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EFFICACY AND TOLERABILITY OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER: A SYSTEMATIC REVIEW

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EFFICACY AND TOLERABILITY OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER: A SYSTEMATIC REVIEW

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LIST OF ABBREVIATIONS

APB – Abductor polis brevis (muscle)
A-rTMS – Acceleracted rTMS
BAI – Beck's Anxiety Inventory
BDI-II – Beck Depression Inventory
BD – Bipolar Disorder
CGIS – Clinical global impressions scale
CTMB – Color Trail Making B Test
cTBS – Continuous Theta Burst Stimulation
DLPFC – Dorso lateral prefrontal cortex
DMPFC – Dorso medial prefrontal cortex
DSM-5 – Diagnostic and Statistical Manual of Mental Disorders 5
DSST – Digit Symbol Substitution Test
DST – Digit Sequencing Test
ECT – Electroconvulsive Therapy
EEG – Electroencefalography
EQ-5D – Summary indices of The EuroQoL EQ-5D Quality of Life Questionnaire
ERD – Widlocher's Depressive Retardation Scale
FC – Functional connectivity
FDA – Food and Drug Administration
GNGT – Go/No Go Task
HAM-A – Hamilton Rating Scale of Anxiety
HAM-D – Hamilton Depression Scale
HDRS – Hamilton Depression Rating Scale
HF – High-frequency
iTBS – Intermittent Theta Burst Stimulation
LF – Low-frequency
MADRS – Montgomery–Åsberg Depression Rating Scale
MDD – Major depressive disorder
MRI – Magnetic ressonance imaging
MSM - Maudsley Staging Method
PICO – Population, Intervention, Comparison and Outcome
piTBS – Prolonged intermittent TBS
pgACC – Pregenual anterior cingulate cortex
PHQ-9 – Personal Health Questionnaire
PTSD – Post-traumatic stress disorder
QIDS-C16 – Quick Inventory of Depressive Symptomatology - Clinician Rated Version
QIDS-SR16 – Quick Inventory of Depressive Symptomatology - Self Rated Version

RCT – Randomized Controlled Trial

RMT – Resting motor threshold

rTMS – Repetitive Transcranial Magnetic Stimulation

SAS – Starkstein's Apathy Scale

SF-36 – 36-item Short-Form Health Survey

sgACC – Subgenual anterior cingulate cortex

SHAPS – Snaith-Hamilton Pleasure Scale

SIOSS – Self-rating idea of suicide scale

SSI – Scale for Suicidal Ideation

TBS – Theta Burst Stimulation

TRD – Treatment resistent depression

WCST – Wisconsin sort cards test

WHO – World Health Organisation

WHOQOL-BREF – World Health Organization quality of life

ABSTRACT

Introduction/Aims

Major Depressive Disorder (MDD) is one of the most common mental disorders worldwide [1]. This clinical condition is likely to have a very negative impact on the functionality and quality of life of the affected individuals. Even though the standard treatment is effective for a large number of patients [2], MDD still has a treatment resistance prevalence up to 30% and can become a long-course mental disorder, with carer burden and high economic costs (Leo Chen et al., 2021) [3].

As a neuromodulation method, repetitive transcranial magnetic stimulation (rTMS) is a non-invasive and non-convulsive technique, which requires no anesthesia and has a safety profile without serious adverse effects and significant tolerability [4].

Along with reasonable response rates between 40-50% and remission rates up to 30% [5], rTMS is being presented as an emergent option for the treatment for MDD, namely for the cases that prove to be refractory to pharmacological treatment.

The principal aim of this literature review is to summarize the most recent evidence in which respects the use of rTMS in the treatment of MDD.

Methods

This systematic review was conducted following PRISMA Guidelines. Literature was systematically searched on PubMed, Embase and Web of Science Care Collection until August 2022, and limited to the last five years. Only randomized controlled trials (RCT) conducted in adults diagnosed with MDD or Treatment Resistant Depression (TRD) were included.

The exclusion criteria were studies including patients with other disorders than MDD and TRD such as bipolar I and II (BD), post-traumatic stress disorder (PTSD), schizophrenia, substance use disorders or major neurocognitive disorder. We did not exclude concomitant anxiety since the comorbidity between depression and anxiety is much more the rule than the exception.

The outcomes evaluated were efficacy, in terms of the reduction of depressive symptomatology and change of depression rating scores, as well as the response and remission rates. Safety and tolerability were evaluated based on the adverse effects reported by the patients across the treatment.

Results

Fourteen eligible studies were included in this systematic review, and all incorporated the RCT method. Twelve of the fourteen studies found that rTMS was as an effective treatment for MDD or TRD and six showed the maintenance of reduction in depression scores and improvement of quality of life after the treatment in follow-up assessments. One paper studied more precisely the response inhibition and cognitive flexibility of the individuals.

The left dorsolateral prefrontal cortex (DLPFC) was the brain target used in twelve of fourteen studies. Only one paper applied rTMS on dorsomedial prefrontal cortex (DMPFC) and one to the left prefrontal cortex (PFC). Three compared the effectiveness between unilateral and bilateral left DLPFC application of rTMS.

In all the included studies, rTMS treatment was globally well tolerated by patients, being the most common adverse effect reported headaches, followed by dizziness, local discomfort or intolerance of the stimulation sensation and local pain. No serious adverse effects were reported in any study.

Conclusions

Evidence for the effectiveness of rTMS for MDD treatment is clear and supported in dozens of well powered RCTs and meta-analyses [6]. However, there is still limited data concerning the long-term therapeutic benefits and the utility/need for maintenance treatment after the acute episode. The identification of predictive factors is of paramount importance to better characterise the patients who could benefit from this treatment, both in the short-term and in the long run. Without relinquishing the prevalence, carer burden and economic costs [3] of this disorder, shorter treatment periods with comparable antidepressant efficacy are of great clinical importance [8], as well as global accessibility and reliability evidence-based protocols [9].

More studies with larger sample size that compare, according to a consistent protocol, the newer forms of rTMS in terms of stimulation parameters across all the treatment arms, are urgently needed so we can place these tools towards clinical practice guidelines.

Keywords: Major Depressive Disorder, Transcranial Magnetic Stimulation, rTMS, Theta Burst Stimulation, Efficacy, Tolerability.

INTRODUCTION

As a worldwide common mental disease, major depressive disorder (MDD) can have important negative consequences on the functionality and quality of life of affected individuals.
According to the World Health Organisation (WHO), depression affects more than 280 million of people worldwide and it is estimated that over 5% of the adults suffer from this disorder in their lifetime with 5.7% being older than 60 years old.
In addition to overall burden, especially when the disorder is recurrent with moderate or severe episodes [1], MDD is associated with an increase in mortality rates, being suicide one of the most significant causes of death [7]. Mortality due to suicide is a major public health concern, being the fourth cause of death between the ages of 15-29 [1].

Although the standard treatment for MDD based on psychotherapy and pharmacotherapy, either alone or in combination, is effective in a substantial number of patients, depression can be a long course mental disorder [2].
According to the conservative estimate of Fang et al. (2021), only 33% of patients using pharmacological treatment achieve a completly remission of symptomatology during the acute phase, and less than 50% of patients fail to achieve remission after multiple medication trials.
Despite several treatment options, treatment resistance prevalence is up to 30%, paired with carer burden and economic costs [3], leading to the circunstance that one in five patients with depression will follow a chronic course, defined as a depressive episode lasting longer than 2 years [10].
Treatment resistance depression (TRD) is defined as the absence of a clinical response despite at least 2 consecutive antidepressant trials, administred at adequate doses for at least 4 to 6 weeks [11]. It can be measured according to some scales such as Thase and Rush Staging Method and Maudsley Staging Method (MSM), Thus, the development of effective therapeutic modalities for TRD is fundamental [12].

Alternative options for the treatment of TRD are the neuromodulation techniques such as electroconvulsive therapy (ECT) and Transcranial Magnetic Stimulation (TMS). Repetitive TMS (r-TMS) is presented as an emergent option with response rates that range between 40-50% and remission rates up to 30% [5].

Repetitive TMS was described for the first time by Barker et al. in 1985, and has been extensively investigated [13-14]. It has been approved in 2008 by the Food and Drug Administration (FDA), which cleared rTMS for treating depression aproving the protocol of 10 Hz frequency applied on the left dorsolateral prefrontal cortex (DLPFC) [10]. This protocol consists of 3000 pulses delivered in 4 trains with 26 seconds interval, over a period of 37.5 min, for 20-30 sessions over a period of 4-6 weeks [15].

As an indirect, non-invasive and non-convulsive tecnhique, which requires no anaesthesia, rTMS has a safety profile without serious adverse effects and significant tolerability, where the most common adverse effect is scalp discomfort or local pain during the treatment (~40%), followed by headaches (20-30%) and fatigue (15-20%) [4]. The generalized tonic-clonic seizure is the most serious adverse reaction of rTMS, but the risk is comparable to that of antidepressant medications [16]. Moreover, it is know that, when applied at regular intervals, the repetition of pulses can lead to long-lasting effects [17].

It has been proposed that the capacity of rTMS of changing the functional connectivity is due to the fact that, when applied on the left DLPFC using a high frequency (HF), it increases the metabolic activity in connected areas, while when it is applied on the right DLPFC using a low frequency (LF), rTMS decreases it [18]. Furthermore, it is suggested that rTMS induce an upregulation of $5HT_{2A}$ receptors in the prefrontal areas and a downregulation and the hippocampus, as well as the GABA and glutamate neurotransmitter system [17]. These mechanisms of action may explain why MDD involves dysregulation of cortical activity, with lower activity in the left DLPFC and higher activity in the right DLPFC [19].

The majority of studies applies rTMS on the left DLPFC, which also has an important role in cognition and mood regulation [9] meaning that TMS provides a unique tool to study brain behaviour relationships [20].

