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New Cranial Electrotherapy Stimulator

The FDA has announced approval of a new cranial electrotherapy stimulator (CES; *Cervella*) for the treatment of anxiety, depression, and insomnia. CES delivers micro pulses of electrical current to the brain and has been shown to reduce anxiety levels, insomnia, and depressed mood. The new device is the first CES to integrate conductive treatment electrodes into noise-cancelling, Bluetooth-enabled headphones. Because the device resembles ordinary headphones, it can be used inconspicuously in anxiety-provoking situations. *Cervella* is also the first CES device that is managed through a free app that provides automated treatment data recording, reminders, and analytics that patients can share with their healthcare provider.

FDA OKs brain stimulator for insomnia, anxiety, depression. Medscape Medical News March 27, 2019. Available at www.medscape.com/viewarticle/910999.

Self-Administered tDCS

Results of an open-label pilot study confirm the feasibility, efficacy, and safety of remotely-monitored, in-home, self-administered transcranial direct current stimulation in patients with depression.

Background: Although tDCS has been shown to reduce depression, the typical treatment course (i.e., weekday sessions over 2–4 weeks) can be an obstacle for patients due to time, cost, and travel constraints. Using specifically designed equipment and procedural modifications, tDCS has been adapted for remotely-supervised, home-based use. Pilot studies in patients with schizophrenia, Parkinson's disease, vascular dementia, and other disorders suggest that home-based tDCS is a viable treatment approach. The adapted protocol has not previously been studied in patients with depression.

Methods: Study subjects were 34 adults with confirmed unipolar or bipolar depression with a current episode duration of ≥ 4 weeks in duration and a Montgomery-Asberg Depression Rating Scale (MADRS) score of ≥ 20 . Antidepressant use was not exclusionary, provided it had been unchanged for ≥ 4 weeks before study entry and throughout treatment. Following a clinic-based training session, during which participants' ability to independently prepare the tDCS equipment

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and operate the device safely was confirmed, participants underwent 4 weeks of acute, in-home tDCS treatment (20–28 sessions). Stimulation parameters, including intensity, duration, total number of sessions, and single-use activation codes for each session, were preprogrammed into the device, and treatment was supervised remotely by clinic or research staff. Participants completed an online treatment diary for each session and mood was assessed with the MADRS, at weeks 2 and 4. Treatment response and remission were defined as a $\geq 50\%$ decrease in MADRS score at week 4 and a final score of ≤ 10 , respectively. Those who met response criteria were offered maintenance treatment with decreasing stimulation frequency for up to 5 months.

Results: In-home tDCS was both feasible and acceptable to patients; 33 of the 34 patients completed the treatment protocol and the single patient withdrawal was unrelated to treatment. During a total of 1149 sessions, the most frequently reported adverse effects included burning, tingling, redness, and itching at electrode placement sites, but these were generally mild to moderate and transient. No serious adverse effects were reported, and there were no occurrences of mania or hypomania.

Patients experienced a significant decrease in depressive symptoms with in-home tDCS. Mean MADRS scores decreased from 27.5 at baseline to 15.5 following treatment (effect size,* 1.53; $p < 0.001$). Treatment response was achieved by 13 patients (38%), and remission by 11 patients (32%). Cognitive testing, administered to about half of the study sample, showed no significant changes from pre- to post-treatment in reaction time, memory, or executive function. At the final follow-up, MADRS improvements were preserved in the 10 patients who opted to receive maintenance treatment.

Discussion: These results provide initial evidence that home-based, remotely-supervised tDCS treatment for depression is both feasible and effective. While the findings are preliminary and require replication, in-home tDCS could substantially improve treatment accessibility and lower costs while providing similar efficacy and safety to in-clinic treatment.

Alonzo A, Fong J, Ball N, Martin D, et al: Pilot trial of home-administered transcranial direct current stimulation for the treatment of depression. *Journal of Affective Disorders* 2019;252:475–483; doi 10.1016/j.jad.2019.04.041. From the University of New South Wales, Australia; and other institutions. **The study was conducted with no specific funding; however, some of the devices and consumables used in the study were loaned or provided by Soterix Medical Inc. The authors declared no competing interests.**

*See Reference Guide.

