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Differences in PHQ-9 Depression Severity Between Adults Receiving Ketamine or Ketamine-Assisted Psychotherapy

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Abstract

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Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Abstract

Treatment-resistant depression (TRD) affects roughly 2.8 million or 1.1% of the United States population. Many traditional treatments of mental disorders including various types of psychotherapy and pharmacotherapy do not provide adequate symptom reduction for clients, and many clients diagnosed with TRD seek out nontraditional treatments such as ketamine and psychedelics for their antidepressant effects. Due to the dissociative nature of psychedelic medication wherein resistance is reduced, and a trance-like state is induced, ketamine-assisted psychotherapy (KAP) has great potential as an adjunct to ketamine therapy. Procedures of KAP have been in development for the last 7 years and a consensus on protocol has been evolving. The purpose of this study was to determine the differences in depression self-report ratings using the PHQ-9 between clients who receive KAP versus clients who receive the infusions alone while controlling for baseline at intake and immediately following 6 infusions cycle. Common Factors conceptual framework was used to frame the study. Quade's Rank ANCOVA was computed to determine that no significant differences exist in depression ratings between ketamine infusion only and KAP group, though paired samples *t* test results indicate statistically significant differences in depression ratings from baseline to follow-up in each treatment group. The positive social change implications are possible new treatment options for individuals who have been struggling with treatment-resistant mental health conditions, contribution to the literature on the effectiveness of KAP for TRD, and to help inform policy changes and establish needs for insurance coverage of ketamine and KAP.

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Dedication

This dissertation would not have been possible without the love and support of my family and friends these past years who have encouraged me to fulfill my dream of becoming a counselor educator and supervisor.

I am forever indebted to my mother, father, and grandparents. You have instilled the value of education in pursuing my dream. With your constant love and sacrifice, I have been able to be successful in my journey to becoming a counselor and educator. You always believed in me, encouraged me, and loved me. Your generosity has made this my dream come true.

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Lastly and most importantly, this dissertation is dedicated to my husband, Anto. Thank you for your support, patience, and understanding. Your love, kindness, and encouragement has inspired me to complete this work. This work would not be what it is, had it not been for you.

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Chapter 1: Introduction to the Study

Introduction

Ketamine clinics and private practices are conducting ketamine-assisted psychotherapy (KAP) across the United States, but there is not enough evidence to support its efficacy in the literature, nor a clear standard for protocol in conducting KAP (Dore et al., 2019). This contrasts with the ACA *Code of Ethics* which advises counselors to use empirically supported treatments or theories for mental health conditions (C.7.a.; ACA, 2014). Treatment-resistant depression (TRD) affects between 20-60% of the population of clients diagnosed with psychiatric disorders (Howes et al., 2021). Zhdanava et al. (2021) noted that the number of adults diagnosed with TRD is 2.8 million or 1.1% of the United States population. Many traditional treatments of depression including various types of psychotherapy and pharmacotherapy do not provide adequate symptom reduction for clients (Akil et al., 2019; Rizvi & Khan, 2019). There is a need for novel treatments for TRD due to the significant impacts TRD inflicts on the lives and livelihood of people in the United States (Zhdanava et al., 2021).

Ketamine is a dissociative anesthetic and was approved in 2019 by the FDA for treatment of depression and suicidality in the form of a nasal spray (U.S. Food and Drug Administration, 2022). Robust evidence for rapid antidepressant and antisuicidal effects of ketamine in various forms including infusions exists regarding evidence-based treatment of major depressive disorder (MDD), but there is limited evidence supporting psychotherapeutic methods during infusions (Walsh et al., 2022). KAP has been in clinical development since roughly 2013, but a consensus on protocol and procedures

continue to develop (Dore et al., 2019). Dore et al. (2019) defined KAP as occurring in three phases: preparation, administration, and integration.

The positive social change implications of this study include possible new treatment options for individuals who have been struggling with treatment-resistant mental health conditions. An additional social change implication is that this study contributed to the literature on the effectiveness of ketamine by identifying the critical problems faced by persons with treatment-resistant conditions and depressive disorders and highlighting the benefits of ketamine and KAP treatment. Accessibility and equity are important in reducing barriers to access among marginalized or lower socioeconomic groups which are already disproportionally affected by treatment-resistant conditions (Walsh et al., 2022). Yet, ketamine treatment is expensive, between 400-2,000 dollars per infusion, not including KAP (KetamineClinicsDirectory.com, 2021). It is not currently covered by insurance plans, as it is considered off label use of the drug at this time (InnovativeKetamine.com, 2021). A potential positive social change impact of this study is that it may help inform policy changes and establish need for insurance coverage of these treatment alternatives for depression and treatment-resistant cases, so that more people may benefit from ketamine and KAP.

In this chapter, I presented information on the background for my study, a brief review of the relevant existing literature, and the gap in the literature which identifies the problem, that practitioners are providing KAP with limited evidence supporting its efficacy, which contrasts with the ACA *Code of Ethics* which advises counselors to use empirically supported treatments or theories for mental health conditions (C.7.a.; ACA,

2014). I provided the hypotheses and described the conceptual framework of common factors which provided the foundation for this research study. Finally, I addressed the potential limitations and significance of this work to the counseling field.

Background

TRD affects between 20-60% of the population of clients diagnosed with psychiatric disorders (Howes et al., 2021). This translates to roughly 1.1% of the U.S. population (Zhdanava et al., 2021). Many traditional treatments of depression including various types of psychotherapy and pharmacotherapy do not provide adequate symptom reduction for clients (Akil et al., 2019; Rizvi & Khan, 2019). For example, the large-scale Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study showed that half of patients responded to an initial trial of an antidepressant (Gaynes et al., 2009). However, only one third of patients with the initial trial reached clinical remission; subsequently only up to one third of clients reached remission following multiple antidepressant trials (Gaynes et al., 2009). For those clients who show insufficient progress, electroconvulsive therapy (ECT), vagus nerve stimulation, and other nontraditional treatments such as ketamine and psychedelics may be used to alleviate mental health disorder symptoms (Bottomley et al., 2020; Rizvi & Khan, 2019; Veraart et al., 2021).

Ketamine and psychedelic-assisted psychotherapy (PAP) are emerging forms of treatment for TRD. PAP is a broad umbrella term which includes a variety of medicines including psilocybin, LSD, DMT, ketamine, and others. KAP falls under the broader term of psychedelic-assisted psychotherapy. Clinical research on psychedelics was widespread

in the 1950s and 1960s (Luoma et al., 2020). In the 1970s, the United States categorized psychedelics as Schedule 1 substances, or reclassified as having no medical purpose or potentiate high risk of abuse (Luoma, et al., 2020). After two decades during which psychedelic research was halted, placebo-controlled clinical trials are just beginning to be published (Luoma et al., 2020). Ketamine in the form of a nasal spray esketamine, also known as Spravado, was named a Schedule III controlled substance that was approved by the FDA in 2019 (U.S. Food and Drug Administration, 2022). Currently, this is the only psychedelic approved by the FDA for the treatment of mental health disorders, though psychedelics in the form of MDMA, psilocybin, LSD, ayahuasca, and ibogaine are now undergoing clinical trials by the FDA for approval in treating mental health disorders (Mitchell et al., 2021). Medical providers have autonomy to determine whether off-label use of ketamine in the form of infusion, oral, intramuscular, or other method of administration is warranted for treatment of various conditions including mental health disorders.

Although researchers have investigated the effectiveness of ketamine on depression, there is minimal evidence demonstrating the efficacy of KAP, the first analytic study being conducted in 2019 (Dore et al., 2019). In my review of the literature, there are four studies that focus specifically on KAP for depression. In addition, little research has been conducted on the lasting effects of ketamine on mental health, and a clear gap in the literature is that there are no existing studies comparing ketamine and KAP regarding change in depression. It is not known to what extent psychotherapy in conjunction with ketamine treatment accounts for decrease in depression and other

mental health symptoms in comparison to ketamine treatment alone (Davis et al., 2021). Psychoactive drugs work synergistically with psychological therapies, however distinct support for assisted psychotherapy during ketamine infusion has not been emphasized in the current use of ketamine for depression (Walsh, 2022). The FDA approved the nasal spray form of ketamine, esketamine, for TRD and did not require adjunctive psychotherapy (Walsh, 2022).

Ketamine-assisted psychotherapy differs from PAP, while both are considered dissociative drugs, they differ in the ways in which they are experienced, as well as in their antidepressant effects (Lennon, 2021). Psychedelics are a class of drug, grouped together due to the quality of the experience they invoke and the common action on serotonin receptors in the brain (Lennon, 2021). Ketamine's dissociative effects cause an experience of freedom from physical reality and lowered inhibition and have been found to have rapid antidepressant effects (Berman et al., 2000; Blier & Blier, 2016; DiazGranados et al., 2010; Griffiths et al., 2021; Phillips et al., 2019). In comparison to ketamine, the history of MDMA as a treatment has been closely tied to the accompanying psychotherapy (Schenberg, 2018). While KAP has been less widely researched and practiced than MDMA assisted psychotherapy, ketamine clinics have begun to introduce similar setting, music, and empathetic presence of a psychotherapist to determine whether the same effects exist in KAP as in PAP (Davey, 2021). I chose to focus this study on ketamine and KAP to contribute to the literature on the potential effects of KAP, as well as the availability of the data, as I work in partnership with a ketamine clinic.

Impact of COVID-19 Pandemic

It is important to note that the COVID-19 pandemic, declared on March 11, 2020 has marked a global health, social, and economic burden, and has contributed to significant challenges for persons struggling with depression (Bueno-Notivol et al., 2021). Bueno-Notivol et al. (2021) found that while the global prevalence of depression was 3.44% in 2017, the pooled prevalence surveyed appeared to be roughly seven times higher during the pandemic. These findings point to the impact which the COVID-19 outbreak has had on mental health and well-being and that the changes which have occurred since the pandemic's beginning contribute to the increased need for new and innovative depression treatment.

The COVID-19 pandemic has gained a major role in intensive care medicine and poses an unprecedented burden on society and the development of medical services (Weinbroum, 2021). Weinbroum (2021) advocated for the use of ketamine when caring for coronavirus patients who suffered from both physical impairments and mental health conditions such as depression. Weinbroum reported that ketamine could be used in the treatment of patients diagnosed with coronavirus due to its many benefits, specifically reduction in depressive symptoms and suicidal thoughts, as well as it's documented safety sedation and anesthesia benefits without depressing cardiovascular or respiratory processes (Weinbroum, 2021).

Problem Statement

TRD imposes a national cost in the United States, accounting for 43.8 billion dollars in incremental costs (Zhdanava et al., 2021). The estimated 12-month prevalence of major depressive disorder (MDD) is 8.9 million adults (Zhdanava et al., 2021). Of those diagnosed with MDD, 2.8 million (30.9%) qualified for TRD (Zhdanava et al., 2021). There is a need for novel treatments for TRD, which has significant negative impacts on the lives of people in the United States (Zhdanava et al., 2021). There is evidence that intravenous ketamine has the potential to be a part of the next wave of management for this disorder (Voineskos et al., 2020).

According to the ACA Code of Ethics: "counselors must use techniques/procedures/modalities that are grounded in theory and/or have an empirical or scientific foundation" (C.7.a; American Counseling Association, 2014). Although researchers have investigated the effectiveness of ketamine on depression, there is minimal evidence demonstrating the efficacy of KAP, the first analytic study being conducted in 2019 (Dore et al., 2019). In my review of the literature, there were four studies that focus specifically on KAP for depression. Practitioners continue to provide KAP despite limited research supporting its efficacy and no published protocols and standards for treatment (Dore et al., 2019). Consequently, this lack of research presents a problem: there is a need for novel treatments for TRD and practitioners continue to provide KAP, yet the ACA *Code of Ethics* calls on counselors to provide empirically supported treatments.

Dore et al. (2019) measured KAP in their quantitative analysis as having three distinct phases: preparation, administration, and integration (wherein psychotherapy occurs). While researchers have investigated the difference between medication and psychotherapy, with combined treatments demonstrating superior outcomes (Kamenov et al. 2019; Karyotaki et al. 2016), the effectiveness of ketamine infusions in comparison to KAP had not yet been analyzed. Given the economic and health impacts of TRD, it is important to determine if medication paired with psychotherapy contributes to superior outcomes than intravenous ketamine alone.

This dissertation study contributes to the counseling profession by providing greater understanding of the impact of ketamine and KAP on the treatment of depression. This research will support professional counselors' practice by evaluating the effectiveness of these new waves of treatment, thus contributing to the existing literature and knowledge needed to use these approaches with clients. Increased use of KAP indicates a need for counselor educators and supervisors to demonstrate teaching and supervision theory and techniques on conducting ethical and effective KAP. Psychedelic-assisted psychotherapy is becoming more commonplace, and efficacy studies are underway. For the counseling profession, this translates to a need for counselor education programs to consider training counselors in the procedures of KAP and PAP.

Purpose of Study

The purpose of this quantitative quasi-experimental study was to determine if there is a statistically significant difference in changes in depression from baseline to immediately following treatment as measured by the PHQ-9, among clients receiving

ketamine infusions compared to clients receiving KAP after controlling for baseline depression severity. The dependent variable is depression severity as measured by the PHQ-9. The independent variable is ketamine infusion with or without KAP. Baseline depression severity is considered a covariate in this study.

