Examining the Efficacy of Combining Psychotherapy and Ketamine Treatments for the Treatment of Emotional Disorders in Adults

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To my wife and daughter – my light.

Special thanks to my parents for the countless times they have supported me through this adventure. Further appreciation to my late grandmother whose belief in me will always hold a special place.

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Abstract

Emotional disorders, including depression, post-traumatic stress disorder, and anxiety, appear to be on the rise in Canada. Counselling, medication, and mental health information are the most common forms of mental health support offered in Canada, often with limited efficacy. Emerging research has shown that ketamine-assisted psychotherapy may be an effective treatment for clients with emotional disorders, especially those who have become treatment resistant. In this paper, a systematic review was completed that examined the efficacy of combining ketamine with psychotherapy for the treatment of depression, post-traumatic stress disorder, and/or anxiety. The goal of this literature review is to determine the efficacy of combining ketamine with psychotherapy for the treatment of emotional disorders in adults and identify gaps in the literature that merit further investigation. Findings suggest that ketamine-assisted psychotherapy may be an effective treatment for emotional disorders in adults with depression, post-traumatic stress disorder, and/or anxiety. A limitation found across studies was that the length of time that relief lasted was variable, and often undetermined as there were inconsistencies in follow-up methods. While the initial findings of a reduction in symptoms from all the studies are promising, further research with control groups, larger sample sizes, consistent evidence-based psychotherapy modalities, consistent ketamine dosing protocols, and longer-term follow-up periods are merited.

Key terms: ketamine, ketamine-assisted psychotherapy, neuroplasticity, and treatment resistant depression.

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Examining the Efficacy of Combining Psychotherapy and Ketamine Treatments for the Treatment of Emotional Disorders in Adults

Chapter One: Introduction

The prevalence of emotional disorders, defined as “any psychological disorder characterized primarily by maladjusted emotional reactions that are inappropriate or disproportionate to their cause” (American Psychological Association, 2025), appears to be on the rise in Canada. According to Stephenson (2023), the proportion of Canadians over the age of fifteen diagnosed with major depressive disorder (MDD) grew from 4.7% in 2012 to 7.6% in 2022. Similarly, the proportion of Canadians over the age of fifteen diagnosed with generalized anxiety disorder doubled from 2.6% to 5.2% from 2012 to 2022 (Stephenson, 2023). In Canada, 64.4% of the population experience at least one potentially psychologically traumatic event (PPTEs) in their lifetime, with 7.7% reporting having received a diagnosis of post traumatic stress disorder (PTSD), and another 6.1% in the process of being diagnosed with PTSD by a health professional (Statistics Canada, 2024).

Under half (48.8%) of Canadians aged fifteen and older meeting the diagnostic criteria for a mood, anxiety, or substance use disorder reported talking to a health professional about their mental health concerns in the past year (Stephenson, 2023). Further, those who did talk to a health professional were most likely to talk to a family doctor (32.4%) compared to a psychologist or psychiatrist. Counselling (43.8%), medication (36.5%), and mental health information (32.0%) were the most common forms of mental health support offered (Stephenson, 2023). Although counselling was the most common form of care received, it was also the service that most commonly did not meet the needs of the patients compared to medication and mental health information based on the reported satisfaction by participants in the Statistics Canada survey (Stephenson, 2023). With the prevalence of emotional disorders on the rise in Canada, new combinations of treatment are merited.

Major Depressive Disorder

The remission rates when utilizing classic antidepressants to treat MDD are quite high, with 40-60% in clinical trials and 20-40% for those studied in naturalistic settings (Hasler, 2020). However, as noted by Hasler (2020), the persistence of symptoms for those diagnosed with MDD increases the chance of relapse and can lead to social and occupational impairments, deficits in cognitive functioning, and a higher risk of suicide.

Research by Hasler (2020) found that the efficacy of combining classic antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs), with psychotherapy to treat MDD has only found small benefits, with studies finding that it is unclear whether the benefits found can be deemed clinically relevant. According to Hasler, the benefits from psychotherapy are found through changes in learning and behaviour. Hasler (2020) suggests that a benefit of combining pharmacotherapy and psychotherapy comes from the neuroplasticity-enhancing effect of psychotropics, which can enhance cognitive restructuring and behavioural change. A limitation noted with classic antidepressants is that they modulate the synapses but do not substantially influencing synaptogenesis (Hasler, 2020). While the classic antidepressants increase brain-derived neurotrophic factor (BDNF), they explain that for plasticity to occur, BDNF release must occur in addition to the activation of synaptogenesis (Hasler, 2020).

Ketamine, when given at a sub-anesthetic dose, has been found to have antidepressant effects (Hasler, 2020). In comparison to classic antidepressants, onset of action of ketamine is more rapid, reduces suicide risk, and is effective for patients who do not respond to certain classical antidepressants. They explain that ketamine leads to fast acting changes in a patient's synaptic function and plasticity far beyond the effects of classical antidepressants. By increasing mTORC1 signaling, synaptic number, and function, the neuroplasticity effects of ketamine can last up to a week or longer and have been shown to correlate with lowering depressive symptoms in patients with MDD (Hasler, 2020). The researcher explains that this shows that the

use of ketamine may have the potential to enhance and sustain the effects of psychotherapy for depression.

Cognitive behavioural therapy (CBT) has been shown in preliminary studies to have the potential of extending the antidepressant effects of ketamine (Hasler, 2020). Hasler (2020) explains that the use of ketamine alters the activity in the brain circuits that are related to reward and motivation. Patients with anhedonia, a lack of interest, enjoyment, or pleasure from life's experiences, were found to be 55% more likely to positively respond to ketamine treatments. The researcher explains this finding with behavioural models of depression that describe low positive reinforcement in a patient's environment as a causal factor reinforcing their depressed state. Behavioural activation, a highly effective intervention used in CBT to increase environmental reinforcement when treating depression, is described by Hasler (2020) as an intervention that shows promise in combination with ketamine to lengthen its antidepressant effects. Hasler (2020) explains that behavioural activation works when the subjective experience of environmental rewards, in comparison to objective rewards, lowers the chance of the patient avoiding the reward. He notes that behavioural activation works best when the human reward pathways are responsive and plastic. As such, the combination of using ketamine and behavioral activation appears to be promising in lengthening the antidepressant effects of the ketamine.

Inflammation has been shown to predict a poor response to CBT, possibly due to negative effects related to cognitive deficits in memory, attention, learning, and fatigue (Hasler, 2020). Further, inflammation has shown to have negative effects on social cognition and behaviours. The use of ketamine may enhance the therapeutic potential of CBT when used in combination due to the anti-inflammatory effects of the medicine. With ketamine shown to rapidly improve social functioning in patients diagnosed with MDD, Hasler (2020) notes that the therapeutic relationship between the practitioner and patient may also improve when combined with psychotherapy. With both the anti-inflammatory effects and ability to improve social

functioning, there appears to be merit in investigating further the combination of CBT and ketamine for the treatment of MDD.

Post Traumatic Stress Disorder

While there are a variety of evidence-based therapies for PTSD, including prolonged exposure, eye movement desensitization and reprocessing (EMDR), cognitive processing therapy, and trauma focused CBT, clinical studies have found that the non-response rate for these interventions ranges from 25%-50% (Davis et al., 2021). Perseverative thoughts, poor therapeutic alliance, and high drop-out rates may all lead to difficulty in managing symptoms. Selective-serotonin reuptake inhibitors (SSRIs) such as paroxetine and sertraline have been approved for the treatment of PTSD but come with limitations such as low response rate (40%) and a delayed symptom relief period of 6-8 weeks. Further, sudden cessation of medication can lead to worsening PTSD symptoms and an increase in anxiety and depression symptoms (Davis et al., 2021).

With the current limitations in treatment for PTSD, preliminary clinical trials using ketamine to treat PTSD have been promising, including rapid reduction in PTSD symptoms within 24 hours with effects sustaining for 15 days (Davis et al., 2021). Limited evidence currently exists for whether psychotherapy could increase the therapeutic benefits of using ketamine when treating PTSD. Davis et al. (2021) found that combining therapy with ketamine through ketamine-assisted psychotherapy (KAP) may increase the ability for the patient to be more reflective and increase therapeutic rapport. Further research is required to determine whether combining therapy with ketamine would be effective for treating PTSD.

Anxiety Disorders

In comparison to MDD, less clinical research has been done on the use of ketamine for anxiety disorders (Whittaker et al., 2021). Whittaker et al. (2021) note that in treatment resistant anxiety, remission rates in clinical trials are between 25-35% and relapse rates for those post-remission are about 30% after 10 years. These findings show a need for more effective

treatments with longer lasting effects. According to the researchers, current pharmacotherapies for anxiety disorders include medications that interact with monoamine and GABA-A systems, which have shown to have a slow onset of action and a high rate of nonresponse in patients. Whittaker et al. (2021) also noted concerns about using benzodiazepines as a long-term treatment for anxiety disorders due to potential for abuse, rapid buildup in patient tolerance, and withdrawal symptoms. Evidence from the studies presented by Whittaker et al. (2021) has shown that medications interacting with the glutamate system may be therapeutically effective for anxiety disorders, recognizing that glutamate is involved in fear extinction. They note that glutamate regulates neuropeptides involved in the stress response linked to anxiety and plays a role in both synaptic and neural plasticity linked to anxiety disorders. There appears to be enough evidence to explore linking ketamine with psychotherapy as a potential therapeutic benefit in the treatment of anxiety disorders.

Research Problem

While evidence demonstrates that ketamine alone has shown to be a potential treatment for depression, anxiety, and PTSD (Whittaker et al., 2021; Davis et al., 2021; Hasler, 2020), less is known about whether combining psychotherapy with ketamine would augment the therapeutic benefits. While there is preliminary research showing the potential for psychotherapy to augment the therapeutic benefits of ketamine for depression using CBT (Wilkinson et al., 2021), a deeper exploration of the research would be beneficial to demonstrate clinical significance of combining the two methods, and whether the combination of psychotherapy and ketamine would also be effective for the treatment of anxiety disorders and PTSD. Further, it is important to demonstrate which psychotherapy modalities would be effective in combination with ketamine, and in turn, which method of ketamine administration (e.g., intravenous (IV), intramuscular, sublingual, or intranasal) would facilitate the greatest benefit. This review seeks to clarify the current literature gap in determining whether combining ketamine treatments with

psychotherapy would augment the therapeutic benefits of ketamine, and if so, which therapeutic modality and method of ketamine administration would be best suited for the treatment.

Rationale/Justification

With the proportion of Canadians over the age of fifteen diagnosed with anxiety and/or depressive disorders increasing (Statistics Canada, 2022) and high prevalence (64.4%) of Canadians experiencing at least one PPTE in their lifetime, new combinations of treatment appear to be merited. Combining psychotherapy with ketamine has shown early clinical success in improving and/or sustaining the therapeutic benefit of ketamine for the treatment of emotional disorders (Wilkinson et al., 2017; Wilkinson et al., 2021; Pradhan et al., 2017; Pradhan et al., 2018; Dore et al., 2019; Shiroma et al., 2020; Keizer et al., 2020; Davis et al., 2021; Zdyb & Hart, 2021; Dames et al., 2022; Yermus et al., 2024). As our understanding of the efficacy of combining ketamine treatments with psychotherapy continues to evolve, and practitioners examine the clinical applications of the new treatment method, it is important that we understand which ketamine administration methods and psychotherapy modalities are most effective. Without understanding which administration methods and modalities are most effective, clinicians may unknowingly utilize less effective ones when applying treatment.

Research Significance

With the prevalence and increased rates of emotional disorders in Canada, it is likely that therapists will frequently encounter clients with one or more of these disorders, both in private and public practice (Stephenson, 2023). Drawing attention to the availability of alternative treatments for emotional disorders when other evidence-based approaches have been unsuccessful or partially successful can enhance the availability of supports for clients. A further benefit includes having another treatment route to offer clients who have become treatment resistant to other therapeutic options. A better understanding of how to combine psychotherapy and ketamine, and when it is appropriate, would support therapists in providing another therapeutic option to their clients.

