psychiatric History																			
	MINI	**X**																	
Patient Reported Outcomes																			
	MADRS	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
	YMRS	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
	C-SSRS	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
	CADSS	**X**	**X**			**X**			**X**			**X**							
	BPRS		**X**			**X**			**X**			**X**		**X**					
	MARRRS-14	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
	MEQ		**X**									**X**							
	UCLA	**X**												**X**					**X**
	ESAS-r	**X**						**X**						**X**					**X**
	PCL-5	**X**												**X**					**X**
	Drug Liking Scale		**X**			**X**			**X**			**X**							
	PSQI		**X**											**X**					**X**
	BSL-23	**X**												**X**					**X**
	MSI-BPD	**X**																	
	CTQ	**X**																	
	QoL.BD	**X**												**X**					**X**
	Blinding Assessment		**X**																
	Mood and cognition battery	**X**						**X**						**X**					
Blood Work		**X**												**X**					
Actigraphy Given to Patient		**X**																	
Actigraphy Taken back from Patient														**X**					
Body Weight			**X**			**X**			**X**			**X**							
IV Ketamine Administration			**X**			**X**			**X**			**X**							
	Pre-ketamine Administration		**X**			**X**			**X**			**X**							

Vital Signs (i.e. BP, HR, RR, SPO_2, Consciousness)	During Ketamine Administration	10 mins.		**X**			**X**			**X**			**X**								
		20 mins.		**X**			**X**			**X**			**X**								
		30 mins.		**X**			**X**			**X**			**X**								
		40 mins.		**X**			**X**			**X**			**X**								
	Post-Ketamine Administration	15 mins.		**X**			**X**			**X**			**X**								
		30 mins.		**X**			**X**			**X**			**X**								
		45 mins.		**X**			**X**			**X**			**X**								
		60 mins.		**X**			**X**			**X**			**X**								
Adverse Events				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
End of Study Questionnaire																					**X**

Table 8. Summary of assessments for KET-BD.

Midazolam Arm		Week/Visit																
		Screen/ Baseline (Week 0)+	Unblinding from Ket-BD trial ++	**Acute Infusion 1**	Follow-up 1/2	**Acute Infusion 2**	Follow-up 1/2	**Acute Infusion 3**	Follow-up 1/2	**Acute Infusion 4**	Follow-up 1/2	**Booster 1**	Weekly Follow-up	**Booster 2-6**	Weekly Follow-up	**Week 4**	**Week 8**	**Week 12**
Assessments																		
Baseline	Sign Informed Consent Form	X																
	Assess inclusion/ exclusion criteria	X																
	Demographics	X																
	Anthropometrics	X		X		X		X		X		X		X		X	X	X
	Medication History	X																
	Blood pressure and Heart Rate	X																
Psychiatric History	MINI	X																
	Continued Consent			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinician Rated Scales	MADRS	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	YMRS	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	C-SSRS	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	CADSS	X		X		X		X		X		X		X		X*	X*	X*
	BPRS			X		X		X		X		X		X		X*	X*	X*
Self-Rated Scales	MARRRS-14	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	UCLA	X														X	X	X
	ESAS-r	X														X	X	X
	PCL-5	X														X	X	X
	PSQI	X														X	X	X
	BSL-23	X														X	X	X
	MSI-BPD	X														X	X	X
	CTQ	X														X	X	X
	QoL.BD	X														X	X	X
	Mood and cognition battery	X														X	X	X
Blood Work		X														X	X	X
Body Weight		X		X		X		X		X		X		X				
IV Ketamine Administration				X		X		X		X		X		X		X*	X*	X*
Vital Signs (i.e. BP, HR, RR, SPO2)	During Ketamine Administration	Every 10 min. x40 min		X		X		X		X		X		X		X*	X*	X*
	Post-ketamine Administration	Every 15 min x1hr		X		X		X		X		X		X		X*	X*	X*
Adverse Events				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
End of Study Questionnaire																		X

Table 9. Summary of assessments for KET-BD-SUSTAIN for participants in the midazolam arm.

