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Ketamine in Postpartum Mood and Anxiety Disorders

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Ketamine in Postpartum Mood and Anxiety Disorders

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Abstract

Postpartum mood and anxiety disorders (PMADs) are a distinctive subset of psychiatric disorders that can have serious consequences for the birthing person and child if not effectively treated. Current treatment options for PMADs can take several weeks to achieve efficacy or are difficult to access. Although literature on ketamine has been focused on preventing PMADs, ketamine is an emerging treatment option for various psychiatric disorders and is starting to show promise in treating PMADs. This project utilized content and thematic analysis to examine electronic medical records (EMRs) of individuals with PMADs at the AIMS Institute to determine benefits of those who received ketamine vs. treatment as usual. Out of five total participants, the majority (n = 4, 80%) had received ketamine while experiencing PMADs. Benefits of participants who received ketamine showed three predominant coded categories: general improvement in mental health symptoms, increased psychosocial self-awareness, and improvement of feelings of self-worth and self-efficacy. This study provides a precedent for the benefit of ketamine treatment in PMADs.

Keywords: ketamine, ketamine assisted psychotherapy, KAP, postpartum, peripartum, anxiety, depression, PMAD, PPD

Ketamine in Postpartum Mood and Anxiety Disorders

Postpartum mood and anxiety disorders (PMADs) are a form of mental illness with unique considerations as they have a range of consequences that can become dangerous for both the birthing individual and developing infant. Effects on maternal health include an increase in adverse maternal physiological and psychological health outcomes, which may include heightened suicidal ideation (Slomian et al., 2019). Suicide is one of the leading causes of maternal death within the United States from 2017-2019 at slightly over 20% (Trost et al., 2022). Effects on infants born to individuals with PMADs include a greater proportion of health concerns, emotional development delays (Slomian et al., 2019), and delays in communication and personal-social development (Mughal et al., 2019). Individuals with PMADs have co-occurring profound physical and life changes, which includes sleep deprivation. Treatment offers are often generalized from standard depression protocols, such as selective serotonin reuptake inhibitors (SSRIs) which, while demonstrating a level of efficacy, and can often take several weeks to achieve full efficacy (Carlini et al., 2023). There is the additional consideration of lactation, where any drug given to the individual must have a demonstrated level of safety for the infant as well (Mughal, 2022). Unfortunately, there are limited approved pharmacologic treatment options specific to PMADs (Viguera, 2024).

Given the serious implications that PMADs can represent it is crucial to identify additional pharmacologic treatments that can be utilized for this unique subset of psychiatric disorders. Ketamine is one such emerging pharmacologic treatment that has shown a wide range of benefits in various psychiatric and mental health disorders (Drozdz et al., 2022) and may provide additional benefit in the treatment of PMADs. Despite ketamine's emergence as a treatment option for mood disorders, which from early literature appears safe during postpartum because of its relatively low risk of transmission during lactation (Wolofson et al., 2022), it has been limited in both its clinical use, and coverage in literature as a treatment modality for

individuals with PMADs. It is possible that this may be due to lack of funding, or hesitancy to study a medication within the perinatal period. The purpose of this DNP project is to examine existing cases of ketamine use in PMADs with the aim of assessing its benefits, safety, and tolerability as a potential treatment option for individuals with PMADs.

Background and Significance

PMADs

Definition

This project uses the term ‘postpartum mood and anxiety disorders’ (PMADs) to encompass a variety of psychiatric disorders related to the period following parturition. There is no universally established definition of PMADs within the psychiatric community. The most current Diagnostic and Statistical Manual of Mental Disorders 5th edition text-revision (DSM-5-TR) uses the term ‘peripartum,’ which includes both during pregnancy and postpartum, to affiliate with psychiatric disorders during this period. This is a change from stating ‘postpartum’ exclusively, as the onset of these disorders can begin as early as late pregnancy and up to one year after parturition (Tebeka et al., 2021). DSM-5-TR defines ‘peripartum onset’ as a mood disorder beginning either in pregnancy or within the first four weeks following delivery (American Psychiatric Association, 2022). However, this timeframe is debated, with literature demonstrating the onset of a PMADs longer after parturition (Tebeka et al., 2021). Many prominent organizations also define postpartum depression as occurring up to a year following birth, but commonly starting within the first several weeks following birth (American College of Obstetrician and Gynecologists, 2024; National Health Service, 2024; UNICEF, n.d.). Further research through the Center for Women’s Health, Massachusetts General Hospital with cohort studies suggest this period may be longer yet and that PMADs may increase likelihood of future depressive episodes (Freeman et al., 2018).

There is no formal diagnosis within the DSM-5-TR for peripartum mood or anxiety disorders; however, the specifier ‘with peripartum onset’ can be added to mood disorders such as depressive and bipolar disorders. For anxiety disorders, there is no peripartum specifier included in the DSM-5-TR (American Psychiatric Association, 2022). Despite its absence in the DSM-5-TR, there is substantial literature regarding peripartum anxiety, indicating that it may be even more prevalent than peripartum depression (Zappas et al., 2021). The international classification of diseases, tenth revision (ICD-10) has some diagnostic codes specifically associated with PMADs: postpartum mood disturbance (O90.6) and postpartum depression (F53.0).

Risks of Untreated PMADs

Treatment of PMADs can be complex as the risks and benefits of a treatment for both the parent and child must be weighed against the risks of untreated PMADs. Slomian et al. (2019) conducted a systematic review of outcomes related to postpartum depression for parents, children, and the bond between the two. For parents, the risks of untreated PMADs are associated with sustained psychiatric concerns, relationship difficulties, overall poorer physical health outcomes, greater postpartum weight retention, increased risk for substance use, and higher likelihood of suicidal ideation. Risks to the child include lower levels of weight gait, increased morbidity and mortality risks; sleep problems; delays in motor, cognitive, and language development; and delays in emotional development and social engagements. Regarding the parent-child bond, postpartum depression was associated with increased difficulties with lactation and chest feeding and impaired bonding, which includes lower levels of closeness, warmth, sensitivity, and attunement. It is worth noting that many of these effects were greater for sustained depression, as opposed to transient, and there were confounding variables that overlap with risk factors for PMADs, such as low socioeconomic status (SES) and large life stressors.

