Literatur und medizinische Studien zu den von uns erfolgreich durchgeführten Therapieverfahren. Studien zur Wirksamkeit von Ketamininfusionen bei schwerer Depression, rTMS Behandungen während der Schwangerschaft und andere Therapiemethoden wie EMDR, Neurofeedback, HRV Biofeedback und tDCS.

Studien zum Einsatz von Ketamin

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

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 treat- ment, on average). The results were analyzed by using descriptive statistics. Results: 25 pa- tients 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 keta- mine therapy exhibited promising lasting effects. Their mood changed considerably, regard- less of whether they only got ketamine infusions or a combination treatment, but combining ketamine with other treatments seems to have a superior effect.

LINK ZUR STUDIE >>>
https://www.journalofpsychedelicpsychiatry.org/_files/ugd/e07c59_588a615cea41456daede945bc9092852.pdf?index=true

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

Studie von Chiara Rolle, Mario Scheib, Anja Frank, Isabella Russ

Fulltext PDF
https://assets.ctfassets.net/e0h7lzmer4zr/1CIGPnJP6p6VzdHszLIYut/d9f306928ddee1a196d5964628f4a6a8/ICMCRJ-2-1091.pdf

Abstract

The most reported symptom of post-COVID syndrome is pronounced fatigue.In this case series, we present the treatment of four patients suffering from Post-COVID syndrome

after more than 3 months since infection, presented diagnostically within the framework of chronic fatigue syndrome (CFS). They were treated with a combination of Low-frequency (1 Hz) repetitive transcranial magnetic stimulation(rTMS) and ketamine intravenous (IV) infusion therapy for a period of 2 to 3 weeks. Three patients experienced significant improvement. Given the promising results further research is indicated.

Keywords:

Post-COVID Syndrome; SARS-CoV-2; Ketamine; rTMS; Chronic Fatigue Syndrome; Neuroplasticit

Citation:

Chiara Rolle, Mario Scheib, Anja Frank, Isabella Russ. 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.Int Clinc Med Case Rep Jour. 2023;2(6):1-7.

Ketamine in COVID-19 patients: Thinking out of the box

Akinosoglou K, Gogos A, Papageorgiou C, Angelopoulos E, Gogos C. Ketamine in COVID-19 patients: Thinking out of the box. J Med Virol. 2021 Jul;93(7):4069-4070. doi: 10.1002/jmv.26681. Epub 2020 Dec 1. PMID: 33215721; PMCID: PMC7753268.

LINK ZUR STUDIE >>>
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7753268/

Dr. Scheib & Sophie Adler: Ketamine-Hypnosis Package (KHP): A Clinical Case Study for the treatment of depression and addiction administering Ketamine with Hypnotherapy

Background
There are few studies on ketamine and its properties to work with addiction (alcohol, opioid, cannabis, and cocaine use disorder). The studies show that ketamine treatment can help reduce craving and support abstinence [14]. Hypnotherapy is an evidence-based treatment gaining popularity for treating addiction, but not everybody can be hypnotized due to different levels of suggestibility. Our clinical practice has observed that people who are not highly hypnotizable, such as patients with obsessive-compulsive disorders, become more suggestible accompanied by our newly developed method called “Ketamine-Hypnosis package” (KHP). In this case report and study, we want to explore and evaluate the potential of KHP in working with addiction. Diagnostic and a qualitative content analysis should give profound insights into the treatment process and method.

Case Report
The subject is a 48-year-old male German Social Worker with treatment-resistant depression, suicidal thoughts, obsessive behavior, and several forms of addiction. The patient received a 10-day treatment at Instituto Dr. Scheib, with Diagnostic, rTMS,

neurofeedback, and four sessions of KHP. Every Ketamine infusion remained with a standard dose of 0.5 mg/kg *R*-Ketamine for about 45 minutes.
Results.
Primary outcome measures included change in depression as measured by the BDI-II with a reduction from 44, highly depressed, to a score of 3, no depression, and change of symptoms measured by the SCL-90 R that showed a clear reduction in almost every factor vs. baseline. The qualitative content analysis of the KHP sessions identified nine categories; Setting, Intervention, Body, Control, Feelings, Insights/Realizations, Addiction, Depression and Imagery. QEEG measurements before and after treatment showed a pattern of over-representation of slow brain activity with closed eyes, which can be observed in fluctuating concentration and volatile impulse control. Follow-Up Data with BDI-II one week after treatment showed factor 3 and 5 weeks after treatment factor 15.

Conclusions.
The 10-day-treatment program improved numerous important treatment outcomes in one substance-dependent adult engaged in hypnotherapeutic modification, including promoting less substance abuse, diminishing craving, and reducing the risk of relapse. Further research is needed to replicate these promising results in a larger sample.

READ THE COMPLETE STUDY
https://ketaminplus.com/wp-content/uploads/2021/01/Ketamine-Hypnosis-Package.pdf

Combining Ketamine, Brain Stimulation (rTMS) and Mindfulness Therapy (TIMBER) for Opioid Addiction.

Basant Pradhan, Garrett Rossi

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Cite this article as: Pradhan B, Rossi G (November 30, 2020) Combining Ketamine, Brain Stimulation (rTMS) and Mindfulness Therapy (TIMBER) for Opioid Addiction. Cureus 12(11): e11798. doi:10.7759/cureus.11798
Abstract

Opioid addiction in the United States currently presents a national crisis despite availability of different treatments. Prior findings suggest that both repetitive transcranial magnetic stimulation (rTMS) and subanesthetic dose of ketamine are efficacious in patients with opioid use disorders (OUD) when administered in isolation. However, their therapeutic value may be undermined by varying clinical responses that tend to dissipate with treatment cessation. There has been no study to date that has used a combination of both for OUD, and there are still many unanswered questions with respect to both. TIMBER (Trauma Interventions using Mindfulness Based Extinction and Reconsolidation of memories) therapy attempts to alter the expression of emotionally charged memories such as traumatic memories, and has been successfully tried in chronic post-traumatic stress disorder (PTSD) and in combination with memory-altering pharmacotherapy like ketamine

infusion. By a combination of extinction and reconsolidation of memory approaches, TIMBER works to not over-flood and/or retraumatize as is seen in other treatment approaches. TIMBER involves a balanced combination of both the memory extinction and memory reconsolidation approaches (rather than extinction-only approaches) which explains its superior efficacy in PTSD and benefit in substance use disorders.

Introduction

Opioid addiction in the United States (US) currently presents a national crisis despite availability of different treatments. Over 2.1 million people were diagnosed with opioid use disorder (OUD) in 2016 [1]. Prior findings suggest that both repetitive transcranial magnetic stimulation (rTMS) and subanesthetic dose of ketamine are efficacious in patients with OUD when administered in isolation [1-4]. However, their therapeutic value may be undermined by varying clinical responses that tend to dissipate with treatment cessation. There has been no study to date that has used a combination of both for OUD, and there are still many unanswered questions with respect to both. Trauma Interventions using Mindfulness Based Extinction and Reconsolidation of memories (TIMBER) attempts to alter the expression of emotionally charged memories such as traumatic memories, and has been successfully tried in chronic post-traumatic stress disorder (PTSD) alone, or in combination with memory-altering pharmacotherapy like ketamine infusion [5-7]. By a combination of extinction and re-consolidation of memory approaches, TIMBER works to not over-flood and/or re-traumatize as is seen in other treatment approaches. At the present time, TIMBER has been shown to be efficacious in targeting trauma memories and their expressions in PTSD patients [6].

TIMBER uses all eight limbs of Yoga including the focused attention meditation and mindfulness meditation, the five-factor model of trauma or addiction experience, and integrates the principles of cognitive behavioral therapy (CBT) (mindfulness-based graded exposure therapy: MB-GET) with the neurobiology of emotionally charged traumatic or addiction memories. With respect to applying the translational model of TIMBER for drug addiction, the key steps are:

1. Inducing a mindful state (calm, alert but non-reactive) by use of a standardized meditation protocol (StaMP).
2. Creating drug-cues evoked controlled arousal response using a scripted brief narrative of the addiction experience by using the Buddha's Five Factor Model (thoughts, feelings, memories, sensations/perceptions, and urges/impulses related to the addiction experience).
3. Using the mindfulness-based graded exposure therapy (MB-GET) and the TIMBER methods to decrease the arousal responses.
4. Using the already created mindful state to cognitively reprocess and reappraise the drug-related emotionally charged memories so that the drug-related emotionally charged memories are extinguished and de-conditioned from the cues and re-consolidated/updated as new memories.

TIMBER involves a balanced combination of both the memory extinction and memory reconsolidation approaches (rather than extinction only approaches) which likely explains its superior efficacies in PTSD and possibly in our future studies on drug addiction as well.

The case series presented here is the extended application of the proof of concept model of TIMBER in three patients with chronic OUD.

Materials & Methods

The study is an open-label proof of concept study designed to test the feasibility and efficacy of ketamine, rTMS, and TIMBER in patients with OUD. The study included three patients all with a diagnosis of OUD. The primary outcome measure was percent reduction in cravings using the opiate use craving scale from baseline to the fifth rTMS session.
The following interventions were used:
1. Ketamine was given as a single infusion of 0.75 mg/kg weight-based dose capped at 745 mg total, administered over a 45 minute period. A one week washout period followed prior to the start of rTMS.
2. rTMS was performed for five sessions of 10 Hz and 3000 stimulation pulses applied to the right dorsolateral pre-frontal cortex (DLPFC) over one to two weeks.
3. Five sessions of TIMBER mindfulness-based therapy was carried out during the same two weeks period that rTMS was performed.
4. Home practice was then carried out two times daily with additional sessions on an as-needed basis whenever cravings were present.
Cravings were measured using the Opiate Craving Scale. Arousal responses were measured by a multi-system biofeedback bundle that comprised of real-time electroencephalogram (EEG), heart rate variability, and breath response pattern guided focused attention and mindfulness meditation practice (three minutes before rTMS, 21 minutes during, and three minutes after administration of rTMS).

Results

In our open-label pilot study sample that consisted of three subjects with opiate use disorder (two with heroin use disorder and one with oxycodone use disorder), the participants rated their craving on the Opiate Craving Scale (OCS: scores range 0-30), five minutes before and five minutes after the rTMS stimulation [8]. They rated their level of mindfulness pre-infusion baseline and after completing five sessions of TMS+mindfulness using the Assessment Scale for Mindfulness Interventions (ASMI) [6,7].
In these three subjects, at baseline, the mean OCS was 23.6 (SD 4.2), which indicates a high level. The OCS reduced to 8.2 (SD 2.7) after five sessions of TMS and mindfulness. Similarly, at baseline, their mean ASMI was 28.45 (SD 9.61). After five sessions of TMS and mindfulness, the mean ASMI was 49. 67 (SD 7.72) indicating a significant increase in mindfulness (Table *1*).

Patient Profile	Cravings at Baseline	Cravings at session Five	Craving Percent Decrease After 5 Sessions	Mindfulness at Baseline	Mindfulness at Session 5	Mindfulness percent Increase After 5-sessions	t-test P-Value (2-tailed), and 95% CI
Combined Patient Data	OCS: 23.66 +/- 3.21	OCS: 8.33 +/- 2.5	65.7%	ASMI: 29 +/- 3.6	ASMI: 49.33 +/- 7.37	41.21%	For OCS: P=0.002, t=6.5, 95% CI=8.8 to 21.85 For ASMI:

	P=0.01 T= 4.2, 95% CI= 33.48 to 7.18

Table 1: Reduction In Opioid Craving and Increase In Mindfulness at Baseline and Session 5

OCS: Opiate Craving Scale, ASMI: Assessment Scale for Mindfulness Interventions

Discussion

Collectively all of these therapeutic interventions show promise as individual treatments for maintenance of abstinence in OUD, particularly improvement in cravings and increased motivation to quit. Significant long-term improvements in complete abstinence have been demonstrated with the use of ketamine following extended inpatient treatment [3,4], and ketamine reduced physiological response during opioid withdrawal [9]. However, these studies on the use of ketamine are limited by their use of low-dose ketamine as the comparison group rather than a true placebo. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation technique currently approved for major depressive disorder. rTMS is currently being pursued as a treatment for substance use disorder. Preliminary data looking at treatment with rTMS to the dorsolateral pre-frontal cortex (DLPFC) has shown reduction in cravings in alcohol, cocaine, and nicotine use disorders [2]. Single session rTMS studies have demonstrated that applying excitatory rTMS to the DLPFC can decrease cue-induced craving in nicotine, cocaine, and alcohol use disordered populations. The mechanism of rTMS success in treating addiction is thought to involve increased dopamine function in the shell region of the nucleus accumbuns [10].

Single session studies have only found small temporary reductions in craving, however more frequent sessions could lead to longer durations and greater reductions in cravings. The largest such clinical trial (n=130 smokers) demonstrated that 13 sessions of DLPFC rTMS resulted in six month tobacco abstinence rates of 33% [2]. Trauma memories lay at the core of the pathogenesis of PTSD. TIMBER therapy attempts to alter the expression of emotionally charged memories such as traumatic memories, and has been successfully tried in chronic PTSD alone or in combination with memory altering pharmacotherapy like ketamine infusion [5,7]. There are many similarities between the emotionally charged memories common in PTSD, and the emotionally charged memories associated with addiction. Exposure to environmental cues such as people, places, or drug paraphernalia lead to a state of arousal and strong emotional response that often results in relapse for patients attempting to maintain sobriety. The use of mindfulness-based graded exposure therapy (MB-GET) and the TIMBER methods to decrease the arousal responses will extinguish drug-related emotionally charged memories while replacing them with new more adaptive memories. TIMBER aims to restructure cognitions and emotions, which prevents reactivity of the underlying memories in trauma [5].

A number of important questions remain. It is unclear how each of these modalities will function in combination and in comparison to a true placebo group. It is unclear what role baseline levels of desire to quit, motivation for treatment, and prior periods of abstinence

have on the achievement and maintenance of abstinence. The groups chosen for the ketamine studies were treatment-seeking and completed three months of residential treatment prior to treatment with ketamine infusion [3,4]. The abstinence rates at one- and two-year follow-up for ketamine are promising; unique genetic and socioeconomic factors must be considered [3,4]. To date there is limited work examining the effect of rTMS on craving in OUD. However, preliminary data indicates significant possibility of reduced craving with multiple sessions of rTMS. While TIMBER methods have been successfully used to treat PTSD, this method has yet to be applied to substance use disorders on a mass scale. TIMBER involves a balanced combination of both the memory extinction and memory reconsolidation approaches (rather than extinction only approaches) and has possible implications for substance use disorder.

Conclusions

Combination therapy with ketamine, rTMS and TIMBER is feasible in patients with OUD. Although an open-label proof of concept study, the data suggests that the combination therapy reduces craving, promotes abstinence, and reduces the amount used in patients with OUD. Combination therapy allows patients to be actively involved in their care by engaging in meditative therapy-based techniques that directly result in a calmer state of mind. This protocol allows concurrent implementation of three individually effective interventions in combination for a compounding synergistic effect.

Link to publication: https://europepmc.org/article/pmc/pmc7779150#free-full-text

The Acute Antisuicidal Effects of Single-dose Intravenous Ketamine and Intranasal Esketamine in Individuals with Major Depression and Bipolar Disorders: A Systematic Review and Meta-analysis

Journal of Psychiatric Research

Available online 11 December 2020

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Highlights

• Single-dose intravenous ketamine/intranasal esketamine has rapid and robust acute effects in reducing suicidal ideation (SI).
• Future high-quality research on the anti-SI efficacy of alternative administration routes (i.e. intramuscular, subcutaneous, oral/sublingual) and formulations of ketamine is needed.
• Dosage, routes of administration, and formulations are factors to be considered for optimizing SI treatment using ketamine.

Abstract

The efficacy of ketamine in reducing suicidal ideation (SI) has been previously reported. We aimed to evaluate acute anti-SI effects of single-dose ketamine in different formulations/routes of administration by pooling results from randomized controlled trials (RCTs). A systematic search was conducted on Cochrane, Embase, Medline, and PubMed from inception to July 1st, 2020. Studies were selected based on pre-determined eligibility criteria. Effect sizes of different formulations/routes at various time points were computed using random-effects models. With data from nine eligible RCTs (n=197), the pooled effect size for anti-SI effects at 24-hour time point was 1.035 (N=6, CI: 0.793 to 1.277, p<0.001) for intravenous (IV) racemic ketamine and 1.309 (N=1, CI: 0.857 to 1.761, p<0.001) for intranasal (IN) esketamine. An additional five RCTs were available for qualitative analysis. RCTs were identified for oral/sublingual ketamine for depression, however, none of these trials reported anti-SI effects preventing quantitative analysis for these routes of delivery. No RCTs for intramuscular (IM) ketamine were identified. The findings suggest that single-dose IV ketamine/IN esketamine is associated with robust reductions in suicidal thoughts at 2-hour, 4-hour, and 24-hour post-intervention. In addition, future studies on IM/oral/sublingual ketamine and comparative studies are warranted to evaluate the anti-SI efficacy of distinct formulations and routes of administration.

Zur Studie>>>
https://pubmed.ncbi.nlm.nih.gov/33360864/

Early symptomatic improvements as a predictor of response to repeated-dose intravenous ketamine: Results from the Canadian Rapid Treatment Center of Excellence

Progress in Neuro-Psychopharmacology and Biological Psychiatry

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Highlights
• Early symptom improvement was associated with greater antidepressant effects following four ketamine infusions.
• ~40% of individuals with early improvement responded to the full treatment course versus 14–19% in non-early improvers.
• 58% of individuals who did not experience early improvement experienced a partial to full response after the fourth infusion.

Abstract

Background
Early symptomatic improvement with monoamine-based antidepressants is predictive of treatment response. The objective of this study was to determine if early symptomatic improvements with intravenous (IV) ketamine predicted treatment response to an acute course of four infusions.

Method
134 adults with treatment resistant depression (TRD) received four ketamine infusions over one to two weeks. Depressive symptoms were measured using the Quick Inventory for Depressive Symptomatology Self-Report16 (QIDS-SR16) at baseline and post-infusions 1, 2, 3, and 4. Early improvement was defined as ≥20% reduction in QIDS-SR16 scores after the first or second infusion. Linear models were used to determine whether early improvement was associated with post-infusion 4 QIDS-SR16 scores after controlling for baseline characteristics.

Results
Early improvement post-infusion 1 (β = −3.52, 95% BCa CI [−5.40, −1.78]) and 2 (β = −3.16, 95% BCa CI [−5.75, −1.59]) both significantly predicted QIDS-SR16scores post-infusion 4. Early improvers had significantly lower QIDS-SR16 scores at post-infusion 4 (post-infusion 1 improvers: *M* = 9.8, *SD* = 4.5; post-infusion 2 improvers: *M* = 10.6, *SD* = 5.7) compared to non-early improvers (post-infusion 1 non-improvers: *M* = 13.7, *SD* = 5.8; post-infusion 2 non-improvers: *M* = 14.1, *SD* = 5.3) when controlling for baseline characteristics. The majority (58%) of individuals who did not improve post-infusions 1 or 2 still experienced an antidepressant response or partial response (≥20% reduction in QIDS-SR16) post-infusion 4.

Limitations
This is a *post-hoc* analysis of an open-label study.

Conclusion
Early improvement was associated with greater antidepressant effects following a course of four ketamine infusions. However, individuals who did not show early improvements still had a high likelihood of experiencing clinically significant symptom reduction after the fourth infusion, suggesting that completing four infusions, regardless of early symptom changes, is appropriate and merited.