Research Question and Hypotheses

RQ – Is there a statistically significant difference in change in depression, as measured by the PHQ-9, from baseline to immediately following treatment between clients receiving ketamine infusions compared to clients receiving ketamine-assisted psychotherapy after controlling for baseline depression severity?

H_0 - There is not a statistically significant difference in change in depression, as measured by the PHQ-9, from baseline to immediately following treatment between clients receiving ketamine infusions compared to clients receiving ketamine-assisted psychotherapy after controlling for baseline depression severity.

H_a - There is a statistically significant difference in change in depression, as measured by the PHQ-9, from baseline to immediately following treatment between clients receiving ketamine infusions compared to clients receiving ketamine-assisted psychotherapy after controlling for baseline depression severity.

Conceptual Framework: The Common Factors

The conceptual framework that grounded this study was the common factors approach to psychotherapy, research, and practice, focusing specifically on common concepts of counseling theories and how they contribute to treatment success. The common factors framework was originated by Saul Rosenzweig in 1936 (Rosenzweig,

1936). The therapists who provided KAP for the clients in this study have differing theoretical orientations to counseling. The common factors approach emphasizes the importance of commonalities among therapy treatment orientations in effecting positive change in their clients' lives (Duncan, 2002).

The logical connections between the common factors framework and the nature of this study were the inclusion of several different therapists with different theoretical approaches to treatment providing KAP in this study. Rather than crediting specific techniques or tools that are beneficial in treating mental health disorders, the common factors approach recognizes various components of the therapeutic relationship as contributing to its success (Duncan, 2002). Since 1936, many theorists have built upon the concepts of the common factors, with most agreeing that it is the personality of the therapist and the quality of the therapeutic alliance which accounts for the positive effects of psychotherapy, rather than the various interventions or intricacies of the many psychological theories (Duncan, 2002). For example, Rogers (2007) identified the central tenets of psychotherapy as unconditional positive regard, empathy, and honesty (Rogers, 2007). In contrast, Jerome Frank (1983) identified the tenets as: an emotionally charged confiding relationship, a healing setting, a rationale, a procedure requiring active participation in client and therapist with the understanding that it will be used to restore the client's health. The common factors approach related to this study, as the concepts demonstrated the significance of the common tenets of various forms of psychotherapy. This was a central conceptual framework, as several therapists provided the KAP in this study.

The clients who received KAP were experiencing a therapeutic relationship during treatment, while those clients who elected out of KAP did not have this experience. The common factors framework relates to the research questions as the focus was to compare two groups of clients, one in which there was a psychotherapeutic relationship wherein the common factors were demonstrated, and the other in which there was not such a therapeutic relationship. The framework relates to data analysis as I used Quade's rank ANCOVA to compare the PHQ-9 outcomes of these two groups of clients.

Nature of the Study

The nature of this study was a quantitative, retrospective quasi-experimental analysis which determined whether differences existed in depression between ketamine infusions compared to KAP. The key study variables included the independent variable ketamine infusion with or without KAP. The dependent variable was PHQ-9 score at baseline and immediately following the sixth and final infusion. Baseline depression severity was considered a covariate. The rationale for using a quantitative approach to this study was to determine whether a relationship existed between ketamine infusion and depression symptoms, and the effectiveness of ketamine infusion with or without accompanying psychotherapy.

To address the research questions in this quantitative study, specific analysis included Quade's nonparametric analysis of covariance (ANCOVA) (see Frankfort-Nachmias & Leon-Guerrero, 2018). Quade's ANCOVA analysis included controlling for baseline severity on the PHQ-9 as well as measuring the outcome of potential change in depression score at end of treatment and one month follow up.

The ketamine provider clinic collected client data. This ketamine clinic was authorized to store and administer ketamine infusions. The clinic staff collected client self-report measures including the PHQ-9, GAD-7, and subjective mood scores via the Osmind app; an app specifically designed for ketamine providers. All data used in this study were archival, I was provided with a deidentified dataset in accordance with a data use agreement between the ketamine clinic and researcher. I had no interaction with clients throughout the course of this study.

Definitions

Baseline severity: Baseline severity referred to the score of the outcome measure at baseline (prior to treatment) (Nunes et al., 2011). Covariation for baseline severity of the outcome measure should be considered for inclusion in studies which aim to contribute to literature on evidence-based treatment (Nunes et al., 2011). Baseline severity is strongly associated with outcome in studies (Nunes et al., 2011).

Common factors: The common factors conceptual approach originated in 1936 by Saul Rosenzweig. The framework states that success is not a reliable guide for validity of a theory to psychotherapy. Rather, implicit common factors among therapists explains the success of psychotherapy. Many theorists have contributed to the conversation on the common factors model and agree that more similarities exist between approaches than differences. For example, Rogers discussed therapist congruence, accurate empathy, and unconditional positive regard as the factors which are most influential common factors of psychotherapy (Rogers, 2007), while Garfield identified the therapist being a sympathetic non-moralizing healer, reassurance and support, promoting successful coping strategies,

facing or confronting a problem, and opportunity to gain understanding about oneself (Garfield, 1997).

Ketamine-assisted psychotherapy (KAP): In the first analytic study on KAP, Dore et al., (2019) described three phases of KAP: preparation, administration, and integration. Preparation includes the anesthesiologist/nurse administering various tests to the patient such as blood work, height, and weight. The patient also signs consent forms. Administration phase involves the patient sitting or lying down for the IM, IV, or other route of administration of ketamine; music may be played at this time (Dore et al., 2019). Integration phase takes place during or after the administration of ketamine with a licensed professional counselor or therapist who uses a particular theoretical orientation such as: CBT, ACT, DBT, EFT, existential, or another orientation. The content of KAP is like an outpatient therapy session; the therapist focuses on the client experience of the session, current and past struggles, anxiety, depression, or other mental health problem. KAP has been in clinical development for several years and a consensus on protocol and procedures is evolving (Dore et al., 2019).

Ketamine infusion: Ketamine infusions are administered to the client by an anesthesiologist or Certified registered nurse anesthetist (CRNA) on site. Ketamine is administered in a dose of 0.5/mg/kg, but some patients respond to doses as low as 0.1 mg/kg and others require higher doses, such as up to 0.75mg/kg (Andrade, 2017). The infusion is typically administered over the course of 40 minutes, but safety and efficacy has been demonstrated in sessions ranging between 2 and 100 minutes (Andrade, 2017).

The Patient Health Questionnaire (PHQ-9): A valid and reliable instrument for the assessment of depression severity. The assessment tool has cut-offs for the severity of depression, including 5, 10, 15, 20 which represent cutoff points for mild, moderate, moderately severe, and severe depression, respectively (Inoue et al., 2012). The PHQ-9 is sensitive to changes in depression over time points (Cameron et al., 2008; Lowe et al., 2004).

Psychedelic renaissance: a term used by psychiatrists and psychotherapists in the past decade, referring to the increase in research on psychedelic substances (Dyck, 2017). In 2014, the *Scientific American* published an editorial calling for the end to the ban on psychedelic drug research and appeal that the U.S. government should move these drugs to the less strict Schedule II classification of substances so that researchers may better research their effects. Research is ongoing which explores whether psychedelics have therapeutic potential (National Institute of Health [NIH], 2017).

Assumptions

The most basic assumption in this quantitative research is that reality is something which can be studied objectively, measured, and analyzed. I tested the hypothesis of this study using deductive forms of logic and statistical analysis. An assumption in quantitative research is that the researcher remains value-free, distant, and independent of the research process. I was a part of the research process; in that I have likely provided KAP to the clients in this study. It is possible that this dual role, acting as both a therapist and researcher, may create conflicts or undue influences on the therapy or research

process. An additional assumption was that clients in this study have provided honest answers to the PHQ-9 outcome measure.

Scope and Delimitations

The delimitations of this study were related to the gap in the literature on the efficacy of ketamine and KAP and will contribute to the literature on whether KAP has an advantage in the treatment of depression. The scope of this research study was to focus on the depression scores as assessed by the PHQ-9, before, immediately after, and one month following infusions. Clients have also provided subjective mood scores, which were in response to the question: "How are you feeling today? 1 (bad) and 10 (great)." However, I have chosen not to include these scores in this analysis due to the lack of existing literature which has validated the use of subjective mood scores in the research on depression severity.

Additionally, a diagnosis of MDD is necessary for inclusion in this study. The purpose of this is that the PHQ-9 is used only to assess for depression severity, not severity of other mental health disorders. I have chosen to include clients who have been provided KAP from several different therapists who employ various theoretical orientations to counseling and psychotherapy. The purpose of this is related to the conceptual framework of this study, the common factors approach which emphasizes the foundational aspects of psychotherapy which lead to treatment success. I have limited this analysis to clients who were 18 years and older at the time of infusion. In addition, the geographical location included clients who received ketamine and KAP from two ketamine clinics in the southeastern region of the United States.

There were several threats to the generalizability of this study including focus on ketamine and KAP for clients diagnosed with MDD which does not include clients with other diagnoses; therefore, it is not possible to make generalizing assumptions about ketamine and KAP's effectiveness with all mental health disorders. Another generalizability threat to consider is selection bias. Clients who opted to have KAP may share characteristics which makes them different from the clients who opted out of KAP. Finally, the maturation effect may contribute to limits of generalizability due to changes in the clients' self-report measures from initial report to the report one month following infusions. These changes may range from client mood changes to changes in work, schooling, health, or other physical, social, or behavioral changes in the client's life.

Limitations

In this study I am using nonprobability sampling, and clients were included based on their accessibility and availability to the infusions and accompanying psychotherapy. Additionally, ketamine is expensive, and the infusions are not covered under insurance plans at this time. A cycle of infusions costs roughly $2,400 dollars, with accompanying psychotherapy the cost may be upwards of $3,200 dollars. This may exclude clients of lower income households. The cost of infusions and accompanying psychotherapy may limit the ability to generalize the results of this study to the general population as there may be some potential economic biases of privilege inherent with clients from higher SES backgrounds.

It is possible that other events which have occurred in the clients' lives may affect the PHQ-9 scores, and it is therefore not plausible to say that all changes in PHQ-9 scores

from baseline, immediately following infusions, and one month following infusions were due solely to the effects of ketamine infusions/KAP. In addition, the Hawthorne effect may impact the internal validity of this research. Defined as the change in subject responses or behavior consequent to awareness of being studied in research, the Hawthorne effect has been found to influence subject responses due to being observed and having behavior assessed (McCambridge et al., 2014). Clients become concerned about social desirability and researcher expectations and may change their responses on self-report measures (McCambridge et al., 2014). This is a proposed limitation associated with using self-report instruments in research.

A consideration and potential bias for this study is that I am employed with the private practice which works in conjunction with the ketamine clinic by providing KAP. Another potential problem could be time required to meet my minimum sample size. Not all clients who were provided ketamine infusions or KAP provide their PHQ-9 data. I needed to ensure that enough client data was collected to make valid inferences.

An additional limitation to this study is lack of comprehensive demographic data. The only demographic data collected by the ketamine clinic includes age, gender, past medical history, location in city and state, referral source, and mental health diagnosis; clients' race/ethnicity is not collected. Racial and ethnic minorities experience poorer health outcomes yet are not included in research studies as often as White people (CDC, 2013). The lack of racial or ethnic identification is a proposed limitation for this study as no generalizations beyond the available sample demographics may be deduced on differences in depression ratings according to client race and ethnicity.

Significance

This study is significant in that it will fill a gap in the understanding and literature on comparison of the efficacy of intravenous ketamine and KAP. Filling this gap is important as KAP has limited empirical evidence, and the ACA *Code of Ethics* calls for counselors to use empirically supported treatments or theories for clients with mental health conditions (C.7.a.; ACA, 2014). Through the results of this study, I intend to provide research on new and developing therapies for clients struggling with chronic and treatment-resistant mental health disorders. My aim in this study is to contribute to the growing literature on the efficacy of KAP by analyzing the differences in PHQ-9 scores between those clients who have received both KAP and the infusions, and the infusions only.

Accessibility to ketamine infusion and KAP treatment is a social change consideration for this study. As previously mentioned, at this time, the six cycles of infusions and KAP together may cost between $2,400-3,200 dollars. It may not be available to those clients who were coming from lower income households, and most treatments are not covered by insurance plans at this time. I aim to impact treatment disparity through this research, by contributing to the literature on the effectiveness of KAP, so that treatment may become more readily available for coverage through insurance providers.

Summary

In this chapter, I have presented the topic of ketamine infusion and KAP in their relevance to the treatment to depression. Practitioners across the United States are

providing KAP without adequate evidence supporting its efficacy, this contrasts with the ACA Code of Ethics which advises counselors to use empirically supported treatments or theories for mental health conditions (C.7.a.; ACA, 2014). I have presented the research questions and discussed the theoretical foundation of the common factors approach. Finally, I have presented the social change implications which include contribution to the knowledge of the developing therapies for the treatment of depression. In Chapter 2, I will provide a review of the literature related to depression, ketamine infusions, and KAP. I will also discuss the common factors conceptual framework.

