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Ketamine Assisted Psychotherapy for Mental Health Conditions

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Abstract

Mental health conditions including depression, anxiety, and post-traumatic stress disorder impact the lives of almost a billion people worldwide. The current standard pharmacological interventions offer limited benefits, but new research in ketamine-assisted psychotherapy (KAP) has shown promising outcomes. This study sought to add to the existing body of research regarding KAP by measuring whether depression, anxiety, and/or spirituality scores improved significantly in participants after one KAP session by measuring Patient Health Questionnaire-9 (PHQ-9) scores, General Anxiety Disorder-7 (GAD-7), and National Institute of Health Healing Experience of All Life Stressors (NIH-HEALS) scores, respectively. A retrospective chart review performed on clinical data from 15 participants from the Advanced Integrative Medical Science (AIMS) Institute in Seattle, Washington showed that improvements in PHQ-9 and NIH-HEALS scores were statistically significant after one KAP session, but there was not a statistically significant improvement to GAD-7 scores following one KAP session. Further research should be conducted to determine whether additional sessions contribute to any significant improvement to GAD-7 scores or greater and sustained improvements to PHQ-9 and NIH-HEALS scores.

Keywords: ketamine assisted psychotherapy; KAP; mental health; depression; anxiety; post-traumatic stress disorder; PTSD; suicide

Ketamine Assisted Psychotherapy for Mental Health Conditions

Mental rigidity, a common sign observed in mental health conditions, is the inability to shift perspectives or adapt to new information. In an ever-evolving world, this hinders a person's capacity to contribute meaningfully, participate fully, and live purposefully. There are many factors as to why global, national, and local mental health has suffered, which will be detailed throughout the extent of this paper. Nonetheless, we acknowledge the universal problems of increased severity of psychiatric conditions and demand of its services, decreased supply of providers, and dismal treatment access, which exist without straightforward solutions and amidst global ambivalence.

Considering the issues listed above, hope remains if we can expand our minds to accept new ways of thinking while working within the context of the U.S. medical system. The use of ketamine and psychotherapy, in particular, seems to be a convincing way to facilitate new neural networks to augment chronically ingrained thinking patterns (i.e., mental rigidity) in a way that can be done safely, legally, and legitimately in our current healthcare paradigm. In this paper, we aimed to answer the question: In patients with a mental health diagnosis in Seattle, does ketamine-assisted psychotherapy, compared to conventional treatments, improve Patient Health Questionnaire-9 (PHQ-9) scores, General Anxiety Disorder-7 (GAD-7) scores, and National Institute of Health Healing Experience of All Life Stressors (NIH-HEALS) scores?

The rationale of this DNP project is to contribute to and deepen the current KAP knowledge base. Analysis and translation of the data will contribute to the significance of the effect of KAP on mood and mental health conditions. This project intends to substantiate the efficacy and effectiveness of KAP as a potential therapeutic modality in psychiatry.

As more research is conducted on the benefits of ketamine, particularly when combined with a psychotherapeutic framework, the positive outcomes may encourage mental health providers to be more open to exploring treatment modalities outside the Western biomedical model. A quantitative study using well established scales is ideal for adding to the body of research that assesses the efficacy of a psychoactive substance, as its assessment is performed in ways that are in line with evidence-based medicine.

Background

This paper focuses primarily on the mental health conditions of depression, anxiety, and post-traumatic stress disorder (PTSD). Since the concept of mental health is shifting towards the perspective that psychiatric conditions lie on an interrelated continuum, or spectrum, the inclusion of PTSD seems appropriate especially with sustained interest in adverse childhood experiences (ACEs) and improvement of healthcare through a trauma-informed lens.

PTSD shares overlapping symptom presentation and is commonly comorbid with depression and anxiety. PTSD can also contribute to the etiology and/or pathogenesis of depressive and anxiety disorders, as trauma exposure in childhood increases likelihood of developing an adult psychiatric condition (Copeland et al., 2018). Traumatic incidents are an unfortunate and frequent occurrence, with up to 60% of children experiencing one event by age 16 and more than 30% experiencing several events (Copeland et al., 2018). PTSD affects more than 50% of sexual assault survivors and is prevalent in up to 25% of conflict-afflicted areas of the world over the course of a year (Hoskins et al., 2021).

Global Mental Health Status

Mental health conditions are amongst the most common debilitating disorders worldwide. In 2022, the World Health Organization (WHO) estimated almost one billion people are living

with a mental disorder globally, with depression and anxiety composing most of these conditions. Mental, or psychiatric disorders, are characterized by deficits in executive functioning due to difficulty coping in response to external and/or internal stressors. Having one mental health disorder predisposes someone to having another mental health condition, such as the frequent co-occurrence of depression with anxiety and vice versa (Momen et al., 2020). Additionally, the likelihood of developing other medical conditions increase with a mental health diagnosis—either due to how our mindset affects our lifestyle choices and socioeconomic status, or that having an illness influences our mental-emotional status (Momen et al., 2020).

Within the Context of COVID-19

Even before the COVID-19 pandemic, rates of mental illness were rising. This affected approximately 280 million people with depression, and approximately 301 million people with anxiety (WHO, 2022, 2021). Although the direct and indirect effects from the pandemic remain to be seen, one study has found depression and anxiety disorders have increased by more than 25% within a year since the onset of COVID-19 (WHO, 2022).

Cost of Burden

Mental health conditions are typically chronic in nature, thus significantly affecting societal costs based on increased utilization of healthcare services, decreased work productivity and economic outcomes, as well as reduced longevity and quality of life (Greenberg et al., 2021). Although schizophrenia is noted to have the highest cost burden of all mental health disorders, depression and anxiety maintain the highest *overall* cost burden due to increased prevalence within the population (WHO, 2017). Estimated cost burden of depression and anxiety collectively reach $1 trillion USD annually (WHO, n.d.).

Mortality and Morbidity

Disability. Alongside financial repercussions, the burden of mental health conditions can lead to increased morbidity and mortality. The WHO has projected that, on average, for every five years lived, one of those years is lived with disability due to mental health conditions (n.d.). Depressive disorders pose a greater threat of disability compared to anxiety disorders with the WHO ranking depressed conditions as the primary cause of chronic (or "non-fatal") health loss (2017). The disease burden of depression is particularly felt in low- and middle-income countries, where greater than 80% of years lived in disability were reported (WHO, 2017).

All mental health conditions are a disability because of impairments to the mind or altered ability to think which can lead to social disengagement or diminished participation in life events (Centers for Disease Control and Prevention [CDC], 2020). Disabilities, specifically mental, will present with modified or reduced completion of self-care-based activities of daily living, like hygiene and grooming, organizing finances and paying bills, cleaning and laundry, or shopping for and assembling a meal (CDC, 2020). Level of disability is based on the individual's experience and perception of their functional status within the context of their unique background and characteristics (CDC, 2020).

Suicidality. The range of disability type, duration, and severity can vary immensely, from a "mild" episode of seasonal depression to the more extreme with death by suicide. When unrelenting, distorted thinking and negative beliefs about the self persist (i.e., mental illness), suicide is a common outcome and is the fourth leading cause of death in individuals ages 15-29 (WHO, 2021). Similar to rates of depression worldwide, the majority (75%) of suicides took place in low-and medium-income countries (WHO, 2017). Factors that increase suicide risk include but are not limited to untreated or worsening mental health conditions, such as

depression, anxiety, and/or PTSD; financial stress, such as loss of a job; and poverty or lower socioeconomic status (Substance Abuse and Mental Health Services Administration [SAMHSA], 2021; WHO, 2017).