Combination therapy with transcranial magnetic stimulation and ketamine for treatment-resistant depression: A long-term retrospective review of clinical use

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A R T I C L E I N F O

Keywords: Psychiatry, Neurology, TMS, Depression, Ketamine, Comorbidity, Biomarker, C ombination
A B S T R A C T
Background: Both transcranial magnetic stimulation (TMS) and infused ketamine are recognized treatments for patients suffering from major depressive disorder (MDD). A novel therapy named combination TMS with ketamine (CTK) is introduced. This retrospective review examined the safety and clinical benefits of CTK in patients suffering from treatment-resistant depression (TRD) during the routine practice of psychiatry in a private clinic.
Methods: TRD patients (N . 28) received a coincident application of high-output TMS (30 minutes) with biomarker-determined ketamine infusions (20 minutes). Frequency of treatment was dependent on patient responsiveness (10–30 sessions). Clinical global impression (CGI) data was collected pre- and post-treatment and then two years later.
Results: The mean reduction in CGI severity for the patient group following CTK was 4.46 0.54 at a 99% confidence interval and was deemed statistically significant using a paired t-test (α . 0.01, t . 22.81 $p < 0.0001$).
This reduction was sustained for two years following treatment completion and this remission was deemed statistically significant by a second paired t-test (α . 0.01, t . 27.36, $p < 0.0001$).
Limitations: Retrospective review of a limited number of patients undergoing CTK in a clinical practice.
Conclusions: This clinical review indicated that CTK is an effective, long-term therapy (after two years) and can be used for TRD patients. The coincident administration of ketamine allowed for higher TMS intensities than otherwise would be tolerated by patients. Further studies for optimization of CTK are warranted.
1. Introduction
Treatment-resistant depression refers to a major depressive disorder (MDD) with a lack of clinically meaningful improvement to an appropriate course (adequate dose over 6–8 weeks) of at least two antidepressants from different pharmacological classes, prescribed for adequate duration, with adequate affirmation of treatment adherence (Little, 2009; EMA Guidelines, 2013). It is estimated that between 15% and 33% of patients will not respond to multiple interventions and therefore be classed as suffering from treatment-resistant depression (Little, 2009).
The sequenced treatment alternatives to relieve depression (STAR*D) trial explored the effectiveness of alternative treatments for treatment-resistant depression patients and predicted that only a third of the 20 million Americans suffering from MDD would achieve remission (Warden et al., 2007). Continued depressive symptoms have been linked to social issues, a greater risk of suicide and mortality and ultimately results in increased health-care costs (Lepine and Briley, 2011; Kellar et al., 2016).
The cause of such depressive disorders remains unclear. However, it is commonly agreed that it relates to a system disorder affecting pathways between cortical, subcortical and limbic sites, along with the neurotransmitter and molecular mediators (Mayberg et al., 2005). Patients with unipolar depression have been shown to have prefrontal abnormalities, predominantly on the left and decreased neuronal activities in the dorsolateral prefrontal cortex (PFC) regions, as well as in the rostral anterior cingulate

cortex (ACC) areas, closely connected to the dorsolateral PFC (Baeken and De Raedt, 2011).
Research has shown a strong negative correlation between the ACC
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Ketamine for Social Anxiety Disorder: A Randomized, Placebo-Controlled Crossover Trial

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Neuropsychopharmacology **volume 43**, pages325–333(2018) Cite this article

Abstract
Many patients with social anxiety disorder (SAD) experience inadequate symptom relief from available treatments. Ketamine is a potent *N*-methyl-D-aspartate receptor antagonist with a potentially novel mechanism of action for the treatment of anxiety disorders. Therefore, we conducted a double-blind, randomized, placebo-controlled crossover trial in 18 adults with DSM-5 SAD and compared the effects between intravenous ketamine (0.5 mg/kg over 40 min) and placebo (normal saline) on social phobia symptoms. Ketamine and placebo infusions were administered in a random order with a 28-day washout period between infusions. Ratings of anxiety were assessed 3-h post-infusion and followed for 14 days. We used linear mixed models to assess the impact of ketamine and placebo on anxiety symptoms. Outcomes were blinded ratings on the Liebowitz Social Anxiety Scale (LSAS) and self-reported anxiety on a visual analog scale (VAS-Anxiety). We also used the Wilcoxon signed-rank test to compare the proportion of treatment responders. Based on prior studies, we defined response as a greater than 35% LSAS reduction and 50%

VAS-Anxiety reduction. We found ketamine resulted in a significantly greater reduction in anxiety relative to placebo on the LSAS (Time × Treatment: $F_{9,115}=2.6$, $p=0.01$) but not the VAS-Anxiety (Time × Treatment: $F_{10,141}=0.4$, $p=0.95$). Participants were significantly more likely to exhibit a treatment response after ketamine infusion relative to placebo in the first 2 weeks following infusion measured on the LSAS (33.33% response ketamine *vs*0% response placebo, Wilcoxon signed-rank test $z=2.24$, $p=0.025$) and VAS (88.89% response ketamine *vs* 52.94% response placebo, Wilcoxon signed-rank test $z=2.12$, $p=0.034$). In conclusion, this proof-of-concept trial provides initial evidence that ketamine may be effective in reducing anxiety.

Effects of ketamine in patients with treatment-refractory generalized anxiety and social anxiety disorders: Exploratory double-blind psychoactive-controlled replication study

Paul Glue, Shona Neehoff, Amandine Sabadel, …
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Article information
Abstract

Background:
We previously reported that ketamine has anxiolytic effects in patients with treatment-resistant generalized anxiety and social anxiety disorders.
Aims:
The purpose of this study was to replicate our earlier report about ketamine‘s anxiolytic activity, using a more robust study design.
Methods:
This was a double-blind, psychoactive-controlled ascending dose study in 12 patients with treatment-resistant generalized anxiety and social anxiety disorders who were not currently depressed. Ascending doses of ketamine (0.25, 0.5, 1 mg/kg) were administered at weekly intervals, and midazolam 0.01 mg/kg, the control, was randomly inserted into the ketamine dose sequence. Assessments included ratings of anxiety and dissociation, safety and tolerability, and blood samples for ketamine pharmacokinetics and BDNF concentrations.
Results:
Improvements in anxiety ratings occurred within an hour of ketamine dosing, and persisted for up to 1 week. A dose-response profile was noted for anxiolytic effects, dissociative side effects, and changes in blood pressure and heart rate after ketamine dosing. Midazolam had minor brief effects on anxiety ratings. Ketamine was safe and well tolerated. Ketamine pharmacokinetics were correlated with dissociation ratings. Serum BDNF concentrations declined over time and were similar for all treatments.
Conclusions:
Ketamine may be a potential therapeutic option for patients with treatment-resistant generalized anxiety and social anxiety disorders.

Single and repeated ketamine infusions for reduction of suicidal ideation in treatment-resistant depression

Jennifer L. Phillips1,2, Sandhaya Norris1,2, Jeanne Talbot1,2, Taylor Hatchard1, Abigail Ortiz 1, Meagan Birmingham1, Olabisi Owoeye1,2, Lisa A. Batten1 and Pierre Blier1,2,3

Repeated administration of subanesthetic intravenous ketamine may prolong the rapid decrease in suicidal ideation (SI) elicited by single infusions. The purpose of this secondary analysis was to evaluate reduction in SI with a single ketamine infusion compared with an active control, and prolonged suppression of SI with repeated and maintenance infusions. Thirty-seven participants with treatment-resistant depression (TRD) and baseline SI first received a single ketamine infusion during a randomized, double-blind crossover with midazolam. Following relapse of depressive symptoms, participants received six open-label ketamine infusions administered thrice-weekly over 2 weeks. Antidepressant responders (≥50% decrease in Montgomery-Åsberg Depression Rating Scale [MADRS] scores) received four further open-label infusions administered once-weekly. Changes in SI were assessed with the suicide items on the MADRS (item 10, MADRS-SI) and the Quick Inventory of Depressive Symptomatology-Self Report (item 12, QIDS-SI). Linear mixed models revealed that compared with midazolam, a single ketamine infusion elicited larger reduction in SI ($P = 0.01$), with maximal effects measured at 7 days postinfusion ($P < 0.001$, Cohen's $d = 0.83$). Participants had cumulative reductions in MADRS-SI scores with repeated infusions ($P < 0.001$), and no further change with maintenance infusions ($P = 0.94$). QIDS-SI results were consistent with MADRS-SI. Overall, 69% of participants had a complete alleviation of SI following repeated infusions. In TRD, single and repeated ketamine infusions resulted in decreases in SI which were maintained with once-weekly maintenance infusions. This study adds to the growing body of research suggesting ketamine as a possible novel treatment strategy for SI in mood disorders.

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Ketamine induces rapid and sustained antidepressant-like effects in chronic pain induced depression: Role of MAPK signaling pathway

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Abstract
Chronic pain produces psychologic distress, which often leads to mood disorders such as depression. Co-existing chronic pain and depression pose a serious socio-economic burden and result in disability affecting millions of individuals, which urges the development of treatment strategies targeting this comorbidity. Ketamine, a noncompetitive antagonist of the *N*-methyl-d-aspartate (NMDA) receptor, is shown to be efficient in treating both pain and depression-related symptoms. However, the molecular

characteristics of its role in chronic pain-induced depression remain largely unexplored. Hence, we studied the behavioral and molecular effects of a single systemic administration of ketamine (15 mg/kg, i.p.) on mechanical hypersensitivity and depressive-like consequences of chronic neuropathic pain. We showed that ketamine transiently alleviated mechanical hypersensitivity (lasting <24 h), while its antidepressant effect was observed even 72 h after administration. In addition, ketamine normalized the upregulated expression of the mitogen activated protein kinase (MAPK) phosphatase 1 (MKP-1) and the downregulated phosphorylation of extracellular signal-regulated kinase (pERK) in the anterior cingulate cortex (ACC) of mice displaying neuropathic pain-induced depressive-like behaviors. This effect of ketamine on the MKP-1 was first detected 30 min after the ketamine administration and persisted until up to 72 h. Altogether, these findings provide insight into the behavioral and molecular changes associated with single ketamine administration in the comorbidity of chronic pain and depression.

Ketamine for suicidal ideation in adults with psychiatric disorders: A systematic review and meta-analysis of treatment trials

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Abstract
OBJECTIVE:
Ketamine may reduce suicidal ideation in treatment-resistant depression. But it is not known how quickly this occurs and how long it persists. We undertook a systematic review and meta-analysis to determine the short- and long-term effectiveness of ketamine for suicidality.
METHOD:
CENTRAL, EMBASE, Medline, and PsycINFO were searched until 12 December 2018. Randomised controlled trials of ketamine or esketamine reporting data on suicidal ideation, self-harm, attempted or completed suicide in adults diagnosed with any psychiatric disorder were included. Two reviewers independently extracted data, and certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation tool. Standardised mean difference was used for continuous outcomes.

RESULTS:
Twenty-five reports from 15 independent trials, with a total of 572 participants diagnosed with predominately affective disorders, were included. The evidence was rated moderate to low. In most trials, ketamine was administered at 0.5 mg/kg via a single intravenous infusion over a 30- to 45-minute period. Only a single trial of intranasal esketamine was identified. At 4 hours post-infusion, treatment with ketamine was associated with a significant reduction in suicidal ideation scores (standardised mean difference = -0.51, 95% confidence interval = [-1.00, -0.03]), which persisted until 72 hours post-infusion (time points between 12 and 24 hours: standardised mean difference = -0.63, 95% confidence

interval = [-0.99, -0.26]; between 24 and 72 hours: standardised mean difference = -0.57, 95% confidence interval = [-0.99, -0.14]), but not thereafter. However, there was marked heterogeneity of results. In a single trial of esketamine, marginal effects on suicidal ideation were observed. In terms of actual suicidal behaviour, there were virtually no data on effects of ketamine or esketamine.

CONCLUSION:
A single infusion of ketamine may have a short-term (up to 72 hours) beneficial impact on suicidal thoughts. While confirmation of these results in further trials is needed, they suggest possible use of ketamine to treat acute suicidality. Means of sustaining any anti-suicidal effect need to be found.

Combination therapy utilizing ketamine and transcranial magnetic stimulation for treatment-resistant depression: a case report

Abstract

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In the present article, we report on the case of a 23-year-old woman with a history of treatment-resistant depression who achieved significant symptom improvement with a novel treatment consisting of ketamine, a dissociative anesthetic, and external neuromodulation with transcranial magnetic stimulation (TMS). This case highlights the need for further investigation of treatments pairing external neuromodulation with dissociative anesthetics.

Despite advances in pharmacological treatment, approximately half of patients fail to achieve full remission, prompting researchers to look beyond conventional antidepressant medications [1]. Recent research has examined transcranial magnetic stimulation (TMS and its variant rTMS), in which an electromagnetic stimulator positioned at the scalp induces a change in local and distant electric field conditions and may cause an associated depolarization of neurons [2]. When used to stimulate the dorsolateral prefrontal cortex, rTMS has been associated with significant antidepressant effects [3], and is an FDA-approved treatment for depression. However, it is difficult to achieve remission with rTMS alone. A separate body of research has investigated intravenous ketamine, an *N*-methyl-D-aspartate (NMDA) antagonist [4–8]. In contrast to typical antidepressant medications that take effect within several weeks, ketamine provides relief within 2 h and lasts between four and seven days, after which relapse is common [4,5]. To date, little is known about the possible synergistic effects of combined rTMS/ketamine treatment for depression.

One study found that a factor underlying treatment resistance in depression is abnormal function in a thalamocortical circuit involving the anterior cingulate cortex (ACC), among other areas [9,11]. Accordingly, the first author hypothesized stimulating the ACC with TMS would restore normal functioning in the relevant circuit, thereby improving response to

ketamine. We report on a depressed patient treated with a novel combined ketamine/TMS technique who showed substantial improvement in depression symptomatology at the end of treatment, and again at follow-up 483 days later. An IRB exemption was obtained from an independent accredited agency.

Case Report. Patient X is a 23-year-old woman who presented with a 9-year history of depression that did not respond to treatment with sertraline, buprorion, paroxetine, or stimulants. She also presented with attention deficit disorder that was treated with amphetamine from intake through follow-up. Her past history included diagnoses of anorexia nervosa and substance abuse (cocaine) that were in full remission at intake. Patient X was systematically assessed for psychopathology by an independent licensed psychologist at the outset of treatment. The primary assessment instruments were the Beck Depression Inventory-II (BDI-II) and the Personality Assessment Inventory (PAI). PAI subscale scores greater than 70 indicate clinically significant difficulties. Results of this assessment suggested that Patient X exhibited moderate levels of depression (BDI-II = 17, PAI DEP T = 84) consisting predominantly of depressed mood (PAI DEP-A T = 83), low self-esteem (PAI DEP-C T = 87), and suicidal ideation (PAI SUI T = 62). In addition, the initial assessment suggested significant difficulties in developing and maintaining a sense of life purpose and self-identity (PAI BOR-I T = 80), problematic alcohol use (PAI ALC = 66), and concentration difficulties (PAI SCZ-T T = 73). After this comprehensive assessment, Patient X's mood was assessed during each treatment by the first author using a visual analog scale. In this measure, Patient X indicated where her mood fell along a continuum from "the worst I can imagine feeling" to "the best I can imagine feeling."

Prior to beginning combined treatment, Patient X was given 2 days of rTMS pretreatment (four treatments per day of 30 min with 45 min of rest between treatments). Combined ketamine/TMS treatment began the following day and continued at weekly intervals for 13 weeks. Fifteen years of observational evidence from our clinic suggested that this duration produced clinically significant results. Combined treatment consisted of 40 min of 1 Hz continuous TMS with an intravenous ketamine infusion administered concurrent to and bracketed within the middle 30 min of TMS, resulting in 5 min of TMS pre- and postinfusion. The dosage of infused ketamine increased gradually from 30 mg at the first treatment to 100 mg at the last treatment. During combined treatment, the TMS head coil (manufactured by Neotonus) was positioned at the midline of the scalp to achieve maximal stimulation of the medial prefrontal area that overlays the anterior cingulate, a region implicated in depression [10]. While direct stimulation of the anterior cingulate is not likely given its subcortical position and the limited electromagnetic field penetration of TMS coils [4], we hypothesized that indirect stimulation of the anterior cingulate via TMS applied to the overlaying scalp region would result in a beneficial effect.

Baseline brain scans were used to ensure accurate coil positioning at each treatment. TMS treatments were administered at 115% of motor threshold at 1 Hz continuous pulsation given that these settings were within safety guidelines and consistent with previous research. Using this method, we hypothesized that the dissociative effects of ketamine along with TMS activation of the anterior cingulate would help reestablish normal oscillatory rhythms in this region, leading to a decrease in depression symptoms.

After the treatment on week three, Patient X reported a substantial improvement in mood and energy levels. Patient X noted that these gains were maintained over the duration of treatment with some fluctuation in mood due to relationship difficulties. Soon after the last

combined treatment, Patient X reported a nondepressed mood with increased motivation and diminished attention difficulties. Combined treatment was followed by regular psychiatric visits 1–2× /month for 14 months. Gains were generally maintained over this span, with Patient X reporting that she was able to begin graduate studies and sustain an intimate relationship. Four hundred and eighty three days after her initial assessment, Patient X was again systematically assessed for psychopathology by an independent licensed psychologist. Results showed substantial decreases in depression (BDI-II = 0, PAI DEP T = 41), suicidal ideation (PAI SUI T = 45), alcohol use (PAI ALC T = 49), and concentration difficulties (PAI SCZ T = 49), along with increased sense of self-purpose (PAI BOR-I T = 56).

Discussion. This case report adds to the literature on improving the efficacy of brain electromagnetic stimulation by administering pharmacological agents that modulate glutamatergic transmission. Whereas previous research suggests that rTMS is somewhat effective in treating depression [3], and that subanesthetic doses of ketamine are temporarily helpful with depression [5–9]; the present case report is the first to suggest that a combined ketamine/rTMS treatment may be a more efficacious treatment for refractory depression than either infused ketamine or rTMS alone. Future research should examine combined ketamine/TMS treatment in a randomized controlled trial.

Declaration of Interest

Dr. Best reports no biomedical financial interests or potential conflicts of interest. Brian Griffin reports no biomedical financial interests or potential conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References

1.Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000;47:351–4. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]

2.Barker AT. An introduction to the basic principles of magnetic nerve stimulation. J Clin Neurophysiol 1991;8:26–37. [Google Scholar]

3.Gross M, Nakamura L, Pascual-Leone A, Fregni F. Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies. Acta Psychiatr Scand 2007;116(3):165–73. [Google Scholar]

4.Deng ZD, Lisanby SH, Peterchev AV. Electric field depth–focality tradeoff in transcrancial magnetic stimulation: simulation comparison of 50 coil designs. Brain Stimul 2013;6(1):1–13. [Google Scholar]

5.Diazgranados N, Ibrahim LA, Brutsche NE, et al. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. J Clin Psychiatry 2010;71:1605–11. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]

6.Murrough JW, Perez AM, Pillemer S, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry 2012;74(4):250–6. [Google Scholar]

7.Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006;63(8):856–64. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
8.Zarate CA Jr, Brutsche NE, Ibrahim L, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. Biol Psychiatry 2012;71:939–46. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
9.Ibrahim L, Diazgranados N, Franco-Chaves J, et al. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs. add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. Neuropsychopharmacology 2012;37:1526–33. [Google Scholar]
10.Mayberg HS, Lozano AM, Voon V, et al. Deep brain stimulation for treatment-resistant depression. Neuron 2005;45(5): 651–60. [Crossref], [PubMed], [Web of Science ®], [Google Scholar]
11.LLínas RR, Ribary U, Jeanmond D, et al. Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc Natl Acad Sci 1999;96(26):15222–7. [Google Scholar]

Is Ketamine Safe to Use for Depression During Pregnancy?

The fast-acting nasal spray esketamine, marketed as SpravatoTM, was recently approved by the Food and Drug Administration (FDA) to treat depression in individuals whose depression has been resistant to at least two medications. Structurally, esketamine is an enantiomer, or mirror image, of ketamine and works by a similar mechanism.1 The antidepressant response is evident within a few days of administration, unlike traditional antidepressants that often take weeks for the patient to feel any improvement in mood. This is particularly advantageous for patients who have suicidal thoughts and need quick resolution of depression symptoms.

While an old anesthetic drug, this new formulation has yet to be explored extensively through clinical studies in the pregnant and breastfeeding population. Interestingly, animal studies conducted don't seem to produce promising results. A new study conducted in 2017 found that offspring of pregnant rats treated with ketamine had impaired learning and memory.2 Another study found that offspring of rats treated with ketamine during the second trimester had long-term neurocognitive dysfunction.3 A study in 2016 found that ketamine exposure during pregnancy in rats resulted in reduced development of certain brain regions in the offspring.4 Thus, at this time, ketamine's effects in pregnancy are concerning and it is not recommended for use during pregnancy. Although the FDA has not assigned a pregnancy category to esketamine, the pharmaceutical provider suggests that SpravatoTM may cause fetal toxicity and should be avoided in pregnant and breastfeeding women.5

This is not to say that women shouldn't seek treatment for depression during pregnancy, however. It is instead recommended that pregnant or potentially soon-to-be pregnant women turn to older antidepressants, such as select serotonin reuptake inhibitors (SSRIs). The more popular antidepressants used during pregnancy include sertraline, escitalopram, or fluoxetine.6 Paroxetine has been associated with an increased risk of cardiac defects in exposed infants with exposure in the 1st trimester.6 Bupropion is another alternative treatment for depression in pregnant mothers. Treatment should be initiated on a case-by-

case basis depending on severity of symptoms and personal history. All of these aspects should be discussed with a physician before initiating therapy. Medication changes should ideally be made prior to pregnancy.6

Common antidepressants in pregnancy:

Medication	**Description**
Bupropion	Animal studies revealed no evidence of harm6
Citalopram	Possible SSRI withdrawal syndrome6
Esketamine	New to the market
Escitalopram	Possible SSRI withdrawal syndrome6
Fluoxetine	Possible SSRI withdrawal syndrome6
Paroxetine	Studies in pregnant women suggested some risk to fetus6

Conclusions

- Esketamine has not been studied extensively in pregnant women, but has shown negative effects on exposed offspring in rats.
- Esketamine is not currently recommended for pregnant women.
- Other antidepressants, such as an SSRI or bupropion, should be considered for depression in pregnancy.
- Medication changes should ideally be made before pregnancy and should be initiated on case-by-case basis with individualized treatment.
- An appropriate dose for an adult is 56 mg (2 sprays total intranasally) administered on day 1 of treatment, then 56-84 mg (2-3 sprays total) twice weekly for 4 weeks.5
- It is important to remember that untreated depression during pregnancy is very risky and mothers should seek treatment for depression during pregnancy.

