



Review article

Accelerated intermittent theta burst stimulation in major depressive disorder: A systematic review

Daan Neuteboom^{a,b,*}, Jasper B. Zantvoord^{a,b}, Roberto Goya-Maldonado^c, Jonas Wilkening^c, Annemieke Dols^{b,d,e}, Eric van Exel^{b,e,f}, Anja Lok^{a,b,g}, Lieuwe de Haan^{a,b}, Karel W.F. Scheepstra^{a,b,h,g}

^a Amsterdam UMC, University of Amsterdam, Adult Psychiatry, Meibergdreef 9, Amsterdam 1105AZ, the Netherlands

^b Amsterdam Neuroscience, Mood, Anxiety, Psychosis, Stress and Sleep, Amsterdam, the Netherlands

^c Department of Psychiatry and Psychotherapy, Laboratory of Systems Neuroscience and imaging in Psychiatry (SNIP-lab), University Medical Center Göttingen, Göttingen, Germany

^d Department of Psychiatry, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, the Netherlands

^e Department of Psychiatry, Amsterdam UMC, Location VUmc, the Netherlands

^f Department of Old Age Psychiatry GGZinGeest, the Netherlands

^g Center for Urban Mental Health, University of Amsterdam, the Netherlands

^h Neuroimmunology Research Group, Netherlands Institute for Neuroscience, Meibergdreef 47, Amsterdam 1105 BA, the Netherlands

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ABSTRACT

Background: Major depressive disorder [MDD] is expected to be the leading cause of overall global burden of disease by the year 2030 [WHO]. Non-response to first line pharmacological and psychotherapeutic antidepressive treatments is substantial, with treatment-resistant depression [TRD] affecting approximately one third of depressed patients. There is an urgent need for rapid acting and effective treatments in this population. Repetitive Transcranial Magnetic Stimulation [rTMS] is a non-invasive treatment option for patients with MDD or TRD. Recent studies have proposed new paradigms of TMS, one paradigm is accelerated intermittent Theta Burst Stimulation [aiTBS].

Objective: This systematic review assesses the efficacy, safety and tolerability of aiTBS in patients with MDD.

Methods: This review was registered with PROSPERO [ID number: 366556]. A systematic literature review was performed using Pubmed, Web of Science and PsycINFO. Case reports/series, open-label and randomized controlled trials [RCTs] were eligible for inclusion if they met the following criteria; full text publication available in English describing a form of aiTBS for MDD or TRD. aiTBS was defined as at least three iTBS treatments sessions per day, during at least four days for one week.

Results: 32 studies were identified describing aiTBS in MDD, 13 studies described overlapping samples. Six articles from five unique studies met eligibility criteria; two open-label studies and three RCTs [two double blind and one quadruple blind]. Response rates directly after treatment ranged from 20.0% to 86.4% and remission rates ranged from 10.0 to 86.4%. Four weeks after treatment response rates ranged from 0.0% to 66.7% and remission rates ranged from 0.0% to 57.1%. Three articles described a significant reduction in suicidality scores. aiTBS was well tolerated and safe, with no serious adverse events reported.

Conclusions: aiTBS is a promising form of non-invasive brain stimulation [NIBS] with rapid antidepressant and antisuicidal effects in MDD. Additionally, aiTBS was well tolerated and safe. However, the included studies had small samples sizes and differed in frequency, intersession interval, neuro localization and stimulation intensity. Replication studies and larger RCTs are warranted to establish efficacy, safety and long term effects.

* Corresponding author at: Amsterdam UMC, University of Amsterdam, Meibergdreef 9, Amsterdam 1105AZ, the Netherlands.

E-mail address: d.neuteboom@amsterdamumc.nl (D. Neuteboom).

1. Introduction

Major depressive disorder [MDD] is a common psychiatric mood disorder, affecting over 280 million people worldwide [estimated 3.8% of the world population] (World Health Organisation, 2021). Depression is associated with impaired social functioning and unemployment and is associated with a wide range of chronic physical illnesses, such as diabetes and cardiovascular disease (Kawakami et al., 2012). In addition, [severe] depression can lead to suicide, which is currently the fourth leading cause of death in the age of 15 to 29. MDD is expected to be the leading cause of overall global burden of disease by the year 2030 [WHO] (World Health Organisation, 2021).

First-line treatment options for MDD include antidepressants and forms of psychotherapy such as cognitive behavioral therapy [CBT] (Davidson, 2010). However, approximately one third of patients with MDD do not respond adequately after receiving two or more evidence-based antidepressant treatment (Rush et al., 2006; Kverno and Mangano, 2021; Valenstein, 2006). Generally, the failure to respond to two or more medication trials of adequate dose and duration in MDD is referred to as treatment resistant depression [TRD] (Valenstein, 2006). Non-invasive brain stimulation [NIBS] such as repetitive Transcranial Magnetic Stimulation [rTMS] has emerged as an effective and safe treatment option for some patients with MDD or TRD (Lefaucheur et al., 2020). rTMS is typically delivered once a day over the dorsolateral prefrontal cortex [dlPFC] in a 1 Hz or 10 Hz protocol over the course of four to six weeks. Response rates of rTMS in MDD or TRD depend on the protocol, [personalized] coil localization or combination therapy (Mutz et al., 2019; Gaynes et al., 2014; Donse et al., 2018; Sackeim et al., 2020). A meta-analysis in 2014 [29 RCTs; totaling 1371 subjects with MDD] found response rates of 29.3% and remission rates of 18.6% of subjects following approximately 13 sessions of high frequency [HF]-rTMS. (Berlim et al., 2014) A more recent meta-analysis in 2019 found that HF-rTMS over the left dlPFC and low frequency [LF]-rTMS over the right dlPFC were associated with higher response rates compared to sham rTMS [odds ratio of 3.17 and 3.65 respectively] (Mutz et al., 2019). However, the daily application over the course of multiple weeks and the delayed time-to-response limits its practicality for both patient and treatment clinics. Newer forms of NIBS such as accelerated forms of intermittent theta burst stimulation [aiTBS] attempt to increase efficacy and reduce time-to-response.

