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Research paper

Transcranial magnetic stimulation for treatment-resistant depression: Naturalistic treatment outcomes for younger versus older patients

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (TMS) has been shown to be safe and effective for treatment-resistant depression (TRD) in the general adult population. Efficacy among older (≥60 years) patients, who have a greater burden of cognitive, physical, and functional impairment compared to their younger counterparts, remains unclear. The current study aimed to characterize antidepressant response to an acute course of TMS therapy among patients aged ≥60 years compared to those < 60 years in naturalistic clinical practice settings.

Methods: Data were retrospectively collected and pooled for adults with TRD (N =231; n =75 aged ≥60 years and n = 156 < 60 years) who underwent an acute course of outpatient TMS therapy at two outpatient clinics. Self-report depression scales were administered at baseline and end of acute treatment. Change on continuous measures and categorical outcomes were compared across older vs. younger patients.

Results: Both age groups showed significant improvements in depression symptoms. Response and remission rates did not differ between groups. Age group was not a significant predictor of change in depression severity, nor of clinical response or remission, in a model controlling for other predictors (all $p > .05$).

Limitations: Limitations include reliance on self-report clinical measures and variability in comorbidity and concurrent pharmacotherapy due to the naturalistic nature of the study.

Conclusions: Results suggest that effectiveness of TMS for TRD is not differentially modified by age. Based on these naturalistic data, age alone should not be considered a contraindication or poor prognostic indicator of the antidepressant efficacy of TMS.

1. Introduction

Repetitive transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation treatment for people with major depressive disorder resistant to first-line pharmacotherapy and psychotherapy interventions ("treatment resistant depression," TRD; American Psychiatric Association, 2010). TMS uses brief magnetic field pulses to induce electrical currents in the cerebral cortex, which impacts a number of processes involved in brain function (Chervyakov et al., 2015). TMS for TRD in the general adult population has demonstrated safety, tolerability, and efficacy in multiple randomized controlled trials (e.g., George et al., 2010; Levkovitz et al., 2015; O'Reardon et al., 2007); similar outcomes have been reported in naturalistic effectiveness research (Carpenter et al., 2012) and retrospective case reviews (Connolly et al., 2012). However, TMS outcomes among older adults (≥60 years) with TRD remain unclear.

Depression is the second most common psychiatric disorder in the elderly (Panza et al., 2010), and about one third of elderly depressed patients have TRD (Mulsant and Pollock, 1998). Compared to their younger counterparts, elderly depressed patients often suffer from a greater burden of cognitive, physical, and functional impairment (Knöchel et al., 2015; Mulsant and Pollock, 1998); poorer course of major depressive disorder (MDD; Licht-Strunk et al., 2007); inadequate antidepressant response or early symptom relapse (Knöchel

Abbreviations: MDD, major depressive disorder; MT, motor threshold; TMS, transcranial magnetic stimulation; TRD, treatment-resistant depression

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et al., 2015; Whyte et al., 2004); and more medication side-effects (Lyness et al., 1996). Older patients may also experience more medical comorbidities and significant psychosocial stressors, such as social isolation and caregiver dependence (Knöchel et al., 2015). Given that depression in older age involves these unique clinical challenges, it is important to understand whether available treatments for TRD can be applied in this population.

The effectiveness of TMS in older adults has been debated in the literature. Meta-analytical evidence based on six of the early TMS-TRD randomized control trials (RCTs) suggested that older age predicted poorer response (Fregni et al., 2006). However, a recent systematic review of both randomized and uncontrolled trials concluded that there was no reliable evidence negating the utility of TMS in elderly people with TRD, largely because most early trials excluded older adults (i.e., those > 60 years; Sabesan et al., 2015), and most studies reviewed by Fregni et al. (2006) used stimulation intensity at 90–110% percent of motor threshold (MT), which is less than what would be considered a standard "dose" in today's clinical practice (i.e., 120% MT). Sabesan et al. (2015) also indicated that TMS has a high degree of tolerability and safety among older elderly patients, leading them to conclude that elderly people with TRD should not be excluded in clinical trials or practice.

Four RCTs to date focused on older people (Jorge et al., 2008; Manes et al., 2001; Mosimann et al., 2004; note that Jorge et al. included two studies). Of note, the most recent of these studies used a stimulation intensity of 110% MT and demonstrated efficacy of TMS in geriatric patients with vascular depression (Jorge et al., 2008). Earlier trials using stimulation intensity equal to or lower than MT found no benefit compared to sham (Manes et al., 2001; Mosimann et al., 2004). However, no studies have yet examined whether elderly patients benefit from a 120% MT protocol, which is now the standard stimulation intensity used in clinical practice (George et al., 2010; O'Reardon et al., 2007).

