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Research paper

Outcome of transcranial magnetic intermittent theta-burst stimulation in the treatment of depression - A Swedish register-based study

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) is an established treatment of depression. The more recently introduced intermittent Theta-burst stimulation (iTBS) has shown significant superiority over sham-stimulation and equal effect sizes to a 10 Hz protocol in one clinical trial. The aim of the current study was to investigate the effectiveness and tolerability of iTBS in a naturalistic, clinical setting. Further, we explored demographical and clinical predictors of response.

Methods: Data was collected from seventeen rTMS-sites in Sweden between January 2018 and May 2021, through the Swedish National Quality register for repetitive Transcranial Magnetic Stimulation (Q-rTMS). We included 542 iTBS-treated patients with unipolar or bipolar depression. Outcome was assessed with Clinical Global Impression Severity and Improvement scores in an intention to treat analysis.

Results: The response rate was 42.1 % and 16.1 % reached remission. The response rate was significantly larger in the oldest age group compared to the youngest (odds ratio 3.46, 95 % confidence interval 1.65–7.22). Less severe level of depression (Montgomery-Åsberg depression rating scale self-assessment < 36) at baseline predicted response and remission. Only <1 % were much or very much worse after treatment. Drop-out rate was 10.9 %. No serious adverse events were reported.

Limitations: Retrospective analysis of register data. No comparison group.

Conclusions: In a clinical setting, iTBS was shown to be safe and tolerable and the response rate was similar to that reported from clinical trials. Older age-group and less severe illness predicted response.

1. Introduction

In 2008, the U.S. Food and Drug Administration (FDA) approved repetitive transcranial magnetic stimulation (rTMS) for the treatment of depressive illness that has not responded to pharmacological treatment. The large-scale randomized controlled trials (RCTs) underlying the approval demonstrated significant antidepressant effect of rTMS over sham treatment, although response and remission rates were modest. For example O'Reardon et al. reported response rates around 24 % and remission rates of 14.2–17.4 % in the rTMS-group (O'Reardon et al., 2007). The study population consisted of unmedicated depression patients with previous treatment failures and placebo response was low; response rates of 15.1–12.3 % and remission rates of 5.5–8.9 % were reported, depending on which rating scale that was used.

The FDA approval facilitated further clinical trials and analyses of naturalistic data collected from clinical practices. In the coming years, studies with different designs and in different settings were published, with higher response and remission rates, than the original studies. An open-label study in 2012, with patients treated with concomitant antidepressant medication had a response rate of 50 %, and 30 % remitted (Carpenter et al., 2012). Another open label study with flexible treatment protocols also reported a remission rate of 30 % (McDonald et al., 2011). A recent large registry study of treatment outcomes of the 10 Hz protocol in clinical settings showed response rates of 58 %–83 % and remission rates of 28 %–62 %. The variability depended on rTMS-protocol and outcome measure (Sackeim et al., 2020a). The highest

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response and remission rates were found in a sample of patients that received left dorsolateral prefrontal cortex (DLPFC) stimulation, completed the treatment course, and were rated with CGI-S. The lowest rates were found in an intention to treat analysis of all subjects assessed with PHQ-9.

Most of the early large-scale studies applied 10 Hz stimulation over the left DLPFC or 1 Hz stimulation over the right DLPFC (Brunelin et al., 2014)(O'Reardon et al., 2007) and a later meta-analysis of RCT's have further validated these treatments as effective (Hyde et al., 2022). The downside of these treatment protocols has been the long treatment duration. In parallel, other patterned protocols such as intermittent theta-burst stimulation (iTBS) of the left DLPFC (Huang et al., 2005) has been developed, delivering a high number of pulses over a short time frame. One small study reported antidepressant effect superior to sham (Li et al., 2014) with the benefit of requiring shorter treatment duration per session than former protocols. In the THREE_D study, the largest rTMS trial so far, Blumberger et al. demonstrated that a just over 3-min iTBS protocol was non inferior to a 37.5-min 10 Hz protocol (Blumberger et al., 2018), with response and remission rates of 47 % and 27 % in a pharmacotherapy-resistant population. Notably, 80 % of the patients in this trial were on concomitant antidepressant medication. A recent meta-analysis, comprising studies using different iTBS protocols, confirmed iTBS superior antidepressant effect over sham (risk ratio 2.40), with a response rate of 39 % (response defined as a >50 % reduction of HRSD-score) (Voigt et al., 2021). Overall, iTBS is considered an effective, safe and tolerable treatment for depression (Stultz et al., 2020) (Chu et al., 2021).