TBS is a paradigm of rTMS that enhances cortical excitability through enhancement of synaptic transmission by mimicking cortical theta rhythms (Di Lazzaro et al., 2008; Bakker et al., 2015; Rounis and Huang, 2020). TBS delivers 600 pulses in only 40 s to three minutes [compared to \approx 18–25 min of rTMS protocols], however equivalent antidepressant results are achieved compared to rTMS (Chung et al., 2015; Blumberger et al., 2018; Prasser et al., 2015). Two main types of TBS are described in clinical research: intermittent TBS [iTBS], in which 2 s of TBS are administered with an 8 s interval across a span of 192 s [totaling 600 pulses], and continuous TBS [cTBS], where TBS is uninterruptedly administered for 40 s [also totaling 600 pulses]. While iTBS generates neuronal excitatory effects reminiscent of high-frequency rTMS, typically applied to the left prefrontal cortex for depression treatment, cTBS is applied on the right hemisphere and appears to yield the opposite outcome – a suppression on neuronal excitability as presumed in low-frequency rTMS [1 Hz] (Chung et al., 2016; Suppa et al., 2016). Accelerated forms of iTBS include multiple sessions applied over a single day during the course of several days, thereby reducing the number of days required to complete the course of treatment and total number of pulses. In addition to a rapid acting antidepressant therapy, it may also be a novel approach for the treatment of acute suicidality in depression. Several recent studies show promising results of one-week accelerated iTBS [aiTBS] as a rapid acting antidepressant. Studies on primarily accelerated cTBS are lacking.

This systematic review provides the first extensive overview of existing literature on the efficacy, safety and tolerability of one-week

aiTBS in MDD.

2. Methods

This systematic review was registered with PROSPERO [ID number: 366556] [see supplementary materials for the registered protocol].

2.1. Eligibility criteria

Case reports/series, open-label designs and randomized controlled trials [RCTs] [1] were eligible for inclusion if they met the following criteria; full text publication available in English [2] and describing a form of aiTBS [3] for MDD [4]. aiTBS was defined as at least three iTBS treatments sessions per day, during at least four days a week, with a total stimulation/treatment duration of one week (Lefaucheur et al., 2020; Desmyter et al., 2014). Studies describing aiTBS for psychiatric disorders other than MDD were excluded. In addition, reviews and meta-analysis, book chapters and conference papers were excluded.

2.2. Information sources, search strategy and selection procedure

To identify eligible studies, a search was conducted on October 28, 2022 and updated on 16-01-2023 using the databases Pubmed, Web of Science and PsychINFO. Search terms included: “major depressive disorder”, “repetitive transcranial magnetic stimulation”, “accelerated intermittent theta burst stimulation”, “theta burst stimulation”, “accelerated transcranial magnetic stimulation”. In addition, reference lists of eligible articles were searched to identify eligible studies. See **Supplementary materials Search strategies** for the complete search strategies for all databases. Covidence guidelines were used to screen all articles found in the initial search (Covidence Systematic Review Software, 2023). Two independent reviewers [D.N and K.S] screened the full-text based on inclusion and exclusion criteria. Any discrepancies were resolved by discussion and consensus between the reviewers.

2.3. Data collection and risk of bias

Author's name, year of publication, design, sample size, treatment characteristics, instruments used to register response and remission, response and remission rates, depressive scores such as the Montgomery Asberg Depression Rating Scale [MADRS] or Hamilton Depression Rating Scale [HDRS], suicidality scores, side-effects/adverse events, drop-out rates and duration of follow-up were collected from eligible studies.

To assess the risk of bias in the included studies, two reviewers [D.N and K.S] independently assessed the included studies according to the Oxford center for Evidence-based Medicine levels of evidence (Philips et al., 2009). Any discrepancies were resolved by discussion and consensus between the reviewers.

2.4. Effect measures

The primary outcomes are short-and long-term efficacy, safety and tolerability of aiTBS in patients with MDD. Efficacy was measured through response and remission rates, based on reduction in depression scales such as the MADRS and the HDRS. In case of cross-over designs, overall response and remission rates and arm specific [active-sham first or sham-active first] were extracted. Safety and tolerability were measured through side-effects, serious adverse events [SAE] and drop-out rates respectively. Short term effect is defined as less than four weeks after initial treatment and long-term effect is defined as more than four weeks after treatment. The secondary outcome was reduction of suicidality.

3. Results

3.1. Study characteristics

A total of six publications from five unique studies [two open-label trials and three RCTs] met inclusion criteria [see Fig. 1. (Page et al., 2021)] (Williams et al., 2018; Cole et al., 2020, 2022; Duprat et al., 2016; Wilkening et al., 2022; Desmyter et al., 2016). For aiTBS parameters see Supplementary Table 2. For demographic factors, study designs and evidence levels/recommendations see Table 1. Key exclusion criteria of the included studies were a primary psychiatric disorder other than MDD, history of psychotic disorder, substance use disorder, major systemic illness, rTMS contraindications (including history of seizure, metallic implants in the head, cardiac pacemakers, pregnancy). Additionally, Cole et al. (2022) also excluded participants with prior

exposure to rTMS or nonresponse to ECT. Duprat et al. (2016) excluded participants who attempted suicide within six months prior start of the study. Among the three RCTs, a total of 64 patients with MDD were included. Two of these RCTs used a cross-over design, whereas one RCT used a parallel design. In the two open-label studies, a total of 25 patients with MDD and three patients with bipolar disorder [BD] were included. The three RCTs and the open label trial by Cole et al. (2020) were given level 1B evidence with grade A recommendation, the open label trial by Williams et al. (2018) was given level 4 evidence with grade C recommendation (Philips et al., 2009).

3.2. aiTBS parameters

See Supplementary Table 2 for an overview of the dlPFC localizing method, motor threshold [MT], iTBS protocol, study protocol and

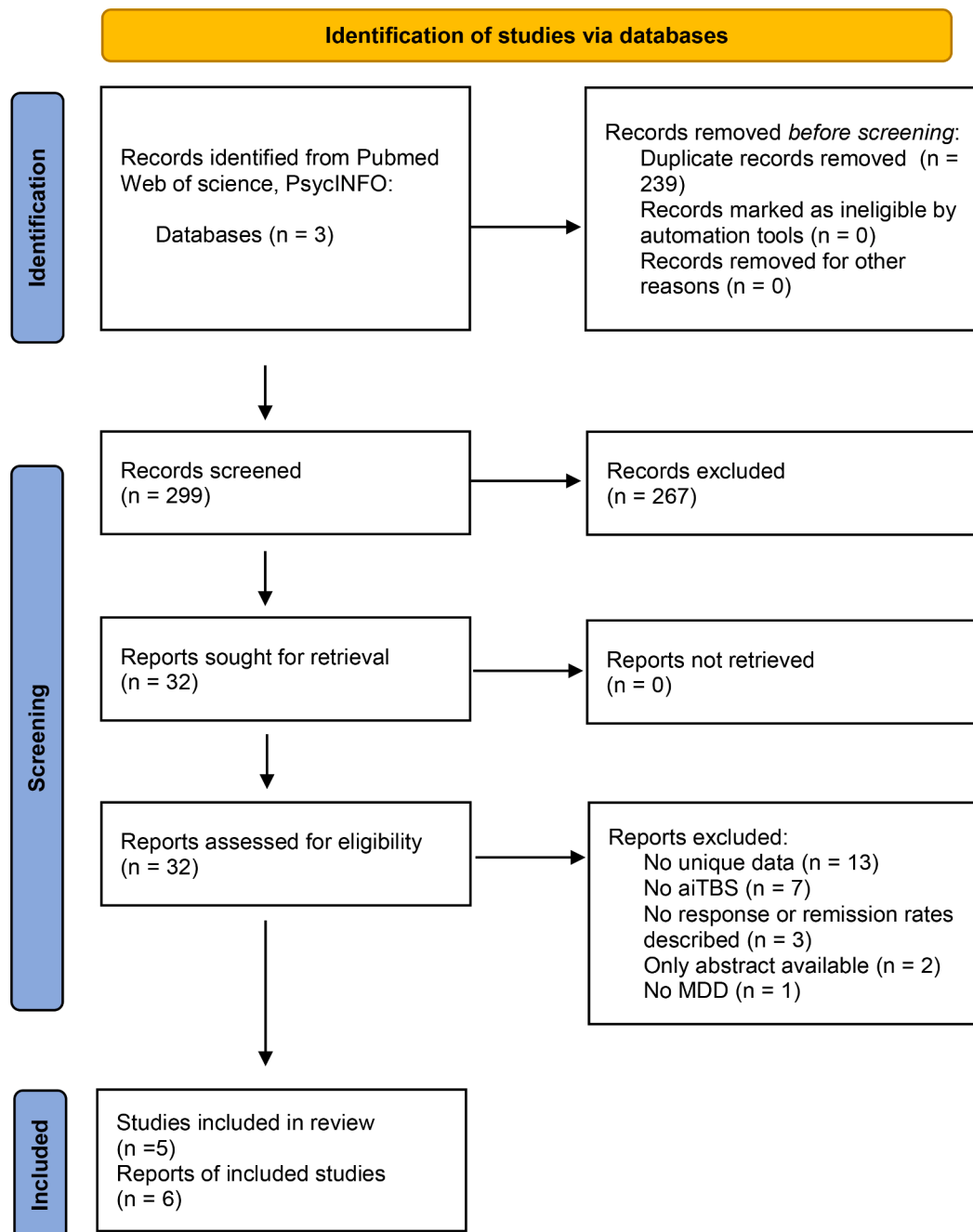


Fig. 1. Prisma flow diagram.

Table 1
Study demographics and study designs.

Authors	Study design	Sample size and diagnosis	Mean age [SD]	Duration of current depressive episode in years [SD]	Medication status	Prior antidepressant medication trials [SD]	Treatment resistance [SD]	Diagnosis criteria/method	Follow-up period	Level of evidence/Recommendation ^o
Duprat et al. (2016)	RCT - cross over Double blind	n = 47 MDD Active-sham first n = 20 Sham-active first n = 21	All: 41.7 [11.8]	All: 3.9 [6.1]	Antidepressant free at least 2 weeks prior start study	–	Thase and Rush staging Method: Stage I: 9/47 Stage II: 24/47 Stage III: 14/47	MINI criteria for MDD At least stage I treatment resistance	2 weeks	1B / A
Williams et al. (2018)	Open-label	n = 6 MDD = 5 BD = 1	56 [12.1]	14.8 [6.8]	–	–	Thase and Rush staging Method: 6/6 had stage V Maudsley Staging Method: 6/6 had score 14/15	SCID-5-CV for MDD or BD Score ≥20 on the HDRS-17	4 weeks	4 / C
Cole et al. (2020)	Open-label	n = 21 MDD = 19 BD = 2	44.9 [17.2]	23.0 [16.3]	Stable antidepressant or medication during study	5.9 [3.5]	Not reported	DSM-5 criteria for MDD or BD Score ≥20 on the HDRS-17	4 weeks	1B / A
Cole et al. (2022)	RCT-parallel Double blind	n = 29 MDD Active: n = 14 Sham: n = 15	Active: 49 [15] Sham: 52 [16]	Active: 8 [14] Sham: 10 [13]	Stable antidepressant or medication free at least 4 weeks prior start study	Active: 5 [2] Sham: 5 [2]	Maudsley Staging Method: Active: 9 [2] Sham: 9 [2]	Score ≥20 on the HDRS-17 and MADRS	4 weeks	1B / A
Wilkening et al. (2022)	RCT – cross over Quadruple blind	n = 81 MDD Active-sham first n = 40 Sham-active first n = 41	All: 35.7 [13.0]	–	59/81 used medication* Stable antidepressant or medication free at least 2 weeks prior start study	–	Active:** 17 [21.0] Sham: 15 [18.5]	SCID-5-CV criteria for MDD	2 weeks	1B / A

RCT = randomized controlled trial, MDD = major depressive disorder, BD = bipolar disorder, HDRS-17 = Hamilton Depression Rating Scale – 17 item, MADRS = Montgomery-Asberg Depression Rating Scale, MINI = Mini International Neuropsychiatric Interview, SCID-5-CV = Structured Clinical Interview for DSM-5 Disorders-Clinician Version, DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, fifth edition.

