

Response and Remission across Transcranial Magnetic Stimulation Protocols for Treatment-Resistant Depression: A Narrative Review

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Abstract

Daily high-frequency repetitive transcranial magnetic stimulation (rTMS) to the left dorsolateral prefrontal cortex (DLPFC) is an established treatment for depression that has not responded to medication, but a standard course takes four to six weeks of sessions that can last close to 40 minutes each. Intermittent theta burst stimulation (iTBS), accelerated schedules and alternative coil designs have all been developed to shorten treatment or improve its effect. This narrative review examines how often patients respond and remit under these approaches, drawing on 13 studies: four randomized trials comparing theta burst stimulation with conventional rTMS, one sham-controlled trial of deep TMS in late-life depression, seven studies of accelerated iTBS and one network meta-analysis of theta burst stimulation against sham. Theta burst stimulation was non-inferior to conventional rTMS in two large trials, and response and remission were similar between the two approaches in two further trials, one of which used connectivity-guided targeting. Deep TMS with the H1 coil produced remission in 40.0% of older adults against 14.8% with sham. Two parallel sham-controlled trials found accelerated iTBS superior to sham, with remission of 57.1% against 0% immediately after a five-day, connectivity-guided protocol, and 34% against 16% at week 5 with a pragmatic protocol delivered over three weeks. Open-label and retrospective studies were more variable, and the only direct comparison with standard iTBS found numerically lower response with a one-week accelerated course. Across 23 randomized trials, left-sided iTBS roughly doubled the likelihood of response compared with sham, although confidence in that evidence was rated low or very low. Theta burst stimulation at standard daily dosing now rests on a solid evidence base. Accelerated iTBS works better than sham, but whether it matches or improves on a standard course has not yet been tested in an adequately powered randomized trial.

Keywords: transcranial magnetic stimulation, theta burst stimulation, treatment-resistant depression, accelerated tms, response, remission

Introduction and background

For patients whose depression has not improved with antidepressant medication, repetitive transcranial magnetic stimulation (rTMS) delivered to the left dorsolateral prefrontal cortex (DLPFC) is a recognized next step [1]. The conventional protocol uses high-frequency (about 10 Hz) stimulation, with sessions lasting roughly 40 minutes, five days a week, over an initial course of about six weeks [1]. Shortening each session would allow a clinic to treat several times as many patients a day with the same equipment [2].

Several lines of work have tried to change this. Intermittent theta burst stimulation (iTBS) delivers triplets of 50 Hz pulses repeated at 5 Hz [3], and a standard 600-pulse session takes about three minutes [1]. Large trials have compared it with conventional rTMS in adults [2] and, using bilateral protocols, in older adults [3]. Coil design has also been revisited: the H1 coil is designed to stimulate deeper and larger brain volumes than a standard figure-of-eight coil [4]. Accelerated protocols go a step further and compress a full course of sessions into days rather than weeks by delivering several sessions a day [5-7].

Most of these studies report response and remission, but the definitions, scales and timepoints differ, and the evidence ranges from large non-inferiority trials to retrospective chart reviews. The aim of this narrative review is to bring together response and remission data across these protocol types, to set out what each study design can and cannot show, and to identify where the evidence is strong and where it remains thin.

Review

Approach

This is a narrative review rather than a systematic review. Thirteen studies were selected to represent the main protocol comparisons in current use: theta burst stimulation against conventional rTMS [2,3,8,9], deep TMS against sham [4], accelerated iTBS against sham, in open-label samples or against standard iTBS [5-7,10-13], and a network meta-analysis of theta burst protocols against sham [1]. Where a study reported response and remission on more than one scale or at more than one timepoint, each is given.

In the primary studies, response meant a reduction of at least 50% from baseline on the stated depression scale (in the deep TMS trial, a reduction of more than 50% on two consecutive weeks). Remission thresholds varied and are given with each study where they matter for interpretation. Table 1 summarizes the 13 studies.

Table 1. Studies included in this review

Study	Design and sample	Protocols compared	Response	Remission
THREE-D, Blumberger et al. 2018 [2]	Multicentre randomized non-inferiority trial; 414 adults aged 18-65 with TRD	10 Hz rTMS (37.5 min) vs iTBS (3 min), daily for 4-6 weeks	HRSD-17 fell from 23.5 to 13.4 (rTMS) and from 23.6 to 13.4 (iTBS); non-inferior	iTBS 32%, as reported by the FOUR-D investigators [3]
FOUR-D, Blumberger et al. 2022 [3]	Randomized non-inferiority trial, open treatment, blinded raters; 172 adults aged 60 and over with TRD	Sequential bilateral rTMS vs bilateral TBS, daily for 4-6 weeks	MADRS: rTMS 32.9%, TBS 44.3% (other scales in Table 2)	MADRS: rTMS 32.9%, TBS 35.4% (other scales in Table 2)
THETA-DEP, Bulteau et al. 2022 [8]	Single-centre randomized trial, raters blinded; 60	10 Hz rTMS (1,600 pulses) vs iTBS (600 pulses), 20	MADRS: rTMS 33.3%, iTBS 36.7%	MADRS: rTMS 14.8%, iTBS 18.5%

Study	Design and sample	Protocols compared	Response	Remission
	adults with treatment-resistant unipolar depression	sessions over 4 weeks		
Morriss et al. 2024 [9]	Five-centre double-blind randomized trial; 255 adults with TRD	Connectivity-guided iTBS (80% RMT) vs rTMS at F3 (120% RMT), 20 sessions over 4-6 weeks	GRID-HDRS-17 at 8 weeks: rTMS 31.3%, iTBS 35.1%	GRID-HDRS-17 at 8 weeks: rTMS 16.9%, iTBS 20.7%
Kaster et al. 2018 [4]	Sham-controlled randomized trial; 52 analyzed, aged 60-85	Deep TMS, H1 coil (18 Hz, 6,012 pulses) vs sham, daily for 4 weeks	HDRS-24: active 44.0%, sham 18.5%	HDRS-24 (primary): active 40.0%, sham 14.8%
Duprat et al. 2016 [5]	Randomized, double-blind, sham-controlled crossover trial; 47 analyzed with medication-resistant depression	Accelerated iTBS week (20 sessions over 4 days) and sham week, in random order	HDRS: 28% at end of procedure; 38% two weeks later	30% of responders in remission
Cole et al. 2022 (SNT) [6]	Double-blind sham-controlled randomized trial, stopped at interim analysis; 29 treated	Connectivity-guided accelerated iTBS, 10 sessions a day for 5 days, vs sham	MADRS immediately after: active 71.4%, sham 13.3%; at 4 weeks: 69.2% vs 7.1%	MADRS immediately after: active 57.1%, sham 0%; at 4 weeks: 46.2% vs 0%
Ramos et al. 2025 [7]	Single-centre triple-blinded sham-controlled randomized trial; 100 adults with TRD	Accelerated iTBS, 3 sessions a day for 15 weekdays (Beam F3), vs sham	HDRS-17 at week 5: active 52%, sham 22%	HDRS-17 at week 5: active 34%, sham 16%
Cole et al. 2020 (SAINT) [10]	Open-label, uncontrolled; 22 patients with TRD	Connectivity-guided accelerated iTBS, 10 sessions a day for 5 days	Remission was the reported outcome	MADRS: 90.5% (19/21); 86.4% (19/22) by intention to treat
Chen et al. 2026 [11]	Open-label pilot, uncontrolled; 8 patients with TRD	Same high-dose schedule without	MADRS at 1 month: 50%	MADRS at 1 month: 12.5%

Study	Design and sample	Protocols compared	Response	Remission
		precision targeting (Beam F3)		
Dragon et al. 2025 [12]	Retrospective analysis of consecutive cohorts; 66 patients	Standard iTBS (4 weeks) vs accelerated iTBS (5 sessions a day for 5 days), 1,200 pulses per session	HAMD-21: standard 38%, accelerated 19%; MDI: 35% vs 16% (not significant)	HAMD-21: standard 29%, accelerated 13%; MDI: 44% vs 25% (not significant)
Batail et al. 2024 [13]	Data letter, uncontrolled; 14 patients aged 60-79	Stanford Accelerated Neuromodulation Therapy (10 sessions a day for 5 days)	Not reported; mean MADRS fell significantly ($p < 0.001$)	Not reported; mean post-treatment MADRS in remission range
Kishi et al. 2024 [1]	Systematic review with network and pairwise meta-analysis; 23 RCTs, 960 patients	Six TBS protocols vs sham	Left iTBS 44.95% vs sham 17.85%; network RR 2.003 (95% CI 1.283-3.126)	Left iTBS vs sham RR 2.162 (95% CI 1.012-4.618)