		Week/Visit								
KET-BD		2	4 (Unblinding)	--	--	--	--	--	--	--
Ketamine Arm		Screen/ Baseline (Week 0)	--	**Booster 1**	Follow-up (Weekly until next booster)	**Booster 2-6**	Follow-up (Weekly until next booster)	**Week 4**	**Week 8**	**Week 12**
Assessments										
Baseline	Sign Informed Consent Form	X								
	Assess inclusion/ exclusion criteria	X								
	Demographics	X								
	Anthropometrics	X		X		X		X	X	X
	Medication History	X								
	Blood pressure and Heart Rate	X								
Psychiatric History	MINI	X								
	Continued Consent			X	X	X	X	X	X	X
Clinician Rated Scales	MADRS	X		X	X	X	X	X	X	X
	YMRS	X		X	X	X	X	X	X	X
	C-SSRS	X		X	X	X	X	X	X	X
	CADSS	X		X		X		X*	X*	X*
	BPRS			X		X		X*	X*	X*
Self-Rated Scales	MARRRS-14	X		X	X	X	X	X	X	X
	UCLA	X						X	X	X
	ESAS-r	X						X	X	X
	PCL-5	X						X	X	X
	PSQI	X						X	X	X
	BSL-23	X						X	X	X
	MSI-BPD	X						X	X	X
	CTQ	X						X	X	X
	QoL.BD	X						X	X	X
	Mood and cognition Battery	X						X	X	X
Blood Work		X						X	X	X
Body Weight		X		X		X				
IV Ketamine Administration				X		X		X*	X*	X*
Vital Signs (i.e. BP, HR, RR, SPO2)	During Ketamine Administration	Every 10 min. x40 min		X		X		X*	X*	X*
	Post-ketamine Administration	Every 15 min x1hr		X		X		X*	X*	X*
Adverse Events				X	X	X	X	X	X	X
End of Study Questionnaire										X

Table 10. Summary of assessments for KET-BD-SUSTAIN for participants in the ketamine arm.

	Total	Midazolam	Ketamine
n	29	15	13
Males	15	7	7
% Female	48.3	46.7	53.9
Age	43.04 (9.79)	41.13 (10.80)	44.31 (8.31)
Caucasian	23	11	11
Primary diagnosis			
BD-I	11	6	4
BD-II	18	9	9
Mean Baseline MADRS (SD)	32.93 (6.11)	31.67 (6.99)	33.92 (4.91)
Mean Baseline C-SSRS (SD)	2.86 (1.92)	2.67 (2.02)	3.31 (1.70)

Table 11. Preliminary baseline demographic data for KET-BD.

