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Doxtator, Mandy HLTH:EX

From: Louie, Betty HLTH:EX
Sent: April 21, 2016 11:03 AM
To: Samra, Kevin HLTH:EX; Hart, Bob HLTH:EX
Subject: RE: rTMS 2016

Kevin,
I could not find any request for a new physician fee related to this.
Betty Louie
Manager, Physician Payment Schedule
Compensation Policy and Programs Branch, MoH
P.O. Box 9649 |Victoria BC V8W 9C4
Betty.Louie@gov.bc.ca| p 250 952-1706 | f 250 952-3133

From: Samra, Kevin HLTH:EX
Sent: Thursday, April 21, 2016 10:57 AM
To: Hart, Bob HLTH:EX; Louie, Betty HLTH:EX
Subject: RE: rTMS
Did you find any information about a repetitive transcranial magnetic stimulation for treatment resistant depression fee item request?

From: Hart, Bob HLTH:EX
Sent: Wednesday, April 6, 2016 2:55 PM
To: Louie, Betty HLTH:EX
Cc: Samra, Kevin HLTH:EX
Subject: FW: rTMS
Betty……have we received a request for the procedure in Kevin's note below….or are you aware of one in the pipe?
Thanks Betty.
Bob Hart
Director, MSP Payment Schedule
Compensation Policy and Programs
Health Sector Workforce Division
Ministry of Health 250-952-1204

From: Samra, Kevin HLTH:EX
Sent: Wednesday, April 06, 2016 2:48 PM
To: Hart, Bob HLTH:EX
Subject: rTMS
Hi Bob,
We are looking at repetitive transcranial magnetic stimulation for treatment resistant depression. I understand a fee item request was put forth for that at some point – do you know the status of that request?
Kevin Samra
Director, Health Technology Review
Partnerships and Innovation Division
Ministry of Health, 5th floor, 1515 Blanshard Street
PO Box 9637 STN PROV GOVT

Victoria, BC V8W 9P1
Tel: 250.952.2346 Fax: 250.952.2109

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TITLE: **Repetitive Transcranial Magnetic Stimulation for Depression: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines**

DATE: 06 October 2015

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Repetitive Transcranial Magnetic Stimulation

Health Technology Review

Business Case

Topic: Repetitive Transcranial Magnetic Stimulation for Major Depressive Disorder

Author: James Murtagh

Document Version and Date: FINAL 14Apr2016

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Repetitive Transcranial Magnetic Stimulation (rTMS)

HTAC Meeting

April 22, 2016

Background

- Clinical Condition
  - Major Depressive Disorder (MDD) - depressed mood and/or notably diminished pleasure in all or most activities, for most of the day, nearly every day for at least two weeks
  - Usually emerges in late adolescence or early adulthood
  - More common in females
  - Recurring problem for >50% of MDD patients

- Prevalence
  - Annual prevalence in Canadians ≥15-years of age, 3.9%
  - Extrapolating to BC population → 156,075 MDD cases

- Current Treatment Pathway
  - 1st line therapy → psychotherapy and/or pharmacotherapy
  - 2nd line therapy → neuromodulation therapy e.g., electro-convulsive therapy (ECT)
  - Inadequate response to two pharmacotherapies = Treatment Resistant Depression (TRD)
  - Up to 35% of MDD cases have TRD → 54,627 cases in BC
  - ECT seldom used even in TRD patients

Background (con't)

- rTMS
  - An emerging neuromodulation therapy
  - Long research history but not widely disseminated in clinical practice
  - Uses focused magnetic field pulses to non-invasively stimulate cortical neurons for the purpose of altering brain function in the area of the brain associated with mood regulation
  - Course of therapy = 30 sessions (15-45 minutes/day, 5days/week, 6 weeks)
  - Widely viewed as safe → treatment typically delivered by non-physician in outpatient setting
  - Generally viewed as 2nd line therapy but some argue for lower threshold for use
  - Treatment protocols still evolving

- rTMS in Canada and BC
  - Health Canada licensed since 2002
  - Insured service Saskatchewan and Quebec
  - Research programs at UBC and Vancouver General Hospital (VGH)
  - Treatment programs at VGH, Mood Disorder Association of BC (MDABC) and Royal Jubilee Hospital
  - VGH clinic only available to Vancouver Coastal residents; patient charges in place at VGH and MDABC

Evidence of Effectiveness – Health Benefits

- CADTH Rapid Review
  - Included literature – 1 HTA, 3 MA, 1 SR and 3 RCT
  - Low to moderate quality evidence (primary studies were small [n≤54 patients]; variation in treatment protocols used across studies; inconsistent finding across some RCTs)
  - Included HTA found rTMS is equivalent in efficacy and superior in safety relative to pharmacotherapies and ECT
  - Included MA's found rTMS to be significantly superior to sham-rTMS but magnitude of efficacy varied across studies
  - Included SR showed positive findings for rTMS but concluded the available evidence was not sufficient to confirm the efficacy of rTMS for TRD
  - Included RCTs compared rTMS to sham r-TMS but produced inconsistent results

- OHTAC
  - Completed HTA post-CADTH Rapid Review
  - Included literature – 29 RCTs (23 compare rTMS to sham rTMS; 6 compare rTMS to ECT)
  - rTMS showed a statistically significant improvement in depression scores but < than the pre-specified clinically important treatment effect
  - Trials of rTMS versus ECT showed a statistically and clinically significant difference between rTMS and ECT in favour of ECT

Evidence of Effectiveness – Health Benefits (con't)

- CADTH Rapid Review Conclusion
  - rTMS is associated with inconsistent superior efficacy relative to sham-treatment and similar efficacy relative to pharmacotherapies
- OHTAC Conclusion
  - some evidence supporting the superior efficacy of rTMS over sham treatment but, overall, the evidence favoured ECT over rTMS for patients with treatment-resistant depression

- ***HTAC Committee Score – Health Benefits***
  - 0 = None
  - 1 = Minimal
  - 2 = Moderate
  - 3 = Substantial