TRD: treatment-resistant depression; RMT: resting motor threshold; GRID-HDRS-17: GRID version of the 17-item Hamilton scale; SNT: Stanford neuromodulation therapy; SAINT: Stanford accelerated intelligent neuromodulation therapy; rTMS: repetitive transcranial magnetic stimulation; iTBS: intermittent theta burst stimulation; TBS: theta burst stimulation; HRSD-17/HDRS-17: 17-item Hamilton scale; HDRS-24: 24-item Hamilton scale; HAMD-21: 21-item Hamilton scale; MADRS: Montgomery-Åsberg Depression Rating Scale; MDI: Major Depression Inventory; RR: risk ratio. Definitions of remission differ between studies.

Theta burst stimulation compared with conventional rTMS

THREE-D was a randomized non-inferiority trial at three Canadian university hospitals in adults aged 18 to 65 with treatment-resistant depression and a score of at least 18 on the 17-item Hamilton Rating Scale for Depression (HRSD-17) [2]. Treatment was open-label, but investigators and outcome assessors were masked to group [2]. Of 414 patients, 205 were randomized to 10 Hz rTMS and 209 to iTBS, delivered to the left DLPFC five days a week for four to six weeks; 192 (94%) and 193 (92%) were assessed for the primary outcome [2]. A 10 Hz session took 37.5 minutes and an iTBS session three minutes [2]. HRSD-17 scores fell from 23.5 to 13.4 with rTMS and from 23.6 to 13.4 with iTBS, and iTBS met the pre-specified non-inferiority margin of 2.25 points [2]. Dropout was 6% (13 of 205) with rTMS and 8% (16 of 209) with iTBS, and headache was the most common treatment-related adverse event in both groups [2]. Self-rated pain during treatment was greater with iTBS [2]. The FOUR-D investigators later reported the iTBS remission rate in THREE-D as 32% [3].

FOUR-D asked a related question in older adults (60 years and over) with treatment-resistant depression, using bilateral protocols in both arms [3]. Standard sequential bilateral rTMS (1 Hz to the right DLPFC, then 10 Hz to the left DLPFC, about 47.5 minutes in total) was compared with bilateral theta burst stimulation (continuous TBS to the right DLPFC, then iTBS to the left, about four minutes) [3]. Of 172 patients randomized, 87 received rTMS and 85 received theta burst stimulation, and 85 (98%) and 79 (93%) were assessed for the primary outcome [3]. Treatment was open, but outcome raters were blinded and worked on a different floor [3]. Mean Montgomery-Åsberg Depression Rating Scale (MADRS) scores improved from 25.6 to 17.3 with rTMS and from 25.7 to 15.8 with theta burst stimulation, which met the non-inferiority margin of 2.75 points (adjusted difference 1.55, lower 95% confidence limit -0.67) [3]. Response and remission were secondary outcomes. Theta burst stimulation was non-inferior on every secondary measure [3]. All-cause dropout was 2.3% (2/87) with rTMS and 7.1% (6/85) with theta burst stimulation ($P = .14$) [3]. The trial planned to enrol 200 participants, but new recruitment was halted in March 2020 because of the COVID-19 pandemic [3].

Remission in FOUR-D was defined separately on each scale: a MADRS score of 10 or less, an HRSD-17 score of 7 or less and a QIDS-SR-16 score of 5 or less [3]. Response and remission on each scale are shown in Table 2 [3].

Table 2. Response and remission in FOUR-D by scale

Scale	rTMS response, n (%)	TBS response, n (%)	rTMS remission, n (%)	TBS remission, n (%)
MADRS	28 (32.9)	35 (44.3)	28 (32.9)	28 (35.4)
HRSD-17	24 (29.6)	31 (41.9)	22 (27.2)	25 (33.8)
QIDS-16	30 (35.7)	35 (44.3)	18 (21.4)	25 (31.6)

Data from the FOUR-D report [3]. Comparisons were tested for non-inferiority (margin 15% for response and 10% for remission) with 90% confidence intervals.

THETA-DEP was a smaller single-centre randomized trial in patients with treatment-resistant unipolar depression who had, on average, failed more than three antidepressant trials [8]. Sixty patients were randomized 1:1 to 10 Hz rTMS (110% of resting motor threshold, 1,600 pulses per session) or iTBS (80% of resting motor threshold, 600 pulses per session), 20 sessions over four weeks, with the left DLPFC targeted by neuronavigation [8]. Raters were blinded to treatment allocation and operators were not [8]. Fifty-four patients (27 in each arm) completed the stimulation sessions [8]. MADRS response at four weeks was 36.7% with iTBS and 33.3% with rTMS ($p = 0.789$), and remission (MADRS below 8) was 18.5% and 14.8% respectively ($p = 1.000$) [8]. Both groups showed a similar reduction in depression scores and improved quality of life at six months [8]. The trial was designed to test superiority, with a sample size based on an expected response of 25% with rTMS and 60% with iTBS, and it was not powered to establish non-inferiority [8].

Morriss and colleagues tested whether personalizing the target would make theta burst stimulation more effective [9]. In a five-centre, double-blind trial in patients with treatment-resistant depression, 255 participants were randomized to 20 sessions over four to six weeks of either connectivity-guided iTBS (n

= 128), delivered at a site chosen from each patient's resting-state functional MRI, or rTMS (n = 127) at the standard F3 site located with structural MRI neuronavigation [9]. The arms were matched for pulses per session, session duration and number of sessions, but iTBS was given at 80% and rTMS at 120% of resting motor threshold [9]. There was no difference on the primary outcome, the GRID 17-item Hamilton Depression Rating Scale assessed at 8, 16 and 26 weeks (adjusted mean difference -0.31, 95% CI -1.87 to 1.24, P = 0.689) [9]. At eight weeks, response was 31.3% (35/112) with rTMS and 35.1% (39/111) with connectivity-guided iTBS, and remission (a score of 8 or less) was 16.9% (19/112) and 20.7% (23/111) [9]. At 26 weeks, response was 30.4% and 34.6% and remission 20.6% and 25.0% [9]. Two serious adverse events, mania and psychosis, were judged possibly related to TMS [9].

Deep TMS with the H1 coil

Kaster and colleagues randomized adults aged 60 to 85 with major depression, who had not responded to at least one adequate or two inadequate antidepressant trials, to active or sham deep TMS [4]. The active protocol used the H1 coil at 18 Hz and 120% of resting motor threshold, 6,012 pulses per session, five days a week for four weeks [4]. Fifty-eight patients were randomized, but the first six were treated with a different coil (H1L) that proved poorly tolerated and were excluded from analysis, leaving 52 in the intention-to-treat sample (25 active, 27 sham) [4]. The primary outcome was remission, defined as a 24-item Hamilton Depression Rating Scale (HDRS-24) score of 10 or less with at least a 60% reduction from baseline on two consecutive weeks [4]. Remission was 40.0% (10/25) with active treatment and 14.8% (4/27) with sham, a number needed to treat of 4.0 (95% CI 2.1 to 56.5) [4]. Response (a reduction of more than 50% on the HDRS-24 on two consecutive weeks) was 44.0% (11/25) against 18.5% (5/27) [4]. Forty-seven patients (90.4%) completed the acute course; all five dropouts were in the active arm [4]. No serious adverse events occurred in the analyzed sample, although one patient treated with the excluded H1L coil had a seizure [4]. There was no difference between active and sham treatment on any cognitive measure [4]. Recruitment ended before the target sample size was reached, when grant funding ended [4].

Accelerated iTBS

Duprat and colleagues ran a registered, randomized, double-blind, sham-controlled crossover trial in 50 patients with medication-resistant major depression [5]. In randomized order, each patient received one week of real accelerated iTBS and one week of sham, with each week consisting of 20 sessions (five a day) over four days at 1,620 pulses per session to the left DLPFC [5]. Three patients dropped out and 47 were analyzed [5]. Depressive symptoms fell significantly and immediately regardless of whether real or sham stimulation came first, and the authors suggested that accelerated protocols may be prone to strong placebo effects [5]. At the end of the two-week procedure, 28% of patients had a reduction of at least 50% on the Hamilton Depression Rating Scale, and this rose to 38% two weeks later, which the authors interpreted as a delayed clinical effect [5]. The authors report that 30% of responders were considered to be in clinical remission [5].