Risk Factors for PMADs

There are a variety of risk factors associated with PMADs stemming from social and psychological or biological and genetic etiologies. Social and psychological risks include history of prenatal mood and/or anxiety disorders, high stress or trauma, lack of social support, lack of spousal/partner support, immigration or high levels of acculturation, and low SES. Biological and genetic risk factors include gestational diabetes, increased inflammatory mediators, abnormal neuroendocrine hormone function, and epigenetic changes. Birthing experiences themselves may also become a risk for PMADs. Negative birth experiences, multiple births, and preterm deliveries have been associated with PMADs. Notably, aspects which have been studied as risk factors and have failed to demonstrate a strong correlation across studies include chronic illness, vitamin D levels, birth via caesarean section, body image dissatisfaction, and pre-pregnancy obesity (Agrawal et al., 2022; Yang et al., 2022).

Pathophysiology

There is emerging research to suggest that PMADs may differ from other psychiatric conditions relating to the disease's pathophysiological processes. Batt et al. (2020) effectively summarizes some of the major differences and similarities in the pathophysiologic processes underlying postpartum depression (PPD) and major depressive disorder (MDD). Neurological changes observed in both PPD and MDD include decreased activation of reward circuitry, reduced binding of serotonin receptors, and decreased activity of gamma-aminobutyric-acid (GABA). Specific to PPD is that the amygdala, commonly known as the fear center of the brain, has a blunted response to negative stimuli whereas in MDD the response is typically heightened.

Many genetic risk factors overlap for both PPD and MDD with specific genetic variances in reproductive and stress hormone pathways having been associated with both types of depression. There are some genetic variances distinctly associated with PPD, and not with

MDD, as compared with non-depressed individuals. PPD also has a much greater level of heritability than MDD and it is believed genetics exert a greater role on the development of depression early in the postpartum period (Batt et al., 2020).

Epigenetic changes are also associated with both conditions. Epigenetics examines the influence of our life factors on the expression of our genes. Both PPD and MDD are associated with early-life stressors, which can create epigenetic changes. PPD has specific epigenetic changes, such as the combination of short homozygous alleles for the serotonin transporter gene with a larger proportional decrease in estradiol following childbirth (Batt et al., 2020). The greater decline in estradiol following childbirth in PPD is associated with epigenetic changes that can decrease synaptic plasticity and brain-derived neurotrophic factor (BDNF) expression (Guintivano et al., 2013).

Hormonally, there are certain findings consistent with both PPD and MDD. This involves stress and its effect on the body via the hypothalamic-pituitary-adrenal (HPA) axis which helps regulate stress hormones such as cortisol in the body. In both forms of depression, there is dysregulation of the HPA axis and stress can play a significant role in triggering both types of depression. In PPD, the depression can be triggered by hormonal fluctuations related to pregnancy and childbirth.

One of the major pathophysiologic processes emerging that is specifically implicated in PMADs involves the neuroactive steroid allopregnanolone, which acts on gamma-aminobutyric-acid alpha (GABA-A) receptors in the brain. Allopregnanolone levels increase during pregnancy and there is a precipitous decline following the end of pregnancy. Research suggests that the levels of allopregnanolone levels influence GABA-A receptor regulation. During pregnancy there is a downregulation of GABA-A receptors because of high allopregnanolone levels. After pregnancy there is a subsequent upregulation of GABA-A receptors to return to baseline in

response to the drop in allopregnanolone levels. In individuals with PMADs, it is thought that the GABA-A receptors do not return to baseline levels (Gunduz-Bruce et al., 2021).

Current Treatment Modalities

Many of the current options for PMADs are drawn from depression treatments, with few treatments focused on the unique aspects of PMADs. The U.S. Food and Drug Administration (FDA) has approved new pharmacological treatments that target the pathophysiology of PMADs with relation to neuroactive steroids. These new treatments are GABA-A positive allosteric modulators (PAMs), which increase a neuron's hyperpolarization and inhibit the possibility of an action potential, making the neuron less excitable (Edwards & Preuss, 2024). Common uses of other medications which are GABA-A PAMs include sedation, seizure management, and alcohol withdrawal. The allopregnanolone analog brexanolone is an emerging GABA-A PAM treatment with demonstrated efficacy. Unfortunately, however, it is not easily accessible and is cost-prohibitive. For example, brexanolone is given by an infusion over 60 hours in a hospital setting and can be upwards of $30,000 in cost (Faden & Citrome, 2020). Another emerging oral GABA-A PAM is zuranolone. Per the prescribing guide, zuranolone is commonly dosed at 50 mg for a 14-day course, which, unlike brexanolone, can be taken at home. It must be taken with an evening meal of around 700 calories, the individual taking it may not drive for 12 hours following dose, and out-of-pocket costs remain highly prohibitive. The pharmaceutical company which makes zuranolone, Biogen, has offered to help with the cost by having the prescription sent to certain specialty pharmacies which work directly with Biogen (Biogen & Sage Therapeutics, 2023). It is unclear how long this is expected to last and with a GoodRx coupon this medication can cost around $15,000 (*Zurzuvae Prices, Coupons & Savings Tips - GoodRX*, n.d.).

Additional medication options to specifically target PMAD pathophysiology include estradiol treatment, often given via transdermal patches. As discussed earlier, the lack of estradiol can have epigenetic effects which may contribute to mood changes in the postpartum

period. Trials using estrogen transdermal patches have shown limited benefit for PMADs thus far (Li et al., 2019). Of studies that have shown a positive effect, the data suggest that, rather than replacing levels of estradiol, the treatments may be more beneficial in stabilizing estradiol fluctuations (Batt, 2020).

While standard depression treatments have been thoroughly studied and are offered to individuals with PMADs, these treatment options do not address the more specific etiologies of PMADs such as changes in neuroactive steroids and hormones. The new development of medications like brexanolone and zuranolone address the fluctuation in neuroactive steroids specific to PMADs, have shown promise in its treatment, and are safe options during lactation. However, they currently remain highly inaccessible for many. Estradiol treatment is in the early phases of being studied for PMADs with unclear efficacy. Although it is safe in lactation with low serum levels in infants, it may decrease milk supply and carries risk of thromboembolic events (National Institute of Child Health and Human Development, 2024)

Ketamine

Ketamine was first developed as a derivative of phencyclidine for use in anesthesia in the 1960s. It demonstrated a good safety profile without respiratory depression, which led to its utilization in the Vietnam war and subsequent wars as a field anesthetic despite concerns about its utilization as a drug of abuse (Domino, 2010; De Rocquigny et al., 2020). It is now commonly used as an anesthetic in many countries and is on the list of the World Health Organization's (WHO) essential medicines (WHO, 2019). The international pursuit of ketamine's psychiatric implications began in the 1970s with landmark studies, such as Khorramzadeh and Lotfy (1973), which found remission of a variety of psychiatric symptoms following ketamine injection lasting up to a year in a study of approximately 100 participants who varied in their psychiatric diagnoses.

