## Title

Mindfulness Meditation as an Adjunct to Esketamine Treatment for Major Depressive Disorder



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# Mindfulness Meditation as an Adjunct to Esketamine Treatment for Major Depressive Disorder

A dissertation submitted in partial satisfaction of the

requirements for the degree

Doctor of Nursing Practice

by

Jennifer Tustison

2025

ABSTRACT OF THE DISSERTATION

Mindfulness Meditation as an Adjunct to Esketamine Treatment for Major Depressive Disorder

by

Jennifer Tustison

Doctor of Nursing Practice

University of California, Los Angeles, 2025

Professor Kristen R Choi, Chair

**Background**: Major Depressive Disorder (MDD) affects approximately 300 million people worldwide. Despite available treatments, many patients do not achieve full recovery with traditional antidepressants, and others lack access to evidence-based care. Esketamine, a glutamatergic agent approved for treatment-resistant depression, and mindfulness meditation represent promising approaches for depression care that may improve neuroplasticity. The neuroplasticity theory of depression posits that reduced neural plasticity contributes to MDD development, with both esketamine and mindfulness potentially addressing this deficit.

**Objectives**: This quality improvement project aimed to implement and evaluate the feasibility and efficacy of adding mindfulness meditation to esketamine treatments for patients with MDD,

with the goal of improving depression outcomes. **Methods:** A quasi-experimental pilot was conducted at an outpatient psychiatric clinic with 19 participants (10 in mindfulness plus esketamine group, 9 in usual care esketamine-only group). Outcome measures included changes in depressive symptoms using the Patient Health Questionnaire-8 (PHQ-8), mindfulness domains of self-compassion and acting mindfully using Five Facet Mindfulness Questionnaire-Short Form (FFMQ-SF) subscales, and Hope, Agency, and Opportunity (HAO) scores. The intervention consisted of structured mindfulness meditations during esketamine treatments. Data were analyzed using t-tests, regression modeling, and Pearson's r correlations. **Results:** Patients receiving the mindfulness adjunct had significantly greater PHQ-8 score reductions (4.70 points) compared to the usual care group (1.00 point; $p = .014$), with a large effect size (Cohen's $d = 1.27$). Within the mindfulness group, self-compassion scores significantly increased ($p < .01$) and were strongly correlated with PHQ-8 score improvements ($r = -0.71$, $p = .032$). Both groups showed excellent treatment adherence. All mindfulness group participants reported satisfaction with the intervention. **Conclusion:** Adding mindfulness meditations to esketamine treatments provided clinically meaningful improvements in depressive symptoms compared to esketamine alone. The strong correlation between increased self-compassion and depression symptom reduction highlights a potential mechanism for this effect. This feasible, well-received intervention offers a promising approach to enhance outcomes for patients with MDD undergoing esketamine treatment. Future research should examine optimal timing, duration, and long-term benefits of this integrative approach.

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The dissertation of Jennifer Tustison is approved.

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This dissertation is dedicated to the memory of my dad, Andy Tustison, I love you and I miss you. Thank you to my mom, Susan, and sisters, Chrissy and Erika, for seeing me through every chapter of this journey, and helping me keep the faith. Thank you to my fiancé, Scott Hay, for lifting me up time and time again throughout this endeavor. I am blessed to have the support of so many people who I love and admire.

TABLE OF CONTENTS

List of Figures and Tables

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2. **Tustison, J.** & Choi, K. R. (Under review). The science of caring in the age of AI.
3. **Tustison, J.**, Brauer, E., Niemi, C., & Choi, K. R. (In preparation). Mindfulness Meditation as an Adjunct to Esketamine for Major Depressive Disorder.

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# CHAPTER ONE: INTRODUCTION

Major Depressive Disorder (MDD) is characterized by low mood, diminished interest, and deteriorations in physical and emotional functioning occurring for two weeks or longer (American Psychiatric Association [APA], 2013). MDD affects approximately 300 million people worldwide and is a primary cause of global disability (Herman et al., 2019). In the United States (US), one in five adults will experience MDD in their lifetime (Lee et al., 2023). One significant barrier to MDD recovery is poor access to evidence-based treatment, as only an estimated 60% of adults with MDD access formal depression care (Han et al., 2017). Another challenge in depression care is that one-third of patients do not achieve full recovery with first-line recommended depression treatment, monoaminergic antidepressants (Corriger & Pickering, 2019).

MDD that does not respond to initial treatment is sufficiently concerning that both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have operationalized a definition of this nonresponse – treatment resistant depression (TRD) – as lack of response to at least two antidepressant medications which have been taken for adequate duration, at recommended doses, with proper adherence to the treatment plan (McIntyre et al., 2023). TRD is considered a subset of MDD (Voineskos et al., 2020), and remission rates for patients meeting TRD criteria are less than 15% (McAllister-Williams et al., 2020).

## Problem Statement

The dual phenomena of gaps in utilization of traditional depression care and failure to achieve remission on traditional antidepressant medications highlight the need to consider alternative approaches, which has led to the investigation of glutamatergic agents such as esketamine (Swainson et al., 2019). There is also an emerging body of evidence on

psychotherapeutic techniques, such as mindfulness meditation, that can serve as complementary treatments to ameliorate depressive symptoms (Reangsing et al., 2020). Although there is rapid growth in research supporting their use, neither mindfulness meditation nor ketamine, alone or in combination, are widely available in practice to all patients with MDD. There is a need to understand how best to implement these alternative, evidence-based MDD treatments in clinical practice, which may improve depression care quality and patient outcomes.

**Scientific Underpinnings: Ketamine**

Ketamine gained notice in medicine in the 1960s, when it was synthesized by Calvin Stevens as an anesthetic agent that offered a safer alternative to phencyclidine (PCP) (Hashimoto, 2019). The FDA approved ketamine for use as an anesthetic in humans in 1970 (Chang et al., 2016). A formal study of ketamine's utility as an antidepressant was conducted several decades later, providing support for further investigation and application of this medication in psychiatry (Berman et al., 2000). In 2017, following multiple supportive studies and concomitant increased interest within the psychiatric community, a task force for the American Psychiatric Association (APA) authored a statement on the use of ketamine in psychiatry, further legitimizing its psychiatric applications (Sanacora et al., 2017). In 2019, the FDA approved intranasal esketamine, the s-enantiomer of ketamine, for TRD in adults which was followed by approval for major depression with suicidal ideation (MDSI) in 2020 (Alario & Niciu, 2022).

Ketamine's antidepressant mechanism of action has yet to be definitively elucidated. Current consensus focuses on ketamine's actions as an antagonist of the N-methyl-D-aspartate receptor (NMDAR) which affects glutamatergic function in the central nervous system (CNS) (Gálvez et al., 2017). The disinhibition hypothesis proposes that ketamine's binding to NMDARs

on gamma-aminobutyric acid (GABA)-secreting interneurons has a net effect of increasing extracellular glutamate levels and activating alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors (Moghaddam et al., 1997). These actions cause release of brain-derived neurotrophic factor (BDNF) and downstream activation of trophic signaling cascades which lead to corticolimbic synaptogenesis and the increased dendritic sprouting thought to be responsible for ketamine's antidepressant effects (Li et al., 2010). A second hypothesis posits direct inhibition of extrasynaptic NMDARs by ketamine with a downstream effect of increased BDNF translation and activation of mammalian target of rapamycin (mTOR) synaptic plasticity (Miller et al., 2016). Research on ketamine for MDD has focused on isolating the s-enantiomer based on the premise that esketamine more potently antagonizes NMDARs when compared to its r-enantiomer counterpart, arketamine (Swainson et al., 2019).

Despite the availability of this new treatment for MDD and TRD, as well as large numbers of patients who could potentially benefit, current data on esketamine utilization suggest that it is not often used in real-world clinical care settings. Studies of esketamine utilization characteristics from large public and private insurance claims datasets have typically only identified a few hundred esketamine claims in recent years, despite the large number of individuals with depression who could potentially benefit from this treatment (Joshi et al., 2023; Karkare et al., 2022).

**Scientific Underpinnings: Mindfulness Meditation**

Mindfulness meditation, rooted in long-standing psychological and spiritual Eastern traditions, has been a subject of interest in Western medicine since John Kabat-Zinn introduced a mindfulness-based stress reduction program in 1979 (Niazi & Niazi, 2011). Mindfulness refers to an open, nonjudgmental, present-focused awareness of thoughts, emotions, physical sensations,

and environmental stimuli (Zhang et al., 2021). Proposed mechanisms of action underlying mindfulness meditation's efficacy in alleviating depressive symptoms include improved attention regulation, greater body awareness, and evolved understanding of and perspective on the concept of selfhood (Hölzel et al., 2011). From a neurobiological perspective, neuroimaging studies suggest that mindfulness meditation correlates to neuroplastic alterations in structures such as the anterior cingulate cortex, insula, fronto-limbic network, and default mode network (Hölzel et al., 2011).

Research on mindfulness-based interventions (MBIs), such as mindfulness meditation, supports the assertion that such practices offer effective treatment strategies for depressive disorders across a broad range of patient populations (Hofmann & Gómez, 2017). However, mindfulness is under-utilized as an approach to mental well-being and not consistently offered in clinical care. For example, an analysis of data from the 2012 National Health Interview Survey (NHIS) found that only 1.9% of American adults reported practicing mindfulness mediation, with higher likelihood of this or other meditation practice among individuals with depression (Burke et al., 2017). While more recent surveys have found higher levels of mindfulness practice, some as high as 35%, these have been smaller and more racially homogenous with predominantly White patients (Lam et al., 2023). Thus, the most recent large-scale, broadly representative survey remains the 2012 NHIS.