United States Mental Health Status

For every five adults in the United States, one has any type of mental illness based on criteria from the *Diagnosis and Statistical Manual of Mental Disorders,* 4th edition (DSM-IV); 1 in 20 U.S. adults have a severe form of mental illness, and 1 in every 6 youth (ages 6-17) have a mental illness (SAMHSA, 2021; National Alliance on Mental Illness [NAMI], 2023). Compared to the global average, U.S. depression rates are worse with a seven percent 12-month prevalence rate (American Psychiatric Association [APA], 2013). The prevalence of depression is even worse in certain age groups, specifically 18–29-year-old individuals who have a three times higher rate than adults over the age of 60 (APA, 2013).

Similar to global patterns, in the United States, depression increases the risk of suicidal thoughts and behavior (WHO, 2017, 2022). In 2020, over 12 million adults in the United States struggled with suicidal ideation; 3 million made plans to kill themselves; and 1.2 million made a plan AND attempted suicide (WHO, 2022). Young adults, who are the highest risk for depression, are also those who have suicide as the fourth leading cause of death (APA, 2013).

Cost of Burden

Major Depressive Disorder. In 2020, major depressive disorder (MDD) cost the United States $326.2 billion, an increase of $110 billion over the past decade (Greenberg et al., 2021). Approximately 61% were workplace related costs since the population surveyed were primarily younger adult workers with employer-based health insurance (Greenberg et al., 2021). Consistent with global costs of burden, MDD contributes to overall loss of productivity, specifically due to

employee absences and 'presenteeism' or reduction of productivity despite being physically present at work (Greenberg et al., 2021).

Anxiety. Although difficult to find a recent estimate of anxiety-related cost burden in the United States, the prevalence of anxiety is higher (44% of adults) and the costs are mostly from loss of productivity (Kavelaars et al., 2023). Similar to depressive disorders, anxiety disorders contribute to increased healthcare costs and indirect costs (absenteeism and presenteeism) and a lower quality of life in the United States (Kavelaars et al., 2023).

Post-traumatic Stress Disorder. In 2018, approximate overall cost burden of PTSD was $232.2 billion, or $19,630 per person with PTSD (Davis et al., 2022). One study comparing U.S. cost burden between civilians and its respective military members observed that the general population utilized greater than 80% of the cost burden associated with PTSD (Davis et al., 2022). Total cost burden for civilians ($189.5 billion) primarily went towards healthcare costs (approximately 35%, or $66.0 billion) and work-related costs (approximately 22%, or $42.7 billion), while total cost burden for military members ($42.7 billion) went towards healthcare (almost 25%, or $10.1 billion) and disability costs (approximately 42%, or $17.8 billion) (Davis et al., 2022). While it may be surprising that civilians require more overall funding due to PTSD, active-duty military represent less than 0.5% of the U.S. population (Council on Foreign Affairs, 2020). However, military members used higher PTSD cost per person cover compared to the general population, due to the increased trauma exposure and inherent risk associated with military activities (Davis et al., 2022).

Washington State Mental Health Status

In the northwest part of the United States, Washington is one of the most progressive states in terms of medical care and access for both patients and healthcare providers. Despite

access and close proximity to major medical schools, medical research, and technology companies, Washington is one of the worst states in the country when it comes to mental health (Sudermann, 2021). Ranked 6th nationally, 22% of Washington state's adult population reported a mental illness, with 8.8% adults having a major depressive episode in a year (Furfaro, 2021; Kaiser Family Foundation [KFF], 2021). Washington also ranks in the top 10 states with the highest prevalence of suicidal ideation in adults (Furfaro, 2021). In those who have died by suicide, the age-adjusted rate in 2019 was higher in Washington than the national average—15.9 and 13.9, respectively (KFF, 2021). Washington state also trends higher in substance use and addiction (Furfaro, 2021).

Despite some of the highest rates of mental illness, Washington also a severe shortage of mental health professionals (Sudermann, 2021). Washington state has only met 16.2% of its mental health treatment needs, compared to 27.7% of the overall United States (KFF, 2022).

Disability Costs

Approximately 25% of the adult population in Washington state have a reported disability (Centers for Disease Control and Prevention [CDC], n.d.). Washington adults with disabilities are significantly more likely to have depression compared to adults without disabilities (47% vs. 18%) (CDC, n.d.). Healthcare costs average $15,068 per person with disability, contributing approximately $19.5 billion per year which represents 37% of the state's healthcare budget (CDC, n.d.).

Universal Barriers to Treatment

Mental health is clearly a problem with the capacity to affect any person regardless of their sociocultural affiliations. However, barriers to treatment are consistently a major obstacle, despite multiple calls to action by the WHO to "transform" global mental health (WHO, 2017,

2022). The scarcity of effective psychiatric care, in addition to barriers of "stigma and discrimination," prevent individuals from seeking early diagnosis and treatment of mental-emotional concerns (WHO, 2022; Mahomed, 2020).

Barriers to accessing care are considerably related to a lack of global prioritization of funding psychiatric research and community mental healthcare (Mahomed, 2020). Globally, countries average 3% of their total medical budget towards mental health, with low- and middle-income countries providing $2 per person for psychiatric care per year (APA, 2016). Greenberg et al. (2021) observed that the percentage of U.S. adults treated for MDD remained the same (at 56%) over the course of a decade despite rates of MDD increasing by 13% over the same time. The rate of incidence should, at minimum, mirror the rate of patients receiving MDD treatment; it was determined that significant treatment needs remained (Greenberg et al., 2021).

Yet there are not as many mental health professionals available to perform the treatment so desperately needed. Before COVID-19, U.S. psychiatrists made up roughly 4% of all medical doctors with over 60% over the age of 55 (Association of American Medical Colleges [AAMC], 2019). Despite some of the highest rates of mental illness, Washington State has a severe shortage of mental health professionals (Sudermann, 2021). Washington state has only met 16.2% of its mental health treatment needs, compared to 27.7% of the overall United States (KFF, 2022).

Although there are initiatives, such as increasing funding and availability of psychiatric residencies, primary care providers are attempting to fill treatment disparities (AAMC, 2019). While primary care providers can prescribe psychiatric medications like antidepressants to bridge gaps in care, they have less training and experience than mental health professionals,

increasing the risk of misdiagnosis or inappropriate prescribing (Radovic et al., 2014; Rolin et al., 2020).

Mental Health Conditions

Epidemiology

Women are more likely than men to be diagnosed with mental health conditions like depression, anxiety, and/or PTSD (NAMI, 2023; U.S. Department of Health and Human Services [HHS], n.d.). People who have been discriminated against due to their race, sexual orientation, and/or gender-identity, are also more likely to have mental health diagnoses (NAMI, 2023). The age of onset for mental illness primarily occurs even before complete maturation of the brain (i.e., in the mid-20s), with 50% beginning by age 14, and 75% by age 24 (NAMI, 2023).

Identification

Diagnostic Criteria. Depression and anxiety are the most common psychiatric conditions diagnosed by medical practitioners both abroad, and within the United States (WHO, 2022; NAMI, 2023). To obtain a mental health diagnosis, specific symptoms and criteria must be met based on guidelines outlined from the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM–5) which is predominantly used in North America, or the *International Classification of Diseases* (10th ed.; ICD-10), which is used throughout the rest of the world (APA, 2013). The most recent updates of these manuals were written in collaboration, so that global definitions of mental disorders are more in alignment. However, ICD-10 diagnostic codes are used universally through billing of medical services and in gathering of disease statistics across all of medicine.

An important caveat which differentiates normal human emotion from a diagnosable, mental disorder is if the symptoms cause "significant distress or impairment," affecting an individual's occupation and economic status, ability to socialize with others, participate in society, and/or other vital areas of function (WHO, 2019; APA, 2013). Importantly, diagnosing mental health conditions must exclude the influence of substances, such as illicit drugs, cannabis, alcohol, or caffeine, and potential underlying medical conditions should be ruled out before a psychiatric diagnosis is made.

