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Viewpoint

Neuroinflammation and Depression: Kynurenine Pathway, BDNF, and the Implications for Psychedelic Therapies

Alicia McCullough, DO and Tyler Kjorvestad, MD

Abstract
This article discusses the relationship between depression and neuroinflammation, which is a process in which the immune system responds to injury or infection in the brain, leading to the activation of immune cells and the release of inflammatory molecules. Recent research has suggested that neuroinflammation may play a key role in the development and progression of depression. Studies have shown that neuroinflammation interacts with the three neurobiological correlates of major depressive disorder: depletion of brain serotonin, dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis, and alteration of the continuous production of adult-generated neurons in the dentate gyrus of the hippocampus. The article also discusses the Kynurenine pathway, which is a critical metabolic pathway responsible for the conversion of tryptophan into several biologically active metabolites, including kynurenic acid, and quinolinic acid. Alterations in the kynurenine pathway may be associated with depression. The article also discusses the impact of brain-derived neurotrophic factor (BDNF) on depression and how psychedelics may offer more sustained benefits compared to other therapies due to anti-neuroinflammatory effects.

INTRODUCTION

Depression is a mental health disorder that affects millions of people worldwide. Recent research has suggested that neuroinflammation may play a key role in the development and progression of depression [1,2,4]. Neuroinflammation is a process in which the immune system responds to injury or infection in the brain, leading to the activation of immune cells and the release of inflammatory molecules [2]. This response can be triggered by a variety of factors, including chronic stress, infection, and injury [4].

Studies have shown that neuroinflammation interacts with the three neurobiological correlates of major depressive disorder: depletion of brain serotonin, dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis, and alteration of the continuous production of adult-generated neurons in the dentate gyrus of the hippocampus [1]. Inflammation can impact hippocampal neurogenesis by increasing extracellular glutamate levels and glutamate neurotransmission [1]. Patients with chronic inflammation are often associated with the emergence of depression symptoms, while diagnosed depressed patients show increased levels of circulating cytokines [2].

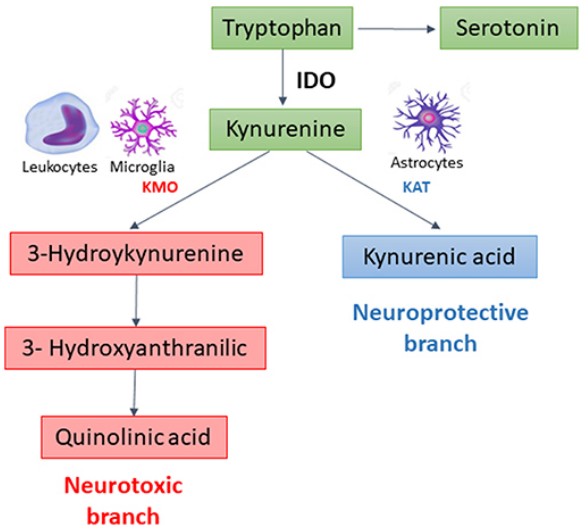
Further studies have revealed the activation of the brain immune cell microglia in depressed patients with a greater magnitude in individuals that committed suicide, indicating a crucial role for neuroinflammation in depression brain pathogenesis [2]. Animals subjected to different stress paradigms show glial cell activation and a surge in proinflammatory cytokines in various brain regions [4]. The concept of sterile inflammation observed in animal models of depression has intrigued many researchers to determine the possible triggers of central immune cell activation [4].

KYNURENINE PATHWAY

An interesting emerging area of clinical research supports interactions between the immune system and the Kynurenine pathway. Kynurenine pathway activation by pro-inflammatory cytokines results in a cascade of

metabolites as potential contributors to the pathophysiology of depression, psychosis, and cognitive deficits [5]. The Kynurenine pathway is a critical metabolic pathway responsible for the conversion of tryptophan into several biologically active metabolites, including kynurenic acid, and quinolinic acid.

