5-2022

Ketamine Use in Refractory Depression

McKenzie K. Kemmet
University of North Dakota

Ketamine Use in Refractory Depression

by

McKenzie K. Kemmet, PA-S

Bachelor of Biological Sciences, North Dakota State University, 2018

Contributing Author: Jay Metzger, MPAS, PA-C

A Scholarly Project

Submitted to the Graduate Faculty of the University of North Dakota

in partial fulfillment of the requirements for the degree of

Master of Physician Assistant Studies

Grand Forks, North Dakota

May 2022

Table of Contents

Acknowledgments……..……..3

Abstract……....4

Introduction……...……..…….5

Statement of the Problem…….5

Research Question……...6

Research Methods……6

Literature Review…….……..…….…..…6

Pathophysiology of Major Depression and Refractory Depression…….……7

Theme One: Efficacy of Typical Antidepressants……...……9

Theme Two: Pharmacological Benefits of Ketamine……...…….13

Theme Three: Efficacy of Ketamine…….…….16

Theme Four: Safety of Ketamine ……...……...18

Discussion……..24

Applicability to Clinical Practice……...27

References……..28

Acknowledgments

I am grateful to have the assistance of my advisor Jay Metzger and instructor Daryl Sieg with this extensive scholarly project. I would like to thank Allison Ranisate for helping with my various interlibrary loan requests and the UND writing center staff for helping with the formatting of this APA-style paper. In addition, I would like to thank Marilyn Klug for reviewing my current research and statistical data used in this literature review, Miriam Tell, a nurse practitioner that discussed ketamine with me in further detail and Andrew Smith that helped edit and proofread my final paper. Lastly, I would like to thank my family and friends for their support and encouragement during my journey to becoming a physician assistant.

Abstract

Despite pharmacological advancements, depression continues to be considered the third leading cause of disability in the world. Although depressive symptoms may decrease within a few weeks after beginning typical antidepressants, there are still about one-third of individuals that fail to respond and do not achieve recovery. The symptoms not resolved by antidepressant therapy ultimately leads to decreased quality of life, decreased productiveness of the individual, increased hospitalizations, higher health care costs, and increased rates of suicide. As a result, the clinical use of ketamine in refractory depression is increasing because of the antidepressant properties found in a multitude of studies.

The goal of this literature review is to determine the most efficacious treatment option for treatment-resistant depression (TRD), whether it be typical antidepressants or the intravenous infusion of ketamine. A comprehensive literature review was completed, with the use of various electronic databases, which included PubMed, Access Medicine, and Clinical Key. The studies included clinical trials, meta-analyses, randomized controlled trials, and systemic reviews. The research suggested evidence of improvement in symptoms of depression and suicidal ideation with the use of IV ketamine. However, the adverse effects associated with the use of ketamine need to be considered before beginning the use of ketamine for treatment. Additional clinical research does need to be done to further investigate the adverse effects associated with the chronic use of ketamine in TRD or refractory depression.

Keywords: treatment-resistant depression, major depression disorder, ketamine, adverse effects, safety, pathophysiology, typical antidepressants

Introduction

The biggest challenge in clinical psychiatry today is TRD, regardless of the pharmacological advancements in therapies. Numerous patients have not had a response to typical antidepressants used in the treatment of major depression. About 44% of patients do not have a response to two separate antidepressant therapies, while 33% of patients do not have a response to four separate antidepressant therapies (Bergfeld et al., 2018). The symptoms not resolved by antidepressant therapy contribute to a decreased quality of life, decreased productiveness of the individual, increased hospitalizations, and higher costs in health care. Lastly, TRD has an excessively high risk of suicide in which 30% of patients will try to commit suicide at least one time throughout their life (Bergfeld et al., 2018). The goal of this literature review is to determine the most efficacious treatment option for TRD, whether it be typical antidepressants or the intravenous infusion of ketamine.

Statement of the Problem

Antidepressants are considered first-line treatment for adults with depression ranging from moderate to severe. A common definition of TRD or refractory depression is when the individual does not respond adequately to typical antidepressants. TRD occurs in two-thirds of the population that are prescribed antidepressants (Davies et al., 2019). In the United States, about 30% of patients with depression are affected by refractory depression (Singh et al., 2017). Refractory depression is a disabling illness associated with an increased risk of suicidal behaviors when typical antidepressants do not provide complete recovery for the patient. As of now, there is no standardized approach to the treatment of individuals with refractory depression.

Research Question

In adult patients with TRD, does the use of typical antidepressants or the infusion of ketamine have greater efficacy in treating refractory depression?

Methods

A comprehensive literature review was completed, with the use of various electronic databases which included PubMed, Access Medicine, and Clinical Key. The keywords used during this search were TRD, MDD, ketamine, adverse effects, safety, pathophysiology, and typical antidepressants. The total number of articles found from the years 2005-2021 using the electronic databases was 905. This was then filtered and narrowed by limiting the age to 19-64 years old, during the years 2018-2021. The studies included clinical trials, meta-analyses, randomized controlled trials, and systemic reviews. After using the exclusion criteria, 66 articles were found that met the inclusion criteria. These remaining articles were then evaluated for further use and application in this comprehensive literature review.

Literature Review

After reviewing the literature on both typical antidepressants and ketamine use for the treatment of major depressive disorders and refractory depression, it appears that many studies have been done to determine the most efficacious treatment. The current literature indicates that the recommended first-line treatment for major depressive disorders is selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs). One-third of individuals taking these antidepressants fail to respond to treatment which is why ketamine may be a prospective first-line antidepressant medication used alone to achieve clinical improvement. Ketamine is a prompt and effective treatment option for depression and helps to reduce suicidal ideation among patients.

