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Crossover to bilateral rTMS: A potential strategy when patients are not responding to unilateral left-sided high frequency rTMS

Pilar Cristancho, M.D.¹, Nicholas T Trapp, M.D.², Shan H Siddiqi, M.D.^{1,3}, David Dixon, Ph.D.¹, J. Philip Miller, A.B.⁴, and Eric J Lenze, M.D.¹

¹Department of Psychiatry, Healthy Mind Lab, School of Medicine, Washington University in St. Louis, Campus Box 8134, 660 S. Euclid Ave, St. Louis MO, 63110. USA

²University of Iowa Hospital and Clinics. 200 Hawkins Drive Iowa City, IA 52242

³Department of Neurology, McLean Hospital and Harvard Medical School, Boston, MA

⁴Division of Biostatistics, School of Medicine, Washington University in St. Louis, Campus Box 8067, 660 S. Euclid Ave. St. Louis MO 63110. USA

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Introduction

What should clinicians do when a depressed patient is not responding to High-Frequency (HF) left unilateral rTMS treatment? Clinical trials using left Dorso Lateral Prefrontal Cortex (DLPFC) rTMS reported remission rates of 14–32.6%^{1–3}, suggesting that most patients will not achieve remission with standard rTMS; moreover, real world patients have a great variation in disease severity, comorbidities and often a high degree of treatment resistance. Therefore strategies to optimize rTMS in clinical practice are needed.

Beneficial strategies include extending the duration of the rTMS course⁴ or switching the stimulation site to the right DLPFC⁵. This prospective case series examines another potential but unstudied strategy: crossing-over to bilateral stimulation, with the addition of low-frequency (LF) right-sided rTMS, when patients are not responding to unilateral rTMS. This strategy is biologically supported, since LF (1Hz) rTMS over the right DLPFC decreases blood flow in circumscribed regions of the right prefrontal cortex, left medial temporal cortex, left basal ganglia and left amygdala⁶ and has demonstrated efficacy and tolerability in major depression⁷. Besides, crossover to bilateral rTMS has been empirically used by clinicians^{8,9}.

Materials and Methods

From 2012–2016, patients in a major depressive episode who consented to research participation received a clinical rTMS protocol administered 5-days a week for 4–6 weeks. Stimulation began with HF rTMS (10Hz) over the left DLPFC (3000–5000 pulses-per-session [pps] range, inter-train interval 15 – 20 seconds range). Patients without sufficient

clinical improvement early in their rTMS course received “off label” (not FDA approved) 1Hz rTMS over the right DLPFC (in addition to and sequentially after the HF left-stimulation). LF stimulation typically began at 600pps and was increased up to 1200pps as per clinician’s judgment. Every 600 pulses of LF rTMS added 11 minutes to the total duration of the rTMS session. We used a Magpro R30 stimulator with a figure of eight coil. Motor threshold (MT) was determined for each left and right hemispheres and stimulation intensity was set at 110%–120% of the MT. The DLPFC was localized for each hemisphere at 6 cm anterior to the motor cortex or by using the Beam F3 system¹⁰. To localize the right DLPFC using the Beam F3 system, we positioned the X and Y software values on the right hemisphere.

Primary outcome was change in Hamilton Depression Rating Scale 17-item (HAM-D); secondary outcomes included depression remission rates (HAM-D = 7) and change in scores on the Quick Inventory of Depressive Symptoms (QIDS), the Generalized Anxiety Disorder-7 scale (GAD7), and the Work and Social Adjustment Scale (WSAS) (measuring functional impairment). Clinical Improvement was determined by the Clinical Global Impressions Scale. Burden of side effects was assessed with the Frequency, Intensity and Burden of Side Effects Rating (FIBSER). Lost to follow-up patients without post-baseline mood assessments were excluded from analysis. We described continuous variables using Means (*M*) and Standard Deviations (*SD*) and categorical variables using total number and percentages. We compared baseline to treatment-end depression scores, anxiety and functional impairment scores and calculated Cohen’s *d* effect sizes.