Research has shown that alterations in the kynurenine pathway may be associated with depression. In particular, the imbalance between kynurenic acid and quinolinic acid can have neuroinflammatory and neurotoxic effects. Elevated levels of quinolinic acid have been linked to neuroinflammation and oxidative stress, which are associated with depressive symptoms. The initial enzymatic reaction in the Kynurenine pathway to convert tryptophan by indoleamine-2,3-dioxygenase (IDO) is activated by proinflammatory cytokines [6].



Microglia and macrophages produce quinolinic acid, which must release for enzymatic conversion to nicotinamide adenine nucleotide (NAD+) by astrocytes and neurons containing quinolinate phosphoribosyl transferase (QPRT). In physiologic conditions, quinolinic acid is catabolized into NAD+ with involvement in cellular respiration, energy production, DNA repair and transcriptional regulation [3].

In a pathogenic state, quinolinic acid accumulation can occur, stimulating NMDA receptors resulting in excitotoxic damage. Specific regions of the brain have been found to have variations in QPRT activity. Of interest, areas of lowest activity have been found within the frontal cortex, hippocampus, and the striatum. The hippocampus and striatum areas are particularly vulnerable to damage, with the combination of NMDA receptor density, paired with limited clearance of quinolinic acid, and calcium influx associated with oxidative stress.

Steiner and colleagues [7] found increased quinolinic acid concentrations in the anterior cingulate gyrus in human subjects during acute depressive episodes. Also noted increased serum IL-1, IL-6, and TNF-α in the same population compared to healthy controls. These pro-inflammatory signaling proteins have been found to activate the

In 2013, Erhardt, et al. [8] compared CSF from people who attempted suicide to healthy controls and found significant elevation in Quinolinic Acid, but not Kynurenic acid. Similar to results found by Steiner, elevated Quinolinic acid was associated with higher IL-6 levels in the CSF. Scores from the Suicide Intent Scale also correlated with Quinolinic acid levels.

New onset depressive symptoms, in previously psychiatrically healthy, with cancer or viral treatments involving Immunotherapy with cytokines has been found in multiple studies. Capuron [9] characterized the progression of cytokine therapy, beginning with sickness behavior; symptoms include anorexia, fatigue, pain, malaise, and fever. A third of the treatment participants were found to have symptoms consistent with depressive disorders, and some developed suicidal ideation.

Additional studies have found sickness disease symptoms include lethargy, depressed mood, disrupted sleep, impaired

concentration, anorexia, social isolation, and loss of interest in personal hygiene. Evidence of elevated proinflammatory cytokines, such as IL-1, IL-6, and TNFα compared to healthy controls [10] Dantzer.

In contrast to quinolinic acid, kynurenic acid is produced primarily by astrocytes, which acts as an antagonist on N-Methyl-D-aspartate (NMDA) and alpha7 nicotinic acetylcholine receptor (α7nAChR) with neuroprotective properties. Kynurenic acid shares some similarities with Ketamine and its derivatives that is already used to treat depressive symptoms via NMDA modulation.

Specifically, Ketamine has been shown to suppress pro-inflammatory cytokines and affect both pro- and anti-inflammatory cytokines in animal models [11]. Microglia are involved in the secretion of cytokines and chemokines as well as other pro-inflammatory mediators after infection or brain damage, and ketamine may regulate microglial activation through inflammatory signaling pathways [12].

Brain Derived Neurotropic Factor

Brain Derived Neurotropic Factor (BDNF) is a protein that plays an important role in neuronal survival and growth, serves as a neurotransmitter modulator, and participates in synaptic plasticity and cognitive function [13-15]. BDNF is highly regulated, and changes in its expression are associated with both normal and pathological aging, psychiatric disease, and structures important for memory processes such as the hippocampus and parahippocampal areas [16]. Studies have shown that BDNF levels are decreased in patients with depression [13, 15]. Antidepressant medication, such as the selective serotonin reuptake inhibitor Fluoxetine have been shown to increase BDNF levels [13, 17,-19]. Additionally, Quinolinic acid has been shown to decrease BDNF levels in the hippocampus and prefrontal cortex which may be mediated by quinolinic acid's effects on glutamate receptors and oxidative stress [13, 17].