Evidence of Effectiveness – Non-Health Benefits

- Benefits to patients
  - Favourable adverse event profile
  - Less incapacitating than ECT
  - Convenience – treatment can be scheduled around activities of daily living
- Benefits to health system
  - Possible reduced reliance on hospital intensive services and some publicly funded pharmacotherapies but these benefits may be unpredictable or small

- ***HTAC Committee Score – Non-Health Benefits***
  - 0 = None
  - 1 = Minimal
  - 2 = Moderate
  - 3 = Substantial

Condition Severity

- Impact on QoL and Mortality Risk
  - Severe impairment in QoL is common and includes occupational impairment, increased risk of unemployment, adverse family dynamics and intergenerational impacts on children
  - Most MDD patients do not commit suicide but suicide rates are slightly higher than in the general population

- ***HTAC Committee Score – Condition Severity***
  - 0 = Minimal impact on QoL or mortality risk
  - 1 = Moderate impact on QoL or mortality risk
  - 2 = Significant impact on QoL
  - 3 = Significant impact on mortality risk

Environmental Impact

- Impact
  - No known impact associated with operation of rTMS devices
  - Disposal impact similar to that of relatively compact solid state electronic devices

- ***HTAC Committee Score – Environmental Impact***
  - 0 = Highly adverse
  - 1 = Mildly adverse
  - 2 = Benign
  - 3 = Positive effects

Illness and Injury Prevention

- Illness prevention
  - rTMS is a therapeutic technology with no confirmed role in illness prevention
- Injury prevention
  - No confirmed role but it is possible there might be some reduction in self-harm among those patients who respond to rTMS treatment

- ***HTAC Committee Score – Illness and Injury Prevention***
  - 0 = Not at all
  - 1 = Minimally
  - 2 = Moderately
  - 3 = Substantively

Marginalized or Disadvantaged Patients

- Addresses avoidable, unfair and remediable health status gaps
  - MDD may contribute to marginalization and disadvantage but the condition is not unique to marginalized or disadvantaged populations

- ***HTAC Committee Score – Marginalized and Disadvantaged Populations***
  - 0 = Intervention does not reduce, or worsens, health inequities
  - 1 = Intervention slightly reduces health inequities
  - 2 = Intervention moderately reduces health inequities
  - 3 = Intervention substantially reduces health inequities

Implementation

- Implementation considerations
  - No physician fee schedule exists and expectations may be high
  - Opinions regarding treatment protocols diverge in BC but have major impact on the economics of rTMS
  - rTMS position in the treatment pathway is uncertain
  - There may be insufficient psychiatrists to oversee rTMS which gives rise to questions re the role of other providers
  - The nature of rTMS treatment demands patients reside within commuting distance for at least 6-weeks...in the absence of wide spread diffusion access and equity issues could be significant

- ***HTAC Committee Score – Implementation***
  - 0 = Substantial implementation requirements and challenges
  - 1 = Moderate implementation requirements and challenges
  - 2 = Minimal implementation requirements and challenges
  - 3 = Few implementation requirements and challenges

Training and Credentialing

- Standards
  - No credentialing or training standards exist but consensus based risk mitigation and safety guidelines have been developed
  - Physician training generally requires out-of-country travel for 3 to 5-days
  - Staff training is accomplished on-the-job under the supervision of a trained physician with support from the equipment vendor

- ***HTAC Committee Score – Training and Credentialing***
  - 0 = Substantial training and credentialing requirements
  - 1 = Moderate training and credentialing requirements
  - 2 = Minimal training and credentialing requirements
  - 3 = No training and credentialing requirements

Risk Registry

- Financial
  - Over-investment in rTMS technology given unknown demand, limited providers and large number on TRD patients non-responsive to rTMS treatment
  - Physician fees could be substantial
  - Costs associated with training and development of guidelines
  - Cost of rTMS devices
- Human resource
  - Psychiatrist interest in and availability to oversee delivery of rTMS treatment
  - Timeframe for training psychiatrists
- Other
  - Indication creep both within the MDD population and for indications outside MDD
  - Potentially very large demand but unpredictable uptake
  - Capacity constraints inherent in rTMS could lead to waitlists
  - Uncertainty regarding protocols
  - Emerging technologies (e.g., deep brain TMS)
  - Unstructured diffusion including the private sector
  - Equity issues related to access outside urban areas

- ***HTAC Committee Score – Risk Registry***
  - 0 = High
  - 1 = Moderate
  - 2 = Minimal
  - 3 = None

Costs and Expenditures

- Total Incremental Costs and Savings
  - There are no studies either confirming or quantifying savings associated with rTMS
  - Response and remission rates are <50% → pool of patients that might generate savings is significantly reduced and savings are further reduced due to poor compliance and/or uptake of alternate therapies
  - Conservative approach → all rTMS costs are incremental and there are no health system savings

- Total Budget Impact
  - Major considerations in budget impact are choice of treatment protocol and patient demand
  - Two protocols are in use in BC, one of which is associated with much higher patient volumes but is considered experimental
  - There is no literature regarding patient demand but other jurisdictions have used estimates ranging from <1% of TRD patients to approximately 16%
  - Four demand scenarios developed for BC → 100%, 16%, 8% and a scenario tied to the number of ECT treatment locations
  - Total budget impact ranges from $2.64 million to $84.62 million

- Total Cost of Implementation
  - Not fully known but major components including device costs and staff training are captured in the budget impact
  - Physician training would be absorbed by the physicians assuming a fee code is established

Total Public and Private Sector Costs

- Service shifts
  - There are no known private sector providers of rTMS in BC and therefore no shift in service provision is expected

- ***HTAC Committee Score – Total Public and Private Sector Costs***
  - 0 = Complete shift to public sector
  - 1 = Substantial shift to public sector
  - 2 = Minor shift to public sector
  - 3 = No shift to public sector

