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

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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
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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:

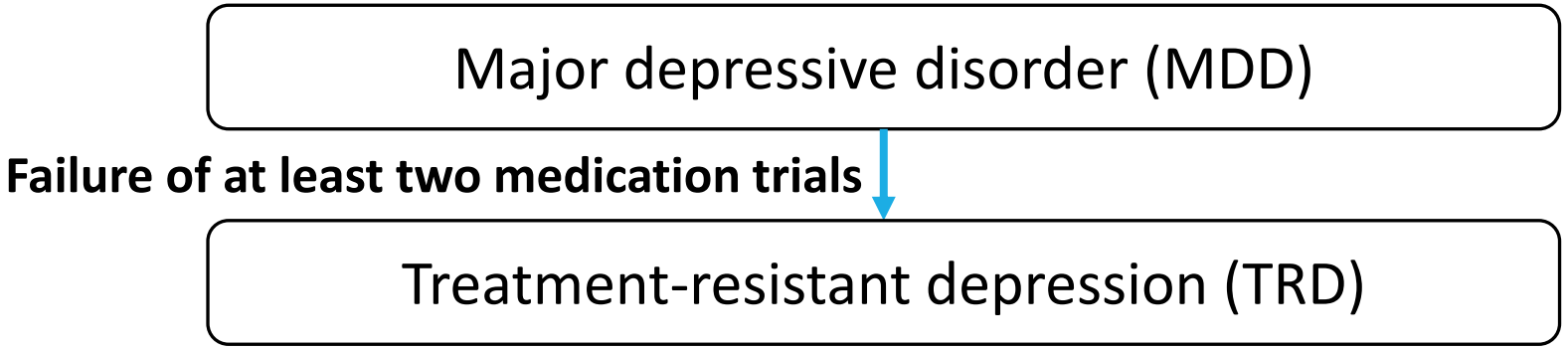
  - 4.7% of Canadians reported a major depressive episode in the last year[3]

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]

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
4. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. AJP 2006;163(11):1905–17.
5. Malhi GS, Parker GB, Crawford J, et al. Treatment-resistant depression: resistant to definition? Acta Psychiatrica Scandinavica 2005;112(4):302–9.

BACKGROUND:
TREATMENT-RESISTANT DEPRESSION



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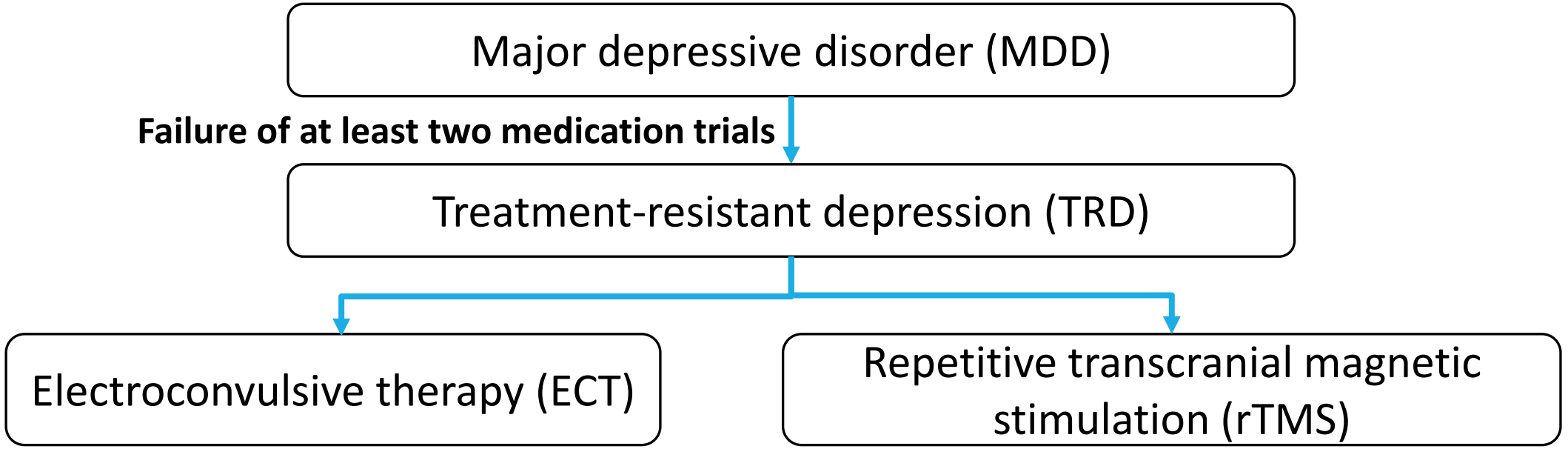

