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Review Article

Utilization of Ketamine for Major Depression

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Abstract

Major depressive disorder (MDD) continues to be a prevalent disease worldwide. While selective serotonin reuptake inhibitors and other medications continue to be prescribed, further research has been conducted toward other treatment modalities. Within the past decade, ketamine, an N-methyl-d-aspartate receptor antagonist, has been extensively studied as a new treatment for MDD. Recent studies show that ketamine at subanesthetic doses provides antidepressant effects. An extensive overview of the latest statistics of MDD and treatment plans are emphasized, with a review of current medications and their subsequent side effects. However, an important factor to consider with ketamine is dissociation, and given ketamine's psychotomimetic side effects, it must be reviewed further. Despite such side effects of hallucinations and depersonalization, studies have shown administration achieves rapid and lasting antidepressant effects. the synergistic effects of ketamine are also analyzed with recent studies to summarize the effects of different treatment modalities. A summary of the latest research studies of ketamine as a possible treatment for MDD is provided. By focusing on the evolution of ketamine as a treatment for MDD, physicians can now utilize newer techniques for depression, with better short-term and long-term outcomes for the patients.

Introduction

Major depressive disorder (MDD) is a common psychiatric diagnosis affecting millions worldwide. While monoaminergic drugs have long been the preferred method of treatment for MDD, they can often take weeks or months to provide a therapeutic effect, with many patients failing to find any relief in their depressive symptoms. Patients who have failed after two oral therapies are considered to have treatment-resistant depression (TRD). Given the high prevalence of MDD and potentially subsequent TRD, there has been a surge of interest in finding new short-acting therapies, novel to the standard methods of treatment. Ketamine was first discovered in the 1970s as an anesthetic medication but has since been extensively studied in multiple research projects. Through antagonism of the N-methyl-D-aspartate (NMDA) receptor, ketamine works to decrease hyperalgesia but has also been found to affect descending inhibitory serotonergic pathways. Research has shown that Ketamine, given regularly in a controlled manner, could be a promising potential treatment for patients with TRD and other depressive disorders, including post-traumatic stress disorder (PTSD), as it has been shown to rapidly reduce suicidality and depression in patients who have failed other therapies.

MDD and other depressive disorders have become increasingly prevalent within the United States, especially since the beginning of the COVID-19 pandemic in 2020.[1,2] Data from the National Survey of Drug Use and Health (NSDUH) reported that around 21.0 million US adults (8.4% of all US adults) experienced a major depressive episode in 2020, an increase from 16.2 million (6.4% of all US adults) in 2016.[3] Despite increased public health efforts and advancements in the field of psychiatry, there is still an increasing amount of depression without a compensatory increase in treatment response.[4] A recent study showed that this phenomenon, otherwise known as the "treatment-prevalence paradox" (TPP), was prevalent in that despite increased efforts to address MDD, the incidence of MDD diagnosis continues to rise.[4,5] The TPP strongly suggests an overdiagnosis of MDD or lack of response in treatment for MDD as the causes for this discrepancy.[6,7]

Many patients who suffer from MDD are hesitant to seek proper treatment, and those who do start taking common antidepressant medications tend to experience high treatment failure rates or minimal improvement in their symptoms.[8] Some randomized control trials (RCTs) have shown that serotonin selective reuptake inhibitors (SSRI), the current standard of treatment, were only 20–30% more effective than that of a placebo.[9] Other medications such as oral monoaminergic drugs carry a dangerous warning of increasing

Keywords: Depression; Ketamine; Anesthesiology; Psychiatry.

Abbreviations: AMPAR, amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BDNF, brain-derived neurotrophic factor; CBT, cognitive behavioral therapy; ECT, electroconvulsive therapy; mTOR, mechanistic target of rapamycin; MDD, major depressive disorder; NMDA, N-methyl-D-aspartate; SSRI, serotonin selective reuptake inhibitor; TRD, treatment-resistant depression; TPP, treatment-prevalence paradox.

