Cost Analysis of Intermittent Theta Burst Stimulation (iTBS) Versus 10Hz Repetitive Transcranial Magnetic Stimulation (rTMS) in Patients With Treatment Resistant Depression

ANDREW B. MENDLOWITZ MBIOTECH, ALAA SHANBOUR MD, JONATHAN DOWNAR MD, FIDEL VILA-RODRIGUEZ MD, ZAFIRIS J. DASKALAKIS MD, WANRUDEE ISARANUWATCHAI* PHD, DANIEL M. BLUMBERGER* MD

PRESENTER: ANDREW MENDLOWITZ
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DISCLOSURE

I have no actual or potential conflict of interest in relation to this topic or presentation.
OUTLINE

1. Background
2. Methods
3. Results
4. Discussion
5. Summary
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1. Background
2. Methods
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5. Summary
BACKGROUND:
TREATMENT-RESISTANT DEPRESSION

- Major depressive disorder (MDD) accounts for 4.3% of the global burden of disease\(^1\)
- Leading cause of disability worldwide\(^2\)

In Canada:
- 4.7% of Canadians reported a major depressive episode in the last year\(^3\)

Of patients with MDD:
- In the STAR*D trial of pharmacotherapy of MDD, the prevalence of treatment-resistant depression (TRD) was 30%\(^4\)
- TRD among MDD patients has been estimated to be as high as 30% to 60% in the literature\(^5\)
- Estimated prevalence of 2% in population\(^6\)

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\(^1\) World Health Organization. Global burden of mental disorders and the need for a comprehensive, coordinated response from health and social sectors at the country level. Report by the Secretariat. Geneva, Switzerland; 2011.
\(^2\) Friedrich MJ. Depression is the leading cause of disability around the world. JAMA 2017;317(15):1517–1517.
\(^3\) Statistics Canada. Mental health profile, Canadian Community Health Survey-mental health (CCHS), by age group and sex, Canada and provinces [Internet]. Ottawa, ON: Government of Canada; 2013
BACKGROUND:
TREATMENT-RESISTANT DEPRESSION

Major depressive disorder (MDD)

Failure of at least two medication trials

Treatment-resistant depression (TRD)
BACKGROUND:
TREATMENT-RESISTANT DEPRESSION

Major depressive disorder (MDD)

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Treatment-resistant depression (TRD)

Electroconvulsive therapy (ECT)

Repetitive transcranial magnetic stimulation (rTMS)
BACKGROUND:
TREATMENT-RESISTANT DEPRESSION

Major depressive disorder (MDD)

Failure of at least two medication trials

Treatment-resistant depression (TRD)

Electroconvulsive therapy (ECT)
- Mainstay therapy for TRD\(^1\)
- Adverse effects\(^1\)
- High cost and logistical demands\(^2,3\)

Repetitive transcranial magnetic stimulation (rTMS)

---

**BACKGROUND:**
**TREATMENT-RESISTANT DEPRESSION**

Major depressive disorder (MDD)

Failure of at least two medication trials

Treatment-resistant depression (TRD)

Electroconvulsive therapy (ECT)

Repetitive transcranial magnetic stimulation (rTMS)

- Introduced in 1985\(^1\)
- Focused magnetic field pulses
- Research has confirmed its efficacy and safety in TRD\(^2\)

Major depressive disorder (MDD)

Failure of at least two medication trials

Treatment-resistant depression (TRD)

Electroconvulsive therapy (ECT)

Repetitive transcranial magnetic stimulation (rTMS)

• Have been extensively compared!
• Slightly different in clinical effect
• rTMS has a much better adverse-effect profile and cost-effective when compared to ECT in TRD$^{1,2}$
Major depressive disorder (MDD)

Failure of at least two medication trials

Treatment-resistant depression (TRD)

Electroconvulsive therapy (ECT)

Repetitive transcranial magnetic stimulation (rTMS)