Overall, MDD represents a large and growing public health concern in the US. Often patients receive "trial and error" approaches to treatment stemming from lack of consensus around optimal management following multiple medication failures (Derakhshanian et al., 2021). There is evidence that both mindfulness and esketamine may be under-utilized as approaches to depression care. Ketamine shows promise as a rapid-acting treatment for MDD, and effects may

be augmented with integration of psychotherapeutic techniques (Drozdz et al., 2022). Mindfulness meditation represents an easily replicated psychotherapeutic technique which has shown benefit in the treatment of depressive conditions (Geurts et al., 2020). New, clinically oriented projects are needed to understand how to best implement the combination of psychotherapeutic techniques, such as mindfulness meditation, with ketamine treatments to improve quality of depression care and alleviate symptoms of MDD (Muscat et al., 2021).

### Clinical Question

A Population, Intervention, Comparison, Outcome, and Time (PICOT) question was developed to guide a quality improvement project to clinically implement mindfulness and esketamine in real-world depression care: In patients diagnosed with MDD (P) how does the addition of mindfulness meditation to intranasal esketamine treatments (I) as compared to intranasal esketamine alone (C) affect symptoms of depression (O) over a two-week period (T)?

## CHAPTER TWO: THEORETICAL FRAMEWORK

The interventions selected for clinical implementation in this quality improvement project are based on the neuroplasticity theory of depression, which has a long history of application in nursing science and nursing clinical interventions (Kennedy, 2021; Vance et al., 2008). While a multiplicity of factors contribute to the development of MDD, the condition is notable for including symptoms of rigid thought and behavior, suggestive of a neural inability to respond and adjust to evolving stimuli (Kashdan & Rottenberg, 2010). The neuroplasticity theory of depression posits that impaired neural plasticity contributes to the development of MDD (Liu et al., 2017). Neuroplasticity refers to the degree to which the brain is able to modulate activity in response to both internal and external stimuli (Puderbaugh & Emmady, 2023). The neuroplasticity model of depression characterizes development of depression as being mediated

by neural alterations engendered by negative life experience and chronic stress, which become entrenched through reductions in overall neuroplasticity in the prefrontal-limbic circuit causing resistance to subsequent positive inputs (Changeux & Danchin, 1976).

An integrative model of neuroplasticity and depression merges concepts from neuroscience and clinical psychology (Price & Duman, 2019). Neuroscience research has demonstrated that depressive behaviors are associated with such neuroplasticity deficits as atrophy of neurons and loss of synapses in the medial prefrontal cortex and hippocampus (Price & Duman, 2019). Neuroplasticity alterations observed in the brains of MDD patients include reduced volume in the hippocampus and amygdala, areas of the brain associated with learning and memory (Kadiyala et al., 2024). A relationship has been shown to exist between the degree of volume reduction and severity of symptoms (Frodl et al., 2008). Post-mortem studies evidence reduced markers of neuroplasticity including decreased synaptic density and reductions in BDNF levels (Kang et al., 2012). Neuroimaging studies on patients diagnosed with MDD illustrate reduced functional integration across corticolimbic structures such as the prefrontal cortex and hippocampus in addition to overall volume loss (Disner et al., 2011).

**Ketamine and Neuroplasticity**

Emerging treatments seek to leverage the phenomenon of neuroplasticity in the treatment of MDD, including ketamine and its derivative, esketamine. BDNF and mTOR are two frequently cited markers of neuroplasticity (Price & Duman, 2019). Studies examining rodent models of ketamine administration for MDD demonstrate increases in BDNF levels as well as increased mTOR signaling, suggestive of neuroplasticity induction (Li et al., 2010). In rodent models, ketamine administration also produces an increased number of synapses in the prefrontal cortex, thus remediating the reduction of synapses caused by stress (Duman et al., 2019). In

human subjects receiving ketamine treatment, neuroimaging techniques that target indirect measures of neuroplasticity have demonstrated a direct correlation between increased plasticity and improvement in depressive symptoms (Kopelman et al., 2023).

### Mindfulness Meditation and Neuroplasticity

Mindfulness meditation has been linked to improvements in emotional regulation with neuroplasticity as a possible mediating mechanism (Lardone et al., 2018). Studies have demonstrated that mindfulness meditation results in improvements in reported depressive symptoms. Neuroimaging has shown that these improvements in depression correspond to brain network remodeling, with alterations to more closely resemble neural networks of healthy controls (Yang et al., 2016). Results of MBI studies suggest that such mindfulness interventions increase BDNF, a modulator of neuroplasticity (Gomutbutra et al., 2020). There is limited research on the integration of formal mindfulness meditation into ketamine treatments with the intention of synergizing effects on neuroplasticity in the treatment of depression.

## CHAPTER THREE: REVIEW OF LITERATURE

A focused literature review was conducted to examine existing research on ketamine and mindfulness in relation to MDD. Databases searched included PubMed, American Psychological Association PsycInfo (APA PsychInfo), Cumulated Index in Nursing and Allied Health Literature (CINAHL), and Web of Science. Inclusion criteria for the review were articles published in the past 10 years, intervention studies, studies of ketamine or esketamine in combination with mindfulness meditation, and studies of patients with MDD. Articles were excluded if they were animal studies or were not relevant to the search topic. First, a search was performed in PubMed using the following search strategy: (((ketamine{Title/Abstract}) OR (esketamine{Title/Abstract})) AND ((mindfulness{Title/Abstract}) OR

(meditation{Title/Abstract}))) AND (depression{Title/Abstract}). This search returned five articles, none of which, upon review, met inclusion criteria. Similar searches were carried out in APA PsycInfo, CINAHL, and Web of Science with similar yields. Due to insufficient article yield, additional hand-searching was done to identify relevant articles. Because no studies specifically examining the use of esketamine and mindfulness meditation for the treatment of depression were found, the search was broadened to include studies on 1) ketamine or esketamine treatment for depression, 2) mindfulness meditation for depression, or 3) the combination of ketamine or esketamine with mindfulness for behavioral conditions other than depression to provide support for further investigation of how these two treatments for MDD can be implemented simultaneously. There were six articles included in the review under these broadened search criteria, summarized in the following paragraphs.

A phase 3, double-blind, active-controlled multicenter study compared safety and efficacy of esketamine nasal spray with initiation of a new antidepressant medication to a placebo nasal spray with initiation of a new antidepressant medication in patients diagnosed with TRD (Popova et al., 2019). Analyzing data with a mixed-effects model using repeated measures, researchers found that the esketamine plus new antidepressant intervention group showed significantly greater reductions in Montgomery-Asberg Depression Rating Scale (MADRS) scores at day 28 of the study. This study provides evidence that treatment with esketamine nasal spray is associated with clinically meaningful and statistically significant improvement in depressive symptoms. Limitations of this study included imperfect blinding secondary to dissociative side effects of esketamine and limited generalizability due to exclusion of patients with significant medical or psychiatric comorbidities (Popova et al., 2019).

MBIs have demonstrated benefit in alleviating symptoms of depression and anxiety (Hofmann & Gómez, 2017). Researchers examined whether a brief MBI reduced depressive symptoms in patients diagnosed with MDD as compared to a control group given an ambient music treatment (Winnebeck et al., 2017). Using a series of repeated measures analysis of variance (ANOVA), researchers found that the MBI group showed a significant increase in mindfulness and a reduction in depressive symptoms. The MBI group also experienced reductions in ruminative tendencies and cognitive reactivity as compared to the control group. Within the MBI group, reductions in depressive symptoms significantly correlated with improvements in measures of mindfulness. Limitations of this study included self-report of symptoms leading to the possibility of reporting bias, no monitoring of medication use by participants, and no formal assessment of therapist adherence to mindfulness teaching protocols. Future studies should address these limitations and assess how long improvements are sustained (Winnebeck et al., 2017).

Additional support for the benefits of mindfulness in MDD comes from a single-blind randomized-controlled trial (RCT) examining effects of a mindfulness-based cognitive therapy intervention for patients diagnosed with MDD (van der Velden et al., 2022). The study used functional magnetic resonance imaging to examine neurocognitive mechanisms associated with both mindful and ruminative states. Study results showed that during induced rumination, subjects in the mindfulness intervention group evidenced decreased frontal connectivity between the salience network and lingual gyrus. As the salience network is believed to play a role in depression symptomology and treatment response, such results support the use of mindfulness interventions in treatment for depressive disorders. Limitations of this study included the lack of an active control group and the fact that participants had the option to opt out of the rumination

condition. Consequently, the findings only generalize to participants willing to participate in rumination induction (van der Velden et al., 2022).

Several studies support the use of mindfulness and ketamine in the treatment of psychiatric disorders other than MDD, though the combination of treatments has not yet been extensively studied in MDD. A double-blind RCT examined whether a single ketamine infusion combined with mindfulness-based behavioral modification improved treatment outcomes in adults diagnosed with cocaine use disorder (CUD) (Dakwar et al., 2019). Participants were randomly assigned to ketamine or a midazolam control group. Each group received preparation with relaxation and body scan exercises and mindfulness-based relapse prevention sessions post-infusion. Researchers found that the combination of ketamine and mindfulness enhanced motivation to change and facilitated engagement with treatment as compared to the midazolam control group. Statistical analyses included logistic regression models to analyze effects of treatment on the primary outcome of end-of-study-abstinence, and a longitudinal mixed-effects model was estimated to examine weekly cocaine use and cocaine craving scores. End of study abstinence in the ketamine group was six times greater than the midazolam group. The ketamine group was 53% less likely to relapse as compared to the midazolam group. At 6-month follow-up, 44% of the ketamine group participants were abstinent as compared to 0% of the midazolam group. Limitations included a small sample size ($N$ = 55), limited generalizability due to exclusion of psychiatric comorbidities, imperfect blinding due to the unique side effect profile of ketamine, and lack of a ketamine-only control group (Dakwar et al., 2019).