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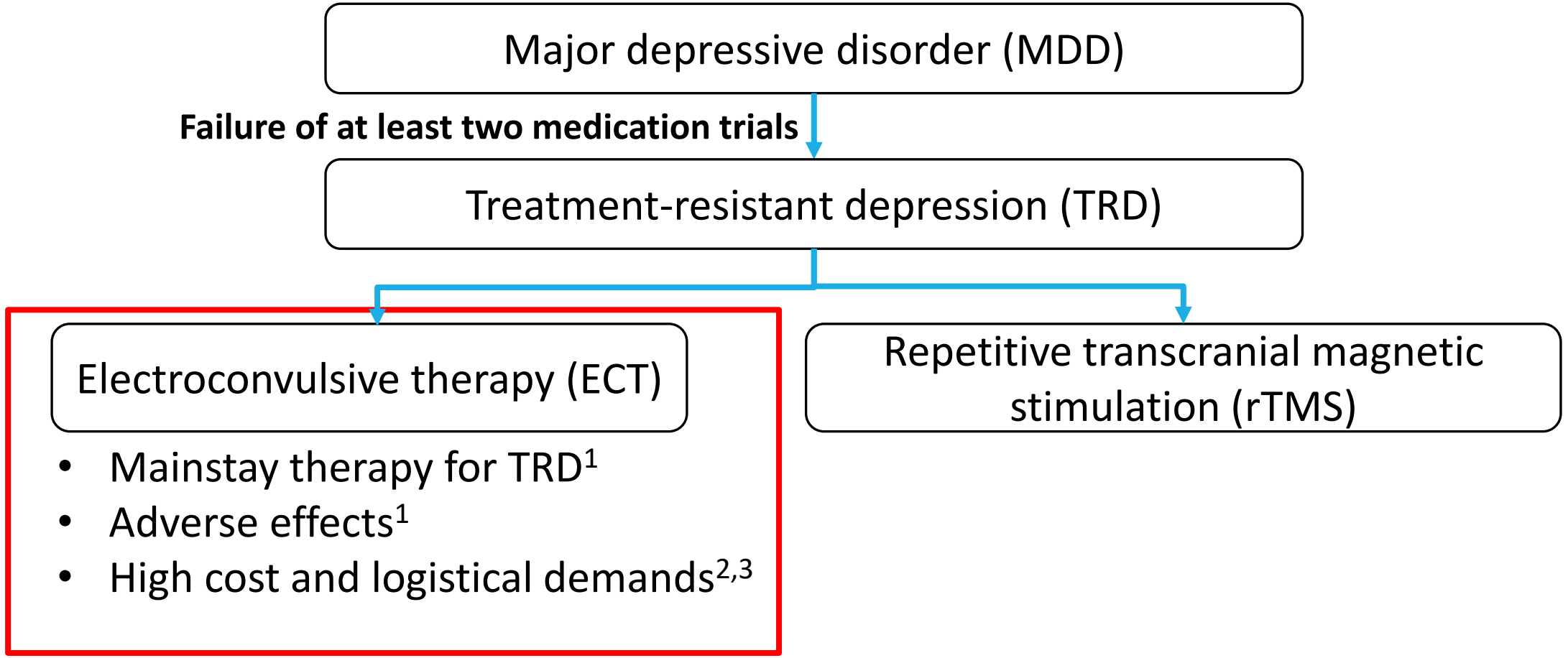


1. Lisanby SH. Electroconvulsive Therapy for Depression. N Engl J Med 2007;357(19):1939–45.
2. Downar J, Blumberger DM, Daskalakis ZJ. Repetitive transcranial magnetic stimulation: an emerging treatment for medication-resistant depression. Canadian Medical Association Journal 2016;188(16):1175–7.
3. Getty SS, Faziola LR. Adverse effects of electroconvulsive therapy on cognitive performance. Ment Illn 2017;9(2).