Nevertheless, and according to Eijndhoven et al. (2020), it remains unclear whether rTMS is a viable treatment option for patients with TRD, since there is an inverse correlation between its antidepressant effect and the level of treatment resistance [21-22].

The main aim of this review is to sumarize the more recent evidence from the literature in which respects the use of rTMS as a treatment of MDD.

Basic Principles of rTMS

Briefly, rTMS uses an electromagnetic coil to induce an electrical current in the underlying cortex, working as a therapeutical tool that modulates the brain region where the multiple stimuli are applied. [6]. It can induce changes in functional connectivity and downstream electrophysiological effects along the frontostriatal and limbic brain network [3].

As an indirect technique, the coil is placed flat on the scalp, and the magnetic field can be reduced by extracerebral tissues such as the scalp, bones and meninges [23]. Thus, TMS preferentially activates neurons oriented horizontally in a plane that is parallel to both the coil and the brain surface [24].

The key parameters of rTMS that characterize the different protocols of this tecnhique consist in frequency, intensity, brain region target and positioning of the coil, pulses per session and duration of the treatment.

Prior to the start of the first treatment session, the intensity of pulses is calculated based on the individual's resting motor threshold (RMT), defined as the lowest TMS intensity necessary to produce

a motor evoked potential (MEP) at least 5 out of 10 consecutive trials when applied in the abductor polis brevis (APB) muscle [25]. According to some rTMS studies, the standard positioning of the DLPFC is defined as 5 cm anterior to the scalp meeting the point at which the MT has been obtained for optimum stimulation of the APB. In addition to this more common method, neuronavigational methods using magnetic resonance imaging (MRI) have been studied in order to locate the DLPFC with more precision.

Beyond the unilateral application, rTMS can be performed bilaterally, where both low frequency rTMS (LF-rTMS) of the right DLPFC and high frequency rTMS (HF-rTMS) of the left DLPFC are applied sequentially in the same session [24].

In each treatment session, rTMS technique applies multiple stimuli in trains, where each train consists of a number of pulses to be delivered. For safety reasons, there must be an interval of no stimulation between these trains.

In addition to the standard depression treatment protocol, a new rTMS protocol was developed which is called theta burst stimulation (TBS). This is a variation of rTMS that allows a short stimulation duration resulting in more powerfull and rapid effects on synaptic plasticity [26].

High frequency (HF; ≥ 5 Hz) rTMS and intermittent theta burst stimulation (TBS) are known to induce neuronal activation whereas low frequency (LF; ≤ 1Hz) rTMS and continuous TBS (cTBS) induce neuronal inhibition [27]. Furthermore, through this new form of rTMS, significant gains in the cost-effectiveness have been achieved [15].

To conclude this overview, rTMS is still evolving and can yield very different results according to the inclusion criteria and protocol.

METHODS

Information sources and search strategy

In order to find literature related with rTMS treatment of MDD, three databases were ellectronically searched: PubMed, Embase and Web of Science Care Collection.

The main aim of this review is to cover the most updated evidence from the literature relative to the use of rTMS as a treatment of MDD. However, due to the fast pace of research advancement in this field, with the use of different protocols providing a wide new option of parameters, we opted to limit the search strategy to the last five years.

Using this timeframe, the latest update of data publication was performed on August 11th, 2022 and all studies between January 1st, 2018 and August 11th, 2022 were included. Furthermore, language restrictions were applied and limited to English written articles.

The search terms are described towards each database in **Table 1**. and the search strategy is further detailed in **Figure 1.**

Databases	Search Terms
PubMed	(“Transcranial magnetic stimulation”[Title/Abstract] OR “TMS” [Title/Abstract] OR “rTMS OT burst stimulation” [Title/Abstract] OR “cTBS” [Title/Abstract] OR “iTBS” [Title/Abstract]) AND (“Major depressive disorder” [Title/Abstract] OR “Major depression” [Title/Abstract] OR “Depression” [Title/Abstract] OR “Depressive” [Title/Abstract]) OR (“Transcranial Magnetic Stimulation” [MeSH]) AND (“Depressive Disorder, Major” [MAJR])
Embase	(“Major depression”/exp AND 'Transcranial magnetic stimulation”/exp) OR (“Transcranial magnetic stimulation”:ab,ti OR TMS:ab,ti OR “rTMS ot Burst Btimulation”:ab,ti OR cTBS:ab,ti OR iTBS:ab,ti) AND (“Major depressive disorder”:ab,ti OR “Major depression”:ab,ti OR Depression:ab,ti OR Depressive:ab,ti) AND [english]/lim AND ([article]/lim OR [article in press]/lim OR [data papers]/lim OR [preprint]/lim)
Web of Science Care Collection	Depression OR Depressive (Title) and Transcranial magnetic stimulation OR TMS OR rTMS OR Burst stimulation OR cTBS OR iTBS (Title) and Article or Letter or Early Access or Editorial Material (Document Types) and English (Languages)

Table 1. Search Strategy.

Eligibility criteria

To define our eligibility criteria, we referred to the PICO (Population; Intervention; Comparison; Outcome) framework, according to the current PRISMA guidelines.

Population and sample characteristics: Our Population was defined as adults (older than 18 years old) and elderly population (older than 65 years old), of both sexes, having a diagnosis of unipolar major depressive disorder (MDD) according to Diagnostic and Statistical Manual of Mental Disorders: DSM-5. Patients diagnosed with treatment resistant depression (TRD) were included.

Treatment Characteristics: The intervention was the repetitive transcranial magnetic stimulation (rTMS) defined as an indirect and non-invasive neuromodulation technique capable of inducing excitability or inhibiton in the neuronal circuits of the motor cortex, by creating a focal magnetic field. Since there is a wide variety of different methodologies and treatment protocols of rTMS, we focused on comparing the therapeutic efficacy and tolerability including every different protocol that met the inclusion criteria. Ten Hz rTMS (standard rTMS), low frequency rTMS (LF-rTMS), acceleracted rTMS (arTMS), Theta Burst stimulation (TBS), aTBS, Intermittent TBS (iTBS), countinous TBS (cTBS), prolonged intermittent TBS (piTBS) protocols, both unilaterally and bilaterally applied, were included.

Comparison: rTMS is being compared within the different existing protocols and also to sham controlled groups. Sham control is considered the “placebo treatment” regarding the rTMS technique.

Outcomes: Papers were included if they reported the outcomes of interest: **efficacy**, based on the reduction of depressive symptomatology, change of depression rating scores and response and remission rates, as well as **safety** and **tolerability**, based on the adverse effects reported and dropout reasons. An additional outcome of this review was the follow-up after the active treatments.

Exclusion criteria

Studies where rTMS was a form of treatment for conditions other than MDD or TRD such as bipolar I or II disorder (BD), post-traumatic stress disorder (PTSD), schizophrenia, substance use disorders or major neurocognitive disorder were excluded as well as the studies performed in adolescents. We did not exclude concomitant anxiety disorders since the comorbidity between depression and anxiety is much more the rule than the exception and also because rTMS decreases anxiety associated with depression [28] and has shown comparable efficacy in cases of comorbidity with anxiety disorders [29].

Study selection

One author (A. Delgado) systematically assessed the titles and the abstracts of publications retrieved, leading to the exclusion of the articles that were deemed to be completely irrelevant to the study. Subsequently, using the search strategy to identify studies who met the eligibility criteria described above, the studies that incorporated the randomized controlled trial (RCT) method were screened. Due to the large sample of trials retrieved, it was given greater importance to double-blinded studies and sham controlled ones. The search strategy is further detailed in **Figure 1.**, which shows the PRISMA flow diagram displaying the search results and process.