Other factors known to impact BDNF include Butyrate, Lion's Mane, Omega 3, and Exercise are all known to impact Brain Derived Neurotropic Factor (BDNF) levels in the brain. Butyrate is a short-chain fatty acid produced by gut bacteria during the fermentation of dietary fiber. Studies have shown that butyrate can increase BDNF levels in the hippocampus and prefrontal cortex, possibly through its effects on histone acetylation and gene expression [20]. Lion's Mane is a mushroom that has been shown to have neuroprotective effects and to increase BDNF levels in the hippocampus and prefrontal cortex [21]. Omega 3 fatty acids are essential fatty acids that are important for brain function and have been shown to increase BDNF levels in the hippocampus and prefrontal cortex [22]. Exercise has also been shown to increase BDNF levels in the hippocampus and prefrontal cortex, possibly through its effects on neurogenesis and synaptic plasticity [23].

IMPLICATIONS FOR PSYCHEDELIC COMPOUNDS

Psychedelics have been shown to have anti-inflammatory effects in the brain, which may be one of the mechanisms underlying their therapeutic potential for neuropsychiatric disorders [24]. Psychedelics have been shown to decrease kynurenic acid levels in the brain, possibly through their effects on serotonin receptors and the kynurenine pathway [24, 25]. Additionally, studies have shown that psychedelics can increase BDNF levels in the brain, possibly through their effects on serotonin receptors and the mTOR pathway [24, 26]. A single dose of psilocybin has been shown to decrease levels of the inflammatory biomarker C-reactive protein (CRP) in healthy humans [27].. Lastly, Psychedelics may exert significant modulatory effects on immune responses by altering signaling pathways

involved in inflammation, cellular proliferation, and cell survival via activating NF-κB and mitogen-activated protein kinases [28].

Psychedelics likely offer more sustained benefits compared to other therapies, including transcranial magnetic stimulation (TMS), transcranial electrical stimulation (TES), electroconvulsive therapy (ECT), photobiomodulation (PBM), transcranial ultrasound stimulation (TUS), deep brain stimulation (DBS), and vagus nerve stimulation (VNS), which have also been reported to attenuate neuroinflammation and reduce the symptoms of depression [3].

In conclusion, neuroinflammation is a key factor that interacts with the three neurobiological correlates of major depressive disorder, leading to the development and progression of depression. Further research is needed to fully understand the mechanisms underlying this relationship and to develop effective treatments for depression that target neuroinflammation.

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. *The Journal of Psychedelic Psychiatry*, *5*(3).

REFERENCES

1. Troubat, R., Barone, P., Leman, S., Desmidt, T., Cressant, A., Atanasova, B., Brizard, B., El Hage, W., Surget, A., Belzung, C., & Camus, V. (2021). Neuroinflammation and depression: A review. *The European journal of neuroscience*, *53*(1), 151–171. https://doi.org/10.1111/ejn.14720
2. Brites, D., & Fernandes, A. (2015). Neuroinflammation and Depression: Microglia Activation, Extracellular Microvesicles and microRNA Dysregulation. *Frontiers in cellular neuroscience*, *9*, 476. https://doi.org/10.3389/fncel.2015.00476
3. Guo, B., Zhang, M., Hao, W. *et al.* (2023) Neuroinflammation mechanisms of neuromodulation therapies for anxiety and depression. *Transl Psychiatry* **13**, 5 https://doi.org/10.1038/s41398-022-02297-y
4. Afridi, R., & Suk, K. (2021). Neuroinflammatory Basis of Depression: Learning From Experimental Models. *Frontiers in cellular neuroscience*, *15*, 691067. https://doi.org/10.3389/fncel.2021.691067
5. Millischer, V., Heinzl, M., Faka, A., Resl, M., Trepci, A., Klammer, C., Egger, M., Dieplinger, B., Clodi, M., & Schwieler, L. (2021). Intravenous administration of LPS activates the kynurenine pathway in healthy male human subjects: a prospective placebo-controlled cross-over trial. *Journal of neuroinflammation*, *18*(1), 158. https://doi.org/10.1186/s12974-021-02196-x
6. Guillemin, G. J., Smythe, G., Takikawa, O., & Brew, B. J. (2005). Expression of indoleamine 2,3-dioxygenase and production of quinolinic acid by human microglia, astrocytes, and neurons. *Glia*, *49*(1), 15–23. https://doi.org/10.1002/glia.20090
7. Steiner, J., Walter, M., Gos, T., Guillemin, G. J., Bernstein, H. G., Sarnyai, Z., Mawrin, C., Brisch, R., Bielau, H., Meyer zu Schwabedissen, L., Bogerts, B., & Myint, A. M. (2011). Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: evidence for