The differences in treatment outcome between studies may depend on the study samples. It is still not known why some patients with depression respond to rTMS and others do not. Attempts to identify putative predictors for antidepressant response have been made through retrospective analyses of clinical studies. A few patient characteristics have been associated with antidepressant response to rTMS. Demographic and clinical parameters such as being younger (Rostami et al., 2017), female gender (De Santis et al., 2014), lower depression severity level (Fitzgerald et al., 2016), psychomotor retardation (Brakemeier et al., 2008), have correlated to treatment effect. However, one large retrospective study found no demographic or clinical parameters associated with response (Bakker et al., 2015). Retrospective analyses have suggested predictors for iTBS antidepressant effect, where the currently most consistent is lower depression severity (Trevizol et al., 2020). Data on the efficacy of iTBS in naturalistic clinical settings has, to our knowledge, not been published.

In 2016, the Swedish National Board of Health and Welfare recommended rTMS for treatment resistant depression in its national guidelines. Since then, rTMS treatment has become increasingly available in Sweden, a country of ten million inhabitants. In 2017 there were six treatment sites in Sweden and in 2020 there were 17. The THREE-D study seems to have had a great impact on clinical rTMS practice in Sweden since the just over 3-min iTBS protocol from that study is the most used protocol in Swedish clinics.

The aim of this study was to investigate the effectiveness and tolerability of iTBS for unipolar and bipolar depression in the clinical setting using data from the Q-rTMS https://ect.registercentrum.se/. Secondary aims were to investigate clinical and demographical predictors of treatment response.

2. Methods

2.1. Data collection

In 2018, the National Quality Register for TMS (Q-rTMS) started collecting data from the Swedish rTMS treatment providers. Clinics using rTMS send patient data regarding diagnosis, patient's age and gender, previous rTMS and/or ECT-treatment, stimulator model, treatment protocol and symptom ratings to the register. The register is non-mandatory but in 2020 94 % of all rTMS treatments were registered (Nordenskjöld et al, 2020), compared to data from the Swedish national patient registry. Data for this study was collected from seventeen Swedish rTMS-sites through the Q-rTMS between January 2018 and June 2021. Both patients who had received iTBS for uni- and bipolar depressive episodes were included (ICD-10 codes F31.3-F31.9, F32.0-F32.9, F33.0-F33.3, F34.1, F34.9, F38.1, F41.2). For subjects who received two or more treatment series, only the first series is included.

2.2. Symptom ratings

Clinical Global Impression - Improvement (CGI-I) and Clinical Global Impression-Severity (CGI-S) ratings were performed by the patients' treating psychiatrist or the psychiatrist in charge of iTBS-treatment. The CGI-S is a one item rating 1–7 of the patient's global symptoms of illness where 1 no symptoms and 7 is the most severely ill. The CGI-I is a one item rating 1–7 of global improvement where 1 is very much improved, 4 is no change and 7 is very much worse (Guy, 1976). Montgomery-Åsberg depression rating scale, self-assessment (MADRS-S) (Svanborg and Åsberg, 2001) and EuroQol Visual Analog Scale (EQ-VAS) (https://euroqol.org/) scores were patient-rated. Post-treatment ratings were completed within one week after the last treatment. The MADRS-S is a self-rating of the severity of nine different symptoms of depression. Each symptom is rated on a scale 0–6 with a maximum score of 54. The EQ-VAS is a visual analog self-rating scale of 0–100 where the patient score their subjective level of health.

