Ketamine Plus Exercise for Major Depressive Disorder: A Randomized Controlled Trial

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KETAMINE PLUS EXERCISE FOR MAJOR DEPRESSIVE DISORDER: A RANDOMIZED CONTROLLED TRIAL

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Abstract

Major Depressive Disorder is the leading cause of disability among mental illnesses worldwide, but existing therapies fail to adequately treat approximately 30-50% of depressed patients. Ketamine has promising rapid antidepressant effects, but these effects are of short duration. Exercise yields moderate antidepressant effects both as a primary treatment and as an adjunct to standard therapies, but has not been investigated as an adjunct to ketamine. This study seeks to determine whether the addition of regular aerobic exercise regimens to ketamine therapy will potentiate or prolong ketamine’s antidepressant effects. We propose a single-blind, randomized controlled trial in which patients will be randomly assigned to receive intravenous ketamine or ketamine plus a structured exercise regimen. The potentiation or prolongation of ketamine’s antidepressant effects with exercise may increase the number of patients responsive to therapy and may reduce the cost and potential adverse effects of ketamine therapy.
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CHAPTER 1: INTRODUCTION

Background

Major Depressive Disorder (MDD) is a highly prevalent and potentially debilitating disorder accounting for significant disability, morbidity, and mortality worldwide. It is estimated that the lifetime prevalence of MDD in the United States is 16.9%, and globally it is the leading cause of disability among mental illnesses. The World Health Organization (WHO) reports that depression is the fourth leading cause of disability among all diseases worldwide, and projects that it will become the second leading cause of disability among all illnesses by 2020. MDD disproportionately affects women, affecting approximately twice as many women as men; this relationship has been observed in numerous countries worldwide. In the United States, individuals with the lowest incomes are twice as likely to be depressed as those with the highest incomes. It has been estimated that between 1/3 and 1/2 of patients with MDD experience a recurrent major depressive episode (MDE) in a given year. Importantly, MDD has been associated with increased risk and severity of numerous medical conditions, an elevated risk of early death, and risk of suicide.

Clinical Presentation and Diagnosis of Major Depressive Disorder

The clinical presentation of MDD varies significantly; each individual presents with a unique pattern of signs and symptoms that occurs over a particular temporal pattern. MDD is characterized by the presence of one or more MDEs, in which an individual experiences an assortment of emotional, cognitive, and somatic symptoms over the course of at least two weeks. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the core symptoms of MDD that commonly manifest during
a MDE include: depressed mood, loss of interest or pleasure in usual activities, feelings of guilt or worthlessness, fatigue, difficulty concentrating, change in appetite or weight, psychomotor agitation or retardation, insomnia or hypersomnia, and suicidal ideation or suicide attempt. These symptoms are typically present on a daily basis and may be either newly present or worsening from an individual’s baseline. One study found that the most commonly reported symptom of MDD is depressed mood, followed by changes in sleep habits and difficulty concentrating. The impact of MDD can be far-reaching and may negatively affect an individual’s sleep habits, diet, interpersonal relationships, occupation, or education.

The diagnosis of MDD is made using a set of diagnostic criteria outlined in the DSM-5. Five of the nine symptoms listed above must be present or worsening within the same two week period, and one of the presenting symptoms must be either depressed mood or loss of interest in one’s usual activities. Importantly, symptoms must not be better explained by the effects of a medical condition and must lead to significant psychosocial distress or impairment in order to qualify for a diagnosis of MDD.

Clinicians frequently utilize screening tools to facilitate the accurate diagnosis of MDD, to develop treatment plans, and to monitor progress throughout the course of a patient’s treatment. The Patient Health Questionnaire-9 (PHQ-9) is a screening tool commonly used in clinical settings. It is convenient for clinicians in that it is relatively brief, is completed by patients, and that each item on the questionnaire correlates with a diagnostic criterion for MDD as outlined in the DSM-5. The Montgomery-Åsberg Depression Rating Scale (MADRS) is another screening tool which was specifically designed to detect changes in depression scores over the course of receiving
antidepressant treatment. The MADRS is commonly used in clinical research settings due to its high sensitivity in detecting changes in depression scores over time as well as its high inter-rater reliability.

Given the broad range of symptoms that characterize MDD, there is significant heterogeneity in the clinical presentation of patients with MDD. Six of the diagnostic criteria outlined in the DSM-5 are considered to be compound because they consist of several symptoms (e.g. “insomnia or hypersomnia” is listed as a single diagnostic criterion). When each individual symptom within the compound diagnostic criteria was considered, there are 14,528 different combinations of symptoms that meet diagnostic criteria for MDD. This lends credence to the notion that what we consider to be MDD may actually represent a spectrum of distinct disorders, each with unique neurobiological underpinnings that have yet to be elucidated.

MDD is a recurrent disorder in which the majority of affected individuals experience a relapsing and remitting course. There is a significant degree of individual variation in the clinical course of MDD; many individuals experience depressive episodes lasting weeks to months, while others continue to experience symptoms for years at a time without relief. The median age of onset for MDD in the United States is 22.7, but the range is wider than that observed in other mental disorders and onset at a younger or older age is not uncommon. Earlier onset of MDD in childhood or adolescence has been associated with a more severe course including increased risk of suicide, more severe symptoms, increased comorbid psychiatric disorders, as well as a more chronic course with more recurrent MDEs. Recurrence is quite common in MDD, with an estimated 31% of patients experiencing a recurrent MDE in a given year in primary care populations.
Additionally, the number of previous MDEs has been associated with an increased risk of recurrence, indicating that each MDE increases the risk of experiencing a subsequent MDE. Subclinical residual symptoms that persist beyond a MDE are another predictor for future recurrence of a subsequent MDE. Individuals who experience residual symptoms following remission of a MDE are more likely to relapse into a subsequent MDE, and relapse more quickly than individuals who relapse but did not experience residual symptoms. The most common residual symptoms include fatigue, difficulty concentrating, forgetfulness, and indecisiveness; these symptoms are less likely to be apparent to clinicians as they are difficult to note objectively and patients may not recognize that they are symptoms related to MDD.

MDD is the most common psychiatric disorder among individuals who commit suicide, which represents the most dire consequence of the disease. The WHO estimates that approximately one million people die annually as a result of suicide. Suicide represents the fourth-leading cause of death among individuals aged 10-65 and the third-leading cause of death among children aged 10-14 in the United States. While completed suicide garners a great deal of attention, unsuccessful suicide attempts and suicidal ideation account for numerous emergency department visits and admissions to psychiatric inpatient institutions every year. Taken together, these statistics highlight that suicide represents a major public health concern and, like MDD overall, is not being adequately addressed by currently available psychiatric treatments.

**Overview of Proposed Etiologies for Major Depressive Disorder**

While a number of risk factors have been identified, the etiology of MDD has been elusive and there is presently a lack of consensus regarding the neural and psychosocial
underpinnings of the disease despite a large body of research devoted to its study. The etiology of MDD is clouded by the heterogeneity of its clinical presentation, course, and response to treatment.

The monoamine hypothesis has classically been accepted as the most commonly held theory regarding the etiology of MDD.\textsuperscript{15} This theory posits that deficiencies in levels of the monoaminergic neurotransmitters serotonin, norepinephrine, and dopamine within diffuse brain regions are the underlying cause of MDD.\textsuperscript{15} Several types of antidepressants including monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors, and selective norepinephrine reuptake inhibitors were developed on the basis of this theory with the intent of increasing synaptic concentrations of monoaminergic neurotransmitters as a means of treating MDD.\textsuperscript{16} This theory is flawed, however, in that it is incapable of properly explaining the delayed response to antidepressant medication and the significant proportion of depressed individuals that fail to respond to antidepressants.\textsuperscript{15}

More recent research has implicated that dysfunction in a number of more specific brain regions and neural circuits may possibly underlie the various manifestations of MDD. A common hypothesis is that chronic stress causes hypothalamic-pituitary-adrenal (HPA) axis dysfunction, leading to chronic elevations of glucocorticoids which has been proposed as an explanation for reduced hippocampal volumes that have been observed in individuals with MDD.\textsuperscript{15} Other research indicates that the various symptoms of MDD may be the result of impaired functional connectivity causing dysfunction in several discrete brain regions, involving numerous neurotransmitters including monoamines as well as histamine, acetylcholine, and glutamate.\textsuperscript{3,17} More recently, the prefrontal cortex
has been identified as a region where impaired functional connectivity may likely occur, potentially explaining alterations in executive functions commonly seen in MDD as well as impaired emotional regulation as a result of loss of top-down regulation of circuitry within the limbic system.\textsuperscript{18}

**Overview of Standard Treatments for Major Depressive Disorder**

Monoaminergic drugs such as selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) are currently the standard of care for pharmacologic treatment of depression. Approximately 60-70\% of patients experience clinically significant symptom relief with currently available pharmacotherapies, but this figure includes patients that may require up to four different treatment steps after failing to respond to first-line medications.\textsuperscript{19} It is noteworthy that only one-third of patients respond fully to antidepressant medication; large clinical trials have shown that half of patients fail to demonstrate at least a 50\% reduction in depressive symptoms after undergoing 12-14 weeks of treatment.\textsuperscript{19} The latency in onset of antidepressant medications is well-documented; many patients require weeks to months to attain clinically significant symptom improvement, and sustained remission of depressive symptoms in the long term is not common.\textsuperscript{2} The side effect profile of antidepressant medications of all pharmacologic classes are significant and well-documented, rendering them intolerable for a significant portion of patients.\textsuperscript{20} Taken together, this speaks to the notion that the efficacy of currently available pharmacotherapies for MDD is limited, which leaves many patients with inadequate or no symptom relief.
Psychotherapies such as cognitive behavioral therapy (CBT) are proven to have similar efficacy as pharmacologic therapies, and psychotherapy in combination with pharmacotherapy has been proven to be more effective than either treatment alone. While generally considered to be cost-effective, psychotherapy frequently poses significant out-of-pocket costs for patients and is therefore either not accessible or only available in suboptimal durations to a significant portion of patients. Due to the shortcomings in efficacy and accessibility of current antidepressant treatments, a significant portion of patients with MDD either achieve suboptimal or no treatment for their depressive symptoms and as a result a large body of research has been devoted to the development of alternative therapies for MDD.

**Overview of Ketamine as a Rapid-Acting Antidepressant**

Ketamine is an N-methyl-D-aspartate receptor (NMDA-R) antagonist that has been used clinically for its anesthetic, sedative, and analgesic properties for over 50 years. As a result of the shortcomings of traditional antidepressant treatments, ketamine has recently received attention for its promising rapid antidepressant effects and potential to serve as an alternative treatment option for patients with MDD.

