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Brain Stimulation for Substance Use Disorders

Preliminary evidence indicates that brain stimulation techniques may be a promising approach for substance use disorders.

Methods: A comprehensive literature search was undertaken to identify studies of repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and deep brain stimulation (DBS) in the treatment of alcohol, tobacco, cocaine, methamphetamine, opioid, and cannabis use disorders. The present review includes only studies whose participants met criteria for DSM-IV substance abuse or dependence or DSM-5 substance use disorders and whose primary or secondary outcomes were related to substance use (e.g., craving, consumption, or abstinence) or drug cue-induced functional imaging changes. A total of 60 studies met criteria; most were preliminary and had sample sizes <40.

Results: rTMS has demonstrated positive effects on craving and consumption in patients dependent on alcohol, nicotine, and cocaine. Effects in methamphetamine dependence have been mixed, and rTMS does not appear to improve cannabis dependence. Studies have shown the effects of tDCS are generally positive in substance use disorders. The treatment reduced cravings and consumption in alcohol, tobacco, cocaine, methamphetamine, opioid, and cannabis dependence. All DBS studies in alcohol, tobacco, cocaine, and opioid use disorders demonstrated positive effects.

Variations in stimulation parameters, differences among the disorders, and heterogeneity in the populations studied, including the presence of comorbid psychiatric disorders in some, appear to impact the efficacy of all 3 neuromodulation techniques in substance use disorders. Effect sizes* were promising but highly variable and were similar for rTMS and tDCS, ranging from small negative effects to very large effect sizes as high as 4. Both of these techniques were more effective when used repeatedly, and tDCS when it was applied for >10 minutes. High-frequency rTMS seems to be more effective than low-frequency. In most studies, both of these techniques were targeted to the dorsolateral prefrontal cortex (DLPFC). Specifically targeting the right DLPFC was more effective than the left. All DBS studies targeted the nucleus accumbens.

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Discussion: While these results suggest neuromodulation may be helpful for patients with substance use disorders, few of the studies followed patients long-term, there were no within-study comparisons of different brain regions or stimulation parameters, and the evidence base includes only a few studies of each treatment modality in each disorder. In spite of the limitations highlighted by this overview, additional study of neuromodulation in substance use disorders appears to be warranted. However, it should be noted that in order to produce improvement, stimulation should target brain regions relating to the reward pathway to reduce craving and consumption.

Coles A, Kozak K, George T: A review of brain stimulation methods to treat substance use disorders. *American Journal on Addictions* 2018; doi 10.1111/ajad.12674. From the Centre for Addiction and Mental Health, Toronto; and the University of Toronto, Canada. F**unded by the Canadian Institutes of Health Research; and other sources. The authors did not include disclosure of potential conflicts of interest.**

***See Reference Guide.**

VNS: Long-Term Effects on Depression

Results of a small, 6-year, naturalistic follow-up study of patients with treatment-resistant depression suggest that vagus nerve stimulation produces lasting improvements in depressive symptoms and quality of life.

Methods: Study subjects (n=10; 6 women) had a diagnosis of major depression that had been resistant to ≥3 antidepressant trials. All patients began receiving VNS at the University of Montreal between November 2007 and April 2010 and were followed for 72 months. Patients' background treatments were continued throughout the study period, but no changes were permitted during the first year of VNS therapy. At baseline and 9 follow-up points, depression and anxiety symptoms were evaluated using the Hamilton Rating Scales for Depression and Anxiety (HAM-D and HAM-A, respectively), and quality of life (mental and physical) was assessed using the 36-item Short Form Survey. Treatment response was defined as a ≥50% decrease in HAM-D score, and remission as a final score of ≤7.

Results: All 10 patients completed the full 6 years of follow-up assessments. Clinically and statistically significant improvement in depression was evident throughout the study, beginning at the 1-month evaluation. The mean HAM-D score decreased from 27 at baseline to 16 at 1 month ($p=0.001$), and then continued to decline, reaching a final mean of 8 at 72 months ($p<0.001$). Response was achieved by 30% of patients at 1 month, by 70% of patients at 12 months, and by 80% of patients at 72 months. Remission rates were 30% at 1 month and 50% at both the 12- and 72-month evaluations. Reductions in anxiety showed a similar pattern. HAM-A scores decreased from 16 at baseline to 10 at 1 month and reached a final mean of 6 at 72 months ($p<0.001$). Quality of life also improved significantly in patients treated with VNS, although the magnitude of improvement was substantially larger on the mental-health versus the physical-health component.