Pathophysiology of Major Depression and Refractory Depression

According to Otte et al. (2016), "Major depressive disorder (MDD) is a debilitating disease that is characterized by at least one discrete depressive episode lasting at least two weeks and involving clear-cut changes in mood, interests, pleasure, changes in cognition and vegetative symptoms" (p. 1). TRD is used to describe a form of MDD that has not responded to one antidepressant in which 50-65% of patients do not have an adequate response or change in their symptoms of depression following initial treatment (Otte et al., 2016). A meta-analysis was done and revealed the variables related to TRD. This included older age, marital status, longer duration of existing depressive episodes, high suicidal risk, anxiety, increased hospitalizations, and other comorbid personality disorders.

MDD is among the most disabling in the realm of psychiatric disorders. Most seen in patients with MDD is a poor response to typical antidepressants. This specific disorder affects a large amount of the population, specifically 320 million people worldwide (Hashimoto, 2019). The estimated inheritability of MDD in a first-degree relative is about 30% and is more commonly seen in females (Mora et al., 2018). By the year 2030, depressive disorders are expected to be the primary source of disease burden worldwide (Mora et al., 2018).

In a review done by Bergfeld et al., (2018), TRD is described as a patient that has failed or did not respond to a minimum of two adequate antidepressant therapies. Treatment for TRD often includes electroconvulsive therapy (ECT) but there have been new treatment options that have gained more recognition over the last 20 years due to a sudden decrease in suicidal ideation (Bergfeld et al., 2018). A sudden decrease in suicidal ideation is significant due to almost 25% of patients with MDD having a history of multiple suicide attempts (Corriger & Pickering, 2019).

"Due to the complex nature of this disorder, and lack of precise knowledge regarding the pathophysiology, effective management is challenging" (Pitsillou et al., 2020, p. 753). MDD is caused by a variety of things and is a result of the interactions between biological, behavioral, psychosocial, and cultural factors. Pitsillou et al., (2020) reports that a chemical balance in the brain is very important and is needed for normal functioning. Thus, MDD is most likely due to a chemical imbalance, but most likely not the only cause. This is concerning the monoamine hypothesis of depression and monoamine oxidase theory which causes a change in mood and ultimately led to the finding of antidepressant therapy.

Regarding the pathophysiology related to MDD and refractory depression, "abnormalities in excitatory and/or inhibitory neurotransmission and neuronal plasticity may lead to aberrant functional connectivity patterns within large brain networks" (Lener et al., 2017, p. 1). Network dysfunction has also been found in studies done on animals and humans with depression, with distorted levels of glutamate (Glu) and gamma-aminobutyric acid (GABA) in the brain. Functional imaging done on the neurochemicals Glu, and GABA demonstrated an antidepressant response to subanesthetic doses of ketamine (Lener et al., 2017).

In studies done on rodents, depressive-like behaviors were produced using either pharmacology or stress. With this behavior change, adjustments in cortical glutamate were observed and have been reversed using monoaminergic antidepressants and ECT (Lener et al., 2017; Iserson K.V. 2016; Nowak et al., 1993; Skolnick et al., 1996). Other studies using magnetic resonance spectroscopy (MRS) and positron emission tomography (PET) have demonstrated variations in the concentrations and the activity in both Glu and GABA which indicates a disruption in either the excitatory or inhibitory neurotransmitters which could play a crucial role in depression (Lener et al., 2017). In addition to imaging done on the brain to further

investigate the changes associated with MDD, biomarkers are also being studied to better predict a patient's response to antidepressants, leading to personalized medicine for the patient. Further research is needed to identify biomarkers in particular depression phenotypes. This research could help to predict an individual's response to antidepressant therapy with greater accuracy.

Theme One: Efficacy of Typical Antidepressants

"Millions of people worldwide suffer from depression, but despite advances in pharmacological therapies, many patients do not experience symptomatic remission or treatment response, even after treatments with several medications" (Mora et al., 2018, p. 2). Mora et al., (2018), found that even with numerous different antidepressant medications out there, about 60% of people do not have relief with the use of a single antidepressant. About 20% of these people fail to respond to any intervention. According to Mora et al. (2018), there are many different classes of antidepressant medications with different molecular mechanisms and only about 50% of people respond to the first trial of antidepressants. According to Davies et al., (2019):

> Depression is a common problem often treated with antidepressant medication. However, many people do not get better with antidepressant treatment and have 'treatment-resistant depression'(TRD). Several different treatment approaches can be tried - such as increasing the dose of the current medication, adding another medication, or switching to a different antidepressant. (p. 3)

For individuals with moderate to severe anxiety, antidepressants are often considered first-line therapy, although about 66% do not respond to this. This may be due to possible intolerance to the medication prescribed, non-adherence to the regimen, or treatment-resistant depression. There are five core types of antidepressants used which include tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), SSRIs, SNRIs, and lastly noradrenergic specific

serotonin antidepressants (NaSSAs) (Davies et al., 2019). The most prescribed antidepressant used to treat depression is an SSRI and this is because of its good tolerability. Since there is not a standardized approach to prescribing antidepressants for individuals with a failed response to the initial medication, the possible next option would be to increase the dose, switch to an antidepressant within the same class, switch to an antidepressant in a different class, or augment with another pharmacological option or psychotherapy (Davies et al., 2019). Combined treatment with psychotherapy and pharmacotherapy is often more effective together than alone.

The antidepressants commonly used for depression have inadequate effectiveness and there is an immense delay in the amount of time for an antidepressant to have therapeutic effects in a patient. According to Hashimoto (2019), an unmet medical need is the development of rapid-acting antidepressants that are effective in patients with TRD and suicidal ideation. There are treatments that exist for TRD, such as traditional antidepressants, ECT, psychotherapy, lithium, or valproate, but due to the slow onset of these treatment options and the resistance seen with this disorder, the act of suicide could occur during this time (Corriger & Pickering, 2019). Most antidepressant agents used for the treatment of MDD focus on the monoamine system and are used to increase the availability of serotonin, norepinephrine, and dopamine in the brain (Pitsillou et al., 2020).