Figures

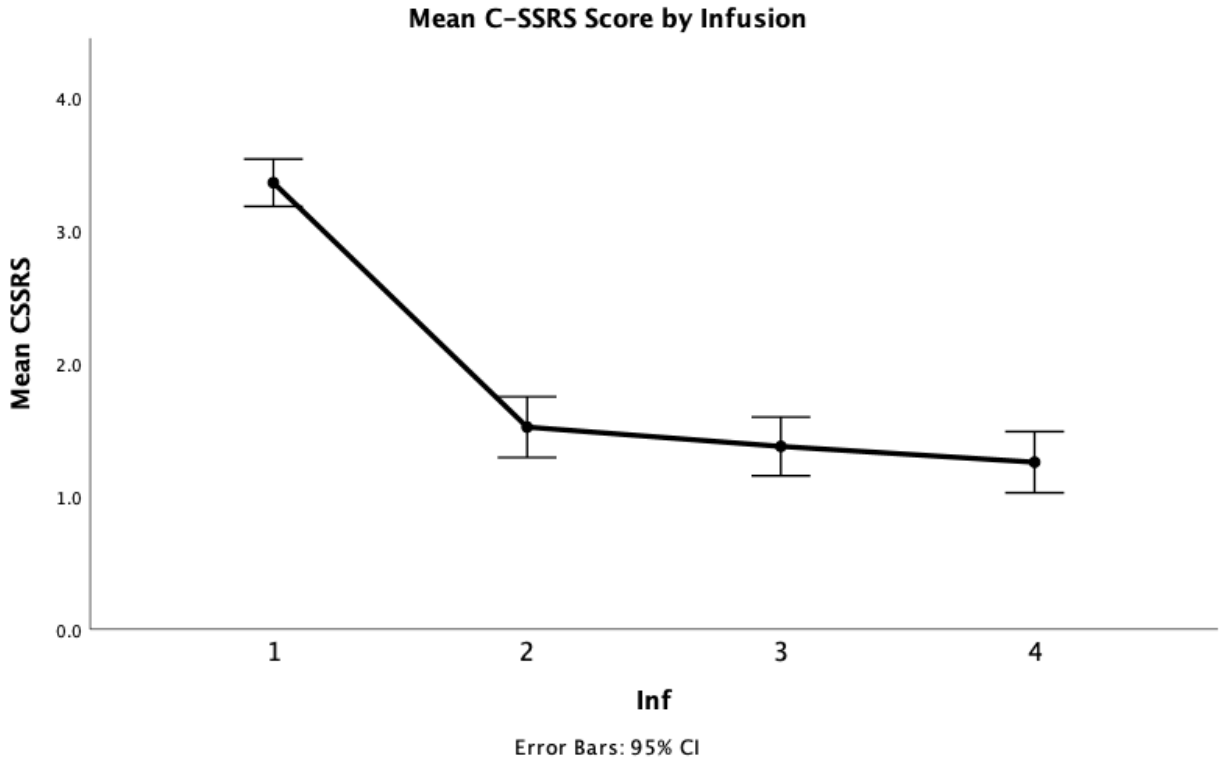

Figure 1. Graph of mean C-SSRS change across infusion time points.

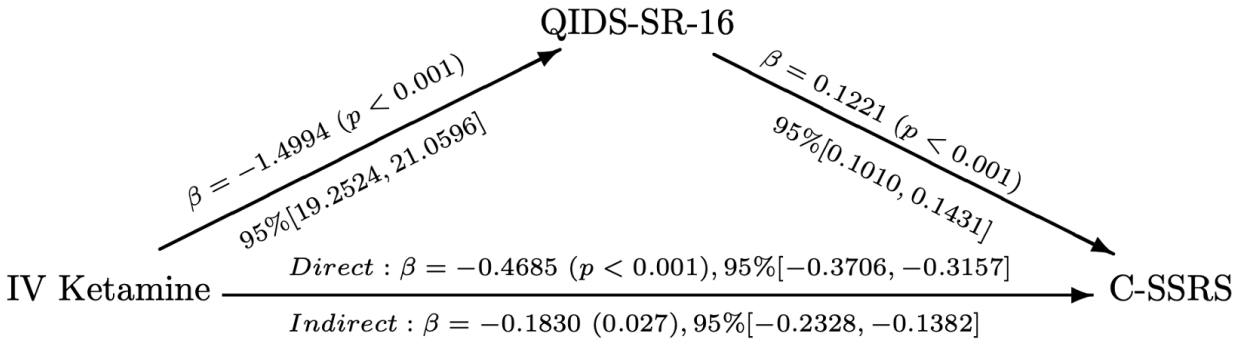

Figure 2. Mediation analysis investigating the effect of depression severity on the efficacy of IV ketamine on suicidal ideation. The mediation variable was depression severity as measured by the QIDS-SR16 at each infusion.

