Published in final edited form as:

J Affect Disord. 2018 January 01; 225: 773–774. doi:10.1016/j.jad.2017.08.033.

Response to Letter to the Editor regarding “Transcranial magnetic stimulation for treatment-resistant depression: Naturalistic outcomes for younger versus older patients”

Christine A. Conelea, Ph.D.^{a,*}, Noah S. Philip, M.D.^{b,c}, Augustin G. Yip^d, Jennifer L. Barnes^d, Matthew J. Niedzwiecki^b, Benjamin D. Greenberg^{b,c}, Audrey R. Tyrka^b, and Linda L. Carpenter^b

^aUniversity of Minnesota, Minneapolis, MN, USA

^bButler Hospital/Alpert Medical School of Brown University, Providence, RI, USA

^cCenter for Neurorestoration and Neurotechnology, Providence VA Medical Center, Providence, RI, USA

^dMc Lean Hospital/Harvard Medical School, Boston, MA, USA

We appreciate the comments of Professor Van den Noort and colleagues regarding our recent report (Conelea et al., 2017). We described a retrospective chart review of adults (N=231) with treatment resistant depression (TRD) who received an acute course of outpatient TMS therapy in a naturalistic clinical practice setting. We found equivalent improvements in depression symptoms between patients aged ≥60 years vs. those <60. We concluded that older age alone should not be considered a contraindication or poor prognostic indicator to TMS therapy, a finding that is consistent with the prior literature (see review by Sabesan et al., 2015).

Professor Van den Noort and colleagues raised three concerns about our study. First, in a manner consistent with prior letters to journal editors (van den Noort et al., 2014), they expressed concern regarding the safety of TMS in the aging brain. We point out that our data were from a chart review of naturalistic treatment outcomes, and as such data were not systematically captured or available in sufficient detail to permit rigorous testing of all safety outcomes. We did not find any differences in serious or non-serious adverse psychiatric events, but side effects were not assessed with standardized instruments. Furthermore, in the majority of cases we have limited contact with our TMS patients after they finish the course of stimulation and return to their outpatient psychiatrists and therapists for maintenance care. We certainly agree that our study alone is insufficient to comprehensively demonstrate TMS safety for all older patients with TRD. However, our impressions of safety from the data we examined are consistent with published findings demonstrating generally good tolerability and at least short-term safety among older patients receiving TMS. For example, in a review of four randomized trials and seven uncontrolled trials of TMS for TRD (total N=136), Sabesan et al. (2015) found no clear evidence of age-related adverse effects, no evidence of

*Correspondence to: Department of Psychiatry, F282/2A West Building, 2450 Riverside Avenue, Minneapolis, MN 55454. ccconelea@umn.edu (C.A. Conelea).

Author Manuscript

differential distribution of side effects between sham vs. active treatment, and overall low dropout rates due to adverse effects. A sizeable and growing literature describes the application of TMS in older populations to probe cortical function in both healthy and clinical populations, and to treat neuropsychiatric illnesses such as vascular depression, mild cognitive impairment, dementia, Alzheimer's disease, stroke, neurodegenerative aphasia, and Parkinson's disease (e.g., Drumond Marra et al., 2015; Liu et al., 2014; Luber et al., 2013; Vonloh et al., 2013). To our knowledge, no research has identified a contraindication to TMS based specifically on older age. When considering TMS therapy for older TRD patients, we argue that available data do not support the blanket exclusion of those age 60 or older. As with all clinical interventions, the risk-benefit ratio of TMS should be considered in the context of individual patient characteristics and in comparison to other available treatments.

Author Manuscript

Author Manuscript

Second, Professor Van den Noot and colleagues wondered why we did not use a standardized clinical interview and relied on patient self-rating scales. Because our study was a retrospective assessment of general outpatient clinic data, and not a prospective research trial, we reported on the measures used in our clinic's routine practice. These include the application of DSM-IV or DSM-V diagnostic criteria during a comprehensive clinical interview to confirm primary diagnosis of major depressive disorder prior to initiation of treatment, and serial measurement of depressive symptom severity during the course of TMS treatment with well-validated, psychometrically sound, patient-reported outcome measures (PROMs). Our clinic uses PROMS that are widely used in depression research trials (Inventory of Depressive Symptomatology-Self-Report, IDS-SR; Rush et al., 2006; 9-Item Patient Health Questionnaire, PHQ-9; Kroenke et al., 2001), widely recognized as reliable indicators of depression severity and change over time, and free of bias imposed by the treating clinician. Unlike structured diagnostic interviews, PROMs do not require the time and resources needed to establish inter-rater reliability. A number of major governmental organizations and medical specialty societies around the world promote the use of PROMs in both routine clinical care and clinical trials research based on the rationale that PROMs improve patient satisfaction and enable clinicians and health systems to evaluate practice quality and effectiveness (Basch et al., 2013; IsHak et al., 2014). We encourage other TMS clinical practice groups to practice measurement-based care and to publish PROM-based outcomes to enhance the field's understanding of TMS therapy effects when delivered in (non-research) routine clinical care. Similar to the case with newer pharmacotherapies, published safety data for repeated application of TMS over very long-term periods (beyond one year) are generally limited for patients of all ages. Reports of safety outcomes for naturalistically-treated TMS samples with their inherent comorbidities and complexities might therefore be considered a particularly important contribution to the collective knowledge base for clinicians using TMS in their practice.