Efficacy was compared in the THREE-D non-inferiority Trial

Conventional 10Hz rTMS

Intermittent theta-burst stimulation (iTBS)
BACKGROUND:

THE THREE-D TRIAL

• Recently, the THREE-D trial was published as the first randomized non-inferiority trial comparing:

1) Conventional 10 Hz rTMS protocol:
   ◦ Approved by the FDA in 2008
   ◦ 3,000 pulses of 10Hz stimulation to the left DLPFC over 37.5 min

2) Intermittent theta-burst stimulation (iTBS) protocol:
   ◦ Differed only in stimulation pattern and number of pulses for a 3 min session duration
   ◦ Approved by the FDA for TRD in August of 2018

• Non-inferior in reducing depression scores on both the Hamilton Rating Scale for Depression (HRSD-17) and the self-report Quick Inventory of Depressive Symptoms

BACKGROUND:

RESEARCH GAP

• Given the evidence from the THREE-D trial that iTBS is non-inferior to 10Hz rTMS:
  • Research is needed to further optimize and inform decisions regarding the efficacy and cost-effectiveness of rTMS compared to other available treatment strategies in MDD
  • There is still a gap in research describing the potential economic impact of implementing iTBS in clinical practice
BACKGROUND:  
RESEARCH GAP  

• Given the evidence from the THREE-D trial that iTBS is non-inferior to 10Hz rTMS:  
  • Research is needed to further optimize and inform decisions regarding the efficacy and cost-effectiveness of rTMS compared to other available treatment strategies in MDD.  
  • There is still a gap in research describing the potential economic impact of implementing iTBS in clinical practice  

The question still remains:  
What is the cost per course and cost per remission for implementing iTBS versus the conventional 10Hz rTMS protocol to treat patients with TRD?
OUTLINE

1. Background
2. Methods
3. Results
4. Discussion
5. Summary
## METHODS
### STUDY OVERVIEW

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>• Patient-level cost analysis</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>• Adults aged 18 to 65 with a diagnosis of MDD who did not respond to adequate pharmacotherapy</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>• Minimum of 4-weeks of iTBS treatment</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>• Minimum of 4-weeks of 10Hz rTMS treatment</td>
</tr>
<tr>
<td><strong>Perspective</strong></td>
<td>• Healthcare system</td>
</tr>
<tr>
<td><strong>Time Horizon</strong></td>
<td>• Duration of the course of treatment per patient following initial assessment</td>
</tr>
</tbody>
</table>
| **Outcomes (2018 USD)** | • Per patient cost per course of treatment  
                              • Per patient cost per remission |
# METHODS

## CONTROLLED-TREATMENT PARAMETERS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>10Hz rTMS</th>
<th>iTBS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base Case</td>
<td>Range</td>
<td>Base Case</td>
</tr>
<tr>
<td>Length of Session</td>
<td>Minutes per session</td>
<td>45</td>
<td>(30 – 60)</td>
</tr>
<tr>
<td>Equipment capacity</td>
<td>Sessions per day</td>
<td>7</td>
<td>(6 – 8)</td>
</tr>
<tr>
<td>Remission rate (%)</td>
<td>Rate of remission</td>
<td>30</td>
<td>(20 – 40)</td>
</tr>
<tr>
<td>Core equipment amortization</td>
<td>Annual period</td>
<td>5</td>
<td>(3 – 10)</td>
</tr>
<tr>
<td>Coil amortization</td>
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## METHODS