BACKGROUND:
TREATMENT-RESISTANT DEPRESSION

Major depressive disorder (MDD)

Failure of at least two medication trials

Treatment-resistant depression (TRD)

Electroconvulsive therapy (ECT)

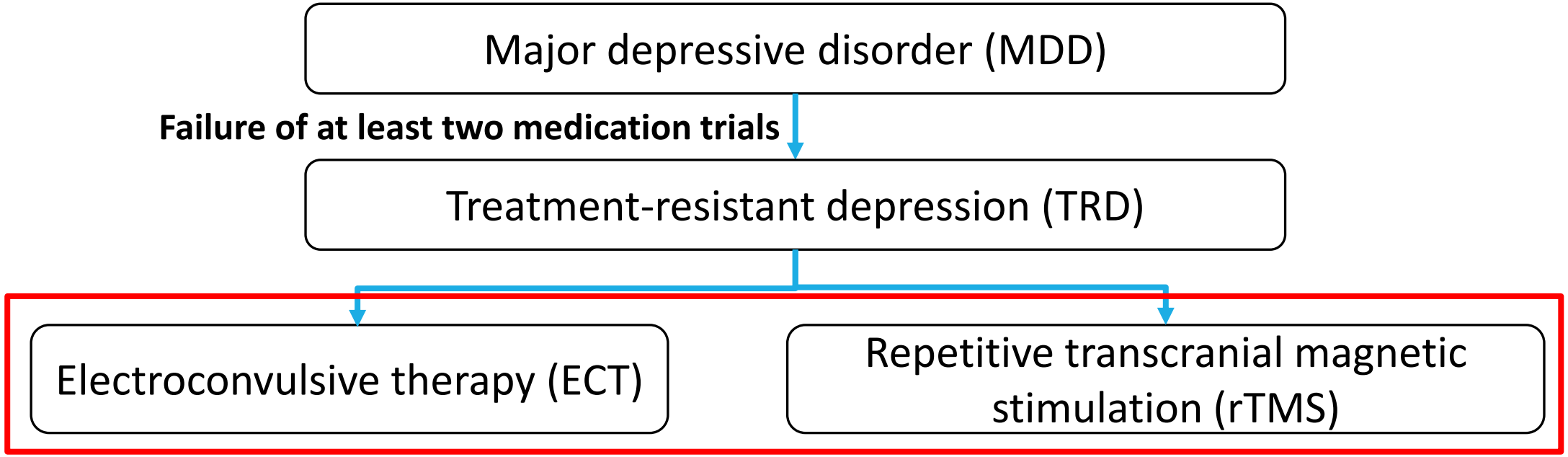
Repetitive transcranial magnetic stimulation (rTMS)

- Introduced in 1985[1]
- Focused magnetic field pulses
- Research has confirmed its efficacy and safety in TRD[2]

1. George MS, Wassermann EM, Williams WA, et al. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport: An International Journal for the Rapid Communication of Research in Neuroscience 1995.
2. Brunoni AR, Chaimani A, Moffa AH, et al. Repetitive Transcranial Magnetic Stimulation for the Acute Treatment of Major Depressive Episodes: A Systematic Review With Network Meta-analysis. JAMA Psychiatry 2017;74(2):143–52.

BACKGROUND:

rTMS vs. ECT

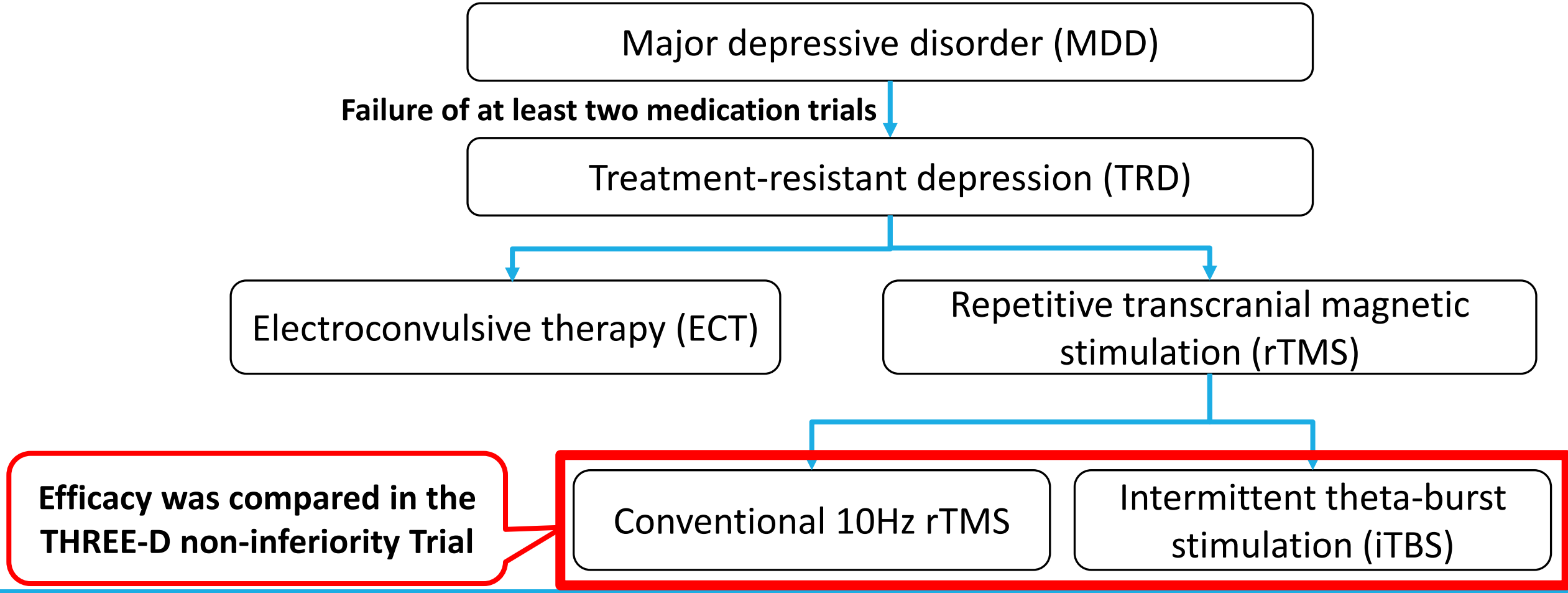


- **Have been extensively compared!**
- Slightly different in clinical effect
- rTMS has a much better adverse-effect profile and cost-effective when compared to ECT in TRD[1,2]

1. Kozel FA, George MS, Simpson KN. Decision analysis of the cost-effectiveness of repetitive transcranial magnetic stimulation versus electroconvulsive therapy for treatment of nonpsychotic severe depression. CNS spectrums. 2004 Jun;9(6):476-82.
2. McClintock SM, Reti IM, Carpenter LL, et al. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. The Journal of clinical psychiatry 2018;79(1).

BACKGROUND:

rTMS Protocols



BACKGROUND:
THE THREE-D TRIAL

- Recently, the THREE-D trial was published as the first randomized non-inferiority trial[1] comparing:

1) Conventional 10 Hz rTMS protocol:

- Approved by the FDA in 2008[2,3]
- 3,000 pulses of 10Hz stimulation to the left DLPFC over 37.5 min[1]

2) Intermittent theta-burst stimulation (iTBS) protocol:

- Differed only in stimulation pattern and number of pulses for a 3 min session duration[1]
- Approved by the FDA for TRD in August of 2018[4]

- 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

1. Blumberger DM, Vila-Rodriguez F, Thorpe KE, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. The Lancet 2018;391(10131):1683–92.
2. Health Quality Ontario. Repetitive transcranial magnetic stimulation for treatment-resistant depression: an economic analysis. Ont Health Technol Assess Ser. 2016 March;16(6):1-51.
3. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biological psychiatry 2007;62(11):1208–16.
4. Brooks M. FDA Clears 3-Minute Brain Stimulation Protocol for Depression. MedScape Medical News Published Online First: 22 August 2018.

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

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- 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?

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METHODS

STUDY OVERVIEW

Design	• Patient-level cost analysis
Population	• Adults aged 18 to 65 with a diagnosis of MDD who did not respond to adequate pharmacotherapy
Intervention	• Minimum of 4-weeks of iTBS treatment
Comparator	• Minimum of 4-weeks of 10Hz rTMS treatment
Perspective	• Healthcare system
Time Horizon	• Duration of the course of treatment per patient following initial assessment
Outcomes (2018 USD)	• Per patient cost per course of treatment • Per patient cost per remission

METHODS

CONTROLLED-TREATMENT PARAMETERS

		10Hz rTMS		iTBS		
Parameter	**Unit**	**Base Case**	**Range**	**Base Case**	**Range**	**Source**
Length of Session	Minutes per session	45	(30 – 60)	15	(10 – 30)	Expert opinion
Equipment capacity	Sessions per day	7	(6 – 8)	20	(15 – 30)	Expert opinion
Remission rate (%)	Rate of remission	30	(20 – 40)	30	(20 – 40)	THREE-D trial[1]
Core equipment amortization	Annual period	5	(3 – 10)	5	(3 – 10)	Expert opinion
Coil amortization	Annual period	1	(1 – 5)	5	(1 – 5)	Expert opinion

1. Blumberger DM, Vila-Rodriguez F, Thorpe KE, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. The Lancet 2018;391(10131):1683–92.