The Stanford protocol was tested against sham by Cole and colleagues in a double-blind randomized trial in treatment-resistant depression [6]. Each patient's left DLPFC target was chosen with resting-state functional MRI as the region most anticorrelated with the subgenual anterior cingulate cortex, and stimulation was given as ten iTBS sessions a day, 18,000 pulses a day, on five consecutive days, at 90% of resting motor threshold adjusted for cortical depth [6]. The trial stopped at its planned interim analysis because of a large effect, by which point 29 participants had been treated (14 active, 15 sham) [6]. Immediately after treatment, remission (MADRS 10 or less) was 57.1% with active treatment against 0% with sham, and response was 71.4% against 13.3% [6]. Four weeks later, at the primary timepoint,

remission was 46.2% against 0% and response 69.2% against 7.1%, with mean MADRS reductions of 52.5% and 11.1% [6]. Across the four-week follow-up, 11 of 14 active participants (78.6%) met remission criteria at least once, against 2 of 15 (13.3%) with sham [6].

Ramos and colleagues tested a simpler accelerated protocol in a single-centre, triple-blinded, sham-controlled trial in São Paulo [7]. One hundred adults aged 18 to 65 with treatment-resistant depression, who had tried on average more than three antidepressants in the current episode, received 45 active or sham iTBS sessions over 15 weekdays: three sessions a day, 30 minutes apart, 1,200 pulses each at 100% of resting motor threshold, with the left DLPFC located by the Beam F3 method rather than neuronavigation [7]. Eighty-nine patients completed the trial [7]. At week 5, HDRS-17 scores had fallen by 54.7% with active treatment and 31.87% with sham (Cohen d 0.65, 95% CI 0.29 to 1.00, $P < .001$) [7]. Response was 52% (26/50) against 22% (11/50) (odds ratio 4.11, 95% CI 1.66 to 10.13), and remission (HDRS-17 of 7 or less) was 34% (17/50) against 16% (8/50) (odds ratio 2.73, 95% CI 1.03 to 7.24) [7]. Scalp pain was more common with active treatment (17.4% against 4.4%) [7]. The sham response was large, peaking at weeks 3 and 4, and the authors noted that their trial did not compare accelerated treatment with a standard once-daily course [7].

Two open-label studies show what the Stanford-type protocol can do without a control group. In the original report, 22 patients with treatment-resistant depression received 50 iTBS sessions (1,800 pulses each, 50 minutes apart, ten a day for five days) at 90% of resting motor threshold adjusted for cortical depth, with connectivity-guided targeting [10]. One patient withdrew; 19 of 21 (90.5%) met remission criteria (MADRS below 11), or 19 of 22 (86.4%) by intention to treat [10]. Chen and colleagues then gave the same high-dose schedule to eight patients without any precision features, targeting the left DLPFC with the Beam F3 method [11]. Patients received 46 sessions on average, and at one-month follow-up response was 50% and remission 12.5%, which the authors judged lower than previously reported for the full Stanford approach [11]. After an optional four weeks of transcranial direct current stimulation, 28.6% and 14.3% had sustained response and remission, falling to 16.7% and 0% at six months [11].

Dragon and colleagues retrospectively analyzed the records of 66 inpatients and outpatients treated for depression (64 unipolar, 2 bipolar) at a German tertiary care hospital between April and September 2023 [12]. Patients treated from April to June received accelerated iTBS (five sessions a day for five days, 25 sessions), and patients treated from July to September received standard iTBS (one session per working day for four weeks); every session delivered 1,200 pulses [12]. Response was 38% (13/34) with standard iTBS against 19% (6/32) with the accelerated course on the 21-item Hamilton Depression Rating Scale (HAMD-21), and 35% (12/34) against 16% (5/32) on the Major Depression Inventory (MDI) [12]. Remission was 29% (10/34) against 13% (4/32) on the HAMD-21 and 44% (15/34) against 25% (8/32) on the MDI [12]. None of these differences was statistically significant (response: HAMD-21 $p = .081$, MDI $p = .068$) [12]. Side effects were reported more often with the accelerated course (15 of 32 patients against 5 of 34), but six patients in the standard iTBS group stopped treatment early because of side effects and were not included in the analysis [12]. The two schedules were delivered to consecutive cohorts rather than to concurrently randomized groups, and there was no sham condition [12].