^o Level of evidence/recommendation by the Oxford center for Evidence-Based Medicine: Levels of Evidence

Level of evidence: level 1A, systematic reviews [with homogeneity] of randomized clinical trials; **level 1B, individual randomized clinical trials [with narrow confidence intervals]**; level 2A, systematic reviews [with homogeneity] of cohort studies; and level 2B, individual cohort studies [including low-quality randomized clinical trials]; Level 3A, systematic reviews [with homogeneity] of case-control studies; Level 3B, Individual case-control studies; **Level 4, case series [or poor quality cohort and case-control studies]**.

Grades of recommendation: **A, consistent level 1 studies**; B, consistent level 2 or 3 studies or extrapolations from level 1 studies; C, **level 4 studies or extrapolations from level 2 or 3 studies**; and D, level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

*Medication including antidepressants, lithium, anticonvulsant, benzodiazepine

**Definition treatment resistance: ≥2 failed medication trials with adequate dose and duration.

number of pulses.

3.3. Antidepressant effects [short term]

See Tables 1 and 2 for outcome measures, findings and criteria for response and remission. Fig. 2 shows a summary of all the findings on responders and remitters [in case of the cross-over studies, only the active-sham group was illustrated]. Wilkening et al. (2022) only reported scores of MADRS and suicide items of the Beck Depression Inventory – II [BDI-II] and HDRS-17 and provided additional data of

response and remission rates for this review.

Duprat et al. (2016) assessed depressive symptoms based on the HDRS-17. In the active-sham group [n = 20], the response rates after zero, one and four weeks were respectively 20.0%, 35.0% and 35.0%. The remission rates after zero, one and four weeks were respectively 10.0%, 25% and 30%.

Williams et al. (2018) assessed depressive symptoms based on the HDRS-17 and reported response and remission rates following active treatment of 83.3% [5/6] and 66.7% [4/6], respectively. The response rates after two and four weeks were respectively 33.3% [2/3] and 0%.

Table 2
Findings.

Authors	Outcome scale depressive symptoms	Baseline depression scores	Response and remission [%]	Outcome scale suicidality	Suicidality	Side effects And drop-outs
Duprat et al. (2016), Desmyter et al. (2016)	HDRS-17 BDI-I BSI	HDRS-17: 21.3 [SD 5.3]	^b Overall response after treatment: 13/41 [31.7] Overall remission after treatment: 6/41 [14.6] ^b Overall response end of study: 17/41 [41.4] Overall remission end of study: 14/41 [34.1] Active – sham response rates at 0,1,3 weeks: 20.0%; 35.0%; 35.0% Active – sham remission rates at 0,1,3 weeks: 10.0%; 25.0%; 30.0% Sham-active response rates at 0,1,3 weeks: 4.8%; 28.6%; 47.6% Sham-active remission rates at 0,1,3 weeks: 0.0%; 4.8%; 38.1%	HDRS/BSI	Baseline: 13.3 [95%CI = 10.5–16.1] After two weeks of treatment 7.53 [95%CI = 4.5–10.5] At 2 week follow-up: 5.26 [95%CI = 2.5–8.2] Overall reduction: 60.5%	Safe and well-tolerated - Discomfort at treatment site - Headache Drop-out: 3 [*]
Williams et al. (2018)	HDRS-17	HDRS-17: 28.8 [SD 6.0] MADRS: 40.3 [SD 8.6]	At end of treatment (week 0): ^b Response: 5/6 [83.3] ^b Remission: 4/6 [66.6] At two week follow-up: Response: 2/6 [33.3] Remission: 0/6 [0] At four week follow-up: Response: 0/6 [0] Remission: 0/6 [0]	Did not report on suicidality	Did not report on suicidality	Safe and well-tolerated - Fatigue - Discomfort at treatment site/facial muscles Drop-out: 1 ****
Cole et al. (2020)	MADRS HDRS-17 C-SSRS BDI-II	HDRS-17: 25.9 [SD 4.8] MADRS: 34.9 [SD 5.3]	ITT at end of treatment (week 0): ^a Response: 19/22 [86.4] ^a Remission: 19/21 [86.4] ITT At 4 week follow-up: Response: 14/21 [66.7] Remission: 12/21 [57.1]	C-SSRS [Suicide items from] HDRS-17 MADRS	Baseline: C-SSRS: 19/21 [90.5%] HDRS-17: 20/21 [95.2%] MADRS: 21/21 [100%] Post treatment remitters: C-SSRS: 21/21 [100%] HDRS-17: 21/21 [100%] MADRS: 20/21 [95.2%]	Safe and well-tolerated - Fatigue - Discomfort at treatment site/facial muscles Drop-out: 1 ***
Cole et al. (2022)	MADRS	Active group: HDRS-17: 24 MADRS: 31 Sham group: HDRS-17: 26 MADRS: 35	^a Overall response: 12/14 [85.7] ^a Overall remission: 11/14 [78.6] ITT response rates at 0,1,2,3,4 weeks: 71.4%; 71.4%; 78.6%; 64.3%; 64.3% ITT remission rates at 0,1,2,3,4 weeks: 57.1%; 64.3%; 50.0%; 57.1%; 42.9% Sham: Overall response: 4/15 [26.7] Overall remission: 2/15 [13.3]	Did not report on suicidality	Did not report on suicidality	Safe and well-tolerated - Fatigue - Discomfort at treatment site - Headache Drop-out: 0
Wilkens et al. (2022)	[Suicide items from] MADRS BDI-II HDRS-17	MADRS: 23.2 [SD 7.6] HDRS-17: 15.0 [SD 4.9] MADRS item 10: 16 [19.8] HDRS-17 item 3: 38 [46.9]	Overall reduction in MADRS score = 29.5% ^a ITT response rates active-sham at 0,1,2,3,4 weeks: 26.8%; 29.3%; 26.8%; 29.3%; 39.0% ^a ITT remission rates active-sham at 0,1,2,3,4 weeks: 24.4%; 29.3%; 26.8%, 29.3%; 39.0% ^a ITT response rates sham-active at 0,1,2,3,4 weeks: 20.0%; 15.6%; 26.7%; 24.4%; 28.9% ^a ITT remission rates sham-active at 0,1,2,3,4 weeks: 15.6%; 15.6%; 24.4%; 22.2%; 15.6%	[Suicide items from] HDRS-17 MADRS BDI-II	50/81 [61.7%] experienced improvement on the C-SSRS 14/81 [17.3%] experienced worsening on the C-SSRS Experienced improvement on the following scales: HDRS-17: 36/81 [44.4%] MADRS: 31/81 [38.3%] BDI-II: 32/81 [39.1%] Worsening on the following scales: HDRS-17: 15/81 [18.5%] MADRS: 14/81 [17.3%] BDI-II: 5/81 [6.2%]	Safe and well-tolerated - Discomfort at treatment site [56.2%] - Headache [52.5%] - Neck pain [21.0%] Drop-out: 11 **