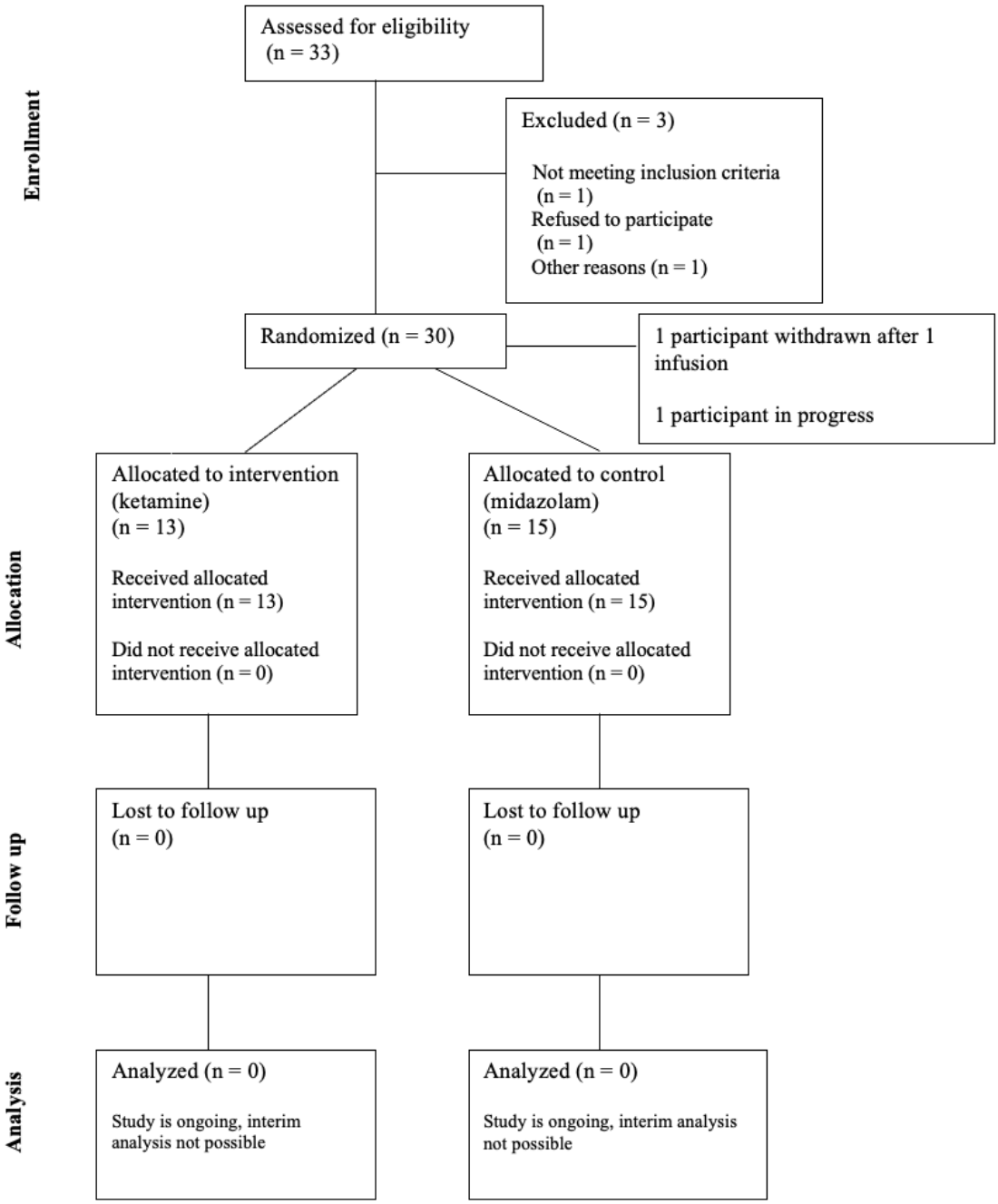

Figure 3. CONSORT diagram for KET-BD.