Theoretical Framework

The theoretical framework used to guide this review is the biopsychosocial framework (Engel, 1977). This framework emphasizes that mental health concerns are affected by biological, psychological, and social factors. Applying this framework to this review emphasizes that utilizing a combination treatment of ketamine and psychotherapy for emotional disorders is multifaceted in its approach. Biologically, ketamine's mechanisms of action, including effects on glutamate receptors, increase in neuroplasticity, BDNF upregulation to induce acute changes in synaptic plasticity, and anti-inflammatory effects appear to offer rapid symptom relief (Zarate & Machado-Vieira, 2017). Psychologically, psychotherapy modalities discussed in this review aim to support clients with expressing their thoughts and emotions to assist them with processing the insights from their ketamine treatments and help them develop coping strategies to manage their symptoms. Regarding the social aspect of the theoretical framework, the studies in this review discuss the importance of the therapeutic alliance and connection with others, particularly Dames et al (2022). The researchers utilize group therapy and emphasize that the intended mechanisms for healing are enabling connection to self and others through experiencing secure attachment, addressing trauma in an environment that provides unconditional positive regard, providing space to regulate the nervous system by co-regulating with others, and exploring individual desires and callings. Integrating biological, psychological, and social factors into this review's framework supports the combination of pharmaceutical intervention, psychotherapy, and social connection for the treatment of emotional disorders.

Definition of Terms

Key terms that are essential to understand in this review are: ketamine, ketamine-assisted psychotherapy (KAP), neuroplasticity, and treatment resistant depression (TRD). Ketamine is a dissociative anesthetic that is used at sub-anesthetic doses for the treatment of mental health disorders, particularly depression (Hasler, 2020). Ketamine is administered

intravenously through IV infusions, intramuscularly with a needle injection, orally with sublingual tablets, or intranasally through a nasal spray.

Ketamine-Assisted Psychotherapy (KAP) includes the combination of ketamine administration with psychotherapy. Psychotherapy can occur before (preparation), during (dosing), or after the administration of ketamine (integration; Dore et al., 2019). In this literature review, psychotherapy is combined with ketamine in either the preparation phase before the ketamine is administered, during the dosing to provide therapeutic support, and/or after the ketamine treatment to help the participant integrate insights from the experience.

Neuroplasticity is a process in the brain that involves the ability of the brain to make adaptive structural and functional changes (Puderbaugh & Emmady, 2020). These changes, described by Puderbaugh and Emmady (2020), are made by the nervous system in response to intrinsic or extrinsic stimuli where reorganization of structure, function, or connections occur.

While there is no universal definition for TRD, a commonly used criteria includes when a client fails to achieve symptom resolution after at least one antidepressant treatment (Parikh & Lebowitz, 2004). As described by Parikh and Lebowitz (2004), there are many factors involved in a client developing resistance to treatment, including factors related to the disorder, the treatment, and/or patient and environmental factors.

Researcher's Positioning Statement

I acknowledge that I have personal, academic, and professional biases within the context of this research topic. Personally, I have witnessed people I know have therapeutic success when combining ketamine with psychotherapy. Seeing people I know benefit from the combination leads me to believe that combining psychotherapy with ketamine would be effective.

Academically, I have examined the use of ketamine as a treatment for depression in previous work, specifically when completing a literature review. The conclusion of the studies I found for that assignment overwhelmingly supported the use of ketamine for the treatment of

depression. I acknowledge that I have a biased view towards how effective ketamine can be based on my previous academic work. Upon reflection, a limitation in my previous academic work related to ketamine was not ensuring I explored studies that went against my hypothesis as well. When completing my literature review, I instead focused on the inclusion of studies that supported my research topic and hypothesis.

Professionally, my family owns and operates a ketamine clinic where patients with a variety of mental health disorders, including depression, anxiety, and PTSD, receive treatment. As a practitioner with the clinic, I have seen firsthand the positive therapeutic effects patients have experienced from the treatment. As we also work in conjunction with another clinic to offer ketamine-assisted therapy, I recognize that I have both a bias and self-interest towards ketamine and psychotherapy being shown to be effective for emotional disorders when combined.

To ensure I remain objective and limit biases, it is important that I search for academic sources that support the efficacy of combining ketamine with psychotherapy and academic sources that do not support the efficacy as well. Finding sources from both sides will support my discussion regarding where further research is required and assist in identifying gaps in the current literature regarding the subject. The discussion and learnings from completing the project will be beneficial whether I am able to find conclusive evidence or not to support my research topic, acknowledging that I am investigating an emerging topic with limited past research.

Overview of the Paper

The rest of this review is divided into five chapters. Chapter two describes the databases and search engines used for the literature review, including a list of all the search parameters. It also includes a description and evaluation of some of the significant studies reviewed, challenges encountered, and significant limitations on the methodology that impacted the interpretation of findings. Chapter three reviews the literature utilizing the themes of combining

ketamine and psychotherapy for the treatment of depression, combining ketamine and psychotherapy for the treatment of PTSD, and combining ketamine and psychotherapy for the treatment of anxiety. Each theme includes sub-themes examining the research design, ketamine protocols, psychotherapy protocols, assessment tools used to measure outcomes, and key findings. Lastly, there is a section that includes examining the ethical considerations. Chapter four includes an examination of the application and integration of ketamine-assisted therapy into clinical practice. This section describes how aspiring practitioners can use the information in their clinical practice and outlines how the findings factor into the ability to do research, including suggesting a different theoretical model. Lastly, chapter five provides a summary of the review and problem addressed with a concluding statement and reflection on learnings.

Chapter Two: Methods of Literature Search

For a research study to be included, the study must have been within the last eight years, have at least 5 participants, and include the use of ketamine and psychotherapy in some form of combination as a treatment for depression, anxiety, or PTSD. Studies that examined the treatment of a combination of disorders (e.g. anxiety and depression) were also included. Studies were found by searching the following databases: PubMed, Google Scholar, PsycINFO, and Frontiers in Medicine.

Key terms used when searching for studies included: *ketamine, ketamine therapy, ketamine-assisted therapy, ketamine-assisted psychotherapy, combination of ketamine and psychotherapy for depression, combination of ketamine and psychotherapy for PTSD, and combination of ketamine and psychotherapy for anxiety*. Only using the search term "*ketamine*" yielded a broad range of studies and other types of literature describing ketamine as medication.

Refining the search terms to *"ketamine"* and *"psychotherapy"* yielded studies relevant to this review, although refining the search criteria to include *"depression", "PTSD",* or *"anxiety"* assisted in filtering out the studies that examined the use of combining ketamine and psychotherapy for other disorders not reviewed in this paper (i.e., substance use disorders). To ensure that studies that may be relevant to this review were not missed, the results of the search terms *"ketamine"* and *"psychotherapy"* were analyzed.

There were 25 studies that initially appeared relevant to this review using the search terms *"ketamine"* and *"psychotherapy"*. Relevancy to this review was determined by first reading the abstracts of each study that would be potentially included. If it could not be determined by the abstract whether a study met the inclusion criteria, then the study was read in full, with attention being focused on the study's research methods section. Out of the 25 studies, 14 were excluded based on one or more of the following criteria: not being within the last eight years, not

utilizing KAP for the treatment of depression, anxiety, and/or PTSD, and/or having less than five participants.

The majority of the studies excluded from this review included the use of KAP for the treatment of substance use disorders, such as cocaine use, alcohol use, heroin use, and opioid use. One of the excluded studies involved using KAP for chronic pain, two involved using KAP for the treatment of obsessive-compulsive disorder, and another investigated the use of KAP for treating an eating disorder. Two studies investigating the use of KAP for MDD were excluded as there were less than five participants in the study, and one of those studies did not take place in the last eight years. While the results of the studies investigating the efficacy of the use of KAP for the treatment of substance use disorders appeared positive, it was decided that increasing the inclusion criteria outside of emotional disorders would be too broad for this review. Further reviews that focus on examining the efficacy of KAP for the treatment of substance use disorders are merited.

Studies relevant to this review were organized in table form, sorting them by year, type of psychotherapy used, method of ketamine administration, assessment tools used, and key findings. Recognizing the various methods of psychotherapy, all psychotherapy methods were included. Studies were only included if they were done in a legal and controlled setting, such as a hospital or government approved clinic. Any method of legal ketamine administration was included, such as IV, sublingual, intramuscular, or intranasal.

In terms of evaluating significant studies reviewed in this literature review, Wilkinson et al. (2021) stands out as the most significant study that contributes the furthest to answering the research question. This is due to the study being recent, utilizing randomization, having a control group, utilizing a psychotherapy modality (CBT) that is evidence based for the treatment of the disorder being examined (depression), ensuring psychotherapists are certified and trained in the psychotherapy modality being used, using consistent ketamine administration protocols (including dosing protocols), having a follow-up period, and utilizing consistent assessment

methods. Wilkinson et al. (2021) found that the group that received ketamine and CBT had a moderately improved score compared to the control group, suggesting that the combination of ketamine and psychotherapy may be an effective treatment for depression. This study was a follow up study to Wilkinson et al. (2017) which did not have a control group but also found that the combination of ketamine and psychotherapy (CBT) may be effective in treating depression.

Other significant studies in this literature review that contributed to answering the research question were Pradhan et al. (2017) and Pradhan et al. (2018) as they were the only other studies in this review that included a control group. Both studies also included randomization, consistent ketamine administration protocols (including dosing protocols), a post treatment follow-up period, and consistent assessment methods. Both studies found that the combination of ketamine and psychotherapy may be an effective treatment for PTSD as both studies found that the group that received ketamine and trauma interventions using mindfulness-based extinction and reconsolidation (TIMBER) showed a reduction in symptoms.

Retrospective studies by Yermus et al. (2024) and Dore et al. (2019) analyzed data from the largest samples in this review, with 346 and 235 participants, respectively. While the results were encouraging regarding the effectiveness of the combination of ketamine and psychotherapy, the lack of control group, high dropout rate, and lack of consistent ketamine protocols and psychotherapy modalities limited the findings.

As noted, the limited number of studies, especially involving a control group, was the most significant challenge encountered in the literature review process. Further, the variability in methods of ketamine administration (including dosing protocols), variability in the types of psychotherapy modalities used, inconsistent and/or short-term follow-up periods, high drop-out rate of participants, and/or small sample sizes made it difficult to compare the results of the studies and make interpretations with the results.

Chapter Three: Review of the Literature

The combination of psychotherapy and ketamine treatment appears to present a promising new opportunity for mental health practitioners for the treatment of emotional disorders in adults. The following literature review aims to evaluate existing literature examining the efficacy of combining ketamine treatments with psychotherapy. The review will include the presentation of key areas related to the combination treatment, identifying and discussing existing gaps in literature, and highlighting the ethical considerations associated with the topic. The goal of the literature review is to explore methods of ketamine combined with psychotherapy to determine if the combination is an effective treatment for emotional disorders. This review will provide insights, including potential benefits and challenges, regarding the combination of ketamine and psychotherapy for the treatment of emotional disorders.

Combining Ketamine and Psychotherapy to Treat Depression

The combination of ketamine treatment and psychotherapy for the treatment of depression shows promising results, especially in cases involving treatment-resistant depression (TRD). Research has shown that ketamine can rapidly reduce suicidal ideation and be an effective treatment for patients who have not responded to other treatment methods, such as anti-depressants (Hasler, 2020). While ketamine has been shown to have rapid-acting antidepressant effects, there are concerns regarding sustaining the effects long term (Wilkinson et al., 2021). Combining ketamine with psychotherapy has been suggested by the authors in this review as a potential treatment option to sustain the antidepressant effects of ketamine. The following analysis will describe the types of ketamine protocols being used, psychotherapy modalities implemented, research designs, assessment tools used to measure outcomes, and key findings from combining ketamine with psychotherapy for the treatment of depression.

Research Design

Within the last eight years only one randomized clinical trial has been completed to examine the efficacy of combining psychotherapy with ketamine for the treatment of depression.

Wilkinson et al. (2021) conducted a randomized clinical trial with 42 participants to examine the efficacy and feasibility of using cognitive behavioural therapy (CBT) following ketamine treatments for treating TRD. Wilkinson et al. (2021) divided their study into two phases. In phase one, ketamine was administered six times over three weeks through IV infusions. There were 42 participants who initially signed consent to participate. Of the 42 participants, 28 achieved a response from the ketamine, meaning they had a 50% or greater reduction in depression severity, and were then randomized into either CBT or treatment as usual (TAU) for an additional 14 weeks of treatment (phase two). Those who did not respond to ketamine were withdrawn from the study. Participants did not receive further ketamine infusions after the completion of phase one. The inclusion criteria for the participants included being treatment resistant to two or more adequate courses of antidepressant medications, a severe depressive episode as measured by the Hamilton Depression Rating Scale (score of 21 or higher), and being aged 18-65. Participants who had an active substance use disorder or schizophrenia were excluded. This being the only study having a control group and randomization of participants strengthened the validity of the researcher's findings. As outlined by the researchers, having a small sample size limits the validity and generalizability of the results.