an immune-modulated glutamatergic neurotransmission?. *Journal of neuroinflammation*, *8*, 94. https://doi.org/10.1186/1742-2094-8-94

8. Erhardt, S., Lim, C. K., Linderholm, K. R., Janelidze, S., Lindqvist, D., Samuelsson, M., Lundberg, K., Postolache, T. T., Träskman-Bendz, L., Guillemin, G. J., & Brundin, L. (2013). Connecting inflammation with glutamate agonism in suicidality. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, *38*(5), 743–752. https://doi.org/10.1038/npp.2012.248
9. Capuron, L., Ravaud, A., Miller, A. H., & Dantzer, R. (2004). Baseline mood and psychosocial characteristics of patients developing depressive symptoms during interleukin-2 and/or interferon-alpha cancer therapy. *Brain, behavior, and immunity*, *18*(3), 205-213.
10. Dantzer R. (2009). Cytokine, sickness behavior, and depression. *Immunology and allergy clinics of North America*, *29*(2), 247–264. https://doi.org/10.1016/j.iac.2009.02.002
11. Spencer, H. F., Berman, R. Y., Boese, M., Zhang, M., Kim, S. Y., Radford, K. D., & Choi, K. H. (2022). Effects of an intravenous ketamine infusion on inflammatory cytokine levels in male and female Sprague-Dawley rats. *Journal of neuroinflammation*, *19*(1), 75. https://doi.org/10.1186/s12974-022-02434-w
12. Donoso, F., Cryan, J. F., Olavarría-Ramírez, L., Nolan, Y. M., & Clarke, G. (2023). Inflammation, Lifestyle Factors, and the Microbiome-Gut-Brain Axis: Relevance to Depression and Antidepressant Action. *Clinical pharmacology and therapeutics*, *113*(2), 246–259. https://doi.org/10.1002/cpt.2581
13. Bathina, S., & Das, U. N. (2015). Brain-derived neurotrophic factor and its clinical implications. *Archives of medical science : AMS*, *11*(6), 1164–1178. https://doi.org/10.5114/aoms.2015.56342
14. Brain Derived Neurotropic Factor. (n.d.). *Science Direct*. https://www.sciencedirect.com/topics/neuroscience/brain-derived-neurotrophic-factor
15. Colucci-D'Amato, L., Speranza, L., & Volpicelli, F. (2020). Neurotrophic Factor BDNF, Physiological Functions and Therapeutic Potential in Depression, Neurodegeneration and Brain Cancer. *International journal of molecular sciences*, *21*(20), 7777. https://doi.org/10.3390/ijms21207777
16. Miranda, M., Morici, J. F., Zanoni, M. B., & Bekinschtein, P. (2019). Brain-Derived Neurotrophic Factor: A Key Molecule for Memory in the Healthy and the Pathological Brain. *Frontiers in cellular neuroscience*, *13*, 363. https://doi.org/10.3389/fncel.2019.00363
17. Castrén, E., & Rantamäki, T. (2010). The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity. *Developmental neurobiology*, *70*(5), 289–297. https://doi.org/10.1002/dneu.20758
18. O'Leary, O. F., Wu, X., & Castren, E. (2009). Chronic fluoxetine treatment increases expression of synaptic proteins in the hippocampus of the ovariectomized rat: role of BDNF signalling. *Psychoneuroendocrinology*, *34*(3), 367–381. https://doi.org/10.1016/j.psyneuen.2008.09.015
19. Huang, G. J., Ben-David, E., Tort Piella, A., Edwards, A., Flint, J., & Shifman, S. (2012). Neurogenomic evidence for a shared mechanism of the antidepressant effects of exercise and chronic fluoxetine in mice. *PloS one*, *7*(4), e35901. https://doi.org/10.1371/journal.pone.0035901