Chapter 2: Literature Review

Introduction

The specific research problem addressed through this study is that practitioners across the United States are providing KAP without adequate evidence supporting its efficacy, this contrasts with the ACA *Code of Ethics* which advises counselors to use empirically supported treatments or theories for mental health conditions (C.7.a.; ACA, 2014). In addition, there is a need for novel treatments for TRD due to its significant negative economic and health impact on persons in the United States (Zhdanava et al., 2021), and ketamine has the potential to be a part of the next wave of treatment for this disorder (Voineskos et al., 2020). The purpose of this quantitative study is to determine if there were statistically significant changes in self-report of depression symptoms from baseline to immediately following treatment, as measured by the PHQ-9, among clients receiving ketamine infusions compared to clients receiving KAP. In this study, there were two treatment groups, both receive ketamine infusions, but one group elected for KAP sessions, while the other group had opted out of KAP sessions.

While ketamine has been used for many decades as an anesthetic in battlefields and emergency rooms (Moghaddam, 2021), it is only within the last 20 years that ketamine has been explored and studied as a part of the *psychedelic renaissance* for its effects on mental health. The research that exists on ketamine has clearly indicated strong positive results in subjects struggling with suicide and TRD within a matter of hours after administration (Matveychuk et al., 2020); however, there is a lack of data indicating the

long-term therapeutic effects of ketamine on the clients' depression symptoms (Blier & Blier, 2016).

In the last five years, KAP protocol has been developing and evolving, and experts have not yet arrived at a consensus for procedures and protocol (Dore et al., 2019). Over time however, analysis of available data, especially from client self-report measures, have contributed to the continued development of a replicable protocol for KAP (Dore et al., 2019). Dore et al. identified KAP as occurring in three distinct phases: preparation, administration, and integration. In preparation, the anesthesiologist/nurse conducts medical screening and provides consent and demographic forms for the client to complete. In the administration phase, the anesthesiologist/nurse provides the ketamine infusion to the client. In the integration phase, a licensed mental health clinician conducts therapy with the client.

In this literature review, I will discuss the current and evidence-based treatments of depression which include psychotherapy and pharmacotherapy, as well as nontraditional methods such as ECT and vagus nerve stimulation. I will also examine the current use and findings of ketamine and KAP in the treatment of depression. I will present the limited empirical studies on KAP in the treatment of depression, as well as the long-term effects of ketamine infusions on mental health diagnoses.

Literature Search Strategy

The keywords I searched in this literature review included the following: *Intravenous Ketamine, Ketamine, Ketamine-Assisted Psychotherapy, Ketamine and Depression, Ketamine and Treatment-Resistant Depression, PHQ-9, Patient Health*

Questionnaire. The databases I searched included Thoreau, APA PsycINFO, SAGE Journals, Pubmed, JSTOR, and Google Scholar.

I reviewed existing literature spanning the past five years, from 2016-2022. Most of the literature I found and used for this study is current, within the last five years. There were some exceptions to this, due to my inclusion of articles which provide historical perspective on the conceptual framework. These few include seminal articles going back to 1936 on the founder of the common factors approach.

Conceptual Framework: Common Factors

The common factors approach to psychotherapy is the conceptual framework for this study. The common factors approach for research and practice focuses on the common concepts of counseling theories and how they contribute to treatment success. The concept of the common factors was originated by Saul Rosenzweig in 1936 in an article (Rosenzweig, 1936). After Rosenzweig's 1936 article, little else was written about the common factors of psychotherapy until the 1950s, when it began to be discussed and explored by a variety of theorists (Duncan, 2002). The central tenets of the common factors framework include the *operation of unverbalized and implicit factors such as catharsis, the personality of the therapist, consistency of the therapeutic ideology as a basis for reintegration*, as well as the *alternative formulation of psychological events* (Duncan, 2002). After this first article on the common factors, several prominent theorists including Carl Rogers and Saul Rozenweig assembled at the 1940 American Orthopsychiatric Society conference to discuss their work with clients in counseling (Duncan, 2002). At this conference, the panelists agreed that more similarities among

therapeutic approaches existed than differences, including *that objectives are similar, the quality of the therapeutic relationship is central, respecting client autonomy, and increasing client's understanding of self* (Duncan, 2002).

In the 1950s, more theorists began placing attention on the common factors approach. In 1955, Hoch commented that despite therapists' various treatment techniques and theories, there are similar therapeutic results, which can lead to the conclusion that theoretical orientations are not as important as the common factors present in therapies (Duncan, 2002). Jerome Frank contributed to the literature on the framework in 1983, as he wrote extensively about the commonalities across therapeutic approaches and identified four common features across orientations: *an emotionally charged confiding relationship with a helping person, a healing setting*, *a rationale*, *a conceptual theme or myth*, and a *ritual*- or procedure requiring active participation in client and therapist with the understanding that it will be used to restore the client's health (Frank, 1983, p. 19-20.)

Carl Rogers also wrote about the common factors inherent in counseling and psychotherapy, or, the *necessary and sufficient conditions* of therapeutic change (Rogers, 2007). Rogers identified three therapist qualities which account for this change, including *being genuine and honest, unconditional positive regard or basic respect,* and *empathy* (Rogers, 2007). He emphasized that under these conditions of therapy, the client would become the arbiter of their own subjective experience, empowering the client and encouraging them to make the needed changes in life (Samstag, 2007).

The nature of this study is inclusion of several different therapists who employ various theoretical orientations to KAP treatment. This coincides with the conceptual

framework of common factors, namely, that it is the commonalities among treatment approaches lend to therapeutic success rather than the differences between modalities (Frank, 1983). Rather than crediting specific techniques or tools that are beneficial in treating mental health disorders, the common factors conceptual framework places emphasis on the quality of the relationship between therapist and client and working toward the agreed upon goals (Duncan, 2002).

Ketamine infusions induce a trance-like state, which may allow for easier access of the aspects of depression, anxiety, or other mental health condition which are often barred from conscious awareness (Wolfson, 2016). Addressing the trauma, attachment, existential struggles, failures, and oppressions, alongside the human need for being, connection, compassion, justice, and morality may take a significant amount of trust between therapist and client over many sessions (Wolfson, 2016). Due to the trance-like state brought on by dissociation, KAP allows for a breakdown of resistance and greater corresponding openness to access the complex innerworkings of a mental health problem (Wolfson, 2016).

While the client's resistance is reduced through ketamine infusion, it is important that the therapist provide the necessary conditions, including an *emotionally charged confiding relationship, a healing setting, a rationale for treatment,* and *active participation in restoring client's health,* as outlined by Jerome Frank (1983, p. 19-20). These vital components of the therapeutic relationship may serve to strengthen the therapeutic alliance, and therefore contribute to the positive results of the ketamine

treatment. The therapeutic relationship, with these common factors, may contribute to stronger treatment outcomes (Wampold, 2015).

Researchers of KAP have demonstrated the importance of therapeutic support and alliance throughout infusions (as indicated by clients' self-report), and this supports the inclusion of the common factors approach as a central tenet of this study. For example, "trust" in the ketamine providers influenced the subjects' willingness to try ketamine and perceived treatment success as found in Griffiths et al. (2021). Jilka et al. (2019) surveyed individuals on the subject of ketamine and client views and found that subjects expressed their desire to have not just monitoring by a physician or nurse, but also a relationship with a counselor or therapist who "understands depression and mental illness" (p. 4).

It is important to note that KAP, wherein a client forms a therapeutic alliance with a therapist, differs from the relationship the client may have with the ketamine infusion provider. The anesthesiologist or anesthetist nurse checks in on the client to assess for physical markers of distress and to ensure that the client has reached necessary levels of dissociation (American Psychiatric Nurses Association [APNA], 2021). This provider does not stay throughout the infusion providing support or fulfilling the common factors of psychotherapy, such as is found in KAP.

Literature Review Related to Key Variables and Concepts

In this section, I present the literature which provides the basis for this research project. I begin by discussing the evidence-based treatment of combined psychotherapy and pharmacotherapy for TRD, followed by the status of depression and depression

treatment in the United States. I will then discuss ketamine and KAP in the treatment of depression.

Psychotherapy and Pharmacotherapy: Combined Treatments

There is evidence that psychotherapy and pharmacotherapy are both tools which have a positive effect on mental health disorders (Kamenov et al. 2017). In their meta-analysis, Kamenov et al. found that compared to control conditions, both psychotherapy and pharmacotherapy had small to moderate effects on functioning, with slight superiority of psychotherapy. The mean effect of psychotherapy on functioning was *g*=.43 with 95% confidence interval, whereas for pharmacotherapy, the effect was *g*=.31 with a 95% confidence interval. Both yielded small to medium effect sizes. Between client functioning and quality of life, the therapies yielded no significant differences (Kamenov et al. 2017). Kamenov et al. found that the combined treatment was significantly superior when compared to either of the treatments alone yielding small effect sizes. Combined treatment was significantly more efficacious compared to medication alone (*g* = .36, 95% CI .11-.62), while studies comparing combined treatment with psychotherapy alone, favored combined treatment, which yielded an effect size (Hedges' *g*) of .39 (95% CI .19-.58). Lesperance (2007, as cited in Kamenov et al., 2017) found that combined treatment of psychotherapy and pharmacotherapy is superior to psychotherapy alone for functioning, yielding an effect size (Hedges' g) of 0.30. Bellino (2006 as cited in Kamenov et al., 2017) found that combined treatment is superior to pharmacotherapy alone for quality of life, yielding an effect size (Hedges' *g*) of 0.42.

Karyotaki et al. (2016) conducted a meta-analysis comparing the efficacy of pharmacotherapy and psychotherapy alone versus a combination of both in the treatment of MDD. Karyotaki et al. included 23 randomized controlled trials with 2184 clients and found that combined psychotherapy with antidepressants was more efficacious in reducing symptoms compared to antidepressants alone after 6 months or longer post-randomization (OR = 2.93, CI 95%, 2.15-3.99, $p < 0.001$). In addition to the study by Kamenov et al. (2017), this study contributes to the literature on the efficacy of the combination of psychotherapy and medications.

Blais et al. (2013) explored the effectiveness of treatment for depression using a sample of 1,322 psychiatric outpatients who received either psychotherapy, pharmacotherapy, or combined treatment. On average, all these treatments produced clinically significant outcomes with effect sizes surpassing no-treatment benchmark, with no significant differences between groups from self-report measures. Blais et al. conducted a one-way ANOVA comparing outcomes between clients by type of treatment and found no significant treatment differences between them ($F(2, 1{,}320) = 1.001$, $p = .36$). While the ANCOVA demonstrated no significant differences between groups, Blais et al. used paired *t* tests results to explore degree of improvement between each treatment group. The results indicated improvement representing a medium effect size (Cohen's *d*) of 0.61 for the pharmacotherapy and combined treatment groups (Cohen's *d*) of 0.66.

Kamenov et al. (2017), Karyotaki et al. (2017), and Blais et al. (2013) provided evidence that the combination of medication and psychotherapy are statistically significantly effective in reducing symptoms of depression. These researchers determined

that patients offered either pharmacotherapy such as antidepressants, or psychotherapy, yielded roughly similar treatment effects, namely the researchers found significant improvement from baseline and no significant between group differences between those offered psychotherapy versus pharmacotherapy. There has been limited research on the combination of intravenous ketamine (pharmacotherapy) and psychotherapy with the first analytic study performed in 2019 by Dore et al., which yielded statistically significant reduction in depressive symptoms.

Depression

According to the National Institute of Mental Health (NIMH, 2021), one in five adults in the U.S. lives with a mental disorder: roughly 51 million people. An estimated one in 25 Americans are diagnosed with a severe mental health disorder which causes significant impairment in functioning and interferes with the ability to conduct major life activities (Centers for Disease Control and Prevention [CDC], 2018). Mental health disorders have led to significant human, societal, and financial impacts in the United States. For example, depression, bipolar disorder, schizophrenia, and obsessive-compulsive disorder are among the top causes for disability in the United States (Johns Hopkins University, 2021). Serious mental illness alone accounts for nearly 200 billion dollars in lost earnings per year (CDC, 2018). Indeed, most people who die by suicide have a diagnosable mental health disorder (Johns Hopkins University, 2021). Persons with severe mental health disorders die on average up to 25 years earlier than others (CDC, 2018).

Treatment for depression is not one-size-fits-all and will often include a trial-and-error process. The American Psychiatric Association guidelines for the treatment of depression recommend the use of psychotherapy with a common antidepressant for first-line therapy (Mithawala & Davis, 2020). In contrast, the Veterans Administration/Department of Defense (VA/DoD) guidelines recommend psychotherapy, either CBT, Interpersonal therapy, or solution-focused therapy, as initial treatment for clients with MDD before moving to the prescription of antidepressant medication (Mithawala & Davis, 2020). For those clients who show insufficient progress in medication or therapy options, ECT and vagus nerve stimulation are also possible treatment options (Mithawala & Davis, 2020). Ultimately, treatments should be highly individualized, and providers should proceed with patience in working with clients with MDD and should provide an abundance of client education on treatment options (Mithawala & Davis, 2020).

TRD is defined as the failure to respond to two or more trials of medication of an adequate dose and duration (Zhdanava et al., 2021). The estimated 12-month prevalence of MDD is 8.9 million adults, with 2.8 million (30.9%) qualifying for TRD. TRD imposes a national cost in the United States. Zhdanava et al. found that the total incremental burden by adults with medication treated MDD was 92.l7 billion dollars, 49.1% in health care costs, 31.1% in productivity costs, and 19.8% in unemployment costs. Adults with TRD account for 43.8 billion or 47.2% of these incremental costs (Zhdanava et al., 2021). TRD is associated with significant and disproportionate health

care costs and implications for productivity at work and unemployment (Zhdanava et al., 2021).