The study by Wilkinson et al. (2021) was a follow up to the open-label study conducted by Wilkinson et al. (2017) with 16 participants to explore the efficacy of combining CBT and ketamine for the treatment of TRD. The researchers were interested in determining whether CBT could prolong the antidepressant effects of ketamine, and whether CBT could improve the treatment outcome of patients who did not have a strong initial positive response to ketamine. The inclusion criteria for the participants included being between the ages of 18-65, having been diagnosed with MDD, and eligibility to receive ketamine. The study by Wilkinson et al. (2017) did not have a control group but did provide a foundation for the follow-up randomized clinical trial by Wilkinson et al. (2021).

Various other research designs were used in the identified studies to examine the efficacy of combining ketamine with psychotherapy for the treatment of depression, including studies by Dames et al. (2022), Zdyb and Hart (2021), Yermus et al. (2024), and Dore et al. (2019). In a case cohort report presented by Dames et al. (2022), 94 adult participants received ketamine-assisted therapy through a 12-week program. Participants were included in the study if they had a history of previous treatment failure and a diagnosis of TRD, chronic anxiety, obsessive-compulsive disorder, suicidality, PTSD, or substance use disorder. While the sample size of this study was larger than the studies by Wilkinson et al. (2017) and Wilkinson et al. (2021), the lack of control group limits the researcher's findings. Zdyb and Hart (2021) conducted an open-label pilot study of 10 participants combining ketamine and the therapeutic reset of internal processes (TRIP) protocol for the treatment of TRD. Inclusion criteria included participant being over the age of 18 and having a diagnosis of TRD. In their study, participants were given low dose sublingual ketamine during a TRIP protocol session. Like Wilkinson et al. (2017) and Wilkinson et al. (2021), the small sample size of the study by Zdyb and Hart (2021) limits the validity of the researcher's findings. Further, similar to Wilkinson et al. (2017) and Dames et al. (2022), the lack of a control group in the study by Zdyb and Hart (2021) limits the ability to determine whether it was the combination of ketamine treatments with psychotherapy that yielded the therapeutic benefit, or if the same results would have been found with the participants receiving either ketamine or psychotherapy alone.

Retrospective studies by Yermus et al. (2024) and Dore et al. (2019) analyzed data from large sample populations over multiple years. Yermus et al. (2024) conducted a retrospective effectiveness study of 346 adults who received KAP at a Field Trip Health Clinic in North America between 2020 and 2022. The study included self-reported outcome data at three months and six months post-treatment. Inclusion criteria for the study included the participants signing a written informed consent, being over age of 18, and having a diagnosis of MDD, bipolar disorder, generalized anxiety disorder (GAD), obsessive compulsive disorder, an eating

disorder, or a significant history of trauma and/or a diagnosis of PTSD. Out of the 346 participants, 177 had a primary diagnosis of MDD. Dore et al. (2019) analyzed self-reported outcome data from 235 patients across three private general psychiatric clinics who received KAP between 2013-2018. Inclusion criteria for the study included the participants being over the age of 18 and having more than two ineffective psychiatric treatments for depression. Out of the 235 patients, 148 met the criteria for major depressive disorder. While both studies by Yermus et al. (2024) and Dore et al. (2019) had large sample sizes, the lack of a control group limits the validity of the findings.

Ketamine Protocols

The method, timing, and dosing of the ketamine used by the participants varied across the studies examined. Wilkinson et al. (2017) divided their study into two phases, with the first phase having participants undergo four IV ketamine infusions twice weekly for two weeks while participating in one CBT session between ketamine infusions. Phase two only included CBT sessions and participants did not receive any additional ketamine. The ketamine dosing protocol used to calculate the dose for all participants was 0.5 mg/kg. A strength of this study is that every participant received a standardized dose (0.5mg/kg) over a consistent time frame (twice weekly for two weeks). This allows for the ability to compare the ketamine protocol with other studies that utilize ketamine intravenously.

Similar to the protocol used by Wilkinson et al. (2017), the ketamine protocol used to calculate the dose for all participants in the study by Wilkinson et al. (2021) was 0.5 mg/kg. A strength of this study is that every participant received a standardized dose (0.5mg/kg) over a consistent time frame (twice weekly for three weeks). This allows for the ability to compare the ketamine protocol with other studies that utilize ketamine intravenously, such as Wilkinson et al. (2017).

In the study conducted by Dames et al. (2022), the participants received ketamine during weeks four, five, and seven of the 12-week study. Ketamine was administered by intramuscular

injections with participants receiving between 1.0 and 1.5mg/kg. The dose was determined through conversation with the participant to ensure it aligned with their goals, intentions, and comfort with being in an altered state of consciousness. While the researchers note that each dose was individually determined to meet the therapeutic goals of each participant, the variability of the dose limits the ability to compare the results with other studies. Further, utilizing intramuscular injections compared to IV infusions further limits the ability to compare the study's outcomes with other studies such as Wilkinson et al. (2017) and Wilkinson et al. (2021).

Zdyb and Hart (2021) gave participants low dose sublingual (oral) ketamine during a TRIP protocol session. The TRIP protocol involved patients participating in a psychotherapy session after taking 75mg of oral ketamine. Participants completed two TRIP sessions with the same dose of 75mg being used per session. Unlike the studies by Wilkinson et al. (2017), Wilkinson et al. (2021), and Dames et al. (2022), the study's ketamine protocol did not determine the dose based on the participant's weight. The rationale for using a fixed dose for each participant was not provided by the researchers. Utilizing a different method of ketamine administration than Wilkinson et al. (2017), Wilkinson et al. (2021), and Dames et al. (2022), and not adjusting the dose by participant weight, limits the ability for the study's outcome to be compared with other studies in this review.

In both studies by Yermus et al. (2024) and Dore et al. (2019), ketamine was administered either sublingually with oral tablets or by intramuscular injection. While the participants in the study by Yermus et al. (2024) received 4-6 guided ketamine sessions, the frequency of sessions in the study by Dore et al. (2019) varied between 1 and 25. Similar to the study conducted by Dames et al. (2022), the dose given to participants in the study by Yermus et al. (2024) was tailored individually for participants and was adjusted throughout the ketamine protocol. The range of doses used was not provided by the researchers. Unique to the study by Yermus et al. (2024), participants first received ketamine treatments at the clinic and then continued the treatments at their own home using sublingual oral tablets. This further increases

the variability of doses as the ketamine sessions were not supervised. As neither the doses used by Yermus et al. (2024) and Dore et al. (2019) were disclosed, and multiple ketamine administration methods were used, the results are limited in terms of comparing the outcomes with other studies in the review.

Psychotherapy Modality

Similar to the variability in ketamine protocols, psychotherapy modalities varied as well. Wilkinson et al. (2017) and Wilkinson et al. (2021) both utilized CBT. Wilkinson et al. (2017) utilized CBT in two phases, with phase one lasting two weeks. CBT sessions in phase one occurred 24-48 hours post ketamine IV infusion (4 CBT sessions and IV infusions over two weeks). Phase two involved participants having one CBT session weekly for weeks 3-8 with no further ketamine being administered. CBT sessions were delivered by a therapist with over ten years of experience with CBT. In the follow up study conducted by Wilkinson et al. (2021), the participants in the CBT group participated in CBT twice a week for weeks four and five, with a similar protocol as Wilkinson et al. (2017) regarding ketamine administration, and then once a week from weeks six to seventeen. Similar to Wilkinson et al. (2017), CBT was conducted by two experienced therapists who had prior training and certification and was based on the Beck Model (Beck et al., 1987). The CBT sessions included psychoeducation, cognitive restructuring, and behavioural activation. The TAU participants in the study by Wilkinson et al (2021) saw a study physician every week or every other week. The visits focused on medication management for oral antidepressants. A strength of the studies of both Wilkinson et al. (2017) and Wilkinson et al. (2021) is that experienced therapists were used who had training and certification in the psychotherapy modality being used. Further, utilizing a consistent psychotherapy modality and timing provides the ability for the reader to compare the results of each study.

In conjunction with the ketamine treatments, participants in the study by Dames et al (2022) took part in a community of practice (CoP) curriculum as the psychotherapy component. The CoP curriculum included group sessions where participants could share their concerns and

passions. The intended mechanisms for healing were described by the researchers as enabling connection to self and others through experiencing secure attachment, addressing trauma in an environment that provides unconditional positive regard, providing space to regulate the nervous system by co-regulating with others, and exploring individual desires and callings. CoP sessions were conducted weekly with each session lasting two hours. While the researchers explained the benefits of utilizing the CoP modality in detail, being that CoP is a group modality causes a limitation in comparing the results of the study with the others in this review as the other psychotherapy modalities were delivered individually. Further, the researchers did not provide information related to the credentials of the therapists and whether they were trained and/or certified in the modality.

A limitation of the studies conducted by Zdyb and Hart (2021), Yermus et al. (2024), and Dore et al. (2019) is that they used non-evidence-based psychotherapies. In the research conducted by Zdyb and Hart (2021), The TRIP protocol was developed by one of the researchers, Dr. Zdyb, and is described as a five-step treatment used to enhance therapeutic impacts of ketamine. The study did not describe the procedures associated with the TRIP protocol. While Zdyb and Hart (2021) state that the psychotherapy is evidence-based, evidence beyond their own publications is lacking to support the efficacy of their treatment modality.

In the study conducted by Yermus et al. (2024), the modalities of psychotherapy used with participants were not defined, making it difficult to compare the results with other studies as it is not known whether the psychotherapies used were evidence-based. The authors explained that psychotherapy occurred after dose one and two, and then after every two ketamine doses thereafter. Regarding the study by Dose et al. (2019), psychotherapy was described as non-manualized, reducing the ability to determine what was used for each patient and to analyze its validity of the intervention. Without determining whether psychotherapy methods are evidence-based and standardized, there are limitations in comparing the results to the other studies in this review. Further, only the studies by Wilkinson et al. (2017) and Wilkinson et al. (2021) discuss

therapist training and/or certification in the psychotherapy modality being used, limiting the validity of the findings of the other studies.

Assessment Tool(s) Used to Measure Outcome

There was variability in the assessment tools used across the studies to measure depressive symptoms. Wilkinson et al. (2017) and Wilkinson et al. (2021) both assessed depression severity for each patient at each visit using the Montgomery-Asberg Depression Rating Scale and the Quick Inventory of Depression Symptomatology Self Report. Patients who responded to the initial treatment were followed up for 3 months after the study ended. A strength in the studies by Wilkinson et al. (2017) and Wilkinson et al. (2021) is that multiple assessment tools were utilized and assessment scores were taken at each visit, allowing the researchers to examine changes throughout the study.

In the research conducted by Dames et al. (2022), out of the 94 participants, 64 screened positive for depression using the Patient Health Questionnaire-9 (PHQ-9). Similarly to Dames et al. (2022), all participants in the studies by Zdyb and Hart (2021) and Yermus et al. (2024) completed the PHQ-9 to measure the severity of their depressive symptoms. All 10 of the participants in the study by Zdyb and Hart (2021) screened positive for depression using the PHQ-9. Yermus et al. (2024) did not provide screening data to state how many of the participants screened positive for depression utilizing the PHQ-9. In the study conducted by Dore et al. (2019), the Beck Depression Inventory (BDI) was used to measure depressive symptoms. The researchers did not specify which version of the BDI was used for the study (BDI vs. BDI-II). While participants in the study by Yermus et al. (2024) had assessment scores completed at baseline, 3 months, and 6 months, the participants in the studies by Dames et al. (2022), Zdyb and Hart (2021), and Dore et al. (2019) had participants complete the assessments pre and post treatment, reducing the ability to determine whether therapeutic changes occurred throughout the treatment protocol.

Key Findings

While there was variability in the ketamine and psychotherapy protocols, an area of consistency was the statistically significant improvement in depressive scores across the studies. While every study showed depressive symptom relief amongst participants, the length of time that relief lasted was variable, and often undetermined as there were inconsistencies in follow-up methods. Further, beyond the study by Wilkinson et al. (2021), a lack of control group in the studies limits the reliability and generalizability of the findings. The following table summarizes the key findings for the treatment of depression.

Table 1: Summary of Key Findings for the Treatment of Depression

Study (N)	Ketamine Administration	Psychotherapy	Key Findings
Wilkinson et al., (2017;2021) N:16 & 42	Intravenous (0.5mg/kg)	Cognitive Behavioural Therapy (CBT)	CBT appeared to extend antidepressant effects of the ketamine in both studies using MADRS*.
Dames et al., (2022) N:94	Intramuscular (1.0-1.5mg/kg)	Community of Practice (CoP) - Group Therapy	79% had significant clinical improvements in PHQ-9** scores.
Yermus et al., (2024) N:346	Sublingual (variable doses)	Non-Manualized	75% reported an improvement in depressive symptoms (PHQ-9).
Zdyb & Hart, (2021) N:10	Sublingual (75mg)	TRIP Protocol	The average PHQ-9 score of participants dropped from 17.9 to 9.5.
Dore et al., (2019) N:235	Sublingual (variable doses)	Non-Manualized	BDI scores decreased by an average of 11.24 points.

