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Ketamine in the Treatment of Depression

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Abstract

Introduction

Depression is one of the most common mental illnesses. Over the course of a lifetime, several percent of the adult population suffers from depression. There are many treatments for depression like pharmacotherapy and psychotherapy. In this article, we wanted to focus on the effectiveness of ketamine in treating depression.

Aim of study

The study aimed to summarize the available knowledge on the use of ketamine in the treatment of depression. The epidemiology, etiology, side effects, and treatment methods, were summarized and described.

Materials and method

The literature available in the PubMed database was reviewed using the following keywords: "Ketamine"," Depression", and "Antidepressants".

Conclusion

Without a doubt, ketamine has proven to be a new advocate for mental health research and therapeutics. After over half a century without novel targets for MDD (Major Depressive Disorder) treatment, the observation of ketamine's rapid antidepressant effects in treatment-resistant depression has become a promising field that could represent a breakthrough in the understanding of MDD, and the possibility of reducing some of the major personal and global burden that depression is responsible for. It seems imminent then that a new era of different

acting antidepressant strategies is upon us, and it is our responsibility to make a critical analysis of the potential benefits and harm inherent to novel therapeutics.

Keywords: Ketamine, Depression, Antidepressants, Psychiatry.

Introduction

According to epidemiological datasets, major depressive disorder is the second highest cause of disability worldwide [1]. Globally, approximately 322 million people are living with depression [2]. Major depressive disorder (MDD) can occur up to 20% over a lifetime [3]. The main manifestations during an episode include feeling sad, empty, or unhappy for most of the day; loss of pleasure in things that previously made you happy; sleep disturbances; exhaustion and lack of energy; changes in appetite; suicidal thoughts and tendencies; cognitive disturbances; and somatic symptoms. Major depressive disorder is diagnosed based on the existence of one or more episodes of major depression, with no manic or hypomaniacal symptoms. It is also referred to as “unipolar depression” [4]. The pathophysiology of depression is not fully elucidated. The contribution of many factors that may contribute as targets for therapy is presumed [5]. Over the decades, several theories have been put forward on the pathophysiology of depression, one of the best studied being the monoamine hypothesis of depression, which indicates disorganization of the 5-hydroxytryptamine (5-HT, serotonin), norepinephrine, and dopamine systems [6]. Over the past several decades, research on the use of subanesthetic doses of intravenous (IV) ketamine in the treatment of major depressive disorder (MDD) and treatment-resistent depression (TRD) has earned interest among researchers [7]. Ketamine is mainly used as an anaesthetic, but there is evidence of its rapid antidepressant effect at doses lower than those that are predominantly used for anaesthesia (e.g., 0.5-1.0 mg/kg administered by infusion over 40-60 minutes). Hence, there is increasing interest in its use for treating depression [8].

Defining depression

We can diagnose major depressive disorder (MDD) when for two weeks, patients have symptoms such as mood swings and lack of feeling pleasure from things that used to make

them happy [9]. The main symptoms of depression include low self-esteem, guilt, fatigue, and sleep problems, among others. Also, people suffering from depression may have cognitive impairments that affect their daily functioning. Depression may have an increased risk of comorbidities such as hypertension, and diabetes [10]. Notable people with MDD that do not react to treatment and are assumed to be patients with treatment-resistant depression [11]. We can say that treatment-resistant depression (TRD) is when patients do not experience improvement in their mood after being treated two or three times with antidepressants at the appropriate dose [12]. The major antidepressants unfortunately have their restrictions related to their mechanism of action, which contains mostly monoaminergic neurotransmission and a later start of action. In patients who have previously failed to respond to regular antidepressant treatment, ketamine has a positive effect on their mental state [13].

In the Beginning

Phencyclidine was first created in 1956 by chemists at the Parke Davis Company. Based on this, analogs were created, such as ketamine, which is much safer due to its shorter duration of action and one-tenth the potency of phencyclidine [14]. Since then, ketamine has become a popular substance as a painkiller as well as an agent used for anaesthesia. The rapid antidepressant effect of ketamine in patients with depression was reported in 2000 [15].