Most studies on ketamine and KAP focus on the inclusion of subjects diagnosed with depression or anxiety (Hyde, 2015). While many clients suffer from comorbid psychiatric diagnoses in the natural world, most randomized trials exclude clients with more than one illness (Hyde, 2015). Hyde reviewed the current research which has been conducted providing evidence of ketamine's efficacy with other diagnoses, including autism, generalized anxiety disorder, social anxiety, PTSD, suicidal thinking, substance use, eating disorders, BPD, and depression with psychosis. Hyde helped elucidate evidence of other diagnoses that may benefit from ketamine treatment, not just TRD. Due to the commonality of depression and the problem of TRD, I have chosen to delimit this study to clients diagnosed with depression. This is due to the estimated 12-month prevalence of MDD being 8.9 million adults and 2.8 million (30.9%) of those diagnosed, qualifying for TRD (Zhdanava et al., 2021).

Ketamine

Ketamine has been acclaimed as one of the most novel discoveries in the treatment of depression in recent decades. Several studies have demonstrated rapid responses to its antidepressant effects in MDD as well as in treatment-resistant cases (Berman et al., 2000; Blier & Blier, 2016; DiazGranados et al., 2010; Griffiths et al., 2021; Phillips et al., 2019). It has gained in popularity over the last two decades with an initial report in 2000 investigating the treatment effects of the drug for depression (Berman et al., 2000).

In this placebo-controlled, double-blind study, Berman et al. (2000) tested the treatment effects of ketamine via infusion in clients with depression. The researchers found that clients in the treatment conditions experienced significant reductions in self-reported scores of depressed mood (paired *t* test, p=.0025), suicidality (p = .02), helplessness (p = .008), and worthlessness (p = .015) which were sustained for several days after infusions. Since Berman et al.'s study, hundreds of articles have been published testing ketamine's efficacy in treating mental health diagnoses (Marcantoni et al., 2020).

Several researchers have reported rapid therapeutic effects in ketamine especially for TRD (Berman et al., 2000; Blier & Blier, 2016; Griffiths et al., 2021; Phillips et al., 2019). Phillips et al. (2021) conducted a randomized double-blind crossover comparison of single infusions of ketamine and a placebo control to 41 clients diagnosed with TRD. After six weeks, clients received six ketamine infusions three times over a 2-week period. Those clients who demonstrated at least a 50% decrease in depressive scores from the MADRS scale, received four additional infusions administered once weekly (Phillips et al., 2021). These rapid effects, which ketamine has on the body in influencing depressive symptoms, sheds new light on the mechanisms in depression and paves a way for new discussion on the genesis of and psychopathology of depression, as well as the possible treatment avenues.

Limited evidence has been elucidated regarding the long-term effects of ketamine. Murrough et al. (2013) conducted a quantitative study with 24 subjects who were provided up to six IV infusions of ketamine three times weekly over a 12-day period.

Murrough et al. recorded patient responses up to 83 days post the last infusion. The researchers noted a large mean decrease in depression scores and a median time to relapse after the last infusion was 18 days (Murrough et al., 2013).

The scope of this study includes adults only, but it is important to note that ketamine clinics across the United States are also providing ketamine to adolescent clients for the treatment of TRD, as innovative treatments for this population are urgently needed (Cullen et al., 2018). Cullen et al. conducted an analysis on 13 adolescent participants with ages ranging from 14.5-18.8 years old and 8 biologically male. The average decrease in depression ratings as indicated by the Children's Depression Rating Scale-Revised (CDRS-R) was 42.5% ($p = 0.0004$) (Cullen et al., 2018). These results demonstrate the potential role of ketamine in the treatment of TRD in adolescents, specifically for youth who report suicidality (Cullen et al., 2018). Suicide is the second leading cause of death in youth ages 10-34, further demonstrating the need for novel treatments in this population (NIMH, 2021).

Ketamine: Mechanisms of Action

Ketamine appears to have a mechanism of action which is separate from other conventional antidepressant medications (Moghaddam, 2020). Ketamine itself has the ability to manipulate several proteins and receptors in the brain (Matveychuk et al., 2020; Moghaddam, 2020). One of the receptors for which ketamine acts is for the neurotransmitter glutamate, but the highest affinity for which ketamine acts is on the N-Methyl-D-aspartate (NMDA) receptor (Moghaddam, 2020). Ketamine selectively acts on receptors which are engaged in certain functions, but leaves others alone (Moghaddam,

2020). Ketamine works by blocking the excitatory action of the NMDA receptor when it is activated, which in high doses of ketamine, may lead to silencing of NMDA neuronal activity (Moghaddam, 2020). When ketamine is administered in smaller doses, it increases brain activity by allowing negatively charged ions into the neuron; ketamine creates an interplay of excitation and inhibition, from which ketamine in low doses has an antidepressant effect (Moghaddam, 2020). Ketamine works also on acetylcholine, opioid, and estrogen receptors, but surprisingly, does not have high affinity to serotonin or dopamine receptors, unlike its antidepressant medication counterparts (Moghaddam, 2020). Matveychuk et al. (2021) noted the existence of neuroanatomical biomarkers of response to ketamine especially on the prefrontal cortex (PFC), hippocampus, and anterior cingulate cortex (ACC) areas in the brain.

Guidelines for Ketamine Off-Label Use for Mental Health Disorders

As stated previously, medical providers have autonomy to determine whether off-label use of ketamine in the form of infusion, oral, intramuscular, or other method of administration is warranted for treatment of various conditions including mental health disorders. The American Psychiatric Association Council of Research Task Force on Novel Biomarkers and Treatments issued an article discussing the guidelines for off-label use of ketamine in the treatment of mental health disorders (Sanacora et al., 2017). Sanacora et al. recommended several components to the evaluation of clients for ketamine treatment; these include comprehensive diagnostic assessment, assessment of baseline severity, history of antidepressant treatment, decision-making on the specific physical examinations according to established guidelines depending on individual

clinical characteristics of the client, review of medical and psychiatric records, and informed consent.

The American Psychiatric Nurse Association (APNA) advises that ketamine should not be used for initial psychiatric treatment and should only be considered after failure of standard psychotherapy treatment or antidepressant trials (2022). Ketamine therapy exclusions include active substance abuse, history of psychosis, current pregnancy, history of increased intracranial pressure, uncontrolled hypertension, unstable cardiovascular disease, or a previous negative response to ketamine (APNA, 2022). There were no current published guidelines outlining the specific training requirements for clinicians administering ketamine at the time of this study (Sanacora et al., 2017). Most clinical trials have documented the ketamine dose administration of 0.5mg/kg per 40 minute IV, consistent with the original report by Berman et al. in 2000 (Sanacora et al., 2017).

The standard operating procedure throughout the ketamine infusion duration should include frequent assessment of the client's mental and physical state, such as respiratory status, blood pressure, heart rate, and consciousness, or other method for assessing responsiveness (Sanacora et al., 2017). The treatment setting should be such that the provider may sufficiently monitor the client to be able to provide immediate care if necessary. Nurses such as psychiatric mental health advanced practice nurses (APRNs) and psychiatric-mental health RNs, and certified registered nurse anesthetists (CRNAs) are working in collaboration with physicians, most notably anesthesiologists, to provide ketamine therapy services in a clinic setting for the treatment of chronic mental health

disorders (APNA, 2021). Most clinics utilize a 2–3-week course of ketamine delivered 2-3 times per week, with a total of six ketamine infusions per cycle (Sanacora et al., 2017). Clients may opt for additional infusions, considered *boosters*, which may occur every 1-2 months or longer following the initial six infusion cycle, but the recommendation for booster varies, based on client self-report of depression severity and discretion of ketamine provider (InnovativeKetamine.com, 2021).

Ketamine-Assisted Psychotherapy

The dissociative quality of ketamine provides an "extraordinary opportunity" for accompanying psychotherapy (KAP; Wolfson & Hatelius, 2016; p. 340). KAP softens the psychological defenses, liberates the mind from depressive mood states, obsession, and fear, and is helpful in reducing the severity of responses to recollection of traumatic events in one's life (Wolfson & Hatelius, 2016). KAP protocol has been developing and evolving since roughly 2013, and experts have not yet arrived at a consensus for procedures and protocol (Dore et al., 2019). Over time however, analysis of available data, especially from patient self-report measures, have contributed to the continued development of protocol for KAP (Dore et al., 2019).

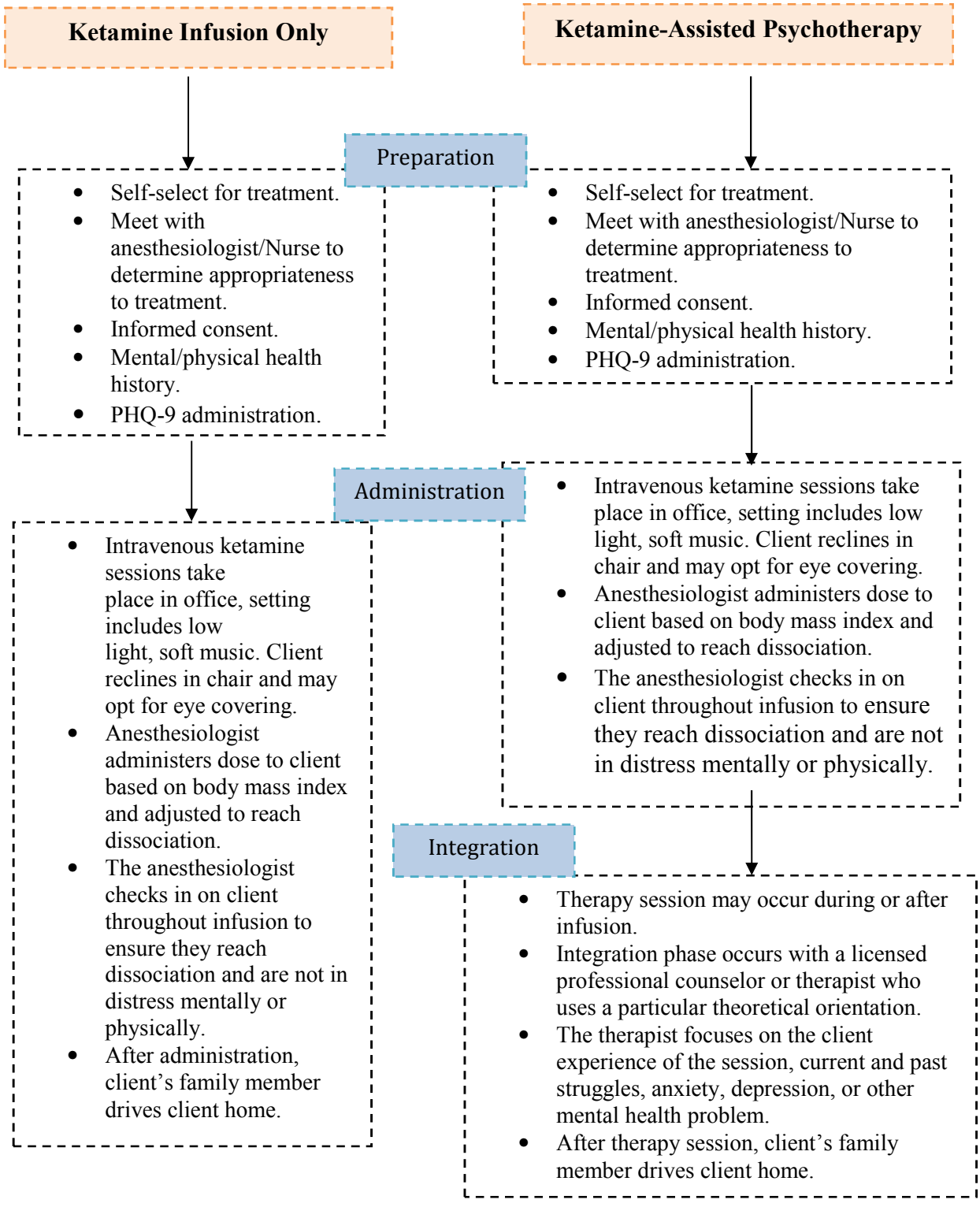
Dore et al. (2019) conducted the first analytic study on KAP. I have confirmed via personal communication that the ketamine clinic uses similar protocol and screening procedures as is used by Dore et al. for KAP. Dore et al. presented the stages as preparation, administration, and integration in KAP. Preparation includes the anesthesiologist/nurse administering various tests to the patient such as blood work, height, and weight. The patient also signs consent forms. Administration phase involves

the patient sitting or lying down for the IM, IV, or other route of administration of ketamine; music may be played at this time (Dore et al., 2019). Integration phase takes place during or after the administration of ketamine with a licensed professional counselor or therapist who uses a particular theoretical orientation such as: CBT, ACT, DBT, EFT, or another orientation. The content of KAP is similar to an outpatient therapy session; the therapist focuses on the client experience of the session, current and past struggles, anxiety, depression, or other mental health problem.

As seen in Figure one below, there are three phases, the first two are shared with the protocol for clients who receive ketamine infusions only.

Figure 1.