Similarly, a study of patients diagnosed with alcohol use disorder (AUD) examined the combination of esketamine treatments and an MBI (Gent et al., 2024). Patients participated in seven days of mindfulness followed by a drug administration visit at which participants were

randomly assigned to receive either oral esketamine or vitamin C placebo. Treatment engagement, alcohol craving, and mindfulness changes were analyzed using multilevel modeling with time and group as fixed effects variables and participants as the random effects variable. The study showed a significant decrease in alcohol cravings for the treatment group but not the placebo group. Limitations of this study included a small sample size ($N$ = 28) and imperfect blinding (Gent et al., 2024), similar to other studies of ketamine.

A study of two precepts of mindfulness meditation – non-judging and opposite diminishing – was conducted to investigate the association between the presence of these factors following ketamine administration and measures of mental well-being (Stocker et al., 2022). The authors described non-judging as cognition that is not dominated by making judgments, and opposite-diminishing as a thought process that is not characterized by thinking in terms of opposites. Using a single group, pre-/posttest design, patients completed the Altered States of Consciousness Inventory (ASCI), a scale with items measuring opposite diminishing and non-judging, and the Beck Depression Inventory-II (BDI-II) following ketamine infusion. Using linear mixed effects models, the researchers examined associations between opposite diminishing and non-judgment to study outcomes, including depression. The study supported the hypothesis that a mental state of non-judging during the ketamine infusion correlated to reduced depression scores. Limitations of this study included lack of a control group, a small sample size ($N$ = 11), a heterogeneous sample, and subjective dosing determination (Stocker et al., 2022).

**Synthesis of Literature Review**

A review of the literature revealed a dearth of studies specific to the examination of ketamine combined with mindfulness meditation for MDD. Consequently, several separate searches were conducted focusing upon discrete facets of the proposed treatment and target

condition. Overall, there was evidence that ketamine alone is effective for treating MDD; that mindfulness alone may reduce symptoms of depression; that the combination of ketamine and mindfulness may improve treatment engagement and decrease cravings in individuals with AUD; and that the combination of ketamine and mindfulness may improve treatment engagement and promote abstinence in CUD. The studies reviewed shared several strengths. Three of the studies used a double-blind RCT design. Use of a double-blind design minimizes risk of several types of bias which reduces risk of type I errors (Ranganathan & Aggarwal, 2018). In addition to three double-blind RCTs, a single-blind RCT and an RCT without blinding were included. In the hierarchy of levels of evidence, RCTs represent the highest level that establishes cause and effect associations in research (Zabor et al., 2020). A strength shared by all six studies was the use of clinically validated screening tools such as the Patient Health Questionnaire-9 (PHQ-9) or Five Facet Mindfulness Questionnaire (FFMQ) to measure changes in symptomology. Frequently, the scores were the primary outcome. Use of a validated screening tool strengthens these studies, as such tools have demonstrated specificity and sensitivity via psychometric testing (Mughal et al., 2020).

Weaknesses in the evidence center around overall scarcity of studies, heterogeneity of research synthesized (i.e., some studies of mindfulness meditation alone, some studies of ketamine alone, combination studies in substance use only), and common limitations shared by studies of ketamine, including imperfect blinding. Ketamine has a distinct side effect profile including feelings of dissociation such that patients are often able to predict whether they received ketamine or placebo which may introduce bias (Dakwar et al., 2019). Additionally, sample sizes were frequently small, ranging from 11 to 197 subjects, which may limit both internal and external study validity as well as power to detect change (Faber & Fonseca, 2014).

Because of the lack of high-quality, well-powered studies on the combination of ketamine and mindfulness for MDD, there is little information to guide best practices in adding mindfulness meditation as a psychotherapeutic technique intended to enhance ketamine or esketamine treatments. While mindfulness has been examined as an adjunct to ketamine treatments in substance use disorders (SUD), which are frequently comorbid with MDD (Hunt et al., 2020), research on MDD specifically remains unclear.

Overall, the literature review highlighted an opportunity to further study how combined ketamine and mindfulness meditation can be implemented in practice, as research supports each individually in the treatment of MDD. Additionally, research supports the combination of the two in addressing psychiatric disorders, though not MDD specifically, and provides evidence for the potential benefit of adding psychotherapeutic protocols to ketamine treatments for MDD. Finally, the review indicated that one of the main tenets of mindfulness meditation, nonjudgment, was uniquely associated with improvement in depressive symptoms following ketamine infusion and thus may be important to target in future mindfulness meditation implementation projects.

## CHAPTER FOUR: METHODS

### Project Design

This was a quasi-experimental pilot for clinical quality improvement that examined the feasibility and potential benefits of implementing mindfulness meditation as an adjunct to esketamine treatments in patients diagnosed with MDD. Pilot data can inform broader quality improvement initiatives for depression care. Outcome measures included changes in depressive symptoms, changes in mindfulness, and changes in sense of hope, agency, and opportunity.

### Ethical Considerations

This project was reviewed by the university's institutional review board (IRB) prior to patient recruitment. The university IRB determined that this project did not require formal IRB approval because it was implemented as a quality improvement initiative, aiming to improve care quality at a single organization. Participation was voluntary and all participants provided informed consent.

**Population Sample and Setting**

The project was set at an outpatient psychiatric clinic in Southern California. The clinic is located in Orange County and has approximately 95,000 to 105,000 patient visits per year, primarily for mood disorders. The clinic is interprofessional, with nurses, physicians, and other allied health professionals on treatment teams. A convenience sample of adults diagnosed with MDD and receiving esketamine treatment in the course of usual depression care was recruited prior to esketamine induction. As a feasibility and implementation pilot, we recruited 10 patients interested in the intervention and four patients for usual-care comparison. Data for an additional five patients who were not captured in the recruitment process were obtained from the clinic's Electronic Health Record (EHR), so that a total of nine patients were included in the usual care group. Inclusion criteria were that patients be aged 18 years or older, read/spoke English, were diagnosed with MDD, and were planning to begin esketamine treatment in the course of usual depression care.

**Procedures**

Patients were provided with an introductory flyer with information on the mindfulness opportunity. Participants in the mindfulness group then completed a web-based survey with a series of questionnaires assessing baseline measures of depression, mindfulness, and sense of hope, agency, and opportunity. These pretest questionnaires were administered prior to

esketamine induction and mindfulness interventions. Participants in the usual care group completed a web-based survey with a questionnaire assessing depressive symptoms. For usual care group participants who did not complete this survey, depressive questionnaire data was obtained retroactively from the EHR, as the same questionnaire is administered by the clinic prior to and following each session of esketamine treatment. Patients self-selected to participate in the mindfulness meditation arm.

The mindfulness group completed esketamine induction as usual, eight esketamine treatments, two treatments per week, over a span of four weeks. This project focused only on the first four sessions, two per week over two weeks, of esketamine induction. A mindfulness meditation was added to the latter half of each of the first four esketamine inductions sessions, as described in detail below. Patients received a link to the prerecorded meditations and had the option of listening over a personal device, or a tablet provided by the clinic. Patients in the usual care group received esketamine induction treatments as usual, per the clinic's protocol, without the addition of a mindfulness meditation.

Following the first four sessions of treatment, the intervention group completed posttest questionnaires which measured depressive symptoms, mindfulness, and sense of hope, agency, and opportunity. The usual care group completed a posttest questionnaire which measured depressive symptoms. Similar to the pretest questionnaire, for usual care participants who did not complete the web-based survey, questionnaire data was obtained from the EHR. Participants in both the mindfulness group and the usual care group were offered the opportunity to receive a ten-dollar gift card for completion of the pretest survey and a twenty-dollar gift card for completion of the posttest survey.

### Mindfulness Meditation Intervention

The mindfulness meditation intervention consisted of web-based, self-guided sessions based on principles of mindful self-compassion (Germer & Neff, 2021). These meditations had been prerecorded and were part of a pre-existing introductory mindful self-compassion meditation program (Germer, 2021). The first meditation was an 18-minute audio recording that was used for sessions one and two, and the second meditation was a 15-minute audio recording that was used for sessions three and four. The 18-minute recording focused upon awareness of breath from a stance of self-compassion, and the 15-minute recording focused upon compassionate present-moment awareness.

### Data Collection and Measures

We assessed project feasibility and implementation metrics, including number of mindfulness sessions completed and patient satisfaction with the adjunct mindfulness meditation. Depressive symptoms were measured using the Patient Health Questionnaire-8 (PHQ-8), as shown in Appendix A, a validated measure for diagnosis of depressive disorders in clinical studies (Kroenke et al., 2009). Mindfulness was assessed using two subscales of the Five Facet Mindfulness Questionnaire: Short-Form (FFMQ-SF), a validated measure, including the self-compassion subscale (5 items), and the acting mindfully subscale (5 items), as shown in Appendix B (Meng et al., 2020). We focused on these subscales because they were most directly targeted by the contents of the mindfulness program. Sense of hope, agency, and opportunity was measured using the Hope, Agency, and Opportunity (HAO) questionnaire, as shown in Appendix C, a validated 4-item questionnaire (Newman-Taylor et al., 2017). Measures were administered via Qualtrics, a digital survey platform. The pretest measures included a survey to gather baseline data such as history of ketamine treatments. Additional demographic data such as age,

gender, ethnicity, and type of insurance provider (public vs private) were obtained from the EHR.

