BRZOZOWSKA, Patrycja, BULSKA, Klaudia, SŁAWEK, Konrad, PIELA, Andrzej, PIOTROWSKI, Jan, HĄDZLIK, Izabela, BIAŁY-KARBOWNICZEK, Julia, NOWIŃSKA, Bianka, ŁUCZAK, Blanka and SŁYCHAN, Katarzyna. The effectiveness of ketamine in medication of treatment-resistant depression - review. Quality in Sport. 2024;16:52628. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.16.52628
https://apcz.umk.pl/QS/article/view/52628

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 14.06.2024. Revised: 20.06.2024. Accepted: 03.07.2024. Published: 10.07.2024.

The effectiveness of ketamine in medication of treatment-resistant depression - review

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Abstract:
In spite of the variety of antidepressant drugs available for treating depressive disorder, treatment resistant depression (TRD) is still prevalent among the population.
Despite being used mainly in anesthesia, and mostly phased out by more modern anesthetics, ketamine shows potential when it comes to depressive disorder treatment.
We've set out to investigate the the relevant body of work to determine the efficacy of ketamine usage in patients with TRD.

Research shows that usage of ketamine used in patients with TRD leads to mood elevation, better cognitive functions, sleep and appetite. Moreover, ketamine is shown to decrease suicidal thoughts and shows potential in acute actions in emergency situations, especially with its faster effects when compared to traditional antidepressants. Some research show significant reduction in suicidal thoughts after just one infusion of ketamine.
Clinicians have developed intranasal, subcutaneous, intramuscular and oral ways of administering ketamine, which, though less bioavailable, when compered to intravenous use, are much more convenient and less expensive for the patients. All those ways of administering the drug have their upsides and downsides, and theres still debate on which is best.
Ketamine shows promise in patients with TRD. Some studies show that up to 70% of people with TRD response to ketamine, which might show efficacy of ketamine usage in those patients
State of knowledge:

Despite extensive research in the field of depression treatment, there's considerable lack of comprehensive reviews of efficacy of ketamine usage in cases where traditional ways of treating depression have failed. In the face of increasing number cases of treatment resistant depression worldwide, this paper aims to gather research papers regarding this topic and synthesize it into comprehensive review.

Keywords: ketamine; treatment-resisant depression; TRD; depression; suicide.

Review methods: PubMed and Google Scholar were browsed for appropriate, useful and recent articles and books regarding chosen topic with the terms “ethics”, „suicide”, “ketamine”, “depression”, “abuse”,“misuse” and “safety”. We identified relevant medical and clinical articles through our professional networks, searched through our personal databases, through above-mentioned online databases and by suggestions from anonymous reviewers. We reviewed articles resulting from these searches and relevant references cited in those articles. Only articles published in English were included.

Introduction:

Major depressive disorder is one of the most frequent psychiatric disorders of developed countries. A variety of antidepressant medications have been discovered and widely used all over the years. However, sometimes they are insufficient in treatment-resisant depression (TRD).

Ketamine has been mostly used for anesthesia, analgesia, sedation and treatment of chronic pain syndromes - it is a rapid-acting general anesthetic and NMDA receptor antagonist used for induction and maintenance of anesthesia during medical procedures. It is commonly used in veterinary medicine, whereas the use as a main anesthetic has been minimized due to psychodysleptic side effects. Usually it is used in hemodynamically critical patients. However, qualities of ketamine have increased interest in its’ use for treatment of depression, both unipolar and bipolar [1,2]. Ketamine reverses synaptic chronic stress pathology after one day of treatment by postsynaptic glutamate activation, resulting in synaptic connectivity restoration that lasts for days or weeks.

How does ketamine affect central nervous system?

Apart from being antagonist of NMDA receptors ketamine also binds to opioid, cholinergic, muscarinic, monoaminergic and nicotinic receptors. Binding to the opioid receptors might be responsible for psychodysleptic effects, according to Hustveit et al [3]. The S(+) enantiomer affects opioid receptors 2-3 times stronger than racemic form of ketamine, thus it is being used in treatment of drug-resistant depression. Fascinating research of Williams et al. revealed that binding nonselective pure opioid receptors by naltrexone reverses antidepressant and anti-suicidal effect of one-time intravenous administration of ketamine in adults suffering from TRD [4]. Moreover, since ketamine is a muscarinic receptors antagonist it inhibits norepinephrine, dopamine and serotonin uptake, which creates the possibility to treat depression - the inhibition results in higher concentration of mentioned neurotransmitters. Studies prove that it leads to mood elevation, better cognitive functions, sleep and appetite [5,6]. Besides antidepressant effect, racemic ketamine can quickly decrease suicidal thoughts within one day and for up to one week in depressed patients with suicidal thoughts [7,8]. It might be significantly helpful in emergency acute crises.