Protocol for Ketamine Infusion Only vs. Ketamine-Assisted Psychotherapy



KAP is performed with the goal of assisting the client in alleviating the debilitating depression they are experiencing. The formats of KAP may often include processing past and current traumas, as ketamine works by reducing the client's emotional resistance and lessening defensiveness (Wolfson, 2016). Other procedures and goals for KAP may include assisting the client in experiencing a new, compassionate, open, and creative connection to the self (Wolfson, 2016). Psychotherapeutic tools and techniques used may be diverse, such as exposure or CBT, but all KAP should be supportive in nature with interpersonal warmth, trust, natural belief in healing, and positive regard to help clients feel safe and secure (Becker, 2016).

Becker (2016) discussed how the mechanisms of ketamine in the brain and the conscious effects of the drug produce themes outlining phenomenological and meaningful experiences for subjects. The transpersonal nature of KAP often highlights themes such as out-of-body experience, awareness of becoming a nonphysical being, emotionally intense visions, feelings of ego dissolution, visitations to mythological realms of consciousness, reexperiencing birth process, and a feeling of cosmic unity with the universe or God (Becker, 2016). Other themes gleaned from in-depth analysis of interviews include dissociation, relaxation, heightened sensory perception, uplifted mood, feeling like 'true self', renewed motivation, communicating with others, increase in positive thoughts, reduction in SI, and life changing impact (Griffiths et al., 2021). In a qualitative and quantitative KAP study by Summer et al. (2021) themes included loss of control, perceptual changes, emotional and mood changes, changes to perspective on life and problems and depression.

The first study demonstrating KAP's effectiveness within an analytic framework was conducted by Dore et al. in 2019. Dore et al. conducted pre and post surveys using the Beck Depression Inventory, Hamilton Anxiety Scale, Patient Health Questionnaire, Childhood Resilience Scale, and Adverse Childhood Event Score for 235 clients of three distinct practices which use similar ketamine and KAP practices. Dore et al. suggested that KAP demonstrated significant decreases in anxiety and depression as seen in the surveys, and number of sessions was positively correlated with improvements in depression scales. These findings were true especially for clients with significant symptom burden and for older clients (Dore et al., 2019).

While there are limited published studies to demonstrate KAP's effectiveness using large sample sizes, case studies and studies using smaller sample sizes are available. Halstead et al. (2021) conducted a case study report on the results of utilizing KAP for a child diagnosed with treatment-resistant PTSD as a result of experiences of racism and sexual abuse. The ketamine infusions paired with psychotherapy led to a decrease in symptoms which was maintained over the course of four months. Summer et al. (2021) provided a qualitative and quantitative analysis on KAP. Thirty-two clients diagnosed with MDD were administered ketamine infusions in a crossover design with an active placebo. Clients' experiences were measured using the MADRS and altered states of consciousness questionnaire. Summer et al. found that reduction in depression on the MADRS is correlated with the altered states of consciousness survey. While Dore et al., (2019), Halstead et al., and Summer et al., demonstrated positive treatment responses to

KAP, Griffiths et al. (2021) found that some clients did not experience antidepressant effects.

In this literature review, I focused on research surrounding ketamine, KAP, and depression. The research on KAP is limited, and to date only one study (Dore et al., 2019) has been conducted using an analytic framework with over 235 subjects. This study yielded positive outcomes for KAP in alleviating symptoms of MDD. Other studies on KAP included in this literature review focused on the protocol, potential benefits, and mechanisms of action which may contribute to positive treatment effects. The literature on ketamine infusions indicates alleviation of depressive symptoms when there are several infusions (usually six in a cycle occurring over 2-3 weeks) and this effect was sustained for several weeks.

Summary and Conclusions

Major themes in the literature include the content, nature, and experiences of subjects who are undergoing KAP. The procedures of KAP are various and can include components of structure-based treatments such as CBT, as well as treatments focusing on meaning making and spiritual enlightenment such as transpersonal counseling. Themes include out-of-body experiences, emotionally visual experiences, mythological visions, and cosmic unity. Despite the reported positive effects, only one study exists in the professional literature which validates the use of KAP in treatment of MDD through use of a quantitative analysis.

There is very little evidence on the efficacy of KAP in the treatment of depression. Additionally, limited research has been conducted exploring the sustained

positive effects of ketamine. These findings elucidate the problem posed; practitioners across the United States are providing KAP without adequate evidence supporting its efficacy; this contrasts with the ACA *Code of Ethics* which advises counselors to use empirically supported treatments or theories for mental health conditions (C.7.a.; ACA, 2014).

Chapter 3: Research Methods

Introduction

The purpose of this quasi-experimental quantitative study is to determine if there was a statistically significant difference in changes in depression from baseline to immediately following treatment as measured by the PHQ-9, among clients receiving ketamine infusions compared to clients receiving KAP. The major sections of this chapter include an explanation of the research design and rationale, methodology, data analysis plan, threats to internal and external validity, and ethical procedures.

Research Design and Rationale

The independent variable in this study is the presence of ketamine infusion with or without KAP. The dependent variable is the PHQ-9 scores at intake, immediately following the sixth (final) ketamine infusion, and one month following the last ketamine infusion. I plan to control for baseline depression severity as a covariate. The research design for this study includes the quasi-experimental design. This design is appropriate to answer the research questions as the purpose is to evaluate the effectiveness of ketamine infusion and KAP without the use of randomization. As a part of the standard practices of the participating clinic, the ketamine providers collected these data in its naturalistic setting. It was not possible to conduct this study using randomization as clients elected to this treatment. I used their subjective scores for the proposed analysis. KAP protocol is continually developing, especially from analysis of research using client self-report measures (Dore et al., 2019).

The purpose of this quasi-experimental retrospective analysis is to analyze client self-report measures of depression severity as indicated on the PHQ-9. This is a quasi-experimental design as I am comparing the treatment of two different treatment groups without the use of randomization. I used archival data from a ketamine clinic which treats clients struggling with depression.

Methodology

Population

I used archival data from a ketamine clinic located in the southeastern United States for this study. The population included were clients who have been diagnosed with MDD receiving outpatient treatment for depression. Clients who were provided ketamine infusions agreed that they had received two rounds of antidepressant medications at sufficient dose and duration with no treatment success. The sample included 73 subjects. The target population included adult clients who were 18 years and older at the time of ketamine infusions. I included clients who sought out and elected for ketamine or KAP on their own volition. There were no recruiting procedures, as I used archival sampling methods. As previously mentioned, the clinic does not collect data on race/ethnicity; this is a proposed limitation of this study.

Sampling and Sampling Procedures

The sampling method was nonprobabilistic and the specific subcategory includes subjective or judgmental sampling, wherein archival data was chosen and analyzed based on the inclusion criteria for the study. The inclusion criteria were identified as data

indicating infusions alone or KAP, a PHQ-9 baseline score and at least one additional PHQ-9 score (i.e., end of treatment or one month follow-up), and a diagnosis of MDD.

The strengths of this sampling method and subcategory included the researcher's ability to select clients based on meeting inclusion criteria and excluding clients who did not meet criteria. Other strengths included the ease with which the sample was collected and that it essentially consumed minimal time for collection. Disadvantages of this sampling method were that due to this method not being random from the population, inferences from the analysis only applied to the specific group being studied, and that this process may be more prone to researcher bias. It may be viewed as being a threat to generalizability when being applied to large population groups.

I collected this sample by use of archival data from a ketamine clinic. The ketamine clinic collected and stored client data on Osmind.org, a website and app which collects and tracks client mood and PHQ-9 scores, among other mental health assessments. This clinic entered into a data use agreement with me as the researcher for this study which provided access to clients' scores via a deidentified dataset. The inclusion criteria for data in this study included those clients who are over 18 years of age at the time of ketamine infusion, and those who were diagnosed with MDD. Exclusion criteria included those clients who had not received at least six ketamine infusions.

As this was an archival analysis, I did not have control over the sample size (see Aberson, 2015). A commonly used standard for sociological research is to use .80 for power, which I used for this analysis (Aberson, 2015). The *a priori* level I have set for this study is the commonly accepted .05 level (Aberson, 2015). A large study by Cuijpers

et al. (2014) compared the effects of antidepressant medications alone and antidepressant medications combined with psychotherapy used a confidence interval of 95% and moderate effect size for Hedges g at .43 in favor of the combined treatment.

In their study on power analyses for ANCOVA designs, Shieh (2019) found that the minimum sample size to run a repeated measures ANCOVA comparison of two groups was 48, which will require at least 24 clients per client group. This estimate used moderate effect sizes. Based on Shieh's article, I used a minimum of 24 clients in each treatment group, namely, clients who were provided ketamine infusion alone versus clients who were provided ketamine infusions with assisted psychotherapy.

Procedures for Recruitment and Participation of Archival Data

For the study sample, I included clients who sought out and elected for ketamine or KAP on their own volition. There were no recruiting procedures, as I used archival sampling methods. The demographic information I collected included age of the client, diagnosis, diagnosed by whom, DOB, gender, referral source, past medical history, whether client received KAP, the dates of each of the six infusions, and the dates of boosters, as well as any medications the client was currently taking. The information I collected is from the ketamine clinic via a deidentified dataset, from which clients provided informed consent for services.

The ketamine clinic offered its clients the option to enroll in an online and app-based software which sends daily mood subjective scoring, as well as weekly reminders to fill out PHQ-9 assessments. The app provided a graph displaying the client's mood changes throughout their treatment. Should the client decline continuing with infusions,

the ketamine providers reach out via telephone to provide support, resources, and referrals per client request. The client was advised that a full ketamine treatment cycle includes six infusions over the course of 2-3 weeks, but clients can opt out of further infusions if necessary or requested. I only included clients who have completed six infusions, as most clinics utilize a 2–3-week course of ketamine delivered 2-3 times per week, with a total of six ketamine infusions per cycle (Sanacora et al., 2017).

Procedures for Gaining Access to Archival Data

I used archival data taken from a ketamine clinic for this study. I used data which came from clients of the ketamine clinic who have been referred by their primary care provider, therapist, another provider, or internet search. Clients' self-report data was collected by the ketamine clinic which offered clients to document PHQ-9 and subjective mood scores on an app which provided logging of these scores and a graph to illustrate client progress over the course of their treatment and beyond treatment. Clients could choose to opt out of logging their subjective mood and PHQ-9 scores and still participate in ketamine infusions and psychotherapy. I have access to the deidentified data set through a data use agreement with the ketamine clinic, which provided this dataset to me at the time of collection. The institutional review board approval number for this study is #07-14-22-0984650.

Instrumentation

The instrument which the ketamine clinic used to measure depression severity was the Patient Health Questionnaire (PHQ-9). The PHQ-9 was developed in 1999 by Kurt Kroenke and his colleagues at Columbia University and was originally created to be

a self-administered diagnostic screening for depression severity (Blackwell & McDermott, 2014). The questionnaire consists of nine items which assess for the symptoms of MDD as classified by the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV-TR; American Psychiatric Association [APA]), though it is still theoretically consistent with the fifth edition of the manual (Blackwell & McDermott, 2014). The total assessment takes roughly five minutes to be completed and can be administered repeatedly to reflect the decline in reported symptoms (Blackwell & McDermott, 2014). The PHQ-9 is available in public domain and freely downloadable; permission is not required to distribute or reproduce the PHQ-9 (Blackwell & McDermott, 2014).

The PHQ-9 was one of the assessment tools offered to the clients by the ketamine clinic as a method by which the client can report their current symptoms as well as view their previous scores and progress in treatment. The clients were offered to download the Osmind app which prompts the user to answer the PHQ-9 assessment questions as well as a daily subjective mood score.

The PHQ-9 is a valid and reliable measure for assessing depression severity (Sun et al., 2020). Sun et al. evaluated the validity and reliability of the PHQ-9 and found that the PHQ-9 scores have a high internal consistency and high test-retest coefficient after two weeks. The correlation coefficient between each item score and the total score of PHQ-9 indicated a strong correlation, ranging from .572 to .813 (Sun et al., 2020). Sun et al. concluded that the PHQ-9 is a rapid, effective, and reliable measure in screening the severity of depression.

Constantini et al. (2021) analyzed 42 articles from several dozen countries on the validity and reliability of the PHQ-9 in primary care settings in clients older than 12 years old, and articles ranging from 1995 to 2018. The overall sensitivity of the instrument ranged from 0.37 to 0.98, positive predictive value from .09 to .92 and negative predictive value from .8 to 1. Constantini et al. determined that the PHQ-9 is validated and recommended for use in a two-stage screening process for depression severity.

Operationalization of Constructs

The key study variables included the independent variable: ketamine infusion with or without KAP. The dependent variable is PHQ-9 score at baseline and immediately following the sixth and final infusion. I included baseline depression severity as a covariate in this analysis.

KAP refers to a therapist, either licensed clinical social worker, licensed professional counselor, licensed marriage and family therapist or clinical psychologist or associate clinician providing therapeutic support as the client undergoes the ketamine infusion procedure. The content of KAP is similar to an outpatient therapy session; the therapist focuses on the client experience of the session, current and past struggles, anxiety, depression, or other mental health problem. KAP has been in clinical development for several years and a consensus on protocol and procedures is evolving (Dore et al., 2019). KAP is typically provided for one hour either during the infusion or for one hour following the infusion.