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Resources:

1.Paddock, Catharine. “The FDA Approve Esketamine Nasal Spray for Severe Depression.” Medical News Today, MediLexicon International, 8 Mar. 2019, www.medicalnewstoday.com/articles/324656.php.

2.Li, Xinran, et al. “Ketamine Administered Pregnant Rats Impair Learning and Memory in Offspring via the CREB Pathway.” Oncotarget, vol. 8, no. 20, 2017, doi:10.18632/oncotarget.15405.

3.Li, Yanan, et al. “Long-Term Neurocognitive Dysfunction in Offspring via NGF/ERK/CREB Signaling Pathway Caused by Ketamine Exposure during the Second Trimester of Pregnancy in Rats.” Oncotarget, vol. 8, no. 19, 2017, doi:10.18632/oncotarget.16042.

4.Dong, C., et al. “Ketamine Exposure during Embryogenesis Inhibits Cellular Proliferation in Rat Fetal Cortical Neurogenic Regions.” Acta Anaesthesiologica Scandinavica, vol. 60, no. 5, 2016, pp. 579–587., doi:10.1111/aas.12689.

5.“SPRAVATO™ Treatment Center.” Spravato Esketomine, www.spravatotreatmentcenter.com/.

6.Payne, Jennifer L., and Samantha Meltzer-Brody. “Antidepressant Use During Pregnancy: Current Controversies and Treatment Strategies.” Clinical Obstetrics and Gynecology, vol. 52, no. 3, 2009, pp. 469–482., doi:10.1097/grf.0b013e3181b52e20.

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A Randomized Controlled Trial of Repeated Ketamine Administration for Chronic Posttraumatic Stress Disorder

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Abstract

Objective:

Posttraumatic stress disorder (PTSD) is a chronic and disabling disorder, for which available pharmacotherapies have limited efficacy. The authors’ previous proof-of-concept randomized controlled trial of single-dose intravenous ketamine infusion in individuals with PTSD showed significant and rapid PTSD symptom reduction 24 hours postinfusion. The

present study is the first randomized controlled trial to test the efficacy and safety of repeated intravenous ketamine infusions for the treatment of chronic PTSD.

Methods:

Individuals with chronic PTSD (N=30) were randomly assigned (1:1) to receive six infusions of ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg) (psychoactive placebo control) over 2 consecutive weeks. Clinician-rated and self-report assessments were administered 24 hours after the first infusion and at weekly visits. The primary outcome measure was change in PTSD symptom severity, as assessed with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), from baseline to 2 weeks (after completion of all infusions). Secondary outcome measures included the Impact of Event Scale–Revised, the Montgomery-Åsberg Depression Rating Scale (MADRS), and side effect measures.

Results:

The ketamine group showed a significantly greater improvement in CAPS-5 and MADRS total scores than the midazolam group from baseline to week 2. At week 2, the mean CAPS-5 total score was 11.88 points (SE=3.96) lower in the ketamine group than in the midazolam group (d=1.13, 95% CI=0.36, 1.91). Sixty-seven percent of participants in the ketamine group were treatment responders, compared with 20% in the midazolam group. Among ketamine responders, the median time to loss of response was 27.5 days following the 2-week course of infusions. Ketamine infusions were well tolerated overall, without serious adverse events.

Conclusions:

This randomized controlled trial provides the first evidence of efficacy of repeated ketamine infusions in reducing symptom severity in individuals with chronic PTSD. Further studies are warranted to understand ketamine’s full potential as a treatment for chronic PTSD.

Ketamin als Hoffnungsträger bei der chronischen posttraumatischen Belastungsstörung

Deborah Brauser, 18. Januar 2021

Wiederholte intravenöse Ketamin-Infusionen verschaffen Patienten mit posttraumatischer Belastungsstörung (PTBS) schnelle Linderung, so neue Forschungsergebnisse.

In der ersten randomisierten kontrollierten Studie zur wiederholten Verabreichung von Ketamin bei chronischer PTBS erhielten 30 Patienten sechs Infusionen mit Ketamin oder Midazolam (als psychoaktives Placebo) über zwei aufeinanderfolgende Wochen.

Es wurden keine ernsthaften TRAE berichtet. Während der Ketamin-Infusion kam es zu einigen dissoziativen Symptomen mit den höchsten Werten gegen Ende der Infusion, die jedoch bis zur nächsten Bewertung 2 Stunden nach der Infusion wieder verschwunden waren.

Die am häufigsten berichtete Nebenwirkung in der Ketamin-Gruppe im Vergleich zu Midazolam waren nach Beginn der Infusion verschwommenes Sehen (53% vs. 0%), gefolgt von Schwindel (33% vs. 13%), Müdigkeit (33% vs. 87%), Kopfschmerzen (27% vs. 13%) und Übelkeit oder Erbrechen (20% vs. 7%).

„Weitreichende Verbesserung“

„Die Ergebnisse in dieser Patientenpopulation zeigen insgesamt, dass wiederholte Ketamin-Infusionen über 2 Wochen mit einer deutlichen, klinisch signifikanten Verbesserung der PTBS-Symptomatik verbunden sind“, schreiben die Untersucher und Feder empfand sie als „sehr zufriedenstellend“.

„Es war auch ermutigend zu hören, was einige der Teilnehmer zu sagen hatten. So berichteten manche davon, wie sich ihre Symptome und Gefühle im Laufe der Ketamin-Behandlung verändert hatten, wobei sie sich stärker fühlten und besser mit ihrem Trauma und ihren Erinnerungen umgehen konnten.“

Sie fügte jedoch hinzu, dass die Studie nicht speziell zur Bewertung von Ketamin bei therapieresistenter PTBS angelegt war. „Einige Patienten hatten bereits mehrere erfolglose Behandlungen hinter sich, während andere noch nie behandelt worden waren. Die Wirksamkeit bei therapieresistenter PTBS ist eine wichtige Frage für zukünftige Untersuchungen“, sagte Feder.

Die Ergebnisse in dieser Patientenpopulation zeigen insgesamt, dass wiederholte Ketamin-Infusionen über 2 Wochen mit einer deutlichen, klinisch signifikanten Verbesserung der PTBS-Symptomatik verbunden sind. Dr. Adriana Feder und Kollegen

Weitere Bereiche, die es wert seien, in Zukunft erforscht zu werden, wären die Wirksamkeit der Behandlung bei Patienten mit verschiedenen Traumaformen und die Frage, ob die Ergebnisse bei Patienten, die Ketamin plus Psychotherapie erhalten, länger anhielten, merkte sie an.

„Ich möchte nicht die Tatsache ignorieren, dass die derzeit verfügbaren Behandlungen bei einer Reihe von Menschen mit chronischer PTBS funktionieren. Da es aber noch viel mehr Menschen gibt, bei denen diese Behandlungen nicht oder nicht ausreichend helfen, ist dies sicherlich ein potenziell sehr vielversprechender Ansatz, der in das Behandlungsrepertoire eines Klinikers aufgenommen werden kann“, sagt Feder.

Weiterlesen bei Medscape
https://deutsch.medscape.com/artikelansicht/4909690?pa=jEL2oItdbSUBx6BSQz0Vvhh4LphfCA612KE3KUYilWMGC2qftgLwu3KfPYKTPRKx56MI7dGTgNawPfsOtJla9Q%3D%3D#vp_3

Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta
Link zur Studie auf Elsevier:
Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta

“Death - rebirth” Psychotherapy with Ketamine
Igor Kungurtsev, M. D.

The recent changes in the former Soviet Union have allowed Russian and American researchers to communicate freely for the first time since the October Revolution. Prior to these changes, the story of Russian psychedelic research had remained a mystery in the West. The following article is one of the first reports of psychedelic research to emerge from Russia as well as the first published outcome study of ketamine-assisted psychotherapy.

Igor Kungurtsev, M.D. is a research associate at the Bekhterev Psychoneurological Research Institute in St. Petersburg, Russia, and a psychiatrist in private practice. Kungurtsev is also Vice Chairman of the St. Petersburg Transpersonal Association, and a member of the Board of Advisors of the Albert Hofmann Foundation. About five years ago, our research team obtained permission from the Central Pharmacological Committee in Moscow to use ketamine as an adjunct to psychotherapy with alcoholics. Ketamine is an anesthetic used in modern medicine which can also be used in subanesthetic doses to safely and reliably induce transpersonal states with profound healing potential. This paper will review the phenomenology of the ketamine state, the procedure for ketamine-assisted psychotherapy, and the preliminary results of our study with alcoholic and neurotic patients. Ketamine, 2-(o-chlorophenyl)-2-(methyl-amino) cyclohexanone HCL, has several advantages over other psychedelics as an adjunct to psychotherapy. It is short acting, the psychoactive effects lasting about an hour. In addition, ketamine is not scheduled like other psychedelics. In lower doses (about one sixth to one tenth of that usually used in surgery), it induces profound transpersonal states. My colleagues and I adopted the transpersonal paradigm as a result of our personal and clinical experience with ketamine before we had become acquainted with the literature on psychedelics and altered states of consciousness.

At first, we attempted to use ketamine solely as a means of increasing the patient's suggestibility. The psychotherapist could then place suggestions of sobriety more deeply into the patient's subconscious. Anesthesiologists have reported that ketamine frequently induces states of confusion, feelings of death and dying, and unpleasant hallucinations. This is known as the "emergence reaction", and is considered to be a negative side effect of ketamine in surgical patients who are unprepared for these psychological effects. Subsequently, we had the idea that we could associate these feelings of death and dying with the smell and taste of alcohol (an aversive conditioning model). Not long after we started our research, however, we came across situations which were incompatible with this paradigm. After ketamine injections, many of our patients reported very strange experiences. They began to report that they felt disconnected from their bodies, and that they were "floating" in strange worlds. Some of them, for the first time in their lives, spoke about God, the meaning of life, and their relationships. Although we tried to help our patients formnegative associations and develop an aversion to alcohol, their experience was more profound and mystical, sometimes with no relationship to our suggestions or psychotherapy.

At this point, I undertook a series of self-administrations which completely changed my conception of the ketamine experience. I tried various dosages in order to choose the level most appropriate for our patients. Three or four minutes after the first injection, I felt this world begin to disappear, and I experienced myself as a point of consciousness which was floating in strange worlds. The most unusual feeling was that I had no body, yet somehow "I" existed. The next development was indescribable. During the first stage, I seemed to

exist only as a point of consciousness, but still, “I” existed. Then there was a stage where even this disembodied sense of self began to disappear, and I felt a real terror of dying. At that moment I managed to surrender and let go. All that remained was awareness; there was no “I” as me, as an individual point of consciousness. It was as if there existed only that which was aware of itself.

This experience profoundly changed my view of ketamine, and gave me new insight into some esoteric concepts of Buddhism and other Eastern philosophies. It profoundly changed my understanding of death and dying as well.

For several days after this session, I had a feeling of inner surrender, as if my life was a game that I was playing very easily. While I performed my daily activities, I was very calm and centered inside. It was a remarkable feeling. After this self-experimentation, we changed our paradigm and adopted a transpersonal approach. We now refer to this treatment as “Death-Rebirth” Psychotherapy. The research is done in a comparatively large hospital for the treatment of alcoholics near St. Petersburg. The patients in this hospital are all voluntary. The psychotherapy is usually limited to the area of alcohol abuse, and the goal of treatment is overcoming their so-called “alcohol denial.” A typical patient in our ketamine program stays in the hospital about one month. During the first phase of therapy, we treat their alcohol withdrawal syndrome and any related anxiety or affective disorders. Then, we start rational, cognitive psychotherapy in order to establish a mental set of sobriety and a negative attitude toward alcohol. However, we go beyond the problem of alcohol abuse to explore broader issues including the patient’s life history, relationships, and world view. Later in the program, we tell them that they will undergo a new treatment which will allow them to see and feel the subconscious roots of their problems. We help our patients understand that their alcohol problem is only a superficial symptom – the manifestation of more deeply rooted problems. On the day of the session, we give the patient an intragluteal injection of about 150 mg. of ketamine (approx. 2 mg. per kg.). We prefer the intramuscular route because the effect is more gradual, and the transpersonal state lasts longer. With an intravenous injection, the effect lasts only about fifteen to twenty minutes, but after an intramuscular injection, it lasts from about forty-five minutes to an hour. We tell the patient that they will enter some unusual states of consciousness and that they may feel detached from their body. We also instruct them to surrender fully to the experience. I gave up our original approach of trying to induce something specific in the patient during the session. Under the influence of ketamine, especially in these doses, one has no direct contact with ordinary reality. The psychotherapist can try to influence the experience, but it will be in vain. We are available, however, to give emotional support if the patient requests it. As with other psychedelics, music also enhances the ketamine experience. We have found composers whose music is particularly conducive for ketamine sessions, such as Jean Michael Jarre or Kitaro. After forty-five minutes to an hour, the patient slowly comes back from the experience. During the recovery period, which takes about an hour and a half or two hours, the patient begins to feel ordinary reality returning, but part of their consciousness is still in another world, another dimension. At this point in the session, the patient usually begins to describe their experience, and we begin some interpretation. After the session, the patient goes to rest, and we ask them to write down a detailed report of their experience that evening. The next day, we have a follow-up session which includes an in-depth discussion of their experience. When several patients have ketamine sessions on the same day, we do it as

group therapy. We gather these patients in a group the day before treatment and the day after, because when they all share the experience, it is usually more powerful. Regarding spiritual experiences induced by ketamine, it is interesting that many people who never thought about spirituality or the meaning of life reported having experiences that one might read about only in spiritual texts or Eastern teachings. At the beginning of ketamine sessions, people often experience the separation of consciousness from the body and the dissolving of the body ego. For many patients, it is a profound insight that they can exist without their bodies as pure consciousness or pure spirit. Many of them said that as a result of their experience, they understood the Christian notion of the separation of the soul and the body, and that they now believe some part of them will continue to exist after death. There were several cases where people reported contact with God, but this is usually not an anthropomorphic figure. They describe an ocean of brilliant white light, sometimes a golden white light, which is filled with love, bliss and energy. After coming back to ordinary consciousness, they feel sure that they have had contact with a higher power. There were also several cases where people saw Jesus Christ approaching them. It seems ironic that so many of our patients, through their own experience, were converted to a more spiritual approach to life, despite living in a country where people have been brought up for generations with atheism.

A second observation is that many patients report the existence of other dimensions or other worlds that are parallel to ours. They usually report that these other dimensions seem as real or more real than our own. Some patients experience this “ego death”, or the dissolving of the individual sense of self, which 1 had experienced. Of course they do not use these terms. They might say, “I ceased to exist, I disappeared, yet still something existed. It was like I became the whole universe or the whole cosmos”. In my experience, I also got the feeling of the collapse of space and time, and I really felt that space and time were illusions. It was as if I had collapsed into a single point with no space and no time, and it was from this point that the whole universe seemed to be manifesting. Another interesting observation, although not a topic of our research, is the correlation between the type of personality and the type of experience under the influence of ketamine. People who are very controlled and have difficulties letting go, or who have problems with relationships, often have negative experiences with ketamine. For them, the dissolving of the individual sense of self is horrible. For other patients who are more relaxed and able to surrender, who have a deep capacity to love, the experience is usually blissful, even ecstatic.

The action of ketamine is somewhat unique in comparison with other psychoactive substances. Stanislav Grof has divided the psychedelic experience and other experiences of altered states of consciousness into three main categories; the psychodynamic level, where people recall the past events of their lives, especially childhood memories; the perinatal level, or the recollection of the birth experience; and the transpersonal level, which includes the mystical experience. “Transpersonal” refers to experiences which go beyond one’s individual personality and involve the transcendence of the spatial or temporal boundaries of ordinary consciousness. One might also experience mythological themes or archetypal figures like the god or goddess, or the expansion of consciousness to encompass the whole cosmos, etc. Ketamine differs from other psychedelics in that in medium doses, it usually it does not engage the psychodynamic level. Instead, it almost “throws” one into the transpersonal realm. The other major psychedelics, such as LSD or

mescaline, are more gradual and gentle, and in medium doses they usually engage the psychodynamic level. To induce transpersonal states, higher doses of these substances are normally required.
Of course, the effects of ketamine are also a function of dosage. In low doses, one remains in contact with ordinary reality, but with eyes closed one can see some strange images. They are not human forms, but usually geometric shapes like spheres or triangles, or simply open spaces. Following treatment, the patient is released from the hospital. Every two or three months, we see them for follow-up visits. We have collected data on patients who have undergone ketamine-assisted psychotherapy after spending one month in the hospital. About sixty eight per cent of these patients remain sober for one year following treatment. This is a very high success rate in comparison with other programs for alcoholism. In the control group, which was composed of patients who were in the same hospital, who were the same average age, and who were in the same stage of the development of alcoholism, the percentage who remained sober for one year was about forty-five to fifty per cent. So we have proven statistically that the ketamine experience is very useful. We believe that these positive results
in maintaining sobriety were not achieved simply because we were more successful in establishing a set of sobriety and a deeper negative attitude toward alcohol, but rather because of changes in the values, relationships, and world view of these patients. They began to see other goals, other values, other pleasures in their lives, and this was the main reason for their sobriety. For us, this was much more interesting than the limited issue of keeping sober. We also administered several psychological tests before and after the ketamine treatment. We gave patients the MMPI, and after the session the scales which indicated anxiety and depression decreased statistically, even though these patients were not primarily neurotic or depressive. The same results were also confirmed by the Zung anxiety and depression scales, but we were interested in more than these clinical symptoms. We also tried to measure changes in values and world view after treatment. It was difficult to find an instrument to measure these changes, but the two scales we found most useful were the Omega Life Changes Questionnaire by Kenneth Ring, and the Self Assessment Spirituality Scale by Charles Whitfield. Kenneth Ring is a professor of psychology at the University of Connecticut who has done extensive research on near death experiences, and he created The Life Changes Questionnaire. It consists of some thirty questions that assess the individual’s values, goals, and attitudes toward material things, etc. Our patients showed the most significant changes in exactly this scale. According to the results of this questionnaire, they shifted to a more spiritual world view. We also used the Self-Assessment Spirituality Scale by Charles Whitfield, an American researcher who has tried to introduce spirituality into recovery from alcoholism. In addition, we developed our own instrument, called the “repertory grid”, which measures psychosemantic fields. It measures the meanings of key words such as life, love, death, despair, Jesus Christ, etc. Through this tool, we can measure changes in the patient’s attitude toward various aspects of life. This scale also showed that our patients shifted to a wider, more spiritual world view.
Our anecdotal observations also confirmed these changes. Some patients began to write poems after their ketamine sessions, while others began to paint. Many of them began to feel more connected with nature and reported, for example, that after treatment they went to the countryside more often. When some patients went back to their families, they

noticed problems in their relationships, or certain idiosyncrasies of their spouses and relatives which they were unaware of before treatment. Ketamine seems to increase the capacity for detached observation. I would also like to relate some unusual anecdotes connected with our research. About one year after we began our study, a group composed of two men and one woman appeared at our hospital who were very strange looking, wore strange clothes, and had strange, shiny eyes that seemed out of focus. They called themselves “magicians”, and said that they sensed in their meditations and magic practice that in this hospital, some people were throwing other souls into the “astral plane”. They had come to see what we were doing, like “astral police”. Prior to this, we had not published the results of our work, and only a few professionals knew about it. Also, this hospital is situated in the suburbs of St. Petersburg, and is not widely known. So we described our work and showed them our hospital. They approved! They also told us that they themselves used ketamine for their underground magic practice. As far as I understood from our conversations, their practice to some extent imitates or closely parallels the practice of Carlos Casteneda. They had gone into the forest and found power spots and power plants, and practiced meditation there. This acquaintance was useful for us because, as it turned out, they had a tremendous volume of underground psychedelic literature, translated into Russian. When we shifted to the transpersonal paradigm, we began a literature search, and we sent requests to several libraries, including the main state library in Moscow. Although they probably had this literature, it was two or three years ago, before the changes in Russia, and they didn’t send it to us. So the magicians gave us, for example, Peter Stafford’s Psychedelics Encyclopedia. Later, there was another interesting episode with these magicians. One of the men told me that they also used mushrooms growing in the forest near the region of St. Petersburg to induce psychedelic states. At first I didn’t believe him, but he gave me a dried specimen, and I identified it in the Psychedelics Encyclopedia as Psilocybe semilanceata. To date, the total number of patients treated with this method is about four hundred. Our results show that ketamine-assisted psychotherapy is significantly more effective in treating alcoholism than standard nondrug psychotherapy. In addition, ketamine-assisted psychotherapy results in positive life changes which
go beyond the limited goal of maintaining sobriety, including profound changes in values, relationships, and world view. In the near future, we plan to continue our work with alcoholic patients and to develop this approach further with neurotic patients using repeated ketamine sessions. Note: The author would like to thank Robert Zanger and Blackbird Willow for their assistance in the preparation of this article.
Reprinted from the Fall 1991 issue of the Albert Hofmann Foundation bulletin.

