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PULSE

A Monthly Update on Advances in Neuromodulation

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Bilateral TBS is Non-inferior to Standard Sequential Bilateral rTMS for Major Depression

Michael K. Leuchter, MD reviewing Blumberger et al. JAMA Psychiatry 2022 September

In the successor to the 2018 THREE-D study, the FOUR-D RCT found that a four-minute protocol of right-sided cTBS followed by left-sided iTBS is non-inferior to one of the gold standard 48-minute protocols of right-sided 1 Hz rTMS followed by HFL

When rTMS is utilized for the treatment of MDD, a typical session of HFL can last up to 37.5 minutes. Additional stimulation sites or other parts of a treatment protocol can lengthen that treatment. With the often-used sequential bilateral method (right-sided 1 Hz rTMS followed by left-sided 10 Hz rTMS, which some evidence suggests may be more effective in the elderly), sessions can last up to 48 minutes. This poses significant barriers to treatment in the forms of time and cost. Blumberger and colleagues already demonstrated the

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noninferiority of iTBS (a three-minute protocol) to 10 Hz stimulation in their 2018 THREE-D study, but this raises the question of how other theta burst forms of stimulation compare to other, more complex, gold standard protocols.

Researchers performed a randomized, rater-blinded study comparing the efficacy of sequential bilateral TBS with sequential bilateral rTMS for treatment-resistant MDD in the elderly. 172 participants over age 60 (mean: 67.1 years; 54% female) with TRD of moderate severity were randomized to receive 20-30 sessions of either TBS (600 pulses right cTBS followed by 600 pulses left iTBS, four minutes per session; 85 participants) or standard rTMS (1200 pulses right 1 Hz followed by 3000 pulses left 10 Hz, 48 minutes per session; 87 subjects), each delivered to the corresponding sides of the DLPFC at an intensity of 120% MT. Partial responders (those with 30-50% improvement) could receive additional treatment sessions. The primary outcome was the change in MADRS score from pre-treatment to the end of treatment, with secondary outcomes including response rates, remission rates, change in the QIDS, and change in the HDRS. Mood scores were collected at baseline, every five treatments, and at one, four, and 12 weeks after completing treatment.

In the TBS group, MADRS scores improved from an average of 25.7 to 15.8 at the end of treatment, with improvement maintained after treatment. In the standard rTMS group, MADRS scores improved from an average of 25.6 to 17.3 at the end of treatment, with improvement also maintained 12 weeks after treatment. Initial statistical testing demonstrated non-inferiority at a 95% confidence level for the primary outcome, as well as for all secondary outcome measures. There was evidence of superiority of TBS compared to standard rTMS in MADRS score benefit at four weeks after treatment. Pain scores were significantly higher in the TBS group compared to the standard rTMS group, and the TBS group required more sessions to reach goal intensity. No other significant differences in side effects or tolerability were observed.

Impact: The FOUR-D RCT demonstrated that sequential-bilateral TBS provides clinical benefits that are similar to gold standard sequential-bilateral rTMS treatment often used in geriatric TRD populations. In both groups, symptom improvements were sustained for at least 3 months, with the trade-off for increased treatment efficiency being decreased tolerability. This further emphasizes and expands on the thrust of the THREE-D study, suggesting that increased clinical use of TBS may help expand access to TMS for the treatment of MDD, even in geriatric populations and even with complex treatment protocols.

Blumberger, D. M., Mulsant, B. H., Thorpe, K. E., McClintock, S. M., Konstantinou, G. N., Lee, H. H., Nestor, S. M., Noda, Y., Rajji, T. K., Trevizol, A. P., Vila-Rodriguez, F., Daskalakis, Z. J.; Downar, J. (2022). Effectiveness of Standard Sequential Bilateral Repetitive Transcranial Magnetic Stimulation vs Bilateral Theta Burst Stimulation in Older Adults With Depression. JAMA Psychiatry. https://doi.org/10.1001/jamapsychiatry.2022.2862

