Repetitive transcranial magnetic stimulation for depression The non-inferiority extrapolation

Ali Amad, Florian Naudet, Thomas Fovet

"Repetitive transcranial magnetic stimulation for depression: *the non-inferiority extrapolation*"

Ali Amad M.D, PhD[1, 2], Florian Naudet M.D, PhD[3], Thomas Fovet M.D, PhD[1]

1. Univ. Lille, CNRS UMR 9193-PsyCHIC-SCALab, & CHU Lille, Department of Psychiatry, F-59000 Lille, France

2. Department of Neuroimaging, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8AF, UK

3. INSERM Centre d'Investigation Clinique 1414, Centre Hospitalier Universitaire de Rennes, Rennes, France

CORRESPONDENCE

Ali Amad

Hôpital Fontan, CHU de Lille, F-59037, Lille cedex, France

Email: ali.amad@chru-lille.fr

Tel: + 33 3 20 44 42 15 **Fax:** +33 3 20 44 62 65

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Over the last 20 years, repetitive transcranial magnetic stimulation (rTMS) has been intensively developed as an antidepressant treatment. The conventional rTMS protocol for depression corresponds to a high-frequency (10 Hz) protocol delivered to the left dorsolateral prefrontal cortex (HF-rTMS). It requires 37.5-minute daily sessions during 4 to 6 weeks. As long session and protocol lengths restrict rTMS treatment capacity, two randomised non-inferiority trials about the effectiveness of accelerated procedures in treatment resistant depression (TRD) were published in high-ranking journals this year (Blumberger et al., 2018; Fitzgerald et al., 2018) .

To assess the efficacy of intensive rTMS versus standard HF-rTMS, Fitzgerald and colleagues (Fitzgerald et al., 2018) conducted a randomised trial involving 115 outpatients with TRD who received either intensive rTMS (i.e., rTMS delivered as 3 sessions/day over 3 days in week 1, 3 sessions/day over 2 days in week 2 and 3 sessions on a single day in week 3) (n = 58) or standard HF-rTMS (n = 57). They concluded to non-inferiority regarding remission rates, response rates, and reduction in depression scores. On the other hand, Blumberger and colleagues (Blumberger et al., 2018) recently published the results of a randomised non-inferiority trial about the effectiveness of theta burst (iTBS) TMS, that can be delivered in 3 minutes, versus HF-rTMS, in patients with TRD. By comparing two groups of nearly 200 patients for each technique, they showed that iTBS was non-inferior to HF-rTMS.

We believe that the choice of a non-inferiority design in the two trials described above deserve major comment especially because of the potential consequences of these studies for clinical practice. Indeed, despite HF-rTMS is often considered as an effective treatment for major depressive disorder (MDD) or for TRD, many trials resulted in "*negative*" findings, particularly when basic methodological prerequisites are respected (for example, when the primary outcome and the intention-to-treat analyses are considered). *In fact, the supposed efficacy of HF-rTMS for MDD or TRD is based on several meta-analyses (e.g* (Brunoni et al., 2017)*) that included about fifty small sample size randomized controlled trials (RCTs) (median number of subjects per study = 32.5, [interquartile range 24-57.3]). Yet, three of the four largest studies failed to show the superiority of active versus sham HF-rTMS in patients with MDD or TRD (see* ***Table 1****). In these 4 studies, the risk of bias was rated as low. This assessment was performed independently in a blind standardized manner by two reviewers (AA and TF) by using the Cochrane Collaboration tool for assessing risk of bias.*

First, O'Reardon et al. failed to show any statistical differences on the primary outcome of a study including 301 participants (positive results were only observed in secondary analyses) (O'Reardon et al., 2007). In a second trial (n=190), the primary efficacy analysis revealed a significant effect of treatment on the proportion of remitters (George et al., 2010). Yesavage et al. recently published a RCT of 164 US veterans with TRD and failed to show any difference in remission rates between the active and sham treatments (Yesavage et al., 2018). In a last study investigating the

efficacy of rTMS as an augmentative treatment for MDD (n=127), no difference was found in the responder rates between the active and the sham treatment groups (Herwig et al., 2007).

These non-significant results should not be taken as strict evidence for null hypothesis (i.e. no difference between active versus sham HF-rTMS) but they undoubtedly indicate that more research is needed before asserting that HF-rTMS is an effective treatment for MDD or TRD. We therefore want to highlight that, in the Fitzgerald or Blumberger et al.'s studies, it is far from certain that HF-rTMS would have been superior to sham. In fact, two options are possible: 1/ accelerated procedures are "equally effective" as HF-rTMS or 2/ both treatments are "equally ineffective". Without any placebo control group, there is currently no sufficient evidence to support one of these two options.

In this context, we are convinced that caution is needed before adopting "accelerated" rTMS procedures as a new standard treatment for MDD and especially for TRD in clinical practice. *Future RCTs should include a placebo arm in large samples to definitely validate the effect of rTMS in MDD and TRD.*

Contributors

AA, FN and TF reviewed the literature and all authors participated in the writing and revision of the successive drafts of the manuscript and approved the final version.

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Conflict of interests

In the past 3 years, AA has relationships (travel/accommodation expenses covered/reimbursed) with Actelion, Otsuka, Astrazeneca. FN and TF have no conflict of interest to disclose in the past 3 years.

	Clinical characteristics in the patients included in the RCT	*Primary outcomes*	*Bias risk assessment**	*Results (standard / modified intention-to-treat analyses)*
O'Reardon et al, 2007	MDD and TRD	Symptom score change as assessed at week 4 with the MADRS	LR/UC/LR/LR/LR/LR/LR	p = 0.057 No significant statistical differences on the primary outcome No other statistical details
George et al, 2010	MDD and TRD	Remission rate (HAM-D score of 3 or less or 2 consecutive HAM-D scores less than 10)	LR/UC/LR/LR/LR/LR/LR	OR = 4.2; 95% CI 1.32-13.24; P = 0.02
Yesavage et al, 2018	TRD	Remission rate (Hamilton Rating Scale for Depression score ⩽ 10)	LR/LR/LR/LR/LR/LR/LR	OR = 1.16; 95% CI 0.59-2.26; P = 0.67
Herwig et al, 2007	MDD and TRD	Response rate (improvement in scores on at least two of the three rating scales by at least 50% after 3 weeks of rTMS)	LR/UC/LR/LR/LR/LR/LR	OR = 1.0; 95% CI 0.5–2.2; P = 0.962

Table 1. Characteristics of the 4 largest studies comparing active versus sham high-frequency repetitive transcranial magnetic stimulation in patients with major depressive disorder (MDD) or treatment resistant depression (TRD).

**RCTs were assessed for methodological quality by using the Cochrane Collaboration tool for assessing risk of bias (https://methods.cochrane.org/bias/resources/cochrane-risk-bias-tool) . The different biases assessed were: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective reporting and 7) other bias. Bias risks were described as "high risk" (HR), "unclear risk" (UR), "low risk" (LR) and "not applicable" (NA).*