Evidence in Cost-Effectiveness Literature

- Economic evaluations
  - Australia, Alberta and Ontario
  - Generally well conducted but conflicting results and some design limitations
  - BC MoH completed a BC-specific evaluation building on the Ontario model using BC cost data and adding measures of mortality and disutility
  - Examined the cost-effectiveness of rTMS compared with ECT and of rTMS compared with antidepressant therapy for treating patients with TRD
  - Concluded that compared to ECT, rTMS would be cost-effective if the willingness-to-pay is less than $113,262 per QALY gained
  - Compared to antidepressant therapy, rTMS is estimated to be cost-effective if the willingness to pay is greater than $79,948 per QALY gained

- ***HTAC Committee Score – Evidence in Cost-Effectiveness Literature***
  - 0 = None
  - 1 = Minimal
  - 2 = Moderate
  - 3 = Substantial

Health Technology Assessment Committee Meeting Agenda HTAC

Date: April 22, 2016
Time: 10:00 am – 12:00 pm
Location: Telepresence (Various Rooms)
Teleconference: **1 877 353-9184**
Participant ID# **5274354**
Moderator: Kevin Samra

ATTENDEES:	Michael McMillan, James Coyle, Darryl Samoil, John Mathieson, Stirling Bryan (tentative), Melinda Mui, Patricia Daly, Stuart Peacock, Nick Foster, Sek Cheung, Katherine Duthie, Glynis Soper, Kevin Samra, Jemal Mohamed, Maureen Neuman
REGRETS:	Heather Davidson
GUESTS:	James Murtagh

No.	Agenda Item	Lead	Information/ Decision	Materials		Time
				Pre-distributed	Supplementary	
1	Approval of Minutes, Agenda, Review of Action Items and Conflicts of Interest Declarations	Chair	Decision	√	☐	10:00 – 10:05
2	Repetitive Transcranial Magnetic Stimulation (RTMS)	James Murtagh	Decision	√	☐	10:05 – 10:30

NR

NR

ACTION ITEMS	PERSON RESPONSIBLE	DEADLINE

NR

NR

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Repetitive Transcranial Magnetic Stimulation (rTMS) Business Case

Summary of Reviewer Comments

Author: James Murtagh

Document Version and Date: v1; 18 April 2016

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BRITISH COLUMBIA

APRIL 22, 2016	TIME 10:00 – 12:00	VIA TELEPRESENCE/TELECONFERENCE
CHAIR	Michael McMillan	
ATTENDEES	James Coyle, Darryl Samoil, Stuart Peacock, Berna Marcelino (for Melinda Mui), Patricia Daly, , Sek Cheung, Nick Foster, Glynis Soper, Kevin Samra, Maureen Neuman, Jemal Mohamed	
REGRETS	Heather Davidson, Stirling Bryan, Katherine Duthie, John Mathieson	
NOTE TAKER	Maureen Neuman	
GUESTS	James Murtagh	

1. NR

NR

NR

2. Repetitive Transcranial Magnetic Stimulation (rTMS) – Presented by James Murtagh

Discussion

HTAC received a presentation from James Murtagh on the assessment of Repetitive Transcranial Magnetic Stimulation (rTMS) for the treatment of Major Depressive Disorder (MDD) and evaluated the technology through the completion of the scoring matrix. Members agreed that health benefits were not well established in the literature, and as a result there was some uncertainty with respect to the cost-effectiveness of the technology. From a patient perspective, it was noted that standards and credentialing would be important if this technology were introduced. HTAC concluded that results were mixed and there was insufficient evidence to recommend funding the technology, despite the technology being in existence for over a decade.

Action items	Person responsible	Deadline
□ Develop Technology Appraisal and Advice (T2A) report for rTMS	HTR Office	May 2016

3.NR

NR

Discussion

NR

Heath Technology Assessment Meeting Minutes HTAC

BRITISH COLUMBIA

DATE: MAY 3, 2016	TIME 3:00 – 5:00	VIA TELECONFERENCE
CHAIR	Heather Davidson	
ATTENDEES	Michael McMillan, James Coyle, Darryl Samoil, Berna Marcelino (for Melinda Mui), Patricia Daly, Stirling Bryan, John Mathieson, Glynis Soper, Kevin Samra, Maureen Neuman, Jemal Mohamed	
REGRETS	Stuart Peacock, Nick Foster, Sek Cheung, Katherine Duthie	
NOTE TAKER	Maureen Neuman	
GUESTS	Tania Conte, Mohsen Sadatsafavi	

1. Approval of Minutes, Agenda, Review of Action Items and Confict of Interest Declarations

No changes to the Minutes for April 22nd. No changes/additions to the May 3 Agenda. Action items were reviewed – T2As for rTMS and NR are under development and will be completed shortly for review and approval by HTAC via email. NR

s.13

NR

NR

Health Technology Assessment Committee
Technology Appraisal & Advice Synthesis

Topic: Repetitive Transcranial Magnetic Stimulation (rTMS)

Report Date: May 24, 2016 (Final)

Disclaimer:

This evidence-informed report was prepared by the secretariat for the British Columbia Health Technology Assessment Committee. Findings and recommendations are based upon a review of the business case submitted to the committee and an evidence review undertaken by the Canadian Agency for Drugs and Technology in Health (CADTH). Findings and recommendations also take into account other BC-specific data and information provided within the business case. It should be noted that other relevant scientific findings may have been reported since the completion of the reference documents used to form the basis of committee recommendations and to complete this report.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

HEALTH TECHNOLOGY ASSESSMENT COMMITTEE RECOMMENDATIONS

1. There is a lack of consistent evidence to recommend the public provision of repetitive transcranial magnetic stimulation (rTMS) for treatment resistant depression at this time. As such, it is recommended that rTMS be performed only in research.
2. It is recommended that the rTMS technology be reviewed again in three years, or when compelling new evidence becomes available.