What makes treating MDD difficult is that the best antidepressant may be different for every person and can only be found through experimental trials. This ultimately leads to prolonging several things that include remission, suffering, and suicidal ideation. “Pragmatic studies indicate that a substantial number of depressed patients do not remit with current first-line antidepressant treatments and after two failed treatment steps the chance of remission with subsequent therapies is around 15%” (Cowen, 2017, p. 1). According to Thomas et al. (2015):

> More than 40% of patients treated for major depressive disorder (MDD) with an appropriate antidepressant dose for an adequate duration fail to respond. Further, approximately half of adults with MDD fail to achieve sustained remission despite various medication trials. (p. 434)

One of the first classes of medications that were used for the treatment were MAOIs. The mechanism of action for this class of medication involves irreversible binding and inactivation of the enzyme monoamine oxidase which inhibits the breakdown of serotonin, epinephrine, norepinephrine, and dopamine (Thomas et al., 2015). This results in the accumulation of these neurotransmitters. This class of medications has limited use due to the adverse effects and the possible interactions it may have with other drugs or an individual's diet. MAOIs also should not be combined with other antidepressants and certain medications due to the risk of serotonin syndrome which can be life-threatening (Thomas et al., 2015).

To manage patients with MDD, the first line of treatment is a second-generation antidepressant. This includes selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs). Second-line agents include TCAs, trazodone, levomilnacipran, and vilazodone while third-line agents for the treatment of depression include MAO inhibitors and reboxetine (Mora et al., 2018). The antidepressant medications that are used currently exert their effects on the monoamine system which is completely different from ketamine which targets the N-methyl-D-aspartate (NMDA) receptors (Nowacka et al., 2019).

According to Bergfeld et al., (2018), the primary clinical challenge in psychiatry is TRD due to patients not responding to consecutive antidepressant therapies. Within the last 20 years, there have been many new drugs that have been formulated and share similar structures and mechanisms of action. Based on 117 studies done on 12 different antidepressants, they found that

escitalopram and sertraline may be the best option when starting treatment for individuals with moderate to severe major depression due to the greatest probable balance between effectiveness and adequacy (Cipriani et al., 2009). Out of the 12 antidepressants used for the acute treatment of major depression, the drugs that had the best response were mirtazapine, escitalopram, venlafaxine, and sertraline. The antidepressants that did not have a great response were duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine. Reboxetine when compared to the other 11 antidepressants was significantly less effective. Thus, the results signify that the two most effective treatments used in the treatment of major depression are mirtazapine and venlafaxine, although they are not the most acceptable drugs. In this study, the adverse effects, toxic effects, symptoms with discontinuation of the medication, and social functioning were not evaluated.

"Despite newer medications, TRD literature indicates that the investigatory endeavors came to a standstill a decade ago" (Pandarakalam, 2018, p. 274). Important key points to consider when prescribing an antidepressant are if it has a fast onset, continued response, continued remission, sustained prevention of relapse, monotherapy, single regime, good tolerability, and the fewest symptoms when discontinuing the medication (Pandarakalam, 2018). An efficient way to manage TRD is the prompt detection of this disorder, followed by aggressive management of remaining symptoms and maintenance treatment. It is advised to prescribe these medications at low doses to avoid adverse reactions. Although starting at a low dose lowers the opportunity for full improvement in symptoms, it could elicit a partial response (Pandarakalam, 2018). In preparation for a further course of treatment, it is vital to differentiate whether there was a partial response or no response at all. If there is no response or significant adverse effects, a change in medication would be indicated (Pandarakalam, 2018).

Theme Two: Pharmacological Benefits of Ketamine

Ketamine has been used for its short-term anesthetic properties and its analgesic properties since the 1970s (Nowacka et al., 2019). “In the areas related to ketamine's psychological effects, pain management and treatment of depression seem most promising” (Nowacka et al., 2019, p. 9). In addition, “Among new applications of ketamine, its antidepressive and antisuicidal properties seem to be particularly promising and create hope for developing effective treatments” (Nowacka et al., 2019, p. 9). It also has been known for having neuroprotective properties by inhibiting the NDMA receptor activation and excitotoxic signaling, reducing the apoptosis of neurons, while also prolonging cerebral perfusion pressure with the activation of the sympathetic nervous system (Nowacka et al., 2019). Regarding inflammation seen with a tissue injury, ketamine can reduce this inflammatory response by cooperating with three main events associated with the inflammatory process. These include the regulation in the recruitment of inflammatory cells, the production of cytokines, and the management of inflammatory mediators (Nowacka et al., 2019).

The mechanism of action (MOA) of ketamine is unknown. A common question associated with the research and studies of ketamine use with treatment-resistant depression is, how does ketamine implement its antidepressant effects? They have a couple of possible MOAs that may account for the effects of ketamine in reducing depressive symptoms. One possible MOA could be through the brain-derived neurotrophic factor (BDNF) and NMDA receptors. Ketamine is a noncompetitive agonist and works by binding to the NMDA receptors and inhibiting ion flow (Nowacka et al., 2019). Ketamine also interacts with a variety of receptors that includes opioid, monoaminergic, cholinergic, muscarinic, and nicotinic. This ultimately leads to the inhibition of the NMDA receptors which leads to decreased eukaryotic elongation

factor 2 (eEF2) kinase activity which results in decreased BDNF translation (Nowacka et al., 2019). This possible mechanism of action was found through the study of mice. Another MOA that could be responsible for the effects of ketamine on TRD is through the mechanistic target of the rapamycin (mTOR) pathway, which could be due to neurotrophic methods (Nowacka et al., 2019). In addition, ketamine could exert its effects on the opioid receptors by serving as an opioid receptor antagonist. Found with the use of ketamine is NMDA mediated antagonism found specifically in the transmembrane located in the brain and the spinal cord. The antagonism of the NMDA receptors triggered by glutamate, which is an excitatory amino acid, is responsible for causing amnesic, psycho sensory, and analgesic effects (Peltoniemi et al., 2016). Ketamine when used for its antidepressant effects works to reverse the neurochemical and psychological disruptions. In addition, ketamine has antagonistic actions at L-type voltage-gated calcium channels, nicotinic and muscarinic acetylcholine receptors, hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, voltage-sensitive sodium channels, and large conductance big potassium (BK) channels (Guatam et al., 2020). It also causes activation of mu and delta-opioid receptors, amino-3-hydroxyl-5-methyl-4-isoxazole propionic acid (AMPA), and GABA receptors (Guatam et al., 2020).

