

Long-Term Effects of Ketamine Infusions in Comparison to Combination Therapy involving additional rTMS, Neurofeedback and Psychotherapy: A Retrospective Survey Study of Subjective Effects

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Abstract

Introduction: The anesthetic Ketamine has been shown to exert rapid effects in a variety of mood disorders, especially in depression. Recent studies have demonstrated that Ketamine can improve neuroplasticity, the brain's ability to adapt and form new neuronal connections [1]. **Aim:** To examine the long-term effects of Ketamine without and in combination with other techniques for induced modulation. **Methods:** 26 patients, some of whom only received ketamine and some of whom additionally received repetitive transcranial stimulation (rTMS), Neurofeedback (NF), and Psychotherapy, were asked to estimate (partially retrospectively) their mood pre-treatment, post-treatment, and at the time of the survey (30 months after treatment, on average). The results were analyzed by using descriptive statistics. **Results:** 25 patients showed better mood at post-treatment and at time of survey than pre-treatment. Patients who received a combination of treatments showed better mood improvements than patients who were solely administered ketamine infusions. **Conclusion:** Patients who received ketamine therapy exhibited promising lasting effects. Their mood changed considerably, regardless of whether they only got ketamine infusions or a combination treatment, but combining ketamine with other treatments seems to have a superior effect.

INTRODUCTION

Ketamine, an NMDA receptor antagonist, is known to have immediate antidepressant effects, unlike other traditional antidepressant medications that take weeks to produce noticeable effects. The primary mechanism of action of ketamine is believed to be the promotion of "brain plasticity synaptic, structural, and functional changes" in the prefrontal cortex's pyramidal neurons, allowing the brain to form new functional networks [1]. Recent studies have also suggested that ketamine may stimulate hippocampal neurogenesis. These underlying mechanisms could explain why ketamine is effective in treating depression, especially treatment-resistant depression (TRD).

Typically, ketamine infusions or ketamine-assisted psychotherapy (KAP) are

only considered after pharmacotherapy, or psychotherapy has failed to produce satisfactory results [2]. The effects of ketamine on mood can be noticed after the first infusion. However, the immediate effects can last for varying lengths of time, with people suffering from TRD reportedly benefiting the most [3].

While several studies have already demonstrated the short-term positive effects of Ketamine, there are few results on the long-term effects to date. The aim of the study was to gather results on the long-term effects of KAP and determine if combination treatment has a superior effect^[4-8]. Repetitive Transcranial Magnetic Stimulation (rTMS), Neurofeedback, and Psychotherapy were employed. rTMS is conducted by applying externally produced alternating magnetic fields, which act on the brain's nerve cells by

stimulating electrical activity and activating (or inhibiting) them and brain networks [9]. Additionally, recent studies suggest another mode of action for rTMS: its glial activation, which leads to anti-inflammatory effects [10]. Regulatory agencies currently recognize repetitive transcranial magnetic stimulation as a viable treatment option for patients suffering from drug-resistant depression (Level A Evidence) and obsessive-compulsive disorder, as well as a potential therapy for fibromyalgia/neuropathic pain, drug addiction, chronic fatigue syndrome (CFS) as a Post-Covid-19 symptom [11], gambling disorder and to treat the consequences of a stroke [9,12,13].

Neurofeedback (NF) is also sometimes referred to as "EEG-Biofeedback". However, it can be applied to a number of other imaging modalities, such as fMRI, PET, and Functional Near-Infrared Spectroscopy (fNIRS). This technique is coupled with a computer screen, allowing the user to see their brain activity represented as either a graphic replica or a game. Additionally, operant conditioning is often used in NF, with rewards given for achieving the desired brainwave, e.g., a reward picture flashes up to the performing person [14]. One mechanism of action is the "autonomic regulation of subcognitive systems", which represents the implicit nature of learning neurofeedback [15]. Neurofeedback is used for both therapeutic and performance-enhancing purposes, and most of the research has focused on attention deficit hyperactivity disorder so far [16]. Furthermore, it is applied as a method to conduct experiments in neuroscience [17]. Ultimately, neurofeedback seeks to help patients learn to control their behavior and attention, as well as their impulsivity, and to self-regulate their brain states.

