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Alternative Pharmacology: Exploring Ketamine Use for Treatment Resistant Mental Health Disorders

Kiersten L. Ash
St. John Fisher University, ka02645@sjfc.edu

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Global Mental Health Crisis

Worldwide, there are millions of people who suffer from mental health challenges that affect their ability to be able to perform and maintain a stable mood and peace of mind. According to the World Health Organization, mental health is defined as the individual state of being that allows people to be able to respond and adjust to life changes and stress. Additionally, the goal is to maintain the functions of living and to respond to inevitable daily life changes that occur every day and is universally stated to be a basic human right (World Health Organization, 2022). Pharmacological interventions are often necessary for the treatment of these mental health diagnoses. However, challenges arise in patients as mental health disorders are subjective and complex with many variations in patient presentation. Symptoms can vary across different age groups, socioeconomic status, previous interventions, sex, past individual experiences, and access to receive health care. With a wide variety of presentations, comorbid mental health diagnoses are commonly seen to co-exist.

The most common mental health disorder seen worldwide is depression, with an estimated number of 280 million people diagnosed. Severe depression can lead to suicide which is the fourth leading cause of death in people aged 15-29 years old (World Health Organization, 2021). Clinically, it has been seen that anxiety often can co-exist alongside depression. To scale, generalized anxiety disorder (GAD) affects 3.1% of the United States overall population which amounts to an estimated 6.8 million American adults. Anxiety is deemed a broad "umbrella term" and anxiety can be classified into specific categories, specifically examining the national statistics of post-traumatic stress disorder (PTSD) which affects women five times more than men. Statistically it affects 3.6% of the entire United States population which amounts to be 7.7 million adults (Anxiety & Depression Association of America, 2022). Depression and anxiety are highly prevalent in populations on a global scale and locally. Due to the advancements and evolution of modern psychiatric medicine over the past few decades, researchers have needed to rapidly develop and increase the options of pharmacological and cognitive treatments to meet the growing demand of patients needing pharmacology assistance.

Challenges with Psychiatric Intervention for Depression, Anxiety, and PTSD

Treatment for depression, anxiety, and post-traumatic stress disorder (PTSD) are extraordinarily complex and require individualized assessments completed by a provider to determine effective pharmacological and nonpharmacological treatment. Nonpharmacological intervention for depression, anxiety, and PTSD management includes targeted methods and variations of therapy that aim at the symptoms that the patient may experience. Limitations to non pharmacological therapy suggest the lack of access and education surrounding these resources. In the United States in 2020, 2.8 million people did not have health insurance (United States Census Bureau, 2021). Financial burdens are strong treatment restrictions due to lack of transportation to access resources and prohibited financial burdens such as co-pays seen at a doctor's office and costly medications prescribed. This would result in statistics being altered due to numerous cases of mental health that are simply not accounted for. People who suffer in silence

are often burdened by poverty and peer stigmas, resulting in an overwhelming sense of hopelessness. For patients who have access to healthcare and have been diagnosed by a psychiatrist, they can be prescribed specific classes of medications.

The most common medication given for long-term treatment of depression, anxiety, and PTSD is the pharmaceutical class of medications known as selective serotonin reuptake inhibitors (SSRIs). However, this class of medication takes two to four weeks, on average, for therapeutic benefits to be seen. Medications for mental health disorders do not provide a definitive cure. SSRIs increase the available amount of serotonin in the brain, which is a neurotransmitter that plays a role in moods, sleep patterns, and emotions (National Health Service, 2021). The SSRI class of medications have recorded numerous side effects and high rates of patient intolerance. Additional considerations and concerns arise regarding the long-term effects, where research is limited. The first SSRI approved in the United States was Fluoxetine, which was introduced to the pharmacy market in 1989. SSRIs do not work for everyone as it is contraindicated in patients with underlying medical problems such as diabetes, impaired kidney function, and seizure disorders. This class of medication requires daily compliance regardless of the significant adverse effects if a dose is missed and the severity of the reported effects can vary based on prescribed dosage. The most common adverse effects seen in compliant patients are fatigue, sedation, impotence, weight gain, sleep pattern disturbances, headache, and nausea. Black box warnings are given due to the risk of suicidal ideation and attempts and risk worsening the state of anxiety and depression (Ferguson, 200, p. 22-27). Due to adverse effects impeding activities of daily life and the length of time it takes for therapeutic outcomes to be seen, medication compliance is the greatest challenge seen in patients with depression, anxiety, and PTSD. Commonly due to polypharmacy, treatment resistance develops in patients who have failed at least two previous trials of antidepressant and anti-anxiety medications regimes.