Lener et al., (2017) found that ketamine is a very good molecular tool to measure the influence of glutamatergic modulation specifically on excitatory and inhibitory neural circuitry in both healthy and depressed individuals with MDD because of the data supporting ketamine's effectiveness and decreased adverse effects when compared to other glutamatergic modulating agents.

Ketamine is known for its rapid onset in reducing depressive symptoms. It is usually seen within 24 hours and can last from four to seven days after a single IV dose. It has also been noted

that ketamine has continuous and collective effects when an individual is given six repeated doses (Guatam et al., 2020). With patients who are in the initial stages of ECT while receiving ketamine, there has been short-term mild improvement. Also, ketamine has significant effects in patients with suicidal ideation with a single dose of IV ketamine within just two hours and can last for a week (Guatam et al., 2020). Due to ketamine's rapid effects on depressive symptoms, it is commonly used in conjunction with ECT. The MOA that may be responsible for the antidepressant effects seen with the use of ketamine could be due to "rapamycin pathway activation, synaptogenesis in the prefrontal cortex and glycogen synthase kinase (GSK)-3 beta inactivation" (Scheuing et al., 2015, as cited in Peltoniemi et al., 2016, p. 1070). Lener et al., (2017) found:

> Ketamine's antidepressant effects were demonstrated over a decade ago in a double-blind, placebo-controlled clinical study of eight depressed patients randomized to receive either a subanesthetic dose (0.5 mg/kg IV over 40 minutes) of ketamine or saline. Four of the eight patients (n=7 completers) had an antidepressant response to ketamine (defined as a reduction of 50% or greater on the Hamilton Depression Rating Scale (HAM-D). (p. 6)

A limitation is the small number of clinical studies done in MDD patients, so it is uncertain how the antidepressant effect associated with ketamine is related to specific levels of Glu and GABA. Additional studies are needed to identify the connectivity alterations correlated with the antidepressant response elicited with ketamine use. This will be further evaluated using functional imaging before, during, and after a ketamine infusion to analyze the changes in Glu/GABA neurochemistry (Lener et al., 2017; Iserson K.V. 2016; Nowak et al., 1993; Skolnick et al., 1996).

The routes of administration determine the bioavailability of ketamine within the body. Due to the first-pass metabolism, oral ketamine is known for having poor bioavailability within the body and is not commonly used in a clinical setting. Only about 7-14% of the oral racemic ketamine and 8-11% of oral S-ketamine reaches systemic circulation (Peltoniemi et al., 2016). Currently, S-ketamine and a racemic mixture of ketamine are used clinically. Because of the higher clearance and sharper concentration-effect curve, the S-ketamine version presents improved titratability (Peltoniemi et al., 2016). After ketamine is absorbed systemically, it is dispersed into the brain and into tissues that are properly perfused.

Theme Three: Efficacy of Ketamine

For more than ten years ketamine has been researched in detail regarding the treatment of major depressive disorders. This began because of a study done in 2000, which involved a randomized controlled trial that demonstrated the relief of depressive symptoms with the use of one subanesthetic dose of ketamine (Nowacka et al., 2019). There are many clinical studies showing ketamine is effective in treating TRD and the suicidal ideation associated with TRD. However, ketamine is generally not offered to patients until they have failed at least two antidepressant therapies (Nowacka et al., 2019).

Lapidus et al., (2014), conducted a study on 18 individuals using intranasal ketamine. This study found that the individuals using intranasal ketamine had significantly reduced depressive symptoms along with anxiety symptoms, within 24 hours of the administered dose. “Depressive symptoms 24 hours post treatment were significantly improved in the ketamine condition compared to placebo ($t=4.39$, $p<0.001$). The estimated mean difference in MARDS score between ketamine and placebo was 7.6 ± 3.7 (95% CI: 3.9 – 11.3)” (Lapidus et al., 2014, p. 6). In addition, a recent study found that one dose of 50 mg intranasal ketamine was associated

with a quick antidepressant response in patients with major depression who failed at least one antidepressant medication (Lapidus et al., 2014). The effect of ketamine on depressive symptoms was observed 40 minutes after the infusion of ketamine. In fact, “ketamine was superior to placebo in improving anxiety symptoms at 24 hours as measured by HAM-A scores [t17=3.06, p=0.007; mean benefit of 4.5 ± 3.2 (95% CI: 1.4–7.6)]” (Lapidus et al., 2014, p. 6).

Ketamine has been associated to have a quick response in decreasing suicidal ideation in random control trials (RCTs). In patients with an increased risk of a suicide attempt, this may be the treatment that is favored due to a response time of two hours. However, studies done on this recently have shown no usefulness with the improvement in suicidal ideation (Corriger & Pickering, 2019). Although, another study showed that ketamine use was beneficial to individuals with the most suicidal ideation and the highest risk. Furthermore, ketamine use was assessed in non-depressed individuals that had suicidal ideation and found that ketamine can influence suicidal ideation in individuals even if they did not have anxiety or depression (Corriger & Pickering, 2019). Studies done by Hashimoto (2019), found response rates 24 hours after ketamine use ranged from about 25% to 85%, while 72 hours after the use of ketamine, the response rates still ranged from 14% to 70%.

