KETAMINE-ASSISTED PSYCHOTHERAPY: CLINICAL OUTCOMES AND SELF-TRANSCENDENCE IN DEPRESSION AND POST-TRAUMATIC STRESS DISORDER

by

Jennifer Fraser Montjoy

A Dissertation Submitted to the Faculty of the

COLLEGE OF NURSING

In Partial Fulfillment of the Requirements

For the Degree of

DOCTOR OF PHILOSOPHY

In the Graduate College

THE UNIVERSITY OF ARIZONA

2 0 2 2

THE UNIVERSITY OF ARIZONA
GRADUATE COLLEGE

As members of the Dissertation Committee, we certify that we have read the dissertation prepared by Jennifer Fraser Montjoy, titled Ketamine-Assisted Psychotherapy: Clinical Outcomes and Self-Transcendence in Depression and Post-Traumatic Stress Disorder and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy.

Kathleen C. Insel, PhD, RN — Date: Jun 27, 2022

Thaddeus W. W. Pace, PhD — Date: Jun 27, 2022

Pamela G. Reed, PhD, RN, FAAN — Date: Jun 27, 2022

Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copies of the dissertation to the Graduate College.

We hereby certify that we have read this dissertation prepared under our direction and recommend that it be accepted as fulfilling the dissertation requirement.

Kathleen C. Insel, PhD, RN — Date: Jun 27, 2022
Dissertation Committee Co-Chair
College of Nursing

Thaddeus W. W. Pace, PhD — Date: Jun 27, 2022
Dissertation Committee Co-Chair
College of Nursing

ACKNOWLEDGMENTS

I would like to express my sincere gratitude to my academic advisors and mentors, Dr. Thaddeus Pace, Dr. Kathleen Insel, and Dr. Pamela Reed, and to my research team, Katie Walsh, DNP, PMHNP-BC, and Zaskia Villa, BS. Without all of your support and efforts this work would not have manifested.

DEDICATION

To the individuals suffering from the invisible wounds overlooked by our current healthcare model; even though your injuries may not be physically or biometrically measurable, your suffering is real. You are not invisible, your well-being matters; this research is dedicated to you.

TABLE OF CONTENTS

TABLE OF CONTENTS – *Continued*

TABLE OF CONTENTS – *Continued*

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Posttraumatic stress disorder (PTSD) treatment response is estimated at 40%. Roughly half of individuals with PTSD have co-occurring depression. Repeated racemic ketamine administration has been effective in treatment-resistant depression (TRD); response in chronic PTSD is less understood. A quasi-experimental, retrospective study was conducted to investigate intramuscular (IM) racemic ketamine administration with concurrent psychedelic-assisted psychotherapy (i.e., ketamine-assisted psychotherapy) (KAP) efficacy in chronic PTSD and TRD.

Relationships between self-transcendence scale (STS) scores and adverse childhood experiences (ACEs) in those who received KAP were also explored. A convenience sample (N =33; M_{age}= 43, SD = 15) was recruited from an outpatient psychiatric clinic in southern Arizona. Data were collected between July 15, 2021, through March 10, 2022. As part of their regular clinic care, participants received between 0.3 mg/kg with gradual titration to 1 mg/kg of IM ketamine, for either three or six KAP sessions in the past 12 months. Two-tailed paired t-tests were used to analyze pre- to post-KAP PTSD symptom severity and depression symptom severity, using the PCL-5 and PHQ-9 respectively. Total mean PCL-5 score was 19.16 points lower (SD = 14.91, $p < .001$) post-KAP with significant improvement (d = 1.28, 95% CI = 0.796, 1.751) in PTSD symptom severity. More of a reduction occurred in PCL-5 score after six sessions (n = 18, M = -21.56, SD = 16.32) compared to three sessions (n = 12, M = -17.75, SD = 11.42). The effect of the number of KAP sessions on PCL-5 score was not statistically significantly for pre- to post-PCL-5 score difference for participants who received three versus six KAP sessions.

Post-hoc findings revealed 86% of participants with chronic PTSD were KAP responders (i.e., had a $\geq$ 10-point reduction in pre- to post-PCL scores). Pre- to post-KAP change in depression symptom severity was statistically significant (d = .976, 95% CI = 0.555, 1.39) with total PHQ-9 mean 8.49 points lower (SE = 1.16) post-KAP PHQ-9. Analyses of the relationship between STS score and PCL-5 and PHQ-9 yielded significant inverse correlations between self-transcendence and post-KAP PTSD symptom severity, $r(31) = -.75$, $p < .001$ and between self-transcendence and post-KAP depression symptom severity, $r(31) = -.84$, $p < .001$. Non-significant, positive correlations resulted between ACEs and post-KAP depression and between ACEs and post-KAP PTSD symptom severity.

These findings provide rationale for further research of IM KAP's effect on chronic PTSD symptom severity; however, findings should be considered preliminary. More research is needed to investigate optimal psychotherapeutic approaches, treatment settings, and individualized dosages in treating individuals with chronic PTSD and developmental trauma.

CHAPTER I: INTRODUCTION AND CONCEPTUAL FRAMEWORK

Introduction

Roughly 48-55% of patients suffering from post-traumatic stress disorder (PTSD) have comorbid major depressive disorder (MDD) (Choi, 2019). Depression treatment response is estimated at 50% (Williams et al., 2016; Paterniti et al, 2017) and PTSD treatment response is approximately 40% (Holmes et al., 2017) in persons treated for both conditions with currently available treatment modalities (e.g., psychotropics, psychotherapy, or both). The underlying causes of poor treatment response remain unclear; however, daily functional impairment, job loss, and poor quality of life experienced by these individuals and their families is evidenced by the annual $200 billion economic burden in the United States (US) alone (Chow et al., 2019). The disabling nature of treatment-resistant depression (TRD) and post-traumatic stress disorder (PTSD), lack of efficacious treatment modalities, and unprecedented suicide rates (Davidson et al., 2019; Weir, 2019) has cultivated a mental healthcare consumer shift from traditional western psychiatry to off-label modalities such as ketamine-assisted psychotherapy (KAP). Furthermore, poor TRD and PTSD treatment outcomes have catalyzed a resurgence in academic research globally, picking up where research in the 1950s and 1960s left off investigating the psychotherapeutic efficacy of entheogenic plants and psychedelic medicines for mental health clinical use.

Research over the last three decades suggests ketamine provides robust, rapid response in adults experiencing treatment-resistant depression (TRD) and suicidality (Singh et al., 2016; Cusins, 2019); however, response and outcomes for the 48-55% with comorbid PTSD are less understood. The monoamine hypothesis has been the primary theoretical focus in psychiatric

treatment for the last 40 years (Krystal et al., 2019), emphasizing psychotropic influences of serotonin, norepinephrine, and dopamine receptors. Consequently, the field of psychiatry has transitioned from a psychotherapeutic model to a predominately biomedical model in treating mental illness with medications (i.e., psychotropics). This approach has provided important data and, for many, reduced suffering. Nevertheless, this shift to a biomedical treatment approach in mental healthcare no longer emphasizes psychotherapy, an assertion exemplified by those spearheading and financing research and development in the field of psychiatry, namely pharmaceutical companies. Interestingly, many of today's non-pharmaceutical interventions evolved from theories generated by some of the greatest minds of the 20th century, Freud, Jung, and Bowlby for example, all of whom were psychiatrists *and* psychotherapists (i.e., psychoanalysts). The shift to a predominately biomedical or pharmaceutical interventional paradigm in psychiatry has been contrary to innumerable investigators reporting the most efficacy (e.g., reduction in depression severity) with a combination of psychotropics (e.g., selective serotonin reuptake inhibitors) and psychotherapy (Cuijpers et al., 2020; Kamenov et al., 2017), compared to either approach as a monotherapy.

Fast forward to present day, racemic ketamine has been the first molecule in decades to offer hope as an intervention for intractable depressive symptoms and suicidality. Researchers have reported robust and immediate depressive symptom relief, including suicidality after receiving ketamine; though the duration of symptom reduction or abatement is less known and continues to be studied (Cusins, 2019). As with previous psychotropic research, ketamine studies in treating psychiatric conditions have been physiologically (e.g., mechanism of action) focused, providing important information. However, very little has been published regarding ketamine's

use as a psychotherapeutic tool in mental healthcare settings and whether factors such as childhood maltreatment and psychospiritual well-being correlate with ketamine treatment outcomes in TRD and PTSD. A retrospective quasi-experimental project was used to investigate ketamine-assisted psychotherapy outcomes in adults treated for TRD and chronic PTSD within the past 12 months.

Significance

Traumatic Stress

Traumatic stress can occur at any time over the course of a person's life. In early life, traumatic stress often arises from enduring and/or severe childhood maltreatment (CM). CM includes emotional or physical neglect, and/or psychological, sexual, or physical abuse occurring prior to age 18. Meta-analyses suggest adults with history of CM are twice as likely to experience chronic depression or persistent episodic depression and are 1.5 times more likely to develop TRD (Nanni, Uher, & Danese, 2012; Nelson et al., 2017). Approximately 45-50% of adults who seek mental health services for TRD endorse history of CM (Nelson et al., 2017; Paterniti et al., 2017), and lifetime prevalence of PTSD among adults who self-report CM is 30-38% (Messman-Moore & Bhuptani, 2017). Li, D'Arcy, and Meng (2015) suggest one-half of global adult depression and anxiety cases are attributable to CM. Contrary to these data, at present, it is not considered best (clinical) practice to screen adults who present with anxiety and/or, depression, for CM (i.e., adverse childhood experiences or ACEs) in healthcare settings (e.g., primary care & women's health clinics) where the majority of these patients seek and receive mental health symptom-related treatment.

Like those with a history of childhood maltreatment, first responders (e.g., fire fighters, paramedics), healthcare providers, and veterans are also at greater risk of developing both PTSD and suicidality compared to the general population. The frequency and intensity of scenarios to which these professionals respond and their job-related responsibilities are important contributing factors in the development of work-related traumatic stress. Suicidality has been reported as significantly higher among first responders who develop job-related PTSD (Stanley, Hom, & Joiner, 2016). Frontline healthcare providers also experience profound stressors in emergency departments and critical care settings, and like community first responders, these clinicians have higher incidence of post-traumatic stress *and* suicide. Suicide is the second leading cause of death among 10 to 34-year-olds (Weir, 2019) and between 2005 to 2016 approximately 66,000 veterans died from suicide (Veterans Administration [VA], 2019). Furthermore, suicide rates have been significantly higher in nurses (51.77/100,00) compared to other adults (36.08/100,000) (Davidson et al., 2019). These data pre-date the intense and unprecedented stressors many frontline healthcare providers have experienced this year during the COVID-19 pandemic.

Pre-COVID-19 data suggest work-related PTSD rates were approximately 14% among physicians compared to 3-4% in the general population (Sendler, Rutkowska, & Makara-Studzinska, 2016), and 50% of emergency department (ED) nurses reported severe job-related traumatic stress symptoms (Ratrout, & Hamdan, 2020). Between 300 to 400 physicians die from suicide each year in the US (Dos Santos, 2017); risk for suicide appears to be significantly higher in female physicians compared to the non-physician population (Dutheil et al., 2019). Female

nurse suicide rates are estimated at 10.41:100,000 compared to 7.41:100,00 among non-nurse females between 2005-2016 (Davidson et al., 2020) in the US.

These data are poignantly relevant at this time as front-line nurses and other clinicians are experiencing repeated intense stressful patient care scenarios due to the COVID-19 pandemic. Many healthcare organizations have instituted no visitor policies; consequently, seriously ill patients are passing away without the presence and comfort of loved ones. Witnessing this suffering and caring for patients in isolation due to the recent pandemic has fallen on first-responders, nurses, and other allied professionals across the US. Adding insult to injury, front-line clinicians are losing friends and colleagues due to work-related exposure to the coronavirus. Implications of these traumatic stressors on our healthcare providers firsthand; given the duration of the COVID-19 pandemic and circumstances related to it, a tsunami of secondary PTSD and moral injury in healthcare providers is on the horizon.

In addition to career, CM may also be a contributing factor for suicide rates among post-deployed veterans with PTSD. Enlistees of the American and Canadian armed forces were reported to have greater frequency of CM (Sher, 2017) compared to non-enlistees. Carroll and colleagues (2017) reported approximately 83.4% of post-deployed veterans seeking treatment for PTSD endorsed at least one form of CM and 41.5% reported four or more. These investigators also found veteran suicidality increased by approximately 23% per each additional type of CM reported. Many veterans seek mental healthcare services for PTSD-related symptoms; unfortunately, suicide attempts remain high in this population contrary to receiving currently available treatment. Of 30,384 veterans treated for PTSD, approximately 3.4% (1,033) attempted suicide within four months of residential treatment discharge between 1993-2011 (Stefanovics &

Rosenheck, 2019). Together these data illustrate the prevalence and potential severity of traumatic stress among veterans, first responders, and frontline clinicians, and the potentially chronic nature of MDD and PTSD.

Fortunately, traumatic stress does not ensure the development of PTSD. Several mitigating factors have been found to promote resilience, particularly during childhood; these include, the presence of loving supportive adults, strong community engagement (e.g., school, extracurriculars), and reliable social support (e.g., spiritual, peer) (Hornor, 2015). There are also epigenetic factors that may increase risk for PTSD. Nemeroff (2016) suggests genetic and environmental (GxE) interactions are strongly associated in the development of traumatic stress disorders. This growing body of research is beyond the breadth of the proposed project; however, researchers of GxE are emphasizing the need for prevention by screening for PTSD and CM in primary care and pediatric settings (Johnson et al., 2013) and other non-psychiatric healthcare settings to promote earlier detection and intervention. Unfortunately, adults living with chronic PTSD have very few efficacious treatment options.

Toxic Stress

What is post-traumatic stress disorder or PTSD? Post-traumatic stress disorder (PTSD) is a diagnosis found in the American Psychiatric Association's (APA) *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-V) (2013). The DSM-V provides criteria and guidelines for assigning (i.e., 'diagnosing') mental health conditions. In short, these criteria include a list of symptoms and potential scenarios considered applicable to specific psychiatric diagnoses (e.g., major depressive disorder [MDD]). For example, some of the symptoms associated with PTSD listed in the DSM-V include hyperarousal, poor sleep quality, re-

experiencing the traumatic event(s), and avoidance (Meyerhoff et al., 2014). DSM-V criteria typically represent the patients' reported symptoms and time-frame parameters for distinguishing acute versus chronic conditions and partial or full symptom remission. The physiological manifestations of traumatic stress conditions (e.g., PTSD) are better represented by a concept termed "toxic stress."

Physiologically, traumatic stress becomes *disordered* when an organism is no longer able to maintain allostasis or allostatic load (Berens et al., 2017) subsequent to repeated and/or severe exposure to psychological distress, neglect, or abuse, a phenomenon known as toxic stress (Johnson et al., 2013). Toxic stress is distinguished by multisystemic compensatory mechanism dysfunction (e.g., extreme, erratic co-activation of the sympathetic & parasympathetic nervous systems) (Payne, Levine, & Crane-Godreau, 2015) and eventual psychoneuroendocrine-immune dysregulation. Chronic toxic stress induces a state of systemic and neurological inflammation associated with a host of comorbidities and premature mortality (Miller, Chen, & Parker, 2011). These comorbidities include numerous psychiatric conditions, cardiovascular disease, metabolic and autoimmune disorders, and neurological pathology. Toxic stress decreases serotonin levels in the brain and negatively affects GABA and glutamate levels, the two most predominant neurotransmitters in the brain (Averill et al., 2017). To date, there are no FDA-approved glutamatergic psychotropics available for the treatment of TRD or PTSD.

Ketamine's Use in Psychiatry

Racemic ketamine is included in the World Health Organization's (WHO) *Essential Medicines List* (WHO, 2015) due to ketamine's global use as an anesthetic and its low-risk profile. Racemic ketamine is considered a safe medication for pediatric, adult, and veterinary

clinical use. It is considered safe due to minimal respiratory effects, ease of titration, rapid onset, predictable duration, and short half-life; sub-anesthetic dosages of ketamine are anxiolytic, analgesic, and neuroprotective (Kolp et al., 2007). After almost 60 years since its inception, racemic ketamine is an inexpensive generic medication; however, because it has not been FDA-approved for TRD and other psychiatric conditions its use in psychiatry is considered off-label use. Consequently, insurance companies do not currently reimburse for psychiatric services when ketamine is administered.

The *off-label* designation of racemic ketamine for treating psychiatric conditions such as TRD has not deterred many patients from undergoing ketamine treatment. This may be for number of reasons: intolerable side effects (e.g., dyspepsia & sexual dysfunction) of currently available psychotropics, the disabling nature of moderate to severe depression, anxiety, and/or PTSD (e.g., concerns about job security), and as discussed, the lack of available efficacious treatment options. Currently, ketamine is being administered for psychiatric conditions by clinicians using two different approaches. One approach aligns with the traditional biomedical model; ketamine hydrochloride is administered intravenously (IV) over approximately 40 minutes in subanesthetic doses (e.g., 0.5mg/kg) (Sanacora et el., 2017) at outpatient infusion clinics. Most ketamine infusion settings are fluorescently lit clinics, patients' blood pressure is taken every five minutes throughout the infusion and heart rhythm is monitored with a three-lead (i.e., 3 wires) connected to medical equipment chair-side. Patients are monitored by medical technicians or medical assistants and discharged approximately one-hour post-ketamine administration. Researchers have reported positive TRD and suicidality outcomes using this

medicalized approach (Conley et al., 2021); the duration of these benefits remain unclear and have been reported as short-term (Mathai et al., 2018) by some investigators.

Over the past decade, a growing subset of clinicians, primarily psychiatrist and psychiatric nurse practitioners in collaboration with psychologists and therapists, have taken a different approach to ketamine treatment. This approach uses ketamine as a psychotherapeutic tool post-administration (i.e., psychoactive phase) of the medication lasting between 40 to 60 minutes (Dore et al., 2019). This approach has emerged for several reasons; primarily as a result of shared subjective experiences by patients. These include a reduction in anxiety, analgesia, and experiences of altered states of consciousness and alterations in sensorium (i.e. *psychedelic*).

Psychedelic substances (e.g., psilocybin, lysergic acid diethylamide, & ketamine) induce non-ordinary states of consciousness (NOSC) during which sensory perception may be temporarily altered (i.e., synesthesia), qualia (i.e., out of body or formlessness) may be experienced (Dore et al., 2019), and/or a spiritual or mystical experience may emerge (Mathai et al., 2018). Though this may sound radical to some in research and medical communities, whether there is therapeutic benefit in ketamine's psychedelic effects continues to be investigated. The notion of psychotherapeutic use and research of psychedelic molecules and their potential as psychotropic tools began in the 1940s and continued well into the 1960s in academic (e.g. Harvard) and clinical settings internationally until 1970 when many of these molecules were banned for recreational use *and* academic and clinical research.

Theoretical Framework

The theoretical framework for the proposed dissertation project is comprised of concepts from the psycho-neuroendocrine-immunology (PNI) framework and Reed's *Theory of Self-*

Transcendence. Research related to the PNI mechanisms underlying development of toxic stress will be discussed in detail in Chapter II. For the purposes of the proposed project, the *P* in PNI will describe two distinct, though interrelated concepts: *psychospiritual* (e.g. existential) and *psychological.* Psychospiritual, within the context of this project, refers to the unconscious mind (i.e., higher self) and/or spiritual or existential beliefs, including but not limited to one's soul or energetic being (i.e. prana, qi), one's place in the world, and one's sense of connection to *Self* (i.e. within or intrapersonally), connection with other humans and non-humans in the physical (i.e. interpersonally), and/or a connectedness with a higher power, the universe, or a collective consciousness (i.e. transpersonally). *Psychological* include aspects of the mind whereby thoughts/thinking, reasoning, and perspectives arise (i.e., egoic identity, resting-state networks including the default-mode network, & executive functioning) and emotions and memories associated with emotional experiences (i.e. limbic regions) arise.

The psychological sequelae of PTSD are discussed in detail in the *Diagnostic Statistical Manual, 5th edition* (2013) as are the diagnostic criteria for assigning PTSD as a diagnosis. Historically, the psychospiritual nature of PTSD have not been discussed in research and even less so in most biomedical, research and clinical settings, including mental healthcare. Consequently, traditional psychotherapies targeting psychospiritual attributes of PTSD and other mental health conditions have been extremely limited. This omission in mental healthcare may offer one explanation to the complex phenomenon whereby patients are not responding or to or getting better with currently available interventions. These patients subsequently receive the designation *treatment-resistant* by their provider(s).

Psychospirituality is a relatively new focus in PTSD and mental health research and has begun gaining recognition in the last 10 years (Bélanger et al., 2018). Due to its relative novelty, the concepts of psychospiritual and psychospiritual injury (i.e., moral injury) are continuing to be studied and refined (Grimell, 2018), theoretically and empirically. The term self-transcendence has been used to contextualize mystical *and* developmental constructs (Reed, 2009) in psychology, social science, and nursing research (Garcia-Romeu, 2010). The *Theory of Self-Transcendence*, developed by Dr. Pamela Reed, describes self-transcendence as intrapersonal, interpersonal, and transpersonal connection and is a process by which vulnerability, active participation, and well-being are emergent and interconnected in the human experience (Reed, 2018). Reed (1991) suggests self-transcendence evolves from a place of vulnerability subsequent to major life stressors (e.g., serious illness, traumatic experience), existential crises (e.g., death of a loved one, angst around one's mortality), and as an attribute of normal human development influenced by personal and circumstantial factors.

Ketamine and other psychedelic-assisted psychotherapeutic interventions may catalyze this process from a safe and more detached perspective. Research to date has attributed outcomes primarily to racemic ketamine's pharmacodynamics or mechanisms of action (Krystal et al., 2019; Vasavada et al., 2020); however, clinical research (Dore et al., 2019; Mathai et al., 2020) suggests the subjective experiences during and following ketamine administration are important and overlooked influences in outcomes. This perspective necessitates a theoretical framework that conceptualizes the physiological mechanisms *and* the subjective, including existential, experiences that frequently arise during the psychoactive phase post-administration. Reed's

theory of self-transcendence and self-transcendence scale (STS) may be a helpful framework and tool in this field of inquiry.