### Data Analysis

R version 4.3.1 was used for statistical analysis (R Core Team, 2021). The sample was characterized using descriptive statistics: frequencies and percentages for binary/categorical variables and measures of central tendency (mean, median, range, standard deviation) for continuous variables. Independent samples t-tests (for continuous variables) and chi-square tests (for categorical variables) were used to compare mindfulness group and usual treatment participants on demographic characteristics. Frequencies and descriptive statistics were also calculated for feasibility and implementation measures within the mindfulness group (e.g. number of sessions completed and drop-out rates). An independent samples t-test was applied to compare mean PHQ-8 change scores between the mindfulness and usual care groups. A simple linear regression model was estimated to assess the relationship between mindfulness group membership and PHQ-8 change score. Paired samples t-tests were then used to examine pre- to posttest differences within the mindfulness group on positive outcomes of mindfulness (HAO, FFMQ-SF self-compassion subscale, and FFMQ-SF acting mindfully subscale). Finally, Pearson's r correlation coefficients were calculated to examine relationships between outcome measures. Results with *p* values less than .05 were considered statistically significant. We assessed data missingness prior to analyses and used complete case analysis for incomplete case data.

## CHAPTER FIVE: RESULTS

The sample consisted of 19 patients undergoing esketamine induction treatment in the course of usual depression care at an outpatient psychiatric clinic. 14 patients were approached

about the mindfulness adjunct opportunity, and of those 14, 10 opted to participate in the mindfulness intervention as an adjunct to usual care. The mindfulness group had more female (60.0%, *n* = 6) than male (40.0%, *n* = 4) patients, while the usual care group had more male (66.7% *n* = 6) than female (33.3%, *n* = 3) patients, though these differences were not statistically significant. In both groups, participants predominantly self-identified as White. In the mindfulness group, self-identified ethnicities were White (60.0%, *n* = 6), Hispanic/Latino (30.0%, *n* = 3), and Asian (10.0%, *n* = 1). In the usual care group, self-identified ethnicities included White (66.7%, *n* = 6), Asian (11.1%, *n* = 1), Hispanic/Latino (11.1%, *n* = 1), and unspecified (11.1%, *n* = 1). There was no statistically significant difference in ethnic identification between groups. The mean age of the mindfulness group (*M* = 34.90 years, *SD* = 12.64) was lower than the mean age of the usual care group (*M* = 49.22 years, *SD* = 19.03), and the difference reached statistical significance (*M* = 14.32 years, *p* = .040). The mindfulness group had no participants with a history of ketamine treatment, while there were two individuals who had received ketamine treatment in the past in the usual care group. The majority of patients had public insurance in both the mindfulness group (70.0%, *n* = 7) and the usual care group (66.7%, *n* = 6), with no significant difference in insurance allocation between groups (*p* = .999). The two groups had similar mean baseline PHQ-8 scores (mindfulness group: *M* = 15.50, *SD* = 5.99; usual care group: *M* = 15.00, *SD* = 5.43; *p* = .85). Participant characteristics are displayed in Table 1.

Completion of esketamine treatment and the mindfulness adjunct was high. All patients in both the mindfulness and usual care groups completed four out of four esketamine treatments in the first two weeks of the induction phase. In the mindfulness group, nine patients completed four out of the four mindfulness meditations, and one patient completed three out of the four

mindfulness meditations. Several patients provided comments about their experiences with mindfulness on the posttest questionnaire, displayed in Table 2. Comments indicated that the meditations were helpful, with some patients indicating a desire for more varied meditation options from which to choose. Patients in the mindfulness group rated their satisfaction with the intervention, with 40.0% ($n$ = 4) reporting they were extremely satisfied and 60.0% ($n$ = 6) reporting they were satisfied, as shown in Table 3.

In assessing changes in PHQ-8 scores, the mindfulness participants had a 4.70-point mean reduction ($M$ = 4.70, $SD$ = 3.06), while the usual care group participants had a 1.00-point mean reduction ($M$ = 1.00, $SD$ = 2.78; $p$ = .014), as shown in Figure 1. Mindfulness group membership (relative to usual care) was associated with a 3.70-point reduction in PHQ-8 scores ($SE$ = 1.35, $R^2$ = 0.31, $p$ = .014) in a simple linear regression model. The effect size, measured by Cohen's d, was $d$ = 1.27, indicating a large effect.

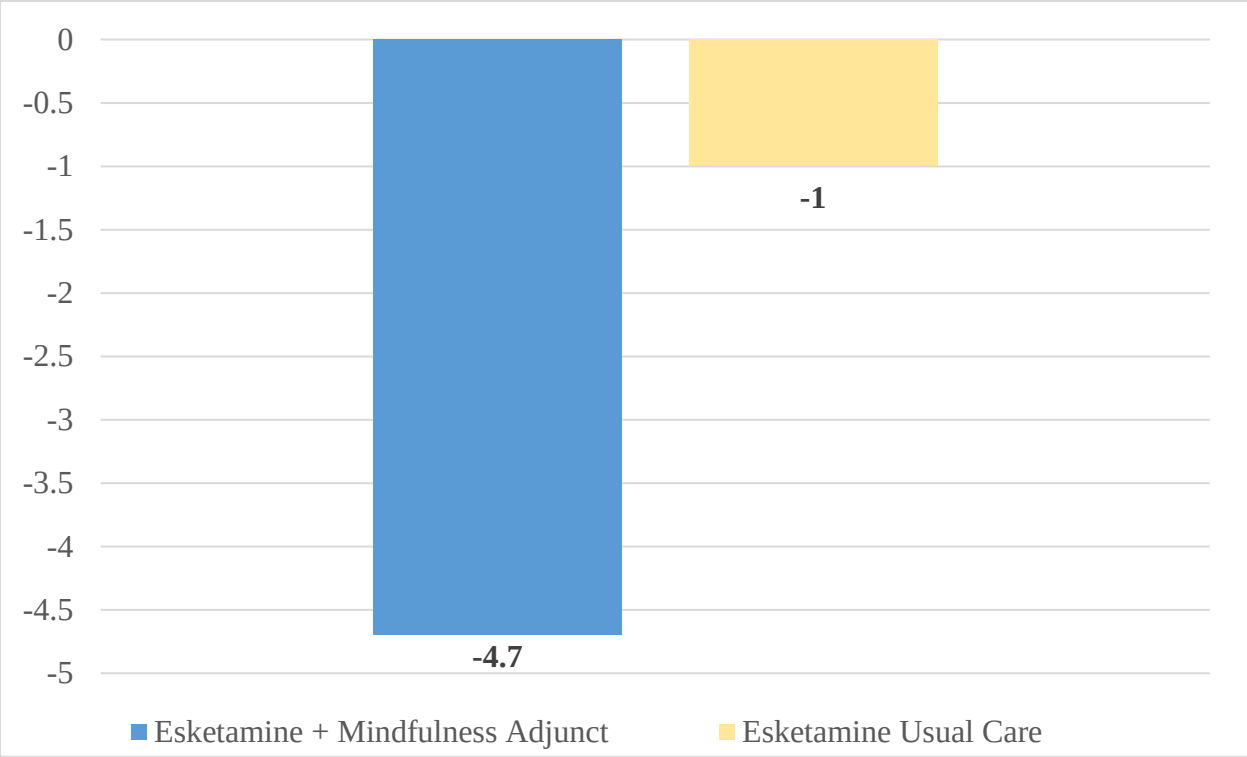
In the mindfulness group, participants had a mean baseline HAO score of 7.44 ($M$ = 7.44, $SD$ = 3.06) and a mean posttest HAO score of 8.89 ($M$ = 8.89, $SD$ = 2.83) for a mean increase in score of 1.45 points ($p$=.140). Mindfulness group participants had a mean FFMQ-SF acting mindfully subscale score of 12.44 ($M$ = 12.44, $SD$ = 4.22) at baseline and a mean posttest score of 15.44 ($M$ = 15.44, $SD$ = 2.22) for a mean change in score of 3.00 points ($p$ = .064). Mindfulness group participants had a mean FFMQ-SF self-compassion subscale score of 11.44 ($M$ = 11.44, $SD$ = 3.83) at baseline and a mean posttest score of 14.78 ($M$ = 14.78, $SD$ = 3.89) for a mean change in score of 3.34 points ($p$ < .01). See Table 4 for changes in mindfulness measures.

In assessing correlations between outcome variables in the mindfulness group, using complete case analysis for the nine patients who completed all questionnaires, there was no

significant correlation between mean PHQ-8 score change and mean FFMQ-SF acting mindfully subscale score change ($r$ = -0.24, $p$ = .518), nor was there a significant correlation between mean PHQ-8 score change and mean HAO score change ($r$ = 0.02, $p$ = .957). There was a significant correlation between mean PHQ-8 score change and mean FFMQ-SF self-compassion subscale score change ($r$ = -0.71, $p$ = .032). See Figure 2 and Table 5 for Pearson's r correlations.