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risks of suicidal ideation and behaviors. Patients must wait weeks to months to experience any form of symptomatic relief.[10] When patients are unable to respond to over two treatment regimens for their depressive symptoms, they are considered to have treatment-resistant depression (TRD) which is associated with greater levels of suicidality and higher risks of repeated hospitalization.[11–13]

Traditional pharmacological methods of treatment

The standard of care for pharmacological treatment of depression has gone largely unchanged for many years.[13] The basis of using these monoaminergic drugs ties into the pathophysiology of MDD, where levels of monoamines such as dopamine, norepinephrine, serotonin, epinephrine, and histamine are seen to be reduced. As such, the traditional pharmacological approach was to address this monoamine shortage by using pharmacological methods to increase their levels.[14] Despite initial success with this approach, there has been a large number of patients reporting no significant improvement in their symptoms, thus necessitating newer treatment methods to be considered.[15–17] With each subsequent generation, monoaminergic medications have become more tolerable, however, the targets and basis behind treatment have remained largely unchanged.[18] There is interest in research beyond the scope of the monoamine hypothesis—such as looking at other signaling cascades associated with stress responses and depressive symptoms.[18,19]

Mechanisms of action of current antidepressant treatments

Monoamine oxidase inhibitors (MAOIs)

MAOIs inhibit the activity of monoamine oxidase, which functions to break down serotonin, norepinephrine, and dopamine in the brain. By inhibiting monoamine oxidase, MAOIs increase the levels of these neurotransmitters in the brain, thus enhancing their neurotransmission. While MAOIs have been shown to have greater efficacy than subsequent generations of antidepressants, they are also much less tolerable. Major side effects of MAOIs include an increased risk of hypertensive crisis, dizziness, sexual dysfunction, and GI upset.

Tricyclic antidepressants (TCAs)

TCAs work by blocking the reuptake of both serotonin and norepinephrine but also affect other neurotransmitter systems, such as acetylcholine and histamine, thus precipitating antimuscarinic effects, including potential cardiovascular complications. Some examples of TCAs include amitriptyline, nortriptyline, and imipramine.

Serotonin-noradrenaline reuptake inhibitors (SNRIs)

SNRIs work by inhibiting the reuptake of both serotonin and norepinephrine, which increases the availability of both neurotransmitters in the synaptic cleft, thus enhancing their neurotransmission. SNRIs include venlafaxine, duloxetine, and desvenlafaxine.

Selective serotonin reuptake inhibitors (SSRIs)

SSRIs increase the availability of serotonin in the synaptic cleft by inhibiting the reuptake of serotonin in the brain, leading to subsequent increased serotonin neurotransmission. With both SSRIs and SNRIs, patients require at least 4–6 weeks to acquire any optimal effect.

Atypical antidepressants

These miscellaneous medications have different mechanisms of action that have been proven to act as an antidepressant. Some examples include bupropion, which works by increasing the levels of dopamine and norepinephrine in the brain, and mirtazapine, which works by enhancing the release of both serotonin and norepinephrine and also blocks certain serotonin receptors.

Ketamine as a treatment for depression

Mechanism of action

Discovered first in the 1960s as an anesthetic, ketamine has been extensively utilized for intraoperative anesthesiology and in acute trauma settings. Ketamine is a phencyclidine derivative, which is a compound primarily classified as a hallucinogen. Through competitive antagonism of the *N*-methyl-d-aspartate (NMDA) receptor, ketamine antagonizes the amplification of pain signals and modulates the central sensory processing of pain for analgesic effects. Higher doses of ketamine work on other receptors, including monoamine transporters, dopamine D2 receptors, and voltage-gated sodium channels. By activating other receptors, major side effects of ketamine start to take effect; primarily, hallucinations, euphoria/dysphoria, agitation, and anxiety. By inhibiting the NMDA receptors on the GABAergic interneuron, ketamine causes a large surge of glutamate activity that works to depolarize the postsynaptic neuron in releasing sodium and calcium. The subsequent ions cause the release of vesicle-filled brain-derived neurotrophic factor (BDNF) into the synaptic cleft.[20] Please see Figure 1 for further analysis of ketamine's molecular mechanism of action as an antidepressant.

Ketamine inhibits NMDA receptors primarily present on inhibitory GABAergic interneurons at lower subanesthetic doses. By inhibiting an inhibitory neurotransmitter, there is a surge of glutamate release from the increased depolarization of the presynaptic neuron, which then binds to and activates postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR). The subsequent Na+ and Ca2+ ions entering the postsynaptic cell activate the voltage-gated calcium channels, which release vesicles filled with brain-derived neurotrophic factor (BDNF) into the synaptic space. BDNF acts upon tropomyosin receptor kinase B (TrkB) to activate the MEK–ERK and PI3K-Akt signaling pathways to produce the mechanistic target of rapamycin (mTOR). mTOR acts as a facilitator of protein synthesis and is believed to play a role in neuroplasticity. The downstream protein synthesis resulting from this cascade ultimately gives rise to increased synapse generation, thought to play a role in ketamine's antidepressant effects.

