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Low frequency right-sided and high frequency left-sided repetitive transcranial magnetic stimulation for depression: The evidence of equivalence



Conflict of interest disclosures

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In their recent letter, Miron and colleagues make a cohesive and robust argument for reappraising the role of low frequency (1 Hz), right-sided repetitive transcranial magnetic stimulation (LFR-TMS) for the treatment of depression, highlighting its many potential advantages over high frequency (≥ 5 Hz) left-sided stimulation (HFL-TMS); these advantages included the ability to use less expensive devices, tolerability, and better safety profile [1]. Such devices may also be better suited to the COVID-19 world where the need for at-home stimulation must carry greater weight. The relative advantages of LFR-TMS become even more critical if it can be shown that this approach has comparable efficacy as HFL-TMS. Consistent with this narrative, multiple studies comparing the efficacy between LFR-TMS and HFL-TMS for depression have failed to detect differences in these approaches, including a meta-analysis of 12 studies ($n = 361$) [2], and a recent large randomized controlled trial ($n = 300$) [3]. While the failure to detect differences using null hypothesis significance testing in these studies is insufficient to establish that LFR-TMS is as efficacious as HFL-TMS, formal equivalence testing of this same data can provide quantitative evidence for the absence of a clinically meaningful difference between these treatment approaches. The aim of this study was to perform equivalence testing of the pooled efficacy outcomes from LFR-TMS and HFL-TMS treatments for depression using the currently available evidence.

Randomized controlled trials of LFR-TMS and HFL-TMS for patients with major depressive episodes were identified through PubMed following the methods described by Cao et al. [2], but extending to June 21, 2020 and defining low frequency stimulation as less than 5 Hz. Treatment response was defined as a 50%

reduction in depression rating scales. This strategy yielded 12 studies assessing treatment response and six reporting remission rates, including 11 of the studies identified and analyzed by Cao et al. [2] and the two arms of the recent large trial by Fitzgerald et al. [3].

Pooled odds ratios for response and remission rates were calculated using the Mantel-Haenszel (MH) fixed effect method as implemented in the 'meta' package from R [4]. Heterogeneity was estimated using the DerSimonian-Laird estimator for τ^2 . Odds ratios (OR) and the corresponding confidence intervals (CI) were converted to effect sizes (Cohen's d) and standard error (SE) estimates using the conversion procedures for meta-analysis provided by Chinn [5], where $d = \ln(OR) * (\sqrt{3}/\pi)$. Equivalence testing for meta-analysis was completed using the two one-sided test (TOST) for meta-analysis in the R 'TOSTER' library with alpha (α) set at 0.05 [6]. The equivalence margin was set at $d = 0.25$, following the work and rationale of Steinert et al. [7] for equivalence testing in meta-analysis of depression treatments. Using the conversion formula noted above [5], this equivalence margin corresponds with OR values between 0.636 and 1.574. Additional analyses were performed using alternative study selection to assess the robustness of these findings. Ninety percent confidence intervals corresponding to $1-2\alpha$ are presented to illustrate equivalence testing using the TOST [6].

Twelve randomized controlled trials were included in the analysis with a total of 627 subjects with major depressive episodes treated with either LFR-TMS ($n = 320$) or HFL-TMS ($n = 307$). Overall, 47% percent (292/627) of these subjects were classified as responders, with reported response rates of 45% (144/320) in subjects treated with LFR-TMS and 48% (148/307) in subjects treated with HFL-TMS. The pooled odds ratio was 1.12 (90% CI: 0.85–1.48), corresponding to an effect size of $d = 0.064$ ($SE = 0.09$) nominally favoring HFL-TMS as shown in Fig. 1. Equivalence testing with a margin of $d = 0.25$ was significant ($Z = -2.02$, $p = 0.022$), indicating evidence to reject the difference hypothesis and accept the equivalence hypothesis for treatment response. A subset of six of these studies ($n = 431$) reported remission rates in addition to response rates, with 26% (57/217) of patients randomized to LFR-TMS achieving remission compared to 25% (54/214) in the HFL-TMS groups. The pooled odd ratio was 0.92 (90% CI: 0.64–1.33), nominally in favor of LFR-TMS (Supplement 1). Equivalence testing with the same margin ($d = 0.25$) was significant ($Z = 1.687$, $p = 0.046$), indicating evidence for equivalence of remission rates. Additional analyses excluding three