Optimizing the Treatment of CRPS With Ketamine

Abstract

Objective:

This study aimed to develop a method that objectively measures the clinical benefits of ketamine infusions to treat complex regional pain syndrome (CRPS), thus making it possible, for the first time, to determine the optimal dosing of ketamine and duration of treatment to treat CRPS.

Materials and Methods:

All patients were diagnosed with hyperalgesia associated with CRPS. Patients underwent an outpatient, 4-day, escalating dose ketamine infusion. Hyperalgesia was measured using pain thresholds. Clinical outcome was determined without knowledge of the patient's pain thresholds throughout treatment.
Results:

We found a correlation between pain thresholds and the intensity of pain reported by the patient at various sites of the body. We found that clinical outcomes correlated with improvement in pain thresholds. There was a plateau in pain thresholds between days 3 and 4 for the lower extremities. There was no plateau in pain thresholds observed for the upper extremities.
Discussion:

Our findings suggest that 4 days of treatment are sufficient for the treatment of CRPS of the lower extremities. For the upper extremities, >4 days may be required. Our study is the first to utilize quantitative sensory testing to direct the treatment of a chronic pain disorder.

KOMPLETTE STUDIE LESENEAD
https://journals.lww.com/clinicalpain/pages/articleviewer.aspx?year=2020&issue=07000&article=00003&type=Fulltext

Mystical-type experiences occasioned by ketamine mediate its impact on at-risk drinking: Results from a randomized, controlled trial

https://journals.sagepub.com/doi/10.1177/0269881120970879
A Single Ketamine Infusion Combined With Motivational Enhancement Therapy for Alcohol Use Disorder: A Randomized Midazolam-Controlled Pilot Trial

Abstract
Objective: Pharmacotherapy and behavioral treatments for alcohol use disorder are limited in their effectiveness, and new treatments with innovative mechanisms would be valuable. In this pilot study, the authors tested whether a single subanesthetic infusion of ketamine administered to adults with alcohol dependence and engaged in motiva- tional enhancement therapy affects drinking outcomes.
Methods: Participants were randomly assigned to a 52- minute intravenous administration of ketamine (0.71 mg/kg, N=17) or the active control midazolam (0.025 mg/kg, N=23), provided during the second week of a 5-week outpatient regimen of motivational enhancement therapy. Alcohol use following the infusion was assessed with timeline followback method, with abstinence confirmed by urine ethyl glucuro- nide testing. A longitudinal logistic mixed-effects model was used to model daily abstinence from alcohol over the 21 days after ketamine infusion.
Results: Participants (N=40) were mostly middle-aged (mean age=53 years [SD=9.8]), predominantly white (70.3%), and largely employed (71.8%) and consumed an average of five drinks per day prior to entering the study. Ketamine significantly increased the likelihood of abstinence, delayed the time to re- lapse, and reduced the likelihood of heavy

drinking days com- pared with midazolam. Infusions were well tolerated, with no participants removed from the study as a result of adverse events.
Conclusions: A single ketamine infusion was found to im- prove measures of drinking in persons with alcohol de- pendence engaged in motivational enhancement therapy. These preliminary data suggest new directions in integrated pharmacotherapy-behavioral treatments for alcohol use dis- order. Further research is needed to replicate these promis- ing results in a larger sample.
Am J Psychiatry 2020; 177:125–133; doi: 10.1176/appi.ajp.2019.19070684

READ THE COMPLETE STUDY
https://ajp.psychiatryonline.org/doi/pdf/10.1176/appi.ajp.2019.19070684

Ketamine-facilitated behavioral treatment for cannabis use disorder: A proof of concept study

ABSTRACT
Background

Sub-anesthetic ketamine infusions may benefit a range of psychiatric conditions, including alcohol and cocaine use disorders. Currently, there are no effective pharmacological treatments for cannabis use disorder.
Objectives

The objective of this uncontrolled proof of concept trial was to test the feasibility, tolerability, and potential therapeutic effects of integrating ketamine infusions with a behavioral platform of motivational enhancement therapy and mindfulness-based relapse prevention in treating cannabis use disorder (CUD).
Methods

Eight cannabis-dependent individuals (four female, four male) receiving motivational enhancement therapy and mindfulness-based relapse prevention behavioral treatments completed this single-blind outpatient 6-week study. Participants received either one or two infusions of ketamine (0.71 mg/kg [infusion 1]; 1.41 mg/kg [infusion 2] for non-responders) during the study. Participants self-reported cannabis use (Timeline Follow-Back) and underwent an assessment of confidence in abstaining from using cannabis (Drug-Taking Confidence Questionnaire) at predetermined time points throughout the study.
Results

Ketamine infusions were well-tolerated and there were no adverse events. Frequency of cannabis use decreased significantly from baseline (B = 5.1, s.e = 0.7) to the week following the first infusion (B = 0.8, s.e = 0.412), and remained reduced at the end of the study (B = 0.5, s.e = 0.3). Participants' confidence in their ability to abstain from cannabis in potentially triggering situations increased significantly from baseline to the end of study.
Conclusions

These findings suggest that combining ketamine with behavioral therapy is feasible,tolerable, and potentially helpful, in treating cannabis-dependent individuals.

ZUR KOMPLETTEN STUDIE
https://www.tandfonline.com/doi/abs/10.1080/00952990.2020.1808982

Psychedelics as a novel approach to treating autoimmune conditions

Abstract
With a rise in the incidence of autoimmune diseases (AiD), health care providers continue to seek out more efficacious treatment approaches for the AiD patient population. Classic serotonergic psychedelics have recently been gaining public and professional interest as novel interventions to a number of mental health afflictions. Psychedelics have also been shown to be able to modulate immune functions, however, while there has been great interest to researching into their psychotherapeutic applications, there has so far been very little exploration into the potential to treat inflammatory and immune-related diseases with these compounds. A handful of studies from a variety of fields suggest that psychedelics do indeed have effects in the body that may attenuate the outcome of AiD. This literature review explores existing evidence that psychedelic compounds may offer a potential novel application in the treatment of pathologies related to autoimmunity. We propose that psychedelics hold the potential to attenuate or even resolve autoimmunity by targeting psychosomatic origins, maladaptive chronic stress responses, inflammatory pathways, immune modulation and enteric microbiome populations.

Komplette Studie auf sciencedirect.com lesen
https://www.sciencedirect.com/science/article/pii/S0165247820303977

Ketamine Metabolites Enantioselectively Decrease Intracellular D-Serine Concentrations in PC-12 Cells

Abstract
D-Serine is an endogenous NMDA receptor co-agonist that activates synaptic NMDA receptors modulating neuronal networks in the cerebral cortex and plays a key role in long-term potentiation of synaptic transmission. D-serine is associated with NMDA receptor neurotoxicity and neurodegeneration and elevated D-serine concentrations have been associated with Alzheimer's and Parkinsons' diseases and amyotrophic lateral sclerosis. Previous studies have demonstrated that the ketamine metabolites (*rac*)-dehydronorketamine and (2*S*,6*S*)-hydroxynorketamine decrease intracellular D-serine concentrations in a concentration dependent manner in PC-12 cells. In the current study, PC-12 cells were incubated with a series of ketamine metabolites and the IC50 values associated with attenuated intracellular D-serine concentrations were determined. The results demonstrate that structural and stereochemical features of the studied compounds contribute to the magnitude of the inhibitory effect with (2*S*,6*S*)-hydroxynorketamine and (2*R*,6*R*)-hydroxynorketamine displaying the most potent inhibition with IC50 values of 0.18 ± 0.04 nM and 0.68 ± 0.09 nM. The data was utilized to construct a preliminary 3D-QSAR/pharmacophore model for use in the design of new and more efficient modulators of D-serine.

Komplette Studie auf journals.plos.org lesen

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0149499

Post-Marketing Safety Concerns with Esketamine: A Disproportionality Analysis of Spontaneous Reports Submitted to the FDA Adverse Event Reporting System

Abstract
Introduction: Esketamine nasal spray received approval for treatment-resistant depression in March 2019. *Objective:* Using the FDA Adverse Event Reporting System (FAERS) database (March 2019–March 2020), we analysed esketamine-related adverse events (AEs) to detect and characterize relevant safety signals. *Methods:* We used the consolidated case/non-case approach to estimate the reporting odds ratio (ROR) and information component (IC) with relevant confidence intervals (95% CI) for esketamine-related AEs with ≥4 counts. Comparisons between serious and non-serious AEs were performed using non-parametric tests. *Results:* The FAERS database contained 962 cases of esketamine-related AEs, with signals detected for several AEs, such as dissociation (ROR = 1,612.64, 95% CI = 1,354.63, 1,919.79; IC = 8.19, 95% CI = 7.96, 8.35), sedation (ROR = 238.46, 95% CI = 202.98, 280.15; IC = 7, 95% CI = 6.75, 7.18), feeling drunk (ROR = 96.17, 95% CI = 61.42, 150.57; IC = 4.84, 95% CI = 4.09, 5.36), suicidal ideation (ROR = 24.03, 95% CI = 18.72, 30.84; IC = 4.31, 95% CI = 3.9, 4.61), and completed suicide (ROR = 5.75, 95% CI = 3.18, 10.41; IC = 2.25, 95% CI = 1.23, 2.94). Signals for suicidal and self-injurious ideation, but not suicide attempt and completed suicide, remained when comparing esketamine to venlafaxine. Females and patients receiving antidepressant polypharmacy, co-medication with mood stabilizers, antipsychotics, benzodiazepines, or somatic medications were more likely to suffer from serious versus non-serious AEs ($\chi2 = 125.29$, $p < 0.001$, $\chi2 = 9.08$, $p = 0.003$, $\chi2 = 8.14$, $p = 0.004$, $\chi2 = 19.48$, $p < 0.001$, $\chi2 = 25.62$, $p < 0.001$, and $\chi2 = 16.79$, $p < 0.001$, respectively). *Conclusions:* Esketamine may carry a clear potential for serious AEs, which deserves urgent clarification by means of further prospective studies.

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https://www.karger.com/Article/Abstract/510703

Safety of Repeated Administration of Parenteral Ketamine for Depression

Abstract
The objective of this study was to investigate the safety of repeated parenteral ketamine for depression. An electronic survey inquiring about the frequency of adverse events was distributed to providers of parenteral ketamine for depression. In addition, the investigators conducted a search of published studies describing six or more repeated parenteral ketamine treatments administered to individuals for depression, and extracted reported adverse events. The survey was sent to 69 providers, of which 36 responded (52% response rate); after eliminating those that were incomplete, 27 were included in the analysis. The providers in the analysis collectively reported treating 6630 patients with parenteral ketamine for depression, one-third of whom received more than 10 treatments. Only 0.7% of patients experienced an adverse eect that required discontinuation of

ketamine. Psychological distress during the treatment was the most frequent cause. Other adverse events were extremely rare (such as bladder dysfunction (0.1%), cognitive decline (0.03%) and psychotic symptoms (0.03%)). Among the 20 published reports of repeated parenteral ketamine treatments, rates of significant adverse events resulting in discontinuation were low (1.2%). The rate of adverse eects reported in the survey and the published literature is low, and suggests that long-term treatment of depression with ketamine is reasonably safe.
Keywords: ketamine; major depressive disorder; depression; addiction

Pdf der kompletten Studie
https://ketaminplus.com/wp-content/uploads/2021/08/safety-of-repeated-administration-of-parenteral-ketamine-for.pdf

Immunoregulation and antidepressant effect of ketamine

Abstract
Major depressive disorder (MDD) is a common mental health disorder that brings severe disease burden worldwide. Traditional antidepressants are mainly targeted at monoamine neurotransmitters, with low remission rates and high recurrence rates. Ketamine is a noncompetitive glutamate *N*-methyl-d-aspartate receptor (NMDAR) antagonist, and its rapid and powerful antidepressant effects have come to light. Its antidepressant mechanism is still unclarified. Research found that ketamine had not only antagonistic effect on NMDAR but also strong immunomodulatory effect, both of which were closely related to the pathophysiology of MDD. Although there are many related studies, they are relatively heterogeneous. Therefore, this review mainly describes the immune mechanisms involved in MDD and how ketamine plays an antidepressant role by regulating peripheral and central immune system, including peripheral inflammatory cytokines, central microglia, and astrocytes. This review summarizes the related research, finds out the deficiencies of current research, and provides ideas for future research and the development of novel antidepressants.

Zur kompletten Studie: https://www.degruyter.com/document/doi/10.1515/tnsci-2020-0167/html

Considering Ketamine for Treatment of Comorbid Pain, Depression, and Substance Use Disorders

Abstract
The use of ketamine for treatment of comorbid pain, depression, and substance use disorders (SUDs) is becoming an option of increasing interest, as multiple clinical studies demonstrate its efficacy. Ketamine’s efficacy in this diagnostically complex population is mechanistically based on a wide array of affected brain areas in addition to presynaptic neurons of the spine. Efficacy has been shown in both depressive and pain disorders with durability lasting 3 to 4 weeks after discontinuation of ketamine. Although ketamine itself is a drug of potential abuse when used recreationally, its lasting effects without repeated daily use have also shown promise for patients with SUDs. Assisted psychotherapy concurrent with ketamine treatment can help dependent patients cultivate new perceptions

and ideals consistent with sobriety. Decreased opiate cravings in patients with SUDs may be related to ketamine's effects on reducing opiate-induced hyperalgesia. Given this and additional properties, ketamine can help reduce opiate medication burden, augment opiates in the hospice setting, or acutely alleviate symptoms of opiate withdrawal. [*Psychiatr Ann.* 2018;48(4):180–183.]

Zur kompletten Studie>>
https://journals.healio.com/doi/10.3928/00485713-20180312-02

The Canadian Network for Mood and Anxiety Treatments (CANMAT) Task Force Recommendations for the Use of Racemic Ketamine in Adults with Major Depressive Disorder

Abstract

Objective: Patients with major depressive disorder often have limited response to first-line and second-line medications; hence, novel pharmacological treatments are needed for treatment-resistant depression (TRD). Ketamine, an *N*-methyl-d-aspartate (NMDA) receptor antagonist, has demonstrated rapid antidepressant effects in patients with TRD. The Canadian Network for Mood and Anxiety Treatments (CANMAT) convened a task force to review the evidence for efficacy and safety of racemic ketamine and to provide recommendations for its use in clinical practice.
Methods: A systematic review was conducted with computerized search of electronic databases up to January 31, 2020 using combinations of search terms, inspection of bibliographies, and review of other ketamine guidelines and consensus statements. The level of evidence and lines of treatment were assigned according to CANMAT criteria. Recommendations were given in question-answer format.
Results: Intravenous (IV) racemic ketamine given as a single infusion has Level 1 evidence for efficacy in adults with TRD. The evidence for multiple infusions, given as an acute series or as ongoing maintenance treatment, is limited to Level 3. Adverse events associated with ketamine infusions include behavioral (e.g., dissociative symptoms) and physiological (e.g., hypertension) events. There is only Level 3 or 4 evidence for non-IV formulations of racemic ketamine. Consensus recommendations are given for clinical administration of IV ketamine including patient selection, facility and personnel issues, monitoring, and maintaining response.
Conclusions: Single-dose IV racemic ketamine is a third-line recommendation for adults with TRD. The need for repeated and maintenance ketamine infusions should be carefully assessed on a case-by-case basis with consideration of potential risks and benefits. Because of limited evidence for efficacy and risk for misuse and diversion, the use of oral and other formulations of racemic ketamine should be limited to specialists with ketamine-prescribing expertise and affiliations with tertiary or specialized centers.

Zur kompletten Studie >>
https://pubmed.ncbi.nlm.nih.gov/33174760/

Response to intravenous racemic ketamine after switch from intranasal (S)-ketamine on symptoms of treatment-resistant depression and post-traumatic stress disorder in Veterans: A retrospective case series

Abstract
Background: Racemic (R,S)-ketamine is a glutamatergic drug with potent and rapid acting antidepressant effects. An intranasal formulation of (S)-ketamine was recently approved by the US Food and Drug Administration (FDA) to be used in individuals with treatment-resistant depression (TRD). There are no data directly comparing outcomes on depression or other comorbidities between these two formulations of ketamine. However, recent meta-analyses have suggested that IV racemic ketamine may be more potent than IN-(S)-ketamine.
Methods: We retrospectively analyzed clinical outcomes in 15 Veterans with comorbid TRD and post-traumatic stress disorder (PTSD) who underwent ketamine treatment at the VA San Diego Neuromodulation Clinic. All Veterans included in this analysis were given at least 6 intranasal (IN)-(S)-ketamine treatments prior to switching to treatment with IV racemic ketamine.
Results: Veterans receiving ketamine treatment (across both IN-(S)-ketamine and IV-(R,S)-ketamine) showed significant reductions in both the Patient Health Questionnaire-9 (PHQ-9), a self-report scale measuring depression symptoms (rm ANOVA $F(14,42) = 12.6$, $p < 0.0001$), and in the PTSD checklist for DSM-5 (PCL-5), a self-report scale measuring PSTD symptoms (rm ANOVA $F(13,39) = 5.9$, $p = 0.006$). Post hoc testing revealed that PHQ-9 scores were reduced by an average of 2.4 ± 1.2 compared to baseline after (S)-ketamine treatments ($p = 0.1$) and by an average of 5.6 ± 1 after IV-ketamine treatments ($p = 0.0003$) compared to pretreatment baseline scores. PCL-5 scores were reduced by an average of 4.3 ± 3.3 after IN (S)-ketamine treatments ($p = 0.6$) and 11.8 ± 3.5 after IV-ketamine treatments ($p = 0.03$) compared to pretreatment baseline scores.
Conclusions: This work suggests that off-label IV-(R,S)-ketamine could be considered a reasonable next step in patients who do not respond adequately to the FDA-approved IN-(S)-ketamine. Further double-blinded, randomized controlled trials are warranted to assess whether IV racemic ketamine is more effective than IN-(S)-ketamine.
Keywords: (S)-ketamine; depression; ketamine.

Komplette Studie:
https://pubmed.ncbi.nlm.nih.gov/35122282/

Ketamine in chronic pain: A Delphi survey

Abstract
Background

There is no recommendation in Europe for the use of ketamine in patients with chronic pain. The heterogeneity of practice highlights the need to seek the advice of experts in order to establish a national consensus. This Delphi survey aimed to reach a national consensus on the use of ketamine in chronic pain in Pain clinics.

Methods

A collaborative four-round internet-based questionnaire was used. It was created after literature search on ketamine administration in chronic pain and included about 96 items. It discussed utility and advantages, adverse events and deleterious aspects, methods of administration, concomitant treatments and assessment of results.

Results

Twenty-eight experts completed all rounds of the survey with a total of 81.3% items reaching a consensual answer. Neuropathic pain represents the first indication to use ketamine, followed, with a good to moderate utility, by other situations (fibromyalgia, complex regional pain syndrome, central neuropathic pain, peripheral neuropathic pain, nociceptive pain, sensitization, opioid withdrawal, palliative care, depression). Experts agreed on the rare occurrence of adverse events. Concerning routes of administration, intravenous infusion with doses of 0.5–0.9 mg/kg/d for 4 days of treatment is preferred. Place of care is hospital, as in- or out-patient, with a quarterly administration of ketamine. Finally, ketamine effectiveness is assessed 1 month after infusion, and experts encourage combination with non-pharmacological treatment.

Conclusions

This Delphi survey established a consensus of pain specialists on the use of ketamine in refractory chronic pain, thus providing a basis for future comparative trials.

Significance

This Delphi survey in chronic pain reached agreement on four main aspects: (1) Priority to treat neuropathic pain with evaluation of effectiveness at 1 month; (2) No deleterious effects in the majority of listed diseases/situations with the absence or <3% of suggested adverse events; (3) 0.5–0.9 mg/kg/d IV infusion; (4) Combination with non-pharmacological treatment.