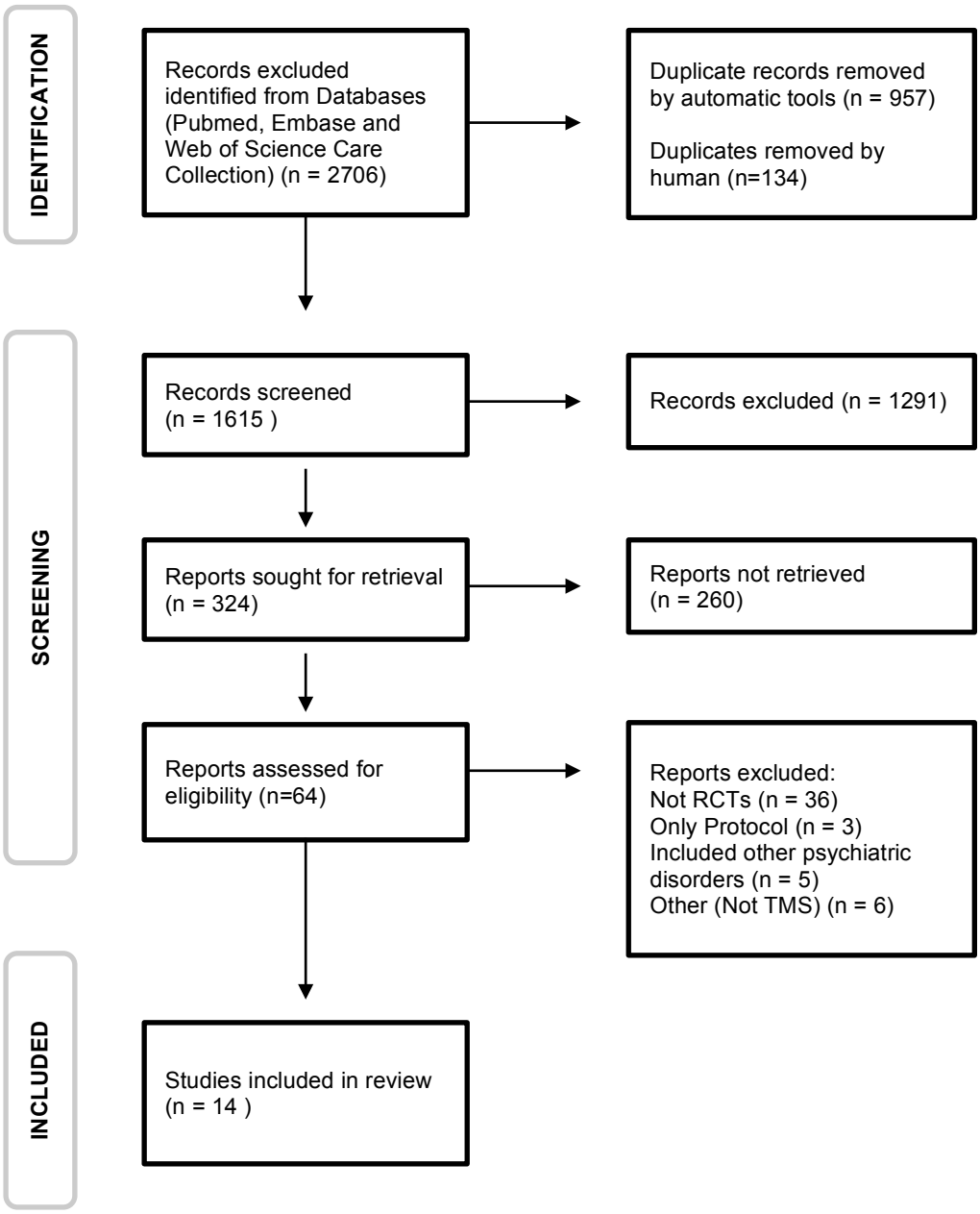

Figure 1. PRISMA flow chart describing the search results.

Data extraction process and data items

The data extracted per study includes the first author, the year of publication, the study design and population, baseline characteristics, the protocol of rTMS used and the objective of the study, and also measurements applied to evaluate the outcomes of interest: efficacy, safety and tolerability of the treatment.

Quality assessment and risk of bias

The quality of the included studies was assessed by one author (A. Delgado), using the Jadad Scoring System, which evaluates three key methodological features of clinical trials: randomization (0-2 points), blinding (0-2 points) and dropouts and withdrawals (0-1 point). The response to each item was either “yes” (1 point) or “no” (0 points) [30]. Ponctuations between 0-2 reveal low quality studies, while 3-5 reveal high quality studies.

RESULTS

After excluding duplicates, we found a total of 1615 articles retrieved from literature on Pubmed, Embase and Web of Science Care Collection.

Of these, 1291 were excluded based on the title or the abstract due to not meeting the pre-defined criteria, resulting in 324 eligible articles.

After that, the selection procedure retrieved 14 articles which meet the eligibility criteria of articles that assessed rTMS as a treatment for MDD: 2 single-blind, randomized sham-controlled rTMS study: Asgharian et al. (2022) and Eijndhove et al. (2020) [25, 10]; 4 double-blinded RCT: Bulteau et al. (2022), Armas-Castañeda et al. (2021), Zhang et al. (2021) and Trevizol et al. (2019) [31-34]; 4 randomized, double-blinded, sham-controlled study: Jagawat et al. (2022), Li et al. (2019), Dunlop et al. (2019) and Blumberger et al. (2021) [35, 8, 36,15]; 1 three arm, single-blind RCT: Chen et al. (2021) [3]; 1 randomized, double-blind, parallel-group design study: Dai et al. (2020) [37]; 1 single-blinded RCT: Filipčić et al. (2019) [38] and 1 two arm single-blind RCT: Fitzgerald et al. (2018) [39].

Even though the study of Chen et al. (2021) had criteria to be excluded due to the fact it includes Bipolar Disorder, we decided exceptionally to include this study once the sample size of these patients was <10% of the total sample, hence with an insignificant impact.

Figure 1. shows the PRISMA flow diagram displaying the search results and process.

Overview of the Extracted Studies

Table 2. shows the summary of the extracted studies. Though the search strategy encompassed studies published in the last five years to the date of the data search (until August 11st, 2022) we organized them by year of publication.

Concerning the geographic areas where the studies were conducted, China and Canada both conducted three studies, followed by Australia which conducted two and the rest of the countries Iran, France, India, Mexico, Netherlands and Croatia all conducted one study each.

All the 14 studies incorporated the RCT method, though in different formats and forms described in **Table 2.**

The sample size for the various trials ranged from n=20 to n=300. The participants in the various studies were all patients diagnosed with MDD or TRD, with the exception of one paper, Chen et al. (2021), which we decided exceptionally to include because the sample size of BD patients included was <10% of the total sample.

Out of the 14 trials, 12 were conducted in an adult population (≥18 years old). Two of the studies were conducted in elderly patients, with age above 60 years [34, 37].

Quality assessement of the included studies

According to Jadad evaluation, 12 in 14 studies showed a high quality score. Five studies had score 5 [15, 31-33, 37]. Three studies had score 4 [8, 34-35] as well as three had score 3 [3, 38-39]. Only two studies [10, 25] showed a low quality score, which translates about 14% of the sample of included studies.

We could not evaluate the Jadad Score of the trial of Dunlop et al. (2019) due to the fact that we did not had access to the Suplementar Material, where the Methods were described in detail, even though it is a double-blinded sham-controlled trial.

This evaluation can be assessed in detail in **Appendix 1.**

Targeted symptoms

In the 14 papers, all evaluated reduction in the severity of depression symptoms in accordance with the score reduction in depression measuring scales, as well as the response and remission rates.

The study of Asgharian et al. (2022) investigated more precisely the response inhibition and cognitive flexibility, relying on the measurements of Go/No-Go tasks (GNGT) and the Wisconsin card sorting test (WCST), respectively.

Target brain region

Usually, standard rTMS protocols for MDD deliver a 10 Hz stimulation to the left DLPFC at an intensity of 120% of the resting motor threshold (RMT) over 4-6 weeks in once-daily stimulation sessions [11].

As Ashgarian et al. (2022) explained, one of the key anatomical regions of interest in depression treatment via rTMS is the dorsolateral prefrontal cortex (DLPFC), an important region for executive function and mood regulation. Hence, for most of the included studies, the brain target for rTMS application was the left DLPFC [3, 8, 10,15, 25, 31-35, 38-39].

Additionally, three papers: Zhang et al. (2021); Chen et al. (2021) and Trevizol et al. (2019), evaluated the differences in effectiveness between unilateral and bilateral left DLPFC. Both Zhang et al. (2021) and Chen et al. (2021) found no statistical differences in the efficacy of rTMS between unilateral left and bilateral DLPFC. In contrast, Trevizol et al. (2019) had significantly higher response and remission rates with the bilateral 10 Hz-rTMS (120% MT) compared with the unilateral 10 Hz-rTMS (120% MT).

Dunlop et al. (2019) was the only paper in which the brain site application was the dorsomedial prefrontal cortex (DMPFC) while Dai et al. (2020) studied the left-prefrontal cortex (PFC).

Transcranial magnetic stimulator and coil position

In the majority of the studies [8,10, 25, 33, 37-38], the stimulation was conducted with a **Magstim Super Rapid (^{2})** stimulator system equipped with an air-cooled, figure-8-coil. Notwithstanding, the study of Filipčić et al. (2019) accurately compared the effectiveness of HF-rTMS between a H1-coil and a figure-8-coil, where the response rate was significantly greater in H1-coil group.
Five in 14 papers [3, 15, 31- 32, 34] used **MagPro X100 or R30 transcranial magnetic stimulator**. This model is equipped with a cool B65 figure-8-coil with dynamic cooling where the coil has two treatment options: active and sham [32]. Blumberger et al. (2021) used the **MagPro X100/R30 stimulato**r equipped with the B70 fluid-cooled coil for active left DLPFC stimulation and the placebo B70 coil. Dunlop et al. (2019) used as well **MagPro R30** stimulator but with a specially designed Active/Sham DB80 coil for all rTMS treatments, with one double-cone coil in contact with the scalp for active treatment, and the opposite coil for sham stimulation.
Two studies did not specify the transcranial magnetic stimulator [35, 39].

According to some rTMS studies, the DLPFC is defined "as 5 cm anterior to the scalp position for optimum stimulation of the abductor pollicis brevis (APB)" [25], which means anterior to the primary motor cortical representation of the hand [8]. In **Table 3.** we can observe that 6 in 14 studies used the standard positioning method. [25, 32-33, 37-39],
In 1 of 14 studies, coil positioning is not mentioned [35].
In 2 of 14 studies, MRI guided neuronavigation was used to target the left DLPFC. [15, 31].
Li et al. (2019) studied specifically the effectiveness of piTBS and HF-rTMS using MRI-guided coil positioning versus standard positioning. The neuronavigation method of coil positioning failed to reveal that was more accurate than the standard method. Along with Trevizol et al. (2019), who likewise compared the two methods of positioning the coil in the scalp and found no differences in the proportion of subjects who were treated using the MRI neuronavigation system and the 5 cm rule in each arm.
In the studies of Eijndhoven et al. (2020) and Chen et al. (2021), the DLPFC was localized according to electroencephalograhy (EEG) method using an international system for electrode placement, were F3 corresponds to the left DLPFC and F4 to the right DLPFC**.** Dunlop et al. (2019) used the same method where surface electrodes were connected to the stimulator and placed bilaterally above the eyebrows for all treatments in order to identify the DMPFC.