*Montgomery-Asberg Depression Rating Scale
**Patient Health Questionnaire-9

Of the 16 participants in the pilot study conducted by Wilkinson et al. (2017), 8 achieved response, with 7 achieving remission from symptoms. Out of the 8 who achieved a response, 2 relapsed within 8 weeks of the last ketamine infusion. The median time to relapse for the

responders was 12 weeks. Follow ups for the participants ended after 3 months post-treatment. The researchers noted that these findings suggest that CBT may be effective in extending the antidepressant effects of ketamine as the majority of patients relapsed following the conclusion of the CBT phase. Unlike the study by Wilkinson et al. (2021), this study did not have a no treatment comparison group, making it difficult to decipher if reduced relapse was a function of CBT, time, patient characteristics, or other factors. The researchers also compared their findings to other ketamine treatment studies that did not include the addition of a psychotherapy component in conjunction with ketamine infusions. They found that the 25% relapse rate at 8 weeks of their study was lower than the relapse rate of similar studies (55-89%) without the adjunct CBT therapy. Limitations described by the researchers were the small sample size, open-label design, and lack of a control group. The researchers suggest that a larger sample size with a longer course of ketamine treatments and CBT sessions should be considered in future studies. Longer term follow-ups to monitor whether participants sustained symptom relief would help determine the effectiveness of the treatment.

In the study conducted by Wilkinson et al. (2021), the CBT group had a moderately improved score compared to the TAU group. The total study duration was approximately seventeen weeks, with no follow-up after the study was completed. Participants self-reported their outcome using the Quick Inventory of Depressive Symptomatology and there was a statistically significant improvement in the CBT group compared to the TAU group. The researchers hypothesized that this may have been due to ketamine improving cognitive control, a cognitive process that has been shown to be positively affected by CBT when reversing inaccurate beliefs and maladaptive thinking. The researchers further hypothesized that the CBT group may have benefited from the ketamine's neuroplasticity effects in combination with the ability of CBT to produce long lasting changes in the brain. They hypothesize that this may have resulted in improved cognitive control, reduced depressive symptoms, and prevention of relapse. The researchers acknowledge that while this pilot study provided data that CBT may

sustain the antidepressant effects of ketamine when used in combination, their results are speculative and further research with larger population groups over a longer period of time is required. Longer term follow-ups to monitor whether participants sustained symptom relief would help to determine the effectiveness of the treatment.

In the study conducted by Dames et al (2022), out of the 64 participants who initially screened positive for depression utilizing the PHQ-9, 49 (79%) were categorized as having mild depressive symptoms on the PHQ-9 or had significant clinical improvements after the 12-week program. In addition, 92% of participants had significant clinical improvements in life/work impairments. The researchers acknowledge that there was a limitation with the study given that there was no control group to compare CoP with and without ketamine. Further, there was no follow-up past 12 weeks post treatment to see if remission of symptoms was maintained. Consistent with other studies, longer term follow-ups to monitor whether participants sustained symptom relief would help determine the effectiveness of the treatment.

In the study by Zdyb and Hart (2021), the average PHQ-9 score of patients before the intervention was 17.9. After two sessions, the average score reduced to 9.5. Individual PHQ-9 scores were not provided by the researchers. No follow-up period was reported by the researchers, limiting the ability to determine how long the reduction of symptoms lasted post treatment. The researchers noted that while the pilot study demonstrated a reduction in depression scores, future studies with a control group only receiving ketamine would be merited. Longer term follow-ups to monitor whether participants sustained symptom relief would help determine the effectiveness of the treatment.

In the study by Yermus et al. (2024), the researchers noted that large treatment effects were observed at three months post treatment and that the effects were sustained at six months. The researchers based the results on their findings on whether a patient met the threshold for a minimal clinically important difference to be determined based on their assessment at baseline, 3-months, and 6-months post treatment. A change of 3 points less in

the PHQ-9 was considered a minimal clinically important difference. For the 315 patients who provided a 3-month PHQ-9 assessment, 75% of the patients reported a 3-point minimal clinically important difference compared to the assessment at baseline. For the 92 patients who provided a 6-month PHQ-9 assessment, 70% reported a 3-point minimal clinically important difference compared to the assessment at baseline. While there were 346 participants in the study at three months post-treatment, only 96 participants remained in the study at six months post-treatment. While the results of the study are promising in terms of rate of relief of symptoms, there are limitations in the validity of the study based on the high drop-out rate of participants.

In the study by Dore et al. (2019), the average BDI score for patients who screened positive for depression decreased by an average of 11.24 points and fell from moderate depression to mild. The decrease in depressive symptoms was considered statistically significant by the researchers compared to baseline scores. Individual data was not made available, and results were only provided at the aggregate level. A further limitation is that there was no follow-up completed with the participants after the study. Future studies with a control group only receiving ketamine and utilizing evidence-based psychotherapy modalities would be merited. In addition, longer term follow-ups to monitor whether participants sustained symptom relief would help determine the effectiveness of the treatment.

In summary, current literature suggests that combining ketamine treatments with psychotherapy may be an effective treatment of depression. Utilizing CBT in combination with ketamine, as presented by Wilkinson et al. (2017) and Wilkinson et al. (2021), appears most promising in reducing depressive symptoms as compared to treatment as usual. While other studies (Dames et al, 2022; Zdyb and Hart, 2021; Yermus et al., 2024; Dore et al., 2019) combining ketamine with psychotherapy provided evidence that the combination may be an effective treatment for depression, there are limitations in making conclusions from the evidence provided due to the studies not having a control group. Further, there are limitations to all the

studies reviewed, including inconsistent and/or short-term follow-up periods, inconsistent use of psychotherapy modalities, and/or ketamine dosing protocols, and small sample sizes. While the initial findings of a reduction in depressive symptoms from all the studies is promising, further research with a control group, larger sample sizes, consistent evidence-based psychotherapy modalities, consistent ketamine dosing protocols, and longer- term studies with follow-up periods are merited.

Combining Ketamine and Psychotherapy to Treat PTSD

The combination of ketamine and psychotherapy for the treatment of PTSD also appears to show promising results. Previous research has suggested that the symptoms of PTSD may cause a loss of synaptic connectivity and that the stress experienced by the symptoms could impair the functioning of the client's synaptic connectivity (Liriano et al., 2019). As synaptic connectivity is mostly mediated by glutamate, the researchers suggest clients may get relief through ketamine as it may enhance synaptic connectivity in neuronal circuits, leading to a reversal in the negative effects of PTSD. The following analysis describes the types of ketamine protocols used, psychotherapy modalities implemented, research designs, assessment tools used to measure outcome, and key findings from combining ketamine with psychotherapy for the treatment of PTSD.

Research Design

In the last eight years, two randomized placebo-controlled studies have been conducted to assess the efficacy of combining ketamine with psychotherapy for the treatment of PTSD. Pradhan et al. (2017) and Pradhan et al. (2018) examined the efficacy of combining a single ketamine treatment with psychotherapy to sustain the therapeutic effects of ketamine to treat PTSD. In the study by Pradhan et al. (2017), the researchers completed a randomized, placebo-controlled, cross-over clinical study with 10 patients. The inclusion criteria for the participants included being between 21-60 years old with chronic, refractory PTSD for at least six months. The participants must have also failed to experience relief of symptoms from at least two

standard PTSD treatments, including CBT and antidepressants. In the study conducted by Pradhan et al. (2018), the researchers completed a randomized, double-blind, placebo-controlled, parallel group study of 20 patients, where one group received IV ketamine and psychotherapy while the control group received saline through IV and psychotherapy. The inclusion criteria for the participants in the study by Pradhan et al. (2018) were the same as Pradhan et al. (2017). In both studies, one group received a single ketamine infusion plus 12 sessions of TIMBER psychotherapy (Timber-K group), while the control group received a single saline infusion plus 12 sessions of TIMBER psychotherapy (Timber-P group). The participants in the Timber-P group switched to Timber-K and received a ketamine infusion after 12 sessions of TIMBER to see if they received a different response from being in the Timber-P group. While there were strengths in these two studies in using a control group, having a small sample size limits the validity and generalizability of the studies' results.

Various other study design methods were to examine the efficacy of combining ketamine with psychotherapy for the treatment of PTSD, including studies by Davis et al. (2021), Shiroma et al. (2020), Dames et al. (2022), Yermus et al. (2024), and Keizer et al. (2020). Davis et al. (2021) completed a retrospective clinical chart review to assess the efficacy of combining ketamine with body-centered psychotherapy for patients in an outpatient clinic between 2018 and 2020. Participants in the study were between 18-70 years of age and met the diagnostic criteria for PTSD. The researchers reviewed de-identified clinical records of self-reported symptoms for 18 patients. This was the first time this type of clinical chart review had been completed to assess the efficacy of combining ketamine with body centered therapy to treat patients with PTSD. The lack of control group in this study and only using self-report measures limits the researchers' findings.

Shiroma et al. (2020) conducted a 10-week pilot study combining ketamine with prolonged exposure (PE) for 12 veterans with at least moderate PTSD symptoms. The inclusion criteria for the study included participants being between the ages of 18-75 and having a clinical

diagnosis of PTSD. Similar to Davis et al. (2021), a limitation of this study was not having a control group. Further, the short timeframe that patients' results were examined limits the findings. As previously noted, Dames et al. (2022) completed a case report for 94 participants who received ketamine-assisted therapy through a 12-week program for the treatment of mental disorders in health care professionals, with priority on treating depression and PTSD. Participants were included in the study if they were an adult and had a history of previous treatment failure, and a diagnosis of TRD, chronic anxiety, obsessive-compulsive disorder, suicidality, PTSD, or a substance use disorder. While the sample size of this study is larger than other studies (Pradhan et al., 2017; Pradhan et al., 2018; Davis et al., 2021; Shiroma et al., 2020), the lack of control group limits the researcher's findings.

Also as previously noted, Yermus et al. (2024) conducted a retrospective effectiveness study for 346 adults who received KAP at a Field Trip Health Clinic in North America between 2020 and 2022. The study included self-reported outcome data at three months and six months post-treatment. Inclusion criteria for the study included the participant signing a written informed consent, being over the age of 18, and having a diagnosis of MDD, bipolar disorder, GAD, obsessive compulsive disorder, an eating disorder, or a significant history of trauma and/or diagnosis of PTSD. Similar to Davis et al. (2021), a strength of this study is the large sample size; however, the lack of control group limits the researcher's findings.

Keizer at al. (2020) completed a case series examining 11 participants who received ketamine infusions in conjunction with psychotherapy for the treatment of PTSD. The inclusion criteria included the participant being an adult and diagnosed with PTSD. Limitations noted by the researchers included not having a control group and having a small sample size.

Ketamine Protocols

The method, timing, and dosing of the ketamine used by the participants varied across the studies examined. In the studies by both Pradhan et al. (2017) and Pradhan et al. (2018), ketamine was administered through one 0.5mg/kg IV infusion during the first week of the clinical

trial. No further ketamine was administered in either trial. A strength of the protocol in both studies is that every participant received a standardized dose (0.5mg/kg) over a consistent time frame. A limitation of this method is that only using one dose makes the results difficult to compare with other studies that use multiple doses, such as Shiroma et al. (2020). Patients reviewed by Davis et al. (2021) received ketamine through sublingual oral tablets. Doses of ketamine ranged from 100mg to 200mg and were given before each body centered therapy session. Patients completed up to six ketamine treatments. The time between ketamine treatments was not disclosed. A limitation of this study was that the variability of the dose given limits the ability to compare the results with other studies. Further, utilizing sublingual tablets compared to IV infusions further limits the ability to compare the study's outcomes with other studies such as Pradhan et al. (2017) and Pradhan et al. (2018). Further, the researchers did not provide dosing protocols used to determine each dose per participant. Without standardized dosing methods, including not adjusting the dose by participant weight, the ability for the study's outcomes to be compared with other studies in this review is limited.

In the study by Shiroma et al. (2020), participants received ketamine through IV infusions weekly for three weeks at a dose of 0.5mg/kg 24 hours prior to their weekly PE psychotherapy sessions. No ketamine was administered after the first three weeks while psychotherapy continued for ten weeks. Similar to Pradhan et al. (2017) and Pradhan et al. (2018), utilizing a standard IV infusion dose of 0.5mg/kg allows the studies' results to be compared with other studies using standardized dosing protocols.