HEALTH TECHNOLOGY ASSESSMENT COMMITTEE FINDINGS

The business case submitted to the Health Technology Committee (HTAC) reviewed the effectiveness of rTMS in the treatment of Major Depressive Disorder, with a focus on Treatment Resistant Depression (TRD). Recommendations were based on the following committee findings:

1. Overall, the clinical effectiveness evidence for rTMS is mixed. Study sample sizes are small, results are inconsistent, and evidence is generally of low to moderate quality. Studies indicated that:
   - the efficacy of rTMS relative to sham was inconsistent. Some studies show rTMS provides better efficacy, and others failed to show any differences between rTMS and sham;
   - rTMS may be similar in efficacy to antidepressant therapy, but is more costly;
   - Electroconvulsive therapy (ECT) is more effective than rTMS, but is more costly. ECT is already an insured service in BC.
2. The cost effectiveness evidence is mixed, and based on evidence of moderate to low quality.
3. Due to the short-term duration of studies, there is little evidence regarding the length of time that the benefit of rTMS persists.
4. If this technology were to be introduced, it is estimated that it would cost between $2.7 - $13.6 million dollars per year. This is based on treating 8% and 16% of all treatment resistant depression patients. Treating all patients with TRD with rTMS would be challenging, and cost as much as approximately $ 84.6 million dollars.
5. Variability in the literature make definitive conclusions about optimal treatment strategies difficult. In other words, rTMS treatment protocols and, to an extent, its place in the clinical pathway are still developing, which could have a significant impact on expected costs and benefits.
6. It is expected that rTMS would be an additional option for physicians treating patients with TRD (rather than replace existing treatments), and therefore significant cost savings to the health system are not anticipated.
7. Research initiatives involving rTMS are in place at the University of British Columbia (UBC) hospital and Vancouver General Hospital (VGH).

INTRODUCTION

Major Depressive Disorder (MDD) is associated with a substantial health, psychosocial and financial burden and is increasingly recognized as a target for chronic disease management. Antidepressants and psychotherapy are usually the first line of therapy prescribed by physicians; however, if two types of antidepressants do not generate a response, then referral to a psychiatrist for Treatment Resistant Depression (TRD) is recommended.

Treatment options for psychiatrists include, in addition to psychotherapy and more intensive pharmacotherapy, neuromodulation therapies, which are typically viewed as the second line of therapy. Electroconvulsive therapy (ECT) is the oldest and most widely used neuromodulation therapy and considered the gold standard. Although the first human studies are now 25-years old, repetitive Transcranial Magnetic Stimulation (rTMS), a less invasive form of neuromodulation therapy, is an emerging therapy for TRD.

rTMS for the treatment of MDD was identified as a topic for the HTR in 2015/16. The Health Technology Review Office (HTRO) requested a rapid review from CADTH, which was completed in October 2015, and James Murtagh & Associates were contracted to develop the business case. HTAC evaluated the business case on April 22, 2016, and findings and recommendations are synthesized in this report.

BACKGROUND

MEDICAL CONDITION

Major depressive disorder (MDD) is characterized by the occurrence of one or more major depressive episodes (MDE) wherein an individual suffers from depressed mood and/or notably diminished pleasure in all or most activities, for most of the day, nearly every day for at least two weeks. It usually emerges in late adolescence or early adulthood, is more common in females, and a recurring problem for more than 50% of MDD patients. MDD which fails to respond to two or more adequate trials from different classes of antidepressants is typically considered to be Treatment Resistant Depression (TRD). Based on a prevalence estimate of 156,076 MDD cases and TRD prevalence of 35%, it is estimated there are 54,627 TRD cases annually in BC.

HEALTH TECHNOLOGY OVERVIEW

Repetitive transcranial magnetic stimulation (rTMS) involves the administration of a series of pulsed magnetic stimuli to the brain for the purpose of altering brain function in the area of the brain associated with mood regulation. The principle equipment necessary to deliver rTMS is a stimulator, which generates brief pulses of strong electrical currents whose frequency and intensity can be varied, and a stimulation coil connected to the stimulator. The coil is placed against the scalp and the magnetic field generated at the coil passes unimpeded through the scalp and skull and induces electrical current in the underlying

tissue, which in turn depolarizes neurons. Neuronal modulation (increasing or decreasing neuronal excitation) depends on the frequency and intensity of stimulation applied but, most importantly, extends beyond the moment when stimulation occurs and the therapeutic potential of rTMS flows from the durability of this modulatory effect.

Standard rTMS treatment is a repetition of individual pulses at a pre-set interval (train of pulses); a typical treatment session involves delivering 3,000 pulses over 37.5 minutes. Patterned rTMS, also known as theta-burst rTMS or intermittent theta-burst stimulation (iTBS) is a relatively new development and treatment involves a repetition of short bursts of pulses at a pre-set interval (train of bursts as opposed to a train of pulses) where a typical session involves delivering 600 pulses in just over three-minutes. Regardless of treatment protocol, rTMS is typically administered once daily, five days a week for four weeks on an outpatient basis.

Unlike electroconvulsive therapy (ECT), rTMS does not require anesthesia, does not aim to induce a seizure and is not accompanied by memory loss. rTMS is generally considered to be a safe procedure without enduring side effects but is contraindicated in patients who may have implanted magnetic sensitive devices depending on proximity to the coil.

rTMS can be delivered by a non-physician but is delivered under the general supervision of a physician. Formal training is available to physicians but not offered in BC or Canada in general. rTMS has been licensed in Canada since 2002. There are four devices licensed in Canada by the following companies: Magstim (1), MagVenture (2), and Brainsway (1).

PATIENT AND STAKEHOLDER PERSPECTIVE

No literature addressing the attitude of clinicians towards rTMS was identified and very little information is available regarding patient perspectives regarding rTMS. BC-based physicians who use rTMS are enthusiastic proponents of the technology. Two clinical experts reviewed an embargoed copy of the business case, which informed the final report. Expert opinion of the evidence reviewed supported that it was very inclusive and comprehensive.

JURISDICTIONAL SCAN

- *British Columbia* – rTMS research programs at UBC hospital and Vancouver General Hospital (VGH); rTMS clinical programs at VGH (with patient charges); rTMS units in place and clinical programs being planned by Mood Disorder Association of BC (with patient charges) and Royal Jubilee Hospital in Victoria (potentially without patient charges).
- *Alberta* – The Alberta Health Technology Decision Process (AHTDP) also examined the possibility of listing rTMS as an insured service. No decision has been made public.

