Repetitive transcranial magnetic stimulation

for adults with treatment resistant major depressive disorder

Technology Guidance from the MOH Medical Technology Advisory Committee

Guidance Recommendations

The Ministry of Health's Medical Technology Advisory Committee has recommended subsidy for:

- ✓ A single course of repetitive transcranial magnetic stimulation (rTMS) therapy of up to a maximum of 24 sessions as initial treatment for adults (aged 18 years or more) with a diagnosis of treatment resistant major depressive disorder (TRD):
  - Who failed to achieve satisfactory improvement despite adequate trialling of at least two different classes of antidepressants, unless these are contraindicated; AND
  - Who have undertaken psychological therapy when appropriate and feasible; AND
  - Who have not received treatment with rTMS previously.
- ✓ A single course of rTMS retreatment of up to a maximum of 15 sessions for adults with TRD:
  - Who have received initial treatment with rTMS and relapsed following remission or satisfactory clinical response, as assessed by a validated tool to measure the severity of major depressive disorder; AND
  - Retreatment should start no sooner than four months after the end of initial treatment.
- ✓ rTMS retreatment for patients with TRD who did not respond to rTMS initial treatment is not recommended.
- ✓ rTMS as maintenance treatment for patients with TRD is not recommended.

Subsidy status

Subsidies should apply to initial rTMS treatment and rTMS retreatment for adults with TRD, in line with stated recommendations.

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Factors considered to inform the recommendations for subsidy

Technology evaluation

1.1 The MOH Medical Technology Advisory Committee ("the Committee") considered the evidence presented for technology evaluation of rTMS in treatment of adults with treatment resistant major depressive disorder (TRD). The Agency for Care Effectiveness conducted the evaluation in consultation with senior clinicians in psychiatry.

1.2 The evidence was used to inform the Committee's deliberations around five core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Overall benefit of the technology to the patient and/or the system;
- Cost-effectiveness (value for money), which covers the incremental benefit and cost of the technology compared with existing alternatives;
- Estimated annual technology cost and the number of patients likely to benefit from the technology; and
- Organisational feasibility, which covers the potential impact of adopting the technology, especially barriers for diffusion.

1.3 Considerations such as ethical or social issues related to the adoption of the technology may also inform the Committee's deliberations.

Clinical need

2.1 The Committee noted that TRD is characterised by lack of satisfactory response to at least two adequate courses of antidepressants. Pharmacological treatment with antidepressants and psychological therapy remain the cornerstone of TRD management.

2.2 Currently, there is a lack of standardised antidepressant therapy recommended for TRD in Singapore. The available treatment strategies for TRD as third-line therapy include: optimisation of antidepressant dose; switching to similar or different class of antidepressant; combination of different classes of antidepressant; augmentation by adding non-antidepressants; and in some cases somatic therapies, such as an electroconvulsive therapy (ECT).

2.3 The Committee further noted that the likelihood of treatment success decreases after multiple trials with subsequent courses of antidepressants. In the target population for this evaluation, ECT is of limited use as it is mostly used in patients with psychotic major depressive disorder.

Overall benefit of technology

3.1 The Committee noted that rTMS is a somatic, non-invasive neurostimulation and neuromodulation treatment technique. rTMS is often used in outpatient setting as adjunctive therapy with antidepressants and psychological therapy. However, in patients who are unable to tolerate or are contraindicated to pharmacotherapy, rTMS can be administered as monotherapy. It can be used as initial treatment, retreatment, and maintenance treatment. The Committee noted that third-line antidepressant medication is the main comparator for rTMS in patients with TRD.

3.2 The Committee agreed that, as a non-invasive treatment, rTMS has an acceptable safety profile with headaches being the most common adverse event. Supportive evidence showed that rTMS showed similar safety outcomes to pharmacological treatments.

3.3 The Committee noted that rTMS combined with antidepressants was superior to sham combined with antidepressants in terms of clinical effectiveness. Based on a meta-analysis by Sehatzadeh et.al 2019 of controlled randomised trials (RCTs), rTMS combined with antidepressant was associated with a significant improvement in remission rates and depression scores compared with sham combined with antidepressants. The mean improvement in depression scores was considered clinically meaningful. No significant difference was observed for response rate, although the results numerically favoured rTMS combined with antidepressants.