Comparative Efficacy of Brain Stimulation Techniques

Results of a comprehensive review and network meta-analysis support the use of nonsurgical brain stimulation techniques as alternative or add-on treatments in adults with major depressive episodes. The analysis considered 18 different active interventions, including multiple variants of ECT and repetitive transcranial magnetic stimulation (rTMS), as well as new techniques such as theta burst stimulation and magnetic seizure therapy. The treatments differed in efficacy, but most were equally well tolerated.

Methods: The analysis included randomized controlled trials, either parallel-group or crossover (but only the first period of crossover trials), in adults with major depressive disorder or bipolar depression. Non-English-language studies, conference abstracts, trials of vagus nerve stimulation, and trials that simultaneously initiated drug or psychological therapies were excluded. Within each major category of treatment, studies were grouped according to methodologic variations and analyzed separately: 4 variants of ECT, 9 of TMS, 3 of theta burst stimulation, and 1 each of magnetic seizure therapy and transcranial direct current stimulation (tDCS). Efficacy was measured using the Hamilton Rating Scale for Depression (HAM-D) or the Montgomery-Asberg Depression Rating Scale (MADRS). The

primary efficacy outcome was response, usually defined as a $\geq 50\%$ decrease in depressive symptoms. Rates of study completion were the indicator of tolerability.

Results: The authors identified 113 trials with a total of 6750 participants. The most frequent comparisons were high frequency left rTMS versus sham, bilateral rTMS versus sham, bi-temporal ECT versus high-dose right unilateral ECT, and tDCS versus sham. Owing to their novelty, newer treatment modalities (e.g., theta burst stimulation, priming TMS) were not well represented; and there were no sham-controlled ECT studies. Most trials (81%) included only patients with resistant depression. In two-thirds of studies, brain stimulation was an add-on to ongoing drug treatment.

In the network meta-analysis, 10 treatments were found to be significantly superior to sham stimulation. (See table.) In pairwise comparisons of active treatments, bitemporal ECT was significantly superior to other ECT protocols and to several other approaches. High-dose right unilateral ECT, priming transcranial rTMS, and bilateral rTMS were all significantly superior to continuous theta burst stimulation. Most treatments had similar discontinuation rates to sham treatment; only priming rTMS was notably better tolerated. There are too few trials evaluating the newer treatments, such as magnetic seizure therapy, to provide reliable evidence of relative efficacy.

Brain stimulation treatments significantly superior to sham treatment	
Treatment	Odds ratio* for response vs sham
Bitemporal ECT	8.91
High dose right unilateral ECT	7.27
Priming TMS	6.02
Magnetic seizure therapy	5.55
Bilateral rTMS	4.92
Bilateral theta burst stimulation	4.44
Low frequency right TMS	3.65
Intermittent theta burst stimulation	3.20
High frequency left rTMS	3.17
tDCS	2.65

Discussion: Treatment guidelines support the use of nonsurgical brain stimulation in the treatment of depression, but these treatments tend to be used sparingly and late in the disease course. ECT may be the most frequently considered modality, but the present results suggest that other treatment protocols also have robust evidence of efficacy.

Study Rating*—18 (100%): This study met all criteria for a systematic review/meta-analysis.

Mutz J, Vipulanathan V, Carter B, Hurlmann R, et al: Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis. *BMJ* 2019; doi 10.1136/bmj.l1079. From King's College London, U.K.; and other institutions. **Funded by the German National Academic Foundation; and other sources. Two of 6 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

*See Reference Guide.

PTSD Treatment Preferences and Outcomes

In a head-to-head comparison study, both prolonged exposure therapy and sertraline (*Zoloft*) were highly effective in treating PTSD, with some evidence of an advantage for prolonged exposure. Patients who were allowed to choose between the 2 treatments were more adherent and had marginally better outcomes than those who were randomly assigned to a treatment.

