Repetitive Transcranial Magnetic Stimulation with and without Internet-delivered Cognitive Behaviour Therapy for the Treatment of Resistant Depression: Patient-centred Randomized Controlled Pilot Trial.

By

Medard Kofi Adu

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

Department of Psychiatry
University of Alberta

Abstract

Background: Major depression is a severe, disabling, and potentially lethal clinical disorder. Only about half of patients respond to an initial course of antidepressant pharmacotherapy. At least 15% of patients with major depression disorder (MDD) remain refractory to any treatment intervention. Repetitive Transcranial Magnetic Stimulation (rTMS) is considered a treatment option for patients with MDD who are refractory to antidepressant treatment as well as cognitive-behavioural therapy (CBT: an evidence-based, structured, intensive, time-limited, symptom-focused form of psychotherapy recommended for the treatment of MDD). It is not known if the addition of iCBT enhances a patient's response to rTMS treatments.

Objectives: The aims of this study are to 1) conduct a scoping review of the literature in support of the use of rTMS for the management of the psychiatric disorders (treatment-resistant depression (TRD), PTSD, bipolar disorder, and obsessive-compulsive disorder (OCD)) 2) conduct a general review of the literature in relation to iCBT for the management of TRD. 3) evaluate the initial comparative clinical effectiveness of rTMS with and without iCBT as an innovative patient-centred intervention for the treatment of participants diagnosed with TRD.

Methods: Five databases were searched (MEDLINE, CINAHL, PsychINFO, SCOPUS, and EMBASE) to identify empirical studies and randomized controlled trials (RCTs) aimed at the treatment of TRD, PTSD, bipolar disorder, and OCD with rTMS. Again, a general search was conducted in the afore-mentioned databases to generate a general review of literature on the use of iCBT for the management of TRD. Regarding the prospective RCT, overall, 78 participants diagnosed with TRD were randomized to one of two treatment interventions; rTMS sessions alone and rTMS sessions plus iCBT. Participants in each group completed evaluation measures at baseline and 6 weeks (discharge) from treatment. The primary outcome measure was the mean

change in the 17-item Hamilton depression rating scale (HAMD-17) from baseline to six weeks. Secondary outcomes included mean changes from baseline to six weeks in the Columbia suicide severity rating scale (CSSRS), which rates suicidal ideations, Quick inventory of depressive symptomatology-self rated scale (QIDS-SR16) for subjective depression, and the EQ-5D-5L to assess the quality of health in participants.

Results: The major findings from the scoping reviews conducted on the efficacy of rTMS were that rTMS application is efficacious in the management of TRD, PTSD, bipolar disorder, and OCD. From the reviewed papers, iCBT seems an effective and promising internet-based intervention for the management of MDD and TRD, with a greater accessibility for the target population.

Regarding the prospective RCT, the majority of participants were females 50(64.1%), aged ≥40 39(50.0%), and had college/university education 54(73.0%). After adjusting for baseline scores, the study failed to find a significant difference in the changes in mean scores for participants from baseline to six weeks between the two interventions under study on the HAMD-17 scale; $F(1, 53) = 0.15$, $p = 0.70$, partial eta squared = 0.003, CSSRS; $F(1, 56) = 0.04$ $p = 0.85$, partial eta squared = .001, QIDS-SR16 scale; $F(1, 53) = 0.04$ $p = 0.61$, partial eta squared = 0.005, and EQ-5D-VAS; $F(1,51) = 0.46$ $p = 0.50$, partial eta squared = .009. However, it found a significant reduction in means scores at week six compared to baseline scores for the combined study population on the HAMD-17 scale (42%), CSSRS (41%) and QIDS-SR16 scale (35%). Additionally, it noted an improvement of about 62% in the quality of life of all participants, as recorded via the EQ-VAS scale.

Conclusion: The scoping reviews suggest that rTMS is effective for management of TRD, PTSD, bipolar disorder, and OCD. Future narratives on effective implementation strategies of

iCBT interventions for the management of TRD should consider issues on specific predictors and impediments of their usage, and address them in future studies and practices.

The RCT failed to demonstrate a significant difference regarding the management of MDD symptoms, subjective MDD, suicidal ideations, and the quality of health between rTMS alone and rTMS plus unguided iCBT on all scales.

Preface

This thesis is an original work by Medard Kofi Adu under the supervisorship of Dr. Vincent I.O. Agyapong. The research project, of which this thesis is a part, was conducted per the Declaration of Helsinki (Hong Kong Amendment) and Good Clinical Practice (Canadian Guidelines). The study received ethical clearance from the Health Ethics Research Board of the University of Alberta (Pro00094208). The study is registered with clinicaltrials.gov: (registration number: NCT04239651; pre-result). Results are expected to be disseminated at several levels, including participants, practitioners, academics/researchers, and healthcare organizations.

Some sections within the various chapters of this thesis are published or submitted/planned for publication. The references from these published or submitted papers are listed in a single refence list at the end of this thesis. This was done to prevent redundancy and to make this write-up more readable. Aside from this change, the text of the papers is presented exactly as published.

Brief details of the included papers are provided below, and highlight the contributions made by Medard Kofi Adu.

Chapter 1.2: This chapter has been published as: **Medard Kofi Adu**, Reham Shalaby, Pierre Chue and Vincent I.O. Agyapong. Repetitive Transcranial Magnetic Stimulation for Treatment of Resistant Depression: A Scoping Review. Behav. Sci. 2022, 12, 195.
Behav. Sci. 2022, 12(8), 263; https://doi.org/10.3390/bs12060195.

Medard Kofi Adu was responsible for design, data curation, data analysis, and drafting the initial manuscript.

Chapter 1.3: This chapter has been published as: **Medard Kofi Adu**, Ejemai Eboreime, Adegboyega Oyekunbi Sapara, and Vincent Israel Opoku Agyapong. The Use of Repetitive Transcranial Magnetic Stimulations for the Treatment of Bipolar Disorders: A Scoping Review.
https://doi.org/10.3390/bs12080263

Medard Kofi Adu was responsible for design, data curation, data analysis, and drafting the initial manuscript

Chapter1.4: This chapter has been published as: **Medard Kofi Adu**, Ejemai Eboreime, Adegboyega Oyekunbi Sapara, Andrew James Greenshaw, Pierre Chue and Vincent Israel Opoku Agyapong. The use of repetitive transcranial magnetic stimulation for treatment of

obsessive-compulsive disorder: A scoping review. *Emerald Publishing Limited* [ISSN 2036-7465], DOI 10.1108/MIJ-05-2021-0002.
Medard Kofi Adu was responsible for design, data curation, and drafting the manuscript. Vincent Agyapong played a supervisory role.

Chapter 1.5: This chapter has been published as: **Medard Kofi Adu**, Ejemai Eboreime, Adegboyega O. Sapara, and Vincent I. O. Agyapong. The Use of Repetitive Transcranial Magnetic Stimulations for the Treatment of Post-Traumatic Stress Disorder: A Scoping Review. *MPDI- Trauma Care 2022, 2, 151–161. https:// doi.org/10.3390/traumacare2020012.*
Medard Kofi Adu was responsible for design, data curation, and drafting the manuscript. Vincent Agyapong played a supervisory role.

Chapter 1.6: This chapter has been submitted to the MDPI – Behavioral sciences journal for possible publication as: Medard Kofi Adu, Reham Shalaby, and Vincent I.O. Agyapong. *The Use of Internet-Based Cognitive Behavioral Therapy (iCBT) In Treatment-Resistant Depression: General Literature Review.*
Medard Kofi Adu was responsible for design, data curation, and drafting the manuscript. Vincent Agyapong played a supervisory role.

Chapter 2: This chapter represents the protocol of this project published as: Rabab M Abou El-Magd, MSc, PhD; Gloria Obuobi-Donkor, BSc; **Medard K Adu**, BSc; Christopher Lachowski, MD; Surekha Duddumpudi, MD; Mobolaji A Lawal, MD; Adegboyega O Sapara, MD; Michael Achor, MD; Maryam Kouzehgaran, MD; Roshan Hegde, MD; Corina Chew, BSc; Mike Mach, BSc; Shelley Daubert, BSc; Liana Urichuk, PhD; Mark Snaterse, BSc; Shireen Surood, PhD; Daniel Li, MD; Andrew Greenshaw, PhD; Vincent Israel Opoku Agyapong, MD, PhD. *Repetitive Transcranial Magnetic Stimulation with and without Internet-Delivered Cognitive-Behavioral Therapy for the Treatment of Resistant Depression: Protocol for Patient-Centered Randomized Controlled Pilot Trial.*
Medard Kofi Adu was responsible for writing the initial draft and reviewing the final draft.

Chapter 3: This chapter represents the main results of the prospective RCT, and has been submitted for publication in JMIR- Mental Health Journal as**: Apparent Lack of Benefit of**

Combining Repetitive Transcranial Magnetic Stimulation with Internet-Delivered Cognitive Behavior Therapy for the Treatment of Resistant Depression: Patient-centered Randomized Controlled Pilot Trial.

Medard K Adu, Reham Shalaby, Ejemai Eboreime, Adegboyega O Sapara, Mobolaji Lawal, Corina Chew, Shelley Daubert, Liana Urichuck, Shireen Surood, Daniel Li, Mark Snaterse , Mike Mach, Pierre Chue, Andrew J. Greenshaw, Vincent I O Agyapong

Medard Kofi Adu was responsible for recruitment of patients, data collection, data analysis and writing the initial draft as well as reviewing the final draft.

Dedication

I dedicate this thesis to my wife, children and the entire family for their prayers, encouragement, and unwavering support during the writing of this thesis.

Acknowledgements

An essential lesson you realize in life is how much any success depended on some critical people who were there at crucial moments in your life. The fact is, you just don't succeed in any endeavor unless you have a team that has been supporting you.

First and foremost, my sincerest gratitude goes out to my supervisor, Dr. Vincent I.O. Agyapong for his unflinching support, guidance and mentorship throughout these years of my academic life. I am most grateful to him for providing such a valuable opportunity to be his student and for creating an enriching academic environment for me to live and thrive in. I appreciate his incredible vision and wisdom, which has propelled me to flourish in the world of academia and in the field of psychiatry.

I express my gratitude towards my co-supervisor Prof. Andrew Greenshaw and the team of indefatigable supervisory committee members, Dr. Pierre Chue, and Dr. Adegboyega Sapara for availing their immense wealth of knowledge and endless enthusiasm for research to me. I am most appreciative of your invaluable guidance for the duration of this project.

I am highly indebted to all the post-doctoral fellows in our research team, Dr. Ejemai Eboreime, Dr. Fola Oluwasina, Dr. Raquel Dias, and Dr. Reham Shalaby for their generous intellectual directions to my study. I also thank my colleague students in our research team for their support. As the learned Isaac Newton put it, "*if I have seen further than others, it is by standing on the shoulders of giants"*.

I acknowledge the support from the Department of Psychiatry, University of Alberta, the Mental Health Foundation and the Douglas Harden Trust Fund for their generosity in funding this work through the scholarship support they granted me.

Finally, my sincere gratitude and appreciation go to the entire staff of rTMS clinics; Addiction and mental health clinic 108 St. building and the Alberta day hospital rTMS clinic for their support and cooperation during my recruitment process.

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Abbreviations

MDD - Major Depression Disorder

TRD – Treatment-resistant Depression

TMS - Transcranial Magnetic Stimulation

rTMS – repetitive Transcranial Magnetic Stimulation

CBT – Cognitive Behavioural Therapy

iCBT – internet-delivered Cognitive Behavioural Therapy

Ham-D– 17 - Hamilton Rating Scale for Depression–17-item

QIDS-SR16 - Quick Inventory of Depressive Symptomatology Self Report–16-item

CSSRS - Columbia Suicide Severity Rating Scale

EQ-5D-5L - EuroQuol 5-Dimension–5-Level

SMA - Supplementary Motor Area

MT - Motor Threshold

RMT - Resting Motor Threshold

DLPFC - Dorsal Lateral Prefrontal Cortex

OFC -- Orbitofrontal Cortex

mPFC - medial Prefrontal Cortex

CAM- Complementary and alternative medicine

CANMAT - Canadian Network for Mood and Anxiety Treatments

DSM - Diagnostic and Statistical Manual of Mental Disorders

ECT - Electroconvulsive Therapy

Y-BOCS - Yale–Brown Obsessive-Compulsive Scale

CGI-I -Clinical Global Impression

HAMA - Hamilton Anxiety Rating Scale

GAF - Global Assessment of Functioning

MCCB - MATRICS Consensus Cognitive Battery

CAPS – Clinician-administered PTSD Scale

BNCE - Brief Neurobehavioural Cognitive Examination

STAI - State Trait Anxiety Inventory

SC-Q - Self-administered Comorbidity Questionnaire

SCID - Structured Clinical Interview for DSM-IV

IPF - Inventory of Psychosocial Functioning

BRMAS - Bech-Rafaelsen mania scale

CRSD - circadian rhythm sleep disorder

SCL-90-R - Symptom Checklist-90-Revised

Chapter 1. Introduction

The introduction chapter is made up of six sections: 1) A general review of treatment resistant depression (TRD); 2) Scoping review of rTMS application in the management of TRD; 3) Scoping reviews of rTMS in bipolar disorder; 4) A scoping review of rTMS in obsessive compulsive disorder (OCD); 5) A scoping review of rTMS in post-traumatic stress disorder (PTSD); 6) A general review of literature on the use of iCBT in TRD.

1.1 : General Review on Treatment-Resistant Depression

According to the Lancet Commission on global mental health and sustainable development, mental health is considered a fundamental human right, and plays an important role in the development of every nation[1]. Accordingly, mental health conditions are gradually being recognized as a major cause of disease burden globally[1]. Mental health conditions in 2017 were evaluated as the second leading cause of burden regarding years lived with disability (YLDs) globally, which became severe health system crises, especially in the low- and middle-income countries[2]. Mental illness has a significant impact on affected individuals, their families, and society at large. It leads to a huge reduction in quality of life, and is considered a major cause of self-harm, parasuicide, and completed suicide in the world.

For this reason, global health policymakers placed mental health on their list of top-priority health policies, and hence, it was added to the Sustainable Development Goals[3, 4]. However, to better manage the socioeconomic burden of mental illness around the world, the apathy of health policymakers, governments, and funders of global health needs to be changed[5].

Mental illnesses have a high prevalence rate. The lifetime prevalence, according to a comparative epidemiological survey conducted on mental disorders in adults across different countries within Europe and America, ranges from 12.2% to 48.6%[6]. Aside from high prevalence, the major treatment gap and the seeming ineffectiveness of treatment interventions are issues of major concern in the mental health field. Despite data in the literature regarding RCTs supporting the efficacy of psychotropic medications, these treatment modalities are under constant criticism and mistrust from patients and their relatives as well as healthcare providers[7].

Major depression disorder (MDD) is among the most prevalent and debilitating psychiatric disorders worldwide[8]. According to the World Health Organization (WHO), MDD contributes significantly to the global burden of disease[9]. More than 264 million people in 2017 alone were believed to be suffering from MDD globally, and it is considered to be the 3rd leading cause of YLDs. MDD is characterized by persistent sadness, lack of interest, altered sleep patterns, and loss of appetite. Affected individuals mostly present with emotional distress, psychosocial disorders, and cognitive impairments with an increased risk of suicide[10]. Although MDD is treatable, expert reviews indicate inadequate treatment resources for its management; therefore, it has become a global priority to widen the coverage of treatment modalities for it[11]. Common

and traditional treatments include pharmacological approaches and psychotherapeutic interventions. However, despite the array of therapeutic evidence for these treatment modalities[12], 20 to 46% of MDD patients do not receive an adequate response, and non-responders are referred to as having TRD [13].

Defining TRD

TRD is a common clinical subtype of MDD that does not respond adequately to traditional antidepressants. Experts have yet to present a standardized definition for this group of MDD patients [14]. However, there are several schools of thought regarding what constitutes a concise definition for TRD. Among these, the consensus seems to centr on the failure of an MDD patient to obtain remission after treatment with at least two trials of antidepressant pharmacotherapy[14]. Several guidelines outline specific characteristics that must be observed before the classification of TRD. However, a consensus has not yet been reached on these staging methods[15]. Therefore, TRD presents several challenges that make it difficult to identify quality therapeutic interventions and their true efficacy in its management.

Classification of TRD

Among the several criteria proposed in the literature to classify TRD is that presented by Thase and Rush[16]. In this model, TRD levels range from a failure of an antidepressant to a non-response to electroconvulsive therapy (ECT). The Massachusetts General Hospital Staging method is another way of classifying TRD[17]. Compared with the Thase and Rush approach, this model is more quantitative and takes into account increases in treatment dosage as well as the extended duration of treatment and the number of treatment failures[17, 18]. Other models include the Souery Operational Criteria for TRD. Unlike other approaches, this staging model defines TRD as a single non-response to an optimum (6-8 weeks) trial of antidepressants[19].

Issues in Diagnosing TRD

A major challenge in diagnosing TRD is the issue of “pseudo resistance”[20]. Pseudo resistance borders on the description of MDD patients who were mistakenly prescribed psychopharmacological agents or patients who discontinued their medications due to reasons such as the unbearable side effects, and non-adherence. Several comorbidities, such as anxiety

disorders, drug/substance use disorders, and personality disorders may complicate clinical assessments and can eventually have a negative effect on treatment response[21, 22]. Another significant difficulty in diagnosing TRD occurs during the process of interviewing patients in clinical assessment where there is the possibility of recall bias in reporting psychopharmacological trials and responses. Data suggest that, for a quality description of the characteristic features and course of TRD, the prospective use of objective clinician-assessed scales, such as the Hamilton Depression Rating Scale[23] and the Inventory of Depressive Symptomatology[24] as well as antidepressant treatment history forms, could be instrumental[25].

Prevalence of TRD

Due to the lack of consensus regarding a standardized definition and uniform criteria for classifying TRD, estimates of prevalence vary significantly in the literature (12%–55%)[26-29]. In the US alone, the estimated annual prevalence of medication-treated MDD was placed at 8.9 million adults, of which 2.8 million (30.9%) had TRD[30]. In Canada, while classifying TRD according to the failure to respond to at least two antidepressant medications from different classes, the overall prevalence was estimated to be 21.7% with no difference in prevalence between men and women or among ethnic groups [31].

In other geographical regions, data from a study that assessed the prevalence and impact of TRD among patients with MDD in four Latin American countries demonstrated that 29% of study participants with MDD were resistant to medication. The results suggested a TRD prevalence of 21% in Mexico, 33% in Argentina, 32% in Colombia, and 40% in Brazil[32]. With regard to Europe, data from a multicentre study of patients diagnosed with TRD demonstrated a prevalence rate of 41% among patients with MDD, while in the UK, a study conducted on patients being treated for MDD in a primary care setting demonstrated that 55% of the patients had TRD[33, 34].