In the study conducted by Dames et al. (2022), the participants received ketamine during weeks four, five, and seven of the 12-week study. The ketamine was administered by intramuscular injections with participants receiving between 1.0 and 1.5mg/kg. The dose was determined through conversation with the participant to ensure it aligned with their goals, intentions, and comfort with being in an altered state of consciousness. While the researchers note that each dose was individually determined to meet the therapeutic goals of each

participant, the variability of the dose limits the ability to compare the results with other studies. Further, utilizing intramuscular injections compared to IV infusions further limits the ability to compare the study's outcomes with other studies (Pradhan et al., 2017; Pradhan et al., 2018; Shiroma et al., 2020).

In the study by Yermus et al. (2024), ketamine was administered either sublingually with oral tablets or by intramuscular injection. The participants received 4-6 guided ketamine sessions. The doses given to participants were tailored individually for the participant and were adjusted throughout the ketamine protocol. The range of doses used was not provided by the researchers. Unique to the study by Yermus et al. (2024), participants first received ketamine treatments at the clinic and then continued the treatments at home using sublingual oral tablets. This further increases the variability of doses as the ketamine sessions were not supervised. As the doses used were not disclosed, and multiple ketamine administration methods were used, the results are limited in terms of comparing the outcomes with other studies in the review.

In the study by Keizer et al. (2020), participants received ketamine continuously through IV infusion for up to 96 hours. The researchers did not disclose the doses used for each participant. Participants engaged in daily psychotherapy while continuing to receive the IV infusion of ketamine. A limitation of this method is the inability to provide it outside of a hospital setting and the intensive nature of the method. Further, the uniqueness of this administration method does not allow for the findings of this study to be compared with other studies in this review.

Psychotherapy Modality

Similar to the variability in ketamine protocols, psychotherapy modalities varied as well. In the studies by both Pradhan et al. (2017) and Pradhan et al. (2018), psychotherapy was conducted utilizing the TIMBER method three times in week one and then weekly from weeks 2-10. The researchers explained that the TIMBER method is a trauma-specific mindfulness based cognitive therapy that targets pathological trauma memories. TIMBER, as described by the

researchers, combines yoga and mindfulness based cognitive therapy (Y-MBCT) with mindfulness based graded exposure therapy (MB-GET; a type of CBT). The researchers stated that combining these psychotherapy interventions can allow cognitive reprocessing and neutral/detached reappraisal of the patient's trauma memories with the hope of changing them in a positive way. A strength of the method used by both studies is the psychotherapy used is both structured and replicable. Utilizing a consistent psychotherapy modality and timing allows for comparison of the results of each study.

Patients reviewed by Davis et al. (2021) underwent body centered therapy augmented by the effects of ketamine. Sessions lasted approximately a hundred and twenty minutes and were facilitated either by one or two therapists using somatic-based interactional psychotherapy. The body centered therapy approach, described as an autonomic nervous system-based body modality, focused on sensation, emotion, imagery, and nervous system reactivity. The researchers explained that the treatment was designed to focus on both relational and personal aspects of the patient's psychological functioning, activating the patient's psychobiological autonomic nervous system to process both psychological and physical experiences, and to establish a physical processing pathway to assist the patient with resolving nervous system reactions. The therapist(s) interacted with the patient the entire session and focused on helping the patient experience nervous system activation without triggering a fear or dissociative response. The hope was to help the client foster adaptive regulation of challenging internal experiences. Non-ketamine sessions were also included in the patient's protocol to integrate insights from the ketamine sessions and assist patients in creating plans for changes in behaviours post-treatment. A strength of this study was described by the researchers as using a trauma-informed approach for psychotherapy. A limitation is that the method is not manualized, limiting the ability to replicate the findings.

In the study by Shiroma et al. (2020), participants received weekly PE sessions in conjunction with ketamine for the first three weeks and then up to 7 additional PE sessions over

the next seven weeks. A strength of the study is the use of a modality that has been previously validated as an effective method for treating PTSD.

Participants in the study by Dames et al (2022) took part in a CoP curriculum as the psychotherapy component. CoP sessions were conducted weekly with each session lasting two hours. While the researchers explained the benefits of utilizing the CoP modality in detail, being that CoP is a group modality, comparing the results of the study with the others in this review is difficult as the other psychotherapy modalities were provided individually. Further, the researchers did not provide information related to the credentials of the therapists and whether they were trained and/or certified in the modality.

In the study conducted by Yermus et al. (2024), the modalities of psychotherapy used with participants were not defined, making it difficult to compare the results with other studies as it is not known whether the psychotherapies used were evidence-based. The authors explained that psychotherapy occurred after dose one and two, and then after every two ketamine doses thereafter. Not knowing which therapeutic modalities were used limits the ability to evaluate the psychotherapy's contribution to the reduction in symptoms.

In the study conducted by Keizer et al. (2020), participants received exposure-based PTSD therapy while receiving ketamine IV infusions. While the researchers noted strengths in combining exposure therapy with ketamine as it allowed participants to revisit traumatic memories during periods of enhanced neuroplasticity, this method is limited in the intensity of completing the treatment for up to five days continuously. Further, cost limitations arise based on the medical care required. As ketamine administration and psychotherapy occurred together, there are limitations in differentiating whether ketamine or psychotherapy would have had similar outcomes separately.

Assessment Tool(s) Used to Measure Outcome

Patients reviewed by Davis et al. (2021) completed the Primary Care Post Traumatic Stress Disorder Checklist-5 (PC-PTSD-5) both at intake and after session six to assess their

PTSD symptoms. Those who had a score of 3 or higher were identified with probable PTSD. Of the 18 patient files reviewed, 15 patients had a score of 3 or higher and were identified with probable PTSD. In the remaining studies (Pradhan et al., 2017; Pradhan et al., 2018; Shiroma et al., 2020; Dames et al, 2022; Yermus et al., 2024; Keizer et al., 2020), either or both of the Posttraumatic Stress Disorder Checklist (PCL) and Clinician Administered PTSD Scale for DSM-V (CAPS-5) were used to assess the PTSD symptoms. The consistent use of assessment methods across these studies is a strength regarding the ability to compare results across studies.

Key Findings

Similar to studies reviewed for the use of psychotherapy and ketamine for depression, there was variability in the ketamine and psychotherapy protocols, including follow up periods. While every study reviewed for PTSD also showed symptom relief amongst participants, the length of time that relief lasted was variable and often undetermined as there were inconsistencies in follow-up methods. In addition, beyond the studies by Pradhan et al. (2017) and Pradhan et al. (2018), lack of control groups in the studies limits the reliability and generalizability of the findings. The following table summarizes the key findings for the treatment of PTSD.

Table 2: Summary of Key Findings for the Treatment of PTSD

Study (N)	Ketamine Method	Psychotherapy	Key Findings
Pradhan et al. (2017;2018) N:10 & 10	Intravenous (0.5mg/kg)	Trauma Interventions using Mindfulness-Based Extinction and Reconsolidation (TIMBER)	TIMBER + ketamine produced longer-lasting relief than control group (PCL*).
Shiroma et al. (2020) N:20	Intravenous (0.5mg/kg)	Prolonged Exposure (PE)	Significant reduction in PTSD symptom severity (CAPS-5**).

Davis et al. (2021) N:18	Sublingual (100-200mg)	Body-Centered Therapy	Moderate reduction in PTSD symptoms (PC-PTSD-5***).
Dames et al., (2022) N:94	Intramuscular (1.0-1.5mg/kg)	Community of Practice (CoP) - group therapy	86% screened negative for PTSD post treatment (PCL).
Yermus et al., (2024) N:346	Sublingual (Variable doses)	Non-Manualized	50% had a decrease of 5 points or more on PCL scores.
Keizer et al. (2020) N:12	Intravenous (Not disclosed)	Exposure-Based Therapy	90% clinically significant reduction on PCL scores.

*Posttraumatic Stress Disorder Checklist
**Clinician Administered PTSD Scale for DSM-V
***Primary Care Post Traumatic Stress Disorder Checklist-5

The clinical study by Pradhan et al. (2017) found that out of the 10 participants in the study, 9 experienced a statistically significant reduction in PTSD symptoms measured using the PCL and CAPS-5. Further, those that received ketamine plus TIMBER had longer sustained symptom reduction (33 days) than those who received saline plus TIMBER (25 days). Pradhan et al. (2018) replicated the results of Pradhan et al. (2017) with the group receiving both ketamine plus TIMBER, obtaining statistically significant symptom relief 34 days compared to the control group sustaining statistically significant symptom relief for 16.5 days. In both studies, all participants eventually relapsed. While the researchers monitored the participants for side effects for 18 months, there was no follow-up treatment conducted once the participants relapsed in symptoms from the Timber-K group. Longer term treatment with multiple ketamine infusions combined with TIMBER to see if participants sustained symptom relief would better determine the effectiveness of the treatment.

In the review by Davis et al. (2021), patients who completed six sessions of body centered therapy augmented by ketamine were shown to have improvement in their PTSD symptoms measured by PC-PTSD-5. Patients who completed six sessions also demonstrated

meaningful improvement in global disability in functioning scores. The researchers noted that while the study showed meaningful improvement in patient PTSD symptoms, including intensity of symptoms, the results were not statistically significant. The researchers explained that the study was underpowered, not representing the population of patients who receive KAP, and since the reduction in PTSD symptoms was only a marginal reduction, the effect size of the finding was medium, suggesting that if the study was fully powered the researchers may have been able to obtain results that were statistically significant. Further, the researchers noted that a randomized controlled trial to test the efficacy of combining ketamine with body centered therapy for the treatment of PTSD would be merited. A limitation of the study was that no long-term follow-up was reported post-treatment. Longer term follow-ups to monitor whether participants sustained symptom relief would help determine the effectiveness of the treatment.

In the study completed by Shiroma et al. (2020), 10 participants completed the treatment protocol with at least one follow-up assessment. All 10 participants' scores on the CAPS-5 reduced significantly following treatment. While the results suggested meaningful improvement for participants, the researchers noted that larger randomized clinical trials were merited. No long-term follow-up was reported post-treatment. Similar to Davis et al. (2021), longer term studies where the participants receive more treatments and have longer term follow-ups would help determine the effectiveness of the treatment.

In the study conducted by Dames et al (2022), out of the 37 participants who initially screened positive for PTSD, 32 (86%) screened negative for PTSD post treatment, measured using the PCL. In addition, 92% of participants had significant clinical improvements in life/work impairments. The researchers acknowledge that there was a limitation with the study in that there was no control group to compare CoP with and without ketamine. Further, there was no follow-up after 2 weeks post treatment to determine if remission of symptoms was maintained. Similar to other studies (Pradhan et al., 2017; Pradhan et al., 2018; Davis et al., 2021; Shiroma

et al., 2020), longer term follow-ups to monitor whether participants sustained symptom relief would help determine the effectiveness of the treatment.

Yermus et al. (2024) noted that large treatment effects were observed at three months post treatment and that the effects were sustained at six months measured with the PCL. A decrease of 5 points in the PCL was considered a minimal clinically important difference. For the 299 patients who provided a 3-month PCL assessment, 50% of the patients reported a 5-point minimal clinically important difference. For the 72 patients who provided a 6-month PCL assessment, 48% reported a 5-point minimal clinically important difference. While there were 346 participants in the study at three months post-treatment, only 96 participants remained in the study at six months post-treatment. While the results of the study are promising in terms of rate of relief of symptoms, there are limitations in the validity of the study based on the high drop-out rate. Similar to other studies (Pradhan et al., 2017; Pradhan et al., 2018; Davis et al., 2021; Shiroma et al., 2020; Dames et al, 2022), longer term follow-up to monitor whether participants sustained symptom relief would better determine the effectiveness of the treatment.

In the study by Keizer et al. (2020), 10 out of the 11 participants were able to engage in psychotherapy during ketamine infusions. One participant who received ketamine infusions required a high ketamine dose to gain the required analgesic effects and was unable to engage in psychotherapy due to the high level of sedation. All 10 participants who were able to engage in psychotherapy during ketamine infusions were found to have statistically significant reductions in PTSD symptoms on the PCL. No long-term follow-up was reported post-treatment. Similar to other studies (Pradhan et al., 2017; Pradhan et al., 2018; Davis et al., 2021; Shiroma et al., 2020; Dames et al, 2022; Yermus et al., 2024), longer term follow-up to monitor whether participants sustained symptom relief would help determine the effectiveness of the treatment.

