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Title Transcranial magnetic stimulation (rTMS) in the treatment of adult treatment-resistant depression

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Aim

The aim of the assessment was to:

1. assess the efficacy and safety of conventional rTMS as adjuvant therapy to the standard therapeutic strategy for treatment-resistant depression during two different treatment phases: acute phase (course of treatment) and consolidation phase (maintenance sessions);
2. compare the new therapeutic strategy including rTMS (alongside medication and psychotherapy) to the two current conventional strategies for treatment-resistant depression: pharmacological optimisation plus psychotherapy in most cases, or use of electroconvulsive therapy in specific cases;
3. compare the organisational impact of the new therapeutic strategy with rTMS to the current conventional strategies.

Conclusions

In view of all the data compiled (meta-analyses with sensitivity analyses, consultations of experts, stakeholders and patient associations):

- for efficacy, the data from the meta-analysis suggest that, in the acute phase of depression, rTMS according to the conventional HF-G protocol (high-frequency stimuli targeting the left dorsolateral prefrontal cortex) has no effect size or a small effect size but with no significant clinical translation;
- for safety, the data from the literature and the working group's opinion suggest that the technology is relatively well tolerated and has minor side-effects;
- for the role in the therapeutic strategy, it is difficult to rank rTMS due to the lack of robust comparative data or its inferior efficacy in relation to current conventional strategies;
- the overall organisational impact is not in favour of the new therapeutic strategy including rTMS compared to the current conventional strategies for cases of treatment-resistant depression (medication alone plus psychotherapy).

Despite a reassuring safety profile, the selected data associated with rTMS (conventional HF-G protocol) provide no evidence of a favourable clinical impact (no pertinent clinical added value compared to a sham procedure, no determination of its role in relation to the current conventional pharmacological optimisation strategy, unacceptable alternative to electroconvulsive therapy). The organisational impact associated with the use of rTMS as adjuvant therapy compared to pharmacological optimisation alone is unfavourable (i.e. the most common current strategy).

Results:

I/ Regarding the efficacy of rTMS (conventional) compared to a sham procedure (8 studies, 475 patients)
In the acute phase of depression, the results of the meta-analyses comparing both treatments, rTMS (conducted according to a conventional protocol) and a sham procedure, show that there is no formal evidence of the specific efficacy of rTMS compared to the sham procedure.
The effect size observed on the reduction in depression severity is not statistically significant; the same applies for remission and clinical response. Moreover, in terms of clinical significance, the effect size observed is small; it is – 2.02 points; 95% CI [-4.93; +0.88]; p=0.17 on an $HDRS_{17}$ scale ranging from 0 to 52 points; therefore, these values have no pertinent clinical translation.
Note that a non-specific effect (i.e. not linked with cortical magnetic stimulation) is however likely as it was observed in the sham arm. This non-specific effect was interpreted by some experts of the working group and in the international literature as being

linked with the associated psychological support and daily social interaction with the care team during the weeks of treatment. The working group agrees to consider that, in terms of clinical relevance, a reduction in the severity of depression of an effect size of Δ ≤ 2 points on the $HDRS_{17}$ rating scale can be deemed to be *"small"*, *"not clinically significant"* or *"non-detectable"*. In keeping with many international studies, the relevance threshold previously set by HAS was more than 3 points.
The data available to date do not suggest any interaction of rTMS with pharmacological treatments left in place (no heterogeneity in subgroup analysis with non-significant interaction test), or any added value significantly attributable to neuronavigation tools (standardised difference of -0.13 SD; 95% CI [-0.48; + 0.22] p=0.47).
In addition, an albeit slight overestimation of the observed effect of rTMS (conventional protocol) is suggested by the exploratory analyses conducted secondarily. It would seem to be linked with the findings of some monocentric studies with a high risk of bias and small sample sizes. The efficacy of rTMS on psychotropic drug reduction, satisfaction, quality of life or functional remission in patients was not reported in the selected studies.
Regarding the efficacy of rTMS (conventional protocol) in the consolidation phase, based on the data published to date, it is not possible to assess the added value, with respect to the standard therapeutic strategy, of a relapse prevention plan with rTMS maintenance sessions set up over a period of 6 months and more.

II/ Ranking of the new strategy with rTMS with respect to current conventional therapeutic strategies

It was not possible to determine the rank and therapeutic added value of adding rTMS (conventional protocol) with respect to the pharmacological optimisation (current conventional treatment), due to a lack of identified robust comparative data (0 studies).
The studies comparing rTMS to electroconvulsive therapy (other current conventional treatment) suggest an inferior efficacy of rTMS in these (sometimes more severe) patients presenting with an initial indication of electroconvulsive therapy. In keeping with the data from the literature review, the expert group was of the view that rTMS is not an acceptable alternative to electroconvulsive therapy (2 studies, 86 patients).