2.3. Outcomes

All subjects who had received at least one iTBS-stimulation were included in the intention to treat (ITT) analyses. The main outcome measure was the post-treatment CGI ratings. Remission was defined as a post-treatment CGI-S score of 1 or 2 (normal or borderline mentally ill), and response was defined as a CGI-I score of 1 or 2 (very much or much improved) (Leucht et al., 2017). Subjects receiving <15 treatments were classified as dropouts. For secondary analyses of MADRS-S and EQ-5D scores, remission was defined as MADRS-S < 10 and EQ5D > 80, and response as 50 % reduction of MADRS-S and 50 % increase of EQ-5D.

2.4. Statistics

Univariable logistic regression models were performed to identify predictors of treatment outcome by investigating the associations of gender, age, unipolar/bipolar status, previous ECT-treatment, baseline MADRS-S rating, and use of benzodiazepines, with the response and remission. Age was stratified into four groups and MADRS-S into five groups to get homogenous groups of comparable sizes, all other variables were dichotomous. All variables were entered into corresponding multivariable models. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and SPSS 22 (IBM Corp, Armonk, NY, USA).

The study was approved by the Swedish Ethical Review Authority, approval number 021–03815 and the need for informed consent was waived because patients were not identifiable in the research database.

3. Results

We identified 695 patients treated with iTBS in the Q-rTMS. Fifty-six subjects had other indications for iTBS than depression and were excluded from the analysis. CGI-I ratings were missing for 97 patients and CGI-S ratings were missing for 86, rendering 542 subjects included in the response analyses and 553 subjects in the remission analyses. Demographic and clinical data of the included subjects and those with missing CGI-I ratings are shown in Table 1.

Table 1
Demographics.

	Study cohort n = 542	Subjects missing ratings n = 97
Gender, female, n (%)	328 (60.5)	52 (53.6)
Age, mean (SD)	43.9 (15.3)	43.0 (15.3)
Number of treatments, mean (SD)	22.6 (7.1)	22.2 (10.3)
Pretreatment EQ VAS, mean (SD)	29.6 (16.0) (n = 450)	33.5 (17.8) (n = 82)

SD = Standard deviation.
EQ VAS = EuroQol visual analog scale.

3.1. iTBS procedure

Intermittent Theta-Burst stimulation was delivered using the Magventure R30 (91 %), Magventure X100 (5 %) or Nextim (4 %) stimulators using a figure of eight coil (93 %) or butterfly figure of eight coil (7 %). All sites used the standard iTBS protocol (Blumberger et al., 2018) of twenty pulse trains of ten 5 Hz Theta-bursts (three 50 Hz pulses), and 8 s inter-train interval, in total 600 pulses in just over 3 min. Treatments were given daily or twice daily. The mean number of treatments per series was 22.3 and 89,1 % (n = 483) of the subjects received at least 15 treatments. Eighty-two percent (n = 429) of the subjects received concomitant antidepressant treatment.

In the ITT analysis, 42.1 % of the subjects responded to the treatment (CGI-I 1 or 2). Five subjects (0.2 %) were much worse or very much worse (CGI-I 6 or 7) after treatment and 16.1 % remitted (CGI-S 1 or 2) (Table 2). Response and remission rates for the groups of unipolar depression (UD) and bipolar depression (BD) respectively were UD: 41.4 % response, 15.6 % remission, BD: 46.5 % response, 18.6 % remission. A sensitivity analysis of missing data was performed with the assumption that all subjects with missing CGI-ratings (n = 97) were either remitters and responders or non-remitters and non-responders. This rendered a response rate ranging from 35.7 to 50.9 % and a remission rate ranging from 13.6 to 28.8 %.