Methods: The study enrolled clinically-referred or self-referred patients with a primary diagnosis of chronic PTSD. All participants initially viewed a video explaining the rationale for each treatment. They were then randomly assigned to receive either their choice or no choice of treatment. Within the no-choice group, a second randomization led to assignment of

medication or prolonged exposure therapy. Patients receiving sertraline also had 10 weekly manualized psychiatrist visits lasting up to 30 minutes. Prolonged exposure therapy consisted of 10 weekly 90–120-minute sessions, also manualized, with recounting of trauma memories and in-vivo exposure. After completing acute treatment, patients were offered 24 months of either 2 optional booster sessions or continued sertraline treatment. The primary study outcome measure was the PTSD Symptom Scale–Interview Version (PSS-I), administered by blinded raters after 10 weeks of acute treatment, and then after 3, 6, 12, and 24 months.

Results: Of 200 patients enrolled (mean age, 37 years; 76% women), 97 were randomized to the choice group and 103 to the no-choice group. Within the choice group, 61 chose prolonged exposure (63%) and 36 chose sertraline (37%). Overall, 149 patients received their preferred treatment, whether by choice or randomly, and 51 received the treatment they did not prefer.

The mean baseline PSS-I score was 30 (possible range for this measure, 0–51). Both treatments were associated with large decreases in scores. Following 10 weeks of acute treatment, mean PSS-I scores were 10.5 in the prolonged-exposure group and 13.3 in the sertraline group ($p < 0.001$ for both groups), with no significant between-group differences. However, patients who received prolonged exposure were significantly more likely than the sertraline group to achieve loss of PTSD diagnosis (69% vs 55%; $p = 0.04$; number needed to treat,* 7). Participants who received their preferred treatment did not have larger symptom reductions than those who did not, but they were more likely to achieve loss of PTSD diagnosis (71% vs 41% at post-treatment; $p < 0.001$; number needed to treat, 3). Treatment gains generally persisted for the 24 months of follow-up in both groups. Secondary outcome measures of depression, anxiety, and disability showed similar efficacy for the 2 treatments. Patients who requested and received prolonged exposure had lower rates of premature treatment discontinuation than patients who preferred prolonged exposure but received sertraline.

Discussion: When given a choice, the majority of study patients (61%) preferred exposure therapy to pharmacotherapy. While both treatments showed good short- and long-term efficacy, patients receiving their treatment of choice had better adherence and were more likely to achieve response, suggesting that accommodating patient preferences between empirically supported treatments can improve outcomes.

Zoellner L, Roy-Byrne P, Mavissakalian M, Feeny N: Doubly randomized preference trial of prolonged exposure versus sertraline for treatment of PTSD. *American Journal of Psychiatry* 2019;176 (April):287–296. doi 10.1176/appi.ajp.2018.17090995. From the University of Washington, Seattle; and Case Western Reserve University, Cleveland, OH.

Funded by the NIMH; and other sources. One study author disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.

*See Reference Guide.

tDCS-Associated Mania

An updated meta-analysis that included 3 recent large-scale trials found a 5-fold increase in risk of treatment-emergent mania or hypomania in patients with unipolar major depression who received transcranial direct current stimulation.¹ The risk increase is comparable to that known to occur with SSRIs.

Background: A previously published meta-analysis found that about 3.5% of patients with depression who received tDCS experienced treatment-emergent mania.² However, those findings indicated the risk was not significantly greater in patients who received active versus sham stimulation.

Methods: All randomized controlled trials comparing active and sham tDCS in patients with major depression ($n = 11$) were identified in the literature. These included the 8 studies evaluated in the previous meta-analysis and an additional 3 large-scale trials published after the

previous analysis. Studies in which no cases of treatment-emergent mania were reported in either treatment group were excluded, leaving a total of 5 studies in the current analysis.

Results: The 5 studies included 731 patients who received either active tDCS (n=367) or sham treatment (n=364). Treatment-emergent mania occurred in 13 patients, 12 of whom received active treatment. In the pooled analysis, emergent mania was significantly more common in the active treatment group (3.3% vs 0.27%; p=0.015; odds ratio,* 5.01). Although the study design precluded assessment of mania severity, at least 1 patient required hospitalization. In the active treatment groups, two-thirds of the emergent mania episodes occurred when tDCS was used in combination with an SSRI.