Several randomized controlled trials (RCTs) have demonstrated that subanesthetic doses of IV ketamine provide significant reductions in depressive symptoms, most notably in suicidal ideation, within four hours following an infusion. However, ketamine’s antidepressant effects are of short duration and tend to diminish within 7-14 days of treatment, which poses a significant barrier to its viability as a depression treatment. Concerns regarding potentially harmful neurobiological side effects of ketamine limit its potential to be used in the long-term to maintain remission of depressive symptoms.
Additionally, ketamine’s potential for abuse raises many questions regarding its viability for use on an outpatient basis for regular, long-term use – particularly in patients with a history of substance abuse. Numerous studies have indicated that future directions in research surrounding ketamine’s use in the treatment of MDD should be focused on developing strategies to prolong its antidepressant effects, limiting the amount of ketamine treatments needed to sustain its antidepressant effects.²,²⁴

**Overview of the Antidepressant Effects of Exercise for Major Depressive Disorder**

The American College of Sports Medicine (ACSM) defines exercise as being purposeful physical activity undertaken with the intention of improving one’s overall health and fitness.²⁶

In addition to numerous benefits on physical health, exercise has been proven to have moderate antidepressant effects in MDD as a solitary treatment,²⁷ with preliminary evidence supporting its use as an adjunct to CBT,²⁸ antidepressant medication,²⁹ and to the combination of CBT and pharmacotherapy.³⁰ Importantly, exercise has been shown to have antidepressant effects comparable to those of antidepressant medication and psychotherapy.³¹ Exercise holds many advantages over pharmaceutical and psychotherapeutic treatments for MDD in that it is less expensive, is not associated with the numerous side effects of psychotropic drugs, and is well-established as being effective in the prevention and treatment of several medical conditions.³²

The WHO recommends the implementation of regular physical exercise, in combination with medication or psychotherapy, as part of the standard treatment of MDD.²⁹ Many clinicians have embraced the utility of exercise in the treatment of depression due to its accessibility, relatively low cost, absence of side effects, and bountiful benefits on many
aspects of physical health.\textsuperscript{33} Taken together, current high-level evidence supports exercise as having moderate antidepressant effects and also supports the notion that exercise may be an effective adjunct therapy for depression. Therefore, it stands to reason that exercise may have the potential to augment the antidepressant effects of ketamine. This study seeks to determine whether the addition of adjunct regular aerobic exercise regimens to existing ketamine treatments will potentiate or prolong ketamine’s antidepressant effects.

**Statement of the Problem**

The rapid antidepressant effects of ketamine are well-established, but a major limitation of ketamine’s clinical utility is its short duration of action. While many patients achieve clinically significant remission of symptoms within 1-4 hours of treatment, many patients experience a relapse in depressive symptoms within 7-14 days. There is currently a paucity of research investigating therapeutic adjuncts to ketamine therapy that may improve its antidepressant effects or prolong its duration. Additionally, not all patients respond clinically to ketamine treatment and few adjunct therapies to potentiate the antidepressant effect of ketamine have been investigated to date.

**Goals and Objectives**

The goals of this study are to determine whether exercise regimens potentiate the initial antidepressant response to ketamine treatment and whether regular exercise prolongs the duration of ketamine’s antidepressant effect. The objectives of this study are to compare reductions in MADRS scores between subjects undergoing ketamine treatment alone and those undergoing ketamine treatment plus an exercise regimen.
**Study design:** The current proposal encompasses a two-arm, single-blind, randomized controlled trial comparing ketamine to ketamine plus an exercise regimen for the treatment of MDD in an adult population.

**Outcomes:** The primary outcome will be mean reductions in MADRS scores at four weeks of follow-up from the last ketamine infusion compared to scores recorded at baseline. Secondary outcomes will be time to extinction of ketamine’s antidepressant effects during follow-up, and mean reductions in depression scores immediately following completion of ketamine therapy.

**Hypothesis**

The addition of adjunct aerobic exercise routines to ketamine treatment will result in greater mean reductions in MADRS scores four weeks after completion of ketamine treatment compared to ketamine treatment alone in adults with moderate-severe MDD.

**Chapter 1 References**


33. Ekkekakis P. Honey, I shrunk the pooled SMD! Guide to critical appraisal of systematic reviews and meta-analyses using the Cochrane review on exercise for depression as example. Mental Health and Physical Activity 2015;8:21-36.
CHAPTER 2: REVIEW OF THE LITERATURE

Introduction
Between July 2018 and April 2019, a comprehensive review of relevant literature was performed using the databases PubMed, Ovid PsycINFO, Scopus, and the Cochrane Library. The literature review included articles published between the dates of 1979-2018; the vast majority of articles were published within the past 10 years and older articles were included as necessary to adequately review relevant literature. The following key search terms were utilized: “depression”, “major depressive disorder”, “depression epidemiology”, “STAR D”, “depression clinical presentation”, “depression ketamine”, “ketamine rapid antidepressant”, “ketamine glutamate”, “depression exercise”, “depression aerobic exercise”, “depression adjuncts”, “exercise BDNF”, “cognitive behavioral therapy”, “ketamine depression exercise”, and “ketamine exercise”. This literature review includes randomized controlled trials (RCTs), systematic reviews, critical appraisals, and meta-analyses. References were mined from the included articles to expand and facilitate the review of relevant literature. The search was limited to articles written in English.

Review of Empiric Studies Investigating Ketamine as a Rapid-Acting Antidepressant with a Single Intravenous Infusion
As a result of the shortcomings of traditional treatments for major depressive disorder (MDD), ketamine has recently received attention for its promising rapid antidepressant effects and its potential to serve as an alternative treatment option for patients with MDD, and particularly for patients with treatment-resistant depression (TRD). In the past 20 years, ketamine has been studied more extensively than other N-methyl-D-aspartate
receptor (NMDA-R) antagonists and has consistently demonstrated impressive antidepressant effects when administered intravenously at subanesthetic doses of 0.5mg/kg in multiple independent clinical trials.\(^1\) While monoaminergic antidepressants have been shown to produce a response rate of approximately 40-47% that takes weeks to months to take effect, ketamine has exhibited a response rate of 65-70% that typically takes effect within two hours of administration,\(^2\) prompting some to label its antidepressant effects as one of the most important discoveries in psychiatry in the past 60 years.\(^3\) The primary limitation to ketamine’s utility as an antidepressant is its short duration of action; several studies have demonstrated that ketamine’s antidepressant effects most commonly subside within 7-14 days of administration, though the effects persist considerably longer for some individuals.\(^4,5\) The following section will review evidence of ketamine’s efficacy as a rapid-acting antidepressant.

Berman et al. (2000) was the first group to investigate the antidepressant effects of ketamine in a double-blind, placebo-controlled, crossover clinical trial.\(^6\) A small sample of eight subjects with MDD was administered either an intravenous (IV) infusion of ketamine (0.5mg/kg) over 40 minutes, or a saline placebo administered intravenously over the same period. Consistent with the crossover design, subjects received both the ketamine and saline placebo treatments in a randomized order, at least one week apart. Changes in depression scores on the 25-item Hamilton Depression Rating Scale (HDRS) following each treatment were compared as the primary outcome; baseline scores measured prior to treatment were compared to scores over the following 72 hours.\(^6\) Treatment with ketamine resulted in significantly greater reductions in HDRS scores than treatment with placebo.\(^6\) Analyses of variance using the Huynh-Feldt correction revealed
significant condition-by-time effects ($F = 3.97$, d.f. 5,30, $p = .02$), but insignificant time effects ($F = 2.62$, d.f. 5,30, $p = .09$) and condition effects ($F = 0.157$, d.f. 1,30, $p = .71$). This revealed impressive reductions in HDRS scores from baseline at each subsequent time point. 50% of subjects exhibited a 50% or greater reduction in HDRS scores at 72 hours post-infusion, while only 12.5% of subjects exhibited such a reduction in HDRS scores following a placebo treatment. The improvements in depression scores due to ketamine treatment reportedly returned to baseline within 7-14 days, though this study was not designed to detect the temporal scale of these changes. Statistically significant reductions, measured with paired t-tests, were noted for the following measures on the HDRS among all subjects: suicidality ($p=.02$), depressed mood ($p=.0025$), worthlessness ($p=.015$), and helplessness ($p=.008$). As a result of the design of this study, some subjects received ketamine seven days prior to receiving a placebo treatment. Although the duration of ketamine’s effects was not well-characterized at the time, it is now known that ketamine’s antidepressant effects last longer than seven days in some individuals. The authors noted that baseline depression scores prior to receiving the placebo treatment were approximately 10 points lower in the group that received ketamine first, though post hoc analyses revealed that there were no statistically significant effects as a result of the order in which ketamine or placebo treatments were administered. It is conceivable that this affected results, but an effect was unable to be detected in this small sample size. The results of this study may have been confounded by the inclusion of subjects with bipolar disorder and panic disorder. Despite the small sample size of this study it demonstrated impressive antidepressant effects for ketamine, generating a great deal of subsequent research seeking to replicate
its effects in larger trials and better characterize the temporal scale of its antidepressant effects.

Zarate et al. (2006)\(^7\) conducted a subsequent study investigating ketamine’s antidepressant effects, replicating the findings of Berman et al.\(^6\) with a larger sample size and a study design that allowed for evaluation of a longer follow-up period. This study was also a randomized, double-blind, placebo-controlled crossover study.\(^7\) A sample of 18 patients with TRD was enrolled to receive IV infusions of ketamine (0.5 mg/kg) and saline placebo over 40 minutes, one week apart, in a crossover design. Selection criteria were similar to those employed by Berman et al.,\(^6\) but subjects with comorbid psychiatric disorders were not included. The primary outcome was changes in depression scores on the 21-item HDRS from baseline to several time points following treatment. The investigators defined a clinically significant response as a 50% or greater reduction in HDRS scores from baseline, while clinical remission was defined as a score of 7 or lower on the HDRS. A fixed-effects linear mixed model was utilized to analyze the differences in depression scores following ketamine and placebo treatments over nine temporal data points from baseline to follow-up at seven days.\(^7\)

Significant drug effects (F\(_{1,203} = 58.24, p<0.001\)) and time effects (F\(_{8,203} = 9.48; p<0.001\)) were observed, indicating a statistically significant benefit for ketamine over placebo in reducing HDRS scores at all time points from 110 minutes post-infusion to seven days post-infusion.\(^7\) The effect size was large at 24 hours post-infusion (d=1.46 [95% CI, 0.91-2.01]) and was moderate-to-large at one-week follow-up (d=0.68 [95% CI, 0.13-1.23]). At 24 hours post-infusion, 71% of subjects receiving ketamine met criteria for a clinical response, compared to 0% of subjects receiving placebo. Additionally, 29% of subjects
receiving ketamine met criteria for clinical remission compared to 0% of subjects receiving placebo. Among subjects who responded to ketamine, 35% maintained their clinical response at one-week follow-up.\textsuperscript{7}

The authors noted that no other depression treatment had yielded as robust a response with a single treatment prior to their study.\textsuperscript{7} The clinical response to ketamine among depressed subjects in this study was greater than response rates observed at 8 weeks for bupropion (62%), selective serotonin reuptake inhibitors (63%), and venlafaxine (65%) in systematic reviews.\textsuperscript{7} This trial replicated the findings of Berman et al.\textsuperscript{6} in a larger sample with stricter exclusion criteria, demonstrating the robustness of ketamine’s clinical effects in MDD. Importantly, it provided more detailed data regarding the rapid onset of ketamine’s antidepressant effects and the course of improvement over a longer follow-up period of seven days.

In addition to the trials conducted by Berman et al.\textsuperscript{6} and Zarate et al.\textsuperscript{7}, several subsequent trials have replicated the efficacy of a single IV infusion of ketamine in rapidly reducing depressive symptoms in MDD as a primary treatment,\textsuperscript{8,9} as well as in bipolar depression.\textsuperscript{10,11} Newport et al. (2015) conducted a systematic review examining six RCTs which investigated the antidepressant effects of a single IV infusion of ketamine against a placebo treatment.\textsuperscript{1} The authors concluded that a single IV infusion of ketamine at 0.5mg/kg over 40 minutes provided a statistically significant reduction in depressive symptoms within 24 hours, with a composite odds ratio (OR) of 9.87 (95% CI=4.37-22.29, $z=5.50$, $p<0.001$) for a clinically significant antidepressant response 24 hours after receiving ketamine.\textsuperscript{1} This solidifies the strong evidence base supporting ketamine’s
antidepressant effects when administered as a single treatment, and stimulated additional research investigating strategies to prolong ketamine’s antidepressant effects.

