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A naturalistic, multi-site study of repetitive transcranial magnetic stimulation therapy for depression

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) was approved in 2008 in the United States, and there are relatively few studies describing its use in regular clinical practice since approval.
Methods: From April 2011 to October 2014, ten sites within the National Network of Depression Centers (NNDC) provided data on 62 evaluable patients with a depressive episode. Treatment was determined naturalistically. Response was assessed by the Quick Inventory of Depressive Symptoms, Self-Report (QIDS-SR) as the primary outcome, and the Patient Health Questionnaire-9 (PHQ-9) and the clinician-rated Clinical Global Impression (CGI) as secondary depression measures.
Results: Enrolled patients exhibited significant treatment resistance, with 70.2% reporting more than 4 prior depressive episodes. Most patients received treatment with standard parameters (10 Hz over the left dorsolateral prefrontal cortex), although 22.6% of the patients received 1 or 5 Hz stimulation at some point. Over 6 weeks of treatment, response and remission rates were 29.4% and 5.9%, respectively, for the QIDS-SR; 39.2% and 15.7%, respectively, for the PHQ-9; and 50.9% and 17.9%, respectively, for the CGI. Moderator analyses revealed no effect of prior depressive episodes, history of ECT or gender, although early life stress predicted a better response to rTMS therapy.
Limitations: The study was an open-label, registry trial, with relatively coarse clinical data, reflecting practice only in academic, depression-specialty centers. Because of the relatively small size and heterogeneity of the sample, type 2 errors are possible and positive findings are in need of replication.
Conclusion: rTMS demonstrates effectiveness in clinical practice within the NNDC, although remission rates appear slightly lower in comparison with other recent naturalistic studies.

1. Introduction

Major depressive disorder (MDD) is one of the most common psychiatric disorders, with an annual incidence of around 7% (Kessler et al., 2005). Repetitive transcranial magnetic stimulation (rTMS) has been studied as a treatment for MDD for more than 20 years, and meta-analytic studies have demonstrated superiority for rTMS over sham stimulation in randomized controlled trials (Allan et al., 2011; Berlim et al., 2014; Gross et al., 2007; Herrmann and Ebmeier, 2006; Kozel and George, 2002; Lam et al., 2008; Schutter, 2010; Slotema et al., 2010; Xie et al., 2013), identifying effect sizes in the range of 0.4–0.6. The FDA cleared the first rTMS device for the treatment of

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depression in 2008, and three more under the 510 (k) mechanism since 2008. In controlled clinical trials, response and remission rates have ranged around 25–50% and 12–35%, respectively (Allan et al., 2011; Berlim et al., 2014; Gross et al., 2007; Herrmann and Ebmeier, 2006; Kozel and George, 2002; Lam et al., 2008; Schutter, 2010; Slotema et al., 2010; Xie et al., 2013). However, since the beginning of rTMS research, the length and intensity of treatment have increased, which has been associated with a more robust therapeutic effect (Gross et al., 2007). Since initial FDA clearance, only a few studies have examined therapeutic response in actual clinical settings using the parameters under which the treatment was approved (> 3000 pulses/session, minimum of 20 sessions, goal of 120% motor threshold). One study of 85 patients from a single academic center reported response and remission rates of 50.6% and 24.7%, respectively (Connolly et al., 2012), while a multi-site, naturalistic study of 307 patients (Carpenter et al., 2012), mostly in non-academic settings, found clinician-rated response and remission rates of 58% and 37%, respectively. However, with limited data, it remains an open question as to how rTMS is faring in regular clinical practice.

Although randomized, sham-controlled studies are necessary to establish efficacy for a therapy, the results of controlled trials may not generalize to clinical practice, which includes greater variation in patient characteristics, medications and rTMS treatment parameters than clinical trials. For patients considering whether or not to undergo treatment with rTMS, response rates in open-label trials, which combine both intrinsic treatment effects as well as placebo expectations, are the best guide to determine anticipated response rates. Therefore, to meet the critical need for naturalistic studies that reflect the evolving state of treatment in practice, the National Network of Depression Centers (NNDC) sponsored a registry study of rTMS therapy for depression. The NNDC is a 22-site consortium of centers focused on depressive disorders, all located in academic medical centers. Ten centers with rTMS operations participated in the registry. The goals of the study were three-fold: (1) characterize the variation in rTMS therapy in regular clinical practice, (2) measure response and remission rates, and (3) explore moderators of treatment response in a naturalistic, clinical setting.