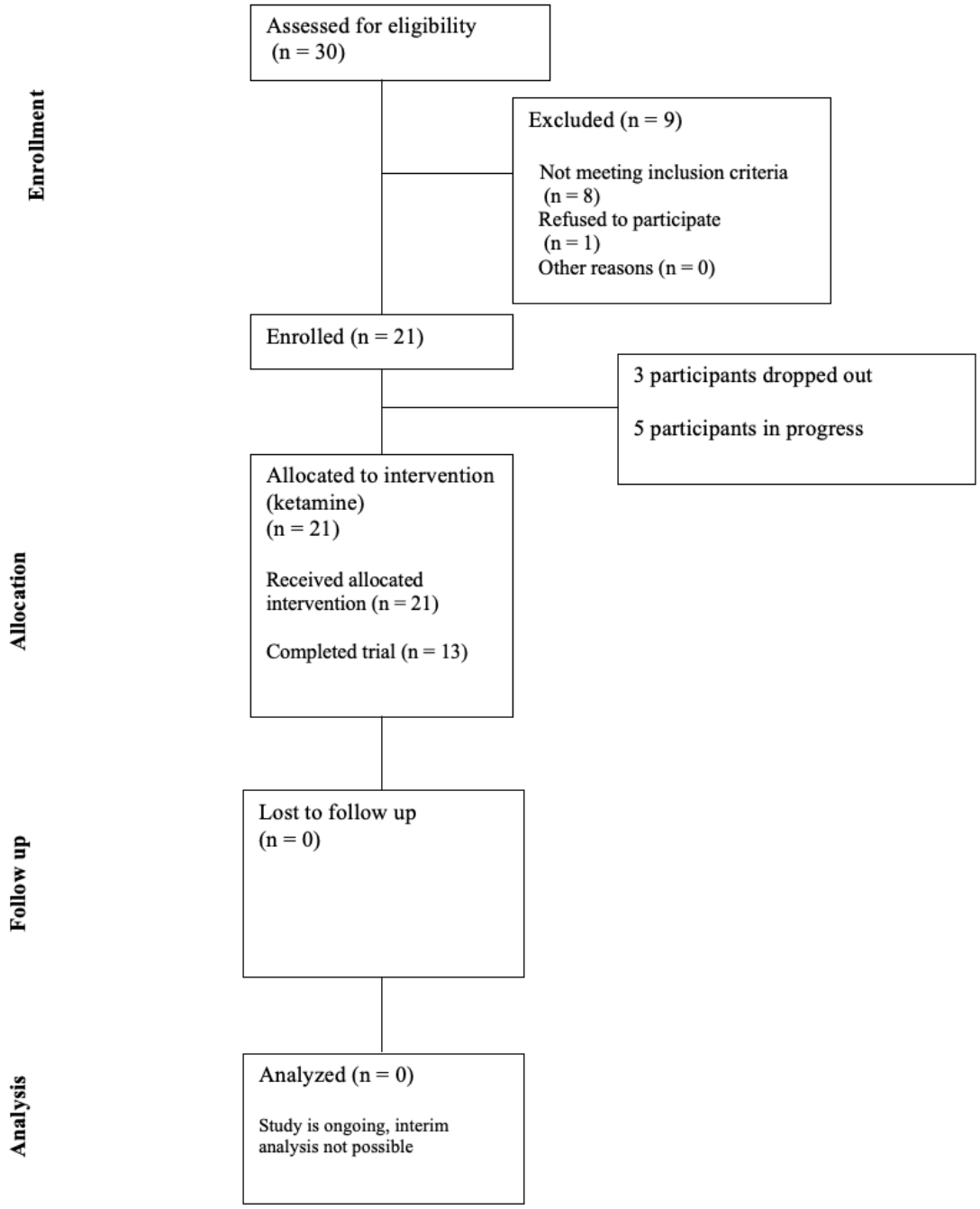

Figure 4. CONSORT diagram for KET-BD-SUSTAIN

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