Recommendation

The Danish Health Technology Council's Recommendation Regarding

Repetitive Transcranial Magnetic Stimulation for the Treatment of Patients with Treatment-Resistant Moderate to Severe Unipolar Depression

The Danish Health Technology Council's recommendation:

The Danish Health Technology Council recommends that repetitive Transcranial Magnetic Stimulation (rTMS) is offered as an adjunct treatment to adult patients with treatment-resistant moderate to severe unipolar depression when standard treatment has not been sufficient. Depression is defined as treatment-resistant when a satisfactory effect has not been achieved after trying at least two treatment courses with antidepressant medication from different pharmacological classes.

About the Recommendation:

The recommendation is based on the premise that, for the majority of the patient population, rTMS will function as an adjunct treatment to standard pharmacological treatment. For a smaller group of patients, rTMS may be a viable alternative to changing standard pharmacological treatment or initiating electroconvulsive therapy (ECT).

In terms of clinical effectiveness and safety, rTMS shows a clinically meaningful difference in effect compared to sham-rTMS concerning both response and remission rates. Furthermore, the evidence indicates that rTMS has a milder side-effect profile than ECT and pharmacological treatment, which can improve treatment satisfaction.

Health economic analysis suggestss that rTMS, when used alongside standard treatments, is cost-effective compared to standard treatment alone, with an incremental cost-effectiveness ratio (ICER) of approximately 200,000 DKK per quality-adjusted life year (QALY). Furthermore, advancements in stimulation protocols may lower treatment costs, as seen in the Central Denmark Region, where Intermittent Theta Burst Stimulation (iTBS) is being adopted over high-frequency rTMS (HF-rTMS). The introduction of rTMS in regional healthcare systems is expected to reduce medication usage and, for some patients, decrease reliance on ECT over time. The Council recommends ongoing

monitoring to assess clinical, patient-reported, and economic benefits, given the existing uncertainties about the long-term effects of rTMS.

Implementing rTMS on a broad scale is anticipated to require expanded treatment capacity and comprehensive staff training to ensure safe delivery, maximize patient outcomes, and guarantee equal access. Consideration should also be given to involving other healthcare professionals who can administer the treatment to minimize resource demands.

The Council considers the evidence for clinical effectiveness and safety to be generally reliable.

The Council emphasizes the need for clear clinical guidelines specifying the appropriate indications for rTMS, as the treatment is not suitable for patients with acute psychotic symptoms, urgent suicidal ideation, or other severe contraindications. Additionally, uncertainty remains regarding withdrawal and maintenance treatment protocols, which should be detailed in future guidelines. The Council is particularly attentive to the scope of any required withdrawal process.

The Council also highlights the risk of indication drift and stresses the importance of offering treatment only to appropriate patient groups. This can be ensured through systematic patient registration and monitoring using a national database.

Overall, the Council believes that rTMS for patients with treatment-resistant moderate to severe unipolar depression, when clinically indicated, provides value relative to the economic costs of implementation.

About the technology	Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive brain stimulation method that uses magnetic impulses to modulate brain activity in specific areas. Its primary core effect is to improve symptoms in treatment-resistant unipolar depression. rTMS has been compared to sham-rTMS, changes in pharmacological treatment, and ECT in the evaluation.
Patient populationen	The recommendation concerns adult patients (over 18 years) with moderate to severe treatment-resistant unipolar depression who have not achieved a satisfactory effect from at least two different antidepressants. Patients with acute psychotic symptoms, urgent suicidal thoughts, or serious somatic conditions are excluded.
Scope of Application	The recommendation is targeted the psychiatric sector, particularly at the regional level, where the treatment of treatment-resistant depression is managed. It is relevant for specialized psychiatric units and clinics equipped with neurostimulation capacity.
Implementation	Implementing rTMS will require developing treatment capacity and training healthcare personnel. Since the technology demands specialized equipment and expertise, regions must ensure staff are proficient in treatment protocols and patient safety. To optimize resources, the involvement of other professional groups in administering treatment should be considered. The establishment of new treatment facilities or the expansion of existing neurostimulation clinics may be necessary to ensure equal access across regions. The Council encourages Danish Regions to consider alternative implementation strategies to ensure broad geographic availability and avoid potential overburdening of hospital-based psychiatric services, which currently handle the treatment.
Procurement	rTMS treatment requires the purchase of specialized medical equipment, which only a few manufacturers supply. It may be advantageous to prepare a joint national procurement to secure competitive prices and consistent quality across regions. When selecting a supplier, compatibility with existing IT systems, operational stability, and the need for support and maintenance should be considered. The regions are advised to coordinate the implementation to achieve economies of scale and ensure unified implementation.