Discussion: While the small cohort of subjects is an important limitation, these study results appear to be the first indicating that VNS produces sustained improvement in symptoms as well as quality of life for as long as 6 years. Clinical improvement occurred earlier in these patients than has been previously reported in VNS studies, but overall response and remission rates were similar to previous reports. The authors note that the rate of remission with VNS in these patients was higher than that generally reported for repetitive transcranial magnetic stimulation and only slightly lower than that reported for ECT.

Trottier-Duclos F, Jodoin V, Fournier-Gosselin M, Richer F, et al: A 6-year follow-up study of vagus nerve stimulation effect on quality of life in treatment-resistant depression: a pilot study. *Journal of ECT* 2018; doi 10.1097/YCT.0000000000000485. From Centre Hospitalier Universitaire de Montreal; and Universite du Quebec a Montreal, Canada. **Source of funding not stated. Two of 7 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Virtual Reality Treatment for Paranoia

As an add-on to standard treatment, virtual-reality-based cognitive behavioral therapy (VR-CBT) led to reduced paranoid ideation and momentary anxiety in patients with psychosis. The treatment also modestly reduced safety behaviors, which could potentially lead to long-term improvement in social interactions.

Methods: Study participants (n=116) were adult outpatients with a psychotic disorder who were experiencing paranoid ideation with avoidance of various public places. All participants received standard treatment, and half were randomly assigned to undergo additional, single-blind VR-CBT. The virtual-reality intervention was designed to avoid some of the limitations of standard exposure-based CBT exercises for paranoid ideation by providing therapist control of the social environment, allowing real-time feedback, and overcoming patients' fears and negative symptoms. The treatment was delivered in virtual environments (e.g., a street or cafe) populated by therapist-operated avatars whose characteristics and behavior were tailored to match the paranoid fears of the patient. Each of the 16 planned sessions consisted of 40 minutes of virtual reality and 20 minutes of discussion and planning. No homework exercises were assigned. The primary outcome was social participation, measured by blinded raters using 4 constructs: amount of time spent with others, momentary paranoia, perceived social threat, and momentary anxiety in company.

Results: At the end of 3 months of treatment, patients in the virtual-reality group had large reductions in momentary paranoia and anxiety, compared with the control group ($p<0.0001$), effects that remained significant at 6-month follow-up ($p\leq0.007$). Treatment had no acute effects on time spent with others. However, at follow-up, time spent with others decreased somewhat in the control group but was unchanged in the VR-CBT group. Treatment had a small positive effect on perceived social threat. Use of safety behaviors (e.g., avoiding eye contact) decreased significantly in the virtual reality group at 3 and 6 months. The treatment was also associated with reduced ideas of persecution, social reference, and self-stigmatization and with improved social functioning. The treatment effect on paranoid ideation was mediated by change in safety behavior (34%) and social cognitive problems (19%). Quality of life did not differ significantly between the groups. The only reported adverse effect of VR-CBT was cybersickness (i.e., visual motion sickness), which caused 1 patient to withdraw from the study

Discussion: The lack of a treatment effect on time spent with others was an unexpected result. The authors suggest that safety behaviors interfere with gathering social information and forming new associations, and the effects of treatment may not be immediate.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Pot-Kolder R, Geraets C, Veling W, van Beilen M, et al: Virtual-reality-based cognitive behavioural therapy versus waiting list control for paranoid ideation and social avoidance in patients with psychotic disorders: a single-blind randomised controlled trial. *Lancet Psychiatry* 2018; doi 10.1016/S2215-0366(18)30053-1. From VU University, Amsterdam; and Amsterdam Public Health Research Institute, the Netherlands; and other institutions. **Funded by Fonds NutsOhra, Stichting tot Steun VCVGZ. The authors declared no competing interests.**

***See Reference Guide.**

Computer-Assisted CBT for Depression

In a randomized comparison, efficacy and acceptability of computer-assisted cognitive behavioral therapy (CCBT) were similar to standard CBT in patients with major depression, despite using one-third the therapist hours.[1]