Author Manuscript

Third, Van den Noort et al. noted that our data were extracted from medical records with Institutional Review Board (IRB) approval and wondered whether efforts were made to obtain patient approval for data use. This was not a prospective clinical trial and the symptom measures were intended to guide clinical care rather than to answer research questions. Since informed consent could not be obtained from patients for a study that was not happening at the time the patients were receiving care, we followed federal regulations

(see CFR 164.501) and received IRB approval for limited use of protected health information pursuant to a waiver of authorization. Our study met the criteria required for this provision of the Privacy Rule, and allowed us to access patients' medical records so that we could extract specific data in an anonymized format to answer our research questions.

Consistent with the recently published consensus recommendations for application of TMS in clinical practice (McClintock et al., 2017), we believe a comprehensive review of health status and physical examination are critical components for evaluating a patient's appropriateness for TMS therapy. Prior to the start of treatment, physicians in our TMS clinics routinely review each candidate's medical, surgical, neurologic and psychiatric conditions, medications, and results of physical examination (along with results of brain imaging or laboratory tests, when indicated). However, we appreciate the continued focus of Professor Van den Noort and colleagues on patient safety in the context of new therapies, particularly for subgroups, such as older patients, who may have relatively greater risk with psychiatric treatments.

References

- Basch E, Torda P, Adams K, 2013 Standards for patient-reported outcome-based performance measures. *JAMA* 310, 139–140. [PubMed: 23839744]
- Conelea CA, Philip NS, Yip AG, Barnes JL, Niedzwiecki MJ, Greenberg BD, Tyrka AR, Carpenter LL, 2017 Transcranial magnetic stimulation for treatment-resistant depression: Naturalistic treatment outcomes for younger versus older patients. *J. Affect. Disord* 217, 42–47. [PubMed: 28388464]
- Drumond Marra HL, Myczkowski ML, Maia Memória C, Arnaut D, Leite Ribeiro P, Sardinha Mansur CG, Lancelote Alberto R, Boura Bellini B, Alves Fernandes da Silva, A., Tortella G, Ciampi de Andrade D, Teixeira MJ, Forlenza OV, Marcolin MA, 2015 Transcranial magnetic stimulation to address mild cognitive impairment in the elderly: A randomized controlled study. *Behav. Neurol* 2015, 287843. [PubMed: 26160997]
- IsHak WW, Mirocha J, Pi S, Tobia G, Becker B, Peselow ED, Cohen RM, 2014 Patient-reported outcomes before and after treatment of major depressive disorder. *Dialogues Clin. Neurosci* 16, 171–183. [PubMed: 25152656]
- Kroenke K, Spitzer RL, Williams JB, 2001 The PHQ-9: validity of a brief depression severity measure. *J. Gen. Intern. Med* 16, 606–613. [PubMed: 11556941]
- Liu AY, Rajji TK, Blumberger DM, Daskalakis ZJ, Mulsant BH, 2014 Brain stimulation in the treatment of late-life severe mental illness other than unipolar nonpsychotic depression. *Am. J. Geriatr. Psychiatry* 22, 216–240. [PubMed: 23891366]
- Luber B, McClintock SM, Lisanby SH, 2013 Applications of transcranial magnetic stimulation and magnetic seizure therapy in the study and treatment of disorders related to cerebral aging. *Dialogues Clin. Neurosci* 15, 87–98. [PubMed: 23576892]
- McClintock SM, Reti IM, Carpenter LL, McDonald WM, Dubin M, Taylor SF, Cook IA, O'Reardon J, Husain MM, Wall C, Krystal AD, Sampson SM, Morales O, Nelson BG, Latoussakis V, George MS, Lisanby SH, National Network of Depression Centers rTMS Task Group, American Psychiatric Association Council on Research Task Force on Novel Biomarkers and Treatments, 2017 Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. *J. Clin. Psychiatry* doi:10.4088/JCP.16cs10905
- Rush AJ, Bernstein IH, Trivedi MH, Carmody TJ, Wisniewski S, Mundt JC, Shores-Wilson K, Biggs MM, Woo A, Nierenberg AA, Fava M, 2006 An evaluation of the quick inventory of depressive symptomatology and the Hamilton rating scale for depression: a sequenced treatment alternatives to relieve depression trial report. *Biol. Psychiatry* 59, 493–501. [PubMed: 16199008]

- Sabesan P, Lankappa S, Khalifa N, Krishnan V, Gandhi R, Palaniyappan L, 2015 Transcranial magnetic stimulation for geriatric depression: Promises and pitfalls. *World J Psychiatry* 5, 170–181. [PubMed: 26110119]
- van den Noort M, Lim S, Bosch P, 2014 Recognizing the risks of brain stimulation. *Science* 346, 1307.
- Vonloh M, Chen R, Kluger B, 2013 Safety of transcranial magnetic stimulation in Parkinson's disease: a review of the literature. *Parkinsonism Relat. Disord* 19, 573–585. [PubMed: 23473718]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript