Technoleg Iechyd Cymru
Health Technology Wales

HEALTH TECHNOLOGY WALES (HTW) GUIDANCE 035 (November 2021)

Transcranial magnetic stimulation to treat people with treatment-resistant major depression

HTW Guidance:

The use of repetitive transcranial magnetic stimulation (rTMS) for the treatment of treatment-resistant major depression is partially supported by the evidence.

The use of rTMS is well tolerated, leads to a medium-term (up to three months) reduction in depression score, and improves response and remission rates compared with sham treatment.

De novo economic modelling is subject to considerable uncertainty. Further research is therefore recommended to better determine the case for cost effectiveness, to establish the long-term efficacy of rTMS including potential maintenance therapy, and to determine the appropriate placement of rTMS in the NHS Wales treatment pathway.

Why did Health Technology Wales (HTW) appraise this topic?

Major depression can have a debilitating impact on a person's life and wellbeing. Symptoms vary but commonly include feelings of hopelessness, low interest or pleasure in activities and reduced self-worth. Depression can affect a person's ability to perform daily tasks or take part in work and social life, as well as impact negatively on relationships with family and friends. Treatment options can include antidepressant medication and talking therapies. However, in some cases antidepressants have limited or no effect on the depression; this is known as treatment-resistant or difficult to treat depression. In some severe cases, electroconvulsive therapy (ECT) is offered, but this is rarely used in Wales. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neurostimulation technique that does not require anaesthesia and can be done in an outpatient setting, with little to no recovery period. It is usually considered for treatment resistant depression, or where antidepressants are unsuitable or poorly tolerated.

The status of HTW guidance is that NHS Wales should adopt this guidance or justify why it has not been followed. HTW will evaluate the impact of its guidance.

Evidence Summary

Refer to Evidence Appraisal Report 035 (EAR035) for a full report of the evidence supporting this Guidance.

Health Technology Wales undertook an evidence review to address the following question: What is the clinical and cost effectiveness of repetitive transcranial magnetic stimulation in people with major depressive disorder that has not responded to antidepressants, when compared standard care?

We identified a recent health technology assessment (HTA) by Ontario Health (2021) that reported evidence on the effectiveness of rTMS for treatment resistant depression, including major depression and bipolar disorder. The Ontario Health report included a meta-analysis of different rTMS modalities versus sham treatment, and systematic reviews comparing rTMS with electroconvulsive therapy.

We adapted and reanalysed the evidence on major depression from the Ontario Health (2021) review for 'standard' rTMS modalities. In total, 29 primary studies were included in the analysis: 20 studies evaluated high-frequency left dorsolateral prefrontal cortex (DLPFC) rTMS, eight evaluated low-frequency right DLPFC rTMS and six evaluated bilateral rTMS. Acute treatment phases in the studies varied between two and six weeks. Some studies reported a follow-up period after the acute treatment phase; this varied between two and 12 weeks.

Compared to sham treatment, high frequency left DLFPC rTMS lowered depression scores and had better response and remission rates, both at the end of the acute treatment phase and at follow-up. There was no difference between low frequency right DLFPC rTMS at end of treatment or follow-up. Bilateral rTMS showed improved reduction in depression score and better response and relapse rates in the follow-up phase, but not during the acute treatment period.

Four systematic reviews were identified comparing rTMS to ECT; all the studies within these reviews evaluated high frequency rTMS. Overall, ECT showed a better reduction in overall depression score than rTMS, but there was no difference in response and remission rates.

Two economic studies were identified in the literature review. A cost-utility analysis conducted as part of the HTA by Ontario Health (2021) found rTMS to be cost effective in comparison to pharmacotherapy and dominant in comparison to ECT (more effective and less costly). A cost-utility analysis by Teng et al. (2021) compared treatment sequences based on combinations of antidepressants (A), rTMS (T) and ECT (E). The authors compared strategies against the least costly strategy (AAAT) and concluded that the most cost-effective strategies were AAAE and AATE. We used the reported results in a fully incremental analysis in which all strategies were compared against each other. The results showed AAAE and AATE to be the only non-dominated strategies. AATE was found to be more costly and more effective than AAAE with a resulting ICER of $46,222 per QALY (£33,742 per QALY).

HTW developed an economic model to estimate the cost-effectiveness of rTMS in comparison to ECT and pharmacotherapy for treatment-resistant major depression. The modelling suggests that rTMS was less costly but also less effective than ECT. The resulting ICER of £15,664 per QALY indicates that rTMS was not cost effective compared with ECT. Note the interpretation of the ICER changes in scenarios where an intervention is less effective and less costly, with values above the £20,000 per QALY threshold considered cost effective because higher values indicate greater savings for each QALY lost. In comparison to pharmacotherapy, rTMS was found to be more effective but more costly. The resulting ICER of £28,214 per QALY indicates that rTMS was not cost effective compared to pharmacotherapy. Sensitivity analyses show the findings for rTMS in comparison to pharmacotherapy to be robust but that there is considerable uncertainty in the analysis comparing rTMS and ECT. In addition, there are elements of uncertainty beyond the

scope of the economic analysis to consider, such as uncertainty around the optimal comparator and where rTMS would be placed in the therapeutic pathway.