Another study was done on 68 patients with TRD. Patients were given 0.5 mg/kg of ketamine over 40 minutes, twice per week, and showed a 69% response rate with a 37.5% remission rate (Sanacora et al., 2017). In addition, ketamine given three times per week had a 53.8% response rate with a 23.1 remission rate (Sanacora et al., 2017). Using the Montgomery-Asberg Depression Rating Scale score, they saw a 27-point reduction in those given ketamine twice weekly while those that received ketamine three times per week only had a 23-point reduction. This score gives evidence that the dosing of ketamine twice per week is more effective

than ketamine dosing three times per week. Recurrent treatment with ketamine has shown to have a substantial benefit that takes place early during treatment, while other reports show a cumulative advantage with continued treatment over time (Sanacora et al., 2017). The number of treatments of ketamine infusion should be restricted to the minimum number of treatments that are needed for a clinical response to occur. The goal of treatment with ketamine is a therapeutic response of three to four weeks, and about one-third of patients do not respond to the treatment entirely. In 2006 there was a study done on 17 individuals with MDD. The study found that a little over 70% of the individuals had a decrease in over half of their symptoms associated with depression within 24-hours after the ketamine had been infused over a 40-minute time span (Singh et al., 2017). The placebo group receiving IV saline had nearly no change in symptoms.

Theme Four: Safety of Ketamine

Right now, the information encompassing the advantages of ketamine use over a short period is restricted, resulting in even larger gaps regarding the safety of ketamine especially when used for prolonged periods (Sanacora et al., 2017). This lack of data makes it hard to give suggestions regarding the duration of the treatment and the dosage. Although there has been an increasing number of cases used to assess the advantages of recurrent use of ketamine in patients who experience major depressive episodes. The data on long-term effectiveness has even less information than the short-term use of ketamine efficacy. In clinics using ketamine, a typical treatment course is two to three weeks during which the ketamine is delivered two or three times weekly. Afterward, there will be a taper period and/or continued treatments. (Sanacora et al., 2017). This treatment is based on each patient's duration of response and is not uniform. With each infusion of ketamine, the risks and benefits should be assessed in addition to the consideration of long-term effects of use.

There are several challenges associated with the use of ketamine that includes an increase in heart rate, blood pressure, cardiac output, myocardial oxygen demand (Guatam et al., 2020). With these side effects, it would not be a reasonable medication for individuals with a history of past cardiovascular events. Not only does it affect the heart, but it also influences the brain due to the powerful stimulation, especially in those with known seizure disorders. Ketamine also can cause cognitive impairment in normally healthy individuals. It does this by depressing the central nervous system ultimately leading to intoxication, changes in perception, false beliefs, problems with speech, and slower response rates. Lastly, chronic use of ketamine has been known to cause toxicity of the urinary tract, leading to increased frequency, urgency, and pain with urination. However, this has been known to resolve itself weeks after stopping ketamine. Common findings associated with the prolonged use of ketamine include bladder instability, overactivity of the detrusor muscle, interstitial cystitis, vesicoureteral reflux, hydronephrosis, papillary necrosis, and finally renal impairment (Guatam et al., 2020). These various adverse effects have been found in multiple studies. With any drug, comes the possibility for abuse, and ketamine is a common drug that is abused recreationally.

The cardiovascular effect associated with the administration of ketamine was an increase in blood pressure for a short period. In a study of 16 individuals experiencing ECT while also receiving 0.8 mg/kg ketamine, there were five circumstances during which the patient experienced a hypertensive episode resulting in their diastolic blood pressure being greater than 100 mmHg (Zhu et al., 2016). In another study conducted in patients who were hospitalized, they were given 0.54 mg/kg of ketamine, which resulted in a slight increase in their blood pressure (Zhu et al., 2016). This was resolved in about 30 minutes after the ketamine infusion was stopped. The effects of ketamine on the patient's blood pressure are possibly associated with the

release of the catecholamines within the body in addition to the inhibition of the norepinephrine reuptake specifically in the nerves in the periphery, and in non-neuronal tissues which are found in the myocardium of the heart (Zhu et al., 2016). If patients have existing heart conditions such as ischemic heart disease or hypertension, ketamine use should be used with caution, and blood pressure should be taken during the ketamine infusion to monitor any possible changes.

Studies have been done in clinical trials on the use of IV ketamine with short-term use but not long-term use. In a study done by Iqbal & Matthew (2020), the most common adverse effects associated with 205 ketamine infusions were drowsiness, dizziness, poor coordination, blurring of vision, and feeling strange. All side effects diminished after the infusion was complete. In another study, 833 healthy volunteers were given a subanesthetic dose of IV ketamine and reported feeling weird, panicky, too high, walls closing in as well as having nightmares, insomnia, a decreased ability to concentrate, crying and unresponsiveness to pain and verbal stimuli (Iqbal & Mathew, 2020). Symptoms that are generally dependent on the dosage and minor include lightheadedness, headache, nausea, changes in vision, drowsiness, and dizziness (Iqbal & Mathew, 2020). Ketamine has both cognitive effects and cardiovascular effects that occur only during the infusion and subside shortly after. The cognitive effects associated with ketamine were revealed after a study was done on 54 healthy volunteers that had effects on memory, specifically episodic, working, and recognition (Iqbal & Mathew, 2020). It also has effects on semantic processing and procedural learning. In addition, in patients with hypertension, their blood pressure typically reached its highest value while the infusion is taking place. After the infusion is complete, blood pressure will return to baseline. When it comes to cardiovascular safety, these changes are not significant due to the doses being administered at a subanesthetic dose (Iqbal & Mathew, 2020).

Another study done by Corriger & Pickering (2019) regarded the safety and potential toxicity of ketamine in patients with depression. Ketamine has been shown overall to be safe and tolerable when given for short periods and at low doses. The adverse effects linked to the use of ketamine were due to high doses for prolonged periods. The most common adverse effects are psychiatric, psychotomimetic, or disassociated in nature (Corriger & Pickering, 2019). These adverse effects with ketamine use can be simply resolved by stopping the infusion. A side effect disclosed in a study was a suicide attempt by a patient. Other mild-moderate adverse effects seen with the use of intranasal (S) ketamine included dizziness, dissociation, altered taste, vertigo, and nausea (Corriger & Pickering, 2019). Furthermore, there are a small number of individuals that experience side effects associated with discontinuing the use of ketamine which include syncope, headache, dissociative syndrome, and ectopic pregnancy (Corriger & Pickering, 2019). Recreational users of ketamine can suffer from adverse effects of the liver, urinary tract, and kidney damage. More studies should be conducted, specifically on individuals who chronically use ketamine for depression (Corriger & Pickering, 2019).