A Mechanism of Action

Ketamine is an arylcycloalkylamine that contains two forms of enantiomers, (S)-ketamine and (R)-ketamine, and has antagonistic effects toward the N-methyl-d-aspartate (NMDA) glutamate receptor [16]. Studies have shown that the R(-) isomer used as an antidepressant is more powerful and has fewer side effects than the S(+) isomer [14]. Katemine's antagonistic action toward the NMDA receptor results in reduced glutamatergic signalling in the brain [17]. A general theory declares that ketamine-induced suppression of tonic NMDA receptor-mediated glutamatergic intake onto GABA-ergic interneurons directs to a decrease in general inhibition, also named disinhibition, leaning the proportion of synaptic transmission toward excitation. The NMDA receptor has a characteristic role in later synaptic signalling and moderating quick antidepressant-like results that cannot be imitated by other means of altering postsynaptic glutamatergic responses [18]. The main limitation of

known monoaminergic-based antidepressants is their delayed therapeutic effect period, which is usually seen after several weeks, unlike ketamine, which exerts a powerful, fast, and relatively maintained antidepressant effect in patients with major depression [19]. Induction of brain-derived neurotrophic factor (BDNF) is one of the most common effects of antidepressants, and the ongoing therapeutic effects of these drugs affect the remodelling of neural circuits. BDNF and its related receptor tropomyosin receptor kinase B (TrkB) are thought to be essential for the prolonged effects of ketamine [20].

Use of ketamine in depression

We can speak of treatment-resistant depression (TRD) when there is no improvement in treatment after the introduction of two antidepressants such as selective serotonin or norepinephrine reuptake inhibitors (SSRIs; SNRIs) [21]. It is possible to identify some factors that may make depression resistant to treatment, including comorbid anxiety disorders and suicidal tendencies, depression at a young age, psychotic depression, long duration of depressive episodes, number of prior hospitalizations, and delayed initiation of treatment [22]. Traditional treatment of depression using pharmacological and non-pharmacological treatments takes a long time and is sometimes ineffective in contrast to the use of ketamine, which gives a fast reduction in depressive symptoms such as suicidal thoughts [23]. The first evidence of the fast and antidepressant result of a dose of ketamine alone was published by Berman and his co-workers [24]. Single intravenous or intranasal administration of racemic ketamine (usually at a dose of 0.5 mg/kg) delivers a more significant reaction within 1 hour, peaking at 4 hours and staying for up to 7 days after administration [13]. One intravenous dose of ketamine results in this improvement in depressive manifestation such as anhedonia and suicidal thoughts although the progress was quick, staying nearly 3 days [25].

Forms of ketamine administration

In addition to the racemic ketamine used to treat depression, there are other alternative formulations and delivery systems for ketamine such as subcutaneous, intranasal, and intramuscular administration of ketamine, which have been discussed in the publications with hopeful outcomes in several studies [26]. The levogyre enantiomer of ketamine (i.e. esketamine) has been approved for the treatment of depression. The intranasal route of

administration appeared to be a superior method as administering the drug in this form has become more convenient, eliminating the need for intravenous infusion sessions [27]. The advantage of esketamine in a nasal spray is also more favourable because it is safer compared to ketamine, which allows its possible use in an outpatient setting [28]. Esketamine intranasal spray can be dosed weekly or biweekly after the initial phase of administration twice a week [29]. Ketamine administered intranasally has limitations, such as decreased bioavailability, as parts of the intranasal spray are swallowed, causing it to undergo first-pass metabolism. In contrast, orally administered ketamine has a high first-pass metabolism rate, but its bioavailability is 16%. Although a small amount reaches the brain, its acceptability to patients is a distinct advantage, especially for long-term use [30]. Oral ketamine has poor bioavailability in contrast to intramuscular administration, which may indicate its lesser use in treating depression. Still, researchers recently found that in a study of 27 people with major depression who were divided into three groups receiving intravenous ketamine at a dose of 0, 5 mg/kg, intramuscular ketamine at a dose of 0.5 mg/kg and intramuscular ketamine at a dose of 0.25 mg/kg, had a 58.86%, 60.29% and 57.36% reduction in depressive symptoms as assessed by the HDRS in each group two hours after the ketamine injection, and the progress was followed for three days [31]. There is little knowledge on racemic ketamine and esketamine administered subcutaneously compared to the most commonly used intravenous protocols. Existing information on ketamine and esketamine administered subcutaneously is a hopeful alternative to TRD, showing robust efficacy and tolerability [32].