The results of the logistic regression analysis of predictors of remission and response are found in Table 3. The univariable analyses identified an association between older age and response but not remission. Compared to the youngest group (<25 years) the odds ratios for remission were 2.22 (95 % CI: 1.24–3.95) for the age-group 26–40, 2.34 (95 % CI: 1.33–4.12) for the age-group 41–60, and 3.46 (95 % CI:1.65–7.22) for the age-group 61–84. Baseline MADRS-S scores >36 predicted both lower response rates and lower remission rates compared to the reference group of MADRS-S scores between 26 and 30 (Table 3). No significant differences in response rate were found for gender, UD vs. BD, previous ECT-treatment or concomitant use of benzodiazepines. The multivariate analyses showed no significant effect of age but a significant effect of MADRS-S < 36 on response rates and MADRS-S 36–40 on remission rates.

To further evaluate if the CGI-scores reflect reduction of depression symptoms and reduced suffering, we performed secondary analyses of the subsets of subjects that had pre- and post-treatment MADRS-S and EQ-VAS ratings. Of the 339 subjects with MADRS-S ratings, response was found in 22.1 % (n = 75), and remission was reached by 12.4 % (n = 42). The mean reduction of MADRS-S score was 8.20 SD 9.05 and median 7.0 range 11–38. EQ-VAS data was registered in 412 subjects. We found a response rate of 49.3 % (n = 203) and a remission rate of 7.2 % (n = 42). The mean post-treatment EQ-VAS score in the CGI-S remission group was 68.6, and in the CGI-I response group 58.5.

Table 2
Response and remission rates.

Response		Remission	
CGI-I	Number of subjects, %	CGI-S	Number of subjects, %
1. Very much improved#	67 (12.4)	1. Normal, not at all ill¤	41 (7.6)
2. Much improved#	161 (29.7)	2. Borderline mentally ill ¤	46 (8.5)
3. Minimally improved	134 (24.7)	3. Mildly ill	146 (26.9)
4. No change	160 (29.5)	4. Moderately ill	185 (34.1)
5. Minimally worse	15 (2.8)	5. Markedly ill	86 (15.9)
6. Much worse	4 (0.7)	6. Severely ill	16 (3.0)
7. Very much worse	1 (0.2)	7. Among the most extremely ill patients	0 (0.0)
		Missing	22 (4.1)
	542 (100)		542 (100)

= The operational definition of response.
¤ = The operational definition of remission.
CGI-I: Clinical Global Impression, improvement.
CGI-S: Clinical Global Impression, severity.

4. Discussion

In this first national register-based cohort study of iTBS for depression we observed a clinician rated response rate of 42.1 %, being on par with the THREE-D clinical trial (17), while the remission rate of 16.1 % was lower. In the subgroup of patients with bipolar depression, response rate was 46.5 % and remission rate 18.6 %. We also identified less severe degree of depressive symptoms, and older age as predictors of beneficial outcome.

When evaluating the clinical usefulness of rTMS, it should be compared to other treatment options. The large rTMS register study by Sackeim et al. presented a response rate (>50 % PHQ-9 reduction) of 57.7 % and remission rate (PHQ-9 < 5) of 27.9 % in the ITT-sample. Other augmentation therapies of depression have shown similar response rates (>50 % MADRS or HDRS-17 reduction), e.g. lithium (50.7 %) and quetiapine (49.5 %) though placebo response rates were above 30 % in these studies, and numbers needed to harm (NNH) was 5 for lithium and 3 for quetiapine (Vázquez et al., 2021). We cannot present NNH figures from our data but the fact that 89.1 % of the patients continued to receive >15 treatments indicates that tolerability is high. Differences in outcome measures and the lack of placebo group in register studies make comparisons between treatments difficult. Differences such as coil configuration, targeting, stimulation frequency and intensity, number of stimulations per session, number of sessions per treatment series and concomitant medication, makes it difficult to predict the likelihood of responding to rTMS. Some of these stimulation parameters have been associated with antidepressant effect and therefore adjusted in later studies allowing for a continuous optimization of the treatment protocols. Examples of such causes of the increasing response and remission rates in open label studies (Kar, 2019) may be the method of identifying the stimulation target(Johnson et al., 2013) (Herbsman et al., 2009), higher stimulus intensity (Fitzgerald et al., 2016) and the number of pulses administered per session (Sackeim et al., 2020b). Clinical, double-blind, head-to-head RCTs are needed to compare rTMS efficacy to pharmacotherapies.

