Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial

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Summary

Background Treatment-resistant major depressive disorder is common; repetitive transcranial magnetic stimulation (rTMS) by use of high-frequency (10 Hz) left-side dorsolateral prefrontal cortex stimulation is an evidence-based treatment for this disorder. Intermittent theta burst stimulation (iTBS) is a newer form of rTMS that can be delivered in 3 min, versus 37·5 min for a standard 10 Hz treatment session. We aimed to establish the clinical effectiveness, safety, and tolerability of iTBS compared with standard 10 Hz rTMS in adults with treatment-resistant depression.

Methods In this randomised, multicentre, non-inferiority clinical trial, we recruited patients who were referred to specialty neurostimulation centres based at three Canadian university hospitals (Centre for Addiction and Mental Health and Toronto Western Hospital, Toronto, ON, and University of British Columbia Hospital, Vancouver, BC). Participants were aged 18–65 years, were diagnosed with a current treatment-resistant major depressive episode or could not tolerate at least two antidepressants in the current episode, were receiving stable antidepressant medication doses for at least 4 weeks before baseline, and had an HRSD-17 score of at least 18. Participants were randomly allocated (1:1) to treatment groups (10 Hz rTMS or iTBS) by use of a random permuted block method, with stratification by site and number of adequate trials in which the antidepressants were unsuccessful. Treatment was delivered open-label but investigators and outcome assessors were masked to treatment groups. Participants were treated with 10 Hz rTMS or iTBS to the left dorsolateral prefrontal cortex, administered on 5 days a week for 4–6 weeks. The primary outcome measure was change in 17-item Hamilton Rating Scale for Depression (HRSD-17) score, with a non-inferiority margin of 2·25 points. For the primary outcome measure, we did a per-protocol analysis of all participants who were randomly allocated to groups and who attained the primary completion point of 4 weeks. This trial is registered with ClinicalTrials.gov, number NCT01887782.

Findings Between Sept 3, 2013, and Oct 3, 2016, we randomly allocated 205 participants to receive 10 Hz rTMS and 209 participants to receive iTBS. 192 (94%) participants in the 10 Hz rTMS group and 193 (92%) in the iTBS group were assessed for the primary outcome after 4–6 weeks of treatment. HRSD-17 scores improved from 23·5 (SD 4·4) to 13·4 (7·8) in the 10 Hz rTMS group and from 23·6 (4·3) to 13·4 (7·9) in the iTBS group (adjusted difference 0·01, lower 95% CI –1·16; p=0·0011), which indicated non-inferiority of iTBS. Self-rated intensity of pain associated with treatment was greater in the iTBS group than in the 10 Hz rTMS group (mean score on verbal analogue scale 3·8 [SD 2·0] *vs* 3·4 [2·0] out of 10; p=0·011). Dropout rates did not differ between groups (10 Hz rTMS: 13 [6%] of 205 participants; iTBS: 16 [8%] of 209 participants); p=0·6004). The most common treatment-related adverse event was headache in both groups (10 Hz rTMS: 131 [64%] of 204; iTBS: 136 [65%] of 208).

Interpretation In patients with treatment-resistant depression, iTBS was non-inferior to 10 Hz rTMS for the treatment of depression. Both treatments had low numbers of dropouts and similar side-effects, safety, and tolerability profiles. By use of iTBS, the number of patients treated per day with current rTMS devices can be increased several times without compromising clinical effectiveness.

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Introduction

Major depressive disorder is a leading cause of disability worldwide.[1] About a third of patients with major depressive disorder do not respond to pharmacotherapy or psychotherapy.[2] For patients with treatment-resistant depression, non-invasive brain stimulation via techniques such as repetitive transcranial magnetic stimulation (rTMS) is an emerging option.[3] rTMS uses powerful, focused magnetic field pulses to induce durable changes in the activity of brain regions that are affected by major depressive disorder.[4,5] Large-scale multicentre trials and meta-analyses over the past 20 years have confirmed the efficacy and safety of rTMS of the left dorsolateral prefrontal cortex in treatment-resistant depression.[6–8]

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Research in context

Evidence before this study

We searched PubMed from Jan 1, 1996, to Dec 7, 2017, with the search terms: "depression", "transcranial magnetic stimulation", and "theta burst stimulation". We restricted the search to reviews and clinical trials in English. Systematic reviews and depression guidelines have recognised repetitive transcranial magnetic stimulation (rTMS) as an evidence-based treatment for patients who have not responded to a minimum of one adequate antidepressant treatment trial. In 2015, the UK National Institute for Health and Care Excellence recommended rTMS as a treatment for depression. Additionally, the US Agency for Healthcare Research and Quality published a meta-analysis that found a mean reduction in Hamilton Rating Scale for Depression (HRSD-17) score of 4·53 points (95% CI −6·11 to −2·96) in patients treated with rTMS compared with sham treatment. The form of rTMS with the most supporting evidence is a high-frequency (10 Hz) protocol, in which rTMS is delivered to the left dorsolateral prefrontal cortex over 37·5 min. Broad access to rTMS treatment has been partly limited by the number of patients who can be treated with existing protocols. A newer form of rTMS, theta burst stimulation (TBS), can be delivered in a similar excitatory protocol to the standard 10 Hz protocol. A treatment of excitatory intermittent TBS (iTBS) can be delivered in slightly more than 3 min. Several small trials and two meta-analyses have suggested that iTBS can be efficacious in treating depression.

Added value of this study

To our knowledge, this is the largest trial of brain stimulation ever done and is the first adequately powered non-inferiority trial to compare the effectiveness of iTBS with that of the standard 10 Hz treatment. Our data robustly show that iTBS is non-inferior in reducing depressive symptoms, increasing response (indicated by a 50% reduction in HRSD-17 score), and achieving remission of symptoms (indicated by an HRSD-17 score of less than 8), with very similar tolerability and safety profiles between the two treatments.