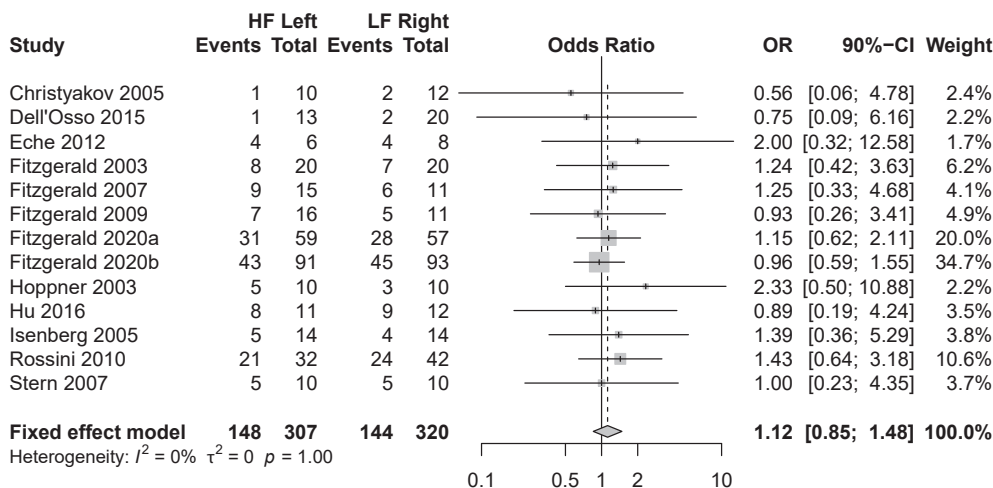


Fig. 1. Meta-Analysis of Depression Response Rates in Subjects Receiving either High Frequency Left-Sided (HF Left) or Low Frequency Right-Sided (LF Right) Transcranial Magnetic Stimulation.

studies in which bipolar depression made up the majority of subjects [8–10] yielded similar results supporting equivalence for response rates (pooled OR = 1.10, 90% CI: 0.82–1.49; equivalence testing $Z = -1.94$, $p = 0.026$ given margin of $d = 0.25$) and trend level results for remission rates (pooled OR = 0.87, 90% CI: 0.59–1.28; equivalence testing $Z = -1.35$, $p = 0.088$).

This study provides statistical evidence of the equivalence of LFR-TMS and HFL-TMS efficacy when used to treat major depressive episodes. As illustrated by the confidence intervals in Fig. 1, neither the individual studies nor the pooled estimates comparing LFR-TMS and HFL-TMS demonstrated that either approach has superior efficacy for treating depressive episodes ($p > 0.1$). These findings confirm previous meta-analyses of LFR-TMS and HFL-TMS outcomes that were unable to detect differences with these two stimulation protocols [2] and suggest there is no statistical evidence that these stimulation protocols differ in efficacy. However, many of these previous studies have been underpowered to demonstrate meaningful equivalence and none have applied the methods of equivalency testing. The current study works to overcome these limitations by combining the statistical power of meta-analysis along with the logic of equivalence testing to define equivalent efficacy outcomes of these two TMS protocols using a conservative margin established for depression treatments [7]. If a true difference between LFR-TMS and HFL-TMS response and remission rates existed larger than the tested equivalency margin ($d = 0.25$), the current results of significant equivalence would be surprising ($p < 0.05$). A difference in efficacy outcomes between LFR-TMS and HFL-TMS protocols may still exist, however, this analysis suggests the difference would be small and unlikely to be clinically meaningful. While the evidence base for HFL-TMS has been well established compared to LFR-TMS, the current finding that these two stimulation protocols have equivalent efficacy provides further support of the need for additional studies to re-evaluate the role of LFR-TMS in the treatment of depression.

CRedit authorship contribution statement

Yosef A. Berlow: Conceptualization, Methodology, Visualization, Writing - original draft, preparation. **Amin Zandvakili:** Conceptualization, Writing - review & editing. **Noah S. Philip:** Conceptualization, Writing - review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2020.10.005>.

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