Ketamine is classified as a dissociative anesthetic with a quick onset of action and a short half-life of 1-3 hours. It is highly lipophilic in nature and is a racemic mixture of an S and R enantiomer (Ezquerra-Romano et al., 2018). This fast therapeutic relief may be of benefit in PMADs, where rapid treatment may aid a faster return to parent-child bonding during a critical time period for neurobiological regulation and attachment development(Chen-Li et al., 2022). Ketamine can be taken via several routes with varying levels of absorption. In order of decreasing levels of absorption, these routes are intravenous, intramuscular (IM), sublingual, oral, and intranasal (Walsh et al., 2022). Ketamine has several mechanisms of action that may be responsible for its effects. It is a non-competitive n-methyl-d-aspartate (NMDA) receptor antagonist and acts on acetylcholine nicotinic receptors and opioid receptors, whilst increasing norepinephrine and dopamine transmission. It increases synaptic plasticity and synaptogenesis (Ezquerra-Romano et al., 2018; Dore et al., 2019) which, within the hippocampus, can demonstrate antidepressant effects specifically in PMADs as suggested by one animal model study (Ren et al., 2022). Ketamine also increases expression of BDNF, commonly thought of as a type of ‘brain fertilizer’ which is characteristically low in depression, and which promotes neuroplasticity (Ota & Duman, 2013).

Additional benefits of ketamine may be derived beyond the pharmacologic effect. Rather, these may be from its experiential effects. Preliminary findings suggest effects of ketamine appear to be due in part to the “mystical-type experience” (Dakwar et al., 2014; Rothberg et al., 2021). It has been found that ketamine’s benefits are protracted in duration when combined with subsequent psychotherapy (Dore et al., 2019; Drozdz et al., 2022; Joneborg et al., 2022), such as seen ketamine-assisted psychotherapy.

Ketamine is considered a safe medication with a good tolerability profile. Side effects of ketamine administration are generally acute and relatively mild, including nausea and vomiting, dizziness, headache, sedation, transient hypertension, blurred vision, agitation, anxiety, and

derealization, the term for feeling as though one's surroundings or reality are not real (Dore et al., 2019; Short et al., 2017). The safety of ketamine during lactation is just as prevalent. An initial study by Wolofson et al. (2022) examined breastmilk of four women who received two doses each of IM ketamine, 0.5 mg/kg and 0.1 mg/kg, where two samples of breastmilk were collected prior to ketamine administration and then at hours 3, 6, 9, and 12 following ketamine administration. Levels of ketamine and metabolites were measured, showing a peak in concentration at 3 hours. A measure frequently used to assess safety of drugs in lactation is the relative infant dose (RID). This measures the proportion of mg/kg/day of the drug received by the infant, relative to the amount taken by the lactating person, and is often considered to be safe at 10% (Hotham & Hotham, 2015). The Wolofson et al. study (2022) additionally demonstrated that ketamine has a low RID of less than <1% for both the low and high doses. They further postulated that, due to ketamine's poor oral bioavailability in adults, even less may be transferred via lactation to infants. Despite this relatively limited RID finding, due to the lack of substantive data, it is recommended to closely monitor infants who are breastfed by individuals receiving ketamine (National Institute of Child Health and Human Development, 2023).

Literature Review

The literature on this topic is still developing with increasing recent interest. The limited human studies in this population are likely due to concerns during lactation and its potential risks in developing infants. Chen-Li et al. (2022) summarizes many of the major studies surrounding prophylactic use of ketamine for postpartum depression. Many randomized control trials are centered around prophylactic treatment with ketamine being used as anesthesia during cesarean section or post-operatively. Dosages ranging from 0.2 mg/kg – 0.5 mg/kg intravenously have been utilized in a double-blind design with a placebo group. Various studies used the Edinburgh Postnatal Depression Scale (EPDS) to examine rates of depression in the

control vs. experimental group. Questionnaire administration timelines vary in studies from 48 hours post-delivery to 6 weeks post-delivery. Overall, the groups who received ketamine generally have lower rates of depression compared to controls. In groups receiving higher doses of ketamine, depression scores were even lower. One of these studies, however, found that the result of this single ketamine dose was no longer effective at four weeks postpartum (Li et al., 2022).

One such study by Yang et al. (2022) examined the effects perioperative ketamine on later development of postpartum depression and added a post-hoc analysis of the control group to identify high-risk groups for developing postpartum depression. Items noted to be associated with high risk included increased stress or mood disorder during pregnancy, domestic violence, self-harm ideations, and heightened prenatal EPDS scores. These criteria were applied to identify potential high-risk individuals within the experimental group. The study found that the prophylactic effect of ketamine was significant only for those identified as high risk in the experimental group, but not for those who were low risk.

There have additionally been studies to examine ketamine in PMADs using animal models. Garcia et al. (2022) conducted a study using mice, where they compared ketamine vs. synthetic allopregnanolone treatments. PMADs were replicated by having the mice undergo a maternal separation with early weaning, which were correlated with behaviors of despair, anhedonia, and disrupted maternal care. Further, these behaviors were correlated with lower allopregnanolone serum levels, decreased GABA and glutamate vesicular transporters in the infralimbic cortex and decreased hippocampal cell proliferation. They found that, while both treatments addressed despair behavior and increased hippocampus synaptogenesis, only the ketamine reversed levels of anhedonia. The researchers add that, while further studies are needed, this may indicate that ketamine could outperform allopregnanolone synthetics, like brexanolone and zuranolone, in the treatment of postpartum depression.

Most notably, each study reviewed urged the importance of further research and to examine the effects of ketamine as a treatment for PMADs rather than only maintaining a prophylactic approach. Despite demonstrated safety during lactation, promising animal model studies, and demonstrated efficacy as a prophylactic treatment, ketamine is still not well studied as a treatment for existing PMADs. This gap in the available literature indicates a need for additional data. Examining current cases of ketamine use in PMADs is a way to fill this gap before more controlled studies are completed.

Methods

Design

A qualitative research design was utilized to conduct a retrospective chart review to understand the impacts of ketamine treatments, including ketamine-assisted psychotherapy (KAP), for individuals with PMADs seeking care at the Advanced Integrative Medical Science (AIMS) Institute, a private healthcare clinic in King County, Washington. Due to the anticipated small number of eligible participants, a qualitative design was selected to allow thematic elements to be showcased and better understand the nuance and impact of ketamine on PMADs.

The Seattle University Institutional Review Board (SU IRB) reviewed this project as part of a modification to an existing outcomes study, the AIMS Medical Outcomes Study (AMOS) (NCT 04512755), which has SU IRB oversight. AMOS is a five-year longitudinal study that examines health-related quality of life outcomes in patients who receive care at AIMS Institute (National Library of Medicine, 2023; AIMS Institute, 2020.). As this project falls under the purview of the AMOS protocol, only a modification was required rather than a standalone IRB proposal.