Results

Demographic and clinical characteristics of the 17 patients were: Mean age 48.7 (13.3 *SD*) years, 9 (52.9%) females, all were Caucasian. All patients had at least three previous antidepressant trials without response. Four patients (23.5%) had a lifetime-history of electroconvulsive therapy, 8 patients (47%) had previous psychiatric hospitalizations, 3 (17.6%) had a previous suicide attempt and 8 (47%) had a history of anxiety disorder. Baseline MT values were $M=52.2$, $SD\pm 8.3$ for the left hemisphere and $M=52.3$, $SD\pm 7.5$ for the right.

All except for one patient, were taking antidepressants. A total of 41% (7/17) patients had medication changes during their rTMS course; however, Ham-D scores at the end-of-treatment did not differ between the group with medication changes ($M=-2.1$, $SD\pm 2.8$) and those without medication changes ($M=-1.4$, $SD\pm 4.8$), $t(15) = 0.37$, $p=0.71$.

Figure 1 shows individual data on Ham-D scores changes throughout the rTMS course. A total of 14 patients crossover to bilateral rTMS after 2 weeks of rTMS, CGI 3 – 4 (minimal improvement or no change); 2 patients after 3 weeks, CGI = 2 and 5 (much improved and minimally worse) and one patient after 4 weeks, CGI = 3. Group results show decreased scores on the Ham-D from the time of crossover to the end of rTMS indicating antidepressant effects (Table 1). The group’s remission was 24% (4/17) and 41.1% patients (7/17) had at least 25% decrease in HAM-D scores. The two patients with bipolar disorder did not remit. The QIDS also showed improvement from the time of crossover to the end-of-

treatment. Similarly, the GAD-7 anxiety scale and the WSAS scales also showed improvement (Table 1). Reported side effects were mild and minimally burdensome, including headache 35% (6/17), anxiety 18% (3/17), fatigue, tooth pain, sleep disturbance and scalp soreness each 12% (2/17).

Discussion

To our knowledge this is the first report of crossover to bilateral rTMS in patients with insufficient clinical improvement in their rTMS course. With this bilateral “augmentation” strategy, patients showed a meaningful decrease in depression scores with a medium effect size, and 24% remitted. These outcomes are comparable with a 24% remission rate with aripiprazole augmentation in patients minimally responsive to antidepressants¹¹. Side effects were minimally burdensome. One controversial aspect of this strategy was our decision to crossover to bilateral treatment before the completion of a full left-side rTMS course. The rationale of this early change is supported by literature documenting depression improvement in clinical trials using a 2-week rTMS (10 sessions) course¹². Likewise, changes in brain metabolism occurred within 2 weeks of rTMS⁶. Nonetheless, it is possible that the improvements we saw would have been obtained simply by continuing the unilateral rTMS. Other limitations include potential confounding effects of concomitant medications and the lack of randomization with a control group.

Nevertheless, we demonstrated that crossover to bilateral stimulation is a feasible and potentially effective strategy when patients are not improving with standard rTMS. A randomized controlled trial comparing crossover vs. standard rTMS is needed to determine the efficacy of this paradigm.

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Figure 1.
Trajectory of Hamilton Depression Scores for Each Patient Crossing Over to Bilateral rTMS. (Triangles denote mean Hamilton Depression scores trajectory)

Table 1

Changes in Depression, anxiety and general functioning scores in patients crossing over to bilateral stimulation (n = 17).

Scale	Baseline Mean (±SD)	Illness severity	Treatment end Mean (±SD)	Score change (units)	Illness severity	Cohen's D effect size	95% Confidence Interval
HAM - D	13.9 (3.9)	moderate-mild	12.2 (5.8)	-1.7	mild	-0.35	-1.01 – 0.34
QIDS	12.5 (4.0)	moderate	9.6(5.7)	-2.9	mild	-0.60	-1.26 – 0.11
GAD - 7	7.9 (5.2)	mild	5.9 (5.1)	-2.0	mild	-0.39	-1.36 – 0.61
WSAS	25.9(8.2)	moderately severe	21.6 (10.0)	-4.3	moderately severe	-0.47	-1.15 – 0.23

Abbreviations: HAM -D, Hamilton Depression Rating Scale; QIDS, Quick Inventory of depressive symptoms; GAD-7, Generalized Anxiety Disorder 7 Scale; WSAS, Work and Social Adjustment Scale.