Table 1. Route of Administration, Bioavailability, and the Therapeutic Starting Dose of Ketamine Racemate [33].

Route of administration	**Bioavailability**	**Starting dose (adults)**
Intravenous (IV)	100%	antidepressant dose: 0.1–0.5 mg/kg over 40–45 minutes
Intraosseous (IO)	93%	antidepressant dose: 0.25–1 mg/kg
Oral	16%-20%	antidepressant dose: 0.5 mg/kg

Intranasal (IN)	45%-50%	antidepressant dose: 50 mg

Clinical effectiveness of ketamine

In a number of studies, scientists have shown that the commonly used ketamine has a rapid and long-lasting antidepressant effect, which has sparked interest in the subject [34]. Several clinical trials have demonstrated the efficacy of ketamine i.v. in patients with TRD. The number of participants in these studies was around 100 participants, but meta-analyses confirmed its clinical efficacy [35]. In a placebo study, hospitalized patients with major depression showed an effective mean reduction in depression severity (14 ± 12 points on the 25-point Hamilton Depression Rating Scale) 72 hours after a single ketamine infusion [36]. Intravenous therapy with ketamine and i.n. esketamine produces euphoric effects, improved mood and reduced suicidal tendencies usually lasting for 3-7 days [37]. Dosing of intravenous racemic ketamine involves administering it two to three times a week for two to three weeks, with dose titration according to tolerance. A meta-analysis that examined the efficacy of intranasal esketamine (five studies, N=774 patients) documented symptom relief in patients with TRD or having acute suicidal thoughts [38]. It has also been shown that using intranasal esketamine together with antidepressant lowers the risk of relapse by 51% among those who accomplish remission and by 70% among those who acquire a stable response to acute therapy [39]. The dosage of esketamine is to use it twice a week for 2-3 weeks at the same dose for a week and then every two weeks thereafter [40]. It has been shown that in order to maintain the short-term efficacy of racemic ketamine administered intravenously, it needs to be administered repeatedly in most cases to maintain its therapeutic benefit [41]. It was noted that intravenous ketamine administration in patients with TRD who were cared for in a community clinic at a higher dose was associated with more treatment-related adverse events compared to lower doses (i.e., 0.75 mg/kg and 0.5 mg/kg) [42]. In another study, the researchers noted that thirty-three patients had a decrease in suicidal thoughts based on the Suicidal Thoughts Scale (SSI) 40 minutes after ketamine infusion as well as after 4 hours. In

ten individuals (30%) who had a score ≥ 4 on the SSI before ketamine administration, all of these individuals had scores below 4 (9 dropped after 40 minutes, and 1 after 80 minutes) [43].