Setting

Located in Seattle, the AIMS Institute is comprised of several types of clinicians

including medical physicians, naturopathic physicians, therapists, and advanced nurse practitioners. The clinic provides a variety of integrative medicine and holistic services in specialty fields including, but not limited to, oncology, neurology, palliative care, and mental health therapy. They offer specialized services such as cannabis-assisted therapy, stellate ganglion block, and ketamine treatments.

The AIMS Institute offers ketamine therapy in a few modalities including, but not limited to, administration via intramuscular or sublingual routes in-clinic and patient utilization of sublingual lozenges, called troches, at home. Patients who have KAP sessions in clinic are seated in a large recliner with the option for relaxing music and an eye mask. Following ketamine administration, a clinician observes them for approximately two hours during their dissociative experience, transcribing any actions taken during this time (e.g., movements, narrations during the experience, summaries after the experience). These notes are later reviewed with patients during their psychotherapy sessions. Ketamine troches may be used at dissociative or sub-dissociative dosing. Patients who utilize at-home ketamine troches may then discuss their experiences during integration psychotherapy sessions. Protocols for participants prior to administration include fasting for 4 hours, using the restroom, and arranging a ride home for after the session. Participants are typically prescribed an anti-nausea medication to utilize prior to administration of ketamine, as nausea is a commonly expected side effect. Chest feeding is not recommended up to 4 hours after IM ketamine administration and up to 6 hours after sublingual ketamine administration. Insurance does not cover ketamine treatments. The direct cost to patients is approximately $500-$700 for KAP treatments (AIMS Institute, 2023).

Patients of this clinic are largely of higher socio-economic status from the greater Seattle metropolitan area; however, they may also be from out of state as the clinic has a partnership with local hotels and many patient visits are able to be conducted via telehealth.

Participants

Participants were selected using a convenience sampling from existing participants who consented and enrolled in the AMOS study. Participants in the AMOS study are all established patients at the AIMS Institute. The inclusion criteria of the study were individuals who: have been seen at the AIMS Institute for any self-described postpartum related mood and/or anxiety disorder, regardless of timeframe; have been consented into the AMOS study; are diagnosed with a mood or anxiety disorder; and/or are prescribed a medication to target mood or anxiety, including ketamine therapy.

The initial inclusion criteria for participants had a previous capping of the postpartum period at 12 months. This change was made both because literature suggests that the definition of postpartum can vary greatly and the study was anticipated to have a low sample size. The intent behind abolishing the time restriction was to capture any available data possible for this project.

Participants were identified via electronic medical record (EMR) analytics using specific diagnoses and ICD-10 codes relevant to PMADs. Individuals were flagged if any of the following diagnoses were explicitly entered into their EMR: MDD, single episode, unspecified postpartum depression (F32.9); postpartum mood disturbance (O90.6); or postpartum depression (F53.0). The EMR analytics enabled a ‘diagnosis contains’ search; any individuals were flagged if their EMR contained a diagnosis that had the term “postpartum” or “pregnancy.” Provider recall further identified patients who may have PMADs; this was solicited by internal email communications and during a morning huddle.

Data Collection

Data collected from each participant’s EMR was stored in a secure, cloud-based platform using a spreadsheet software program. General participant information collected included: participant identifier, age, marital status, date of delivery, psychiatric diagnoses,

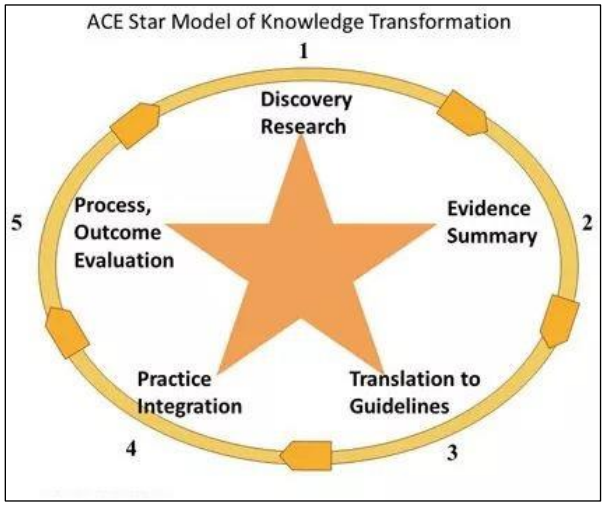
medications, and notable medical and/or obstetric history. This data included appointment dates and qualitative data about participants' narratives that pertained to discussing PMAD symptoms, PMAD treatment (ketamine or treatment as usual), and effects of treatment. Data collected was within the period identified by participants during which PMADs were a concern. This created variability in the number of appointments and length of treatment for data collection for each participant.

Theoretical Framework

This project used the ACE Star Model of Knowledge Transformation as the theoretical framework. This framework conceptualizes the process by which evidence is incorporated into practice. It is comprised of five distinct points/phases (see Figure 1). Discovery research includes identifying primary research on a topic, such as randomized control trials. Evidence summary involves synthesizing the known information about the topic, like systematic reviews. Translation to guidelines utilizes research findings to create evidence-based guidelines. In practice integration evidence-based guidelines are applied. Process, outcome evaluation assesses the impact, such as efficacy and efficiency of care, of the new evidence-based practice on patient care (Stevens, 2013).

Figure 1

ACE Star Model of Knowledge Transformation



This project will focus primarily on steps one, discovery research, and two, evidence summary. The data collected regarding ketamine use in PMADs will contribute to the research available. The literature review of this project summarizes the existing research specific to ketamine use during PMADs. In the future insights gleaned from this project may be utilized in guiding evidence-based practices.

Data Analysis

Data analysis was conducted via content and thematic analysis (Hsieh & Shannon, 2005). Participant narrative themes were clustered via categorical aggregation and assigned codes based on anticipated features or behaviors observed in individuals who have improved mental health outcomes. Each specific feature was assigned only one code. Coder judgement was utilized to decide which code most closely fit. These codes were: 1) increased feelings of connectedness; 2) increased psychosocial self-awareness; 3) improvement in mental health symptoms; 4) improvement in feelings of self-worth and self-efficacy; and 5) other, with narrative description included. It was anticipated that additional categories may emerge within code #5 should there be repeated themes. Thematic analysis was planned to identify any re-emerging themes, which would later be defined and placed into its own unique code.