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COST PARAMETERS (in 2018 USD)

		10Hz rTMS		iTBS		
Parameter	**Unit**	**Base Case**	**Range**	**Base Case**	**Range**	**Source**
Core Equipment	Equipment package cost	50,000	(37,500 – 62,500)	73,000	(54,750 – 91,250)	Manufacturer suggested
Maintenance	Annual cost	2,500	(1,875 – 3,125)	2,500	(1,875 – 3,125)	Expert opinion
Coil	Cost of coil	19,000	(14,250 – 23,750)	19,000	(14,250 – 23,750)	Manufacturer Suggested
Technician Services	Hourly wage	30	(20 – 40)	30	(20 – 40)	Expert opinion
Initial Assessment	Cost per assessment	160	(100 – 500)	160	(100 – 500)	Medicare and Medicaid[1]
Ongoing assessments	Cost per assessment	120	(100 – 300)	120	(100 – 300)	Medicare and Medicaid[1]

1. U.S. Centers for Medicare and Medicaid Services. Physician fee schedule search. 2018.

METHODS

ANALYSIS

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

1) Cost of technician = $C_{Technician\ wage} * Session\ Duration * N_{Tx\ sessions}$

2) Cost of equipment = $\left(\frac{\frac{C_{annual\ cost}}{Weekdays\ per\ year}}{Equipment\ Capacity}\right) * N_{Tx\ sessions}$

3) Cost of physician assessments = $C_{initial\ appointment} + C_{ongoing\ appointments} * N_{weeks\ of\ TX}$

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

5) **Cost per remission** = $\frac{C_{\ Course\ of\ tX}}{Remission\ rate}$

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

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THREE-D TRIAL RESULTS

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

RESULTS

AVERAGE PER PATIENT COSTS

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

RESULTS

COURSE OF TREATMENT COST PER PATIENT

	10Hz rTMS		iTBS	
Parameter	**Mean (USD), SD**	**Mean(CAD), SD**	**Mean (USD), SD**	**Mean(CAD), SD**
Total cost of course of treatment	$1,844 (304)	$2,309 (381)	$1,108 (166)	$1,387(208)
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- iTBS yielded a savings of US$735 (CAN$920.22) per course compared to 10Hz rTMS