Controversies and limitations

While ketamine therapy for people with TRD is considered effective, some concerns have been noted regarding long-term treatment, safety, tolerability and the risk of developing substance use disorders [44]. The large majority of available studies on ketamine for the treatment of depression focus on its efficacy and assess less on its safety and potential for addiction [45]. The safe dose of ketamine used in anesthesiology as an anesthetic is 1 to 3mg/kg. Doses of ketamine from 0.1 to 1 mg/kg in the treatment of depression caused short-term adverse neuropsychiatric changes, neurocognitive and sensorimotor disturbances, and a temporary increase in heart rate and blood pressure [46]. The most common side effects after using ketamine in antidepressant doses include headache, dizziness, dissociation, increased blood pressure and heart rate, vision problems nausea, drowsiness and restlessness [47]. Researchers in another study also registered that the most common adverse events following ketamine infusions up to 4 hours later included dizziness, blurred vision, headache, sickness or vomiting, dehydrated mouth, lacking coordination, poor concentration and anxiety. Ketamine exhibits cardiovascular stimulation due to reduced catecholamine reuptake which results in increased heart rate and blood pressure [48]. In another study in which 205 doses were administered in 97 patients, about 30% of them noticed hemodynamic modifications such as a temporary increase in heart rate and mean blood pressure, with a mean increase in systolic pressure of 19.6 ± 12.8 mmHg and a mean growth in diastolic pressure of 13.4 ± 9.8 mmHg [49]. Seventeen percent of patients showed significant dissociative manifestation (sensation of being out of body or sensing that time passes slower or faster than normal) directly after the ketamine intake, which vanished by 2 hours after its administration [50]. The majority of studies that administered intravenous ketamine reported more psychotomimetic or dissociative side effects than studies that used the oral, subcutaneous, intramuscular route of ketamine administration. It was observed that 36% of studies that administered intravenous ketamine reported psychotomimetic side effects, compared to 72% of studies that used this form of ketamine [45]. It is worth noting that there is a chance of long-term side effects with repeated administration of (es)ketamine such as uropathy, hepatobiliary complications cognitive impairment and tolerance are observed in rodent models and in ketamine abusers

but the doses of ketamine that were used in these studies were higher than those that are mostly used to treat depression [51][52]. Limitations of ketamine in the treatment of depression also include multiple administrations, which are expensive, and some patients cannot financially afford it [53].

Risk of addiction

Ketamine is used, among other things, to reduce the symptoms of schizophrenia, severe depression as well as in the treatment of chronic pain, and also for recreational purposes, which can sometimes lead to its abuse and consequently addiction [54]. Ketamine's significant role in the treatment of mental disorders faces a serious challenge because ketamine can house toxic effects, and its abuse can provoke serious harm to some individuals and society [55]. It has been shown that ketamine and its derivative, methoxetamine, can trigger a reinforcing stimulus that can provoke self-administration and conditioned place preference in rats, by which it can be concluded that ketamine has the potential for drug abuse [56]. Ketamine has empowering and rewarding properties, making it a famous recreational drug in the “rave” context, and non-medical usage of ketamine has steadily expanded worldwide over the past several decades [57]. Chronic ketamine use can cause the positive and negative symptoms that usually occur in schizophrenia, including hallucinations, detachment, delusions, in healthy volunteers with high amounts of ketamine [58]. Ketamine in most cases is a safe drug, but its abuse can cause great harm to those who are addicted to it [59]. The rapid antidepressant effect of ketamine is an innovative method of treating depression but can lead to its abuse, so it is worth bearing this in mind when using it and introducing it in treatment carefully in appropriate doses so as not to lead to dependence on it [55].

Potential Antisuicidal Effects of Ketamine

In addition to its antidepressant effect, ketamine also has an effect on such depressive symptoms as suicidal tendencies and thoughts. It has been reported that its intravenous administration (0.5 mg/kg over 40 minutes) causes a significant reduction in suicidal tendencies 24 hours after a single dose (monotherapy) in 26 patients with TRD, according to the results of the latent association test, as well as in the MADRS suicidal tendency object

(mean decrease of 2.08 points, with 81% of patients scoring 0 or 1 after infusion). The reduction in suicidal tendencies was maintained at the same level for 12 days with the use of ketamine three times a week [60]. Another study found that ketamine uses in patients with MDD showed a reduction in suicidal thoughts (percentage of patients experiencing a 50% decrease in suicidal thoughts scale) of 55% 24 hours after intake. Ketamine demonstrated a reduction in clinically significant suicidal thoughts in depressed patients within 24 hours compared to midazolam, which is substantial in their treatment as this dangerous manifestation needs to be reduced fast to prevent a suicide attempt [61]. One potential reason for the antisuicidal effect of ketamine, may be related to a decrease in nocturnal wakefulness [62]. It was shown that in patients who made an attempt on their lives, the time taken to make the decision was about 10 minutes or less in 74% [63]. The progress after ketamine treatment is noteworthy because patients who have suicidal thoughts are mostly resistant to treatment, and those who suffer from severe depression are more likely to have an increased number of suicide attempts [64].