Implications of all the available evidence

Excitatory rTMS can be delivered to the left dorsolateral prefrontal cortex by use of an iTBS protocol with no reduction in clinical effectiveness for major depressive disorder, compared with standard 10 Hz rTMS treatment. A course of treatment requires daily attendance on weekdays for 4 to 6 weeks; however, treatment sessions can now be completed in just over 3 min. The ability to deliver effective treatment efficiently could increase the treatment capacity of clinics offering rTMS.

rTMS is approved by the US Food and Drug Administration (FDA) and is covered by many public and private insurers in the USA and other countries. However, adoption of this treatment has been slow, partly due to high cost and low capacity. The conventional, FDA-approved protocol requires 37·5 min of 10 Hz stimulation per session.[7] Long session lengths restrict treatment capacity and increase the cost per session. Reduced session lengths could therefore improve the accessibility and cost-effectiveness of rTMS.

A newer form of rTMS called theta burst stimulation (TBS) has been developed.[9,10] Unlike 10 Hz stimulation, TBS mimics endogenous theta rhythms, which can improve induction of synaptic long-term potentiation.[10] One form of TBS, intermittent TBS (iTBS), delivers 600 pulses in just 3 min, yet shows similar or more potent excitatory effects than conventional 10 Hz stimulation.[11] Several pilot trials[12–14] and two meta-analyses[8,15] indicate that iTBS is superior to sham treatment for treatment-resistant depression. However, the key practical question is whether iTBS performs comparably to the existing standard of care. If 3 min iTBS sessions were non-inferior to the standard, FDA-approved 37·5 min 10 Hz sessions, then the capacity, cost, and accessibility of rTMS would improve several-fold, greatly improving its clinical usefulness.

We therefore conducted a randomised, multicentre, non-inferiority trial to compare iTBS with conventional 10 Hz rTMS in patients with treatment-resistant depression. We hypothesised that iTBS would achieve non-inferior reductions in depressive symptoms and non-inferior rates of response and remission compared with the standard 10 Hz rTMS protocol. We also aimed to compare safety and tolerability outcomes in terms of self-reported adverse events, treatment-associated pain, and numbers of all-cause dropouts.

Methods

Study design and participants

The study was a randomised, multicentre, non-inferiority trial. Participants were recruited after referral to specialty neurostimulation centres at three Canadian academic health centres (Centre for Addiction and Mental Health, Toronto, ON; Toronto Western Hospital, Toronto, ON; University of British Columbia Hospital, Vancouver, BC).

We recruited adults aged 18–65 years who had a Mini-International Neuropsychiatric Interview-confirmed diagnosis of major depressive disorder, as a single or recurrent episode. A patient met inclusion criteria if their current episode showed a 17-item Hamilton Rating Scale for Depression (HRSD-17)[16] score of at least 18, they showed no clinical response to an adequate dose of an antidepressant (based on an antidepressant treatment history form score of more than 3 in the current episode) or were unable to tolerate at least two separate trials of antidepressants of inadequate dose and duration, and they had received a stable antidepressant regimen for at least 4 weeks before treatment, which continued during treatment. Exclusion criteria included substance abuse or dependence in the past 3 months, active suicidal intent,

pregnancy, bipolar disorder, any psychotic disorder or current psychotic symptoms, previous rTMS treatment, a lifetime history of non-response to an adequate course—ie, a minimum of eight treatments—of electroconvulsive therapy, personality disorder deemed to be the primary pathology, an unstable medical illness, substantial neurological illness, abnormal serology, or the presence of a cardiac pacemaker, intracranial implant, or metal in the cranium. Participants were also excluded if they were taking more than 2 mg lorazepam (or an equivalent) or any antizconvulsant or if more than three adequate antidepressant trials had failed (determined by antidepressant treatment history form).[17,18] Ethics approval was granted by the research ethics boards of all three institutions. A local data and safety monitoring board oversaw the study. All participants provided written, informed consent.

Randomisation and masking

Participants were randomly allocated (1:1) to groups receiving either 10 Hz rTMS or iTBS of the left dorsolateral prefrontal cortex. Randomisation tables of a fixed size were made before each site started recruitment with a computer-based algorithm that generated randomly permuted blocks, which were stratified by study site, and groups were balanced regarding degree of medication resistance (more than one *vs* one or fewer adequate trials in which the patient did not respond to treatment), since this variable was previously associated with poor response to rTMS.[7] The randomisation tables were used by staff outside the study team to produce opaque, sealed envelopes, labelled with a participant-specific randomisation identification number and containing a treatment allocation code. After collection of patient details and antidepressant treatment history form score, participants were assigned a randomisation identification number by study staff. The randomisation identification number was obtained and treatment allocation accessed after participants received their baseline MRI by the treatment technician. Participants and treatment technicians were, by necessity, aware of the treatment condition, but staff assessing treatment outcomes were segregated in a different clinic area and were masked to treatment condition. Participants were instructed not to discuss their treatment allocation with these staff or other participants.

Procedures

Before treatment, participants had high-resolution anatomical MRIs, and each treatment session used real-time MRI-guided neuronavigation with a Visor neuronavigation system (ANT Neuro, Enschede, Netherlands) for coil positioning. The left dorsolateral prefrontal cortex target was located in each participant by reverse co-registration from the MNI152 stereotaxic coordinate (x–38, y+44, z+26), which was previously identified as optimal on the basis of clinical outcomes and whole-brain functional connectivity.[19] rTMS was delivered with a MagPro X100 or R30 stimulator, equipped with a B70 fluid-cooled coil and high-performance cooler (MagVenture, Farum, Denmark).