RESULTS

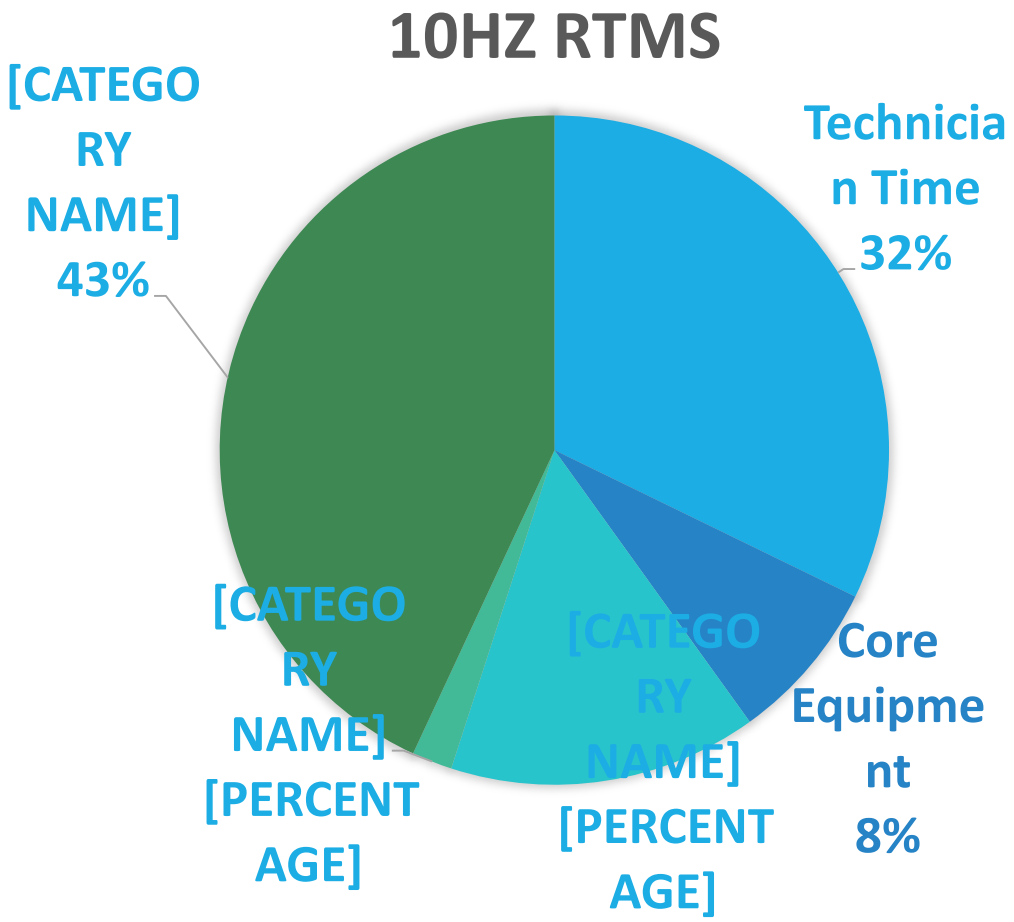
COST OF REMISSION PER PATIENT

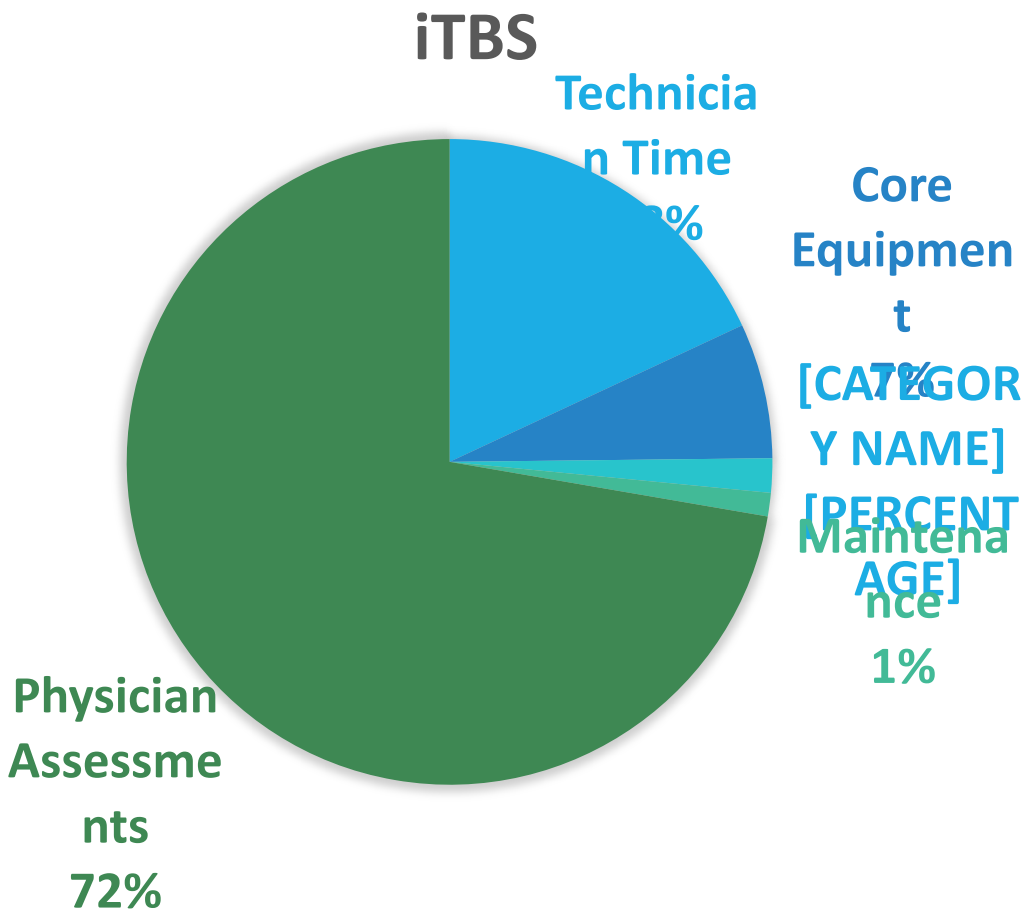
	10Hz rTMS		iTBS	
Parameter	**Mean (USD), SD**	**Mean(CAD), SD**	**Mean (USD), SD**	**Mean(CAD), SD**
Total cost of course of treatment	$1,844 (304)	$2,309(381)	$1,108 (166)	$1,387(208)
Total cost of remission	$6,146 (1,015)	$7,695(1271)	$3,695 (552)	$4,626(691)

- iTBS yielded a savings of US$2,451 (CAN$3,069) per remission compared to 10Hz rTMS

RESULTS

AVERAGE PER PATIENT COSTS BY CATEGORY





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**

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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]

1. McClintock SM, Reti IM, Carpenter LL, et al. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. The Journal of clinical psychiatry 2018;79(1).
2. National Institute for Health and Care Excellence. Repetitive transcranial magnetic stimulation for depression. London, UK: 2015.
3. Health Quality Ontario. Repetitive transcranial magnetic stimulation for treatment-resistant depression: an economic analysis. Ont Health Technol Assess Ser. 2016 March;16(6):1-51.

