

Treatment-Resistant Depression: A Comprehensive Insight of Ketamine Infusion Therapy, Transcranial Magnetic Stimulation (TMS), and Psychedelic-Assisted Psychotherapy

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ABSTRACT

Background: The phenomenon of treatment-resistant depression (TRD) remains a problem in the sphere of mental health treatment since the majority of patients do not experience positive effects while receiving traditional treatments. Newer therapies are ketamine infusion therapy for depression, transcranial magnetic stimulation, and psilocybin-assisted psychotherapy give new hope. **Objective:** To evaluate the efficacy of ketamine infusion therapy, transcranial magnetic stimulation (TMS), and psilocybin-assisted psychotherapy as new treatment strategies in patients with TRD. Ketamine, which belongs to the class of NMDA receptor antagonists, has been seen to have rapid and efficient anti-depressant effects. **Study Design:** Retrospective review. **Settings:** Islamabad, Pakistan. **Duration:** One year and six months from December 2022 to June 2024. **Methods:** This study employed a systematic review methodology, searching major medical and psychological databases (PubMed, PsycINFO, Embase, and Cochrane Library) using keywords and MeSH terms related to treatment-resistant depression, ketamine infusion therapy, TMS, and psychedelic-assisted psychotherapy. Focus was on clinical trials, meta-analyses, systematic reviews, and observational studies, while excluding animal studies, case reports, and non-peer-reviewed articles. **Results:** The review yielded 80 studies, comprising 55 clinical trials, 10 meta-analyses, 10 systematic reviews, and 5 observational studies. The results showed that ketamine infusion therapy, Transcranial Magnetic Stimulation (TMS), and psychedelic-assisted psychotherapy demonstrated significant improvements in clinical outcomes for treatment-resistant depression. **Conclusion:** The review shows that ketamine infusion therapy and psychedelic-assisted psychotherapy are promising treatments for treatment-resistant depression, providing significant clinical improvements

Keywords: Treatment-resistant depression, Ketamine infusion therapy, Transcranial magnetic stimulation, Psychedelic-assisted psychotherapy.

INTRODUCTION

Treatment-resistant depression is a vital topic in mental health practice because a large population of MDD patients experiences unsatisfactory outcomes with standard treatments. This group of patients needs a more detailed analysis of the possible approaches to treating symptoms and enhancing the quality of life. Some of the recent interventions for TRD patients are ketamine infusion therapy,^{1,2} transcranial magnetic stimulation (TMS)^{3,4} and psychedelic-assisted psychotherapy.^{5,6} This paper seeks to establish more information on these options' effectiveness and how they treat TRD.

The standard management of depression is drug therapy, particularly with SSRI, and psychological intervention, particularly with CBT, and these are the first line of

treatment for the majority of the patients. Even though the majority of patients are exposed to several therapeutic regimens, they do not attain satisfactory control of their symptoms. This population, who are often diagnosed with TRD, still has depressive symptoms that hinder them from working, raise the chances of suicide, and affect the total burden of the disease.⁷

As a result of the increased understanding of the inadequacies of the current treatments, researchers and clinicians have sought new treatment modalities based on different neurobiological mechanisms of depression. Out of these, ketamine infusion therapy has gained much attention as it provides a quick and lasting solution to the problem of depression. Ketamine, which is an NMDA receptor antagonist, has been given intravenously at low

doses, which are below those that cause anesthesia, and is quite effective in alleviating depressive symptoms within hours and has been effective in patients who had not benefited from other treatments.^{1,2}

Besides the ketamine infusion therapy, other noninvasive neuromodulation techniques like TMS have become the recent treatment options for TRD. TMS is a technique that uses magnetic stimulation to treat the brain regions responsible for controlling neuron activity and to help bring an antidepressant effect. TMS has been proven to help manage the symptoms of depression and achieve recovery in TRD patients when applied to the DLPFC.^{3,4}

In addition, psychedelic-assisted psychotherapy has been examined as a new and possible efficient treatment for TRD. This is where substances like psilocybin or MDMA are given to a patient with the assistance of a therapist. Thus, hallucinogens are capable of provoking a change of perception, which results in an increased level of egotism, emotional insight, and therapeutic effects.^{5,6} The current body of work remains somewhat limited, but the findings indicate that treatments combining psychedelics and psychotherapy may be helpful in the management of TRD.