Frequency, Intensity of Stimulation, Pulses per Session and Duration of Treatment

The frequency of rTMS ranged from 1 Hz to 50 Hz. Low frequency <1Hz has neuronal inhibitory effects while 5-25 Hz, considered high frequency, has excitatory neuronal effects in the brain.
The 10 Hz HF-rTMS is the most extensively investigated frequency and already considered the

'standard' rTMS protocol [40]. Being this the standard protocol, as expected it is the most frequently used, 10 in 14 [3, 8, 10, 31, 33-35, 37-39], displayed this frequency.
Also, Chen et al. (2021) and Li et al. (2019) used 10 Hz-rTMS as an active control.
Different forms of rTMS, more precisely the Theta Burst Stimulation (TBS), were applied in 4 of 14 papers [3, 8, 15, 31]. According to Chen et al. (2021), TBS is a novel patterned form of rTMS, that applies triplet bursts of gamma frequency (50 Hz) pulses at theta frequency (5 Hz) intervals. Two forms of TBS have been described: intermittent TBS (iTBS), where 2 seconds of 50/5 Hz TBS are applied every 10 seconds over 192 seconds (600 total pulses) and continuous TBS (cTBS), where 50/5 Hz TBS is applied continuously for 40 seconds (600 total pulses).

The intensity of treatment ranged between 80% Motor Threshold (MT) to 120% MT.
According to Zhang et al. (2021), "the resting MT was considered as the minimum TMS intensity sufficient to produce a predefined motor-evoked potential (the right-hand fingers twitching appears visibly) in the contralateral abductor pollicis brevis (APB) in 5 out of 10 trials when the hand was relaxed". Five in 14 studies applied 120% Intensity of the MT [3,15, 34, 38-39], three used a 110% MT [10, 31-32], four a 100% MT [8, 33, 35 and 37], one a 85% MT [25] and two used a 80% MT [3, 31]. Even though, according to Li et al. (2019), the effect sizes between studies using intensities <100% MT and 100% to 120% MT were not significantly different.

The number of sessions varied between 10 [8, 25, 35] and 60. There were two trials applying 60 sessions: Zhang et al. (2021) and Blumberger et al. (2021). Considering that the majority of the studies applied a total of 20 sessions [3, 10, 31, 37-39]. The pulses per session presented a broader variety within the trials, ranging between 600 and 3500.

The duration of the active treatment varied from 10 days to 12 weeks, wherein merely 8 in 14 studies reviewed treatment through follow-up [3, 8, 10, 15, 31-32, 36, 39]. Concerning the follow-up assessment, the most extended one belonged to Bulteau et al. (2022) trial, that saw a reduction in depression scores and quality of life improvement at 6 months.
The rest of studies, most of them assessed patients after 12 weeks [8, 15, 32, 36], after 8 weeks [3], after 4 weeks [39] or after only 1 week [10].
All this informations can be accessed in **Table 3.**

Tolerability and Side Effects

The overall effectiveness of any treatment intervention must acknowledge both its efficacy and the safety and tolerability factors [9]. Concerning the rTMS neuromodulation technique, the treatment is globally well tolerated by patients, being the most common adverse effect reported headaches, followed by dizziness, local discomfort or intolerance of the stimulation sensation and local pain.

Even though the headaches are, most of the time, temporary and no analgesic treatment is required, in the study of Armas-Castañeda et al. (2021), it was one of the dropout reasons.
Exacerbation of tinnitus was observed in one patient out of 35 of rTMS group in the study of Li et al. (2019).
Additional adverse effects reported were asthenia, nausea, chest tightness, anxiety, insomnia and lightheadedness.
No serious adverse effects such as epiletic seizures occurred during any study.

Outcome Measures

Regarding the diversity of scales to measure the reduction in the severity of depression symptoms, most of the studies, more precisely 10 in 14, used the Hamilton Depression Rating Scale (known as HDRS or HAM-D) as an outcome measure. Futher scales such as Beck Depression Inventory (BDI-II), Quick Inventory of Depressive Symptomatology (QIDS), Personal Health Questionnaire (PHQ-9), Montgomery–Åsberg Depression Rating Scale (MADRS), Clinical Global Impression (CGI) were employed to measure some of the primary or secondary outcomes.
To ascertain the anxiety severity, two papers used either Beck's Anxiety Inventory (BAI) or Hamilton Rating Scale of Anxiety (HAM-A). Likewise, the Scale for Suicidal Ideation (SSI) and Reduction in self-rating idea of suicide scale (SIOSS) were used in two studies to resort suicidal ideation.
Health-related quality of life was assessed using three different scales: the 36-item Short-Form Health Survey (SF-36), the EQ-5D Quality of Life Questionnaire and the World Health Organization WHOQOL-BREF quality of life.
Cognitive assessment was performed using Go/No-Go tasks (GNGT) and the Wisconsin Card Sorting Test (WCST), respectively, to measure response inhibition and cognitive flexibility, in one paper.
In the study of Jagawat et al. (2022*)* executive functions were tested with Digit Symbol Substitution Test (DSST) for assessing information processing speed, Color Trail Making B Test (CTMB) for assessing focused attention, Digit Sequencing Test (DST) for assessing working memory, and finally Stroop test for assessing response inhibition.
Bulteau et al. (2022) studied potential treatment response predictors such as anhedonia and apathy, resorting, respectively, the Snaith-Hamilton Pleasure Scale (SHAPS) and Starkstein's Apathy Scale (SAS). Certain moods, anxiety, retardation, suicidal ideation, and other signs of depression were considered using the French HARD diagram and Widlocher's Depressive Retardation Scale (ERD). All the scales can be observed in **Table 2.**

For most of the studies, the primary outcome was the longitudinal change in the depression scores from baseline to the end of the treatment. Secondary outcomes were the response and remission rates, quality of life, and level of depression at pre-defined moments following the post-treatment [10, 15, 32-33, 36-38]. For 4 in 14 studies, the response rate was also considered in the primary outcome

[3, 8, 31, 34, 39].
Armas-Castañeda et al. (2021)'s trial defined response rate as a 50% or greater reduction in HAM-D scores after repetitive transcranial magnetic stimulation. Remission was defined as scores ≤7 on HAM-D after rTMS.
Whereas in the Fitzgerald et al. (2018)'s trial, the definition of response of a 35% improvement from baseline to week 8 on the MADRS.
One paper in 14, Asgharian et al. (2022), focused their primary outcome regarding the effects of rTMS on the change in the depression scores, response inhibition and cognitive flexibility. Along with Jagawat et al. (2022), which focused their primary outcome regarding the effects of rTMS on executive functioning and correlation between mood changes and executive functioning [25, 35].

The degree of refractoriness was defined in 5 out of 14 trials, where TRD was defined by Thase and Rush staging method stage II on the studies of Jagawat et al. (2022) and Chen et al. (2020) using Maudsley Staging Method (MSM) on the studies of Bulteau et al. (2022); Eijndhoven et al. (2020) and Li et al. (2019). MSM is described as the failure to respond to two treatment programs using different antidepressants at normally effective dosages over a 6- week period during current depressive episode [10].
The safety and tolerability outcomes were assessed by adverse event reporting, assessments during the treatment with different variables were measured at inclusion, baseline, during the treatment and the follow-up.

Outcome Results

Considering the antidepressant efficacy of rTMS, already approved by Food and Drug Administration (FDA) in 2008, all the 14 papers results can be seen in detail in **Table 3.**
Almost all studies found a significantly reduction in the severity of depression due to rTMS treatment [3, 8, 15, 25, 31-35, 37-39]. Only two trials: Eijndhoven et al. (2020) and Dunlop et al. (2019) found no significative differences between active rTMS treatement and sham control.
Six in 14 trials showed the maintenance of reduction in depression score and improvement of quality of life after the treatment [8, 15, 31-32, 36, 39].

With the aim of comparing the efficacy and tolerability of the different forms of rTMS treatment, were studied:

iTBS versus 10 Hz rTMS
Bulteau et al. (2022) failed to demonstrate superiority of iTBS to 10Hz rTMS inTRD patients.
Li et al. (2019) found significantly greater decreases in piTBS group compared to the sham group.

aTBS at 80% MT and 120% MT versus active control (10 Hz rTMS)
Chen et al. (2021) found that both the response and the remission rates did not differ significantly from

the three groups. There was no significant difference in antidepressive efficacy between sub and supra-threshold bilateral aTBS. The aTBS was not associated with more rapid antidepressive effects.

arTMS versus standard rTMS

Fitzgerald et al. (2018) found no significant difference in remission and response rates and MADRS score between the two groups. There was a significant improvement in performance of cognition tests in both groups. Accelerated treatment was associated with a higher rate of reported treatment discomfort.

Different frequencies

Zhang et al. (2021) compared **5Hz**-rTMS with **10Hz**-rTMS and found no statistical differences in the efficacy between the two treatments.

Dunlop et al. (2019) compared **1Hz**- rTMS with **20 Hz**-rTMS and a sham control in the DMPFC. Although there was a significant main effect of treatment across all arms, active rTMS was not superior to sham.

Filipčić et al. (2019) studied **10Hz**-rTMS using a figure-8-coil and **18Hz**-rTMS using a H1-coil and found better response rate and greater reduction of depression severity in the H1-coil group, but without a significant difference in the remission rate between the two rTMS modalities.

Number of sessions per week

Armas-Castañeda et al. (2021) found no significant differences between the two active groups (applying rTMS either 5 or 2 sessions per week). In contrast, comparisons of each active group to its corresponding sham group did show significant differences.

Number of sessions per day

Blumberger et al. (2021) studied once-daily iTBS versus twice-daily iTBS and found that twice-daily iTBS does not accelerate the response to treatment and does not differ from once-daily treatment in terms of improving depressive symptoms in patients with TRD.