Burden and Economic Implication of TRD

Study findings suggest that TRD presents a disproportional socioeconomic burden for patients, their relatives, and the healthcare system in general[32]. TRD is a costly condition characterized by highly significant medical and mental health care costs. Compared to non-TRD, patients with

TRD appear to have a greater cost of outpatient medical care and are twice as likely to be hospitalized due to mental health or medical health concerns[35, 36]. On admission, TRD patients have a six times increase in overall healthcare costs compared to non-TRD patients ($42,344 vs. $6,512)[35]. Furthermore, TRD is characterized by an increase in indirect costs, such as poor productivity and lack of employment for patients and their relatives. However, data regarding the accurate evaluation of the related indirect costs of TRD are limited or missing in the literature[27].

According to data from previous studies, Patients with TRD have greater levels of healthcare resource utilization than MDD patients without TRD and the population at large. This highlights the wide treatment gap that exists for TRD[37-39]. In a related study conducted in the US, in a year following their diagnosis, patients with TRD had an annual healthcare payment of on average $3,000 higher compared to MDD patients without TRD[39]. Furthermore, the total 12-month burden of medicated-treated MDD for the entire US population was reported to be $92.7 billion, of which $43.8 billion representing 47.2% was attributed to TRD alone. The share of TRD on the healthcare burden was estimated at 56.6% ($25,8 billion) with 47.7% ($8.7 billion) representing the unemployment burden[30].

Therapeutic Options for Managing TRD

Since the establishment of the concept of TRD in 1974[40, 41], several studies have been conducted to evaluate the optimum treatment modalities[42, 43]. In the management of TRD, several psychopharmacological and nonpharmacological agents must be considered, especially when patients are believed to have failed at least two optimized therapies.

Adjunctive Therapy for TRD

Augmentation or adjunct treatment for TRD involves the use of additional treatment to the primary therapy, which is usually a first-line antidepressant medication[44]. Examples of adjunctive treatments for TRD include lithium, a naturally-occurring salt. Therapeutic evidence in support of adjunctive antidepressant therapy with lithium derives from studies on tricyclic antidepressants[45]. Again, in a meta-analysis, the data suggest that lithium is as effective adjunct therapy as a commonly-prescribed second-generation antipsychotic[46]. Triiodothyronine (T3) is a type of thyroid hormone mostly prescribed in the augmentation of

antidepressant therapy in TRD[47]. T3 is more tolerable than lithium and requires less monitoring.

Another common augmentation therapy for TRD are second-generation antipsychotic medications (SGAs). SGAs have been evaluated as adjunctive therapies in combination with the well-known first-line treatment modalities. These include selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs)[14]. SGAs are believed to have effects on serotonin receptors and, hence, may be effective when combined with SSRIs or SNRIs in managing patients with TRD. Examples of SGAs that have evidence as adjunct therapy with antidepressants in the management of TRD include olanzapine[48], risperidone[49, 50], quetiapine[51, 52], and aripiprazole[53, 54]. For instance, in a sample of 28 patients, olanzapine was evaluated in combination with fluoxetine, and the results suggest a 60% response[48]. In another study, a daily dosage of 300mg of Quetiapine demonstrated around 48% response with remission of about 24.5% when combined with SSRIs. It has since been cleared as an adjunctive treatment for managing MDD by the FDA[51, 52].

Dose Optimizing, Combining, and Switching Strategies

Regarding dose optimizing, combining, and switching strategies, the National Institute for Health and Care Excellence (NICE) and CANMAT have each developed protocols concerning the management of patients with MDD. Therefore, for patients who seek psychopharmacology, SSRIs or SNRIs become their first-line treatment strategy while older versions of antidepressant medications are reserved for treatment trials when treatments with SSRI or SNRI have been exhausted[14]. Therapeutic evidence in support of the effectiveness of switching to medication from the same class of antidepressant treatments in MDD is limited in the literature. However, data from several studies suggest that switching classes of medication after treatment non-response to an initial class of antidepressant significantly increases the rate of response[14]. In studies conducted by Thase et al[55] and Peselow et al[56], each evaluated switching from SSRI or SNRI medications to tricyclic antidepressants, resulting in a total response rate of 44% to 73%. Monoamine oxidase inhibitors (MAOIs) such as phenelzine, tranylcypromine, and moclobemide, are effective antidepressants for the management of MDD. Therefore, studies have also evaluated the effectiveness of switching from TCA[57, 58] to an MAOI, with a resultant response rate of up to 60%.

With the substantial advances in pharmacological interventions for TRD, there is enough evidence in the literature that supports the effectiveness of antidepressants for the management of TRD despite some limitations[59, 60]. Other supportive evidence suggests that adjunctive treatment protocols that combine different classes of antidepressant medications yield better treatment outcomes in TRD[61]. However, patients with challenges regarding treatment strategies based solely on psychotropic medications find it difficult to comply with the treatment protocols due to issues such as the negative effects of the drugs, availability and high cost of the medications, hindrances due to religious and cultural beliefs, and for some, their personal beliefs about these medications[62].

Psychotherapy in TRD

For the TRD patients with a special preference for nonpharmacologic treatment strategies, psychotherapy becomes the cornerstone of effective treatment interventions[63]. Although group therapy is effective, individual psychotherapy is deemed a major alternative to the traditional psychopharmacologic treatment intervention[64]. Overall, data regarding the use and efficacy of psychotherapy are limited but promising, given significant evidence from RCTs that suggest that the different forms of psychotherapy are effective for the management of TRD[63]. Over the past decades, psychotherapy has gone through cycles of theoretical and technical advancements such that it becomes difficult for clinicians and therapists to refer or decide the unique modality of psychotherapy for the right patient needing it[65, 66].

Specific Psychotherapeutic Strategies in TRD

Cognitive-Behavioural Therapy

Cognitive-behavioural therapy (CBT) is deemed the most frequently-evaluated individual psychotherapy in the management of TRD. Cognitive and behaviourally-inclined treatment strategies assess the maladaptive thoughts and behaviours that contribute to the worsening of symptoms in TRD[63]. Treatment modalities that educate patients to recognize and remedy cognitive distortions, increase behavioural activation, and enlighten them on efficient means to control acute stressors are an important aid to the recovery of patients with TRD[64]. Despite the evidence in support of the effectiveness and extensive use of CBT for TRD, access to treatment

is limited. This is because insufficient resources and qualified therapists are available to attend to the high number of patients needing it[67]. In addressing this limitation, CBT has been modified and can now be administered through computer and internet-based programs. These internet-based CBT (iCBT) require less therapist time and can be accessed by many patients needing it anytime, anywhere, and at a lower cost[68, 69]. An example of iCBT intervention programs for depression includes the self-guided MoodGYM program[70] and the cognitive-behavioural Beating the Blues (BTB) program, which was developed in the UK and is made of 8 web-based modules[71, 72].

iCBT interventions differ in the extent to which they provide guidance or support. The intervention can be delivered through self-guidance or by therapist guidance. During the active phase of iCBT intervention, participants are supported by a therapist who provides guidance and individual feedback to each participant after the completion of each module[73]. The therapist usually communicates with participants via the internal messaging function of the iCBT platform. The therapist is usually a clinician with training in CBT[74]. Participants within the unguided iCBT treatment intervention do not receive any form of support from a therapist or a coach. They get no individualized feedback, however, after completion of each session, a standardized message is automatically delivered to them through the application platform to congratulate them and encourage them to continue with the other modules[74]. Evidence demonstrates that the clinician-supported iCBT is associated with superior efficacy regarding the management of TRD than the self-guided iCBT, which is characterized by relatively poorer outcomes and higher dropout rates[73].

Acceptance and Commitment Treatment

Acceptance and commitment treatment (ACT) is another form of psychotherapy that is effective in the management of individuals diagnosed with TRD. ACT helps TRD patients to identify, evaluate, and accept their negative emotions and thoughts by discouraging experiential avoidance and helping them improve their psychological flexibility and self-care[75]. The expected outcome of ACT is that, when a patient can effectively deal with or minimize the struggle with unwanted thoughts and emotions, it becomes easier to pay attention to realistic strategies and goals in the management of the symptoms in TRD[75].

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) is one of the oldest strategies to treat severe neuropsychiatric conditions. ECT was introduced in 1934 and is still in use in mental health care practice[76]. Ever since its introduction, ECT has stood the test of time as one of the effective treatment modalities in the management of patients with TRD. Despite ECT consistently producing high remission rates in TRD, it is very often the last resort for MDD patients who have failed to adequately respond to or are intolerant to multiple trials of psychopharmacologic treatments[77, 78]. In support of its efficacy and safety, bifrontal and right unilateral electrode placement in ECT was evaluated in a RCT among TRD patients, and resulted in no significant differences observed between the two sites[79].

Generally, ECT is relatively effective in the management of TRD, and believed to produce quick improvements[80-82] and a response rate from 50% to 60%[83, 84]. ECT is evaluated to produce great outcomes in suicidal patients. The rapid improvement in TRD that comes with ECT intervention is especially advantageous for patients with suicidal ideations[85-87]. Despite the efficacy of ECT, the intervention is characterized by high relapse rates, especially within the first month of its application[88]. To avoid this, clinicians often suggests combining ECT with antidepressant treatments[89] or following ECT with maintenance ECT in the management of patients with TRD[84, 90]. Regarding the safety and tolerability of ECT, the most common adverse effect is cognitive impairment[91] of which loss of memory function is the key effect[76, 83]. Other commonly-witnessed side-effects after ECT include headaches[92], nausea[93], and vomiting[94].

Repetitive Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation (rTMS) was developed in the late 1980s for the management of MDD[95]. Since then, several studies have evaluated its efficacy in other psychiatric conditions. The application of rTMS intervention to manage TRD was approved by Health Canada in 2002, the US Food and Drugs administration (FDA) in 2008, and other health bodies in Israel, the European Union, and Australia[14]. Several studies have suggested that rTMS is effective in the management of TRD, with response rates from 30.6 to 64.7%[96-101].

Technological advances in the development and use of rTMS have seen it delivered in different formats that increase its therapeutic efficacy. An example is Deep rTMS. In this approach, the

stimulus is applied with rTMS coils of different designs. These designs include double-cone coils[102], Hesel-coils (H-coils)[103], and halo coils[104], which allow pulses to target deeper areas of the cortex[105]. Deep TMS devices (H1-coil) were approved in 2013 by the FDA for the management of MDD. This approval was based on the outcomes of a study where the remission rate for dTMS was 32.6% against 14.6% for sham rTMS[106]. Other versions include heta-burst stimulation (TBS) and Accelerated rTMS protocols.

The subsequent sections of this paper highlight the use and efficacy of rTMS in TRD and other mental health conditions through scoping reviews in the literature.

1.2: Repetitive Transcranial Magnetic Stimulation for Treatment of Resistant Depression: A Scoping Review of the Literature.

Medard Kofi Adu, Reham Shalaby, Pierre Chue, and Vincent I. O. Agyapong.

Repetitive Transcranial Magnetic Stimulation for the Treatment of Resistant Depression: A Scoping Review. Behav. Sci. 2022, 12(6), 195; https://doi.org/10.3390/bs12060195. Available at: https://www.mdpi.com/2076-328X/12/6/195

Abstract:

Treatment-resistant depression (TRD) is associated with significant disability and, due to its high prevalence, results in a substantive socio-economic burden at a global level. TRD is the inability to accomplish and/or achieve remission after an adequate trial of antidepressant treatments. Studies comparing repetitive transcranial magnetic stimulation (rTMS) with electroconvulsive therapy (ECT) and pharmacotherapy have revealed the therapeutic efficacy of rTMS in TRD. These findings suggest a crucial role for rTMS in the management of TRD. This article conducts a comprehensive scoping review of the literature concerning the use of rTMS and its therapeutic efficacy as a treatment modality for TRD. PubMed, PsycINFO, Medline, Embase, and Cinahl were used to identify important articles on rTMS for TRD. The search strategy was limited to English articles. Articles were included if they reported on a completed randomized controlled trial (RCT) of rTMS intervention for TRD. The exclusion criteria involved studies with rTMS for the treatment of conditions other than TRD, and study and experimental protocols of rTMS on TRD. In total, 17 studies were eligible for inclusion in this review. The search strategy spanned studies published in the last five years, to the date of the data search (14 February 2022). The regional breakdown of the extracted studies was North American (n = 9), European (n = 5), Asian (n = 2) and Australian (n = 1). The applied frequencies of rTMS ranged from 5 Hz to 50 Hz, with stimulation intensities ranging from 80% MT to 120% MT. Overall, 16 of the 17 studies suggested that rTMS treatment is effective, safe and tolerated in TRD. For patients with TRD, rTMS appears to provide significant benefits through the reduction of depressive symptoms, and while progressive evidence supports the same, more research is needed to define standardized protocols of rTMS application in terms of localization, frequency, intensity, and pulse parameters.

Keywords: treatment-resistant depression; major depressive disorder; repetitive transcranial magnetic stimulation; mental health; treatment

INTRODUCTION

Major depressive disorder (MDD) is a mood disorder characterized by depressed mood and /or lack of interest or pleasure in previously rewarding or enjoyable activities, fatigue, disturbed sleep, loss of appetite, and somatic and psychological symptoms[107, 108]. MDD is a significant public health concern that affects approximately 300 million people globally, is a major leading cause of morbidity and contributes immensely to the global burden of disease [109, 110]. Effective treatment of MDD is available in the form of psychopharmacology, psychotherapy, electroconvulsive therapy (ECT), and other non-invasive brain stimulation methods [111] but affected patients frequently experience relapses and persistent life dysfunction [112] with associated suicidal ideation [113].

When a patient with MDD cannot attain remission or adequate therapeutic response while being treated with one or more antidepressants, the patient is said to have developed treatment-resistant depression (TRD) and is diagnosed as such [114]. Since 50 to 60% of MDD patients fail to attain reasonable therapeutic response despite being treated with antidepressants, TRD is relatively common in clinical practice [17]. The most basic definition of TRD is the inability to accomplish and or achieve remission after an adequate trial of antidepressant treatment[17, 115]. TRD is associated with delayed and high-cost inpatient times of treatment[115]. The suffering and disability associated with chronic, unremitting depressive illnesses are enormous; and TRD is considered responsible for the greatest healthcare burden associated with depressive disorders[116]. From the earliest conceptualization of TRD in 1974 [40, 41, 117], numerous studies have been conducted to determine the most effective treatment strategy [42, 43].

As a result of the potentially high direct and indirect medical costs, which further increase the severity of TRD, clinicians are in search of empirical evidence to guide in the most effective treatment [36]. A wide variety of treatment choices, including pharmacological and nonpharmacological interventions and somatic treatments are available for the management of TRD [118]. However, the decreasing therapeutic efficacy of antidepressant medications following at least two failed treatments, coupled with their potential side effects[28, 119], has led to research into alternative treatment modalities, including repetitive transcranial magnetic stimulation (rTMS)[118].

As one of the current modes of treatment for MDD[120, 121], the transcranial magnetic stimulation (TMS) technique was identified and developed by Barker et al. in 1985 [122].

Subsequently, other researchers modified the technique to deliver TMS in repeated pulses at short intervals, which became known as rTMS[120]. rTMS has since been studied and evaluated by researchers for its potential therapeutic effect on many neurological and mental health conditions worldwide [123].

Studies comparing repetitive transcranial magnetic stimulation (rTMS) with electroconvulsive therapy (ECT) and pharmacotherapy have revealed evidence of the therapeutic efficacy of rTMS in TRD; which suggests a key role for rTMS in the management of TRD [121]. An advantage of rTMS over other somatic treatments like ECT includes features such as not requiring anesthesia and the fact that it can be delivered in an office setting, coupled with fewer treatment-associated side effects[124].

Approved by the US Food and Drug Administration (US FDA) for TRD [121], rTMS can be transmitted with a low (1 Hz) or high frequency (10 Hz). While high-frequency rTMS is deemed to produce a stimulating effect on the cerebral cortex, low-frequency rTMS is believed to emit an inhibitory effect [125]. There has been a steady increase in the stimulation dosages of rTMS application from the early rTMS trials [126]. These increases include the stimulation intensity relative to the motor threshold and the number of pulses used in each treatment session. For instance, instead of the usual 10 to 20 trains of 10Hz stimulation used for a high-frequency left-sided rTMS application [96, 127], current trials apply up to about 75 trains for every treatment application daily [128, 129]. This strategy has become the standard in many settings.

Studies suggest an imbalance in the efficient functioning of the frontal lobe in individuals diagnosed with depression [130]. Hence, researchers have treated patients with low-frequency rTMS to the right dorsolateral prefrontal cortex (DLPFC) or high-frequency stimulation to the left DLPFC [131, 132]. It has been found that intermittent theta-burst stimulation (iTBS) delivered over 3 minutes is non-inferior to a standard 37·5 min treatment session at 10 Hz [133]. Furthermore, both low and high frequencies of rTMS application targeted to either the left or right DLPFC have the same therapeutic efficacy [134]. However, there were fewer side effects with low-frequency right-sided application[134].

The most effective treatment for TRD remains uncertain due to limited validated pharmacological and psychotherapeutic approaches [135, 136]. Given this limited evidence, rTMS has been evaluated as a strategy [137]. Thus, increasing studies have focused on rTMS application in individuals diagnosed with TRD. The approval by the FDA for its use in the

treatment of TRD reflects the evolving research on rTMS for which the optimal technique of application continues to be investigated. rTMS is becoming a common treatment modality whose parameters are still being defined. This review seeks to map an up-to-date synthesis of literature evidence supporting the therapeutic efficacy of rTMS in TRD while acknowledging that rTMS is a general approach rather than a single entity.

Methodology

To identify literature concerning rTMS for the treatment of TRD, five databases (PubMed, Embase, PsycINFO, CINAHL, and Medline) were searched electronically. The authors developed and executed a search strategy within the designated databases, which included terms related to "treatment-resistant depression", "repetitive transcranial magnetic stimulation", "randomized control trials", and "treatment". The main focus of this review is to synthesize evidence and assess the scope of current and updated literature on the use of rTMS in TRD. Also, due to the use of newer techniques and parameters for rTMS applications, we opted to explore these recent updates in this review, therefore the search strategy was limited to the last five years of data publication (from 2017 to Feb 2022). Language restrictions were applied, and only articles published in English were included. Two researchers independently screened the titles and abstracts and reviewed all full-text articles that met the inclusion criteria. Conflicts that arose out of the review process were discussed and resolved by the two reviewers.

We calculated Cohen's Kappa Statistics, following the equation below, to report inter-rater reliability at the stage of full text review of the potential articles, where 0 = agreement equivalent to chance, (0.1 – 0.20) = slight agreement (0.21 – 0.40) = fair agreement, (0.41 – 0.60) = moderate agreement, (0.61 – 0.80) = substantial agreement, (0.81 – 0.99) = near perfect agreement, and 1 = perfect agreement[138, 139].

$$\text{Kappa} = \frac{\text{Observed agreement} - \text{chance agreement}}{1 - \text{chance agreement}}$$

Inclusion and Exclusion Criteria

Articles were included if they reported on a completed randomized controlled trial (RCT) of rTMS as a treatment intervention for TRD, and were published within the last five years.