20. Bathina, S., & Das, U. N. (2015). Brain-derived neurotrophic factor and its clinical implications. *Archives of medical science : AMS*, *11*(6), 1164–1178. https://doi.org/10.5114/aoms.2015.52
21. Miranda, M., Morici, J. F., Zanoni, M. B., & Bekinschtein, P. (2019). Brain-Derived Neurotrophic Factor: A Key Molecule for Memory in the Healthy and the Pathological Brain. *Frontiers in cellular neuroscience*, *13*, 363. https://doi.org/10.3389/fncel.2019.00363
22. Ziaei, S., Mohammadi, S., Hasani, M., Morvaridi, M., Belančić, A., Daneshzad, E., Saleh, S. A. K., Adly, H. M., & Heshmati, J. (2023). A systematic review and meta-analysis of the omega-3 fatty acids effects on brain-derived neurotrophic factor (BDNF). *Nutritional neuroscience*, 1–11. Advance online publication. https://doi.org/10.1080/1028415X.2023.2245996
23. Yang, T., Nie, Z., Shu, H., Kuang, Y., Chen, X., Cheng, J., Yu, S., & Liu, H. (2020). The Role of BDNF on Neural Plasticity in Depression. *Frontiers in cellular neuroscience*, *14*, 82. https://doi.org/10.3389/fncel.2020.00082
24. Kurtz, J. S., Patel, N. A., Gendreau, J. L., Yang, C., Brown, N., Bui, N., Picton, B., Harris, M., Hatter, M., Beyer, R., Sahyouni, R., Diaz-Aguilar, L. D., Castellanos, J., Schuster, N., & Abraham, M. E. (2022). The Use of Psychedelics in the Treatment of Medical Conditions: An Analysis of Currently Registered Psychedelics Studies in the American Drug Trial Registry. *Cureus*, *14*(9), e29167. https://doi.org/10.7759/cureus.29167
25. Pilecki, B., Luoma, J. B., Bathje, G. J., Rhea, J., & Narloch, V. F. (2021). Ethical and legal issues in psychedelic harm reduction and integration therapy. *Harm reduction journal*, *18*(1), 40. https://doi.org/10.1186/s12954-021-00489-1
26. Tupper, K. W., Wood, E., Yensen, R., & Johnson, M. W. (2015). Psychedelic medicine: a re-emerging therapeutic paradigm. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*, *187*(14), 1054–1059. https://doi.org/10.1503/cmaj.141124
27. Burmester, D. R., Madsen, M. K., Szabo, A., Aripaka, S. S., Stenbæk, D. S., Frokjaer, V. G., Elfving, B., Mikkelsen, J. D., Knudsen, G. M., & Fisher, P. M. (2022). Subacute effects of a single dose of psilocybin on biomarkers of inflammation in healthy humans: An open-label preliminary investigation. *Comprehensive psychoneuroendocrinology*, *13*, 100163. https://doi.org/10.1016/j.cpnec.2022.100163
28. Szabo A. (2015). Psychedelics and Immunomodulation: Novel Approaches and Therapeutic Opportunities. *Frontiers in immunology*, *6*, 358. https://doi.org/10.3389/fimmu.2015.00358

Original Research

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

Johanna Kreßner, BS, Anja Frank, MA, Mario Scheib MD

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 ofther 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."