Year	First Author	Country	Study Design	TMS	Measurement (Scales)	Objective of the study
2022	Fatemeh Asgharian	Iran	Single-blind, sham-controlled RCT	HF-rTMS	BDI-II GNGT WCST	Efficacy of HF-rTMS on depression, response inhibition, and cognitive flexibility
2022	Samuel Bulteau	France	Double-blind RCT	iTBS; HF-rTMS	MADRS BDI-13 CGI-S SF-36 HARD ERD SHAPS SAS	iTBS versus HF-rTMS
2022	Saadgi Jagawat	India	Double-blind randomized sham control study	HF-rTMS	HAMD DST, DSST, Stroop test and CTMB	Efficacy of HF-rTMS on executive functioning
2021	Gabriela Armas-Castañeda	Mexico	Double-blind RCT	HF-rTMS	HAMD HAMA	Two versus five sessions per week of 5 Hz-rTMS
2021	Tingting Zhang	China	Double-blind RCT	LF-rTMS; HF-rTMS	HDRS-24 CGI	Unilateral versus Bilateral HF-rTMS
2021	Leo Chen	Australia	Three arm, Single-blind RCT	aTBS; HF-rTMS	QIDS-C_{16} BAI SSI QUIDS-SR_{16} EQ-5D	aTBS versus HF-rTMS
2021	Daniel Blumberger	Canada	Double-blind randomized sham control study	iTBS	HDRS-17 BDI-II QUIDS-SR_{16}	Once versus twice daily iTBS
2020	P. van Eijndhoven	Netherlands	Single-blind, sham-controlled RCT	HF-rTMS	HDRS-17	Efficacy of HF-rTMS

2020	Lilei Dai	China	Randomized, double-blind, parallel-group design study	HF-rTMS	HAMD-24 SIOSS	Efficacy of HF-rTMS in elderly patients
2019	Cheng-Ta Li	China	Randomized, Double-Blind, Sham-Controlled Study	piTBS; rTMS	HDRS-17	Efficacy of piTBS and HF-rTMS using MRI-guided coil positioning versus standard positioning
2019	Katharine Dunlop	Canada	Double-blinded sham-controlled trial	LF-rTMS; HF-rTMS	HDRS-17	Efficacy of LF-rTMS and HF-rTMS on DMPFC
2019	Igor Filipčić	Croatia	Single-blind RCT	HF-rTMS	HAMD-17 WHOQOL-BREF	Efficacy of HF-rTMS using a H1-coil versus figure-8-coil
2019	Alisson Trevizol	Canada	Double-blinded RCT	LF-rTMS; HF-rTMS	HDRS-17	Unilateral versus Bilateral rTMS
2018	Paul Fitzgerald	Australia	Two arm, single-blind RCT	Hf-aTMS; HF-rTMS	HDRS MADRS BDI SSI	a-rTMS versus HF-rTMS

Table 2. Summary of the included studies.

Year	First Author	Parameters; Brain region; Duration	Intervention group; Sample size; Age	Outcomes (Primary and secondary)	Safety and tolerability (adverse effects measurement)	Efficacy (results)	Limitations
2022	Fatemeh Asgharian	**Protocol:** 20 Hz rTMS (85% MT) Sham control **Brain Region:** Left-DLPFC **Positioning:** 5 cm rule standard localization **Duration:** 2 weeks **Pulses per session:** 2500 pulses/session in a total of 10 sessions	**Sample size:** 28 female patients with MDD *rTMS group* = 14 *Sham group* = 14 **Age:** 25-45 years	**Outcomes:** Measured using BDI-II, GNGT and WCST.	No adverse effects mentioned.	**BDI-II:** rTMS significantly decreased the depression severity. **GNGT:** rTMS enhanced accuracy and decreased reaction time. **WCST:** perseverative and non-perseverative errors and failure to maintain a set index significantly decreased following rTMS.	Small sample size Lack of follow-up Inability to know if the improvement in cognitive function was a direct benefit of the TMS or if it was just due to alleviation of the patients' depression.
2022	Samuel Bulteau	**Protocol:** iTBS (80% MT) 10 Hz rTMS (110% MT) **Brain Region:** Left-DLPFC **Positioning:** MRI guided neuronavigation **Duration:** 4 weeks **Pulses per session:** 1600 pulses/session for rtMS and 600 pulses/session for iTBS in a total of 20 sessions **Follow up:** 6 months after active treatment (M1, M3, M6)	**Sample size:** 60 patients with TRD *iTBS group* = 30 *rTMS group* = 30 **Age:** 18-75 years	**Primary outcome:** Response rate (MADRS) at W4 relative to baseline. **Secondary outcome:** Remission rate, quality of life and level of depression (W4, M3 and M6)	**Moderate to severe:** Asthenia (rTMS: 6%; iTB: 13%) Headaches (rTMS: 3%; iTBS: 17%)	**Response rates:** iTBS – 36.7% 10 Hz rTMS – 33.3% **Remission rates:** iTBS – 18.5% 10 Hz rTMS – 14.8% **HARD**, **ERD**, **SHAPS**, and **SAS scores:** dropped significantly at the M1 follow-up but did not differ significantly between groups, with the except for the apathy score (SAS), which	Some patients used lamotrigine. (Neurophysiological effects of TMS can be modified by lamotrigine)

						showed greater improvement in the iTBS group. **Follow-up at 6 months:** showed for both treatments a reduction in depression scores and quality of life improvement.	
2022	Saadgi Jagawat	**Protocol:** 10 Hz rTMS (100% MT) Sham control **Brain Region:** Left – DLPFC **Positioning :** Not mentioned. **Duration:** 2 weeks **Pulses per session:** 3000 pulses/session in a total of 10 sessions	**Sample size:** 20 patients with TRD *rTMS group* = 14 *Sham group* = 10 **Age:** 18-50 years	**Primary outcome:** Change of HAM-D score at W2 relative to baseline **Other outcomes:** Change of DST, DSST, Stroop Test and CTMB scores	No adverse effects mentioned.	The severity of depression reduced significantly due to rTMS treatment. **HAM-D** and **stroop tests scores**: significant positive correlation in active group.	Small sample size Homogeneous population More sessions of rTMS could produce better results Effects of medication and its compliance could not be ruled out.
2021	Gabriela Armas-Castañeda	**Protocol:** *Group 1:* 5 Hz rTMS (110% MT; 5 sessions/week) *Group 2:* 5 Hz rTMS (110% MT; 2 sessions/week) *Group 3:* sham control (5 sessions/week) *Group 4:* sham control (2 sessions/week)	**Sample size:** 91 university students with MDD *Group 1* = 25 *Group 2* = 25 *Group 3* = 25 *Group 4* = 25	**Outcomes:** Change of HAM-D and HAMA scores at W2 relative to baseline Reponse and remission rates.	**Dropped out reasons:** *Group 2 (3/25 patients)* - lack of time, lack of immediate response, headache *Group 3 (3/25*	**HAM-D** and **HAMA**: no significant differences between the final total scores in the active groups (*1 and 2*). In contrast, comparisons of each active group to its corresponding sham	Standard positioning (5cm rule) can be subject to anatomical inaccuracies. Sample of young university

		Brain Region: Left – DLPFC **Positioning:** 5 cm rule standard localization **Duration:** 2 weeks **Pulses per session:** 1500 pulses/session in a total of 15 sessions **Follow-up:** patients in active rTMS; every 15 days for 3 months after active treatment	**Age:** 18-35 years		*patients)* - lack of time *Group 4 (3/25 patients)* - symptomatology got worse	group (*1* vs. *3, 2* vs. *4)* did show significant differences. **Response rates:** *Group 1* and *2* – 100% **Remission rates:** *Group 1* – 68.2% *Group 2* – 80% **Follow-up at 3 months:** showed the maintainance of improvement in both active rTMS groups.	subjects (28.6% which rTMS was the first therapeutic approach)
2021	Tingting Zhang	**Protocol:** *Group 1:* 10 Hz rTMS (100% MT; left-DLPFC) *Group 2:* 5 Hz rTMS (100% MT; left-DLPFC) *Group 3:* 10 Hz rTMS (100% MT; bilateral) *Group 4:* 5 Hz rTMS (100% MT; bilateral) **Brain Region:** Left – DLPFC and bilateral DLPFC **Positioning:** 5 cm rule standard localization **Duration:** 12 weeks; in a total of 60 sessions **Pulses per session:** 1200 pulses/session in 10 Hz-rTMS group and 600 pulses/session in 5 Hz-rTM	**Sample size:** 221 patients with MDD *Group 1* = 55 *Group 2* = 53 *Group 3* = 57 *Group 4* = 56 **Age:** 18-65 years	**Primary outcome:** Change of HDRS-24 score at W6, W12 relative to baseline **Secondary outcome:** CGI score and response rate.	Generally, well tolerated and there were no serious side effects. **Mild to moderate:** Bodily pain, such as headache, toothache, dizziness, and numbness in the scalp. Temporary. **Severe:** no seizures occurred in any treatment group. **Dropouts:** symmetrical among the four treatment	**HDRS score:** *Week 6* - 56.5% *Week 12* - 59.7% **CGI score:** *Week 6* – 48.3% *Week 12* – 49.8% **Response rates:** *Week 6* – 63.8% *Week 12* – 67.4% There were no statistical differences in the efficacy of rTMS between unilateral left and bilateral DLPFC, and between 5 and 10Hz for treating MDD	Lack of a placebo arm. Participants were requested to be free of any medication during the study period, it is unlikely and unethical to set a sham- control group with MDD.

					groups. Most of the dropouts emerged after the W6.		
2021	Leo Chen	**Protocol:** *Group 1:* a TBS (80% MT) *Group 2:* aTBS (120% MT) *Active control:* 10 Hz rTMS **Brain Region:** Bilateral - DLPFC *(groups 1* and *2*) Left - DLPFC (*active control*) **Positioning:** Using the algorithm developed by Beam et al; were placed over F3 for left-DLPFC and F4 for the right-DLPFC **Duration:** *Groups 1 and 2:* 10 days (total of 20 sessions) *Active control:* 4 weeks (total of 20 sessions) **Pulses per session:** 1200 pulses/session in *groups 1* and *2* and 3000 pulses/session in active control; in a total of 20 sessions **Follow-up:** 8 weeks after active treatment (W1, W2, W4, W8)	**Sample size:** 300 patients with TRD or MDE in BD (<10%). **Age:** adults over the age of 18 years	**Primary outcome:** Response and remission rates at W4 (QIDS-C16). **Seconday outcomes:** QIDS-SR16, SSI and EuroQol EQ-5D	**Mild to moderate:** *Group 2* declared intolerance of the stimulation sensation. **Severe:** No serious adverse effect; no induction of seizure or manic episodes. **Dropouts:** *Group 2* (4 patients) - difficulty of tolerating the stimulation sensation	**Global response rate:** 43.7% (did not differ significantly from the three groups) **Global remission rate:** 28.2% (after 8 weeks follow-up. Did not differ significantly from the three groups) **QIDS- C_{16} score:** *Week 4* – greater reduction for the active control. The aTBS was not associated with more rapid ATD effects. Bilateral sequential TBS did not have superior ATD effect to unilateral 10 Hz rTMS. There was no significant difference in ATD efficacy between sub and supra-threshold bilateral aTBS.	Follow-up was not possible for most of the patients. Lack of sham-control. Comparisson of bilateral TBS with unilateral rTMS. Not curate the classes of the antidepressants/ mood stabilizer.