The appropriate mechanism for patient engagement was determined and the patient perspective was considered where possible.

Appraisal Panel considerations

- The Appraisal Panel heard patient evidence highlighting the impact that depression can have on patient and family lives with feelings of hopelessness, losing the ability to perform daily tasks or take part in society, and breakdown of family relationships. It was explained that for some people, therapeutic options such as antidepressants and ECT can have little impact or a diminishing effect over time. There is a negative public perception and stigma around the use of ECT, which can influence a person's decision on whether or not to have this treatment. Conversely, patient evidence suggested that rTMS is well received by patients and their families and is associated with improvements in mental health and quality of life, a lower incidence of side effects, and less social stigma.
- The Appraisal Panel also heard from clinical experts about the potential benefits of adding rTMS to the current treatment pathway for people with major depression. The Appraisal Panel were informed that rTMS would be expected to be offered much earlier in the clinical pathway than ECT and that currently ECT is rarely used in Wales, except in the cases of most severe depression. In this regard, it was explained that rTMS may therefore offer an additional treatment for patients who are not responding to pharmacotherapy and, compared to ECT may be more acceptable to patients and more easily delivered in an outpatient setting with quicker recovery. It was also explained, however, that there are significant practical challenges surrounding the implementation of rTMS as well as uncertainty about the long-term benefits of this treatment and its ability to avoid the need for other interventions in the future.
- The Panel were informed of an ongoing three-month pilot within Hywel Dda University Health Board, which is evaluating the use of rTMS in a small cohort of patients. The expert involved in the pilot reported on the organisational challenges faced in implementing the pilot, including the acquisition of additional space and resource requirements. The estimated completion date for the pilot is March 2022.
- The Appraisal Panel considered the clinical evidence and concluded that rTMS is a safe and clinically effective treatment for treatment-resistant major depression, particularly in the short to medium term. However, the Panel acknowledged the uncertainty about the long-term benefits of rTMS and its potential use as maintenance treatment in patients with severe depression.
- The Appraisal Panel considered the economic evidence for rTMS and discussed the limitations that exist with the published evidence and the HTW health economic modelling which are largely driven by the clinical uncertainties around the optimal role of rTMS in the care pathway and th e most appropriate comparator.
- The Appraisal Panel discussed the differing conclusions of the HTW economic analysis and the economic analysis conducted as part of the HTA by Ontario Health (2021). The HTW health economist explained that the contrasting results were driven by three main differences between the analyses. Firstly, different costs were applied in the HTW model to reflect the UK NHS context. Secondly, the Ontario Health model included quality of life values reflecting the acute phase of treatment with a notable quality of life decrement for people receiving ECT. This was not included in the HTW analysis as it had been based on assumptions rather than direct evidence. Thirdly, there were differences in key clinical inputs, most notably the probability of relapse and remission in people treated with ECT.

- The Panel concluded that while the evidence of clinical benefit would support adoption, there is considerable uncertainty around the economic impact of rTMS, which requires further clarification before adoption can be fully supported.
- The Panel therefore recommends that further research be undertaken to establish the long-term efficacy of rTMS including: potential maintenance therapy; to determine the appropriate placement of rTMS in the NHS Wales treatment pathway; and to establish the likely economic impact of rTMS in managing patients with severe and treatment-resistant depression.

Responsibilities for consideration of this Guidance

Health Technology Wales (HTW) was established by Ministerial recommendation[1,2] to support a strategic, national approach to the identification, appraisal and adoption of non-medicine health technologies into health and care settings. The HTW Appraisal Panel comprises senior representation from all Welsh boards with delegated authority to produce guidance 'from NHS Wales, for NHS Wales'. The status of HTW guidance is 'adopt or justify'. There is an expectation from Welsh Government that HTW guidance is implemented with adoption regularly audited by HTW.[3]

The guidance in this document is intended to assist Welsh care system decision makers to make evidence-informed decisions when determining the place of health technologies and thereby improve the quality of care services.

The content of this HTW guidance was based upon the evidence and factors available at the time of publication. An international evidence base was reviewed and external topic experts and HTW committee members consulted to contextualise available evidence to Wales. Readers are asked to consider the generalisability of the evidence reviewed to NHS Wales and that new trials and technologies may have emerged since first publication and the evidence presented may no longer be current. It is acknowledged that evidence constitutes only one of the sources needed for decision making and planning.

This guidance does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgment in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

No part of this guidance may be used without the whole of the guidance being quoted in full. This guidance represents the view of HTW at the date noted. HTW guidance is not routinely updated. It may, however, be considered for review if requested by stakeholders, based upon the availability of new published evidence which is likely to materially change the guidance given.

Standard operating procedures outlining HTW's evidence review methods and framework for producing its guidance are available from the HTW website.

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Declarations of interest were sought from all reviewers. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control and the views expressed are those of Health Technology Wales.

Chair, Health Technology Wales Appraisal Panel

1. National Assembly for Wales, Health and Social Care Committee. Access to medical technologies in Wales. December 2014.
2. Response to Recommendations from the Health & Social Care Committee: Inquiry into Access to Medical Technologies in Wales. February 2015.
3. Gething, V. Letter to all Health Board Chairs re Funding for Sacral Nerve Stimulation in Wales. VG_01655_17. September 2017.