Data regarding treatment with ketamine was aggregated separately from data regarding treatment without ketamine or treatment as usual. The data within the treatment as usual category was reviewed from encounter notes from any participant with PMADs who did not receive any ketamine treatment or from participant narratives regarding prior treatments before beginning ketamine treatment.

Results

The initial search yielded 93 results which contained many ineligible results such as repeated results, cis-gendered male patients, patients who had not consented to the medical study, and patients who never had a postpartum period while at the clinic. Application of criteria

identified 14 patients as having a PMAD, of which 5 had consented to the AMOS study. Of these 5 eligible participants, 4 received ketamine while identifying PMAD as a presenting concern.

Demographics

All 5 participants were in their 30s (33-39 years old) and identified their gender as female. Most participants were married. All participants had some type of psychiatric diagnosis and/or clinician notes that indicated PMADs at the time of the encounter. Psychiatric diagnoses predominantly included anxiety disorders, trauma disorders, and PMADs. Table 1 showcases participant demographics and diagnoses entered in the EMR.

Table 1

Participant Demographic and Diagnostic Information

ID	Age	Postpartum Depression/ Anxiety	Conditions Arising in the Perinatal Period	Depressive Disorders	Anxiety Disorders	Trauma Disorders	Substance Abuse
1	39	X		X	X	X	
2	38		X	X	X	X	
3	37	X	X		X		
4	36				X	X	X
5	33	X				X	

Treatment and Appointments

Participants had between 3-19 appointments at the AIMS Institute when they had a PMAD. The average number of appointments was 11, with a median of 8. Participant 4 had the lowest number of appointments addressing PMADs, with only 3 appointments identified. The length of treatment represents the time span, measured in days, where the appointments in which PMADs were still a presenting concern occurred. The average length of treatment in days was 101, with a median of 140 days, and a span of 176 days. The most common reasons for discontinuing care specific to addressing PMADs were PMAD was no longer a presenting issue,

and/or participants were no longer engaging in treatment (e.g., no show for appointment). Table 2 outlines each participant's treatment information.

Table 2

PMAD Treatment at AIMS

Participant ID	Number of Appointments	Length of Treatment (Days)	Discontinuation Reason
1	19	140	Participant stipulated consent only until specific date
2	17	182	PMAD no longer presenting concern
3	7	54	Ceased clinic engagement
4	3	26	Ceased clinic engagement
5	8	150	PMAD no longer presenting concern

Ketamine Treatment Group

The methods of ketamine administration included in-clinic intramuscular (IM) injection, in-clinic sublingual administration, and sublingual ketamine troches taken at home. Table 3 shows information on participant ketamine treatment. At the AIMS Institute, the protocol for dosing of IM ketamine starts at 1.5 mg/kg, barring medical or psychological indications for lower or higher dosing, and can be adjusted for subsequent sessions if tolerated. Doses administered to participants IM ranged from 105 mg to 180 mg, with an average dose of 140 mg and a median dose of 125 mg intramuscularly. Ketamine sublingual troches are 100 mg per troche and dosing can vary between 100 mg – 300 mg. The dose of sublingual ketamine administered to participants in clinic was 300 mg. The dose of troches used at home was 100 mg – 300 mg. Notably participant 5 used ketamine as needed daily, rather than on a session basis, for the indication of pain and commonly used between 100 mg – 300 mg each day as indicated by clinician notes. Side effects reported by participants included dizziness, mild nausea (with no reported episodes of emesis), and headache. All side effects reported were mild and resolved within a day. Clinician notes did not include any indication regarding any side effects noted for infants. Ketamine sessions are followed by an integration session, a form of psychotherapy focused on exploring themes that arose during a ketamine session.

Table 3

Ketamine Treatment Information

Participant ID	In-Clinic Ketamine		At-Home Ketamine	Side Effects	Integration Therapy at AIMS
	IM	SL	SL		
1	4	0	1	Y	5
2	5	0	0	Y	5
3	0	1	0	N	1
5	0	0	PRN	Y	0

Abbreviations: intramuscular (IM); sublingual (SL); as needed dosing between 100-300 mg daily (PRN)

Treatment as Usual Group

The 'treatment as usual' data was derived from participants' discussions of any other psychiatric pharmacotherapy and/or psychotherapy for PMADs that occurred outside of ketamine treatment. Tables 4 and 5 show participant psychiatric medications, and psychotherapy modalities. Commonly taken medications were psychiatric medications, such as serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). Supplement use varied widely; however, were predominantly taken for a psychiatric indication. The psychotherapy modalities that participants had engaged in predominantly included only three forms: cognitive behavioral therapy, eye movement desensitization and reprocessing therapy, and individual psychotherapy (non-specified form of psychotherapy).

Participant discussion of treatment effects were mainly derived from appointments before initiating ketamine. Participant 4 was the primary 'treatment as usual' participant, the only individual who had not had ketamine treatment within the project parameter. Unfortunately, this participant also had a very small number of appointments, thus the amount of data to draw from was limited. From the available data, the primary alternative treatment utilized was SSRI/SNRI treatment, which was described as not being effective or not providing enough benefit for their PMAD. One participant discussed weight gain due to SSRI treatment. No other treatments were

prescribed and/or recommended by the AIMS Institute clinicians for PMAD outside of co-occurring ketamine administration.

Table 4

Participant Psychiatric Medications

ID	Age	SSRI/ SNRI	AD	MS/ AC	STIM	a-A	BZD	P-RX	HERB/ BOT	ZZZ
1	39	X				X			X	X
2	38	X		X			X	X		
3	37	X		X						
4	36	X		X		X			X	
5	33	X	X	X	X	X	X	X	X	X

Abbreviations: selective serotonin reuptake inhibitor (SSRI); serotonin norepinephrine reuptake inhibitor (SNRI); other antidepressants (AD); mood stabilizer (MS); anticonvulsant (AC); stimulants (STIM); alpha agonist (a-A); benzodiazepine (BZD); pain medications (P-RX); herbal (HERB); botanical (BOT); sleep aids (ZZZ)

Table 5

Participant Psychotherapy Modalities

ID	Age	CBT	EMDR	IPT
1	39		X	
2	38	X	X	X
3	37			X
4	36	X	X	
5	33		X	X

*Abbreviation: c*ognitive behavioral therapy (CBT); eye movement desensitization and reprocessing (EMDR); individual psychotherapy (IPT)

Content and Thematic Coding

Table 6 outlines the frequency that each code occurs, disaggregated to each participant. After the “other” category was reviewed for themes, four new codes (#6-9) emerged. Upon identifying the new codes, data was subsequently reviewed from Code #5 and re-coded into the respective new codes.