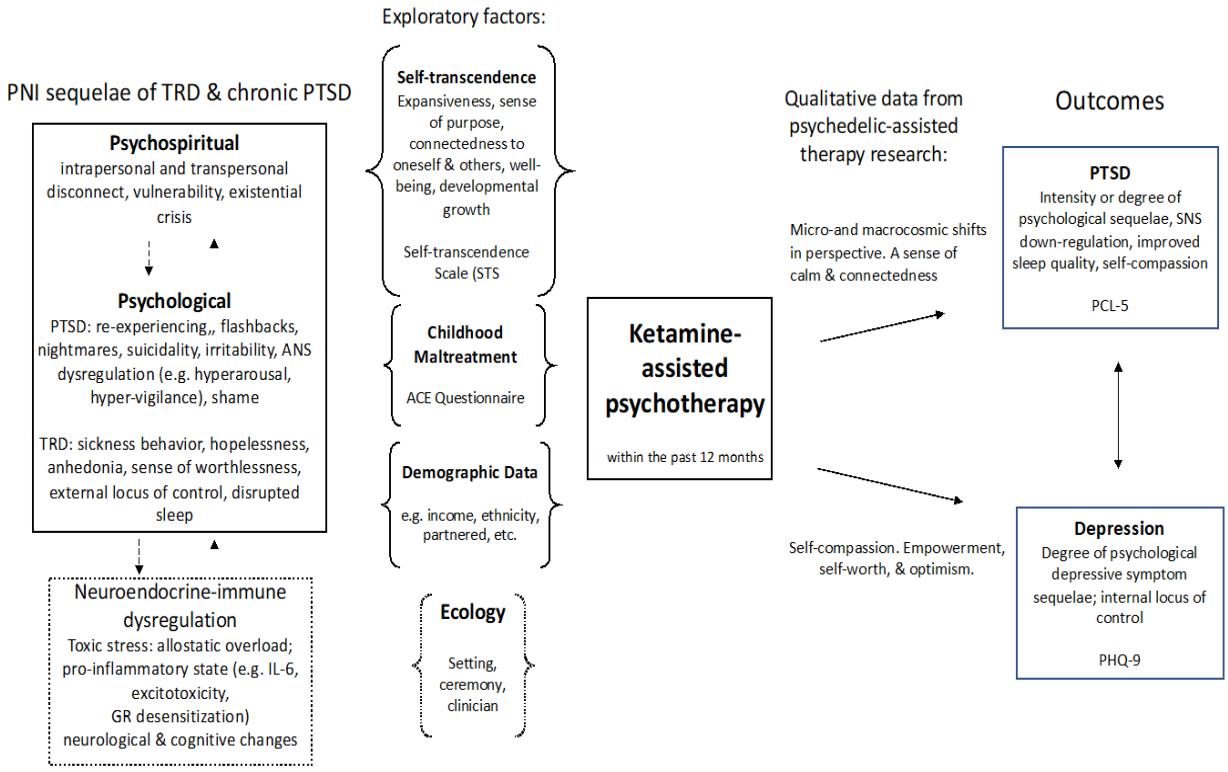
The epistemological worldview guiding the proposed project's conceptual framework is *intermodernism*. Intermodernist tenets that have been integral in the development of the proposed project are the philosophy that bench science is integral to the evolution of clinical practice and that clinical practice influences and drives bench science (Reed, 2019). These two areas of scientific inquiry are not mutually exclusive; instead, they are interconnected and are both needed to move the social and bioscience fields forward. Intermodernism also encompasses '*holism*' (Bell & Koithan, 2006), a deviation from the reductionist, *Cartesian* perspective (Sturmberg, 2016; Bell & Koithan, 2006), and positivist worldview that human beings are comprised of mechanistic and non-dynamic parts. The physiological, psychological, and psychospiritual elements of PTSD are interrelated and inextricable; therefore, a holistic paradigm is foundational for the proposed project's conceptual framework and methodological approaches. To achieve this, Reed's (1991) *Theory of Self-Transcendence* and a PNI framework (Birney, 1991, Bennet, 1997; McCain et al., 2005) are being used to model the relationships within and between the concepts of interest and are depicted in Figure 1.

The PNI concepts related to the sequelae of TRD, and PTSD appear on the left side of the model and diagram the relationships between these concepts. The intervention (KAP within the last 12 months) is shown in the center; contextual and personal factors (e.g., demographics, childhood maltreatment) are depicted to the left of the intervention and are exploratory factors in the proposed project. KAP outcome concepts of interest are self-transcendence, to assess psychospiritual well-being, depression severity, and PTSD symptom severity are shown on the

right side of the model. The construct *ecology* is also depicted in the conceptual model as this too influences the approaches in ketamine treatment modalities and likely affects psychiatric treatment outcomes. Within the ecology construct are setting (e.g., environment/surroundings), clinician and client dynamic, and ceremony (e.g., protocol around administering the medication). Ecology and Rogers' concept of integrality (1992) are important factors to consider in ketamine and other psychedelics being used medicinally in clinical research. Ecology will be further explored in future KAP research; ecology and other relevant constructs beyond the breadth of this project are depicted within the framework below by dotted outlines.

Figure 1

Conceptual Framework Model: Psych-neuroendocrine-immunology (PNI) and Self-transcendence in Ketamine-assisted Psychotherapy



(Concepts directly addressed in this research are bolded.)

Purpose and Aims

The purpose of the present study was to evaluate PTSD and depression symptom outcomes in adults aged ≥ 18 years who received ketamine-assisted psychotherapy (KAP) in the past 12 months for treatment resistant depression (TRD) and post-traumatic stress disorder (PTSD) as a component of their previous psychiatric clinical care, and whether psychospiritual well-being, depression symptom severity, and PTSD symptom severity differed between individuals with and without reported history of childhood maltreatment (CM). The study was guided by the following specific aims.

Aim 1: To Compare Depression Severity and PTSD Symptom Severity Pre- and Post-KAP

Hypothesis 1a - There will be a reduction in post-KAP depression severity compared to pre-treatment.

Hypothesis 1b - There will be a reduction in post-KAP PTSD symptom severity compared to pre-treatment.

Aim 2: To Describe Self-Transcendence Post-KAP

Hypothesis 2 - Self-transcendence will be moderate to high or ≥ 31 post-KAP.

Aim 3: To Examine Associations Between Self-Transcendence and PTSD Symptom Severity and Self-Transcendence and Depression Severity Post-KAP and Between Adverse Childhood Experiences and PTSD Symptom Severity and Between Adverse Childhood Experiences Self-Transcendence and Depression Severity Post-KAP

Hypothesis 3a - There will be an inverse association between self-transcendence and PTSD symptom severity.

Hypothesis 3b - There will be an inverse association between self-transcendence and depression symptom severity.

Definition of Terms

Intravenous (IV) Ketamine

IV ketamine refers to the administration of ketamine hydrochloride over 40 minutes using weight-based (e.g., 0.5 mg/kg) dosages in medical settings typically managed by anesthesiologists. Non-mental health clinicians provide patient care including continuous three-lead EKG monitoring and automatic blood pressure measures every five minutes throughout the infusion; ecology (e.g., methods surrounding medication administration & setting) and therapeutic processing and support are not foci of this ketamine modality.

Ketamine-Assisted Psychotherapy (KAP)

KAP is a modality that induces a non-ordinary state of consciousness during which sensory perception may be temporarily altered (i.e., synesthesia), qualia (i.e., boundaryless or formlessness) may be experienced, and/or a spiritual or mystical states may arise inducing a noetic (i.e., revelatory) experience. Providers facilitating this experience by maintaining a safe container, paying close attention to the ecology of facilitating the experience, and assist patients/participants with processing and contextualizing the session(s). A thorough medical screening is obtained to determine medical safety and to rule out any contraindications. Vital signs are obtained pre- and post-medication administration. The intention of providers using this modality is transmutation and healing resulting in durable well-being.

Psyche

Psyche translates from Greek to English as *soul*; in psychoanalytic theory psyche represents the whole mind, conscious and unconscious.

Psychospiritual Injury

Psychospiritual injury connotes severe unaddressed violations of one's energetic body (e.g., sexual assault, childhood maltreatment), morals and/or beliefs (e.g., job-related moral injury, childhood maltreatment) resulting in intrapersonal, interpersonal, and/or transpersonal disconnect.

Psychological Sequelae of Post-Traumatic Stress Disorder (PTSD)

Psychological sequelae of PTSD are hallmark symptoms experienced and reported by individuals after an extreme, harrowing experience(s). These symptoms, listed in detail in the DSM-5 (2013) may include re-experiencing, sickness behavior, flashbacks, hopelessness, nightmares, suicidality, irritability, and/or hyper arousal, and may develop after single or repeated psychologically and/or physically traumatic experiences at any time across the lifespan.

Racemic Ketamine

Racemic ketamine is the original, FDA-approved anesthetic and analgesic molecule comprised of two enantiomers in equal parts, *R*-and *S*-ketamine. Racemic ketamine is the predominant molecule that has been investigated for efficacy in treating mental health conditions.

Self-Transcendence

Self-transcendence is process by which one experiences temporal boundary expansion and intrapersonal (i.e., within one's self) and transpersonal (i.e., beyond the self) connection or re-connection resulting in healing and subsequent sense of well-being.

Toxic Stress

Toxic stress conceptualizes the measurable (e.g., cytokines, cortisol, neuroimaging) physiological psychoneuroendocrine-immune (PNI) dysregulation and pro-inflammatory state arising in chronic PTSD.

Treatment Resistant Depression

Treatment resistant depression is the designation for two failed treatment interventions (APA, 2017), provided for adequate duration and dose, with minimal or temporary efficacy in treating major depressive disorder.

Summary

It is a common misconception that post-traumatic stress disorder (PTSD) only applies to combat veterans; however, approximately 8% of the general population will develop PTSD at least once during their lifetime (Feder et al., 2020). Given the chronicity and severity of stressors related to COVID-19 being experienced by frontline healthcare clinicians over the last year, the need for efficacious modalities in treating PTSD is an ongoing critical issue in mental healthcare. Healthcare clinicians and veterans have higher than average suicide rates; unremitting depression and chronic PTSD are risk factors in developing suicidality. Furthermore, there is a gap in research and mental health practice in assessing psychospiritual well-being. In the next chapter,

current literature pertaining to ketamine's use in psychiatric research and in clinical settings and gaps in research related to TRD, PTSD, and psychospiritual well-being will be discussed.

CHAPTER II: LITERATURE REVIEW

Introduction

The human stress response involves complex, dynamic psychoneuroendocrine-immune (PNI) systems. These recursive neuroendocrine-immune feedback mechanisms will be the focus of this section. Broadly, the neuroendocrine-immune mechanisms involved in the human stress response are embedded in the limbic, autonomic, endocrine, and immune systems. These mechanisms are interrelated and communicate between the central nervous system (CNS) and numerous sites nested throughout the human body. The holistic nature of the human stress response underscores the multisystemic health implications and early mortality associated with chronic traumatic stress. Understanding the mechanisms that become dysregulated and why is essential in the development of future efficacious traumatic stress interventions. Stress responses potentiated by environmental stimuli (e.g., work-related experience, witnessing violence) that eventually lead to psychopathological states like PTSD begin in the limbic system.

The limbic system is responsible for olfaction, autonomic and neuroendocrine regulation, learning, memory, emotions, and other functions (Reibau, 2015). Structurally, the limbic system is comprised of the olfactory tracts, thalamus, prefrontal cortex, hippocampus, fornix, cingulate gyrus, and hypothalamus. Chemical messengers and corresponding receptors are responsible for communication within the CNS, including the limbic system. These messengers or neurotransmitters include, but are not limited to, serotonin, dopamine, norepinephrine (NE), and amino acids: glutamate and gamma aminobutyric acid (GABA). Serotonin has been implicated in mood states, anxiety, and sleep (Daruna, 2012). Dopamine is associated with pleasure and reward (e.g., addiction) and motivational behavior. NE is also involved in sleep-wake cycles,

attention, and mood (Sherin & Nemeroff, 2011); NE is integral in immune system activation and the sympathetic nervous system's *fight, flight, freeze* response.

Glutamate is an excitatory CNS neurotransmitter, its counterpart GABA is inhibitory; these two neurotransmitters predominate the cortex and limbic system comprising 75%-85% of synaptic connections (Averill et al., 2018; McCance & Heuther, 2018). Glutamate and GABA mediate neuronal function (Meyerhoff et al., 2014), sleep/wake cycles, cognition and focus, emotional memory, and anxiety levels. GABA, within the limbic system, plays an important role in fear conditioning and fear extinction (Averill et al., 2018). Glutamate mediates neuroplasticity by promoting brain-derived neurotrophic factor (BDNF) (Krystal et al., 2019); however, in excess, glutamate is neurotoxic (Zhou & Danbolt, 2014) by inducing neuronal excitotoxicity. Excitotoxicity has been associated with several neurodegenerative diseases.

Limbic system response to external stimuli begins with the thalamus. The thalamus is the relay center for the limbic system; all sensory information except olfaction, synapse in the thalamus (Haines & Terrell, 2013). The thalamus relays sensory input to the sensory cortex; if a stimulus is perceived as non-threatening the sensory cortex transmits this information to the hippocampus. The hippocampus consolidates short-term, explicit memories into long-term memories; thus, has an important role in learning and cognition. Once information has synapsed in the hippocampus, it is relayed to the amygdala. The amygdala assigns emotional significance to sensory input and establishes emotional memory (Riebau, 2015). Consequently, the hippocampus, pre-frontal cortex (PFC), and the amygdala are important brain regions for emotion and emotional regulation (Sherin & Nemeroff, 2011). In a life-threatening scenario or exposure to an extreme stressor (e.g., the presence of a rattlesnake), sensory input is relayed

directly from the thalamus, bypassing the cortex and hippocampus, to the amygdala activating the hypothalamic-pituitary-adrenal (HPA) axis.

HPA-axis activation begins with the hypothalamus; the hypothalamus controls the autonomic nervous system (ANS), and moderates several homeostatic functions including temperature regulation, hunger and satiety, sexual behavior, sleep-wake cycle, pleasure and punishment responses, mood and affect, visceral and somatic responses, and endocrine system mechanisms (McCance & Huether, 2018; Reibau, 2015; Daruna, 2012). The ANS is comprised of the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS). The SNS is activated by the hypothalamus' release of corticotropin-releasing factor and the anterior pituitary transmitting adrenocorticotropic hormone to the adrenals. The adrenal cortices release glucocorticoids (e.g., cortisol) and the adrenal medullae release norepinephrine (NE) catalyzing anti- and pro-inflammatory immune responses, respectively. These mechanisms physiologically prepare humans for the metabolic demands required to manage environmental stressors and to maintain allostasis (i.e., the pre-stress response state).

Glucocorticoids (GC) moderate gene expression of T-helper cells and between receptor-ligand complex and transcription factors (e.g., nuclear factor kappa B [NF-κB]) that inhibit proinflammatory mediators (e.g., interleukin [IL]-6, tumor necrosis factor [TNF]-α) (Pace et al., 2012; Danese & Baldwin, 2017). However, the degree to which GC are effective depends on cell-membrane GC receptor sensitivity, not GC levels independently (Busillo & Cidlowski, 2013). GC receptor sensitivity is vital for metabolic health and for moderating neurogenesis and neuroplasticity (Bekhbat, Rowson, & Neigh, 2017). Specific immune cells have adrenergic receptors activated when the adrenals release NE; once activated a cascade immune system

response is initiated. Antibody and lymphocyte (e.g., natural killer cells) production increases, temporarily in a healthy stress response, promoting the release of pro-inflammatory (e.g., cytokines, TNF-α) and anti-inflammatory (e.g., cytokines, GC) constituents. NE and GC attenuate inflammation through numerous recursive feedback mechanisms.

Anti-inflammatory cytokines (e.g., IL-10 moderate GC release by signaling the HPA-axis (Miller, Chen, & Parker, 2011). Cytokine communication is transmitted through several routes: 1) TNF-α and IL-1β act upon afferent vagus nerve fibers resulting in CNS microglia release; 2) humoral cytokines cross the permeable blood-brain barrier (BBB); 3) active transport across the BBB using the transmembrane pathway; and 4) circulating cytokines activate astrocytes and endothelial cell receptors that are located at the BBB (i.e., signal transduction pathway) (Danese & Baldwin, 2017). In an acute stress response, these finely tuned recursive feedback mechanisms protect and if needed heal the human body and nervous systems. However, chronic activation of these systems eventually leads to allostatic overload, the consequences of which are systemic pro-inflammation and neurotoxicity, a phenomenon termed toxic stress.

Physiology of Toxic Stress and PTSD Sequelae

One important mechanism associated with toxic stress is immune cell glucocorticoid receptor desensitization (e.g., monocytes) to GCs (e.g., cortisol) (Shankoff et al., 2012). Glucocorticoid desensitization has been associated with hypercortisolemia and subsequent dysregulation of NF-κB (Pace et al., 2012). Hypercortisolemia, over time, increases vulnerability to development of metabolic disorders (e.g., DM) and increased NF-κB which has a critical role in mediating inflammation. Researchers have reported dysfunction of glucocorticoid receptor sensitivity and NF-κB in persons with traumatic stress conditions (e.g., PTSD) (Pace et al., 2012;

Bekhbat, Rowson, & Neigh, 2017). A combination of glucocorticoid receptor desensitization and pro-inflammatory cytokines left unchecked are key components in the development of systemic inflammation and consequently medical and psychiatric co-morbidities.

Elevated pro-inflammatory cytokines (e.g., IL-6, TNF), indicative of toxic stress, have been found in participants with ongoing depression, emotional and behavioral dysregulation, and chronic PTSD (Johnson et al., 2013). Toxic stress has been associated with elevated NE, downregulation of GABA, increased glutamate (Sherin & Nemeroff, 2011), impaired brain-derived neurotropic factor (BDNF), reduced binding of serotonin receptors (Daruna, 2012), and delays in auditory, visual, and somatosensory-evoked potentials (Horner, 2015). BDNF is a critical mediator in neuroplasticity (e.g., synaptic healing & branching) and neurogenesis, particularly in the hippocampus (Calabrese et al., 2014). Over time these alterations in brain chemistry change the brain structurally further affecting mood, behavior, and cognitive functioning.

The subjective experiences and behaviors associated with PTSD are linked to the physiological alterations of toxic stress. Elevated NE levels have been implicated in flashbacks and hyperarousal (Sherin & Nemeroff, 2011); decreased serotonin (5HT) levels have been associated with impulsivity, irritability, aggressive behavior, depression, and suicidal ideation. Lower 5HT has also been associated with a heightened startle response and intrusive memories, hallmark experiences in persons with PTSD. The prevalence of comorbid PTSD and TRD and the reduction of 5HT receptor sensitivity and 5HT levels may another factor contributing to the endemic poor treatment outcomes with currently available interventions. Decreased GABAergic activity and excessive glutamate have also been identified in persons with PTSD (Averill et al.,

2017) resulting in excitotoxicity and neuronal death. Increases in glutamate inhibit BDNF, reducing neuroplasticity (Calabrese et al., 2014) in the brain regions where GABA and glutamate predominate (e.g., limbic regions & cortex).

Brain imaging of research participants with chronic PTSD have shown reduced hippocampal, ventromedial PFC, and anterior cingulate cortex volume (Sherin & Nemeroff, 2011; Sripada et al., 2012; Teicher, Anderson, & Polcari, 2012). Researchers have also reported blunted basal ganglia activation and amplified amygdala activity (Danese & Baldwin, 2017), and/or dysfunction of the insula and the dorsolateral PFC (Ben-Zion et al., 2020). Sequelae of these neurological changes often present clinically as depressive or anxiety-and arousal-related symptoms. These may include poor sleep quality, learning difficulties, impaired memory, reduced reward response, agitation, anxiety, restlessness, hypervigilance, and/or a heightened startle response (Nemeroff, 2016); abnormal emotional reactivity (Berens et al., 2017) and difficulty emotionally self-regulating may also be present.

Behaviors believed to arise from these pro-inflammatory neurological changes are impulsivity, poor decision-making, addictive behavior (e.g., substance misuse, gambling, excessive consumption), fidgeting or pacing, and/or suicidal gestures (Teicher, Anderson, & Polcar, 2012). Anxiety and depressive symptoms are also psychological sequelae associated with a pro-inflammatory state (Lindert et al., 2014) and a phenomenon is known as *sickness behavior*. Sickness behavior is induced by pro-inflammatory cytokines (e.g., tumor necrosis factor-alpha [TNF-α], IL-6) and results in lethargy, reduced social behavior, anhedonia, changes in appetite, and cognitive alterations (Shattuck & Muehlenbein, 2016). These pro-inflammatory neurological and behavioral changes can become disabling professionally and strain personal relationships,

furthering the experience of isolation. Individuals with chronic PTSD often present with several medical comorbidities (Felitti et al., 1998; Wang & Young, 2016), these may include hyperlipidemia, obesity, cardiovascular disease, type II diabetes mellitus, autoimmune conditions, neurodegenerative conditions, and/or irritable bowel syndrome (i.e., gastrointestinal symptoms). Research findings examining several anti-inflammatory mechanisms of racemic ketamine and how these mechanisms may contribute to rapid improvement in TRD and suicidality will be discussed in more detail.

Currently, available psychotropics for treating TRD and PTSD have been driven by the biomedical paradigm, including the monoamine hypothesis (Averill et al., 2017). Consequently, available psychotropics are believed to target serotonin, NE, and/or dopamine receptors. There is currently one (intranasal) medication with FDA approval for TRD that targets glutamate receptors; to date, there are no FDA-approved glutamatergic medications for PTSD. Given the comorbidity of TRD and PTSD (approximately 50%) and data supporting rapid robust improvements in suicidality and depressive symptoms post-ketamine treatment (Krystal et al., 2019), further exploration and analyses of racemic ketamine treatment outcomes in co-morbid PTSD are warranted.

Ketamine in Treating Depression and PTSD

Ketamine hydrochloride (i.e., racemic ketamine) was developed in 1962 and is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist (Krystal et al., 2019). NMDA receptors are embedded in the glutamate system and there is a growing body of research supporting aberrant glutamatergic activity in persons with PTSD (Meyeroff et al., 2014; Averill et al., 2017; Ben-Zion et al., 2020) and mood disorders (e.g., TRD, bipolar) (Esterlis et al.,

2018). Racemic ketamine can be administered intravenously (IV), intramuscularly, orally, sublingually (SL), rectally, and intranasally. The primary routes of administration and estimated bioavailability of ketamine for each route are: IV (100%), IM (93-95%), and SL (15-25%) (Dore et al., 2019). Since the late 1980s racemic ketamine has been investigated for efficacy in treating several psychiatric conditions including addiction, alcoholism, depression, anxiety, and obsessive-compulsive disorder (Kolp et al., 2007); however, racemic ketamine remains only approved as an anesthetic and analgesic in the US by the Food and Drug Administration (FDA).

Ketamine's mechanism of action has been theorized as NMDA antagonism resulting in pyramidal (i.e., excitatory) cell disinhibition, which in turn activates [alpha]-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors upregulating brain-derived neurotrophic factor (BDNF) (Aleksandrova, Phillips, & Wang, 2017). AMPA and BDNF promote synaptogenesis in and between the PFC and hippocampus, the brain regions prone to atrophy and reduced neuronal activity subsequent to TRD and chronic PTSD. Over time, as a result of increased BDNF and upregulation of AMPA receptors, there is a reversal in hippocampal and PFC atrophy and augmentation of dendritic branching (i.e., neuroplasticity).

A few small studies have reported downregulation of pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β) in animal and human models post ketamine-administration and an association between elevated pro-inflammatory cytokines at baseline and greater response in depression symptom severity compared to participants with lower pro-inflammatory cytokines at baseline (Zhang et al., 2021). In their literature review, Zhang and colleagues further discuss research findings reporting upregulation of IL-10, an anti-inflammatory cytokine; improvement in the kynurenine pathway (critical for catecholamine [e.g., 5HT] production); attenuation of

pro-inflammatory cytokine gene expression; microglial reactivity; and cytotoxicity post-ketamine administration. These findings are preliminary, however, may offer additional insight into underlying (anti-inflammatory) mechanisms resulting in rapid improvement of suicidality for many individuals post-ketamine administration.