**Figure 1**

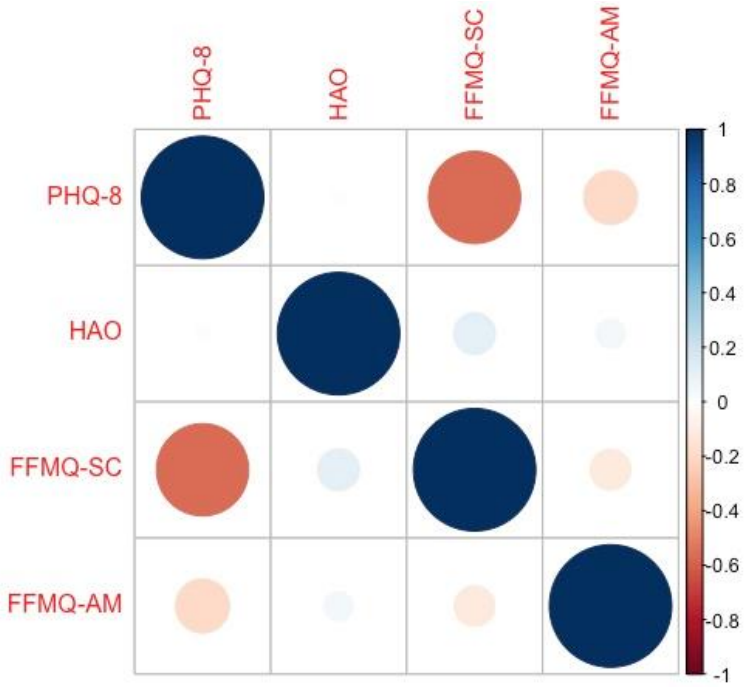
*PHQ-8 Score Reductions After Two Weeks of Esketamine Treatment*




*Legend.* This figure shows the magnitude of reduction in Patient Health Questionnaire-8 (PHQ-8) scores after two weeks of esketamine treatment among 19 adults in Southern California. All patients received esketamine and 10 patients received a mindfulness meditation adjunct during each session. Differences in mean PHQ-8 score changes between the two groups were statistically significant ($p$ = .014).

**Figure 2**

*Pearson r Correlations Between Outcome Measures*




*Legend.* This figure visualizes the direction and magnitude of Pearson r correlations shown in Table 5 for four outcome measures used in an implementation of mindfulness meditation with nine patients receiving esketamine treatment for depression from 2024-2025 in Southern California. Larger circles denote larger correlation magnitude. There were 10 total participants, but one did not complete outcome measures. PHQ-8= Patient Health Questionnaire-8; HAO= Hope, Agency, & Opportunity questionnaire; FFMQ-SC= self-compassion subscale of the Five Facet Mindfulness Questionnaire: Short-Form; FFMQ-AM= acting mindfully subscale of the Five Facet Mindfulness Questionnaire: Short-Form.

**Table 1**

*Patient Demographics*

| | Overall | | Esketamine + Mindfulness | | Esketamine Usual Care | | |
|---|---|---|---|---|---|---|---|
| | *N* | % | *n* | % | *n* | % | *p* |
| Age (*M* [*SD*]) | 19 | 41.7 (17.3) | 10 | 34.90 (12.64) | 9 | 49.22 (19.03) | .040 |
| Gender | | | | | | | .483 |
| Male | 10 | 52.6 | 4 | 40.0 | 6 | 66.7 | |
| Female | 9 | 47.4 | 6 | 60.0 | 3 | 33.3 | |
| Unspecified | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | |
| Race/ethnicity | | | | | | | .582 |
| White | 12 | 63.2 | 6 | 60.0 | 6 | 66.7 | |
| Asian | 2 | 10.2 | 1 | 10.0 | 1 | 11.1 | |
| Hispanic/Latino | 4 | 21.1 | 3 | 30.0 | 1 | 11.1 | |
| Black | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | |
| Other | 1 | 5.3 | 0 | 0.0 | 1 | 11.1 | |
| History of ketamine treatment | 2 | 10.5 | 0 | 0.0 | 2 | 22.2 | .408 |
| Insurance Carrier | | | | | | | .999 |
| Public | 13 | 68.4 | 7 | 70.0 | 6 | 66.7 | |
| Private | 6 | 31.7 | 3 | 30.0 | 3 | 33.3 | |
| Baseline PHQ-8 score (*M* [*SD*]) | | | 10 | 15.50 (5.99) | 9 | 15.00 (5.43) | .852 |
| PHQ-8 change score (*M* [*SD*]) | | | 10 | -4.70 (3.06) | 9 | -1.00 (2.78) | .014 |

*Note.* This table summarizes the demographic and clinical characteristics of a sample of 19 adults who received esketamine for depression from 2024 to 2025 in Southern California, either alone or with an adjunctive mindfulness meditation added to each session. There were 10 mindfulness participants and nine usual care participants.

**Table 2**

*Meditation Group Participant Comments, n = 6*

| |
|---|
| “Helped add to the process, I would also like a deep body scan meditation” |
| “Both meditations were helpful, but I really liked the second one. I listened to it twice during one session. The Spravato makes me a little anxious and breathe heavily, so I found the meditations to be calming” |
| “I found both meditations to be useful / helpful, and I've listened to lots of meditations over the years” |
| “Good content, I would like the option of a female voice” |
| “I liked the breathing meditation, but I definitely had a different (good) experience with the second meditation. It’s one I want to continue to use in and out of ketamine therapy. I also definitely agree with listening to the meditations during the second half of the session, after the acute effects have worn off.” |
| “Gave me something to focus on which I liked” |

*Note.* Comments left by meditation participants on written posttest questionnaire.

**Table 3**

*Mindfulness Group Participant Satisfaction Scores*

| Satisfaction with Adjunct Meditation | *n* | % |
|---|---|---|
| Extremely Satisfied | 4 | 40.0 |
| Satisfied | 6 | 60.0 |
| Neither Satisfied nor Dissatisfied | 0 | 0.0 |
| Dissatisfied | 0 | 0.0 |
| Extremely Dissatisfied | 0 | 0.0 |

*Note.* This table shows satisfaction with care ratings for 10 patients who received esketamine for depression from 2024 to 2025 in Southern California.

**Table 4**

*Pre-/Posttest Changes in Mindfulness Measures*

| | Pretest | | Posttest | | *p* |
|---|---|---|---|---|---|
| | *M* | *SD* | *M* | *SD* | |
| HAO Score | 7.44 | 3.06 | 8.89 | 2.83 | .141 |
| Self-compassion score | 11.44 | 3.83 | 14.78 | 3.89 | <.010 |
| Acting mindfully score | 12.44 | 4.22 | 15.44 | 2.22 | .064 |

*Note.* This table shows pre-/posttest differences in measures of positive benefits of mindfulness during esketamine treatment among nine adults (i.e., all mindfulness participants with complete data) who received esketamine for depression from 2024 to 2025 in Southern California. HAO=Hope, Agency, and Opportunity (0-16 points); self-compassion (5-25 points) and acting mindfully (5-25 points) scores were derived from each respective subscale of the Five Facet Mindfulness Questionnaire: Short-Form (FFMQ-SF).

**Table 5**

*Pearson r Correlations Between Outcome Measures*

| | PHQ-8 | HAO | FFMQ-SC | FFMQ-AM |
|---|---|---|---|---|
| PHQ-8 | 1.00 | 0.02 | -0.71* | -0.24 |
| HAO | | 1.00 | 0.24 | 0.10 |
| FFMQ-SC | | | 1.00 | -0.08 |
| FFMQ-AM | | | | 1.00 |

*Note.* This table shows Pearson r correlations for four outcome measures used in an implementation of mindfulness meditation with nine patients receiving esketamine treatment for depression from 2024-2025 in Southern California. There were 10 total participants, but one did not complete all outcome measures. PHQ-8= Patient Health Questionnaire-8; HAO= Hope, Agency, & Opportunity questionnaire; FFMQ-SC= self-compassion subscale of the Five Facet Mindfulness Questionnaire: Short-Form; FFMQ-AM= acting mindfully subscale of the Five Facet Mindfulness Questionnaire: Short-Form. *Value is significant at the .05 level.

## CHAPTER SIX: DISCUSSION

Based on these findings, a brief mindfulness meditation program as an adjunct to standard esketamine treatment for MDD showed promising results in a small clinical sample, the majority of whom were publicly insured. Participation in the mindfulness intervention demonstrated clinically significant improvement in depressive symptoms, with a 4.70-point mean PHQ-8 score reduction compared to a 1.00-point mean score reduction in the usual care group ($p$ = .014). This represented a large effect size ($d$ = 1.27). This result can be considered

clinically significant, as the average minimal clinically important difference (MCID) estimate for the PHQ-9, from which the PHQ-8 is derived, is a 3.70-point change (Bauer-Staeb et al., 2021). The PHQ-8 (0-24 points) has one fewer item than the PHQ-9 (0-27 points). Thus, utilizing the PHQ-9 MCID of 3.70 points would be a conservative estimate of clinically significant change on the PHQ-8. Among mindfulness participants, improvements in self-compassion scores were strongly correlated with depression symptom reduction.

Treatment adherence was excellent across both groups, with all participants completing the entirety of the first four sessions of the first two weeks of the esketamine induction protocol and high completion rates of mindfulness meditations. The lack of participant drop-out and high completion rates of the mindfulness meditation adjunct suggest that mindfulness group participants found that the addition of a meditation was feasible and acceptable. Nine participants completed all four meditation sessions, and one participant completed three of the four sessions. Anecdotally, the dissociative effects of esketamine contributed to the missed session.