Komplette Studie:
https://onlinelibrary.wiley.com/doi/full/10.1002/ejp.1914?casa_token=nnUX13IGqIgAAAAA%3AHyzcBeqhLuqas16n4FVp1i3nbVYQZoOM3vWbTC5TpDDC4nuH4UF3wTHJfSMRQ2W2nCUf5Qt0wzJscPUhttps://pubmed.ncbi.nlm.nih.gov/35122282/

Comparative Effectiveness of Intravenous Ketamine and Intranasal Esketamine in Clinical Practice Among Patients With Treatment- Refractory Depression: An Observational Study

Abstract

Objective: Ketamine has been redeveloped as a rapid-acting antidepressant for treatment-resistant depression (TRD). There is a paucity of literature comparing subanesthetic intravenous (IV) ketamine and US Food and Drug Administration (FDA)-approved intranasal (IN) esketamine for TRD in real-world clinical settings. We compared the efficacy and time to achieve remission/response with repeated ketamine and esketamine.
Methods: An observational study of adults with TRD received up to 6 IV ketamine (0.5 mg/kg over 40 minutes) or up to 8 IN esketamine (56- or 84-mg) treatments from August 17, 2017, to June 24, 2021. Depressive symptoms were measured utilizing the 16-item

Quick Inventory of Depressive Symptomatology self-report (QIDS-SR) before and 24 hours after treatment. Cox proportional hazard models were used to evaluate associations between time to response (≥ 50% change in QIDS-SR score) and remission (QIDS-SR score ≤ 5).
Results: Sixty-two adults (median age = 50 years, 65% female) received IV ketamine (76%, n = 47) or IN esketamine (24%, n = 15). Neither baseline-to-endpoint change in QIDS-SR score nor response/remission rates were significantly different between groups. Time to remission, defined as number of treatments (adjusting for age, body mass index [BMI], sex, and baseline QIDS-SR score), was faster for IV versus IN treatment (HR = 5.0, *P* = .02).
Conclusions: Intravenous ketamine and intranasal esketamine showed similar rates of response and remission in TRD patients, but the number of treatments required to achieve remission was significantly lower with IV ketamine compared to IN esketamine. These findings need to be investigated in a randomized control trial comparing these two treatment interventions.

https://pubmed.ncbi.nlm.nih.gov/36724113/

Ketamine for the Treatment of Major Depression: A Systematic Review and Meta-Analysis

Abstract
Background: There is growing interest in glutamatergic agents in depression, particularly ketamine, a glutamate N-methyl-d-aspartate (NMDA) receptor antagonist. We aimed to assess the efficacy of ketamine in major depressive episodes.
Method: We searched EMBASE, PsycINFO, CENTRAL, and Medline from 1962 to January 2014 to identify double-blind, randomized controlled trials with allocation concealment evaluating ketamine in major depressive episodes. Clinical remission, response and depressive symptoms were extracted by two independent raters. The primary outcome measure was clinical remission at 24 h, 3 days and 7 days post-treatment. Analyses employed a random-effects model.
Results: Data were synthesized from seven RCTs employing an intravenous infusion and one RCT employing intranasal ketamine, representing 73 subjects in parallel arms and 110 subjects in cross-over designs [n = 34 with bipolar disorder (BD), n = 149 with major depressive disorder (MDD)]. Ketamine was associated with higher rates of clinical remission relative to comparator (saline or midazolam) at 24 h [OR 7.06, number needed to treat (NNT) = 5], 3 days (OR 3.86, NNT = 6), and 7 days (OR 4.00, NNT = 6), as well as higher rates of clinical response at 24 h (OR 9.10, NNT = 3), 3 days (OR 6.77, NNT = 3), and 7 days (OR 4.87, NNT = 4). A standardized mean difference of 0.90 in favor of ketamine was observed at 24 h based on depression rating scale scores, with group comparisons revealing greater efficacy in unipolar depression compared to bipolar depression (1.07 v. 0.68). Ketamine was associated with transient psychotomimetic effects, but no persistent psychosis or affective switches.
Conclusion: Our meta-analysis suggests that single administrations ketamine are efficacious in the rapid treatment of unipolar and bipolar depression. Additional research is

required to determine optimal dosing schedules, route, treatment schedules, and the potential efficacy of other glutamatergic agents.

https://pubmed.ncbi.nlm.nih.gov/25010396/

Ketamine and esketamine in suicidal thoughts and behaviors: a systematic review

Abstract
Background: More than 2% of the general population experience suicidal ideas each year and a large number of them will attempt suicide. Evidence-based therapeutic options to manage suicidal crisis are currently limited.
Objectives: The aim of this study was to overview the findings on the use of ketamine and esketamine for the treatment of suicidal ideas and acts.
Design: Systematic review.
Data sources and methods: PubMed, article references, and Clinicaltrials.gov up to June 30, 2022. Meta-analyses published within the last 2 years were also reviewed.
Results: We identified 12 randomized controlled trials with reduction of suicidal ideation as the primary objective and 14 trials as secondary objectives. Intravenous racemic ketamine was superior to control drugs (placebo or midazolam) within the first 72 h, in spite of large placebo effects. Adverse events were minor and transient. In contrast, intranasal esketamine did not differ from placebo in large-scale studies. Limitations, clinical considerations, and opportunities for future research include the following points: large placebo effects when studying suicidal ideation reduction; small concerns about blinding quality due to dissociative effects; no studies on the risk/prevention of suicidal acts and mortality; lack of studies beyond affective disorders; no studies in adolescents and older people; lack of knowledge of long-term side effects, notably liability for abuse; no robust predictive markers; limited understanding of the mechanisms of ketamine on suicidal ideas; need for improved assessment of suicidal ideation in clinical trials; need for studies in outpatient settings, emergency room, and liaison consultation; need for research on ketamine administration; limited knowledge on the positive and negative effects of concomitant treatments.
Conclusion: Overall, there is compelling evidence for a favorable short-term benefit-risk balance with intravenous racemic ketamine but not intranasal esketamine. The place of ketamine will have to be defined within a multimodal care strategy for suicidal patients. Caution remains necessary for clinical use, and pharmacovigilance will be essential.

https://pubmed.ncbi.nlm.nih.gov/36776623/

Ketamine-assisted psychotherapy provides lasting and effective results in the treatment of depression, anxiety and post traumatic stress disorder at 3 and 6 months: Findings from a large single-arm retrospective effectiveness trial

Abstract
IMPORTANCE Ketamine-Assisted Psychotherapy (KAP) is an emerging treatment option to alleviate treatment resistant affective disorders, but its long term effectiveness remains unclear.

OBJECTIVE To examine the treatment effects of KAP on anxiety, depression, and post traumatic stress disorder (PTSD) at 1, 3, and 6 months post treatment.
DESIGN, SETTING, AND PARTICIPANTS This retrospective single-arm effectiveness trial included self-reported outcomes from 1806 adults with a history of depression, anxiety, or PTSD who had not responded to prior treatment interventions and received KAP administered across 11 Field Trip Health clinics in North America between March 13, 2020 and June 16, 2022.
INTERVENTION KAP consisting of 4-6 guided ketamine sessions (administered via intramuscular injection or sublingual lozenge) with psychotherapy-only visits after doses 1 and 2 and then after every 2 subsequent doses. Mean number of doses administered was 4, SD=3, and mean number of psychotherapy sessions was 3, SD=2.
MAIN OUTCOMES AND MEASURES Primary outcomes were changes in depression, anxiety, and PTSD at 3 months relative to baseline, assessed respectively using the 9-item Patient Health Questionnaire (PHQ-9), the 7-item Generalized Anxiety Disorder measure (GAD-7), and the 6-item PTSD Checklist (PCL-6). Secondary outcomes were changes at 1 and 6 months relative to baseline.
RESULTS Large treatment effects were detected at 3 months (d's=0.75-0.86) that were sustained at 6 months (d's=0.61-0.73). Case reductions (identified based on cut-off values) ranged from 39-41% at 3 months and 29-37% at 6 months. 50-75% reported a minimal clinically important difference at 3 months and 48-70% at 6 months.
CONCLUSIONS AND RELEVANCE KAP produced sustained reductions in anxiety, depression, and PTSD, with symptom improvement lasting well beyond the duration of dosing sessions. These effects extended to as much as 5 months after the last KAP session. Given the growing mental health care crises and the need for effective therapies and models of care, especially for intractable psychiatric mood related disorders, these data would support the consideration of KAP as a viable alternative. Further prospective clinical research should be undertaken to provide further evidence on the safety and effectiveness of ketamine within a psychotherapeutic context.

https://www.medrxiv.org/content/10.1101/2023.01.11.23284248v2

Repurposing ketamine to treat cocaine use disorder: integration of artificial intelligence-based prediction, expert evaluation, clinical corroboration and mechanism of action analyses

Abstract
Background and aims: Cocaine use disorder (CUD) is a significant public health issue for which there is no Food and Drug Administration (FDA) approved medication. Drug repurposing looks for new cost-effective uses of approved drugs. This study presents an integrated strategy to identify repurposed FDA-approved drugs for CUD treatment.
Design: Our drug repurposing strategy combines artificial intelligence (AI)-based drug prediction, expert panel review, clinical corroboration and mechanisms of action analysis being implemented in the National Drug Abuse Treatment Clinical Trials Network (CTN). Based on AI-based prediction and expert knowledge, ketamine was ranked as the top candidate for clinical corroboration via electronic health record (EHR) evaluation of CUD patient cohorts prescribed ketamine for anesthesia or depression compared with matched

controls who received non-ketamine anesthesia or antidepressants/midazolam. Genetic and pathway enrichment analyses were performed to understand ketamine's potential mechanisms of action in the context of CUD.
Setting: The study utilized TriNetX to access EHRs from more than 90 million patients world-wide. Genetic- and functional-level analyses used DisGeNet, Search Tool for Interactions of Chemicals and Kyoto Encyclopedia of Genes and Genomes databases.
Participants: A total of 7742 CUD patients who received anesthesia (3871 ketamine-exposed and 3871 anesthetic-controlled) and 7910 CUD patients with depression (3955 ketamine-exposed and 3955 antidepressant-controlled) were identified after propensity score-matching.
Measurements: EHR analysis outcome was a CUD remission diagnosis within 1 year of drug prescription.
Findings: Patients with CUD prescribed ketamine for anesthesia displayed a significantly higher rate of CUD remission compared with matched individuals prescribed other anesthetics [hazard ratio (HR) = 1.98, 95% confidence interval (CI) = 1.42-2.78]. Similarly, CUD patients prescribed ketamine for depression evidenced a significantly higher CUD remission ratio compared with matched patients prescribed antidepressants or midazolam (HR = 4.39, 95% CI = 2.89-6.68). The mechanism of action analysis revealed that ketamine directly targets multiple CUD-associated genes (BDNF, CNR1, DRD2, GABRA2, GABRB3, GAD1, OPRK1, OPRM1, SLC6A3, SLC6A4) and pathways implicated in neuroactive ligand-receptor interaction, cAMP signaling and cocaine abuse/dependence.
Conclusions: Ketamine appears to be a potential repurposed drug for treatment of cocaine use disorder.
https://pubmed.ncbi.nlm.nih.gov/36792381/

Active mechanisms of ketamineassisted psychotherapy: A systematic review

Abstract
Background: Few studies have evaluated the efficacy of ketamine-assisted psychotherapy (KAP) in the treatment of treatment-resistant depression (TRD) and substance use disorders (SUD).
Methods: A systematic review of clinical trials reporting on the efficacy of KAP and discussing mechanisms of action, identified on PubMed and PsycInfo.
Results: Five randomized-controlled trials reported on the efficacy of KAP treatment and discussed active mechanisms. Four of the studies treated adults with SUD and a single study treated adults with TRD. Overall, KAP had a significant positive effect on primary outcome measures compared to controls, however, the data is mixed. The study examining KAP for TRD found no benefit.
Limitations: Lack of large, replicated clinical trials. No studies actively examining mechanisms of action.
Conclusion: Evidence suggests that temporary neural changes caused by ketamine such as n-methyl-d-aspartate receptor (NMDAR) inhibition and increase of synaptic neuroplasticity affect treatment outcomes of KAP. Based on reports of preliminary findings, we speculate that adjunct psychotherapy, changes in perspective, and spirituality may also play a role.

https://pubmed.ncbi.nlm.nih.gov/35905796/

Generic ketamine performs strongly in depression trial

A low-cost version of ketamine to treat severe depression has performed strongly in a double-blind trial that compared it with placebo.
In research published today in the British Journal of Psychiatry, researchers led by UNSW Sydney and the affiliated Black Dog Institute found that more than one in five participants achieved total remission from their symptoms after a month of biweekly injections, while a third had their symptoms improve by at least 50 per cent.

Zur kompletten Studie>>>
https://www.technologynetworks.com/drug-discovery/news/generic-ketamine-performs-strongly-in-depression-trial-376270

The Possible Application of Ketamine in the Treatment of Depression in Alzheimer's Disease

Abstract
Depression is a leading cause of disability globally, with a prevalence of 3.8% among the whole population, 5% of the adult population, and 5.7% of the elderly population over 60 years of age. There is evidence that depression is linked to certain neurodegenerative diseases, one being Alzheimer's disease (AD). The efficacy of conventional antidepressants to treat depression in AD is conflicting, especially regarding selective serotonin reuptake inhibitors (SSRIs). A recent systemic review and meta-analysis of 25 randomized controlled trials including fourteen antidepressant medications showed no high efficacy in treating AD patients' symptoms. However, ketamine, a nonselective N-methyl-D-aspartate (NMDA) receptor antagonist, can mediate a wide range of pharmacological effects, including neuroprotection, anti-inflammatory and anticancer properties, multimodal analgesia, and treatment of depression, suicidal attempts, and status epilepticus. Esketamine, which is ketamine formulated as a nasal spray, was approved by the Federal Drug Administration (FDA) in March 2019 as an adjuvant drug to treat treatment-resistant depression. NMDA receptor antagonists treat AD through offsetting AD-related pathological stimulation of subtypes of glutamate receptors in the central nervous system. Recent clinical findings suggest that ketamine may provide neuroprotection and reduce neuropsychiatric symptoms associated with AD. In the present investigation, we evaluate the potential role of ketamine and its postulated mechanism in AD management.

Zur kompletten Studie>>>
https://pubmed.ncbi.nlm.nih.gov/35466206/

New Frontiers in Ketamine Research: From Mechanisms of Action to Novel Psychiatric Treatment Approaches

Abstract
Ketamine, initially developed as a safer alternative to phencyclidine, has emerged as a groundbreaking treatment in psychiatric practice. It gained popularity after its approval by

the FDA in 1970 for its analgesic properties and ability to induce altered consciousness while maintaining vital functions. In the 1990s, researchers discovered its rapid and potent antidepressant effects, especially in patients with treatment-resistant depression. The mechanism of action of ketamine involves blocking N-Methyl-D-Aspartate receptors, leading to the release of inhibitory signals and increased glutamate levels. This process triggers a series of events promoting neuron growth and synaptic plasticity relevant to antidepressant outcomes. Various administration methods have been explored, including intravenous, intranasal, oral, subcutaneous, and intramuscular routes, each with its own advantages and limitations. IV ketamine administration has been widely used, but intranasal and sublingual forms are gaining popularity due to improved accessibility and safety. The FDA and European Medicines Agency approved intranasal S-ketamine for treatment resistant depression and depressive symptoms. Ketamine treatment is being extensively researched for its impact on various psychiatric domains, including resistant depression, suicidal crises, anxiety disorders, substance use disorders, and others. Preliminary evidence suggests potential benefits in conditions such as obsessive compulsive and personality disorders, although further research is needed. Ketamine's safety profile is generally favorable, with mild, temporary, and self-limiting side effects. However, caution is advised in individuals with uncontrolled hypertension, cardiovascular conditions, a history of psychosis, or substance abuse. Contraindications also apply to pregnant women. Ketamine interactions with other medications should be carefully considered, especially regarding benzodiazepines, and lamotrigine use. To optimize ketamine treatment in psychiatric diseases, guidelines recommend it as a third-line option after multiple unsuccessful antidepressant treatments for treatment resistant depression. Intravenous racemic ketamine has Level 1 evidence supporting its efficacy, while the evidence for non-intravenous formulations is limited. International guidelines vary slightly, but overall, the use of ketamine shows great potential in addressing challenging psychiatric conditions. This update highlights the expanding literature on ketamine in psychiatric treatment, focusing on its applications in treatment-resistant depression and its potential to revolutionize acute psychiatric emergency departments. Moreover, it provides insights into administration methods, safety considerations, and international guidelines for optimized ketamine usage in psychiatric practice.

Zur kompletten Studie>>>
https://www.sciencepublishinggroup.com/journal/paperinfo?journalid=653&doi=10.11648/j.ajpn.20231103.12

Novel ketamine and zinc treatment for anorexia nervosa and the potential beneficial interactions with the gut microbiome

Abstract
Anorexia nervosa (AN) is a severe illness with diverse aetiological and maintaining contributors including neurobiological, metabolic, psychological, and social determining factors. In addition to nutritional recovery, multiple psychological and pharmacological therapies and brain-based stimulations have been explored; however, existing treatments have limited efficacy. This paper outlines a neurobiological model of glutamatergic and γ-aminobutyric acid (GABA)-ergic dysfunction, exacerbated by chronic gut microbiome

dysbiosis and zinc depletion at a brain and gut level. The gut microbiome is established early in development, and early exposure to stress and adversity contribute to gut microbial disturbance in AN, early dysregulation to glutamatergic and GABAergic networks, interoceptive impairment, and inhibited caloric harvest from food (e.g., zinc malabsorption, competition for zinc ions between gut bacteria and host). Zinc is a key part of glutamatergic and GABAergic networks, and also affects leptin and gut microbial function; systems dysregulated in AN. Low doses of ketamine in conjunction with zinc, could provide an efficacious combination to act on NMDA receptors and normalise glutamatergic, GABAergic and gut function in AN.

Zur kompletten Studie>>>
https://pubmed.ncbi.nlm.nih.gov/36907256/

Studien zu Neurofeedback

Healing the Neurophysiological Roots of Trauma: A Controlled Study Examining LORETA Z-Score Neurofeedback and HRV Biofeedback for Chronic PTSD

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DOI: https://doi.org/10.15540/nr.6.2.54
Keywords: Traumatic stress, PTSD, EEG biofeedback, LORETA, Z-score neurofeedback, Neurophysiology

ABSTRACT

Introduction: Posttraumatic stress disorder (PTSD) has been linked to abnormalities within three neural networks: default mode (DMN), salience (SN), and central executive (CEN). This study examined the effectiveness of LORETA *z*-score neurofeedback (LZNF) training for altering current source within these networks and reducing symptoms associated with PTSD. **Methods:** Twenty-three adults with chronic PTSD were randomly assigned to 15 sessions of either LZNF (*n*= 12) or heart rate variability biofeedback (HRVB; *n* = 11). Psychosocial and physiological assessments were completed at baseline and postintervention. **Results:** The LZNF group showed very large, statistically significant decreases in symptoms on the PTSD Checklist for DSM-V (PCL-5; $p = .003$, $d = 2.09$) and Beck Anxiety Inventory (BAI; $p = .003$, $d = 2.13$). The HRVB group also showed very large decreases on the PCL-5 ($p = .006$, $d = 1.40$) and medium effects on the BAI ($p = .018$, $d = 0.76$). Between-group comparisons showed medium to large effects of group type in favor of LZNF (PCL-5 $d = 0.57$; BAI $d = 0.94$), although not statistically significant. LZNF Responders ($n = 9$) demonstrated very large, statistically significant decreases in abnormal *z*-scores within all targeted networks (DMN $p = .012$, $d = 0.96$; SN $p = .008$, $d = 1.32$; CEN $p = .008$, $d = 1.33$). **Conclusion:** The positive outcomes of this study provide preliminary evidence to support LZNF training as a specific, effective, and tolerable intervention for adults with chronic PTSD.

Comparing the Effectiveness of Neurofeedback and Transcranial Direct Current Stimulation on Sleep Quality of Patients With Migraine

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Basic and Clinical Neuroscience, 2020
Abstract:
Introduction: Migraine is considered one of the most common primary headache disorders. Migraine attacks may occur due to a lack of sleep. Furthermore, sleep is regarded as one of the smoothing factors of migraine pain. Patients with sleep disorders often suffer from headaches when they wake up compared with healthy individuals.
Methods: This research was a quasi-experimental study with a pretest-posttest design and a 2-month follow-up. The samples included 20 migraine patients within the age range of 15 to 55 years who were selected as volunteers for treatment by the neurologists and psychiatrists during 2017. The initial evaluation was then conducted based on the inclusion and exclusion criteria and using the Ahvaz migraine questionnaire, and Pittsburgh sleep quality index. The patients were randomly assigned to two neurofeedback (n=10) and transcranial direct current stimulation (tDCS) (n=10) groups and evaluated three times. The obtained data were analyzed by the repeated measures ANCOVA and Chi-square test in SPSS.
Results: Based on the scores of both groups, no significant difference was observed between neurofeedback and tDCS groups. However, based on the results, neurofeedback decreased sleep latency, whereas tDCS increased sleep efficiency. Overall, these two treatments were effective in improving subjective sleep quality and sleep quality.
Conclusion: Both neurofeedback and tDCS treatments could significantly enhance sleep quality of the patients in the posttest and 2-month follow-up. Given the effectiveness of both treatments, neurofeedback and tDCS are recommended to be used for improving the sleep status of patients with migraine.