Home-based tDCS Yields Positive Results for Adults with Osteoarthritis

David Lee reviewing Martorella et al. Brain Stimulation 2022 Jun

An RCT of remote-supervised, home-based tDCS self-administered over three weeks suggests the treatment can effectively improve knee pain in older adults with osteoarthritis

Osteoarthritis (OA) is a highly prevalent and debilitating condition in older adults that can gravely compromise daily activities and quality of life. Standard management involves analgesics such as NSAIDs, but their efficacy is limited and can involve significant adverse effects. Strong evidence has implicated central sensitization in the pathophysiology of OA knee pain, prompting the authors' previous work which demonstrated the efficacy tDCS for OA in a clinic setting. Seeking to expand on these results, here the authors aimed to investigate remote-supervised tDCS administered by patients in their own home.

In this double-blind phase II RCT, 120 participants with knee OA pain were randomized into either treatment or sham groups. In both groups, participants received a brief training on use of the device and placement of electrodes, with the anode over primary motor cortex (M1) and cathode over the supraorbital region (SO). Thereafter, participants self-administered treatment at home while receiving real-time remote instructions via secure teleconferencing, including a single-use activation code for the device provided daily which controlled sham vs. active settings on the device. A fixed-position headgear ensured appropriate placement of the saline-soaked sponge electrodes on each use. Participants received 20 minutes of stimulation daily for three weeks (15 total), with sham stimulation only providing 30s of actual current outside of the 30s ramp-up/-down periods. Each participant's pain intensity was evaluated at baseline,

at the end of 3 weeks, and at 3 months, using the numeric rating scale (NRS). The change in pain intensity was statistically assessed using Wilcoxon rank-sum test. The Western Ontario and McMaster Universities OA Index (WOMAC) was also examined for efficacy, and a custom "tDCS Experiences Questionnaire" was used to assess acceptance and tolerability.

The researchers found that the NRS was significantly lower at 3 weeks in the treatment group (score Δ= -24) compared to the sham group (score Δ = -1; d= 1.20, p<0.0001). At 3 months, NRS remained significantly lower in the treatment group compared to sham (score Δ = -14 vs. -0.4, respectively; p <0.01). WOMAC scores did not differ significantly between the two groups at 3 weeks (d=0.23, p=0.10) or 3 months (d=0.02, p=0.56). The tDCS experience questionnaire showed participants generally endorsed ease of use (mean = 9.41/10), efficacy of remote supervision using teleconference (mean = 9.41/10), and lack of serious adverse effects (data not shown).

Impact: In this phase II double-blind RCT, self-administered home-based tDCS to M1 with remote teleconference supervision effectively improved the intensity of knee OA pain after three weeks of treatment, with pain score improvements lasting up to 3 months. Self-administered tDCS may serve as an important option for older adults who may be limited in mobility, and who may have contraindications to conventional medical therapy including NSAIDs. Lack of improvement in WOMAC scores raises the question of whether pain relief was associated with improvement in function and activity level. This question should be examined in future studies, along with whether tDCS might be useful for fibromyalgia or other forms of pain. Future work can focus on optimizing the intensity and duration of tDCS therapy to guide individualized treatment plans and investigate whether less resource-intensive remote-monitoring could achieve similar results.

Martorella G, Mathis K, Miao H, Wang D, Park L, Ahn H. Self-administered transcranial direct current stimulation for pain in older adults with knee osteoarthritis: A randomized controlled study. Brain Stimulation. 2022 Jun 8. https://doi.org/10.1016/j.brs.2022.06.003

ECT More Efficacious than Ketamine for TRD in Recent Small-Scale Meta-Analysis

Collin M. Price, MD reviewing Rhee et al. JAMA Psychiatry 2022 Oct

This systematic review and meta-analysis of head-to-head trials suggests that ECT may be more effective than intravenous or intramuscular ketamine in treating patients with TRD. However, the quality of included studies was limited, highlighting a gap in the current literature

ECT has long been considered the gold standard treatment for TRD, but utilization has been limited by many factors including stigma, lack of infrastructure, and notable cognitive side effects. Ketamine, an NMDA receptor antagonist used for decades as an anesthetic, has recently shown promise as a rapid-acting antidepressant, though trials have thus far been small and the clinical effects may be short lived. This meta-analysis sought to compare these two potentially life-saving treatments by assessing the current literature of head-to-head studies.

