MARCH 2024 / ISSUE 37

PULSE

A Monthly Update on Advances in Neuromodulation

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Potential Benefits of rTMS for Cannabis Use Disorder (CUD)

Harinee Maiyuran, MD, reviewing Sahlem et al. Drug and Alcohol Dependence Nov 2023

In this phase-II randomized trial, active rTMS in participants with cannabis use disorder (CUD) decreased days-per-week use when compared to those receiving placebo treatment, showing the promise of rTMS as a treatment for CUD.

Cannabis use disorder (CUD) is becoming increasingly common in the United States, and options for treatment are few and far between. rTMS has shown promise in the treatment of other substance use disorders, including tobacco use disorder, leading to recent curiosity as to its potential in managing CUD. Thus far, rTMS targeting the left dorsolateral prefrontal cortex (LDLPFC) has been most promising in decreasing cravings and cannabis use. Could rTMS significantly increase abstinence from cannabis when compared to sham rTMS?

This double-blind, sham-controlled trial examined 51 participants

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(age 30.2±9.9, 37.5% female) with at least moderate cannabis use disorder (and no other significant substance use disorder) at either the Medical University of South Carolina (MUSC) or Stanford University. Participants were randomized to receive 20 sessions of either active or sham rTMS over five weeks, with two sessions per visit (separated by ≥30 min) and twice-weekly visits. Active stimulation sessions consisted of 4000 pulses of 10Hz stimulation delivered at 120% MT to LDLPFC; sham stimulation used a sham coil. Participants also met with a therapist for motivational enhancement therapy (MET) during three visits. Participants completed various validated rating scales, though the primary outcome was abstinence, defined as self-reported weeks without any cannabis use, confirmed by a 25% decrease in urine cannabinoids compared to the prior level and absolute cannabinoids <200ng/mL. Cravings were measured by the Marijuana Craving Questionnaire Short-Form (MCQ-SF). The two main hypotheses were that the active group would demonstrate decreased cravings and increased abstinence. Participants were followed for 4 weeks after completing treatment. Statistical analyses consisted of a generalized linear mixed-effects model (GLMM) for craving scores and days-per-week use and a Poisson regression model examining abstinence. Though participants completed several scales, the marijuana problem scale (MPS) was the only one that predicted outcomes and was therefore used in the final models.

Active rTMS recipients reported mildly numerically increased abstinence rates (15.5%) after treatment than those who received sham rTMS (9.3%), though this was not statistically significant (rate ratio = 1.66 [95% CI: 0.84, 3.28]; p=0.14). Interestingly, abstinence was higher in the sample treated at Stanford than at MUSC. Craving levels (MCQ-SF) decreased in both groups after treatment, though this lacked statistical significance. The MPS total score was able to significantly predict abstinent weeks and correlated with abstinence, in particular in the final two weeks of follow-up, suggesting that the decrease was greater in the active-rTMS group than the sham group. No serious adverse events were reported, with headaches and fatigue being most common across both the active and sham rTMS groups. Though results show that rTMS helped decrease cravings and increase abstinence in CUD, it was not shown to be significant in this study.

Impact: This study sheds light on the possibility that rTMS can benefit those with CUD, despite its lack of significance in decreasing cravings and increasing abstinence. Given the safety of the treatment and its promising results, further studies should be done to explore the benefits of rTMS in CUD in different contexts. The MPS was a strong predictor and moderator of rTMS outcomes in this study, making it a good candidate to help determine personalized treatments for patients with CUD. Baseline differences between MUSC and Stanford demonstrate a significant difficulty in CUD research: the complexity of varying use patterns in different environments, cultures, and lifestyles.

