Interactions of the Placebo Effect and Transcranial Magnetic Stimulation

To the Editor: We read with interest the case report "The Enhanced Placebo Effect of Transcranial Magnetic Stimulation" by Hadi and colleagues.[1] The authors[1] report that the patient's response to treatment sessions of transcranial magnetic stimulation (TMS) might represent placebo effect. The authors[1] speculate that this placebo effect may have been produced by patient beliefs concerning use of a medical device and mention several other factors by which this placebo response may have been effectuated, such as patient expectations or exposure to a therapeutic relationship.

What exactly is meant by placebo effect? The *Oxford Dictionary of English*[2] defines *placebo* as a harmless pill, medicine, or procedure prescribed more for the psychological benefit to the patient than for any physiologic effect, and/or a substance that has no therapeutic effect (inert), used as a control in testing new drugs. While not explicitly stated, this patient's TMS sessions and the subsequent singular sessions to which the patient responded were apparently not sham TMS but actual TMS, so it is unlikely that the authors[1] were suggesting that the TMS treatment per se is a placebo.

Published in 1955, the article titled "The Powerful Placebo"[3] informs us of the prolonged period of time during which the effects of placebo have been represented in the medical literature. Four decades later, that article was reviewed by Kienle and Kiene,[4] who concluded that those responses considered to be placebo effects were in fact not placebo. Research and time have edified us and will likely continue to do so.

Did this patient experience an enhanced placebo response or a placebo response at all? While the patient improved following a single session of TMS given 6 months after the end of his first series of treatments, he again became symptomatic within 2 months. This shorter duration of improvement may underscore the findings and conclusions of Huang et al[5] concerning the importance of optimizing and timing treatment interventions. Further, rTMS has been reported to have effects on molecular and cellular and neuronal circuitry within the brain that outlast the time of the active treatment.[5–7] We might therefore conclude this patient[1]simply experienced a rapid and good response to treatment, not a placebo response.

Placebo is recognized as "a powerful determinant of health"[8] and consists of objective neurobiological pathways.[9] Some of the factors mentioned by the authors[1] have neurobiological effects, which have been documented. The term *placebo* has been defined and redefined and developed a noxious twin, the nocebo. Could something inert have a biochemical correlate or neurobiological pathway? Or is it not the inert substance but the neural response based on prior experience to it or some similar stimulus that could be either common or idiosyncratic. In this patient,[1] we conclude that both known and unknown factors likely contributed to his clinical response. Placebo remains a ubiquitous part of patient care[10] but may simply represent all the unknowns, those things not yet identified or defined but potentially relevant to health outcomes.

Dr Hadi was shown this letter and declined to reply.

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__Published online:__ March 18, 2021.
__Potential conflicts of interest:__ None.
__Funding/support:__ None.
Prim Care Companion CNS Disord 2021;23(2):20lr02874

__To cite:__ Bartlett J, Upshaw WN, Obregon D. Interactions of the placebo effect and transcranial magnetic stimulation. *Prim Care Companion CNS Disord*. 2021;23(2):20lr02874.
__To share:__ https://doi.org/10.4088/PCC.20lr02874