Journal of Exploratory Research in Pharmacology **2023** vol. 8(4) | 295–298
DOI: 10.14218/JERP.2023.00023

Mini Review

Efficacy of Ketamine Therapy in the Treatment of Refractory Major Depressive Disorder

Helena van Oers*

Durban Oncology Centre, Durban, South Africa

Received: March 21, 2023 | **Revised:** May 25, 2023 | **Accepted:** June 19, 2023 | **Published online:** July 25, 2023

Abstract

Major depressive disorder (MDD) is a prevalent and highly debilitating illness that causes significant functional impairment in many patients. Conventional pharmacotherapy, such as monoaminergic antidepressant agents, usually takes several weeks to improve symptomatology and has some adverse side effects, and in many cases, patients show clinical non-response. This has resulted in a quest to identify novel means of targeting the illness. Ketamine, a glutamate N-methyl-D-aspartate receptor antagonist, has been widely researched as an alternative intervention. Originally developed as an anesthetic, ketamine has been shown to exert an antidepressant effect at subanesthetic doses. A single dose of ketamine has been shown to have a rapid effect in resolving serious depressive symptoms including suicidal ideation with antidepressant effects. However, further research is needed as, in longer-term use, ketamine has the potential to be abused and certain psychological side effects, including psychotomimetic or dissociative effects, must be considered. This review highlights some of the benefits and risks of the use of ketamine in the treatment of MDD.

Introduction

Major depressive disorder (MDD) is among the most disabling and potentially life-threatening illnesses globally and has been ranked by WHO as the third greatest cause of the burden of disease while being projected to rank first by 2030.[1,2] MDD is diagnosed when an individual exhibits persistent depressive episodes, anhedonia (a decrease in interest in pleasurable activities), feelings of worthlessness and/or guilt, low energy levels, impaired concentration, changes in appetite and sleep patterns, psychomotor retardation, agitation, or SI. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition,[3] to be diagnosed with MDD, a patient must experience at least five of these symptoms, of which one is depression or anhedonia and which results in interpersonal or occupational impairment.[2]

The etiology of MDD is believed to be multifactorial and includes biological, genetic, environmental, and psychosocial factors. Historically, MDD has been considered to be primarily influenced by anomalies in the functions of neurotransmitters, especially serotonin, norepinephrine, and dopamine. Conventional and widely-used antidepressants such as selective serotonin receptor inhibitors (SSRIs) and serotonin-norepinephrine receptor inhibitors (SNRIs) aim at modulating the monoaminergic system. However, an important limitation of SSRIs is the delayed onset of action, as they typically take about 14 days to begin exerting an effect and have the potential to worsen any pre-existing anxiety or suicidality during this time, especially in younger populations. Other possible side effects which limit the effectiveness and use of these conventional therapies may include insomnia, nausea, headaches, and sexual dysfunction, which negatively impact the patient's quality of life. Moreover, a significant proportion of patients fail to respond to treatment at all.[4,5]

Treatment of refractory MDD

Among those individuals who receive first-line treatment for MDD, up to 60% do not achieve remission[6] and a significant proportion of patients fail to achieve clinically notable benefits even with multiple antidepressant interventions. Patients with Treatment-Resistant Depression (TRD) continue to have residual depressive symptoms that affect both function and quality of life and increase the risk of suicide. Thus, alternative intervention for refractory cases is an important clinical need.[7]

TRD is a subset of MDD. While there is a lack of broad consensus on the definition of TRD, it may be described as depressive symptomatology that does not remit after two or more regimens of first-line antidepressant pharmacotherapy at optimal dose and

Keywords: Ketamine; Esketamine; Pharmacotherapy; Treatment-resistant depression; Non-conventional antidepressants.

Abbreviations: MDD, major depressive disorder; NMDA, N-methyl-D-aspartate; SI, suicidal ideation; TRD, treatment-resistant depression.

