Barriers to Using Ketamine for the Treatment of Depression

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Contents

Abstract

Depressive disorders are prevalent in the United States. Current treatment paradigms take weeks to reach clinical efficacy and may leave patients at risk for suicide during the initial weeks of treatment. Intravenous (IV) ketamine infusions have shown promise in the rapid relief of depression symptoms, including efficacy in treatment-resistant depression and relief of suicidal ideation. Initial research has shown ketamine therapy to be safe and effective. Despite a plethora of information in support of the safety and efficacy of ketamine, there is reluctance of both patient and provider in utilizing ketamine's unique potential. We used a grounded-theory approach to perform a meta-analysis literature review exploring the barriers preventing widespread acceptance of ketamine therapy. We found fear or moral objection to psychoactive effects, potential side effects, and history of abuse as a street drug to be inhibiting factors among patients. Among healthcare providers, barriers included lack of accessibility, addictiveness, abuse potential, and refusal of insurance policies to cover treatment. We present arguments to challenge objections and question concerns as the vast benefit of ketamine therapy far outweighs potential harms. We give recommendations for further research and call for a more rational approach to U.S. drug policy with a focus on objective evidence and an elimination of unwarranted restriction of personal freedoms.

Keywords: ketamine, depression, efficacy, barriers, bias, perceptions

Barriers to Using Ketamine for the Treatment of Depression

Depressive disorders such as Major Depressive Disorder (MDD) affect the lives of millions of people (Center for Disease Control, 2018). The adverse effects of depression include degradations to interpersonal relationships, cognitive functioning, mental health, sleep patterns, caretaking ability, and occupational productivity (Bhutta, 2007). Depression is a widely prevalent mental illness, affecting 10%-19% of the population worldwide and approximately 18% of the population in the United States (U.S.) (Strasburger et al., 2017). Untreated MDD is associated with high rates of suicide. According to a report by the National Center for Health Statistics, "Suicide is the 10th leading cause of death for all ages in the United States… second leading cause of death for ages 10–34 and the fourth leading cause for ages 35–54" (Center for Disease Control, 2020) There were 48,344 deaths from suicide in the U.S. in 2018 (National Institute of Mental Health, 2020).

Current antidepressant therapies leave much to be desired with regard to efficacy and side effect profiles, leaving a care gap in the treatment of depression. This need for effective therapies could potentially be fulfilled by ketamine, yet ketamine therapy has been slow to gain acceptance in treatment paradigms.

To understand the bias facing ketamine therapy, it may be helpful to explore public perceptions of other frequently used substances and how they compare with ketamine. Substances of interest may include opioids, cocaine, amphetamines, caffeine, cannabis, alcohol, nicotine, psilocybin, lysergic acid diethylamide (LSD), and other prescription or illicit substances. Some characteristics to consider are current standard of care, history of the

substance, legal status, psychoactive effects, potential harms vs. benefits, addictiveness, political factors, and cultural climate.

This review explores the barriers in using ketamine as a treatment option for depressive disorders such as MDD and will consider ideas such as what barriers researchers and providers face for ketamine to be considered a viable treatment option, whether ketamine's association with illicit drugs impacts patient openness to treatment, and whether ketamine's psychedelic properties discourage healthcare providers from recommending it. By understanding patient and provider attitudes, perceptions, biases, and beliefs regarding ketamine as a treatment option, areas of focus for further education or investigation can be identified. Future research may provide greater insight into strategies for increasing provider and/or patient accessibility for this breakthrough.

Methods

The data collected were obtained through mixed-method research. Qualitative and quantitative studies were collected and interpreted to describe bias towards ketamine use in MDD and identify factors which may influence bias. Peer-reviewed articles were gathered to show the efficacy and safety of using ketamine to treat MDD.

Background and Literature Review

Current Depression Therapies

First-line screening and initiation of therapy for depression is commonly managed by Primary Care providers (Siu & US Preventative Services Task Force, 2016). Depression treatment guidelines currently include pharmacologic therapy as well as non-pharmacologic

approaches such as Cognitive Behavioral Therapy (CBT), with a combined approach showing the most therapeutic results for treatment-resistant depression (TRD) (Pandarakalam, 2018).

There are many medications currently used for managing depression including selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), dopamine-reuptake inhibitors, norepinephrine–serotonin inhibitors (5-HT2 receptor antagonists), and tricyclic antidepressants (Epocrates, 2020; Gautam et al., 2017). Patients and health care providers may face challenges in finding a medication that each patient's unique body chemistry is responsive to, as well as managing symptoms while waiting several weeks for the patient to achieve therapeutic effect. The lack of clear criteria and effective interventions in treating severe cases further increases the difficulty.