Ketamine: An alternative pharmacological treatment for Depression, Anxiety, and PTSD

As the mental health crisis soars worldwide, alternatives for the demand of alternative pharmacology interventions are imperative to provide available and effective options to patients who have treatment resistance. In adult patients diagnosed with depression, anxiety, and/or PTSD, the effectiveness of ketamine administration as an off label pharmacological intervention was evaluated compared to patients who did not receive ketamine treatment. The comparison was based on outcomes and improvement of overall reported quality of life. Ketamine is a non-competitive (DMNA) N-methyl-D-aspartate and glutamine receptor antagonist. Glutamine is a necessary substrate providing a direct source of energy for the central nervous system which stimulates the production of other excitatory and inhibitory neurotransmitters. Ketamine is approved by the FDA for anesthesia uses for humans and animals. The increase of interest surrounding the administration of ketamine has provoked interest within psychiatry due to the rapid therapeutic effects seen within minutes of administration. SSRIs target monoamine neurotransmitters, such as serotonin, dopamine, and adrenaline. Ketamine targets glutamine, which is the most prevalent chemical messenger in the brain and has significant systemic antidepressant effects. The physiology of how ketamine works in psychiatry alongside

neurology has limited studies available due to the newer prevalence of off label use and legal limitations surrounding stigma in research. However, it is suspected that ketamine can have brisk antidepressant properties in patients due to changes in the neural circuit. This means positive therapeutic effects are observed longer than other available psychiatric medication (Makin, 2019).

After evaluating the pathophysiology of depression, studies have indicated that depression over a long duration can cause a chronic state of inflammation throughout the brain and body and elicits a neurological immune response. This supports the pathophysiology of why patients who experience treatment resistance have a decreased tolerance to alternative treatments because histamine release directly affects serotonin receptors (Kopra et al., 2021). With the immediate effects of ketamine seen in patients with depression, there have also been trials evolving the use of ketamine in treatment of patients with anxiety, specifically PTSD. PTSD treatment options are far more limited than depression due to individual disease complexity, lack of therapeutic options, and the possibility that victims who have experienced traumatic events are statistically less likely to seek relief and treatment of symptoms. In terms of pharmacological management, SSRIs are the only FDA approved PTSD treatment and as previously discussed, SSRIs have a high rate of noncompliance due to the adverse manifestations. PTSD treatment is complex; however, ketamine is the only antidepressant medication that has relief of suicidal thoughts within hours of administration. The examination of the psychological properties and effectiveness of the administration of ketamine to patients with treatment resistance mental health disorders needs to be further examined to determine efficacy, safety, and durability of symptom relief.

Purpose Statement

The purpose of this narrative review was to dissect past and current literature regarding the psychopharmacological properties of the current available treatments for depression, anxiety, and PTSD and compare the impact of past interventions in comparison to the use of ketamine in psychological disease processes.

Methods

Search Strategies

A methodical search was conducted through CINAHL and PubMed. The following medical subject headings were used “Ketamine Infusions AND depression AND Anxiety” AND “Ketamine Treatment AND Depression AND Anxiety” AND “Ketamine Treatment AND PTSD AND Depression” AND “Ketamine Infusion AND PTSD AND Anxiety” AND “Ketamine Therapy OR Ketamine Infusions AND Depression” AND “Ketamine Therapy OR SSRI Depression Treatment” AND “Ketamine Therapy AND SSRI Treatment AND Depression” AND “Ketamine Therapy OR Depression Treatment” AND “Ketamine Therapy OR PTSD Treatment” AND “Ketamine Treatment AND PTSD Treatment AND Depression Treatment” and “Intravenous Ketamine Infusions AND Depression OR PTSD.”

Inclusion and Exclusion Criteria

Database searches resulted in an average of 117 articles. Inclusion criteria included peer reviewed articles, published within 2017-2022, and included adult participants over 18 years old, in all geographical regions. Sample size variation was seen due to limited researched data. Exclusion criteria included articles published before 2017 and articles that included pediatric populations, and articles that did not have PDF capability.