Exclusion criteria involved studies with rTMS as a form of treatment for conditions other than TRD; studies and experimental protocols of rTMS on TRD; studies with rTMS as combined therapy with pharmacotherapy or any other interventions; and studies of rTMS treatment on treatment-resistant bipolar depression.

Data Extraction

A qualitative descriptive approach was used during extraction to categorize the included studies based on the name of authors, year of publication, study design, number of participants, targeted brain region, targeted symptoms, measurement tools, duration of treatment, coil/rTMS stimulations, outcome/significant improvements/effect size, assessment and follow-up, conclusion and side effects of the intervention as displayed in table 3.

Results

We identified 85 studies from the electronic databases through the search strategy and the use of the Covidence software. The software automatically screened and removed 16 duplicate studies; 69 studies were screened against the eligibility criteria set based on the title and abstract only. The screening was done independently by two reviewers, and where conflicts in classification existed, the articles in question were discussed, and a consensus was reached between the two reviewers. The title and abstract screening brought the total records left for full-text screening to 30 studies after 39 were deemed irrelevant and excluded from the records. The remaining items were full text screened by the two reviewers and 13 studies were excluded from the study. Studies were excluded primarily based on wrong intervention, where the studies used CBT but not specifically internet-based. In other studies, the target population had conditions other than TRD. There were studies with poor study designs and sometimes with wrong outcomes. A total of 17 studies were eligible and extracted for this scoping review. Figure 1.2.1. shows the PRISMA flow diagram displaying the search results and process.

Table 1.2.1: Agreement of the two researchers for full text review

		Researcher R.S.		
		Yes	No	Total
Researcher M.A.	Yes	15	4	19
	No	1	10	11
	Total	16	14	30

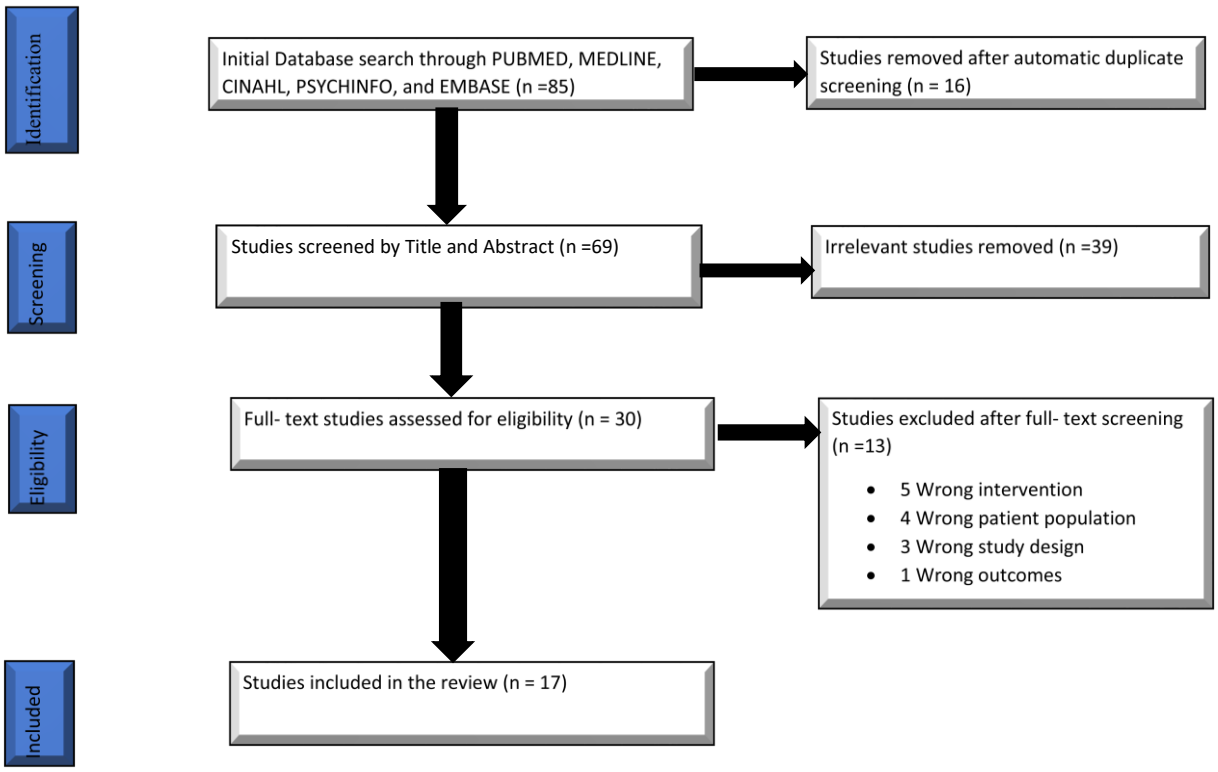
Observed agreement= 25/30= 0.83

Chance agreement= (16/30) * (19/30) + (14/30) * (11/30) = 0.34 + 0.17 = 0.51

Kappa= (0.83- 0.51)/(1-0.51) = 0.65

Kappa denotes a substantial agreement between the two researchers.

Figure 1.2.1: PRISMA flow chart describing the search results



Overview of the Extracted Studies

Though the search strategy encompassed studies published in the last five years to the date of the data search (Feb. 14, 2022), we did not find any paper published in 2022 that met the inclusion criteria. Out of the 17 reviewed studies, we found (n=4. 23.5%) each within 2019 and 2020 and (n=3, 17.6%) from 2017, 2018, and 2021 respectively. Most of the studies were conducted in the USA (n=7); Canada conducted two studies, and the UK, Greece, China, Netherlands, Australia, France, Croatia, and Japan each conducted one study.

All 17 studies incorporated the RCT method but using different formats and forms such as parallel, double-blind, open labels, and single, two or four arms. The sample size for the trials ranged from (n= 27 to n= 414). The participants were all patients diagnosed with TRD or patients who failed at least two adequate trials of different major classes of antidepressants. Of the 17 papers, 15 were conducted in adult populations age ≥18. Two of the studies were conducted on older adults age 60 and above. Only 1 study evaluated the effectiveness of rTMS in adolescents with a diagnosis of TRD.

Targeted Symptoms

All 17 studies evaluated the reduction in the severity of depression symptoms, the rate of responses or remissions, and the reduction in depression measuring scales. Several studies investigated other confounding factors that positively or negatively affect the results of rTMS. For instance, Carpenter et al. (2017) and Kavanaugh et al. (2018) targeted the effectiveness and safety of a 2-coil rTMS device in their study subjects. Zhao et al. (2019) investigated the effects of rTMS on serum levels of brain-derived neurotrophic factor, interleukin-1b, and tumour necrosis factor-alpha in elderly patients with refractory depression.

rTMS Protocol

In most studies (n= 7), stimulation was conducted with a Magstim Super Rapid stimulator system[140-146]. Four studies also applied the MagProX-100 or R30 stimulator[133, 147-149]. The NeuroStar XPLOR was utilized by two studies [150, 151]. The MagVentureRX-100[152], Magstim VR simulator[153], Medtronic MagPro 30[126], and YRDCCY- 1TMR[154] stimulators were applied in one study each. The Figure-8 coil was the most used (n=7), followed

by the B65-A/P coil (n=4). The remaining studies used either the B70 fluid field-cooled coil or the 70mm Double Air film coil.

Targeted Brain Region of rTMS

The brain site for rTMS application employed by the studies ranged from the left PFC (n=5) [140, 144, 147, 148, 151], and the left DLPFC (n=4) [133, 146, 150, 154]. Four studies indicated DLPFC without specifying left or right [143, 145, 149, 153]; with one study evaluating the effectiveness between left and right DLPFC[126]. Two of the remaining studies[141, 142] assessed the effectiveness of left DLPFC against dorsomedial PFC; and one study evaluated the differences in effectiveness between unilateral and bilateral left DLPFC [152].

Outcome Measures

A wide range of scales was used to measure positive symptoms and reduction in symptoms scales, including; the Hospital Depression Rating Scale (HDRS) was the outcome measure in 9 of 17 studies, while the Hamilton Depression Scale (HAM-D) was used in 6 studies. Other scales, such as the Clinical Global Impression – Severity (CGI-S), Quick Inventory of Depressive Symptomatology (QIDS), Personal Health Questionnaire (PHQ-9), and Beck Depression Inventory (BDI-II) were also used to measure some of the primary or secondary outcomes. Blumberger et al. (2018) defined their primary outcome as the reduction in HDRS-17 score from baseline to the end of treatment (20 or 30 treatments). If participants received most scheduled sessions, and a 4-week, 5-week, or 6-week assessment was available, they were assessed for the primary endpoint. Safety outcomes included adverse event reporting, neurocognitive assessments, vital signs, and Columbia Suicide Rating Scale (C-SSRS) and Young Mania Rating Scale (YMRS) assessments for the various studies.

Table 1.2.2: Summary of studies using rTMS for the treatment of TRD

Author (Year)	Country of origin	Study design	Age range	Number of participants	Targeted Brain Region	Targeted symptom	measurement	Duration of treatment	Coil/ rTMS Parameters/Stimulation method	Outcome/significant improvements/Effect size	Assessment and follow-up	Conclusion	Side effects
Rosen et al. (2021)	USA	RCT	27 - 78 years	49	DLPFC	Change in depression symptoms	HAM-D 24 item	5 - 12 calendar days	MagPro R30 stimulator with a B65-A/P coil (10 Hz,4s on, 10 s off, 120% MT, 4000 pulses/session, 25 min per session) daily in blocks of 5 for a min. of 20 sessions (80,000 pulses), max. of 30 sessions (120,000 pulses)	Average stimulation location for responders vs. non-responders differed in the active but not in the sham condition (P = .02) Average responder location derived from the active condition showed significant negative functional connectivity with the subgenual cingulate (P < .001), while the non responder location did not (P = .17)	Baseline and acute phase	Clinical response to rTMS is related to accuracy in targeting the region within DLPFC that is negatively correlated with subgenual cingulate. Results support the validity of a neuro-functionally informed rTMS therapy target in veterans	None reported
Theleritis et al (2017)	Greece	Parallel-group RCT	18 - 59 years	98	L- DLPFC	Change in depressive symptom severity	HDRS CGI-S	3weeks	Magstim ultrarapid stimulator with a figure-8 magnetic coil. 40 trains of 20 Hz at 100% MT for 2s and intertrain 1 minute, yielding 1,600 pulses per session	Twice-daily sessions might be more effective in both response and remission rates. Patients who had lower baseline HDRS (OR = 0.75, P = 0.014) and CGI-S scores (OR = 0.18, P = 0.001) were more likely to achieve remission	Baseline, and at the end of the first, second, third, and fifth week (follow up)	Twice per day, active HF-rTMS might be more effective than once per day, active HF-rTMS Practically none of the subjects in either sham group achieved remission	Discomfort at the site of stimulation Exacerbation of preexisting headache
Kavanaugh et al (2018)	USA	Double-blind, sham-controlled trial	18 - 70 years	84	L- DLPFC & dorso-medial PFC	Neurocognitive safety of the 2-coil device	HAM-D 24 CGI QLESQ-SF	4 - 6 weeks	2 Magstim Rapid2 stimulators. 70 mm figure-eight coil 10 Hz 120 MT of 4 s and 26 s rest Total of 3,000 pulses per session	No observed negative neurocognitive effects of the 2-coil rTMS device. A significant effect of active rTMS was observed on the quality of episodic memory. Baseline quality of episodic memory predicted depression treatment response and remission	Baseline, one month	2-coil rTMS device is a cognitively safe treatment for TRD that may possess episodic memory-enhancing capabilities	Nil

Carpenter et al. (2017)	USA	Randomized double-blind sham-controlled trial	18 - 70 years	92	L- DLPFC & dorso-medial PFC	Safety and efficacy of an investigational 2-coil rTMS device on depression symptoms	HAM-D 24 C-SSRS ATRQ	4 - 6 weeks	2 Magstim Rapid2 stimulators. single Magstim 70 mm figure eight coil 10Hz120MT in trains of 4 s 26 s rest. 20 daily rTMS. A total 3,000 pulses per session	n = 75 showed significantly greater improvement (mean HAMD-24 change) over time for the active (n = 38) versus sham (n = 37) group after 20 sessions (F = 7.174; p = 0.008) & also at the one-month follow-up (F = 6.748; p = 0.010) Effect size (Cohen's d) for 4-week efficacy of rTMS with the two-coil device (ITT d = 0.58; PP = 0.52)	Baseline, Four weeks	Significant antidepressant effects after only 4-weeks of treatment and was well tolerated	Headache Muscle twitch/spasms
Trevizol et al. (2019)	USA	RCT	≥60 years	43	Unilateral & bilateral L- DLPFC	The primary outcome was the remission of depression.	HDRS SCID-II	3 weeks	Magventure RX-100 Stimulation with a cool B-65 figure-of-8 coil. 120% of RMT 10Hz 15 sessions at 5 sessions/week over three weeks	Participants receiving bilateral rTMS experienced greater remission rates (40%) compared to unilateral (0%) or sham (0%) groups Response to rTMS in the HDRS similarly favoured the efficacy of bilateral rTMS	Baseline, week 3 week 6	Sequential bilateral treatment may be an optimal form of rTMS when used for TRD in older adults	nil
DM Blumberger et al. (2018)	Canada	Randomized non-inferiority trial	18 - 65 years	414	L-DLPFC	Change in the score of depression symptoms as read on HRSD-17	HRSD-17 QIDS-SR BSI-A DS-30	Five days a week for 4–6 weeks	MagPro X100 or R30 stimulator with B70 fluid-cooled coil. 10Hz rTMS at 120% RMT 4s on and 26 s off; 3000 pulses/ session; total of 37·5 min. 120% RMT iTBS triplet 50 Hz bursts, repeated at 5 Hz; 2s on and 8 s off; 600 pulses/ session; a total of 3min 9s	HRSD-17 scores improved from 23·5 (SD 4·4) to 13·4 (7·8) in the 10 Hz rTMS group and from 23·6 (4·3) to 13·4 (7·9) in the iTBS group (adjusted difference 0·103, lower 95% CI –1·16; p=0·0011)	Baseline, after every five treatments and one week. Four weeks, and 12 weeks after treatment	iTBS is non-inferior to standard 10 Hz rTMS in reducing depressive symptoms.	Headache
Iwabuchi et al. (2019)	Canada	RCT	18 - 70 years	27	DLPFC	rTMS Treatment response in TRD	HAM-D BDI	4 weeks	Magstim Su- per Rapid 2 Plus 1 stimulator 70 mm Double Air Film Coil. iTBS at ten bursts of 3 pulses 80%MT at 50 Hz applied at 5 Hz repeated at five runs of 600 pulses with 5 min rest. rTMS at 75 trains of 10 Hz 4 s per train rest 26 s intertrain intervals	rTMS treatment response rate was (55% for rTMS, 69% for iTBS). HAMD scores were significantly reduced at both one month ($p < .001$) and three months ($p < .001$) compared to baseline.	Baseline, Four weeks, 12 weeks	The study demonstrates that resting-state connectivity signatures can predict response to rTMS treatment in patients with resistant depression (irrespective of methodological variations in stimulus delivery)	Nil

BARBINI et al., (2021)	UK	Randomized single-blinded study	-	80	DLPFC	Depressive symptoms in TRD	HDRS	3 weeks	rTMS applied MagstimVR stimulator with a figure-8 coil over the DLPFC	rANOVA (F=2.766, p=0.043) & post-hoc in HDRS-17 showed significantly better scores in favour of group B (rTMS plus BLT) every week (p<0.025, T1: 22.075 vs 17.200; T2: 16.100 vs 12.775; T3: 12.225 vs 8.900)	Baseline, week 1, week 2, week 3	The antidepressant effect of rTMS was enhanced and accelerated by its combination with BLT in treating resistant depression. Both treatment protocols were effective in reducing depressive symptomatology	Nil
P.F.P. van Eijndhoven, et al. (2020)	Netherlands	RCT	Adults	31	L- PFC	Depression symptoms in severe TRD patients	HDRS	4 weeks	Magstim Rapid 2 TMS with a focal, 8-figure shaped 70 mm coil. 110%RMT, 10 Hz 60 trains. 5 s with a resting period of 25 s between each train. 30 min with ,3000 pulses/session, 5 days for 4 weeks, a total of 60,000 pulses	Interim analysis in the form of a mixed ANOVA indicated that there was a main effect of time (F (1,30)=25.4;p < 0.01), but not for treatment (F(1.30)=1.5; p = 0.23), and there was no interaction between time and treatment (F(1,30)=0.45; p= 0.50)	Baseline, after 5, 10, 15, 20 sessions and one-week post-treatment	"Standard" 4-week rTMS treatment is not effective in chronic, severe TRD	Mild to moderate headache
Kito et al. (2019)	Japan	Randomized open-label trial	25 - 75 years	30 (28 completed)	L- PFC	Remissions in depression symptoms	QIDS PHQ-9 YMRS	4-6 weeks	MagPro R30 magnetic stimulator and a Cool-B65 coil. rTMS at 120%MT, 10HZ a total of 3000 pulses/d 5 days a week, for 4-6 weeks (Standardized rTMS) conventional rTMS 75 trains "4s on and 26 sec off" for 37.5 mins with 3000 pulses	13/30 patients (43.3%) showed remission at week 6 There were no significant differences in the remission rate between the conventional 37.5- and 18.75-minute protocol groups (46.7% and 40.0%, respectively)	Baseline, week 2, week 4, and week 6	Compared with conventional, rTMS with 18.75-minute protocol might be equally effective and clinically beneficial in saving the treatment session length	Stimulation pain or discomfort
Filipčić et al. (2020)	Croatia	Two-arm, unicentric, double-blind pilot randomized trial	18 - 68 years	28	DLPFC	Change in depression symptoms and rate of remissions	HDRS BDI-II	10 - 15 days	Magstim Rapid2 stimulator at 120% MT Each session lasted for 20 min at 18 Hz: 2-s trains; 20-s intertrain intervals; 55 trains; a total of 1,980 pulses per session or 3,960 pulses per day	HDRS scores decreased by 13 (95% CI 11–17; 59%, 95% CI 45–73%) and 13 (95% CI 11–14; 62%, 95% CI 54–69%) points in the 10- and 15-day protocols, respectively	Baseline and daily adTMS	adTMS with H1-coil regimen twice daily for ten days or 15 days can be a safe and effective alternative for the treatment of TRD	Nil