DISCUSSION

SESSION COSTS

Compared to ECT:

- ECT is associated with a cost ranging from $300 to $1,000 per treatment session[1]

In the US:

- Costs ranging from $6,000 to $12,000 for an acute course of 20 to 30 rTMS sessions[2]
- 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

1. Ross EL, Zivin K, Maixner DF. Cost-effectiveness of electroconvulsive therapy vs pharmacotherapy/psychotherapy for treatment-resistant depression in the united states. JAMA Psychiatry 2018;75(7):713–22.
2. Health Quality Ontario. Repetitive transcranial magnetic stimulation for treatment-resistant depression: an economic analysis. Ont Health Technol Assess Ser. 2016 March;16(6):1-51.

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[1]
- Only considered direct costs associated with treatment
- Does not consider accelerated courses of treatment[2]

1. Milev RV, Giacobbe P, Kennedy SH, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 4. Neurostimulation Treatments. Canadian journal of psychiatry 2016;61(9):561–75.
2. Duprat R, Desmyter S, van Heeringen K, et al. Accelerated intermittent theta burst stimulation treatment in medication-resistant major depression: a fast road to remission? Journal of affective disorders 2016;200:6–14.

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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.

St. Michael's
Inspired Care. Inspiring Science.

UNIVERSITY OF TORONTO

camh
Centre for Addiction and Mental Health

theta
Collaborative

Thank You!

SUPPLEMENTARY

RESULTS

AVERAGE PER PATIENT COSTS BY CATEGORY

	10Hz rTMS		iTBS		
Parameter	**Mean (SD)**	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**	**P Value**
Cost of technician time	594 (107)	675 (450 – 675)	200 (35)	225 (150 - 225)	<0.0001
Cost of core equipment	145 (26)	164 (109 – 164)	75 (13)	84 (56 – 84)	<0.0001
Cost of coil	275 (50)	312 (208 – 312)	19 (3)	22 (15 – 22)	<0.0001
Cost of maintenance	36 (7)	41 (27 – 41)	13 (2)	14 (10 - 14)	<0.0001
Cost of physician assessments	794 (115)	880 (640 – 880)	801 (112)	880 (640 – 880)	0.5189