Review of Empiric Studies Investigating the Efficacy of Repeated Ketamine Infusions

Based on the findings of several blinded, randomized, placebo-controlled trials demonstrating the efficacy of a single subanesthetic dose of ketamine as a rapid-acting antidepressant of short duration, Murrough et al. (2013) conducted a novel open-label study investigating the effects of repeated ketamine infusions on the time-course of its antidepressant effects. Inclusion and exclusion criteria were similar to those employed by Berman et al. and Zarate et al. Subjects were administered up to six IV infusions of ketamine (0.5mg/kg) over 40 minutes, over a period of 12 days. The primary outcome was changes in Montgomery-Åsberg Depression Rating Scale (MADRS) scores from baseline to follow-up. One of the defining aspects of this study was that subjects were followed up for up to 83 days, representing a follow-up period several months longer than what had been utilized in prior studies and allowing for a better evaluation of the temporal course of ketamine’s antidepressant effects.

Similarly to previous studies investigating the effects of a single ketamine infusion, 71% of subjects demonstrated a clinically significant reduction in MADRS scores following up to six ketamine treatments over 12 days. A significant and robust decrease in MADRS scores was observed at two hours after the first ketamine infusion (18.9 +/- 6.6, p<0.001), which was generally maintained for the duration of the ketamine treatment period as evidenced by a mean decrease in MADRS scores from 31.8 to 12.9 (p<.001). This replicated the finding from prior studies that statistically significant improvements
in depression scores were first evident at two hours post-infusion in many subjects, with 94% of responders showing a significant response within four hours of receiving an infusion. Among individuals that showed a significant response, the median time to relapse of depressive symptoms to pre-treatment baseline levels was 18 days, with the 24th and 75th percentiles respectively being 11 days and 27 days. Importantly, this study revealed that response within four hours of receiving a ketamine treatment was highly predictive of response at study end (95% sensitive, 71% specific), providing important implications regarding the early identification of likely responders to treatment going forward.

The selection criteria and methodology that was utilized was very similar to those utilized by studies of ketamine as a single infusion, strengthening the internal validity of the study and the generalizability of the results. Utilizing the MADRS as the primary outcome improved the sensitivity of the results, given that the MADRS is better suited to track changes in depression scores as a result of an intervention than the HDRS or the Beck Depression Inventory (BDI). This study provided a significantly improved characterization of the temporal scale of ketamine’s antidepressant effects, demonstrating that ketamine’s effects were lost within 2-3 weeks of receiving an infusion in the majority of responders. However, this study revealed that proportions of patients may relapse sooner, while others enjoy a more prolonged antidepressant effect. The data presented in this study provided preliminary evidence that repeated ketamine infusions may provide a longer lasting antidepressant effect than that conferred by a single dose.

Singh et al. (2016) expanded upon the findings of Murrough et al. with a randomized, double-blind, placebo-controlled, dose-frequency study investigating the effects of IV
ketamine at different dose frequencies in subjects with TRD.\textsuperscript{13} Investigators enrolled 67 subjects and utilized similar selection criteria to previous studies.\textsuperscript{5-7} Subjects were randomized to undergo one of four treatment regimens over a two week period: ketamine twice per week, saline placebo twice per week, ketamine three times per week, or saline placebo three times per week. Ketamine was administered according to the protocol described previously.\textsuperscript{5-7} The primary outcome was mean change in MADRS scores from baseline to day 15, after completion of ketamine therapy. Subjects were followed for an additional two weeks following completion of two weeks of ketamine or placebo treatments; MADRS scores were recorded daily during this time.\textsuperscript{13}

Subjects who received ketamine twice per week showed a significantly greater mean reduction in MADRS scores at day 15 compared to those receiving placebo (ketamine, -18.4 [SD=12.0]; placebo, -5.7 [SD=10.2]; \( p < .001 \)).\textsuperscript{13} A similar significant mean reduction in MADRS scores was observed in subjects receiving ketamine three times per week compared to placebo (ketamine, -17.7 [SD=7.3]; placebo, -3.1 [SD=5.7]; \( p < .001 \)).

There was no significant difference in reductions in MADRS scores between groups receiving ketamine twice per week and the group receiving ketamine three times per week. Additionally, improvements in MADRS scores did not differ significantly between groups at follow-up on day 29, indicating that twice-weekly dosing was sufficient to provide a rapid and sustained antidepressant response as opposed to thrice-weekly dosing that was studied by Murrough et al. previously.\textsuperscript{5} The authors conclude that twice-weekly dosing would be preferable given these findings, since less frequent dosing would likely reduce burden on patients and clinics, and reduce costs associated with treatment.\textsuperscript{13}
This study has several limitations. The primary limitation was that a significant portion of subjects did not complete the study due to loss to follow-up; 83.8% of patients completed the first 15 days of the study, and only 36.8% of patients completed the entire 4-week study. The authors report that the vast majority of subjects who discontinued prior to the end of the study had withdrawn due to lack of efficacy of the saline placebo treatment. Furthermore, while this study provided valuable information regarding the dose-frequency characteristics of ketamine’s antidepressant effects, it was not powered to detect a statistically significant difference between the two regimens. Due to the shorter follow-up period than employed by Murrough et al., conclusions cannot be drawn regarding the longer-term duration of ketamine’s effects in each dose-frequency regimen. The results of the study are reassuring overall in that they successfully replicated the findings from Murrough et al. that ketamine’s effects seem to be prolonged with repeated administration.

The evidence base for the efficacy of ketamine as a rapid-acting antidepressant is robust; ketamine is the best studied and the most effective antidepressant among other glutamatergic agents. Ketamine’s antidepressant effects have been shown to be superior to a number of similar agents, including memantine, lanicemine, nitrous oxide, traxoprodil, D-cycloserine, and rapastinel. The primary limitation to the utility of ketamine as an antidepressant is its short duration of action. Studies of ketamine administered in repeated doses demonstrate relapse rates of 55%-89% within one month of receiving treatment, and to date there is a paucity of research investigating the maintenance of its effects in the long-term. As a result, several authors have cited the
need for future studies investigating strategies to enhance and prolong ketamine’s antidepressant effects.¹⁵¹³⁻¹⁷

Review of Empiric Trials Investigating Therapeutic Adjuncts to Ketamine for Major Depressive Disorder

The short duration of ketamine’s antidepressant effects has generated interest in the development of strategies to prolong its effects, which is desirable for a number of reasons. Considering that ketamine’s antidepressant effects take effect much more quickly and appear to be of greater magnitude than existing therapies for MDD, it is unsurprising that its efficacy has generated research into developing strategies to compensate for its shortcomings as an antidepressant drug. Reducing the amount of treatments necessary to sustain its antidepressant effects would theoretically reduce the risk of adverse effects associated with long-term use, reduce the abuse potential associated with ketamine use, and reduce the costs associated with more frequent use. However, there is currently a paucity of research regarding possible therapeutic adjuncts.¹ This section will discuss the two RCTs that have been published to date investigating possible adjuncts to ketamine to bolster its antidepressant effects.

Ibrahim et al. (2012) conducted a randomized, double-blind, parallel, placebo-controlled, flexible-dose trial investigating whether ketamine’s antidepressant effects would be prolonged with the addition of riluzole, a fellow NMDA-R antagonist which has been shown to possess antidepressant and neuroplasticity-promoting effects via modulation of glutamate activity, similar to ketamine.¹⁶ The investigators hypothesized that ketamine and riluzole would exhibit synergistic effects given similarities in their mechanisms of action. This study included 42 subjects with selection criteria similar to that described in
previous studies. All subjects were administered a single IV infusion of ketamine (0.5mg/kg) over 40 minutes in an open-label design; 4-6 hours after treatment, subjects were randomized to receive riluzole (100-200mg/day) or placebo for four weeks. The primary outcome was change in MADRS scores from baseline to various time points following ketamine administration, as well as to daily MADRS scores for the subsequent 28 days.

A linear mixed model was used to analyze the data, which showed significant reductions in MADRS scores over the course of the study (F=8.81, d.f.=28, 297, \( p<.001 \)). This was an expected result given that all subjects received ketamine treatment, and is consistent with effects demonstrated previously. However, the analysis failed to show a significant difference between the treatment groups, or for the interaction between treatment groups and time (treatment: F=0.00, d.f.=1, 40, \( P=0.99 \); time x treatment: F=1.20, d.f.=28, 297, \( P=0.23 \)). These results indicate that riluzole failed to potentiate ketamine’s antidepressant effects. The linear mixed model failed to show significant interactions for the secondary outcomes of scores on the BDI or HRDS.

The generalizability of this study is limited by the fact that all subjects had been hospitalized for treatment of their depression for 46 days prior to starting the study. The authors hypothesized that the overlapping mechanisms of riluzole and ketamine may have interfered with one another, rather than potentiate each other. However, the authors noted that riluzole demonstrated a non-significant increase in time-to-relapse compared to the placebo group (17.2 vs. 9.8 days), which may hold clinical significance despite its lack of statistical significance. They additionally posed that the severity of depressive symptoms in TRD may have masked the effects of riluzole.
More recently, Wilkinson et al. (2017) conducted an open-label study investigating whether IV ketamine plus parallel treatment with cognitive behavioral therapy (CBT) would produce antidepressant effects superior to those conferred by ketamine as a solitary treatment. Specifically, this study sought to determine whether CBT could prolong ketamine’s antidepressant effects or improve the therapeutic response in subjects who do not demonstrate an initial response to ketamine treatment. All subjects underwent IV ketamine infusions (0.5mg/kg over 40 minutes) twice per week for the first two weeks of the study. All subjects additionally engaged in 12 sessions of CBT concurrently with the ketamine treatments – two sessions per week during the first two weeks, then weekly sessions during the subsequent 8 weeks. Subjects were followed for up to three months following the ten-week study period. The primary outcome was the proportion of subjects exhibiting a clinical response or remission, defined as a greater than 50% reduction in baseline MADRS scores or a MADRS score less than 9, respectively.

The results demonstrated that 43.8% of subjects achieved remission of depressive symptoms, with 50% of subjects overall demonstrating a clinically significant response, similar to response rates reported previously. Subjects that demonstrated a response to ketamine showed a significantly maintained response for the first three weeks of the study, but failed to maintain a significant improvement in MADRS scores after three weeks. The median time to relapse after ketamine treatment among subjects who responded was 12 weeks, with only 25% of subjects (n=2) relapsing by 8 weeks.

This represents a markedly prolonged antidepressant effect of ketamine compared to those observed in previously published trials, but the small sample size and absence of a control condition in this study limits interpretation and generalizability of this data.
Additionally, the results may be confounded by the concurrent use of psychotropic medications by study subjects, which may have caused overestimation of the true effect of CBT in prolonging ketamine’s antidepressant effect; previous studies utilized a “washout” period to control for this factor.\textsuperscript{5,7,13} Overall, the preliminary results of this study are promising and suggest that CBT may enhance or prolong the duration of ketamine’s antidepressant effects.