Nowacka et al., (2019) also found similar adverse effects associated with ketamine use including an increase in heart rate and blood pressure along with respiratory depression which is not remarkable. The drug does not affect the function of the kidney or liver but has been known to cause injury to the kidney and multiorgan dysfunction with prolonged use of ketamine (Nowacka et al., 2019). In addition, it produces psychodysleptic effects which can result in hallucinations, conscious dreams, feelings of floating, a disruption in mood, body image, and the perception of time (Nowacka et al., 2019). The effects are dependent on the dose that is administered in which anxiety and feelings of paranoia develop with elevated doses. There are

also neural effects associated with the use of ketamine due to the activation of several areas in the brain.

The use of intranasal ketamine only showed mild symptoms of dissociation, in addition to psychosis-like symptoms and increased hemodynamic parameters. The intranasal ketamine was well tolerated by the individuals. Overall, a randomized study demonstrated the safety of the intranasal ketamine and its effectiveness in the quick decline in depressive symptoms found in patients with MDD and mild TRD with a 50 mg single of ketamine (Lapidus et al., 2014). Although, when compared to another study, the antidepressant effects associated with the intranasal ketamine were less than the effects found with the IV administration of ketamine. This could be due to the amount of ketamine found in the blood in which 84 ng/mL were found at 40 minutes with intranasal ketamine (Lapidus et al., 2014). In contrast, the mean ketamine levels found with IV infusion of ketamine at 40 minutes was 200 ng/mL (Lapidus, et al., 2014). The adverse effects associated with the use of intranasal ketamine included psychosis and dissociation. In addition, hemodynamic changes have been noted. The hemodynamic changes associated with the use of intranasal ketamine were not significant enough to need treatment and had resolved within four hours after administration. In addition to these symptoms, some individuals had strange feelings, poor memory, and weakness or fatigue (Lapidus et al., 2014). No significant adverse events occurred with the use of ketamine during this study.

The long-term side effects of IV ketamine use have not been studied in clinical trials. This makes the safety associated with the chronic use of ketamine undetermined (Iqbal & Mathew, 2020). The long-term effects typically seen with the chronic use of ketamine include cognitive impairment, cystitis, and substance abuse and should be considered with infusions of ketamine for a prolonged period (Sanacora et al., 2017). Cognitive impairment could be due to

neurotoxicity which can result with higher doses of ketamine for long periods. It has also been shown to affect the urinary system in which there is increased urgency, frequency, sporadic hematuria, nocturia, dysuria, pain in the bladder, and male erectile dysfunction (Iqbal & Mathew, 2020). Gastrointestinal side effects can also be a result of using IV ketamine at higher doses for a prolonged period. This can lead to abnormal liver function labs, dilation of the common bile duct, and choledochal cysts eventually resulting in liver fibrosis (Iqbal & Mathew, 2020). The worry associated with patients who use ketamine daily for depression is due to the prolonged adverse side effects linked to the misuse of ketamine. The significant side effects are ulcerative cystitis that is ketamine-induced which is also known as a 'ketamine bladder' (Singh et al., 2017). A 'ketamine bladder' causes symptoms such as pain with urination, increased frequency of urination and may become a chronic issue. Another issue associated with the use of ketamine is hepatotoxicity which is commonly seen when ketamine is used more frequently and at higher doses (Singh et al., 2017).

The adverse effects associated with ketamine use typically occur with a high dose or treatment for a prolonged period and can produce neurotoxicity, cognitive dysfunction, and other negative effects that are related to mental status, psychotic symptoms, cardiovascular events, and uropathic effects (Zhu et al., 2016). Neurotoxicity is most often due to chronic ketamine use at higher doses. The side effects associated with neurotoxicity include impairment in memory, specifically episodic memory, sedation, ataxia, and psychomimetic effects (Zhu et al., 2016). Chronic ketamine use at low doses should be safe and effective in maintaining an antidepressant response to this medication. More research is needed to find the most favorable dosage and route of administration in patients needing ketamine treatment for longer periods. A study done on 54 volunteers that received a total of two infusions of ketamine at doses of 0.4-0.8 mg/kg revealed

decreased episodic and working memory, semantic processing, recognition memory, and procedural learning (Zhu et al., 2016). Another study was done on 12 individuals at doses of 50-100 ng/mL and showed even stronger effects on memory. The adverse effects of ketamine on mental states have been commonly described as mild and temporary. This was shown in a study done on 833 healthy individuals. Of the 833 individuals receiving subanesthetic doses of IV ketamine, only ten had significant adverse effects related to their mental status (Zhu et al., 2016). The immediate adverse effects went away within minutes after stopping the infusion of ketamine and almost all remaining adverse effects were absent after four days. Lastly, a meta-analysis done specifically on eight randomized controlled trials demonstrated that one dose of ketamine resulted in brief psychotomimetic effects but did cause ongoing psychosis (Zhu et al., 2016).

Ultimately, IV ketamine used for a short period is generally safe at subanesthetic doses with only minor side effects that subside after the infusion is complete (Iqbal & Mathew, 2020). The factors that alter the safety and tolerability of IV ketamine are correlated to the dosing in which higher doses have greater side effects (Iqbal & Mathew, 2020).