2. Methods

2.1. Subjects

From April 2011 through October 2014, 81 subjects consented to participate in the registry study. Patients were recruited from amongst those who had sought clinical treatment with TMS in one of the participating centers. Eligibility criteria were minimal to encourage a sample representative of standard clinical practice in a tertiary care center: (1) receiving rTMS for their depressive disorder, as determined by their attending psychiatrist; (2) at least 18 years of age; (3) literate in English; (4) without a diagnosis of schizophrenia or schizoffective disorder; and (5) no contra-indications to receiving rTMS. rTMS parameters and length of treatment were determined by the treating clinician, working with the patient. The cost of rTMS treatment was born by patients or their insurance companies. Other treatments, such as pharmacotherapy and psychotherapy, varied naturalistically. All subjects signed an informed consent document, describing the risks and benefits of participating in the registry, as approved by the local Institutional Review Board of each site.

2.2. Outcome measures

Standard measures were used to track outcome, including the following self-report measures: (1) Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR): a 16-item patient self report measure which assesses the 9 DSM-IV symptom criteria for a major depressive episode (Rush et al., 2003); (2) Patient Health Questionnaire-9 (PHQ-9): a 9-item depression symptom severity scale (Gilbody et al., 2007); (3) Work and Social Adjustment Scale (WSAS): a 5-item scale assessing the impact of the patient's symptoms on work and home life (Mundt et al., 2002); (4) Generalized Anxiety Disorder Assessment (GAD-7): a 7-item scale assessing the degree of anxiety experienced by the patient (Spitzer et al., 2006); (5) Adverse Childhood Experiences (ACE): a 10-item self-report scale assessing potentially traumatic experiences during childhood (Chapman et al., 2004). Patients also completed a 10-point pain intensity rating, and the Columbia Suicide Severity Rating Scale (Posner et al., 2007), adapted for self-report. Clinicians completed the Clinical Global Impression scale (CGI; severity, CGI-S, and change, CGI-I), single-item global ratings of severity and improvement with treatment (Guy and Bonato, 1970).

The registry was designed to acquire ratings at the initiation of rTMS treatment, and then for every week thereafter for the course of treatment. The QIDS-SR was the primary outcome measure, and the other measures were treated as secondary outcomes. Information about diagnosis, prior treatment and treatment response was based on the clinician's interview and best judgment.

2.3. Analysis

Analysis included categorical and continuous measures of change on the primary and secondary outcome measures. Change was measured in the first 6 weeks of treatment, the standard endpoint for other rTMS studies in depression (Carpenter et al., 2012; Connolly et al., 2012; O'Reardon et al., 2007). Some patients had no treatments after baseline measurement; others had only 2 or 3 weeks of treatment, but a majority had at least 4 weeks of treatment and assessments. We excluded subjects from this analysis who had less than 4 weeks of assessments after baseline for reasons clearly not related to treatment, such as becoming lost to follow-up, moving away or withdrawing consent to participate in the registry. The remaining patients were included in an intent-to-treat analysis for QIDS-SR and PHQ-9 scores, including patients with less than 4 weeks of treatment, but at least one assessment after baseline. All-cause discontinuation of therapy, relevant to delivering the therapy, before 4 weeks includes important information, such as treatment non-response, logistical burden of daily sessions or the cost of treatment (often born by the patient). Hence, these data points were included.

For categorical responses, we defined treatment *response* as the following: a 50% or greater drop in QIDS-SR or PHQ-9 scores, or a CGI-I score ≤2 ("Much improved"), on the last assessment in 6 weeks of treatment. Remission was defined as a QIDS-SR or PHQ-9 score < 5 or CGI-S score as ≤2 ('Borderline mentally ill"), from the last observation in 6 weeks of treatment. For the QIDS-SR and PHQ-9 analysis, patients had to have a baseline score > 5.

For measurement of continuous change, we employed a mixed-model, multiple regression with random coefficients and AR(1) structure, modeling weekly change from baseline with baseline rating as a co-variate. This model was run for the primary and secondary self-report measures. In a moderator analysis of self-report depression measures (QIDS-SR and PHQ-9), we examined the effects of gender, number of prior depressive episodes, failed antidepressant courses, prior history of ECT, ACE scores and stimulation site. Since the number of observations varied between subjects, this mixed approach incorporated all observations by first modeling symptom change at the subject level, and then between subjects.

3. Results

3.1. Subjects entered into analysis

There were 62 evaluable patients from the 81 patients enrolled in the study (Fig. 1). The number of evaluable subjects from each site