dIPFC = dorsolateral Prefrontal Cortex, fcMRI = functional connectivity Magnetic Resonance Imaging, SCC = subcallosal cingulate, DMN = Default Mode Network, MT = Motor Threshold, EEG = electroencephalogram, Hz = Hertz, ISI = intersession interval, MADRS = Montgomery-Asberg Depression Rating Scale, HDRS-17 = Hamilton Depression Rating Scale - 17-item, BDI-I/II = Beck Depression Inventory - I/II, PHQ-9 = Patient Health Questionnaire-9, BSI = Brief Symptom Inventory, ITT = Intention To Treat, BSI= Brief Symptom Inventory, C-SSRS = Columbia-Suicide Severity Rating Scale,.

- ^a Response was defined as a reduction of $\geq 50\%$ in MADRS score, and remission was defined as MADRS score ≤ 10 .
- ^b Response was defined as a reduction of $\geq 50\%$ in HDRS-17score, and remission was defined as HDRS-17 score ≤ 7 .
- ^c Duprat and colleagues did not elaborate on suicide risk, however as part of the same data set, they did report results on suicidal ideation in a separately published article [Desmyter et al. 2016].
- ^{*} Drop-out due to severe suicide attempt in one patient, one week after sham-iTBS. Another patient received iTBS sessions during two weeks rather than one week stimulation and one week sham [patient was both responder and remitter]. Third patients improved depressive symptoms after discontinuation of antidepressants and therefore did not start with the aiTBS.
- ^{**} Drop-out due to rTMS unrelated reasons [e.g. cold], medications changes, worsening of depressive symptoms, time limitations for scheduling time visits. No drop-outs due to rTMS side effects.
- ^{***} Drop-out due to anxiety after the first day of stimulation [previously known with anxiety].
- ^{****} Drop-out due to non-response after day four.