2021	Daniel Blumberger	**Protocol:** iTBS (120% MT) once-daily iTBS (120% MT) twice-daily Sham control for both groups **Brain Region:** Left – DLPFC **Positioning:** MRI guided neuronavigation **Duration:** 30 treatment days **Pulses per session:** 600 pulses/session twice-daily or 1200 pulses/session once daily; in a total of 60 sessions. **Follow-up:** 12 weeks after active treatment (W1, W4 and W12)	**Sample size:** 208 patients with TRD **Age:** 18-59 years	**Primary outcome:** Change of HDRS-17 score at day 10 relative to baseline **Secondary outcome:** Change of HDRS-17 score at day 30 relative to baseline **Other outcomes:** BDI-II, QIDS-SR16 (days 10 and 30)	**At least one side-effect:** *iTBS once-daily* – 87% *iTBS twice-daily* – 84% In both groups, the most common side effect was headache (66% in *once-daily;* 70 % in *twice-daily*). Followed by: dizziness, nausea, fatigue, insomnia, anxiety/agitation/panic; back/neck pain.	**Response and remission rates:** did not differ between the active groups and did not reveal a significant difference in change in HRSD-17 and BDI-II scores. Twice-daily iTBS does not accelerate response to iTBS and is not different from once-daily treatment in terms of improving depressive symptoms in patients with TRD. **Follow-up at 12 weeks:** statistically significant difference in favor of the twice-daily group.	The design of the protocol, lasting 30 treatment days may have led to an expectancy effect and negatively biased early treatment effects. The current analysis also does not considerer a number of biological measures, which may aid in discriminating participants. Interval of 54 min between sessions may have been to short or too long for some individuals.
2020	P. van Eijndhoven	**Protocol:** 10 Hz rTMS (110% MT) Sham control **Brain Region:** Left-DLPFC **Positioning:** DLPFC was localized according to EEG method using an international	**Sample size:** 31 patients with TRD *rTMS group* = 15 *Sham group* = 16	**Primary outcome:** Change of HDRS score one week after the last treatment in comparison to baseline.	Treatment was overall well tolerated by the patients. **Mild to moderate:** *Headache* *10 Hz rTMS* – 60%	**Antidepressive response:** No differences between real and sham rTMS. **HDRS score:** *10 Hz rTMS* – reduction of 13%	The method of sham stimulation used could have caused small effects within the brain (was applied by tilting the coil 45° away from the

		system for electrode placement **Duration:** 4 weeks **Pulses per session:** 3000 pulses/session in a total of 20 sessions **Follow-up:** 1 week after active treatment		**Secondary outcome:** Response and remission rates	*Sham Control* – 62.5% **Severe:** no serious adverse events, such as epileptic seizures.	*Sham Control* – reduction of 18% **Remission:** no patients fulfilling the criteria.	scalp) A substantial number of patients even had undergone ECT prior to participating in this trial, contributing to a very high level of treatment resistance.
2020	Lilei Dai	**Protocol:** 10 Hz rTMS (100% MT) + routine drug therapy with escitalopram oxalate (initial dose 5mg, then 10mg, then > 20mg) Sham control **Brain Region:** Left-PFC **Positioning:** Not mentioned. **Duration:** 4 weeks **Pulses per session:** 800 pulses/session in a total of 20 sessions	**Sample size:** 103 patients with MDD and suicidal ideation *rTMS group* = 48 *Sham control* = 55 **Age:** 60-80 years	**Primary outcome:** Change of HAM-D24 at W2 and W4 relative to baseline. SIOSS at W2 and W4 relative to baseline. **Secondary outcome:** Response and remission rates.	**Mild to moderate:** *rTMS group* – dizziness, nausea and chest tightness (10.4%) *Sham control* – nausea, mouth dryness, constipation and headache **Severe:** no serious adverse events, such as epileptic seizures. **Dropouts:** *rTMS group* - 14 patients *Sham control* - 7patients	**HAM-D score:** rTMS group achieved a significant lower score. **SIOSS score:** substantial effect to reduce the suicidal ideation in rTMS group. No optimism improvement. **Response rates:** rTMS group – 52.1% Sham control – 32.7%	Need of longitudinal follow-up.

2019	Cheng-Ta Li	**Protocol:** piTBS in monotherapy (100% MT) 10 Hz rTMS monotherapy (active control) (100% MT) Sham control TBS Sham control rTMS **Brain Region:** Left-DLPFC (**Positioning:** MRI guided neuronavigation and 5cm rule standard localization **Duration:** 2 weeks **Pulses per session:** 1800 pulses/session for piTBS and respective sham and 1600 pulses/session for rTMS and respective sham; in a total of 10 sessions **Follow-up:** 12 weeks after active treatment	**Sample size:** 105 patients with MDD *piTBS group*= 35 *rTMS group* = 35 *Sham TBS* = 35 *Sham rTMS* = 35 **Age:** 21-70 years	**Primary outcome:** Change of HDRS-17 at W2 relative to baseline. Response and remission rates. **Secondary outcome:** Antidepressant effects of MRI navigation method compared to the standard	**Mild to Moderate:** *Headache* (temporary and no analgesic requirement)– 14% *Dizziness* (temporary) – 12% *Exacerbation of tinnitus* – 1 patient in the rTMS group **Severe:** no serious adverse events, such as epileptic seizures.	**Depression Scores:** significantly greater decreases in piTBS group compared to the sham group. **MRI navigation method:** failed to reveal that was better than the standard method. **Follow-up:** Most of the piTBS responders and rTMS responders remained responders 3 months after treatment (W14).	Need of future studies with larger samples. The follow-up period was open label, and antidepressant use was allowed for nonresponders. Head shapes in Chinese populations are rounder than those of their Caucasian counterparts.
2019	Katharine Dunlop	**Protocol:** 20 Hz rTMS 1Hz rTMS Sham control rTMS **Brain region:** DMPFC **Positioning:** EEG method using electrode placement **Duration:** total of 30 sessions, twice daily. **Follow-up:** 12 weeks (at W1, W4 and W12) after active treatment	**Sample size:** 120 patients with TRD **Mean age:** 39.44 years	**Primary outcome:** Change of HDRS-17, measured every 5 days, relative to baseline. And also W1, W4, W12 pos-treatment.	No adverse effects mentioned.	Although there was a significant main effect of treatment across all arms, active DMPFC-rTMS was not superior to sham. Both participants and assessors were unable to accuracy determine whether patients received active or placebo stimulation. **Follow-up:** showed the maintenance of improvement in 20 Hz rtMS group and in placebo.	

2019	Igor Filipčić	**Protocol:** 18 Hz rTMS with H1-coil (120% MT) 10 Hz rTMS with figure-8-coil (120% MT) Control group (only pharmacotherapy) **Brain Region:** Left-DLPFC **Positioning:** 5 cm rule standard localization (BeamF3) **Duration:** 4 weeks **Pulses per session:** 1980 pulses/session for H1-coil rTMS and 3000 pulses/session for figure-8-coil rTMS in a total of 20 sessions	**Sample size:** 228 patients with MDD *H1-coil group*= 72 *Figure-8-coil group*= 75 *Control group* = 81 **Age:** 20-70 years	**Primary outcome:** Patients achieving remission defined as HAM-D17 score **Secondary outcomes:** Change in symptoms by HAM-D17, Response rate, Change in quality of life by WHOQOL-BREF and safety and tolerability	**Mild to Moderate:** *H1-coil group* - headache (29%), site discomfort (4%), site pain (7%), muscle twitching/spasms or jaw pain (12%), lightheadedness or dizziness (6%) and insomnia (7%). *Figure-8-coil group* - headache (20%), site discomfort (1%), site pain (7%), lightheadedness or dizziness (3%), anxiety (1%) and insomnia (7%). *Control group* - headache (4%), dizziness (1%), anxiety (3%), fatigue (3%), nausea (1%) and insonia (5%). **Severe:** no serious adverse events.	**Remission rate:** significantly greater in both rTMS groups. *H1-coil group* – 60% *Figure-8-coil group* – 43% *Control group* – 11% **HAM-D17:** *H1-coil group* – decreased 59% *Figure-8-coil group* – decreased 41% *Control group* – decreased 17% **Response rate:** significantly greater in H1-coil group. *H1-coil group* – 67% *Figure-8-coil group* – 44% *Control group* – 24% **WHOQOL-BREF score:** no significant differences between the three groups.	Patients treated with either of the rTMS modalities were monitored daily, while the control group was monitored only at baseline and after the 4-weeks of treatment. Lack of a sham control for both active groups. Lack of long-term outcomes and neurocognitive assessments.
2019	Alisson Trevizol	**Protocol:** Unilateral 10 Hz rTMS (120% MT) Bilateral 1 Hz and 10 Hz rTMS (120% MT) Sham rTMS B**rain Region:**	**Sample size:** 43 patients with MDD *Unilateral* = 11 *Sham* = 12 *Bilateral rTMS* = 20	**Primary outcome:** Change in HDRS score and remission and response rates.	**Moderate to severe:** *Unilateral* - insomnia (1/11) and headache (1/11). *Bilateral rTMS* -	**Remission rate:** differed significantly between treatment. *Unilateral* - 0% *Sham* - 0% *Bilateral rTMS* - 40%	Small sample. Unbalanced number of participants across the three groups.