Benadhira,et al. (2017)	France	Randomized sham-controlled study	22 - 79 years	58	L-DLPFC	Depression symptoms of TRD	HDRS	1 month (phase 1) 11 months (phase 11)	Magstim Super Rapid stimulator with figure-8 70-mm coils 10 Hz at 110%MT 25 trains of 8 s interval of 30 s, for 5 days per week, for 1 month (20 sessions, M1) for a total of 2,000 pulses per session.	Phase I, 35 patients were responders (60%) and 16 were partial responders (28%) 16 patients (28%) were in remission after one month of active rTMS HDRS scores, a significant difference was found between baseline and M1 ($t(57) = 17.476$; $p<0.001$)	Baseline, weekly during the first month (M1) & monthly for the maintenance phase (M2 to M6	rTMS could represent a novel strategy for preventing relapse in TRD patients who respond to rTMS treatment Weekly maintenance sessions could be useful, showing beneficial effects during the fourth month of treatment.	Nil
Roach et al. (2020)	USA	Clinical trial	≥18 years	61	L- DLPFC	To test whether depressive symptoms changed significantly throughout treatment	PHQ-9	4 - 6 weeks	NeuroStar TMS 120%MT at 10Hz 4 s followed by 10- to 26-s rest for a total of 3.000 pulses/ session. 5 days a week for 4 to 6 weeks, for a total of 90,000 pulses	Average (SD) pretreatment and posttreatment PHQ-9 scores were 15.8 (6.2) and 12.6 (7.6), respectively. Statistically significant reduction in post–PHQ-9 was demonstrated ($P < 0.001$) with 69% of patients lowering their ratings & 31% demonstrating reliable change (improvement >5.64) Effect size (Cohen d = 0.46 on the paired t-test of pre–/post–PHQ-9)	Baseline, week 4, week 6	rTMS for TRD is an adequate treatment or augmentation option for ADSMs with MDD	Nil
Yesavage, et al. (2018)	USA	A double-blind, sham-controlled randomized clinical	18 - 80 years	164	L- PFC	Remission of depression symptoms And the severity of depression symptoms	HRSD BDI	3 weeks	MagPro R30 device with Cool-B65-A/P coil. 10 Hz, 120%MT 5 sessions over 5 to 12 days A total of 4,000 pulses/ session.	Overall remission rate was 39%, with no significant difference between the active and sham groups No significant effect of treatment (odds ratio, 1.16; 95%CI, 0.59-2.26; P = .67)	Baseline, end of treatment & 24-week follow up.	This study supports the clinical observation that a combination of interventions, including rTMS, effectively achieves symptom remission in 39.0% of veterans with MDD who were previously treatment-resistant.	Headache Naso-pharyngitis Suicidal ideation
Croarkin, et al. (2021)	USA	Double-blind, randomized, sham-controlled trial	12 - 21 years	103 Sham (n = 55) Active (n= 48)	L- PFC	Change in the HAM-D 24 score	HAM-D, MADRS, CDRS-R, QIDS-A17-SR, CGI-S	6 weeks	NeuroStar XPLOR TMS 120%MT 10 pulses per sec (10 Hz) for 4 s, and with an interval of 26 s Each treatment session was 37.5 mins (75 trains) for 3,000 pulses per session.	Improvement in HAM-D-24 scores was similar between the active (−11.1 [2.03]) & sham groups (−10.6 [2.00]; P = 0.8; difference [95% CI], −0.5 [−4.2 to 3.3]) Response rates were 41.7% in the active group and 36.4% in the sham group (P = 0.6) Remission rates were 29.2% in the active group and 29.0% in the sham group (P = 0.95)	Baseline Week 4 and Weeks 6	Left prefrontal 10-Hz TMS monotherapy in adolescents with TRD is feasible, tolerable, and safe. A statistically significant difference between 6 weeks of sham and active TMS was not observed.	Suicidal ideation, worsening depression during week 4, suicide attempt during week 6

Fitzgerald et al. (2020)	Australia	Four arm RCT	Adults	300	L- DLPFC & R- DLPFC	Response and remission rates of depression symptoms	HRSD-17	4 weeks	Medtronic Magpro30 magnetic stimulators with fluid-filled 70mm figure-8 coils rTMS at 120% RMT 10Hz for groups (1 and 2), 1Hz for groups (3 and 4). (left standard= 50 trains, left high = 125 trains, right standard= 20 min, right high = 60 min, all per day in a single session)	The rate of response exceeded 45% in all groups. No significant difference between groups on initial analysis of the primary or secondary outcome measures (response rates:standard left = 52.5%, high left = 47.3%, standard right = 49.1%, high right = 48.4%) Greater remission rate with high compared to moderate dose left-sided treatment when controlling for illness duration	Baseline and after 1, 2, 3, and 4 weeks	No consistent association between the antidepressant effect of rTMS & the number of TMS pulses provided across the ranges investigated in this study Increasing TMS pulse number in individual sessions seems unlikely to be a method to substantially improve clinical outcomes.	Nil
Zhao et al (2019)	China	RCT	≥ 60 years	58	L- DLPFC	Serum levels of brain-derived neurotrophic factor (BDNF), interleukin (IL)-1b, and tumour necrosis factor (TNF)-a in elderly patients with refractory depression.	HAM-D 24	1 month	YRDCCY-I TMR apparatus 10 Hz at 80% MT	BDNF levels gradually increased with treatment duration in the rTMS group and were significantly higher compared with the control group. In contrast, IL-1b and TNF-a levels gradually decreased and were significantly lower than in the control group None of the serum factors was affected by rTMS in healthy individuals	Baseline, at 48 hours and 1, 2, 3, and 4 weeks after the first TMS treatment	rTMS increased serum BDNF levels and decreased serum IL-1b and TNF-a levels in patients with depression but had no effect on any of these factors in healthy individuals Results suggest that rTMS may increase BDNF and decrease IL-1b and TNF-a serum levels in elderly patients with refractory depression.	Nil

MT= Motor Threshold, SMA= supplementary motor area; HAM-D 24= Hamilton Rating Scale for Depression–24-item; BDI–II = Beck Depression Inventory, DLPFC = dorsal lateral prefrontal cortex, OFC= orbitofrontal cortex, RMT= resting motor threshold, CGI-I= Clinical Global Impression. HAM -A= Hamilton Anxiety Rating Scale, HRSD= Hamilton Rating Scale for Depression, YMRS=Young Mania Rating Scale, GAF= Global Assessment of Functioning, MCCB= MATRICS Consensus Cognitive Battery. QIDS= Quick Inventory of Depressive Symptomatology, BNCE= Brief Neurobehavioural Cognitive Examination, Questionnaire, SCID= Structured Clinical Interview for DSM-IV, IPF= Inventory of Psychosocial Functioning, BRMAS= Bech-Rafaelsen mania scale, CRSD= circadian rhythm sleep disorder, SCL-90-R= Symptom Checklist-90-Revised, mPFC= medial prefrontal cortex

Outcome Results

Regarding the antidepressant efficacy of rTMS per the findings of this review, all 17 included studies deemed it effective for the treatment of TRD, except for one study in which the authors concluded that standard 4-week rTMS treatment was not effective in chronic, severe, TRD patients [144].

Efficacy of 2-coil rTMS Device

This review also included studies focusing on important confounding factors that either enhance or inhibit the efficacy of rTMS in patients with TRD. For instance, in their study, Kavanaugh et al. (2018) [141] examined neurocognitive data from a randomized, double-blind, sham-controlled trial of an investigational 2-coil rTMS device in TRD patients. The 2-coil rTMS device is reported to stimulate deeper areas of the brain than standard TMS devices, which primarily stimulate cortical brain areas and may therefore have different neurocognitive adverse effects. The patients received 20 minutes of daily rTMS with 10Hz stimulation in active and sham groups. Neurocognitive safety was evaluated at baseline and within 72 hours of the final treatment session. There were no observed negative neurocognitive effects of the 2-coil rTMS device. The results revealed a significant effect of active rTMS on the quality of episodic memory; baseline quality of episodic memory predicted depression treatment response and remission. The results were consistent with another RCT conducted by Carpenter et al. (2017) in which the researchers concluded that delivery of rTMS with the 2-coil device produced significant antidepressant effects after only 4-weeks of treatment and was well tolerated, with an effect size (Cohen's d) f (ITT d = 0.58; PP = 0.52)[142].

Tolerability and Side Effects

The overall effectiveness of any treatment intervention must acknowledge its efficacy as well as any safety and tolerability factors. In this regard, rTMS treatment appears to be reasonably well-tolerated, and the most common side effects were transient headaches, dizziness, and scalp discomfort at the stimulation site. However, Croarkin et al. (2021) [51] reported that one participant in both the sham group and active group developed suicidal ideation. The researchers classified this as not related to the study device. In that same study, a patient developed worsening depression during week four, and another had a suicide attempt during week 6. Still,

all these adverse effects were classified as unrelated to the study device. Yesavage, et al. (2018) [47] also reported cases of suicidal ideation in 3 active and four sham participants, although no suicides or seizures occurred during the study.

Frequency, Intensity of Stimulation, and Duration of Treatment

The frequency of rTMS ranged from as low as 5Hz to as high as 50 Hz. The majority of the studies (13 out of 17) applied the 10Hz frequency, and two studies applied the 50Hz frequency. The intensity of stimulation reviewed in the included studies also ranged from 80% to 120% motor threshold but most of the studies (11) applied the 120% motor threshold in their investigations. The duration of active rTMS treatments ranged from 3 to 6 weeks, while the only maintenance treatment reviewed lasted about 11 months. Concerning the number of magnetic pulses given per treatment session, the range varied from 600 to 4,000 pulses.

Variations in Brain Target

Accuracy in targeting functional brain networks is deemed essential for the treatment efficacy of rTMS in TRD. One study tested whether variations in targeting precision contributed to the failure to find an advantage of active over sham treatment [149]. In this study, the researchers used data from a failed clinical trial of rTMS in veterans to test whether treatment response was associated with rTMS coil location in the active but not sham stimulation, and compared fMRI functional connectivity between those stimulation locations. The results indicated the response to rTMS related to accuracy in targeting the region within DLPFC that is negatively correlated with subgenual cingulate.

Comparing the Efficacy and Tolerability of the Different Forms of rTMS

To establish the true efficacy of rTMS in depression-related conditions, studies are beginning to focus attention on the different forms of rTMS, and compare their effectiveness and tolerability to the standard rTMS. For instance, Blumberger et al. (2018) [133] aimed to evaluate the clinical effectiveness, safety, and tolerability of iTBS compared with standard 10 Hz rTMS in treatment-resistant depression adult patients. Participants were randomized to receive iTBS or 10Hz rTMS. Both groups were assessed at 4-6 weeks for the primary outcome. The HRSD-17 scores for the 10HZ rTMS improved from a baseline of 23·5 (SD 4·4) to 13·4 (7·8) and from 23·6 (4·3) to

13·4 (7·9) in the iTBS group. The adjusted difference was (0·103, lower 95% CI –1·16; p=0·0011). The conclusion was that iTBS is non-inferior to standard 10 Hz rTMS in reducing depressive symptoms in TRD patients, with the advantage that using iTBS can increase the number of patients treated in a day without affecting the clinical efficacy of the treatment.

Maintenance rTMS Treatment

Regarding the efficacy of maintenance rTMS after acute response in depression, Benadhira et al. (2017)[146] evaluated the role of maintenance rTMS in TRD patients who responded to one month of active rTMS in an open-labelled study (phase I). They assessed the benefits of a randomized protocol of maintenance rTMS for up to 11 months (phase II). Clinical assessment was at baseline, weekly during the first month, and then monthly for the maintenance phase. The results indicated that the antidepressant effect of maintenance rTMS sessions appeared three months after the treatment (Month 4). Maintenance rTMS was well tolerated, and no side effects were thus reported. The study suggests that rTMS could represent a novel strategy for reducing relapse in TRD patients who respond to rTMS treatment. This result contrasts with a trial in which patients were randomized to once-a-month rTMS maintenance treatment and an observation-only group. The result failed to predict any statistically significant difference between the two groups at the end of a 1-year study period [155].

Relationship between Pulse Number and Response to rTMS in TRD

The stimulation dosage of rTMS application has increased steadily from the early stages of rTMS trials to date. These increases include the stimulation intensity relative to the motor threshold and the number of pulses used in each treatment session. However, very few studies have sought to evaluate the differences in pulse numbers and the response of rTMS in patients. Fitzgerald et al. (2020)[126] investigated whether the response to rTMS is greater when applied at a higher pulse than a lower pulse. The participants were grouped into four treatment groups:

Standard dose HFL-rTMS: 50 trains of 10 Hz rTMS; 4.5s trains at 120% RMT with a 20.5 s inter-train interval (2250 pulses/session).

1. High dose HFL-rTMS:125 trains of 10 Hz rTMS; 4.5 s trains at 120% RMT; 15.5 s inter-train interval (5625 pulses/session).

2.Standard dose LFR-rTMS: 1continuous train of 1 Hz rTMS; 20 min. at 120% RMT (1200 pulses).
3.High dose LFR-rTMS: 2 trains of 1 Hz rTMS; 30 min. at 120% RMT (3600 pulses/session).

The treatment was applied for four weeks, five days/week for 20 sessions. In terms of results, there was no consistent association between the antidepressant effect of rTMS and the number of TMS pulses across the ranges. Thus, increasing TMS pulse in individual sessions did not seem to substantially improve clinical outcomes.

Effect of rTMS on Serum BDNF, IL-1b, and TNF-a Levels in TRD

Inflammatory factors such as interleukin (IL)-1 [156], tumour necrosis factor (TNF)-a [157], nuclear factor-kappaB (NF-jB) [158], and brain-derived neurotrophic factor (BDNF) have been implicated in the causative mechanism of depression[159]. However, there are limited studies on the specific effects of rTMS on these inflammatory factors in patients with TRD. In the study by Zhao et al. (2019) [154], elderly depressed patients were randomized into two groups of 29, with one group receiving rTMS and the other as a control group, while another group of 30 healthy volunteers were given rTMS. Serum levels of BDNF, IL-1b, and TNF-a were measured before the study and at 48 hours and 1, 2, 3, and 4 weeks after the first TMS treatment. rTMS increased serum BDNF levels and decreased serum IL-1b and TNF-alpha levels in patients with depression but had no effect on any of these factors in healthy individuals.

Discussion

The studies included in this review were RCTs published between 2017 and 2022 (though none of the eligible studies was extracted from 2022). Overall, these studies are characterized by their varying sample sizes,from small to high, and are heterogeneous in terms of demographic and clinical variables and choices of brain targets of rTMS stimulation, treatment duration, and stimulus intensity. The 17 studies reviewed suggest that rTMS has a robust therapeutic effect in the treatment of TRD. The regional breakdown of the extracted studies revealed that most studies (n=9) were conducted in North America. Depression is a global burden and a debilitating condition that exacts a serious personal, social, and economic toll [160] and is associated with extreme consequences such as increased mortality, disability, and secondary morbidity [161].

The World Health Organization has reported that depression ranks among the leading causes of disability worldwide [162].

All but one study [144] reported consistent improvements in depressive symptoms through higher or accelerated doses and patient-centred stimulation protocols across the major outcome domains. These positive outcomes were enhanced by the accurate and advanced neuro-navigational technologies, the degree of precision in the techniques of detecting the DLPFC, and the application of modern coil geometries. Since rTMS treatment is rapidly gaining popularity as a treatment modality for TRD, attention should focus on global accessibility, reliability, and efficacy through standardized protocols and evidence-based guidelines.

Though the primary objective of all 17 studies was the reduction and remission of depressive symptoms in TRD patients, some of the studies evaluated other confounding factors that affect the efficacy of rTMS intervention in the management of TRD. Two of the 17 studies evaluated a 2- coil rTMS device[141, 142]. Although the antidepressant mechanism of multi-coil stimulation and whether it differs from that of standard single-coil stimulation is still being investigated, studies have reported that the depth and direction of electromagnetic field capable of penetrating the scalp and tissues of the brain to activate neurons during the process of rTMS application depend on the shape and size of the coil through which current is passed [128, 129]. Until recently, most rTMS depression interventions have been performed using the figure-8 or butterfly-shaped coils deemed to emit relatively superficial cortical stimulations. However, the pathophysiology of depression is assumed to involve deeper frontal brain regions [163, 164]. Therefore, the 2-coil rTMS device was designed to target brain pathways for possible deeper cortical stimulations and may represent a novel technique to neurostimulation for patients with TRD.

There were limited data on maintenance rTMS treatment for TRD. Only one of the 17 reviewed papers evaluated the efficacy of maintenance rTMS after an acute response in the treatment of TRD. Its results indicated that the antidepressant effect of maintenance rTMS sessions appeared three months after the treatment. Maintenance rTMS was well tolerated, and no side effects were reported [146]. This result contrasts with an earlier study that investigated 12-month outcomes comparing two maintenance TMS approaches; a scheduled, single TMS session delivered monthly versus an observation-only group, which found no significant group differences on any

outcome measure [155]. This suggests that, although rTMS could represent a novel strategy for reducing relapse in TRD patients who respond to rTMS treatment, there is little information on its maintenance use. As explained in the literature, maintenance treatment is not the mere reintroduction of rTMS in situations of a relapse but rather an intentional, timely scheduled regimen of rTMS treatment for a fixed period after an acute rTMS treatment [120]. Much more research needs to be conducted, and the true effect of maintenance rTMS treatment in TRD ascertained.

Regarding brain targets, the DLPFC was the most frequent (n=9) rTMS site targeted with the primary preference for the left DLPFC; none of the studies applied rTMS to the right DLPFC. Only one study compared the relationship between pulse number and response to rTMS in depression between the left and right DLPFC [126]. The left PFC was also utilized in six studies, which reported improvement in depressive symptoms. The left DLPFC represents an essential brain region for neurocognitive performance connecting to the frontosubcortical brain regions [165]. The dysfunctions of this brain region are believed to be involved in the pathogenesis of symptoms of depression and cognitive impairment[97, 101]. Stimulation of the DLPFC is significantly associated with enhancing the neurocognitive domains, and rTMS appears to reduce depressive symptoms with subsequent improvement in the neurocognitive functions of TRD patients [128, 166, 167].

According to our findings, all 17 reviewed studies applied rTMS with a high frequency ranging from 18Hz to 50Hz in their subjects. Studies have it that the effectiveness of rTMS treatment to modulate neural activities much depends on the frequency applied and other stimulation parameters [168]. High-frequency rTMS over the DLPFC has been used in most recent trials, a choice guided by positive outcome results for this approach[169]. This may explain the positive outcomes found by our reviewed studies since the rTMS targets were mostly over left-DLPFC with high frequencies. Again, our results revealed a trend where all included papers applied rTMS with high stimulus intensity, ranging from 80 MT to 120 MT. Though not all RCTs that apply higher stimulating intensities end up with larger effect sizes, stimulus intensity is deemed an essential component in inducing lasting changes in cortical excitability, which is believed to be responsible for the antidepressant effect rTMS[169]. This report is consistent with our findings since all studies applied high stimulating intensities and still had the desired treatment effects.