Populations in each group were similar on all measured demographics, with the exception of age. The mindfulness group had a lower mean age ($M$ = 34.90 years, $SD$ = 12.64) than the usual care group ($M$ = 49.22 years, $SD$ = 19.03; $p$ = .040). This age disparity is consistent with trends in prevalence of meditation use in the US, where it is more common among individuals aged 25-44 years old and less common among those aged 45 and older (Davies et al., 2024). There was underrepresentation of non-White participants in this project, which parallels studies finding that non-Hispanic African American and Hispanic populations are less likely to initiate esketamine treatment (Liberman et al., 2023). One possible explanation for this disparity is that non-White and Hispanic/Latinx participants were underrepresented in clinical trials of esketamine, which may be related to lower real-world uptake (Monahan et al., 2023). Racial

disparities may also be related to cost barriers, practical access challenges (e.g., time, transportation), and structural disadvantages that contribute to inequities in mental healthcare access and utilization (Cook et al., 2018). The majority of participants in the mindfulness group (70.0%, *n* = 7) were publicly insured, which suggests this may represent an effective intervention for low-income Americans, who have been shown to have higher rates of chronic unmet mental healthcare needs (Yang et al., 2019).

Consistent with previous studies, esketamine treatment alone corresponded with a reduction in depressive symptoms over a short time period (two weeks), with greater gains for participants who used mindfulness. Trends in depression symptom reduction are similar to those observed by Popova et al. (2019), who noted a reduction in depressive symptoms after eight treatments on day 28. Previous studies have also found that mindfulness alone can have significant positive effects in patients diagnosed with MDD (Winnibeck et al., 2017). Consistent with our expectations based on the benefits of mindfulness alone and esketamine alone, we observed possible synergistic benefits when these two modalities were combined.

The synergistic benefits of mindfulness plus esketamine observed in depression align with previous studies examining the use of mindfulness and ketamine to treat mental health conditions other than depression, such as SUD. Previous studies of SUD have found that treatments combining mindfulness and ketamine improve symptoms of these disorders (Dakwar et al., 2019; Gent et al., 2024). There are high comorbidity rates between SUD and MDD, so our results taken together with prior studies of mindfulness and ketamine in SUD may be especially significant for patients with dual diagnoses (Amendola et al., 2022: Li et al., 2020; Philogene-Khalid et al., 2020). Treating SUD frequently leads to depression improvement (Chan et al., 2014) while treating depression can lead to improvements in SUD (Agabio et al., 2018).

Although this project did not measure comorbid SUD, implementing mindfulness with ketamine or esketamine treatment may benefit patients with comorbidities and should be studied in future research.

Improvements in self-compassion scores were strongly correlated to reduced depressive symptoms ($r$ = -0.71, $p$ < .01), indicating that mindfulness focused upon principles of self-compassion may be particularly beneficial to patients, and supporting this as a promising area of future research. The correlation between self-compassion and reduction in depressive symptoms is consistent with current medical literature which shows that self-compassion can play a prominent role in reducing depressive symptoms in a variety of patient populations (Han & Kim, 2023). Consistent with the neuroplasticity theory of depression used to guide this project, one of the proposed mechanisms for this reduction involves the effect that self-compassion has upon activity in the dorsal anterior cingulate cortex and the right dorsolateral prefrontal cortex, with decreased activity in these circuits correlating with reductions in depressive symptoms (Liu et al., 2020). While participants did show improvements on mean change in acting mindfully scores, ($M$ = 3.00 points, $p$ = .064), the correlation between improvement in these scores and reduction in PHQ-8 scores did not reach statistical significance ($r$ = -0.24, $p$ = .518). Similarly, while mindfulness group participants showed improvements in HAO scores, mean change did not reach clinical significance ($M$ = 1.45 points, $p$ = .141). As a feasibility pilot, this project may have been under powered to detect meaningful changes in these parameters, or it is possible that the contents of the mindfulness sessions did not sufficiently target acting mindfully and HAO domains. Self-compassion has been previously linked to reductions in depressive symptoms and increases in markers of neuroplasticity, which may explain why we observed a significant

relationship between the self-compassion subscale of the FFMQ-SF and PHQ-8 score changes. Self-compassion may be an important mechanism to target in future interventions for depression.

**Strengths / Limitations**

Patients were recruited via convenience sampling at a single clinic, representing a potential source of bias. Additionally, patients self-selected into the mindfulness group, which may have introduced bias as these individuals could have been particularly motivated to consider mindfulness meditation as a way of enhancing esketamine treatment. As a feasibility pilot, this project included 19 patients, which is appropriate for assessing feasibility of implementation but may not have been sufficient to detect statistically significant change in symptom measures such as the HAO or FFMQ-SF acting mindfully subscale. Study strengths included the use of validated measures, the inclusion of a usual care group for comparison, testing of a highly feasible intervention, and addressing a key gap in the literature.

**Implications for Research and Clinical Practice**

This project provides data on the feasibility of combining mindfulness meditation and esketamine in the treatment of MDD as a strategy to improve depression care quality. The results of this project contribute to clinical practice through the provision of a novel, integrative approach to the alleviation of distressing symptoms in patients diagnosed with MDD. Adoption of this approach by outpatient psychiatric centers can offer patients a complementary treatment strategy that will enhance efficacy of esketamine treatments, potentially improving remission rates in MDD, thus lowering the burden exacted by this condition. The findings of this project highlight key areas for future research and efforts to improve clinical care more broadly. Results of this project show that mindfulness has strong potential as an esketamine adjunct, and future

studies and implementations of mindfulness may consider emphasizing self-compassion facets of the practice since this factor was highly correlated with depression symptom improvement.

Key areas for future research include determining optimal timing and duration of mindfulness interventions, examining the patient experience of this combination, and determining long-term benefits of this integrative approach. Future research can expand on this pilot project by conducting larger RCTs that establish causal relationships and refine treatment protocols. Including larger populations will allow for sufficient power to detect significant changes in symptom measures. Greater ethnic diversity in future projects will yield more generalizable findings. Investigation of the integration of mindfulness and other neuroplasticity-enhancing treatments may offer additional novel therapeutic paradigms which offer more comprehensive, personalized treatment options for patients diagnosed with MDD. Future studies and quality improvement projects can explore models of integrating mindfulness into regular depression care and how these models can be sustained. Additionally, larger-scale mindfulness implementation projects in mental healthcare systems can contribute to improved care quality as evidenced by metrics such as patient satisfaction scores.

## CONCLUSION

This project implemented a combination of mindfulness meditation and intranasal esketamine treatment in patients diagnosed with MDD, finding evidence for feasibility, acceptability, and potential synergistic benefits of the two treatment modalities. The addition of mindfulness to esketamine provided both a statistically and clinically significant improvement in depressive symptoms as compared to usual care, with a robust correlation between reduction in depressive symptoms and improvement in the mindfulness domain of self-compassion. Given the rising prevalence of MDD and the limitations of current monoaminergic antidepressant

treatments, innovative approaches, such as esketamine with mindfulness meditation, offer promising avenues for improving patient outcomes.

# APPENDICES

## Appendix A

**Eight-Item Patient Health Questionnaire (PHQ-8)**

| **Over the last 2 weeks, how often have you been bothered by any of the following problems?** | **Not at all** | **Several days** | **More than half the days** | **Nearly every day** |
|---|---|---|---|---|
| 1. Little interest or pleasure in doing things | 0 | 1 | 2 | 3 |
| 2. Feeling down, depressed, or hopeless | 0 | 1 | 2 | 3 |
| 3. Trouble falling or staying asleep, or sleeping too much | 0 | 1 | 2 | 3 |
| 4. Feeling tired or having little energy | 0 | 1 | 2 | 3 |
| 5. Poor appetite or overeating | 0 | 1 | 2 | 3 |
| 6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down | 0 | 1 | 2 | 3 |
| 7. Trouble concentrating on things such as reading the newspaper or watching television | 0 | 1 | 2 | 3 |
| 8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual | 0 | 1 | 2 | 3 |

Scoring:
0-4: no significant depressive symptoms
5-9: mild depressive symptoms
10-14: moderate depressive symptoms
15-19: moderately severe depressive symptoms
20-24: severe depressive symptoms

**Appendix B**

**Five Facet Mindfulness Questionnaire: Short-Form (FFMQ-SF)**

Below is a collection of statements about your everyday experience. Using the 1-5 scale below, please indicate, in the box to the right of each statement, how frequently or infrequently you have had each experience in the past month (or other agreed time period). Please answer according to what really reflects your experience rather than what you think your experience should be.