Sahlem GL, Kim B, Baker NL, et al. A preliminary randomized controlled trial of repetitive transcranial magnetic stimulation applied to the left dorsolateral prefrontal cortex in treatment seeking participants with cannabis use disorder. Drug and Alcohol Dependence. 2024;254:111035. doi:10.1016/j.drugalcdep.2023.111035

Prefrontal Short-Term rTMS No Different from Sham in Treating Alzheimer's Disease (AD)

Lara Tang, reviewing Moussavi et al. Neurotherapeutics 2024 Jan 29

This study demonstrated that both active and sham rTMS targeting DLPFC led to similar clinical benefits for patients with mild-to-moderate Alzheimer's Disease (AD). This improvement was observed to remain for up to two months during post-treatment follow-up.

While prior work has demonstrated that rTMS may improve cognition in patients with AD, little is known about how it should be administered (e.g., frequency of pulses, intensity of stimulation, duration of treatment) for optimal clinical outcomes. In addition to investigating the efficacy of rTMS in patients with mild-to-moderate AD, this trial sought to identify rTMS protocol parameters in DLPFC stimulation that might provide clinical benefit in patients with AD and to characterize the duration of benefit after treatment.

This double-blind, placebo-controlled, multi-site clinical trial randomized patients diagnosed with mild-to-moderate AD (n=156, 71 female, mean age 74.0 ± 8.1) into three groups: 2 weeks (5 days/week) of active rTMS (R2), 4 weeks (5 days/week) of active rTMS (R4), or 4 weeks of sham rTMS (S4). Active stimulation consisted of 1500 pulses of 20 Hz stimulation (30 pulses per train with 10s ITI) at 90-100% MT applied in a sequential bilateral manner to DLPFC (left then right) using structural MRI neuronavigation. Patients were

randomized based on age (< or > 70) and AD severity. Score changes in the Alzheimer Disease assessment scale-cognitive subscale (ADAS-Cog) from baseline to post-treatment was used as the primary outcome measure. ADAS-Cog was measured at five separate time points during the trial duration (3, 5, 12, 20, and 28 weeks from the start of treatment) for up to 6 months. Secondary outcome measures included changes in neuropsychiatric/behavioral symptoms and activities of daily living using standardized measures.

There were no significant differences in ADAS-Cog scores at different time points across the three groups (R2, R4, S4), although the ADAS-Cog scores were significantly different between weeks within the same intervention groups ($p<0.00001$). Furthermore, rates of responders (with degree of response defined based on significant improvement and/or stabilization in ADAS-Cog or secondary measures at weeks 5 or 8) were over 70% higher in all three groups across all study sites. These improvements in ADAS-Cog lasted for roughly 2 months in all groups and gradually worsened, returning to baseline by the end of the follow-up period.

Impact: This study of DLPFC-targeted rTMS showed no difference in the impact of excitatory stimulation on cognitive function in mild-to-moderate AD with rTMS performed for 2 or 4 weeks and sham rTMS. Interestingly, it also highlighted that there was no cognitive decline in any of the three groups throughout the duration of the trial, including the sham intervention. This study highlights many of the difficulties that arise when studying a slowly progressive illness like AD, the possible issues with using certain sham TMS coils that generate low voltage active fields and provides further evidence that rTMS in AD may need to target alternative areas. Results from this study do not exclude the use of rTMS in patients with AD. However, this study suggests that further research is needed to understand how rTMS can be effectively and clinically utilized in AD.

Moussavi Z, Uehara M, Rutherford G, et al. Repetitive transcranial magnetic stimulation as a treatment for Alzheimer's disease: A randomized placebo-controlled double-blind clinical trial. Neurotherapeutics. Published online February 14, 2024. doi:10.1016/j.neurot.2024.e00331

Vagus Nerve Stimulation (VNS) for Depression May Reduce the Number of Psychiatric Hospitalizations and Subsequent Neuromodulatory Treatments

Erin M Hegarty, reviewing Kavakbasi et al. Brain Sci. 2024 January

This small prospective observational study of patients with treatment-resistant depression (TRD) studied the effects of vagus nerve stimulation (VNS) on adjunctive medication burden, number of ECT and/or ketamine treatments administered, and rate of hospitalization after 12 months. Statistically significant reductions in depression severity, number of maintenance ECT/ketamine treatments, number of hospitalizations, and total medication burden were all observed. However, hospitalizations and total medication burden improvements were of limited clinical utility in this study.