**Limitations to Ketamine’s Use as an Antidepressant**

While generally considered safe when administered at subanesthetic doses, ketamine possesses sympathomimetic properties that cause transient elevations in heart rate and blood pressure which represent a potential safety concern for certain patient populations.\textsuperscript{17} One review of clinical trials using ketamine found that approximately 30\% of subjects receiving subanesthetic doses exhibited tachycardia >110 beats per minute, systolic blood pressure readings >180mm Hg, or diastolic blood pressure readings >110mm Hg.\textsuperscript{17} As a result of these properties ketamine should be used judiciously in depressed populations with comorbid cardiovascular disease.\textsuperscript{14}

The two most notable adverse effects of subanesthetic doses of ketamine are transient dissociation and psychotomimetic symptoms that are very commonly observed during intravenous infusion,\textsuperscript{17} rendering it intolerable for a small proportion of individuals.\textsuperscript{3} Ketamine has a number of undesirable side effects, the most common of which are dizziness, visual changes, drowsiness, impaired coordination, and “feelings of disconnect from reality”.\textsuperscript{17} These adverse effects are most prominent two hours after receiving an infusion, and typically resolve in 4-24 hours.\textsuperscript{17} However, these adverse effects have little effect on the tolerability of ketamine; meta-analyses have shown that there are no
significant differences between ketamine and control groups regarding all-cause discontinuation.\textsuperscript{17} Furthermore, when side effects are considered to be clinically significant, symptomatic treatment is often sufficient – for example, oral clonidine has been used for hypertension prophylaxis.\textsuperscript{17}

Ketamine’s psychotomimetic dissociative properties confer an abuse potential associated with medical risks, further limiting its utility.\textsuperscript{3,17} Ketamine is commonly abused as a “club drug”, with over 2 million teenagers and adults in the United States reporting they had used ketamine recreationally in their lifetime in 2006 and abuse rates steadily increasing worldwide in the past several decades.\textsuperscript{18} Chronic ketamine abuse – at doses much higher than those used for depression – has been associated with neurotoxicity including cognitive dysfunction, memory impairments, and white matter abnormalities, as well as with severe urologic pathology.\textsuperscript{14}

There is a large population of depressed individuals that may benefit from repeated infusions ketamine, which at this point appears to be safe in the short term.\textsuperscript{14} Several studies point to the need for future studies to evaluate the long-term safety of ketamine use as well as strategies to mitigate its adverse effects and abuse potential.\textsuperscript{14}

**Review of the Antidepressant Effects of Exercise**

The role of exercise as a treatment option for patients with MDD has historically been the subject of debate; conflicting results in randomized controlled trials and meta-analyses have led many to question the true benefit that exercise has on depressive symptoms in MDD. There is considerable variation in the study populations, clinical settings, methodologies, nature of exercise interventions, control groups, and statistical analyses among RCTs that makes comparisons between studies difficult. Additionally, the vast
and heterogeneous body of literature dedicated to the study of exercise in depression further complicates comparisons between studies. This review will summarize high-level evidence which supports exercise as having moderate antidepressant effects when utilized as a primary treatment for MDD, as well as evidence that supports the efficacy of exercise as an adjunct to standard psychological and pharmacological treatments.

A 2013 Cochrane Review performed a systematic review and meta-analysis of the literature investigating the antidepressant effects of exercise against placebo, psychological, and pharmacological control therapies. The investigators included RCTs that were designed to directly compare exercise with standard therapy, placebo therapy, or no therapy in adults that met diagnostic criteria for MDD. The authors reviewed 39 clinical trials that met inclusion criteria for the study, and extracted data from 37 of those trials for meta-analysis. Using data from primary and secondary outcomes from these trials, the authors calculated effect sizes and standardized mean differences to examine the overall pooled effect of exercise on depression rating scores. The authors additionally carried out several subgroup analyses to examine whether effect sizes were influenced by type, frequency, or intensity of exercise.

Among studies that compared exercise to either a control treatment or to no treatment, analyses revealed a moderate clinical effect for exercise on depressive symptoms (SMD -0.62, 95% CI -0.81 to -0.42). Analyses of studies that examined the effects of exercise at long-term follow-up showed a small effect favoring exercise (SMD -0.33, 95% CI -0.63 to -0.03). There was no significant difference between exercise and psychological therapies (SMD -0.03, 95% CI -0.32 to 0.26) or between exercise and pharmacotherapy (SMD -0.11, 95% CI -0.34 to 0.12). When the authors analyzed the six trials that they
classified as high quality studies (utilized adequate allocation concealment, blinded outcome assessment, and intention-to-treat analysis), the effect of exercise on depressive symptoms was not statistically significant (SMD -0.18, 95% CI 0.97 to 1.04).\textsuperscript{19}

This study was one of the largest and most comprehensive reviews of the use of exercise for depression. One of the key findings was that exercise was found to be no more effective than psychological or pharmacological treatments in reducing depressive symptoms, indicating that it is at least as effective as available treatments and is a viable treatment option for patients with depression. Additionally, the authors concluded that exercise had been shown to be moderately more effective than a control treatment in improving the symptoms of MDD,\textsuperscript{19} indicating that for some patients exercise represents a viable option for a primary depression treatment. This study found a small effect size for the benefits of exercise at follow-up,\textsuperscript{19} indicating that the benefits of exercise seem to persist after the cessation of an intervention, although it was unclear whether subjects continued to exercise on their own during the follow-up phases of the included studies.

Ekkekakis\textsuperscript{20} published a comprehensive critical appraisal of the Cochrane review by Cooney et al.\textsuperscript{19} Ekkekakis noted that the effect size for exercise in treating depression had decreased by 44\% from 2001 to 2013 (SMD of -1.10 to -0.62, respectively), with sequential decreases in the SMD with each periodic update of the review.\textsuperscript{20} He argues that this is a result of flawed selection criteria employed by Cooney et al. The central argument supporting this assertion is that the authors included studies in which exercise plus a standard treatment (psychotherapy or antidepressant medication) was compared to standard treatment alone in “exercise versus no-treatment control” comparisons, which is methodologically flawed and likely caused an underestimation of the effect size of
exercise for depression. Additionally, Ekkekakis argues that the inclusion of trials comparing exercise to interventions such as tai-chi or yoga would further underestimate the efficacy of exercise as these treatments may influence depressive symptoms and are not equivalent to inactive treatment. Subsequent meta-analyses incorporated Ekkekakis’ recommendations and found larger effect sizes for exercise in treating MDD.

Schuch et al. (2016) performed a subsequent meta-analysis on the antidepressant effects of exercise while controlling for publication bias, which had not been done in previous systematic reviews. Importantly, the inclusion criteria were designed based on Ekkekakis’ criticism of the flawed methodology utilized by Cooney et al. in the 2013 Cochrane review. The authors excluded studies in which exercise plus an established treatment was compared to another established treatment, as Ekkekakis argued that this likely led to the “shrinkage” of the pooled SMD observed in the study by Cooney et al. Furthermore, the authors excluded studies in which tai chi, yoga, or qi going were used as control intervention as they utilize behaviors such as meditation and deep breathing that have been shown to have an effect on depressive symptoms and may underestimate the effects of exercise.

The primary outcome of this study was the pooled mean change in depression scores from baseline to post-exercise intervention, compared to changes in depression scores in control groups, represented by the SMD. Trim and fill and fail-safe n analyses were also utilized to control for publication bias. The authors reported a large effect size in favor of exercise (SMD = 0.98, 95% CI 0.68 to 1.28, p < 0.001, Q = 135, p < 0.01). The effect size was recalculated to control for publication bias with Dival and Tweedie’s trim and fill method, revealing a larger effect size (SMD =1.11, 95% CI 0.79 to 1.23, p<0.001).
Furthermore, the authors calculated a fail-safe number of 1,057 studies with negative results for an exercise intervention required to nullify the significance of their results.\textsuperscript{21}

After employing more rigorous inclusion criteria and controlling for publication bias, this study reported a large effect size for exercise in reducing depressive symptoms when compared to an inactive control group,\textsuperscript{21} which supports exercise as an effective primary treatment for MDD. The authors attributed the larger effect size to their adaptation of Ekkekakis\textsuperscript{20} recommendations.\textsuperscript{21} The authors concluded that their analyses suggest that publication bias typically led to an underestimation of the antidepressant effects of exercise, and may have led to underestimation of the true effects of exercise on reducing MDD symptoms in prior meta-analyses. The authors contend that their overall results support the use of exercise as an evidence-based treatment for the treatment of MDD.\textsuperscript{21}

Schuch et al. provided robust evidence supporting the use of exercise as a primary treatment for MDD given its large effect size when compared to non-active controls.\textsuperscript{21} However, in order to determine the effect size of exercise as a primary treatment for MDD, the authors excluded studies in which exercise plus standard treatment was compared to standard treatment alone.\textsuperscript{21} While necessary for the goals of their study, this precluded their study from evaluating the effects of exercise as an adjunct to standard therapies such as medication or psychotherapy.

Kvam et al. (2016) conducted a meta-analysis examining the effects of exercise as either a primary treatment or as an adjunct to antidepressant medication.\textsuperscript{22} The authors used data to calculate effect sizes using random effects models. Similarly to Schuch et al.,\textsuperscript{21} the authors excluded studies in which tai-chi, or yoga were used as controls groups. The
primary outcome was the calculation of effect sizes using Hedges’ $g$, representing the difference between exercise and control groups in reducing depression scores.\textsuperscript{22}

The authors reported a statistically significant, moderate to large effect of exercise over all control conditions ($g = -0.68$, 95% CI -0.92 to -0.44, $p < 0.001$). However, this effect was small and no longer statistically significant at follow-up ($g = -0.22$, 95% CI -0.53 to 0.09, $p = .16$). The smaller effect size for exercise at follow-up is consistent with the findings of Cooney et al.\textsuperscript{19} The authors suggest that the antidepressant effects of exercise are likely of short duration and require continuous activity to maintain their effect, and in many studies the exercise intervention ceased prior to follow-up.\textsuperscript{22} No comment was made on whether compliance with exercise regimens was upheld during follow-up.

For part of their study, Kvam et al. investigated the effects of exercise against non-active controls only. Similarly to Schuch et al., the authors found a large effect size favoring exercise over no intervention ($g = -1.24$, 95% CI -1.83 to -0.65, $p < 0.001$). They additionally directly compared the effects of exercise on MDD to standard treatments, including psychotherapy and antidepressant medication. Similarly to the findings of other analyses,\textsuperscript{19,21} the authors found that there were small, non-significant effects for exercise compared to psychotherapy ($g = -0.22$, 95% CI -0.65 to 0.21, $p = .31$) or antidepressant medication ($g = -0.08$ (95% CI -0.33 to 0.18, $p = .55$)),\textsuperscript{22} indicating that exercise is comparable to either standard treatment for MDD.\textsuperscript{22}

The authors analyzed four studies in which exercise was added as an adjunct to antidepressant medication, and was the first meta-analysis to do so.\textsuperscript{22} Combination therapy generated a moderate effect over medication alone that was not statistically significant ($g = 0.50$, 95% CI -1.10 to 0.11, $p = .11$). The authors acknowledged the
limited applicability of this figure given it was based on four studies and that further research of combination therapy is warranted. Despite the limitations and need for future studies, the authors contend that evidence supports the use of exercise as primary treatment or as an adjunct to standard therapy for MDD.\textsuperscript{22}

Babyak et al. (2000) conducted a study comparing the long-term antidepressant effects of exercise, medication, and exercise plus medication;\textsuperscript{23} the results of this study were not included in the meta-analysis by Kvam et al.\textsuperscript{22} Investigators enrolled 156 adults age 50 or older with a diagnosis of MDD that had previously completed a study (A Study of Medical Information and Lifestyles in Eindhoven, “SMILE”)\textsuperscript{24} in which they underwent four months of treatment with aerobic exercise, sertraline (50-200mg/day), or aerobic exercise plus sertraline (50-200mg/day). The SMILE study compared depression scores at baseline and at four months with the primary outcome being mean changes in the HDRS.\textsuperscript{24} While patients in the medication group showed improvements in depression scores more quickly, there were no statistically or clinically significant differences between groups at the end of the four-month study.\textsuperscript{24} All three treatment groups demonstrated significant reductions in depression scores at four months which were not significantly different (exercise group, 60.4%; sertraline group, 65.5%; combination group, 68.8%; $p = .67$).\textsuperscript{24} Babyak et al. sought to investigate the impact of continued exercise beyond the study period on depressive symptoms at long-term follow-up, ten months after completion of the SMILE study.\textsuperscript{23}

At 10-month follow-up, subjects in the exercise-only group demonstrated significantly lower rates of MDD (exercise, 30%; sertraline, 52%; combination, 55%; $p = .028$) and increased likelihood of being in either partial or full remission (OR = 6.10, $p = .01$) than
subjects in the other two study groups. 64% of subjects in the exercise group and 66% of subjects in the combination group continued to exercise, while 48% of subjects in the sertraline groups started to exercise during the follow-up period. Multiple logistic regression analysis revealed that among subjects from all three groups, those who exercised regularly during the follow-up period were significantly less likely to meet diagnostic criteria for MDD at 10-month follow-up ($p<.0009$); this figure included adjustments for baseline depression, age, gender, and antidepressant use during the follow-up period.