The drug's bioavailability and it's chemical properties

Available ketamine drugs are racemic mixtures of both enantiomers. The esketamine's half life is longer than racemic ketamine - 5 hours vs 2-4 hours [9]. Ketamine is usually administered intranasally or intravenously. The target frequency with intravenous use has not been stated yet - the researchers proved no significant differences in efficacy between administration twice a month, twice per week or three times per week [10]. Recommendations state that IV ketamine should be started at concentration of 0,5 mg per kg and infusion should take 40 minutes. However, studies prove efficacy at doses of 0,5-1,0 mg per kg with no additional advantages of 1,0 mg/kg dose over 0,5 mg/kg dose [11]. Dosage of ketamine should be adjusted to weight, including increasing the dose at obese or overweight patients [6]. On the other hand, important note is that some adverse effects such as increased blood pressure were observed as dose-dependent [12]. It might be a side effect resulting from antagonizing muscarinic receptors. The intranasal doses range between 56-84 mg of esketamine or 50-150 mg of racemic ketamine twice per week. The bioavailability is 100% for intravenous ketamine and estimates at 30%–50% for intranasal esketamine. The intravenous administration is quite impractical and limiting for patients, it is also quite expensive. As a results there is the need for further research in order to find a better alternative between intranasal, subcutaneous, intramuscular and oral ways. Arabzadeh et al suggest that oral ketamine might be a successful adjuvant to sertraline [13]. Australian clinicians discovered that subcutaneous delivery route was well tolerated and repeated

treatment might result in higher likelihood of remission and longer time to relapse [14]. Intramuscular administration of ketamine alleviates symptoms of depression in a comparable way to IV [15]. Intranasal administration of S-ketamine is gaining popularity since it is well tolerated by patients, delivery route is quite comfortable and there were no reported cases of its abuse [16]. However, these patients often experience dissociation manifested by anxiet, confusion, derealization and depersonalization [17,18]. It happens more often as higher doses (86 mg) are used [19].

Is ketamine a good treatment option?

Depression is the leading cause of disability in the world, affecting nearly 300 million individuals globally. According to WHO estimates, by 2030, depression will become the most common disease in the world.

Usually, you have to wait 2 to 4 weeks for the first effects of taking antidepressants [20]. In the case of a single intravenous administration of ketamine, this time is shorter. This effect lasts for 3-7 days [21]. The minimum dose assessed in studies and meta-analyses was 0.5 mg/kg ketamine administered over 40 minutes. Lower doses should probably be considered ineffective [22]. It is important to note that current research, analysis and knowledge relates to the effectiveness of ketamine and (S)-ketamine when administered intranasally or intravenously. Ketamine is a safe and effective treatment option for patients suffering from not responding to conventional treatment and treatment-resistant depression (TRD).

It should be remembered that this is not an ideal drug that all TRD patients will respond to. Most studies have shown a 50-70% response rate in TRD.

It was proven that in the case of the group of patients treated with ketamine, where long-term observation was carried out, there were no cases of unfavorable medical effects, persistence of psychomimetic effects, addiction to psychoactive substances, which could be observed to a small extent at the beginning of drug administration [23].

Scientists reached slightly different conclusions in the case of the pediatric population. A significant study in the field of schizophrenia suggests that repeated exposure to ketamine-like drugs during development can consistently disrupt neurodevelopment and lead to severe long-term cognitive and behavioral consequences.

As one of the main prepsychotic symptoms of schizophrenia in adolescence is depression, repeated administration of esketamine as an antidepressant could pose a significant risk for at least some individuals in this highly vulnerable group [24].

A paper published in 2019 found that one short-term study showed statistically meaningful antidepressant effects of esketamine vs placebo, while a long-term withdrawal trial showed

that esketamine is significantly beneficial in terms of extending time to relapse, compared to placebo.

Repeated ketamine infusions may offer an effective, durable, and safe treatment for a clinically complex and high-risk population that has been historically difficult to treat. One study reported an 80% remission rate for posttraumatic stress disorder patients and a 93.3% response rate for TRD. In this study, they also concluded that the median time to relapse of symptoms in patients with treatment-resistant depression who responded to a series of ketamine infusions was 20 days [26]. Another study found that adding five ketamine infusions significantly increased the response rate from 13.0% to 67.5% and the remission rate from 7.8% to 48.1% [26].

Ketamine and suicide

The number of suicides in the world is constantly increasing. A particularly high risk of suicide occurs in patients suffering from treatment-resistant depression.

Based on scientific research, conclusions can be drawn regarding the impact of intravenous ketamine and esketamine treatment on reducing suicide rates.

In a randomized controlled trial [28] the impact of a single administration of ketamine, midazolam, and a psychoactive placebo substance on patients with TRD was analyzed. Twenty-four hours after infusion, clear suicidal thoughts were significantly reduced only in the group receiving ketamine. The study found that a single ketamine infusion significantly reduced suicidal thoughts in patients with TRD within 24 hours of administration. These effects persisted for at least a week in some patients. The best results were obtained in patients who exhibited heightened suicidal tendencies [28].