Neurofeedback and Attention-Deficit/Hyperactivity-Disorder (ADHD) in Children: Rating the Evidence and Proposed Guidelines

Martijn Arns · C. Richard Clark · Mark Trullinger · Roger deBeus · Martha Mack · Michelle Aniftos

Abstract
Stimulant medication and behaviour therapy are the most often applied and accepted treatments for Attention-Deficit/ Hyperactivity-Disorder (ADHD). Here we explore where the non-pharmacological clinical intervention known as neuro- feedback (NFB), fits on the continuum of empirically supported treatments, using standard protocols. In this

quantitative review we utilized an updated and stricter version of the APA guidelines for rating ‘well-established’ treatments and focused on efficacy and effectiveness using effect-sizes (ES) and remission, with a focus on long-term effects. Efficacy and effec- tiveness are compared to medication and behaviour therapy using benchmark studies. Only recent systematic reviews and meta-analyses as well as multi-centre randomized controlled trials (RCT’s) will be included. Two meta-analyses confirmed significant efficacy of standard neurofeedback protocols for parent and teacher rated symptoms with a medium effect size, and sustained effects after 6–12 months. Four multicenter RCT’s demonstrated significant superiority to semi-active control groups, with medium-large effect sizes end of treatment or follow-up and remission rates of 32–47%. Effectiveness in open- label studies was confirmed, no signs of publication bias were found and no significant neurofeedback-specific side effects have been reported. Standard neurofeedback protocols in the treatment of ADHD can be concluded to be a well-established treatment with medium to large effect sizes and 32–47% remission rates and sustained effects as assessed after 6–12 months.

Treatment Efficacy and Clinical Effectiveness of EEG Neurofeedback as a Personalized and Multimodal Treatment in ADHD: A Critical Review

Abstract
Purpose

Recent reviews have proposed that scientifically validated standard EEG neurofeedback (NF) protocols are an efficacious and specific treatment for attention-deficit hyperactivity disorder (ADHD). Here, we review the current evidence for the treatment efficacy and clinical effectiveness of NF in ADHD to investigate whether NF treatment personalization (standard protocols matched to the electrophysiological features of ADHD) and combination with other interventions (psychosocial, sleep hygiene and nutritional advice) might yield superior long-term treatment outcomes relative to non-personalized NF and medication monotreatments.
Methods

The electronic databases PubMed and PsycINFO were systematically searched using our key terms. Of the 38 resulting studies, 11 randomized controlled trials (RCTs) and open-label studies were eligible for inclusion. Studies were analyzed for effect sizes and remission rates at the end of treatment and at follow-up. The effects of personalized and multimodal NF treatments were compared to non-personalized NF monotreatments and with two benchmark medication studies.
Results

The analysis of RCTs indicated that the long-term effects of personalized NF interventions were superior to non-personalized NF and comparable to those of medication alone or in combination with behavioral intervention. The analysis of open-label trials further indicates

that the interaction of NF with parental interventions, sleep and nutritional advice might yield superior clinical effectiveness relative to NF and medication monotreatments.
Conclusion

Personalized and multimodal NF interventions seem to yield superior treatment efficacy relative to NF alone and superior clinical effectiveness relative to medication. We propose that treatment outcomes may be further enhanced by adjusting NF non-specific factors (eg, reinforcement contingencies) to specific ADHD characteristics (eg, reward sensitivity). Future NF research should focus on the systematic evaluation of the treatment outcomes of personalized and multimodal treatments.

Komplette Studie: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7920604/

Neurofeedback training in major depressive disorder: A systematic review of clinical efficacy, study quality and reporting practices

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- PMID: 33587957
- DOI: 10.1016/j.neubiorev.2021.02.015

Abstract

Major depressive disorder (MDD) is the leading cause of disability worldwide. Neurofeedback training has been suggested as a potential additional treatment option for MDD patients not reaching remission from standard care (i.e., psychopharmacology and psychotherapy). Here we systematically reviewed neurofeedback studies employing electroencephalography, or functional magnetic resonance-based protocols in depressive patients. Of 585 initially screened studies, 24 were included in our final sample (N = 480 patients in experimental and N = 194 in the control groups completing the primary endpoint). We evaluated the clinical efficacy across studies and attempted to group studies according to the control condition categories currently used in the field that affect clinical outcomes in group comparisons. In most studies, MDD patients showed symptom improvement superior to the control group(s). However, most articles did not comply with the most stringent study quality and reporting practices. We conclude with recommendations on best practices for experimental designs and reporting standards for neurofeedback training.
Keywords: Biofeedback; Electroencephalography; Functional magnetic resonance imaging; Major depressive disorder; Neurofeedback; Neuroimaging; Real-time fMRI; Self-regulation.

Komplette Studie:
https://pubmed.ncbi.nlm.nih.gov/33587957/

Efficacy of neurofeedback as a treatment for people with subjective tinnitus in reducing the symptom and related consequences: a systematic review from 2010 to 2020

Abstract
Background and objective

Tinnitus is a symptom experienced by millions of people around the world, generating psychological, physical and social consequences. There are different therapeutic options that seek to reduce the symptom and the related consequences. One of the newest alternatives is training with Neurofeedback, a neuromodulation technique that looks for modify brain activity. The objective of this research was to determine the efficacy of Neurofeedback treatment parameters in reducing the perception of tinnitus and in reducing the behavioral consequences triggered by the symptom, through a systematic review between 2010 and 2020.
Materials and methods

The data search was carried out in Spanish and English on PubMed/MedLine, EBSCO Host, Embase, Scopus, CENTRAL, SpringerLink and OpenGrey databases. The systematic review was carried out according to the stages established by PRISMA and five studies were identified to be included in the qualitative analysis.
Results

All studies demonstrated that NFB training for tinnitus decreases symptom perception and related consequences. At the neural level, there was an increase in the activity of the alpha wave and a decrease in the activity of delta, gamma and beta.
Conclusions

Neurofeedback has a modulating effect on brain activity patterns. However, although all the studies reported a decrease in the consequences related to the symptom at the behavioral level after treatment, due to the lack of development of this technique for the symptom and the characteristics of the studies reviewed, it cannot be certainty of efficacy on behavioral and neurophysiological consequences.

Komplette Studie:
https://www.sciencedirect.com/science/article/abs/pii/S2173573522001119

Efficacy of bio- and neurofeedback for depression: a meta-analysis

Abstract
Background: For many years, biofeedback and neurofeedback have been implemented in the treatment of depression. However, the effectiveness of these techniques on depressive symptomatology is still controversial. Hence, we conducted a meta-analysis of studies extracted from PubMed, Scopus, Web of Science and Embase.
Methods: Two different strings were considered for each of the two objectives of the study: A first group comprising studies patients with major depressive disorder (MDD) and a second group including studies targeting depressive symptomatology reduction in other mental or medical conditions.

Results: In the first group of studies including patients with MDD, the within-group analyses yielded an effect size of Hedges‘ g = 0.717, while the between-group analysis an effect size of Hedges‘ g = 1.050. Moderator analyses indicate that treatment efficacy is only significant when accounting for experimental design, in favor of randomized controlled trials (RCTs) in comparison to non RCTs, whereas the type of neurofeedback, trial design, year of publication, number of sessions, age, sex and quality of study did not influence treatment efficacy. In the second group of studies, a small but significant effect between groups was found (Hedges‘ g = 0.303) in favor of bio- and neurofeedback against control groups. Moderator analyses revealed that treatment efficacy was not moderated by any of the sociodemographic and clinical variables.
Conclusions: Heart rate variability (HRV) biofeedback and neurofeedback are associated with a reduction in self-reported depression. Despite the fact that the field has still a large room for improvement in terms of research quality, the results presented in this study suggests that both modalities may become relevant complementary strategies for the treatment of MDD and depressive symptomatology in the coming years.

Komplette Studie
https://pubmed.ncbi.nlm.nih.gov/34776024/

Studien über repetitive transkranielle Magnetstimulation (rTMS)

The role of left prefrontal transcranial magnetic stimulation in episodic migraine prophylaxis

Amin et al. The Egyptian Journal of Neurology, Psychiatry and Neurosurgery (2020) 56:19
The Egyptian Journal of Neurology, https://doi.org/10.1186/s41983-019-0140-5 Psychiatry and Neurosurgery
RESEARCH
Randa Amin1, Tamer Emara1*, Samia Ashour1, Mahmoud Hemeda1, Nahed Salah Eldin1, Salma Hamed1, Sara Shouman2 and Mohamed Shouman3
Abstract
Objective: The aim of the study was to examine the prophylactic role of repetitive transcranial magnetic stimulation (rTMS) on the frequency, and severity of migraine attacks in episodic migraineurs who failed medical treatment.
Methods: A randomized double-blinded placebo-controlled study was designed to assess the effect of 5 Hz rTMS applied over the left dorsolateral prefrontal cortex (LDLPFC) in 33 migraineurs. Patients were followed up for 1 month before receiving rTMS, and for another month after the sessions by a headache diary. The primary outcome measure was the achievement of 50% reduction in the number of migraine attacks. Secondary outcome measures included migraine days, assessment of migraine attack severity, disability by HIT-6, and side-effects to the procedure.
Results: The study revealed that 69.2% of the active treatment group achieved 50% or more reduction in the number of migraine attacks versus 25% of cases in the control group (p = 0.02). The absolute number of migraine attacks was reduced by 3.1 vs 1.5 in the active and control group, respectively. The number of cases with severe HIT-6 scores was

reduced by 46.2% in active treatment group versus a 7.1% reduction in the control group (p = 0.02).
Conclusion: High-frequency rTMS applied to LDLPFC can reduce the number of migraine attacks by 50% or more in almost 70% of a sample of episodic migraineurs with a concomitant decrease in functional disability.
Trial registration: ClinicalTrials.gov, Identifier: NCT04031781. Registered 23 July 2019—retrospectively registered
at https://clinicaltrials.gov/ct2/show/NCT04031781?term=Migraine+Prophylaxis&recrs=ce&type=Intr&cond=Migraine&rank=9

A systematic review and meta-analysis of rTMS effects on cognitive enhancement in mild cognitive impairment and Alzheimer's disease

Ying-hui Chouab Viet Ton Thata MarkSundmana
https://doi.org/10.1016/j.neurobiolaging.2019.08.020

Abstract
Repetitive transcranial magnetic stimulation (rTMS), a noninvasive brain stimulation technique, has emerged as a promising treatment for mild cognitive impairment (MCI) and Alzheimer’s disease (AD). Currently, however, the effectiveness of this therapy is unclear because of the low statistical power and heterogeneity of previous trials. The purpose of the meta-analysis was to systematically characterize the effectiveness of various combinations of rTMS parameters on different cognitive domains in patients with MCI and AD. Thirteen studies comprising 293 patients with MCI or AD were included in this analysis. Random-effects analysis revealed an overall medium-to-large effect size (0.77) favoring active rTMS over sham rTMS in the improvement of cognitive functions. Subgroup analyses revealed that (1) high-frequency rTMS over the left dorsolateral prefrontal cortex and low-frequency rTMS at the right dorsolateral prefrontal cortex significantly improved memory functions; (2) high-frequency rTMS targeting the right inferior frontal gyrus significantly enhanced executive performance; and (3) the effects of 5–30 consecutive rTMS sessions could last for 4–12 weeks. Potential mechanisms of rTMS effects on cognitive functions are discussed.
us leo.

Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS)

Jean-Pascal Lefaucheur et al (2020)
Abstract

A group of European experts reappraised the guidelines on the therapeutic efficacy of repetitive transcra- nial magnetic stimulation (rTMS) previously published in 2014 [Lefaucheur et al., Clin Neurophysiol 2014;125:2150–206]. These updated recommendations take into account all rTMS publications, includ- ing data prior to 2014, as well as currently reviewed literature until the end of 2018. Level A evidence (definite efficacy) was reached for: high-frequency (HF) rTMS of the primary motor cortex (M1) contralat- eral to the painful side for neuropathic pain; HF-rTMS of the left dorsolateral

prefrontal cortex (DLPFC) using a figure-of-8 or a H1-coil for depression; low-frequency (LF) rTMS of contralesional M1 for hand motor recovery in the post-acute stage of stroke. Level B evidence (probable efficacy) was reached for: HF-rTMS of the left M1 or DLPFC for improving quality of life or pain, respectively, in fibromyalgia; HF-rTMS of bilateral M1 regions or the left DLPFC for improving motor impairment or depression, respec- tively, in Parkinson's disease; HF-rTMS of ipsilesional M1 for promoting motor recovery at the post-acute stage of stroke; intermittent theta burst stimulation targeted to the leg motor cortex for lower limb spas- ticity in multiple sclerosis; HF-rTMS of the right DLPFC in posttraumatic stress disorder; LF-rTMS of the right inferior frontal gyrus in chronic post-stroke non-fluent aphasia; LF-rTMS of the right DLPFC in depression; and bihemispheric stimulation of the DLPFC combining right-sided LF-rTMS (or continuous theta burst stimulation) and left-sided HF-rTMS (or intermittent theta burst stimulation) in depression. Level A/B evidence is not reached concerning efficacy of rTMS in any other condition. The current recom- mendations are based on the differences reached in therapeutic efficacy of real vs. sham rTMS protocols, replicated in a sufficient number of independent studies. This does not mean that the benefit produced by rTMS inevitably reaches a level of clinical relevance.

rTMS in der Schwangerschaft

Nervenheilkunde 2020; 39(04): 213-221
DOI: 10.1055/a-1113-0084
Schwerpunkt

Transkranielle Magnetstimulation zur Behandlung von Depressionen bei Schwangeren Eine Übersicht
Transcranial magnetic stimulation in the treatment of depression during pregnancy A review
Tobias Hebel, Martin Schecklmann, Berthold Langguth
Zusammenfassung
Gegenstand und Ziel In dieser Übersichtsarbeit sollen die Wirksamkeit und Sicherheit der repetitiven transkraniellen Magnetstimulation (rTMS) für die Patientengruppe depressiv erkrankter Schwangerer evaluiert werden.
Material und Methoden Es wurde eine Datenbankrecherche auf Pubmed durchgeführt, um alle relevanten Original- und Übersichtsarbeiten zu dem Thema zu identifizieren und zu analysieren
Ergebnisse Zusätzlich zu einer Reihe von Fallberichten existieren 3 kontrollierte Studien zur Behandlung depressiver Schwangerer mittels rTMS. Der Datenlage nach scheint die rTMS sowohl für die schwangeren Patientinnen als auch ihre ungeborenen Kinder sicher zu sein. Es wurden keine postnatalen negativen Wirkungen auf die Kindesentwicklung berichtet.

Schlussfolgerung rTMS stellt eine vielversprechende Behandlungsoption dar. Weitere Studien mit größeren Teilnehmerzahlen sind notwendig, um den Stellenwert der rTMS in einer multimodalen Depressionsbehandlung in der Schwangerschaft zu klären.

Transcranial magnetic stimulation during pregnancy

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Transcranial Magnetic Stimulation for the Treatment of Cocaine Addiction

Abstract

Objective:

The aim of this paper is to present the clinical data analysis results from a service delivering repetitive transcranial magnetic stimulation (rTMS) for people with cocaine-use disorder (CUD).
Methods:

The study was a retrospective investigation of routinely collected data on patients receiving rTMS between 2018 and 2019. Measures used were a cocaine craving Visual Analogue Scale (VAS), Hospital Anxiety and Depression Scale (HADS) and Patient Health Questionnaire (PHQ-9) self-rated depression measures.

Results:

The outcome data of 10 patients with CUD were analysed. There was a statistically significant reduction and a large effect size on CUD and depression scales. Conclusions: Reductions in craving and depression indicate the potential benefits to patients and to society of rTMS in treating CUD. Further sufficiently powered RCTs are warranted with studies focusing on the optimization of rTMS treatment and exploring the underlying mechanisms.

ZUR KOMPLETTEN STUDIE
https://www.scirp.org/journal/paperinformation.aspx?paperid=100492

Longitudinal effects of rTMS on neuroplasticity in chronic treatment-resistant depression

Abstract:
Major depressive disorder (MDD) is amongst the most prevalent of psychiatric disorders. Unfortunately, a third of patients will not respond to conventional treatments and suffer from treatment-resistant depression (TRD). Repetitive transcranial magnetic stimulation (rTMS) has been proven effective in treating TRD. The research suggests that rTMS acts via neuroplastic effects on the brain, which can be measured by changes in hippocampal and amygdala volume as well as cortical thickness. This sham-controlled study investigates longitudinal effects of rTMS on the volumes of the hippocampus and amygdala and cortical thickness in patients with chronic TRD. 31 patients received 20 sessions of high-frequency rTMS (N = 15) or sham treatment (N = 16) over the left dorsolateral prefrontal cortex during 4 consecutive weeks. Using structural magnetic resonance imaging, we investigated longitudinal treatment effects on hippocampus and amygdala volume as well as thickness of the paralimbic cortex. We found no clinical differences between the active and sham rTMS group. Longitudinal changes in hippocampal and amygdala volume did not differ significantly, although males showed a significant decrease in left amygdala volume, irrespective of treatment group. Changes in cortical thickness of the paralimbic cortex differed significantly between the active and sham groups. Most notably, the increase in cortical thickness of the isthmus of the left cingulate gyrus was greater in the active as compared to the sham rTMS group. Our data suggest that rTMS can induce neuroplastic changes, particularly in cortical thickness, independent of treatment response. We also found longitudinal changes in amygdala volume in males. For clinical effects to follow these neuroplastic effects, more intensive rTMS treatment might be needed in chronically depressed patients. Trial registration number: ISRCTN 15535800, registered on 29-06-2017.

Zur kompletten Studie
https://www.researchgate.net/publication/341267074_Longitudinal_effects_of_rTMS_on_neuroplasticity_in_chronic_treatment-resistant_depression

Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment-Resistant Depression

Abstract

Objective:

New antidepressant treatments are needed that are effective, rapid acting, safe, and tolerable. Intermittent theta-burst stimulation (iTBS) is a noninvasive brain stimulation treatment that has been approved by the U.S. Food and Drug Administration for treatment-resistant depression. Recent methodological advances suggest that the current iTBS protocol might be improved through 1) treating patients with multiple sessions per day at optimally spaced intervals, 2) applying a higher overall pulse dose of stimulation, and 3) precision targeting of the left dorsolateral prefrontal cortex (DLPFC) to subgenual anterior cingulate cortex (sgACC) circuit. The authors examined the feasibility, tolerability, and preliminary efficacy of Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT), an accelerated, high-dose resting-state functional connectivity MRI (fcMRI)–guided iTBS protocol for treatment-resistant depression.

Methods:

Twenty-two participants with treatment-resistant depression received open-label SAINT. fcMRI was used to individually target the region of the left DLPFC most anticorrelated with sgACC in each participant. Fifty iTBS sessions (1,800 pulses per session, 50-minute intersession interval) were delivered as 10 daily sessions over 5 consecutive days at 90% resting motor threshold (adjusted for cortical depth). Neuropsychological testing was conducted before and after SAINT.

Results:

One participant withdrew, leaving a sample size of 21. Nineteen of 21 participants (90.5%) met remission criteria (defined as a score <11 on the Montgomery-Åsberg Depression Rating Scale). In the intent-to-treat analysis, 19 of 22 participants (86.4%) met remission criteria. Neuropsychological testing demonstrated no negative cognitive side effects.

Conclusions:

SAINT, an accelerated, high-dose, iTBS protocol with fcMRI-guided targeting, was well tolerated and safe. Double-blinded sham-controlled trials are needed to confirm the remission rate observed in this initial study.

Zur kompletten Studie >>
https://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2019.19070720

HEART RATE DECELERATION (HRD) AS A LOW COST SCALABLE INDICATOR OF TARGET ENGAGEMENT DURING SAINT FOR TREATMENT RESISTANT DEPRESSION (TRD)

HEART RATE DECELERATION (HRD) AS A LOW COST SCALABLE INDICATOR OF TARGET ENGAGEMENT DURING SAINT FOR TREATMENT RESISTANT DEPRESSION (TRD) John Coetzee 1,2, Clive Veerapal 2, Fahim Barmak 2, Seble Adinew 2, Nolan Williams 2. 1 Rehabilitation Service, Veterans Affairs Palo Alto Health Care System (VAPAHCS), Palo Alto, CA, USA; 2Psychiatry and Behavioral Sciences,Stanford University School of Medicine, Stanford, CA, USA Abstract Prior research has shown that repetitive transcranial magnetic stimulation (rTMS) and intermittent theta burst stimulation (iTBS) can induce acute time-limited heart rate deceleration (HRD) when applied to the left dorsolateral prefrontal cortex (L-DLPFC), and that the amount of deceler- ation may related to treatment response for patients with treatment resistant depression (TRD) (Iseger et al. 2020). This deceleration appears to result from activation of a neural circuit involving L-DLPFC, subgenual anterior cingulate cortex (sgACC), and vagus nerve, and may be useful as an indicator of target engagement that is less costly and more scalable than neuroimaging with functional magnetic resonance imaging (fMRI) or electroencephalography (EEG). In this study, we will extend prior HRD results to data from a now completed sham-controlled study involving the application of a novel form of iTBS treatment, Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT), in which 30 patients with treatment resistant depression (TRD) underwent iTBS 10 times a day for 5 days with treatments spaced 1 hour apart. Heart rate data was collected using a Neuroconn ECG device. We hypothesize that HRD will be evident during treatment application, in the active condition. We further hypothesize that the amount of HRD (reflected in the slope of the RR intervals) will be predictive of both treatment response and remission, according to the MADRS, at the im- mediate post and one-month follow up timepoints, in the active condition. We also hypothesize that the amount of HRD will be predictive of the amount of reduction in anhedonia at the immediate post and one-month follow up timepoints (as reflected by questions 7 and 8 of the MADRS). Analysis will be conducted using Kubios and SPSS. These results will contribute to the growing body of work indicating HRD can serve as a low cost and scalable marker of target engagement during neuromodulation for depression. Keywords: heart rate deceleration, TMS, iTBS

Non-invasive neuromodulation for tinnitus: A meta-analysis and modeling studies

MathildeLefebvre-Demers, NicolasDoyon, ShirleyFecteau

Abstract

Background

Patients with tinnitus often have poor quality of life, as well as severe anxiety and depression. New approaches to treat tinnitus are needed.