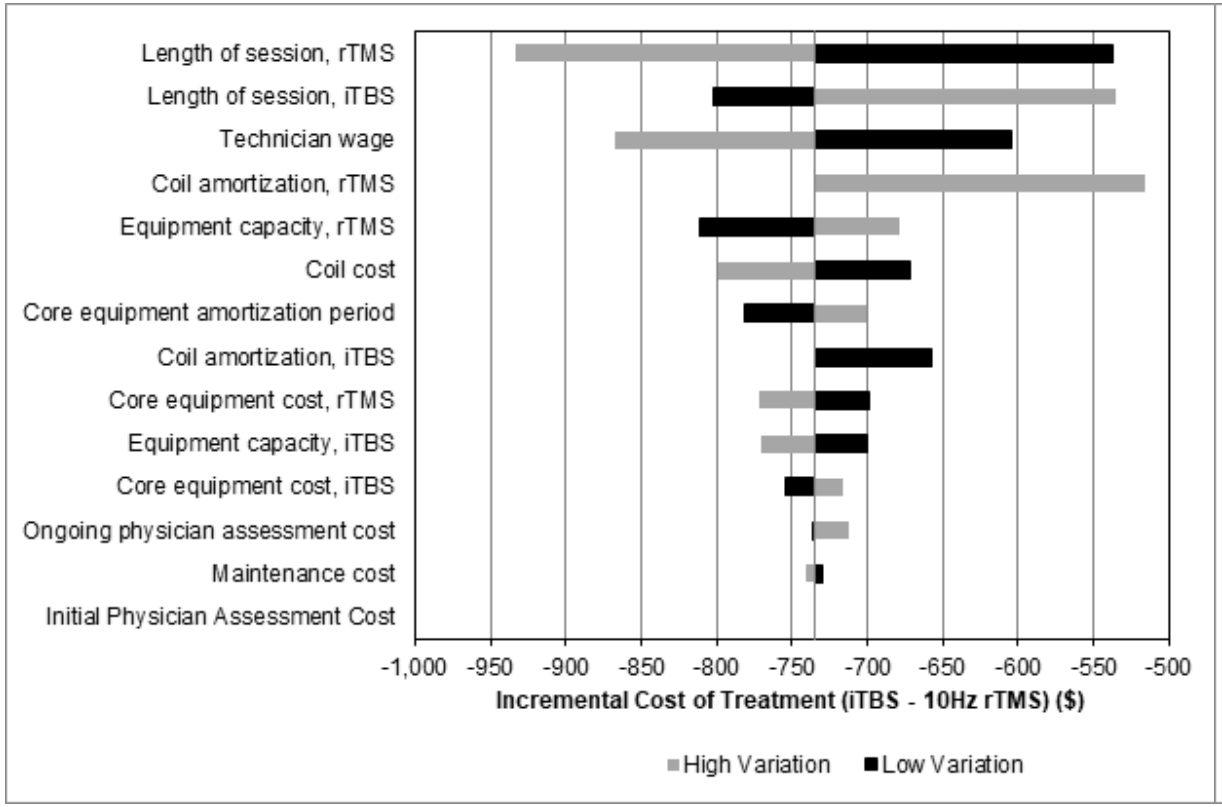
RESULTS

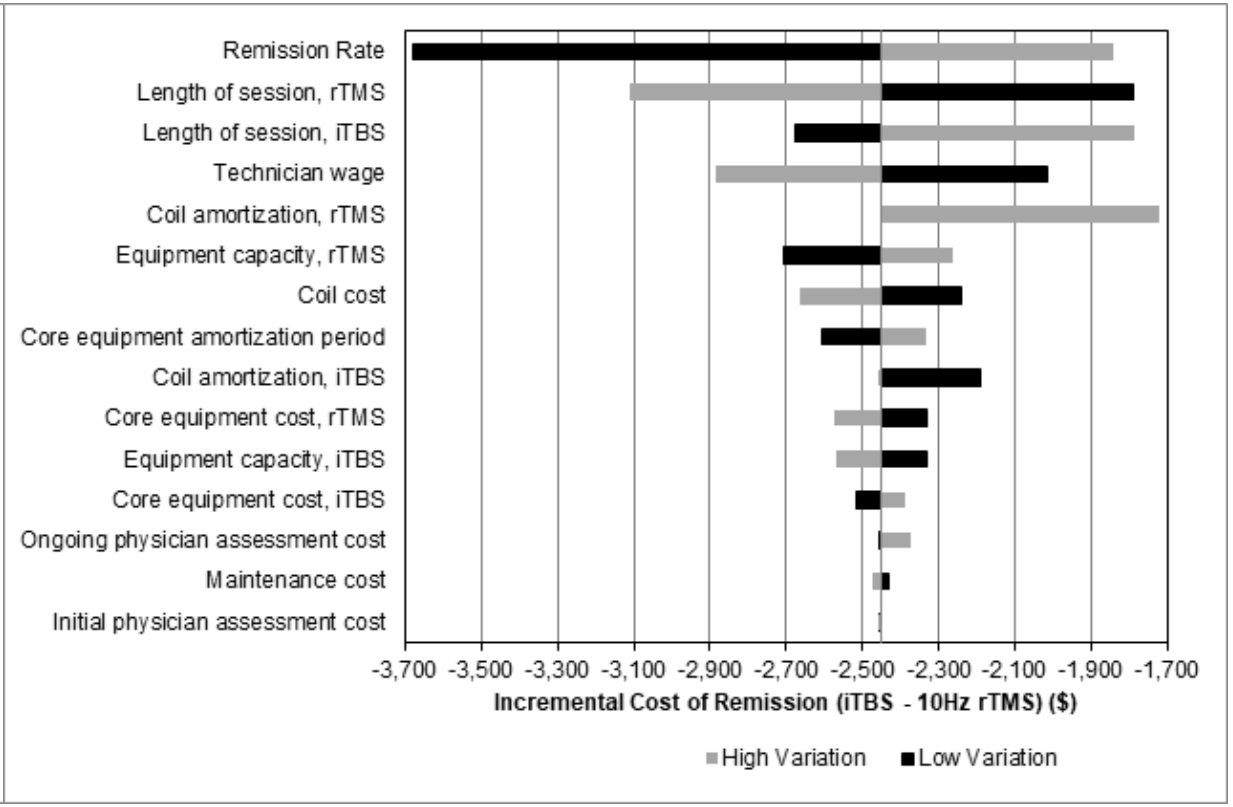
INCREMENTAL COSTS

	Incremental Cost (iTBS – 10Hz rTMS)	
Parameter	**Mean (SD)**	**95% Confidence Interval**
Cost of treatment	-735 (24)	-783 – -688
Cost of remission	-2,451 (81)	-2,610 – -2,293

RESULTS

DETERMINISTIC SENSITIVITY ANALYSES





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