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| Never or very rarely true | Not often true | Sometimes true, sometimes not true | Often true | Very often or always true |

| Item | Facet | Item score/ Reverse keyed items | Final score |
|---|---|---|---|
| I'm good at finding the words to describe my feelings | Describes experiences | | |
| I can easily put my beliefs, opinions, and expectations into words | Describes experiences | | |
| I watch my feelings without getting carried away by them | Non-reactivity | | |
| I tell myself that I shouldn't be feeling the way I'm feeling | Self-compassion | 6- | |
| It's hard for me to find the words to describe what I'm thinking | Describes experiences | 6- | |
| I pay attention to physical experiences, such as the wind in my hair or the sun on my face | Observing inner events | | |
| I make judgments about whether my thoughts are good or bad | Self-compassion | 6- | |
| I find it difficult to stay focused on what's happening in the present moment | Acting mindfully | 6- | |
| When I have distressing thoughts or images, I don't let myself be carried away by them | Non-reactivity | | |
| Generally, I pay attention to sounds, such as clocks ticking, birds chirping, or cars passing | Observing inner events | | |
| When I feel something in my body, it's hard for me to find the right words to describe it | Describes experiences | 6- | |
| It seems I am "running on automatic" without much awareness of what I'm doing | Acting mindfully | 6- | |
| When I have distressing thoughts or images, I feel calm soon after | Non-reactivity | | |

| | | | |
|---|---|---|---|
| I tell myself I shouldn't be thinking the way I'm thinking | Self-compassion | 6- | |
| I notice the smells and aromas of things | Observing inner events | | |
| Even when I'm feeling terribly upset, I can find a way to put it into words | Describe experiences | | |
| I rush through activities without being really attentive to them | Acting mindfully | 6- | |
| Usually, when I have distressing thoughts or images, I can just notice them without reacting | Non-reactivity | | |
| I think some of my emotions are bad or inappropriate and I shouldn't feel them | Self-compassion | 6- | |
| I notice visual elements in art or nature, such as colors, shapes, textures, or patterns of light and shadow | Observing inner events | | |
| When I have distressing thoughts or images, I just notice them and let them go | Non-reactivity | | |
| I do jobs or tasks automatically without being aware of what I'm doing | Acting mindfully | 6- | |
| I find myself doing things without paying attention | Acting mindfully | 6- | |
| I disapprove of myself when I have illogical ideas | Self-compassion | 6- | |

## Appendix C

## The Hope, Agency, and Opportunity (HAO) Questionnaire

| | None of the time 0 | Rarely 1 | Some of the time 2 | Often 3 | All of the time 4 |
|---|---|---|---|---|---|
| Hope:<br>Seeing a future for yourself<br>Believing that difficulties in your life will get better<br>Having things that you want to do<br><br>Do you believe that you can live well, and pursue your aspirations and goals? | | | | | |
| Agency (sense of control):<br>Having choice and information about the support you receive<br>Feeling that you are able to take control of difficulties in your life<br>Knowing how to keep yourself well<br><br>Do you have a sense of control over your life? | | | | | |
| Opportunity:<br>Developing and supporting the things you are good at<br>Supporting the roles that you already have eg family member, student, job role<br>Having the chance to get involved in your local community<br><br>Can you build a full and meaningful life of your choice, with opportunities to be a part of wider society? | | | | | |
| Working Relationships:<br>Being listened to by health and social care professionals and people that support you<br>Working together to build a care plan that fits you<br>Feeling that people supporting you believe in your recovery<br><br>Do your relationships with staff foster hope, agency, and opportunity for recovery? | | | | | |

## TABLE OF EVIDENCE

| CITATION | PURPOSE | SAMPLE/SETTING | METHODS (Design, Interventions, Measures) | RESULTS | DISCUSSION, INTERPRETATION, LIMITATIONS |
|---|---|---|---|---|---|
| Dakwar, E., Nunes, E. V., Hart, C. L., Foltin, R. W., Mathew, S. J., Carpenter, K. M., Choi, C., Basaraba, C. N., Pavlicova, M., & Levin, F. R. (2019). A single ketamine infusion combined with mindfulness-based behavioral modification to treat cocaine dependence: A randomized clinical trial. *American Journal of Psychiatry*, *176*(11), 923–930. **https://doi.org/10.1176/appi.ajp.2019.18101123** | Examine whether a single ketamine infusion in combination with mindfulness-based behavioral modification improves treatment outcomes in adults with cocaine use disorder | Sample:<br><br>-Eligibility criteria: individuals seeking treatment for cocaine dependence, medically healthy, under age 70, cocaine dependence diagnosis per Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, no psychiatric comorbidity<br><br>-Exclusion criteria: history of psychotic or dissociative symptoms, individuals with benzodiazepine or opioid use disorder<br><br>Sample Size:<br><br>n=55<br><br>Setting:<br><br>-New York State Psychiatric Institute | Design:<br><br>-double-blind randomized controlled trial (RCT)<br><br>Procedure/Intervention:<br><br>-ketamine or midazolom infusion over 40 minutes<br><br>-preparation with relaxation or breathing exercises, body scan practice during infusion, mindfulness-based relapse prevention (MBRP) session the same afternoon<br><br>-four total sessions of MBRP completed during inpatient phase<br><br>Measurement:<br><br>-Cocaine-Related Vulnerabilities<br><br>-Five-Factor Mindfulness Questionnaire (FFMQ)<br><br>-Perceived Stress Scale-self-reported drug use | Analysis:<br><br>-logistic regression to analyze effect of treatment on primary outcome of end-of-study-abstinence<br><br>-longitudinal mixed-effect model to analyze weekly cocaine use, weekly craving scores<br><br>Results:<br><br>- ketamine group 53% less likely to relapse compared to midazolam group<br><br>-at 6-month follow-up interview, 44% of ketamine group participants abstinent as compared to 0% midazolam group | Discussion/Interpretation:<br><br>-support that ketamine enhances motivation to change and facilitates engagement with treatment<br><br>-ketamine was well-tolerated and promoted abstinence<br><br>Limitations:<br><br>-small sample size<br><br>-homogenous sample largely African American and male<br><br>-minimal psychiatric comorbidities hamper generalization<br><br>-imperfect blinding<br><br>-no ketamine-only group so unable to determine what role mindfulness played in abstinence |

| CITATION | PURPOSE | SAMPLE/SETTING | METHODS (Design, Interventions, Measures) | RESULTS | DISCUSSION, INTERPRETATION, LIMITATIONS |
|---|---|---|---|---|---|
| Gent, E. M., Bryan, J. W., Cleary, M. A., Clarke, T. I., Holmwood, H. D., Nassereddine, R. O., Salway, C., Depla, S., Statton, S., Krecké, J., & Morgan, C. (2024). Esketamine combined with a mindfulness-based intervention for individuals with alcohol problems. *Journal of Psychopharmacology*, *38*(6), 541–550. https://doi.org/10.1177/02698811241254834 | To study whether the combination of esketamine treatments and a mindfulness-based intervention (MBI) in patients diagnosed with alcohol use disorder (AUD) caused greater engagement with the mindfulness intervention and whether that enhanced engagement translated to an effect on alcohol-related outcomes | Sample:<br><br>-over age 18<br><br>-score between 8 and 40 on AUD Identification Test thus meeting criteria for hazardous drinking or moderate to severe AUD<br><br>-Exclusion criteria: history of schizophrenia or psychosis, in treatment for substance use disorder, high blood pressure (>140/90) at initial screening, body mass index (BMI) less than 16 or greater than 35, taking any medication contraindicated for use with ketamine, taking any medication that could produce a false positive urine screen for ketamine, any display of alcohol withdrawal based on assessment of on-site psychiatrist<br><br>Sample Size:<br><br>n=28<br><br>Setting:<br><br>-Academic research center | Design:<br><br>-double-blind RCT<br><br>Procedure/Intervention:<br><br>-subjects recruited from community using social media advertising<br><br>-assigned mindfulness practice to complete daily for seven days at initial screening visit<br><br>-at drug administration visit, received either oral esketamine or vitamin C placebo<br><br>Measurement:<br><br>-engagement in mindfulness measured using four-item questionnaire<br><br>-FFMQ<br><br>-Alcohol Craving Questionnaire Short-Form Revised (ACQ-SF-R)<br><br>-dissociative states measured using clinician-administered-dissociative states scale (CADSS)<br><br>-depressive symptoms measured using Patient Health Questionnaire-8 (PHQ-8) | Analysis:<br><br>-engagement, alcohol craving, mindfulness changes analyzed using multilevel modeling<br><br>-mediation analysis used to determine whether changes in engagement mediated changes in alcohol cravings<br><br>Results<br><br>-significant decrease in alcohol cravings from pre- to post-drug administration for esketamine group but not placebo group<br><br>-esketamine enhanced psychological engagement with daily MBI as compared to placebo | Discussion/Interpretation:<br><br>-first study exploring whether esketamine enhances engagement in MBI and whether this engagement has an influence on treatment outcomes<br><br>- support for hypothesis that esketamine leads to increased engagement in treatment<br><br>-clinical implications include suggestion that ketamine may reduce probability of individuals dropping out of MBIs, and, in turn, decrease likelihood of relapse<br><br>-support for proposition that ketamine may act as catalyst for greater mindfulness practice<br><br>Limitations:<br><br>-limited sample size<br><br>-imperfect blinding |