A study by the National Institute of Mental Health concluded that a significant portion of patients treated with antidepressants for MDD do not achieve remission (2020). Less than a third of patients had achieved remission even with the use of four different antidepressant medications by 12 weeks of therapy, with only 33% achieving remission of symptoms with continued treatment for a full year (Strasburger et al., 2017). Gautam et al. (2017) describe this same struggle with treatment failure and call for the development of new therapies to address the failures of current options. With approximately two thirds of MDD patients failing to achieve remission of symptoms, a huge number of people are living with unmet mental health needs and the need for new and more effective treatments is urgent (Jilka et al., 2019).

Potential Roles of Ketamine

A lack of evidence-based guidelines in the clinical care of TRD is a likely contributor to the poor rates of successful treatment in MDD (Pandarakalam, 2018). With no such standards

available, each clinician is left to their own personal experience and judgement to decide what to do when patients fail treatment. In his review, Pandarakalam emphasized the need for further quality research based on clear and justifiable rationale to establish guidelines that meet the criteria of evidence-based medicine for TRD. This gap in treatment standards presents a potential role for ketamine. Joanna Szarmach and her colleagues found the antidepressant effects of ketamine and esketamine to be well established in the growing body of evidence, including efficacy in TRD and rapid reduction of suicidal ideation (Szarmach et al., 2019). They assert that ketamine and esketamine warrant consideration for patients who fail to achieve sustained remission of depressive symptoms with monoamine antidepressants.

The need for fast and effective treatment options to increase safety of patients with suicidal ideation or suicidal behavior is another area ketamine holds promise. MDD increases the risk of death by suicide, making the need for safe treatments with rapid onset of therapeutic effect critical (Nemeroff, 2018; Strasburger et al., 2017). Anti-suicide interventions may be most effective in emergencies when clinical decisions must be made quickly and often without known patient history (Zhan et al., 2019). The rapid-onset effect of ketamine offers potential as a bridge therapy for patients as they wait for first-line antidepressants to take effect (Malhi et al., 2016).

Ketamine's safety has been demonstrated in its use in both adult and pediatric populations. Though the majority of studies on ketamine refer to its use in the adult population, it has been used with pediatric patients for years. Bhutta (2007) illustrates some of its current applications in anesthesia and analgesia, with potent sedation, short duration, amnesia, and without causing hemodynamic or respiratory compromise. Low-dose ketamine infusion during and after surgery can improve analgesia with minimal adverse effects (Golembiewski, 2017).

Ketamine also offers potential for acute pain management in the emergency care setting (Reynolds, 2017) and treatment of bipolar disorder/fear of harm phenotype in pediatric patients (Papolos et al., 2013).

Ketamine's applications and clinical benefits in the treatment of depressive disorders are being recognized by many in the medical community. In 2019, the U.S. Food and Drug Administration (FDA) approved Spravato (esketamine), a nasally administered enantiomer of ketamine, for breakthrough and fast track status. Tiffany Farchione, M.D., acting director of the Division of Psychiatry Products in the FDA's Center for Drug Evaluation and Research, said "There has been a long-standing need for additional effective treatments for treatment-resistant depression, a serious and life-threatening condition" (U.S. Food and Drug Administration, 2019). Despite clear therapeutic uses for ketamine therapy, legal and public acceptance of therapeutic ketamine has been slow to develop. Reservations regarding ketamine therapy may be due to its historical context.

History of Ketamine

In the 1950s, the healthcare industry was looking for a rapid anesthesia drug with minimal side effects for surgical procedures. Adnan Bhutta (2007) chronicles the history of the first compounds created to fill this need as coming from the pharmaceutical company, Parke-Davis. They created a class of drugs they called cyclohexylamines, from which they selected phencyclidine (PCP) for initial testing (Bhutta, 2007; Mion, 2017). Bhutta detailed that PCP was not ideal due to severe and extended psychotomimetic response in most patients. In 1962, Parke-Davis synthesized ketamine, a PCP derivative with shorter duration and less adverse effects. Georges Mion (2017) reported ketamine was first marketed in Belgium for veterinary use

in 1968. Mion continued, stating the FDA did not approve the medication for human consumption until 1970, at which point the first commercial brand, Ketalar, came into use. Adnan Bhutta (2007) wrote of the widespread acceptance of ketamine in healthcare with its potent anesthetic and analgesic properties, quick action, and safe respiratory and hemodynamic profiles. Ketamine was introduced into the pediatric population with its proven safe profile, as well as veterinary medicine, and battlefield emergencies. Ketamine quickly became the most widely-used anesthetic in the Vietnam war (Denomme, 2018).