Treatment

Initial strategies. First-line, standard of care treatments for depression, anxiety, and PTSD all include psychotherapy and/or pharmacotherapy, specifically antidepressant selective serotonin reuptake inhibitors (SSRIs) like fluoxetine, sertraline, citalopram, escitalopram, among several others (Stahl, 2021b). Proposed mechanism of action for SSRIs is based on the monoamine hypothesis that a deficiency in neurotransmitters leads to the production of mental disorders. Specifically, a deficiency in serotonin was correlated with depression; so, an SSRI's objective is to increase the amount of serotonin, but also to desensitize reuptake receptors from the neuronal synapse (Stahl, 2021b). The latter involves genomic alterations and is the rationale as to why SSRIs must be titrated up over the course of six to eight weeks before treatment efficacy can be determined (Stahl, 2021b). However, antidepressant medications do not work for everyone. Treatment often involves multiple trials of various medications, requiring investment of time, potentially causing unfavorable side effects depending on the medication, all without guarantee of reaching the goal of symptom remission.

SSRIs for depression. STAR*D, the largest, most comprehensive study on antidepressants, found that approximately one in three patients reach remission of major

depressive symptoms on the first trial of the antidepressant citalopram, with 10-15% having a partial response (HHS, 2006). After a total of four antidepressant trials, 70% of the STAR*D participants were without depression symptoms, yet each subsequent trial resulted in an even smaller likelihood of symptom resolution (HHS, 2006). The remaining 30% of the participants did not obtain remission, thus continued to experience depressed mood. Another study found similar results, with 20-30% of patients having no improvement despite following recommended treatment (Lent, 2019). Additionally, many patients have difficulty tolerating side effects from antidepressants, commonly involving decreased libido and/or sexual dysfunction, changes in weight or appetite, gastrointestinal upset, sedation, insomnia, agitation, or QT prolongation which can lead to cardiac arrhythmias (Lent, 2019; Lexi-Drugs, 2022).

SSRIs for anxiety and trauma. When SSRIs are used to treat anxiety conditions, the effect size of those medications is only small to medium (Gomez et al., 2018). Higher doses are also usually needed to treat anxiety conditions which also increase a patient's risk of unfavorable side effects, such as agitation and anxiety, insomnia, sexual dysfunction, diarrhea and gastrointestinal upset, and cardiovascular effects, such as QT prolongation and orthostatic hypotension, among others (Gomez et al., 2018). Benzodiazepines, such as alprazolam (Xanax), are the most efficacious drugs for anxiety disorders with a moderate effect size, but they are not recommended as a first-line treatment since they are highly addictive, can cause potentially deadly withdrawal symptoms, or lead to respiratory depression when used with other sedatives or recreational drugs (Gomez et al., 2018). Additionally, long-term use of benzodiazepines contributes to cognitive impairment which can be irreversible, increasing the risk of dementia (Zetsen et al., 2022). The application of SSRIs for treatment of PTSD has also shown a small

effect size, yet overall clinically significant benefits in a systematic review and meta-analysis of 115 randomized controlled trials (Hoskins et al., 2021).

Resistant treatment strategies. Depression that is unresponsive to two or more trials of antidepressant medication is considered treatment resistant depression (TRD). People with TRD tend to have more severe, chronic forms of depression that accompany higher rates of disability. Since typical, first-line therapies were attempted without ideal response, the next course of treatments, unfortunately, are often more invasive with higher risk of adverse effects.

Electroconvulsive therapy. The current gold standard treatment for TRD is electroconvulsive therapy (ECT) (Basso et al., 2020; Lent, 2019; Sonmez et al., 2019; Veraart et al., 2021). ECT is more efficacious and addresses symptoms more rapidly than antidepressants, but it is not without significant downsides (Basso et al., 2020). The procedure is known to cause temporary cognitive impairments, especially with executive functioning and verbal and visual memory domains, and patients who have experienced post-ECT memory impairment describe the experience as highly distressing (Basso et al., 2020; Veraart et al., 2021). Patients must be put under general anesthesia for ECT, which increases the cost and possible risks involved (Lent, 2019). There is also significant stigma attached to ECT, partially because it has been depicted negatively in movies and television shows for years, which can make patients hesitant to agree to this type of treatment (Lent, 2019).

Transcranial magnetic stimulation. Another option for TRD is transcranial magnetic stimulation (TMS), yet there are multiple reasons it has not become a popular alternative to ECT. The devices needed to perform the treatments are expensive, they are not available at all clinics, and the standard protocol of daily treatments over a series of four to six weeks would be difficult for many patients to afford or make time for (Pridmore & Pridmore, 2021; Sonmez et al., 2019).

While it is an effective treatment for TRD, TMS is also not quite as effective as ECT. Some patients that fail to benefit from TMS will go on to have positive results with ECT (Pridmore & Pridmore, 2021). TMS also has the potential to damage intracranial devices and pacemakers (Pridmore & Pridmore, 2021).

Perhaps the most disappointing finding about TMS came from Sonmez et al.'s (2019) systematic review and meta-analysis of studies focused on accelerating the TMS protocol to shorten the standard treatment length. They discovered that, even when TMS treatment was accelerated, clinical improvement still seemed to have a delayed onset with patients not reaching full improvement potential until weeks after treatment (Sonmez et al., 2019). Yet again, patients with severe depression and high risk of suicide are being asked to wait for an undetermined amount of time for a new treatment option to provide relief from their suffering.

Ketamine as a Potential Mental Health Intervention

Medical Use

Ketamine has received significant attention as a possible alternative to address depression, suicide, and other mental health conditions. Approved by the Food and Drug Administration (FDA) in the 1970s as a dissociative anesthetic, it is still used in medical and veterinary applications today. Ketamine can maintain respiratory functioning while providing pain coverage and adequate sedation and has demonstrated overall good safety and tolerability (Li & Vlisides, 2016). Combined with the unique effect of detachment from reality, psychiatric interest in use of ketamine treatment and the resurgence of psychedelics to promote healing with spiritual exploration has created an explosion of research in this domain (Barber & Aaronson, 2022).

Psychedelic Use

While many different psychedelics and/or hallucinogens are currently being researched for their potential mental health benefits, ketamine is unique in which it is the only substance that is FDA-approved and used primarily within the framework of biomedicine. Because it was created in a lab, it can be dosed more accurately than plant-derived medicines. Additionally, it has not been used historically for spiritual-related practices or ceremonies, so it can be researched in a clinical or laboratory setting, outside of traditional rituals and cultural context (Ona et al., 2021). Whereas plant-based psychoactive substances that have been used for generations, such as peytote, ayahuasca, and iboga, pose a greater risk of cultural appropriation (Ona et al., 2021). Research without regard to the application and intention of historically used natural medicines disrespects the communities from which they are deeply rooted and may also result in less-than-ideal research outcomes as the synergistic benefits from combining the substances within a community and cultural context are lost (Ona et al., 2021).

Overcoming Medical versus Non-Medical Use Bias

Proposing ketamine as a viable treatment for mental health conditions has been controversial due to its potential for addiction as a classified Schedule III drug under the Controlled Substances Act. The effects of sedating dissociation and hallucinations can be intriguing for recreational drug users and has gained the association of being a party drug ("Special K") commonly used at raves (Dodge, 2021; Drug Enforcement Administration [DEA], 2020). Although availability and use of ketamine has increased over the past couple years, non-medical use and abuse is still uncommon in the United States with less than 1% prevalence (Harrison, 2021). Critics of expanding ketamine use are understandably skeptical of increased access to a substance that induces altered states of consciousness, that is commonly used in conjunction with other drugs (such as MDMA or ecstasy) and could increase public-health

burden of disease through HIV and hepatitis if used via injection, or STIs and sexual trauma if used as a date rape drug (Harrison, 2021; DEA, 2020).