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

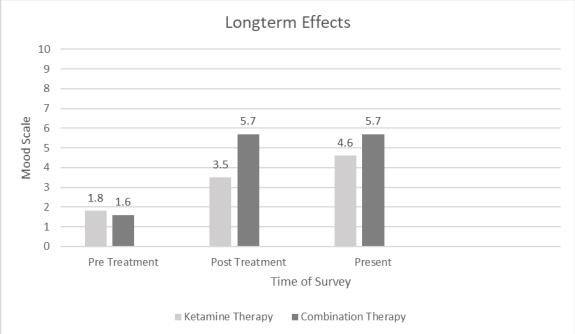

Figure 1: Assessment of mood before, after treatment, and mood at the time of the study

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

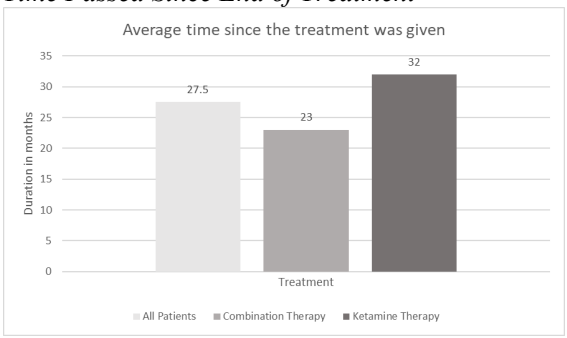

Figure 2: Average duration since the end of treatments in months

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.

Abbreviations

CFS	Chronic Fatigue Syndrome
CGI	Clinical Global Impression
KAP	Ketamine-assisted Psychotherapy
NF	Neurofeedback
NMDAR	*N*-Methyl-D-Aspartate Receptor
rTMS	Repetitive Transcranial Magnetic Stimulation

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Kreßner, J; Frank, A; Scheib M (2023, September). Long-Term Effects of Ketamine Infusions in Comparison to Combination Therapy involving additional rTMS, Neurofeedback and Psychotherapy: A Retrospective Survey Study of Subjective Effects. *The Journal of Psychedelic Psychiatry*, 5(3).

REFERENCES:

1. Aleksandrova, L. R., & Phillips, A. G. (2021). Neuroplasticity as a convergent mechanism of ketamine and classical psychedelics. Trends in pharmacological sciences, 42(11), 929–942. https://doi.org/10.1016/j.tips.2021.08.003
2. Bahji, A., Vazquez, G. H., & Zarate Jr, C. A. (2021). Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. Journal of affective disorders, 278, 542-555. https://doi.org/10.1016/j.jad.2020.09.071
3. Alnefeesi, Y., Chen-Li, D., Krane, E., Jawad, M. Y., Rodrigues, N. B., Ceban, F., Di Vincenzo, J. D., Meshkat, S., Ho, R. C. M., Gill, H., Teopiz, K. M., Cao, B., Lee, Y., McIntyre, R. S., & Rosenblat, J. D. (2022). Real-world effectiveness of ketamine in treatment-resistant depression: A systematic review & meta-analysis. Journal of psychiatric research, 151, 693–709. https://doi.org/10.1016/j.jpsychires.2022.04.037
4. Duman, R. S., Li, N., Liu, R.-J., Duric, V. & Aghajanian, G. (2012). Signaling pathways underlying the rapid antidepressant actions of ketamine. *Neuropharmacology, 62*(1), 35-41. https://doi.org/10.1016/j.neuropharm.2011.08.044
5. Hasler, G. (2020). Toward specific ways to combine ketamine and psychotherapy in treating depression. CNS spectrums, 25(3), 445-447. https://doi.org/10.1017/S1092852920000916
6. Hirota, K. & Lambert, D. (1996). Ketamine: its mechanism(s) of action and unusual clinical uses. *British journal of anaesthesia, 77*(4), 441-444. https://doi.org/10.1093/bja/77.4.441
7. Schoretsanitis, G. & Hasler, G. (2015). *Ketamin als Behandlungsoption.* Paper presented at the Swiss Medical Forum. http://dx.doi.org/10.4414/smf.2015.02420
8. Wei, Y., Chang, L. & Hashimoto, K. (2020). A historical review of antidepressant effects of ketamine and its enantiomers. *Pharmacology Biochemistry and Behavior, 190*, 172870. https://doi.org/10.1016/j.pbb.2020.172870
9. Lefaucheur, J.-P., Aleman, A., Baeken, C., Benninger, D. H., Brunelin, J., Di Lazzaro, V.et al. (2020). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018). *Clinical neurophysiology,*