After the war, ketamine used throughout the conflict found its way into illegal use in the many countries it had been distributed (Mion, 2017). One of the most notable side effects of ketamine is its psychoactive property, which consequently led to its abuse and designation as a schedule III drug in the U.S. (Bhutta, 2007). Han et al. (2016) depicted ketamine as one of the most abused drugs around the world and the third most common in Taiwan and China. Several countries have implemented laws to restrict illicit use, possession, manufacturing, and distribution of ketamine, with many establishing lengthy prison sentences for offenders (Han et al., 2016; Mion, 2017).

Pharmacology

Though ketamine is an old drug, its mechanism of action is still actively being researched. By 2007, Bhutta discussed that ketamine was widely known to be an N-methyl D-aspartate (NMDA) receptor antagonist, a pathway of the glutamatergic excitatory system. The action of ketamine blockade on NMDA receptors reduces the frequency of channel opening when given at low doses, and additionally blocks open channels at higher doses. Bhutta recognized there was a growing recognition of other receptors being involved, such as nicotinic

acetylcholine, D2-dopamine, serotonin 5-HT2, adrenergic, muscarinic, and opiate receptors. He also points to anti-inflammatory effects caused by nuclear factor kappa B suppression resulting in decreased tumor necrosis factor, interleukin 6, and interleukin 8 levels.

Currently, Wei et al. (2020) discussed the advances in our understanding. NMDA receptor antagonism results in a disinhibition of pyramidal cells, sharply increasing glutamatergic activity, but antidepressant effects fail to materialize unless followed by activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. This shows why NMDA antagonists other than ketamine have failed to show antidepressant effects. Monoaminergic system involvement continues to be explored and shows conflicting data. Rapid production of brain-derived neurotrophic factor (BDNF) has been shown to be necessary for rapid antidepressant effects (Strasberger et al., 2017), with subsequent tropomyosin receptor kinase B (TrkB) activation shown to also be necessary (Wei et al., 2020). Wei et al. (2020) found the long-lasting antidepressant effects appear to rely on the BDNF-TrkB cascade. Further areas of potential importance they identified with currently conflicting or insufficient evidence include mammalian target of rapamycin complex 1 and extracellular-signal-regulated kinase receptors, low-voltage-sensitive T-type calcium channels, opioid receptors, Transforming growth factor β1, and the brain-gut-microbiota axis. This wide array of potential mechanisms, especially considering the varying effectiveness of (R)-ketamine, (S)-ketamine, and (R,S)-ketamine on different subtypes of depression, demonstrates that there is still much room for growth in the understanding of depression and it's treatment.

While ketamine's cellular pharmacologic effects are still under investigation, some alternative methods are being used to measure its psychological and systemic effects. Reed et al.

(2018) used functional MRI in a double-blind study to measure the effects of ketamine on the brain in individuals with MDD versus a healthy control group. They went on to report that ketamine has shown signs of stabilizing the emotional and attentional processes of the brain.

In clinical findings, Mandal et al. (2019) demonstrated ketamine's substantial antidepressant effect. In their study, six doses of IV ketamine were given over two weeks. The participants reported significant improvement of depression and anxiety within the first hour of receiving the first dose. Therapeutic effects persisted beyond 1 month after the last infusion. Adverse effects were transient, lasting less than one hour. This study supports findings that in addition to rapid onset, the therapeutic effects of ketamine can be long lasting and may continue to be effective for months post infusion (Witt et al., 2020).

Rapid onset of therapeutic effect differentiates ketamine from current antidepressant treatments, offering the advantage of near-immediate relief from depression and suicidal ideation (Strasburger et al., 2017). The gap between initiation of current antidepressant medications and onset of therapeutic effect leaves many MDD patients at risk of suicide (Mandal et al., 2019; Zhan et al., 2019). This evident transient antidepressant effect could be greatly beneficial to patients being treated for MDD, instead of waiting for several weeks to months for traditional first-line antidepressants to work (Nemeroff, 2018). Ketamine's rapid-onset offers a promising treatment for these patients (Strasburger et al., 2017).

Safety and Side Effects

Discovering how ketamine works with the body's chemistry is of little importance unless it is also shown to be safe. Fortunately, ketamine's use for over half a century has allowed for thorough documentation of its safety profile. Ketamine's side effects must be considered against

the side effects known to be caused by other depression treatments when choosing between therapeutic options.