Table 6

Frequency of Code Occurrence in Participants with PMADs

Code	Participant				
	1	2	3	4	5
1. Increased feelings of connectedness	5	0	1	0	0
2. Increased psychosocial self-awareness	21	1	2	0	0
3. Improvement in mental health symptoms	16	8	3	0	3
4. Improvement in feelings of self-worth and self-efficacy	20	0	3	0	0
5. Other, provide detail	0	5	0	1	1
6. Feelings of release/freedom	12	1	0	0	0
7. Feeling safe/at peace, centered/relaxed, whole/grounded	5	4	2	0	0
8. Increased hopefulness/future oriented talk	1	0	2	0	1
9. Discussed spirituality/transcendental or dissociative experiences	3	2	3	0	0

There was significantly more data available to code from participant appointments where they had ketamine treatment for PMADs compared to treatment as usual. For the ketamine treatment group, 122 total code occurrences emerged compared to only 4 code occurrences for the treatment as usual group. In the ketamine treatment group, Figure 2 shows the proportional aggregated frequency occurrence for each code and Table 7 shows the aggregated frequency occurrence for each code. The three most common themes that emerged in the ketamine treatment group were: #3 improvement in mental health symptoms (n = 29); #2 increased psychosocial awareness (n = 24); and #4 improvements in feelings of self-worth and self-efficacy (n = 23). Due to limited data, no figure could be generated for the proportional occurrence of each code in the treatment as usual group.

Figure 2

Proportional Aggregated Frequency of Code Occurrence, Ketamine Treatment Group (n=4)

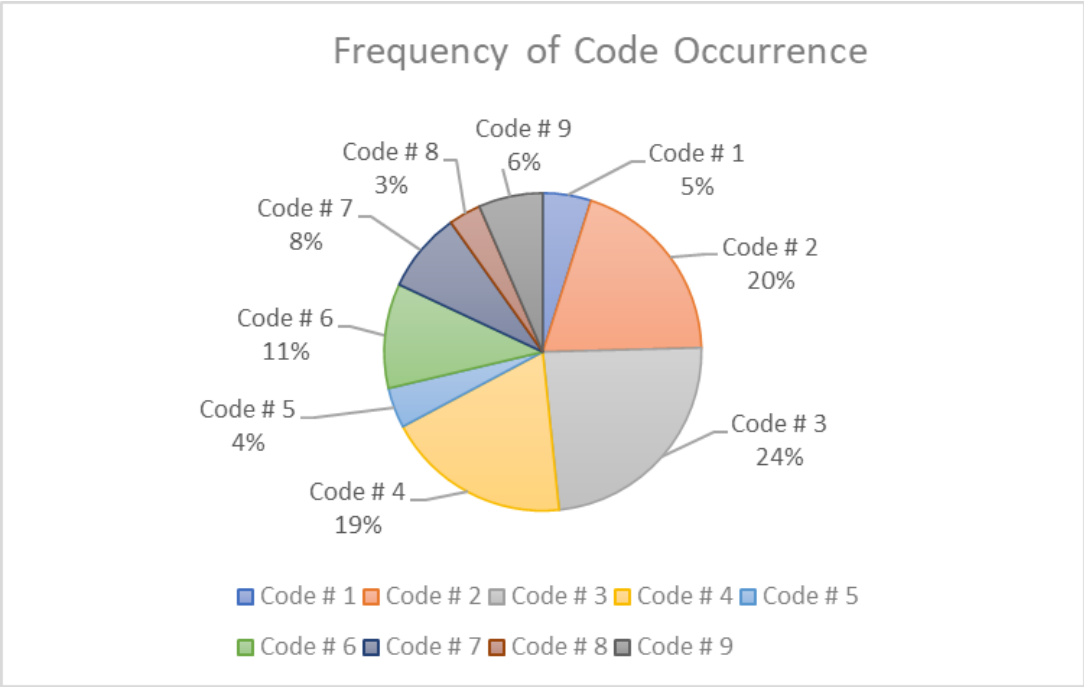


Table 7

Aggregated Frequency of Code Occurrence, Ketamine Treatment Group (n = 4)

Code	Frequency of Occurrence
1. Increased feelings of connectedness	6
2. Increased psychosocial self-awareness	24
3. Improvement in mental health symptoms	29
4. Improvement in feelings of self-worth, and self-efficacy	23
5. Other, provide detail	5
6. Feelings of release/freedom	13
7. Feeling safe/at peace, centered/relaxed, whole/grounded	10
8. Increased hopefulness/future oriented talk	4
9. Increased spirituality/transcendental or dissociative experiences	8

Table 8

Frequency of Code Occurrence, Treatment as Usual Group (n=1)

Code	Frequency of Occurrence
1. Increased feelings of connectedness	0
2. Increased psychosocial self-awareness	0
3. Improvement in mental health symptoms	1
4. Improvement in feelings of self-worth, and self-efficacy	0
5. Other, provide detail	3
6. Feelings of release/freedom	0
7. Feeling safe/at peace, centered/relaxed, whole/grounded	1
8. Increased hopefulness/future oriented talk	0
9. Increased spirituality/transcendental or dissociative experiences	0

Discussion

Demographics

Participant demographics were consistent with expected risk factors for PMADs, as they included a history of prenatal psychiatric conditions. Most participants had a trauma disorder diagnosis (n = 4), and/or an anxiety disorder diagnosis (n = 4). Depressive disorders were less prevalent than expected (n = 2). Research suggests high stress and history of prenatal psychiatric disorders can be a strong risk factor for developing PMADs (Agrawal et al., 2022), so these factors are likely to be prevalent within the larger population of people who have PMADs.

Participant demographics are unlikely to be representative of the population of individuals with PMADs. Inferring that participants could afford ketamine treatment, it is likely that the sample is of higher SES. Individuals of lower SES are more likely to experience PMADs (Agrawal et al., 2022) and may benefit from ketamine treatment, but may not be able to access it due to its costs. Although there are other factors that increase risk for or are correlated with

PMADs, such as lack of spousal support, increased inflammatory mediators, and epigenetic changes, this information is not known for the existing participants.

Treatment and Appointments

In planning this project, it was assumed that only a small percentage of participants with PMADs would have received ketamine treatment, but most (n = 4, 80%) had received ketamine. Even participant 4, categorized as treatment as usual, had historically engaged in KAP at the AIMS Institute prior to pregnancy and sought to re-initiate treatment; however, ceased engagement before receiving ketamine treatment for PMADs. This skewed representation towards ketamine treatment and limits the ability to compare ketamine treatment outcomes against treatment as usual. It does increase the data on the effects of ketamine treatment for PMADs. Based on the literature, it would be expected a greater proportion of individuals with PMADs would receive ‘treatment as usual’ comprised of first-line treatment options such as SSRIs, SNRIs, and/or psychotherapy (Viguera, 2024). While all participants in this study were engaged in at least some of these treatment modalities, most of the data collected occurred while ketamine was taken concurrently.