Each participant's resting motor threshold (RMT) was determined by use of visual observation in accordance with standard clinical practice.[20] 10 Hz rTMS used conventional FDA-approved parameters (120% RMT stimulation intensity; 10 Hz frequency; 4 s on and 26 s off; 3000 pulses per session; total duration of 37·5 min).[6,7] iTBS was delivered at the same site and intensity (120% RMT), differing only in stimulation pattern and total number of pulses (triplet 50 Hz bursts, repeated at 5 Hz; 2 s on and 8 s off; 600 pulses per session; total duration of 3 min 9 s).[9] Initial treatment comprised 20 sessions in total, which consisted of once-daily sessions (on weekdays; ie, five sessions a week).

An HRSD-17 score[16] was determined by trained research staff at baseline, after every five treatments, and 1 week, 4 weeks, and 12 weeks after treatment. Participants with an improvement in HRSD-17 score of more than 30% from baseline, but who did not achieve remission, received ten additional sessions in accordance with consensus guidelines.[20] Participants missing scheduled sessions because of illness or scheduling conflicts received additional sessions at the end of the treatment course to achieve the intended course length. However, participants missing 4 consecutive treatment days were withdrawn.

Secondary outcome measures were also recorded at baseline, after every five treatments, and 1 week, 4 weeks, and 12 weeks after treatment. These measures included the 30-item inventory of depressive symptoms (IDS-30),[21] the Brief Symptom Inventory–Anxiety Subscale (BSI-A)[22] (both evaluated by the same person who assessed HRSD scores), and the self-rated 16-item quick inventory of depressive symptoms (QIDS-SR).[23]

At each session, adverse events were also self-reported; participants self-rated pain intensity of the rTMS procedure on a verbal analogue scale (from 1 [no pain] to 10 [intolerable pain]). Previous rTMS trials indicate that participants rapidly become accustomed to pain over the initial sessions.[24] Thus, to ensure tolerability, stimulation intensity was adaptively titrated upward as quickly as possible to the target intensity of 120% RMT, without exceeding maximum tolerable pain (appendix). We recorded the number of sessions required to reach 120% RMT by session-end, and the number of sessions required to start the session at this target intensity. We also recorded the number of serious adverse events and reasons for treatment discontinuation when such events occurred.

See Online for appendix

Outcomes

The primary outcome was reduction in HRSD-17 score from baseline to the end of treatment (either 20 or 30 treatments). If participants received most scheduled sessions and a 4-week, 5-week, or 6-week assessment was

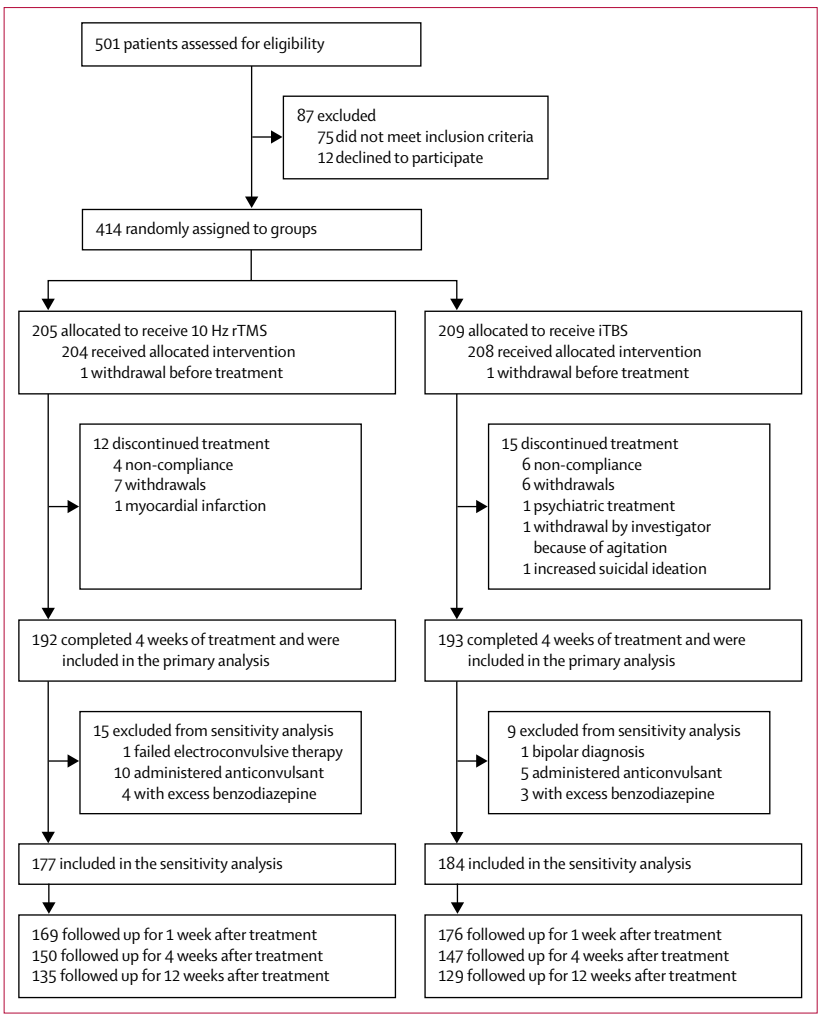

Figure 1: **Trial profile**
rTMS=repetitive transcranial magnetic stimulation. iTBS=intermittent theta burst stimulation.

available, they were assessed for the primary endpoint. In the same population of participants, we also assessed response (by HRSD-17, IDS-30, and QIDS-SR scores; defined as score reductions of ≥50% from baseline), remission (defined as HRSD-17 scores <8, IDS-30 scores <14, and QIDS-SR scores <6), and improved scores on the IDS-30, BSI-A, and the QIDS-SR as secondary outcomes.