3.3 The Committee noted that the evidence base for rTMS as retreatment is limited. Based on one single-arm open label study, most of the rTMS retreatment resulted in improved outcomes in patients. Despite this limitation, there is a clinical need for rTMS retreatment in patients who have relapsed following remission or satisfactory clinical response to the initial course of rTMS. The Committee noted that only a single course of rTMS retreatment was recommended by ACE's reference agency – the Medical Services Advisory Committee (MSAC) in Australia.

3.4 The Committee agreed that the current evidence base for rTMS as ongoing maintenance treatment for TRD is currently premature.

3.5 The Committee noted that key limitations of the clinical evidence of rTMS include variable study parameters, treatment protocols, definition of remission, level of treatment resistance, and use of rTMS in monotherapy or as adjunctive therapy, and the small sample size included in the studies.

Cost effectiveness

4.1 An in-house cost-effectiveness model compared initial rTMS combined with antidepressants with antidepressants alone for patients with TRD. The Committee noted that patients with TRD treated with rTMS experienced more QALYs but also incurred higher medical costs compared with patients treated with antidepressants alone.

4.2 In the base case analysis where only a single course of initial rTMS treatment was included, the incremental cost-effectiveness ratio (ICER) was less than $15,000 per QALY gained. A scenario analysis included one course of rTMS as initial and retreatment each, rTMS became less costly and more effective (i.e. dominant) compared with antidepressants alone.

4.3 The Committee noted that the cost-effectiveness results were sensitive to probability of losing remission after antidepressant and rTMS therapy, and the health utility of remission after acute treatment.

Estimated annual technology cost

5.1 The Committee noted that the budget impact for subsidising rTMS therapy is uncertain as the number of patients with TRD that is eligible for rTMS treatment may exceed the current utilisation due to capacity constraints of rTMS services in Singapore. Based on current rTMS services capacity, the annual cost to the government is estimated to be less than $0.5M. However, the demand for rTMS services is likely to increase with the introduction of subsidy, given there is likely more eligible patients currently not seeking treatment. If more specialist outpatient clinics (SOCs) choose to offer rTMS treatment post subsidy, the estimated annual budget can exceed $5M.

Organisational feasibility

6.1 The committee acknowledged the importance of the development and use of standard rTMS treatment protocol across all institutions. Institutions offering rTMS service need to collect patient characteristics and rTMS treatment outcomes in electronic database. Treatment outcomes such as response, remission, cognitive outcomes, and adverse events should be measured in a systematic way, collated, and recorded in individual patient care records. The prescribing clinicians should clearly define the type of rTMS treatment (i.e. initial treatment, retreatment, or maintenance treatment) for subsidy eligibility assessment. The institutions should capture rTMS treatment type and number of rTMS sessions centrally. Patient outcomes should be measured at regular intervals that are not limited to baseline and at the end of rTMS treatment.

6.2 The Committee noted that institutions providing rTMS services should ensure proper and continued training and accreditation of rTMS practitioners. A rTMS operator who is trained to manage seizures should always be present with the patient and have immediate access to appropriate equipment to manage seizures before the arrival of emergency response teams.

6.3 As with all new clinical services, institutions that would like to offer rTMS services need to apply for MOH's approval for re-designation of the Levels of Medical Capabilities (LMC), if applicable. Institutions may submit their applications and their standard protocols to MOH Hospital Services Division (HSD). Applications will be assessed based on consideration to alignment with national interests, available manpower, infrastructure, supporting services, and clinical governance frameworks.

Recommendation

7.1 Based on the evidence presented, the Committee recommended subsidy for a single course of rTMS therapy of up to a maximum of 24 sessions as initial treatment for adults (aged 18 years or more) with a diagnosis of TRD,

- who have failed to achieve satisfactory improvement despite adequate trialling of at least two different classes of antidepressants, unless these are contraindicated; AND
- who have undertaken psychological therapy when appropriate and feasible; AND
- who have not received treatment with rTMS previously.

7.2 Given the unmet clinical need, the Committee recommended subsidy for a single course of rTMS retreatment of up to a maximum of 15 sessions for adults with TRD

- who have received initial treatment with rTMS and relapsed following remission or satisfactory clinical response, as assessed by a validated tool to measure severity of major depressive disorder; AND
- Retreatment should start no sooner than four months after the end of initial treatment.