We identified less severe depressive symptom level as a predictor of iTBS response and remission. This corroborates the retrospective finding from the THREE-D study that milder depression is more likely to respond to iTBS (Trevizol et al., 2020). Since there is no published sham-controlled RCT using the 3-min, 600 pulses, 120 % of motor threshold iTBS stimulation protocol, for depression, it is not possible to estimate the placebo effect. However, the definition of response as a 50 % reduction of a depression severity score could inflate response rates in the less severely depressed group due to placebo effects. Nevertheless, a recent meta-analysis of placebo effects in RCTs of treatment resistant depression showed a mean response rate of 21.2 % and mean remission rate of 13.0 % (Jones et al., 2021), over different treatment modalities. Thus, placebo effects in treatment resistant depression tend to be

Table 3
Predictors of remission and response.

		Remission			Response		
		n (%)	OR (95%CI)	p	n (%)	OR (95 %)CI	p
Gender	Female	337 (61)	Reference		328 (61)	Reference	
	Male	216 (39)	1.20 (0.76–1.90)	0.443	214 (39)	1.25 (0.88–1.77)	0.214
Age	17–25	81 (15)	Reference		80 (15)	Reference	
	26–40	189 (34)	0.56 (0.28–1.13)	0.107	181 (33)	2.22 (1.24–3.95)	0.007
	41–60	216 (39)	0.68 (0.35–1.33)	0.258	212 (39)	2.34 (1.33–4.12)	0.003
	61–84	67 (12)	1.61 (0.75–3.45)	0.222	69 (13)	3.46 (1.65–7.22)	0.001
Indication	Unipolar	454 (82)	Reference		443 (82)	Reference	
	Bipolar	99 (18)	1.20 (0.68–2.12)	0.533	99 (18)	1.25 (0.80–1.93)	0.327
Previous ECT	Yes	364 (66)	Reference		354 (65)	Reference	
	No	177 (32)	1.02 (0.21–4.90)	0.98	170 (31)	0.966	0.862
	Missing	12 (2)	–	–	18 (3)	–	
Baseline MADRS-S	9–25	71 (13)	0.85 (0.38–1.87)	0.679	68 (13)	0.75 (0.37–1.51)	0.420
	26–30	59 (11)	Reference		59 (11)	Reference	
	31–35	96 (17)	0.58 (0.27–1.26)	0.167	101 (19)	0.65 (0.34–1.24)	0.193
	36–40	89 (16)	0.27 (0.11–0.67)	0.005	92 (17)	0.33 (0.17–0.66)	0.002
	41–52	60 (11)	0.30 (0.11–0.83)	0.020	56 (10)	0.73 (0.40–1.33)	0.010
	Missing	178 (32)	–	–	166 (31)	–	–
Use of bensodiazepines	Yes	391 (71)	Reference		383 (71)	Reference	
	No	145 (26)	0.87 (0.50–1.51)	0.612	142 (26)	0.83 (0.59–1.23)	0.349
	Missing	17 (3)		–	17 (3)		

Odds ratios with 95 % confidence intervals and logistic regression of predictors of treatment response and remission. ECT - Electroconvulsive therapy. MADRS-S – Montgomery-Asberg Depression Rating Scale, Self Rating.

modest. Placebo response has also been relatively low in iTBS studies of unipolar depression using another stimulation protocol (mean change in HDRS-17: −17.4 %) (Li et al., 2014) and bipolar depression using the THREE-D protocol (mean change in MADRS: −27 %) (McGirr et al., 2021a).