- *Saskatchewan* – rTMS is an insured service in Saskatchewan. The fee schedule includes a technical component of $81.60 for instances where the rTMS unit is owned by and treatment staff employed by the physician and a corresponding professional component of $51.00.
- *Quebec* – rTMS is an insured service in Quebec. The physician fee is $350.00 for the first visit and $175.00 for subsequent visits.
- *Ontario* – OHTAC has recommended rTMS be publicly funded for patients with TRD when ECT has failed or is contraindicated. The Ministry of Ontario Health & Long Term Care has yet to announce a decision. Ontario assumed a physician fee equal to that for ECT ($85.92) for each treatment session.

HEALTH TECHNOLOGY REVIEW MEETING PROCESS

The HTA Committee met on April 22, 2016, to review the business case on the assessment of repetitive Transcranial Magnetic Stimulation (rTMS) in the treatment of Major Depressive Disorder (MDD). The chair led a review of the business case, and the committee evaluated it based on the HTR multi-criteria evaluation framework. A consensus score was established for each criterion. The committee concluded by developing its recommendations. The Health Technology Review rating scale is attached as Appendix B. No conflicts of interest were declared by committee members.

ASSESSMENT CRITERIA

EFFECTIVENESS

Health Benefits

Definition: The clinical effectiveness of the health technology compared with the insured treatment or current clinical practice including any safety issues identified in the literature. The health gain expected from use of the technology, including the expected impact on the underlying condition in terms of survival gains (or losses), and changes in health-related quality of life, morbidity and adverse events.

Consensus score: 1 – Minimal

Rationale: A CADTH rapid review of the evidence was undertaken. It included one health technology assessment (HTA), three meta-analyses, one systematic review, and three randomized control trials (RCTs). The available evidence was assessed as being of low to moderate quality. The findings were as follows:

- The included HTA, which assessed the clinical effectiveness and cost-effectiveness of rTMS for patients with TRD who had failed at least two courses of antidepressants, found rTMS to be at least equivalent in efficacy and superior in safety relative to pharmacotherapies and ECT.
- The three included meta-analyses reported rTMS to be statistically significantly superior to sham rTMS, but the magnitude of the efficacy varied across studies.

- The included systematic review found that seven of ten included RCTs showed positive findings associated with rTMS and negative findings in three, but the authors concluded that the available evidence was not sufficient to confirm the efficacy of rTMS for treatment resistant depression.
- The three included RCTs, which compared rTMS to sham rTMS, produced inconsistent results; two RCTs did not show differences while the third RCT provided positive findings favouring rTMS.

The CADTH rapid review concluded that rTMS is associated with inconsistent superior efficacy relative to sham treatment and similar efficacy relative to pharmacotherapies.

After the CADTH rapid review, the Ontario Health Technology Advisory Committee (OHTAC) completed a meta analyses aimed at examining the efficacy of rTMS in patients with treatment resistant unipolar depression and concluded that there is some evidence showing a small treatment effect between rTMS and sham (about two points) and that the evidence suggest ECT is more effective than rTMS.

The committee concluded that given the conflicting results and low to moderate quality of studies, the marginal benefit relative to sham rTMS, lack of long-term studies, and superior effectiveness of ECT, there was minimal evidence of health benefits with rTMS.

Non-Health Benefits

Definition: The non-health benefits that can be expected from the use of this technology not captured in the health benefits criterion. Examples of non-health benefits include autonomy, convenience, comfort and confidence.

Consensus score: 1 – Minimal

Rationale: rTMS is generally considered to be a safe procedure without enduring side effects. rTMS has a more favourable adverse event profile than ECT or pharmacotherapies, and is less incapacitating and arguably more convenient for patients than ECT. Benefits to the health system may include reduced reliance on hospital intensive services (ECT requires anesthesia and recovery room resources) and funded pharmacotherapies, but these benefits were deemed to be unpredictable or small.

The committee concluded that the non-health benefits were likely between minimal to moderate, but difficult to assess due to lack of evidence.

CONDITION SEVERITY

Definition: The extent to which the underlying health condition affects a patient's quality of life and risk of mortality from the condition.

Consensus score: 2 – Significant impact on Quality of Life (QoL)

Rationale: Severe impairment in quality of life is common for the majority of MDD patients. MDD is associated with substantial health, psychosocial and financial burden, including occupational impairment, increased risk of unemployment, adverse family dynamics and intergenerational impacts on children. Most MDD patients do not commit suicide but suicide rates are slightly higher in this population than the general population. In BC, about 917 patients received ECT in 2014/15.

The committee noted the condition has a significant impact on the quality of life for most patients (and a significant impact on the risk of mortality for the most serious cases).

ENVIRONMENTAL IMPACT

Definition: How the use of the technology affects the environment.

Consensus score: 2 – Benign

Rationale: There are no known environmental impacts associated with operation of rTMS devices. Disposal is similar to that of relatively similar compact solid state electronic devices.

The committee concluded that the impact of rTMS on the environment is benign.

COSTS

EVIDENCE OF COST-EFFECTIVENESS

Definition: Discussion on the evidence of cost-effectiveness.

Consensus Score: 1 – Minimal

Rationale:

Economic analyses of rTMS have been completed in Australia, Alberta and Ontario, and compared the cost-effectiveness of rTMS to ECT and antidepressant therapy in patients with TRD. These studies were generally well conducted but there were some conflicting results and design limitations. As a result, a BC-specific economic analysis was developed by the BC Ministry of Health.

The BC analysis built upon the Ontario model by using BC cost data and adding measures of mortality and disutility used in the Australian model. The BC analysis concluded that antidepressant therapy is more cost-effective than rTMS when the willingness to pay is less than $79,948 per QALY gained; however, ECT is considered more cost-effective than rTMS if the willingness to pay is greater than $113,262 per QALY gained.