***Correspondence to:** Helena van Oers, Durban Oncology Centre, Durban 4001, South Africa. ORCID: https://orcid.org/0000-0003-2251-9981. Tel: +27 82 469 0035, E-mail: fransvo@dtinc.co.za

How to cite this article: van Oers H. Efficacy of Ketamine Therapy in the Treatment of Refractory Major Depressive Disorder. *J Explor Res Pharmacol* 2023;8(4):295–298. doi: 10.14218/JERP.2023.00023.

duration in the course of a current depressive episode.[7] Treatment resistance includes persistent symptoms of a low mood, repeated depressive episodes, and poor response to medication or other therapeutic interventions, including brain stimulation such as electroconvulsive therapy, repetitive transcranial magnetic stimulation, magnetic seizure therapy, deep brain stimulation as well as psychotherapy.[1,6]

Recent studies have shown that patients with MDD having episodes of TRD have a significantly higher risk of self-harm, a greater than 20% increase in all-cause mortality, increased use of health resources, comorbidities such as anxiety disorders, obsessive-compulsive disorders, and fatigue when compared to patients without TRD episodes. Increased incidence of substance abuse was also found to be higher among these patients. One study also found that MDD episodes with TRD were of substantially longer duration than MDD without TRD.[7]

Research has suggested that the risk factors for the development of TRD include age, age at onset, psychiatric comorbidities, duration of, a history of abuse, and treatment-related factors.[7]

The efficacy of ketamine in TRD

In the quest for more rapid-acting treatments, newer theories have emerged that suggest MDD may be closely associated with more complex neuroregulatory systems, and the examination of novel molecular targets beyond the monoamine system has become marked in order to gain clinically groundbreaking advances in MDD therapeutics.[2,8]

Recent research involving in vivo brain imaging and studies of gene expression has implicated abnormalities in glutamatergic signaling in the pathophysiology of MDD and agents that modulate this system have significant therapeutic potential. In particular, ketamine, a non-competitive NMDA receptor antagonist, which has been in use primarily in veterinary and pediatric anesthesia and has well-established safety and efficacy qualities as an analgesic and anesthetic in these contexts, has been recently studied for use off-label as a treatment for psychiatric disorders.

A key factor in ketamine's efficacy is its role as an efficient glutamate receptor modulator. Ketamine works by blocking NMDA receptors in the brain, which increases levels of the neurotransmitter glutamate causing synaptogenesis or neurotransmission along new pathways.[4] As glutamate is the primary excitatory neurotransmitter in the central nervous system and any disruption in glutamate function or the operation of glutamatergic transmission may impair neural health, this has a significant effect on limiting the progression of many neurodegenerative and psychiatric diseases[4,9,10] and affects mood, thought patterns, and cognition[11] Moreover, recent studies have found that ketamine is better at crossing the blood-brain barrier than SSRIs, SNRIs and other widely used antidepressants.[12] This is the first non-monoaminergic agent that has demonstrated rapid-onset efficacy in the treatment of MDD and thus represents a pharmacologically novel therapeutic option for adults with TRD.[8,13]

Several studies have shown that antidepressant effects in patients with TRD were observed within approximately 2 hours of a single subanesthetic intravenous infusion of ketamine, after the acute, dissociative, and euphoric side effects subsided, with the effects gradually decreasing at seven days post-infusion—although twice weekly infusions have been demonstrated to prolong the antidepressant effect for up to 15 days.[4] This finding is especially significant for individuals needing immediate intervention such as those with concurrent SI or patients with personality disorders where high levels of suicidality render research on ketamine a priority.[9,10,14–17]

Moreover, ketamine has been demonstrated to be effective in other psychiatric contexts, including Bipolar Disorder, Social Anxiety, Generalized Anxiety Disorder, Obsessive Compulsive Disorder, Post-traumatic Stress Disorder, and eating disorders.[10]

Routes of administration

Although there is consensus regarding the therapeutic role of ketamine in depression, the comparative effects of different formulations of ketamine are less clear and the psychoactive and therapeutic effects have also been found to vary substantially by dose and route of administration.[10,18] Ketamine is a 1:1 racemate of two enantiomers, S-ketamine (esketamine) and R-ketamine. One of these enantiomers, S-ketamine (esketamine), binds more potently to the NMDA receptor than R-ketamine and thus has an anesthetic effect that is approximately 2 times higher but produces less lethargy and cognitive impairment.[9,19]

Ketamine and esketamine are similar as they have the same molecular makeup but esketamine has been shown to be not only more potent but also better tolerated than ketamine.[19] Recent research suggests that esketamine reduces the risk of relapse by between 50 and 70%.[16] The most researched formulations and routes of delivery of ketamine in TRD are intranasal (IN) esketamine and intravenous or parenteral (oral, sublingual, and IN) racemic ketamine.[13,20]