Methods: This noninferiority study was conducted at 1 institution that had developed a standard CBT program (University of Pennsylvania) and another institution that had implemented

the Good Days Ahead computer-assisted CBT program (University of Louisville). The study was designed to minimize potential allegiance bias by distributing both types of therapy between therapists at both institutions. Study subjects were patients who met DSM-IV criteria for major depression and did not have psychosis, bipolar disorder, or alcohol or drug dependence. Participants were required to discontinue any previous antidepressant medication. Standard CBT was delivered in up to 20 sessions (50 minutes each) over 16 weeks, with up to 1000 minutes of therapist time. Therapists delivering CCBT provided up to 325 minutes of patient contact in 25-minute sessions distributed over 16 weeks. The internet-based component included 9 self-study modules covering the standard elements of CBT. The primary study outcome measure was the Hamilton Rating Scale for Depression (HAM-D), with a 4-point difference between the groups demonstrating noninferiority. Outcomes were assessed upon treatment completion and then 3 and 6 months later.

Results: A total of 154 patients were randomly assigned to CBT or CCBT. About 80% of patients in both groups completed treatment. Patients in the CBT group received a mean of 13.3 hours of therapist time, compared with 5 hours for the CCBT group. At study entry, depression severity was moderate as indicated by an average baseline HAM-D score of about 20.

At week 16, mean HAM-D scores were 9.2 in the CBT group and 8.9 in the CCBT group, well below the noninferiority threshold (between-group effect size,* 0.05). Both groups experienced marked improvement during treatment, with within-group effect sizes of 2.4 and 2.0 for CCBT and CBT, respectively. Remission rates were 43% and 42%, respectively. The results of treatment did not differ between the study sites, which indicates investigator allegiance and differences in familiarity with CCBT did not influence the results.

Treatment effects were maintained at the 3- and 6-month evaluations, with no differences between groups in measures of symptoms or function. Patients who received CCBT finished the program with a higher level of knowledge about the methods of CBT, which they retained throughout follow-up. Among the 55 participants who remitted and remained in follow-up, there were 2 relapses in the CBT group and 4 in the CCBT group.

Discussion: Previous studies of CCBT have generally compared it with treatment-as-usual or with an inactive control condition. A few small studies have compared CCBT with standard CBT, with similar results to those of the present, relatively large study. Although well designed, the present study had important limitations, according to both the authors and an accompanying editorial.[2] Because it delivers a reduced "dose" of therapist time, CCBT may not be appropriate for patients with more severe or longstanding depression or those with comorbidity.

[1]Thase M, Wright J, Eells T, Barrett M, et al: Improving the efficiency of psychotherapy for depression: computer-assisted versus standard CBT. *American Journal of Psychiatry* 2018;175 (March):242–250. From the University of Pennsylvania, Philadelphia; and other institutions. **Funded by the NIMH. Two of 8 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

[2]Kocsis J: Internet-based psychotherapy: How far can we go [editorial]? *American Journal of Psychiatry* 2018;175 (March):202–203. From New York-Presbyterian Hospital and Weill Cornell Medicine, New York, NY. **The author declared no competing interests.**

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Behavioral Avoidance and OCD Outcomes

Moderate-to-high baseline levels of avoidance predict a poorer response to exposure and response prevention (ERP) therapy for obsessive-compulsive disorder, according to a post-hoc analysis of a clinical trial. Measuring avoidance, which can be done using an auxiliary item on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), could help clinicians identify patients who might benefit from additional clinical support in completing exposure assignments.

Methods: The randomized trial enrolled 100 adults with OCD who remained symptomatic despite ≥12 weeks of SRI therapy. Patients were randomly assigned to augmentation of ongoing medication with ERP, an atypical antipsychotic, or placebo. ERP consisted of 2 planning sessions plus 15 sessions with exposures (90 min each), in addition to between-session self-directed exposure homework. Avoidance was measured at baseline with a Y-BOCS auxiliary item in which raters ask the patient to estimate, on a scale of 1–4, the extent to which they avoid places, situations, or people because of obsessional thoughts or the need to perform compulsions. For the present analysis, the ratings were grouped as none/mild and moderate/extreme. Adherence to ERP was measured with the Patient EX/RP Adherence Scale (PEAS), which rates the quantity and quality of exposures and the degree of success of response prevention. The primary outcome of the clinical trial was change from baseline in the Y-BOCS. Effects of baseline avoidance were analyzed separately for each treatment group.