In an effort to identify the most intolerable aspects of current antidepressant medications, Ashton et al. (2005) explored why patients were noncompliant with prescribed treatments for depression. They asked patients currently prescribed SSRIs, monoamine oxidase inhibitors (MAOIs), and SNRIs for the most common reasons why they stopped taking their medication. Reasons given included anxiety, lack of efficacy, troubles remembering to take the medication, weight gain, anorgasmia, lack of interest in sex, troubles having an erection, and loss of energy. These symptoms may strain relationships, potentially worsening symptoms of depression. This data illustrates that side effect profiles of medications currently considered the standard of care often diminish quality of life more than the depression itself for many patients.

In addition to rapid and sustained therapeutic effect, evidence supports the safety of short term ketamine therapy for MDD when used appropriately and within the limits of studied parameters (Szarmach et al., 2019). Nemeroff (2018) explained that when adverse events occur, it is usually with very high doses given for prolonged periods of time and relieved with cessation. Corriger & Pickering (2019) found in their literature review of several meta-analyses, that ketamine demonstrated good safety and tolerability profiles at low-doses and with short term treatment in studies versus placebo or other comparators and as an adjuvant before ECT. A review by Short et al. (2020) lists potential side effects of ketamine such as hallucinogenic or dissociative effects, urinary tract symptoms, liver toxicity, cognitive changes, and potential for dependence. Findings by Han et al. (2016) included some patients experiencing reduction of

frontal gray matter, tachycardia, increased cardiac output, hypertension, changes in liver function, changes in bladder function, and respiratory depression related to ketamine use.

Each individual ultimately has the choice whether or not to take a medication, but, as emphasized by Kraus et al. (2019), the significant proportion of MDD patients who are diagnosed with TRD have an ongoing risk for decompensation and suicide without viable treatment options. They reported findings that ketamine therapy had significant transient side effects including dissociative symptoms, floating, tachycardia, hypertension, increased irritability and anxiety, impaired vision, and nausea, but at subanesthetic levels these were well-tolerated. Grunebaum et al. (2017) also found that the side effects of ketamine are usually minimal, and do not last longer than a couple of hours.

Obstacles to Ketamine's Implementation

Ketamine holds promise as a therapeutic treatment option for individuals with depressive disorders, yet faces some unique obstacles with implementation. Jilka et al. (2019) discussed reasons individuals may be reluctant to accept ketamine as a viable treatment option, such as its psychoactive effects and history of abuse as a street drug. They also discuss reluctance among healthcare providers due to a lack of wide accessibility, the potential to be addictive, it is often not covered by insurance, and it may be misused if not administered by a trained health care provider. They posited that decreased access and availability to ketamine therapy perpetuates the stigma in which these restrictions were founded.

When the FDA approved Spravato (esketamine), they applied caveats such as conditional availability due to "the risk of serious adverse outcomes resulting from sedation and dissociation caused by Spravato administration, and the potential for abuse and misuse of the drug" (U.S.

Food and Drug Administration, 2019) Distribution of esketamine was only allowed through their Risk Evaluation and Mitigation Strategy system and IV ketamine was notably excluded from their announcement, leaving the use of IV ketamine infusions for depression considered off-label. Insurance companies and the treatments they cover are different for each company, though searches of multiple companies, such as Aetna and United Healthcare, all suggest a lack of coverage.

Aetna (2020) stated on their website that they consider all forms of ketamine experimental when use for generalized and social anxiety disorders, depression, or substance use disorder. They claim that clinical value has not been established for these indications. Aetna is not alone in its position on ketamine infusions. United Healthcare's policy claims ketamine injection is investigational and not medically necessary for psychiatric disorders, chronic pain, or migraines (United Healthcare, 2020).

Gatekeeping by insurance companies in the approval and coverage of ketamine infusions is a substantial financial barrier to accessing ketamine as an option for most patients. Until the FDA recognizes IV ketamine as a treatment for depression, many patients are forced to pay for treatments out of pocket. A survey performed by Jilka et al. (2019) found that if patients were prescribed ketamine for long term use, some patients would consider purchasing ketamine illegally if it was cheaper, illustrating that the cost of ketamine could become a barrier to prescribing.

Another concerning factor for the use of ketamine is the potential for abuse and addiction. Ketamine is a powerful medication and so it is of little surprise that ketamine became a popular drug outside of the medical field. Society has long known humans are prone to

addictive behaviors, especially when it comes to substances that can alter one's thoughts and perceptions of life. Illicit use of ketamine led it to be compared in the minds of many to PCP as a drug of abuse, which ironically was the anesthetic agent ketamine was created to replace (Denomme, 2018). The U.S. Drug Enforcement Administration (DEA) describes ketamine as addictive and harmful, similar to PCP and other hallucinogenic substances such as mescaline, LSD, GHB, and rohypnol (Drug Enforcement Administration, 2020). The DEA portrays these substances as dangerous drugs of abuse and makes claims about the physical and social dangers of ketamine, including that it is used in facilitating sexual assault (Drug Enforcement Administration, 2017).

