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# The role of low-frequency repetitive transcranial magnetic stimulation in major depression: A call to increase the evidence base

*To the Editor,*

Repetitive transcranial magnetic stimulation (rTMS) is an effective intervention in major depressive disorder (MDD), with superior tolerability over medication [1]. Unfortunately, its widespread adoption has been impeded by high operational costs, decreasing accessibility.

These issues arise in part from the current protocols being favored, namely high-frequency (HF) rTMS, using figure-of-eight (Fo8) coils and targeting the left dorsolateral prefrontal cortex (L-DLPFC), and Deep TMS (using the H1 coil). The most recent rTMS guidelines considers them both to have the highest evidence, with level A ratings of "definite efficacy" [2].

An alternative that has now been studied for over 2 decades is low-frequency (LF) rTMS, usually 1 Hz right DLPFC (R-DLPFC) stimulation. Several RCTs have already demonstrated the superiority of R-DLPFC LF-rTMS over sham in MDD, and its efficacy has been confirmed in multiple meta-analyses. An oft-cited meta-analysis from 2012 (8 RCTs, 263 patients) suggested superior response (38.2% vs 15.1%) and remission rates (34.6% vs. 9.7%) vs. sham ($p = 0.007$ and $p < 0.0001$, RR 2.14, 95% CI = 1.02–4.47), with a number needed to treat (NNT) of 5 [3]. Higher number of pulses (>1200) was associated with higher response rates, and there were no differences in dropout rates between both groups. Superiority over sham of R-DLPFC LF-rTMS (OR 2.37, 95% CI = 1.52–3.68) was also confirmed in the most recent and largest meta-analysis on rTMS (81 RCTs, 4233 patients) [4]. Despite these encouraging results, the sham-controlled R-DLPFC LF-rTMS RCTs have been small N, single-center trials. The issue of blinding in rTMS has also often been contentious, and even though recent trials have successfully used surface electrodes placed above the eyebrows, this was not the case of the aforementioned LF rTMS RCTs. Blinding integrity was also not assessed. Given all of this, the most recently published rTMS guidelines [2] gave R-DLPFC LF-rTMS a rating of "probable antidepressant efficacy" (Level B).

Conversely, the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines from 2016 gave R-DLPFC LF-rTMS level I evidence and ranked it as first line equally with L-DLPFC HF-rTMS, considering them equally efficacious [1]. The most recent and largest meta-analysis (12 RCTs, 361 patients) confirmed this observation, showing similar response (OR 1.08, 95% CI = 0.88–1.34, $p = 0.50$) and remission rates (OR 1.29, 95% CI = 0.54–3.10, $p = 0.56$) [5]. Unfortunately, most of the RCTs done on the subject were also of small N (largest 74), thus bringing once again the issue of lack of power and type-II error. Nevertheless, a recent and large ($n = 300$) four-arm RCT, not included in this meta-analysis (2 R-DLPFC LF-rTMS arms and 2 L-DLPFC HF-rTMS arms, 150 in each group), also concluded that both protocols had similar efficacy [6].

Beyond the issue of efficacy, LF-rTMS offers several advantages over the other FDA-approved protocols. There indeed is evidence that LF-rTMS causes less pain and has a higher safety profile - even in epilepsy patients - who show *reductions* of seizure frequency [7–9]. More importantly though, the greatest potential of LF-rTMS may lie in the potential to improve accessibility, tolerability, safety, and equipment costs associated with the technique, which should spark the interest of clinics and healthcare policy-makers. Indeed, 1 Hz rTMS only requires very basic stimulators, which could be much more affordable than usual setups required for HF and Deep TMS. Our group also recently published a case series on easy-of-use non-cooled non-focal parabolic coils [10]. These could be an affordable alternative to cooled coils, while also offering a solution to targeting issues given their non-focality. Additionally, given its safety and simplicity of administration on large coils, 1 Hz rTMS could potentially offer a pathway toward the development of devices suitable for home use. Home-based 1 Hz rTMS would address the two most significant downsides of rTMS over medication: the need for patients to come to clinics for treatment, and the cost of the treatment sessions. A device capable of delivering basic 1 Hz stimulation currently costs in the range of $15,000 – amortized over a 5-year use period, this would equate to under $9 a day, which is comparable to many antidepressant medication regimens. Home rTMS would also facilitate maintenance treatments, a still unresolved issue in rTMS [1]. Finally, treatment at home decreases patient contact, social distancing now being a necessary, albeit unfortunate new reality of the COVID-19 "pandemic era" [11].

Before this can become a reality, we need to clearly establish the efficacy of 1 Hz rTMS. Indeed, critics will point out, and rightly so, that the aforementioned evidence is insufficient, given the lower quality of the evidence compared to HF or rTMS. We thus believe that properly powered RCTs with adequate blinding are therefore needed, which could even take the form of an eventual home-based trial.

As a community of healthcare providers and scientists, we believe that we should always strive for innovations allowing maximal accessibility to novel treatments on behalf of our patients. We believe that a form of 'accessibility-optimized' LF-rTMS protocol could eventually offer comparable convenience and cost to medications, while preserving the efficacy and tolerability of the technique. This would help make rTMS more accessible to the population worldwide, creating a pathway toward meaningful reductions in the overall prevalence of depression and anxiety in the

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general population, beyond what has been achieved via conventional therapies to date.

## Declaration of competing interest

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