Participants 1 and 2 had IM ketamine in clinic and integration psychotherapy at AIMS had the greatest number of codes and appointments. While this seemingly indicates greater benefit, it is worth acknowledging additional reasons the number of codes may be inflated. Having more appointments means having more available data to code. The clinician's notes were also richer and more detailed for these participants to be more in line with the structure of ketamine assisted psychotherapy for PMADs. Finally, ketamine administration sessions that occurred in clinic allowed more opportunities for noting participant reported benefits compared to participants using ketamine at home while unobserved.

It seems the set and setting may have a greater effect on benefit than the route of administration of ketamine. Participant 3 who utilized sublingual ketamine in clinic with a

subsequent integration session had only one round of ketamine therapy before discontinuing treatment. This one session, however, yielded many codes. Participant 1, who had one sublingual ketamine session at home after four IM sessions in clinic, had the least number of codes generated for their sublingual session compared with their IM sessions. Participant 5 had the second fewest number of codes, despite having the median number of appointments. They were taking sublingual ketamine troches 100 mg -300 mg/day, as needed, in their home for pain management. They did not have a ketamine 'session,' so to speak, that was an intentional time to use ketamine for psychotherapeutic purposes. Thus, participant 5 did not engage in any integrative psychotherapy that would accompany a ketamine 'session.' The focus of their appointments while experiencing a PMAD was predominantly medical. The correlation between coded benefits and the setting in which ketamine is taken seems to reflect what is shown in the literature regarding the beneficial effects of ketamine being associated with its mystical effects (Dakwar et al., 2014; Rothberg et al., 2021) and that benefits become protracted with integrative psychotherapy (Dore et al., 2019; Drozdz et al., 2022; Joneborg et al., 2022).

For participants 1 and 2 who had the greatest engagement with ketamine, the types of comments that were made over the course of ketamine sessions shifted from themes of release and relaxing to themes of deeper understanding of self and acknowledging longer lasting benefits of ketamine in later sessions. This also seems consistent with literature that repeated ketamine assisted psychotherapy sessions may provide greater benefit (Drozdz et al., 2022; Joneborg et al., 2022).

Content and Thematic Coding

For the ketamine treatment group, the most frequently reported theme was related to the generally encompassing code of 'improvement in mental health symptoms' (code #3, n = 29). Samples of participant statements include, *"life feels pleasurable...[it] felt daunting in the past;" "[I] feel [my] executive function is being repaired;"* and *"[I] felt really good."* One participant

described being *“less in my head.”* Due to the broad nature of this code, as well as the wide-reaching psychiatric benefits known to be associated with ketamine (Kew et al., 2023) it seems appropriate that this code should be the most prevalent in the ketamine group.

This is in stark contrast to the treatment as usual group in which the most frequently reported code was ‘other’ (#5, n=3), and was entirely related to themes of ineffective treatments such as SSRIs/SNRIs and psychotherapy. While remaining conscious of the limited data, the findings indicate that treatment as usual was not as beneficial as ketamine. This finding was likely affected by the small disproportionate sample size and it may be possible that individuals who had not had success with other forms of treatment were more likely to seek out ketamine treatment.

The mechanisms behind the efficacy of ketamine assisted psychotherapy are thought to be due in part to creating a more positive change in mindset and increased synaptic neural plasticity which may correlate with cognitive flexibility (Joneborg et al., 2022). This seemed to be reflected in the themes that were most prevalent. The theme of ‘increased psychosocial self-awareness’ (code #2, n = 24) had a high reported frequency within the ketamine treatment group. One participant shared, *“prior to ketamine, [I] was so wound up... [felt] bound... stuck."* Within the context of being in a dissociative ketamine session, another participant stated, *"I was trying to look and dig a little deeper inside me"* and reflected that *"being a mom, I am always serving someone else."* Increased psychosocial self-awareness (code #2, n=0) was not coded for treatment as usual. Although it can be difficult to draw conclusions with such limited data, this type of benefit occurring rapidly over a session of treatment would not be expected with SSRI/SNRI or psychotherapy treatments which provide benefit over a longer period.

The theme ‘improvements in feelings of self-worth and self-efficacy' (code #4, n = 23) was also predominant in the ketamine treatment group. Participant statements evoked confidence and self-assuredness, such as, *“I have inner resources.”* One participant reflected,

“A lot of the things I think I want to be, I am. I need to remember that... A good mom. Strong. Confident. Beautiful. I love myself.” This theme reflects what would be expected based on the literature of ketamine treatment.

Statements assigned to code #5, which held any outlying themes, were analyzed and resulted in four newly defined codes. Many of these codes were defined using synonyms to capture the theme as it emerged within the data. Participant ‘feelings of release and freedom’ (code #6, n = 13) accounted for 11% of the total codes. One participant stated, *“I'm able to let go of the stresses of life.”* In one participant’s last session she expressed feeling *“my body releasing the trauma”* and was *“able to let go into the experience.”* This theme which reflects a release of stress and/or trauma is consistent with the literature of ketamine’s efficacy in post-traumatic stress disorder (Kew et al., 2023; Liriano et al., 2019). Many participants in this study had a trauma disorder (n = 4), which can also be a risk factor for PMADs. Ketamine may play a multifactorial role in treating PMADs by also addressing some of the psychopathology associated with increased risk.

The theme of ‘feeling safe/at peace, centered/relaxed, whole/grounded’ (code #7, n = 10) was defined using multiple words to capture the theme accurately as it emerged within the data. Participant statements included: "*I feel more rooted and centered inside me*" and *“[KAP] feels very soothing, peaceful*”. Clinician notes included, “*KAP helped the participant feel more relaxed”.*

Though occurring less frequently with the aggregate data, there are noteworthy codes that showcase some of the unique benefits associated with ketamine. Though the themes of ‘increased hopefulness/future oriented talk’ (code #8, n = 4, 3% of total occurrences) and ‘increased spirituality/transcendental or dissociative experiences’ (code #9, n = 8, 6 % of total occurrences) had some of the lowest number of occurrences, statements within these codes demonstrate some of the unique benefits of ketamine. Participant statements that showcase this

include: *“[I] went to a place in my mind where all things are possible.”* Participants also describe feeling like being *“on a roller coaster”* or they felt like *“Alice going down the rabbit hole.”* One participant commented, *“I did connect to the more ancient parts of me”* while discussing the dissociative experiences, which are more of a hallmark of ketamine. These effects may be small but are noted in the literature to correlate in a large way with the potential benefits of ketamine treatment (Dakwar et al., 2014; Rothberg et al., 2021).