Objective

Evaluate the effects of non-invasive neuromodulation on tinnitus through a metaanalysis and modeling study. The main hypothesis was that real as compared to sham neuromodulation that decreases tinnitus will modulate regions in line with the neurobiological models of tinnitus.

Methods and results

The systematic review, conducted from Pubmed, Cochrane and PsycINFO databases, showed that active as compared to sham repetitive transcranial magnetic stimulation (rTMS) reduced tinnitus, but active and sham transcranial direct current stimulation did not significantly differ. Further, rTMS over the auditory cortex was the most effective protocol. The modeling results indicate that this rTMS protocol elicited the strongest electric fields in

the insula. Also, rTMS was particularly beneficial in women. Finally, the placebo effects were highly variable, highlighting the importance of conducting sham-controlled trials.
Conclusion

In sum, neuromodulation protocols that target the auditory cortex and the insula may hold clinical potential to treat tinnitus.

Komplette Studie:
https://www.sciencedirect.com/science/article/pii/S1935861X20303016

Neuronavigation-Guided rTMS for the Treatment of Depressive Patients With Suicidal Ideation: A Double-Blind, Randomized, Sham-Controlled Trial

Abstract
During the last decade, the problem of suicide has become more serious in individuals with depression. Repetitive transcranial magnetic stimulation (rTMS) is an effective treatment for major depressive disorder (MDD). This study aims to investigate the efficacy of MRI-based neuronavigation-guided daily high-dose rTMS for rapidly improving suicidal ideation in treatment-naive MDD patients. In the present 1-week double-blind study, 42 treatment-naive MDD patients with suicidal ideation were randomly assigned to the treatment of escitalopram oxalate tablets (10 mg/d) in combination with either active (n = 21) or sham (n = 21) rTMS. The TMS coil was positioned over a specified target location (-44, 40, 29) in left dorsolateral prefrontal cortex（DLPFC）based on MRI data. The severity of suicidal ideation was measured by the Beck Scale for Suicide Ideation (BSI). The 24-item Hamilton Depression Rating Scale (HAMD-24) and Montgomery–Asberg Depression Rating Scale (MADRS) were utilized to assess the severity of depression. The Wisconsin Card Sorting Test (WCST), Continuous Performance Test (CPT) and Stroop Color–Word Test (SCWT) were adopted to assess executive function. In contrast to the sham group, the active rTMS group showed a significantly greater BSI score reduction at the third day and the seventh day ($p < 0.001$). Moreover, the active rTMS group showed a significantly greater HAMD ($p < 0.001$) and MADRS ($p < 0.001$) score reduction at the seventh day in comparison with the sham group. The present findings suggested that the neuronavigation-guided high-dose rTMS may be a novel method to rapidly reduce suicidal ideation and mitigate depressive symptom.

Komplette Studie: https://www.sciencedirect.com/science/article/pii/S1935861X20303016

Efficacy and safety of simultaneous rTMSetDCS over bilateral angular gyrus on neuropsychiatric symptoms in patients with moderate Alzheimer's disease: A prospective, randomized, sham-controlled pilot study

Abstract

Background: Treating neuropsychiatric symptoms (NPS) in Alzheimer's disease (AD) remains highly challenging. Noninvasive brain stimulation using repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) is of considerable interest in this context.
Objective: To investigate the efficacy and safety of a novel technique involving simultaneous application of rTMS and tDCS (rTMSetDCS) over bilateral angular gyrus (AG, P5/P6 electrode site) for AD-related NPS.
Methods: Eighty-four AD patients were randomized to receive rTMSetDCS, single-rTMS, single-tDCS, or sham stimulation for 4 weeks, with evaluation at week-4 (W4, immediately after treatment) and week-12 (W12, follow-up period) after initial examination. Primary outcome comprising Neuropsychiatric Inventory (NPI) score and secondary outcomes comprising mini-mental state examination (MMSE), AD assessment scale-cognitive subscale (ADAS-cog), and Pittsburgh sleep quality index (PSQI) scores were collected and analyzed by a two-factor (time and treatment), mixed-design ANOVA.
Results: rTMSetDCS produced greater improvement in NPI scores than single-tDCS and sham at W4 and W12 (both P < 0.017) and trended better than single-rTMS (W4: P . 0.058, W12: P . 0.034). rTMSetDCS improved MMSE scores compared with single-tDCS at W4 (P . 0.011) and sham at W4 and W12 (both P < 0.017). rTMSetDCS also significantly improved PSQI compared with single-rTMS and sham (both P < 0.017). Interestingly, rTMSetDCS-induced NPI/PSQI improvement was significantly associated with MMSE/ADAS-cog improvement. tDCS- and/or rTMS-related adverse events appeared slightly and briefly.
Conclusions: rTMSetDCS application to bilateral AG can effectively improve AD-related NPS, cognitive
function, and sleep quality with considerable safety.

Zur kompletten Studie>>>
https://pubmed.ncbi.nlm.nih.gov/36460293/

Novel Therapeutic Approaches for Alzheimer's Disease: An Updated Review

Abstract
Alzheimer's disease (AD) is a progressive neurodegenerative disease and accounts for most cases of dementia. The prevalence of AD has increased in the current rapidly aging society and contributes to a heavy burden on families and society. Despite the profound impact of AD, current treatments are unable to achieve satisfactory therapeutic effects or stop the progression of the disease. Finding novel treatments for AD has become urgent. In this paper, we reviewed novel therapeutic approaches in five categories: anti-amyloid therapy, anti-tau therapy, anti-neuroinflammatory therapy, neuroprotective agents including N-methyl-D-aspartate (NMDA) receptor modulators, and brain stimulation. The trend of therapeutic development is shifting from a single pathological target to a more complex mechanism, such as the neuroinflammatory and neurodegenerative processes. While drug repositioning may accelerate pharmacological development, non-pharmacological interventions, especially repetitive transcranial magnetic stimulation (rTMS) and

transcranial direct current stimulation (tDCS), also have the potential for clinical application. In the future, it is possible for physicians to choose appropriate interventions individually on the basis of precision medicine.

ZUR KOMPLETTEN STUDIE>>>
https://pubmed.ncbi.nlm.nih.gov/34360973/

Efficacy of non-invasive brain stimulation on cognitive and motor functions in multiple sclerosis: A systematic review and meta-analysis

Abstract
Objective: In this study, we aimed to investigate the effects of non-invasive brain stimulation (NIBS) on cognitive and motor functions in patients with multiple sclerosis (pwMS).
Methods: A literature search was performed in the Cochrane Library, Embase, PubMed, Web of Science, Medline, CNKI, and Wan fang. The time interval used for database construction was up to December 2022, and the language was not limited. The collected trials were subsequently screened, the data were extracted, the quality was evaluated, and the effect sizes were computed using STATA/MP Version 13 for outcome analysis. Standard mean difference (SMD) and 95% confidence interval (CI) were calculated for domain of interest.
Results: In total, 17 articles that examined 364 patients with multiple sclerosis were included in this analysis. Non-invasive brain stimulation did not improve the overall cognitive function [SMD = 0.18, 95% CI (-0.32, 0.69), *P* = 0.475] but helped improve motor function in patients [SMD = 0.52, 95% CI (0.19, 0.85), *P* = 0.002]. Moreover, this study specifically indicated that non-invasive brain stimulation improved alerting [SMD = 0.68, 95% CI (0.09, 1.26), *P* = 0.02], whereas non-invasive brain stimulation intervention improved motor function in patients aged <45 years [SMD = 0.67, 95% CI (0.23, 1.10), *P* = 0.003] and in patients with expanded disability status scale scores (EDSS) <3.5 [SMD = 0.82, 95% CI (0.22, 1.42), *P* = 0.007]. In particular, NIBS contributed to the improvement of spasticity in pwMS [SMD = 0.68, 95% CI (0.13, 1.23), *P* = 0.015].
Conclusion: These results of this present study provide evidence that non-invasive brain stimulation could improve alertness in pwMS. Furthermore, NIBS may help pwMS with motor function and those who are under 45 years of age or with EDSS < 3.5 improve their motor function. For the therapeutic use of NIBS, we recommend applying transcranial magnetic stimulation as an intervention and located on the motor cortex M1 according to the subgroup analysis of motor function. These findings warrant verification.

ZUR KOMPLETTEN STUDIE >>>
https://pubmed.ncbi.nlm.nih.gov/36779055/

Explore the durability of repetitive transcranial magnetic stimulation in treating post-traumatic stress disorder: An updated systematic review and meta-analysis

Abstract

The objective was to synthesize results from studies that assessed symptom relief after repetitive transcranial magnetic stimulation (rTMS) treatment for post-traumatic stress disorder (PTSD) and investigate the long-term effectiveness of rTMS for treating PTSD. We searched multiple databases for relevant randomized controlled trials of rTMS for PTSD treatment up to 1 January 2023. Two researchers evaluated the studies and focused on the CAPS and PCL as outcome indicators. We used STATA17 SE software for the data analysis. Eight articles involving 309 PTSD patients were analysed in a meta-analysis, which found that rTMS had a significant and large effect on reducing core post-traumatic symptoms [Hedges'g = 1.75, 95% CI (1.18, 2.33)]. Both low and high-frequency rTMS also significantly reduced symptoms, with the latter having a greater effect. rTMS was shown to have a long-term effect on PTSD, with all three subgroup analyses demonstrating significant results. Interestingly, no significant difference in symptom relief was found between the follow-up and completion of treatments [Hedges'g = 0.01, 95% CI (-0.30, 0.33)], suggesting that the treatment effect of rTMS is stable. The meta-analysis provides strong evidence that rTMS is effective in reducing the severity and symptoms of PTSD in patients, and follow-up studies confirm its long-term stability.

ZUR KOMPLETTEN STUDIE >>>
https://pubmed.ncbi.nlm.nih.gov/37452747/

In Older Adults the Antidepressant Effect of Repetitive Transcranial Magnetic Stimulation Is Similar but Occurs Later Than in Younger Adults

Background: Treatment resistant depression is common in older adults and treatment is often complicated by medical comorbidities and polypharmacy. Repetitive transcranial magnetic stimulation (rTMS) is a treatment option for this group due to its favorable profile. However, early influential studies suggested that rTMS is less effective in older adults. This evidence remains controversial.
Methods: Here, we evaluated the rTMS treatment outcomes in a large international multicenter naturalistic cohort of >500 patients comparing older vs. younger adults.
Results: We show that older adults, while having similar antidepressant response to younger adults, respond more slowly, which may help to explain differences from earlier studies when the duration of a treatment course was shorter.
Conclusions: Such evidence helps to resolve a long-standing controversy in treating older depressed patients with rTMS. Moreover, these findings provide an important data point in the call to revise policy decisions from major insurance providers that have unfairly excluded older adults.

ZUR KOMPLETTEN STUDIE >>>
https://www.frontiersin.org/articles/10.3389/fnagi.2022.919734/full

Cortical and subcortical microstructure integrity changes after repetitive transcranial magnetic stimulation therapy in cocaine use disorder and relates to clinical outcomes

Abstract
Cocaine use disorder (CUD) is a worldwide public health condition that is suggested to induce pathological changes in macrostructure and microstructure. Repetitive transcranial

magnetic stimulation (rTMS) has gained attention as a potential treatment for CUD symptoms. Here, we sought to elucidate whether rTMS induces changes in white matter (WM) microstructure in frontostriatal circuits after 2 weeks of therapy in patients with CUD and to test whether baseline WM microstructure of the same circuits affects clinical improvement. This study consisted of a 2-week, parallel-group, double-blind, randomized controlled clinical trial (acute phase) (sham [n = 23] and active [n = 27]), in which patients received two daily sessions of rTMS on the left dorsolateral prefrontal cortex (lDLPFC) as an add-on treatment. T1-weighted and high angular resolution diffusion-weighted imaging (DWI-HARDI) at baseline and 2 weeks after served to evaluate WM microstructure. After active rTMS, results showed a significant increase in neurite density compared with sham rTMS in WM tracts connecting lDLPFC with left and right ventromedial prefrontal cortex (vmPFC). Similarly, rTMS showed a reduction in orientation dispersion in WM tracts connecting lDLPFC with the left caudate nucleus, left thalamus, and left vmPFC. Results also showed a greater reduction in craving Visual Analogue Scale (VAS) after rTMS when baseline intra-cellular volume fraction (ICVF) was low in WM tracts connecting left caudate nucleus with substantia nigra and left pallidum, as well as left thalamus with substantia nigra and left pallidum. Our results evidence rTMS-induced WM microstructural changes in fronto-striato-thalamic circuits and support its efficacy as a therapeutic tool in treating CUD. Further, individual clinical improvement may rely on the patient's individual structural connectivity integrity.

Keywords: MRI; NODDI; addiction; cocaine use disorder; diffusion; transcranial magnetic stimulation.

READ COMPLETE STUDY>>>
https://pubmed.ncbi.nlm.nih.gov/38357782/

Reduced executive and reward connectivity is associated with smoking cessation response to repetitive transcranial magnetic stimulation: A double-blind, randomized, sham-controlled trial

Abstract

Repetitive transcranial magnetic stimulation (rTMS) can reduce cue-elicited craving, decrease cigarette consumption, and increase the abstinence rate in tobacco use disorders (TUDs). We used functional magnetic resonance imaging (fMRI) to investigate the effect of 10 sessions of rTMS on cortical activity and neural networks in treatment-seeking smokers. Smoking cue exposure fMRI scans were acquired before and after the 10 sessions of active or sham rTMS (10 Hz, 3000 pulses per session) to the left dorsal lateral prefrontal cortex (DLPFC) in 42 treatment-seeking smokers (≥ 10 cigarettes per day). Brain activity and functional connectivity were compared before and after 10 sessions of rTMS. Ten sessions of rTMS significantly reduced the number of cigarettes consumed per day (62.93%) compared to sham treatment (39.43%) at the end of treatment ($p = 0.027$). fMRI results showed that the rTMS treatment increased brain activity in the dorsal anterior cingulate cortex (dACC) and DLPFC, but decreased brain

activity in the bilateral medial orbitofrontal cortex (mOFC). The lower strength of dACC and mOFC connectivity was associated with quitting smoking (Wald score = 5.00, p = 0.025). The reduction of cigarette consumption significantly correlated with the increased brain activation in the dACC (r = 0.76, p = 0.0001). By increasing the brain activity in the dACC and prefrontal cortex and decreasing brain activity in the mOFC, 10 sessions of rTMS significantly reduced cigarette consumption and increased quit rate. Reduced drive-reward and executive control functional connectivity was associated with the smoking cessation effect from rTMS. TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT02401672.
Keywords: ACC; DLPFC; Executive control circuitry; Reward circuitry; Smoking cessation; TMS; Tobacco use disorder.

READ COMPLETE STUDY>>>
https://pubmed.ncbi.nlm.nih.gov/37996557/

A generalizable functional connectivity signature characterizes brain dysfunction and links to rTMS treatment response in cocaine use disorder

Abstract
Cocaine use disorder (CUD) is a prevalent substance abuse disorder, and repetitive transcranial magnetic stimulation (rTMS) has shown potential in reducing cocaine cravings. However, a robust and replicable biomarker for CUD phenotyping is lacking, and the association between CUD brain phenotypes and treatment response remains unclear. Our study successfully established a cross-validated functional connectivity signature for accurate CUD phenotyping, using resting-state functional magnetic resonance imaging from a discovery cohort, and demonstrated its generalizability in an independent replication cohort. We identified phenotyping FCs involving increased connectivity between the visual network and dorsal attention network, and between the frontoparietal control network and ventral attention network, as well as decreased connectivity between the default mode network and limbic network in CUD patients compared to healthy controls. These abnormal connections correlated significantly with other drug use history and cognitive dysfunctions, e.g., non-planning impulsivity. We further confirmed the prognostic potential of the identified discriminative FCs for rTMS treatment response in CUD patients and found that the treatment-predictive FCs mainly involved the frontoparietal control and default mode networks. Our findings provide new insights into the neurobiological mechanisms of CUD and the association between CUD phenotypes and rTMS treatment response, offering promising targets for future therapeutic development.

READ COMPLETE STUDY>>>

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10168499/

Studien über den Einsatz von Virtual Reality

Virtuelle Expositionstherapie bei Angststörungen

Y. Shiban
Der Nervenarzt volume 89, pages 1227 – 1231 (2018)

Zusammenfassung

Angststörungen zählen zu den häufigsten psychischen Störungen in Deutschland. Mit der Expositionstherapie steht eine effektive Methode zur Behandlung von Angststörungen zur Verfügung. Im Rahmen der Expositionstherapie werden Patienten systematisch mit dem gefürchteten Objekt bzw. der gefürchteten Situation konfrontiert. Die Expositionstherapie kann dabei in vivo oder in sensu erfolgen. In den letzten Jahren wurde zudem vermehrt der Einsatz der Expositionstherapie in virtuo zur Behandlung von Angststörungen – insbesondere Phobien – untersucht. Bei der Expositionstherapie in virtuo werden Patienten mit einer virtuellen Version des gefürchteten Objekts bzw. der gefürchteten Situation konfrontiert. Eine Vielzahl an Studien belegt die Wirksamkeit der Expositionstherapie in virtuo, insbesondere im Hinblick auf die Behandlung spezifischer Phobien. Vorteile der Expositionstherapie in virtuo liegen in der Kontrollierbarkeit des gefürchteten Stimulus bzw. der gefürchteten Situation und in einem – im Vergleich zur Exposition in vivo – geringeren organisatorischen Aufwand bei der Durchführung der Konfrontation. Nachteile der Expositionstherapie in virtueller Realität liegen vor allem in der Gefahr der Simulatorkrankheit. Mit der Entwicklung kostengünstiger benutzerfreundlicher Systeme kann die virtuelle Expositionstherapie zunehmend Einzug in die psychotherapeutische Praxis finden. Hinsichtlich der weiteren Entwicklung der virtuellen Expositionstherapie ist insbesondere der Einsatz der erweiterten Realität als vielversprechende Behandlungsalternative zu erwähnen. Eindeutige Wirksamkeitsnachweise für diese Art der Konfrontationstherapie stehen noch aus.

Soziales Kompetenztraining in Virtueller Realität bei sozialer Angst. Validierung relevanter Interaktionssituationen

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Zusammenfassung

Theoretischer Hintergrund: Soziale Kompetenztrainings sind wichtige Werkzeuge bei der Psychotherapie der Sozialen Angststörung. Die Durchführung in Virtueller Realität (VR)

könnte die Verfügbarkeit und Effektivität erhöhen, allerdings besteht ein Bedarf an validierten VR-Szenarien. *Fragestellung:* Geprüft wird die Validität von zwei in Anlehnung an das Gruppentraining sozialer Kompetenzen von Hinsch und Pfingsten (2015) entwickelten VR-Szenarien. Es wird angenommen, dass die durch das Szenario ausgelösten Komponenten sozialer Angst auf subjektiver, psychophysiologischer und kognitiver Ebene signifikant zwischen höher (HSA) und niedriger (NSA) sozial ängstlichen Personen differenzieren. *Methode:* Insgesamt durchliefen *N* = 55 HSA und NSA Studierende zwei VR-Szenarien vom Typ „Recht durchsetzen“. Zusätzlich wurde experimentell die Blickkontaktdauer des virtuellen Gesprächspartners variiert. Hauptoutcome war die erlebte Angst in den Rollenspielen. Zusätzlich wurden Herzschlagfrequenz, Hautleitfähigkeit sowie die Einschätzung der eigenen Kompetenz erfasst. *Ergebnisse:* HSA im Vergleich zu NSA berichteten für beide Szenarien signifikant höhere Angst sowie negative Verzerrungen in Bezug auf die Einschätzung der eigenen Kompetenz. Zusätzlich zeigte sich eine physiologische Aktivierung während der Rollenspiele, aber keine Differenzierung zwischen beiden Gruppen. Beide VR-Szenarien wurden als realistisch empfunden. *Schlussfolgerungen:* Virtuelle Interaktionsszenarien können zu Trainingszwecken genutzt werden und Soziale Kompetenztrainings in VR haben ein

Studien über HRV Biofeedback

Feasibility and Efficacy of the Addition of Heart Rate Variability Biofeedback to a Remote Digital Health Intervention for Depression

Applied Psychophysiology and Biofeedback
https://doi.org/10.1007/s10484-020-09458-z
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Abstract

A rise in the prevalence of depression underscores the need for accessible and effective interventions. The objectives of this study were to determine if the addition of a treatment component showing promise in treating depression, heart rate variability-biofeedback (HRV-B), to our original smartphone-based, 8-week digital intervention was feasible and whether patients in the HRV-B (“enhanced”) intervention were more likely to experience clinically significant improvements in depressive symptoms than patients in our original (“standard”) intervention. We used a quasi-experimental, non-equivalent (matched) groups design to compare changes in symptoms of depression in the enhanced group (n = 48) to historical out- come data from the standard group (n = 48). Patients in the enhanced group completed a total average of 3.86 h of HRV-B practice across 25.8 sessions, and were more likely to report a clinically significant improvement in depressive symptom score post-intervention than participants in the standard group, even after adjusting for differences in demographics and engagement between groups (adjusted OR 3.44, 95% CI [1.28–9.26], *P* = .015). Our findings suggest that adding HRV-B to an app-based, smartphone-delivered, remote intervention for depression is feasible and may enhance treatment outcomes.