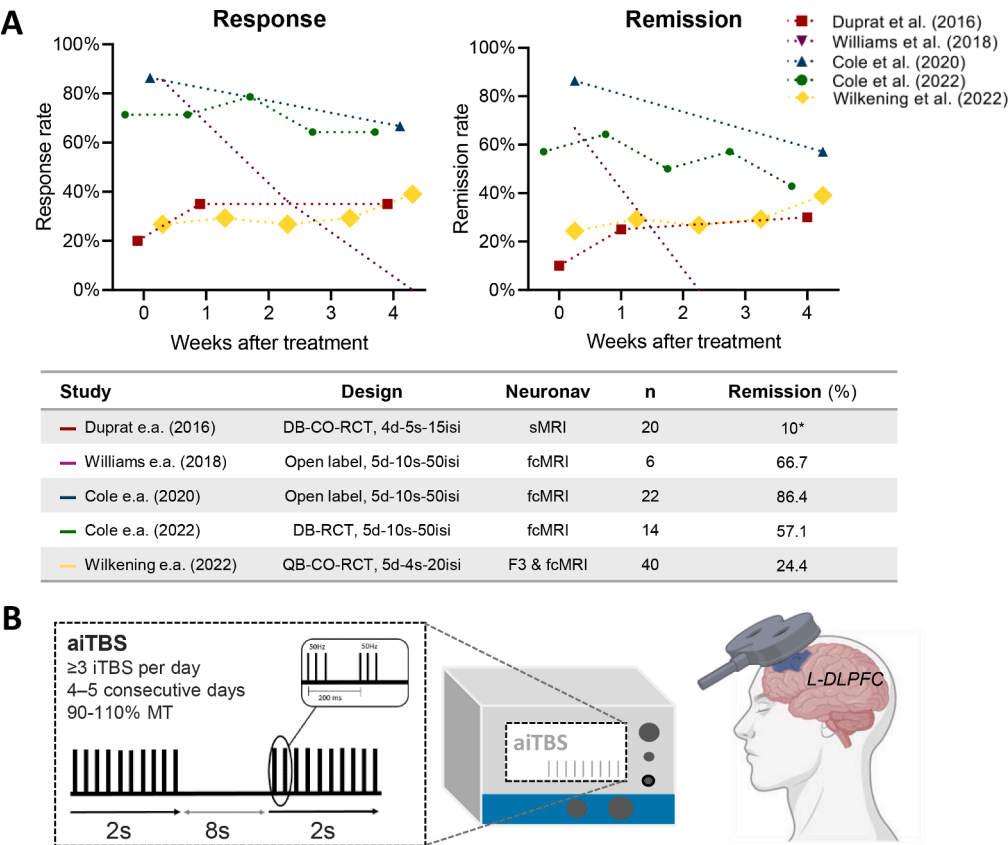


Fig. 2. Summarizing figure including [A] acute response- and remission rates until four weeks follow up with study designs and remission rates directly after treatment. Size represents the number of patients. [B] accelerated intermittent Theta Burst Stimulation [aiTBS] definition of treatment parameters. Hz; Hertz, ms; Milliseconds, Q/DB-CO-RCT; Quadruple/Double-Blind Cross-Over Randomized Controlled Trial, MT; Motor Threshold, L-dIPFC; Left Dorsolateral Pre Frontal Cortex; sMRI: structural MRI; fcMRI: functional connectivity guided MRI; F3: Beam F3 method. *: No ITT data available.

None of the patients remained remitted at two or four weeks of follow-up.

Cole et al. (2020) assessed depressive symptoms based on the MADRS. The study reported ITT response and remission rates following active treatment of 86.4% [19/22] and 86.4% [19/22]. The ITT responses and remission rates after the four week follow-up period were 66.7% [14/21] and 57.1% [12/21]. The mean number of days to reach response was 2.30 days and the mean number of days to reach remission was 2.63 days.

Cole et al. (2022) assessed depressive symptoms based on the MADRS. The response in the intention to treat analysis [ITT] rates after zero, one, two, three and four weeks were respectively 71.4%, 71.4%, 78.6%, 64.3% and 64.3%. ITT remission rates after zero, one, two, three and four weeks were respectively 57.1%, 64.3%, 50.0%, 57.1% and 42.9%.

Wilkening et al. (2022) defined response and remission in line with the Cole et al. studies. For the ITT analysis, the Last Observation Carried Forward [LOCF] was used. In the active-sham group [n = 40] the ITT

response rates after zero, one, two, three and four weeks were respectively 26.8%, 29.3%, 26.8%, 29.7% and 39.0%. In the same group, the ITT remission rates after zero, one, two, three and four weeks were respectively 24.4%, 29.3%, 26.8%, 29.3% and 39.0%.

3.4. Antidepressant effects [long term]

None of the studies reported on antidepressant effects at follow up longer than four weeks after treatment.

3.5. Anti-suicidal effects

A total of three studies reported on anti-suicidal effects following aiTBS. Duprat et al. (2016) did not elaborate on suicide risk, however as part of the same data set, they did report results on suicidal ideation in a separately published article (Desmyter et al., 2016). See Table 2 for an overview of all extracted data.

Desmyter et al. (2016) assessed suicidality with the 21-items Beck

Scale for Suicide Ideation [BSI] and reported an overall reduction in BSI scores of 60.5%. No worsening of suicidal ideation was found. [Cole et al. \(2020\)](#) assessed suicidality with subscales of Colombia-Suicide Severity Rating Scale [C-SSRS], item 3 of HDRS-17 and item 10 of MADRS. Following aiTBS, a significant reduction was found on all measures. All patients remitted on C-SSRS and item 3 of HDRS-17, 20/21 [95.2%] remitted on item 10 of MADRS. 80–100% of the patients remained in remission four weeks after aiTBS. No worsening of suicidal ideation was observed. [Wilkening et al. \(2022\)](#) assessed suicidality with C-SSRS and item 3 of HDRS-17, item 10 of MADRS and item 9 of BDI-II. 50/81 [61.7%] experienced improvement on the C-SSRS and 14/81 [17.3%] experienced worsening on the C-SSRS over the six week period of the study. On the items of HDRS-17, MADRS and BDI-II improvement was found in respectively 38.3 to 44.4% of the patients. A worsening in suicidality items was observed in 6.2–18.5% of the patients.

3.6. Adverse events

See **Supplementary Table 3** for all reported adverse events. None of the studies reported major adverse events, especially no seizures, or affective switching. In the study by [Duprat et al. \(2016\)](#) one patient attempted suicide, one week after being treated with sham aiTBS. Only two studies specified prevalence per adverse event ([Cole et al., 2022](#); [Wilkening et al., 2022](#)). Most common adverse events by [Cole et al. \(2022\)](#) were fatigue and headache [57%], neck/back discomfort [50%], discomfort at stimulation site [36%] and anxiety [29%]. [Wilkening et al. \(2022\)](#) reported scalp pain [56%], headache [53%] and neck/back discomfort [30%]. [Duprat et al. \(2016\)](#) reported that the majority of the patients reported fatigue, headache and discomfort at stimulation site. [Cole et al. \(2020\)](#) reported fatigue, discomfort at stimulation site and anxiety. Side effects that were reported were especially observed at the start of the treatment and spontaneously improved or improved after analgesic medication.

3.7. Tolerability

A total of four studies reported drop-outs [16 out of 184 patients = 8.7%, total n also including patients who received sham treatment]. In the study by [Duprat et al. \(2016\)](#), there were three drop-outs. One patient attempted suicide, one week after being treated with sham aiTBS. A second patient received two weeks of aiTBS treatment, rather than one week of stimulation and one week of sham [patient both responded and remitted]. The third patient did not start the trial as the depressive symptoms improved significantly after discontinuation of antidepressants. A total of 11 patients dropped-out in the study of [Wilkening et al. \(2022\)](#) however these drop-outs were not due to side effects of the treatment rather due reasons such as a cold/upper airway infection, medication changes or worsening of depressive symptoms. The study by [Cole et al. \(2020\)](#) reported one drop-out due to anxiety after the first day of stimulation, in a patient already known to experience anxiety. In the open-label study by [Williams et al. \(2018\)](#) there was one drop-out after day four because the patient wished to discontinue the treatment due to a lack of improvement.