Quality Appraisal

Through analysis of the selected four articles, the quality of the articles using the hierarchy of evidence rating system in literature, which is defined by a chart by Melnyk & Fineout-Overholt (2015), each article was ranked from Level I to Level VII. Level I articles are of the highest evidence quality and encompass articles that are systemic reviews of relevant randomized control trials and include clinical practice guidelines for randomized control trials (RCTs). Level I evidence is the top standard and most reliable form of evidence. As the chart of evidence descends through Level II to Level VII, the quality of evidence decreases. All articles that met criteria for review are displayed in Table 1. The highest quality of evidence analyzed in Table 1 was Level II evidence ranked as the Randomized Control Study that is well designed (Pathak et al., 2021).

Results

Following database searches highlighting exclusion criteria, the results populated yielded 28 articles. Through a single reviewer, abstract screening was performed. Fifteen out of the 28 articles were individually analyzed and read, and 11 were excluded due to not meeting generalized quality appraisal criteria such as being written over 5 years ago or the lack of clinical application to the outcome being evaluated. Following literature analysis, four articles were selected to have met quality appraisal criteria and Table 1 illustrates the outcome of analysis.

Study Quality

The articles were cross compared in terms of relevant subjective quality of evidence. They were rated as excellent, moderate, and fair. All four articles were cross analyzed on the type of study, clinical significance, applicability to the overall relevance to supported claims, and then compared the sample size with the overall quality of study design (Brown, 2018). When evaluating Table 1 with outlined criteria, Table 1 contained excellent and fair articles. Excellent articles entail having a large sample size, valid study design, and included randomized control trials that yielded to be clinically applicable and with an overall appropriate design. The table had one article categorized as excellent (Pathak et al., 2021). Moderate articles consisted of well-designed case-control studies with appropriate sample sizes within reasonable limits for comparison, and then addressed the bias that contributed directly relevant to the variation of the outcome. In Table 1, two articles were put in the category of moderate (Hartberg et al., 2017; Wang et al., 2019). Ranked as the lowest quality of evidence, fair articles entail a small sample size and provided limited qualitative studies and displayed as more descriptive based. One article in Table 1 was deemed fair due to being a cross sectional analysis (Pennybaker et al., 2021). Fair articles failed to address bias or how the study results were clinically applicable to the question appropriate for the relevant research question.

Intervention Variability

When comparing the four articles outlined in Table 1, intervention varied widely among comparison of the articles, and no articles had the same length of intervention. Two weeks of oral ketamine administration was completed with a sample size of 37 people (Hartberg et al., 2017). A 4-week period of intravenous ketamine was seen in (Wang et al., 2019); however, this study had only one participant, limiting sample size, isolating gender response, and the analysis of the

Table 1

Literature Evidence Table

Title	Author/Date	Outcome Measures/ Variables	Design	Sample	Results	Rank/Quality
Impacts of oral ketamine augmentation on hospital admissions in treatment-resistant depression and PTSD: a retrospective study	Hartberg et al., 2017	-Hospital admission before and after ketamine treatment -Number of days inpatient -PTSD -Oral ketamine	Retrospective Cohort	N= 37	-Reduced number of hospital admissions and inpatient days after oral ketamine therapy	Level IV: Case Control Personalized medication dosages Duration of therapy varied among patients Moderate
Repeated ketamine injections in synergy with antidepressants for treating refractory depression: A case showing 6-month improvement	Wang et al., 2019	-Cognitive function - Intravenous injection -Ketamine -Refractory depression improvement	Case Analysis	N=1	-Higher dose intravenous ketamine shows improvement in depression symptoms who do not respond to standard intravenous dosage	Level VI: Single qualitative study Moderate
Anti-suicidal efficacy of ketamine infusion in suicidal patients of depression disorder	Pathak et al., 2021	-Ketamine dosage -Depression symptom management - Suicidal thoughts	Randomized Control Study	N=60	-Suggests that ketamine has strong anti-suicidal properties and improved depression symptoms after treatments	Level II: Bigger Sample Size Single Blinded Study Excellent
Age affects temporal response but not durability, to serial ketamine infusions for treatment refractory depression	Pennybaker et al., 2021	-Depression symptoms -Ketamine -Treatment refractory depression -geropsychiatry	Cross Sectional Study	N=49	-Younger patients have a faster response and improvement in depression symptoms after 6 serial ketamine infusions	Level V: Cohort largely male Veterans only Large age range (24-77 years old) Fair

