LETTER TO THE EDITOR

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Safety, tolerability, and feasibility of deep transcranial magnetic stimulation for late-life depression with comorbid major or mild neurocognitive disorder

Major depressive disorder (MDD) is highly comorbid with Alzheimer's disease (AD) and its prodrome, mild cognitive impairment (MCI) (Enache *et al.*, 2011; Ismail *et al.*, 2017), but effective treatments for depression with comorbid AD or MCI do not exist. Although repetitive transcranial magnetic stimulation (rTMS) is approved for treatment-refractory depression, older populations, particularly AD, are likely to exhibit cortical atrophy and other age-related changes in brain morphology and connectivity that attenuate its efficacy (Iriarte and George, 2018).

Deep TMS (dTMS) is a form of noninvasive brain stimulation that modulates the excitability of cortical targets at greater depths than conventional TMS (Deng *et al.*, 2014). dTMS has been successfully used in late-life depression (Kaster *et al.*, 2018) but carries heightened risk of seizure, a particular concern in AD which is associated with increased seizure risk (Amatniek *et al.*, 2006).

As part of an ongoing trial (NCT 03665831), we report the feasibility and tolerability of dTMS in three patients with MDD and comorbid MCI or AD. Patients were free of psychotropic medications due to seizure risk. dTMS treatment consisted of 20 daily sessions over 4 weeks using an H1-coil positioned over the left prefrontal cortex (Zangen *et al.*, 2005). dTMS was applied in 2 15.5-min blocks of 1980 pulses (55 2s trains at 18 Hz, 20s intertrain interval) separated by 15–20 min. Stimulation was titrated upwards from 80% to target 120% of resting motor threshold (RMT) over week 1.

Patient 1 was a 78-year-old female with mild AD and MDD with failed escitalopram, duloxetine, bupropion, and trazodone trials. Medical history included hyperlipidemia, irritable bowel syndrome, frequent headaches, and chronic fatigue. Cumulative Illness Rating Score for Geriatrics (CIRS-G) was 6. Montreal Cognitive Assessment (MoCA) score was 20. RMT ranged from 50% to 70% maximum stimulator output (MSO). On two sessions, stimulation intensity was reduced to 110% RMT due to uncomfortable movements in the forearm. Acetaminophen 500 mg QAM was taken prophylactically to reduce risk of dTMS-induced headaches.

The patient approached a clinical response, with baseline Montgomery–Asberg Depression Rating Scale (MADRS) decreasing from 26 to 14 after 4 weeks. At 1-month follow-up, MADRS was 17 (Figure 1). Adverse effects included facial muscle twitches, lightheadedness, anxiety, headache, and neck and jaw discomfort.

Patient 2 was a 78-year-old female with MCI and MDD with failed fluoxetine, sertraline, bupropion, mirtazapine, and figure-8-coil rTMS trials. Medical history included hypercholesterolemia, osteoarthritis, noncardiac syncope, gallbladder removal, falls, and chronic initial insomnia (CIRS-G = 7). MoCA score was 25. RMT varied from 50% to 55% MSO.

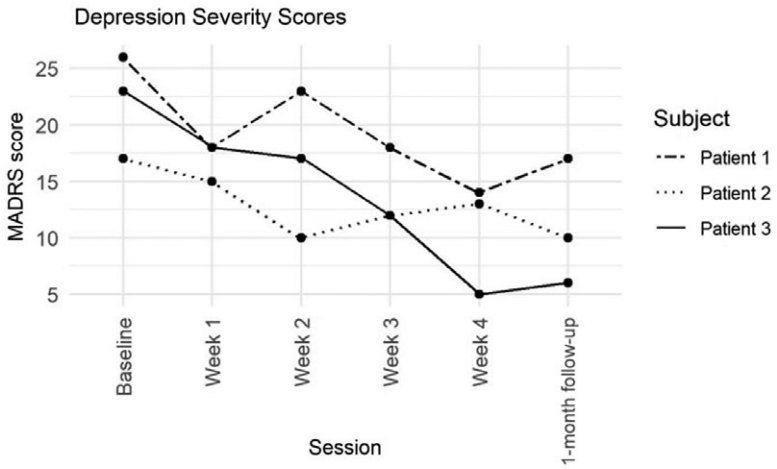
Baseline MADRS of 17 decreased to 13 following 20 treatments and 10 at 1-month follow-up (Figure 1). Adverse effects included facial muscle twitches, involuntary movements in arm and hand during pulses, and insomnia. Transient mild imbalance and moderate memory problems were reported after sessions 6 and 10, respectively. Chronic insomnia was not worsened.

Patient 3 was a 76-year-old male with MCI and MDD with failed mirtazapine and sertraline trials. Medical history included hypertension, hypercholesterolemia, Parkinsonism, and AV conduction block (CIRS-G = 8). Insomnia, anxiety, headaches, lightheadedness, nausea, and fatigue were prominent depression symptoms. MoCA was 17. RMT fluctuated from 69% to 71% MSO. As stimulation exceeding 95% RMT was intolerable due to scalp discomfort, the patient received only 3 sessions at 100%–105% RMT.

The patient showed a clinical response with baseline MADRS decreasing from 23 to 4 after 20 treatments. MADRS was 5 at 1-month follow-up. After 15 sessions, the patient spontaneously reported significant improvements in mood, stating he felt "more like himself than he had in years". Sleep and morning fatigue improved. Adverse effects were facial muscle twitches, restlessness, vibration sensations, and scalp discomfort during pulses. Preexisting insomnia and anxiety symptoms did not worsen.

Summary

All patients attended 20 daily dTMS sessions over 4 weeks and showed a reduction of depression



Subject ID	Baseline MADRS	Week 1	Week 2	Week 3	Week 4	1-month follow-up
Patient 1	26	18	23	18	14	17
Patient 2	17	15	10	12	13	10
Patient 3	23	18	17	12	5	6

Figure 1. Depression severity scores as rated by MADRS over the 4-week course of dTMS and at 1-month follow-up. Patient 3 showed a clinical response to dTMS, defined as 50% reduction in baseline MADRS following 4 weeks of dTMS.

symptoms, with one clinical responder and another approaching a clinical response. Reported mild to moderate adverse effects did not impact the treatment. No seizures, visual hallucinations, or manic symptoms occurred. For patients with depression and comorbid MCI or AD, and other medical comorbidities, a 20-day treatment course of prefrontal dTMS appears safe and well-tolerated. Given the lack of effective treatments for depression in this clinical population, dTMS is a viable option that warrants continuing investigation.

ClinicalTrials.gov identifier

NCT 03665831.

Conflicts of interest

B.H., J.M., and L.M. received funding from the Centre for Aging and Brain Health Innovation. Brainsway, Inc. loaned the dTMS device and contributed toward the costs of facility renovations to accommodate the device. D.B. reports nonfinancial support from Magventure, and Brainsway, Inc., CIHR, Brain Canada, and NIH grants. N.V. has no conflicts of interest to declare.

Description of authors' roles

All authors participated in the study design, data collection or interpretation, and preparation of this manuscript.

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