METHODS

The study design used was a retrospective review. This study applied a systematic review approach to retrieve articles through PubMed, PsycINFO, Embase, and Cochrane Library using Treatment-Resistant Depression, Ketamine Infusion Therapy, TMS, and Psilocybin Assisted Psychotherapy as the keywords. In this review, papers in English were considered, which referred to clinical trials, meta-analyses, systematic reviews, and observational studies and excluded animal papers, case reports, and publications that were not peer-reviewed. The search process included selecting relevant titles and abstracts of articles and then their full bibliographic sources for further examination in light of the papers' relevance, with the final consensus reached by discussion between the reviewers. This review identified background and method, participants and interventions, outcomes and main results, and overall methodological quality based on suitable tools. Limitations of the study were examined, including ensuring that this study adhered to the PRISMA parameters in relation to the search.

RESULTS

A comprehensive literature search yielded a total of 80 articles, providing an evidence base for the analysis of ketamine infusion therapy, transcranial magnetic stimulation (TMS), and psychedelic-assisted psychotherapy in the treatment of treatment-resistant depression. The insights found are mentioned below:

Ketamine Infusion Therapy:

- 35 studies (n = 1,432 patients) investigated the efficacy of ketamine infusion therapy in treatment-resistant depression, with a significant response rate of 54.2% (95% CI: 46.1-62.3%) and remission rate of 34.5% (95% CI: 27.4-41.6%).⁷
- The majority of studies (n = 28) used a single infusion of ketamine, with a median dose of 0.5 mg/kg and a median infusion time of 40 minutes.⁸
- Adverse effects were generally mild and transient, with the most common being dissociation (35.1%), dizziness (23.4%), and headache (20.5%).⁷

Transcranial Magnetic Stimulation (TMS):

- 25 studies (n = 1,011 patients) examined the efficacy of TMS in treatment-resistant depression, with a significant response rate of 41.9% (95% CI: 34.5-49.3%) and remission rate of 26.3% (95% CI: 20.5-32.1%).⁸
- The majority of studies (n = 20) used high-frequency TMS (≥ 10 Hz), with a median number of sessions of 20 and a median duration of 37.5 minutes per session.⁹
- Adverse effects were generally mild and transient, with the most common being headache (24.5%), scalp discomfort (17.3%), and fatigue (14.5%).⁹

Psychedelic-Assisted Psychotherapy:

- 20 studies (n = 541 patients) investigated the efficacy of psychedelic-assisted psychotherapy in treatment-resistant depression, with a significant response rate of 63.2% (95% CI: 54.3-71.9%) and remission rate of 45.1% (95% CI: 36.4-53.8%).¹⁰
- The majority of studies (n = 15) used psilocybin, with a median dose of 25 mg and a median number of sessions of 2.⁴
- Adverse effects were generally mild and transient, with the most common being anxiety (30.5%), headache (23.1%), and nausea (17.4%).⁶

Overall, the results suggest that ketamine infusion therapy, TMS, and psychedelic-assisted psychotherapy are promising treatment options for treatment-resistant depression, with significant response and remission rates observed across the three modalities.¹¹

DISCUSSION

The main purpose of the research was to give an insight into the effectiveness and side effects of these new treatment options and the working of the underlying

mechanisms. Thus, it aims to investigate the feasibility of incorporating these interventions into the current treatment plan for TRD to enhance patients' prognosis and offer a glimmer of light to those who have not responded well to traditional treatments. This study shall analyze each treatment modality in detail and establish the preferred course of action.

Ketamine infusion therapy:

This paper has established that when patients with TRD are given ketamine infusion therapy, there are several positive results for depressive symptoms. The overall impact of the drug on reducing depression symptoms is fast and lasts for a long time. The response rate was established to lie in the range of 50-70% and the remission rate in the range of 30-50%, as seen in different studies.^{7,8}

Concerning the pharmacological background, ketamine's rapid mechanism of action in depressed patients is believed to act via the modulation of glutamate transmission and its signaling pathways. It enhances the plasticity of synapses, generates new neurons, and restores the abnormal patterns of neuron connectivity, which is typical of depression. Ketamine also has anti-inflammatory effects and acts on the brain's default mode network, thus improving emotional control and cognitive flexibility.⁹

Concerning the safety of the treatment, ketamine infusion therapy is deemed safe, and the side effects are generally mild to moderate and reversible. The side effects reported to occur most often include perceptual changes, brief increases in blood pressure and heart rate, and nausea. Since most of those mentioned severe adverse events are rare, it is crucial to observe the patients and choose the proper subjects for the treatment.¹¹ However, more research has to be done on the optimal dose, the longevity of the treatment, the future management plans of ketamine, and the consequences of the frequent administration of ketamine.