Racemic ketamine may also moderate thalamaco-neocortical and limbic electrophysiological potential (Liriano, Hatten, & Schwartz, 2019), reducing communication between sensory signaling, executive functioning (i.e., thinking brain), and emotional processing. Neuroimaging researchers (Vasavada et al., 2020) recently published that ketamine may moderate functional connectivity between limbic regions and resting-state networks (e.g., default-mode network, central executive network, & salience network). In sub-anesthetic doses this temporarily alters proprioception, reducing awareness of one's body position and movement, inducing a sense of expansiveness or formlessness (Dore et al., 2019). Electroencephalography (EEG) has revealed increased delta and theta activity throughout the cerebral cortex (Kolp et al., 2014) post-ketamine administration. Delta and theta states are associated with deep relaxation, "quieting of the thinking mind," and trance or meditative states. This may be another factor contributing to ketamine's efficacy in treating anxiety-related conditions (Glue et al., 2017) and why ketamine merits further investigation in chronic PTSD outcomes.

Outcomes and methods have varied significantly in research investigating intravenous (IV) ketamine efficacy in treating TRD (Schenberg, 2018); study foci have included: efficacy of IV ketamine administration compared to efficacy of other molecules; outcomes using a single ketamine infusion compared to a series of infusions, and racemic ketamine infusions compared to other treatment modalities (Kryst et al., 2020). Use of concurrent psychotherapy has not been

a component in this biomedical research model; however, these studies have provided important data regarding ketamine's mechanisms of action and psychiatric and neurological outcomes post-ketamine administration. Most studies have used 0.5mg/kg infused intravenously (IV) over 40 minutes. Robust positive outcomes in TRD have been reported with multiple (e.g., 3-6) IV ketamine infusions over 2-3 weeks in contrast to minimal efficacy 24 hours post-single IV ketamine infusion (Caddy et al., 2015; Sanacora et al., 2017). Other novel research suggests multiple ketamine infusions to be comparable in efficacy to a series of 12 ECT treatments (Allen et al., 2015) in reducing treatment resistant depression-related symptoms.

Despite the prevalence and comorbidity of chronic PTSD and the previously discussed robust symptom response in depressive symptoms post-ketamine administration, very little has been published on the topic of comorbid PTSD outcomes. The currently limited available research indicates ketamine may be efficacious in reducing chronic PTSD symptom severity. There have been mixed findings regarding racemic and s-ketamine administration following acute traumatic stress, most study outcomes suggest ketamine lacks efficacy in acute PTSD (Liriano, Hatten, & Schwartz, 2019; Feder et al., 2020). To date, there has been one small (n = 15) open-label trial (Albott et al., 2018) using six racemic ketamine IV over 12 days for co-occurring depression and chronic PTSD and one double-blind cross-over RCT (n = 41) (Feder et al., 2014), using a single IV infusion of ketamine and placebo (midazolam).

Participants in the open-label study (Albott et al., 2018) continued any psychotropics they had been prescribed prior to the study's commencement; after undergoing six ketamine infusions 12 of the 15 participants experienced PTSD symptom remission (i.e., no longer met DSM-V criteria for PTSD) lasting a median time of 41 days. Participants of the RCT (Feder et al., 2014)

were not taking any psychotropics during the study, 29 received one IV infusion of racemic ketamine and one IV infusion of placebo (midazolam) two weeks apart. Efficacy of the ketamine infusion was greater than placebo, seven participants reported sustained improvement up to two weeks while, similar to the single infusion method in the TRD research, most participants reported recurrence of PTSD symptoms after 48 hours. Both studies reflect ketamine administration without concomitant psychotherapy.

Ketamine-Assisted Psychotherapy (KAP)

Outside the field of mental healthcare, the consensus regarding ketamine administration has been to avoid the dissociative effects (i.e., psychedelic or non-ordinary states of consciousness [NOSC]) induced by administration of racemic ketamine, hence the IV infusion over 40 minutes. The temporary alterations in sensory perception and thought processes have been purported as unwanted side effects (Dore et al., 2019). Undoubtedly, there are clinical settings where these experiences are unwanted (e.g., emergency departments, during medical procedures, etc.) and potentially psychologically harmful in patients undergoing medical procedures or treatment. However, these sensory and perceptual alterations may be of benefit when used psychotherapeutically in safe, controlled outpatient psychiatric settings. Interestingly, one secondary analysis study reported a positive association between more robust and durable depression treatment response (Luckenbaugh et al., 2014) when participants (n = 108) reported dissociation during ketamine administration.

This assertion and phenomenon of interest is not new to psychiatry; NOSC were being investigated in academia and in clinical psychotherapeutic settings in earnest in the 1950s until 1970. During that time, research was focused primarily on psilocybin, derived from fungi, and

lysergic acid diethylamide (LSD) modeled from ergot; these molecules were administered for research with concurrent psychotherapy, using a psychodynamic approach. Phanke (Majić, Schmidt, & Gallinat, 2015), one of a handful of pioneers of this research at Harvard during the 1960s published experiences as reported by participants which included: a sense of unity, transcendence of space and time, and improved attitudes regarding oneself, others, and life in general post-treatment.

The first meta-analysis on the safety of LSD for clinical use was presented at a scientific conference in 1960 (Carhart-Harris & Goodwin, 2017). Investigators reported findings of safety and efficacy when LSD was administered in therapeutic settings in treating mood disorders, substance abuse (e.g., alcoholism), and existential suffering; however, in 1970 the US congress passed the 'Controlled Substances Act' under the Nixon administration outlawing recreational use and academic research of these molecules. Three decades would pass before academia was permitted by the FDA to resume this research.

In 2000, Johns Hopkin psychopharmacologist and researcher Roland Griffiths received FDA approval to investigate psilocybin's potential as a psychotropic in the US. Since then, numerous, blinded placebo-controlled studies have been published on psychedelics and outcomes related to end-of-life anxiety, TRD, and spiritual (i.e., mystical) healing experiences (Belser et al., 2017). In September of 2019, Johns Hopkins opened the privately funded Center for Psychedelic and Consciousness Research led by Griffiths and his team. Academic institutions worldwide are now investigating psychedelics' applications for numerous psychiatric conditions including the University of Arizona (e.g., psilocybin's efficacy in the treatment of obsessive-

compulsive disorder). Another outcome from the last two decades of therapeutic psychedelic research is a modality called psychedelic-assisted psychotherapy (PAP).

PAP emphasizes intention, mindset, and setting (i.e., environment) to optimize the likelihood of healing and/or transformative experiences during the psychoactive post-administration phase of the medication. Components of PAP, regardless of the molecule being studied (e.g., MDMA, ketamine, psilocybin) are inclusion of music, comfortable furniture for patients to either lie supine or recline, an eye cover to promote introspection, and the ongoing presence of trained licensed mental healthcare professionals (Schenberg, 2018). Several psychiatric providers have participated in phase I and II clinical trials using PAP and the 3,4-methylenedioxymethamphetamine (MDMA) molecule investigating its efficacy for TRD and chronic PTSD. This approach has also been applied in clinical practice utilizing ketamine, a modality called ketamine-assisted psychotherapy (KAP).

Racemic ketamine or ketamine hydrochloride has been used concurrently with psychotherapy in several countries outside of the US since the 1970s in the treatment of numerous psychiatric conditions (Kolp et al., 2007), including heroin addiction, alcohol use disorder, obsessive-compulsive disorder (OCD), disordered eating, end of life anxiety, and depression. However, there have been very little data published regarding concurrent psychotherapy during or immediately following (e.g., intramuscular) ketamine administration in treating chronic PTSD. In 2019, a seminal paper was published (Dore et al., 2019) discussing robust, positive TRD, anxiety, and comorbid PTSD outcomes using ketamine-assisted psychotherapy (KAP) in three private psychiatric practices (n = 235). Of particular interest, the investigators shared that participants with a history of developmental trauma (i.e., childhood

maltreatment) with a PTSD diagnosis reported the most improvement in their depression and anxiety-related symptoms.

Self-Transcendence and Ketamine-Assisted Psychotherapy

Psyche translates from Greek as 'soul' in English. Psychoanalysts consider the concept of psyche to include the conscious and unconscious aspects of the mind. For the proposed project, psyche will be synonymous to psychospiritual, referring to the Jungian concept of 'self' (Kelly, 2002). In Sanskrit this inner self or core (consciousness) is termed *Ātman* and is considered "a metaphysical self, embodied in a biological self" (Bhawuk, 2011, p. 64). 'Self' is the observer or awareness (i.e., consciousness), separate from the egoic mind or "I" (i.e., selfhood, self-identity, or parts) (Schwartz, 2013). These tenets of psyche (or psychospirituality) are generally excluded in western psychology and traditional biomedical treatment. Colonialization and acculturation of European practices and beliefs (e.g., anthropocentrism; wendigo) (Porter, 2019) as well as mass genocide almost extinguished ancient ancestral teachings and beliefs pertaining to human beings' relationship with the Earth and the universe (i.e., cosmos, ether) and practices and principles that have prevailed for tens of thousands of years (Harner, 1990). Regardless, the desire and human need to relate to and feel connected within and beyond one's 'self' endures.

In the 1960s Maslow recognized the importance of intrapersonal connection; he also spoke to the human need of transpersonal connection (Grob & Bossis, 2017). Transpersonal is broadly defined as beyond ego or non-ego (Kelly, 2002). As self-expansive organisms, humans are energetically inseparable with the environment in a continuous, dynamic process, a concept Martha Rogers termed integrality (Armstrong & Kelly, 1995; Reed, 2016). Most providers and scientists are trained or taught to view research and clinical practices through the traditional

biomedical lens; concepts such as spirituality and transpersonal connection are frequently overlooked or considered by some to be 'magical thinking.' This limited connotation has left a void in mental health research and subsequently for many non-religious patients experiencing existential challenges that feel isolated and lost. The transpersonal perspective, like intrapersonal, is metaphysical in nature, not magical nor religious and includes principles of human beings as interconnected energetic beings, interrelated to one another and to everything including the cosmos (Maslow, 1968). As transpersonal beings, humans are comprised of nested, complex-adaptive systems and are simultaneously complex-adaptive systems that are embedded within systems within systems (Friedman, 2018) all inextricably linked.

The word 'trauma' also originates from Greek and translates to English as injury or wound (Thompson & Walsh, 2010). Subjectively, psychospiritual wounds result in a sense of disconnect within or intrapersonally (i.e., self-detachment) (Frankl, 1966) and/or transpersonally (i.e., existential crisis), beyond oneself. Qualitative research has identified guilt, shame, betrayal and intrapersonal and/or transpersonal mistrust, a desire for forgiveness, and changes in faith or spiritual beliefs as themes of the lived experience of PTSD (Starnino et al., 2019). Existential crisis results in questioning one's purpose in the world or in this life, and/or loss of faith in the existence of something greater than oneself (Harris et al., 2015). More specifically, there is a sense of intrapersonal disconnect from 'self' (i.e., higher self, wise self), between oneself and others (e.g., loved ones, animals or nature) or interpersonally, and/or between oneself and the universe (i.e., spirit, God, energetic dimension, etc.) or transpersonally.

Several terms have been used to describe the phenomenon of psychospiritual wound or injury by researchers depending on the population and scenario(s) being investigated. Moral

injury describes an internalized consequence of performing job-related duties that go against an individual's personal beliefs and/or ethics (e.g., combat). Moral injury results in feelings of guilt and shame; like veterans, frontline healthcare providers are particularly vulnerable to moral injury and secondary traumatic stress. Secondary traumatic stress (Cocker & Joss, 2016) arises from witnessing the suffering of others (e.g., adults, children during war time), or animals (e.g., veterinary medicine), hearing about another's traumatic experience(s), or bearing witness to the extreme distress of others on a repeated basis, requisites of many clinicians. Over time, this results in psychological and physical exhaustion that may outwardly present as apathy or dehumanization (Riethof & Bob, 2019). Mealer and Jones (2013) refer to this subset of nurses as wounded healers or walking wounded. This traumatic-stress phenomenon has also been called 'burnout syndrome' (Riethof & Bob, 2019); these individuals may experience extreme helplessness, vulnerability, exhaustion, and loss of purpose (i.e., existential crisis).

Psychospiritual injury may also arise from traumatic events in childhood (e.g., CM). Psychospiritual injury originating in early childhood contributes to attachment styles that unconsciously dictate individuals' ability to connect with others and often prevents development of healthy relationships (Dozier, Stovall-McClough, & Albus, 2008) and lack of self-efficacy. Children who survive CM, without the protective presence of adequate loving and supportive caregivers, develop core beliefs such as *I am a bad person* (i.e., it's my fault)*, I am not loveable, the world is unsafe* and *people are not to be trusted* (Thompson & Walsh, 2010). These beliefs when unidentified and untreated persist into adulthood (Dozier et al., 2008) resulting in a phenomenon Viktor Frankl (1966) termed, existential vacuum or may develop into chronic PTSD. Life may seem meaningless or there may be an ongoing sense of alienation and

disconnect, and/or a sense of emptiness, the antithesis of self-transcendence. Behaviors and situations arising from these beliefs and perceived disconnect may include abusive relationships, substance and/or alcohol misuse, self-harming (e.g., cutting, disordered eating) (Felitti et al., 1998), suicidality, and reckless impulsive behaviors (e.g., gambling).

Summary

Chronic PTSD results in physiological dysregulation (i.e., toxic stress) and lack of psychospiritual well-being; therefore, interventions and related assessment measures need to address both physiological and psychospiritual outcomes. To date, there are no FDA-approved psychotropics or clinical interventions designed to treat both physiological dysregulation and psychospiritual injury concurrently. Ketamine-assisted psychotherapy and other molecules currently in phase III clinical trials (e.g., psilocybin, MDMA) using concurrent psychotherapy may bridge this gap in mental healthcare. The next section will discuss study design and methodology for the proposed dissertation project.

CHAPTER III: METHODS

The study investigated psychological and psychospiritual (i.e., existential) outcomes in treatment-resistant depression (TRD) and post-traumatic stress disorder (PTSD) in adults who have received ketamine-assisted psychotherapy (KAP) in the past 12 months. An additional objective of the project was to explore whether adverse childhood experiences correlate with post-KAP PTSD symptom severity and post-KAP depression symptom severity. In this chapter, the study design, including methods, setting, sample, measures, procedures, and protection of human subjects, will be discussed.

Study Design

The project was a quasi-experimental two-group pre-/post-intervention design (Kazdin, 2017) and included a convenience sample from a clinical site in the southwestern United States (US). Data were collected from recruited adult participants post-intervention. That is, adults who had already received KAP in the previous 12 months were eligible for inclusion. Pretest and posttest depression and PTSD symptom measures were obtained from participants' secure electronic health records. Self-transcendence data were collected post-treatment in addition to the childhood maltreatment measure, the 'Adverse Childhood Experience' (ACE) questionnaire, if participants had not previously completed one. As part of their clinical care participants had received 0.3 mg/kg with gradual titration up to a maximum of 1 mg/kg of racemic ketamine IM for three or six KAP sessions.

Setting

Participants were recruited from an urban setting in the southwestern US. The outpatient clinic provided mental health services including psychotherapy, psychotropic medication

management, and ketamine-assisted psychotherapy (KAP) predominately to working professionals who were commercially insured. The two providers were American Nurses Credentialing Center (ANCC) board-certified psychiatric mental health nurse practitioners (across the lifespan) (i.e., PMHNP-BC).

Sample

Ethnicities of the patient population served at the Tucson clinic are approximately 77% white, 15% Latino, 5% two races or more, 2% African American, and 1% Asian. Post-institutional review board approval, a convenience sample was recruited. Inclusion criteria were adults aged 18 years or older who had participated in ketamine-assisted psychotherapy (KAP) within the previous 12 months. Participants were able to read, write, and speak English. Inclusion criteria to have received KAP was failure of ≥ 2 psychiatric interventions for depression and/or chronic PTSD. Medical and psychiatric exclusion criteria for KAP (Dore et al., 2019; Kolp et al., 2014) were untreated hypertension, history of cardio-or cerebrovascular disease, history of aneurism, not currently prescribed a mood stabilizer for lifetime history of bipolar I or II diagnosis, active mania or hypomania, diagnosis of a thought disorder (e.g., psychosis), lifetime history of severe brain injury, or being pregnant.

Following the initial psychiatric and medical evaluation for KAP, the treatment protocol for the clinical care of participants consisted of being scheduled for three initial KAP sessions along with a brief psychiatric follow-up assessment on the fourth or fifth day following the third KAP session. Psychiatric assessment at this post-third KAP session follow-up also consisted of subjective feedback of KAP treatment tolerability over the course of the first three sessions and reported symptom changes. Additional domains discussed during this appointment included

sleep quality, appetite, energy level, as well as psychiatric interview questions related to changes in affect regulation and distress tolerance. A humanistic, collaborative approach was employed in deciding the next best steps for each individual (e.g., no additional KAP sessions, vs. an additional three KAP induction sessions for a total of six); ultimately, treatment was based on mutual agreement by the psychiatric provider and each client.

As part of routing clinical care of the sample, psychometrics (e.g. PCL-5, PHQ-9) were obtained at baseline (i.e. prior to intake), after the third KAP session, and when applicable, after the sixth KAP session four days post-treatment. However, collected measures were not typically reviewed or considered in the decision-making process for continuing or discontinuing KAP treatment. Alternatively, the psychiatric provider relied on the psychiatric assessment and encouraged participants' self-efficacy, advocacy, and inclusion in making decisions related to their healthcare and healing.

Participants were administered between 0.3 mg per kg with titration up to 1 mg per kg or 20 mg to 70 mg racemic ketamine IM in either a 3-KAP or 6-KAP session induction series over one to three weeks, respectively, with at least one day in between KAP sessions. IM racemic ketamine dosage titration during the course of KAP treatment is illustrated in Table 1. A two-dose approach was used; the second IM dose was administered 12-minutes after the initial dose given the onset and half-life of IM-administered ketamine. Ketamine dosages administered were based on each individual's response, tolerability, and sensitivity to the medicine. Each KAP session was a total of 2.5 hours, and biometrics (e.g., heart rate, blood pressure) were obtained prior to ketamine administration and 1-hour post-booster dose administration at each session. Psychotherapeutic approaches used during participant preparation, intra-KAP session, and post-

KAP sessions were Jungian (e.g., metaphors, archetypes), principles from internal family systems (Schwartz, 2013) (e.g., defenses, protector parts; somatic-focused IFS), and tenets from attachment theory (e.g., attachment styles, transference).

Table 1

Intramuscular KAP Dosage Titration

	1st KAP Session	**2nd KAP Session**	**3rd KAP Session**	**4th KAP Session**	**5th & 6th KAP Sessions**
IM Dose I	10 mg-15 mg	10 mg-15 mg	15 mg – 20 mg	20 mg - 25mg	25 mg – 35 mg
IM Dose II (booster)	10 mg–15 mg	20 – 25 mg	20 mg – 25 mg	25 mg – 30 mg	25 mg – 35 mg
Session total	**20 mg to 30 mg**	**30 mg to 40 mg**	**40 mg to 45 mg**	**45 mg to 55 mg**	**50 mg up to 70 mg***

Note. Dosages and titration were based on individual's sensitivity and tolerability to the medication and experience.

Sample Size

An *a priori* power analysis was conducted using G*Power software (Faul, Erdfelder, Lang, & Buchner, 2007); a two-tailed paired t-test was used to determine the recommended sample size for within-subject pretest-posttest analysis. Effect size for depression and PTSD symptom severity in the limited available research papers had been reported as large; however, among these published reports one study had a small sample (n = 15) (Albott et al., 2019), and the other paper had a much a larger sample (n = 235) (Dore et al., 2019). Therefore, a more conservative medium effect size (0.5), was selected for calculating the sample size for this study. With an alpha of 0.05, and power of 0.8, the recommended sample size was N = 34 participants.

Measures

Psychological Measures

The '9-item Patient Health Questionnaire' (PHQ-9) (Spitzer, Kroenke, & Williams, 1999) was used to assess depression symptom severity; the 'PTSD Checklist for DSM-5' (PCL-5) (Weathers et al., 2013) was used to measure PTSD symptom severity; and the 'Adverse

Childhood Experience' (ACE) (Felitti et al., 1998) questionnaire was used to determine childhood maltreatment severity. Whether or not participants were KAP responders was determined by criteria by Weathers and colleagues (i.e., had a ≥ 10-point reduction in pre- to post-PCL scores (Weathers et al., 2013). These three measures, target population, foci, psychometrics, estimated completion time and respondent are listed in Table 2 below and the instruments are listed in Appendix A.

Table 2

Psychological Measures

Measure	Population & Type of Measure	Focus	Psychometrics	Estimated Completion Time
Patient Health Questionnaire (**PHQ-9)** 9-item	≥ 18 years old	Depression Symptom Assessment & Severity	Internal Consistency (Cronbach's α = .86) - .89; Test-Retest Reliability	5 minutes
Post-traumatic Stress Disorder Checklist for DSM-5 **(PCL-5)**	≥ 18 years old	DSM-V PTSD criteria & PTSD Symptom Severity	Internal Consistency (α = .95); Test-Retest Reliability	15 minutes
Adverse Childhood Experience **(ACE)** Questionnaire	≥ 18 years old	Childhood Maltreatment (e.g., Emotional Neglect & Abuse) Assessment	Internal Consistency (Cronbach's α = .88); Test-Retest Reliability	5 minutes

The PHQ-9 (Spitzer, Kroenke, & Williams, 1999) is a 9-item Likert-type scale that can be used to diagnose major depressive disorder and to assess depression severity in adults. Scores range from 0 – 27 with increasing depression symptom severity as scores increase. These ranges are 1 - 4, 5 – 9, 10 – 14, 15 – 19, and ≥ 20 representing minimal, mild, moderate, moderately severe, and severe respectively (Kroenke, Spitzer, & Williams, 2001). In two studies (n = 3000) using convenience samples and conducted in primary care and obstetrical clinics. Internal consistency was very good (Cronbach's α = .86 -.89), and excellent test-retest reliability has been reported. The PHQ-9 has also been found to have stability (e.g., test-retest & inter-rater) and was

sensitive to change. AUC was .95 for major depression. No modifications were made to this instrument.

The PCL-5 is a 20-item self-report measure with a Likert-type scale that can be used to assess PTSD symptom severity. The PCL-5 has four subscales aligned with DSM-5 criteria, these are alterations in arousal and reactivity, negative changes in cognition and mood, intrusion, and avoidance (Sveen, Bondjers, & Willebrand, 2016). Scores range from 0 – 80, with cumulative scores $\geq$ 31 typically indicating post-traumatic stress disorder (PTSD) per the DSM-V criteria, and scores $\leq$ 31 indicating sub-threshold PTSD sequelae. Two studies (N = 278) and (N = 558) of trauma-exposed (e.g., auto collision) college students (Blevins et al., 2015); demonstrated strong internal consistency (α = .94) as well as test-retest reliability (r = .82), PCL-5 scores were moderately correlated with related constructs (e.g., depression; r = .60). The strongest correlations were found between the PCL-5 and three other PTSD instruments: PCL, PDS, and DAPS (rs = .85, .85, and .84, $p < .01$).