		Left-DLPFC Bilateral **Positioning:** MRI guided neuronavigation and 5 cm rule standard localization **Duration**: 3 weeks (total of 15 sessions) **if non-remitters ->** additional 15 sessions (total 30 sessions in 6 weeks)	**Age:** 60-85 years		none reported. *Sham* - none reported. **Dropout rate =** 9.3% (3/4 because they could not tolerate the treatment)	**Response rate:** *Unilateral* - 0% *Sham* - 16.7% *Bilateral rTMS* - 45% **Dropout rate:** did not differ significantly across groups. *Unilateral* - 18.2% *Sham* - 8.3% *Bilateral rTMS* 5% No differences in the proportion of subjects who were treated using the MRI neuronavigation system and the 5-cm rule in each arm. By six weeks, 39 participants (90.7%) had completed treatment.	Different DLPFC localizing methods. Lack of a formal method of assessing anxiety symptoms and the use of different psychotropic medications,
2018	Paul Fitzgerald	**Protocol:** A-10 Hz rTMS (120% MT) 10 Hz rTMS (120% MT) **Brain Region:** Left-DLPFC **Positioning:** 5 cm rule standard localization **Duration:** *A-rTMS* – 3 weeks; W1: 3 sessions/day for 3 days, W2: 3 sessions/day for 2 days; W3: 3 sessions/day for 1 day. *Standard rTMS* – 4 weeks; 5	**Sample size:** 115 patients with MDD and TRD stage II. *A-rTMS group* = 58 *Standard rTMS group* = 57 **Mean age:** 49.0 years	**Primary outcome:** Change of HDRS and MADRS at W4 and W8 relative to baseline. Remission and response rates **Secondary outcome:** Change over time	**Mild to Moderate:** *A-rTMS group* – headache (27.5%) and site disconfort (18.9%). Transient. *Standard rTMS group* – headache (15.7%) and site disconfort (3.5%). **Severe:** no serious adverse events.	**Remission and Response rates:** no significant difference in between the two groups. **MADRS scores:** no difference between the two groups between baseline and week 8. **Cognition:** There was significantly improved	

	sessions/week **Pulses per session:** 3500 pulses/session in a total of 18 sessions for A-rTMS; 3150 pulses/session in a total of 20 sessions for standard rTMS **Follow-up:** 4 weeks after active standard treatment, 5 weeks after active a-rTMS		in depression severity	**Dropouts:** *A-rTMS group* = 3 patients (two due to treatment discomfort; one due to worsening of migraine) *Standard rTMS group* = one patient due to failure of efficacy,	performance on the **trail making test** in the accelerated group and in digital **symbol coding** in the standard treatment group. Accelerated treatment was associated with a higher rate of reported treatment discomfort. **Follow-up:** maintenance of improvement in both groups.

Table 3. Characteristics and outcomes of the included studies.

DISCUSSION

The 14 studies included in this review were RCTs published within the last five years, between 2018 and 2022.

The main objective was to review the more recent literature relative to the treatment effects of rTMS for MDD. In this context, and due to the heterogeneity of the 14 included studies, the main challenge of this review has to do with the interpretation of the level of treatment efficacy of rTMS for MDD and the characterization of patients who could benefit from this treatment.

The difficulties in interpreting the results result not only from the different sample sizes (that range between 20 and 300), but also due to the fact that different protocols, target regions and methods of evaluating the results were used.

Notwithstanding the diversity of the studies, results were generally consistent. Twelve out of 14 studies [3, 8, 15, 25, 31-35, 37-39] found rTMS effective as a treatment and only 2 studies [10 and 36] found no significant reduction in the depressive symptoms according to the used scales, along with no significant difference compared to the sham control.

In the study of Blumberger et al. (2021) this may have occured because the design of the protocol, “lasting 30 treatment days may have led to an expectancy effect and negatively biased early treatments”.

In the study of Eijndhoven et al. (2020), the method of sham stimulation consisted in tilting the coil 45^{o} away from the scalp which may have caused small therapeutical effects and a substantial number of participants had undergone electroconvulsive therapy (ECT) before participating in this trial, contributing to a very high level of treatment resistance. This report is consistent with the findings of Kar et al. (2019), which studied predictors of response and found that the patients who had shown poor response to ECT, often poorly respond to TMS [41].

Concerning the study of Dunlop et al. (2019), although there was a significant main effect of treatment across all arms, active DMPFC-rTMS was not superior to sham.

Moreover, despite the evidence for the effectiveness of rTMS for MDD is clear and supported in dozens of well powered RCTs and meta-analyses [6], the main goal should now be focused on the identification of objective clinical or biological makers with predictive value that may guide the clinicians in appropriate selection of patients who could benefit from rTMS.

Four studies in 14 [8, 10, 31, 39] found possible relations between clinical predictors and the outcomes. In the study of Bulteau et al. (2022) the main clinical predictors of positive outcomes identified for iTBS and left HF-rTMS were lower baseline depression scores, older age, lack of benzodiazepine use, fewer past treatment failures, lower baseline anxiety and current employment.

Potential treatment response predictors were anhedonia, assessed using the Snaith-Hamilton Pleasure Scale (SHAPS) and apathy, using Starkstein's Apathy Scale (SAS).

In contrast with these results, the age factor was further explored in the study of Cotovio et al. (2022) where a large international cohort, with more than 500 patients were evaluated comparing older

versus younger patients under rTMS for MDD, and found that that older adults, while having similar antidepressant response to younger adults, respond more slowly [42]. This may be explained by factors such as underlying medical condition of the elderly or due to underlying cortical atrophy [41].
In fact, according to Cotovio et al. (2022), a recent metanalysis of RCTs supported that rTMS is a clinically effective antidepressant treatment in older patients [43] and there are suggestions that rTMS has similar antidepressant efficacy in the older and younger patients [44-45].

Moreover, in the review of Kar et al. (2019), other patient related factors have been studied: a meta-analysis, which included 54 sham-controlled trials, revealed that gender might be a positive predictor of response as studies showing good antidepressant response to rTMS had mostly female patients [46]. They also found that patterns of clinical symptoms of depression may predict the rTMS related therapeutic response, depressed mood and guilt feelings being the negative predictors, whereas psychomotor retardation being the positive predictor of response. The cognitive and affective symptoms of depression significantly predict the response to rTMS treatment in comparison to the somatic symptoms (Kar et al. (2019)).
While Li et al. (2019) found that HDRS-17 changes in the 1st week were the most important variable for predicting antidepressant responses, Fitzgerald et al. (2018) found that a significantly greater percentage of patients who were non-responders were taking no current antidepressant medication.
In addition, in the study of Eijndhoven et al. (2020), the level of treatment resistance may be the most contributing factor to estimate the probability of treatment response in TRD patients instead of the level of chronicity. These findings lead to the conclusion that it is important to identify risk factors involving the development of TRD and its different stages, “along with applicable measurements that can be used broadly, improving the characteristics and homogeneity of the therapeutical protocol” [10].
Furthermore, most of the sudies [15, 25, 32-34, 36, 37-39] didn’t include a measure of treatment resistance and consequently we cannot further explore the relation between level of treatment resistance and and the degree of response.

From the four papers [3, 8, 31, 39] that compared standard rTMS with other protocols, Bulteau et al. (2022) failed to demonstrate superiority of iTBS to 10 Hz rTMS in TRD, even though the response and remission rates were no significantly different.
Notwithstanding, there is a growing effort in the field to enhance rTMS cost-effectiveness through time-saving protocols, and in this context iTBS already obtained approval from FDA in 2018 [31].
Chen et al. (2021) also found no significant difference in the global response and remission rates between aTBS and 10 Hz rTMS, meaning that aTBS was not associated with more rapid effects.
In addition, Li et al. (2019) studied piTBS and 10 Hz rTMS both in monotherapy and found significantly greater decreases in piTBS group compared to the sham group and the odds ratio for responses was high. This report is consistent with the systematic review and meta-analysis of Chu et al. (2020), mentioning that TBS was more efficient in terms of time and energy than the standard rTMS, providing a significant antidepressant effects along with favorable tolerability [47].

Finally, Fitzgerald et al. (2018) found no significant difference between arTMS and 10 Hz rTMS, meaning that even though the efficacy is not superior, it can be used as a possible option of treatment. According to the systematic review and meta-analysis of Sonmez et al. (2019), aTMS has utility for adressing the pratical limitations of standard TMS and optimizing the dosing of this treatment [12].

Two out of 14 studies [33-34] studied unilateral compared to bilateral application of rTMS.
Zhang et al. (2021) found no statistical differences in the efficacy of rTMS between unilateral and bilateral DLPFC. This finding was in line with the results of the meta-analysis of Sehatzadeh et al. (2019), which studied 23 RCTs over two decades comparing the efficacy of rTMS applied unilateral or bilaterally [48].
In contrast, in the study of Trevizol et al. (2019), bilateral application of rTMS differed significantly in terms of response and remission rates. This may be explained because of the “dysfunction in both right and left DLPFC in patients with MDD, pointing to the “promotion system” related to goal-directed activity in the left DLPFC, and the “prevention system” related to anxiety and avoidance assigned to the right DLPFC” [34].