This study represents lower-level evidence that exercise appears to be at least as efficacious as antidepressant medication in the treatment of MDD, which was supported in the meta-analyses reviewed previously. Additionally, subjects in the exercise group demonstrated significantly lower likelihood of relapse and higher likelihood of remission at ten-month follow-up. Importantly, regular exercise during the follow-up period was associated with a lower likelihood of relapse at follow-up, indicating that exercise may have a role in prolonging the antidepressant effects of treatments with shorter duration, such as psychotherapy or ketamine. Exercise did not augment the effects of antidepressant medication in this study, which limits the generalizability of exercise as a potential adjunct to other standard treatments. However, it was noted that a number of subjects spontaneously reported that they felt that sertraline interfered with the benefits of exercise. It is conceivable that the commonly reported side effects of sertraline such as fatigue or drowsiness contributed to this and interfered with synergy between exercise and medication. These adverse effects have not been reported in subjects receiving
ketamine therapy, rendering it unlikely that ketamine’s effects would negate the benefits of exercise.

**Review of Relevant Methodology**

The following section will review the methodology that has been employed in prior studies and justify the methodology to be used in the present proposal.

**Study Design**

The proposed study will be a single-blind, randomized controlled trial comparing ketamine to ketamine plus an exercise regimen for the treatment of MDD in an adult population. The use of an RCT design is consistent with previous trials investigating the antidepressant effects of ketamine as both a single infusion\(^6,7\) and as repeated infusions,\(^5,13\) and is also consistent with the design of numerous studies examining the antidepressant effects of exercise as a primary treatment or as an adjunct to standard treatments.\(^{19,21-23,26}\) The use of an RCT design in this study will optimize our ability to directly observe the impact of the addition of exercise regimens to established ketamine treatment protocols.

Unlike previous studies investigating the antidepressant effects of ketamine and exercise, the present study will not utilize a placebo control. The primary purpose of this study is to investigate whether exercise regimens augment the antidepressant effects of ketamine, and the study is designed to compare ketamine treatment alone to ketamine plus an exercise regimen in a similar population. Given that placebo controls for exercise such as yoga, stretching, and mindfulness have been demonstrated to influence depression symptoms and may confound results,\(^{20}\) a placebo control for exercise will not be utilized in this study. Instead, ketamine treatment alone will serve as a control group.
Study Population

The population that will be recruited for this study includes male and female adults, ages 18-65, that meet criteria for a clinical diagnosis of MDD based on criteria outlined in the DSM-5. The severity of depression will be moderate-severe, as measured by a score $\geq 20$ on the MADRS, in order to target a population most likely to respond to the exercise intervention. The population for this study was adapted from a number of RCTs investigating the antidepressant effects of ketamine.\textsuperscript{5-7,13,23,26} In the exercise literature, older adults were included in several trials but an upper age limit will be employed in this study given concerns regarding the safety of ketamine use in older populations.\textsuperscript{17}

Selection Criteria

The present study will utilize selection criteria based on methodology previously reported in a number of RCTs investigating the antidepressant effects of ketamine. These trials were all designed in a similar fashion and utilized a very similar set of inclusion and exclusion criteria.\textsuperscript{5-7,13,23,26} The inclusion criteria that will be employed in the present study will include a current diagnosis of MDD according to DSM-5, a current major depressive episode (MDE) of at least four weeks duration, moderate-severe depression as measured by a score $\geq 20$ on the MADRS, and being free of antidepressant medication for at least 2-4 weeks. Additionally, all subjects must demonstrate good overall health as evidenced by a comprehensive medical history, physical exam, and routine diagnostic studies.\textsuperscript{5-7,13,23,26}

The exclusion criteria will include a history of bipolar disorder or psychosis, a substance use disorder within the past three months (with the exception of tobacco use), medical contraindication to exercise, and current use of antidepressant medication.\textsuperscript{5-7,13,23,26} An
additional inclusion criterion that will be employed is a low-active lifestyle, defined as performing less than 20 minutes of exercise less than three times per week, in order to target a population most likely to benefit from exercise.\textsuperscript{27,28} The present study will enroll subjects with MDD rather than those with TRD, given that the vast majority of the literature on the antidepressant effects of exercise has been studied in MDD, and sparse evidence for the efficacy of exercise for TRD exists.

**Exercise Intervention**

There is a significant degree of variation in the type, intensity, frequency, duration, and setting of exercise interventions for MDD that have been studied in RCTs. As a result of this variation, the methodology for the present study will be adapted from evidence from systematic reviews and meta-analyses that provide higher-level evidence supporting the use of particular exercise interventions.\textsuperscript{19,21,22,29-32} For the exercise intervention in this study, subjects will ride on stationary bicycles at a moderate intensity, for 45-minute sessions, three times per week, for a total duration of three months. These parameters have been associated with the greatest effect sizes of exercise in reducing depressive symptoms.\textsuperscript{19,21,22,29-32} The exercise sessions will occur in a group setting under the supervision of a qualified fitness professional, which has been shown to improve compliance.\textsuperscript{19,21,22,27,31,33}

The definition of moderate intensity exercise will be adapted from the American College of Sports Medicine (ACSM). The ACSM defines moderate intensity exercise as activity that occurs at 64–76\% of an individual’s estimated maximum heart rate (HR).\textsuperscript{34} The ACSM states that an acceptable method for estimating maximum HR is using the
equation, \((\text{Max HR} = 220 – \text{age})\).\(^{34}\) The stationary cycling that will be utilized in this study complies with the definition of exercise as outlined by the ACSM.\(^{34}\)

The exercise intervention in this study will begin one day after the administration of the first ketamine treatment, in order to optimize the potential synergy between the two treatments without affecting baseline depression scores prior to the first ketamine treatment. Subjects in the ketamine plus exercise group will continue their exercise regimen throughout the follow-up phase because doing so has been associated with an increased likelihood of being in partial or full remission from an MDE.\(^{23,26}\)

**Ketamine Control**

All subjects in this study will be administered ketamine according to a standardized dose, route, frequency, and duration. All of the studies cited previously administered ketamine as an intravenous infusion, at a dose of 0.5mg/kg delivered over a 40-minute period.\(^{1,2,5-7,13}\) This protocol will be adapted for the present study.

All subjects will receive three ketamine infusions per week for two consecutive weeks, over a total period of 12 days. This is based on the frequency outlined by Murrough et al.\(^5\) This contrasts with data from Singh et al., who demonstrated that administration of ketamine twice per week for two weeks did not appear inferior to the protocol outlined by Murrough et al.\(^{13}\) However, the study by Murrough et al. was designed with a significantly longer follow-up period which provided a more robust characterization of the temporal scale of ketamine’s antidepressant effects. Therefore, the schedule studied by Murrough et al. will be adopted for this study.\(^5\)
Primary and Secondary Outcomes

The primary outcome in the present study will be the mean change in MADRS scores from a pre-treatment baseline to scores at four weeks of follow-up from the last ketamine infusion. Two previous studies measured changes in MADRS scores from baseline to the end of a two week period of repeated ketamine infusions as their primary outcome.\textsuperscript{5,13} However, these studies were designed to detect the efficacy of repeated infusions of ketamine in reducing depressive symptoms over a two week period. Change in MADRS scores was also the primary outcome in the study by Ibrahim et al. which investigated riluzole as an adjunct to ketamine therapy.\textsuperscript{16} Since our study is designed to detect the efficacy of exercise as an adjunct to enhance and prolong ketamine’s antidepressant effects, we will compare baseline MADRS scores to those taken four weeks after the last ketamine treatment. The time point of four weeks was selected based on the observation that ketamine’s antidepressant effects had subsided by 27 days in the majority of subjects in two prior trials studying repeated infusions of ketamine over a two week period.\textsuperscript{5,13}

A secondary outcome of interest will be the time to extinction of observed reductions in MADRS scores as measured by Kaplan-Meier analysis.\textsuperscript{16} Extinction will be defined as a relapse to a $\leq 50\%$ reduction of an individual’s baseline MADRS score; this was the definition of relapse utilized in a number of previous studies.\textsuperscript{5,13,16} Additional secondary outcomes will include the Beck Depression Inventory-II (BDI-II), Clinician-Administered Dissociative States Scale (CADSS), Brief Psychiatric Rating Scale (BPRS), and Visual Analog Scale of Mood States (VAS). The BDI-II provides a comparison measure to changes in MADRS scores, while the CADSS, BPRS, and VAS are measured to evaluate the psychotomimetic effects of ketamine on subjects during and
following infusions. This is most consistent with secondary outcomes employed in numerous past studies investigating ketamine’s antidepressant effects.\textsuperscript{5-7,13,16,23}

**Sample Size**

This study will utilize an alpha of 5% and a beta of 20% to power the study to 80%, similar to previous trials evaluating exercise as a treatment for MDD.\textsuperscript{28} We aim to detect a 9.5% difference in mean reductions in MADRS scores between the two groups, which has been demonstrated to be a statistically significant reduction in MADRS scores in a prior study comparing exercise to mind-body awareness as adjuncts to antidepressant medication.\textsuperscript{35} This is similar to the effect sizes reported for exercise in reducing depressive symptoms when compared to other active treatments in several meta-analyses.\textsuperscript{19,21,22} This effect size is above the minimum clinically important difference (MCID) that has been documented for the MADRS scale.\textsuperscript{36} We anticipate a 15% loss to follow-up based on prior studies and will correct the sample size for this variable.\textsuperscript{35,37} Calculations for the sample size are in Appendix I.

**Statistical Analysis**

There is a significant degree of variation in the methodologies utilized for statistical analysis in the literature for both ketamine and exercise for depression. The primary outcome of mean change in MADRS scores will be analyzed with paired \( t \)-tests and repeated measures analysis of variance (ANOVA), comparing baseline scores to scores measured four weeks following the last ketamine infusion. The secondary outcome of scores on the BDI-II will be analyzed with the same methodology. This is most similar to the methods employed by studies of exercise as an adjunct to standard treatments for depression.\textsuperscript{28}
The secondary outcome of time to extinction of observed reductions in MADRS scores will be analyzed with Kaplan-Meier analysis. Extinction will be defined as a relapse to a ≤50% reduction from an individual’s baseline MADRS scores; this was the definition of relapse utilized in a number of previous studies.\textsuperscript{5,13,16}

**Review of Possible Confounders**

This study is designed to optimally control for factors that may confound the results. Both the ketamine and exercise interventions were designed such that all subjects undergo as similar a treatment as possible. All subjects in both study groups will receive ketamine at the same dose, route, duration, and frequency. Some past studies were flexible in allowing subjects to determine the intensity of exercise they performed in clinical trials\textsuperscript{31}; the internal and external validity of these studies were limited as a result of the variability in exercise regimens that subjects performed. The exercise intervention for this study was designed such that all subjects in the ketamine plus exercise group undergo exercise of the same type, intensity, duration, and frequency to control for confounding factors.

Past studies have utilized control conditions such as yoga, tai chi, meditation, and stretching under the assumption that they represent an inactive control group. However, subsequent studies have demonstrated that these behaviors may influence depression scores and therefore represent a source of confounding.\textsuperscript{20-22} For this reason, the present study will not utilize an active control group as a direct comparison to exercise.