The ACE is a 10-item questionnaire designed for adults aged 18 years or older to assess for childhood maltreatment, including neglect, abuse, witnessing abuse, and household dysfunction (Felitti et al., 1998). The scale can be used as dichotomous (categorical) for evaluating general types of childhood maltreatment and as continuous data by adding the "Yes" responses for totaled ACE score, as will be the case for the proposed project. Higher ACE values, specifically $\geq$ 4, have been strongly associated with poorer physical and mental health and premature mortality in adulthood (CDC, 2020) (e.g., cardiovascular, autoimmune disease, depression, substance abuse). For the purposes of the proposed project, total ACE scores were analyzed for association with PHQ-9, PCL-5, and self-transcendence scale (STS) scores post-

KAP sessions. Data analyzed from a 2018 study of college athletes (N = 141) who were administered the ACE questionnaire one year apart yielded the test-retest coefficient to be on the lower end of acceptable ($r = .71$, $p < .001$) (Zanotti et al., 2018). ACE scores have been strongly and positively correlated with risk of developing depression in adult men and women ($p < 0.0001$) (Chapman, 2004); this further supports use of the ACE questionnaire in the proposed project.

Psychospiritual Measures

Tenets of Reed's (1991) Self-transcendence Scale (STS) relating to ketamine-assisted psychotherapy (KAP) are interpersonal, intrapersonal, transpersonal, and temporal shifts in perceived boundaries and developmental progression. The latter can be stunted due to CM, and as discussed, unhealthy attachment styles. KAP may provide an opportunity to process and begin healing early childhood (attachment) wounds, thus transcending spiritually and/or developmentally. Chronic PTSD results in a profound sense of separateness by those experiencing it; this sense of alienation and isolation is perceived within and between self and the outside world. This sense of isolation has been reported to abate post-induction of non-ordinary states of consciousness in clinical trials of psilocybin (Belser et al., 2018) and in a small number of published ketamine papers (Kolp et al., 2007) when administration was provided in a safe therapeutic setting.

Participants have also reported a profound sense of intrapersonal and transpersonal expansiveness and connection (Mathai et al., 2018) post-ketamine administration, concepts included in Reed's (1987) 'theory of self-transcendence' and measured by the 'self-transcendence scale' (STS). The STS is comprised of 15 questions using a Likert-type scale with

responses ranging from 1 – 4, “not at all” to “very much;” cumulative STS score ranges are 15 – 30, 31 – 45, and 46 – 60 representing low, moderate, and high levels self-transcendence (Reed, 2015), respectively. Other reasons for selecting the STS for assessment of psychospiritual well-being were its previous use in adult and older adult participants (i.e., similar population); its use in other studies evaluating depression in which a significant inverse relationship between self-transcendence and depression ($r = -.33$, $P < 0.01$) (Reed, 2018) were reported (Table 3). Another study’s investors reported an inverse correlation between self-transcendence with suicide and depression (Reed, 2018). Strong, positive correlations have been demonstrated between self-transcendence, hope, purpose in life, and cognitive and emotional well-being (Coward, 1996) in healthy middle-aged adults. Finally, STS was found to have internal consistency (Cronbach’s α = .8 -.94) and test-retest reliability (Coward, 1996), including several mental health-related investigations (Reed, 1986; Reed, 1989; Reed, 1991).

Table 3

Psychospiritual Measures

Measure	Population	Focus	Psychometrics	Estimated Completion Time
Self-Transcendence Scale **(STS)**	≥ 18 years old	Vulnerability [intrapersonal, transpersonal, temporal] Expansion, Well-being	Internal Consistency Cronbach’s α = .8 - .94; Test-Retest Reliability	10 minutes

Procedures

Data Collection and Management

Informed consent was obtained electronically using a secure electronic platform (Appendix C). Baseline depression (e.g., PHQ-9), and PTSD symptom severity (e.g., PCL-5)

data had been obtained within two weeks prior to starting the KAP sessions and between days four to seven days after the third KAP treatment and, if applicable, four to seven days after their sixth KAP session. The pretest-posttest PHQ-9 and PCL-5 measures were in patients' secure electronic health records (EHR); the STS, informed consent, and the study's completed demographic documents were saved using a secure platform (IntakeQ). The STS was collected post-KAP only and retrospectively; therefore, causality and correlation could not be accurately determined as many participants completed the STS months after their final KAP session concluded. Three forms including the demographic form, ACE questionnaire, and self-transcendence scale (STS) (Appendix A) were obtained and took approximately 35 minutes to complete (Table 4). Measures and forms were provided electronically in fillable formats via a secure platform called IntakeQ. The small scale of the study and the retrospective design made data collection and management feasible, secure, and cost effective.

Table 4

Respondent Measures and Estimated Completion Time

Measure / Item	Estimated Time for Completion
Demographic Form	15-20 minutes
ACE Questionnaire	5 minutes
STS	10 minutes
TOTAL = 3	**Minutes = 35 - 40**

Data Analysis

Participants' data were deidentified and entered in IBM's SPSS version 27 software (2020) for analysis. Descriptive statistics (Appendix A) (mean, median, mode, standard deviation) included participants' socioeconomic information, relationship status, race and ethnicity, and level of education. Effect size was determined using Cohen's *d.*

Aim 1: To Compare Depression Severity and PTSD Symptom Severity Pre- and Post-KAP

Hypothesis 1a - There will be a reduction in post-KAP depression severity compared to pre-treatment.

Hypothesis 1b - There will be a reduction in post-KAP PTSD symptom severity compared to pre-treatment.

Aim 1 Analysis

Paired t-tests were used to analyze changes in depression symptom severity (PHQ-9) and PTSD symptom severity (PCL-5) pre-treatment to post-KAP treatment. Only final PHQ-9 and PCL-5 scores (e.g., after three or six KAP sessions) were used in the paired t-test analysis.

Aim 2: To Describe Self-Transcendence Post-KAP

Hypothesis 2 - Self-transcendence Scale scores will be moderate to high or $\geq$ 31 post-KAP.

Aim 2 Analysis

Descriptive statistical analysis was used to describe participants' STS scores.

Aim 3: To Examine Associations Between Self-Transcendence and PTSD Symptom Severity and Self-Transcendence and Depression Severity Post-KAP and Between Adverse Childhood Experiences and PTSD Symptom Severity and Between Adverse Childhood Experiences Self-Transcendence and Depression Severity Post-KAP

Hypothesis 3a - There will be an inverse association between self-transcendence and PTSD symptom severity.

Hypothesis 3b - There will be an inverse association between self-transcendence and depression severity.

Aim 3 Analysis

Pearson's correlation was used to analyze associations between self-transcendence scores (STS) and depression symptom severity (PHQ-9), between STS scores and post-KAP trauma symptom severity (PCL-5), and between ACE scores and post-KAP PTSD symptom severity measures (PCL-5), and between ACE scores and depression symptom severity (PHQ-9).

Protection of Human Subjects

Recruitment and Informed Consent

Informed consents were obtained during a secure virtual meeting by a research team member not directly involved in participants' care. During the virtual encounter, the same IRB script (Appendix B) was used to obtain informed consent. Informed consent included a copy of the Health Insurance Portability and Accountability Act (HIPAA) regarding the maintenance and protection of participants' confidentiality and protected health information (PHI), and permission to review participants' electronic health record (EHR) (Appendix C).

Potential Risks to Human Subjects

The study included pre-/post-measures; however, as a retrospective design, participants had previously received the intervention (KAP) in the past 12 months. Adverse reactions or side effects were assessed and documented as part of clinical care, however, if adverse reactions or side effects occurred, they most likely occurred during the ketamine-assisted psychotherapy (KAP) treatment or within one-hour post-treatment (e.g., nausea). There were no potential physical or health risks associated with the project. Based on previous research and power analysis, the aim was to recruit 35 participants. The study was conducted with guidance from the

University of Arizona College of Nursing faculty after institutional review board (IRB) approval through the university (Appendix D).

Sources of Materials and Protection Against Risks

Post-recruitment, the principal investigator (PI) created an Excel spreadsheet key to deidentify participants. The master key was only accessible to the PI in a password-protected file. Pre-treatment and post-treatment measures (e.g., PHQ-9, PCL-5) used for analyses were located in participants' secure electronic health records (EHR). Measures obtained post-recruitment were sent and returned via a secure, the HIPAA-compliant app, IntakeQ.

Importance of Knowledge to be Gained and Potential Benefits

Potential benefits and the importance of information gained from the proposed project were additional insights into the use of a novel modality, ketamine-assisted psychotherapy (KAP), in the treatment of chronic PTSD. Approximately 50% of persons diagnosed with PTSD have co-occurring depression (Choi, 2019). As discussed, annual suicide rates in young to middle-aged adults in the last decade has been unprecedented and is now the second leading cause of death in this demographic. More than 8,000 US veterans (VA, 2019), 300 to 400 physicians (Dos Santos, 2017), and approximately 9,000 nurses (Davidson et al., 2020) die from suicide each year. Unfortunately, for many who seek help to ease their suffering, currently available treatments are ineffective. For example, 3.4% of 30,384 veterans who were treated for PTSD in a residential program attempted suicide within four months of being discharged (Stefanovics & Rosenheck, 2019). If a novel intervention reduced suicide rates by 3% each year in the US, approximately 500 veterans and healthcare providers' lives could be saved and

countless friends, colleagues, and families could be spared the pain and loss of a loved one resulting from suicide.

Chronic PTSD and TRD are complex conditions; underlying factors contributing to unremitting PTSD and depression are not well understood, contrary to the pervasiveness of both conditions. A second potential benefit of this project was in determining whether KAP may be efficacious in adults with TRD and/or chronic PTSD with a history of childhood maltreatment (i.e., CM; ACEs). If KAP is efficacious in this population, using the PNI framework, KAP responders with a history of ACE might experience a shift from a state of toxic stress to allostasis. Over time, an allostatic state could improve overall health, reducing systemic inflammation associated with numerous chronic medical conditions (e.g., autoimmune, cardiovascular disease). Finally, the project findings provided information about a novel modality that encompasses the traditional biomedical framework *and* includes a humanistic, holistic paradigm exploring the psychospiritual aspects of chronic PTSD and TRD. This notion is not new to nursing; however, these tenets of human well-being continue to be overlooked in allopathic mental healthcare.

Summary

This project was the first psychedelic-assisted psychotherapy study to use Reed's Self-transcendence scale (STS). Additionally, it was one of very few studies exploring ACE association with TRD and chronic PTSD. If KAP positively influenced existential well-being, KAP may be investigated for efficacy in additional healthcare settings (e.g., palliative or hospice care); for example, KAP may ease the suffering of patients with terminal diagnoses experiencing psychospiritual or existential angst in addition to analgesia.

CHAPTER IV: RESULTS

Participants' data were collected between July 15, 2021, through March 10, 2022. Participants (N = 33) received a total of three (n = 12) or six (n = 20) KAP sessions, except one participant who had a total of five inductions sessions due to travel and was not able to complete a sixth KAP session. Ketamine was administered intramuscularly (IM), exclusively (i.e. no other routes of ketamine administration were used). Per methods specified in Chapter III, each participant had a 30-minute virtual psychiatric assessment appointment with their KAP provider on day four or five after their third KAP session, to determine whether or not three additional sessions (for a total of six) were warranted to achieve the desired clinical outcome.

Post-KAP PTSD symptom severity measures (PCL-5) and post-KAP depression symptoms severity measures (PHQ-9) were obtained electronically between days four to seven after the third day and, when applicable, sixth KAP session. Self-transcendence scales (STS) were administered after participant recruitment and consent were obtained. Participant measure data entry was verified by two of the study investigators before statistical analyses began. Pre-KAP PCL measures were missing for two of the participants recruited; however, post-KAP PCL scores were collected for the entire (N = 33) sample. Descriptive statistics (i.e., mean, median, mode, range and standard deviation) were used to describe participants' socioeconomic information, relationship status, race and ethnicity, and level of education (Table 5).

Table 5

Sociodemographic Characteristics of Participants

	n	%
Gender		
Female	21	63.6
Male	11	33.3
Non-binary	1	3
Race		
White	29	87.8
Multiracial	2	6.1
Indigenous or Native	2	6.1
Ethnicity		
White, Hispanic	2	6.1
Other	6	18.2
White, Non-Hispanic	2	75.7
Marital Status		
Divorced	5	15.2
Domestic Partner/Married	18	57.5
Single	9	27.3
Widowed	1	3.0
Highest Educational Level		
HS/GED	6	18.2
Assoc/Technical Degree	3	9.1
Bachelor	8	24.2
Master	9	27.3
Doctoral	7	21.2
Income		
< $25,000	10	30.3
$25,000 - $49,999	7	21.2
$50,000 - $74,999	3	9.1
$75,000 or more	11	33.2
Declined	2	6.1

Note. N = 33. Participants were on average 43 years old, ages ranged from 20 to 69 years-old (SD = 15).

Descriptive Statistics

A total of 33 participants were recruited; sociodemographic descriptive statistics are depicted in Table 5. Of the 33 participants, 21 identified as female, 11 as male, and 1 as non-binary. Ages ranged from 20 to 69 (M = 43, SD = 15) years-old; 57.5% were married or resided with a domestic partner, 15.2% were divorced, 27.3% were single, and 3% were widowed. Participants' races were 6.1% Indigenous or Native American, 87.8% (n = 29) were White, and

6.1 % (n = 2) were Multiracial. Ethnicities were self-reported as 18.2 % (n = 6) Other, 6.1% (n = 2) Hispanic, and 75.8% (n = 25) as non-Hispanic.

Participants reporting annual household income of less than $25,000 comprised 30.3% of the sample; 21.2% of participants reported household earning between $25,000 - $49,999 annually; 9.1% reported household earnings between $50,000 - $74,999 annually; and 33.3% reported household earnings of $75,000 or more annually (Table 5). Two participants (6.1%) opted not to share their household income. Regarding highest educational degree, 18.2% received a high school diploma or GED, 9.1% held an Associate's or technical degree, 24.2% had earned a Bachelor degree, and 48.5% held Master's or Doctoral degrees.

Twenty-five (75.5%) of the participants were taking at least one concurrent psychotropic at the time of their KAP inductions sessions, and 15 (45.5%) were engaged in psychotherapy (with a therapist outside of the practice). Childhood maltreatment was measured with the ACE questionnaire. Sample (N = 33) ACE score mean was 4.45 (SD = 2.84), 66.7% (n = 22) participants reported $\geq$ 4 ACEs. Twenty-one (63.6%) of the participants met DSM-V criteria for chronic PTSD at baseline (i.e. pre-KAP); 71.4% of these participants with PTSD were females, 23.8% were males, and 4.7% were non-binary. Four participants were veterans, two veterans were female and two were male. All minority participants met diagnostic criteria for chronic PTSD at baseline, except one.

Meeting the Assumptions of Parametric Testing

Pre- and post-KAP depression symptom severity scores (N = 33) and pre-KAP (N = 31) and post-KAP (N = 33) PTSD symptom severity scores were analyzed using a Shapiro-Wilk test (Field, 2015), depicted in Table 6 below. Results indicated normal distribution of each study variable except post-PCL-5 scores, W (31) = 0.87, p = 0.001, these data were positively skewed. Distributions of pre- to post KAP depression symptom severity scores and PTSD symptom severity scores and mean change scores are depicted below (Figure 2 to Figure 7). Additionally, ACE questionnaire (N = 33, M = 4.45, SD = 2.84) and STS score (N = 33, M = 44, SD = 9.83) distributions are displayed.

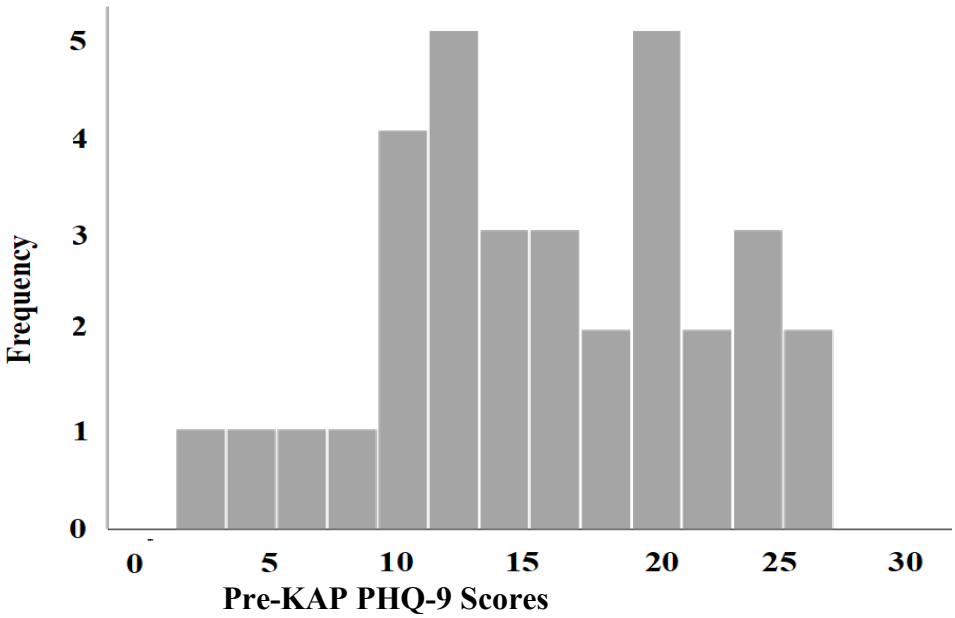
Table 6

Shapiro-Wilk Test of Raw Data Normality

	Statistic	df	Sig.
Pre-PhQ-9	.966	33	.407
Post-PhQ-9	.941	33	.088
Pre-PCL-5	.967	31	.446
Post-PCL-5	.866	31	.001
PHQ-9 Change	.970	33	.527
PCL-5 Change	.962	31	.323

Figure 2

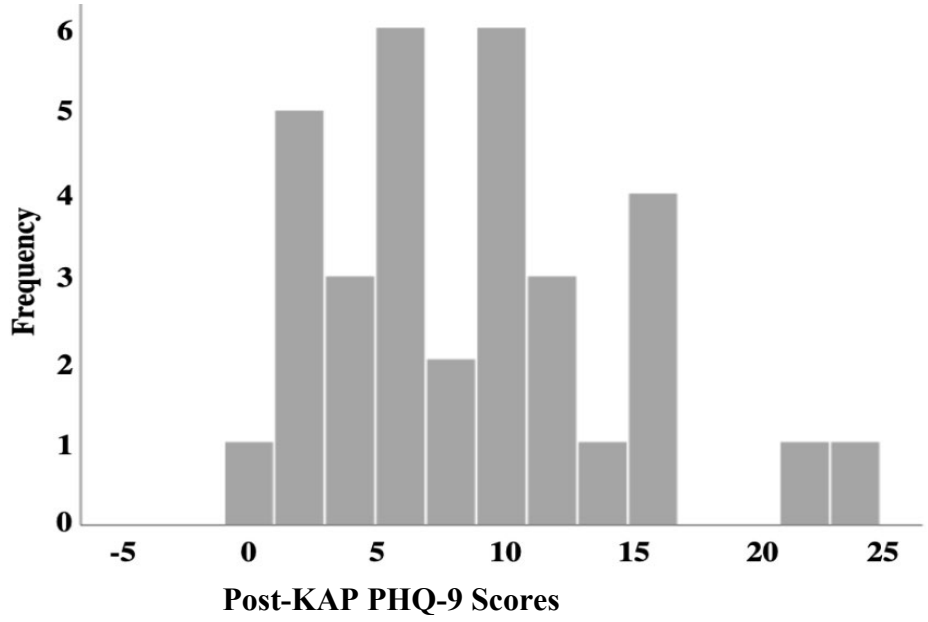
Pre-KAP PHQ-9 Score Distribution



Note. (N = 33, M = 14.97, SD = 6.27)

Figure 3

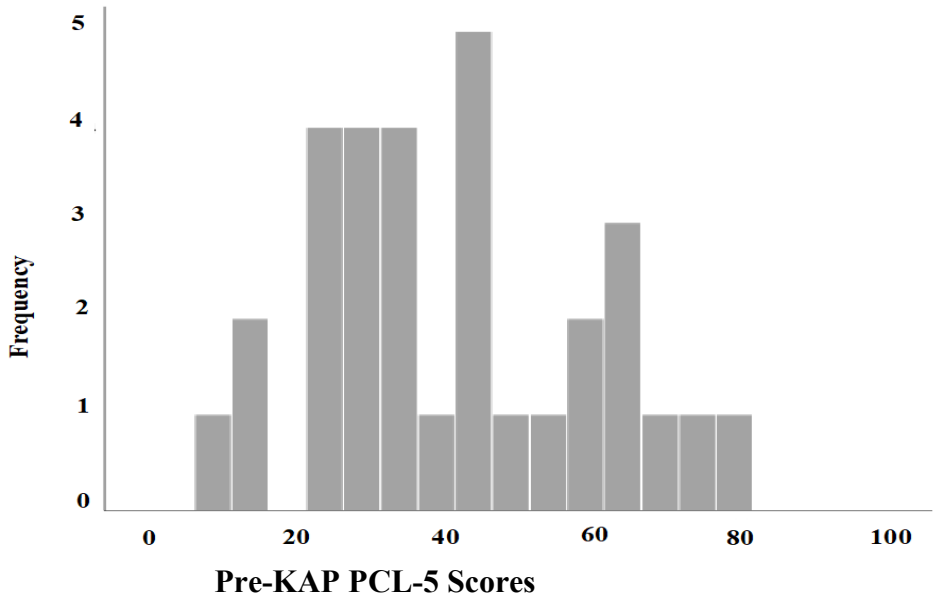
Post-KAP PHQ-9 Score Distribution



Note. (N = 33, M = 8.48, SD = 5.73)

Figure 4

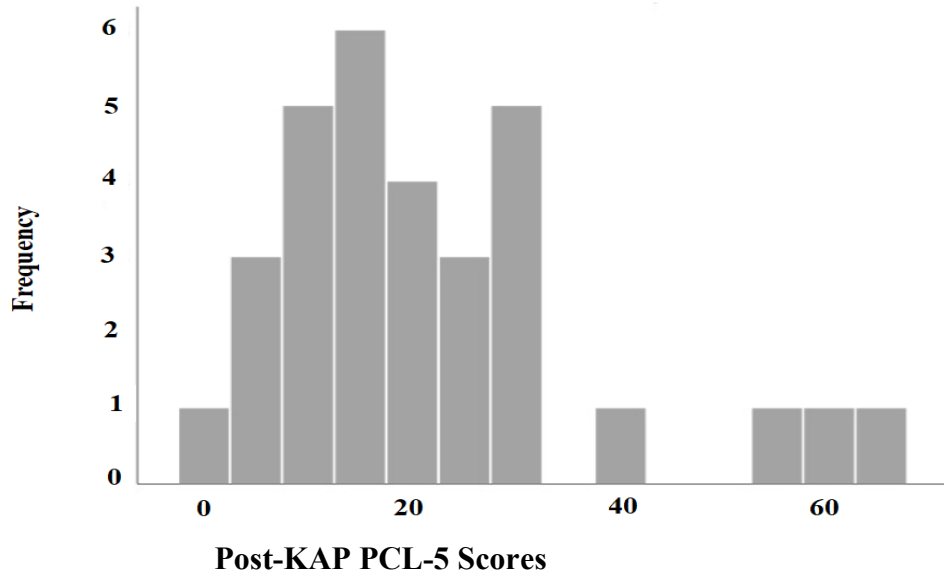
Pre-KAP PCL-5 Score Distribution



Note. (N = 31, M = 40.87, SD = 18.46)