Discussion

MDD and TRD are very complicated disorders due to the complexity of interactions found between genetic and environmental factors. Treating both disorders is complicated and usually done on a trial-and-error basis using first-line antidepressants such as SSRIs or SNRIs. There are five main classes of antidepressants used in the treatment of MDD and TRD including TCAs, MAOIs, SSRIs, SNRIs, and NaSSAs (Davies et al., 2019). In an analysis based on a total of 117 studies and 25,928 individuals, Cipriani et al., (2009) found that mirtazapine, escitalopram, venlafaxine, and sertraline were more effective than duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine in terms of response to the antidepressant. Regarding

the tolerability of antidepressants, escitalopram, sertraline, citalopram, and bupropion were better tolerated by patients. This study ultimately found escitalopram and sertraline to be the best antidepressant option for individuals with moderate to severe major depression due to the greatest probable balance between effectiveness and adequacy (Cipriani et al., 2009). When patients fail to respond to an initial antidepressant medication there are other options that include increasing the dose, switching the antidepressant to the same class, switching the antidepressant to a different class, or augmenting with an additional pharmacological option or psychotherapy (Davies et al., 2019). When a patient does not respond to a minimum of two adequate therapies, they are said to have TRD according to Bergfeld et al., (2018). In fact, 44% of patients do not have an adequate response to two separate antidepressant therapies, and 33% of patients do not have a response to four separate antidepressant therapies (Bergfeld et al., 2018). These statistics indicate high rates of TRD in addition to the high risks of suicides.

"Among new applications of ketamine, its antidepressive and antisuicidal properties seem to be particularly promising and create hope for developing effective treatments" (Nowacka et al., 2019, p. 9). Ketamine has rapid-acting properties in which an initial reduction in depressive symptoms occurred within two hours of the ketamine infusion. Reduction in depressive symptoms were maximized after 24 hours and were sustained for a week after the administration of ketamine (Lener et al. 2017). Lapidus et al., (2014) found:

> Patients showed significant improvement in depressive symptoms at 24 hours following ketamine compared to placebo [$t=4.39$, $p<0.001$; estimated mean MADRS score difference of 7.6 ± 3.7 (95% CI: 3.9 – 11.3)]. Eight of 18 patients (44%) met response criteria 24 hours following ketamine administration, compared to 1 of 18 (6%) following placebo ($p=0.033$). (p. 2)

Not only does ketamine reduce depressive symptoms, but it also has been shown to reduce suicidal thoughts in individuals with suicidal ideation (Nowacka et al., 2019). Ever since ketamine has been used for the treatment of depression, there have been more clinical trials used to study the adverse reactions associated with this drug. The adverse reactions associated with the drug ketamine are diverse and affect many systems within the body. The major systems affected by this drug include the heart, brain, and kidneys. In a study done by Guatam et al., (2020), the most common adverse reactions affecting the heart were an increased heart rate, blood pressure, cardiac output, and myocardial oxygen demand. Symptoms associated with the kidney include bladder instability, overactivity of the detrusor muscle, interstitial cystitis, vesicoureteral reflux, hydronephrosis, papillary necrosis, and renal impairment (Guatam et al., 2020). Lastly, the effects ketamine has on the brain consist of lightheadedness, headache, nausea, changes in vision, drowsiness, and dizziness (Iqbal & Mathew, 2020). Symptoms are mostly dependent on the dosage and are seen with higher doses of ketamine. These symptoms generally diminish after the infusion of ketamine is stopped. Although, some adverse effects have lasted up to four days after the infusion of ketamine. Clinical studies do suggest that the safety and tolerability of this drug are good with low doses or with short-term treatment. Further clinical research does need to be done to further investigate the adverse effects associated with the chronic use of ketamine in TRD.

Applicability to Clinical Practice

Despite various pharmacological advancements, depression continues to be considered the third leading cause of disability in the world. Depression is a common problem seen in clinical practice and is often treated with antidepressants which are considered first-line treatment for adults with depression ranging from moderate to severe. Although, almost half of the patients

treated with these antidepressants fail to respond even when they are treated with two separate antidepressant medications. Those that do not get better with antidepressant treatment are said to have TRD. Increasing studies done on the drug ketamine indicate that it may be a prospective first-line antidepressant medication used to achieve clinical improvement. Ketamine is a prompt and effective treatment option for depression and helps to reduce suicidal ideation among patients. This evidence-based literature review will provide valuable information that will allow advanced practice providers to offer the most efficacious treatment for patients with TRD.

References

Bergfeld, I. O., Mantione, M., Figee, M., Schuurman, P. R., Lok, A., & Denys, D. (2018). Treatment-resistant depression and suicidality. Journal of affective disorders, 235, 362–367. https://doi-org.ezproxylr.med.und.edu/10.1016/j.jad.2018.04.016

Berman, R. M., Cappiello, A., Anand, A., Oren, D. A., Heninger, G. R., Charney, D. S., & Krystal, J. H. (2000). Antidepressant effects of ketamine in depressed patients. *Biological psychiatry*, *47*(4), 351–354. https://doi.org/10.1016/s0006-3223(99)00230-9

Cipriani, A., Furukawa, T. A., Salanti, G., Geddes, J. R., Higgins, J. P., Churchill, R., Watanabe, N., Nakagawa, A., Omori, I. M., McGuire, H., Tansella, M., & Barbui, C. (2009). Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet (London, England), 373(9665), 746–758. https://doi-org.ezproxylr.med.und.edu/10.1016/S0140-6736(09)60046-5

Corriger, A., & Pickering, G. (2019). Ketamine and depression: a narrative review. Drug design, development, and therapy, 13, 3051–3067. https://doi-org.ezproxylr.med.und.edu/10.2147/DDDT.S221437

Cowen P. J. (2017). Backing into the future: pharmacological approaches to the management of resistant depression. Psychological medicine, 47(15), 2569–2577. https://doi-org.ezproxylr.med.und.edu/10.1017/S003329171700068X

Davies, P., Ijaz, S., Williams, C. J., Kessler, D., Lewis, G., & Wiles, N. (2019). Pharmacological interventions for treatment-resistant depression in adults. The Cochrane database of systematic reviews, 12(12), CD010557. https://doi-org.ezproxylr.med.und.edu/10.1002/14651858.CD010557.pub2