The authors performed a keyword search in PubMed, MEDLINE, the Cochrane Library, and Embase for terms related to depression, ECT, and ketamine, and selected studies that compared groups receiving ECT and ketamine using standardized depression measures (e.g., MADRS, HRDS). Additional outcomes of interest included improvements in suicidal ideation (SI) and cognitive measures, and adverse effects such as suicidal behavior, worsened cognition, pain, nausea, and dissociative phenomena. Outcomes were converted to Hedges g standardized mean difference (SMD), and relative risk (RR) was used for safety-related outcomes. The selected studies were also assessed for risk of bias and methodological quality.

The authors included six clinical trials with 340 patients (n=162 for ECT, n=178 for ketamine), comprised of five RCTs and one naturalistic, open-label study. The studies all recruited patients deemed candidates for ECT, with five studies requiring a diagnosis of a Major Depressive Episode, and one study including either unipolar or bipolar depression. The studies ranged from 1-4 weeks in duration, with sample sizes of 18–186 and mean ages of 37.5–52.5 years. The ketamine arms involved 1–9 sessions administered every 1–3 days of ketamine 0.5 mg/kg given intravenously or intramuscularly, with one trial including a second ketamine arm receiving 1.0 mg/kg orally on a similar schedule. The ECT arms consisted of 1–16 sessions administered every 2-3 days, with pulse widths of 0.3–1.5 ms and electrode positions that included right unilateral, bilateral, and bifrontal. ECT was found to have superior outcomes on depressive symptom measures, with an overall pooled SMD favoring ECT over ketamine of -0.69 (95% CI: -0.48–0.89; I^2=39%). Four of the six studies reported on adverse

events, and ketamine was found to have lower risks than ECT for headache (RR=0.37; 95% CI: 0.18–0.76) and muscle pain (RR=0.23; 95% CI: 0.13–0.38), but higher risk of dissociative symptoms (RR=5.04; 95% CI: 3.03–8.36). Cognitive effects were assessed in two studies, with one showing the ketamine group performing better than the ECT group (d=0.40, p= 0.04) in overall neurocognitive testing but with no group differences for immediate or visual memory; the other study reported no group differences on a Wechsler Memory Scale. SI was reported as an outcome in one study, which found ECT and ketamine were both effective at reducing SI without a significant difference between them, while one study reported on suicidal behavior as a serious adverse event and found no significant difference between ECT or ketamine. The methodological quality of included studies was deemed low to moderate, with authors noting deviations from intended interventions, difficulties with blinding, and at least one study with a higher dropout rate in the ketamine group compared to the ECT group, though there was no evidence of reporting bias in individual studies or publication bias.

Impact: This systematic review and meta-analysis of six head-to-head clinical trials of ECT vs. ketamine found that ECT may yield slightly greater improvements in depressive symptoms and that each treatment has unique adverse effect profiles. This study was limited by the quality of the included studies, which generally had small sample sizes, heterogenous intervention protocols, and short follow-up periods. Other limitations include the limited ketamine dosage ranges examined and absence of comparison to oral or intranasal ketamine administration (which are more commonly used than injection). The authors also note a significant lack of research on long-term outcomes and relapse prevention, particularly for ketamine. While providing some insight into the relative risks and benefits of ECT and ketamine for TRD, this study primarily highlights the need for larger, more rigorous studies in this area.

Rhee TG, Shim SR, Forester BP, et al. Efficacy and Safety of Ketamine vs Electroconvulsive Therapy Among Patients With Major Depressive Episode: A Systematic Review and Meta-analysis [published online ahead of print, 2022 Oct 19]. JAMA Psychiatry. 2022;10.1001/jamapsychiatry.2022.3352. doi:10.1001/jamapsychiatry.2022.3352

Persistent Racial, Gender, and Socioeconomic Disparities in DBS for Parkinson's Disease

Tashalee R. Brown, MD, PhD reviewing Cramer et al. Annals of Neurology 2022 Aug

Despite increased use of DBS in the treatment of Parkinson's Disease, multiple demographic disparities persist in access to DBS

DBS is superior to medical management alone in selected patients with severe Parkinson's Disease (PD). However, previous studies have identified significant disparities in who receives DBS, such as Black patients with PD being 5-8x less likely to receive DBS compared to White patients.