article was to evaluate the range of improvement of depression symptoms compared alongside hospital admission rates over a measured six-month period. In the largest sample size of 60 participants, the ketamine intervention length was one week. Lastly, in the article by Pathak et al. (2021) with 49 participants, the intervention length included biweekly ketamine administration over a period of 3 weeks. There were no observed changes in the result of reported depression symptoms that correlated when evaluating if there was a suggested link of reported improvement compared with the intervention length (Hartberg et al., 2017; Pathak et al., 2021; Pennybaker et al., 2021; Wang et al., 2019). It is important to additionally note that articles had no direct correlation impacting results due to longer intervention length based on the number of participants. Additionally, the doses of ketamine varied in every patient in each article due to patient specific weight-based dosing and ketamine tolerance. All articles yielded intervention to have a positive and therapeutic effect of long-term depression symptoms management measured during the administration of oral or intravenous ketamine routes.

Discussion

The four articles were evaluated extensively in this critical appraisal to determine the impact of oral and intravenous controlled ketamine administration and the impact observed in the adult participants in an overall reduction of the debilitating symptoms that accompany mental health disorders. When exploring ketamine for an off-label use in alternative psychopharmacology method, it is imperative to note that subjective depression symptoms are highly individualized and widely vary among individuals. This is based on multiple factors such as personal events, socioeconomic status, and the variation of different trials of depression treatment prior to the trial ketamine administration. Each study conducted screened the patients individually for depression using different scales and methods of data collection. When ketamine is given as a sub-anesthetic dose at 0.5mg/kg diluted within 100 mL of normal saline, the patients can continue their personal current oral antidepressant treatment in adjunct. Results of bilateral pharmacology yielded a significant rapid decrease in the patient's suicidal ideations. This showed that ketamine has a different mechanism of action than first line antidepressants currently available. Ketamine yielded rapid suicidal symptom relief and is seen as the only pharmacological method that can treat suicidal ideations in less than 24 hours. A 57% reduction rate was seen within six hours of the first serial infusion (Pathak et al., 2021). Treatment resistant depression puts patients at greater risk of symptom relapse, disability, and higher medical costs when compared to patients who are responsive to current market oral antidepressant medications.

For PTSD, a single intravenous infusion rate of 0.5 mg/kg over 40 minutes results yielded a significant decrease in subjective depression symptoms in veterans. Reduction rates in symptoms yielded 40-80% of treatment resistant depression patients who are veterans with co-existing PTSD, responded within 3 to 72 hours of treatment (Pennybaker et al., 2021). When increasing the intravenous ketamine infusion rate to 0.75mg/kg in patients with treatment resistant depression (TRD), it showed to have more positive and effective results than the standard dose of 0.5mg/kg. This is due to the rapid infusion technique of dosing to be able to cross the blood-brain barrier quicker yielding a faster treatment outcome (Wang et al., 2019). It is important to note however, due to the off-label use, that ketamine

intravenous infusion therapy is an invasive process that requires continuous cardiac and blood pressure monitoring. Ketamine can induce tachycardia and is contraindicated in patients diagnosed with hypertension.

IV and IM routes of administration led to the invasive barriers that psychiatrists and physicians face for more widely spread accepted universal use. In contrast, some beneficial results yielded that ketamine has no evidence of tolerance building and does not cause respiratory depression unlike other anesthetics (Hartberg et al., 2017). When looking for alternatives to IM injection and intravenous infusion for a less invasive treatment, physicians have also explored the use of ketamine in an oral form. Benefits to oral administration are less invasive and decrease the chance of injection related infections or topical skin irritation. The known standard intravenous psychiatric dosing was the same dose rate of oral ketamine (0.5mg/kg) and was administered orally to patients twice daily and the doses titrated by a 20-50% dose increases at subsequent treatments. Final doses that patients received ranged from 0.5-7.0 mg/kg to target and minimize effects as ketamine has psychoactive properties and manifestations. The goal was aimed to have minimal disassociating effects while being able to yield therapeutic responses.