Route of administration is an important factor in the use of ketamine for disorders such as TRD, in which repeated dosing may be indicated. Intravenous delivery is widely used in clinical settings due to its superior bioavailability and dose control, while esketamine is usually given in the form of a nasal spray.[10,21]

Some studies suggest oral and intranasal formulations of ketamine are optimal for TRD, but there is still little data regarding the potential link between the rapidity of onset of action and the route of administration.[22]

Risks of ketamine use

While the clinical effectiveness of ketamine in TRD has been demonstrated, studies show that this varies considerably among patient populations, which has implications for general use.[23] Many important factors regarding ketamine use still need to be defined and relatively little is known about the overall risks of ketamine use as an antidepressant.[22,24] There is a dearth of research aimed at identifying optimal dosing strategies for ketamine use and common adverse side-effects of ketamine have been found.[25] These include transient and dose-dependent dizziness, headache, nausea, blurred vision, cardiovascular symptoms, neurotoxicity, cognitive dysfunction, and dissociative and psychotomimetic effects.[10] Such adverse effects tend to manifest in acute, low-dose treatments whereas extended exposure may put patients at risk of neurotoxicity and drug dependence. Since ketamine is associated with an increased risk of drug abuse, it cannot be recommended in routine clinical practice.[22,25] Ketamine abuse may lead to chronic cystitis, hepatotoxicity, and gall bladder pathology in addition to the psychiatric symptoms of impaired cognition and chronic dissociative effects.[25]

Experience with ketamine administration in patients with TRD indicates that higher doses of intravenous ketamine are associated with increased rates of treatment-related adverse events such as dissociation when compared with lower dosing. Thus, clinicians administering ketamine should be aware of the greater probability

of adverse events and potential safety issues when administering comparatively higher doses of intravenous ketamine.[13]

Other concerns

Ketamine use for TRD raises a complex set of ethical concerns. Given the rising popularity of off-label ketamine use for TRD, there is consensus that clinicians and professional bodies must ensure that guidelines for safe practice are administered, all experimental and trial data are made known through national registries, and that both the risks inherent in ketamine treatment and the patients themselves continue to be monitored.

In addition, ensuring equitable access to treatment resources is imperative for optimal treatment benefit. The associated cost and financial accessibility hold socioeconomic and ethical implications for practice and, where patients do access treatment facilities, they may experience different standards of care between treatment sites. These are issues that warrant further examination.[26]

Further directions

Scant research exists into the use of ketamine with other supportive interventions such as psychotherapy. It is thought that ketamine may assist in the creation of adaptive new neural pathways in the brain if treatment occurs within the context of a supportive environment and with the inclusion of concurrent psychotherapeutic interventions.[27] Some preliminary studies show that adjunct psychotherapy may prolong the antidepressant effect of ketamine, leading to a less frequent need for administration.[25,28]

Additionally, ketamine may improve treatment adherence and patient engagement, which makes it a valuable psychotherapeutic adjunct.[9] Ketamine's demonstrated antidepressant effect may be linked with the psychotherapeutic process, generating rapid change, increasing treatment engagement, and lowering the patient's defensiveness through relief from distressing symptomology.[29] As such, further research into this association is warranted.

Conclusions

Current neuroscience research has redefined the perception of TRD from a monoaminergic neurotransmitter system model where there is dysfunction of specific parts of the brain toward the finding that depression is a much more complex network disorder. The need for rapid-acting antidepressant therapies at the receptor level with targeted synaptogenesis and improved neural connectivity has led to studies of agents outside current models. Research on ketamine treatment for TRD is still in the relatively early stages but numerous studies have established that ketamine is a safe, effective, fast-acting, and sustained antidepressant that markedly reduces adverse symptoms associated with depression, even in patients who are resistant to conventional pharmacotherapy.

Further research into the risks of ketamine use is necessary. A lack of guidelines regarding the therapeutic monitoring of ketamine therapy for depression has implications for expanding the use of this treatment. Dose optimization, alternative routes of administration, and the role of concurrent pharmacotherapy in the antidepressant effects of ketamine are some of the issues that remain to be answered. Further work is needed to gain a more reliable understanding of ketamine's abuse liability and its side effects in the clinical setting. Moreover, the use of ketamine as an adjunct to other forms of anti-depressant therapy, such as concurrent psychotherapy, requires further investigation.