Overall, rTMS treatment in managing TRD seems safe and tolerable. All 17 studies reported on treatment side effects and tolerability of rTMS. The most common side effects across all studies were scalp pain, transient headaches, dizziness, and discomfort at the stimulation site but these did not lead to discontinuation of the treatment. However, two studies reported cases of suicidal ideation and worsening depressive symptoms but no suicides or seizures occurred during treatment s[147, 151]. Consistent with data from earlier studies [170-173], our results add to the evidence that supports the safe and tolerable nature of rTMS in TRD.

Cost and Policy Implications for rTMS in TRD

The global burden of disease study 2010 ranked MDD as the 2nd leading cause of disability globally, accounting for an estimated 2.5% of global disability-adjusted life-years and 8.2% of global years lived with disabilities[174]. Among the many treatment modalities for the management of TRD, rTMS is considered a clinically safe, productive, and patient's preferred treatment modality in resistant depression. However, the treatment benefits of rTMS need to be weighed against its treatment-related cost. A study evaluated the cost-effectiveness of rTMS vs ECT for TRD from Singapore's societal perspective. The results demonstrated that, compared to ECT, rTMS was associated with lower total cost (SGD 23,072 vs SGD 34,922) and quality-adjusted life yeas (QALYs) (0.6862 vs. 0.7243) over one year. Thus, rTMS was considered highly cost-effective relative to ECT[175]. Their result was consistent with a prospective economic evaluation of ECT and rTMS in the United States. The model provided support for the economic benefit of rTMS versus ECT alone in nonpsychotic depression. Their results revealed the cost of acute treatment of rTMS was $1,422.00 versus $7,758.40 for ECT [176].

The comparative cost-effectiveness can help to inform decisions on resource allocation and treatment utilization. Globally, healthcare resources are mostly scarce relative to needs or wants, and the essence of an economic evaluation is to inform the choices that decision makers face in critical situations. Yet, there is a paucity of literature on the cost-utility analysis of TRD management. Therefore, investigating the resource implications and cost-effectiveness of rTMS offers crucial information that may help the choice of treatment for people with treatment-resistant depression. Future studies should focus on studying the cost-benefit analysis of rTMS in TRD.

Limitations

This review has several limitations. A main one relates to the small number of studies included for qualitative synthesis and analysis. However, our search strategy considered only studies published in English and within the last five years (2017 – 2022). Secondly, although we tried to identify all necessary studies for this review per our eligibility criteria, we may have missed some relevant studies, particularly those published in other languages. Finally, the eligibility criteria only took into account RCTs, and further, no meta-analysis was run on the reported data.

Conclusion

rTMS treatment is gaining popularity in the treatment of depressive conditions, and evidence supports the efficacy of rTMS in TRD. The treatment is considered effective, safe, and tolerable in the management of TRD. However, while progressive evidence supports its efficacy in an acute setting, there is limited literature to support long-term benefits and maintenance treatment in patients with TRD. Large-scale clinical trials are needed to compare the therapeutic efficacy and efficiency of the newer forms of rTMS with the consistency of stimulating parameters across all treatment arms. Finally, to establish a standardization of rTMS application, more studies are required to address frequency, intensity, pulse numbers, and localization.

1.3: The Use of Repetitive Transcranial Magnetic Stimulations for the Treatment of Bipolar Disorders. A Scoping Review

Medard Kofi Adu, Ejemai Eboreime, Adegboyega Oyekunbi Sapara, and Vincent Israel Opoku Agyapong. Behav. Sci. 2022, 12(8), 263; https://doi.org/10.3390/bs12080263 Available at: https://www.mdpi.com/2076-328X/12/8/263

Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a relatively new, noninvasive neuromodulation technique that involves the application of magnetic pulses on hyperactive or hypoactive cortical brain areas. rTMS is considered a highly therapeutic tool in many neuropsychiatric conditions. Despite its wide and continuous usage for the treatment of psychiatric disorders, information about the use rTMS in bipolar disorders is limited and not well-established literature.

Objectives: This scoping review intends to (1) explore the relevant literature available regarding the use of rTMS for the management of bipolar disorders. 2) garner evidence in support of its use in the treatment of bipolar disorders and for recommendations on future clinical and research work.

Method: We developed an operationalized search strategy, which was applied to electronically-conduct data search in five research databases (MEDLINE, CINAHL, Psych INFO, SCOPUS, and EMBASE) using all identified keywords and index terms across all the databases to identify evidence-based studies. We included articles published with randomized control designs that aimed to treat bipolar disorders with rTMS. A total of 9 studies were eligible for this review. The search results are up-to-date as of the final date of electronic data search, December 20, 2020. Only full-text published articles written in English were reviewed. Review articles on treatment with rTMS for conditions either than bipolar disorders were excluded.

Conclusion: The application of rTMS as a treatment intervention for bipolar disorders looks promising despite the diversity in terms of its outcomes and its clinical significance. However, to draw a definite conclusion on the clinical effectiveness of the technique, more randomized controlled studies with well-defined stimulation parameter needs to be conducted with large sample sizes.

Key words: Repetitive transcranial magnetic stimulation, bipolar disorder, mental health; and treatment

Introduction

Bipolar disorder is a chronic episodic mood illness characterized by manic episodes that come with an alternating episode of depression[177]. It has an unpredictable course, and can result in deficiencies in cognition, functional, and occupational functions[177-179]. Bipolar disorder is among the main causes of youth disability[180], and results in an elevated rate of mortality, especially death caused by suicide[181]. Bipolar disorder is deemed to have the highest risk of suicide compared to all other mental health conditions[182]. Suicidal tendencies in bipolar disorder vary, and depend upon the phase of the condition. Primarily, suicidal behaviour in the illness occurs during the mixed phase and the depression phase[183, 184].

Individuals with the diagnosis of bipolar disorders have a greater prevalence of medical and psychiatric comorbidities. The lifetime prevalence of bipolar disorders is over 1% of the global population irrespective of socioeconomic status, race or nationality, with the annual prevalence estimated at 0.6% for the US population. [180, 185]. There is a high prevalence in men compared to women, with the prevalence ratio at 1.1:1[185]. The most common and strongest risk factor is having a family history of the condition; and the chances increase with the degree of kinship to affected individuals[181].

The basic step in the treatment of bipolar disorder is the confirmation of the presence of mania or hypomania. Also, since the approach to therapy differs for various clinical features such as depression, hypomania, mania, mixed affective state, and euthymia, the state of the mood of the patient should be defined[177, 186]. Several factors affect the therapeutic efficacy of the pharmacological and psychotherapeutic intervention in the management of bipolar disorders, and should be observed to optimize efficacy[187]. These factors may include the many medical and psychiatric comorbidities, the effect of previous or current medications, and the willingness of patients to receive and adhere to treatment protocols[181].

Psychopharmacological agents are considered the first-line treatment for bipolar disorder; and their therapeutic efficacy has been tested across the different phases of the illness[188]. Despite their proven effectiveness, pharmacological agents for the management of bipolar disorder present with some limitations, which become a matter of concern. Notable among them is the rate of non-response to adequate pharmacotherapy[189], the unbearable side effects with their related nonadherence and discontinuation of the medication[190, 191], and the possible increased medical burden due to the different medication prescribed by clinicians to cater for the

different symptoms and comorbidities [192, 193]. Amid these limitations and the quest for alternative efficacious treatment intervention[193], transcranial magnetic stimulations (TMS) have been evaluated and found to be a treatment option for patients with bipolar disorder[194].

TMS was introduced as focal brain stimulation in 1985 as a safer and painless way of studying the central nervous system, especially to stimulate motor cortex and to assess the human central motor pathways[122]. TMS has become a major research tool in mental health care due to its ability to produce an explicit effect on a number of measures of brain function[195, 196].

TMS is a noninvasive treatment technique in which brain networks are modulated by the application of magnetic current in the hypoactive or hyperactive cortical areas of the brain[197]. Magnetic pulses are introduced by placing an electromagnetic coil over the patient's scalp. The magnetic pulses from the coil then penetrate the skull into the cortical region of the brain with a resultant activation of neural changes in the brain[198]. The magnetic pulse can be delivered in a repeated manner to produce a long-term change in the neural activity[199]. There can either be an increase or decrease in cortical excitability through a high frequency application- (>5Hz) or low frequency application of –(1Hz) stimulation[200, 201]. TMS, when delivered in trains of repetitive pulses (rTMS), is very flexible and, depending on the brain target and frequency applied, could inhibit or induce local and remote brain activity[202]. An optimum rTMS is achieved when delivered in a train of repetitive pulses with similar stimulus intervals[199, 203].

Several technological advances have been made to the application of rTMS. The current generation of rTMS studies has borne the notable limitations in earlier clinical trials and sought to solve them[204]. The modern generation of studies demonstrate better outcomes through higher or accelerated dosing protocols[205, 206], extended treatment durations[207], patient centred stimulation frequencies[208], and a clear outline for bilateral stimulations[209].

Generally, rTMS treatments are comparatively simple and easy to administer, and well-tolerated by patients[210]. Major advantages of rTMS are its relative safety and lack of major side-effects[211] and its cost-effectiveness as an alternative to more costly treatment interventions, such as electroconvulsive therapy[212].The most common side effect reported by patients is temporal pain in the scalp, which normalizes with moderate increase in the intensity of rTMS[213]. Furthermore, vasovagal syncope may also be present at the initial phases of the treatment, and care must be taken to keep the patient seated. Earplugs can help reduce the clicking sound during rTMS[214].

rTMS has been cleared for use in Canada and in the United States since 2002 and 2008 respectively[215, 216]. It is advocated and recommended by the National Institute for Health and Care Excellence (NICE), 2015) and sanctioned by the Food and Drug Administration (FDA) as a treatment for treatment-resistant depression in the USA[217, 218].

The high number of publications on superficial brain stimulation for mental disorders is based on rTMS for major depression disorder[219]. Base on its versatility and efficacy, rTMS use has been expanded to other major mental health conditions, including bipolar disorder [220]. The proof of the therapeutic benefits of rTMS, as reviewed by some European expects[221], drew attention to the analgesic effect of high frequency (HF) rTMS of the motor cortex and the antidepressant effect of HF rTMS of the dorsolateral prefrontal cortex.

rTMS has been evaluated to be effective in randomized double-blind sham-controlled trials (RCT) in treating unipolar depression, however, it is unclear whether its efficacy extends to bipolar depression[222]. Data from a study suggest that rTMS appears superior to sham rTMS for the management of bipolar depression over 2 weeks[223], while a second study found a less significant difference in response between the rTMS and the sham group in 23 patients[224]. Although the indication for the application of rTMS in bipolar disorders is strong, the evidence is mixed and limited.

Generally, scoping reviews aim to assess the literature for the potential size and scope of research on specific topics of interest[225]. Thus, this review paper aims to explore the literature and inform on current research and main findings related to the potential therapeutic efficacy of the application of rTMS across symptomatic and remitted stages of bipolar disorder.

METHODS

A search strategy was developed and applied to electronically conduct data searches in five databases (MEDLINE, CINAHL, Psych INFO, SCOPUS, and EMBASE) using all identified keywords and index terms across all the databases to identify empirical studies and randomized controlled trials. Key terms included: repetitive transcranial magnetic stimulations, obsessive compulsive disorder, post-traumatic stress disorders, bipolar disorders and treatment. Although a larger search strategy involving results for the use of rTMS for treatment of three major mental disorders (OCD, PTSD and Bipolar Disorders), this paper reports only on and discusses the results for bipolar disorders. Table 1 shows a sample of the search strategy on Medline.

Table 1.3.1: Medline search strategy

Search strategy	Results
Exp *stress disorders, post-traumatic/ or (PTSD or ((posttraumatic or post traumatic or combat or war or trauma*) adj1 (stress* or neurosis or neuroses or nightmare*)) or ((traumatic or acute) adj (stress disorder* or stress symptom*)) or shell shock* or shellshock*).mp.	46,596
Exp obsessive-compulsive disorder/ or bipolar disorder	54,776
(Bipolar or bi-polar or manic-depress* or mania or obsessive-compulsive disorder* or OCD).mp.	102,961
1 or 2 or 3	147,991
Transcranial magnetic stimulation/	11,653
(Repetitive transcranial magnetic stimulation or rTMS).mp.	5,423
5 or 6	13,372
4 and 7	492

Inclusion and Exclusion Criteria

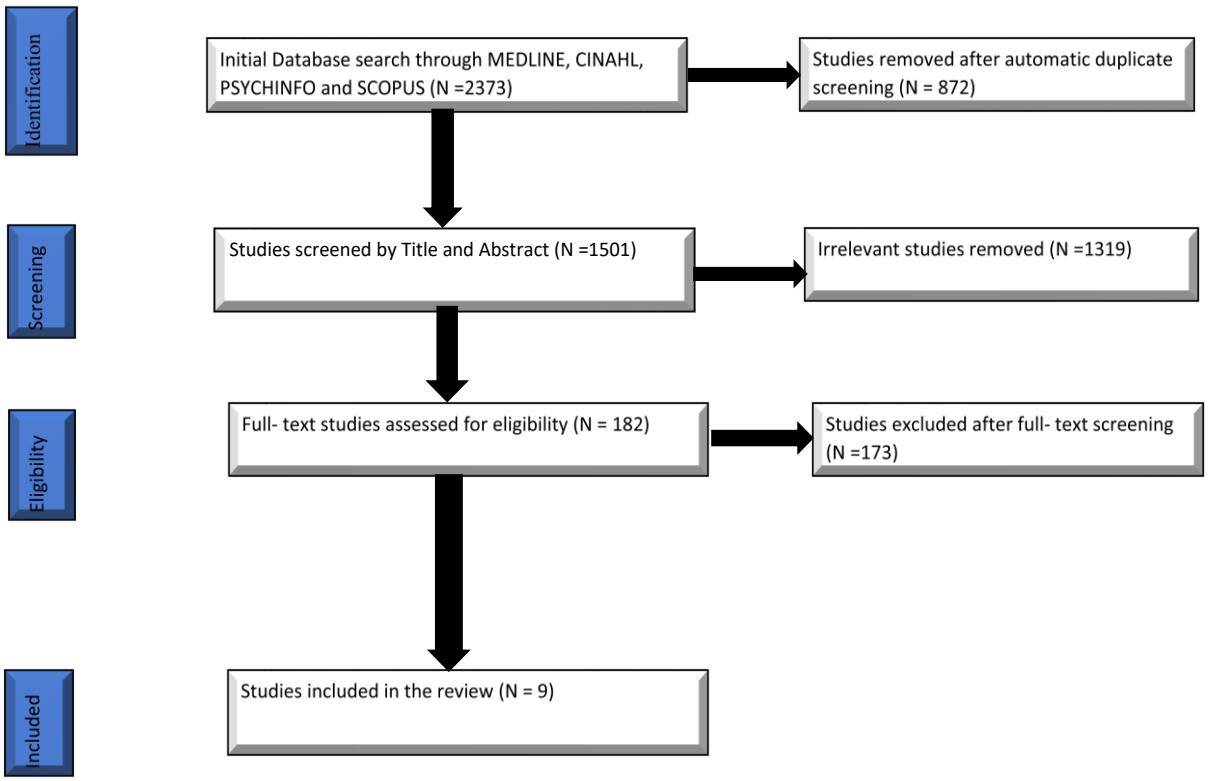
Inclusion criteria included studies involving completed randomized controlled trials (RCT) of rTMS as treatment intervention for bipolar disorders. Open label trials on bipolar disorders using rTMS as a treatment intervention were also included. The review only utilized full text articles and studies published in English.

Exclusion criteria included studies with rTMS as a treatment for conditions other than bipolar disorders, studies with rTMS treatment for bipolar disorders with comorbidities, studies with rTMS as a combined therapy with pharmacotherapy or any other interventions, study protocols as well as experiments of rTMS not designed for treatment for bipolar disorders, and systematic reviews and meta-analysis.

Two independent reviewers (MKA; EE) were employed to screen titles, abstracts and full texts and found articles that conformed to the objectives of the scoping review. Thematic classifications were done by the two reviewers. Where conflicts in classification existed, the articles in question were scrutinized and consensus reached between the two reviewers.

Through the search strategy and the use of the Covidence software, we identified a total of **2,373** studies from the electronic databases searched. The Covidence software automatically screened and removed **872 studies** as duplicates from the searched items. The remaining items (**1,501**) were screened against the eligibility criteria set by the authors, and based on the title and abstract only. The title and abstract screening brought the total records left for full text screening to **182** studies after the exclusion of **1,319** items. The remaining items were full-text screened by the two reviewers, who excluded **173** studies from the study. A total of **9** studies were then eligible for this scoping review. Figure 1.3.1 describes the PRISMA—flow diagram summarizing search process and results

Figure 1.3.1: PRISMA flow diagram summarizing search process and resource



RESULTS

Summary of Results

A qualitative descriptive approach was used to categorize the reviewed studies based on name of authors, year of publication, country of origin, study design, sample size, targeted brain regions, targeted symptoms, measurement tools, duration of treatment, coil/rTMS stimulations, outcome/significant improvements, assessment and follow-up, conclusion, and side effects of the intervention. All nine studies under review applied RCT designs, which include the parallel, double-blind, and open-labels methods. The study sample ranged from (n= 11 to n= 76). The detailed methodological information extracted and summarized from the various studies is presented in table 1.3.2.