A large percentage of patients with depression can be classified as having difficult-to-treat (DTD) depression, which differs from treatment-resistant depression (TRD) in that the depression never fully remits, causing long-term deficits in functioning and quality of life. Psychiatrists often turn to procedural interventions like ECT and ketamine in patients with DTD and TRD. For patients with DTD, maintenance treatments can become increasingly cumbersome, given the degree of time and effort they require. This study examined the impact of VNS on not only the reduction in depressive symptoms but also the impact on practical, quality-of-life measures such as change in the number and/or dose of medications, number of hospitalizations, and change in frequency of maintenance treatments of ECT/ketamine.

Twenty patients (n=14 female, mean age 52.6 years) with unipolar (n=16) or bipolar (n=4) DTD (without psychosis or significant substance use disorders) from Germany were included in this prospective naturalistic study. All patients had failed several medications (mean 5.8 ± 3.7 in current episode, 12.2 ± 6.3 overall), and the average length of patients' current depressive episodes was 28.4 months. 90% had received ECT in the past, and 25% of patients had comorbid PTSD. They were implanted with a LivaNova VNS device as part of the RESTORE-LIFE trial and began titration of their VNS within 10 days of implantation with a goal output current of 1.5 mA (0.25 mA steps). 20 Hz stimulation with a 250 µs pulse width and 30s on separated by a 5 min off time was applied. Outcomes assessed included MADRS score, number of psychiatric hospitalizations,

number of ketamine or ECT treatments, and medication burden/"drug load". Each patient's "drug load" score was calculated, where 1 is equal to the smallest dose constituting an adequate trial of a given medication (e.g., a score of 2 for one drug would indicate the patient was on double this dose), and the sum of all prescribed antidepressant medications for a patient yielded the "total drug load." For this study, patients were followed for 12 months after implantation. T-tests and Mann-Whitney U tests were used to examine descriptive statistics. In contrast, a multivariate analysis of covariance (MANCOVA) was used to describe changes from the year leading up to implantation to follow-up one year after implantation.

The mean MADRS score significantly decreased from baseline (27.3) to 12 months (15.3, p=0.001) in all patients, with those previously demonstrating a response to ECT showing significantly greater response to VNS (baseline=30.2, end follow-up=9.3) than prior non-responders (baseline=26.0, end follow-up=21.4; responder vs non-responder Z=-2.918, p=0.002). The average number of medications decreased significantly, from 3.3 at baseline to 2.9 at the 12-month follow-up (Z=2.11, p=0.035).

However, the drug load score did not significantly change from baseline to the end of follow-up. Though there was a statistically significant reduction in the mean number of hospitalizations per month in the two years before VNS compared to the year following (pre=0.083, post=0.0625, Z=1.975, p=0.048), 45% of patients still had at least one hospitalization for depression in the twelve-month follow-up period, and the decrease was modest. In the 9 patients receiving concurrent ECT or esketamine maintenance therapy, there was a statistically significant reduction in the number of maintenance treatments received from 10.6 during the first six months post-implant compared to 5.1 during the final 6 months post-implant (Z=-2.530, p=0.011). However, in patients with known maintenance treatment history in the year preceding VNS, the change in maintenance treatments in the year following implantation was not statistically significant. One interesting observation of this study was the high rate of comorbid hypothyroidism, as 11 of the 20 subjects received supplemental thyroid hormones for this. This may support previous research showing higher rates of hypothyroidism in patients with more severe forms of depression. Rates of adverse events varied from 30% to 50%, with the highest rate being at 12 months follow-up. The most common side effect of VNS was voice change or hoarseness during stimulation; no adverse events were significant, and no patients discontinued treatment due to adverse events.