In summary, current literature suggests that combining ketamine treatments with psychotherapy may be an effective treatment of PTSD. Pradhan et al. (2017) and Pradhan et al. (2018) demonstrated evidence with the most reliability through their randomized, placebo-

controlled studies. While other studies (Davis et al., 2021; Shiroma et al., 2020; Dames et al 2022; Yermus et al. 2024; Keizer et al., 2020) combining ketamine treatments with psychotherapy provided evidence that the combination may be an effective treatment for PTSD, there are limitations in making conclusions due to the studies not having a control group. Further, there are limitations to all the studies reviewed, including inconsistent and/or short-term follow-up periods, inconsistent use of psychotherapy modalities and/or ketamine dosing protocols, and small sample sizes. While the initial findings of a reduction in PTSD symptoms from all the studies is promising, further research with control groups, larger sample sizes, consistent evidence-based psychotherapy modalities, consistent ketamine dosing protocols, and longer-term studies with follow-up periods are merited.

Combining Ketamine and Psychotherapy to Treat Anxiety

The combination of ketamine and psychotherapy for the treatment of anxiety appears to have early positive results. Although, according to Liriano (2019), ketamine treatments for anxiety are controversial. The researcher notes that ketamine dampens NMDA receptor activity and as such the treatment could theoretically increase feelings of anxiety instead of providing relief. Little current research has examined the effects of combining ketamine treatments with psychotherapy to treat anxiety. The following analysis will describe the types of ketamine protocols being used, psychotherapy modalities implemented, research designs, assessment tools used to measure outcome, and key findings from combining ketamine with psychotherapy for the treatment of anxiety.

Research Design

There have not been any studies in the last eight years that have solely examined the efficacy of combining psychotherapy with ketamine for the treatment of anxiety. Instead, anxiety disorder symptoms were examined in studies that combined disorders, primarily MDD and PTSD (Dames et al., 2022; Yermus et al., 2024; Dore et al. 2019).

In the case report presented by Dames et al. (2022), 55 of the 94 participants participating in the 12-week ketamine-assisted therapy program screened positive for GAD during intake into the study. As noted, participants were included in the study if they had a history of previous treatment failure and a diagnosis of TRD, chronic anxiety, obsessive-compulsive disorder, suicidality, PTSD, or substance use disorder. In the retrospective effectiveness study completed by Yermus et al. (2014), 157 of the 346 participants in the study had a primary diagnosis of GAD. This study also included participants with other diagnoses, including MDD, bipolar disorder, obsessive compulsive disorder, an eating disorder, or a significant history of trauma and/or diagnosis of PTSD. Out of the 235 patients examined in the study by Dore et al. (2019), 55 met the criteria for GAD. In this study patients were also included if they met the screening criteria for other disorders, including MDD and PTSD. As noted, while the studies (Dames et al., 2022; Yermus et al., 2024; Dore et al., 2019) had large sample sizes, the lack of a control group limits the validity of the findings. Further, none of the three studies had a primary focus of treating GAD, likely limiting the ability to interpret how the results may have been different if treating GAD was a primary focus of the study. Further research studies treating anxiety as the primary focus are merited.

Ketamine Protocols

As previously mentioned, the method, timing, and dosing of ketamine varied across studies. Unique to the study by Yermus et al. (2024), participants first received ketamine treatments at the clinic and then continued the treatments at their own home using sublingual oral tablets. This further increases the variability of doses as the ketamine sessions were not supervised. As neither the doses used by Yermus et al. (2024) or Dore et al. (2019) were disclosed, and multiple ketamine administration methods were used, the results are limited in terms of comparing the outcomes with other studies in the review.

Psychotherapy Modality

Similar to the variability in ketamine protocols, psychotherapy modalities varied as well. Participants in the study by Dames et al (2022) took part in a CoP curriculum as the psychotherapy component, described in detail previously. In the study conducted by Yermus et al. (2024), the psychotherapy was not defined, making it difficult to compare the results with other studies as it is not known whether the psychotherapies used were evidence based. Regarding the study by Dose et al. (2019), the psychotherapy component was described as non-manualized, reducing the ability to determine what was used and to analyze the validity of the intervention. Without determining whether psychotherapy methods are evidence based and standardized, there are limitations in comparing the results of the studies by Yermus et al. (2024) and Dore et al. (2019) with others in this review.

Assessment Tool(s) Used to Measure Outcome

In the research by Dames et al. (2022), the Generalized Anxiety Disorder-7 (GAD-7) was utilized at baseline, 3 months, and 6 months post-treatment. Yermus et al. (2024) also utilized the GAD-7, completing the assessment with participants before and after the 12-week program. Dore et al. (2019) utilized the Hamilton Anxiety Rating Scale (HAM-A).

Key Findings

Similar to studies reviewed for the use of psychotherapy and ketamine for depression and PTSD, there was variability in the ketamine and psychotherapy protocols, including follow up periods. While every study reviewed for anxiety also showed symptom relief amongst participants, the length of time that relief lasted was variable and often undetermined as there were inconsistencies in follow-up methods. In addition, no studies used a control group, limiting the reliability and generalizability of the findings. The following table summarizes the key findings for the treatment of anxiety.

Table 3: Summary of Key Findings for the Treatment of Anxiety

Study (N)	Ketamine Method	Psychotherapy	Key Findings
Dames et al., (2022) N:94	Intramuscular (1.0-1.5mg/kg)	Community of Practice (CoP) - group therapy	91% improved GAD-7* scores.
Yermus et al., (2024) N:346	Sublingual (Variable doses)	Non-Manualized	68% showed a 3-point or higher improvement in GAD-7 score.
Dore et al., (2019) N:235	Sublingual (Variable doses)	Non-Manualized	Average HAM-A** score decreased by 5.5 points.

*Generalized Anxiety Disorder-7
** Hamilton Anxiety Rating Scale

In the study conducted by Dames et al (2022), out of the 55 participants who initially screened positive for GAD utilizing the GAD-7, 50 (91%) of those participants went into a milder category of the GAD-7 or had significant clinical improvements after the 12-week program. In addition, 92% of participants had significant clinical improvements in life/work impairments. The researchers acknowledge that there was a limitation with the study in that there was no control group to compare CoP with and without ketamine. Further, there was no follow-up past 12 weeks post treatment to determine if the remission of symptoms was maintained. Longer term follow-ups to monitor whether participants sustained symptom relief would help determine the effectiveness of the treatment.

In the study by Yermus et al. (2024), the researchers noted that large treatment effects were observed at three months post treatment and that the effects were sustained at six months. A change of 3 points less in the GAD-7 was considered a minimal clinically important difference. For the 305 patients who provided a 3-month GAD-7 assessment, 68% of the patients reported a 3-point minimal clinically important difference compared to the assessment

at baseline. For the 72 patients who provided a 6-month GAD-7 assessment, 65% reported a 3-point minimal clinically important difference compared to the assessment at baseline. While there were 346 participants in the total study at three months post-treatment, only 96 participants remained in the study at six months post-treatment. While the results of the study are promising in terms of rate of relief of symptoms, there are limitations in the validity of the study based on the high drop-out rate.

In the study by Dore et al. (2019), the average HAM-A score for patients who screened positive for anxiety decreased by an average of 5.5 points and fell from moderate anxiety to mild. The decrease in anxiety symptoms was considered statistically significant. Individual data was not made available, and results were only provided at the aggregate level. A further limitation is that there was no follow-up completed with the participants after the study. Future studies with a control group only receiving ketamine and utilizing evidence-based psychotherapy modalities are merited. In addition, longer term follow-up to monitor whether participants sustained symptom relief would help determine the effectiveness of the treatment.

In summary, current literature suggests that combining ketamine treatments with psychotherapy may be an effective treatment for anxiety. While studies by Dames et al (2022), Yermus et al. (2024), and Dore et al. (2019) demonstrated that combining ketamine treatments with psychotherapy provided evidence that the combination may be an effective treatment for anxiety, there are limitations in making conclusions from the evidence provided due to the studies not having a control group. Further, similar to the studies on depression and PTSD, there are limitations to all the studies reviewed, including inconsistent and/or short-term follow-up periods, inconsistent use of psychotherapy modalities and/or ketamine dosing protocols, and small sample sizes. While the initial findings of a reduction in anxiety symptoms from all the studies are promising, further research with a control group, larger sample sizes, consistent evidence-based psychotherapy modalities, consistent ketamine dosing protocols, and longer-term studies with follow-up periods are merited. As noted, with none of the three studies having

a primary focus of treating GAD, there are limitations in the ability to interpret how the results may have been different if treating GAD was a primary focus of the study. Further research where treating anxiety is the primary focus are merited.

Summary of Findings

The purpose of this literature review was to evaluate the effectiveness of combining ketamine and psychotherapy for the treatment of depression, PTSD, and anxiety. The evidence in this review suggests that the combination of ketamine and psychotherapy, especially CBT, appears to be effective in reducing symptoms for those diagnosed with depression, including those diagnosed with TRD. The length of time that the reduction of symptoms lasted for those diagnosed with depression was variable, and often undetermined due to the lack of post study follow ups. With a median time of 12 weeks until symptoms relapsed after receiving the ketamine infusion, the study by Wilkinson et al. (2017) demonstrated that including CBT with ketamine may sustain the antidepressant effects of ketamine for those diagnosed with depression, even if the diagnosis is classified as treatment resistant. Participants receiving ketamine infusions and CBT outperforming those who received TAU over the 17-week study (Wilkinson et al., 2021) provides further evidence that the combination of ketamine and psychotherapy, especially CBT, appears to be effective for the treatment of depression and TRD. The limited follow-ups past the active treatment phases limits the ability to determine how long symptom relief lasts, demonstrating the need for studies with long-term follow-up.

The combination of ketamine treatments and psychotherapy may be effective in the treatment of PTSD. However, similar to the findings for depression, the symptom relief from combining ketamine with psychotherapy has only been determined on a short-term basis during the active treatment phases of the studies and the results have not demonstrated to be consistent in the longer-term. This is demonstrated by both Pradhan et al. (2017) and Pradhan et al. (2018) where the participants receiving KAP sustained remission of symptoms a month after treatment, significantly longer compared to the control group. Similar to the findings for

depression, the limited follow-ups past the active treatment phase limits the ability to determine how long symptom relief lasts, demonstrating the need for longer term studies with follow-ups.

With little research in this review including the treatment of anxiety, and only as a secondary diagnosis, there is currently too little research on the treatment of anxiety utilizing KAP to draw firm conclusions about its efficacy. Further research with anxiety as the primary diagnosis, a control group, and long-term follow-up periods is needed to determine whether KAP is effective for the treatment of anxiety.

The lack of long-term follow-ups in the studies reviewed also limits the ability to determine how long symptom reduction lasts for the treatment of depression and PTSD. Longer term studies with follow-ups could determine how long initial symptom relief lasts and if further treatment would be required to maintain symptom relief.

With limited studies in this review having a control group, there are limitations in determining whether it is the combination of ketamine and psychotherapy that provided the relief of symptoms, or if it was ketamine or psychotherapy alone that led to symptom relief. Further, it is difficult to draw conclusions on ketamine dosing because studies use too many different dosing methods. The lack of consistent ketamine dosing protocols, including method of ketamine administration and amount of ketamine used, makes it difficult to determine the appropriate dose for treatment. A similar limitation occurs with the inconsistent use of psychotherapy and assessment methods. Not knowing which psychotherapy methods are effective in combination with ketamine makes it difficult to determine which method(s) to use when providing KAP. Also, not utilizing consistent assessment methods limits the ability to compare the results of different studies. Future research with longer term studies with follow-ups, treating anxiety as the primary diagnosis, consistent ketamine administration methods and dosing amounts, consistent psychotherapy and assessment methods, and research designs that include a control group are merited to better determine the effectiveness of utilizing KAP for emotional disorders.

Ethical Considerations

The *Canadian Code of Ethics for Psychologists* (Canadian Psychological Association [CPA], 2017) states that psychologists must maximize benefit to their clients by striving to provide the best reasonably accessible service for those seeking psychological services. This includes services that are relevant and tailored to the client's needs and based on the best available evidence. As summarized in this literature review, there are limitations in the evidence that KAP is effective for the treatment of depression, PTSD, and anxiety. When considering maximizing the benefit for a client, there appears to be an ethical concern with suggesting KAP. The current literature does not appear to justify suggesting to a client with an emotional disorder that they should pursue KAP over established evidence-based psychotherapy treatment modalities discussed in this review, such as CBT, PE, and others. Where there appears to be more favour in suggesting KAP to a client is when their diagnosis has been labelled as "treatment resistant" and they have already exhausted avenues of conventional psychotherapy without relief. For example, Wilkinson et al. (2020) only included participants who were diagnosed with TRD, stating that the participant had to have a history of being treatment resistant to two or more adequate courses of antidepressant medications. While Wilkinson et al. (2020) did not require that participants also be resistant to conventional, evidence-based psychotherapy modalities, requiring that the participant first try other evidence-based treatment methods first is a framework that can be applied to ensuring practitioners maximize benefit to their clients.