However, highly-regulated medically supervised use of ketamine by a licensed provider for psychiatric conditions is distinctly different in application from promoting widespread non-medical ketamine use, of which the former is supported by this paper. There has not been a considerable change in prevalence of ketamine abuse since the 2019 introduction of an FDA-approved ketamine nasal spray, also used under physician supervision (Harrison, 2021). In considering risks of potential harms and benefits, ketamine is still a viable alternative for those with non-responses to standard depression treatment (Thase & Connolly, 2022). Overcoming negative bias due to preconceived notions of ketamine and its history of recreational use can leave medical professionals and patients alike with many questions and concerns (Dodge, 2021). Potential vulnerability to misinformation should not be ignored and will be an important area to emphasize in patient educational efforts.

Review of Literature

Pharmacokinetics of Ketamine

Ketamine is available in multiple formulations for several different routes of administration, including intravenous (IV), intramuscular (IM), subcutaneous, sublingual (SL), intranasal (IN), and rectal. Ketamine is also available in several chemical forms, including racemic ketamine (R- and S-isomers of ketamine) and S-ketamine (or esketamine). Esketamine is believed to contain more desired therapeutic actions through analgesia with less side effects compared to racemic ketamine (Andrade, 2017). The only FDA-approved form of ketamine for treating MDD is esketamine via an intranasal route (brand name Spravato). All other forms of ketamine used for MDD or other mental health conditions are considered off-label.

Distribution and Absorption

The volume of distribution of ketamine is 2.1 to 3.1 L/kg (Lexicomp, 2023). Its absorption depends on the route of administration, with the intravenous route having the highest rate of absorption. Anesthetic effect is reached, from most rapid to slowest (with respective route of administration): within 30 seconds (IV); and 3-4 minutes (IM) (Lexicomp, 2023). Analgesic effect is reached, from most rapid to slowest (with respective route of administration): within 10 minutes (IN); 10-15 minutes (IM); and 30 minutes (SL) (Lexicomp, 2023). IM has the highest bioavailability (93%), followed by IN (35-50%), and SL (20-30%) (Lexicomp, 2023).

Metabolism and Excretion

Ketamine undergoes metabolism through the liver via N-dealkylation, hydroxylation, and conjugation (Lexicomp, 2023). Norketamine, the first metabolite that is produced from N-dealkylation, has 33% potency compared to the original ketamine compound (Lexicomp, 2023). Within the liver, CYP2B6 and CYP3A4 are major metabolizers of ketamine, while CYP2C9 is a minor metabolizer (Lexicomp, 2023). Ketamine is primarily excreted in urine via the kidneys (91%), and through the gastrointestinal tract as feces (3%) (Lexicomp, 2023).

Pharmacodynamics of Ketamine

Therapeutic Effects

Ketamine is a noncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptors (Stahl, 2021a). When ketamine binds to the phencyclidine site of these glutamate receptors, there is increased glutamate release downstream, as well as stimulation of other glutamate receptors including α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Stahl, 2021a). The antidepressant effects of ketamine have been attributed to activation of the AMPA receptors leading to activation of signal transduction cascades, which cause increased density of

dendritic spines and expression of synaptic proteins (Stahl, 2021a). This process enhances synaptic neuroplasticity through long-term potentiation or strengthening of neuronal transmission (Joneborg et al., 2022; Runge et al., 2020). Synaptic pruning occurs in conjunction with increased dendritic spine density leading to memory consolidation and potentially fear extinction, which is why ketamine is believed to improve cognitive flexibility in individuals who struggle to adapt to environmental changes, including those with depression, anxiety, and PTSD (Joneborg et al., 2022; Runge et al., 2020; Elsouri et al., 2022; Stahl, 2021a).

Adverse Effects

Rare adverse effects that are important to monitor during ketamine treatments include the risk of transient laryngospasm in a patient undergoing endoscopy or an active and/or severe respiratory condition, such as pneumonia, asthma, or COPD (Lexicomp, 2023). The cardiovascular system is more commonly affected by ketamine, which causes sympathetic stimulation to increase blood pressure, heart rate, and cardiac output within minutes of administration (Lexicomp, 2023). Those undergoing ketamine treatments are recommended to receive ongoing vitals to ensure normal cardiorespiratory functioning, since ketamine can also cause arrhythmias and worsen underlying heart issues (Lexicomp, 2023). In someone without cardiac disease or heart failure, blood pressure should return to baseline approximately 15 minutes of reaching peak effects, with peak occurring within minutes of absorption (Lexicomp, 2023).

Since the majority of the excretion occurs through the kidneys and bladder, the urinary and renal systems should also be monitored with long-term use of ketamine (Ou et al., 2020). Lower urinary tract symptoms (LUTS; dysuria, frequency, urgency, incontinence) are more likely to occur initially, with possible kidney-related damage thereafter, including irreversible

hydronephrosis (Lexicomp, 2023; Ou et al., 2020). Due to this frequency, urinary analysis, renal labs (glomerular filtration rate [GFR], creatinine) and renal ultrasound should be considered in people who use ketamine and are presenting with LUTS (Ou et al., 2020). Ou et al. (2020) also recommends that urologists and nephrologists maintain clinical suspicion of ketamine use as the cause of undetermined hydronephrosis, which their study defined as "a poor renal outcome and strong predictor of renal function decline in chronic ketamine [users]" (p.1).

"Emergence reactions" can also occur, where patients can experience hallucinations and/or vivid dreaming up to 24 hours after treatment. This is more likely with higher doses, IV administration, and if the treatment was given in a noisy or stimulating environment (Lexicomp, 2023). Mood and thought changes, such as irritability, confusion, and elevated mood, are also reported (Lexicomp, 2023). However, despite the change in perception and cognition, one study found no significant alterations in neurocognition with repeated ketamine sessions at twice weekly, with a dose of 0.5 – 1.0 mg/kg, and at frequency of up to 8-10 sessions (Dai et al., 2022).

Other symptoms can include gastrointestinal upset (nausea and vomiting), increase in intraocular pressure, and pain or rash at injection site (if receiving via injection) (Lexicomp, 2023). It is also important to note that there is a risk of ketamine addiction and withdrawal (Lexicomp, 2023). However, it should be noted that the therapies discussed in this paper are provided by healthcare providers with an active DEA license to prescribe scheduled drugs, and that these ketamine prescriptions are dispensed in a regulated and legal manner.

Psychedelic Effects

The dissociative state that is induced while using ketamine can also be described as an adverse effect yet may also be involved in the ability of ketamine to promote changes in mindset.

It is also important to note that the benefits of ketamine treatment may have to do partly with the patient's experience rather than simply biological changes in the brain. Dore et al. (2019) supported this by noting that researchers initially "attempted to discover a metabolite or analog of ketamine that lacks the psychedelic effects yet retains antidepressant effects," viewing the psychedelic effects as an unwanted side effect, yet studies found that ketamine does not show antidepressant benefits when its psychoactive effects are purposely avoided (p. 190). Ketamine treatment has also been found to be more effective when prescribed at higher, psychedelic doses rather than lower, sub-psychedelic doses further supporting the idea that the psychedelic experience is necessary to utilize the full benefits of ketamine (Joneborg, 2022).

Current Knowledge of Ketamine and Mental Health Conditions

Potential Treatment for Resistant Depression

Interestingly, studies are finding that ketamine has a faster onset of action than both TMS and ECT (Basso et al., 2020). In their naturalistic observational study comparing the antidepressant and neurocognitive effects of ECT and ketamine, Basso et al. (2020) noted that while ECT and ketamine seemed to be equally effective, "the same antidepressant effects that were achieved within four weeks of ECT treatment could be achieved within two weeks of ketamine administration." Ketamine was also found to improve neurocognition, particularly in attention and executive functioning, while ECT exhibited a small, worsening of neurocognitive functioning (Basso et al., 2020). Veraart et al. (2021) agreed that ketamine treatment seemed to have faster antidepressant effects than ECT and fewer adverse effects; however, they cautioned that more research needs to be done with larger sample sizes. Their systematic review could only find six articles that met their inclusion criteria. The lack of quantity of studies is a clear gap in the existing research.