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<td>Annual period</td>
<td>5 (3 – 10)</td>
<td>5 (3 – 10)</td>
</tr>
<tr>
<td>Coil amortization</td>
<td>Annual period</td>
<td>1 (1 – 5)</td>
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<td>15 (10 – 30)</td>
<td>Expert opinion</td>
</tr>
<tr>
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<td>Sessions per day</td>
<td>7 (6 – 8)</td>
<td>20 (15 – 30)</td>
<td>Expert opinion</td>
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<tr>
<td>Remission rate (%)</td>
<td>Rate of remission</td>
<td>30 (20 – 40)</td>
<td>30 (20 – 40)</td>
<td>THREE-D trial(^1)</td>
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<td>Annual period</td>
<td>5 (3 – 10)</td>
<td>5 (3 – 10)</td>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Core Equipment</strong></td>
<td>Equipment package cost</td>
<td>50,000</td>
<td>(37,500 – 62,500)</td>
<td>73,000</td>
<td>(54,750 – 91,250)</td>
<td>Manufacturer suggested</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td>Annual cost</td>
<td>2,500</td>
<td>(1,875 – 3,125)</td>
<td>2,500</td>
<td>(1,875 – 3,125)</td>
<td>Expert opinion</td>
</tr>
<tr>
<td><strong>Coil</strong></td>
<td>Cost of coil</td>
<td>19,000</td>
<td>(14,250 – 23,750)</td>
<td>19,000</td>
<td>(14,250 – 23,750)</td>
<td>Manufacturer suggested</td>
</tr>
<tr>
<td><strong>Technician Services</strong></td>
<td>Hourly wage</td>
<td>30</td>
<td>(20 – 40)</td>
<td>30</td>
<td>(20 – 40)</td>
<td>Expert opinion</td>
</tr>
<tr>
<td><strong>Initial Assessment</strong></td>
<td>Cost per assessment</td>
<td>160</td>
<td>(100 – 500)</td>
<td>160</td>
<td>(100 – 500)</td>
<td>Medicare and Medicaid</td>
</tr>
<tr>
<td><strong>Ongoing assessments</strong></td>
<td>Cost per assessment</td>
<td>120</td>
<td>(100 – 300)</td>
<td>120</td>
<td>(100 – 300)</td>
<td>Medicare and Medicaid</td>
</tr>
</tbody>
</table>

METHODS

ANALYSIS

Costs were broken down per session then multiplied by each THREE-D patient’s number of treatment sessions:

1) Cost of technician = \( C_{\text{Technician wage}} \times \text{Session Duration} \times N_{Tx \text{ sessions}} \)

2) Cost of equipment = \( \frac{C_{\text{annual cost}}}{\text{Weekdays per year}} \times \frac{1}{\text{Equipment Capacity}} \times N_{Tx \text{ sessions}} \)

3) Cost of physician assessments = \( C_{\text{initial appointment}} + C_{\text{ongoing appointments}} \times N_{\text{weeks of TX}} \)

4) Cost of treatment course = \( C_{\text{physician assessments}} + C_{\text{Technician}} + C_{\text{core equipment}} + C_{\text{coil}} \)

5) Cost per remission = \( \frac{C_{\text{Course of tx}}}{\text{Remission rate}} \)
METHODS

ANALYSIS

Incremental cost of treatment and cost of remission:

• Non-parameter bootstrapping to generate bias-corrected uncertainty intervals around incremental costs

• Deterministic sensitivity analyses to determine the effect of parameter uncertainty on study results
OUTLINE