The future of research and clinical applications

Although ketamine plays a significant role in the treatment of depression what is increasingly being used is the non-competitive S-enantiomer esketamine ((2S)-2-(2-chlorophenyl)-2-(methylamino)cyclohexane-1-one) as a development of traditional ketamine, which has 3-4 times stronger affinity for the NMDA (N-methyl-D-aspartic acid) receptor than its R-enantiomer, arketamine [65]. Esketmine, as an NMDA antagonist, by its action generates an increased release of glutamate, which stimulates GLUR2 (glutamate receptor) which in turn improves neurotrophic signaling. This reaction has a powerful impact on brain functions that regulate feelings and mood. Intranasal use of esketamine shows that its bioavailability is about 50%. 20-40 minutes after its administration, the plasma concentration of esketamine is maximum and the average half-life (T ½) is 4-12 hours [66]. In the meta-analysis of subgroup analysis, researchers found differences between ketamine and esketamine. The efficacy results revealed a benefit for racemic ketamine. One example of why there are contrasts between the two is the biological differences between racemic and ketamine. The observed dissimilarities in efficacy may be due to the more subordinate dosage of esketamine used in the studies or the lower bioavailability after intranasal (compared to intravenous) administration. Doses for intravenous infusions are recalculated relying on what

weight the patient has, while for esketamine administered nasally, doses are fixed (28-84 mg) regardless of body weight [26].

Ketamine has demonstrated the ability to tailor therapy to individual patients' needs. It has been proven in investigations that ketamine can also be useful and safe treatment for juveniles with depression [67]. Furthermore, ketamine is effective in treating postoperative depression and pain intensity. Postoperative depression has been defined as a significant contributor to postoperative pain, lowered cognitive function, longer time spent in the hospital, and morbidity [68]. Moreover, evidence has been shown in studies that ketamine infusion can also be sufficient in treating treatment-resistant anxiety and anxiety with treatment-resistant depression (TRD). Nevertheless, there is less knowledge on this issue compared to the information available on ketamine treatment for depression [69]. Patients who have both anxiety disorders and TRD are complex to treat, as their symptoms are often more severe and they are more likely to relapse [70]. However, several small studies over a dozen years that validated the concept gradually increased interest, revealing strong evidence that ketamine-enhanced therapies helped initiate a sustained but time-limited therapeutic effect quickly [71]. Psychotherapy and pharmacotherapy show similar efficacy when used separately, while in combination they show even greater effectiveness in treating mental disorders compared to when they are used independently, especially in people with comorbidities [72]. Psychotherapy along with ketamine therapy is used as a treatment for many disorders including but not limited to chronic neuropathic pain [73], opioid dose reduction [74], major depressive disorder (MDD), generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), attention deficit hyperactivity disorder (ADHD) and substance use disorder (SUD) [75].

Conclusions

In conclusion, ketamine is undoubtedly an effective drug for the treatment of MDD (Major Depressive Disorder). Its rapid antidepressant effect is its main benefit, especially in treatment-resistant depression, where the speed of drug therapy is of paramount importance. The use of ketamine to abolish symptoms of depression should be individualized and patient centered. Longer follow-up periods of ketamine treatment are needed to understand its long-term effects better. Higher doses of ketamine are associated with more pleasing antidepressant

effects after a single session. Nevertheless, its side effects, such as headache, dizziness, dissociation, elevated blood pressure and heart rate, vision problems, nausea, drowsiness, and anxiety, should be considered. Ketamine plays a significant role in the treatment of MDD and a new era of antidepressant strategies with different effects is coming, and we must critically analyze the potential benefits and harms of new therapies.

Authors contributions

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