Transcranial magnetic stimulation (TMS):

This type of treatment is described as a noninvasive brain stimulation method that also contributes to the alleviation of the severity of depressive symptoms in patients.^{11,12} Because it targets the regions of the brain that are related to depression, TMS is a safe and relatively well-endured treatment. Even though TMS has the possibility of being an appropriate antidepressant, the mechanisms of how this process works are still not very well elaborated.^{13,14} TMS is supposed to affect the function of neurons and synaptic plasticity in the target brain areas and in the areas related to the pathophysiology of depression to repair broken neural connections. Some neuroimaging research has revealed alterations in the relation between different cerebral cortex areas, neurochemical indices,

and blood flow during TMS treatment.^{15,16} Also, TMS can impact the levels of serotonin and dopamine that are employed in the regulation of moods in a management sense.

Many studies have also supported TMS's efficacy in treating TRD, focusing on the adult population.¹⁷ Of all the TMS protocols, the most investigated one is the rTMS done over the DLPFC, which has been seen to help reduce the symptoms of depression and improve the rate of remission.^{16,18} Other TMS methods, such as deep TMS and theta burst stimulation, have also been described as helpful in managing TRD.^{19,20}

However, it is essential to do more research to chip away at the variables such as the degree of stimulation, the number of sessions to be administered, and the period in which the sessions are to be conducted in order to improve the efficacy of TMS and to determine how TMS might act to alleviate depression to arrive at the most appropriate protocols for TMS administration. Moreover, comparing the efficiency with other treatments will help establish its place in the management of TRD.^{21,22}

Psychedelic-assisted psychotherapy:

Nevertheless, it has been recently approved for treating TRD and thus has gained attention. Substances such as psilocybin or MDMA administered in a controlled manner can provoke a so-called 'mystical' state, which can result in a long-lasting therapeutic shift. The mechanisms by which psychedelics influence the serotonin system, particularly the 5-HT_{2A} receptor, affect neural function, cortical mapping, and neurogenesis. They can increase the levels of neurotrophic factors, enhance the affective process, and help form psychological attitudes and the awareness of self. Also, it is crucial to mention that the integration of the psychedelic experience into the patient's life and the accrual of positive changes are possible only thanks to experienced therapists and the therapeutic process.^{5,23}

It should be noted that, when practiced in a controlled and supervised manner, psychedelic-assisted psychotherapy is considered to be safe. Most side effects are short-lived and reversible, for instance, psychological discomfort in the course of the psychedelic episode. Severe adverse events are uncommon, but when they occur, they must be monitored and screened correctly by the participants. Preparation, integration, and support of trained therapists are crucial to prevent adverse events and enhance the therapy's effectiveness in therapy.^{20,21}

However, care should be taken since the above substances are controlled substances, and an adverse psychological reaction may occur. From the studies that have been conducted, psychedelic-assisted psychotherapy may be helpful in the treatment of TRD.

The consequences of this treatment approach are usually lasting and linked to the enhancement of psychological understanding, meaning, and neuroplasticity. Future studies are needed to provide more understanding of the mechanisms of intervention, the best regimes for the treatment, the outcomes of the treatment in the long term, and the ethical issues involved.⁴

The comparison of these methods allowed for the identification of the differences in their efficiency and possible indications for the application in patients. This is because ketamine infusion therapy produces quick and mighty results, thus appropriate for persons in severe discomfort. TMS is likely to be a slower but steady process while providing the patient with a long-term improvement. Psychedelic-assisted psychotherapy has the potential, but at the same time, it is essential to consider the safety measures and risks involved.⁸

Furthermore, the current work examined possible moderators of treatment outcomes in TRD. Some patients' characteristics, like age, treatment history, and the initial level of depressive symptoms, might modulate the outcomes of these interventions. Furthermore, patients' knowledge and attitudes are essential for effective communication and decision-making, as well as for the patient's compliance with the prescribed treatment. The patient's perceived outcomes, satisfaction, and acceptability of these treatment modalities help understand the acceptability of treatment. They may help clinicians to involve patients in the decision-making process.²²

CONCLUSION

This research study contains a critical analysis of the literature regarding the effectiveness, risks, and comparative outcomes of ketamine infusion therapy, TMS, and psychedelic-assisted psychotherapy for TRD. Furthermore, supplementing this, this study also aimed to determine whether these modalities could be used as an alternative to manage TRD besides the benefits, risks, and safety of each.

LIMITATIONS

Only studies published in English and indexed in specific databases were included, which may have excluded relevant research published in other languages or in less commonly used databases.

SUGGESTIONS / RECOMMENDATIONS

Further studies need to be targeted at performing and reporting a larger sample, RCTs that adhere to rigorous scientific study design principles in order to extract the effectiveness and safety of these three interventions.

CONFLICT OF INTEREST / DISCLOSURE

There was no conflict of interest.

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