Discussion: Most depression treatments are associated with a modest risk of inducing mania. While the absolute risk with tDCS was small (3.3%) in the present analysis, it was significantly increased compared with sham treatment, and the focus on patients with unipolar depression suggests it was not associated with unrecognized bipolar disorder.

Study Rating*—16 (89%): This study met most criteria for a systematic review/meta-analysis. However, individual study quality does not appear to have been assessed.

¹Berlow Y, Zandvakili A, Carpenter L, Philip N: Transcranial direct current stimulation for unipolar depression and risk of treatment emergent mania: an updated meta-analysis. *Brain Stimulation* 2019; doi 10.1016/j.brs.2019.03.025. From Brown University, Providence, RI; and other institutions. **Funded by the NIMH; and other sources. The authors declared no competing interests.**

²Brunoni A, et al: Treatment-emergent mania/hypomania during antidepressant treatment with transcranial direct current stimulation (tDCS): a systematic review and meta-analysis. *Brain Stimulation* 2017;10 (March–April):260–262.

*See Reference Guide.

Gluten-Free Diet in Schizophrenia

In a randomized, controlled, pilot study in patients with schizophrenia and evidence of gluten sensitivity, a gluten-free diet was associated with robust improvement in negative symptoms.

Background: Historical research has associated low wheat consumption with a reduced incidence of schizophrenia. Foods made from wheat or certain other grains contain gluten, a component of which, gliadin, can induce sensitivity, distinct from celiac disease. About one-third of patients with schizophrenia have antibodies to gliadin (AGA IgG)—3 times the rate of the general population. Brain inflammation in schizophrenia may be due to leakage of these antibodies through the blood-brain barrier.

Methods: The 5-week diet study was conducted in adults with a confirmed diagnosis of schizophrenia or schizoaffective disorder who screened positive for AGA IgG and were not currently on a gluten-free diet. The study excluded patients with antibodies indicative of celiac disease. Participants were admitted to the research hospital for the entire study and continued on stable dosages of their antipsychotic medication. Each afternoon, all participants received a protein shake, which was based on rice flour (gluten-free) or gluten flour (controls). All meals for the intervention and control groups were prepared by the hospital staff and were gluten free. Although this was primarily a feasibility study, improvement in schizophrenia symptoms was measured using the Scale for the Assessment of Negative Symptoms (SANS) and the Brief Psychiatric Rating Scale (BPRS).

Results: The investigators screened 375 adults with schizophrenia, of whom 27% had AGA IgG. This group included 5 with celiac disease, who were excluded. After further evaluation, 16 patients were enrolled and 14 completed the study, 7 in each group.

The gluten-free diet was not associated with greater improvement in BPRS positive-symptom scores. However, negative symptoms were moderately improved in the gluten-free group

(effect size,* 0.53). Among the SANS subscales, the gluten-free diet was associated with substantial improvements in avolition (effect size, 0.43) and affective blunting (effect size, 0.71), and smaller improvements in anhedonia (effect size, 0.24) and alogia (effect size, 0.12). The gluten-free group also showed global improvements on the Clinical Global Impression scale (effect size, 0.75). Overall effects on cognitive function were modest, but there were medium-to-large effects on tests of attention and verbal learning. Clinical effects of the diet were evident in patients who followed the gluten-free diet for 8 weeks after discharge.

Discussion: Previous studies failed to demonstrate conclusively an association of wheat or gluten intake with schizophrenia, possibly because these studies lacked a biological marker for gluten sensitivity. The present results, although preliminary, support screening for AGA IgG in persons with first-episode schizophrenia and those at risk. This research group is currently conducting a large-scale clinical trial of a gluten-free diet, specifically targeting negative symptoms.

Kelly D, Demyanovich H, Rodriguez K, Cihakova D, et al. Randomized controlled trial of a gluten-free diet in patient with schizophrenia positive for antigliadin antibodies (AGA IgG): a pilot feasibility study. *Journal of Psychiatry & Neuroscience* 2019; doi 10.1503/jpn.180174. From the University of Maryland School of Medicine, College Park; and other institutions. **Funded by the NIMH. Four of 21 authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

*See Reference Guide.

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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.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Number Needed to Treat (NNT): Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective the treatment.

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.

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