The American Psychiatric Nurses Association (APNA) provides considerations for ketamine providers. Ketamine treatment is recommended for adults with moderate to

severe depression, and for clients who have no sustained change following adequate antidepressant trials, different medication combinations, and/or ECT or TMS trials (APNA, 2022). In addition, the APNA advises that clients have demonstrated no sustained change in CBT or individual psychotherapy to be eligible for infusions (APNA, 2022). The APNA suggests exclusions of ketamine infusion when clients are experiencing active substance abuse, pregnancy, uncontrolled hypertension, and cardiovascular disease. In addition, the APNA advises against providing ketamine to clients who have had history of psychosis, intracranial pressure, or history of negative response to ketamine. Ketamine infusions are administered to the client by an anesthesiologist or anesthetist nurse on site. Ketamine is administered in a dose of 0.5/mg/kg, but some patients respond to doses as low as 0.1 mg/kg and others require higher doses, such as up to 0.75mg/kg (Andrade, 2017). The infusion is typically administered over the course of 40 minutes, but safety and efficacy has been demonstrated in sessions ranging between 2 and 100 minutes (Andrade, 2017).

Baseline severity refers to the score of the outcome measure prior to treatment (Nunes et al., 2011). Covariation for baseline severity of the outcome measure should be considered for inclusion in studies which aim to contribute to literature on evidence-based treatment (Nunes et al., 2011). Baseline severity has been found to be strongly associated with outcome in studies (Nunes et al., 2011). There is no required baseline severity to qualify for a ketamine infusion, only diagnosis of MDD and failure to respond to at least two rounds of antidepressant medications of sufficient dose and time; this is considered TRD (Zhdanava et al., 2021).

The Patient Health Questionnaire (PHQ-9) is a valid and reliable instrument for the assessment of depression severity. The PHQ-9 is sensitive to changes in depression over time points (Cameron et al., 2008; Lowe et al., 2004). For the purposes of this study, I will use the PHQ-9 scores at intake and immediately following the sixth, and final, infusion. The assessment tool has cut-offs for the severity of depression, including 5, 10, 15, 20 which represent classification points for mild, moderate, moderately severe, and severe depression, respectively (Inoue et al., 2012). The PHQ-9 provides the following instruction to the client: "Over the last 2 weeks, how often have you been bothered by the following problems?" An example item has been provided below:

"Feeling down, depressed, or hopeless?"

Not at all= 0

Several Days: +1

More than half the days: +2

Nearly every day: +3

The scale of measurement for the PHQ-9 is ratio, because there is a proportionate interval between data points, with a true zero.

Client Selection

At the clinic setting for this study, clients self-selected for ketamine infusion, and/or KAP. Some clients are referred by their primary care provider, therapist, friend or family member, or may have found the ketamine clinic via internet search. The ketamine clinic offers KAP to all clients who contact the clinic to be scheduled for infusions, clients self-select their preferred methods of treatment. Clients are required to have a

mental health diagnosis from a licensed professional to be eligible for treatment. Clients must agree that they have received two rounds of antidepressant medications at sufficient dose and duration with no treatment success; this is considered TRD (Zhdanava et al., 2021).

Ketamine Infusion and Ketamine-Assisted Psychotherapy Protocol

Since roughly 2013, protocol for KAP has been developing and a consensus on procedures continues to develop and has not yet been established (Dore et al., 2019). However, for the purposes of this study, I used the stages of KAP including preparation, administration, and integration originally outlined by Dore et al. (2019). I have confirmed via personal communication that the ketamine clinic site for this study uses similar protocol as is used by Dore et al. for KAP. Preparation includes the anesthesiologist/nurse administering various tests to the patient such as blood work, height, and weight. The patient also signs consent forms. The administration phase involves the patient sitting or lying down for the ketamine infusion, music may be played at this time (Dore et al., 2019). The ketamine clinic adjusts the dose for the client to reach dissociation. In contrast to MAPS protocol for psychedelic-assisted psychotherapy which calls for PAP to occur during the administration of the medicine (Mithoefer, 2015), KAP sessions may occur during or after the ketamine infusion. The integration phase takes place with a licensed professional counselor or therapist who uses a particular theoretical orientation such as: CBT, ACT, DBT, EFT, or another orientation. The content of KAP is similar to an outpatient therapy session; the therapist focuses on the client experience of

the session, current and past struggles, anxiety, depression, or other mental health problem.

Ketamine infusion protocol includes the same preparation and administration stages as for KAP, however, there is no integration phase wherein the licensed clinician provides psychotherapy for the client. Following administration, the client is assessed for any markers of physical distress or instability and is driven home from the clinic by a friend or loved one. Clients undergo the same infusion dosage, duration, and frequency as clients who opt for assisted psychotherapy.

Data Analysis Plan

The statistical software I used for this analysis is Statistical Package for the Social Sciences (SPSS). Before delving into the statistical analysis once the archival data has been entered into SPSS, I examined the quality of the data which I had collected for this analysis. One of the important considerations for data cleaning included looking for outliers in the data. For example, should the client indicate very mild or severe depression on the PHQ-9, at the initial intake, immediately following the last infusion, I investigated the extreme number in the data set (ACAPS, 2016).

Collecting or entering the data required repeated cycles of screening for lack of or excess of data or outliers, whether data were missing, or extreme records were present (ACAPS, 2016). I used two separate Excel sheets to maintain the original and edited the second excel sheet to monitor changes (ACAPS, 2016).

Missing data refers to answers which have been omitted by the client in the research (ACAPS, 2016). The most conservative course, and the one in which I took, was

to leave the data unchanged, accepting the missing data point as a valid response (ACAPS, 2016). I did not correct or change the data from the respondent, nor was I able to remeasure the respondent's answer, as I used archival data. Regarding PHQ-9 data, I used the method of excluding cases pairwise in SPSS. Inclusion criteria included indicating whether subjects received infusions alone or KAP, a PHQ-9 baseline score and at least one additional PHQ-9 score (i.e., end of treatment or one month follow-up), and a diagnosis of MDD.

Research Questions and Hypotheses

The research questions and hypotheses were as follows:

RQ – Was there a statistically significant difference in change in depression, as measured by the PHQ-9, from baseline to end of sixth and final infusion, between clients receiving ketamine infusions compared to clients receiving ketamine-assisted psychotherapy after controlling for baseline depression severity?

H_0 - There was not a statistically significant difference in change in depression, as measured by the PHQ-9, from baseline to end of sixth and final infusion, between clients receiving ketamine infusions compared to clients receiving ketamine-assisted psychotherapy after controlling for baseline depression severity.

H_a - There was a statistically significant difference in change in depression, as measured by the PHQ-9, from baseline to sixth and final infusion between clients receiving ketamine infusions compared to clients receiving ketamine-assisted psychotherapy after controlling for baseline depression severity.

I used Quade's Rank ANCOVA with repeated measures for this data analysis. The ANCOVA with repeated measures statistical test measures the mean of two or more variables based on repeated observations while controlling for a baseline covariate (Wan, 2019). The parametric ANCOVA is based on the assumption that the dependent and covariate is linear and the relationship between the dependent variable and the covariate does not differ across the conditions in the experiment (Schneider et al., 2015). In conducting an ANCOVA, it is assumed that the variables have distribution shapes which are close to normal, that the relationship between the variables are linear, and that the variance is homogenous across groups (Warner, 2013). ANCOVAs are also based on the assumption of no treatment by co-variate interaction or homogeneity of regression (Warner, 2013).

Once I had cleaned the data and sorted it in SPSS, I determined that the infusion only group scores were not evenly distributed, and therefore, I used Quade's Rank ANCOVA which is better suited for nonparametric statistical analyses. All other assumptions for this analysis including homogeneity of regression and variance were met. According to McSweeney and Porter who compared rank transformed ANCOVA to parametric ANCOVA, the rank transform approach was only slightly less powerful than the parametric ANCOVA design (1988). Furthermore, nonparametric tests for the same designs are generally more powerful than their parametric counterparts when parametric assumptions are violated (McSweeney & Porter, 1988).

I began by testing the assumptions and preliminary data screening included ensuring that all distributions were approximately normal with no extreme outliers and

that all relations between pairs of variables and covariates are somewhat linear (Warner, 2013). I tested this by running basic data checks in SPSS including histograms and descriptive statistics to provide information on the frequency distribution and sample size. Then I ran regression analyses for the separate groups: those who have received ketamine infusions versus those who have received KAP. Finally, by running the ANCOVA in SPSS, I tested for the assumption of homogeneity of the dependent variable (Warner, 2013). As states previously, because assumptions of normal distribution of the ketamine infusion only group was violated, I changed the chosen statistical test to Quade's Rank ANCOVA to transform the original scores by replacing each observation in the dependent variable and covariate with its respective rank across all levels of the independent variable.

In ANCOVA designs, it is essential that the baseline score be adjusted, otherwise the estimated treatment effects may be skewed or biased (Clifton & Clifton, 2019). Extreme scores documented at baseline are much more likely to skew the results than lower baseline scores (Clifton & Clifton, 2019). To avoid bias in the treatment results, I included baseline as a covariate in this analysis.

Threats to Validity

As this was a retrospective study, data which I included in this study had been previously collected by the ketamine clinic. This study may have higher external validity than true experimental studies, due to its applicable nature to the natural world. Rather than the results being brought out of laboratory settings, clients opted into having ketamine infusions or KAP out of their own volition.

In contrast to experimental design, a disadvantage of quasi-experimental design is the lack of randomization of clients and use of a control group. This limits the ability for the researcher to justify cause-and-effect conclusions from the study. However, quasi-experimental designs are being increasingly employed in research to achieve a greater balance between external and internal validity (Handley et al., 2018).

Considerations for external validity included sampling bias, history, and experimenter effects. The sample included clients with MDD who had completed six ketamine infusions. This would exclude the clients who had elected for ketamine infusions who have other mental health diagnoses, those who have completed less than six infusions, and those who were under 18 years of age at the time of ketamine infusion. As there were several therapists providing KAP, me included, the characteristics and effectiveness of each of the therapists may have affected the outcomes of the treatment and thus clients' responses to the PHQ-9. Controlling for individual counselor characteristics, including differences in effectiveness between theoretical orientations, was beyond the scope of this study.

As previously discussed, it is possible that other events which have occurred in the clients' lives may have affected the PHQ-9 scores, and it was therefore not plausible to say that all changes in PHQ-9 scores from baseline to immediately following the sixth and final infusion were due solely to the effects of ketamine infusions or KAP. The Hawthorne effect may have impacted the internal validity of this research. Defined as the change in subject responses or behavior consequent to awareness of being studied in research, the Hawthorne effect has been found to influence subject responses due to being

observed and having behavior assessed (McCambridge et al., 2014). Clients become concerned about social desirability and researcher expectations and may change their responses on self-report measures (McCambridge et al., 2014). This was a proposed limitation associated with using self-report instruments in research.

Ethical Procedures and Considerations

Due to the use of archival data for this study, the ethical concerns appeared to be minimal. The ketamine treatment center and I had entered into a data use agreement wherein I will be provided a deidentified data use agreement. Clients' data was collected by the ketamine clinic which offered the clients the option to document PHQ-9 and subjective mood scores on an app which provided logging of these scores and a graph to illustrate client progress over the course of their treatment and beyond treatment.

I had a dual role in the research, as I had likely provided KAP to some clients who had provided their PHQ-9 scores used for this research. I managed conflict of interest as I did not reveal my role as a researcher. I did not disclose to clients my hypothesis for this research project. The ketamine clinic released the dataset to me as the researcher, specifically for the purposes of archiving and analysis for this project.

I ensured client privacy by using a separate list of code-to-name matchups and using client codes to label the data which was collected. The agency attains written consent from each client prior to providing ketamine infusions. The identity of the ketamine clinic will not be disclosed for this project to further mask the identity of the clients.

The data I exported into excel was deidentified and remained confidential. I stored data in an excel document on my computer, which I protected with a password, and access into the computer required a password. Only I as the researcher, and the Walden University faculty which were involved in this project viewed the raw data. As the researcher, I provided the results of the study to the ketamine clinic in a document between 1-2 pages in length. I plan to purge the excel sheet which contained the deidentified dataset information from my computer five years following IRB approval for this research project. I completed the necessary ethical training to conduct this archival analysis study. At the time of data collection and throughout, I fully accepted the responsibility for the ethical conduct of this research project and continue to be committed to protecting the human clients as required by state and federal law and regulations.

An important ethical consideration for this research was related to access to the ketamine infusions. Persons who live in a poor or low-income household have been linked to increased risk for mental health problems which can persist throughout the life span (Hodgkinson et al., 2017). Despite the need for mental health services, persons of lower socioeconomic status are least likely to be provided high-quality care (Hodgkinson et al., 2017). The *Access to Care* Data from Mental Health America (MHA) in 2018 reported 55.8% of adults with a mental illness did not receive mental health treatment, with access slowly improving from 59% in 2011. This figure represents the individuals who are reporting an unmet need for their mental health, who are seeking treatment and are facing barriers to getting the help needed (MHA, 2018). Systemic barriers to

accessing care were identified as: lack of insurance or adequate insurance, lack of available treatment types such as inpatient or individual therapy, lack of available providers, and insufficient finances to cover the costs of treatment (MHA, 2018). It is possible that lower socioeconomic status clients are unable to afford ketamine infusions, despite the need for adequate mental health treatment for this population. It is possible that fiscal privilege increases access to effective and innovative treatments.