The stimulation of the DLPFC is significantly associated with the enhancement of the neurocognitive domains, and rTMS appears to reduce depressive symptoms, with a subsequent improvement in the neurocognitive functions, which is in line with the results of Asgharian et al. (2022) and Jagawat et al. (2022).

Another parameter that may affect rTMS effectiveness using DLPFC as the target region is the positioning of the coil. As per standard technique, this region of the cortex is positioned 5 cm anterior to the motor cortex across the curvature of the scalp. However, due to anatomical variations in brain size and morphology this measurement may not be accurate [41], by chance even mentioned as a limitation of the study of Li et al. (2019), referring that “the head shapes in Chinese people are rounder than the Caucasian warning that the results can be influenced by this fact”. On the other hand, and according to Kar et al. (2019), the activation of parts of DLPFC in MDD also varies across patients leading to that an innaccurate targeting may affect the clinical outcome.
Functional neuroimaging and electroencephalography guided DLPFC are likely to improve the clinical outcome [41], once they are capable of incorporate the anatomical variability across patients. Four in 14 papers [8, 15, 31, 34] applied MRI guided neuronavigation in order to localize the DLPFC, even though those that compared the neuroimaging method didn’t find a significant difference in the outcomes [8, 34].

So far, figure-8-coil is the most used shape of coil to perform rTMS, emiting relatively superficial cortical stimulations [9].
In the paper of Filipčić et al. (2019), they compared a H1-coil with a figure-8-coil observing a better response rate and greater reduction of depression severity in the H1-coil group, but without a significant difference in the remission rate between the two rTMS modalities.

H1-coil can lead to deeper stimulations of the cortex, remaining a non-invasive stimulation, that has estimated to reach approximately 4 cm [38].
The brain structures involved in depression are predominantly the left DLPFC, hippocampus, subgenual anterior cingulate cortex (sgACC) [41] as well as pregenual ACC (pgACC) [49]. Even though sgACC is deeply seated in the brain and could not be stimulated by TMS [41] in the paper of Jing et al. (2020), the stimulation of DLPFC may take antidepression effects through the sgACC-DLPFC network. This may happen due to the connectivity between left DLPFC and sgACC. Furthermore, when studying the functional connectivity (FC) between this two stimulation targets, it was found that the FC of sgACC and DLPFC was more negative in responders than in non-responders making sgACC a potential effective region for rTMS, even when applied only on left DLPFC [49].

In which concerns the tolerability and efficacy of rTMS technique, our results were in line with the systematic review and meta-analysis of Wang et al. (2022) that included 53 randomized sham-controlled trials and found that TMS may significantly increase the risk of non-serious adverse events, mostly mild and transient, including headaches, discomfort and local pain at the stimulation site. Our results are also consistent with the data found by the systematic review and meta-analysis of Valiengo et al. (2022), that included 14 RCTs and 26 studies, concluding that rTMS is an effective, safe, and well-tolerated treatment for MDD in older adults and that it should be considered in the treatment of this vulnerable population.

Looking closely, there were limited data on the maintenance rTMS treatment for MDD. None of the included studies reported any results on this issue. Only 8 out of 14 studies reviewed follow-up treatment [3, 8, 10, 15, 31-32, 36, 39] in terms of monitoring the maintenance of improvement and the reduction of symptomatology in the course of a pre-established time after the end of the rTMS treatment.
While maintenance of treatment, as explained in the literature, is not the mere reintroduction of rTMS in situations of a relapse, but an intentional, timely scheduled regimen of rTMS treatment for a fixed period after acute treatment [51]. According to the protocol of Bulteau et al. (2020) that intends to study the cost-utility analysis of curative and maintenance of rTMS for TRD, bringing up the economical side involved in this, known as being a prevalent disease, indeed debilitating and costly. This protocol [51] proposes a health-economic prospective, randomized, double-blind, multicenter study where two treatment strategies can be offered after the rTMS treatment of the acute phase: either they apply a rTMS cure if a relapse or recurrence occur, or they propose a systematic maintenance of rTMS after the initial rTMS used in the acute phase, being the primary endpoint to investigate the incremental cost-effectiveness ratio over 12 months. Even though this investigation is still in progress (see ClinicalTrials.gov, NCT03701724), the discussion point will be if in the case of significant decrease in the depression costs and expenditures associated with a good long-term prognosis (sustained response and remission) and tolerance, rTMS could be considered as an efficient treatment within the options for resistant unipolar depression.

Further research in this area will be of paramount importance once rTMS is gaining popularity as a treatment option for MDD and TRD, being essential to focus on the global accessibility and reliability of this treatment through standardized protocols and evidence based-guidelines [9].

To finalize, in the paper of Armas-Castañeda et al. (2021), the sample size included university students, ages between 18-35 years old, where the protocol applied was two versus five sessions of 5Hz rTMS per week, directed to the left DLPFC, for two weeks.
This paper showed response rates with the active treatment of 100% for both active groups and remission rates of 68.2% (5 sessions/week) and 80% (2 sessions/week). Another important aspect is that 28.5% of the participants had not any previous depressive episode and, as a young sample, were free of risk factors as medical comorbidities, chronic depression and suicide ideation. Furthermore, the follow-up at three months showed the maintenance of improvement in both active groups. This may lead us to think of rTMS as a future first-line therapy for young people with first depressive episodes, without any other risk factors, which also is consistent with the paper of Fregni et al. (2006) recommending rTMS for patients of younger age and less treatment resistance for a positive outcome [52].

LIMITATIONS

The main difficulty to assess efficacy of rTMS treatment in depression relates to the small number of studies included for qualitative synthesis and analysis. However our research strategy considered only papers written in english and published within the last five years.
Secondly, as the principal aim of this review was to review the more recent literature relative to the treatment effects of rTMS for MDD, very heterogeneous studies were included making the process of analysis more difficult. Most of the existing trials are limited by the small sample size, major variations in the characteristics of the treatment including a wide variety of TMS protocols used and parameters of outcome measurement. Importantly, the lack of consensus when measuring the treatment resistance makes it difficult to evaluate and compare the different results according to the inclusion criteria, as well as the lack of follow-up occurring in the most part of the studies.

For those that compared rTMS with a sham control, the technique used to perform the placebo may have influenced the results. Five in 14 studies [10, 25, 34, 35, 37] used the same stimulation coil that is used for active rTMS, but in a rotation of 45º [10, 35] or 90º (tangencial to the skull) [25, 34, 37] which may have caused small therapeutical effects. Three in 14 studies [8, 15, 32] used a sham coil that reproduces auditory sensation of the active treatment coil [15].

CONCLUSION

Despite the huge variety of methodologies and treatment protocols, this systematic review was in line with the existing evidence that support rTMS as an effective, safe, and tolerable treatment for MDD and TRD. As a neuromodulation technique that is achieving protagonism in the treatment of this prevailing disorder, there is still limited data concerning the long-term benefits and need for maintenance treatment after the acute phase setting. The identification of objective clinical or biological makers with predictive value on the treatment response would be highly valuable for guiding the clinicians to better characterise the patients who could benefit from this treatment, positioning these tools towards clinical practice guidelines.

Repetitive TMS is been studied for MDD and especially for TRD, but if we focus on some trials that studied younger populations, great results were found with remission and response rates way above the ones for TRD patients [32, 52] . This may lead us to think of rTMS as a future first-line therapy for young people with first depressive episodes, without any other risk factors.

Notwithstanding and according to Amad et al. (2021), even though meta-analyses are considered the most robust type of studies, “they can no longer be considered as indisputable gold standard but rather methods with their advantages and disadvantages that are also logically induced by the bias and confounding factors”. Particularly concerning to this topic, where a wide variety of TMS protocols are used and compared simultaneously in a single analysis.

Without relinquishing the economical implication of this disease, and considering time as an important element, shorter treatment periods with comparable antidepressant efficacy are of great clinical importance [8], as well as global accessibility and reliability evidence-based protocols [9].

Thus, future clinical studies with larger sample size are needed, along with a more accurate protocol that consistently compares newer forms of rTMS in terms of stimulation parameters across all of the treatment arms.

CONFLICTS OF INTEREST

The author declare no potential conflict of interest.

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Appendix 1: Jadad Score Calculation for included Studies

Item	Score
1. Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1
2. Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?	0/1
3. Was the study described as double blind?	0/1
4. Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	0/1
5. Was there a description of withdrawals and dropouts?	0/1
6. Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).	0/−1
7. Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0/−1
Guidelines for Assessment	

Randomization: A method to generate the sequence of randomization will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.
Double blinding: A study must be regarded as double blind if the word “double blind” is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos, or dummies is mentioned.
Withdrawals and dropouts: Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

Year	First Authour	Items 1 and 2	Items 3 and 4	Item 5	Item 6	Item 7	Final Score
2022	Fatemeh Asgharian	1 + 1	0 + 0	0	0	0	2
2022	Samuel Bulteau	1 + 1	1 + 1	1	0	0	5
2022	Saadgi Jagawat	1 + 1	1 + 1	0	0	0	4
2021	Armas- Castañeda	1 + 1	1 + 1	1	0	0	5
2021	Tingting Zhang	1 + 1	1 + 1	1	0	0	5
2021	Leo Chen	1 + 1	0 + 0	1	0	0	3
2021	Daniel Blumberger	1 + 1	1 + 1	1	0	0	5
2020	P. van Eijndhoven	1 + 0	0 + 0	0	0	0	1
2020	Lilei Dai	1 + 1	1 + 1	1	0	0	5
2019	Cheng-Ta Li	1 + 0	1 + 1	1	0	0	4
2019	Katharine Dunlop	1 + 1	not	possible	to	evaluate	_
2019	Igor Filipčić	1 + 1	0 + 0	1	0	0	3
2019	Alisson Trevizol	1 + 0	1 + 1	1	0	0	4
2018	Paul Fitzgerald	1 + 1	0 + 0	1	0	0	