There were statements within the ketamine group that were not assigned a code and remained ‘other’ (code #5, n = 5). These statements predominantly include a null response to ketamine. Participant statements included: *“[ketamine was] nothing remarkable”,* “[*I had] no dream like experiences”* and *“second KAP [session] didn't feel like falling”.* These statements contrast with the rest of the codes which all indicated a certain benefit. This also provides a humbling reminder that although ketamine treatment remains promising for PMADs, it will not be effective for everyone. Future research in this field may help clarify the situations in which ketamine treatment would be most appropriate.

Participant 2 had the highest occurrence of code #5 largely reporting null codes. While this null effect may be unique to this individual, the way their treatment was done may also affect their experience. This participant also had a statement that they didn’t *“remember [the] experience during deeper portions*” during an IM ketamine session in clinic. This lapse in memory is likely due to the dissociative experience, similar to difficulty recalling a dream. Certain ketamine sessions would include immediate recounting of what the participant had experienced; however, this dissociative experience was not documented. It is possible that, like a dream, recalling the experience afterwards may help to encode the memory of what was experienced. The benefits of ketamine are thought to be attributable, in part, to its mystical and dissociative effects (Dakwar et al., 2014; Rothberg et al., 2021). Perhaps, without exploring the dissociative effects of the ketamine session, this participant’s benefits were attenuated.

Limitations

There were several limitations to this study design. The pre-determined codes have subjective influences, as they were based on this researcher's experience in witnessing a ketamine session and discussions around commonly reported benefits. Additionally, there were no pre-determined codes for any null or negative experiences. A few of the remaining statements within category #5 reflected this.

While there can be benefits to thematic analysis, such as showcasing the data as it presents rather than restricting it to preset definitions, it can also be incredibly subjective to individual interpretation. The assigning of codes and coding the data were all completed by one person. Thus, the analysis is susceptible to bias and does not have inter-rater reliability.

Each reported benefit was only assigned one code, which created situations for having to decide between two or more codes at times to see which could fit best. This created another opportunity for bias to be present within interpreting results. Further, it is possible that allowing multiple codes where appropriate could better capture the data's nature.

There was great variability in the amount and character of clinician charting. Some clinicians wrote lengthy notes, comprised primarily of direct patient quotes which were much easier and richer to code. Other clinicians would quickly summarize with statements such as, "helped with PTSD." These simpler statements likely contributed to code #3 having the highest frequency of occurrence. It is possible that some elements of patient narrative may have been lost based on how the clinician chose to document the visit. As this project was also a retrospective chart review, there was no standardization of documentation or forethought to document very thoroughly with patient narrative to better capture these themes.

Having objective measures to analyze in addition to the qualitative elements may have further bolstered the data's quality. Having common well validated measures, such as the Generalized Anxiety Disorder-7 (GAD-7) questionnaire for anxiety and Patient Health

Questionnaire-9 (PHQ-9) questionnaire for depression, would have certainly added another layer to this project. Although this was planned for, there was such limited data available that was not conducive to analysis or meaningful interpretation. Only three participants had completed questionnaires and, of these three, only two had completed one set of questionnaires to elucidate any trend or change to mental health parameters.

Future Directions

There are several opportunities for future projects with this particular study. Starting with, most simply, having another individual repeat and re-code the data. This can improve the quality of data analysis by reducing bias and providing some measure of inter-rater reliability. Alternately, if there were multiple coders in a future project, the study could adopt a similar approach between content and thematic analysis to determine prevalent themes. Coding data after such analysis would likely create a higher quality of evidence. Further, this type of project could be expanded to other clinics or facilities that offer ketamine to see if these facilities have also treated individuals with PMADs. Comparing the general findings of this study to other clinics could add to the existing database and see if the general findings can be replicated. Finally, the results of this project could be used to create a more formalized method of charting to track benefits, safety, and tolerability to future clinic patients with PMADs as well as their infants, especially when receiving ketamine treatment.

Sustainability Plan

Ketamine is a promising new medication for a variety of psychiatric conditions, including PMADs but is limited in its accessibility to those of a lower SES. Ketamine treatments are rarely available in community health settings, despite the relatively low cost of a vial of ketamine itself (*Ketamine: Drug Information*, 2024). Further, ketamine treatments are not covered by insurance. At the AIMS Institute, out-of-pocket costs for an individual KAP session in clinic is just over $700 (AIMS Institute, 2022). This is unfortunate as low SES is a risk factor for PMADs (Agrawal et al.,

2022), implying that many may benefit from ketamine therapy, but cannot access it due to the current structures for covering costs of therapy and hours of medical monitoring. Although this project had a low number of participants who are unlikely to be representative of the greater population of individuals with PMADs, this project still contributes to the body of research on the use of ketamine in psychiatry, specifically for treatment of PMADs. With more data, it is possible for ketamine treatment to shift from an experimental status to become more accessible across community settings.

Implications for Advanced Nursing Practice

The role of the advanced practice nurse is critical in the treatment of patients with a variety of conditions and across a variety of settings. PMADs are a unique subset of psychiatric disorder requiring better identification and treatment options. Empowering advanced practice nurses with knowledge of PMADs and emerging treatment options research can help improve patient care. Ketamine treatment provides one such avenue for addressing PMADs in a unique way that may provide relatively rapid relief of symptoms. Moreover, its lactation safety profile and very mild side effects with resolution of these effects within a day makes ketamine a practical treatment option for individuals with PMADs. It is within the scope of advanced practice nurses to prescribe ketamine and utilize it as a treatment modality for their patients.

Conclusion

Ketamine therapy, including KAP, is emerging as a promising treatment option for a variety of psychiatric disorders (Dore et al., 2019). In this study it is found that ketamine provided most benefit for general improvement in mental health symptoms, increased psychosocial self-awareness, and improvement of feelings of self-worth and self-efficacy. PMADs represent a severe and concerning form of psychiatric illness that may be addressed by ketamine in a unique manner which may be just as effective, if not more, than current FDA approved treatments (García-Baos, 2022). However, there is a limited number of high quality

randomized controlled trials to better understand the efficacy of this treatment and durability of its effects in various conditions. To better understand ketamine's role in perinatal mental health, randomized control trials of ketamine for PMAD prophylaxis should be compared to ketamine treatments for existing PMADs. Projects like this can help fill this gap in the literature and provide a precedent for ketamine treatment in PMADs.

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