METHODS

This retrospective cohort study was conducted at Clinic Dr. Scheib in Mallorca

(Spain), where most patients seeking treatment receive a diagnosis of depression (approximately 80%), with a proportion of these patients exhibiting comorbidities such as addiction and anxiety disorders, among others. N: 116 patients who received treatment between April 2017 and February 2021 were invited to participate in the study. The data for this study were obtained from the medical clinic's software and via SurveyMonkey. All participants were informed and provided consent that their data would be published and shared. The study was conducted in accordance with the ethical guidelines of the clinic. Patients who completed a full treatment and completed the study were included. Patients who did not fully participate or had insufficient patient information were excluded. All patients were treated with Ketamine-assisted psychotherapy, and in combination, some received repetitive transcranial magnetic stimulation (rTMS), hypnosis, or neurofeedback (NF). Patients received an average of 5 ketamine infusions (0.5 mg/kg). Most patients stayed on average 23 weeks. Some patients solely received ketamine infusions ($n = 5$; 19.23%), but the majority ($n = 21$; 80.77%) received psychotherapy ($n = 17$; 65.38%), neurofeedback ($n = 6$; 23.06%) or TMS ($n = 9$; 34.62%) in addition to ketamine infusions.

The study was conducted using SurveyMonkey and was completed by patients over a period of four weeks. Patient names were abbreviated, enabling the results to be compared with their corresponding medical records. The survey questionnaire comprised items such as "On a scale from 1-10, how do you feel?" utilizing a 10-point Likert scale with anchor points ranging from 0 (very poor) to 10 (excellent) and collected data at three-time points: "Before," "After," and "Present."

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RESULTS

Twenty-six patients aged 19 to 82 years participated in the study, with an average of 2.5 years since treatment (ranging from 3 to 49 months). 25 out of 26 patients reported sustained improvements in their mood after the treatment (see Figure 1). The mood before the treatment was measured on a scale from 0 (very bad) to 10 (very good) with a median of $Mdn = 2$ and $M = 1.7$, indicating a bad mood. The mood immediately after the treatment and the present state was rated on average "6." Therefore, the average number has tripled, and the mood has gone from a "very bad" to a "good" rating.

Comparison of Long-term Effects in Ketamine vs. Combination Therapy

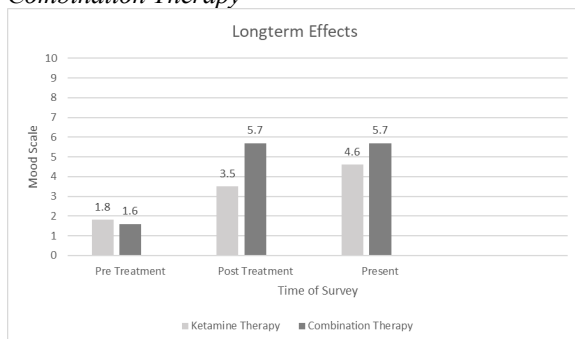


Figure 1: Assessment of mood before, after treatment, and mood at the time of the study

Of particular note is that the treatments were administered a significant amount of time ago (see Figure 2), with patients receiving treatment an average of 2 years and four months ago. Patients who received only ketamine treatment received it even further back, with an average of 2 years and seven months ago.

Time Passed Since End of Treatment

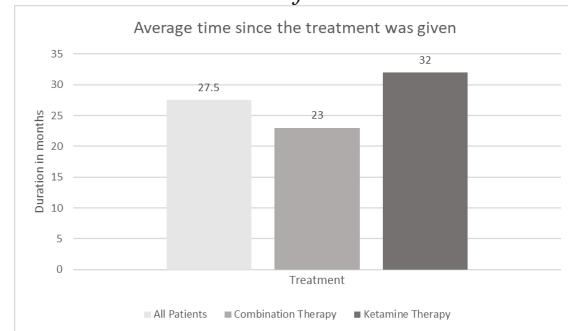


Figure 2: Average duration since the end of treatments in months

DISCUSSION AND CONCLUSION

The combination therapy was administered on average one year and 11 months ago. Both patient groups reported improvements in mood even after two years, indicating a long-term positive effect of ketamine infusions. No conclusive results were found in terms of differentiating between patients who benefited more or less from ketamine infusions. However, it can be concluded that the combination of ketamine, rTMS, and psychotherapy demonstrated a particularly positive effect.