Figure 5

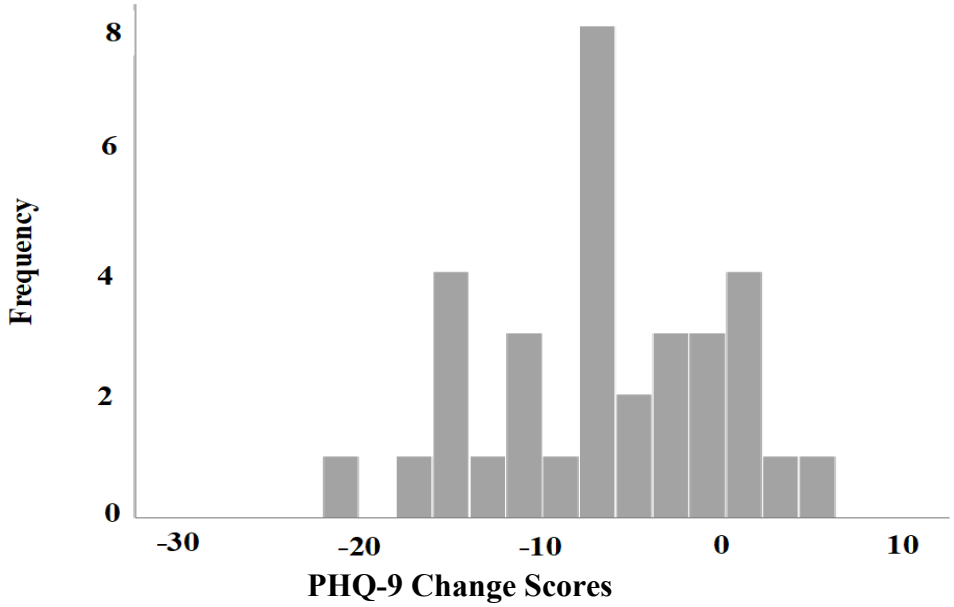
Post-KAP PCL-5 Score Distribution



Note. (N = 33, M = 21.65, SD, 19.41)

Figure 6

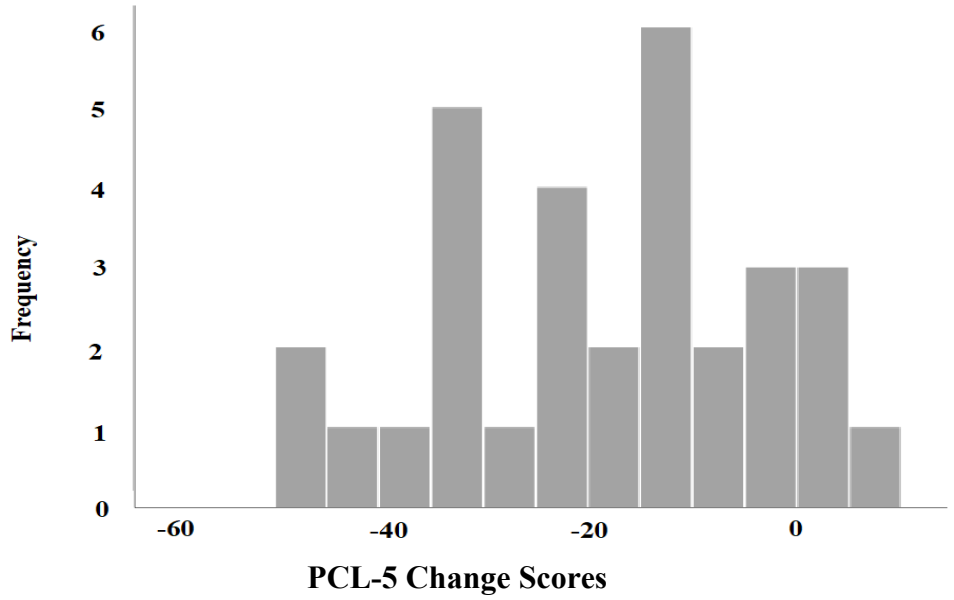
PHQ-9 Change Distribution



Note. (N = 33, M = -7.06, SD = 6.34)

Figure 7

PCL-5 Change Distribution



Note. (N = 31, M = -19.23, SD = 14.91

Aim 1: To Compare Depression Severity and PTSD Symptom Severity Pre- and Post-KAP

Hypothesis 1a - There will be a reduction in post-KAP depression severity compared to pre-treatment.

Hypothesis 1b - There will be a reduction in post-KAP PTSD symptom severity compared to pre-treatment.

Aim 1 Analyses

To address Hypotheses 1a and 1b, a 2-tailed paired t-test was used to analyze pre- to post-KAP PTSD symptom severity (PCL-5) scores and depression symptom severity (PHQ-9) scores. Analyses revealed a significant overall (N = 31) decrease in PTSD symptom severity from before to after KAP (M = 19.16, SD = 14.98, SEM = 2.69, CI: 13.67, 24.65, t = (df) 7.12, $p < .001$, $d = 1.28$). Similarly, there was a significant decrease in overall (N = 33) depression symptom severity from before to after KAP (M = 6.49, SD = 6.64, SEM = 1.16, CI: 4.13, 8.84, t = (df) 5.61, $p < .001$, $d = .97$). Of note, post hoc analysis revealed that change in depression symptom severity and PTSD symptom severity were found to be strongly associated with one another, $r (31) = .71$, $p < .001$ (Figure 8).

Pre- to post-KAP depression symptom severity and PTSD symptom severity statistics were also compared between participants who received three (n = 12) or six (n = 20) total KAP sessions. Tables 8 and 9 and Figures 9 and 10 illustrate these data. Descriptive statistical analysis indicated that six KAP sessions may result in lower PTSD symptoms severity A post hoc two-way ANOVA was performed to examine the effect of three versus six KAP sessions on PTSD symptom severity, as well as a post-hoc Shapiro-Wilk's test of residuals (Table 7) to recheck the split data (i.e., three versus six session mean scores pre-and post-KAP) for normality. Pre-and

post-KAP PHQ-9 and PCL-5 mean scores were normally distributed ($p > .05$) for participants who received three or six total KAP sessions with the exception of post-KAP PCL-5 scores after three ($p = .03$) and after six ($p = .04$) sessions. Upon assessment of the studentized residuals, there were no values greater than ±3 *SD* indicating no outliers.

There was not a statistically significant interaction between the number of KAP sessions and PTSD symptom severity, ($F(1, 28) = .140$ $p = .711$) or within groups, ($F(1, 28) = .490$, $p = .49$). There was a statistically significant difference in pre- to post-PTSD symptom severity within-subjects independent of the number of KAP sessions, ($F(1, 28) = 52.25$, $p < .001$). A second two-way ANOVA was performed to evaluate the effect of the number of KAP sessions' (e.g., three or six) on depression symptom severity. Similarly, there was not a statistically significant interaction between depression symptom severity and the number of KAP sessions, ($F(1, 30) = .137$ $p = .714$) or within-groups, ($F(1, 30) = .041$, $p = .841$). Depression symptom severity scores pre- to post-KAP was statistically significant ($F(1, 30) = .30$, $p < .001$) independent of the number of KAP sessions.

Table 7

Shapiro-Wilk Test of Residuals' Normality

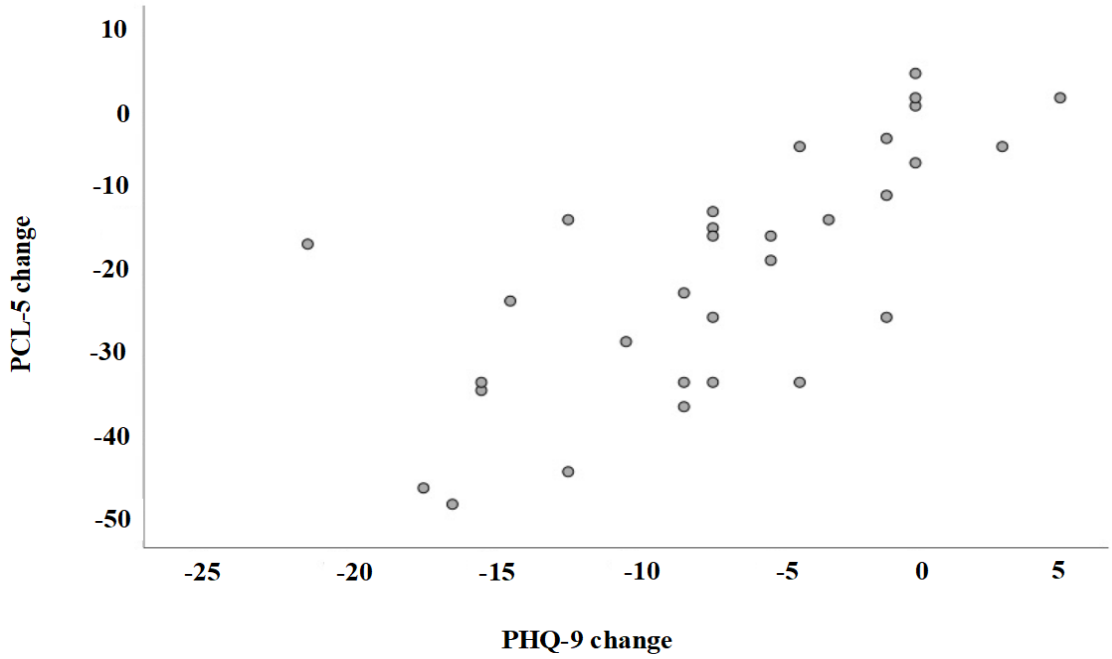
	# of KAP Sessions	Statistic	df	Sig.
Pre-PHQ-9	3	.859	12	.05
	6	.939	20	.23
Post-PHQ-9	3	.945	12	.57
	6	.914	20	.08
Pre-PCL-5	3	.948	12	.6
	6	.962	18	.65
Post-PCL-5	3	.838	12	.03
	6	.893	18	.04

Additional post-hoc findings were, 86% of participants with chronic PTSD ($n = 21$) were considered KAP responders or experienced a $\geq$ 10-point reduction in their cumulative PCL-5

scores pre- to post-KAP (Weathers et al., 2013) after three or six sessions. Eighty-one percent of the participants with a baseline diagnosis of chronic PTSD (n = 21) no longer met diagnostic criteria for PTSD after receiving three or six KAP sessions based on post-treatment psychiatric assessment and confirmed by cumulative post-KAP treatment PCL-5 scores $\leq$ 31, indicating sub-threshold PTSD sequelae (Sveen, Bondjers, & Willebrand, 2016) within five days after their last KAP session. Four participants from the overall sample (N = 33) had PCL-5 scores $\geq$ 31 at the conclusion of their KAP treatment, two of these participants received three KAP sessions and two received a total of six KAP sessions (Table 8 & 9).

Figure 8

Correlation Between PTSD Symptom Severity Change and Depression Symptom Severity Change



Note. r (31) = .71, p < .001

Table 8

Pre- to Post-KAP PHQ-9 and PCL-5 Change by Number of KAP Sessions

	# KAP Sessions	N	Mean	SD	Std Error	95% CI	Lower Bound	Upper Bound	Min	Max
PHQ-9 Change	3	12	-7	6.58	1.9		-11.88	-2.82	-21	5
	5*	1	.00							
	6	20	-6.5	6.31	1.41		-10.40	-4.50	-17	3
Total		33	-7.06	6.34	1.10		-9.31	-4.81	-21	5
PCL-5 Change	3	12	-17.75	11.42	3.3		-25.01	-10.49	-36	2
	5*	1	5						5	5
	6	18	-21.56	16.32	3.85		-29.67	-13.44	-48	2
Total		31	-19.23	14.91	2.68		-24.70	-13.76	-48	5

**Note.* One participant received five KAP sessions due to a scheduling conflict that arose during treatment.

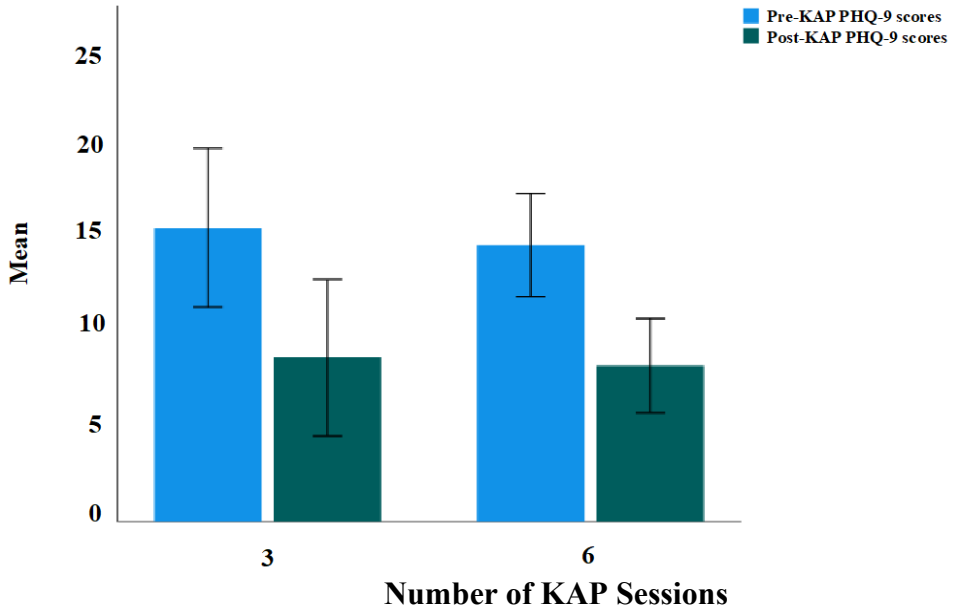
Table 9

Pre- and Post-KAP PHQ-9 and PCL-5 Mean Scores for Three vs. Six Sessions

# of KAP Sessions	N	Mean	SD
PHQ-9			
Pre-3 KAP Sessions	12	15.83	6.74
Post-3 KAP Sessions	12	8.83	6.16
Mean Score Change -7			
Pre-6 KAP Sessions	20	14.9	5.97
Post-6 KAP Sessions	20	8.4	5.42
Mean Score Change -6.5			
PCL-5			
Pre-3 KAP Sessions	12	41.67	18.37
Post-3 KAP Sessions	12	23.92	19.08
Mean Score Change -17.75			
Pre-6 KAP Sessions	18	41.33	19.07
Post-6 KAP Sessions	18	19.78	14.26
Mean Score Change -21.55			

Figure 9

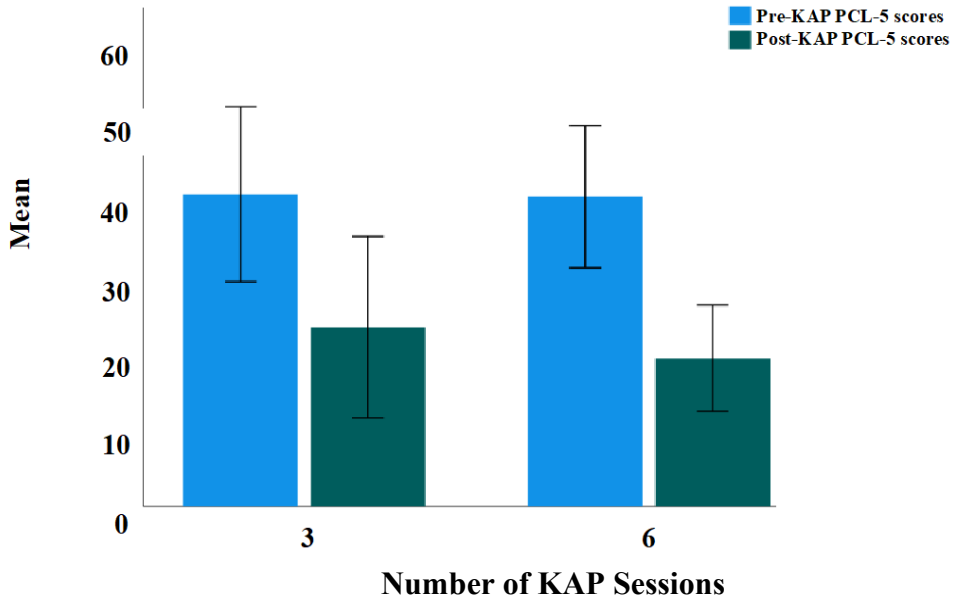
PHQ-9 Scores Pre- to Post-KAP by Total Number of KAP Sessions



Note. Error bars depict the standard error of the mean.

Figure 10

PCL-5 Scores Pre- to Post-KAP by Total Number of KAP Sessions



Note. Error bars depict the standard error of the mean.

Aim 2: To Describe Self-Transcendence Post-KAP

Hypothesis 2 - Self-transcendence Scale scores will be moderate to high or ≥ 31 post-KAP.

Aim 2 Analyses

Self-transcendence scale (STS) scores were collected post-KAP only. Self-transcendence (STS) scores between 31 – 45 and 46 – 60 indicate moderate to high levels of self-transcendence, respectively (Reed, 1987). Ninety-four percent of participants' self-transcendence scale scores were ≥ 31, and 6% were ≤ 30. A one-sample t-test, using a test value of 31, revealed that post-KAP STS scores of participants in the sample were above the cutoff of moderate self-transcendence (M = 44, SD = 9.84, SEM = 1.71, CI: 9.51, 16.49, t = (df) 7.59, $p < .001$).

Frequencies of responses for individual items on the self-transcendence scale (STS) are depicted in Table 10.

Table 10

Self-transcendence Scale Responses (N=33)

	Not at all	Very little	Somewhat	Very much
Having hobbies or interests I can enjoy.	3%	36.4%	33.3%	27.3%
Accepting myself as I grow older.	6%	15.2%	60.6%	18.2%
Being involved with other people, or my community when possible.	3%	24.2%	51.5%	21.2%
Adjusting well to my present life situation.	6%	24.2%	45.5%	24.2%
Adjusting to changes in my physical abilities.	6%	12.1%	63.6%	18.2%
Sharing my wisdom or experience with others.	6%	30.3%	33.3%	30.3%
Finding meaning in my past experiences.	3%	21.2%	30.3%	45.5%
Helping others in some way.	0	27.3%	39.4%	33.3%
Having an ongoing interest in learning.	3%	24.2%	33.3%	36.4%
Able to move beyond some things that once seemed so important.	6%	9%	60.6%	24.2%
Accepting death as a part of life.	3%	12.1%	39.4%	45.5%
Finding meaning in my spiritual beliefs.	18.2%	18.2%	27.3%	36.4%
Letting others help me when I may need it.	0	24.2%	54.5%	21.2%
Enjoying my pace of life.	6%	39.4%	36.4%	18.2%
Letting go of past regrets	6%	24.2%	45.5%	24.2%

Aim 3: To Examine Associations Between Self-Transcendence and PTSD Symptom Severity and Self-Transcendence and Depression Severity Post-KAP and Between Adverse Childhood Experiences and PTSD Symptom Severity and Between Adverse Childhood Experiences Self-Transcendence and Depression Severity Post-KAP

Hypothesis 3a - There will be a positive association between CM and PTSD symptom severity measurements post-KAP.

Hypothesis 3b - There will be a positive association between CM and depression symptom severity measurements post-KAP.

Aim 3 Analyses

Pearson's correlations were performed at the 2-tailed level to determine associations between self-transcendence and post-KAP PTSD symptom severity, and between self-transcendence and post-KAP depression symptom severity (Table 11). Analyses revealed a statistically significant inverse correlation between self-transcendence and post-KAP PTSD symptom severity, r (31) = -.75, p < .001 (Figure 11), and a statistically significant inverse correlation between self-transcendence and post-KAP depression symptom severity, r (31) = -.84, p < .001 (Figure 12).

Table 11

Correlations Between STS and Post-KAP PHQ-9 and Between STS and Post-KAP PCL-5 Scores

		Post-PHQ-9	**Post-PCL-5**	**STS**
Post-PHQ-9	Pearson Correlation	1	.725**	-.843**
	Sig. (2-tailed)		<.001	<.001
Post-PCL-5	Pearson Correlation	725*	1	-.753**
	Sig. (2-tailed)	<.001		<.001
STS	Pearson Correlation	-.843**	-.753**	1
	Sig. (2-tailed)	<.001	<.001	

Note. (N = 33, correlation is significant at the 2-tailed level).

Figure 11

Self-transcendence Scale and Post-KAP PTSD Symptom Severity

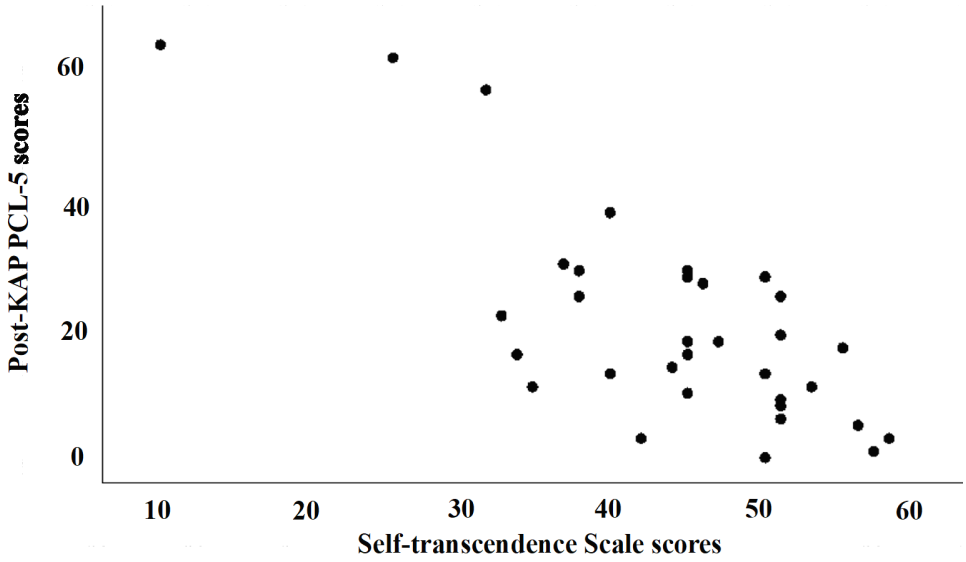
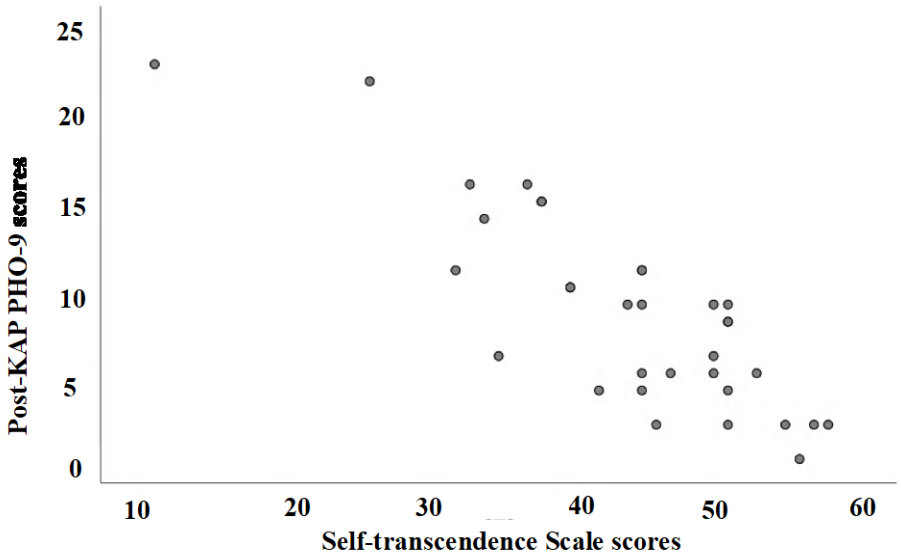


Figure 12

Self-transcendence Scale and Post-KAP Depression Symptom Severity



Pearson's correlations were also performed at the 2-tailed level to determine associations between ACE scores and post-KAP depression symptom severity, and between ACE scores and post-KAP PTSD symptom severity (Table 12). A positive, but non-significant correlation was found between ACE scores and post-KAP depression symptom severity (r (31) = .099, p = .582); this is depicted as a scatterplot below (Figure 13). Similarly, a non-significant, but positive trend correlation was found between ACE scores and post-KAP PTSD symptom severity (r (31) = .251, p = .159) (Figure 14).