In contrast, Ontario found rTMS is cost-effective compared with sham when willingness to pay is greater than $98,242 per QALY and ECT is cost-effective compared with rTMS when willingness to pay is greater

than $37,640 per QALY. The other studies provided significantly different results based on model assumptions. As a result, the Committee concluded that cost-effectiveness evidence was mixed, and the robustness of the economic analyses were based on imprecise assumptions, and evidence of low to moderate quality.

The committee concluded that since health benefits were not well established in the literature, as a result, there is some uncertainty with respect to the cost-effectiveness of the technology.

BUDGET IMPACT ANALYSIS (BIA)

The budget impact looked at a number of different scenarios based on a variety of assumptions (see Appendix 1). Estimated annual incremental costs are between $6.8 million and $13.6 million using patient demand scenarios ranging from 8% (4,370) to 16% (8,740) using the standard treatment protocol. Incremental annual costs based on the same scale as ECT were estimated at $2.9 million, which would provide the capacity to serve an estimated 4% (1,875) of TRD patients using the standard treatment, or up to an estimated 9% (4,791) of TRD patients if only the iTBS treatment protocol is used.

There are no studies either confirming or quantifying savings associated with rTMS. Only one other jurisdiction (Australia) incorporated any cost savings with the introduction of rTMS, which were modest overall (4% of total projected costs), and these were based on assumptions (not evidence). Health system savings are expected to be unpredictable or small due to a patient response and remission rate of <50% and, furthermore, poor compliance or uptake of existing therapies. As such, a conservative approach to cost estimation was taken, where costs associated with rTMS, as presented in the BIA (Appendix 1), were considered to be fully incremental.

Demand Scenarios

The BIA includes four demand scenarios – 100%, 16%, 8% and a scenario based on the number of ECT treatment locations. There is no literature regarding patient demand but other jurisdictions used estimates ranging from <1% of TRD patients to approximately 16%. Two protocols are in use in BC, one of which (iTBS) is associated with much higher patient volumes due to shorter treatment time but is still considered experimental.

Estimated Patient Volumes

There is no literature addressing the uptake of rTMS. The Australian BIA assumes a very low uptake. The Alberta BIA treated demand as non-quantifiable and resorted to a specific number of devices (seven) as recommended by a group of experts, which could serve up to 524 TRD patients. The Ontario BIA assumed a range of 7.5% to 16% based on a number of diffusion scenarios, including per capita ECT supply.

Estimated Cost of rTMS Devices

Purchase prices for units capable of performing both the standard and iTBS protocols range from approximately $65,000 to $100,000+. The BIA assumes the purchase cost of a MagVenture R30/TBS at

$68,500. Treatment coils, whose lifespan is linked to the number and intensity of treatment sessions, are priced in the range of $8,000 to &10,000. Extended warranties are available but are seldom purchased. Device costs in the BIA are amortized over the estimated 10-year lifespan of the device.

Currently, there are three clinical rTMS units in BC: two are in public hospitals and one is in a clinic sponsored by a patient advocacy group (two are not yet in operation). Operating full-time they could serve, at most, 350 patients per year.

Salaries and Benefits

The BIA assumes salary and benefit costs based on all devices operating full-time (7.5 hours/day, 250 days/year) and treatments performed by a Registered Nurse. The BIA does not incorporate physician fees. No consistent approach to physician fees is evident across jurisdictions (see Jurisdictional Scan for approaches within Canada). Physicians are seldom routinely present at treatment sessions beyond initiation. Physician training would be absorbed by the physician assuming a fee code is established. Nursing training costs are not explicitly addressed in the BIA, but are implicit in that this training would be accomplished through a combination of manufacturer/vendor resources and on-the-job training with a trained physician during clinic operations.

PUBLIC/PRIVATE SECTOR COSTS

Consideration of a shift in services or costs from the private to public sector or vice versa was not applicable as no rTMS clinics are known to be operating in the private, for-profit sector in BC.

ADDITIONAL FACTORS

ILLNESS OR INJURY PREVENTION

Definition: The extent to which the intervention provides or supports primary illness or injury prevention, maintenance of well-being, and/or harm reduction.

Consensus Score: 0 – Not at all

Rationale: rTMS is a therapeutic technology with no direct implications for primary prevention to health.

MARGINALIZED AND DISADVANTAGED PATIENTS

Definition: Whether the intervention seeks to improve the health status of groups for whom there is an avoidable, unfair and remediable health status gap.

Consensus Score: 0 – Does not reduce health inequities

Rationale: MDD may contribute to marginalization or disadvantage but it is not unique to marginalized or disadvantaged populations. It is worth noting that inequities among MDD patients may impact access, and MDD is more prevalent in women, who are less likely to be referred to a psychiatrist. Age and location (rural vs. urban) may also impact access to a psychiatrist.

IMPLEMENTATION

IMPLEMENTATION CONSIDERATIONS

Definition: High level implementation considerations for the technology.

Consensus Score: 1 – Moderate implementation requirements and challenges

Rationale: The Business Case outlines the following considerations for implementation:

- Physician fee code – No physician fee schedule currently exists for rTMS and practice in other jurisdictions is inconsistent. It is doubtful psychiatrists would engage in treatment planning and an extended period of treatment oversight without compensation. It should be noted that physicians are seldom routinely present at treatment sessions beyond initiation.
- Provincial guidelines – Opinions regarding rTMS treatment protocols vary but have dramatic implications for the economics of rTMS. Nine patients can be treated per day with the standard protocol compared to 23 with iTBS. No clinical guidelines were identified in the literature review.
- Clinical pathway – Treatment eligibility and the appropriate use of rTMS in the treatment pathway will need to be considered. E.g. as first line of therapy or maintenance therapy.
- Providers – There may be insufficient psychiatrists to oversee rTMS, which gives rise to question about the role of other providers.
- Access – rTMS treatment demands patients reside within commuting distance for at least six weeks. In the absence of wide spread diffusion, access and equity issues could be significant.

The committee noted rTMS requires more time than ECT, which would result in moderate implementation challenges.

TRAINING AND CREDENTIALING

Definition: How training, credentialing and privileging, if required, will be carried out, referring to Canadian and international specialty society guidelines where available.