Summary of the Evalution Report

About the Evaluation	The Danish Health Technology Council's recommendation is informed by an analysis report on rTMS for treating patients with treatment-resistant moderate to severe unipolar depression. The analysis addresses the central question: Should rTMS be offered as an adjunct treatment for adult patients with treatment-resistant unipolar depression?
Clinical Effect and Safety	The purpose of the Clinical Effectiveness and Safety perspective is to evaluate whether there are differences in effectiveness and safety between rTMS and the selected comparators (sham-rTMS, changes in pharmacological treatment, and ECT) for treating unipolar treatment-resistant depression without psychotic or manic symptoms. Thirty-four relevant studies were identified. No comparative studies were found for the outcomes of quality of life and recurrence rate, and the results for these outcomes are based on health technology assessments (HTAs) from Health Technology Wales and Ontario Health. Meta-analyses demonstrated a clinically relevant difference in effect in favor of rTMS compared to sham-rTMS in terms of both response and remission rates, with the quality of evidence rated as moderate. rTMS rarely causes serious side effects, although more instances of headache and discomfort at the site of stimulation were reported compared to sham-rTMS. Compared to changes in pharmacological treatment, rTMS showed a higher remission rate, but the evidence is weak. No systematic difference in effectiveness was found between rTMS and ECT, but ECT is associated with more cognitive side effects. The expert panel assessed that rTMS generally has a milder side effect profile.
Patient Perspective	The patient perspective is based on three sources: published literature, expert statements from the expert panel, and a 2024 survey from the Depression Association. The purpose is to explore patient preferences for treatment and the factors influencing their choices. No clear preferences were identified in the literature, but factors such as previous experiences, expected effectiveness, concerns about side effects, knowledge about the treatment, reputation, and practical considerations like transportation play a role. Patients generally report a positive experience with rTMS, with many experiencing symptom improvement, although long travel times for treatment can be challenging. Side effects from rTMS are milder than those from pharmacological treatments and ECT, influencing treatment preferences. The expert panel believes that rTMS can increase treatment satisfaction and reduce the stigma associated with treatment-resistant depression.
Organizational Implicaitons	The data for Organizational Implications consist of scientific literature, expert statements from the expert panel, and gray literature, including regional treatment descriptions and guidelines. The expert panel analyzed

	average treatment courses with and without rTMS. ECT has long been the only neurostimulation treatment for patients with moderate to severe depression, particularly for those with urgent suicidal thoughts or treatment-resistant depression. For this latter group, alternative treatments have been lacking, which rTMS can now address. As the demand for alternative treatments rises alongside the growing prevalence of depression, a positive recommendation for rTMS will require more TMS clinics and machines in Denmark. There will be organizational requirements for implementing and managing rTMS treatments. The expert panel highlights the need for increased knowledge about neurostimulation across the healthcare system. Additionally, they note that the Danish Psychiatric Association is currently developing national guidelines for ECT and neurostimulation.
Health Economics	The health economic perspective indicates that rTMS, as an adjunct to standard treatment, is cost-effective, with an ICER of approximately 200,000 DKK/QALY. The cost-effectiveness analysis (CEA) suggests that patients could gain up to 17 weeks of remission over three years when receiving rTMS in addition to standard treatment. The expert panel considers remission the most valuable outcome for patients. The budget impact analysis (BIA) estimates that regions will incur costs of around 45 million DKK over five years for the implementation of rTMS. However, long-term savings are expected, such as reduced use of ECT. A positive recommendation for rTMS will result in increased demand on healthcare staff. The expert panel believes that the health benefits from rTMS justify the resource demands and can lead to fewer hospitalizations, reduced medication use, and a decrease in ECT treatments. However, the process of tapering off and maintaining treatment has not been fully evaluated in the scientific literature, creating uncertainty about the long-term effects. The expert panel believes that sustained remission significantly improves patient quality of life, although the lack of data affects the economic outcomes.

About the Danish Health Technology Council's Recommendation

The Danish Health Technology Council's recommendation is directed towards the regions to assist in decision-making regarding the use of a given health technology or the organization of a treatment area. The evaluation report provides a comprehensive review of the following perspectives: 1) clinical effectiveness and safety, 2) patient perspective, 3) organizational implications, and 4) health economics.

This recommendation is based on the Danish Health Technology Council's evaluation report concerning rTMS for the treatment of patients with treatment-resistant moderate to severe unipolar depression. The report was developed by the expert panel and the secretariat in collaboration. The evaluation report was prepared following the evaluation design as well as the Danish Health Technology Council's process manual and methodology guide. The expert panel's terms of reference,

along with other relevant documents, are available on the Danish Health Technology Council's website.

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