Results showed that the milligrams needed for patients typically had a decrease in trends of dosage administered over time to be therapeutically effective. Supporting evidence could ease concerns that arise about physiological damage to the body or developed drug dependence and reliance (Hartberg et al., 2017). Ketamine's safety can be reassured when a negative correlation was seen comparing a patient's BMI and having no impact or significant change seen in the antidepressant symptom response. When evaluating factors that could impact treatment and outcomes, as the age of the patient increased, the affected trajectory of symptom response when comparing to younger patients was a unilateral degree of symptom improvement (Pennybaker et al., 2021). Single dosages of ketamine have shown to have significant positive improvement on depression symptoms; however, more adopted and wide variety of usage are primarily centered around the primary concerns of bladder toxicity, addiction habits, and risks associated with a hypertensive crisis if a patient had undiagnosed hypertensive disease process (Hartberg et al., 2017). Ketamine administration, whether oral or intravenous, yielded rapid improvement of reported symptoms alongside improvement of other co-existing conditions such as anxiety, PTSD, bipolar disorder, and associated symptoms in 100% of patients in all of the studies.

Limitations included variation in the duration of therapeutic responses among individuals and often the most beneficial treatment was in an adjunct with their current oral antidepressants. In addition to psychiatric treatment, it is important to note that chronic pain and depression are prevalent and correlated. Pain can precipitate psychological issues that contribute to a patient's overall quality of life and mental state. Due to ketamine having a variety of effects on cholinergic, serotonin, norepinephrine, dopamine, L-type sodium channels, and opiate receptors, ketamine is favorable for patients who suffer from neuropathic sourced pain. This makes ketamine additionally favorable for off label use for pain management as pain relief has a pathophysiology in the central nervous system by inhibiting neurons in the spinal cord through glutamate release (Sexton et al., 2018). Ketamine overall can have a highly beneficial impact in the brain for psychiatric symptoms; pathological pain

symptom improvement has been demonstrated, and ketamine is currently FDA approved for the primary use of an anesthesia induction agent.

Evidence Based Recommendations

In evaluating many articles, evidence-based recommendations yield to show that with additional reliable research trials, positive effects of oral or intravenous ketamine infusion could be revolutionary in medicine. This could allow the promotion of autonomy and the ability to let patients reach therapeutic benefits through alternative pharmacology in patients who suffer from depression, TRD, PTSD, anxiety, bipolar disorder, and neuropathic pain. As ketamine targets receptors safely in the brain, the main concerns in the perspective of the provider are the most common report of nausea and dissociation during ketamine administration. There is potential for the use of ketamine in adjunct with antidepressants to decrease the time to directly see beneficial mental health and systemic effects in patients. With more studies with a larger sample size, ketamine is yielding greater therapeutic benefits than adverse effects. One consideration to keep in mind is that current marketed antidepressants allow patients the ability to drive and operate machinery; due to ketamine being dissociative and a controlled substance, patients who are either on intravenous or oral therapy are not permitted to drive for 12 hours after administration. However, durability in symptom improvement and decrease in the need for dosages over time proves that tolerance is not seen in this medication, and withdrawal effects are not seen. With current available oral medications, patients must titrate their doses slowly, and a therapeutic response can take weeks. With ketamine use, suicidal ideations, depression symptoms, and neuropathic pain will show improvement within hours and even minutes within the intervention. This makes ketamine favorable for acute settings, such as an emergency medication for psychiatry and acute neuropathic pain. With an increase in need for pharmacological alternatives due to previous intolerance of medications and the positive effects that have already been seen, physicians can see a greater improvement in patients' overall quality of life after ketamine augmentation.

Conclusion

In conclusion, psychiatric disorders are much more prevalent than reported in the United States and worldwide. When exploring alternatives with patients who have not been successful with treatment opportunities, ketamine therapy allows a new gateway in improvement of quality of life which helps promote hope for patients who chronically suffer from debilitating symptoms. In New York specifically, ketamine clinics have been rapidly developing and allow patients to get acute intervention without the need for hospitalization. Currently in the United States, the mental health crisis has soared to levels which overwhelm and overpopulate hospitals and affect the quality of care provided. The treatment patients receive is seen to decrease, which is a major contributing factor to increased suicide rates and recorded treatment failure. Having ketamine as an adjunct to be able to administer in a quiet and controlled environment can impact the lives of millions of patients providing relief from debilitating thoughts and feelings. It is fascinating to evaluate such positive overall long term impacts it can have on patients. Ketamine therapy use can improve the quality of life of individuals who have not yet found relief in symptom management.

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