Summary

The purpose of this quantitative study was to determine if there was a statistically significant difference in changes in depression from baseline to the sixth and final infusion as measured by the PHQ-9, among clients receiving ketamine infusions compared to clients receiving KAP. In this chapter, I described the research design and methodology. I discussed the specific procedures of conducting an archival data analysis and the subsequent statistical tests I ran as well as the alpha level, effect size, and minimum number of clients for this study to have determined valid inferences from the data. I also presented the threats to external and internal validity to this quasi-experimental design and addressed the ethical procedures necessary when conducting archival data analysis with human clients. In the next chapter of this dissertation, I will present the findings of this research.

Chapter 4: Results

Introduction

The purpose of this quasi-experimental quantitative study was to determine if there is a statistically significant difference in changes in depression from baseline to immediately following treatment as measured by the PHQ-9, among clients receiving ketamine infusions compared to clients receiving KAP. For the first phase, I conducted a Quade's Rank ANCOVA analysis to examine the differences of the mean values of the dependent variable (follow-up PHQ-9 score) while controlling for baseline (initial score), between clients who received ketamine infusion alone, versus those who have received KAP.

In the second phase of this analysis, I conducted a paired samples *t* test to examine the effects of each treatment group more closely from baseline to follow up. In this chapter, I list and discuss the data collection procedures, assumptions, and results of the statistical analysis. The research question and hypotheses for this study are as follows:

RQ – Is there a statistically significant difference in change in depression, as measured by the PHQ-9, from baseline to end of treatment, between clients receiving ketamine infusions compared to clients receiving ketamine-assisted psychotherapy after controlling for baseline depression severity?

H_0 - There is not a statistically significant difference in change in depression, as measured by the PHQ-9, from baseline to end of treatment, between clients receiving ketamine infusions compared to clients receiving ketamine-assisted psychotherapy after controlling for baseline depression severity.

H_a - There is a statistically significant difference in change in depression, as measured by the PHQ-9, from baseline to end of treatment, between clients receiving ketamine infusions compared to clients receiving ketamine-assisted psychotherapy after controlling for baseline depression severity.

Data Collection

The private practice clinic provided a deidentified list of the clients who have received KAP and the dates and times of the appointments. The ketamine clinic provided a deidentified dataset which included all the clients who have received ketamine infusions, some demographic information including gender, date of birth, and diagnosis. I then matched the subjects based on date and time of the ketamine infusion with the clinic, and KAP with the private practice, between the two datasets. Unfortunately, the ketamine clinic and private practice did not list race and ethnicity as a variable when the dataset was provided; the clinic does not routinely collect these demographic variables and therefore were unavailable for this analysis. Other information which I included in the dataset from the ketamine clinic were: date and time of ketamine infusions and dates and scores on PHQ-9 assessments.

I examined an initial dataset from the ketamine clinic in June 2021 and a second up-to-date dataset in August 2022 (including all the data which the clinic has collected since its inception in May 2020), which yielded a total of 354 subjects. Out of 354 subjects, 228 did not provide at least one PHQ-9 score, therefore 126 have provided at least two scores on the PHQ-9 assessment. Out of the 126 subjects, nine subjects were excluded for not receiving a full cycle of six ketamine infusions, 16 were excluded for

not having an MDD diagnosis on file, 28 were excluded as they did not have a baseline PHQ-9 score recorded before receiving the infusion. Seventy-three subject cases remained after data cleaning which had both baseline and immediately following sixth infusion PHQ-9 scores. I compared these 73 cases which met the criteria for inclusion in this study with the deidentified dataset from the private practice which provides KAP, and matched 24 cases that had psychotherapy in the hour concurrently or immediately following each infusion.

Unfortunately, 18 subjects out of the 73 did not provide one month follow-up scores. My initial research question included analyzing changes in depression severity from baseline, immediately following treatment, to one month follow-up between infusion only and KAP groups. To meet the minimum sample size to conduct an ANCOVA of at least 24 subjects per group (Shieh et al., 2019), I excluded the one-month follow-up scores.

Out of the 73 cases, 24 subjects have received KAP, and 49 have received ketamine infusions only. The age range is 18 to 69, with a mean age of 40.51. The total sample is 37% male, 60.3% female. One subject was transgender male (1.4%) and one subject was transgender female (1.4%).

I consolidated the datasets based on time and date of ketamine infusion and KAP sessions and transferred the dataset into SPSS with numbers assigned to each subject. I began the data cleaning processing including checking for numbers outside the norm for age or outside the range of values in the PHQ-9. I coded sex of subject as male =1, female =2, transgender male =3, transgender female =4. I ensured that minimum and

maximum values were within the possible range on each variable. I ensured that no missing cases exist in the dataset.

A total of three therapists provided KAP to the 24 subjects and were assigned to each subject on the deidentified dataset. One therapist is a 40-year-old male; he is a doctoral level licensed professional counselor with five years of post-licensure experience. The other two therapists who provided KAP in this study had a CBT orientation to treatment. One therapist is a female, pre-licensed social worker with two years of post-graduate counseling experience. The third therapist and author of this study is a female and had less than one year of post-licensure counseling experience as a professional counselor at the time of data collection.

Assumptions

I began by testing the assumptions for an ANCOVA design but found that an assumption was not met. I began by checking the linearity of the relationship between the dependent variable and the covariate. I ran the Shapiro-Wilk test which I found to be significant for the infusion only group (p=.018) and not significant for the KAP group. Thus, the assumption of linearity was violated. The skewness level for the infusion only group and the KAP group was .334 and .478, respectively. The kurtosis levels for the infusion only group and the KAP group was .668 and .918 respectively. Thus, skewness and kurtosis indicated normality. Other assumptions for ANCOVA design include the assumption of no treatment by covariate interaction that is required to meet homogeneity of regression slopes assumption; this appeared to be satisfied as I found it to be not significant at .159. Homogeneity of variances assumption is above .05 at .73 for baseline

and follow up is .186. Therefore, assumptions for homogeneity of variance and homogeneity of regression slopes were met. However, since the data for the infusion only group is not linear, I was justified in using nonparametric statistics.

According to Harwell and Serlin (1988), nonparametric ANCOVA models such as Quade's Rank ANCOVA is an alternative to parametric ANCOVA designs. Quade's Rank ANCOVA involves transformation of the original scores by replacing each observation in the dependent variable and covariate with its respective rank across all levels of the independent variable when one or more of the assumptions for a parametric ANCOVA design are not met (Harwell & Serlin, 1988). In Quade's Rank ANCOVA design, the procedures include separate transformations of the covariate (baseline PHQ-9) and dependent variable (follow up PHQ-9), substituting ranks instead of the original observations across treatment groups (Olejnik & Algina, 1984). The ranked data is then analyzed using the same procedures as used with a parametric ANCOVA (Olejnik & Algina, 1984). According to McSweeney and Porter (1988), who compared rank transformed ANCOVA to parametric ANCOVA, the rank transform approach was only slightly less powerful than the parametric ANCOVA design. Furthermore, nonparametric tests for the same designs are generally more powerful than their parametric counterparts when parametric assumptions are violated (McSweeney & Porter, 1988).

Quade's Rank ANCOVA Results

I conducted a quasi-experimental study to determine statistically significant differences between KAP and ketamine infusion alone on PHQ-9 depression severity scores at follow up while controlling for baseline score. There was not a significant

difference between the KAP group and infusion only group on follow up PHQ-9 score after controlling for baseline score, F (1,71) = 3.433, p = .068.

Paired Samples T Test Results

As a posthoc analysis, I conducted a paired-samples *t* test to compare PHQ-9 scores at baseline and follow up for subjects who received KAP and those who received ketamine infusions alone. For both treatment groups together (73 clients), there was a significant difference in the scores for the KAP and infusion only groups together at baseline (M= 17.71, SD= 5.638) to follow up scores (M= 7.89, SD=5.451), t(72)=16.325, p = >.001. The effect size was d = 1.770873.

Table 1

Paired Samples T Test

				95% CI for mean difference		
t	df	p	Mean Difference	Lower	Upper	Cohen's d
16.325	72	<.001	9.822	8.623	11.021	1.7708

Because I noticed a large difference between the pre and post scores between the two groups, I conducted a paired samples t-test to compare PHQ-9 scores at baseline and follow up for subjects who received KAP alone. Out of 24 clients, there was a significant difference in scores from baseline (M=16.17, SD= 5.322) to the follow up scores (m= 8.08, SD=4.643), t(23)=8.529, p= >.001. The effect size was d = 1.619.

I conducted a paired samples t-test to compare PHQ-9 scores at baseline and follow up for subjects who received ketamine infusions alone. Out of 49 clients, there

was a significant difference in scores from baseline (M=18.47, SD= 5.687) to the follow up scores (m= 7.80, SD=5.849), t(48)= 14.363, p= >.001. The effect size was d= 1.849.

Summary

In summary, according to a nonparametric Quade's Rank ANCOVA analysis, there was not a statistically significant difference in PHQ-9 depression severity scores between subjects who received ketamine infusions alone and those who received KAP between baseline initial intake and immediately following final infusion. However, results from a paired samples t-test indicated that KAP and ketamine infusion only groups are both statistically significant in reducing depression severity according to the PHQ-9 from intake to immediately following treatment. In Chapter 5, I provide interpretation of my findings in relation the existing research literature and within the context of the Common Factors theoretical framework. I also discuss limitations of this study, recommendations for continued research in ketamine treatment, and social change implications.

Chapter 5: Discussion, Conclusions, Recommendations

Introduction

The purpose of this retrospective quasi-experimental study was to determine if there is a statistically significant difference in changes in depression from baseline to immediately following treatment among clients receiving ketamine infusions compared to clients receiving KAP. In this quantitative analysis, I used archival sampling methods to examine PHQ-9 depression severity among subjects diagnosed with MDD who are receiving ketamine infusions or KAP. In this chapter, I describe the findings as well as relate them to existing literature on ketamine and KAP for MDD. I discuss the findings within the context of the common factors which was the conceptual framework for this study. I also discuss the limitations, recommendations for future research on this topic, and social change implications.

The key findings of this quantitative, retrospective study indicated that there was no statistically significant difference as measured by the PHQ-9 depression severity measure, between subjects who have received ketamine infusion vs. KAP, from baseline to end of treatment. There were significant changes from intake to end of treatment according to the paired samples t-test for both groups individually, yielding effect sizes of $d = 1.6$ and $d = 1.8$ for KAP group and ketamine infusion only group, respectively.

Interpretation of the Findings

Interest in ketamine and KAP as treatments for mental health conditions has increased dramatically from 2010 to 2020 (Walsh et al., 2022). Recent FDA approval of ketamine in the form of a nasal spray in 2019 and the broader reemergence of

psychedelic medicines as demonstrated by FDA trials for psilocybin and MDMA demonstrate the accelerating interest in psychedelics as healing medicines for mental health disorders (Walsh, 2022). However, differences in the effectiveness of ketamine infusion alone vs. KAP had not been investigated prior to this study.

The key findings of this quantitative and retrospective analysis are that there was no statistically significant difference as measured by the PHQ-9 depression severity measure, between subjects who have received ketamine infusion vs. KAP, from baseline to end of treatment. According to my findings from a paired samples t-test, there were significant reductions in depression severity from intake to end of treatment for both infusion alone and KAP groups, yielding effect sizes of $d = 1.6$ and $d = 1.8$ for KAP group and ketamine infusion only group, respectively. The findings of the current study indicated that while ketamine and KAP are highly effective treatments for MDD, there was no significant difference in effectiveness when compared to one another.

There has been limited research on the combination of intravenous ketamine (pharmacotherapy) and psychotherapy with the first analytic study performed in 2019 by Dore et al., which yielded statistically significant reduction in depressive symptoms. While there are several qualitative studies demonstrating the subjective benefits of KAP on perceived depression reduction and improved quality of life (Becker et al., 2016; Griffiths et al., 2021; Halstead et al., 2021; Summer et al., 2021), through the paired samples *t* tests, I found that intravenous ketamine and KAP each provide statistically significant reductions in depression from baseline to follow up. This study extends knowledge for the counseling field by using quantitative methods to analyze reductions in

depression severity from KAP which have been highlighted in the qualitative literature (Becker et al., 2016; Griffiths et al., 2021; Halstead et al., 2021; Summer et al., 2021) but very minimally in the quantitative literature (Dore et al., 2019).

The conceptual framework for this study was common factors. The common factors framework emphasizes the importance of commonalities among therapy treatment orientations in effecting positive change in clients' lives (Duncan, 2002). Rather than crediting specific techniques or tools that are beneficial in treating mental health disorders, thus emphasizing the differences between theoretical orientations to treatment, the common factors approach recognizes various commonalities among approaches as responsible for therapeutic success (Duncan, 2002). For example, Rogers (1957) identified the central tenets of psychotherapy as *unconditional positive regard, empathy*, and *honesty* (Rogers, 1957), while Jerome Frank (1983) identified the tenets as: *an emotionally charged confiding relationship, a healing setting, a rationale, a procedure requiring active participation in client and therapist with the understanding that it will be used to restore the client's health*.

The average decrease in depression severity for the KAP group was not statistically significant when compared to the ketamine infusion only group. Therefore, in this study, aspects of the therapeutic relationship within KAP as highlighted by the common factors approach did not contribute to a significantly different outcome as compared to the group of clients who did not receive therapeutic support. In sum, the relationship did not make a significant difference in depression severity reduction from baseline to follow-up. This finding is contrary to current literature which supports the use

of psychopharmacology and psychotherapeutic interventions combined as yielding superior outcomes than each intervention alone (Kamenov et al., 2017; Karyotaki et al., 2017, Blais et al., 2013).