1. Background
2. Methods
3. Results
4. Discussion
5. Summary
## RESULTS

### THREE-D TRIAL RESULTS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>10Hz rTMS (n=192)</th>
<th>iTBS (n=193)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Mean (SD)</td>
<td>43.4 (12.1)</td>
<td>41.8 (10.7)</td>
<td>0.1645</td>
</tr>
<tr>
<td>Episode length, Mean (SD)</td>
<td>23.8 (28.7)</td>
<td>21.8 (24.6)</td>
<td>0.4910</td>
</tr>
<tr>
<td>Men, N (%)</td>
<td>81 (42.2%)</td>
<td>74 (39.4%)</td>
<td>0.442</td>
</tr>
<tr>
<td>Previous ECT, N (%)</td>
<td>4 (2.1%)</td>
<td>15 (7.8%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Receiving psychotherapy, N (%)</td>
<td>73 (38.0%)</td>
<td>80 (41.5%)</td>
<td>0.492</td>
</tr>
<tr>
<td>Any anxiety diagnosis, N (%)</td>
<td>113 (58.9%)</td>
<td>100 (51.8%)</td>
<td>0.165</td>
</tr>
<tr>
<td>Treatment sessions, Mean (SD)</td>
<td>26.4 (4.8)</td>
<td>26.7 (4.7)</td>
<td>0.5427</td>
</tr>
<tr>
<td>Missed treatment sessions, Mean (SD)</td>
<td>0.094 (0.5)</td>
<td>0.13 (0.8)</td>
<td>0.5920</td>
</tr>
<tr>
<td>Interrupted sessions, Mean (SD)</td>
<td>0.12 (0.4)</td>
<td>0.063 (0.3)</td>
<td>0.0744</td>
</tr>
<tr>
<td>Rescheduled sessions, Mean (SD)</td>
<td>3.04 (3.8)</td>
<td>2.24 (3.7)</td>
<td>0.0355</td>
</tr>
</tbody>
</table>
### RESULTS

#### AVERAGE PER PATIENT COSTS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>10Hz rTMS</th>
<th>iTBS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (USD), SD</td>
<td>Mean(CAD), SD</td>
</tr>
<tr>
<td>Total cost of course of treatment</td>
<td>$1,844 (304)</td>
<td>$2,309(381)</td>
</tr>
<tr>
<td>Total cost of remission</td>
<td>$6,146 (1,015)</td>
<td>$7,695(1271)</td>
</tr>
</tbody>
</table>
# RESULTS

## COURSE OF TREATMENT COST PER PATIENT

<table>
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<tr>
<th>Parameter</th>
<th>10Hz rTMS</th>
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- iTBS yielded a savings of **US$735 (CAN$920.22)** per course compared to 10Hz rTMS
## RESULTS

### COST OF REMISSION PER PATIENT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>10Hz rTMS Mean (USD), SD</th>
<th>10Hz rTMS Mean(CAD), SD</th>
<th>iTBS Mean (USD), SD</th>
<th>iTBS Mean(CAD), SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cost of course of treatment</td>
<td>$1,844 (304)</td>
<td>$2,309(381)</td>
<td>$1,108 (166)</td>
<td>$1,387(208)</td>
</tr>
<tr>
<td>Total cost of remission</td>
<td>$6,146 (1,015)</td>
<td>$7,695(1271)</td>
<td>$3,695 (552)</td>
<td>$4,626(691)</td>
</tr>
</tbody>
</table>

- iTBS yielded a savings of **US$2,451 (CAN$3,069)** per remission compared to 10Hz rTMS
RESULTS
AVERAGE PER PATIENT COSTS BY CATEGORY

10HZ RTMS

- Technician Time: 32%
- Core Equipment: 8%
- [CATEGORIZED NAME]: 43%

 iTBS

- Physician Assessments: 72%
- Core Equipment: 7%
- Maintenance: 1%

[CATEGORIZED NAME] [PERCENTAGE]
[CATEGORIZED NAME] [PERCENTAGE]
RESULTS

COST-SAVINGS IN CONTEXT

• Although these results demonstrate significant cost-savings, context is important!

• To accomplish these cost-savings:
  • For iTBS, assuming a single patient per session this translates to ~5,220 patients per year needed per one device (coil and core equipment)
    • Translates to 104,400 sessions per year (assuming minimum of 4-weeks of treatment)
  • For 10Hz rTMS, translates to ~1,827 patients per year needed per one device
    • Translates to 7,308 sessions per year (assuming a minimum of 4-weeks of treatment)

• Also assumes capacity is constant and not changing
OUTLINE

1. Background
2. Methods
3. Results
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DISCUSSION

COVERAGE

Varied coverage criteria between countries:

• In the US, rTMS is covered by federal and commercial healthcare insurers for the treatment of patients with MDD who have not achieved remission with conventional pharmacotherapy\(^1\)