Heart Rate Variability Biofeedback Increased Autonomic Activation and Improved Symptoms of Depression and Insomnia among Patients with Major Depression Disorder

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Published online 2019 Apr 30. doi: 10.9758/cpn.2019.17.2.222
PMCID: PMC6478078
PMID: 30905122
I-Mei Lin,1,* Sheng-Yu Fan,,* Cheng-Fang Yen, Yi-Chun Yeh, Tze-Chun Tang, Mei-Feng Huang, Tai-Ling Liu, Peng-Wei Wang, Huang-Chi Lin, Hsin-Yi Tsai, and Yu-Che Tsai“ src=“blob:https://www.psychosomatik.com/61724f14-b840-4c3c-bf1c-de47cbec0d0e“ alt=“corresponding author“ border=“0″ class=“Apple-web-attachment Singleton“ style=“width: 0.0729in; height: 0.0937in; opacity: 1;“>
Abstract

Objective
Autonomic imbalance is considered a psychopathological mechanism underlying major depressive disorder (MDD). Heart rate variability (HRV) is an index for autonomic activation. Poor sleep quality is common among patients with MDD. HRV biofeedback (BF) has been used for regulating autonomic balance among patients with physical illness and mental disorders. The purpose of present study was to examine the effects of HRV-BF on depressive symptoms, sleep quality, pre-sleep arousal, and HRV indices, in patients with MDD and insomnia.
Methods
In this case-controlled study, patients with MDD and Pittsburgh Sleep Quality Index (PSQI) score higher than 6 were recruited. The HRV-BF group received weekly 60-minute protocol for 6 weeks, and the control group who have matched the age and sex received medical care only. All participants were assessed on Beck Depression Inventory-II, Back Anxiety Inventory, PSQI, and Pre-Sleep Arousal Scale. Breathing rates and electrocardiography were also performed under resting state at pre-testing, and post-testing conditions and for the HRV-BF group, also at 1-month follow-up.
Results
In the HRV-BF group, symptoms of depression and anxiety, sleep quality, and pre-sleep arousal were significantly improved, and increased HRV indices, compared with the control group. Moreover, in the HRV-BF group, significantly improved symptoms of depression and anxiety, decreased breathing rates, and increased HRV indices were detected at post-testing and at 1-month follow-up, compared with pre-testing values.

Heart Rate Variability Biofeedback Improves Emotional and Physical Health and Performance: A Systematic Review and Meta Analysis

published: 08 May 2020
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●Robert Huseby,
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Applied Psychophysiology and Biofeedback (2020)
Abstract

We performed a systematic and meta analytic review of heart rate variability biofeedback (HRVB) for various symptoms and human functioning. We analyzed all problems addressed by HRVB and all outcome measures in all studies, whether or not relevant to the studied population, among randomly controlled studies. Targets included various biological and psychological problems and issues with athletic, cognitive, and artistic performance. Our initial review yielded 1868 papers, from which 58 met inclusion criteria. A significant small to moderate effect size was found favoring HRVB, which does not differ from that of other effective treatments. With a small number of studies for each, HRVB has the largest effect sizes for anxiety, depression, anger and athletic/artistic performance and the smallest effect sizes on PTSD, sleep and quality of life. We found no significant differences for number of treatment sessions or weeks between pretest and post-test, whether the outcome measure was targeted to the population, or year of publication. Effect sizes are larger in comparison to inactive than active control conditions although significant for both. HRVB improves symptoms and and functioning in many areas, both in the normal and pathological ranges. It appears useful as a complementary treatment. Further research is needed to confirm its efficacy for particular applications.

Neuromodulation Applied to Diseases: The Case of HRV Biofeedback

Abstract

The vagus or “wandering” nerve is the main branch of the parasympathetic nervous system (PNS), innervating most internal organs crucial for health. Activity of the vagus nerve can be non-invasively indexed by heart-rate variability parameters (HRV). Specific HRV parameters predict less all-cause mortality, lower risk of and better prognosis after myocardial infarctions, and better survival in cancer. A non-invasive manner for self-activating the vagus is achieved by performing a slow-paced breathing technique while receiving visual feedback of one’s HRV, called HRV-biofeedback (HRV-B). This article narratively reviews the biological mechanisms underlying the role of vagal activity and vagally mediated HRV in hypertension, diabetes, coronary heart disease (CHD), cancer, pain, and dementia. After searching the literature for HRV-B intervention studies in each condition, we report the effects of HRV-B on clinical outcomes in these health conditions, while evaluating the methodological quality of these studies. Generally, the levels of evidence for the benefits of HRV-B is high in CHD, pain, and hypertension, moderate in cancer, and poor in diabetes and dementia. Limitations and future research directions are discussed.

Komplette Studie:
https://www.mdpi.com/2077-0383/11/19/5927?trk=public_post_comment-text

Heart rate variability biofeedback in chronic disease management: A systematic review

Abstract
Background
Heart rate variability biofeedback (HRVB) is a non-pharmacological intervention used in the management of chronic diseases.

Method
A systematic search was performed according to eligibility criteria including adult chronic patients, HRVB as main treatment with or without control conditions, and psychophysiological outcomes as dependent variables.

Results
In total, 29 articles were included. Reported results showed the feasibility of HRVB in chronic patients without adverse effects. Significant positive effects were found in various patient profiles on hypertension and cardiovascular prognosis, inflammatory state, asthma disorders, depression and anxiety, sleep disturbances, cognitive performance and pain, which could be associated with improved quality of life. Improvements in clinical outcomes co-occurred with improvements in heart rate variability, suggesting possible regulatory effect of HRVB on autonomic function.

Conclusions
HRVB could be effective in managing patients with chronic diseases. Further investigations are required to confirm these results and recommend the most effective method.

Komplette Studie:
https://www.sciencedirect.com/science/article/pii/S0965229921000911

Studien über transkranielle Gleichstromsimulation (tDCS)

Therapeutic Role of Transcranial Direct Current Stimulation in Alzheimer Disease Patients: Double-Blind, Placebo-Controlled Clinical Trial

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First Published April 3, 2019
https://doi.org/10.1177/1545968319840285
Abstract

Objective

To explore the neuropsychological effects and levels of tau protein (TAU), amyloid β 1-42 (Aβ 1-42), and lipid peroxidase after 10 sessions of anodal transcranial direct current stimulation (tDCS) in patients with mild to moderate Alzheimer disease (AD). *Patients and methods*. A total of 46 consecutive patients with probable AD participated in this study. They were classified randomly into 2 equal groups: active versus sham. Each patient received 10 sessions of anodal tDCS over the left and right temporoparietal region for 20 minutes for each side with the cathode on the left arm. Patients were assessed using the Modified Mini Mental State Examination (MMMSE), clock drawing test, Montreal Cognitive Scale (MoCA), and the Cornell Scale for depression. Serum TAU, Aβ 1-42, and lipid peroxidase were measured before and after the 10th session. *Results.* There was a significant improvement in the total score of each cognitive rating scale (MMMSE, clock drawing test, and MoCA) in the real group, whereas no such change was observed in the sham group. The Cornell depression score improved significantly in both groups. There was a significant increase in serum Aβ 1-42 (P = .02) in the real but not in the sham group, with a significant Treatment condition × Time interaction (P = .009). There was no significant effect on tau or lipid peroxidase in either group but a significant positive correlation between changes of Aβ1-42 and MMMSE (P = .005) and MoCA (P= .02). *Conclusion.* The observed cognitive improvements were complemented by parallel changes in serum levels of Aβ 1-42.

A systematic review and meta-analysis on the effects of transcranial direct current stimulation in depressive episodes

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First published: 26 February 2020
https://doi.org/10.1002/da.23004

Abstract

Background
Transcranial direct current stimulation (tDCS) has shown mixed results for depression treatment.
Objective
To perform a systematic review and meta-analysis of trials using tDCS to improve depressive symptoms.
Methods
A systematic review was performed from the first date available to January 06, 2020 in PubMed, EMBASE, Cochrane Library, and additional sources. We included randomized, sham-controlled clinical trials (RCTs) enrolling participants with an acute depressive episode and compared the efficacy of active versus sham tDCS, including association with

other interventions. The primary outcome was the Hedges' *g* for continuous depression scores; secondary outcomes included odds ratios (ORs) and number needed to treat (NNT) for response, remission, and acceptability. Random effects models were employed. Sources of heterogeneity were explored via metaregression, sensitivity analyses, subgroup analyses, and bias assessment.

Results

We included 23 RCTs (25 datasets, 1,092 participants), most (57%) presenting a low risk of bias. Active tDCS was superior to sham regarding endpoint depression scores ($k = 25$, $g = 0.46$, 95% confidence interval [CI]: 0.22–0.70), and also achieved superior response ($k = 18$, 33.3% vs. 16.56%, OR = 2.28 [1.52–3.42], NNT = 6) and remission ($k = 18$, 19.12% vs. 9.78%, OR = 2.12 [1.42–3.16], NNT = 10.7) rates. Moreover, active tDCS was as acceptable as sham. No risk of publication bias was identified. Cumulative meta-analysis showed that effect sizes are basically unchanged since total sample reached 439 participants.

Conclusions

TDCS is modestly effective in treating depressive episodes. Further well-designed, large-scale RCTs are warranted.

A review of transcranial direct current stimulation (tDCS) for the individualized treatment of depressive symptoms

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Mayank V.Jogab Danny J.J.Wangb Katherine L.Narrac
https://doi.org/10.1016/j.pmip.2019.03.001Get rights and content

Highlights

- TDCS of the left dorsolateral prefrontal cortex can reduce depressive symptoms.
- TDCS may be less suited for treatment-resistant depression.
- Combining tDCS with pharmaco- or psychotherapies may enhance therapeutic outcomes.
- Optimizing tDCS parameters to individual patients can improve physiological response.

Abstract

Transcranial direct current stimulation (tDCS) is a low intensity neuromodulation technique shown to elicit therapeutic effects in a number of neuropsychological conditions. Independent randomized sham-controlled trials and meta- and mega-analyses demonstrate that tDCS targeted to the left dorsolateral prefrontal cortex can produce a clinically meaningful response in patients with major depressive disorder (MDD), but effects are small to moderate in size. However, the heterogeneous presentation, and the neurobiology underlying particular features of depression suggest clinical outcomes might benefit from empirically informed patient selection. In this review, we summarize the status of tDCS research in MDD with focus on the clinical, biological, and intrinsic and extrinsic factors shown to enhance or predict antidepressant response. We also discuss research strategies for optimizing tDCS to improve patient-specific clinical outcomes. TDCS appears suited for both bipolar and unipolar depression, but is less effective in treatment resistant depression. TDCS may also better target core aspects of depressed mood over

vegetative symptoms, while pretreatment patient characteristics might inform subsequent response. Peripheral blood markers of gene and immune system function have not yet proven useful as predictors or correlates of tDCS response. Though further research is needed, several lines of evidence suggest that tDCS administered in combination with pharmacological and cognitive behavioral interventions can improve outcomes. Tailoring stimulation to the functional and structural anatomy and/or connectivity of individual patients can maximize physiological response in targeted networks, which in turn could translate to therapeutic benefits.

Studien zu EMDR

25 years of Eye Movement Desensitization and Reprocessing (EMDR): The EMDR therapy protocol, hypotheses of its mechanism of action and a systematic review of its efficacy in the treatment of post-traumatic stress disorder

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y Benedikt L. Amannc,d,∗

Abstract

Eye movement desensitization and reprocessing (EMDR) is a relatively new psychot- herapy that has gradually gained popularity for the treatment of post-traumatic stress disorder. In the present work, the standardised EMDR protocol is introduced, along with current hypot- heses of its mechanism of action, as well as a critical review of the available literature on its clinical effectiveness in adult post-traumatic stress disorder. A systematic review of the published literature was performed using PubMed and PsycINFO databases with the keywords «eye movement desensitization and reprocessing» and «post-traumatic stress disorder» and its abbreviations «EMDR» and «PTSD». Fifteen randomised controlled trials of good methodologi- cal quality were selected. These studies compared EMDR with unspecific interventions, waiting lists, or specific therapies. Overall, the results of these studies suggest that EMDR is a useful, evidence-based tool for the treatment of post-traumatic stress disorder, in line with recent recommendations from different international health organisations.

Journal of EMDR Practice and Research
Volume 13, Issue 4

The Status of EMDR Therapy in the Treatment of Posttraumatic Stress Disorder 30 Years After Its Introduction

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●Hofmann, Arne
●Farrell, Derek
●Lee, Christopher W.
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Vol 13Issue 4

DOI: 10.1891/1933-3196.13.4.261
Abstract
Given that 2019 marks the 30th anniversary of eye movement desensitization and reprocessing (EMDR) therapy, the purpose of this article is to summarize the current empirical evidence in support of EMDR therapy as an effective treatment intervention for posttraumatic stress disorder (PTSD). Currently, there are more than 30 randomized controlled trials (RCT) demonstrating the effectiveness in patients with this debilitating mental health condition, thus providing a robust evidence base for EMDR therapy as a first-choice treatment for PTSD. Results from several meta-analyses further suggest that EMDR therapy is equally effective as its most important trauma-focused comparator, that is, trauma-focused cognitive behavioral therapy, albeit there are indications from some studies that EMDR therapy might be more efficient and cost-effective. There is emerging evidence showing that EMDR treatment of patients with psychiatric disorders, such as psychosis, in which PTSD is comorbid, is also safe, effective, and efficacious. In addition to future well-crafted RCTs in areas such as combat-related PTSD and psychiatric disorders with comorbid PTSD, RCTs with PTSD as the primary diagnosis remain pivotal in further demonstrating EMDR therapy as a robust treatment intervention.

EMDR Therapy's Efficacy in the Treatment of Pain

Journal of EMDR Practice and Research Volume 13, Issue 4
●Tesarz, Jonas
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●Bernardy, Kathrin
●Seidler, Günter H.
Journal of EMDR Practice and Research Vol 13 Issue 4 DOI:
10.1891/1933-3196.13.4.337
Abstract
Chronic pain is the most common global cause of functional and quality of life limitations. Although there are many effective therapies for the treatment of acute pain, chronic pain is often unsatisfactory. Against this background, there is currently an urgent need to develop innovative therapies that enable more efficient pain relief. Psychosocial factors play an important role in the development and persistence of chronic pain. Especially in patients with high levels of emotional stress, significant anxiety, or relevant psychological comorbidity, classical pain therapy approaches often fail. This is in line with the results of recent pain research, which has shown that dysfunctions in emotion processing have a significant influence on the persistence of pain symptoms. The recognition that pain can become chronic through maladaptive emotional processing forms the pathophysiological basis for the application of eye movement desensitization and reprocessing (EMDR) in the treatment of chronic pain. In this sense, EMDR can be used as an established method for desensitizing and processing of emotional distress from trauma therapy specifically for processing emotional stress in patients with chronic pain. Against this background, it is not surprising that the implementation of EMDR for patients with chronic pain is expanding. However, the increasing clinical use of EMDR in the treatment of chronic pain has also led to a reputation to test the efficacy of EMDR in pain management through randomized clinical trials. In addition to numerous case control studies, there are now also six

randomized controlled clinical trials available that demonstrate the efficacy and safety of EMDR in the treatment of different pain conditions. However, in order to overcome several methodological limitations, large multicenter studies are needed to confirm the results.

Desensitizing addiction: Using eye Movements to reduce the intensity of substance-related Mental imagery and craving

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Eye movement desensitization and reprocessing (EMDR) is an effective treatment for posttraumatic stress disorder. During this treatment, patients recall traumatic memo- ries while making horizontal eye movements (EM). Studies have shown that EM not only desensitize negative memories but also positive memories and imagined events. Substance use behavior and craving are maintained by maladaptive memory associa- tions and visual imagery. Preliminary findings have indicated that these mental images can be desensitized by EMDR techniques. We conducted two proof-of-principle studies to investigate whether EM can reduce the sensory richness of substance-related mental representations and accompanying craving levels. We investigated the effects of EM on (1) vividness of food-related mental imagery and food craving in dieting and non-dieting students and (2) vividness of recent smoking-related memories and cigarette craving in daily smokers. In both experiments, participants recalled the images while making EM or keeping eyes stationary. Image vividness and emotionality, image-specific craving and general craving were measured before and after the intervention. As a behavioral outcome measure, participants in study 1 were offered a snack choice at the end of the experiment. Results of both experiments showed that image vividness and crav- ing increased in the control condition but remained stable or decreased after the EM intervention. EM additionally reduced image emotionality (experiment 2) and affected behavior (experiment 1): participants in the EM condition were more inclined to choose healthy over unhealthy snack options. In conclusion, these data suggest that EM can be used to reduce intensity of substance-related imagery and craving. Although long-term effects are yet to be demonstrated, the current studies suggest that EM might be a useful technique in addiction treatment.
Front. Psychiatry 7:14. doi: 10.3389/fpsyt.2016.00014

Desensitization of Triggers and Urge Reprocessing for Pathological Gambling: A Case Series

Hwallip Bae • Changwoo Han • Daeho Kim

Abstract

This case series introduces the desensitization of triggers and urge reprocessing (DeTUR), as a promising adjunctive therapy in addition to comprehensive treatment package for pathological gambling. This addiction protocol of eye movement desensiti- zation and reprocessing was delivered to four male inpatients admitted to a 10-week inpatient program for pathological gambling. The therapist gave three 60-min weekly sessions of the DeTUR using bilateral stimulation (horizontal eye movements or alterna-

tive tactile stimuli) focusing on the hierarchy of triggering situations and the urge to initiate gambling behaviors. After treatment, self-reported gambling symptoms, depression, anxiety, and impulsiveness were all improved, and all the participants reported satisfaction with the therapy. They were followed up for 6 months and all maintained their abstinence from gambling and their symptomatic improvements. Given the efficiency (i.e., brevity and efficacy) of the treatment, a controlled study to confirm the effects of the DeTUR on pathological gambling would be justified.

Cognitive Behavioral Therapy versus Eye Movement Desensitization and Reprocessing in Patients with Post- traumatic Stress Disorder: Systematic Review and Meta-analysis of Randomized Clinical Trials

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Abstract

Background
Post-traumatic stress disorder (PTSD) is prevalent in children, adolescents and adults. It can occur alone or in comorbidity with other disorders. A broad range of psychotherapies such as cognitive behavioral therapy (CBT) and eye movement desensitization and reprocessing (EMDR) have been developed for the treatment of PTSD.
Aim
Through quantitative meta-analysis, we aimed to compare the efficacy of CBT and EMDR: (i) relieving the post-traumatic symptoms, and (ii) alleviating anxiety and depression, in patients with PTSD.
Methods
We systematically searched EMBASE, Medline and Cochrane central register of controlled trials (CENTRAL) for articles published between 1999 and December 2017. Randomized clinical trials (RCTs) that compare CBT and EMDR in PTSD patients were included for quantitative meta- analysis using RevMan Version 5.
Results
Fourteen studies out of 714 were finally eligible. Meta-analysis of 11 studies (n = 547) showed that EMDR is better than CBT in reducing post-traumatic symptoms [SDM (95% CI) = -0.43 (- 0.73 – -0.12), p = 0.006]. However, meta-analysis of four studies (n = 186) at

three-
month follow-up revealed no statistically significant difference [SDM (95% CI) = -0.21 (-0.50 – 0.08), p = 0.15]. The EMDR was also better than CBT in reducing anxiety [SDM (95% CI) = -0.71 (-1.21 – -0.21), p =0.005]. Unfortunately, there was no difference between CBT and EMDR in reducing depression [SDM (95% CI) = -0.21 (-0.44 – 0.02), p = 0.08].
Conclusion
The results of this meta-analysis suggested that EMDR is better than CBT in reducing post- traumatic symptoms and anxiety. However, there was no difference reported in reducing depression. Large population randomized trials with longer follow-up are recommended to build conclusive evidence.