This retrospective database analysis examined the National Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project and the Agency for Healthcare Research and Quality from 2002 to 2018.The authors identified hospitalized patients with PD ≥ 18 years of age admitted for DBS placement based on ICD-9 and ICD-10 codes; exclusion criteria included other neurodegenerative diagnoses, secondary Parkinsonism, and ≥ 2 medical comorbidities. Patient demographics analyzed included sex, age, race (White, Black, and Other, according to the NIS database structure), payer, and income quartile classification based on patients' zip code (derived from the Claritas database). Statistical analysis utilized sampling weights, clusters, and strata from the NIS database. A multivariate logistic model assessed the odds of a PD admission undergoing DBS with and without an interaction term for year and race. A chi-squared test examined the association between insurance type and year, stratified by race.

Patients with PD were more likely to receive DBS during the time period 2010–2013 (OR = 1.45, CI = 1.07–1.97) and 2014–2018 (OR = 1.71, CI = 1.25–2.34) compared to 2002–2005. A growth in the number of DBS treatments was most evident in the Medicare/Medicaid patient population; however, private insurance was associated with increased odds of DBS compared with Medicare/ Medicaid (OR = 1.64, CI = 1.53–1.76), and higher income quartiles were associated with increasing odds of undergoing DBS implantation (all p<0.001). Black patients with PD were less likely to undergo DBS than White patients with PD (OR = 0.21, CI = 0.17–0.27), whereas patients with a race classified as "Other" were just as

likely as White patients to undergo DBS implantation (OR = 0.99, CI = 0.87–1.12). There were no significant differences in this interaction when adjusting for the number of comorbidities, suggesting that comorbidities do not underlie the racial disparity. Women were significantly less likely to undergo DBS than men (OR = 0.79, CI = 0.75–0.83), a difference which remained significant when stratified by White (OR = 0.80, CI = 0.76-0.85) or Other (OR = 0.68, CI = 0.59-0.79) but not Black (OR = 0.69, CI = 0.45-1.07) race. Likewise, older age (OR = 0.48 per decade, CI = 0.47–0.49) and the presence of ≥2 comorbidities (OR = 0.07, CI = 0.06–0.07) both decreased the likelihood of undergoing DBS implantation.

Impact: This retrospective database analysis revealed that although DBS placement for PD has increased over the past decade, significant racial, gender, and insurance-based disparities remain in DBS placement. Although not designed to assess the causes of these disparities, this study nonetheless highlights potential gaps in care for PD patients, and the authors note that causes are likely complex and multifactorial. Potential targets for intervention include systemic factors in the healthcare system, provider implicit bias, and patient-specific factors such as medical mistrust. They argue for interventions for changing physicians' behaviors through utilizing strategies such as individuation and perspective taking to combat implicit bias. They also recommend identifying and mitigating structural barriers (i.e., socioeconomic status, access to transportation) that preclude access to DBS and surgical care in general.

Cramer SW, Do TH, Palzer EF, Naik A, Rice AL, Novy SG, Hanson JT, Piazza AN, Howard MA, Huling JD, Chen CC, McGovern RA. Persistent Racial Disparities in Deep Brain Stimulation for Parkinson's Disease. Ann Neurol. 2022 Aug;92(2):246-254. doi: 10.1002/ana.26378. Epub 2022 May 10. PMID: 35439848.

Abbrevations

cTBS (continuous theta burst stimulation)
DBS (deep brain stimulation)
dTMS (deep transcranial magnetic stimulation)
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)
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)

ADHD (attention-deficit/hyperactivity disorder)
AUD (alcohol use disorder)
GAD (generalized anxiety disorder)
MDD (major depressive disorder)
OCD (obsessive compulsive 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)
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)
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)
OFC (orbitofrontal cortex)
SMA (supplementary motor area)