Acknowledgments

None.

Funding

None.

Conflict of interest

The author declares that there are no conflict of interests.

References

[1] Voineskos D, Daskalakis ZJ, Blumberger DM. Management of Treatment-Resistant Depression: Challenges and Strategies. Neuropsychiatr Dis Treat 2020;16:221–234. doi:10.2147/NDT.S198774, PMID: 32021216.

[2] Bains N, Abdijadid S. Major Depressive Disorder. [Updated 2023 Apr 10]. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559078/.

[3] American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed. Washington, DC: American Psychiatric Association; 2013. doi:10.1176/appi.books.9780890425596.

[4] Bratsos S, Saleh SN. Clinical Efficacy of Ketamine for Treatment-resistant Depression. Cureus 2019;11(7):e5189. doi:10.7759/cureus.5189, PMID:31565597.

[5] Carboni E, Carta AR, Carboni E, Novelli A. Repurposing Ketamine in Depression and Related Disorders: Can This Enigmatic Drug Achieve Success? Front Neurosci 2021;15:657714. doi:10.3389/fnins.2021.657714, PMID:33994933.

[6] Rybak YE, Lai KSP, Ramasubbu R, Vila-Rodriguez F, Blumberger DM, Chan P, *et al*. Treatment-resistant major depressive disorder: Canadian expert consensus on definition and assessment. Depress Anxiety 2021;38(4):456–467. doi:10.1002/da.23135, PMID:33528865.

[7] Lundberg J, Cars T, Lööv SÅ, Söderling J, Sundström J, Tiihonen J, *et al*. Association of Treatment-Resistant Depression With Patient Outcomes and Health Care Resource Utilization in a Population-Wide Study. JAMA Psychiatry 2023;80(2):167–175. doi:10.1001/jamapsychiatry.2022.3860, PMID:36515938.

[8] Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, *et al*. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am J Psychiatry 2013;170(10):1134–1142. doi:10.1176/appi.ajp.2013.13030392, PMID:23982301.

[9] Brendle M, Ragnhildstveit A, Slayton M, Smart L, Cunningham S, Zimmerman MH, *et al*. Registered clinical trials investigating ketamine and esketamine for treatment-resistant depression: A systematic review. J Psychedelic Studies 2023;6(3):176–187. doi:10.1556/2054.2022.00234.

[10] Walsh Z, Mollaahmetoglu OM, Rootman J, Golsof S, Keeler J, Marsh B, *et al*. Ketamine for the treatment of mental health and substance use disorders: comprehensive systematic review. BJPsych Open 2021;8(1):e19. doi:10.1192/bjo.2021.1061, PMID:35048815.

[11] Lengvenyte A, Strumila R, Olié E, Courtet P. Ketamine and esketamine for crisis management in patients with depression: Why, whom, and how? Eur Neuropsychopharmacol 2022;57:88–104. doi:10.1016/j.euroneuro.2022.02.004, PMID:35219097.

[12] Breeksema JJ, Niemeijer A, Kuin B, Veraart J, Kamphuis J, Schimmel N, *et al*. Holding on or letting go? Patient experiences of control, context, and care in oral esketamine treatment for treatment-resistant depression: A qualitative study. Front Psychiatry 2022;13:948115. doi:10.3389/fpsyt.2022.948115, PMID:36506427.

[13] McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrough JW, Berk M, *et al*. Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. Am J Psychiatry 2021;178(5):383–399. doi:10.1176/appi.ajp.2020.20081251,