131(2), 474-528. https://doi.org/10.1016/j.clinph.2019.11.002

10. Luan D, Zhao MG, Shi YC, Li L, Cao YJ, Feng HX, Zhang ZJ. Mechanisms of repetitive transcranial magnetic stimulation for antidepression: Evidence from preclinical studies. World J Psychiatry. 2020 Oct 19;10(10):223-233. doi: 10.5498/wjp.v10.i10.223. PMID: 33134113; PMCID: PMC7582130.
11. Rolle, C., Scheib, M. H. W., Frank, A., & Russ, I. (2022, September 22). Treatment of Chronic Fatigue Syndrome (CFS) in Post-SARS-CoV-2 Infection through combined outpatient-Neuromodulation Therapy with Repetitive Transcranial Magnetic Stimulation (rTMS) and Ketamine IV Therapy - A Case Series. *OSF Preprints*. https://doi.org/10.31219/osf.io/qzgc
12. Aceves-Serrano, L., Neva, J. L., & Doudet, D. J. (2022). Insight Into the Effects of Clinical Repetitive Transcranial Magnetic Stimulation on the Brain From Positron Emission Tomography and Magnetic Resonance Imaging Studies: A Narrative Review. Frontiers in neuroscience, 16, 787403. https://doi.org/10.3389/fnins.2022.787403
13. Neva, J. L., Hayward, K. S., & Boyd, L. A. (2020). Therapeutic Effects of Repetitive Transcranial Magnetic Stimulation (rTMS) in Stroke: Moving Toward an Individualized Approach. *The Wiley Encyclopedia of Health Psychology*, 169-179. https://doi.org/10.1002/9781119057840.ch20
14. Schneider, E. (2020). Frequenzbandtraining. In K.-M Haus, C. Held, A. Kowalski, A. Krombholz, M. Nowak, E. Schneider, G. Strauß, & M. Wiedemann (Eds.), *Praxisbuch Biofeedback und Neurofeedback* (3rd ed., pp. 42—57). Springer. https://doi-org.ipu.idm.oclc.org/10.1007/978-3-662-59720-0
15. Gaume, A., Vialatte, A., Mora-Sánchez, A., Ramdani, C., & Vialatte, F. B. (2016). A psychoengineering paradigm for the neurocognitive mechanisms of biofeedback and neurofeedback. In *Neuroscience and Biobehavioral Reviews,* 68, pp. 891–910. Elsevier Ltd. https://doi.org/10.1016/j.neubiorev.2016.06.012
16. Haus, K.-M., Held, C., Kowalski, A., Krombholz, A., Nowak, M., Schneider, E., Strauß, G., & Wiedemann, M. (2020). *Praxisbuch Biofeedback und Neurofeedback*. Springer. https://doi-org.ipu.idm.oclc.org/10.1007/978-3-662-59720-0
17. Enriquez-Geppert, S., Huster, R. J., & Herrmann, C. S. (2017). EEG-neurofeedback as a tool to modulate cognition and behavior: A review tutorial. *Frontiers in Human Neuroscience*, *11*. https://doi.org/10.3389/fnhum.2017.00051
18. Best, S. R., Pavel, D. G. & Haustrup, N. (2019). Combination therapy with transcranial magnetic stimulation and ketamine for treatment-resistant depression: A long-term retrospective review of clinical use. *Heliyon, 5*(8), e02187. https://doi.org/10.1016/j.heliyon.2019.e02187
19. Pradhan, B. & Rossi, G. (2020). Combining Ketamine, Brain Stimulation (rTMS) and Mindfulness Therapy (TIMBER) for Opioid Addiction. *Cureus, 12*(11). https://doi.org/10.7759%2Fcureus.11798
20. Mathers, F., Levine, S. & Arns A. (2018). Long-Term Maintenance of Patients Treated with Ketamine for