III/ Safety of conventional rTMS

The intrinsic safety of a conventional protocol conducted in accordance with any contraindications[1] and the framework of the recommended technical parameters does not appear to give rise to any concerns in view of the data available. These data suggest that a conventional rTMS protocol is a relatively well-tolerated procedure with minor side-effects. The proportion of patients deciding to discontinue their treatments early is in the region of 5 to 15% in the studies reviewed. The reasons reported stemmed more from personal constraints than physical discomfort associated with the treatment. According to the experts of the working group, the safety profile of the procedure is satisfactory and the adverse events observed would not appear to be a frequent reason for discontinuing treatment (pain at stimulation site, post-procedure headache).

IV/ Organisational impact of conventional rTMS as adjuvant therapy to the current conventional strategy in treatment-resistant depression

The benefit-risk balance of this procedure in the indication of acute-phase treatment-resistant depression is assessed with regard to the new organisational constraints required in relation to the current conventional therapeutic strategy (pharmacological optimisation + psychotherapy).
The international literature review (revealing debates within the specialism, in which some French teams are involved), and the opinion of the consulting group experts and of the stakeholders consulted have shown that the need to conduct daily sessions over 4 to 6 weeks gives rise to genuine organisational constraints in the context of a conventional protocol.
According to the patient associations and the data provided by healthcare professionals, they appear not to be in favour of the health technology in its current form (1 daily session over several weeks) in terms of additional impact:

- on the care process (burden of equipment and installation, preparation to administer the new treatment),
- on the capabilities and expertise required of "actors" such as patients, patients' families and healthcare professionals (technical complexity, care team face-to-face time, and financial impact).
- on society as a whole, the target population being very large epidemiologically (if looking at the relatively broad eligibility criteria in the studies), issues of equity and of difficulty accessing outpatient care in specialist centres effectively depend on the place of residence or the level of autonomy of these patients who tend to be vulnerable. Similarly, the social, occupational and financial impacts of this new strategy on patients and their friends and family also need to be taken into account (daily transportation required). Additional hospital stays may be needed to make it possible for some fragile patients to complete their course of treatment.

Methods:

Based on recent meta-analyses, HAS identified randomised comparative studies up to November 2021 with a systematic review. To conduct its own meta-analyses, four new randomised studies, not included in the many previous systematic reviews and older

[1] In particular, presence of a cochlear or metal/electronic implant near the stimulation site, current pregnancy, or documented epileptic disease

studies, but eligible based on explicit criteria were selected (add-on rTMS, 15 to 30 sessions, 1 daily session, recommended technical efficacy and safety parameters in 2021). This quantitative analysis also included non-reporting data collected from the corresponding authors of certain papers. To ensure the methodological homogeneity and clinical applicability of the findings, the many randomised studies assessing former protocols no longer in line with recommendations and current practice were excluded from the analyses (frequency < 10hz, intensity < 100% of the motor threshold, stimuli per session < 1000/1200, train > 5 seconds). Secondary analyses of an exploratory nature were conducted to study the robustness of the main findings and identify the predictive factors of response in the acute phase of depression (risk of study bias, optimal type of sham procedure or not, number of sessions administered, potentiation effect of rTMS as add-on treatment versus as strict monotherapy, added value of neuronavigation or not). These analyses were discussed with a multidisciplinary expert group and were reviewed by professional and patient stakeholders.

Recommendations

HAS has not recommended that National Health Insurance provide financial cover for conventional rTMS and/or new protocols in so-called rapid sessions (e.g. theta burst). Conclusions were reviewed by the Medical Device and Health Technology Evaluation Committee Santé (CNEDiMTS), HAS's specialised appraisal committee, and adopted by the member of the HAS board.

Further research

Feedback from healthcare professionals has reported currently unvalidated clinical uses of rTMS (non-treatment-resistant patients, retention of maintenance sessions over several years, new rapid protocols as first-line treatment, equipment variants subject to very little assessment, sharing of equipment available for other indications that have not been assessed and recommended by professionals). It is necessary to compile robust data in the context of clinical trials making it possible to compare the different stimulation protocols to the current conventional strategy in order to optimise current stimulation protocols and make the best possible selection of patients actually likely to respond to rTMS in the indication of treatment-resistant depression. It should be noted in this regard that there are a large number of ongoing clinical research studies trialling new so-called rapid protocols (e.g. theta burst) or aimed at optimising the management of cases of treatment-resistant depression particularly using functional imaging and other technical advanced electrophysiological investigations. These easier-to-implement protocols, which are under development, could be the subject of a subsequent HAS assessment, following the publication of new data.

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