These barriers have not stopped ketamine's use for the treatment of depression, however. In 2018, there were an estimated 60-100 ketamine clinics in the U.S. (Nemeroff, 2018). A search of Google Maps (*Google Maps*, n.d.), showed the state of Utah alone has a total of thirteen clinics listed as currently offering ketamine infusions with an unknown number not listed.

An article written by Jilka et al. (2019) looked into biases that can affect ketamine being used as a treatment option for MDD, by using a mixed-methods study. They shared, "Most participants agreed that a psychiatrist should prescribe ketamine, or in some instances a GP, providing their knowledge of ketamine was sufficient" (p.4). Jilka et al. would conclude that many of the participants would prefer a psychiatrist begin the treatments, and if the patients tolerated the infusions well, then the care could then be transferred to their primary care provider, preferring they had formal education on ketamine's use and prescribing. (Jilka et al., 2019)

Ketamine's Comparison to Other Substances

Legal Psychoactive Substances

Many substances influence a person's state of mind, though not all as profoundly as ketamine. As Greisen et al. (2019) describe in their research, alcohol, nicotine, and caffeine are examples of psychoactive substances that can be purchased and used recreationally, even being celebrated in many ways in societies around the world. They go on to discuss that U.S. advertising for nicotine is restricted by the FDA and the substance carries a more negative perception, whereas advertising for alcohol products are only limited by voluntary standards self-applied by the industry. This means they are essentially unregulated, which is why advertisements are commonly seen in the U.S. making them appear appealing and beneficial in their effects. Some brands are even considered "youth brands" as their advertising content targets younger people and results in frequent use by minors. Thorlton and Colby (2017) lay out a similar picture where caffeinated drinks are openly advertised to children despite harmful consequences. They explain that the FDA has difficulty monitoring or controlling the levels of caffeine included in such beverages as it is up to the manufacturer to choose whether their product is considered a dietary supplement or a nutrition product, each with varying labelling requirements and with vague rules regarding proprietary blends. Reporting of adverse events is mandatory for dietary supplements, but is voluntary for nutrition products, creating a loophole for manufacturers.

Cannabis is currently going through a transitional phase in U.S. culture. It has been legalized for recreational use and sale in many states, decriminalized in others, and nationwide public perception is changing to a more favorable view despite its continued designation as a schedule I substance by the federal government (McGinty et al., 2017). The DEA defines

schedule I substances as those considered to have high potential for abuse, no accepted medical use, and a lack of accepted safety for use under medical supervision (Drug Enforcement Administration, 2020). Schedules II through V are controlled substances considered to have some risk of adverse effects or addiction but are allowed by the DEA to be used medically for their benefits. Scheduled substances are usually only obtainable through a prescription and are always tracked by the DEA (Drug Enforcement Administration, 2012).

Social, political, religious, and moral conceptions color the ways in which individuals see the world. This becomes an issue when drug policy officials allow moral frameworks to displace scientific ones. As described by Kathleen Frydl (2019), dogmatic characterizations of substance use and addiction as *evil* are commonplace in the U.S. legal system, at times serving as a form of moral credential for politicians without regard to real objective evidence. Frydl goes on to illustrate how this rhetorical sleight-of-hand can apply to other venues of health. Venereal diseases, for instance, are caused by pathogenic organisms when considered from a scientific viewpoint, but could be portrayed to result from sexual promiscuity when viewed through the lens of religious morality. With this in mind, it isn't hard to see why alcohol, statistically the drug with the most harmful and least beneficial effects, is widely viewed from a positive perspective (Nutt et al., 2010; Morgan et al., 2013). Alcohol is comfortably couched in the culture of most societies, with the concept of a drinking culture being completely absent in historical societies, which instead accepted alcohol use and abuse to be a part of life instead of a social problem (Beccaria, 2015).