A number of neurobiologically plausible mechanisms for an age-related TMS treatment effect have been posited, including atrophy of cortical gray matter (with associated greater coil-to-cortex distance), reduced synaptic connectivity, declining axon conduction velocities, and aging-related changes in lateralization, myelination, cerebrovascular function, and immune-inflammatory control (Bashir et al., 2014; Berlingeri et al., 2013; Knöchel et al., 2015; Kozel et al., 2000). Each of these factors could presumably alter the electromagnetic and anatomic properties of cortical tissue underneath the TMS coil, thereby altering the effect of TMS induced currents.

However, there have been remarkably few studies investigating this age-effect hypothesis directly (Riva-Posse et al., 2013), and it is difficult to draw any meaningful conclusions due to marked methodological variability in terms of coil placement, "dosing," (e.g., stimulation frequency and intensity, number of pulses), and treatment duration. To our knowledge, no previous observational study or controlled trial has specifically examined the treatment outcome of TMS therapy in older individuals using more modern parameters (i.e., high frequency stimulation to the left dorsolateral prefrontal cortex (DLPFC), delivered at 120% MT). The current study aimed to characterize the therapeutic response to TMS among TRD patients aged ≥60 years compared to those < 60 years, through retrospective analysis of outcome data routinely collected on all patients who received an acute course of treatment at two collaborating outpatient TMS clinics in Providence, Rhode Island prior to April 30, 2016. The age of 60 was chosen as a cut-off based on research by Sabesan et al. (2015), who reported that few adults over age 60 have been included in efficacy studies (average age range 27–61). Based on prior literature suggesting benefit for elderly patients (Jorge et al., 2008; Sabesan et al., 2015), we hypothesized that older patients would show similar changes in depression symptoms compared to younger patients.

2. Methods

2.1. Sample

Collection and analysis of data extracted from medical records was approved by the Institutional Review Boards (IRBs) at Butler Hospital (BH) and the Providence Veterans Administration Medical Center (VA). The BH and VA outpatient TMS clinics use the same TMS devices, share psychiatrists and staff that train together, follow similar procedures, and routinely administer the same depression assessment scales at baseline and serially during an acute course of TMS therapy. The pooled data represent 231 adults from BH (n =196) and the VA (n =35) treated with TMS during the period of February 2009 to April 2016. Data were included for analysis in this naturalistic outcomes study if the patient met the following inclusion criteria: 1) primary DSM-IV or V diagnosis of MDD (single or recurrent episode without psychotic features); 2) resistance to or intolerance of ≥1 trials of antidepressant medications; 3) no previous TMS therapy exposure; 4) a TMS-trained psychiatrist determined that TMS represented an appropriate treatment option; and 5) standard clinical assessments of depressive symptom severity were completed at pre-treatment baseline and at least once after the course of daily TMS treatments was initiated.

2.2. Treatment

The NeuroStar TMS Therapy system (Neuronetics, Inc., Malvern, PA) was used to deliver high-frequency (5 Hz or 10 Hz; Philip et al., 2015) stimulation over left DLPFC, typically with a schedule of 5 TMS sessions per week for 6 weeks, followed by 6 additional treatments in a taper schedule over three weeks. If remission was achieved prior to treatment number 30, the taper phase would begin earlier. In several cases at the BH site, the acute course was extended by additional treatments, for a maximum of 50 sessions. MT assessment occurred at the initial treatment session for determination of stimulation intensity, and was re-checked as clinically indicated through the acute course. External coordinates for coil placement over DLPFC were calculated by the device for a site 5.5 cm anterior from the MT location along a left superior oblique plane; adjustments were made for individual patients by the TMS physicians as needed to manage comfort and/or more accurately approximate the F3 location as defined by the international 10–20 system (Beam et al., 2009). Individual treatment sessions were delivered at 120% for a total of 3000 pulses. Consistent with common clinical practice, the total number of pulses per daily session could be increased to 4000 in cases where patients had not demonstrated substantial clinical improvement after the third week of treatment (George et al., 2010).

Consistent with the clinical practice in both settings, patients continued their ongoing (ineffective) psychiatric medications when they initiated the course of TMS. In the event of TMS-medication interactions, medication dose reductions and/or medication discontinuations were directed by TMS physicians so the course of TMS could be continued. Prescribing psychiatrists were discouraged from making other changes to a patient's medication regimen during the course of TMS therapy. For patients engaged in regular psychotherapy when they started TMS, there was no recommendation for change in schedule.

2.3. Measures

Demographic and clinical characteristics were extracted from medical records. Adverse events were retrospectively identified by examining clinically documented reasons for premature termination of the acute TMS course and categorized as serious and non-serious.

2.3.1. Outcome measures

Baseline and endpoint reports of depressive symptom severity were compared using the Inventory of Depressive Symptomatology–Self