Statistical analysis

A threshold of 3 points on the HRSD scale has been specified by the National Institute for Health and Care Excellence to determine a clinically meaningful difference between active pharmacotherapy and placebo.[25,26] The initial power analysis specified a very conservative non-inferiority margin of 1·75 points difference in HRSD-17 score between iTBS and 10 Hz rTMS; this calculation used large previous randomised control trials of 10 Hz rTMS in treatment of depression and assumed an endpoint HRSD-17 SD of 5 points.[6,7,27,28] An interim analysis at 100 participants revealed endpoint SDs of about 8 points in both groups. As a result, a revised non-inferiority margin of 2·25 points was specified to attain a necessary sample size. Importantly, the revised non-inferiority margin of 2·25 points was less than the lower bound of the 95% CI of the treatment effect between rTMS and sham on the HRSD-17, reported in a 2014 meta-analysis[29] by the Agency for Healthcare Research and Quality (mean reduction 4·53; 95% CI –6·11 to –2·96). With this non-inferiority margin, a minimum total sample size of 320 treatment-completers was required to achieve 80% power at α=0·05. To account for attrition and ensure adequate power at 1 week after treatment, we aimed to enrol more than 400 participants.

For the primary outcome analysis, baseline-adjusted change was estimated from an ANCOVA model, with the final HRSD-17 score as the outcome and baseline HRSD-17 score as the adjustment covariate, with the aforementioned non-inferiority margin of 2·25. Following standard practice for non-inferiority studies, a one-sided test at the 5% significance level and a one-sided 95% confidence interval was computed. A per-protocol analysis was chosen, since intention-to-treat analyses can bias results toward non-inferiority.[30] The null hypothesis was that the baseline-adjusted mean final HRSD-17 score for 10 Hz rTMS would be at least 2·25 points better than for iTBS, and the alternative (non-inferiority) hypothesis was that the baseline-adjusted mean final HRSD-17 score for 10 Hz rTMS would be less than 2·25 points better than for iTBS. The same non-inferiority margin of 2·25 was used for IDS-30 and QIDS-SR secondary outcomes. A non-inferiority margin of 15% was used to compare proportions of responders (≥50% score improvement from baseline on each scale). A non-inferiority margin of 10% was used to compare proportions of remitters (within HRSD-17, IDS-30, and QIDS-SR scales). The non-inferiority margins for response and remission were chosen to be less than the raw mean difference between active and sham rTMS for response (21% difference) and remission (14% difference) that were reported in a 2014 meta-analysis.[29] For tolerability comparisons, each participant's mean self-reported pain score across all treatments was calculated. The prevalence and proportion of participants reporting side-effects and adverse events were calculated and compared with Wilcoxon rank-sum test, Pearson's chi-squared test, and Fisher's exact test. The number of treatments were compared with independent samples *t* tests. The proportion of serious adverse events in both groups was compared with a Fisher's exact test. R (v 3.4.3) was used for statistical analyses. This trial is registered with ClinicalTrials.gov, number NCT01887782.

Role of the funding source

The funder of the study (Canadian Institutes of Health Research) and the device manufacturer (MagVenture) that provided equipment had no role in study design,

data collection, data analysis, data interpretation, or writing of the report. The corresponding author (DMB) and statistician (KET) had full access to all the data and the corresponding author (DMB) had final responsibility for the decision to submit for publication.

Results

From Sept 3, 2013, to Oct 3, 2016, 501 participants with major depressive disorder were enrolled, of whom 87 (17%) were ineligible or declined to participate. 414 participants were randomly assigned to receive treatment (205 [50%] 10 Hz rTMS and 209 [50%] iTBS) and two (one from each group) withdrew participation after having an MRI but before receiving treatment. Of the remaining participants, 192 (94%) participants from the 10 Hz rTMS group and 193 (92%) from the iTBS group completed most of the course of 4 weeks of treatment (with 12 participants from the 10 Hz rTMS group and 15 participants from the iTBS group discontinuing treatment) and were analysed for the primary outcome (figure 1).

13 (6%) of 205 participants in the 10 Hz rTMS group and 16 (8%) of 209 participants in the iTBS group (including the two participants who were randomised but did not receive treatment) discontinued treatment before 20 sessions (χ^2=0·27 ; p=0·6004). Among the 10 Hz rTMS group participants, six could not adhere to the treatment schedule, three could not tolerate the treatment, one could not commit to treatment, two discontinued due to lack of perceived benefit, and one had a myocardial infarction that led to hospital admission (deemed unrelated to the rTMS treatment). Among the iTBS group participants, six could not adhere to the treatment schedule, two could not tolerate treatment, one could not commit to treatment, and four withdrew due to lack of perceived benefit. Three participants in the iTBS group had serious adverse events: one with agitation that led to hospital admission, one with worsening suicidal ideation, and one other hospital admission for worsening depression.

Table 1 provides the baseline characteristics of the study participants. Randomisation was successful with respect to the distribution of participants with previous treatment failure across groups. Training sessions across sites and assessments of reliability across staff ratings showed an intra-class correlation coefficient of 0·996 between HRSD scores.

HRSD-17 scores at the end of treatment showed an estimated adjusted difference of 0·103 points between the groups (favouring iTBS), with a lower 95% CI of –1·16 points (favouring 10 Hz rTMS treatment; table 2), which was smaller than the non-inferiority margin of 2·25 points (p=0·0011).

On all secondary outcome measures of change in depression scores on other inventory checklists and response and remission rates, iTBS also showed non-inferiority to 10 Hz rTMS, except for the reduction of scores on the IDS-30 (table 2; figure 2).