4. Discussion

This systematic review provides preliminary evidence that an accelerated form of iTBS is a safe, tolerable and effective form of NIBS, with a rapid onset of antidepressant effect in patients with MDD. This review on a total of 102 patients found response rates of 20%–86.4% and remission rates of 10%–86.4% immediate after three to five consecutive days of treatment. Additionally, suicidality rapidly decreased which remained decreased at least two weeks after treatment. The treatment was safe and well tolerated and no serious adverse events were reported [including seizures or manic switching].

The response and remission rates by the Stanford group ([Williams](#)

[et al., 2018](#); [Cole et al., 2020, 2022](#)) are equivalent to or possibly superior to current approved treatment options in MDD [including antidepressants, psychotherapy and cognitive behavioral therapy] ([Rush et al., 2006](#)). A report by [Rush et al. \(2006\)](#) including 3681 participants with MDD found an overall cumulative remission rate of 67% following one or more adequate evidence-based treatment options, including antidepressants, psychotherapy and cognitive behavioral therapy(). These remission rates are similar to the Stanford group, however these rates are remarkably higher compared to [Duprat et al. \(2016\)](#) and [Wilkening et al. \(2022\)](#). A potential explanation is that most patients in the included studies had at least some level of treatment resistance, whereas 90% of the patients in the Rush study ([Rush et al., 2006](#)) did not meet the general definition of treatment resistant depression [at least two medication trials of adequate dose and duration].

In addition, the studies by the Stanford group ([Williams et al., 2018](#); [Cole et al., 2020, 2022](#)) show preliminary evidence that the effectiveness of aiTBS is equivalent, but more rapid compared to established treatment options such as HF-rTMS, ECT and [es]ketamine. However, these studies had a small sample size and only one study had a RCT design. A possible explanation for the higher response and remission rates compared to other established treatment options such as HF-rTMS is that once-daily treatment is a suboptimal dose for high refractoriness and may require more pulses and therefore more sessions to produce antidepressant effects. In comparison, a meta-analysis in 2014 found response rates of 29.3% and remission rates of 18.6% of subjects following approximately 13 sessions of HF-rTMS ([Berlim et al., 2014](#)). Additionally, response rates of other treatment options for TRD, such as electroconvulsive therapy [ECT] and [es]ketamine are 48% and 60% respectively ([Heijnen et al., 2010](#); [Ionescu et al., 2021](#)). The included studies in this systematic review did not report major adverse events and the studies that performed neuropsychological testing did not demonstrate negative cognitive side effects, suggesting that these protocols might potentially be more acceptable for patients. In comparison, ECT is associated with severe cognitive side effects on executive functioning and memory that may persist for several months ([Berlim et al., 2013](#); [Petersen and Miskowiak, 2018](#)). In conclusion, aiTBS is a rapid and safe antidepressant treatment option with possible equivalent effects of established treatment options such as ECT or HF-rTMS.

Furthermore, another promising accelerated TBS paradigm includes sequential bilateral iTBS/ctBS, described by [Chen et al. \(2021\)](#) in a large multi-center trial with 300 TRD patients(). This largest accelerated TBS study thus far showed a similar efficacy and speed of response between accelerated bilateral TBS versus regular HF-rTMS, but was given during the course of 2 weeks. Other promising forms of neuromodulation include Vagus Nerve Stimulation Therapy [VNS] and Deep Brain Stimulation [DBS] ([Carreno and Frazer, 2017](#); [Kisely et al., 2018](#)). However, both are surgical brain stimulation options and far more invasive in comparison to aiTBS. Additional research is needed to compare efficacy, safety and long-term effects of aiTBS to other treatment options for MDD. Due to the limited reports on long-term effects, future studies should prioritize the long-term treatment effects and maintenance protocols of aiTBS with or without concomitant use of antidepressants. This is especially important as relapse rates after neuromodulation are high and MDD in the majority of patients is chronic with a recurrent pattern. Moreover, the use of accelerated protocols have the potential to optimize time and costs, as multiple sessions can be applied over a single day. Reducing the number of treatment days may lead to improvement of cost-effectiveness, increase the number of patients to be treated in a given time frame and increase accessibility for patients. This is possibly where the true potential of aiTBS lies, rather than in superior efficacy to alternatives. Future studies should evaluate such practicalities and the cost effectiveness of aiTBS in a real world clinical setting.

All studies reported that aiTBS was safe, well-tolerated and no major adverse events occurred. Most reported adverse events were fatigue, headache and discomfort at stimulation site, comparable to regular rTMS protocols. No seizures or affective switches were observed. These

findings support the evidence on safety of TMS and TBS protocols (Lefaucheur et al., 2020; Blumberger et al., 2018; Health Quality Ontario, 2016). It is important to consider the unlikelihood of a seizure to occur, with estimated risks of <0.003% in rTMS and <0.002% in TBS (Health Quality Ontario, 2016; Rossi et al., 2009; Oberman et al., 2011). To evaluate the prevalence of these rare adverse events, more and large-scale naturalistic studies with long term follow-up are warranted.

In line with literature on rTMS and suicidality, Duprat et al. (2016), Desmyter et al. (2016) and Cole et al. (2020), Page et al. (2021) found improvement of suicidality and no worsening of suicidal ideation after treatment (Lefaucheur et al., 2020; Abdelnaim et al., 2020; Pan et al., 2020). Wilkening et al. (2022) also reported an improvement in severity of suicidality, however a worsening of suicidality in 6.2 to 18.2% of the patients was also observed. The increase in suicidal ideation was limited and therefore no evidence was found that aiTBS systematically increased suicidal ideation. This is in line with Abdelnaim et al. [2019] who found that suicidal ideation improved or remained stable after rTMS in 88.3% of MDD patients and worsened in 11.7% of MDD patients (Abdelnaim et al., 2020). All together, these findings suggest that aiTBS is a potential therapy option to rapidly reduce suicidal ideation, for example in an inpatient setting.