Tri-Council Policy Statement

The *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* ([TCPS2], 2022) published by the Canadian Institutes of Health Research outlines three core principles for conducting ethical research. The first, respect for persons, recognizes the intrinsic value of people and involves treating persons involved in research with respect and ensuring participants maintain their autonomy. The authors explain that an important mechanism for

respecting persons is ensuring that researchers obtain free, informed, and ongoing consent. The majority of the studies used in this review state that informed consent was collected from the participants (Wilkinson et al., 2021; Wilkinson et al., 2017; Dames et al., 2022; Yermus et al., 2024; Dore et al., 2019; Pradhan et al., 2018; Pradhan et al., 2017; Shiroma et al., 2020; Keizer et al., 2020). The other two studies in the review did not state whether informed consent was collected (Zdyb & Hart, 2021; Davis et al., 2021). The study by Davis et al. (2021) stated that the research was exempt from review as determined by the institutional review board at Ohio State University. The study by Zdyb & Hart (2021) was conducted in an outpatient clinic and did not state whether informed consent was collected, or if the study obtained permission from an ethics review committee. It is important to ensure that informed consent is collected by the participants to ensure that participants are treated with respect and maintain their autonomy throughout their participation in the study.

The second core principle listed in the TCPS2 (2022) is concern for welfare. This is described by the authors as an impact on a person's physical, mental, and spiritual health. Regarding physical welfare, the researchers in the studies used for this review ensured that medical assessments were completed before the participants received the treatment. To ensure the welfare of participant's mental health, the participants all engaged with health professionals throughout the treatment process, including nurses, physicians, and psychologists. Examples of how researchers supported the participant's physical and mental health during the studies include completing comprehensive testing during intake to ensure safety for the treatment (Davis et al., 2021), having an interdisciplinary team of health professionals to support participants (Dames et al., 2022), and completing ongoing health monitoring during the treatment (Wilkinson et al., 2017; Wilkinson et al., 2021). While a limitation in this review is the lack of consistency in the disclosure of clinical health and safety protocols used for the study, it is suggested that future research utilizing KAP includes having an interdisciplinary team of health professionals, comprehensive testing during intake, and ongoing health monitoring during

treatment and follow-up periods. The spiritual health of participants was only mentioned in one study used for this review (Dames et al., 2022). The researchers in the study by Dames et al. (2022) ensured that spiritual health practitioners were included in the interdisciplinary team, alongside nurses, medical doctors, and clinical counsellors. In future research, it would be beneficial for researchers to consider how to ensure the spiritual health of participants can be maintained throughout the study. Spiritual health can be assessed through a spiritual assessment that evaluates a person's spiritual beliefs, needs, and hopes in a clinical context (Henry & Gilley, 2024). By having the participant complete a spiritual assessment, the researchers can both build therapeutic alliance with the participant and allow them to express their goals and reasons for treatment decisions (Henry & Gilley, 2024). Further, it is important for clients to be provided with the ability to attain continued psychological support after their KAP session to ensure they have a safe space to process their journey and the insights that can come from it (Pilecki, 2021).

The third core principle listed in the TCPS2 (2022) is justice. The authors explain that justice refers to the obligation to treat people fairly and equitability. Regarding justice, the studies used in this review included exclusion and inclusion criteria that was based on the diagnosis of mental health disorders and meeting minimum standards of health criteria to ensure the treatments were safe. By using diagnostic and health criteria, the researchers ensured that inclusion in the studies was done in a fair and equitable way.

Chapter Four: Application to Clinical Practice

While initial findings from the literature show that combining ketamine with psychotherapy for the treatment of emotional disorders is promising, it does not provide enough evidence for clinicians to suggest KAP to their clients as a first-line treatment. Longer-term studies with larger participant groups that include multiple follow-up assessments to ensure the longevity of the treatment relief are merited. Further, completing studies with randomization and a control group would help clinicians better understand whether it was the combination of the ketamine treatment(s) with psychotherapy that was providing relief or if it was the ketamine treatment(s) or psychotherapy alone that was providing relief. To assist in comparing study results more effectively, a standardization of ketamine administration protocols and modalities of psychotherapy used would also be beneficial.

While further research would be beneficial, the findings from the literature provide evidence that current and aspiring counselling practitioners can consider KAP as a potential treatment option for their clients who are considered resistant to previous forms of treatment. There are various factors that practitioners should consider when suggesting KAP, or any psychedelic therapy, as a potential treatment (Pilecki, 2021). First, it is important that clients are aware of the limitations in the current research for KAP and the risks and benefits when choosing a method that does not have a lengthy research history and is not yet considered an evidence-based approach. Second, clients should only do KAP with practitioners who have completed the specialized training required to work with clients who are in an altered state of consciousness (Pilecki, 2021). Third, there are cultural factors regarding the interpretation of the client's psychedelic experience, as there is variability in cultural views towards different symbols and messages that may arise in a client's psychedelic journey (Pilecki, 2021). Further, minoritized populations are not sufficiently represented in research regarding KAP, and other therapeutic psychedelics (Rojas et al., 2024). Rojas et al. (2024) note that issues of race, culture, ritual, and socioeconomic status should be included in KAP treatment planning and

research. Fourth, clients should be aware of the shift in power dynamics favouring the practitioner that occurs when a client is utilizing a medicine that alters their state of consciousness. It is important that the practitioner approaches factors like touch and suggestibility with appropriate ethical boundaries (Pilecki, 2021). Lastly, clients should be provided with the ability to attain continued psychological support after their KAP session to ensure they have a safe space to process their journey and insights that can come from it (Pilecki, 2021).

Recommendations for Clinical Practice

Acknowledging the findings of the literature review and the applications to clinical practice, especially for psychologists in Alberta, I recommend the following theoretical model for counsellors to refer to when considering KAP for clients who have been diagnosed with an emotional disorder. The first step would be for the client to complete a treatment that is evidence based for the presenting diagnosis. For example, if the client has been diagnosed with depression, determine whether the symptoms can be treated by anti-depressants and/or psychotherapy with a modality that is evidence based for the disorder. If the client does not respond to treatment and their symptoms are considered treatment-resistant, move on to step two.

The second step would be to determine whether the client is an eligible candidate for KAP. Factors include whether the client has the financial means to pay for treatment or is able to access public financial means, and that the client does not have any conditions that would exclude the client from KAP, including: a history of primary psychotic or affective disorders such as schizophrenia, schizoaffective disorder, or bipolar disorder, experiencing recent or current symptoms of mania or hypomania, prior adverse reactions to psychedelic substances, recent or current suicidal ideation and/or suicide attempts, significant trauma histories; and have not learned sufficient coping skills or developed a plan for safety, and/or diagnoses that manifest in

emotional and/or behavioural dysregulation and have not learned sufficient coping and regulation skills (College of Alberta Psychologists [CAP], 2025).

If the client does not have any conditions referred to in the second step, refer the client to a physician to complete a medical assessment and discuss the psychedelic medicine's mechanisms of action, risks and benefits, potential interactions with other medicines, risks and types of adverse reactions, and side effects. The primary physician is responsible for prescribing the medicine for the client.

If the client is deemed suitable for KAP by a physician and wishes to participate in treatment, the following treatment plan is suggested in accordance with the findings from CAP (2025) and the literature review:

1. *Preparation phase*: The client meets with a registered psychologist eligible to provide psychedelic-assisted therapy for a therapy session to help the client explore their intentions for the KAP session(s). The psychologist aims to build trust and rapport and help the client psychologically prepare for the session(s).
2. *Active phase***:** Within a week after the preparation therapy session, the client completes a ketamine treatment with an authorized health professional.
3. *Integration phase*: Within 1-3 days after the ketamine treatment, the client meets with the same psychologist as the preparation therapy session to help the client explore their psychedelic experience and make meaning to it. It is important that the psychologist assess the client's symptoms utilizing assessment tools that have demonstrated reliability and validity for the disorder/symptoms being assessed to determine if the client has achieved relief. The psychologist should ensure they are using therapeutic modalities that are considered evidence based and appropriate for the client's presenting concern and diagnosis.

The client then repeats the ketamine treatments and integration therapy as needed, alternating between receiving ketamine treatments and therapy sessions. The ratio of ketamine

treatments to integration therapy is not likely going to be 1:1. In accordance with the findings of the literature review (Wilkinson et al., 2017; Wilkinson et al., 2021), the client is likely to do more therapy sessions than ketamine treatments. The frequency of the treatments and therapy should be determined in collaboration with the primary physician and the psychologist, with the primary physician responsible for ketamine treatment and the psychologist responsible for therapy. Further, as KAP becomes more available as a treatment in Alberta, research conducted in both Alberta and Canada would be merited.

Application to Clinical Practice in Alberta

While those in various counselling roles (e.g. Canadian certified counsellors, registered professional counsellors, social workers with psychotherapy training) may be encouraged by the early promising results of KAP and wish to promote the option to clients, psychologists in Alberta face many restrictions. As of June 2025, psychologists in Alberta must follow the standards of practice guideline for *psychedelic-assisted psychotherapy* (College of Alberta Psychologists [CAP], 2025). The practice guideline provides information regarding the scope of practice for psychedelic-assisted psychotherapies, including KAP, for psychologists in Alberta. In accordance with the practice guideline, as psychologists do not have authority under the *Health Professions Act* to prescribe and administer medication, including Ketamine, psychologists must refrain from making any recommendations to their clients regarding the use of psychedelic treatments. Further, psychologists must not diagnose the need for psychedelic-assisted therapy as it is outside their scope of practice. Instead, the practice guideline encourages clients to speak to their primary physician, psychiatrist, and/or nurse practitioner about psychedelic treatment options. While psychedelic treatments are outside the scope of practice, the practice guideline suggests that psychologists remain aware of basic knowledge regarding psychedelic treatments as it is likely that they will come across clients who are also doing them or are interested in them. The practice guideline suggests that psychologists refer clients to other health professionals with greater knowledge and expertise in the subject.

In accordance with the CAP guideline, psychologists who provide psychedelic-assisted therapy must be familiar with and align their practice with the current legislation in Alberta. The practice guideline describes three types of legislation that psychologists must be familiar with when providing psychedelic-assisted therapy, including the *Mental Health Services Protection Act*, 2018, the *Mental Health Services Protection Regulation with psychedelic drug treatment services, January 16, 2023,* and the *Psychedelic Drug Treatment Services Standards, March 2023.* Together, this legislation establishes the legal framework for clinics offering psychedelic treatment, provides regulations that clinics and practitioners must follow when providing psychedelic treatment, and provides further licensing instruction and minimum standards related to providing psychedelic treatment in Alberta.

As described by the CAP practice guideline, psychologists who are supporting clients who receive treatment with psychedelic medicine should do so in a collaborative practice model where the psychologist can consult with the prescribing physician as required. While psychologists should be aware of the psychedelic medicine's mechanisms of action, risks and benefits, potential interactions with other medicines, risks and types of adverse reactions and side effects, the psychologist is expected to differ from the prescribing physician to have discussions with the client receiving the psychedelic treatment. Further, in accordance with the practice guideline, psychologists in Alberta who wish to provide psychedelic-assisted therapy must have five years' experience as a fully registered psychologist.

Chapter Five: Conclusions and Recommendations

Summary

This review examined whether combining ketamine with psychotherapy (KAP) is an effective treatment approach for adults diagnosed with emotional disorders. KAP may be effective for the treatment of emotional disorders, but there are limitations in current research. Limitations include small sample sizes, short term studies with limited follow ups, inconsistent ketamine administration methods and dosing protocols, inconsistent psychotherapy and assessment methods, and lack of control groups. The strongest evidence that KAP may be an effective treatment approach is for the treatment of depression, particularly TRD, and for the treatment of PTSD. There currently is a lack of evidence to support the use of KAP for the treatment of anxiety. KAP appears best suited as a secondary treatment method, after an evidence based primary method of treatment has not been successful.