This perspective of alcohol use may provide the simplest explanation to how a substance can gain a positive reputation: it merely must be experienced and enjoyed by enough people in a

society that attempts to restrict it will not be tolerated. History shows that most attempts to outlaw alcohol use will be met with disapproval of the population who enjoy its use. Such legislation against the will of the populace is likely to encourage the formation of criminal organizations who will accept the risk of legal consequences in order to capitalize on the financial opportunities of supplying the newly created demand (Beccaria, 2015). Even modern legal policy fails when it doesn't adequately satisfy the desires of the populace. Simon Cohn (2016) put it this way when discussing the difficulties faced by policymakers in England:

> Although effective policies were supported in the abstract, specific proposals were consistently rejected because they were not thought to map onto the fundamental causes of excessive drinking, which was not attributed to alcohol itself but instead its cultural context. Rather than being influenced by the credibility of evidence, or assessed according to likely gains set against possible losses, such responses were established dynamically as people interacted with others to make sense of the topic. This has significant implications for policy-makers, suggesting that existing beliefs and knowledge need to be taken into account as potentially productive rather than obstructive resources. (p. 203)

This phenomenon can be considered in reverse to explain the societal resistance to ketamine or other promising psychedelic substances being studied. Social and political contexts are being used by policymakers to restrict the use of objectively beneficial therapies in favor of subjectively negative perceptions. What must be considered is why those inaccurate perceptions would be used to justify limitations of freedom on the individual and, more absurdly, to stifle the

development of promising new therapies which have the potential to eliminate suffering and increase social functioning of those with depression.

Illicit Psychoactive Substances

Ketamine is often considered an illicit drug alongside other drugs of abuse. The DEA website lists *drug facts* for various substances, though the information is without citation and the sources for their information is absent. This raises concern for the validity of the information, especially when it often deviates from scientific research, such as in the cases of LSD and psilocybin, which both have death listed as a potential side effect (Drug Enforcement Administration, 2020). According to the National Center for Biotechnology Information fact page for LSD, there are no known cases of death from overdose and the lethal dose in humans is estimated to be 0.2-1mg/kg (2020b). The standard dose of LSD is approximately 0.1mg, so for the average 70kg person, the minimum expected lethal dose would be 14mg, or 140 doses, with a likelihood that it could be as much as 700 doses.

Psilocybin has a similar profile, identifying behavior in uncontrolled settings to be the greatest health risk (National Center for Biotechnology Information, 2020a). Though no human lethal dose is given, the LD50 of psilocybin for mice is listed as 285mg/kg. An average dose of psilocybin is approximately 15mg, which would equate to 1,330 doses to reach the LD50 in a 70kg human. A person would have to consume about 3.2kg of dried psilocybe cubensis mushrooms to reach such a level.

With the remarkable safety profiles of LSD and psilocybin, safety is unlikely the reason for outlawing them. Rather, historical accounts trace the origins of the “war on drugs” to Richard

Nixon's desire for a villain to unite the public against the counterculture of the 1960s and to distract from his growing accumulation of political scandals, both of which threatened his reelection (Davis & Minutaglio, 2018). Political and social perceptions likely continue to play a decisive role in the prohibition of many substances, but when the powerful mind-altering effects of ketamine are considered an adverse or side effect, perhaps one of the major benefits it provides is discounted.

Dakwar et al. (2014) found in their research investigating ketamine use in the treatment of cocaine addiction, that higher scores on Hood's Mysticism Scale (HMS) mediated the desire to quit cocaine use. Peter Hendricks (2018) proposed that the psychedelic-occasioned mystical experience elicits a profound sense of awe, defined as "a discrete emotion experienced in the presence of a vast stimulus requiring accommodation of mental structures" (p. 331). He elaborates that this feeling of awe promotes the construct of the "small self," meaning it leads one to a decreased sense of ego and a greater feeling of unitive experience with others. He argues that the psychological effects of the experience are a major facilitator of the beneficial impact. This idea of the enhanced empathy of those who have had a psychedelic experience may explain some of his earlier findings with colleagues. Hendricks et al. (2018) explored data on 480,000 prisoners within the U.S. criminal justice system who had completed the National Survey on Drug use and Health from 2002-2014. They found that classical psychedelic use at any time in an individual's life was associated with reduced rates of antisocial criminal behavior such as violent crime and theft. The benefits of psychedelic substances appear to extend beyond the individual, helping them function in the larger society.

Harms Versus Benefits

As the Swiss chemist and physician Paracelsus said, “All things are poison and nothing is without poison; only the dose makes a thing not a poison,” establishing the basic principle of modern toxicology (American Chemistry Council, 2020) This is often shortened to “the dose makes the poison,” elucidating that all substances have the potential to be either beneficial or harmful, it is merely required that consideration be given to the effects they have and the dosage at which useful effects are harnessed and undesired effects are minimized. This principle is well illustrated by the widespread medical use of opioids and amphetamines as prescription medications while heroin and methamphetamines rank as some of the most harmful street drugs (Nutt et al, 2010).