• United Kingdom’s National Institute for Health and Care Excellence (NICE) has recommended rTMS for treatment of medication-resistant depression\(^2\)

In Canada:

• Treatment is currently funded under the provincial health insurance plans only in Quebec and Saskatchewan\(^3\)

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DISCUSSION

SESSION COSTS

Compared to ECT:

• ECT is associated with a cost ranging from $300 to $1,000 per treatment session¹

In the US:

• Costs ranging from $6,000 to $12,000 for an acute course of 20 to 30 rTMS sessions²
• Reimbursement falls in the range of $120 to $250 per session among public and private coverage plans

In Canada:

• $60 to $200 per session where publicly or privately funded rTMS is available

In Europe:

• In private clinics or large centres costs can fall in the range of $60 to $300 or higher per session

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DISCUSSION

STRENGTHS AND LIMITATIONS

Strengths:

• Usage of THREE-D data, one of the first comparisons between rTMS protocols
  ○ Designed to be generalizable to real-world clinical practice

Limitations:

• Range of possible estimates for parameters associated with equipment lifespan and equipment capacity

• Results are context specific!

• Does not consider follow-up maintenance treatments

• Only considered direct costs associated with treatment

• Does not consider accelerated courses of treatment


OUTLINE

1. Background
2. Methods
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SUMMARY

• This study demonstrates the potential economic impact of implementation of iTBS in treatment of patients with TRD when compared to 10Hz rTMS.

• Impact of a shorter session duration on technician time and treatment capacity has the potential to result in significant cost-savings per patient and per remission.

• In the context proposed (per one device and if the suggested treatment capacity is met), iTBS may be an economically viable intervention for achieving meaningful reductions in the system-wide prevalence and burden of disease for MDD.
ACKNOWLEDGEMENTS

The authors thank the clinical research staff and patient participants of the THREE-D study and the local Data and Safety Monitoring Board Members.
Thank You!
SUPPLEMENTARY
## RESULTS

**AVERAGE PER PATIENT COSTS BY CATEGORY**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>10Hz rTMS</th>
<th>iTBS</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median (IQR)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Cost of technician time</td>
<td>594 (107)</td>
<td>675 (450 – 675)</td>
<td>200 (35)</td>
</tr>
<tr>
<td>Cost of core equipment</td>
<td>145 (26)</td>
<td>164 (109 – 164)</td>
<td>75 (13)</td>
</tr>
<tr>
<td>Cost of coil</td>
<td>275 (50)</td>
<td>312 (208 – 312)</td>
<td>19 (3)</td>
</tr>
<tr>
<td>Cost of maintenance</td>
<td>36 (7)</td>
<td>41 (27 – 41)</td>
<td>13 (2)</td>
</tr>
<tr>
<td>Cost of physician assessments</td>
<td>794 (115)</td>
<td>880 (640 – 880)</td>
<td>801 (112)</td>
</tr>
</tbody>
</table>
## RESULTS

### INCREMENTAL COSTS

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<tr>
<th>Parameter</th>
<th>Incremental Cost (iTBS – 10Hz rTMS)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Cost of treatment</td>
<td>-735 (24)</td>
</tr>
<tr>
<td>Cost of remission</td>
<td>-2,451 (81)</td>
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</tbody>
</table>
RESULTS

DETERMINISTIC SENSITIVITY ANALYSES

[Diagrams showing incremental costs of treatment (iTBS - 10Hz rTMS) and remission rates with variation in different factors such as length of session, technician wage, coil amortization, equipment capacity, core equipment cost, ongoing physician assessment cost, maintenance cost, and initial physician assessment cost.]
METHODS

ASSUMPTIONS AND CONTEXT

Significant assumptions drive the estimates of cost per course of treatment and per remission for this study:

1) Constant treatment capacity
2) Each patient undergoes a single treatment session per workday
3) Implementation translates to one core equipment package and coil
4) Maintenance is only required annually
5) Technician setup time is 15 minutes