Impact: This study indicates that VNS not only significantly improves depressive symptom burden in DTD patients but may also improve quality of life by reducing medication and maintenance treatment burden. Although improvement in medication burden was modest, knowing that VNS may take years to realize its antidepressant potential (with an adequate trial generally being considered two years), this may further improve at follow-up times after a year. This may also explain why the reduction in maintenance ECT/ketamine treatments was greater in the latter six months than in the first six months after implantation. This pattern can provide a helpful "roadmap" for psychiatrists caring for patients with a VNS and other adjunctive treatments, both in laying expectations for patients and in guiding their prescription patterns.

Kavakbasi E, Bauermeister H, Lemcke L, Baune BT. Impact of Adjunctive VNS on Drug Load, Depression Severity, and Number of Neuromodulatory Maintenance Treatments. Brain Sci. 2024;14(2):159.

Vagus Nerve Stimulation Observed as Effective for Narcolepsy Management

Michael K. Harinee Maiyuran, MD, reviewing Winter Y et al. Brain Stimulation 2024 Jan 4, MD reviewing Roth et al. J Clinical Medicine 2024 Jan 31

In this open-label prospective comparative study, patients with depression or epilepsy and with or without narcolepsy received VNS treatment, and sleepiness and cataplexy were measured and compared in those with and without narcolepsy. Subjects with narcolepsy had significant improvement in daily sleepiness following VNS treatment.

Narcolepsy is defined by changes in sleep-wake cycle regulation, with two general types. NT1, or Narcolepsy type 1, results from decreased orexin-producing neurons, leading to difficulties maintaining wakefulness, predisposition to sleepiness, and cataplexy. Comorbidities of narcolepsy include obesity,
This open-label phase IV study obstructive sleep apnea,

hyperlipidemia, hypertension, depression, and anxiety. Pharmacotherapy for narcolepsy and its comorbidities often result in polypharmacy and drug-drug interactions. Thus, neuromodulation modalities are being more heavily considered as treatments. Vagus nerve stimulation (VNS), currently used for epilepsy and depression, has been shown to increase alertness and energy. The mechanisms of how VNS impacts sleep and alertness are of great interest, and theories range from stimulation of the locus coeruleus to altering regional blood flow facilitating orexin receptor upregulation. Could VNS therefore demonstrate benefit in narcolepsy?

This study examined 36 patients (mean age 31.5 ± 8.2 years) implanted with VNS (n=18 with narcolepsy, n=18 without) for either epilepsy (n=22) or depression (n=14). Narcolepsy diagnosis was confirmed based on Internal Classification of Sleep Disorders criteria in addition to a multiple sleep latency test; 10 patients had NT1, and 8 had NT2. Epworth Sleepiness Scale (ESS) scores were greater than 10 for all patients, including those without narcolepsy. Regarding pharmacotherapy, 8 patients were on modafinil, 3 on methylphenidate, 7 on pitolisant, 4 on solriamfetol, 4 on sodium oxybate, 5 on SSRIs, and 2 on clomipramine (several subjects were being prescribed multiple of the aforementioned medications). Medications remained the same for at least the three months prior to the study and through the last follow-up appointment. Controls were patients without narcolepsy but with either depression or epilepsy necessitating VNS. This allowed for discernment between any improvements in sleepiness related to narcolepsy and other etiologies. VNS stimulation was applied both day and night, initially with the same parameters (output current of 0.25 mA, signal frequency of 30 Hz, pulse width of 250 μs, signal off-time of 5 min, and signal on-time of 30 s during the day time), then increased by 0.25 MA every two weeks, up to 2.0 mA. This target dose was reached in all subjects without notable side effects and was maintained during the six months of observation after treatment. ESS was measured one week before VNS implantation then at three and six months after implantation. Cataplexy frequency was measured by calculating weekly cataplexy rate/frequency (WCR) at these time points. Beck Depression Inventory-II (BDI-II) measured depression. Patient diaries were used to assess safety. A t-test and ANOVA were used to assess inter-group differences at baseline and ESS, WCR, and BDI-II changes, respectively. Multiple regression analysis was used to assess whether the improvement inESS after VNS was due to improvements in depression or to direct improvement in narcolepsy symptoms themselves.