Batail and colleagues, in a data letter responding to FOUR-D, reported 14 patients aged 60 to 79, drawn from the group's clinical studies, who had received Stanford Accelerated Neuromodulation Therapy [13]. As described in the letter, this connectivity-guided accelerated iTBS protocol delivers ten sessions a day of 1,800 pulses each, 50 minutes apart, over five days, for 90,000 pulses in total [13]. Mean MADRS scores fell significantly from baseline to the end of treatment ($p < 0.001$), and the mean post-treatment

score was within the remission range [13]. The letter does not report a response or remission rate for these 14 patients. The remission rate of about 80% that it quotes comes from the authors' earlier sham-controlled trial in adults aged 27 to 73 [13], described above [6], not from this older group.

Network meta-analysis of theta burst stimulation against sham

Kishi and colleagues included 23 randomized trials (960 patients, mean age 41.88 years, 60.78% female) of theta burst stimulation in major depressive disorder or bipolar depression, with or without treatment resistance, and assessed every trial with version 2 of the Cochrane risk of bias tool [1]. In the network meta-analysis, three of the six protocols had a higher response rate than sham: iTBS to the left DLPFC (risk ratio 2.003, 95% CI 1.283 to 3.126), continuous TBS to the right DLPFC combined with iTBS to the left DLPFC (risk ratio 1.897, 95% CI 1.110 to 3.244), and iTBS to the occipital lobe [1]. In pairwise meta-analysis, left-sided iTBS remained superior to sham (risk ratio 2.290, 95% CI 1.437 to 3.649), while the combined bilateral protocol did not reach significance (risk ratio 1.745, 95% CI 0.926 to 3.286) [1]. Pooled response rates were 44.95% with left-sided iTBS against 17.85% with sham in the corresponding trials, and 43.42% with the combined bilateral protocol against 25.80% with sham [1]. The left-sided iTBS comparison included the Stanford sham-controlled trial, and left-sided iTBS remained superior to sham when that trial was excluded (risk ratio 2.111, 95% CI 1.316 to 3.386) [1]. Left-sided iTBS also had a higher remission rate than sham (risk ratio 2.162, 95% CI 1.012 to 4.618, 15 trials) [1]. No protocol differed from sham in all-cause discontinuation (17 trials) [1]. Most trials were judged to have some concerns for risk of bias, and confidence in the network estimates was generally low or very low [1].

Discussion

The clearest finding across these studies is that theta burst stimulation at standard daily dosing performs about as well as conventional rTMS. Two large non-inferiority trials, one in younger adults with unilateral stimulation and one in older adults with bilateral stimulation, both met their pre-specified margins [2,3], and two further trials, one in patients with more extensive treatment failure and one using connectivity-guided targeting, found similar response and remission with the two approaches [8,9]. None of these trials showed that theta burst stimulation is better than rTMS. FOUR-D tested its response and remission comparisons for non-inferiority [3], and THETA-DEP was neither powered nor designed to show equivalence [8]. The practical gain is time: a session of a few minutes rather than 40 minutes or more [1,3].

Remission rates in the theta burst arms ranged from 18.5% in THETA-DEP [8] to 32% in THREE-D and 31.6% to 35.4% in FOUR-D, depending on the scale [3]. These figures are not directly comparable. THETA-DEP used 20 sessions, a lower stimulation intensity for iTBS (80% of resting motor threshold) and a remission threshold of a MADRS score below 8, compared with 10 or less in FOUR-D, in patients who had failed more medication trials [3,8]. Its authors noted that their rates were lower than those seen after six weeks of treatment in THREE-D [8].

Deep TMS with the H1 coil produced a large difference from sham in older adults, on the pre-specified remission endpoint as well as on response [4]. Older adults have historically responded less well to rTMS, and one suggested reason is age-related prefrontal atrophy increasing the distance between scalp and cortex [4]. The result is encouraging, but it comes from 52 analyzed patients in a trial that stopped before reaching its target sample, and the wide confidence interval around the number needed to treat reflects that [4].