However, as stated previously, both groups demonstrated statistically significant changes in depression severity as compared to baseline at intake. These findings are consistent with other findings in the literature, that highlight the effectiveness of ketamine infusions and KAP treatments and will help guide the integration of this treatment into therapeutic and psychiatric practice. Further research is needed to determine whether there is value in psychotherapy added to the infusion experience.

Limitations of the Study

There were several limitations to this study. In this study, I used nonprobability sampling methods, and clients were included based on their accessibility and availability to the infusions and accompanying psychotherapy. My sample was not random due to the archival sampling method and limited number of clients who met inclusion criteria for this study. Therefore, I was unable to determine if the population was well represented which is a limitation to generalizability.

Limitations also include lack of socioeconomic data including household income and demographic factors beyond age and gender. Ketamine is expensive and the infusions are not covered under insurance plans at this time. A cycle of infusions costs roughly $2,400 dollars, with accompanying psychotherapy the cost may be upwards of $3,200 dollars. This may exclude clients of lower income households. The cost of infusions and accompanying psychotherapy may serve as a limitation in generalizing the

results of this study to the general population as there may be some potential economic biases of privilege inherent with clients from higher SES backgrounds. Affordability and access to care is a major concern for both practitioners and clients who seek this treatment (Dore et al., 2019).

An additional limitation to this study is lack of comprehensive demographic data including race and ethnicity. The only demographic data collected by the ketamine clinic includes age, gender, past medical history, location in city and state, referral source, and mental health diagnosis; clients' race/ethnicity was not collected. As stated previously, racial and ethnic minorities experience poorer health outcomes, yet are not included in research studies as often as White people are (Center for American Progress, 2020; CDC, 2013). The lack of racial or ethnic identification was a proposed limitation for this study as no generalizations beyond the available sample demographics may be deduced on differences in depression ratings according to client race and ethnicity across ketamine infusion or KAP. Additional research which includes racial and ethnic demographic data of the population would be warranted as it relates to effectiveness of ketamine infusions and KAP.

In addition, the Hawthorne effect may have impacted the internal validity of this research. Defined as the change in client responses or behavior consequent to awareness of being studied in research, the Hawthorne effect has been found to influence client responses due to being observed and having behavior assessed (McCambridge et al., 2014). Clients become concerned about social desirability and researcher expectations

and may change their responses on self-report measures (McCambridge et al., 2014). This is a proposed limitation of using self-report measures in quantitative studies.

The sample only included clients with MDD who had completed six ketamine infusions. This excluded the clients who elected for ketamine infusions who have other mental health diagnoses, those who have completed less than six infusions, and those who were under 18 years of age at the time of ketamine infusion. The scope of this study included adults only, but it is important to note that ketamine clinics across the United States are also providing ketamine to adolescent clients for the treatment of TRD. The results of this study are applicable to adults only, however, previous research by Cullen et al., (2018) indicated the potential role of ketamine in the treatment of TRD for adolescents, especially those who report suicidality (Cullen et al., 2018). Further research should investigate effectiveness of ketamine infusions alone versus KAP for adolescents, as novel treatments for this population are urgently needed (Cullen et al., 2018).

As there were several therapists providing KAP, me included, the characteristics and effectiveness of each of the therapists may have affected the outcomes of the treatment and thus clients' responses to the PHQ-9. I described the clinician sample which included three professionals including two licensed professional counselors and one associate social worker. Despite this, controlling for individual counselor characteristics, including differences in effectiveness between theoretical orientations was beyond the scope of this study, yet would be important to identify in future studies whether there exist differences across theoretical approaches, degree and licensure, and years of experience providing KAP.

Recommendations

There are several strengths and limitations due to the nature of this study which pose some considerations for future research. This study used archival data from a small ketamine clinic in the southeastern region of the United States. I conducted this study without randomization, controlling, or excluding variables, which may contribute to high knowledge translation into clinical practice. Due to the retrospective nature of this study and use of archival data, it was not possible to utilize random sampling which would increase ability to generalize, by isolating and manipulating variables. Recommendations for further research that are grounded in the strengths of this study include continued research on the effectiveness of ketamine and KAP in real world settings. Allowing for randomization in highly controlled environments, while may be more costly, require increased time and may be more logistically challenging, would help to confirm ketamine and KAP's effectiveness. Large sample sizes also allow for greater investigation into validity and reliability in comparison to small samples studies which may require stringent parameters, and greater likelihood for type 2 errors. Additional considerations to increase study validity and reliability include determining study mortality or participant drop out.

One of the inclusion criteria for this study included diagnosis of MDD. However, only 10 out of the 73 subjects were exclusively diagnosed with MDD. Most clients in this study had comorbid diagnoses including generalized anxiety disorder, ADHD, PTSD, and alcohol use disorder. Future researchers may choose to exclude subjects with more than one diagnosis to increase internal validity and reliability. In addition, there was no

required baseline severity to qualify for a ketamine infusion, only diagnosis of MDD and failure to respond to at least two rounds of antidepressant medications of sufficient dose and time; this is considered TRD (Zhdanava et al., 2021). Future researchers may choose to include subjects based on a certain depression severity at intake to further contribute to the study's reliability and validity. Other considerations which were beyond the scope of this study include controlling for concomitant medications and physical health conditions.

Inclusion of race and ethnicity may contribute to a valuable investigation on effectiveness of KAP and ketamine infusions. The lack of racial or ethnic identification was a proposed limitation for this study as no generalizations beyond the available sample demographics may be deduced on differences in depression ratings according to client race and ethnicity across ketamine infusion or KAP. Future research is needed on optimal dose, route, and frequency that foregrounds accessibility for low income and marginalized communities which are already disproportionally affected by conditions for which this treatment may be effective (Walsh, 2022).

Recommendations for future research includes emphasis on developing KAP protocol in research and clinical work. For example, the *Multidisciplinary Association for Psychedelic Studies* has created a treatment manual for MDMA, and Yale has created a manual for mental health treatment using psylocibin. These manuals are focused on using one or two certain theoretical orientations, whereas common factors, the theoretical foundation of this study, focuses on commonality among theoretical orientations. More research is warranted to better specify therapeutic modalities best suited for KAP (Walsh,

2022). In future studies, researchers who hope to investigate the differences between ketamine and KAP, or how to bolster the effects of ketamine through psychotherapeutic methods, can conduct adherence tests to ensure that therapists are meeting certain standards in their approach and techniques used to be deemed the orientation they follow.

Ketamine's effects have been investigated in the literature with some researchers measuring residual effects 7-21 days after final treatment (Li, et al., 2022; Marcantoni et al., 2021; McMullen et al., 2021). However, it is unknown whether prolonged risks associated with long-term use of ketamine exist. Despite the limited adverse effects in short term usage, this prolonged use of ketamine remains an important consideration for future research (Walsh, 2022).

Implications

Social Change Implications

The findings from this research study strongly indicate that both ketamine and KAP are highly effective in reducing depression severity from baseline at intake to immediately following sixth and final infusion. The positive social change implications of this study include potential new treatment options for individuals who have been struggling with TRD. As stated previously, TRD affects between 20-60% of the population of clients diagnosed with psychiatric disorders (Howes et al., 2021). Zhdanava et al. (2021) noted that the number of adults diagnosed with TRD is 2.8 million or 1.1% of the United States population (Zhdanava, 2021). Traditional treatments often do not provide adequate symptom reduction leading to the treatment-resistant diagnosis (Akil et al., 2019; Rizvi & Khan, 2019), which has contributed to the need for new and effective

treatments. This study has contributed to the literature supporting the efficacy of these treatments.

An additional social change implication is that this study contributed to the literature on the effectiveness of ketamine by considering the critical problems faced by persons with treatment-resistant conditions and depressive disorders and highlighting the benefits of ketamine and KAP treatment. As stated previously, accessibility and equity are important in reducing barriers to access among marginalized or lower socioeconomic groups which are already disproportionally affected by treatment-resistant conditions (Walsh et al., 2022). While ketamine is a relatively new and developing treatment for TRD, it is expensive, between 400-2,000 dollars per infusion, not including KAP (KetamineClinicsDirectory.com, 2021). Ketamine infusions and KAP are not currently covered by health plans and has high out-of-pocket costs. Therefore, these treatments are not accessible to a large swath of the population. A potential positive social change impact of this study is that it can inform policy changes and establish need for insurance coverage of these treatment alternatives for depression, so that more people may benefit, especially those of low socioeconomic status and those already suffering from lack of effective and available treatments.

There are organizations which are working to make a difference in the broader and systemic level for ketamine access. The Ketamine Taskforce, created in 2019, was created by a group of ketamine providers and advocates who are lobbying and advocating for insurance coverage of ketamine services (Ketamine Taskforce, 2022). Osmind is a software company and Public Benefit Corporation which stores and tracks ketamine and

other psychedelic mental health assessments and patient information (Osmind, 2022). In early 2022, Osmind published the largest real-world analysis of ketamine infusion therapy for MDD (McInnes et al., 2022). Osmind conducts large research analyses through ORKA (Osmind Real-World Ketamine Analyses) with the goal of improving access of ketamine to persons struggling with mental health problems (Osmind, 2022). This research is currently being used by the Ketamine Taskforce to advocate for insurance coverage. Additionally, the Taskforce recommends that clients who receive ketamine services submit the McInnes (2022) article to their insurance company when seeking partial or full reimbursement.

Methodological, Empirical, and Theoretical Implications

The methodological implications from this study are varied. The findings from this study suggest that future research on KAP may include need for larger sample sizes and randomization to analyze different variables including demographics as well as theoretical orientation of clinician and years of experience. Larger sample sizes and randomization would address some concerns of this study related to validity and reliability and allow for greater generalizability to "real world" settings. Other considerations which were beyond the scope of this study include controlling for concomitant medications and physical health conditions.

It is worth noting that there are a few studies which have investigated the long-term benefits of ketamine infusions on depression severity (Li, et al., 2022; Marcantoni et al., 2021; McMullen et al., 2021). The researchers in these studies investigated the differences in depression reduction from 7 days to 21 days following last ketamine

treatment. From my search of the literature, there are no existing studies demonstrating the lasting effects of KAP. There is a need to identify the multimodality strategies which would prolong the therapeutic effects of ketamine, which includes psychotherapeutic approaches.

Due to the nature of this study, clients who had been diagnosed with MDD were included in the analysis, but this did not exclude subjects who had also been diagnosed with generalized anxiety disorder, ADHD, PTSD, alcohol use disorder, or another mental health problem. This study reflects what is occurring in the "real world" of those seeking treatment, which includes high rates of comorbid disorders alongside TRD. Most research on KAP focuses on its effects on depressive disorders alone, which may exclude relevant considerations for comorbidity in mental or physical health conditions which impact an individual's need for treatment. Considerations for future research include accounting for comorbidity to generalize findings to the "real world" settings.

Recommendations for Practice

Unlike the Multidisciplinary Association for Psychedelic Studies and the Psilocybin Assisted Therapy Association, ketamine does not have an association which has published protocols, standards for practice, or manuals, though there are several organizations who provide their own training and certification. The stages of KAP as outlined in this study, namely, preparation, administration, and integration were modeled after Dore et al. (2019). It is important for practitioners who are interested in conducting KAP to conduct sufficient review of the literature on the benefits and risks associated with treatment.

It is important to note that ketamine has not been found to benefit every client who seeks out this treatment. For example, some clients become nauseated, and some do not respond to ketamine even under high doses (Dore et al., 2019). Others struggling with rigid personality structures find entering the trance state, wherein dissociation may occur, extremely difficult and report yielding little sustained positive change in their symptoms (Dore et al., 2019). It is important for clinicians to provide a thorough informed consent and conduct the necessary mental and physical health assessments prior to treatment. It is also recommended that clinicians seek appropriate supervision and consultation to ensure adherence to ethical and legal standards for practice. While ketamine has been used in much higher doses for medical purposes in emergency rooms and battlefields for several decades prior to mental health treatment, the American Counseling Association calls for clinicians to remain adequately trained and knowledgeable in the specific areas of their practice (A.9.b.; American Counseling Association, 2014), actively working to prevent physical or psychological harm to our clients (C.2.a; American Counseling Association, 2014). Recommendations for practice include staying abreast of current research on KAP, safety precautions, and published protocols to ensure successful treatment, as well as engaging in supervision and consultation should a clinician begin to integrate KAP into their clinical work.

Conclusion

Ketamine infusions and KAP are evolving and unique methodologies in the treatment of TRD. Over the course of the last decade, research on the effectiveness of these treatments is increasingly prevalent (Walsh et al., 2022). In this study, I presented a

comparison of ketamine infusions and KAP from a ketamine clinic in the southeastern region of the United States. Findings from the current study support the efficacy of both ketamine infusions and KAP in reducing depression severity scores from baseline at intake till the end of the six-infusion cycle among clients diagnosed with MDD. However, findings in the current study did not indicate statistically significant difference between infusions only and KAP. This study contributes to the growing literature on possible new treatment options for individuals who have been struggling with treatment-resistant mental health conditions. In addition, I conducted this research to help inform policy changes and establish needs for insurance coverage of ketamine and KAP to improve access and accessibility for those who urgently need new and novel treatment for their mental health conditions.

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