	10 Hz rTMS group (n=205)	iTBS group (n=209)
Age, years	43·2 (12·2)	41·6 (10·8)
Women	119 (58%)	127 (61%)
Men	86 (42%)	82 (39%)
Duration of education, years	16·1 (3·2)	16·4 (3·1)
Left-handed	17 (8%)	25 (12%)
Age of onset, years	21·9 (11·6)	20·3 (10·9)
In current employment	70 (34%)	80 (38%)
Baseline HRSD-17 score	23·6 (4·4)	23·7 (4·4)
Baseline QIDS-SR score	17·3 (3·9)	17·0 (5·2)
Baseline IDS-30 score	40·0 (10·3)	39·1 (9·9)
Baseline BSI-A score	10·5 (5·4)	9·8 (5·3)
Depressive episode duration, months	23·9 (28·8)	22·8 (25·7)
Previous electroconvulsive therapy	4 (2%)	16 (8%)
Anxiety comorbidity	120 (59%)	108 (52%)
Receiving psychotherapy during the episode	79 (39%)	88 (42%)
Receiving pharmacotherapy during treatment		
Benzodiazepine	71 (35%)	68 (33%)
Antidepressant	163 (80%)	155 (74%)
Antidepressant combination	48 (23%)	43 (21%)
Antipsychotic augmentation	40 (20%)	37 (18%)
Lithium augmentation	7 (3%)	6 (3%)
ATHF score	6·2 (3·3)	6·3 (3·5)
Previous treatment history		
Unable to tolerate two trials	16 (8%)	16 (8%)
One failed antidepressant	92 (45%)	93 (44%)
Two failed antidepressants	59 (29%)	57 (27%)
Three failed antidepressants	38 (19%)	43 (21%)

Data are mean (SD) or number of participants in each group (% of total). rTMS=repetitive transcranial magnetic stimulation. iTBS=intermittent theta burst stimulation. HRSD-17=17-item Hamilton Rating Scale for Depression. QIDS-SR=16-item Quick Inventory of Depressive Symptomatology (self-rated). IDS-30=30-item Inventory of Depressive Symptomatology. BSI-A=Brief Symptom Inventory-Anxiety. ATHF=Antidepressant Treatment History Form.

Table 1: **Baseline demographic and clinical characteristics**

145 (71%) of 204 participants in the 10 Hz rTMS group and 146 (70%) of 208 participants in the iTBS group reported at least one side-effect during treatment (χ^2=0·04; p=0·843; table 3). In both groups, the most common side-effect was headache. In the 10 Hz rTMS group, the median number of side-effects was 4·0 (IQR 0–8·2) and the average number of side-effects during treatment was 5·5 (SD 6·2); in the iTBS group, the median was 3·0 (0–8·0) and the average was 5·1 (6·4; F [1,410]=0·65; p=0·419). The distribution of participants reporting side-effects over the course of treatment is shown in the appendix. The median and average pain score across sessions was lower for 10 Hz rTMS treatment (median 2·9, IQR 1·9–4·3; mean 3·4, SD 2·0) than for iTBS treatment (3·6, 2·1–5·3; 3·8, 2·0; F [1,410]=6·45; p=0·011), although this difference was modest. The distribution of average pain scores among participants in each treatment group is shown in the appendix.

	Number of participants assessed (10 Hz rTMS group/ iTBS group)	10 Hz rTMS group	iTBS group	Estimated adjusted difference	Lower 90% CI*	Upper 90% CI	p value
HRSD-17							
Baseline	385 (192/193)	23·5 (4·4)	23·4 (4·3)	..	..	..	..
After treatment	385 (192/193)	13·4 (7·8)	13·4 (7·9)	0·103	−1·16	1·36	0·0011
1 week after treatment	345 (169/176)	13·5 (8·0)	13·2 (8·1)	0·346	−1·00	1·69	0·0008
4 weeks after treatment	297 (150/147)	13·6 (7·9)	13·8 (8·5)	−0·273	−1·74	1·19	0·013
12 weeks after treatment	264 (135/129)	14·1 (8·6)	13·6 (8·5)	0·349	−1·23	1·97	0·0043
Baseline (SA)	361 (177/184)	23·5 (4·3)	23·4 (4·2)	..	..	..	..
After treatment (SA)	361 (177/184)	13·1 (7·6)	13·1 (7·9)	−0·052	−1·35	1·25	0·0028
Response	385 (192/193)	91 (47%)†	95 (49%)†	1·83%	−6·55%	10·2%	0·0005
Remission	385 (192/193)	51 (27%)†	61 (32%)†	5·21%	−2·41%	12·8%	0·0005
IDS-30							
Baseline	385 (192/193)	40·1 (10·5)	38·7 (9·7)	..	..	..	..
After treatment	385 (192/193)	24·5 (14·5)	24·5 (14·6)	−0·914	−3·07	1·25	0·15
1 week after treatment	345 (169/176)	24·5 (15·3)	23·9 (14·6)	−0·135	−2·52	2·25	0·072
4 weeks after treatment	294 (149/145)	25·6 (16·6)	24·8 (15·6)	−0·117	−2·89	2·66	0·1
12 weeks after treatment	263 (134/129)	24·9 (16·1)	23·2 (14·6)	0·809	−2·17	3·79	0·046
Response	385 (192/193)	76 (40%)†	76 (39%)†	−0·21%	−8·40%	8·00%	0·0015
Remission	385 (192/193)	49 (26%)†	48 (25%)†	−0·65%	−7·93%	6·60%	0·017
QIDS-SR							
Baseline	384 (192/192)	17·4 (3·9)	17·0 (5·2)	..	..	..	..
After treatment	379 (189/190)	10·9 (6·1)	10·6 (6·1)	0·159	−0·81	1·12	<0·0001
1 week after treatment	340 (166/174)	10·7 (6·5)	10·3 (6·1)	0·217	−0·86	1·29	<0·0001
4 weeks after treatment	286 (144/142)	11·0 (6·9)	11·0 (6·5)	−0·014	−1·27	1·24	0·0018
12 weeks after treatment	264 (135/129)	11·1 (6·6)	10·9 (6·4)	−0·528	−1·79	0·73	0·012
Response	379 (189/190)	76 (40%)†	76 (40%)†	−0·21%	−8·49%	8·10%	0·0017
Remission	379 (189/190)	37 (20%)†	50 (26%)†	6·60%	−0·46%	13·70%	<0·0001
BSI-A							
Baseline	384 (192/192)	10·5 (5·4)	9·6 (5·3)	..	..	..	..
After treatment	363 (182/181)	7·1 (5·5)	6·4 (5·1)	0·155	−1·16	1·36	<0·0001