Based on the results, the treatments significantly contribute to the improvement of a patient's mental state.

Similar results were obtained in the study by Best et al., in which 28 patients with treatment-resistant depression were treated with ketamine and rTMS. The Clinical Global Impression (CGI) rating scales, which measure symptom severity, treatment response, and treatment efficacy, were used to capture scores before, immediately after, and two years after treatment. CGI scores were significantly reduced at two years compared to the baseline [18]. Pradhan and Rossi add that repeated treatments require significantly improved scores. In particular, rTMS should be applied multiple times to ensure that the changes in brain activity last longer [19].

Another factor contributing to the long-term positive effect of ketamine appears to be the increased willingness to change instigated by the treatment. Prior to treatment, many patients experienced severe depression, making it difficult to manage their lifestyles independently. The immediate mood improvement resulting from ketamine infusions led to increased self-efficacy among many patients. During the initial phase of the survey, conducted via telephone contact, patients reported improvements in their relationships, financial situations, and work statuses. This led to an overall enhancement of their lifestyles as existing conflicts were resolved and acute stress decreased.

Additionally, other studies about the long-term effects of ketamine have shown a high drop-out rate^[20]. The high drop-out rate can also be explained by the fact that the mood improved after only a few treatments, and therefore, no further treatments were undertaken.

The study demonstrated the positive and lasting effects of ketamine infusions explicitly. On average, patients experienced significant mood changes, and the positive effects were not limited to the immediate post-treatment period. Still, they were also sustained up to two and a half years later. The data indicate combining ketamine infusions with rTMS and psychotherapy leads to the best outcomes. Several patients valued ketamine infusions, particularly during acute crises.

The findings of the present study suggest a surprising sustainability and even improvement in patients who had only received ketamine infusions, which is not consistent with previous research^[21]. This outcome may be attributed to the higher motivation level of the patients, as well as the pre-selection process that takes place when patients travel to Mallorca. The pharmacologically- induced period of improvement may have played a significant role in facilitating important, life-

changing decisions that produced a sustained antidepressant effect.

Further systematic studies are warranted to investigate the impact of life events following ketamine infusions and the possible synergistic effects of rTMS, neurofeedback, and psychotherapy.

LIMITATIONS

The study has some limitations due to the characteristics of the clinic where it was conducted, resulting in a small sample size with a relatively low response rate and a non-standardized procedure with different variables. Although most patients seeking treatment showed depressive symptomatology, some patients came for other diagnoses, which could potentially bias the results if only patients who experienced positive results participated in the survey. Additionally, the study primarily includes patients with high socioeconomic status, who had to pay for the treatments themselves. It is important to note that the study was conducted during the COVID-19-related lockdown, where the overall population experienced increased depressive and anxiety symptoms and higher overall stress rates. Furthermore, adolescents and younger people were found to be more affected. Further research is needed to investigate the influence of life events after ketamine infusions and the potential synergistic effects of rTMS, neurofeedback, and psychotherapy^[22,23].

The present study does not claim to be representative. Instead, it should be considered a clinical case series that provides insight into the long-term effects of ketamine, particularly when combined with other treatments. These findings could serve as a basis for further research on a larger scale.

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Abbreviations

| | |
|-----|---------------------------------|
| CFS | Chronic Fatigue Syndrome |
| CGI | Clinical Global Impression |
| KAP | Ketamine-assisted Psychotherapy |
| NF | Neurofeedback |

| | |
|--|--|
| NMDAR | N-Methyl-D-Aspartate |
| Repetitive Transcranial Magnetic Stimulation | Repetitive Transcranial Magnetic Stimulation |

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