Concomitant use of antidepressant medications represents another possible source of confounding. Several past studies investigating ketamine for depression utilized a “washout” period in which all antidepressant medications were discontinued for two
weeks (four weeks for fluoxetine) prior to beginning ketamine treatment.\textsuperscript{5,7,13} Similarly, the present study will require subjects to discontinue antidepressant medications for a period of time prior to starting the study. The use of other psychotropic medication will be permitted but will be measured as a baseline demographic in order to ensure that both study groups are as similar as possible regarding concomitant use of medication.

Variation in baseline activity levels would likely confound the changes in depression scores in subjects in the ketamine plus exercise group. In order to control for this factor, this study will utilize sedentary lifestyle as a selection criterion. This was adapted from prior studies that defined a low-active lifestyle as receiving less than 20 minutes of exercise, less than three times per week.\textsuperscript{27,28}

**Conclusion**

In this chapter, we reviewed the efficacy of ketamine as a rapid-acting antidepressant, both as a single infusion and as a series of repeated infusions over a period of approximately two weeks. The utility of ketamine as an antidepressant agent is limited by its short duration, with most individuals experiencing a recurrence of depressive symptoms within two weeks of their last dose. Furthermore, ketamine’s utility is limited by concerns for abuse and its safety when used in the long-term.

In order to address the shortcomings of ketamine’s antidepressant effects, two strategies have been investigated as possible therapeutic adjuncts to ketamine to prolong its antidepressant response. The results have been mixed, but preliminary evidence suggests that ketamine’s antidepressant effects may be amenable to augmentation strategies.
Exercise has been proven to possess antidepressant effects that are comparable to existing psychological and pharmacologic treatments for depression but come without the adverse effects of medication or the costs associated with psychotherapy. Research has indicated that moderate to vigorous aerobic exercise of at least 30 minutes duration, performed under supervision of an exercise professional 3-4 times per week, for a period of at least three months provides optimal improvement in depressive symptoms in adults with MDD and may be an effective augmentation strategy when used with existing depression treatments. The current proposal will be designed to evaluate the efficacy of aerobic exercise as a therapeutic adjunct to potentiate or prolong the antidepressant effects of ketamine therapy for the treatment of moderate-severe MDD in adults.

Chapter 2 References


20. Ekkekakis P. Honey, I shrank the pooled SMD! Guide to critical appraisal of systematic reviews and meta-analyses using the Cochrane review on exercise for depression as example. Mental Health and Physical Activity 2015;8:21-36.


CHAPTER 3: METHODS

Study Design

The proposed study will be a prospective, single-blind, randomized controlled trial (RCT) investigating whether the addition of exercise regimens will prolong or potentiate the antidepressant effects of ketamine in a population of adults with major depressive disorder (MDD). This study is specifically designed to compare changes in depression scores between two study groups: one group receiving ketamine treatment and a second group receiving ketamine treatment plus an exercise regimen to perform (subsequently referred to as the “ketamine only” and “ketamine plus exercise” groups, respectively). Depression scores measured at baseline will be compared to scores following treatment and scores throughout a three-month follow-up period.

This study will be carried out in two phases. Phase I will be the ketamine treatment phase. During Phase I, all subjects in both study groups will receive intravenous (IV) ketamine infusions three times per week for a total of two weeks. The subjects in the exercise group will begin their exercise regimens at the beginning of this phase. Phase II will be the three-month follow-up phase. During Phase II, the subjects in the ketamine group will not undergo any additional treatment but will report to the clinic for evaluation once per week for four weeks, and subsequently every other week for eight weeks during the remainder of the follow-up period. The subjects in the exercise group will continue their exercise regimens and will also report for evaluation according to the same schedule without receiving any additional ketamine treatments.
Study Population and Sampling

The study population will include adult males and females ages 18-65 with a diagnosis of moderate-severe MDD that live in the state of Connecticut. Convenience sampling will be utilized to obtain the study population, in order to facilitate the operationalization of the recruitment process. Subjects will be sampled from outpatient primary care and psychiatry clinics in New Haven and Fairfield counties.

Selection Criteria

Inclusion criteria will include meeting criteria for diagnosis of MDD according to diagnostic criteria within the DSM-5, current major depressive episode (MDE) of at least four weeks duration, a score $\geq 20$ on the Montgomery-Åsberg Depression Rating Scale (MADRS), and low-active lifestyle defined as $< 20$ minutes of exercise $< 3$ times per week. Additionally, all subjects must be in good health as determined by a comprehensive medical history, physical exam, urinalysis, urine toxicology screen, electrocardiogram, complete blood count, and basic metabolic panel.

Exclusion criteria will include a lifetime history of bipolar disorder or psychotic disorder, substance use disorder in the past three months (with the exception of tobacco use), medical conditions precluding participation in exercise, medical contraindication to receiving ketamine, current use of antidepressant medication, and pregnant or nursing women. Other comorbid psychiatric disorders will be permitted if MDD is determined to be the primary complaint.

Subject Protection and Confidentiality

The proposed study will require the approval of the Institutional Review Board (IRB) through the Yale University Human Investigation Committee (HIC). All study personnel
will be required to complete Yale Human Subjects Protection training as well as training on the Health insurance Portability and Accountability Act (HIPAA). Only pertinent subject identifiers will be collected. All confidential patient information and data to be collected will be stored on secured networks with password protection. Informed consent will be obtained from all subjects prior to enrollment in the study. Subjects will be informed that their participation is entirely voluntary and that they may withdraw from the study at any time.

**Recruitment**

Subjects will be recruited with the use of advertisements placed at local hospitals, outpatient primary care and psychiatry clinics, local psychotherapy practices, local universities, local grocery stores, online, and in local newspapers. Subjects will also be recruited on the basis of referrals from local physicians and advanced practice practitioners.

**Study Variables and Measures**

**Independent Variable**

The independent variable in this study will be the prescription of an exercise regimen, which will only be prescribed to the exercise study group. Subjects in the exercise group will begin exercising the day after their first ketamine infusion and will continue exercising throughout the follow-up period. Subjects in the ketamine only group will be instructed to maintain their usual baseline activity levels during both phases of the study. The exercise intervention will be performed in a group setting and will be supervised by an exercise physiologist. Subjects will be encouraged to ride on stationary bicycles in 40-
minute sessions, at a moderate intensity (64-76% of estimated maximum heart rate), three
times per week. The stationary bicycles will be equipped with heart rate monitors for
continuous biofeedback during sessions, allowing subjects to titrate their efforts to
maintain moderate intensity exercise throughout the session to the best of their ability.

**Dependent Variable**

The dependent variable in this study will be changes in baseline MADRS scores at
various time points following ketamine infusions and throughout the follow-up period.

**Control Condition**

The control condition in this study will be the prescription of ketamine infusions.
Subjects in both study groups will receive ketamine treatments of the same dose, route,
duration, and frequency. For each individual treatment, ketamine will be administered
intravenously at a dose of 0.5mg/kg over a period of 40 minutes. All subjects will receive
a ketamine infusion three times per week for two weeks, in the first two weeks of the
study (Phase I).

**Primary and Secondary Outcomes**

The primary outcome will be the mean change in MADRS scores from baseline to scores
at four weeks after the last ketamine treatment. Secondary outcomes will include time to
extinction of reductions in MADRS scores during follow-up, mean change in MADRS
scores from pre-treatment baseline to post-treatment follow-up at study day 13 (24 hours
after the final ketamine treatment), suicidality (as a separate item on the MADRS), and
scores on the Visual Analog Scale of Mood States (VAS), Clinician-Administered
Dissociative States Scale (CADSS), Brief Psychiatric Rating Scale (BPRS), and the Beck
Depression Inventory-II (BDI-II) measured throughout the study.
Baseline characteristics

The following baseline characteristics will be measured prior to the start of the study: age, sex, race, years since initial diagnosis of MDD, number of lifelong MDEs, duration of present MDE, number of past treatments, prior antidepressant use, current medications, comorbid psychiatric disorders, baseline MADRS scores, BMI, and lifetime substance use disorder.

Methodology Considerations

Blinding of Intervention: Subjects will not be blinded to the exercise intervention, given that it will not be feasible to blind subjects to whether or not they are exercising. Evaluators will be blinded to the study groups that subjects have been assigned to.

Blinding of Outcome: All evaluators will be blinded to the primary and secondary outcomes.

Assignment of Intervention: Subjects will be randomly allocated to either the ketamine only group or the ketamine plus exercise group, in a 1:1 fashion, using a computer-generated algorithm.

Adherence: Adherence with exercise regimens will be monitored by several certified exercise physiologists, who will be present at all exercise sessions throughout the study and will take attendance and also monitor subjects’ heart rate during exercise sessions. Adherence with ketamine treatments will be monitored by the research nurse at infusion appointments.

Adverse events: Psychotomimetic effects will be measured using the VAS, CADSS, and BPRS. All adverse effects of ketamine treatment will be recorded by the research nurse.
All adverse events related to the exercise intervention will be documented by the exercise physiologist.

**Data Collection**

Subject eligibility will first be assessed via telephone screening and by a preliminary medical record review. At the screening visit, our research team will explain the overall study plan to potential subjects and review the consent form. Subjects will have an initial screening evaluation that will include psychiatric history, medical history, physical examination, and laboratory assessment. Other detailed procedures are described in Table 1. If the examination and test results are acceptable and the subject meets the inclusion and exclusion criteria, the subject will be invited to the 6 ketamine infusion visits. During the ketamine infusion sessions, rating scales (MADRS, BDI-II, BPRS, CADSS, VAS) will be measured at -60, 0, +60, and +240 minutes. The exercise intervention in the ketamine plus exercise group will begin one day after the first ketamine treatment will continue throughout the follow-up phase.

**Sample Size Calculation**

This study will utilize two-sided hypothesis testing with an alpha of 5% and a beta of 20%, which will power the study to 80%. We aim to detect a 9.5% difference in mean reductions in MADRS scores between ketamine treatment alone and ketamine treatment plus an exercise regimen at four weeks post-treatment.\(^1\) Based on these parameters, we will require a sample size of 52 total subjects, with 26 subjects assigned to each study group. The sample size was calculated using Power and Precision software (Power and Precision. Version 4. Biostat, Inc. Englewood, NJ). We anticipate a 15% loss to follow-
up; correction for this variable leads to a total sample size of 60 subjects with 30 subjects per treatment group. Calculations for the sample size can be found in Appendix I.