Table 12

Correlations Between ACE and Post-KAP PHQ-9 Scores and Post-KAP PCL-5 Scores

		Post-PHQ-9	**Post-PCL-5**	**ACE**
Post-PHQ-9	Pearson Correlation	1	.725*	.099
	Sig. (2-tailed)		<.001	.582
Post-PCL-5	Pearson Correlation	.725*	1	.251
	Sig. (2-tailed)	<.001		.159
ACE	Pearson Correlation	.099	.251	1
	Sig. (2-tailed)	.582	.159	

Note. N = 33; correlations at the 0.01 level (2-tailed).

Figure 13

Scatter Plot Reflecting the Relationship Between ACE Scores and Post-KAP PHQ-9 Scores

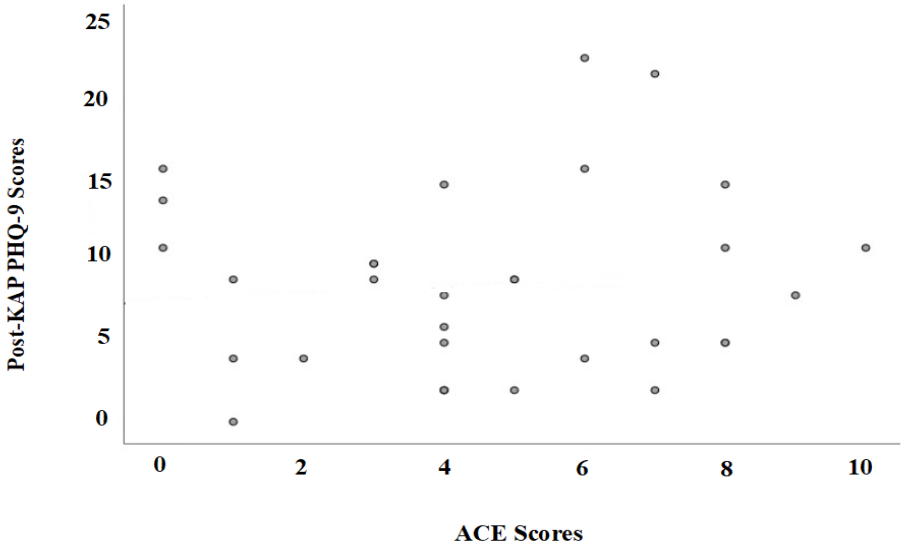
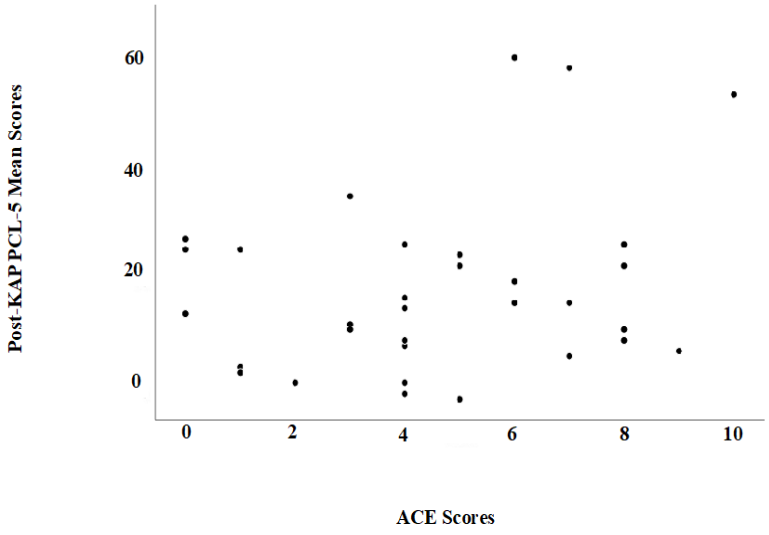


Figure 14

Scatter Plot Reflecting the Relationship Between ACE Scores and Post-KAP PCL-5 Scores



Summary

In summary, results indicated a significant decrease in pre-to post-KAP depression symptom severity and significant decreases in pre- to post-KAP PTSD symptom severity. The effect sizes of these pre- to post-changes exceed Cohen's (1988) parameter for large effect (i.e., *d* =.80) in pre- to post-KAP depression symptom severity scores (PHQ-9; *d* = .97) and pre- to post-PTSD symptom severity scores (PCL-5; *d* = 1.28). Further analyses revealed significant strong, inverse relationships between self-transcendence and post-KAP PTSD symptom severity, and between self-transcendence and post-KAP depression symptom severity. Pearson's correlation was used to determine the presence of associations between adverse childhood experiences (ACE) scores and post-KAP depression symptom severity (PHQ-9) scores and between ACE and post-KAP PTSD symptom severity (PCL-5) scores. These analyses yielded a small, non-significant, positive association between ACE scores and post-KAP PTSD symptom severity and a small, non-significant, but trend positive association between ACE and post-KAP depression symptom severity. Comparison and further discussion and of these findings follow in Chapter V.

CHAPTER V: DISCUSSION

Research investigating concurrent psychotherapy in adults with treatment-resistant depression (TRD) and chronic post-traumatic stress disorder (PTSD) with racemic ketamine administration is limited in the literature. This is due in part to the novelty of psychedelic-assisted psychotherapy research and to the complexities of investigating interventions that do not precisely fit into the biomedical research model. Humans' psychological states, relational responses to other humans (i.e., trauma history & attachment styles), and various situations arising from a myriad of confounding factors can all be challenging to empirically capture and are, therefore, often excluded in randomized-control trial designs. Consequently, there are limitations in existing research on psychedelic-assisted psychotherapy for TRD and chronic PTSD, and ultimately in translation to clinical practice; intravenous ketamine administration for treatment of TRD exemplifies this assertion.

Reported findings on IV ketamine administration for treatment of TRD have been positive; however, there is no inclusion of psychotherapy in IV ketamine infusion studies. This omission is reflected in ketamine's use in clinical practice, types of clinical settings, and the specialty of providers offering patients with mental health conditions (e.g., TRD) this intervention. The consequences, at present, are not knowing whether concurrent psychotherapy may further augment the outcomes or duration of ketamine administration. The purpose of this dissertation project therefore was to retrospectively investigate efficacy of intramuscularly administered ketamine-assisted psychotherapy in depression and PTSD symptom severity and to explore self-transcendence and childhood maltreatment in relation to depression symptom severity and PTSD symptom severity post-KAP.

Interpretation of Findings

KAP's effect in reducing treatment-resistant depression symptom severity was consistent with the previous literature (Lee et al., 2015; Conley et al., 2021). Given the co-occurrence and interrelated symptoms of chronic PTSD and major depressive disorder, it was not surprising to find that changes in PTSD symptom severity and change in depression symptom severity were strongly associated in this study. Participants received six (n = 20) or three (n = 12) induction KAP sessions; interestingly, the change in depression symptom severity between the group who received three sessions was comparable to the group that received six IM KAP sessions. This finding was a deviation from the literature (Lee et al., 2015; Conley et al., 2021) suggesting that five to six initial ketamine administrations may be the most efficacious in persons with treatment-resistant depression. There are several potential factors for this variance, such as the small sample size in this study and the distinct differences in approach between KAP and IV ketamine infusions. This variance may also be related to the provider's clinical approach in reassessing individuals after three KAP sessions and collaboratively deciding with participants whether or not a total of six sessions is warranted.

To date, this is the only study to investigate clinical outcomes of intramuscular (IM) racemic ketamine administration, exclusively, in conjunction with individual psychotherapy (i.e. KAP) in individuals experiencing chronic PTSD. Notable findings were the PTSD symptom severity improvement pre- to post-KAP. It is important, for context, to note that these findings were at or within five days post-treatment. Comparable to the study's sample as a whole (N = 33), 75% of participants with a chronic PTSD diagnosis were taking at least one psychotropic.

Consistent with currently sparse literature on racemic ketamine's use in treating chronic PTSD, multiple administrations within 2-3 weeks provided the most robust reduction in PSTD symptom severity (Albott et al., 2018; Feder et al., 2021). However, IM KAP may provide more positive responses for more participants (86%) compared to IV administration without concurrent psychotherapy (67%; Feder et al.). Again, the number of total KAP sessions did not have a statistically significant effect on PTSD symptom severity change; however, the psychiatric provider's approach of reassessing participants after three sessions and promotion of participant agency in determining whether additional KAP induction sessions (e.g., six versus three) merits further investigation. Associations between ACEs and post-KAP depression symptom severity scores and between ACEs and post-KAP PTSD symptom severity scores were not found in this study. Surprisingly, these results did not replicate previous findings (Dore et al., 2019) suggesting an association between childhood maltreatment (i.e. ACE scores) and KAP treatment response. However, a significant improvement was yielded in PTSD symptom severity in participants with chronic PTSD, most of whom (67%) had ACE scores ≥ 4.

Concurrent psychotherapeutic support has not historically been a precept in IV ketamine infusion research or in clinical practice. The prevailing practice has been to administer racemic ketamine dosages based strictly on participants' weight, and to infuse the medication slowly IV over 40 minutes (Conley et al., 2021) to reduce or minimize sensory and cognitive alterations. Patients are typically in large rooms with other patients, where several patients are medically monitored simultaneously by one technician or nurse. Conversely, ketamine-assisted psychotherapy (KAP) provides a more humanistic, patient-centered approach (Dore et al., 2019). Working within this humanistic framework, patient preparation, and support prior to and during

KAP sessions is imperative; the non-ordinary state induced by ketamine is not avoided or controlled medicinally (e.g. administration of midazolam or lorazepam) by the KAP clinician. Specialized training has enabled KAP providers to psychotherapeutically assist and support patients when needed, typically negating the need for additional IV sedatives or anxiolytics.

Another departure, and potential explanation, in this study's depression symptom severity findings, is the provider to patient ratio. With KAP, there is a 1:1 or even 2:1 (clinicians) to (patient) ratio; for example, a licensed mental health clinician was with each patient throughout the KAP session for participants in this study. Also, within the humanistic framework, and given that the bioavailability of IM racemic ketamine is approximately 93-94% (Li & Vlisides, 2016), the need for 5- to 6 venipunctures during the initial series is negated. IM administration also eliminates the potential for multiple venipunctures (e.g. IV infiltration, missed IV attempts) within a single IV infusion session. Thus, reducing discomfort as needle gauges (i.e., sizes) are significantly smaller for intramuscular medication administration, in contrast to IV needles and IV catheters. There are also not repeated venipunctures with IM administration, which decreases the risk of infection and the potential for developing phlebitis. The differences in approaches may offer some insight into this study's depression symptom severity findings after three versus six KAP sessions; however, additional research that includes psychiatric reassessment after three KAP sessions is needed to determine whether this finding is replicated or isolated to this study.

Adverse Events

No adverse events arose directly from this retrospective study nor were any adverse experiences reported by participants related to their KAP treatment. Dizziness and nausea were

reported by approximately 30% of participants. No participants reported vomiting. The anti-emetic ondansetron was offered by the KAP providers during KAP sessions when needed.

KAP and Self-transcendence

This project was the first ketamine study to include Reed's (1987) self-transcendence scale (STS). Noteworthy findings included compelling associations between self-transcendence scale scores and post-KAP PTSD symptom severity, and between self-transcendence scores and post-KAP depression symptom severity. Ideally, self-transcendence would have been measured before and after KAP to analyze changes in overall scores and to further explore specific changes in self-transcendence domains. Preliminary findings and strength of association in this study between the self-transcendence scores and depression symptom severity scores and between self-transcendence and PTSD symptom severity scores post-KAP provide a strong rationale for further investigation. The findings lend support to Reed's 'theory of self-transcendence' as an underpinning for the study's theoretical framework.

Limitations

These findings should be considered in light of several limitations. First, the study used a retrospective design and included a small convenience sample. Retrospective research findings, though useful, carry a greater risk of bias and reduced reliability in contrast to prospective observational or randomized-controlled trial research designs. The study's clinical site works primarily with higher acuity patients, many of whom have exhausted traditional, available psychiatric treatment options and typically have higher mental health condition acuity. Consequently, outcomes from this study likely reflect higher psychometric scores (e.g. depression symptom severity; PTSD symptom severity PCL; suicidality) compared to patients in

most outpatient mental healthcare settings potentiating inflated effect size, and potentially reducing the generalizability of the findings. Finally, the STS was collected retrospectively after participant recruitment; therefore, the STS scores were not synchronous with the post-KAP PCL-5 and PHQ-9 data. The post-KAP STS scores were obtained up to a several months after the post-KAP PCL-5 and PHQ-9 scores for some participants.

There is a growing body of literature on racemic ketamine's use in treating unremitting depression (Lee et al., 2015; Conley et al., 2021). However, very little has been published regarding racemic ketamine's use in treating chronic PTSD. Consequently, the *a priori* estimated effect size was based on the sparse existing literature and analysis was set for medium effect. The *a priori* recommended sample size was 34; a total of 33 participants were recruited and there were two missing pre-KAP PCL-5 scores. In the pre- to post-KAP PCL-5 score paired t-test analysis, the Hedges' correction fell within one-tenth (1.26; CI: .786, 1.73, $p < .001$) of the Cohen's *d* (1.28; CI: .796, 1.75, $p < .001$). Finally, best efforts were made in the recruitment and data collection procedures to exclude the principal investigator who is also the practice owner. Understandably, this scenario may raise scrutiny to the discerning reader; therefore, it is important to mention the research team was comprised of two additional CITI-certified research members that were not directly involved in the participants' care. The additional research team was comprised of another board-certified psychiatric nurse practitioner with a Doctorate in Nursing Practice (DNP) and a Bachelor's of Science-prepared (BS) research assistant. Participant information was de-identified and the research assistants were tasked with recruitment and data collection. Participation in the study was voluntary.

Future Directions in KAP Research

Currently, the world is two years into the COVID-19 pandemic; the enduring and intense trauma being experienced by frontline healthcare clinicians, including nurses. Outside of wartime, this has not occurred on a scale of this magnitude in the past 100 years since the influenza pandemic of 1918. The psychological implications of the COVID-19 pandemic have yet to be fully realized and are of grave concern for mental healthcare providers given the current paucity of available effective PTSD and TRD treatment options. Limitations in efficacious interventions and subsequent consumer demand have initiated a slow shift away from the current traditional treatment options that have dominated mental healthcare for the past 40 years.

Interventions using ketamine in research and clinical practice are guided by theoretical frameworks specific to disciplines and specialties of the bench scientists (e.g. psychopharmacologist, neuropsychiatry) and clinicians (e.g. psychotherapists, psychiatric providers). For example, theory guiding psychological and psychiatric treatment and approaches to patient care vary considerably from theory guiding anesthesiology and emergency medicine training and care, and yet the majority of outpatient ketamine clinics treating patients for mental health conditions are managed by non-mental healthcare clinicians. This raises ethical concerns regarding the quality of and appropriateness of the care being provided, particularly in vulnerable (e.g. mental health) patient populations. Lack of preparation prior to the induction of a non-ordinary or altered state of consciousness in settings without mental healthcare clinicians may be a contributing factor for attrition in previous human research investigating racemic ketamine's use in treating PTSD and attrition in medical, non-psychotherapeutic settings, a phenomenon that has not yet been, but merits, further exploration.

Very little has been published on combining psychotherapy with racemic ketamine administration, in general. Only 25% of participants with enduring PTSD post-KAP, in this study, were participating in individual psychotherapy when they began KAP treatment, in contrast to approximately one-half of the participants who no longer met DSM-V criteria for chronic PTSD who were receiving individual psychotherapy when they sought KAP services. More research is warranted to investigate whether or not psychotherapy preceding KAP influences KAP treatment outcomes. Additionally, research comparing participant outcomes with and without concurrent psychotherapy during ketamine administration and longitudinal KAP research are also needed. Given the significant statistical correlations between post-KAP depression symptom severity scores and the Self-transcendence scale (STS) scores and post-KAP trauma symptom severity scores and STS scores, the inclusion of the STS in future KAP and psychedelic-assisted psychotherapy research is warranted.

The few published papers investigating concomitant psychotherapy with ketamine administration have not used IV ketamine administration; instead, these studies have retrospectively reported clinical outcome findings when a combination of intramuscular (IM) and /or oral (i.e. troches) (Dore et al., 2019) racemic ketamine was used for anxiety and depression symptom severity, and participants were administered ketamine in-office and were prescribed sublingual ketamine lozenges for home use. Another small study retrospectively reported on the efficacy of sublingual ketamine (Davis, Mangini, & Xin, 2021) with concomitant psychotherapy in-office. More KAP research using mixed methods (i.e. qualitative & quantitative) designs would be helpful for further exploration of ketamine dosage titration protocols and to compare findings between IM, sublingual, and oral routes of administration in outpatient settings.

Conclusions

A humanistic approach is of particular importance when working with individuals experiencing mental health challenges. This vulnerable population has typically exhausted available treatment options when seeking treatments like KAP or IV ketamine infusions. Due to the dissociative and psychedelic effects of ketamine, preparing persons prior to administration, regardless of route of administration, is imperative and even more so when individuals have a history of developmental trauma. The potential for psychological harm and further attachment injury (Dozier et al., 2008) is much higher in persons who have experienced childhood maltreatment which is typically reflected by higher (i.e., ACE scores ≥ 4).

This study's findings suggest a series of three repeated IM KAP sessions reduce chronic PTSD symptom severity and that IM KAP may be an efficacious intervention in treating individuals experiencing chronic PTSD. This study replicated prior findings for ketamine's use in treating TRD; however, the findings suggest that three repeated IM KAP sessions may be as efficacious as six KAP sessions or six repeated IV ketamine infusions without concurrent psychotherapy in treating TRD. Outcomes of this small study substantiate the need for further investigation of using IM KAP for the treatment of TRD and chronic PTSD, as well as further inquiry into the existential (i.e., psychospiritual) nature of participants' suffering in determining whether or not the psychedelic or mystical experience catalyzes or augments the efficacy of racemic ketamine administration.

APPENDIX A:

DATA COLLECTION FORMS

Demographic Data Collection Form

Participant #: _____

Date of data collection: _____

Date(s) of KAP sessions: _____

1. Gender: ☐1 Male ☐2 Female

2. What is your age? _____

3. Are you fluent in English? ☐1 Yes ☐2 No

4. What is your preferred language for communicating?

☐1 English
☐2 Spanish
☐3 American Sign Language
☐4 Other (please list): _____

5. What is your highest level of education?

☐1 No formal education
☐2 Less than high school graduate
☐3 High school graduate/GED
☐4 Vocational training
☐5 Some or in-progress college/Associate's degree
☐6 Bachelor's degree (BA, BS)
☐7 Master's degree (or other post-graduate training)
☐8 Doctoral degree (PhD, MD, EdD, DDS, JD, etc.)
☐9 Do not wish to answer

6. Current marital status (Check **one**)

☐1 Single
☐2 Married
☐3 Separated
☐4 Divorced
☐5 Widowed
☐6 Other (please specify) _____
☐7 Do not wish to answer

Do you consider yourself Hispanic or Latino?

☐1 Yes ☐2 No ☐3 Do not wish to answer

7. How would you describe your primary racial group?

- ☐1 American Indian/Alaska Native
- ☐2 Asian
- ☐3 Black or African American
- ☐4 Native Hawaiian or Other Pacific Islander
- ☐5 White
- ☐6 More than one race
- ☐7 Other (please specify) _____
- ☐8 Do not wish to answer

8. Which category best describes your yearly household income? Do not give the dollar amount, just check the category.

- ☐1 Less than $25,000
- ☐2 $25,000 - $49,999
- ☐3 $50,000 - $74,999
- ☐4 $75,000 or more
- ☐5 Do not wish to answer
- ☐6 Do not know for certain

Occupational Status

9. What is your primary occupational status? (Check **one**)

- ☐1 Employed full-time
- ☐2 Employed part-time
- ☐3 Student
- ☐4 Homemaker
- ☐5 Retired
- ☐6 On sick leave, or on disability benefits
- ☐7 Unemployed or temporarily laid off
- ☐8 Other (please specify) _____

Mental Health Medications & Recent Sleep Information

1. Please list all medications, supplements, and/or herbs you were taking during the time of your ketamine-assisted psychotherapy (KAP) sessions:

_____

_____

_____

_____

2. If there have been changes in your mental health medications since your KAP sessions, please list which medication and what changes have been made (e.g., no longer taking, increase or decrease in dose of medication):

_____

_____

_____

3. Are you currently working with a therapist? (this may be a psychologist, therapist, or psychiatric provider)

□1 Yes □2 No

4. How long have you been working with this therapist? If no current therapy, mark N/A.

□0 N/A □1 < 1 month □2 1-2 months □3 2-3 months □4 3-4 months □5 > 4 months

5. How often are you currently meeting with your therapist?

□0 Twice per week □1 Once per week □2 Every 2 weeks □3 Once per month □4 When needed

6. How would you describe your sleep quality over the last 2 weeks:

□1 Poor □2 Fair □3 Good □4 Very good □5 Excellent

7. On average, how long does it take for you to fall asleep most nights?

□1	□2	□3	□4	□5
0 – 15 minutes	16 – 30 minutes	31 – 45 minutes	46 – 60 minutes	> 1 hour

8. Over the last 2 weeks, on average, how often did you wake up during the night?

□1	□2	□3	□4
0 – 1	2 – 3	3 – 4	5 or more

Self-Transcendence Scale (STS)

Self-Transcendence Scale *(with permission from Pamela Reed, PhD, RN, FAAN*)

DIRECTIONS: Please indicate the extent to which each item below describes you. There are no right or wrong answers. I am interested in your frank opinion.