Current studies showcasing antidepressant effects of ketamine

Once studies found that lower/subanesthetic doses of ketamine could provide antidepressant effects, a significant surge of interest in studying ketamine took place and has continued over the past decade or so. Ketamine can be administered by a variety of routes including the oral, sublingual, transmucosal, intranasal, intravenous, intramuscular, and subcutaneous routes. The relationship between the route of admission, dosing, timing of doses, and resulting effect is complex, given that ketamine has major effects on multiple organ systems, especially, and significantly, the cardiovascular system. Further studies should be conducted towards deciding optimal routes of administration, given that these factors are limiting for ketamine to be prescribed in an outpatient setting.[21] There is some evidence that the mechanism of Ketamine's antidepressant effects comes from downstream signaling as a result of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) activation. Studies have shown that applying an antago-

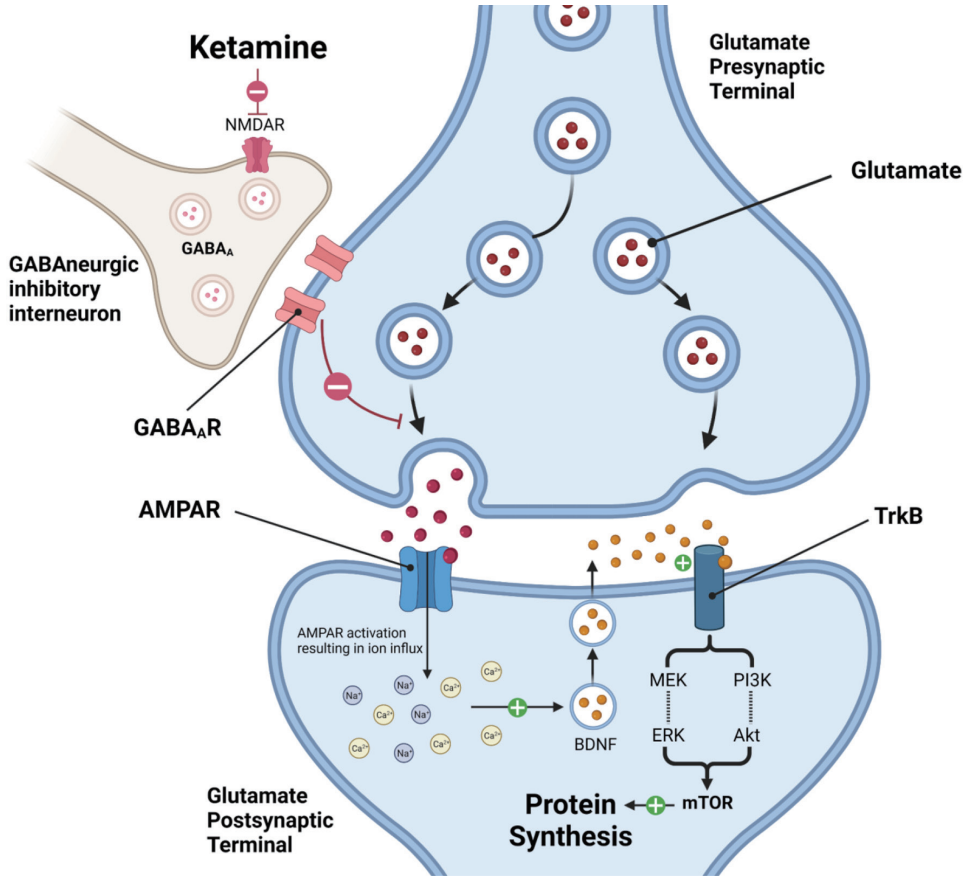

Fig. 1. Mechanism of ketamine as an antidepressant.

nist to AMPAR greatly diminishes the resulting antidepressant effect, which suggests that much of ketamine's ability to function as an antidepressant comes from the downstream effects of AMPAR activation, notably the activation of tropomyosin receptor kinase B (TrkB) resulting in the production of the mechanistic target of rapamycin (mTOR).[22]

A recent study conducted in 2011 focused on the administration of ketamine to induce antidepressant-like effects in rats. Intraperitoneal ketamine of 10 mg/kg was administered 30 minutes prior to inducing escape failures for learned helplessness and subsequent antidepressant effects. One of the controls was a specific inhibitor of the AMPA receptor to measure learned helplessness and depression by utilizing the tail suspension test. Through multiple reviews, this study concluded that the anti-depressant effects of ketamine were partially abolished in the cohort of subjects that had direct AMPA receptor antagonism, suggesting that AMPA receptor activations play a crucial role in the antidepressant-like effects of ketamine.[23]