Restricting substances like ketamine to use only by medical professionals trained in its proper administration will continue to be a challenge requiring modification of societal approaches to how substance use, abuse, and addiction are regarded in both legal and medical venues. Morgan et al. (2013) surveyed current users of various drugs and had them rate their experiences with each drug. The drugs were classified into groups, and then ranked by benefit to harm. Ketamine fell under the high benefit, low harm category, ranked fifth as a drug of choice, and ranked high on benefits for an individual’s state of mind, enjoyment and pain relief. Ketamine was ranked eighth overall in terms of harms, higher than the two types of cannabis and ecstasy, which appears to be a result of higher ratings on measures of craving, bingeing and long-term physical risk, concurrent with recent reports of dependence on ketamine.

Negative views of ketamine may be unwarranted when its benefits and harms are examined through the lens of objective scientific evidence. In a report by Papolos et al. (2013),

researchers discovered in patients six to nineteen years of age, “Ketamine administration was associated with a substantial reduction in measures of mania, fear of harm, and aggression. Significant improvement was observed in mood, anxiety, behavioral symptoms, attention/executive functions, insomnia, parasomnias, and sleep inertia. Treatment was generally well-tolerated” (p. 431). Zhan et al. (2019) likened the benefits of ketamine treatment to electroconvulsive therapy (ECT), with both treatments decreasing suicidal thoughts but with ketamine offering fewer neurocognitive side effects. Mandal et al. (2019) found patients reporting relief of suicidal ideation still present one month post-infusion.

Management Strategies

Education on Ketamine Therapy

As stated by Jilka et al. (2019), patients would prefer someone familiar with ketamine to prescribe it as a treatment. Educating providers as well as the patients on how ketamine works, common side effects, and benefits would help people overcome some of the biases they previously had of this medication. Fear of the unknown can explain much of the reluctance to use ketamine for the treatment of depression. Skepticism will persist for both provider and patient unless viable and credible evidence that ketamine is a safe treatment for MDD is available.

Further Research on Bias

Further research on bias should explore both patient and provider attitudes. Qualitative investigation of patients and families affected by MDD and current or potential ketamine

recipients through interviews and questionnaires would help reveal previous biases patients may have of ketamine and further explore societal stigma. The interviews would provide an opportunity to see if religion or social class affects the decision of receiving ketamine infusions for MDD. Obtaining a general census of local providers' knowledge of ketamine and its uses would be beneficial in looking into biases of prescribing ketamine. How familiar family practice providers are with ketamine may be of note, as it is more commonly used in surgery or emergency departments.

Integration of Ketamine Therapy into Treatment Guidelines

As the body of knowledge regarding ketamine treatment of MDD evolves, further understanding of therapeutic indications, dosage, and timing will help guide the development of treatment guidelines for ketamine. These studies can help in moving ketamine through the process of becoming a verified treatment by the FDA.

Discussion

Reducing Bias

Awareness of inherent bias is the first step to lessen the influence that bias can have upon one’s actions and interpretations of the world, as an unknown problem can not be addressed. It is disingenuous to expect for bias to be completely eliminated. It is more realistic and effective to expect that one will have biases, to be as aware of them as possible, and to take actions to lessen the effects of the bias.

With new scientific finding comes changes in understanding, and thus elimination of preconceived judgments or ideas. Bias is minimized when societies use results of scientific findings and evidence with credible sources to shape policies. Bias can be difficult to identify, however, when individuals or companies deceive others for financial gain. One example of this deception is the pharmaceutical company, Purdue, misrepresenting the dangers and addictiveness of opioids (Van Zee, 2009). Purdue has been fined over $8 billion for deceptive and illegal marketing of Oxycontin, which contributed to the current U.S. opioid crisis and the deaths of over 450,000 Americans since 1999 (Hoffman & Benner, 2020). This illustrates the importance of diligent investigation and research from independent sources free from conflicts of interest.

Another way to decrease bias is to consider a different perspective. References and sources of information which differ from one's own opinions and experiences must be sought and considered. Once all views are considered, reflection upon the different perspectives and experiences can be done and then the implications of the information can be determined.