Data for 10 Hz rTMS and iTBS are mean score (SD), unless otherwise indicated. For estimated adjusted difference values, positive values indicate a greater change in the iTBS group and negative values indicate a greater change in the 10 Hz rTMS group. p values indicate the significance of rejecting the null hypothesis, based on the change in symptoms in the two groups compared with the non-inferiority margin of 2·25 for change, and on a non-inferiority margin of 15% for the proportion of responders and 10% for the proportion of remitters. rTMS=repetitive transcranial magnetic stimulation. iTBS=intermittent theta burst stimulation. HRSD-17=17-item Hamilton Rating Scale for Depression. SA=sensitivity analysis population. IDS-30=30-item Inventory of Depressive Symptomatology. QIDS-SR=16-item Quick Inventory of Depressive Symptomatology (self-rated). BSI-A=Brief Symptom Inventory–Anxiety Subscale. *Data are the lower 95% CI of the one-sided test for non-inferiority. †Data are n (% of participants assessed).

***Table 2*: Change in depression severity scores from baseline to final treatment and at follow-up, and number of participants showing response and remission**

Serious adverse events were seen in one (<1%) of 205 participants in the 10 Hz group (a myocardial infarction) and three (1%) of 209 participants in the iTBS group (one withdrawal by the investigator because of agitation that led to hospital admission, one participant with worsening suicidal ideation, and one hospital admission for worsening depression), with no significant difference in the number of serious adverse events between groups (Fisher's exact test, p=0·6232).

24 participants (15 participants from the 10 Hz rTMS group and nine participants from the iTBS group) were found to be ineligible for the study after discovery of exclusionary criteria during case report form monitoring or data cleaning at the end of the trial. Sensitivity analyses excluding these participants also indicated non-inferiority of iTBS for the primary outcome (table 2). Sensitivity analyses for all primary and secondary outcomes with ineligible participants excluded are in the appendix. Additional prespecified analyses of HRSD-17 scores also suggested non-inferiority of iTBS at 1 week, 4 weeks, and 12 weeks after treatment (table 2; figures 2 and 3). Further sensitivity analyses using a one-sided 97·5% CI and a linear mixed-effects model to account for missing data during active treatment and follow-up phases are presented in the appendix. Among participants who completed a 4-week assessment, the number of treatment sessions did not differ between the 10 Hz rTMS (mean 26·4, SD 4·8) and iTBS (26·7, 4·7) groups (t [1,383]=0·62; p=0·5359). 64 (33%) of 192 participants in the 10 Hz rTMS group and 61 (32%) of 193 participants in

the iTBS group completed treatment—ie, achieved remission or had less than 30% improvement—at 4 weeks (χ^2=0·13; p=0·7175). The mean number of treatment sessions given beyond 20 treatments did not differ between the 10 Hz rTMS group (mean 9·83, SD 0·93) and the iTBS group (9·76, 1·17; t [1,257]=0·59; p=0·56).

Discussion

To our knowledge, this is the first randomised non-inferiority trial comparing iTBS treatment with 10 Hz rTMS, the current standard rTMS treatment for treatment-resistant depression. The findings provide strong evidence that iTBS is non-inferior to standard 10 Hz rTMS in reducing depressive symptoms. Non-inferiority was seen in clinician-rated and self-reported measures and in continuous and categorical outcomes (ie, change in scores and response and remission incidence). Furthermore, the non-inferior reduction in depressive symptoms was also observed at 1 week, 4 weeks, and 12 weeks after treatment. Self-reported adverse events and serious adverse events did not significantly differ between the groups. Mean pain ratings were significantly higher for iTBS, but this result did not translate into higher dropout rates. These findings indicate that the 3 min iTBS protocol might serve comparably to the standard 37·5 min 10 Hz rTMS protocol as an intervention for treatment-resistant depression.

A response rate of 49% and remission rate of 32% following iTBS treatment for treatment-resistant depression is encouraging and clinically meaningful, given that these participants had not responded to an average of one to two adequate antidepressant medication trials and about 50% of the participants had failed two adequate trials. For comparison, the proportion of participants who achieved remission after treatment with switch or augmentation pharmacotherapy in the STAR*D trial was 14·3% after two failed trials and 13% after three failed trials.[31,32] The proportions of participants achieving remission in the 10 Hz rTMS and iTBS groups (27% and 32%) are similar to or higher than those in the original rTMS multicentre trials that preceded regulatory approval (15·5–29·9%) and markedly higher than the proportion of remissions after sham treatment in those trials (9% and 5%).[6,7] Furthermore, the overall reduction in HRSD-17 scores (about 10·1 points in the iTBS group and about 9·9 points in the 10 Hz rTMS group) is greater than that reported in the sham groups of those multicentre trials (which showed a reduction of about 3·5 points).[6,7] Taken together, the response, remission, and change in scores of participants in the 10 Hz rTMS group would preserve assay sensitivity[33] (ie, performed as expected and would have shown efficacy compared with sham treatment) compared with the previous sham results. Despite the reliable and consistent reduction in depression symptoms observed, further efforts are needed to identify the mechanisms of rTMS response and phenotypes that could preferentially respond to different forms of stimulation[34] to enhance overall outcomes.