Consensus Score: 1 – Moderate training and credentialing requirements

Rationale: There is no established training or credentialing standard for rTMS. Consensus-based risk mitigation safety guidelines for TMS stimulus parameters do exist. Some stakeholders take the position that training should include a formal course in rTMS with hands on experience under the supervision of a seasoned practitioner. Such training is not generally offered within Canada. In some hospitals, a

Registered Nurse delivers the therapy. Training for nursing staff would be accomplished through a combination of manufacturer/vendor resources and working with a trained physician on the job during clinic operations.

The committee noted that from a patient perspective, training standards and credentialing will be important if this technology were introduced.

RISK REGISTRY

Definition: Risks to successful implementation.

Consensus Score: 1 **–** Moderate risk

Rationale: The business case identified the following risks to the project:

- Potential over investment in rTMS technology given unknown demand, limited providers and potential number of TRD patients that would be non-responsive to rTMS treatment
- Physician fees could be substantial
- Costs associated with training and development of guidelines
- Costs associated with purchase of more expensive rTMS devices
- Psychiatrist interest and availability to be trained and deliver rTMS treatment
- Capacity constraints could generate waitlists
- Indication creep both within and outside the MDD population (potentially very large demand but unpredictable uptake)
- Uncertainty with respect to protocols
- Uncertainty with respect to emerging technologies (e.g. deep brain TMS)
- Unstructured diffusion into the private sector
- Equity issues related to access outside of urban areas.

The committee concluded that overall risks were moderate, but risk of scope creep was high.

HEALTH TECHNOLOGY ASSESSMENT COMMITTEE FINDINGS

The business case submitted to the Health Technology Committee (HTAC) reviewed the effectiveness of rTMS in the treatment of Major Depressive Disorder, with a focus on Treatment Resistant Depression (TRD). Recommendations were based on the following committee findings:

1. Overall, the clinical effectiveness evidence for rTMS is mixed. Study sample sizes are small, results are inconsistent, and evidence is generally of low to moderate quality. Studies indicated that:
    - the efficacy of rTMS relative to sham was inconsistent. Some studies show rTMS provides better efficacy, and others failed to show any differences between rTMS and sham;
    - rTMS may be similar in efficacy to antidepressant therapy, but is more costly;

- Electroconvulsive therapy (ECT) is more effective than rTMS, but is more costly. ECT is already an insured service in BC.

2. The cost effectiveness evidence is mixed, and based on evidence of moderate to low quality.
3. Due to the short-term duration of studies, there is little evidence regarding the length of time that the benefit of rTMS persists.
4. If this technology were to be introduced, it is estimated that it would cost between $2.7 - $13.6 million dollars per year. This is based on treating 8% and 16% of all treatment resistant depression patients. Treating all patients with TRD with rTMS would be challenging, and cost as much as approximately $ 84.6 million dollars.
5. Variability in the literature make definitive conclusions about optimal treatment strategies difficult. In other words, rTMS treatment protocols and, to an extent, its place in the clinical pathway are still developing, which could have a significant impact on expected costs and benefits.
6. It is expected that rTMS would be an additional option for physicians treating patients with TRD (rather than replace existing treatments), and therefore significant cost savings to the health system are not anticipated.
7. Research initiatives involving rTMS are in place at the University of British Columbia (UBC) hospital and Vancouver General Hospital (VGH).

REFERENCES

1. Murtagh J. Repetitive Transcranial Magnetic Stimulation Health Technology Review Business Case (unpublished). April 2016.
2. CADTH Rapid Review. Repetitive Transcranial Magnetic Stimulation for Depression: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines. October 2015.

APPENDIX A – BUDGET IMPACT ANALYSIS – RTMS IN BRITISH COLUMBIA

			Scenario 1		Scenario 2		Scenario 3		Scenario 4	
	Scenario Description	Source	All TRD Patients Treated		16% of TRD Patients Treated		8% of TRD Patients Treated		rTMS Units = ECT locations (n=25)	
A	TRD Population	Table 3	54,627		54,627		54,627		54,627	
B	Treated Population	Note 1	54,627		8,740		4,370		1,875/4,791	
C	Course of Therapy (# of sessions)	Note 2	30		30		30		30	
D	Required or Available Treatment Sessions	BxC	1,638,810	1,638,810	262,200	262,200	131,100	131,100	56,250	143,750
E	Treatment Protocol		**Standard**	**iTBS**	**Standard**	**iTBS**	**Standard**	**iTBS**	**Standard**	**iTBS**
F	Maximum Sessions/Device/Year	Note 3	2,250	5,750	2,250	5,750	2,250	5,750	2,250	5,750
G	rTMS Units Required or Available	D/F	729	286	117	46	59	23	25	25
	Device Costs									
H	rTMS Units	Note 4	$49,936,500	$19,591,000	$8,014,500	$3,151,000	$4,041,500	$1,575,500	$1,712,500	$1,712,500
I	Planning coils	Note 5	$7,200	$7,200	$7,200	$7,200	$7,200	$7,200	$7,200	$7,200
J	Total Device Cost	H+I	$49,943,700	$19,598,200	$8,021,700	$3,158,200	$4,048,700	$1,582,700	$1,719,700	$1,719,700
K	Device Lifespan		10 years	10 years	10 years	10 years	10 years	10 years	10 years	10 years
L	**Annual Device Costs**	J/K	**$4,994,370**	**$1,959,820**	**$802,170**	**$315,820**	**$404,870**	**$158,270**	**$171,970**	**$171,970**
	Treatment Costs (excluding device)									
M	Salaries & Benefits	Note 6	$66,184,452	$25,965,368	$10,622,196	$4,176,248	$5,356,492	$2,088,124	$2,269,700	$2,269,700
N	Treatment Coils	Note 7	$10,711,400	$2,146,200	$1,715,000	$343,000	$862,400	$176,400	$372,400	$196,000
	Other Consumables									
O	Caps	Bx$20	$1,092,540	$1,092,540	$174,800	$174,800	$87,400	$87,400	$37,500	$95,820
P	Miscellaneous supplies	Dx$1	$1,638,810	$1,638,810	$262,000	$262,200	$131,100	$131,100	$56,250	$143,750
Q	**Annual Treatment Cost**	M+N+O+P	**79,627,202**	**$30,842,918**	**$12,774,196**	**$4,956,248**	**$6,437,392**	**$2,483,024**	**$2,735,850**	**$2,705,270**
R	**Total Annual Cost**	L+Q	**$84,621,572**	**$32,802,738**	**$13,576,366**	**$5,272,068**	**$6,842,262**	**$2,641,294**	**$2,907,820**	**$2,877,240**
S	**Total Cost/Treatment Session** (excluding physician fees)	R/D	**$51.64**	**$20.02**	**$51.78**	**$20.11**	**$52.19**	**$20.15**	**$51.69**	**$20.02**