TABLE 1.3.2: Summary of studies using rTMS for the treatment of bipolar disorders

Author (Year)	Country of origin	study design	Number of participants	Targeted Brain Region	Targeted symptom	Measurement	Duration	Coil/ rTMS Parameters/ Stimulation method	Outcome/significant improvements	Assessment and follow-up	Conclusion	Side effects
Nahas et al. (2003) [226]	USA	RCT	23 participants	Left prefrontal rTMS	Depressive symptoms of bipolar affective disorder	HDRS, YMRS, HAM-A, GAF	2 weeks	5 Hz, 110% MT, 8 sec on, 22 off, over 20 min.	% change in HRSD at 2 weeks compared with day 1 of treatment (clinical response defined as >50% decline in HRSD or <10)	Day 1 and day 10	Daily left prefrontal rTMS appears safe in depressed BPAD subjects, and the risk of inducing mania in BPAD subjects on medications is small	Nil
Dell'Osso et al. (2011) [227]	Chicago USA	A 1-Year Follow-Up Study (prospective study)	11 patients	Right dorsolateral prefrontal cortex	Depressive recurrences Manic recurrences Mixed recurrences	HAM-D score, YMRS	3 weeks	(1 Hz), 110% MT,300 stimuli/d for 3 weeks	Results showed that the achievement of remission after acute rTMS was predictive of maintenance of response at 1 year	From the beginning of the study (T1) and at 3 (T2), 6 (T3), and 12 months (T4),	This first report on the long-term discontinuation effects after acute rTMS suggests that immediate remission is predictive of sustained benefit after 1 year	Nil
M.L. Myczkowski et al. (2018) [228]	Brazil	Randomized, placebo-controlled trial	50 patients	Left DLPFC,	Symptoms of depression, anxiety, and mania, as well as rTMS adverse effects	YMRS,	4 weeks	H1-coil 55 trains at 18 Hz and 120% MT total of 1980 pulses/day or 39,600 pulses per treatment for 8 wks, 4 wks of 20 daily sessions and a follow-up	Deep TMS treatment for bipolar depression, cognitive improvement in all domains was observed. This suggests that deep rTMS is a safe antidepressant intervention in bipolar patients, with marked	Baseline and after 4 and 8 weeks.	This exploratory study provide evidence on the cognitive safety of H1-coil TMS for BD patients. Putative pro-cognitive effects of rTMS in BD were not observed	Nil

								of 4 wks with no TMS sessions	cognitive impairment			
L.-L. Yang et al. (2019) [229]	China	Single-blind randomized controlled trial	60 patients	left DLPFC,	Cognitive impairment in BD participants in remission	HDRS, YMRS, MCCB	10 days	High speed figure-of-eight coil. fifty 5-s, 10-Hz trains delivered at 110% of the MT at 30-s interval for 10 days	High-frequency rTMS improves neurocognitive function in bipolar disorder	Baseline clinical assessments and follow-up clinical assessments	Short-term rTMS can improve cognitive function in BD patients	Mild dizziness
Y. B. Yang et al. (2020) [230]	Canada	retrospective chart review	76 patients	L-DLPFC	change in clinician-rated depressive symptoms	HRDS-21,	Between 2 and 6 weeks	Magstim Super Rapid-2 device 10 Hz, 3,000 pulses, 4 s trains and 26s intertrain interval,120%MT	Patients with BD are less likely to achieve clinical response than those with unipolar depression with high-frequency L-DLPFC rTMS	baseline HRDS-21	The study suggests that patients with BD are less likely to achieve clinical response than those with unipolar depression with high-frequency L-DLPFC rTMS	Nil
A.L. PHILLIPS et al. (2020) [231]	USA	Naturalistic retrospective patient data study	71 patients	L-DLPFC	Depression response and remission rates among patients with bipolar disorder	QIDS, HRDS	2 weeks, followed by 2 weeks of once-daily rTMS, for a total of 28 sessions with 2daily	10 Hz rTMS 100% to120%MT over 3,000 pulses per session. F3 coil positioning	TRD Patients with bipolar TRD responded equally well as patients with unipolar TRD and showed trends for a possible early response	2 weeks, followed by 2 weeks of once-daily rTMS, for a total of 28 sessions with 2 daily	The literature supports the use of high-frequency rTMS over the LDLPFC in the treatment of bipolar TRD	Nil

							sessions skipped			sessions skipped		
Dell_Osso et al. (2009) [232]	Italy	An open-label design	11 right-handed patients	R- DLPFC	Efficacy of low-frequency rTMS in bipolar disorders	HAM-D, CGI-S, YMRS	3 weeks	1 Hz and at 110%MT 8-figured coil for a total of 15 days with five trains of 60 stimuli, 300 stimuli per session	Augmentative low frequency rTMS of the right DLPFC combined with brain navigation was effective and well tolerated in a small sample of drug-resistant bipolar depressive patients	After baseline assessment symptoms were assessed weekly throughout	Augmentative low-frequency rTMS of the right DLPFC combined with brain navigation was effective and well tolerated in a small sample of drug-resistant bipolar depressive patients	Nil
F RACHID et al. (2017) [233]	Switzerland	A naturalistic clinical treatment	22 participants (10 received 5Hz and 12 received 10Hz)	L-DLPFC	Changes in depressive symptoms and effects of 5Hz and 10Hz	MADRS CGI-S	4 weeks	5Hz or 10 Hz. rTMS over the LDLPFC. 120% to 130% of MT, 40 to 60 trains, 10 seconds 2000 to 3,000 pulses per session	Study demonstrated clinical response, safety, feasibility, and 100% adherence rates using 5 or 10 Hz rTMS in a routine clinical setting in patients with treatment-resistant unipolar and bipolar depression.	baseline, week 1, week 2, week 3, and at week 4	rTMS applied to the left dorsolateral prefrontal cortex was safe and effective in an important subset of outpatients with a moderate to severe MDE in a naturalistic setting	nil
P.B. Fitzgerald et al. (2016) [234]	Australia	A parallel design two arm double blind rando-mised controlled trial	49 participants	sequential manner: to the right DLPFC and then the left DLPFC in the same order in all subjects	Changes in depressive symptoms	YMRS HAMD	4 weeks	70mm figure of 8 coils. 1 Hz R-DLPFC in a single train of 1000 pulses and L-DLPFC 10 H 10% RMT.	No significant difference in mean reduction in depression rating scale scores or response rates between active and sham stimulation.	Baseline to week 4.	The study failed to demonstrate a significant benefit of sequential bilaterally applied TMS in a group of patients with bipolar depression.	nil

MT—motor threshold, DLPFC—dorsal lateral prefrontal cortex, RMT—resting motor threshold, CGI-I—clinical global impression, HRSD—Hamilton Rating Scale for Depression, YMRS—Young mania rating scale, GAF—Global Assessment of Functioning, MCCB—MATRICS consensus cog-nitive battery, QIDS-quick inventory of depressive symptomatology, BRMAS—Bech–Rafaelsen mania scale.

Outcome Measures

The following scales were used to measure outcomes and reduction in symptoms scales: HDRS, YMRS, HAM-A, GAF, MADRS, and CGI-S. Safety outcomes measures included adverse effects reporting, neurocognitive assessments, and vital signs assessments.

Frequency, Intensity of Stimulation, Duration of Treatment, and Brain target

The data gathered from the included studies support the use of both high [228, 229, 231, 233] and low frequency rTMS [226, 232] at 110% or 120% motor threshold; and there was no clear superiority between the effects of the low or high frequency rTMS. The treatment duration of rTMS application ranged from 2 to 6 weeks for all the included studies. Six of the nine studies applied rTMS over the L-DLPFC[226, 228-231, 233] , 2 over the R-DLPFC[227, 232], with the remaining study applying rTMS to left and right DLPFC. Despite the diversity in the choices of target to the brain regions, there seem to be no clinical difference between the target sites (left versus right DLPFC).

Results

Of the nine studies under review, seven reported significant positive outcomes and significant bipolar disorder symptoms improvement. Two studies failed to identify any superiority of active rTMS over sham with respect to bipolar disorder symptoms. The results suggest that rTMS treatment was well tolerated with no significant side effects, however, some study participants made a few reports of mild headache, dizziness, and scalp pain, which improved spontaneously after completing the sessions of rTMS.

DISCUSSIONS

Summary of Main Results

The nine studies under review in the present scoping review demonstrate that rTMS may be a safe and clinically efficacious treatment intervention for a difficult-to-treat condition such as bipolar disorder. The review recorded some significant improvements in symptoms of study subjects. However, the efficacy of rTMS on bipolar disorder was inconclusive due to the limited number of studies under review. Overall, rTMS appeared to be related to mild side-effects, and was well tolerated by patients.

Targeted Brain Regions

Of the six studies[226, 228-231, 233] that evaluated the efficacy of rTMS applied over the L-DLPFC, overall, their results supported the idea that L-DLPFC is a safe site and effective for the treatment of the symptoms of bipolar disorders. For instance**,** in the study by M.L. Myczkowski et al. (2018)[228], in a randomized placebo-controlled trial of 50 participants over the left DLPFC evaluated the clinical efficacy and safety of H1coil rTMS for bipolar disorder patients from a cognitive perspective. The H1 coil is clinically important since cognitive dysfunction is common and debilitating in such patients, persisting even after adequate treatment. The results demonstrate cognitive improvement in all domains of bipolar depression. This suggests that deep rTMS is a safe antidepressant intervention in bipolar patients with marked cognitive impairment.

On the other hand, a previous review conducted on the efficacy of rTMS in bipolar disorder demonstrated that rTMS targeting the R-DLPFC was effective at reducing symptoms compared with sham[235]. This result is consistent with our findings where the two studies[227, 232] that applied rTMS over the R-DLPFC yielded some consistent positive outcomes in the symptoms of bipolar disorder among study participants.

Furthermore, the long-term efficacy after acute augmentative rTMS over the R-DLPFC in bipolar depression was evaluated by Dell'Osso et al. (2011) in a one-year follow-up study of 11 subjects[227]. After one year of follow-up, results indicated that the achievement of remission after acute rTMS was predictive of maintenance of response at one year. On the other hand, the absence of acute rTMS response predicted the absence of subsequent response in the long term.

Several factors may have accounted for the differences in effectiveness of the application of rTMS across the major domains of bipolar disorder. For instance, the sample sizes (n= 11 to 76) were too small from which to draw a definite conclusion. Secondly, a very important factor may be that the rTMS treatment was delivered at different phases of the bipolar illness and targeted different clinical symptoms. This would strongly affect the clinical outcomes and efficacy.

Thirdly, the different measuring tools used to evaluate similar outcomes across studies make it difficult to compare and evaluate the results against similar study findings. It is therefore difficult to understand which rTMS parameters lead to the most significant outcomes and treatment response in bipolar disorder. However, due to the several comorbidities and presentation of bipolar disorder, it may seem unrealistic to think uniquely of an optimal or even a standardized

rTMS protocol that will work across studies of the different comorbidities, even if they target similar symptoms.

Furthermore, an important factor noticed is evaluation of the longevity and time course effects of rTMS. The majority of studies reviewed evaluated the treatment outcomes of the various interventions immediately after the last session of rTMS and up to a few months following, with only a handful extending beyond this timeframe (Dell'Osso et al. 2011). Considering the chronic, debilitating and highly prevalent nature of bipolar disorders, evaluating the long-term therapeutic effects of rTMS intervention is of great importance. Therefore, it would be of high clinical significance and research value to estimate the sustainability of treatment effects and, specifically, maintenance strategies following response or remission with rTMS.

Tolerability/Side Effects of rTMS

The general essence of any treatment modality must acknowledge its effectiveness, safety, and tolerability concerns. rTMS is generally noted in the literature to be tolerable with mild side effects in the patients to whom they are applied. Findings from this review suggest that the rTMS application was highly tolerated with mild side effects such as mild headache, dizziness, localized scalp pain, and stimulation of facial nerves during administration.

Finally, neurocognitive processes can be enhanced by rTMS in bipolar disorder patients in remission. rTMS is deemed relatively safe, simple, and effective in treating cognitive dysfunction in bipolar disorder patients. Despite some evidence that rTMS may produce clinical significance in the treatment of bipolar disorders, the pathophysiology and clinical complexities of bipolar depression remain in need of further exploration for more precise treatment modalities. More research is therefore needed in the area of rTMS to determine the specifics in stimulation parameters, effective treatment durations and the brain region with the most significant effect.

Limitations

Finally, this scoping review acknowledges some limitations. First and foremost, our search strategy considered only studies published in English. Although every effort was made to identify all relevant studies for this review per our eligibility criteria, we might have missed some important studies without knowing. Therefore, while the data evaluated suggest that rTMS has the potential to be a clinically significant and effective therapeutic intervention to manage the

symptoms of bipolar disorders, more robust RCTs with higher sample sizes, longer treatment durations and better stimulation parameters need to be conducted before a firmer conclusion can be drawn. Again, the heterogeneity of bipolar spectrum disorder and the fact that each study targeted different phases of the illness make it difficult to generalize the outcome.

CONCLUSION

Although the data gathered from the studies reviewed are diverse in their outcomes and clinical viability, enough evidence shows that rTMS is a promising treatment intervention for bipolar disorders. However, to draw a definite conclusion of the clinical effectiveness of this treatment technique, more studies with well-defined stimulation parameters must be conducted with large sample sizes.

1.4: The use of Repetitive Transcranial Magnetic Stimulation for treatment of obsessive-compulsive disorder: A Scoping Review.

Adu, M. K., Eboreime, E., Sapara, A. O., Greenshaw, A. J., Chue, P., & Agyapong, V. I. O. (2021). The use of repetitive transcranial magnetic stimulation for treatment of obsessive-compulsive disorder: a scoping review. Ment Illn, 13(1), 1-13. doi:10.1108/mij-05-2021-0002. Available at: https://www.emerald.com/insight/content/doi/10.1108/MIJ-05-2021-0002/full/html.

Abstract

Purpose

This paper aims to explore the literature regarding the use of repetitive transcranial magnetic stimulation (rTMS) as a mode of treatment for obsessive-compulsive disorder (OCD); and to evaluate the evidence to support the use of rTMS as a treatment option for OCD.

Design/Methodology/Approach

The authors conducted electronic data search in five research databases (MEDLINE, CINAHL, Psych INFO, SCOPUS and EMBASE) using all identified keywords and index terms across all the databases to identify empirical studies and randomized controlled trials. The authors included articles published with randomized control designs, which aimed to treat OCD with rTMS. Only full-text published articles written in English were reviewed. Review articles on treatment for conditions other than OCD were excluded. The Covidence software was used to manage and streamline the review.

Findings

Despite inconsistencies in the published literature, the application of rTMS over the supplementary motor area and the orbitofrontal cortex has proven to be promising in efficacy and tolerability compared with other target regions, such as the prefrontal cortex, for the treatment of OCD. Despite the diversity in outcomes and the clinical variability of the studies under review, rTMS appears to be a promising treatment intervention for OCD.

Research Limitations/Implications

The authors of this scoping review acknowledge several limitations. First, the search strategy considered only studies published in English. Although every effort was made to identify all relevant studies for this review per the eligibility criteria, the authors may have missed some relevant studies, especially those published in other languages.

Originality/Value

This review considered the varying literature on the application of rTMS and what are considered gaps in knowledge in this area to evaluate and provide information on the potential therapeutic effects of rTMS for OCD.

Keywords: Post-traumatic stress disorder, bipolar disorders, repetitive transcranial magnetic stimulations, treatment, obsessive-compulsive disorder.

Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive neuromodulatory intervention that affects neural activity through rapidly alternating magnetic fields. The stimulation operates through Faraday's law of electromagnetic induction, where the rapidly alternating electric current in the stimulating coil placed over the scalp generates a magnetic field that moves across the skull and produces electric currents in the neural tissue beneath [236]. This magnetic field has the capacity to penetrate the skull to stimulate cortical activity. Pulses can be delivered in a repeated manner to induce long-term changes in neural activity[199] as an increase or a decrease in cortical excitability through relatively high (>5 Hz) or low frequency (1 Hz) stimulation[200, 201]. Repetitive transcranial magnetic stimulation (rTMS) is very flexible and, depending on the site and frequency, it can inhibit or induce local and remote brain activity[202]. Typical rTMS comprises a train of repetitive pulses with similar stimulus intervals[199, 203].

Barker (1985) introduced TMS as a safe, and painless, non-invasive means of applying focal brain stimulation to stimulate the motor cortex and assess human central motor pathways[122]. rTMS has become an integral research tool in psychiatric treatment to exert explicit effects on a range of measures of brain function[195, 196]. rTMS has been evaluated quite extensively as a therapeutic tool for several psychiatric disorders, and is accepted as a brain-system-based, neuromodulation treatment for impacting direct targets involved in the neural circuitry of these disorders[237].

A previous review of rTMS studies identified limitations in earlier clinical trials, and recommended further research[204]. Results of more recent studies report improved rTMS outcomes through higher or accelerated dosing regimens[205, 206], extended treatment durations[207], patient-centred stimulation frequencies[208], and bilateral stimulation[209]. Further, they define more accurate and advanced neuro-navigational technologies[238] and more precise techniques for detecting the dorsolateral prefrontal cortex (DLPFC)[239] with newer coil geometries[240]. With these advancements, new rTMS studies report higher scores in remission and response, ranging from 30%–35% and 40%–55%, respectively[206, 241, 242].

Generally, rTMS treatments are simple and relatively easy to administer, non-invasive and typically well tolerated by patients[243]. A major benefit of rTMS is its relative safety, being devoid of major adverse side-effects[211]. It is a highly cost-effective alternative to more expensive treatment methods, such as electroconvulsive therapy[212]. The most frequent

negative effect noticed by patients is temporary pain in the scalp, although with a moderate increase in the intensity of rTMS, it should be normalized[213]. Vasovagal syncope may also manifest at the initial stages of treatment so caution is taken to keep patients seated. In addition, earplugs can help reduce the clicking sound experienced during rTMS administration[214]. rTMS was approved in Canada in 2002 and in the USA in 2008[215, 216]. In 2015, it was also approved by the National Institute for Health and Care Excellence for treatment-resistant depression in the UK[217, 218].

The large literature on superficial brain stimulation for mental disorders is based on rTMS for major depression disorder[219]. Based on its versatility and efficacy, rTMS use has now been investigated in other psychiatric conditions, including bipolar disorders, psychotic disorders, anxiety disorders, obsessive-compulsive disorder (OCD) and post-traumatic stress disorders (PTSD)[220]. Evidence-based guidelines for the therapeutic use of rTMS[244] drew attention to the analgesic effect of high frequency (HF) rTMS of the motor cortex and the antidepressant effect of HF rTMS of the DLFPC. Similar encouraging outcomes have been reported for neuropsychiatric conditions, such as schizophrenia and motor stroke. rTMS is also capable of regulating cortical plasticity and brain network movements. The outcome depends on the selected cortical section and the different stimulating parameters such as the frequency, design and the potency of stimulations[245, 246]. Many studies, including a meta-analysis, confirm the antidepressant effects of rTMS of the DLFPC[247, 248] but there seems to be conflicting outcomes in relation to anxiety disorders[128, 249].

Although antidepressants or psychotherapy alleviate the symptoms of patients with OCD, this condition can be very debilitating and presents with a greater degree of non-response to conventional treatments[250]. Despite the wide use of rTMS to manage mental disorders and the continual interest in research for newer treatments for OCD, the therapeutic use of rTMS still focuses on depression[251], and much less is known and evaluated for its use in managing OCD.

In view of the above considerations, the clinical effectiveness of rTMS should be assessed in relation to its potential to provide OCD patients with safe and lasting improvement in quality of life [225, 252]. This scoping review aims to identify what we know and what we consider are gaps in our knowledge in this area to evaluate and inform on the potential therapeutic effects of rTMS for OCD.

Methods

We developed an operationalized search strategy, which was applied to an electronically conducted data search in five research databases (MEDLINE, CINAHL, Psych INFO, SCOPUS and EMBASE) using relevant keywords and index terms across all the databases to identify empirical studies and randomized controlled trials (RCTs).