PMID:33726522.
[14] Shiroma PR, Thuras P, Wels J, Albott CS, Erbes C, Tye S, *et al*. A randomized, double-blind, active placebo-controlled study of efficacy, safety, and durability of repeated vs single subanesthetic ketamine for treatment-resistant depression. Transl Psychiatry 2020;10(1):206. doi:10.1038/s41398-020-00897-0, PMID:32591498.
[15] Dai D, Miller C, Valdivia V, Boyle B, Bolton P, Li S, *et al*. Neurocognitive effects of repeated ketamine infusion treatments in patients with treatment resistant depression: a retrospective chart review. BMC Psychiatry 2022;22(1):140. doi:10.1186/s12888-022-03789-3, PMID:35193541.
[16] Price RB, Kissel N, Baumeister A, Rohac R, Woody ML, Ballard ED, *et al*. International pooled patient-level meta-analysis of ketamine infusion for depression: In search of clinical moderators. Mol Psychiatry 2022;27(12):5096–5112. doi:10.1038/s41380-022-01757-7, PMID:36071111.
[17] Gałuszko-Węgielnik M, Chmielewska Z, Jakuszkowiak-Wojten K, Wiglusz MS, Cubała WJ. Ketamine as Add-On Treatment in Psychotic Treatment-Resistant Depression. Brain Sci 2023;13(1):142. doi:10.3390/brainsci13010142, PMID:36672123.
[18] Bahji A, Vazquez GH, Zarate CA Jr. Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta-analysis. J Affect Disord 2021;278:542–555. doi:10.1016/j.jad.2020.09.071, PMID:33022440.
[19] Correia-Melo FS, Leal GC, Carvalho MS, Jesus-Nunes AP, Ferreira CBN, Vieira F, *et al*. Comparative study of esketamine and racemic ketamine in treatment-resistant depression: Protocol for a non-inferiority clinical trial. Medicine (Baltimore) 2018;97(38):e12414. doi:10.1097/MD.0000000000012414, PMID:30235716.
[20] Swainson J, Klassen LJ, Brennan S, Chokka P, Katzman MA, Tanguay RL, *et al*. Non-parenteral Ketamine for Depression: A Practical Discussion on Addiction Potential and Recommendations for Judicious Prescribing. CNS Drugs 2022;36(3):239–251. doi:10.1007/s40263-022-00897-2, PMID:35165841.
[21] Kowalczyk M, Kowalczyk E, Kwiatkowski P, Łopusiewicz Ł, Sienkiewicz M, Talarowska M. Ketamine-New Possibilities in the Treatment of Depression: A Narrative Review. Life (Basel) 2021;11(11):1186. doi:10.3390/life11111186, PMID:34833062.
[22] Karrouri R, Hammani Z, Benjelloun R, Otheman Y. Major depressive disorder: Validated treatments and future challenges. World J Clin Cases 2021;9(31):9350–9367. doi:10.12998/wjcc.v9.i31.9350, PMID:34877271.
[23] Alnefeesi Y, Chen-Li D, Krane E, Jawad MY, Rodrigues NB, Ceban F, *et al*. Real-world effectiveness of ketamine in treatment-resistant depression: A systematic review & meta-analysis. J Psychiatr Res 2022;151:693–709. doi:10.1016/j.jpsychires.2022.04.037, PMID:35688035.
[24] Acevedo-Diaz EE, Cavanaugh GW, Greenstein D, Kraus C, Kadriu B, Zarate CA, *et al*. Comprehensive assessment of side effects associated with a single dose of ketamine in treatment-resistant depression. J Affect Disord 2020;263:568–575. doi:10.1016/j.jad.2019.11.028, PMID:31791675.
[25] Sanacora G, Katz R. Ketamine: A Review for Clinicians. Focus (Am Psychiatr Publ) 2018;16(3):243–250. doi:10.1176/appi.focus.20180012, PMID:31975918.
[26] Peskin E, Gudin J, Schatman ME. Increased Demand for Ketamine Infusions and Associated Complexities. J Pain Res 2023;16:295–299. doi:10.2147/JPR.S403323, PMID:36744115.
[27] Muscat SA, Hartelius G, Crouch CR, Morin KW. An Integrative Approach to Ketamine Therapy May Enhance Multiple Dimensions of Efficacy: Improving Therapeutic Outcomes With Treatment Resistant Depression. Front Psychiatry 2021;12:710338. doi:10.3389/fpsyt.2021.710338, PMID:34899408.
[28] Drozdz SJ, Goel A, McGarr MW, Katz J, Ritvo P, Mattina GF, *et al*. Ketamine Assisted Psychotherapy: A Systematic Narrative Review of the Literature. J Pain Res 2022;15:1691–1706. doi:10.2147/JPR.S360733, PMID:35734507.
[29] Yavi M, Lee H, Henter ID, Park LT, Zarate CA Jr. Ketamine treatment for depression: a review. Discov Ment Health 2022;2(1):9. doi:10.1007/s44192-022-00012-3, PMID:35509843.