Psychologists must maximize benefit to their clients by striving to provide the best, reasonably accessible service for their clients (CPA, 2017). This includes services that are relevant and tailored to the client's needs and based on the best available evidence. As found in this literature review, there are limitations in the evidence that KAP is effective for the treatment of depression, PTSD, and anxiety. The current literature does not appear to justify suggesting to a client with an emotional disorder that they should pursue KAP over established evidence-based psychotherapy treatment. Where there appears to be more favour in suggesting KAP is when their diagnosis has been characterized as "treatment resistant" and they have already exhausted avenues of conventional psychotherapy without relief.

There are various factors that practitioners should consider when suggesting KAP, or any psychedelic therapy, as a potential treatment option (Pilecki et al., 2022). It is important that clients are aware of the limitations in the current research for KAP and the risks and benefits for the client when choosing a method that does not have as much quality of research and is not yet considered an evidence-based approach. Clients should only do KAP with practitioners who

have completed the specialized training required to work with clients who are in an altered state of consciousness and ensure they are provided with the ability to attain continued psychological support after KAP sessions.

Psychologists in Alberta who want to provide KAP must ensure they follow the standards of practice guideline for *psychedelic-assisted psychotherapy* (CAP, 2025) when working with psychedelics. A collaborative practice model where clients have access to a psychiatrist/physician, psychologist, and authorized health professional who can administer psychedelic therapy is suggested as the preferred model for psychedelic therapy (CAP, 2025).

Research Questions

Further possible research questions that would be merited based on the findings of this paper, including:

1. *Ketamine administration*: Investigating which method(s) of ketamine administration are most effective in combination with psychotherapy for the treatment of emotional disorders. At present, we do not know if specific ketamine administration methods are differentially effective when combined with psychotherapy because there are too few studies and different dosing protocols. Additional studies that compare administration methods and standardized dosing protocols would help clinicians understand which ketamine administration method(s) are preferred when offering KAP.
2. *Psychotherapy modalities*: Examining which modalities of psychotherapy (e.g., CBT, exposure therapy, internal family systems therapy, client-centered therapy, narrative therapy, dialectal behaviour therapy, etc.) are most effective in combination with ketamine for the treatment of emotional disorders will identify combination methods that are most effective in maximizing symptom relief. At present, we also do not know if specific psychotherapy methods are differentially effective when combined with ketamine because there are too few studies and different psychotherapy methods being used. Additional studies that compare psychotherapy

methods in combination with ketamine would help clinicians understand which psychotherapy method(s) are preferred when offering KAP.

3. *Protocol timing*: Determining how frequently ketamine should be administered during a KAP protocol, and how often clients should receive psychotherapy in conjunction with the ketamine, would assist clinicians in determining an effective treatment plan. Based on the inconsistent timing of the administration of ketamine and psychotherapy, we do not yet know the most effective protocol timing for KAP.

Reflections of Student Learning

This paper both enhanced my academic knowledge and personal interest in the field of KAP. While I felt that I had a good foundation of knowledge regarding KAP, the analysis of the literature broadened my understanding of the limitations that this field is facing. I had not previously considered that KAP may be best as a secondary option for treatment-resistant disorders. The evidence, or lack thereof, from the literature has made me consider the ethical implications of suggesting KAP to a client, especially one who has not yet tried conventional methods. This shift in my opinion was enhanced as CAP released their practice guideline for *psychedelic-assisted psychotherapy* while I was completing this project. Until that practice guideline, there had not been any formal direction from CAP regarding the implications of psychologists working in the field of psychedelics. As I hope to register with CAP once I graduate, there are multiple new implications for myself as a practitioner that are essential to learn, including the inability to work in the field until five years post-registration. This paper allowed me to gain both academic knowledge and practice guideline knowledge that will be essential when I register as a psychologist. Further, my view towards the best practices for KAP has shifted. I now recognize how important it is to have collaborative practice when working with a client in KAP, and the importance of a client working with the most appropriate professional at each stage. I am looking forward to staying involved in psychedelics as I grow my career and am excited to follow the new research as it continues to emerge.

References

American Psychological Association. (2018) *Emotional disorders - APA dictionary of psychology*, https://dictionary.apa.org/emotional-disorder

Beck, A. T., Rush, A. J., Shaw, B. E., & Emery, G. (1987). *Cognitive therapy of depression*. The Guilford Press.

Canadian Institute of Health Research. (2022). *Tri-council policy statement – ethical conduct for research involving humans*. Canadian institutes of health research, natural sciences and engineering research council of Canada, and social sciences and humanities research council of Canada. https://ethics.gc.ca/eng/documents/tcps2-2022-en.pdf

Canadian Psychological Association (2017). *Canadian code of ethics for psychologists* (4th ed.). Canadian Psychological Association. https://cpa.ca/docs/File/Ethics/CPA_Code_2017_4thEd.pdf

College of Alberta Psychologists. (2025). *Psychedelic-assisted psychotherapy practice guideline*. https://www.cap.ab.ca/Portals/0/adam/Content/fQCpza4q7EGXC_psrgnCvA/Link/Psychedelic-Assisted%20Psychotherapy%20-%20June%202025.pdf

Davis, A. K., Mangini, P., & Xin, Y. (2021). Ketamine-assisted psychotherapy for trauma-exposed patients in an outpatient setting: A clinical chart review study. *Journal of Psychedelic Studies*, *5*(2), 94-102. https://doi.org/10.1556/2054.2021.00179

Dames, S., Kryskow, P., & Watler, C. (2022). A cohort-based case report: The impact of ketamine-assisted therapy embedded in a community of practice framework for

healthcare providers with PTSD and depression. *Frontiers in Psychiatry*, *12*. https://doi.org/10.3389/fpsyt.2021.803279

Dore, J., Turnipseed, B., Dwyer, S., Turnipseed, A., Andries, J., Ascani, G., Monnette, C., Huidekoper, A., Strauss, N. & Wolfson, P. (2019). Ketamine assisted psychotherapy (KAP): Patient demographics, clinical data and outcomes in three large practices administering ketamine with psychotherapy. *Journal of psychoactive drugs*, *51*(2), 189-198. https://doi.org/10.1080/02791072.2019.1587556

Government of Alberta. (2023, January 16). *Mental health services protection regulation*, Alta. reg. 114/2021. King's Printer Alberta. https://kings-printer.alberta.ca/570.cfm?frm_isbn=9780779856190&search_by=link

Engel, G. L. (1977). The need for a new medical model: A challenge for biomedicine. *Science*, *196*(4286), 129-136. https://doi.org/10.1126/science.847460

Hasler, G. (2020). Toward specific ways to combine ketamine and psychotherapy in treating depression. *CNS spectrums*, *25*(3), 445-447. https://doi.org/10.1017/S1092852919001007

Henry, N. L., & Gilley, N. (2024). *Spiritual assessment*. StatPearls Publishing, Treasure Island, FL. https://www.ncbi.nlm.nih.gov/books/NBK599554/

Khan, K. S., Kunz, R., Kleijnen, J., & Antes, G. (2003). Five steps to conducting a systematic review. *Journal of the royal society of medicine*, *96*(3), 118-121. https://doi.org/10.1177/014107680309600304

Keizer, B. M., Roache, J. D., Jones, J. R., Kalpinski, R. J., Porcerelli, J. H., & Krystal, J. H. (2020). Continuous ketamine infusion for pain as an opportunity for psychotherapy for

PTSD: A case series of ketamine-enhanced psychotherapy for PTSD and pain (KEP-P2). *Psychotherapy and Psychosomatics*, *89*(5), 326-329. https://doi.org/10.1159/000507095

Liriano, F., Hatten, C., & Schwartz, T. L. (2019). Ketamine as treatment for post-traumatic stress disorder: A review. *Drugs in context*, *8*. https://doi.org/10.7573/dic.212305

Parikh, R. M., & Lebowitz, B. D. (2004). Current perspectives in the management of treatment-resistant depression. *Dialogues in clinical neuroscience*, *6*(1), 53–60. https://doi.org/10.31887/DCNS.2004.6.1/rparikh

Pilecki, B., Luoma, J. B., Bathje, G. J., Rhea, J., & Narloch, V. F. (2021). Ethical and legal issues in psychedelic harm reduction and integration therapy. *Harm Reduction Journal*, *18*(40). https://doi.org/10.1186/s12954-021-00489-1

Pradhan, B. K., Wainer, I. W., Moaddel, R., Torjman, M. C., Goldberg, M., Sabia, M., M., Parikh, & Pumariega, A. J. (2017). Trauma Interventions using mindfulness based extinction and reconsolidation (TIMBER) psychotherapy prolong the therapeutic effects of single ketamine infusion on post-traumatic stress disorder and comorbid depression: A pilot randomized, placebo-controlled, crossover clinical trial. *Asia Pac J Clin Trials Nerv Syst Dis*, *2*, 81. https://doi.org/10.4103/2542-3932.211589

Pradhan, B., Mitrev, L., Moaddell, R., & Wainer, I. W. (2018). d-Serine is a potential biomarker for clinical response in treatment of post-traumatic stress disorder using (R, S)-ketamine infusion and TIMBER psychotherapy: A pilot study. *Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics*, *1866*(7), 831-839. https://doi.org/10.1016/j.bbapap.2018.03.006

Psychologists' Association of Alberta. (2025). *2025 PAA recommended fee schedule*. https://psychologistsassociation.ab.ca/resources/recommended-fee-schedule/

Puderbaugh, M., & Emmady, P. D. (2020). *Neuroplasticity*. StatPearls Publishing, Treasure Island, FL.

Rojas, D., Zelman, D. C., Hauson, A. O., & Alexander, I. (2024). Exploring cultural competence, inclusivity, and diversity in ketamine assisted psychotherapy: A phenomenological study. *Journal of Psychoactive Drugs*, *57*(3), 243–253. https://doi.org/10.1080/02791072.2024.2341811

Shiroma, P. R., Thuras, P., Wels, J., Erbes, C., Kehle-Forbes, S., & Polusny, M. (2020). A proof-of-concept study of subanesthetic intravenous ketamine combined with prolonged exposure therapy among veterans with posttraumatic stress disorder. *J. Clin. Psychiatry*, *81*(6), 10118. https://doi.org/10.4088/JCP.20L13406

Stephenson, E. (2023, September). *The Daily: Mental disorders and access to mental health care*. Statistics Canada, Government of Canada. https://www150.statcan.gc.ca/n1/daily-quotidien/230922/dq230922b-eng.htm

Statistics Canada. (2024, December). *Posttraumatic stress disorder among adults in Canada*. Government of Canada. https://health-infobase.canada.ca/ptsd-survey/

Whittaker, E., Dadabayev, A. R., Joshi, S. A., & Glue, P. (2021). Systematic review and meta-analysis of randomized controlled trials of ketamine in the treatment of refractory anxiety spectrum disorders. *Therapeutic advances in psychopharmacology*, *11*. https://doi.org/10.1177/20451253211056743

Wilkinson, S. T., Wright, D., Fasula, M. K., Fenton, L., Griepp, M., Ostroff, R. B., & Sanacora, G. (2017). Cognitive behavior therapy may sustain antidepressant effects of intravenous ketamine in treatment-resistant depression. *Psychotherapy and Psychosomatics*, *86*(3), 162-167. https://doi.org/10.1159/000457960

Wilkinson, S. T., Rhee, T. G., Joormann, J., Webler, R., Ortiz Lopez, M., Kitay, B., Fasula, M., Elder, C., Fenton, L. & Sanacora, G. (2021). Cognitive behavioral therapy to sustain the antidepressant effects of ketamine in treatment-resistant depression: A randomized clinical trial. *Psychotherapy and psychosomatics*, *90*(5), 318-327. https://doi.org/10.1159/000517074

Yermus, R., Bottos, J., Bryson, N., De Leo, J. A., Earleywine, M., Hackenburg, E., Kennedy, S., Kezemidis, M., Kratina, S., McMaster, R. & Lo, C. (2024). Ketamine-assisted psychotherapy provides lasting and effective results in the treatment of depression, anxiety, and post-traumatic stress disorder at 3 and 6 months: Findings from a large retrospective effectiveness study. *Psychedelic Medicine*, *2*(2), 87-95. https://doi.org/10.1089/psymed.2023.0021

Zarate, C. A., & Machado-Vieira, R. (2017). Ketamine: Translating mechanistic discoveries into the next generation of glutamate modulators for mood disorders. *Molecular psychiatry*, *22*(3), 324-327. https://doi.org/10.1038/mp.2016.249

Zdyb, T., & Hart, M. (2021). Efficacy of oral ketamine combined with psychotherapy for treatment resistant depression. *European Journal of Medical and Health Sciences*, *3*(4), 106-108. https://doi.org/10.24018/ejmed.2021.3.4.979