As you respond to each item, think of how you see yourself at this time of your life. Circle the number that is the best response for you.

At this time of my life, I see myself as:	**Not at all**	**Very little**	**Some what**	**Very much**
1. Having hobbies or interests I can enjoy	1	2	3	4
2. Accepting myself as I grow older.	1	2	3	4
3. Being involved with other people, or my community when possible.	1	2	3	4
4. Adjusting well to my present life situation.	1	2	3	4
5. Adjusting to changes in my physical abilities.	1	2	3	4
6. Sharing my wisdom or experience with others.	1	2	3	4
7. Finding meaning in my past experiences.	1	2	3	4
8. Helping others in some way.	1	2	3	4
9. Having an ongoing interest in learning.	1	2	3	4
10. Able to move beyond some things that once seemed so important.	1	2	3	4
11. Accepting death as a part of life.	1	2	3	4
12. Finding meaning in my spiritual beliefs.	1	2	3	4
13. Letting others help me when I may need it.	1	2	3	4
14. Enjoying my pace of life.	1	2	3	4
15. Letting go of past regrets.	1	2	3	4

Thank you very much for completing these questions. On the back of this sheet, please write down any additional comments that may help us understand your views.

Patient Health Questionnaire 9-Item (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(circle the number)*	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Little interest or pleasure in doing things.	0	1	2	3
2. Feeling down, depressed, or hopeless.	0	1	2	3
3. Trouble falling or staying asleep or sleeping too much.	0	1	2	3
4. Feeling tired or having little energy.	0	1	2	3
5. Poor appetite or overeating.	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down.	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television.	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual.	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way.	0	1	2	3
Column totals ____ + ____ + ____ + ____				
= *Total Score* _____				

If you answered 1, 2, or 3 for *any* questions, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	**Somewhat difficult**	**Very difficult**	**Extremely difficult**
☐	☐	☐	☐

PTSD Checklist for DSM-5 (PCL-5)

Instructions: Below is a list of problems that people sometimes have in response to a very stressful experience. Please read each problem carefully and then circle one of the numbers to the right to indicate how much you have been bothered by that problem in the past month.

In the past month, how much were you bothered by:	**Not at all**	**A little bit**	**Moderately**	**Quite a bit**	**Extremely**
1. Repeated, disturbing, and unwanted memories of the stressful experience?	0	1	2	3	4
2. Repeated, disturbing dreams of the stressful experience?	0	1	2	3	4
3. Suddenly feeling or acting as if the stressful experience were actually happening again (as if you were actually back there reliving it)?	0	1	2	3	4
4. Feeling very upset when something reminded experience?	0	1	2	3	4
5. Having strong physical reactions when something reminded you of the stressful experience (for example, heart pounding, trouble breathing, sweating)?	0	1	2	3	4
6. Avoiding memories, thoughts, or feelings related to the stressful experience?	0	1	2	3	4
7. Avoiding external reminders of the stressful experience (for example, people, places, conversations, activities, objects, or situations)?	0	1	2	3	4
8. Trouble remembering important parts of the stressful experience?	0	1	2	3	4
9. Having strong negative beliefs about yourself, other people, or the world (for example, having thoughts such as: I am bad, there is something seriously wrong with me, no one can be trusted, the world is completely dangerous)?	0	1	2	3	4
10. Blaming yourself or someone else for the stressful experience or what happened after it?	0	1	2	3	4
11. Blaming yourself or someone else for the stressful experience or what happened after it?	0	1	2	3	4
12. Having strong negative feelings such as fear, horror, anger, guilt, or shame?	0	1	2	3	4

In the past month, how much were you bothered by:	Not at all	A little bit	Moderately	Quite a bit	Extremely
13. Loss of interest in activities that you used to enjoy?	0	1	2	3	4
14. Feeling distant or cut off from other people?	0	1	2	3	4
15. Trouble experiencing positive feelings (for example, being unable to feel happiness or have loving feelings for people close to you)?	0	1	2	3	4
16. Irritable behavior, angry outbursts, or acting aggressively?	0	1	2	3	4
17. Taking too many risks or doing things that could cause you harm?	0	1	2	3	4
18. Being “super alert” or watchful or on guard?	0	1	2	3	4
19. Feeling jumpy or easily startled?	0	1	2	3	4
20. Having difficulty concentrating?	0	1	2	3	4
21. Trouble falling or staying asleep?	0	1	2	3	4

Weathers, F. W., Litz, B. T., Keane, T. M., Palmieri, P. A., Marx, B. P., & Schnurr, P. P. (2013). The PTSD Checklist for DSM-5 (PCL-5) – Standard [Measurement instrument]. Available from https://www.ptsd.va.gov/

Adverse Childhood Experience (ACE) Questionnaire

Adverse Childhood Experience Questionnaire for Adults

California Surgeon General's Clinical Advisory Committee

aces aware
SCREEN. TREAT. HEAL.

Our relationships and experiences—even those in childhood—can affect our health and well-being. Difficult childhood experiences are very common. Please tell us whether you have had any of the experiences listed below, as they may be affecting your health today or may affect your health in the future. This information will help you and your provider better understand how to work together to support your health and well-being.

Instructions: Below is a list of 10 categories of Adverse Childhood Experiences (ACEs). From the list below, please place a checkmark next to each ACE category that you experienced prior to your 18th birthday. Then, please add up the number of categories of ACEs you experienced and put the *total number* at the bottom.	
Did you feel that you didn't have enough to eat, had to wear dirty clothes, or had no one to protect or take care of you?	☐
Did you lose a parent through divorce, abandonment, death, or other reason?	☐
Did you live with anyone who was depressed, mentally ill, or attempted suicide?	☐
Did you live with anyone who had a problem with drinking or using drugs, including prescription drugs?	☐
Did your parents or adults in your home ever hit, punch, beat, or threaten to harm each other?	☐
Did you live with anyone who went to jail or prison?	☐
Did a parent or adult in your home ever swear at you, insult you, or put you down?	☐
Did a parent or adult in your home ever hit, beat, kick, or physically hurt you in any way?	☐
Did you feel that no one in your family loved you or thought you were special?	☐
Did you experience unwanted sexual contact (such as fondling or oral/anal/vaginal intercourse/penetration)?	☐
Your ACE score is the total number of checked responses	

Do you believe that these experiences have affected your health? ◯ **Not Much** ◯ **Some** ◯ **A Lot**

Experiences in childhood are just one part of a person's life story.
There are many ways to heal throughout one's life.

Please let us know if you have questions about privacy or confidentiality.

5/5/20

PDF available at: https://www.acesaware.org/wp-content/uploads/2020/02/ACE-Questionnaire-for-Adults-Identified-English.pdf

APPENDIX B:

PARTICIPANT RECRUITMENT SCRIPT

Hello. My name is _____

I am calling on behalf of a doctoral student at the University of Arizona College of Nursing. We are calling to ask if you would consider participating in a research project. This student is studying ketamine-assisted psychotherapy treatment outcomes in patients who have received ketamine-assisted psychotherapy in the past year. We are looking for about 30 adults 18 years old or older who speak and read English without difficulty.

If you decide to participate in the study, you will be asked to answer some questions during a live, private virtual appointment. The questionnaires will ask questions about how you have been feeling and doing since receiving ketamine-assisted psychotherapy. The virtual appointment will last about 1 to 1.5 hours total and will be scheduled at a time convenient for you.

Your participation in this study is voluntary. You may decide not to participate, or to stop participating at any time. Refusing to participate will not affect the care you receive with your mental health provider.

Thank you for considering participating in this study.

APPENDIX C:

PARTICIPANT INFORMED CONSENT

University of Arizona
Consent to Participate in Research

Study Title: Ketamine assisted psychotherapy: Clinical Outcomes and Self-transcendence in depression and post-traumatic stress disorder

Principal Investigator: Jennifer Montjoy

You are being asked to participate in a research study. Your participation in this research study is voluntary and you do not have to participate. This document contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to ask questions before making your decision whether or not to participate.

- The purpose of the study is to research outcomes of patients who have received ketamine-assisted psychotherapy in the past 12 months.
- Participation includes completing 3-5 questionnaires in one meeting and will take approximately one hour of your time.
- There are no expected risks or benefits from participating in this study.

Confidentiality & Protected Health Information

Your name (identity) will not be used in any report. Identifiable research data will be encrypted and password protected.

Your responses will be assigned a code number. The list connecting your name to this code will be kept in an encrypted and password protected file. Only the research team will have access to the file. When the study is completed and the data have been analyzed, the coded participant list will be destroyed. Once completed, assessment measures will be uploaded and saved to your secure electronic medical record for continuity of your mental healthcare.

The information that you give in the study will be anonymous. Your name will not be collected or linked to your answers.

Information that identifies you will only be used for future research or shared with another researcher after obtaining your consent
The information that you provide in the study will be handled confidentially. However, there may be circumstances where this information must be released or shared as required by law. The University of Arizona Institutional Review Board may review the research records for monitoring purposes.

Participant (Your) Rights:

For questions, concerns, or complaints about the study you may contact:

Jennifer Montjoy PMHNP-BC
PhD Student University of Arizona
College of Nursing
jmontjoy@email.arizona.edu
520.334.5122

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects' research at The University of Arizona reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact the Human Subjects Protection Program Director at 520-626-8630 or online at http://rgw.arizona.edu/compliance/human-subjects-protection-program.

Signing the consent form

I have read this form, and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study. I am not giving up any legal rights by signing this form. I will be given a copy of this form.

Printed name of participant	**Signature of participant**
	AM/PM **Date and time**

Investigator/Research Staff

I have explained the research to the participant or the participant's representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or to the participant's representative.

Printed name of person obtaining consent	**Signature of person obtaining consent**
	AM/PM **Date and time**

APPENDIX D:

THE UNIVERSITY OF ARIZONA INSTITUTIONAL REVIEW BOARD APPROVAL

THE UNIVERSITY OF ARIZONA
Research, Discovery & Innovation

Human Subjects Protection Program

1618 E. Helen St.
P.O Box 245137
Tucson, AZ 85724-5137
Tel: (520) 626-6721
http://rgw.arizona.edu/compliance/home

Date:	July 06, 2021
Principal Investigator:	Jennifer Fraser Montjoy
Protocol Number:	2106896953
Protocol Title:	Ketamine assisted psychotherapy: Clinical Outcomes and Self-transcendence in depression and post-traumatic stress disorder.
Determination:	Approved
Expiration Date:	July 01, 2026

Documents Reviewed Concurrently:

Data Collection Tools: *Montjoy_Participant Chart Review Form.docx*
Data Collection Tools: *Montjoy_Participant Forms_Instrument Measures .docx*
HSPP Forms/Correspondence: *Advisor Confirmation Email.pdf*
HSPP Forms/Correspondence: *Confirmation for Scientific Review and Department Review.pdf*
HSPP Forms/Correspondence: *Montjoy_IRB_application_June_29_2021.pdf*
HSPP Forms/Correspondence: *Montjoy List of Research Personnel.pdf*
Informed Consent/PHI Forms: *Montjoy_PARTICIPANT CONSENT FORM_final.docx*
Informed Consent/PHI Forms: *Montjoy_PARTICIPANT CONSENT FORM_final.pdf*
Other Approvals and Authorizations: *Montjoy_EHR site authorization_Resilience Behavioral Health Solutions (4).pdf*
Other Approvals and Authorizations: *Montjoy_Site EHR Letter_Flagstaff.pdf*
Recruitment Material: *Montjoy_Dissertation Project Flyer 12 May 2021 (1).pptx*
Recruitment Material: *Montjoy_RECRUITMENT SCRIPT_final.docx*

Regulatory Determinations/Comments:

- The project is not federally funded or supported and has been deemed to be no more than minimal risk.
- The project listed is required to update the HSPP on the status of the research in 5 years. A reminder notice will be sent 60 days prior to the expiration noted to submit a 'Project Update' form.

This project has been reviewed and approved by an IRB Chair or designee.

- The University of Arizona maintains a Federalwide Assurance with the Office for Human Research Protections (FWA #00004218).
- All research procedures should be conducted according to the approved protocol and the policies and guidance of the IRB.
- The Principal Investigator should notify the IRB immediately of any proposed changes that affect the protocol and report any unanticipated problems involving risks to participants or others. Please refer to Guidance Investigators Responsibility after IRB Approval, Reporting Local Information and Minimal Risk or Exempt Research.
- All documents referenced in this submission have been reviewed and approved. Documents are filed with the HSPP Office.

REFERENCES

Albott, C. S., Lim, K. O., Forbes, M. K., Erbes, C., Tye, S. J., Grabowski, J. G., ... & Shiroma, P. R. (2018). Efficacy, safety, and durability of repeated ketamine infusions for comorbid posttraumatic stress disorder and treatment-resistant depression. *The Journal of Clinical Psychiatry, 79*(3). https://doi-org.ezproxy4.library.arizona.edu/10.4088/JCP.17m11634

Aleksandrova, L. R., Phillips, A. G., & Wang, Y. T. (2017). Antidepressant effects of ketamine and the roles of AMPA glutamate receptors and other mechanisms beyond NMDA receptor antagonism. *Journal of Psychiatry & Neuroscience, 42*(4), 222-229.

Allen, A. P., Naughton, M., Dowling, J., Walsh, A., ... & Clarke, G. (2015). Serum BDNF as a peripheral biomarker of treatment-resistant depression and the rapid antidepressant response: A comparison of ketamine and ECT. *Journal of Affective Disorders*, *186*, 306-311. https://doi-org.ezproxy2.library.arizona.edu/10.1016/j.jad.2015.06.033

Allen, A. P., Naughton, M., Dowling, J., Walsh, A., ... & Dinan, T. G. (2018). Kynurenine pathway metabolism and the neurobiology of treatment-resistant depression: Comparison of multiple ketamine infusions and electroconvulsive therapy. *Journal of Psychiatric Research*, *100*, 24-32. https://doi-org.ezproxy2.library.arizona.edu/10.1016/j.jpsychires.2018.02.011

Averill, L. A., Purohit, P., Averill, C. L., Boesl, M. A., Krystal, J. H., & Abdallah, C. G. (2017). Glutamate dysregulation and glutamatergic therapeutics for PTSD: Evidence from human studies. *Neuroscience Letters*, *649*, 147-155. https://doi.org/10.1016/j.neulet.2016.11.064

Armstrong, M., & Kelly, A. (1995). More than the sum of their parts: Martha Rogers and Hildegard Peplau. *Archives of Psychiatric Nursing, 9*(1), 40-44.

Bekhbat, M., Rowson, S. A., & Neigh, G. N. (2017). Checks and balances: The glucocorticoid receptor and NFκB in good times and bad. *Frontiers in Neuroendocrinology*, *46*, 15-31. https://doi.org/10.1016/j.yfrne.2017.05.001

Bennett, M. P. (1996). Multidimensional factors affecting well-being: A PNI based model for therapeutic nursing intervention. *Nursing Faculty Publications*. Paper 46.

Bélanger, S. A., Cramm, H., Fletcher, K., & Demers, J. S. (2018). PTSD vs. moral injury: A scoping review. *Journal of Military, Veteran and Family Health*, *4*(1), 2-4.

Ben-Zion, Z., Zeevi, Y., Keynan, N. J., Admon, R., … & Hendler, T. (2020). Multi-domain potential biomarkers for post-traumatic stress disorder (PTSD) severity in recent trauma survivors. *Translational Psychiatry, 10*(1), 208. https://doi.org/10.1038/s41398-020-00898-z

Berens, A. E., Jensen, K. G., & Nelson, C. A. (2017). Biological embedding of childhood adversity: From physiological mechanisms to clinical implications. *BMC Medicine*, *15*(1), 135. doi:10.1186/s12916-017-0895-4

Bernstein, D. P., Fink, L., Handelsman, L., & Foote, J. (1994). *Childhood trauma questionnaire (CTQ)* [Database record]. APA PsycTests. https://doi.org/10.1037/t02080-000

Bhawuk, D. S. (2011) Indian concept of self. In: *Spirituality and Indian psychology*. *International and cultural psychology*. New York, NY; Springer. doi.org/10.1007/978-1-4419-8110-3_4

Birney, M. H. (1991). Psychoneuroimmunology: A holistic framework for the study of stress and illness. *Holistic Nursing Practice, 5*(4), 32-28.

Blevins, C. A., Weathers, F. W., Davis, M. T., Witte, T. K., & Domino, J. L. (2015). The posttraumatic stress disorder checklist for *DSM-5* (PCL-5): Development and initial psychometric evaluation. *Journal of Traumatic Stress, 28*, 489-498. doi:10.1002/jts.22059

Busillo, J. M., & Cidlowski, J. A. (2013). The five Rs of glucocorticoid action during inflammation: Ready, reinforce, repress, resolve, and restore. *Trends Endocrinol Metab*, *24*(3), 109-19. doi: 10.1016/j.tem.2012.11.005

Caddy, C., Amit, B. H., McCloud, T. L., Rendell, J. M., Furukawa, T. A., McShane, R., Hawton, K., & Cipriani, A. (2015). Ketamine and other glutamate receptor modulators for depression in adults. *The Cochrane Database of Systematic Reviews*, *9*, CD011612. https://doi.org/10.1002/14651858.CD011612.pub2

Calabrese, F., Rossetti, A. C., Racagni, G., Gass, P., Riva, M. A., & Molteni, R. (2014). Brain-derived neurotrophic factor: A bridge between inflammation and neuroplasticity. *Frontiers in Cellular Neuroscience*, *8*, 430. https://doi.org/10.3389/fncel.2014.00430

Carhart-Harris, R. L., & Goodwin, G. M. (2017). The therapeutic potential of psychedelic drugs: Past, present, and future. *Neuropsychopharmacology*, *42*(11), 2105-2113. https://doi.org/10.1038/npp.2017.84

Carroll, T. D., Currier, J. M., McCormick, W. H., & Drescher, K. D. (2017). Adverse childhood experiences and risk for suicidal behavior in male Iraq and Afghanistan veterans seeking PTSD treatment. *Psychological Trauma: Theory, Research, Practice, and Policy*, *9*(5), 583-586. https://doi.org/10.1037/tra0000250

Center for Disease Control and Prevention. (CDC). (2020). *About the CDC-Kaiser ACE study*. https://www.cdc.gov/violenceprevention/aces/about.html

Chapman, D. P., Whitfield, C. L., Felitti, V. J., Dube, S. R., Edwards, V. J., & Anda, R. F. (2004). Adverse childhood experiences and the risk of depressive disorders in adulthood. *J Affect Disord*, *82*(2), 217-225. doi: 10.1016/j.jad.2003.12.013. PMID: 15488250

Choi, J. I. (2019). Predictors of the co-occurrence of posttraumatic stress disorder and depressive disorder in psychiatric outpatients. *Comprehensive Psychiatry, 90*, 40-45. https://doi.org/10.1016/j.comppsych.2018.12.005

Chow, W., Doane, M. J., Sheehan, J., Alphs, L., & Le, H. (2019). Economic burden among patients n with major depressive disorder: An analysis of healthcare resource use, work productivity, and direct and indirect costs by depression severity. *AJMC*. https://www.ajmc.com/journals/supplement/2019/economic-burden-mdd-analysis-healthcare/economic-burden-mdd

Cocker, F., & Joss, N. (2016). Compassion fatigue among healthcare, emergency and community service workers: A systematic review. *International Journal of Environmental Research and Public Health*, *13*(6), 618. https://doi.org/10.3390/ijerph13060618

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*. New York, NY: Routledge Academic.

Conley, Norwood, A. E. Q., Hatvany, T. C., Griffith, J. D., & Barber, K. E. (2021). Efficacy of ketamine for major depressive episodes at 2, 4, and 6-weeks post-treatment: A meta-analysis. *Psychopharmacology, 238*(7), 1737–1752. https://doi.org/10.1007/s00213-021-05825-8

Coward, D. D. (1996). Self-transcendence and correlates in a healthy population. *Nursing Research*, *45*, 116-121.

Cuijpers, P., Noma, H., Karyotaki, E., Vinkers, C. H., Cipriani, & Furukawa, T. A. (2020). A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. *World Psychiatry*, *19*, 92-107. doi:10.1002/wps.20701

Cusins, C. (2019). Ketamine as a rapid antidepressant. Shapero, B. G. et al. (eds.). In *The Massachusetts General Hospital Guide to Depression, Current Clinical Psychiatr,* 139-145. doi: 10.1007/978-3-319-97241-1_10

Dames, Kryskow, P., & Watler, C. (2022). A Cohort-based case report: The Impact of ketamine-assisted therapy embedded in a community of practice framework for healthcare providers with PTSD and depression. *Frontiers in Psychiatry*, 12, 803279. https://doi.org/10.3389/fpsyt.2021.803279

Danese, A., & Mcewen, B. S. (2012). Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiology & Behavior, 106*(1), 29-39.

Danese, A., & Baldwin, J.R. (2017). Hidden wounds? Inflammatory links between childhood trauma and psychopathology. *Annual Review of Psychology, 68*, 517-544. doi: 10.1146/annurev-psych-010416-044208

Daruna, J. H. (2012) *Introduction to psychoneuroimmunology* (2nd ed.). Waltham, MA: Elsevier.

Davidson, J. E., Proudfoot, J., Lee, K., & Zisook, S. (2019). Nurse suicide in the United States: Analysis of the Center for Disease Control 2014 national violent death reporting system dataset. *Archives of Psychiatric Nursing*, *33*(5), 16-21. https://doi.org/10.1016/j.apnu.2019.04.006

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

Department of Veterans Affairs. (VA). (2018). Department of Veterans Affairs, Veterans Health Administration, Office of Mental Health and Suicide Prevention. *Veteran Suicide Data Report, 2005–2016*. https://www.mentalhealth.va.gov/docs/data-sheets/OMHSP_National_Suicide_Data_Report_ 2005-2016_508-compliant.pdf

DePierro, J., Lepow, L., Feder, A., & Yehuda, R. (2019). Translating molecular and neuroendocrine findings in posttraumatic stress disorder and resilience to novel therapies. *Biological Psychiatry*, *86*(6), 454-463. https://doi-org.ezproxy2.library.arizona.edu/10.1016/j.biopsych.2019.07.009

Dos Santos, M. (2017). Physician suicide. *European Psychiatry*, *41*(S1), S886-S886. doi:10.1016/j.eurpsy.2017.01.1795

Dore, J., Turnipseed, B., Dwyer, S., Turnipseed, A., Andries, J., Ascani, G., ... & Wolfson, P. (2019). Ketamine assisted psychotherapy (KAP): Patient demographics, clinical data and outcomes in three large practices administering ketamine with psychotherapy. *Journal of Psychoactive Drugs*, *51*(2), 189-198.

Dozier, M., Stovall-McClough, K. C., & Albus, K. E. (2008). Attachment and psychopathology in adulthood. In J. Cassidy & P. R. Shaver (Eds.), *Handbook of attachment: Theory, research, and clinical applications* (pp. 718-744). New York, NY: The Guilford Press.