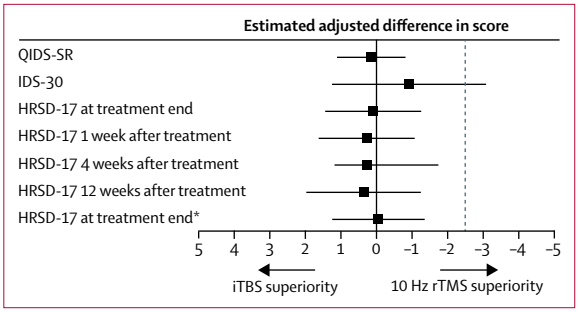

Figure 2: **Estimated adjusted differences in depression scores from baseline to the end of treatment, comparing 10 Hz rTMS treatment and iTBS treatment**

Data are estimated adjusted differences with lower and upper 90% CIs. Dotted line is the non-inferiority margin (2·25 points), determined with a one-side lower 95% CI. iTBS=intermittent theta burst stimulation. rTMS=repetitive transcranial magnetic stimulation. QIDS-SR=16-item Quick Inventory of Depressive Symptomatology. IDS-30=30-item Inventory of Depressive Symptomatology. HRSD-17=17-item Hamilton Rating Scale for Depression (self-rated). *Data are from the sensitivity analysis population.

	Number of participants reporting each adverse event (%)*	
	10 Hz rTMS group (n=204)	iTBS group (n=208)
Headache	131 (64%)	136 (65%)
Nausea	22 (11%)	14 (7%)
Dizziness	8 (4%)	18 (9%)
Unrelated medical problem†	47 (23%)	46 (22%)
Fatigue	14 (7%)	16 (8%)
Insomnia	14 (7%)	10 (5%)
Anxiety or agitation	8 (4%)	9 (4%)
Back or neck pain	7 (3%)	6 (3%)
Unrelated accidents	2 (1%)	3 (1%)
Vomiting	1 (<1%)	1 (<1%)
Tinnitus	1 (<1%)	3 (1%)
Migraine aura	3 (1%)	4 (2%)
Abnormal sensations	2 (1%)	4 (2%)

rTMS=repetitive transcranial magnetic stimulation. iTBS=intermittent theta burst stimulation. *p>0·05 on Fisher's exact tests for each pair of proportions. †Predominantly common infections such as colds and flus.

Table 3: **Adverse events**

There were no discernible differences in self-reported adverse events following iTBS treatment versus 10 Hz rTMS treatment, and there was no difference between the groups in the number of participants who could not complete treatment because they could not tolerate it. Dropout rates were very low in both groups (6–8%), particularly compared with the incidence of discontinuation of 25% reported in a meta-analysis[35] of 117 antidepressant medication trials. Mean pain scores (out of 10 points) were 3·8 points in the iTBS group and 3·4 points for the 10 Hz rTMS group; although this

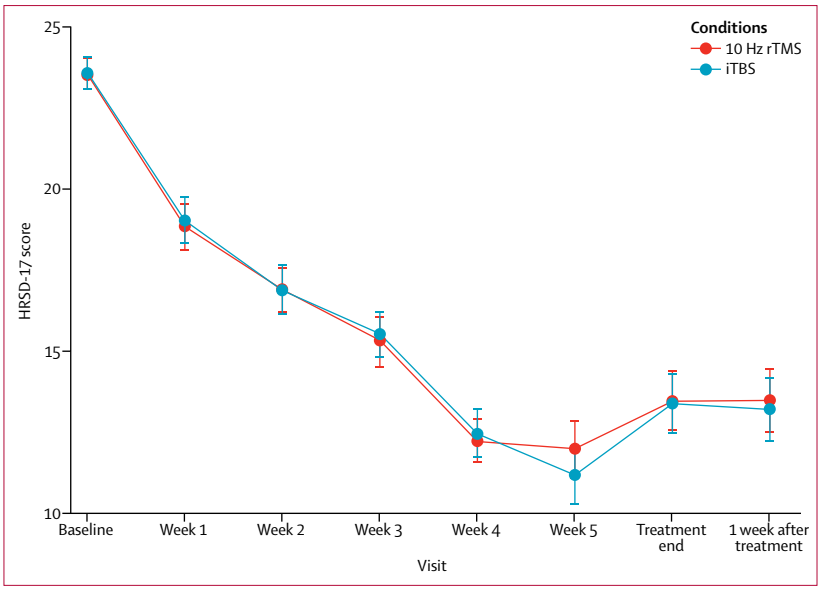

Figure 3: **Change in HRSD-17 scores over time, comparing the 10 Hz rTMS and iTBS treatment groups**
Data are mean scores with lower and upper 90% CIs.

difference reached statistical significance, it did not translate into increased discontinuation rates. Importantly, verbal analogue scale pain ratings do not account for the duration of the participants' reported pain, which was about a tenth as long in the 3 min iTBS sessions compared with the 10 Hz rTMS sessions. The pain rating observed in this trial was somewhat higher than in other iTBS trials; this discrepancy is probably related to the stimulation intensity of 120% and the larger coil diameter used in this trial.

It is important to recognise two key distinctions of the selected parameters for iTBS. First, we did not match the number of pulses of iTBS to the 10 Hz rTMS (3000 pulses per session). However, previous preclinical data suggested that doubling the number of iTBS pulses does not strengthen the excitatory effect and might, in fact, have an inhibitory effect.[36] To avoid the risk of such a reversal effect, and to maximise the advantage of the shorter duration of iTBS we applied a single, standard run of 600 pulses of iTBS.[9] Second, we matched the stimulation intensity at 120% RMT in both groups because a previous meta-analysis[37] had identified inadequate stimulation intensity as a potential reason for lower efficacy in earlier rTMS trials, and current guidelines recommend stimulation of at least 110% RMT for conventional protocols.[20,38] The original neurophysiological studies of iTBS used a lower intensity of 80% of the active motor threshold;[9] previous pilot studies[12–14] of iTBS in major depressive disorder used similarly low intensities, possibly because of uncertainty over the safety of iTBS at higher intensities. TMS safety guidelines[39] recognise the paucity of data on iTBS in non-motor regions, and do not stipulate a maximum stimulation intensity. The data from this trial and others[40,41] indicate that iTBS could be delivered safely at 120% RMT in prefrontal regions without reducing tolerability.