Key terms included: rTMS, OCD, post-traumatic stress disorder, bipolar disorders and treatment. This was a larger search strategy involving results for the use of rTMS for the treatment of three major mental disorders (OCD, PTSD and bipolar disorders). This paper reports only on and discusses the results for OCD. Table 1.4.1. shows a sample of the search strategy for Medline.

Table 1.4.1: Medline search strategy

#	**Search strategy**	**Results**
1	Exp *stress disorders, post-traumatic/ or (PTSD or ((posttraumatic or post traumatic or combat or war or trauma*) adj1 (stress* or neurosis or neuroses or nightmare*)) or ((traumatic or acute) adj (stress disorder* or stress symptom*)) or shell shock* or shellshock*).mp	46,596
2	Exp obsessive-compulsive disorder/ or bipolar disorder/	54,776
3	(Bipolar or bi-polar or manic-depress* or mania or obsessive-compulsive disorder* or OCD).mp	102,961
4	1 or 2 or 3	147,991
5	Transcranial magnetic stimulation/	11,653
6	(Repetitive transcranial magnetic stimulation or rTMS).mp	5,423
7	5 or 6	13,372
8	4 and 7	492

Two independent reviewers (Medard Adu and Ejemai Eboreime) screened the title, abstract and full text and found relevant articles that conformed to the objectives of the scoping review. Thematic classifications were done by the first reviewer (MA), with decisions analyzed by the second reviewer (EE). Where conflicts in classification arose, the articles in question were scrutinized, and consensus was reached between the two reviewers.

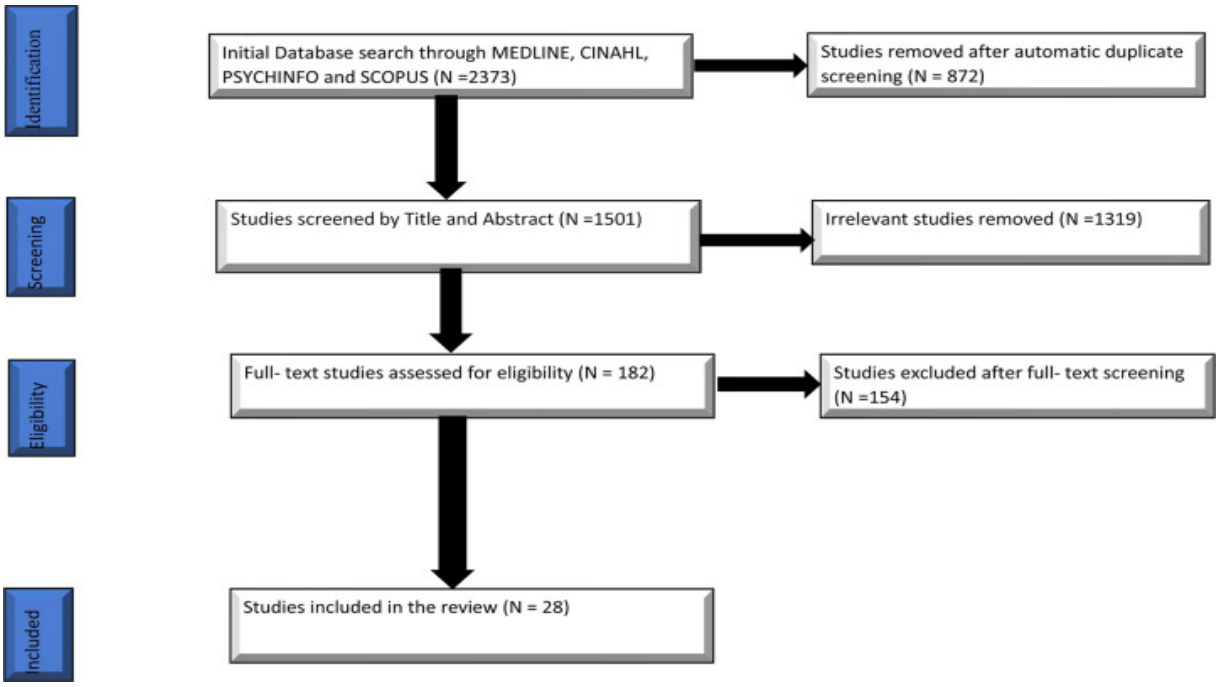
Inclusion and Exclusion Criteria

Inclusion criteria included studies involving a completed RCT of rTMS as a treatment intervention for OCD, open label trials on OCD using rTMS as a treatment intervention, full text articles and studies published in English. Exclusions included studies involving rTMS as a form of treatment for PTSD, bipolar disorders, OCD with comorbidities or studies involving any other conditions other than OCD, as well as those examining rTMS as a combined therapy with pharmacotherapy or any other interventions, systematic reviews, meta-analysis and study protocols and experiments with rTMS that were not designed for treatment for OCD.

Results

Through the search strategy and the use of the Covidence software, we identified a total of 2,373 studies from the electronic databases searched. The Covidence software automatically screened and removed 872 studies as duplicates. The remaining items (1,501) were screened against the eligibility criteria set by the authors based on the title and abstract only, yielding 182 remaining records for full-text screening. In total, 154 studies were excluded in the full-text screening phase, leaving a final pool of 28 studies eligible for inclusion in this scoping review (Figure 1).

Figure 1.4.1: PRISMA flow diagram summarizing search process and results



Many of the studies examined rTMS as a stand-alone treatment intervention for OCD, with most of them comparing the use and efficacy of rTMS to sham treatment. Relevant and detailed methodological information was extracted and summarized from the various studies and presented in Table 1.4.2

Table 1.4.2: Summary of studies using rTMS for the treatment of OCD

Author (Year)	Country of origin	study design	Number of participants	Targeted Brain Region	Targeted symptom	Measurement	Duration of treatment	Coil/ rTMS Parameters/Stimulation method	Outcome/significant improvements	Assessment and follow-up	Conclusion	Side effects
P. S. Sachdev et al. (2007) [253]	Australia	Double-blind, randomized, sham controlled followed by open-label phase	18 Adults	Left DLPFC	Obsessive symptoms	YBOCS MADRS BDI STAI-I	2 weeks	Focal 8-shaped 70 mm coil, with 30 trains of 5 s each, at 10 Hz and 110% MT, with 25-s inter-train intervals (1,500 stimuli per session)	This study did not support the efficacy of high frequency left DLPFC rTMS given over 2 weeks in OCD as there was no improvement in obsession scores	Weekly throughout the study and after 1 and 6 months of the last treatment	2 weeks of rTMS over the left DLPFC is ineffective for treatment-resistant OCD.	Transient headache, localized scalp pain
Kang et al. (2009)[254]	Republic of Korea	A double-blind sham-controlled investigation	21 patients	Right DLPFC	Effect of rTMS on cognitive functions Anxiety symptoms Obsessive compulsive symptoms	YBOCS MADRS	10 days	Focal 8-shaped 70 mm coil, with daily sessions for the first 2 weeks. At 1 Hz and (100% and 110%) RMT, at 10 mins. (1,200 stimuli /d)	The study did not show any clinically meaningful efficacy of sequentially applied low-frequency rTMS over a right DLPFC and SMA of patients with OCD	At baseline, after 1 and 2weeks of stimulation and 2 weeks after the final session	The study did not show any clinically meaningful efficacy of sequentially applied low-frequency rTMS over a right DLPFC and SMA of patients with OCD	Transient headache, localized scalp pain
A. Mantovani et al. (2009)[255]	USA	This trial consisted of two phases: (1) 4-wk double blind, and (2) 4-wk open-label	21 Patients with 8 females.	Coil was positioned over pre-SMA,	Increases in right hemisphere MT and normalization of baseline hemispheric asymmetry of cortical excitability	HAMD 24, YBOCS CGI-S, BDI-II HAMA-14	4-wk double blind, and 4-wk open-label	A vacuum cooled 70-mm figure-of-eight coil. Stimulation of 1-Hz, 20-min train at 100% MT, once a day, 5 d/wk., for 4 wk. (in phase 1) to 8 wk. (in phase 2	There was an average of 25% reduction in the YBOCS compared to a 12% reduction in those receiving sham. For the 4 wk. and for the 8 wks. 28.2 +-5.8 to 14.5+-3.6	Every 2 weeks and self-rating forms filled at the end of every week	There was an average of 25% reduction in the YBOCS compared to a 12% reduction in those receiving sham. For the 4 wks. and for the 8 wks. 28.2 +-5.8 to 14.5+-3.6	Nil
Sachdev et al.,	Australia	Single-blind,	12 patients	Right DLPFC	To compare the efficacy of	YBOCS,	2 weeks	Active RDLPFC10	Global reduction in YBOCS score _	At baseline, 2 weeks,	Significant improvement in	Nil

(2001)[256]		randomized, non sham controlled		And L DLPFC	both RDLPFC and LDLPFC	MADRS, BDI, STAI-I		sessions, RDLPFC, 10 Hz, 110% MT, 15 min, 30 trains, 5s on, 25 s off, fi g-8 coil Active LDLPFC idem, LDLPFC	40% from baseline to wk. 2 and wk. 6	6 weeks	relieving OC symptoms, reducing clinical severity, or improving treatment response; for both LDLPFC and LDLPFC	
Gomes et al. (2012)[257]	Brazil	Randomized double-blind trial	22 right-handed outpatients (women: 13; men: 9), age 18 to 60 years	Coil positioned over pre-SMA	To assess the efficacy of low-frequency rTMS to the SMA in treatment-resistant OCD and further examine the duration of a significant clinical effect	HAMD YBOCS	2 weeks	Focal 8-shaped,70-mm coil with 1-Hz, 20-min trains (1,200 pulses/day) at 100% MT. Once per day, 5 days per week, for 2 weeks	No significant reduction in Y-BOCS for baseline but at 2 wks, there was a significant reduction for the active group. No significant difference between groups for anxiety and depression symptoms	Baseline, after rTMS treatment, and 14 weeks after the end of rTMS treatment	No significant reduction in Y-BOCS for baseline but at 2wks, there was a significant reduction for the active group. No significant difference between groups for anxiety and depression symptoms	mild headache, scalp discomfort, cervical pain
M. Xiaoyan et al. (2014)[258]	China	Double blind sham-controlled study	46patients completed after 2 treatments 9 inpatients and 37 outpatients. Aged between 18 and 60	bilateral DLPFC	Obsessive, depressive, and anxiety symptoms in OCD patients	HAMD YBOCS HRSD, CGI	2 weeks	A 9 cm circular coil. 80% MT. Daily for 5 sessions a wk. for 2 wks. with 20min. each min included 4 s of active stimulation and 56 s of rest	The result showed that there were changes in scores of YBOCS, HRSD, and HAMA over time following both α-TMS and sham treatments	Baseline, after the 5th and 10th sessions of treatment, and 1 wk. after completing the entire treatment	αEEG-guided TMS may be an effective treatment for OCD and related anxiety	Mild headache
C Nauczyciel et al (2014)[259]	France	A randomized, double-blind, crossove	19 patients	Right orbitofrontal cortex (OFC)	Reduction in clinical symptoms, as measured on the Y-BOCS	YBOCS MADRS CGI	2 per day for 1 week	DB-80 butterfly double-cone coil with 120% MT, 1 Hz, 1,200 pulses	At day 7, a significant decrease in Y-BOCS scores, was observed compared with	Assessments were performed before and after each sequence,	Results of this preliminary study suggest that the OFC is a possible neuroanatomical target for OCD	Nil

		r design						per session over the right OFC. 10 sessions, 2 per day over 1 week	baseline, at day 35, no difference was observed in this decrease from the Y-BOCS baseline between active and sham stimulations	as well as 1 month after the end of the last session.	treatment, especially rTMS	
L. Donse et al. (2017) [260]	Nethe rlands	An open-label design	22 patients	Bilateral SMA and right dorsolateral prefrontal cortex (DLPFC)	Role of sleep disturbances in OCD and its predictive value for rTMS treatment nonresponse.	Y-BOCS, BDI, PSQI	10 sessions	Using a figure-8 coil with a frequency of 1 Hz, 1000 pulses per session, 110% MT.10 sessions over the SMA	Study confirms that some sleep disturbances are more prevalent in OCD patients than healthy subjects	Baseline and after the 10 sessions	Findings suggest that CRSD variables can predict treatment non-response to rTMS in a sample of treatment-resistant OCD patients	Nil
Y.-J. Lee et al. (2017)[261]	Repu blic of Korea	An open–label pilot study	9 adults aged 18 or older	SMA	Obsession and compulsion symptoms of OCD	BAI Y-BOCS, BDI CGI-GI SCL-90-R	5days a week for 4 weeks	70 mm, 8 shaped coils.1 Hz, 20 min train (1,200 stimuli/day) at 90–100% RMT, once a day, 5 days a week, for 4 weeks, in 20 sessions	Symptoms in treatment-resistant OCD patients significantly decreased after 20 sessions of 1 Hz rTMS over the SMA	Baseline, after 2 weeks, and after 4 weeks of rTMS treatment	Findings suggest that 1 Hz rTMS over the SMA can be an efficient and safe add-on therapeutic method in treatment-resistant patients with OCD	Mild headache and mild dizziness
Kumar et al (2018) [262]	India	A retrospective open study	25 patients	LF-rTMS over left-OFC	Symptoms of OCD. Factors affecting response to rTMS	Y-BOCS	4 weeks	1-Hz at 110% TM 5-second train duration, intertrain interval of 10 seconds, and 240 trains per session. 20 sessions 5 days per wk. for 4 wks	Significant reduction in the mean YBOCS scores after completion of 20 sessions of rTMS from baseline, whereas no further significant change in YBOCS scores 1 month after completion of rTMS treatment	Baseline and 1 month after the treatment	There is a role of applying LF-rTMS over Lt-OFC as an augmentation strategy in ameliorating clinical symptoms among patients with medication-refractory OCD	Localized scalp discomfort, headache
Arumugham et al.	India	A randomiz	40 patients	Low-frequency	Reduction in clinical	HAM-D	3 weeks	Fluid cooled figure-of-eight	Low-frequency rTMS over pre-	0, 1, 2, 3, and 12	Low-frequency rTMS over pre-	Headache,

(2018)[263]		ed controlled trial	with 36 patients in analysis-19 received active rTMS and 17received sham	rTMS over pre-SMA	symptoms, as measured on the Y-BOCS.	YBOCS CGI-S HAM-A		coil (MCF-B70 butterfly coil. 1,200 stimuli per day at 1 Hz in 4 trains of 300 sec, with intertrain interval of 2 min, at 100% MT	SMA was not superior to placebo in reducing symptoms of OCD in partial/poor responders to SSRIs	weeks using YBOCS	SMA may not be effective as an augmenting agent in partial/poor responders to SRIs	sedation, concentration difficulties, and failing memory
Singh et al (2019)[264]	India	Retrospective review and analysis of records	79 patients	Left-OFC and over bilateral SMA	reduction in clinical symptoms, as measured on the Y-BOCS.	YBOCS	4 weeks	70-mm figure 8 air-film coil.1-Hz at 110% RMT, 5-sec train duration, intertrain interval of 10 sec, and 240 trains per session. Each session consisted of 1,200 pulses/d delivered in 3590 seconds. A total of 20 sessions of rTMS 5 days per week for 4 weeks	Significant reduction in the mean YBOCS score after 20 sessions of rTMS, as compared with baseline YBOCS score	First day before the beginning of rTMS session and after the completion of twentieth rTMS session	This study provided evidence for overall effectiveness of adjunctive 1-Hz rTMS treatment over either SMA or OFC in patients with medication-refractory OCD	Nil
C. G. Mansur et al. (2011)[265]	Brazil	Parallel, double-blind randomized trial	30 patients 18 - 65 years	R-DLPFC	Scores on the YBOCS and CGI-I scale	HAM-D YBOCS CGI-S HAM-A CGI-I	6 weeks	Figure-8 coil 10 Hz and at 110% MT. 30 sessions (1/d, 5 d/wk.).40 trains – 5 s per train, with a 25-s intertrain interval. Total 60,000 pulses	rTMS, over rDLPFC, was not found to be superior to sham rTMS in relieving OC symptoms, reducing clinical severity, or improving treatment response	Baseline; after 2 and 6 wk. Treatment; and after 2 and 6 wk. follow-up	Active rTMS over the rDLPFC does not appear to be superior to sham rTMS in relieving OC symptoms, reducing clinical severity, or improving treatment response,	Mild headache, scalp discomfort, cervical pain, mood swings
R, Rostami	Asia	Retrospective	65 patients	DLPFC or SMA	Y-BOCS	Y-BOCS	3 days per	70-mm figure-8- coil (air film	Significant reduction in OCD	Baseline and after	An overall significant	Headache and

et al. (2020)[266]		study				BDI-II CGI-I BAI	week for 7 weeks	coil). 120% of AMT. 1 Hz, for 30 min, total of ,1800 pulses per session. once a day, 3 days per week for 7 weeks, in 20 sessions (36,000 pulses)	symptoms and anxiety / depressive states were observed after 20 sessions of rTMS	the 20th session of rTMS	reduction in OCD symptoms and anxiety / depressive states were observed after 20 sessions of rTMS	dizziness
Ruffini et al. (2009)[267]	Italy	A randomized controlled investigation	23 patients 18 -75 years	left OFC	OCD symptoms, mood, and anxiety	YBOCS, HDRS, HARS	5 sessions per week for 3 weeks	70-mm 8-shaped coil.10 min 1 Hz left-sided subthreshold rTMS 80% MT. 15 sessions (1 per day, 5 per week for 3 weeks)	Significant improvement in OCD symptoms in OCD patients with benefits lasting up to 10 weeks after the end of rTMS treatment	Baseline, after 15 rTMS sessions, and every 2 weeks for 3 months after the end of rTMS	Low-frequency rTMS of the left OFC produced significant but time-limited improvement in OCD patients compared to sham treatment.	Nil
A. Mantovani et al. (2006)[268]	USA	Open-label pilot study	10 righthanded outpatients	SMA.	YBOCS, CGI	YBOCS, YGTSS, CGI, HARS HDRS, SAD, BDI SCL-90,	10 days	70-mm figure-of-eight coil, SMA for 10 daily sessions at 1 Hz, 100% MT, 1200 stimuli/day	Significant improvement in OCD and TS symptoms with benefits lasting up to 3 months. Improvements in depression and anxiety were also seen	Baseline and after 1 and 2 wk. of stimulation. and 1 and 3 months follow up on CGI	Slow rTMS to SMA resulted in a significant clinical improvement and a normalization of the right hemisphere hyperexcitability, thereby restoring hemispheric symmetry in motor threshold.	Nil
J Praško et al. (2006)[269]	Czech Republic	A randomized, double blind, sham controlled study.	33 right-handed patients	left DPLFC	General psychopathology	CGI, HAMA, Y-BOCS BAI	2 weeks	Air cooled, figure-of-eight 70-mm coil.1 Hz at 110% MT. 10 sessions. 30 min. (5 per week for 2	Low frequency rTMS of left prefrontal cortex had no impact on the symptomatology in the patients suffering with	Week 0, week 2 and week 4	Low frequency rTMS administered over the left DPLFC during 10 daily sessions did not differ from sham rTMS in	nil

								weeks. 1,800 pulses per session	SSRIs resistant OCD		facilitating the effect of serotonin reuptake inhibitors in OCD patients	
K.A.M. Elbeh et al. (2016)[270]	Egypt	Double blind randomized clinical trial	45 patients	Right DLPFC	Effects of 1Hz and 1oHz on scales	Y-BOCS, HAM-A, CGI-S	2 weeks	70mm figure-8 coil 1 Hz-rTMS at 100% RMT, 4 trains, each of 500 pulses with a 40 s and 10 Hz rTMS at 100% RMT applied in 10 trains of 200 pulses, with 20 s. total of 2,000 pluses (5 days/week) 2 weeks.	1 Hz rTMS over the right DLPFC has medium term effect on obsessive-compulsive symptoms and anxiety	Before and after the last treatment session and 3 months later	There was a significantly larger percentage change in GCI-S in the 1Hz group versus either 10Hz or sham. We conclude that 1Hz-rTMS, targeting right DLPFC is a promising tool for treatment of OCD	Transient headache
Pelissolo et al. (2016)[271]	France	Sham-controlled trial	40 patients	pre-SMA	Efficacy of 1-Hz rTMS over pre-SMA	Y-BOCS, CGI-S,	4 weeks	70-mm figure-8 coil.1 Hz, 26-min sessions (four 5-min trains interval of 2 min, 1,500 pulses/d), at 100% of RMT	Low-frequency rTMS delivered to pre-SMA during 4 weeks had no better effects on drug refractory OCD patients than sham stimulation	Baseline and 4 weeks and follow-up (week 12)	Low-frequency rTMS applied to the pre-SMA seems ineffective for the treatment of OCD patients at least in severe and drug-refractory cases such as those included in this study	Headache
H.J. Seo, *et al*. (2016)[272]	Korea	A Randomized Controlled Trial.	27 patients	Right DLPFC	OCD symptoms, mood, and anxiety symptoms	YBOCS, CGI-S HAMD	3 weeks	TAMAS stimulator with a figure-eight coil.1 Hz, 20-minute trains (1,200 pulses/ day) at 100% MT once per day 5 days per week. for 3 weeks	LF rTMS over the right DLPFC appeared to be superior to sham rTMS for relieving OCD symptoms and depression in patients with treatment-resistant OCD	Baseline and every week during the treatment period.	LF rTMS over the right DLPFC appeared to be superior to sham rTMS for relieving OCD symptoms and depression in patients with treatment-resistant OCD	localized scalp pain, Headache