Dutheil, F., Aubert, C., Pereira, B., Dambrun, M., Moustafa, F., Mermillod, M., Baker, J. S., Trousselard, M., Lesage, F. X., & Navel, V. (2019). Suicide among physicians and health-care workers: A systematic review and meta-analysis. *PloS One*, *14*(12), e0226361. https://doi.org/10.1371/journal.pone.0226361

Esterlis, I., Holmes, S. E., Sharma, P., Krystal, J. H., & DeLorenzo, C. (2018). mGluR5 and stress disorders: Knowledge gained from receptor imaging studies. *Biol Psychiatry*, *84*(2), 95-105. doi:10.1016/j.biopsych.2017.08.025

Faul, F., Erdfelder, E., Lang, A.-G. & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*, 175-191.

Feder, A., Parides, M. K., Murrough J. W. et al. (2014). Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: A randomized clinical trial. *JAMA Psychiatry, 71*(6), 681-688. doi: 10.1001/jamapsychiatry.2014.62

Felitti, R. F., Anda, D., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., Koss, M. P., & Marks, J. S. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The adverse childhood experiences (ACE) study. *Am J Prev Med, 14*(4), 245-258. doi: 10.1016/s0749-3797(98)00017-8

Frankl, V. E. (1966). Self-transcendence as a human phenomenon*. Journal of Humanistic Psychology, 6*(2), 97-106. https://doi.org/10.1177/002216786600600201

Friedman, H. L. (2018). Transpersonal psychology as a heterodox approach to psychological science: Focus on the construct of self-expansiveness and its measure. *Archives of Scientific Psychology, 6*(1), 230-242. http://dx.doi.org/10.1037/arc0000057

Garcia-Romeu, A., Himelstein, S., & Kaminker, J. (2015). Self-transcendent experience: A grounded theory study. *Qualitative Research*, *15*(5), 633-654.

Glue, P., Medlicott, N. J., Harland, S., Neehoff, S., Anderson-Fahey, B., Le Nedelec, M., Gray, A., & McNaughton, N. (2017). Ketamine's dose-related effects on anxiety symptoms in patients with treatment refractory anxiety disorders. *Journal of Psychopharmacology* (Oxford, England)*, 31*(10), 1302-1305. https://doi.org/10.1177/0269881117705089

Grimell, J. (2018). Veterans, the hidden wounds of war, and soul repair: Veteranen, die verborgene Wunde des Krieges und die Heilung seelischer Verletzungen. *Spiritual Care*, *7*(4), 353-363.

Grob, C. S., & Bossis, A. (2017). Humanistic psychology, psychedelics, and the transpersonal vision. *The Journal of Humanistic Psychology*, *57*(4), 315-318. doi: 10.1177/0022167817715960

Haines, D. E., & Terell, A. C. (2013). *Fundamental neuroscience for basic and clinical applications*. Philadelphia, PA: Elsevier/Saunders.

Harner, M. J. (1990). *The way of the shaman*. San Francisco, CA: Harper & Row.

Harris, J., Park, C., Currier, J., Usset, T., & Voecks, C. (2015). Moral injury and psycho-spiritual development: Considering the developmental context. *Spirituality in Clinical Practice, 2*(4), 256-266.

Hartberg, J., Garrett-Walcott, S., & De Gioannis, A. (2018). Impact of oral ketamine augmentation on hospital admissions in treatment-resistant depression and PTSD: A retrospective study. *Psychopharmacology*, *235*(2), 393-398. https://doi-org.ezproxy2.library.arizona.edu/10.1007/s00213-017-4786-3

Holmes, S., Girgenti, M., Davis, M., Pietrzak, R., Dellagioi, N., Nabulsi, N., ... & Esterlis, I. (2017). Altered metabotropic glutamate receptor 5 markers in PTSD: In vivo and postmortem evidence. *Proceedings of the National Academy of Sciences of the United States, 114*(31), 8390-8395.

Hornor, G. (2015). Childhood trauma exposure and toxic stress: What the PNP needs to know. *Journal of Pediatric Health Care*, *29*(2). doi: 10.1016/j.pedhc.2014.09.006

IBM Corp. Released 2020. *IBM SPSS Statistics for Windows, Version 27.0*. Armonk, NY: IBM Corporation.

Johnson, S. B., Riley, A. W., Granger, D. A., & Riis, J. (2013). The science of early life toxic stress for pediatric practice and advocacy. *Pediatrics*, *131*(2), 319-327. doi: 10.1542/peds.2012-0469

Kazdin. (2008). Evidence-based treatment and practice. *The American Psychologist,* 63(3), 146–159. https://doi.org/10.1037/0003-066X.63.3.146

Kazdin, A. E. (2017). *Research design in clinical research* (5th ed.). Boston, MA: Pearson. ISBN:9780205992089

Kamenov, K., Twomey, C., Cabello, M., Prina, A., & Ayuso-Mateos, J. (2017). The efficacy of psychotherapy, pharmacotherapy and their combination on functioning and quality of life in depression: A meta-analysis. *Psychological Medicine, 47*(3), 414-425. doi: 10.1017/S0033291716002774

Kelly, S. M. (2002). Space, time, and spirit: The analogical imagination and the evolution of transpersonal theory: Part one: Contexts: Theoretical and historical. *Journal of Transpersonal Psychology*, *34*(2), 73-86.

Kolp, E., Krupitsky, E., Young, M. S., Jansen, K., Friedman, H. & O'Connor, L. (2007). Ketamine-enhanced psychotherapy: Preliminary clinical observations on its effects in treating death anxiety. *International Journal of Transpersonal Studies,* 1-17.

Kolp, E., Krupitsky, E., Sylvester, M. Friedman, H., … & Kolp, A. (2014). Ketamine psychedelic psychotherapy: Focus on its pharmacology, phenomenology, and clinical applications. *International Journal of Transpersonal Studies*, *33*, 112-118.

Kryst, J., Kawalec, P., Mitoraj, A. M., Pilc, A., Lasoń, W., & Brzostek, T. (2020). Efficacy of single and repeated administration of ketamine in unipolar and bipolar depression: A meta-analysis of randomized clinical trials. *Pharmacological Reports: PR*, *72*(3), 543-562. https://doi.org/10.1007/s43440-020-00097-z

Krystal, J. H., Abdallah, C. G., Sanacora, G., Charney, D. S., & Duman, R. S. (2019). Ketamine: A paradigm shift for depression research and treatment. *Neuron,* pp. 774-778. https://doi.org.10.1016/j.neuron.2019.02.005

Lee, E. E., Della-Selva, M. P., Liu, A., & Himelhoch, S. (2015) Ketamine as a novel treatment for major depressive disorder and bipolar depression: A systematic review and quantitative meta-analysis. *General Hospital Psychiatry*, *37*(2), 178-184. doi:10.1016/j.genhosppsych.2015.01.003.

Li, L., & Vlisides, P. E. (2016). Ketamine: 50 years of modulating the mind. *Frontiers in Human Neuroscience*, *10*. https://doi-org.ezproxy2.library.arizona.edu/10.3389/fnhum.2016.00612

Li, M., D'Arcy, C., & Meng, X. (2016). Maltreatment in childhood substantially increases the risk of adult depression and anxiety in prospective cohort studies: Systematic review, meta-analysis, and proportional attributable fractions. *Psychological Medicine*, *46*(4), 717-730. doi:10.1017/S0033291715002743

Lindert, J., von Ehrenstein, O. S., Grashow, R., Gal, G., Braehler. E., & Weisskopf, M. G. (2014). Sexual and physical abuse in childhood is associated with depression and anxiety over the life course: Systematic review and meta-analysis. *International Journal of Public Health, 59*(2), 359-372. doi: 10.1007/s00038-013-0519-5

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

Loureiro, J. R., Leaver, A., Vasavada, M., Sahib, A. K., … & Narr, K. L. (2020). Modulation of amygdala reactivity following rapidly acting interventions for major depression. *Human Brain Mapping*, *41*(7), 1699-1710. https://doi-org.ezproxy2.library.arizona.edu/10.1002/hbm.24895

Luckenbaugh, D. A, Niciu, M. J., Ionescu, D. F., Nolan, N. M., Richards, E. M., Brutsche, N. E., ... & Zarate, C. A. (2014). Do the dissociative side effects of ketamine mediate its antidepressant effects? *Journal of Affective Disorders, 159*, 56-61.

Majić, T., Schmidt, T. T., & Gallinat, J. (2015). Peak experiences and the afterglow phenomenon: When and how therapeutic effects of hallucinogens depend on psychedelic experiences. *Journal of Psychopharmacology, 29*(3), 241-253. https://doi.org/10.1177%2F0269881114568040

Mathai, D. S., Meyer, M. J., Storch, E. A., & Kosten, T. R. (2020). The relationship between subjective effects induced by a single dose of ketamine and treatment response in patients with major depressive disorder: A systematic review. *J Affect Disord*, *264*, 123-129. doi: 10.1016/j.jad.2019.12.023

Marx, B. P., Schnurr, P. P., Lunney, C., Weathers, F. W., Bovin, M. J., & Keane, T. M. (2019). *The brief inventory of psychosocial functioning (B-IPF)*. (Measurement instrument). https: //www.ptsd.va.gov

Maslow, A. H. (1968). *Toward a psychology of being*. Princeton, NJ: Von Nostrand.

McCance, K. L., & Huether, S. E. (2018). *Pathophysiology: The biologic basis for disease in adults and children (8th ed.).* V. L. Brashers & N. S. Rote (Eds.). St. Louis, MO: Elsevier.

Mealer, M., & Jones, J. (2013). Posttraumatic stress disorder in the nursing population: A concept analysis. *Nursing Forum, 48*(4), 279-288. https://doi-org.ezproxy1.library.arizona.edu/10.1111/nuf.12045

Messman-Moore, T., & Bhuptani, P. (2017). A review of the long-term impact of child maltreatment on post-traumatic stress disorder and its comorbidities: An emotion dysregulation perspective. *Clinical Psychology: Science and Practice*, *24*(2), 154-169. doi: https://doi-org.ezproxy4.library.arizona.edu/10.1111/cpsp.12193

Meyerhoff, D. J., Mon, A., Metzler, T., & Neylan, T. C. (2014). Cortical gamma-aminobutyric acid and glutamate in post-traumatic stress disorder and their relationships to self-reported sleep quality, *Sleep*, *37*(5), 893-900. https://doi.org/10.5665/sleep.3654

Miller, G. E., Chen, E., & Parker, K. J. (2011). Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving towards a model of behavioral and biological mechanisms. *Psychological Bulletin*, *137*(6), 959-997. http://doi.org/10.1037/a0024768

Nanni, V., Uher, R., & Danese, A. (2012). Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: A meta-analysis. *Am J Psychiatry, 169*, 141-151.

Nelson, J., Klumparendt, A., Doebler, P., & Ehring, T. (2017). Childhood maltreatment and characteristics of adult depression: Meta-analysis. *British Journal of Psychiatry*, *210*(2), 96-104. doi:10.1192/bjp.bp.115.180752

Novotney, A. (2020). Stopping suicide in the military. *Monitor on Psychology, 51*(1). http://www.apa.org/monitor/2020/01/ce-corner-suicide

Nemeroff, C. B. (2016). Paradise lost: The neurobiological and clinical consequences of child abuse and neglect. *Neuron, 89*(5), 892-909. doi: 10.1016/j.neuron.2016.01.019

Pace, T. W., Wingenfeld, K., Schmidt, I., Meinlschmidt, G., Hellhammer, D. H., & Heim, C. M. (2012). Increased peripheral NF-kB pathway activity in women with childhood abuse-related posttraumatic stress disorder. *Brain, Behavior, and Immunity*.

Paterniti, S., Sterner, I., Caldwell, C., & Bisserbe, J. C. (2017). Childhood neglect predicts the course of major depression in a tertiary care sample: A follow-up study. *BMC Psychiatry*, *17*(1), 113. https://doi.org/10.1186/s12888-017-1270-x

Payne, P., Levine, P. A., & Crane-Godreau, M. A. (2015). Somatic experiencing: using interoception and proprioception as core elements of trauma therapy. *Frontiers in Psychology.* https://doi.org/10.3389/fpsyg.2015.00093

Porter J. (2018). The horror genre and aspects of Native American Indian literature. In: Corstorphine, K. & Kremme, L. (eds) *The Palgrave handbook to horror literature*. London, UK: Palgrave Macmillan. doi: 10.1007/978-3-319-97406-4_4

Pradhan, B., D'Amico, J. K., Makani, R., & Parikh, T. (2016). Nonconventional interventions for chronic post-traumatic stress disorder: Ketamine, repetitive trans-cranial magnetic stimulation (rTMS), and alternative approaches. *Journal of Trauma & Dissociation*, *17*(1), 35-54. https://doi-org.ezproxy2.library.arizona.edu/10.1080/15299732.2015.1046101

QuickFacts. (2019). *QuickFacts: Flagstaff, Arizona; Tucson, Arizona. U.S. Census Bureau*. https://www.census.gov/quickfacts/fact/table/flagstaffcityarizona,tucsoncityarizona/HSG495218

Ratrout, H. F., & Hamdan, M. A. (2020). Secondary traumatic stress among emergency nurses: Prevalence, predictors, and consequences. *International Journal of Nursing Practice, 26*(1). https://doiorg.ezproxy3.library.arizona.edu/10.1111/ijn.12767

Reed, P. G. (2019). Intermodernism, a philosophical perspective for development of scientific nursing theory. *Advances in Nursing Science*, *42*(1),17-27. doi: 10.1097/ANS.0000000000000249

Reed, P.G. (2018). Theory of self-transcendence. In M. J. Smith & P. R. Liehr (Eds.), *Middle range theory for nursing (4th ed.)* (pp. 119-146). New York, NY: Springer. ISBN: 9780826159915

Reed, P. G. (2018). A philosophy of nursing science and practice: Intermodernism. In P. G. Reed & N. B. C. Shearer (Eds). *Nursing knowledge and theory innovations: Advancing the science of practice (2nd ed.)*, 21-46. New York, NY: Springer.

Reed, P. G. (2017) NURS706 Theory development and evaluation. Guidelines for group presentation on theory critique. *Pam's Notes*. Unpublished University of Arizona, College of Nursing: Tucson, AZ.

Reed, P. G. (2016) NURS705 Ontological foundations: Worldviews in nursing. *Pam's Notes*. Unpublished. University of Arizona, College of Nursing: Tucson, AZ.

Reed, P. G. (2009). Demystifying self-transcendence for mental health nursing practice and research. *Archives of Psychiatric Nursing, 23*(5), 397-400. https://doi.org/10.1016/j.apnu.2009.06.006

Reed, P. G. (1986). Developmental resources and depression in the elderly. *Nursing Research,* 35, 368–374.

Reed, P. G. (1989). Mental health of older adults. *Western Journal of Nursing Research,* 11(2), 143-163.

Reed, P. G. (1991). Self-transcendence and mental health in oldest-old adults. *Nursing Research,* 40(1), 5 – 11.

Riebau, D. (2015). Limbic system lectures. *Nursing 352 Neuropsychiatry course*, Vanderbilt University College of Nursing. Unpublished: Nashville, TN.

Riethof, N., & Bob, P. (2019). Burnout syndrome and logotherapy: Logotherapy as useful conceptual framework for explanation and prevention of burnout. *Frontiers in Psychiatry*, *10*(382). https://doi.org/10.3389/fpsyt.2019.00382

Rogers, M. E. (1992). Nursing science and the space age. *Nursing Science Quarterly, 5,* 27-34.

Ross, E. L., & Soeteman, D. I. (2020). Cost-effectiveness of esketamine nasal spray for patients with treatment-resistant depression in the United States. *Psychiatry Online.* https://doi.org/10.1176/appi.ps.201900625

Sahib, A. K., Loureiro, J. R. , Vasavada, M. M., Kubicki, A, … & Narr, K. L. (2020). Single and repeated ketamine treatment induces perfusion changes in sensory and limbic networks in major depressive disorder. *European Neuropsychopharmacology*, *33*, 89-100. https://doi-org.ezproxy2.library.arizona.edu/10.1016/j.euroneuro.2020.01.017

Sanacora, G., Frye, M. A., McDonald, W. Mathew, S. J., ... & Nemeroff, C. B (2017). A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry*, *74*(4), 399-405. doi: 10.1001/jamapsychiatry.2017.0080

Schenberg E. E. (2018). In psychedelic-assisted psychotherapy: A paradigm shift in psychiatric n research and development. *Frontiers in Pharmacology*, *9*, 733. doi: 10.3389/fphar.2018.00733nn7.

Shattuck, E., & Muehlenbein, M. (2016). Towards an integrative picture of human sickness behavior. *Brain Behavior and Immunity, 57*, 255-262.

Singh, J. B., Fedgchin, M., Daly, E. J., De Boer, P, … & Van Nueten, L. (2016). A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. *The American Journal of Psychiatry*, *173*(8), 816-826. https://doi.org/10.1176/appi.ajp.2016.16010037

Schwartz, R. C. (2013). Moving from acceptance toward transformation with internal family in systems therapy (IFS). *Journal of Clinical Psychology*, *69*(8), 805-816. doi:10.1002/jclp.22016

Sendler, D. J., Rutkowska, A. & Makara-Studzinska, M. (2016). How the exposure to trauma has hindered physicians' capacity to heal: Prevalence of PTSD among healthcare workers. *Eur. J. Psychiatry, 30*(4), 321-324.

Sher, L. (2017). Commentary: Adverse childhood experiences and risk for suicidal behavior in male Iraq and Afghanistan veterans seeking PTSD treatment. *Frontiers in Public Health*, *5*, 72. https://doi.org/10.3389/fpubh.2017.00072

Smith, M. (Ed). (2018). *Middle range theory for nursing* (4th ed.). New York, NY: Springer. ISBN: 9780826159915

Spitzer, R. L., Kroenke, K., & Williams, J. B. (1999). Patient health questionnaire study group. Validity and utility of a self-report version of PRIME-MD: The PHQ primary care study. *JAMA*, *282*, 1737-1744.

Sripada, R. K., King, A. P., Welsh, R. C., Garfinkel, S. N, … & Liberzon, I. (2012). Neural dysregulation in posttraumatic stress disorder: Evidence for disrupted equilibrium between salience and default mode brain networks. *Psychosomatic Medicine*, *74*(9), 904-911. https://doi.org/10.1097/PSY.0b013e318273bf33

Stanley, I., Hom, M., & Joiner, T. (2016). A systematic review of suicidal thoughts and behaviors among police officers, firefighters, EMTs, and paramedics. *Clinical Psychology Review*, *44*, 25-44. https://doi.org/10.1016/j.cpr.2015.12.002

Starnino, V. R., Sullivan, W. P., Angel, C. T., & Davis, L. W. (2019). Moral injury, coherence, and spiritual repair. *Mental Health, Religion & Culture*, *22*(1), 99-114.

Stefanovics, E. A., & Rosenheck, R. A. (2019). Predictors of post-discharge suicide attempt among veterans receiving specialized intensive treatment for posttraumatic-stress disorder. *The Journal of Clinical Psychiatry*. doi: 10.4088/jcp.19m12745

Stinson, C. K., & Kirk, E. (2006). Structured reminiscence: An intervention to decrease depression and increase self-transcendence in older women. *Journal of Clinical Nursing, 15*(2), 208-218. doi: 10.1111/j.1365-2702.2006.01292.x

Sveen, J., Bondjers, K., & Willebrand, M. (2016). Psychometric properties of the PTSD checklist for DSM-5: A pilot study. *European Journal of Psychotraumatology*, *7*, 30165. https://doi.org/10.3402/ejpt.v7.30165

Teicher, M. H., Anderson, C. M., & Polcar, A. (2012). Childhood maltreatment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum. *PNAS*, *109*(9), E563-E572. doi: 10.1073/pnas.1115396109

Thompson, N., & Mary Walsh, M. (2010). The existential basis of trauma. *Journal of Social Work Practice*, *24*(4), 377-389. doi: 10.1080/02650531003638163

U.S. Census Bureau. (2022). Race and Ethnicity in the United States: 2010 Census and 2020 Census. https://www.census.gov/library/visualizations/interactive/race-and-ethnicity-in-the-united-state-2010-and-2020-census.html

Vasavada, M. M., Loureiro, J., Kubicki, A., Sahib, A, … & Leaver, A. M. (2020). Effects of serial ketamine infusions on corticolimbic functional connectivity in major depression. *Biological Psychiatry CNNI*. https://doi.org/10.1016/j.bpsc.2020.06.015

Walker, A., McKune, A., Ferguson, S., Pyne, D. B., & Rattray, B. (2016). Chronic occupational exposures can influence the rate of PTSD and depressive disorders in first responders and military personnel. *Extreme Physiology & Medicine*, *5*(8). https://doi.org/10.1186/s13728-016-0049-x

Wang, X. & Kattan, M.W. (2020). Cohort studies: Design, analysis, and reporting. *CHEST*, 158(1). https://doi.org/10.1016/j.chest.2020.03.014

Wang, Z., & Young, M. R. (2016). PTSD: A disorder with an immunological component. *Frontiers in Immunology, 7*(219). DOI: 10.3389/fimmu.2016.00219

Weathers, F. W., Litz, B. T., Keane, T. M., Palmieri, P. A., Marx, B. P., & Schnurr, P. P. (2013). *The PTSD checklist for DSM-5 (PCL-5) – Standard (measurement instrument)*. https://www.ptsd.va.gov/

Weir, K. (2019). U.S. suicide rates have risen in recent years, while rates in other nations have fallen. What can we learn from their examples? *American Psychological Association, 50*(3).

Wiles, N., Thomas, L., Abel, A., Barnes, M., … Lewis, G. (2014). Clinical effectiveness and cost-effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: the CoBalT randomised controlled trial. *Health Technology Assessment*, *18*(31), 1-167 doi: 10.3310/hta18310. https://www.ncbi.nlm.nih.gov/books/NBK261988

Williams, L. M., Debattista, C., Duchemin, A. M., Schatzberg, A. F., & Nemeroff, C. B. (2016). Childhood trauma predicts antidepressant response in adults with major depression: Data from the randomized international study to predict optimized treatment for depression. *Translational Psychiatry*, *6*(5), e799. https://doi.org/10.1038/tp.2016.61

World Health Organization. (WHO). (2015). *Essential medicines and health products: WHO recommends against international control of ketamine*. https://www.who.int/medicines/access/controlled-substances/recommends_against_ick/en/

Zanotti, D. C., Kaier, E., Vanasse, R., Davis, J. L., Strunk, K. C., & Cromer, L. D. (2018). An examination of the test-retest reliability of the ACE-SQ in a sample of college athletes. *Psychological Trauma, 10*(5), 559-562.

Zhou, Y., & Danbolt, N. C. (2014). Glutamate as a neurotransmitter in the healthy brain. *Journal of Neural Transmission, 121*(8), 799-817. https://doi.org/10.1007/s00702-014-1180-8

Zhang, N., Yao, L., Wang, P. & Liu, Z. (2021). Immunoregulation and antidepressant effect of ketamine. *Translational Neuroscience*, 12(1), 218-236. https://doi.org/10.1515/tnsci-2020-0167