Gautam, C. S., Mahajan, S. S., Sharma, J., Singh, H., & Singh, J. (2020). Repurposing Potential

of Ketamine: Opportunities and Challenges. Indian journal of psychological medicine, 42(1), 22–29. https://doi-org.ezproxylr.med.und.edu/10.4103/IJPSYM.IJPSYM_228_19

Hashimoto K. (2019). Rapid-acting antidepressant ketamine, its metabolites, and other candidates: A historical overview and future perspective. Psychiatry and clinical neurosciences, 73(10), 613–627. https://doi.org/10.1111/pcn.12902

Iqbal, S. Z., & Mathew, S. J. (2020). Ketamine for depression clinical issues. Advances in pharmacology. (89), 131–162. https://doi org.ezproxylr.med.und.edu/10.1016/bs.apha.2020.02.005

Iserson K.V. (2016). Improvised Medicine: Providing Care in Extreme Environments, 2e. McGraw Hill. https://accessmedicine-mhmedical-com.ezproxy.library.und.edu/content.aspx?bookid=1728&sectionid=115698841

Lapidus, K. A., Levitch, C. F., Perez, A. M., Brallier, J. W., Parides, M. K., Soleimani, L., Feder, A., Iosifescu, D. V., Charney, D. S., & Murrough, J. W. (2014). A randomized controlled trial of intranasal ketamine in major depressive disorder. Biological psychiatry, 76(12), 970–976. https://doi-org.ezproxylr.med.und.edu/10.1016/j.biopsych.2014.03

Lener, M. S., Niciu, M. J., Ballard, E. D., Park, M., Park, L. T., Nugent, A. C., & Zarate, C. A., Jr (2017). Glutamate and Gamma-Aminobutyric Acid Systems in the Pathophysiology of Major Depression and Antidepressant Response to Ketamine. Biological psychiatry, 81(10), 886–897. https://doi-org.ezproxylr.med.und.edu/10.1016/j.biopsych.2016.05.005

Mora, C., Zonca, V., Riva, M. A., & Cattaneo, A. (2018). Blood biomarkers and treatment response in major depression. Expert review of molecular diagnostics, 18(6), 513–529. https://doi-org.ezproxylr.med.und.edu/10.1080/14737159.2018.1470927

Nowacka, A., & Borczyk, M. (2019). Ketamine applications beyond anesthesia - A literature review. European journal of pharmacology, 860, 172547. https://doi-org.ezproxylr.med.und.edu/10.1016/j.ejphar.2019.172547

Nowak, G., Trullas, R., Layer, R. T., Skolnick, P., & Paul, I. A. (1993). Adaptive changes in the N-methyl-D-aspartate receptor complex after chronic treatment with imipramine and 1-aminocyclopropanecarboxylic acid. *The Journal of pharmacology and experimental therapeutics*, *265*(3), 1380–1386.

Otte, C., Gold, S. M., Penninx, B. W., Pariante, C. M., Etkin, A., Fava, M., Mohr, D. C., & Schatzberg, A. F. (2016). Major depressive disorder. Nature reviews. Disease primers, 2, 16065. https://doi-org.ezproxylr.med.und.edu/10.1038/nrdp.2016.65

Pandarakalam J. P. (2018). Challenges of Treatment-resistant Depression. Psychiatria Danubina, 30(3), 273–284. https://doi.org/10.24869/psyd.2018.273

Peltoniemi, M. A., Hagelberg, N. M., Olkkola, K. T., & Saari, T. I. (2016). Ketamine: A Review of Clinical Pharmacokinetics and Pharmacodynamics in Anesthesia and Pain Therapy. Clinical pharmacokinetics, 55(9), 1059–1077. https://doi org.ezproxylr.med.und.edu/10.1007/s40262-016-0383-6

Pitsillou, E., Bresnehan, S. M., Kagarakis, E. A., Wijoyo, S. J., Liang, J., Hung, A., & Karagiannis, T. C. (2020). The cellular and molecular basis of major depressive disorder: towards a unified model for understanding clinical depression. *Molecular biology reports*, *47*(1), 753–770. https://doi-org.ezproxylr.med.und.edu/10.1007/s11033-019-05129-3

Sanacora, G., Frye, M. A., McDonald, W., Mathew, S. J., Turner, M. S., Schatzberg, A. F., Summergrad, P., Nemeroff, C. B., & American Psychiatric Association (APA)

Council of Research Task Force on Novel Biomarkers and Treatments (2017). A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders. JAMA Psychiatry, 74(4), 399–405. https://doi-org.ezproxylr.med.und.edu/10.1001/jamapsychiatry.2017.0080

Scheuing, L., Chiu, C., Liao, H., & Chuang, D. (2015). Antidepressant mechanism of ketamine: Perspective from preclinical studies. *Frontiers in Neuroscience, 9*.doi:10.3389/fnins.2015.00249

Skolnick, P., Layer, R. T., Popik, P., Nowak, G., Paul, I. A., & Trullas, R. (1996). Adaptation of N-methyl-D-aspartate (NMDA) receptors following antidepressant treatment: implications for the pharmacotherapy of depression. *Pharmacopsychiatry*, *29*(1), 23–26. https://doi.org/10.1055/s-2007-979537

Thomas, S. J., Shin, M., McInnis, M. G., & Bostwick, J. R. (2015). Combination therapy with monoamine oxidase inhibitors and other antidepressants or stimulants: strategies for the management of treatment-resistant depression. Pharmacotherapy, 35(4), 433–449. https://doi-org.ezproxylr.med.und.edu/10.1002/phar.1576

Zhu, W., Ding, Z., Zhang, Y., Shi, J., Hashimoto, K., & Lu, L. (2016). Risks Associated with Misuse of Ketamine as a Rapid-Acting Antidepressant. Neuroscience Bulletin, 32(6), 557–564. https://doi-org.ezproxylr.med.und.edu/10.1007/s12264-016-0081-2