Potential Treatment for Anxiety and PTSD

While TRD seems to be the diagnosis most heavily researched when it comes to treatment with ketamine, there are also studies supporting its efficacy in treating both anxiety and PTSD. Ahuja et al. (2022) studied 452 patients who received ketamine treatment at a private outpatient psychiatric clinic, where 54% of patients had a diagnosis of generalized anxiety disorder. They found that median GAD-7 scores improved 50% from 14.0 at baseline to 7.0 following the patients' final ketamine treatments (Ahuja et al., 2022). Feder et al. (2021) focused their research on the diagnosis of PTSD and found that within 24 hours of ketamine treatment patients experienced improvements to their negative and intrusive thoughts, avoidant behaviors, and overall quality of mood. Those improvements also continued to be present almost a month after treatment (Feder et al., 2022). Further studies are needed to close the gap between the number of studies specifically focused on TRD and the much smaller number of studies focused on other mental health diagnoses.

Types of Ketamine Treatments for Mental Health Conditions

Clinics and providers who offer off-label ketamine treatments for mental health conditions through two methods: IV therapy or through ketamine-assisted psychotherapy (KAP). The process of evaluation and management of both therapies are similar, where patients are screened for applicability and potential contraindications to receiving ketamine are typically offered antiemetics prior to treatment, and are monitored by a medical professional (Pasricha, 2022). IV ketamine and KAP differ in which the former focuses on the drug itself, while the latter incorporates psychotherapy with ketamine to facilitate a transformation.

IV Therapy

According to Lexicomp (2023), use of IV ketamine is recommended for treatment-resistant MDD at an initial dose of 0.5 mg/kg. Infusions can occur 1-3 times per week, typically administered over the course of 40 minutes. Dose increases can occur up to 1.0 mg/kg depending on patient response.

Long-term ketamine infusions have not been studied past 6 weeks and the ideal treatment time has yet to be established. After a 2-week course of 3 ketamine infusions per week, one study reported immediate improvements in depression one hour after administration, with effects sustained at 2- and 4-weeks post-infusion (Mandal et al., 2019). Although many studies report an immediate antidepressive effect that may be helpful for acute suicidality, IV ketamine alone is not a feasible option given that its therapeutic effects have undetermined effect after cessation of treatment. Reduced antidepressant effect diminishes within 10-14 days after discontinuation of ketamine for depression, while the benefit of decreased suicidal ideation lasts up to 7 days (Thase & Connolly, 2022). Additionally, it is expensive (approximately $750 per treatment in the greater Seattle area) and poses another significant barrier to mental health treatment (Pasricha, 2022).

Ketamine Assisted Psychotherapy

In general, current psychiatric practice standards recommend the use of pharmacotherapy in conjunction with psychotherapy for best outcomes when treating mental health issues (Rush, 2022; HHS, 2006). However, most of the studies are related to ketamine monotherapy for depression and other mental health conditions, without concurrent psychotherapy. The discrepancy in lack of studies for KAP is contradictory to what should be recommended to patients with severe depression (Rush, 2022). Specifically, providers have found that ketamine

may be more effective when administered "within a psychotherapeutic framework" which is contrary to the Western biomedical framework and focused only on ketamine's chemical properties (Dore et al., 2019, p. 190). Medical resource, UpToDate, specifically notes that ketamine therapy is complemented by cognitive-behavioral therapy, particularly during transition to maintenance treatment (Thase & Connolly, 2022).

There are no specific KAP guidelines about type of psychotherapy or pharmacotherapy at this time. Though KAP procedures closely mirror the work of psychedelic-assisted psychotherapy (PAP), which has also received a resurgence in research interest (Barber & Aaronson, 2022). Over the course of multiple sessions spread across different days, sessions are divided into: (1) preparation (including evaluation of applicability, education about side effects and potential risks, discussing patient intentions and goals); (2) dosing that is supervised by a licensed provider or facilitator who supports the patient emotionally (or medically if needed) through their ketamine experience; and (3) integration, where the experience is reflected and reviewed (Barber & Aaronson, 2022; AIMS Institute, n.d.). The appeal of KAP and PAP is its dynamic in creating mindfulness and insight, by breaking down previously held notions, and emerging with a new sense of perspective (Fischman, 2022; Barber & Aaronson, 2022). Due to variability observed in the quality and quantity of both ketamine and KAP research, this study aims to add meaningful, considerate research to further differentiate outstanding questions on efficacy, safety, and applicability in clinical settings for patients with mental health conditions.

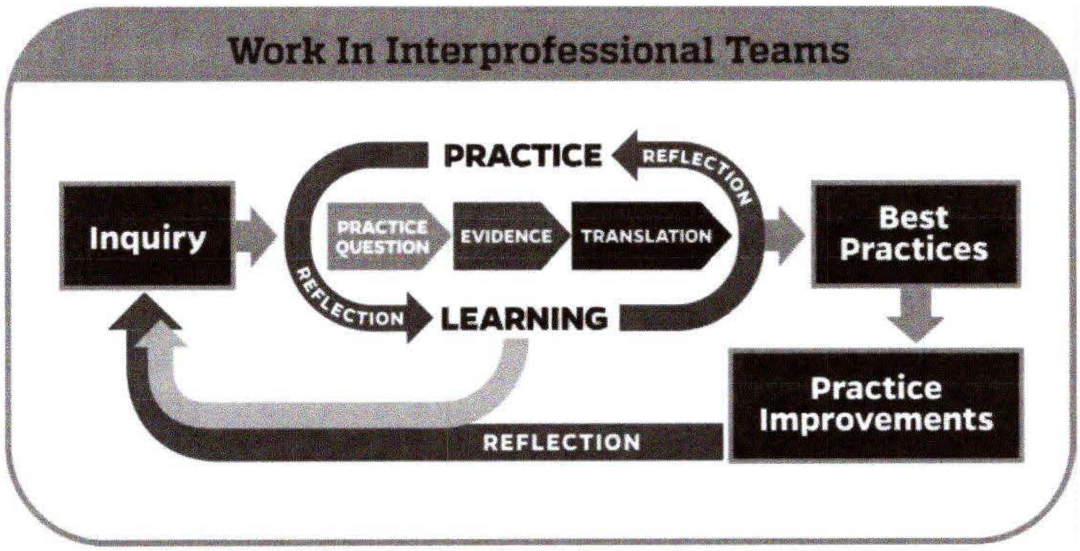
Theoretical Framework

This study uses the John Hopkins Nursing Evidence-Based Practice Model (JHNEBP) as its theoretical framework. The goal of the JHNEBP Model is inherently interchangeable with the ideology of evidence-based medicine (EBM) from which Western biomedicine is based. The

emphasis of both the JHNEBP Model and EBM is to continually combine the most recent research findings with the best clinical practices to deliver the highest quality patient care possible (Dang et al., 2022). The JHNEBP Model (Figure 1) was designed to further support the decision-making process of the practicing nurse using a three-step process: 1) practice question; 2) evidence; and 3) translation (Dang et al., 2022). Conceptually, the JHNEBP model aligns well with the Seattle University College of Nursing's objective to prepare its DNP graduates to apply research within clinical practice, emphasizing quality care at individual and systems-based levels (Seattle University, n.d.).