Table 1. Procedures involved from screening visit to visit 16

<table>
<thead>
<tr>
<th>Visit</th>
<th>1 Screening</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8 F/U</th>
<th>9-12 Weekly</th>
<th>13-16 Q 2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>-14-0</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>10</td>
<td>12</td>
<td>13</td>
<td>19,26,33</td>
<td>54, 68, 82, 94</td>
</tr>
<tr>
<td>Exercise intervention</td>
<td>3 times a week</td>
<td>3 times a week</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Ketamine Infusions</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Informed Consent</td>
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<tr>
<td>Inclusion/Exclusion</td>
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<td></td>
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<tr>
<td>Demographics</td>
<td>X</td>
<td></td>
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<tr>
<td>SCID</td>
<td>X</td>
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<tr>
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<tr>
<td>Physical Exam</td>
<td>X</td>
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<tr>
<td>CBC, Chemistry, Urinalysis</td>
<td>X</td>
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<tr>
<td>Urine toxicology/pregnancy</td>
<td>X</td>
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<tr>
<td>BP, Pulse</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MADRS, BDI-II</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BPRS, CADSS, VAS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Adverse Event</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: Structured Clinical Interview (SCID), Montgomery-Asberg Depression Rating Scale (MADRS), Beck Depression Inventory-II (BDI-II), Brief Psychiatric Rating Scale (BPRS), Clinician-Administered Dissociative States Scale (CADSS), Visual Analog Scale (VAS) of Mood States, Complete Blood Count (CBC), blood pressure (BP)

Statistical Analysis

All data collected in the proposed study will be analyzed using an intention-to-treat protocol. P-values <0.05 will be considered statistically significant for all analyses. All statistical analyses will be performed using the Statistical Package for the Social Sciences (IBM; SPSS version 25). The primary outcome of mean change in MADRS scores will be analyzed using a paired t-test, which will compare MADRS scores measured at baseline to those measured at four weeks following the last ketamine infusion. The
secondary outcome of time to extinction of observed reductions in MADRS scores will be analyzed using Kaplan-Meier analysis. This will measure MADRS scores throughout the entire three-month follow-up period. This measure will be a dichotomous outcome defined by whether subjects maintained a >50% reduction in baseline MADRS scores periodically throughout the follow-up period of the study. An additional secondary outcome of mean reduction in MADRS scores between groups after the completion of Phase I (ketamine treatment) will be analyzed with a paired t-test. The secondary outcomes of scores on the VAS, CADSS, BPRS, and BDI-II will be measured with paired t-tests. Baseline characteristics between groups will be analyzed appropriately; continuous variables will be analyzed with paired t-tests and categorical variables will be analyzed with Chi-Square tests. Analysis of Variance (ANOVA) will be performed on any differences in baseline characteristics that are found to be statistically significant following randomization of study groups.

**Timeline and Resources**

We plan to complete this study in 26 months as follows: (a) IRB approval and training research staff (3 months), (b) recruitment of 60 subjects (20 months; 3 subjects/month), and (c) data analysis and manuscript preparation (3 months). The Co-Principal Investigators (physician assistant student and psychiatrist) will be responsible for project oversight, clinical oversight, medical evaluation, recruitment, infusion day procedures, data analyses, and manuscript preparation. Three research assistants will be responsible for recruitment, scheduling, orienting, and consenting subjects, administering self-rated rating scales, coordinating laboratory work, working with the investigational pharmacy, and overseeing the accuracy of the record form. The administration of ketamine to
subjects will require the assistance of a registered nurse. A pharmacist will be required for the preparation and allocation of ketamine infusions to study subjects. Four exercise physiologists will be required to supervise subjects undergoing exercise routines. A statistician will be utilized to lead data analysis for the study.

**Chapter 3 References**

CHAPTER 4: CONCLUSION

Advantages and Disadvantages

The design of this study provides a number of advantages that optimize the probability of providing positive results to confirm the study hypothesis. The utilization of a randomized controlled trial (RCT) design allows for direct observation and measurement of the efficacy of exercise as an adjunct to ketamine treatment for major depressive disorder (MDD), and is consistent with prior trials investigating the antidepressant effects of both ketamine and exercise. The use of the Montgomery-Åsberg Depression Rating Scale (MADRS) as the primary outcome is best suited to track changes in depression scores in the setting of antidepressant treatment.¹

The internal validity of this study is strengthened by rigorous inclusion criteria that are designed to target a population that is most likely to respond to exercise as a treatment for MDD while balancing control for possible confounders. Specifically, the inclusion of adults with baseline MADRS scores ≥20 and low baseline activity levels will enhance the probability of demonstrating a clinically significant response to exercise.

The exclusion criteria are primarily designed to control for confounding factors. The exclusion of subjects with comorbid psychiatric disorders, history of recent substance use disorder, and medical contraindication to exercise strengthens the internal validity of the study but simultaneously limits the generalizability of its results given that MDD may be comorbid with any of these conditions. The exclusion of subjects currently using antidepressant medication is necessary to most closely examine the true antidepressant effects of ketamine with exercise.
The exercise regimen to be utilized in this study is most consistent with research literature that specifically demonstrates antidepressant effects in adults with MDD. This regimen was tailored to the type, frequency, duration, and setting of exercise that has shown the largest antidepressant effects in the literature. The protocol of ketamine treatments is also adapted directly from a series of studies that consistently demonstrated ketamine’s antidepressant effects, allowing for close evaluation of whether exercise augments ketamine therapy for MDD.

This study has several limitations. The most significant limitation in the design of this study is that it is not a placebo-controlled, double-blind study. This study is designed to evaluate the efficacy of exercise as an adjunct to ketamine treatment, and is not designed to evaluate the efficacy of ketamine given that its antidepressant effects are well-established; for this reason, ketamine treatment alone was chosen as the control condition. The study was not blinded given that it is not practical to blind subjects to whether or not they are physically exercising, and comparison conditions such as yoga, tai chi, and stretching have been shown to influence depressive symptoms and potentially underestimate the effect of exercise. However, evaluators will be blinded to the study groups that subjects have been assigned to.

The use of exercise professionals to supervise exercise sessions was employed based on findings that it improves compliance and provides for greater improvements in depressive symptoms in prior studies. However, in real-world settings the use of fitness instructors can be costly and may hinder access to exercise, decreasing the generalizability of our results.
Finally, there are concerns with the use of ketamine to treat MDD given its abuse potential. Ketamine infusions will be administered in a supervised research setting, minimizing the potential for abuse in study subjects. Additionally, subjects with a history of substance use disorders will be excluded to improve validity and reduce confounding. Other concerns include the acute side effect profile of ketamine. As with any medication, investigators will educate patients about the risks and benefits of ketamine treatment and patients with contraindications to ketamine use will be excluded from the study.

**Clinical Significance and Implications**

The primary implications of this study surround the possibility of augmenting and prolonging ketamine’s antidepressant effects, which is desirable for several reasons. Given its short duration, ketamine would need to be administered frequently to sustain its antidepressant effects in the long-term. The adverse effects of long-term ketamine use are unknown, and questions remain regarding its abuse potential. The ability to administer ketamine less frequently is therefore desirable, and this could be achieved by prolonging its effects with an augmentation strategy such as adjunct exercise regimens. Less frequent administration of ketamine would also theoretically reduce the cost and improve convenience for patients.

**Chapter 4 References**


15. Ekkekakis P. Honey, I shrunk the pooled SMD! Guide to critical appraisal of systematic reviews and meta-analyses using the Cochrane review on exercise for depression as example. Mental Health and Physical Activity 2015;8:21-36.

APPENDIX

Appendix I: Sample Size Calculations

\[ k = \frac{n_2}{n_1} = 1 \]

\[ n_1 = \frac{(\sigma^2_1 + \sigma^2_2/K)(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2} \]

\[ n_1 = \frac{(7.3^2 + 7.3^2/1)(1.96 + 0.84)^2}{5.7^2} \]

\[ n_1 = 26 \]

\[ n_2 = K \times n_1 = 26 \]

\[ \Delta = |\mu_2 - \mu_1| = \text{absolute difference between two means} \]
\[ \sigma_1, \sigma_2 = \text{variance of mean #1 and #2} \]
\[ n_1 = \text{sample size for group #1} \]
\[ n_2 = \text{sample size for group #2} \]
\[ \alpha = \text{probability of type I error} \]
\[ \beta = \text{probability of type II error} \]
\[ z = \text{critical Z value for a given } \alpha \text{ or } \beta \]
\[ k = \text{ratio of sample size for group #2 to group #1} \]

Correction for anticipated loss to follow-up:

We anticipate 15% loss to follow-up based on prior studies.

\[ 0.15 \times 52 = 7.8 \rightarrow 52 + 7.8 = 59.8 \]

We will round up for total sample size of n= 60, providing 30 subjects per study group.
Appendix II: Montgomery-Åsberg Depression Rating Scale (MADRS)

The following was adapted from the original publication of the MADRS by Montgomery and Åsberg (1979).\(^7\)

<table>
<thead>
<tr>
<th>1. Apparent Sadness</th>
<th>6. Concentration Difficulties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representing depressivity; gloom and despair. (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate on depth and inability to brighten up.</td>
<td>Representing difficulties in collecting one's thoughts in one's own mind. Rate according to intensity, frequency, and degree of incapacity produced.</td>
</tr>
<tr>
<td>0 No sadness</td>
<td>0 No difficulties in concentrating.</td>
</tr>
<tr>
<td>1 Looks dispirited but does brighten up without difficulty.</td>
<td>1 Occasional difficulties in collecting one's thoughts.</td>
</tr>
<tr>
<td>2 Appears sad and unhappy most of the time.</td>
<td>3 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.</td>
</tr>
<tr>
<td>3 Looks miserable all the time. Extremely despondent.</td>
<td>5 Unable to read or converse without great effort.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Reported Sadness</th>
<th>7. Lack of initiative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or feeling of being beyond help without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.</td>
<td>Representing a difficulty getting started or slowness in initiating and performing everyday activities.</td>
</tr>
<tr>
<td>0 Occasional sadness in keeping with the circumstances.</td>
<td>0 Hardly any difficulty in getting started. No sluggishness.</td>
</tr>
<tr>
<td>1 Sad or low but brightens up without difficulty.</td>
<td>1 Difficulties in starting activities.</td>
</tr>
<tr>
<td>2 Pensive feelings of sadness or gloominess. Mood is still influenced by external circumstances.</td>
<td>3 Difficulties in starting simple routine activities which are carried out with effort.</td>
</tr>
<tr>
<td>3 Continuous or uneasy sadness; misery or despondency.</td>
<td>5 Complete lack of initiative. Unable to do anything without help.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Inner Tension</th>
<th>8. Inability to feel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representing feelings of ill-defined discomfort, edginess, inner turmoil mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.</td>
<td>Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.</td>
</tr>
<tr>
<td>0 Placid. Only reflecting inner tension.</td>
<td>0 Normal interest in the surroundings and in other people.</td>
</tr>
<tr>
<td>1 Occasional feelings of edginess and ill-defined discomfort.</td>
<td>1 Reduced ability to enjoy usual interest.</td>
</tr>
<tr>
<td>2 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.</td>
<td>3 Loss of interest in surroundings. Loss of feelings for friends and acquaintances.</td>
</tr>
<tr>
<td>3 Unrelenting dread or anguish. Overwhelming panic.</td>
<td>5 The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Reduced Sleep</th>
<th>9. Passimistic Thoughts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.</td>
<td>Representing thoughts of guilt. Inferiority, self-reproach, selfishness, remorse and ruin.</td>
</tr>
<tr>
<td>0 Sleeps as usual.</td>
<td>0 No passimistic thoughts.</td>
</tr>
<tr>
<td>0 Slight difficulty dropping off to sleep or slightly reduced light or fitful sleep.</td>
<td>1 Fluctuating ideas of guilt, self reproach or self-deprecation.</td>
</tr>
<tr>
<td>3 Sleep reduced or broken by at least two hours.</td>
<td>3 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly passimistic about the future.</td>
</tr>
<tr>
<td>5 Less than two or three hours sleep.</td>
<td>5 Delusions of ruin, remorse or unreadable sin. Self-accusations which are absurd and unanswerable.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Reduced Appetite</th>
<th>10. Suicidal Thoughts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representing the feeling of loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.</td>
<td>Representing the feeling that life is not worth living. That a natural death would be welcome, suicidal thoughts, and the preparations for suicide. Suicidal attempts should not influence the rating.</td>
</tr>
<tr>
<td>0 Normal or increased appetite.</td>
<td>0 Enjoys life or takes it as it comes.</td>
</tr>
<tr>
<td>1 Slightly reduced appetite.</td>
<td>1 Weary of life. Only fleeting suicidal thoughts.</td>
</tr>
<tr>
<td>3 No appetite. Food is tasteless.</td>
<td>3 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.</td>
</tr>
<tr>
<td>5 Needs persuasion to eat.</td>
<td>5 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.</td>
</tr>
</tbody>
</table>

Total Score: ____________________________
Appendix III: Clinician-Administered Dissociative Symptoms Scale (CADSS)

The following table represents an example of the questions that appear on the CADSS, adapted from Bremner et al. (1998).