How the DLPFC is located is another source of variation. In an earlier randomized trial of 51 patients with treatment-resistant depression, 10 Hz rTMS targeted with MRI-based neuronavigation gave a better MADRS outcome at four weeks than the standard 5 cm scalp method ($p = 0.02$) [14]. More recent trials complicate that picture. Personalized, connectivity-guided iTBS was no better than rTMS at a structurally neuronavigated standard site over 26 weeks [9], and a pragmatic accelerated protocol located with the Beam F3 scalp method was clearly superior to sham [7]. When the high-dose Stanford schedule was given without connectivity-guided targeting or depth-adjusted intensity, remission at one month was 12.5% in a small open-label sample [11], well below the rates reported with the full protocol [6,10]. Whether individualized targeting adds to accelerated dosing therefore remains an open question, and differences in targeting method are worth keeping in mind when comparing trials.

Accelerated iTBS is the area where the evidence has moved most and is still least settled. Two parallel sham-controlled trials now show that it works better than sham. The Stanford trial found very large differences in remission, but it treated only 29 patients, was stopped early at a planned interim analysis, and used a demanding protocol of ten sessions a day with MRI-guided targeting [6], so its estimates rest on a very small sample. The remission rates of around 90% seen in the open-label study [10] were not reproduced at the same level once a sham group was added [6]. The São Paulo trial was larger, used a protocol that a standard clinic could deliver, and found a more moderate but still clear advantage over sham [7]. The São Paulo trial and the earlier crossover study both recorded a substantial sham response with intensive schedules [5,7], which makes sham-controlled designs especially important in this field.

What none of these trials answers is whether accelerated iTBS is better than, or even as good as, a standard daily course. The only direct comparison found numerically lower response and remission with a one-week accelerated course than with four weeks of standard iTBS [12]. Those differences did not reach statistical significance, and the design has clear limits: consecutive cohorts rather than randomization, outcome measured within days of the last session, and exclusion of the six patients who stopped standard iTBS because of side effects [12]. Its protocol, 1,200 pulses five times a day, was also far lower in dose than the Stanford schedule [6,12]. The crossover trial showed response rising between the end of treatment and a two-week follow-up [5], so studies that measure outcome only immediately after an accelerated course may miss part of the effect. The data from Batail and colleagues add a small, uncontrolled signal in older adults [13].

The network meta-analysis supports left-sided iTBS over sham across a broader trial base than any single study here, with a response rate roughly twice that of sham and a higher remission rate [1]. The evidence for other theta burst protocols is weaker, and the authors' own rating of confidence in the estimates as low or very low is a reason for caution [1].

Limitations

This review covers 13 studies selected to represent the main protocol comparisons, not the full literature, and it did not follow a systematic search. The populations differ: THREE-D, FOUR-D, THETA-DEP and the deep TMS trial enrolled patients with treatment-resistant depression defined in different ways [2-4,8], Dragon and colleagues analyzed routine clinical patients with depression [12], and the network meta-analysis included trials with and without treatment resistance as well as bipolar depression [1]. Response and remission were measured on different scales and at different timepoints, and remission thresholds were not the same across studies. For these reasons the findings are presented study by study rather than

pooled. Four of the seven accelerated iTBS studies were not randomized trials [10-13], and the largest sham-controlled accelerated trial treated 100 patients [7].

Conclusions

Theta burst stimulation at standard daily dosing is non-inferior to conventional rTMS in both younger and older adults with treatment-resistant depression and takes a fraction of the session time. Deep TMS with the H1 coil shows a clear effect over sham in late-life depression, although the trial was small. Accelerated iTBS is superior to sham in two randomized trials, including a pragmatic three-sessions-a-day protocol that does not need neuroimaging, but intensive schedules also carry a large sham response, and remission rates have been lower under sham-controlled conditions than in open-label work. No adequately powered randomized trial has yet compared accelerated iTBS with a standard daily course. That comparison, with follow-up beyond the end of treatment, is the trial the field now needs before accelerated protocols can be recommended in place of standard daily treatment.

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