We also found a positive association between older age and treatment response. In the first decade of rTMS treatment, studies suggested that lower age was associated with antidepressant response (Aguirre et al., 2011) while more recent studies have shown opposite results (Trevizol et al., 2020) or no age factor (Conelea et al., 2017). One reason for this might be that later studies have used magnetic field strengths around 120 % of the motor threshold while earlier studies used around 100 % or less (Fitzgerald et al., 2016). In this study, 91.5 % ($n = 431$) of the subjects were treated with 120 % of motor threshold. Also, the inverse correlation between age and effect has been described in studies using 10 Hz or 1 Hz stimulation, but not in in the iTBS. Although the impact of age on treatment effect remains unclear, our results do not support treatment guidelines with an upper age limit for iTBS.

A recently published RCT of iTBS treatment of bipolar depression showed low effectiveness and no significant difference from sham treatment and was stopped due to futility (McGirr et al., 2021a). We found no significant difference in response and remission rates between unipolar and bipolar depression and the trend was toward higher rates in the bipolar group. The response rate of 46.5 % is almost twice the rate of 23.8 % that McGirr et al. found in the open-label phase of their study (McGirr et al., 2021b). In the study by McGirr et al. more than half of the sample had a diagnosis of bipolar disorder type I, in our registry data it is not possible to reliably differentiate between type I or type II. Thus, we do not know if the samples are comparable in this regard. Further, the numbers should be compared with caution due to different definitions of response and difference in sample sizes. This discrepancy emphasizes the need for larger sham-controlled studies of iTBS for bipolar depression, also differentiating the outcome analyses between bipolar type I and type II.

In studies of antidepressant treatments, psychiatric comorbidity can influence the results and cause smaller effect sizes (Perlman et al., 2019). This is partly because symptoms of e.g. personality disorders, and side-effects of drug treatments for other psychiatric disorders may add noise to data acquired via depression rating scales such as MADRS or HAM-D (Lisinski et al., 2020; Hieronymus et al., 2021). In this study we used CGI as the outcome measure. CGI is not sensitive to specific symptoms but a patient with comorbid diagnoses may present symptoms of illness at evaluation, leading to a higher CGI-score. In a clinical trial of antidepressant treatment, the main outcome should include ratings of depression symptom severity. In the clinical practice, it is important for the patient to reduce suffering and regain function. Hence, we chose to use CGI complemented by MADRS-S and EQ-VAS as outcome variables. Bearing in mind that MADRS-S and EQ-VAS suffered from more missing data, we found that the response rate was numerically highest using EQ-VAS, followed by CGI-I and MADRS-S while the rank order for remission rate was CGI-S > MADRS-S > EQ-VAS. These statistically non-significant differences should be interpreted with caution but might indicate that iTBS-treatment alleviates other symptoms than the nine MADRS-S items and that clinicians who rely too much on MADRS-S may underestimate the treatment effect as well as the burden of sub-syndromal illness.

Since the study has no comparison group, we cannot distinguish treatment effects from those that are not attributable to the direct iTBS effect. Sham-controlled RCT's of iTBS are few and small sampled (Li et al., 2014, 2020; Plewnia et al., 2014; Chistyakov et al., 2015; Duprat et al., 2016; Caeyenberghs et al., 2019) and analyses of unspecific effects in the placebo groups have not been reported. One can only speculate if for example the physical exercise and behavioral activation, visiting the treatment facility daily, as well as interaction with the staff at the rTMS units, may have added to the antidepressant effect and general feeling of well-being.

The use of register data infers some limitations. The iTBS protocol was not standardized and the allocation of patients to iTBS may be subject to selection bias based on clinical presentation and site effects due to local routines. The main outcome variable is not specific for depression and inter-rater variability was not measured.

This large register-based study shows that the antidepressant response rate of iTBS in the clinical settings is on par with randomized controlled trials, while remission rate was lower. The study also indicates that patients with different demographical or clinical characteristics may respond differently on group level. Further clinical trials are necessary to optimize iTBS treatment protocols for different patients or groups of patients. A large sham-controlled RCT of iTBS treatment of depression is also warranted.

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Conflict of interest

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All authors participated in designing the study. Author KP undertook the statistical analysis. Author CJE wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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