Treatment-Resistant Depression. http://dx.doi.org/10.13140/RG.2.2.31684.07043

21. Wilkinson, S. T., Wright, D., Fasula, M. K., Fenton, L., Griepp, M., Ostroff, R. B.et al. (2017). Cognitive behavior therapy may sustain antidepressant effects of intravenous ketamine in treatment-resistant depression. *Psychotherapy and psychosomatics, 86*(3), 162-167. https://doi.org/10.1159/000457960
22. Berger, K., Riedel-Heller, S., Pabst, A., Rietschel, M., & Richter, D. (2021). Einsamkeit während der ersten Welle der SARS-CoV-2-Pandemie–Ergebnisse der NAKO- Gesundheitsstudie. Bundesgesundheitsblatt-Gesundheitsforschung-Gesundheitsschutz, 64(5), 683-690. https://doi.org/10.1007/s00103-021-03340-7
23. Riedel-Heller, S., & Richter, D. (2021). Psychische Folgen der COVID-19 Pandemie in der Bevölkerung [Psychological consequences of the COVID-19 pandemic in the population]. Paper presented at the Public Health Forum.

Book Review

The Psychedelic Handbook, by Rick Strassman: A Review

Gershom Hernandez, MD

Rick Strassman, a pioneer in psychedelic research, puts forth an easily accessible volume discussing the various psychedelics. It is a broad scope discussion that is as engaging as it is informative. With reminders of the risks and cautious approach one should take towards psychedelic ingestion, as well as psychedelic research, he dedicates the book to an in-depth exploration of the various psychedelics, the ensuing implications, and practical approaches. The book excels at the accessible descriptions and explanations.

In the first section, *What Are Psychedelics*, he explains the history and effects. Overviews of the experiences and risks are incorporated into the fascinating history of psychedelics. Particularly interesting was the inclusion of the nomenclature of various psychedelics and how it relates to the experience. Strassman provides cultural and historical contexts initially, then delves into areas of research. His own research into DMT shaped the foundations of his understanding of the cultural, medical, and metaphysical uses of psychedelics. He consistently comes back to DMT, unsurprisingly, given his meticulous and extensive research on DMT.

Strassman does not hesitate to discuss the metaphysical implications of psychedelics, along with current research and often relates this subject to his experiences administering DMT. He mentions links between psychedelic use and the experiences of dreams, spirituality, near death experiences and alien contact. These phenomena have lacked significant study; however, Strassman includes them and refers back to these common experiences throughout the book. Unabashedly, he confronts these subjects that tend to be common experiences in psychedelics that are not often mentioned in clinical research, due to the difficulties in studying such abstract phenomena. The topic was a refreshing insight into his own interpretations of these events and how they relate to the larger picture of humanity and spirituality as a whole.

The second part, *How Do Psychedelics Work*, describes its aim in a clear and direct manner, allowing for complex concepts to be understood easily. Here, the book addresses metaphysical, Freudian, and even Buddhist models of the mind in order to relate these concepts to grasp the importance of understanding the mystical experiences of common to users of psychedelics. This section does not shy away from speculative subject matters, but rather addresses them as areas of investigation. The mind body connection is emphasized heavily.

Part III, *The Psychedelic Drugs*, covers each psychedelic in depth. Pharmacology, history, botany, and legal status are discussed practically and using common language and even slang terms for the drugs included. This section is packed with information.

Part IV, *Practical Guidelines*, wraps up with potential implications of the previous three sections. Here is included a section on How to trip, which focuses on the suggestions for one's own individual psychedelic journey. The insights gathered from studies, researchers, and spiritual practices are compiled in a brief objective description. This subsection neither persuades nor encourages the exploration of a psychedelic. Descriptions of set and setting, micro and macro doses, and spiritual growth are explained to objectively attempt to avoid negative outcomes, should one choose to partake in a psychedelic experience.

Overall, Strassman excels at compiling the available knowledge with his own insightful analysis, while remaining as objective as one

can be when describing the controversial, subjective, and mystical aspects of psychedelics. This book is a valuable resource for those with no knowledge of psychedelics as well as those interested in broadening their knowledge.

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