Studies aimed at understanding ketamine's use as an antidepressant have suggested that its psychotomimetic side effects play some role in facilitating its antidepressant effects. However, because of its addictive potential and side effect profile, many providers are concerned about its long-term administration, thus necessitating further research into mitigating its psychotomimetic side effects and addictive potential. These studies suggest that the R-ketamine enantiomer is able to facilitate antidepressant effects with limited psychotomimetic side effects and reduced addictive properties, which suggests enantiomerically pure R-ketamine as a potential novel treatment with reduced side effects.[24–26] While S-ketamine seems to produce psychotomimetic effects and with greater addictive potential, these side effects could play some role in producing its antidepressant effect.[26–28] Current ketamine infusion treatment involves a racemic mixture of both R- and S-ketamine. A ketamine intranasal spray (esketamine/Spravato) of enantiomerically pure S-ketamine was approved by the FDA in 2019 as a treatment option for patients who have TRD. Early case reports showed acute resolution of depression and suicidality in patients in patients who had taken the spray.[29] suggesting a potential role for ketamine in the treatment of depression. More recent clinical trials following FDA approval have shown that treatment of esketamine and an oral antidepressant together can even lead to longer-lasting effects and can prevent relapse of symptoms.[30,31]

Unique qualities of ketamine treatments

As discussed previously about ketamine's mechanism of action, ketamine is unique in that it affects multiple receptors at higher doses, similar to other select medications. With a half-life of 45 minutes, ketamine can work on cholinergic, aminergic, opioid, and voltage-gated sodium channel receptors with increasing doses, having a modulatory role in sedation and analgesia.[32] It also allows for spontaneous respiration by not affecting the pharyngeal and laryngeal reflexes, especially important during extubation for anesthesia. As a cyclohexanone derivative, ketamine creates a dissociative effect on the patient that has been actively analyzed for

analgesia and sedation. From realizing its dissociative properties, ketamine was further studied as a synergistic medication, given its effect on multiple receptors. In 2004, a research study focused on the synergistic effect between ketamine and morphine for analgesic purposes. They found that humans who received both ketamine and morphine as opposed to morphine alone experienced a greater amount of pain relief in their burns, opening the door for central sensitization.[33] Along with affecting the other receptors, ketamine at higher doses blocks high-affinity dopamine D2 receptors. With its increasing popularity as a "club drug" in the 1990s, the addicting ketamine attracted younger generations for its role in producing delirium, slowing down the perception of time, and altering states of consciousness.[34] A study analyzed the effects of chronic ketamine use in the said population, which revealed atrophy of the frontal, parietal, occipital cortices, prefrontal lobes, brain stem, and corpus striatum. If administered in a controlled environment to limit its potential abuse, ketamine's psychotomimetic effects could have a strong potential role in the treatment of analgesia and even depression.

Dissociative effects and their role in ketamine treatments

While ketamine has been shown to be a promising treatment option for TRD, it is associated with robust psychotomimetic side effects. These side effects limit its potential as a treatment choice, as there are concerns over treatment safety and potential substance abuse. Discussion on the topic generally takes place over whether these side effects are necessary for ketamine treatment efficacy or if they are merely an unintended off-target effect.[35] Studies performed on ketamine's full psychotomimetic effect profile shows that dissociation is the most closely correlated psychotomimetic side effect to treatment effectiveness though it is still unclear whether dissociation is an unintended off-target effect of ketamine or if the subjective experience itself plays a key role in facilitating its antidepressant effects.[36] Some studies suggest that dissociation should be viewed as a facilitator of depression treatment, rather than an unintended side effect.[37] This association is typically compared in parallel to that of other dissociatives that can produce similar antidepressant effects, albeit through different mechanisms of action with the resolution of depression thought to be associated with subjective dissociative experiences produced by these substances.[38] Studies regarding dissociatives suggest that the subjective experience during dissociation has a psychological role, rather than a physiological one, in producing positive mood changes and treating depression.[39] Clinical studies have shown that other NMDA receptor antagonists with little to no dissociative properties are unable to produce a comparable response to that of ketamine. While these NMDA receptor antagonists were able to produce antidepressant effects, they are shorter-lived and less profound.[40,41] However, some clinical trials have suggested that there is no real correlation between the response to ketamine as an antidepressant and its acute dissociative effects.[42,43] These studies have suggested that dissociation, rather than being a feature of ketamine's antidepressant effect, is an unintended side effect associated with its mechanism of action, unrelated to its antidepressant effect.[44] Research continues to be carried out to evaluate the safety of ketamine as an antidepressant due to its dissociative properties. As mentioned before, the R-ketamine enantiomer seems to have a reduced side effect profile while retaining its antidepressant effectiveness, making it a promising safer treatment option than that of current ketamine infusions and S-ketamine.[25] An analysis of literature has been conducted to assess if studies are able to correlate dissociation with treatment outcome but concluded that there is too much variation between studies to truly make a conclusion about the relationship.[45] The variation between studies suggests that there is a need for further research to determine whether or not dissociation truly plays a role in ketamine treatment efficacy.