Note 1 – Treated population is either total TRD population, a % of that population or, in Scenario 4 a function of device capacity where the number of devices is fixed [(FxG)/30]
Note 2 – Number of sessions per course of therapy varies across studies. The norm in all BC facilities is 30 which falls between the low and high values in the literature.
Note 3 – Full-time unit is available 7 hours/day, 250 days/year. Standard protocol requires 43 minutes (9 sessions/day) and iTBS requires 18 minutes (23 sessions/day). [9x250=2,250; 23x250=5,750]
Note 4 – Line G x estimated cost of MagVenture R30/TBS ($68,500)
Note 5 – Planning coils are optional but included here. Coils have useful life of 10 years. The cost of two coils is incorporated here to reflect lifespan of the device.
Note 6 – It is assumed all devices operate full-time, 7.5 hours/day, 250 days/year. Hourly RN salary ($48.42) is from Appendix 2. [Line G x 7.5 x 250 x $48.42]
Note 7 – Treatment coils cost $9,800 each and expire based on use or time (5-years), whichever occurs first. Standard protocol coils are good for 1,500 sessions; iTBS protocol coils are good for 5,750 sessions. Coil costs equal (Line D/ 1,500 or 5,750)x$9,800.

APPENDIX B – HEALTH TECHNOLOGY ASSESSMENT COMMITTEE MEMBERS

Health Authority Representatives

Name	Health Authority	Position
Dr. Darryl Samoil	Fraser Health	Chief Medical Information Officer
Dr. Nick Foster	Provincial Health Services Authority	Vice President Consolidated Services, Clinical & Systems Transformation and Special Projects
James Coyle	Interior Health	Director, Health Systems Evaluation
Dr. John Mathieson	Island Health	Island Health Medical Director (Imaging)
Michael McMillan (Co-chair)	Northern Health	Chief Operating Officer, Northern Interior Health Service Delivery Area
Dr. Patricia Daly	Vancouver Coastal Health	Chief Medical Health Officer and Vice President, Public Health

Other Members

Name	Organization	Position
Melinda Mui	BC Clinical and Support Services	Vice President, Supply Chain
Heather Davidson (Co-chair)	Ministry of Health	Assistant Deputy Minister, Partnerships and Innovation Division
Stirling Bryan (Health Technology Assessment Expert)	Vancouver Coastal Health Research Institute University of British Columbia	Director, Centre for Clinical Epidemiology & Evaluation Professor, School of Population & Public Health
Stuart Peacock (Health Economist)	BC Cancer Agency	Distinguished Scientist - BC Cancer Agency, Professor and Leslie Diamond Chair in Cancer Survivorship – SFU, and Co-Director, Canadian Centre for Applied Research in Cancer Control
Katherine Duthie (Ethicist)	Fraser Health	Contract Ethicist, Research and Special projects
Vacant (Physician)		
Sek Cheung (Public Member)	Patient Voices Network	Public member

Secretariat

Name	Organization	Position
Kevin Samra	Ministry of Health	Director, Stakeholder Relations & Transformation
Jemal Mohamed	Ministry of Health	Senior Economist
Maureen Neuman	Ministry of Health	Senior Policy Analyst

APPENDIX C – CRITERIA SCORING LEGEND

SCORED CRITERIA	DEFINITION	SCORE			
		0	1	2	3
Effectiveness (health benefits)	The health gain expected from use of the technology; and any safety issues identified in the literature.	None	Minimal (see definitions at the bottom of document)	Moderate	Substantial
Effectiveness (Non-health benefits)	The non-health benefits that can be expected from the use of this technology not captured in the health benefits criterion. Examples include autonomy, convenience, and comfort.	None	Minimal	Moderate	Substantial
Condition severity	The extent to which the underlying health condition affects a patient's quality of life and their risk of mortality.	Condition has minimal impact on quality of life or risk of mortality	Condition has moderate impact on quality of life or risk of mortality	Condition has significant impact on quality of life	Condition has significant impact on risk of mortality
Environmental Impact	How the technology affects the environment.	Highly adverse	Mildly adverse	Benign	Positive effects
OTHER CRITERIA	**DEFINITIONS**				
Illness and injury prevention	The extent to which the intervention targets primary illness or injury prevention, maintenance of well-being, and/or harm reduction.	Not at all	Minimally	Moderately	Substantially
Marginalized and Disadvantaged Patients	Does the intervention seek to improve the health status of groups for whom there exists an avoidable, unfair and remediable health status gap?	Intervention does not reduce, or worsens, health inequities	Intervention slightly reduces health inequities	Intervention moderately reduces health inequities	Intervention substantially reduces health inequities
Implementation Considerations	What is the degree of challenge in achieving implementation of this intervention and any other factors that may be relevant such as such as political hurdles; infrastructure requirements; other specific challenges?	Substantial implementation requirements and challenges	Moderate implementation requirements and challenges	Minimal implementation requirements and challenges	Few implementation requirements and challenges
Training and Credentialing	The introduction of a new technology may require the training, credentialing and privileging of medical professionals.	Substantial training and credentialing requirements	Moderate training and credentialing requirements	Minimal training and credentialing requirements	No training and credentialing requirements
Risk registry	What is the level of risk associated with a positive decision?	High	Moderate	Minimal	None