Figure 1

Diagram of John Hopkin's Nursing Evidence Based-Practice Model (Dang et al., 2022)



Methods

Setting

The authors worked with researchers/practitioners from the Advanced Integrative Medical Science (AIMS) Institute in Seattle, Washington. The AIMS Institute was founded to provide integrative care, research, and education, focusing primarily on oncology, psychiatry,

chronic pain, and palliative medicine. They offer a variety of holistic treatment options that include cannabis, KAP, and stellate ganglion blocks (AIMS Institute, n.d.).

Project Type

The doctoral project involved collaboration with researchers to answer clinical questions. This was a data-driven, systematic process. The research data generated and analyzed may be applied to clinical practice and support evidence-based practice, which qualifies as a DNP project (Moran et al., 2020). This project involves analyzing a subset of data extracted from two of the AIMS Institute's existing outcomes studies: the AIMS Cancer Outcomes Study (ACOS) and the AIMS Medical Outcomes Study (AMOS) (National Library of Medicine [NLM], NCT04495790; NCT04512755). Both are five-year longitudinal studies that examine any changes to patient reported outcomes while receiving integrative care at AIMS (National Institute of Health (NIH), 2020; AIMS Institute, n.d.).

Study Design

The study methodology for this doctoral project was a retrospective chart review of patients who are participants in the AIMS Institute's ACOS and AMOS studies. These are "observational, prospective case series outcomes studies on the effects of integrative specialty medical care" (NIH, 2020). This qualifies as a case series outcomes study because it includes a description of the characteristics and outcomes among a group of individuals all exposed to KAP over a period of time, without a control group or randomization (Torres-Duque et al., 2020).

Ethical Considerations

Seattle University's Institutional Review Board (IRB) has identified this DNP project, consisting of retrospective chart review, as "Not Human Participant Research (NHPR)." No further IRB review was deemed necessary. Both AMOS and ACOS studies have been approved

by the IRB at Seattle University in Seattle, Washington, and the authors of this paper were approved as research assistants for these studies.

Participants

Study participants consisted of adolescent and adult patients with established care at the AIMS Institute who consented to take part in the ACOS or AMOS studies (NIH, 2020; AIMS Institute, n.d.). Participants for this DNP project had the following inclusion criteria: a mental health-related ICD-10 diagnosis; receiving KAP treatment at the AIMS Institute between November 1, 2020-October 31, 2022; receiving KAP at least twice; and submitting at least two PHQ-9, two GAD-7, or two NIH-HEALS questionnaires. The last criterion was chosen to ensure that there was sufficient data to assess pre- and post-KAP set of data for each study participant.

The exclusion criteria had specific rationales. As a baseline cannot be established, participants who did not complete a questionnaire prior to their first KAP treatment were excluded. Participants who did not complete a questionnaire after their first KAP session and prior to a consecutive KAP session were not included, as the participant's status between consecutive sessions is unknown. To reduce the effect of questionnaire response bias, AIMS Institute staff members were also excluded.

Data Collection

As of 2020, the AIMS Institute has been gathering data from consented patients through the electronic health record (EHR) programs ChARM EHR and Osmind. ChARM is used to systemize general medical data, such as patient diagnoses and demographics. Osmind, a mental health specific EHR, allows for online distribution of standardized questionnaires that patients complete, providing a quantitative measurement of their mental health status.

These questionnaires and what they assess, respectively, include: PHQ-9 for depression, GAD-7 for anxiety, and NIH-HEALS (Healing Experience of All Life Stressors) to understand healing in the context of chronic illness (NIH, 2020). The PHQ-9 and GAD-7 are two of the best validated, most reliable, and most used self-report scales to track depression and anxiety (Kroenke et al., 2016). Adverse Childhood Experiences (ACEs) and resilience scores are also collected to ascertain if there is a relationship between these metrics and the presence and severity of mental health diagnoses (AIMS Institute, n.d).

The authors reviewed the AIMS Institute's patient database to filter for eligible study participants based on inclusion and exclusion criteria. Thereafter, charts were reviewed for pertinent participant data as defined by the study. The data gathered for this DNP project included the dates of each participant's KAP sessions as well as the dates and results of all their submitted standardized questionnaires. The data sets have been entered into an electronic spreadsheet and stored in a password-protected cloud drive.

Data Analysis

Most data were analyzed with descriptive statistics. Microsoft Excel software was used for statistical analysis. Due to small participant size, Wilcoxon signed rank tests were performed between baseline and second questionnaire scores with an established significance level of $\alpha < 0.05$.

Results

Of the 307 patients who received KAP in the specified time frame, 16 were staff members. There were 230 patients who consented to take part in the AMOS or ACOS studies, now considered participants. Of the 230 participants, those who completed at least two questionnaires were as follows: 112 for PHQ-9 questionnaires, 104 for GAD-7 questionnaires,

and 86 for NIH-HEALS questionnaires. Once the final exclusion criteria were applied, a total of 15 participants were evaluated.

Demographics

The 15 participants ranged in age from 18-69 years with an average participant age of 43.33 years. Most participants were in their 30s (n=5) or 40s (n=5). Participants identified their gender as female (n=7) and male (n=8). The average ACE and Resilience scores were 4.13 ± 2.03 (SD) and 8.4 ± 4.53 (SD), respectively. Table 1 outlines each participant's characteristics.

Table 1

Participant Demographics and Characteristics

Participant ID	Age	Gender	ACE Score	Resilience Score
1	42	Female	1	9
2	52	Male	6	12
3	46	Male	4	8
4	34	Male	2	12
5	33	Female	5	12
6	49	Female	6	0
7	57	Male	5	6
8	34	Female	3	14
9	38	Female	2	13
10	34	Female	8	8
11	44	Male	4	7
12	48	Male	6	3
13	18	Male	1	14
14	52	Male	5	1
15	69	Female	4	7

The number of ICD-10 diagnosis for each participant ranged from 2-6, with a mode of 2 and a mean of 4 diagnoses. A majority of participants had a diagnosis of other personal history of psychological trauma, not elsewhere classified (n=7); major depressive disorder (n=6); or

adjustment disorder (n=6). The next most common diagnoses were generalized anxiety disorder (n=4); suicidal ideation (n=4); post-traumatic stress disorder (n=4); anxiety, unspecified (n=3); dysthymic disorder (n=3); and substance use disorder (n=3). The least common diagnoses were attention deficit hyperactivity disorder (n=1); worries (n=1); disappearance or death of family member (n=1); sleep disorder, unspecified (n=1); bipolar II disorder (n=1); alcohol use disorder (n=1); other psychoactive substance abuse, uncomplicated (n=1); and sex addiction (n=1).

Questionnaire Scores

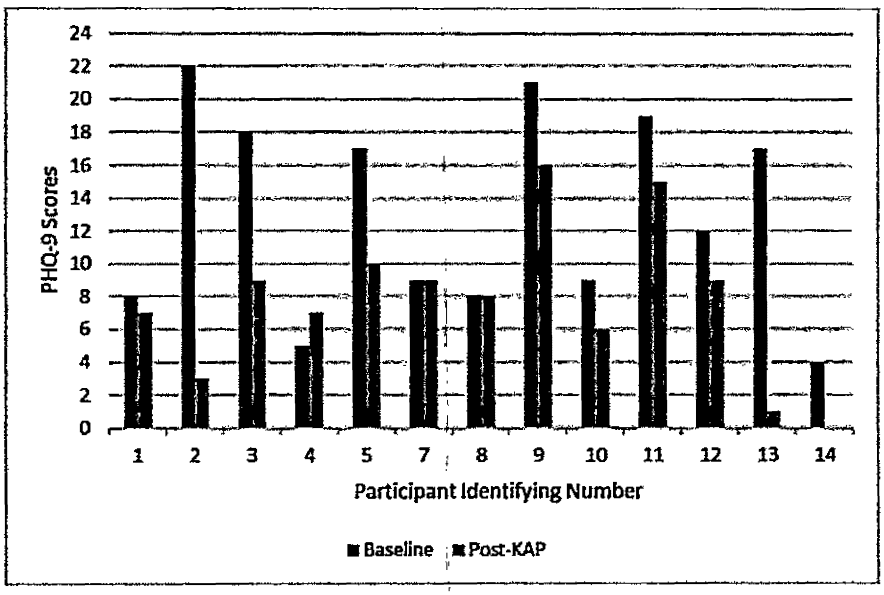
Baseline metrics were established using the most recent questionnaire scores that preceded a participant's first KAP session. Changes were calculated by comparing the difference between the baseline questionnaire score and the most recent questionnaire score that followed a participant's first KAP session.