The Stanford group (Williams et al., 2018; Cole et al., 2020, 2022) reported similar response and remission rates after treatment of 71.4% – 86.4% and 57.1 – 86.4%, with depressive symptoms increasing four weeks after treatment. Contrasting the studies by the Stanford group, Duprat et al. (2016) and Wilkening et al. (2022) found substantial lower response and remission rates. However, both studies identified an delayed increase in response and remission rates two weeks after the treatment had ended. Variations in protocols seemingly affected the degree of clinical response and remission and the persistence of antidepressant effects.

One of these variations is the Identification of the target brain region. The Stanford group targeted the left dlPFC most anti-correlated with the sgACC with fcMRI. Additionally, stimulation was delivered at 90% of MT with a depth correction. Duprat et al. (2016) identified the dlPFC based on structural MRI and delivered stimulation at 110% MT without depth correction. Wilkening et al. (2022) targeted the dlPFC in half the patients based on conventional F3 point and the other half based on dlPFC site most anti-correlating with the DMN with resting state functional MRI. Studies have identified the importance of precise targeting, as different targets can lead to different outcomes in symptom reduction (Opitz et al., 2013). The effects of TMS or iTBS can propagate to other disturbed brain networks depending on the dlPFC site that is stimulated, possibly explaining the variety of responses found in the studies. In addition, it is unclear to what degree adjusting the stimulation intensity [MT] for the coil-to-cortex distance contributes to the variety of response and remission rates.

Moreover, the number of pulses in the studies ranged from a total of 32,400 to 90,000 pulses after completing the course of treatment. A pilot study in 2021 found that a higher number of pulses of rTMS in 29 MDD patients enhanced reduction in depressive symptoms (Johansson et al., 2021). Possibly, the number of pulses and daily sessions by Duprat et al. (2016) [32,400 pulses] and Wilkening et al. (2022) [36,000] were at a suboptimal dosage, as high refractory patients may require more pulses to produce antidepressant effects (Teng et al., 2017).

Also, previous studies have suggested the importance of interval duration, as the duration is important in the degree of neuroplasticity on excitatory circuits (Cao and Harris, 2014; Kramár et al., 2012; Tse et al., 2018; Nettekoven et al., 2014). The ISI was 50 min [Stanford group (Williams et al., 2018; Cole et al., 2020, 2022)] 15 min [Duprat et al., 2016] and 20 min [Wilkening et al., 2022]. In a study conducted in rats, ISI of TBS between 50 and 90 min produced a cumulative effect on neuroplasticity through synaptic strengthening. The cumulative effect on neuroplasticity is thought to be less, or not produced at all, if the interval intersession is shorter than 40 min (Cao and Harris, 2014; Kramár et al., 2012; Tse et al., 2018; Nettekoven et al., 2014). Tse et al.

2018, however, identified that a 15 min ISI can increase cortical excitability that lasts up to 60 min post stimulation (Tse et al., 2018). Systematic investigations are required to confirm if the amount of cumulative effects are [linearly] dependent on the ISI.

In summary, the high level of heterogeneity between the studies makes it challenging at this moment to generalize conclusions on the best aiTBS parameters to optimize treatment efficacy. Additional research is required to assess the optimal treatment parameters. Large scale RCTs are warranted to establish optimal methodology. We also suggest research groups to use similar nomenclature to describe the aiTBS protocols, such as the designation aiTBS-5d-10s-50isi used here.

Several limitations were identified in this systematic review. First, publication bias could be a serious concern due to the rarity of the available studies. However, due to the limited studies available and small sample size [$n = 102$] a publication bias analysis such as a funnel plot could not be performed (Page et al., 2023). Future studies are warranted to overcome this limitation. In addition, only studies published in English were eligible for inclusion and the number of databases used were limited. Therefore, relevant studies published in other languages could have been overlooked. Second, generalizing the overall results is hindered by the large heterogeneity of the studies. Additionally, due the heterogeneity, limited included studies and small sample size [$n = 102$] no meta-analysis was performed. Third, there is a risk of type I or II errors due the relatively small sample sizes. Fourth, there was a consistent lack of long-term follow-up, making it unclear whether initial antidepressant effect is persistent or whether delayed clinical effects occur. Fifth, the cross-over design [Duprat et al., 2016]; (Wilkening et al., 2022)] could have resulted in potential carryover effects from one condition to the other, limiting the ability to separate delayed effects. Additionally, delayed clinical effects were only observed in one condition [active stimulation first]. In both cross-over studies, both arms experienced clinical improvement to some extent at all time points, regardless of order. This indicates that accelerated forms of iTBS [including setup of neuronavigation] are prone to placebo effects, similar to previously studies in rTMS and iTBS (Pan et al., 2020; Burke et al., 2022; Brunoni et al., 2009; Razza et al., 2018). Furthermore, Duprat et al. (2016) only included patients who were antidepressant free at least two weeks prior start of the trial, making it difficult to generalize the results in a real-life setting as most patients will have antidepressant medication. Lastly, due to the limited number of patients with bipolar depression, no definitive conclusions of aiTBS in bipolar depression could be drawn.

5. Conclusion

Accelerated intermittent theta burst stimulation is a promising, tolerable and safe form of non-invasive brain stimulation with rapid antidepressant efficacy and anti-suicidal effects in patients with MDD. Studies performed thus far are small, short term and treatments parameters differ, making generalizability difficult. Replication RCTs with a credible control condition in larger sample studies are warranted to evaluate efficacy and long term effects and to establish optimal treatment methodology.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.psychres.2023.115429](https://doi.org/10.1016/j.psychres.2023.115429).

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