Synergistic use of ketamine with traditional methods of treatment

Ketamine has been analyzed for its potential to be used synergistically with other traditional methods of treatment. Oral antidepressants were studied with concurrent use of ketamine, with results showing that the antidepressant effects were prolonged in patients with TRD.[30] This finding has opened up discussion and the potential to use sub-dissociative doses of ketamine alongside other treatments to enhance their effects. A study from 2017 showed that the coadministration of ketamine and fluoxetine had significant antidepressant effects on rats; however, the combination of ketamine and quetiapine did not produce similar results. The aforementioned ketamine/fluoxetine combination concurrently showed an increase in the antioxidant activity of superoxide dismutase, leading to decreased oxidative damage, and opening future studies towards anti-inflammatory properties for neuroprotection.[46] Alongside oral antidepressants, studies have shown that the administration of ketamine in patients undergoing electroconvulsive therapy (ECT) results in increased cognitive functioning compared to patients who receive ECT alone. Patients who receive ECT are typically those who have TRD and have failed psychotherapy and medication management. The possibility of harmful behaviors between the start of treatment and the response to ECT is also a major challenge given that ECT takes some time to achieve its optimal effect. A study was conducted in 2015 to analyze the relationship between ketamine and ECT for its synergistic effects on the recovery of patients. Given the strong concern for ketamine's potential for cognitive impairments, especially at certain doses, further studies will continue to be conducted for proper research. This research analyzed 22 patients with MDD who underwent ECT and received ketamine and propofol vs. only propofol. While the results were not statistically significant in showing a reduction in depression severity between the two groups, this study does point towards a better recovery time for cognitive performance in the group who received ketamine compared to the control group.[47]

Cognitive behavioral therapy (CBT) and other conservative forms of treatment, including psychotherapy, have been shown to sustain and enhance the effects of ketamine as an antidepressant, further supporting ketamine's synergistic theoretical effects. There are very limited studies that evaluate ketamine-assisted psychotherapy for TRD. One study from 2022 concluded that adjunct psychotherapy may play a role in the treatment of TRD, but patients were found to have temporary neural changes.[45] A separate clinical trial from 2021 assigned patients to receive CBT alongside intravenous ketamine vs. the control group of only ketamine for TRD. Subjects in the CBT group showed clinically and statistically significant improvement towards the end of the study, which further supports this treatment approach.[48] The synergistic properties that ketamine has been shown to demonstrate alongside other methods of treatment suggest clinical use as a potentiating agent. Further research on using ketamine as a potentiating or synergistic agent alongside well-established traditional forms of treatment is needed before making any conclusions; this proposed use of ketamine at sub-dissociative doses to potentiate the effects of more well-established treatment options could be a theoretically safer option for patients with TRD.

Future directions

Because of its success in treating previously treatment-resistant patients, using ketamine as a glutamate modulator has sparked interest in using drugs with similar mechanisms of action as new potential treatments for depression. Like ketamine, propofol is also able to induce antidepressant effects, and xenon, which also has theoretical use as an anesthetic, has been shown to be successful in the rapid reduction of depressive symptoms and anxiety symptoms in animal models.[49,50] However, because of its potential for abuse and addiction, there are valid concerns about the long-term repeated use of ketamine**.** Despite many case studies and short-term studies reporting treatment success, there is still limited data on the long-term repeated administration of ketamine and its longitudinal risks and complications in patients with TRD and other psychiatric illnesses. Future large-scale longitudinal studies regarding treatment efficacy and safety are strongly encouraged before ketamine can be widely administered safely in an outpatient setting for TRD.

Conclusion

FDA approval of ketamine as a potential treatment for TRD has undoubtedly already affected how the treatment of MDD, alongside other psychiatric disorders, will be approached. In this review, we presented the efficacy of ketamine as a treatment for depression and identified major targets of its mechanism of action. While previous treatment centered on monoaminergic modulation, ketamine treatment relies upon NMDA receptor antagonism leading to downstream AMPAR blockade, which may explain its considerable efficacy for those who have failed treatment with first-line monoaminergic drugs such as SSRIs. The success of ketamine treatment has revealed the complex pathogenesis of MDD; there is hope that future studies on ketamine may lead to the exploration of new pharmacological targets and future drug development.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Manuscript planning (RD and AA), manuscript drafting (RD), manuscript writing (RD and AA), critical revision of article (RD and AA). All authors have made a significant contribution to this study and have approved the final manuscript.

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