PHQ-9

There were 86.67 % (n=13) of participants who completed one post-KAP PHQ-9 questionnaire before completing another KAP session. Figure 2 illustrates the PHQ-9 scores for each participant prior to and after the first KAP session. The average baseline PHQ-9 score was 13 ± 6.23 (SD) with scores ranging from 4-22 points. After the first KAP session, scores had an average of 7.69 ± 4.68 (SD) with scores ranging from 0-16 points. This was an average decrease of 5.31 ± 6.2 (SD) points. The score range for PHQ-9 is 0-27 with the higher scores indicating worsening severity of depression symptoms. The Wilcoxon signed rank test calculated w_s=2, rejecting the null hypothesis (α=0.05 of 10).

Figure 2

Paired PHQ-9 Scores

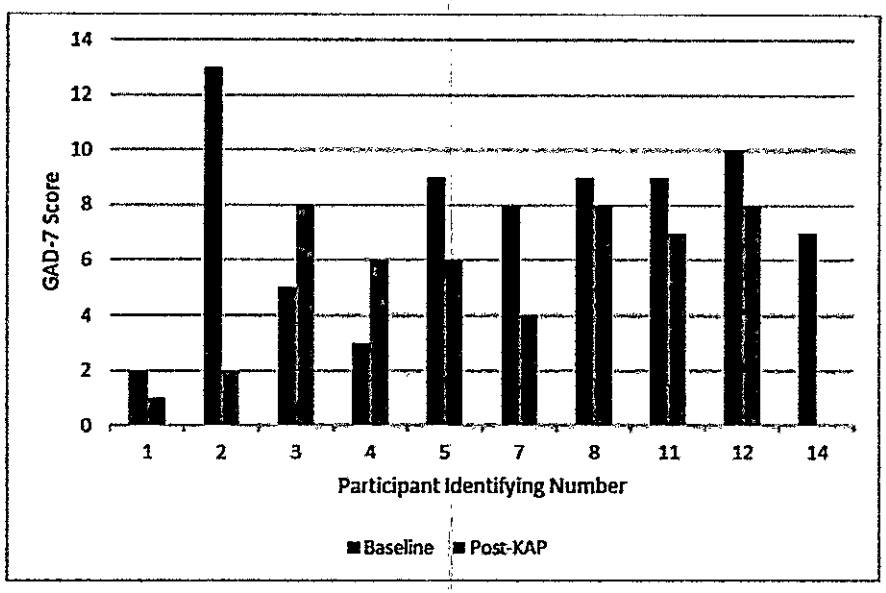


GAD-7

There were 66.67 % (n=10) of participants who completed one post-KAP GAD-7 questionnaire before completing another KAP session. Figure 3 illustrates the GAD-7 scores for each participant prior to and after the first KAP session. The average baseline GAD-7 score was 7.5 ± 3.34 (SD) with scores ranging from 2-13 points. After the first KAP session, participant scores averaged 5 ± 3.06 (SD) with scores ranging from 0-8 points. This was an average decrease of 2.5 ± 4.22 (SD) points. The score range for GAD-7 is 0-27 with higher scores indicating worsening severity of anxiety symptoms. The Wilcoxon signed rank test calculated w_s=12. This did not reject the null hypothesis (α=0.05 of 8).

Figure 3

Paired GAD-7 Scores

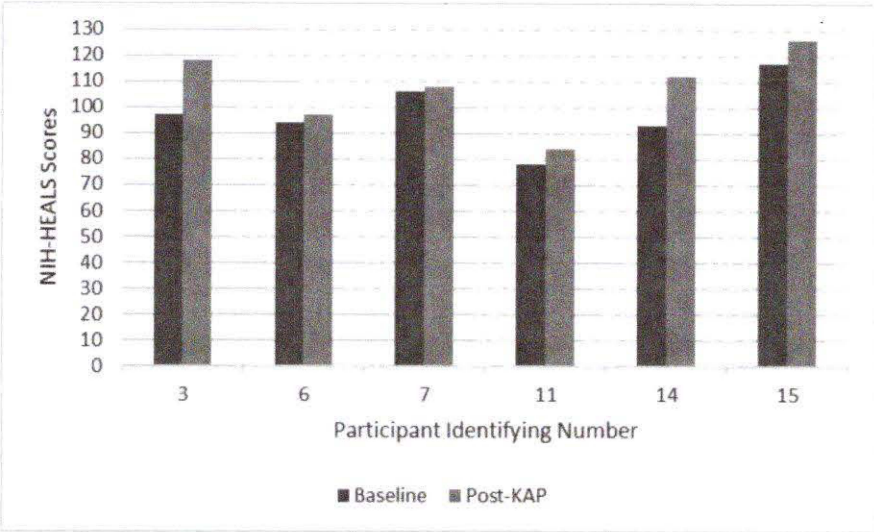


NIH-HEALS

There were 40 % (n=6) of participants who completed one post-KAP NIH-HEALS questionnaire before completing another KAP session. Figure 4 illustrates the NIH-HEALS scores for each participant prior to and after the first KAP session. The average baseline NIH-HEALS score was 98.14 ± 12.13 (SD). The participants' baseline scores ranged from 78-117 points. After their first KAP session, scores had an average of 107.5 ± 15.07 (SD) with scores ranging from 84-126 points. There was an average increase of scores by 10 ± 8.15 (SD) points. The score range for NIH-HEALS is 35-175, with higher scores indicating greater positive transformation in response to challenging life events. The Wilcoxon signed rank test calculated w_s=0, rejecting the null hypothesis (α=0.05 of 0).

Figure 4

Paired NIH-HEALS Scores



Discussion

The results of this study found that the improvement in PHQ-9 and NIH-HEALS scores for patients after one KAP session was statistically significant, but the improvements observed in the GAD-7 did not reach statistical significance following one KAP session. Since KAP has been most widely studied as a treatment for depression, it is not surprising that scores related to depression showed the most significant improvements. These findings further corroborate existing research data. While only a limited number of participants completed NIH-HEALS questionnaires, all of them had an improvement in their scores following one KAP session. The statistically significant improvement in their scores suggests that KAP can improve an individual's ability to experience positive growth following difficult life events - an outcome which these authors believe has not been studied in existing research. Most research regarding KAP has shown that multiple treatments are ideal for improving patient outcomes, so analysis of scores following consecutive KAP sessions may have shown different results.

While the GAD-7 questionnaire results were not statistically significant, there were some interesting findings. Of the four participants diagnosed with generalized anxiety disorder, only one completed two GAD-7 questionnaires, making it difficult to comment on KAP's effectiveness when it comes to treating generalized anxiety disorder. The two participants with the greatest improvements in GAD-7 scores, participant 2 and 14, did not have a diagnosis of generalized anxiety disorder. Participant 2 had major depressive disorder and adjustment disorder with anxiety, while participant 14 had a long history of physical trauma and chronic pain but no diagnosis specific to psychiatry.