Prioritization of self care and emotional health is also important in overcoming bias. Van Ryn (2016) states:

> Converging lines of research suggest that self-care and emotional regulation skills are crucial to providing high-quality, unbiased care. Studies have shown that when people have sufficient motivation, resources, information, time and awareness to be mindful, their judgement, behavior and decision-making are much less likely to be undermined by implicit biases. However, when illness, fatigue, stress, anxiety or competing demands command more of their mental resources, their cognitive processing capacity may be

> compromised, allowing implicit biases and attitudes to hijack perceptions, expectations and evaluations of patients. (Van Ryn, 2016)

Bias does not exist only on a personal level, but infiltrates many of our societal infrastructures. An overhaul of the U.S. schedules of controlled substances with an emphasis on rational use of scientific evidence and a stringent elimination of financial, religious, and political bias would allow for a clearer, unencumbered understanding of what current evidence supports (Morgan et al., 2013; Nutt et al., 2010). As society decreases the bias against ketamine and other therapeutic measures that are clinically supported by evidence, progress can transition away from criminalization of substance use. Criminalization policies are harmful, ineffective, and perpetuate bias, so efforts should be made to transition to harm reduction models of substance use with increased access to treatment for addiction (Beccaria, 2015; Koh et al., 2018).

Areas for Further Research

With the mechanism of action of ketamine not yet completely understood, and with the accessibility and acceptability of ketamine still growing, there are many opportunities for further research involving it. With a quick onset of therapeutic effect, ketamine poses the following possibility: Could ketamine be used as an interim rapid, short-term relief of suicidal ideation while patients are waiting on therapeutic effects of first-line treatments? (Witt et al., 2020, Corriger & Pickering. 2019). Until first-line antidepressants take therapeutic effect, can high risk or actively suicidal patients be temporarily stabilized with ketamine? (Mandal et al., 2019). Szarmach et al. (2019) supports this potential therapeutic use for ketamine, saying "The unmet need for improved pharmacotherapies for TRD means the use of ketamine and esketamine is warranted therapeutic option in patients who fail to achieve a sustained remission of depressive

symptoms with drugs with monoamine-based mechanisms of action" (p.1). Zhan et al. (2019) further supports this potential use of ketamine, suggesting it as possible approach for providing patients that are at high risk for suicide with a rapid-onset antidepressant effect. "It matters especially because anti-suicide interventions may be most effective in emergencies, and quick clinical decisions must be made, even in the absence of diagnosis and treatment history" (p. 210).

Though ketamine's safety in short-term and low-dose treatment is becoming established as safe, there remains a need for further research and evidence on the long term effects and safety of ketamine therapy (Jilka et al., 2019). There is currently little information and research involving high-dose or long-term administration of ketamine for treatment of MDD (Corriger & Pickering, 2019). Before ketamine is to be considered as a long-term therapy for TRD, its safety with long-term use must be determined.

Further research and more clinical trials are necessary to determine if sustained relief of suicidality can be achieved with ketamine therapy (Witt et al., 2020). Low-dose ketamine is currently known to have a transient effect in treatment of MDD. More information is needed regarding the efficacy of long-term and repeated infusions of ketamine (Nemeroff, 2018).

Additionally, an area of need for further research is the discovery of new antidepressant therapies. Kraus et al. (2019) described ketamine as "arguably the most significant development in psychiatry during the past few decades. The paradigm-shifting nature of the rapid antidepressant response to ketamine in patients was a significant breakthrough in neuropsychopharmacology and a turning point in antidepressant research" (p. 2033). Pandarakalam (2018) describes how new biological understandings of depression are developing, with new possible antidepressants emerging, including antidepressants that are not

monoamine inhibitors. These new antidepressants help to prevent the trigger of stress hormones associated with depression (Pandarakalam, 2018, p. 281).

Conclusion

Depression has an extensive impact on quality of life, both for patients who suffer from it and those around them. Finding effective tools to combat this condition should be considered of urgent importance. Ketamine therapy stands to be one such tool, offering immediate relief of acute suicidal ideation and depressive symptoms from a single treatment. Such a profound improvement in the treatment of a serious condition should be an acceptable, accessible treatment option.

No amount of data, evidence, and educational material can change the minds of those who do not base their practice on evidence. This often seems to be how the U.S. Controlled Substances Act operates, with a paucity of evidence for many of the substances it categorizes and controls. More objective methods for the assignment of substances to control categories should be developed, as the current method harbors an unacceptable level of discrepancy between existing evidence and substance assignment. Policy must be examined through an objective scientific lens with more effective methods for updating the laws.

For the Family Nurse Practitioner, it is our responsibility to be aware of the best evidence-based treatments we can provide for our patients. We must strive to maintain awareness of new therapies and advocate for our patients whose quality of life we may improve. It is imperative that we use our knowledge, skills, and position as leaders in healthcare to be involved in the legal process and eliminate barriers that condemn our patients to unnecessary suffering.

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