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|---|---|---|---|---|---|
| Popova, V., Daly, E. J., Trivedi, M., Cooper, K., Lane, R., Lim, P., Mazzucco, C., Hough, D., Thase, M. E., Shelton, R. C., Molero, P., Vieta, E., Bajbouj, M., Manji, H., Drevets, W. C., & Singh, J. B. (2019). Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: A randomized double-blind active-controlled study. *American Journal of Psychiatry*, *176*(6) , 428–438. https://doi.org/10.1176/appi.ajp.2019.19020172 | Compare efficacy and safety of administration of esketamine nasal spray with initiation of new antidepressant to placebo nasal spray with initiation of new antidepressant medication in patients diagnosed with treatment resistant depression (TRD) | Sample:<br><br>-eligibility criteria: between 18 and 64 years old, diagnosed with single-episode of recurrent major depressive disorder (MDD) without psychotic features, meet study definition of TRD, medically stable, able to self-administer intranasal medication<br><br>-exclusion criteria: current or recent homicidal ideation/intent or suicidal ideation or behavior, diagnosis of certain psychiatric disorders, uncontrolled hypertension, seizures<br><br>Setting:<br><br>-conducted across 39 outpatient referral centers<br><br>Sample Size:<br><br>-n=197 | Design:<br><br>-phase 3, randomized, double-blind, active-controlled multicenter study<br><br>Method/Procedure:<br><br>-randomized to treatment with esketamine (56 or 84mg) nasal spray or placebo nasal spray administered twice weekly<br><br>-antidepressant (escitalopram, sertraline, duloxetine, or venlafaxine) selected by investigator based upon review of treatment response questionnaire<br><br>Measures:<br><br>-Montgomery-Asberg Depression Rating Scale (MADRS) performed by independent, remote raters<br><br>-Sheehan Disability Scale (SDS)<br><br>-Patient Health Questionnaire-9 (PHQ-9)<br><br>- Generalized Anxiety Disorder 7-item (GAD-7)<br><br>-EuroQol-5-dimension-5 level (EQ-5D-5L)<br><br>-CADSS | Analysis:<br><br>-primary efficacy endpoint analyzed using mixed-effects model using repeated measures<br><br>Results:<br><br>-esketamine plus antidepressant group had significantly greater reductions in MADRS score at day 28<br><br>-improvement in esketamine group noted at earlier time points<br><br>-most common adverse events – dissociation, nausea, vertigo, dysgeusia, dizziness – observed more frequently in esketamine group | Discussion/Interpretation:<br><br>-flexible-dose study, dose-response relationships not evaluated<br><br>-intent of trial to assess short-term efficacy and safety<br><br>-support for clinically meaningful and statistical improvement in depressive symptoms for esketamine plus antidepressant group<br><br>Limitations:<br><br>-generalizability limited due to exclusion of patients with significant medical or psychiatric comorbidities, exclusion of substance dependence<br><br>-adverse effect profile of esketamine may have affected blinding for study patients |

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| Stocker, K., Hartmann, M., Reissmann, S., Kist, A., & Liechti, M. E. (2022). Buddhist-like opposite diminishing and non-judging during ketamine infusion are associated with antidepressant response: An open-label personalized-dosing study. *Frontiers in Pharmacology*, *13*. https://doi.org/10.3389/fphar.2022.916641 | Investigate whether non-judging and opposite diminishing occasioned by the use of ketamine relate to improved mental well-being | Sample:<br><br>-3 females, 8 males<br><br>-mean age 48.6 years old<br><br>-inclusion criteria: minimum age 18 years old, depressive disorder diagnosis, met health requirements for ketamine administration<br><br>-exclusion criteria: acute suicidality, any disease sensitive to increased blood pressure or heart rate, substance use disorders<br><br>Sample Size:<br><br>n=11<br><br>Setting:<br><br>-anesthesia day clinic | Analysis:<br><br>-data from 45 sessions assessed<br><br>-linear-mixed effect model computed using patient as random intercept effect<br><br>-two separate models with either opposite diminishing or non-judging as fixed effect predictors<br><br>Results:<br><br>-reductions in BDI-II average 9.6<br><br>-significant correlation between opposite diminishing and non-judging<br><br>-opposite diminishing and non-judging associated with antidepressant responses | Analysis:<br><br>-data from 45 sessions assessed<br><br>-linear-mixed effect model computed using patient as random intercept effect<br><br>-two separate models with either opposite diminishing or non-judging as fixed effect predictors<br><br>Results:<br><br>-reductions in BDI-II average 9.6<br><br>-significant correlation between opposite diminishing and non-judging<br><br>-opposite diminishing and non-judging associated with antidepressant responses | Discussion/Interpretation:<br><br>-support that opposite diminishing and mental state of non-judging during infusion associated with reduced depression scores<br><br>-opposite-diminishing positively associated with distressing experience, consistent with observations from classic psychedelics<br><br>Limitations:<br><br>-lack of control group<br><br>-small sample size<br><br>-imbalanced male to female ratio<br><br>-subjective determination of dosing |

| CITATION | PURPOSE | SAMPLE/SETTING | METHODS (Design, Interventions, Measures) | RESULTS | DISCUSSION, INTERPRETATION, LIMITATIONS |
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| van der Velden, A. M., Scholl, J., Elmholdt, E. M., Fjorback, L. O., Harmer, C. J., Lazar, S. W., O'Toole, M. S., Smallwood, J., Roepstorff, A., & Kuyken, W. (2022). Mindfulness training changes brain dynamics during depressive rumination: A randomized controlled trial. *Biologic Psychiatry*, *93*(3), 233–242. | Use functional magnetic resonance imaging (fMRI) to examine neurocognitive mechanisms associated with mindfulness-based cognitive therapy (MBCT) for recurrent depression | Sample:<br><br>-recruited from general practices and local psychiatric units<br><br>-inclusion criteria: diagnosed with MDD, with or without current episode, three or more previous episodes, age 18 or older, if on antidepressants on a stable dose for 8-week minimum<br><br>-exclusion criteria: certain psychiatric diagnoses, persistent self-injury requiring clinical management, formal simultaneous psychotherapy, previous completion of certain mindfulness programs, extensive meditation experience, antipsychotic medication or benzodiazepine use<br><br>Sample Size:<br><br>n=80 | Intervention/Procedure:<br><br>-MBCT group consisted of pre-class interview, weekly classes with homework, four booster sessions every three months after completion of program<br><br>-treatment as usual (TAU) no psychotherapeutic intervention<br><br>-rumination induction during fMRI<br><br>-mindfulness meditation as part of fMRI<br><br>Measures:<br><br>-Perceived Stress Scale<br><br>-Quick Inventory of Depressive Symptomatology Self-Report<br><br>-FFMQ<br><br>-Rumination Response Scale<br><br>-fMRI measures of neural connectivity; default mode network and salience network primary networks of interest | -decreased salience network connectivity to lingual gyrus during ruminative state<br><br>-improvements in ability to sustain and control attention to body sensations<br><br>-MBCT compared with TAU reduced depressive symptoms and increased dispositional mindfulness skills and interoceptive awareness | Discussion/Interpretation:<br><br>-MBCT group showed decreased frontal connectivity between salience network and both lingual gyrus and occipital cortex during induced rumination<br><br>-change in salience network connectivity to lingual gyrus mediated by ability to sustain and control attention to body sensations<br><br>-supports role of salience network in depression symptomology and treatment response<br><br>Limitations:<br><br>-lack of active control group<br><br>-did not measure whether MBCT teachers adhered to treatment protocol<br><br>-participants had the option of opting out of the rumination condition, so findings only generalize to participants willing to participate in rumination induction |

| CITATION | PURPOSE | SAMPLE/SETTING | METHODS (Design, Interventions, Measures) | RESULTS | DISCUSSION, INTERPRETATION, LIMITATIONS |
|---|---|---|---|---|---|
| Winnebeck, E., Fissler, M., Gärtner, M., Chadwick, P., & Barnhofer, T. (2017). Brief training in mindfulness meditation reduces symptoms in patients with a chronic or recurrent lifetime history of depression: A randomized controlled study. *Behaviour Research and Therapy*, *99*, 124–130. https://doi.org/10.1016/j.brat.2017.10.005 | Investigate whether a brief MBI has efficacy in reducing -MBI group showed significantly greater depressive symptom reduction than control group symptoms of depression in acutely depressed patients | Sample:<br><br>-Inclusion criteria: current diagnosis of MDD, chronic or recurrent lifetime history of depression with onset before age 19, BDI-II score above 19, age 25 to 60, fluency in spoken and written German<br><br>-Exclusion criteria: history of psychosis or mania, current eating disorder, obsessive compulsive disorder (OCD), current self-harm, current substance abuse or dependency, history of traumatic brain injury (TBI), simultaneous treatment with cognitive behavioral therapy (CBT)<br><br>Sample Size:<br><br>-n=74 | Design:<br><br>-RCT, patients randomly assigned to MBI or control training<br><br>Intervention/Procedures:<br><br>-series of two 1.5-hour weekly individual sessions plus third 50-minute follow-up session delivered by clinical psychologist followed by daily home practice<br><br>-MBI group engaged in formal meditation practice twice daily using recorded guided meditations<br><br>-control group provided psychoeducation and given ambient music for twice-daily rest periods<br><br>Measures:<br><br>-Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition, Text Revision (DSM-IV-TR)<br><br>-BDI-II<br><br>-Ruminative Response Style Questionnaire – brooding subscale (RRSQ-B)<br><br>-FFMQ | -MBI group showed significantly greater depressive symptom reduction than control group<br><br>-MBI group showed significant increases in mindfulness, significant reductions in ruminative tendencies and cognitive reactivity<br><br>-within MBI group, reductions in BDI-II scores significantly correlated with changes in FFMQ subscales<br><br>-no adverse events | Discussion/Interpretation:<br><br>-brief MBI may have significant positive effects in patients diagnosed with MDD<br><br>-consistent with growing body of literature supporting MBIs for treatment of depressive symptoms<br><br>-MBI did not use guided meditations with prolonged periods of silence to reduce possibility of patients engaging in maladaptive thinking<br><br>Limitations:<br><br>-largely self-report introduced possibility of reporting bias<br><br>-small sample size<br><br>-medications used during study not monitored<br><br>-therapist adherence not formally assessed<br><br>-future studies should assess how far improvements may be sustained |

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