<table>
<thead>
<tr>
<th>Subjective Items</th>
<th>r</th>
<th>No. Endorsed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At this time, in this room:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Do things seem to be moving in slow motion?</td>
<td>.55***</td>
<td>33 (48%)</td>
</tr>
<tr>
<td>2. Do things seem to be unreal to you, as if you are in a dream?</td>
<td>.70***</td>
<td>28 (41%)</td>
</tr>
<tr>
<td>3. Do you have some experience that separates you from what is happening; for instance, do you feel as if you are in a movie or a play, or as if you are a robot?</td>
<td>.61**</td>
<td>32 (47%)</td>
</tr>
<tr>
<td>4. Do you feel as if you are looking at things from outside of your body?</td>
<td>.77***</td>
<td>24 (35%)</td>
</tr>
<tr>
<td>5. Do you feel as if you are watching the situation as an observer or spectator?</td>
<td>.53**</td>
<td>36 (53%)</td>
</tr>
<tr>
<td>6. Do you feel disconnected from your own body?</td>
<td>.57**</td>
<td>24 (35%)</td>
</tr>
<tr>
<td>7. Does your sense of your own body feel changed; for instance, does your own body feel unusually large or unusually small?</td>
<td>.61**</td>
<td>20 (29%)</td>
</tr>
<tr>
<td>8. Do people seem motionless, dead, or mechanical?</td>
<td>.62***</td>
<td>23 (34%)</td>
</tr>
<tr>
<td>9. Do objects look different than you would expect?</td>
<td>.71***</td>
<td>15 (22%)</td>
</tr>
<tr>
<td>10. Do colors seem to be diminished in intensity?</td>
<td>.71**</td>
<td>23 (34%)</td>
</tr>
<tr>
<td>11. Do you see things as if you were in a tunnel, or looking through a wide angle photographic lens?</td>
<td>.81***</td>
<td>28 (41%)</td>
</tr>
<tr>
<td>12. Does this experience seem to take much longer than you would have expected?</td>
<td>.49**</td>
<td>29 (43%)</td>
</tr>
<tr>
<td>13. Do things seem to be happening very quickly, as if there is a lifetime in a moment?</td>
<td>.61***</td>
<td>21 (31%)</td>
</tr>
<tr>
<td>14. Do things happen that you later cannot account for?</td>
<td>.85***</td>
<td>22 (32%)</td>
</tr>
<tr>
<td>15. Do you space out, or in some other way lose track of what is going on?</td>
<td>.74***</td>
<td>37 (54%)</td>
</tr>
<tr>
<td>16. Do sounds almost disappear or become much stronger than you would have expected?</td>
<td>.71**</td>
<td>33 (48%)</td>
</tr>
<tr>
<td>17. Do things seem to be very real, as if there is a special sense of clarity?</td>
<td>.45**</td>
<td>34 (50%)</td>
</tr>
<tr>
<td>18. Does it seem as if you are looking at the world through a fog, so that people and objects appear far away or unclear?</td>
<td>.74**</td>
<td>25 (37%)</td>
</tr>
<tr>
<td>19. Do colors seem much brighter than you would have expected?</td>
<td>.61**</td>
<td>18 (26%)</td>
</tr>
</tbody>
</table>

| Observer Items                                                                 |       |                  |
| 20. Did the subject seem eerie or strange, or in some other way give you an uncomfortable feeling? | .52** | 17 (25%)         |
| 21. Did the subject blank out or space out, or in some other way appear to have lost track of what was going on? | .59** | 20 (29%)         |
| 22. Did the subject appear to be separated or detached from what is going on, as if not a part of the experience or not responding in a way that you would expect? | .54** | 23 (34%)         |
| 23. Did the subject say something bizarre or out of context, or not speak when you would have expected it? | .25*  | 8 (12%)          |
| 24. Did the subject behave in a bizarre, unexpected manner, or show no movement at all, being stiff and wooden? | .35** | 7 (10%)          |
Appendix IV: Brief Psychiatric Rating Scale (BPRS)

Adapted from the original publication of the BPRS by Overall et al. (1962).  

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Somatic Concern: Degree of concern over present bodily health. Rate the degree to which physical health is perceived as a problem by the patient, whether complaints have a realistic basis or not.</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Anxiety: Worry, fear, or over-concern for present or future. Rate solely on the basis of verbal report of patient's own subjective experiences. Do not infer anxiety from physical signs or from neurotic defense mechanisms.</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Emotional Withdrawal: Deficiency in relating to the interviewer and to the interviewer situation. Rate only the degree to which the patient gives the impression of failing to be in emotional contact with other people in the interview situation.</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Conceptual Disorganization: Degree to which the thought processes are confused, disconnected, or disorganized. Rate on the basis of integration of the verbal products of the patient; do not rate on the basis of patient's subjective impression of his own level of functioning.</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Guilt Feelings: Over-concern or remorse for past behavior. Rate on the basis of the patient's subjective experiences of guilt as evidenced by verbal report with appropriate affect; do not infer guilt feelings from depression, anxiety or neurotic defenses.</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Tension: Physical and motor manifestations of tension &quot;nervousness&quot;, and heightened activation level. Tension should be rated solely on the basis of physical signs and motor behavior and not on the basis of subjective experiences of tension reported by the patient.</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Mannerisms and Posturing: Unusual and unnatural motor behavior, the type of motor behavior which causes certain mental patients to stand out in a crowd of normal people. Rate only abnormality of movements; do not rate simple heightened motor activity here.</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Grandiosity: Exaggerated self-opinion, conviction of unusual ability or powers. Rate only on the basis of patient's statements about himself or self-in relation-to-others, not on the basis of his demeanor in the interview situation.</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>Depressive Mood: Despondency in mood, sadness. Rate only degree of despondency do not rate on the basis of inferences concerning depression based upon general retardation and somatic complaints.</td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>Hostility: Animosity, contempt, belligerence, disdain for other people outside the interview situation. Rate solely on the basis of the verbal report of feelings and actions of the patient toward others; do not infer hostility from neurotic defenses, anxiety, nor somatic complaints. Rate attitude toward interviewer under 'uncooperativeness'.</td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>Suspiciousness: Brief (illusional or otherwise) that others have now, or have had in the past, malicious or discriminatory intent toward the patient. On the basis of verbal report, rate only those suspicions which are currently held whether they concern past or present circumstances.</td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>Hallucinatory Behavior: Perceptions without normal external stimulus correspondence. Rate only those experiences which are reported to have occurred within the last week and which are described as distinctly different from the thought and imagery processes of normal people.</td>
<td></td>
</tr>
<tr>
<td>13.</td>
<td>Motor Retardation: Reduction in energy level evidenced in slowed movements. Rate on the basis of observed behavior of the patient only; do not rate on the basis of patient's subjective impression of own energy level.</td>
<td></td>
</tr>
<tr>
<td>14.</td>
<td>Uncooperativeness: Evidence of resistance, unfriendliness, resentment, and lack of readiness to cooperate with the interviewer. Rate only on the basis of the patient's attitude and responses to the interviewer and the interview situation; do not rate on basis of reported resentment or uncooperativeness outside the interview situation.</td>
<td></td>
</tr>
<tr>
<td>15.</td>
<td>Unusual Thought Content: Unusual, odd, strange or bizarre thought content. Rate here the degree of unusualness, not the degree of disorganization of thought processes.</td>
<td></td>
</tr>
<tr>
<td>16.</td>
<td>Blunted Affect: Reduced emotional tone, apparent lack of normal feeling or involvement.</td>
<td></td>
</tr>
<tr>
<td>17.</td>
<td>Excitement: Heightened emotional tone, agitation, increased reactivity.</td>
<td></td>
</tr>
<tr>
<td>18.</td>
<td>Disorientation: Confusion or lack of proper association for person, place or time.</td>
<td></td>
</tr>
</tbody>
</table>
Appendix V: Beck Depression Inventory-II (BDI-II)

Adapted from the Manual for the Beck Depression Inventory-II.\textsuperscript{61}
### Beck Depression Inventory

#### Baseline

**Patient Inits:**

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>11. Agitation</strong></td>
<td>0: I am no more restless or wound up than usual. 1: I feel more restless or wound up than usual. 2: I am so restless or agitated that it's hard to stay still. 3: I am so restless or agitated that I have to keep moving or doing something.</td>
</tr>
<tr>
<td><strong>12. Loss of Interest</strong></td>
<td>0: I have not lost interest in other people or activities. 1: I am less interested in other people or things than before. 2: I have lost most of my interest in other people or things. 3: It's hard to get interested in anything.</td>
</tr>
<tr>
<td><strong>13. Indecisiveness</strong></td>
<td>0: I make decisions about as well as ever. 1: I find it more difficult to make decisions than usual. 2: I have much greater difficulty in making decisions than I used to. 3: I have trouble making any decisions.</td>
</tr>
<tr>
<td><strong>14. Worthlessness</strong></td>
<td>0: I do not feel I am worthless. 1: I don't consider myself as worthwhile and useful as I used to. 2: I feel more worthless as compared to other people. 3: I feel utterly worthless.</td>
</tr>
<tr>
<td><strong>15. Loss of Energy</strong></td>
<td>0: I have as much energy as ever. 1: I have less energy than I used to have. 2: I don't have enough energy to do very much. 3: I don't have enough energy to do anything.</td>
</tr>
<tr>
<td><strong>16. Changes in Sleeping Pattern</strong></td>
<td>0: I have not experienced any change in my sleeping pattern. 1a: I sleep somewhat more than usual. 1b: I sleep somewhat less than usual. 2a: I sleep a lot more than usual. 2b: I sleep a lot less than usual. 3a: I sleep most of the day. 3b: I wake up 1-2 hours early and can't get back to sleep.</td>
</tr>
<tr>
<td><strong>17. Irritability</strong></td>
<td>0: I am no more irritable than usual. 1: I am more irritable than usual. 2: I am much more irritable than usual. 3: I am irritable all the time.</td>
</tr>
<tr>
<td><strong>18. Changes in Appetite</strong></td>
<td>0: I have not experienced any change in my appetite. 1a: My appetite is somewhat less than usual. 1b: My appetite is somewhat greater than usual. 2a: My appetite is much less than before. 2b: My appetite is much greater than usual. 3a: I have no appetite at all. 3b: I crave food all the time.</td>
</tr>
<tr>
<td><strong>19. Concentration Difficulty</strong></td>
<td>0: I can concentrate as well as ever. 1: I can't concentrate as well as usual. 2: It's hard to keep my mind on anything for very long. 3: I find I can't concentrate on anything.</td>
</tr>
<tr>
<td><strong>20. Tiredness or Fatigue</strong></td>
<td>0: I am no more tired or fatigued than usual. 1: I get more tired or fatigued more easily than usual. 2: I am too tired or fatigued to do a lot of the things I used to do. 3: I am too tired or fatigued to do most of the things I used to do.</td>
</tr>
<tr>
<td><strong>21. Loss of Interest in Sex</strong></td>
<td>0: I have not noticed any recent change in my interest in sex. 1: I am less interested in sex than I used to be. 2: I am much less interested in sex now. 3: I have lost interest in sex completely.</td>
</tr>
</tbody>
</table>
Bibliography


33. Ekkekakis P. Honey, I shrunk the pooled SMD! Guide to critical appraisal of systematic reviews and meta-analyses using the Cochrane review on exercise for depression as example. Mental Health and Physical Activity 2015;8:21-36.