The discrepancy could potentially be attributed to these participants not recognizing they have an anxiety disorder. One study comparing self-reported versus 'unrecognized anxiety' found that 44% of its participants could identify having an anxiety disorder, yet up to 11% of the participants had anxiety symptoms yet did not recognize that they had a diagnosable disorder (Kavelaars et al., 2023). Unrecognized anxiety, as well as subthreshold anxiety (where there are some symptoms, but doesn't *quite* meet GAD criteria), are still important to consider and screen for since they also contribute to increased healthcare costs, decreased productivity, and diminished life quality (Kavelaars et al., 2023). These burdens are directly correlated with severity of anxiety symptoms and present a compelling argument for why anxiety should be treated earlier and more aggressively, to prevent disability and likelihood of developing a comorbid diagnosis (Kavelaars et al., 2023).

Additionally, the providers who diagnosed these study participants may not have had time or enough information to yield a GAD diagnosis which is also why anxiety is commonly missed (and undertreated) in primary care settings (Kavelaars et al., 2023). Lastly, perhaps these participants had subthreshold anxiety, yet their symptoms were severe enough to elicit a higher

GAD-7 score at baseline and had an effective therapeutic response to ketamine which dropped their scores overall. In the case of participant 14, the reduction in anxiety score may have been related to improved management of chronic pain since ketamine is also used for this condition.

The PHQ-9 findings were statistically significant, which further corroborate that KAP has associated improvements for persons with treatment resistant depression. The average decrease in PHQ-9 scores between baseline and first KAP session was 5.31 ± 6.2 (SD) points, which reduced the average participant score from moderate depression down to mild depression. Of the PHQ-9 participants, 5 were female and 8 were male, supporting the data's external validity for both genders. Of the 6 patients with major depressive disorder, only 1 did not complete two PHQ-9 questionnaires. This contrasts with the GAD-7 questionnaires where patients with the diagnosis most associated with the screener were least likely to have completed it. In the case of the PHQ-9 questionnaires, the participants with the greatest improvements in scores following KAP (participant 2 and participant 13) also both had diagnoses of major depressive disorder. This may suggest that KAP is more effective in treating the symptoms of patients with depression than patients with anxiety, but further research on larger populations would be needed to confirm this.

Although this study did not specifically focus on ACEs, it is interesting to compare how our participant population compares to the CDC's reported statistics. The CDC reported that 61% of adults have at least one ACE and 16% have four or more, but 100% of our participants had at least one ACE and 67% (n=10) had four or more (CDC, 2021). The CDC also reported that females are at greater risk for experiencing four or more ACEs, but in our population 57% of females (n=4) reported four or more ACEs while 75% of males (n=6) reported four or more ACEs (CDC, 2021). These comparisons suggest that our population is not representative of the

greater population in the United States when it comes to ACEs. This may be because patients with higher ACEs are more likely to investigate new types of therapy and treatments such as KAP. In our study we did not find a noticeable correlation between higher ACEs and depression or suicidal ideation, but that may have been due to our small sample size.

Limitations

One of the most significant limitations of this study was the lack of completed patient questionnaires following KAP sessions. Since the Osmind patient portal sends reminders to complete questionnaires at regular time intervals rather than times specific to an individual's KAP sessions, there is a likelihood that a participant did not complete a questionnaire after each KAP session. Non-response bias also limited the usable data in this study as participants did not always fill out questionnaires when prompted to do so.

Implications for Future Research

Possible ways to minimize non-response bias in the future, to help gather more correlational data for future research, would be to have providers administer questionnaires to patients in person prior to their KAP sessions and integration sessions, rather than rely on automated prompting. This could potentially negatively impact provider's rapport with patients and disrupt their workflow; however, this may produce a valid result observed in the research between KAP and mental health outcomes.

The large amount of data available for retrospective chart review at the AIMS Institute allows for a variety of topics for investigation in future research projects. Potential ideas include but are not limited to looking for correlations between specific diagnoses related to improvement in questionnaire scores following KAP; correlations between ACE scores or resiliency scores and changes in questionnaire scores following KAP; and looking for correlations between the

number of KAP sessions and changes in questionnaire scores following KAP. The latter suggestion may be of particular interest to help providers decide the optimal number of KAP sessions. Another potential area for future research would be to incorporate new questionnaires to answer more specific questions, such as using the Columbia Suicide Severity Rating Scale to help determine whether KAP has an effect on suicidal ideation. Additionally, the WHO Disability Assessment Schedule (WHODAS 2.0) could be an assessment used to track changes in disability throughout the duration of KAP treatments.

Sustainability Plan

Ketamine is a Schedule III controlled substance that is being used off-label for depression and other psychiatric conditions. Currently is not readily available to potential patients since it is considered experimental, and thus not covered by insurance. Patients who engage in ketamine infusions or KAP pay for the treatment out of pocket—which can be thousands of dollars depending on the clinic and frequency of treatment. At present, only those who have financial means can access ketamine—which is unfortunate given that people with lower socioeconomic status (SES) are at an increased risk for depression and suicide (Hoebel et al., 2017; WHO, 2017).

Due to KAP treatment barriers, the participants in this study are likely unrepresentative of the greater Seattle population. Therefore, the results from this research cannot necessarily be extrapolated to all patients presently because of skewed participant demographics related to disproportionately higher SES. Despite the lack of patient participant diversity, this research is still necessary to broaden KAP research, with the intention to increase treatment access to mental healthcare and reduce the morbidity and mortality of mental illnesses. More evidence must be

obtained to inform if KAP should remain experimental, or if it is a reasonable treatment option for those with chronic, unremitting mental health diagnoses.

Yet before KAP can be broadly recommended as a therapy beyond patients with depression, even more research and primary literature is needed to clarify questions about pharmacokinetics, such as optimal dose and form of ketamine which vary in their absorption depending on the route of administration (i.e., oral, intramuscular, or intravenous). Tolerability and side effects are not necessarily as much of a concern due to decades-long evidence showing ketamine to be a safe, reliable anesthetic. However, additional information about duration of treatment, frequency of treatments, how to incorporate KAP with other complementary treatment strategies such as pharmacotherapy, psychotherapy, and brain stimulation (i.e., ECT and TMS), can support ketamine-based therapies from being considered experimental, to becoming a clinically accepted and insurance-covered treatment for mental health conditions.

Implications for Advanced Nursing Practice

Although investigations of KAP have gained significant interest, clinical research in nursing practice is "mostly invisible" (Denis-Lalonde & Estefan, 2020). Despite nurses' comprising a significant portion of the healthcare field, there is an "absence of nursing collaboration and nurse leaders" within psychedelic research (Penn et al., 2021). Given that nurse practitioners and nurse anesthetists can prescribe and provide ketamine infusions in Washington state, the role of the nurse undoubtedly will be vital towards guiding and advancing this promising avenue of medicine.

Additionally, the results from this DNP project can be used as scaffolding to "generate opportunities for future work among different [DNP project] approaches" (Moran et al., 2020, p. 240-241). Our research contributions can be used for subsequent quality improvement projects,

program development and evaluations, and policy analyses created and facilitated by other DNP candidates and colleagues. As the breadth of knowledge surrounding ketamine-based treatments continues to grow, it is vital to maintain diversity, equity, and inclusivity in research and clinical practice, so we may grow towards a healthier, more just, and humane world.

Conclusion

Current treatments for mental health conditions are lacking in efficacy and can be intolerable due to side effects. This study contributed to the growing body of research supporting KAP as a safe and effective treatment for depression and other mental health conditions by demonstrating statistically significant improvements in depression and spirituality scores after just one KAP session. KAP is also a treatment that brings together the expertise of a variety of clinicians including prescribers and therapists, which could potentially maximize patient benefits and allows for continuing research from a variety of fields and frameworks. The authors hope that reading this paper has helped to answer some questions and encouraged the reader to ask new research questions of their own, with the goal of furthering our ability to work with our patients to maximize their mental health and wellbeing.

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