The primary, statistically significant outcome was an improvement in ESS in patients with narcolepsy, from baseline 15.9 ± 2.5 to 11.2 ± 3.3 ($p < 0.05$) at three months, and to 9.6 ± 2.8 ($p < 0.01$) at six months. Those without narcolepsy did not have significant improvement in ESS, indicating that the improvement in daytime sleepiness after VNS was independent of improvement in depression or epilepsy. Though there was a trend that VNS improved/decreased cataplexy, the relationship was insignificant, and more rigorous studies are necessary to consolidate this finding. A sham-controlled trial of VNS for narcolepsy would be of great utility in validating the findings of this study.

Impact: This open-label prospective comparative study showed that VNS appears to be a safe and effective treatment for those with narcolepsy for whom pharmacologic management has not been sufficient in controlling sleepiness. Though this study is small, open-label, and not sham-controlled, it demonstrates promising improvements in narcolepsy symptoms that warrant further exploration.

Winter Y, Sandner K, Bassetti CLA, et al. Vagus nerve stimulation for the treatment of narcolepsy. Brain Stimulation. 2024;17(1):83-88. doi:10.1016/j.brs.2024.01.002

cTBS (continuous theta burst stimulation)
DBS (deep brain stimulation)
dTMS (deep transcranial magnetic stimulation)
ECT (electroconvulsive therapy)
HFL (high frequency left, 10 Hz stimulation to left DLPFC)
HF-rTMS (high frequency repetitive transcranial magnetic stimulation; 10 Hz unless otherwise stated)
iTBS (intermittent theta burst stimulation)
MST (magnetic seizure therapy)
TBS (theta-burst stimulation; TMS delivered as triplet burst pulses at 50 Hz, repeated at 5 Hz)
TENS (transcutaneous electrical nerve stimulation)
TMS (transcranial magnetic stimulation)
rTMS (repetitive transcranial magnetic stimulation)
tDCS (transcranial direct current stimulation)
tACS (transcranial alternating current stimulation)

BOLD (blood oxygen level dependent)
DTI (diffusion tensor imaging)
EEG (electroencephalography)
EMG (electromyography)
fMRI (functional magnetic resonance imaging)
MRI (magnetic resonance imaging)
MT (motor threshold)
RMT (resting MT)

ADHD (attention-deficit/hyperactivity disorder)
AUD (alcohol use disorder)
GAD (generalized anxiety disorder)
MDD (major depressive disorder)
OCD (obsessive compulsive disorder)
PTSD (post-traumatic stress disorder)
SUD (substance use disorder)
TRD (treatment resistant depression)

BAI (Beck Anxiety Inventory)
BDI (Beck Depression Inventory)
CGI (clinical global impression scale)
HAM-A (Hamilton Anxiety Rating Scale)
HAM-D / HDRS (Hamilton Depression Rating Scale)
MADRS (Montgomery-Asberg Depression Rating Scale)
MoCA (Montreal Cognitive Assessment)
PANSS (Positive and Negative Symptom Scale)
QIDS (Quick Inventory of Depressive Symptomatology)
YBOCS (Yale-Brown Obsessive Compulsive Scale)

ANOVA (analysis of variance)
AUC (area under the curve)
CI (confidence interval)
FDA (United States Food and Drug Administration)
ICA (independent component analysis)
ITT (intention to treat)
OR (odds ratio)
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)
RCT (randomized controlled trial)
ROC (receiver operating characteristic)
SMD (standard mean difference)

BA (Brodmann area)
DLPFC (dorsolateral prefrontal cortex)
DMPFC (dorsomedial prefrontal cortex)
M1 (primary motor cortex)
mPFC (medial prefrontal cortex)
OFC (orbitofrontal cortex)
SMA (supplementary motor area)