Despite the strengths of the study, several limitations should be considered. One limitation is the absence of a placebo condition to blind participants to treatment allocation. Since previous studies have addressed the efficacy of iTBS versus sham rTMS in major depressive disorder,[12–14] our study question concerned the performance of iTBS versus the current standard of care (10 Hz rTMS for 37·5 min) rather than versus sham. Nonetheless, a period of sham stimulation following active iTBS might have enabled matching of session duration between groups. However, this would have required delivering active and sham stimulation in the same session, which would have unblinded the participants, since active and sham rTMS are easily distinguishable if administered to the same patient sequentially, even with careful calibration.[42] Notably, iTBS participants received a much shorter period of therapeutic contact than 10 Hz rTMS participants during each session; thus, non-specific effects should have been more powerful in the 37·5 min 10 Hz rTMS group compared with the 3 min iTBS group. iTBS therefore achieved non-inferiority despite the handicap of a much shorter period of non-specific therapeutic contact. We used a one-sided test with a 95% CI, whereas 2016 regulatory guidance recommendations for non-inferiority trials, released after the end of this trial, now recommend a one-sided test with a 97·5% CI.[43] To mitigate this limitation, we have conducted a sensitivity analysis using a one-sided test with a 97·5% CI (appendix) and the results were not altered for any of the primary or secondary outcome findings. Another limitation is the inclusion of 24 participants in the trial who met varying exclusion criteria. These participants were included because of staff misunderstanding or participant information received after treatment start. We have done sensitivity analyses to mitigate this limitation that removed the excluded participants and the findings were unchanged. Another potential limitation is the use of MRI-guided neuronavigation in every session—an approach that is not feasible or cost-efficient for most rTMS clinics. However, we have previously shown that the same stereotaxic target used in this trial can be accurately localised without MRI via a scalp-measurement-based heuristic known as BeamF3, which has been made available in a free online tool.[44] Thus, the present findings can be generalised more broadly to rTMS clinics where MRI-guidance is unavailable. Finally, the finding of non-inferiority at 4 weeks and 12 weeks after treatment should be interpreted with caution because the sample size was reduced by attrition and because participants could alter their medications.

In conclusion, we found that iTBS has non-inferior effectiveness and a similar adverse event profile and

acceptability compared with the standard, FDA-approved 10 Hz rTMS protocol for treatment-resistant depression. A typical iTBS treatment session (including setup) takes about 5–10 min, compared with about 45 min for standard 10 Hz rTMS. Therefore, the number of patients treated per machine, per day can be tripled or quadrupled by use of iTBS. The effectiveness of 3 min sessions reported here could also facilitate efforts to accelerate rTMS courses from weeks to days via several daily sessions.[45,46] More broadly, the potential for increased capacity, improved access, reduced waiting times, and potentially reduced costs per remission should have a positive effect, aiding health insurers and governments in implementing wider coverage of rTMS as an increasingly practical intervention for patients with medication-resistant depression.

Contributors

DMB and JD conceived and designed the study. FV-R, KET, PG, SHK, RWL, and ZJD provided input on the study design. KF, YN, and YK provided medical care and determined the motor thresholds of participants. DMB, KET, and JD developed the plan for statistical analyses. KET analysed the data. All authors contributed to the interpretation of data. DMB, FV-R, and JD drafted the manuscript. All authors made revisions to the manuscript. DMB had final responsibility for submission of the manuscript.

Declaration of interests

DMB reports research grants from the Canadian Institutes of Health Research (CIHR), US National Institutes of Health, Weston Brain Institute, Brain Canada, the Temerty Family Foundation (through the Centre for Addiction and Mental Health Foundation and the Campbell Research Institute), and Brainsway; reports receiving in-kind equipment support for investigator-initiated studies (including this study) MagVenture; is the site principal investigator for three sponsor-initiated studies for Brainsway; and has been on an advisory board for Janssen Pharmaceutical. FV-R reports research grants from CIHR, Brain Canada, Michael Smith Foundation for Health Research, and Vancouver Coastal Health Research Institute; reports receiving in-kind equipment support for this investigator-initiated trial from MagVenture; and has been on an advisory board for Janssen. YN reports research grants from Japan Health Sciences Foundation, Meiji Yasuda Mental Health Foundation, and Mitsui Life Social Welfare Foundation; and reports receiving in-kind equipment support for another investigator-initiated study from MagVenture. PG reports research grants from the CIHR and the US National Institutes of Health; has been an unpaid consultant for St Jude Medical; and has served on an advisory board for Bristol-Myers Squibb. SHK reports research grants or consulting or speaking honoraria from Abbott Laboratories, Allergan, AstraZeneca, Bristol-Myers Squibb, Brain Canada, CIHR, Janssen Pharmaceutical, Lundbeck, Lundbeck Institute, the Ontario Mental Health Foundation, Ontario Brain Institute, Ontario Research Fund, Otsuka Pharmaceutical, Pfizer, Servier Laboratories, St Jude Medical, Sunovion Pharmaceuticals, and Xian Janssen Pharmaceutical. RWL reports research grants or consulting or speaking honoraria from Akili Interactive, Asia-Pacific Economic Cooperation, Allergan, AstraZeneca, Bristol-Myers Squibb, Canadian Depression Research and Intervention Network, Canadian Network for Mood and Anxiety Treatments, Johnson and Johnson, Lundbeck, Lundbeck Institute, MagVenture, Pfizer, St Jude Medical, Otsuka, and Takeda. ZJD reports research grants and equipment in-kind support for an investigator-initiated study from Brainsway and Magventure. JD reports research grants from CIHR, the National Institute for Mental Health, Brain Canada, the Canadian Biomarker Integration Network in Depression, the Ontario Brain Institute, the Klarman Family Foundation, the Arrell Family Foundation, and the Edgestone Foundation; reports travel stipends from Lundbeck and ANT Neuro; reports in-kind equipment support for this investigator-initiated trial from MagVenture; and is an advisor for BrainCheck. KET, KF, and YK declare no competing interests.

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