Results: Of the 40 patients who received ERP, 37 completed treatment. The mean Y-BOCS score decreased after ERP, from 27 to 13 ($p<0.001$). Avoidance was moderately and negatively correlated with PEAS scores (correlation coefficient,* -0.49; $p=0.002$), indicating that patients with significant avoidance were less adherent to ERP procedures.

Pretreatment Y-BOCS scores were not predictive of posttreatment scores. Moderate-to-high levels of pretreatment avoidance were significantly associated with posttreatment scores ($p=0.01$) in the ERP group. Pretreatment avoidance did not predict the outcome of drug or placebo treatment. Patients with high baseline avoidance were less likely to achieve wellness (defined as a Y-BOCS score ≤12) than those with lower avoidance scores. The relationship between high baseline avoidance and poor outcome was mediated by poor adherence, which accounted for nearly 50% of the relationship.

Discussion: Although ERP is effective in OCD, fewer than half of patients achieve minimal symptoms. Assessing baseline avoidance could help clinicians identify patients at risk for poor treatment adherence and suboptimal ERP outcomes.

Wheaton M, Gershkovich M, Gallagher T, Foa E, et al: Behavioral avoidance predicts treatment outcome with exposure and response prevention for obsessive-compulsive disorder. *Depression and Anxiety* 2018; doi 10.1002/da.22720. From Barnard College, New York, NY; and other institutions. **Funded by the NIMH; and the New York State Office of Mental Hygiene. Two of 5 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

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Inflammatory Marker and ECT Response

Levels of the inflammatory marker interleukin 6 (IL-6) were predictive of response to ECT in patients with treatment-resistant depression, particularly in women. This finding supports the concept of an "inflammatory subtype" of depression that is associated with female gender and that may respond poorly to antidepressant medications.

Methods: Inflammatory markers were measured in 29 patients (15 women) scheduled to undergo ECT. Patients were experiencing a current major depressive episode, had ≥2 prior episodes, and had experienced nonresponse to ≥2 antidepressants. They received ECT 3 times a week for a total of 6–22 sessions. Inflammatory cytokines—IL-1beta, IL-6, IL-8, and TNF-alpha—and C-reactive protein (CRP) were measured in blood samples obtained at baseline, between the second and third ECT treatments, and within a week after completing the series. Depressive symptoms were measured using the Montgomery-Asberg Depression Rating Scale (MADRS).

Results: The mean MADRS score decreased from 40 at baseline to 31 at the end of treatment ($p<0.001$). Mean levels of IL-6 nearly tripled, and CRP increased by a factor of 5.5 after the first ECT exposures and returned to previous levels by the end of treatment.

Higher baseline levels of IL-6 predicted larger reductions in the MADRS at the end of treatment. The relationship was stronger in women than in men (p=0.02 and p=0.10, respectively). Baseline CRP also predicted response in women (p=0.04), but not in men. Baseline levels of inflammatory markers did not differ between the sexes. Improvement on the MADRS was not associated with pretreatment levels of the other markers or with changes over time in any of the markers.

Discussion: This finding, if replicated, suggests inflammatory markers could help identify patients who might be prioritized for advancement to ECT. The association of baseline IL-6 with clinical outcome was independent of other clinical variables such as age, symptom severity, and duration of the current illness episode. Previous research has shown cytokines become elevated after a single ECT session but then return to previous levels. These transient elevations may represent acute stress-induced inflammation and do not affect clinical outcome.

Kruse J, Congdon E, Olmstead R, Njau S, et al: Inflammation and improvement of depression following electroconvulsive therapy in treatment-resistant depression. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m11597. From the University of California at Los Angeles. **Funded by the NIH. The authors declared no competing interests.**

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Correlation Coefficient (r): A measure of the closeness of the relationship between 2 variables. The value of r can range from -1 to 1. An r value near 1 indicates a strong positive relationship. An r-value close to zero indicates no relationship, and a negative r-value indicates a negative relationship.

Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.