In a retrospective analysis of patients with TRD who received ketamine, a significant reduction in suicidal ideation was observed. This study underscored the potential of ketamine as a rapid intervention treatment for patients in a suicidal crisis.

These and other studies despite potential concerns regarding addiction suggests that the benefits of ketamine may outweigh the risks, especially in the context of patients in acute suicidal crisis [29].

Discussion:

The use of ketamine in both of the available forms of administration has shown promising results in the treatment of depression. Infusions as well as intranasal administration have been found useful clinically.

Our findings indicate that ketamine infusions significantly reduced suicidal ideation, with moderate to large effect sizes observed within one day, extending up to one week post-

administration. Patients treated with ketamine were significantly more likely to be free of suicidal thoughts at all post-infusion time points. The change in depressive symptom severity was strongly correlated with the change in suicidal ideation, accounting for 10% to 46% of the variance in suicidal ideation changes. Importantly, even after adjusting for improvements in depressive symptoms, ketamine's effects on suicidal ideation remained significant. This suggests that ketamine has a distinct impact on suicidal ideation that is only partially dependent on the overall change in depressive symptoms.These results suggest that ketamine's positive effects on suicidal ideation are promising, especially considering the limited treatment options for patients at risk of suicide. In the present study, 54.9% of patients were free of suicidal ideation 24 hours after a single ketamine infusion, and 60.0% were free of suicidal ideation one week post-infusion [29].
Alternatively to the infusions, intranasal esketamine, administered at doses of 28, 56, and 84 mg, has shown effectiveness in treating treatment-resistant depression (TRD). Evidence indicates strong and sustained efficacy during the double-blind treatment phase, particularly at the 56 and 84 mg doses. Improvements in depressive symptoms continued during the open-label phase, even with reduced dosing frequency, and lasted for up to 2 months after stopping esketamine [31].

All of the currently available data suggests that ketamine is emerging as a safe and effective treatment for treatment-resistant depression (TRD) and is gaining popularity nationwide. However, the main obstacle to its widespread adoption is the lack of education among healthcare providers and patients. Despite the availability of extensive written information on ketamine's safety and efficacy, a significant knowledge gap remains. Given the widespread internet access and the prevalence of social media in society, these platforms are revolutionizing healthcare. Social media increases patient awareness, reduces barriers to accessing reliable online health resources, encourages patients to take an active role in their health decisions, and serves as an educational tool for both providers and patients [29].

Conclusions:

Ketamine is an effective and fast-acting treatment for patients with treatment-resistant depression (TRD). It is well tolerated, with most side effects being temporary and resolving after discontinuation of the drug. It is primarily administered intravenously (IV) and intranasally (IN) due to its antidepressant and anti-suicidal effects. Ketamine is well tolerated not only as a single infusion but also as multiple subanesthetic infusions. Repeated administrations of ketamine infusions show cumulative and long-lasting antidepressant effects. Patients who respond positively to ketamine experience sustained reductions in depressive symptoms, even with once-weekly infusions. These results offer new insights into effective

dosing strategies for ketamine in individuals with treatment-resistant depression. Future research should focus on refining administration protocols to facilitate the integration of ketamine therapy into routine clinical practice [31].

Recently intranasal esketamine has been approved for use in TRD as an adjunct to oral antidepressants.Intranasal esketamine, administered at doses of 28, 56, and 84 mg, has shown effectiveness in treating treatment-resistant depression (TRD). Evidence indicates strong and sustained efficacy during the double-blind treatment phase, particularly at the 56 and 84 mg doses. Improvements in depressive symptoms continued during the open-label phase, even with reduced dosing frequency, and lasted for up to 2 months after stopping esketamine [30].

These results indicate that intranasal esketamine may provide a new treatment option for patients who are difficult to treat. The rapid onset of esketamine's action is a unique advantage over currently available antidepressants. However, concerns about sedation, dissociation, and potential misuse and abuse require that esketamine be administered in a healthcare facility where patients can be monitored for at least 2 hours after administration. Despite its intranasal administration, which could allow for self-administration, esketamine must be supervised by a healthcare provider [26].

Disclosures

Author's contribution:

Conceptualization Methodology: PB, KB, JB-K, Software: not applicable; Check: PB, KB, KS, AP, Formal analysis: PB, BN, KS, BŁ, Investigation: IH, JP, Resources: not applicable; Data curation: Writing - rough preparation: KB, IH, JP, AP, Writing - review and editing: BN, KS, BŁ, JB-K, Visualization: PB, KB, Supervision: PB, KB, Project administration: PB
Receiving Funding: not applicable
All authors have read and agreed with the published version of the manuscript

Funding Statement: This Research received no external funding.

Institutional Review Board Statement: Not applicable.
Informed Consent Statement: Not applicable.
Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article's bibliography.
Conflicts of Interests: The authors declare no conflict of interest.

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