A. Talaei et al. (2009)[273]	Iran	A case report	40-year-old female	SMA	OCD symptoms, mood, and anxiety symptoms	Y-BOCS	10 sessions	10 sessions with 110%, 1 Hz and of 30 minutes per day (a total of 1,200 pulses per day	Significant decrease in compulsive behaviours	Before the first rTMS session and after every session	Significant decrease in compulsive behaviours and obsessive thoughts	Nil
Badawy et al. (2010)[274]	Egypt	Randomized control trial	60 patients	LDLPFC	Mixed OCD symptoms and compulsive symptoms only	Y-BOCS	15 sessions	High frequency r-TMS (20Hz).5 sessions per week for 3 weeks. high frequency r-TMS (20Hz)	While r-TMS was not effective as a single treatment for OCD patients, it was effective as add-on treatment for OCD patients	Before the first r-TMS session and after completion of the 15 sessions	While r-TMS was not effective as a single treatment for OCD patients, it was effective as add-on treatment for OCD patients	Nil
Elmadany, et al. (2014)[275]	Egypt	Randomized control trial	20 patients (9 males and 1 female)	Left prefrontal area of the brain	OCD symptoms	Y-BOCS CGI	20Hz 2 secs for 20 min in 8 sessions every 48 hours	figure-8 or butterfly-shape coil. 5 cm forward and 2 cm to the below the centr of the head. MT 90%; 20Hz 2 secs for 20 min in 8 sessions every 48 hours	OCD patients have better response to r TMS for obsession symptoms more than compulsions especially those on pharmacological treatment.	Before the first r-TMS session and after completion of the last	OCD patients after r-TMS has a better response especially those accompanied with pharmacological treatment	Nil
B. D, Greenberg et al. (1997)[276]	USA	Brief report	12 patients	Right lateral prefrontal, a left lateral prefrontal and midoccipital site on separate days, randomized	Obsessive compulsive symptoms	Y-BOCS HARS	20 Hz/2 seconds per min for 20 min	Cadwell High Speed Magnetic Stimulator and a figure-8-shaped coil. 80%MT, 20 Hz/2 seconds per min for 20 min.	Results suggest that right prefrontal rTMS might affect prefrontal mechanisms involved in OCD	Baseline and poststimulation	Results suggest that right prefrontal repetitive transcranial magnetic stimulation might affect prefrontal mechanisms involved in OCD	Nil
Hegde et	India	Retrospe	17	Pre-SMA	OCD	Y-	3 weeks	70-mm figure-	Only 1 patient met	Baseline	Low-frequency	Mild

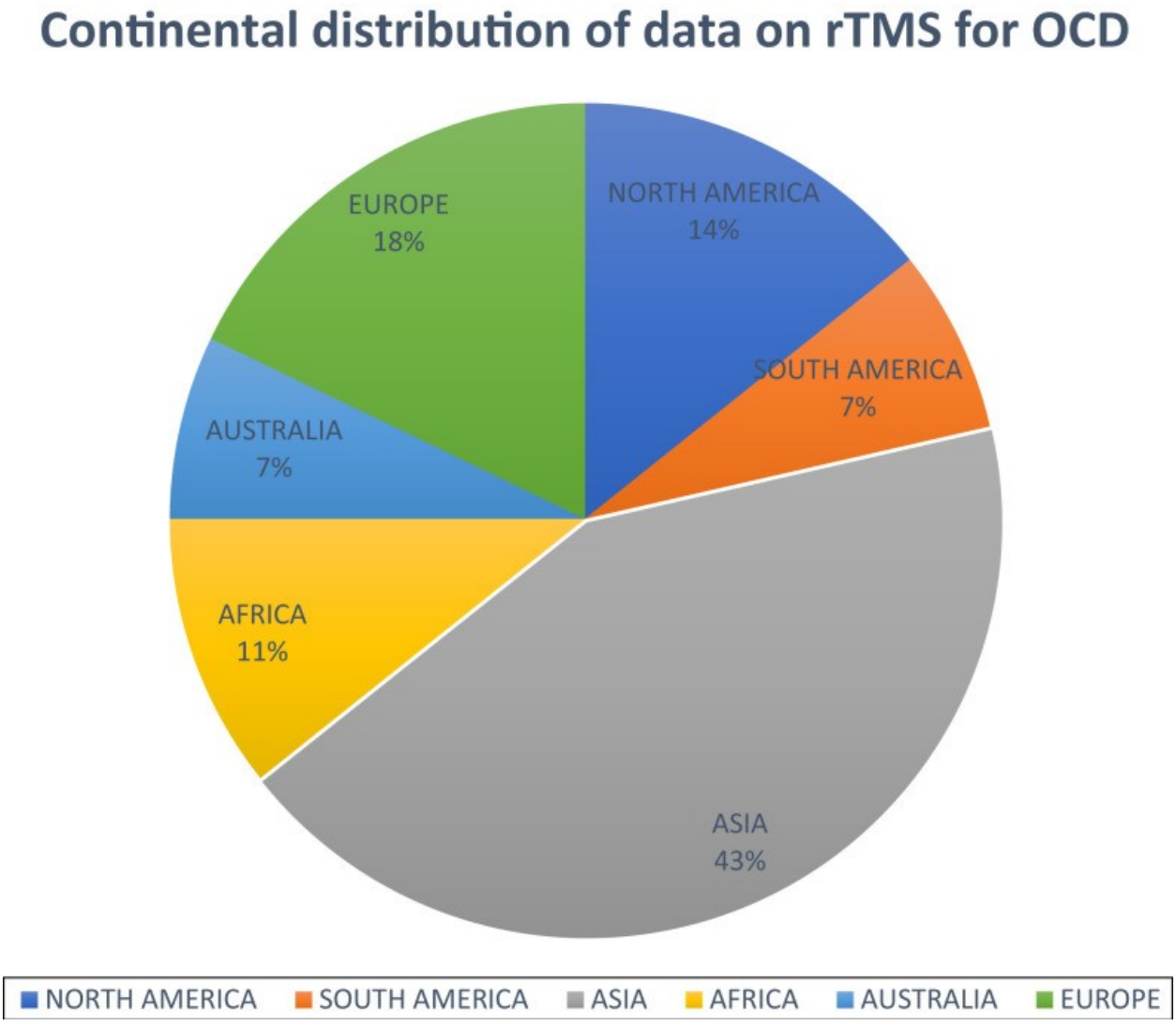
al (2016) [277]		ctive analysis study	patients		symptoms	BOCS CGI-S		8 coil 1-Hz at 100% MT over the pre-SMA 20 minutes, in 4 trains of 300 seconds (1,200 pulses per sitting	the criteria for response after 1 month of treatment initiation	and 1 month after initiation	rTMS over the pre-SMA may not be effective in treatment refractory OCD	headache
L Carmi et al (2019) [278]	Israel	Prospecti ve multicent r randomiz ed double-blind placebo-controlle d trial	100 patients	Dorsal mPFC	Safety, tolerability, and efficacy of dTMS in OCD	YBOC S, CGI-S HAM D CGI-I	6 weeks	H-shaped coil design, 100% RMT. 20 Hz dTMS 2-second pulse trains and 20-second intertrain intervals, for a total of 5 0trains and 2,000 pulses per session	Significant differences between the groups were maintained at follow-up	Baseline and 1 month follow up	High-frequency dTMS over the mPFC and anterior cingulate cortex significantly improved OCD symptoms and may be considered as a potential intervention for patients who do not respond adequately to pharmacological and psychological interventions	1 patient had suicidal thoughts
M. Haghighi et al. (2015)[27 9]	Iran	Randomi zed, single-blind, sham, controlle d clinical trial with cross-over design	21 patients	L-DLPFC	OCD symptoms	Y-BOCS , CGI	4 weeks	70 mm double air film coil. 100% RMT at 20 Hz, in 750 total pulse. 25 min per cortex site, totaling 50 min for a session	Both self- and expert-reported symptom severity reduced in the rTMS condition as compared to the sham condition. Full- and partial responses were observed in the rTMS-condition, but not in the sham-condition.	Baseline, after two, and after four weeks of treatment	The pattern of results from this single-blind, sham- and cross-over design suggests that rTMS is a successful intervention for patients suffering from treatment-resistant OCD	Nil
Modirrou sta et al. (2015)[28 0]	Cana da	Open-label study	10 patients	mPFC	Effect of low-frequency deep rTMS over the	Y-BOCS	2 weeks	Double-cone coil at 110% RMT 1 Hz, 150 pulses	Significant reduction in OCD symptoms	Baseline, after 10 sessions same day	Results suggest the use of low frequency deep rTMS as a	Electric shocking sensation and

					mPFC of patients with OCD			(overall 1,200 pulses in one session) for 10 sessions		as last rTMS treatment, 1 month after last session	promising and robust intervention in OCD symptom reduction.	insomnia

MT= Motor Threshold, SMA= supplementary motor area Y-BOCS= Yale–Brown Obsessive-Compulsive Scale; Ham-D–24= Hamilton Rating Scale for Depression–24-item; BDI–II, DLPFC = dorsal lateral prefrontal cortex, OFC= orbitofrontal cortex, RMT= resting motor threshold, CGI-I= Clinical Global Impression. HAMA= Hamilton Anxiety Rating Scale, HRSD= Hamilton Rating Scale for Depression, YMRS=Young Mania Rating Scale, GAF= Global Assessment of Functioning, MCCB= MATRICS Consensus Cognitive Battery. QIDS= Quick Inventory of Depressive Symptomatology, CAPS= Clinician Administered PTSD Scale, BNCE= Brief Neurobehavioural Cognitive Examination, STAI= State Trait Anxiety Inventory, SC-Q= Self-Administered Comorbidity Questionnaire, SCID= Structured Clinical Interview for DSM-IV, IPF= Inventory of Psychosocial Functioning, BRMAS= Bech-Rafaelsen mania scale, CRSD= circadian rhythm sleep disorder, SCL-90-R= Symptom Checklist-90-Revised, mPFC= medial prefrontal cortex.

We examined the geographical distribution of studies conducted on rTMS treatment for OCD globally, as presented in Figure 2. Of the total of 28 studies included in our review, 12 (43%) were conducted in Asia; North America and South America had 4 (14%) and 2 (7%) studies, respectively; Europe had 5 (18%); Africa had 3 (11%); and Australia had 2 (7%) studies. This indicates that research on rTMS in OCD is being conducted across all continents but the quantity and scope vary widely across geographical jurisdictions. Table 1.4.2. summarizes the main findings for these included studies.

Figure 1.4.2: Number of studies extracted from the various continents (*n* = 28)



Study designs vary widely, including 18 RCTs, 4 open-label trials, 4 retrospective analysis, 1 brief report and 1 case report. All these studies sought to evaluate the efficacy and effectiveness of rTMS for the treatment of OCD. Sample sizes ranged from 10 to 100 subjects across included studies, with a mean sample size of 31.68. The studies were heterogeneous in terms of features of clinical variability, such as the severity of OCD symptoms, duration of sickness and rate of resistance to pharmacotherapy. The location of rTMS stimulation varied among studies as did treatment duration and stimulus intensity. Of the 28 studies, 19 used 70 mm figure-8-shaped coils because of their ability to induce more focal current compared to circular coils. The remaining studies variously used the 9 cm circular coil, DB-80 butterfly double-cone coil, and the H-shaped coil design. Duration of treatment varied across studies, from two weeks to seven weeks. In total, 19 studies applied rTMS with a low frequency and eight applied HF ranging from 10 Hz to 20 Hz; the one remaining study compared effects of low and HF treatment protocols.

In total, 19 studies (68%) reported significant positive outcomes, and the other 9 studies reported no significant symptom improvement. In each study, rTMS application was reported as well tolerated with no significant side effects, although there were a few reports of mild side effects, such as mild headache, dizziness and scalp pain, across the studies.

Discussion

The 28 studies under review suggest that rTMS has potential as a safe and clinically efficacious treatment intervention for OCD. Despite the diverse outcome measures included in this selection of studies, there were some consistent significant OCD symptom improvements.

Many factors may have accounted for the varying effectiveness of the application of rTMS across the studies and major domains of outcomes. For instance, rTMS treatment protocols and stimulation parameters vary greatly across studies, with poorly defined intervention protocols. Another factor is that different measuring tools are used to evaluate similar outcomes across studies, making a comparative evaluation of results difficult. It also makes it difficult to understand which rTMS parameters led to the most significant outcomes and treatment response.

However, due to the diverse nature and presentation of mental conditions, it may seem unrealistic to think uniquely of an optimal or even a standardized rTMS protocol that will work across studies of the different conditions, even if they target similar symptoms. One important aspect of rTMS, as identified in this review, is its versatility, which allows for the development

and adaption of protocols addressing similar symptoms from different conditions with potentially positive outcomes.

Targeted Brain Regions of Repetitive Transcranial Magnetic Stimulation

The pathophysiology of OCD, according to structural and functional neuroimaging studies, is linked with the dysfunction of the orbitofronto-striato-pallido-thalamic circuitry, which includes the orbitofrontal cortex (OFC), Dorsolateral prefrontal cortex (DLPFC), medial PFC as well as the thalamus[281, 282]. Modulation of this circuitry by neurosurgical mechanisms and by means of deep brain stimulation has proven effective in reducing symptoms of OCD [283]. Bearing in mind the possibility of rTMS in modulating cortical and subcortical structures of the brain, the possible therapeutic effects of rTMS have been extensively studied and evaluated in the literature in the quest to normalizing hyper- or hypo-active brain regions by targeting dysfunctional cortico- ubcortical circuits in people with OCD.

For many of the studies extracted, the rTMS stimulation was at either the left-DLPFC or the right-DLPFC, and with high or low frequency rTMS. The overall accepted rationale is that the DLPFC could be a starting point for the induction of remote stimulation in the cortico-subcortical circuits connected. For most of the trials, the left-dorsolateral prefrontal cortex (LDLPFC) and right- dorsolateral prefrontal cortex (RDLPFC) were stimulated with the "5 cm method" where the figure-8 coil was centred on a point at 5 cm rostral to and in the same sagittal line as the optimal area for activating the right or left abductor pollicis brevis muscles during motor threshold (MT) assessment[253, 269, 276]. As prefrontal mechanisms are implicated in OCD, Greenberg et al. (1997) undertook a non-sham-controlled, single-blind rTMS study on the evidence of PFC hypermetabolism and hyper perfusion in untreated OCD patients. The preliminary results suggest that DLPFC rTMS had modest, lateralized effects on compulsions but not on obsessions.

From the data extracted, another brain region studied for the administration of rTMS is the OFC. As indicated earlier, the OFC performs a very important function in the pathophysiology of OCD because obsessions and compulsions are deemed to be mediated at least in part by the hyperactivity in the orbitofrontal-subcortical circuits and the increase in functional activity in the OFC. Inspired by the fact that OFC rTMS may seem OCD-specific, a randomized, single blind sham-controlled study was conducted by Ruffini et al. (2009). The researchers evaluated the

efficacy of LF-rTMS over the left OFC with a low frequency (1 Hz) rTMS at 80% RMT for three weeks. There was a significant reduction in Yele-Brown obsessive compulsive scale (YBOCS) scores for the active group after the 3rd and 10th weeks compared to sham treatment.

The supplementary motor area (SMA) is one of the most recent brain targets used for the application of rTMS. Evidence suggests that the motor and premotor cortex are hyperexcitable in OCD. An open-label trial conducted by Mantovani et al. (2006) sought to evaluate whether low-frequency rTMS to the SMA could normalize overactive motor cortical regions and thereby improve symptoms of patients with OCD. There was clinical improvement at the end of the first week of the treatment with rTMS and, by the second week, there was a statistically significant improvement in the reductions seen in Yele-Brown obsessive compulsive scale (YBOCS), Clinical Global Impression, Beck depression inventory (BDI), Hamilton depression rating scale (HDRS), Hamilton anxiety rating scale (HARS) and Symptom Checklist-90. Following the publication of this study, many of the most recent trials on rTMS application for the treatment of drug resistant OCD focused on the SMA[261, 264, 271, 273, 284-286]. Results suggest that 1 Hz rTMS over the SMA could be an efficient and safe add-on therapeutic method in treatment-resistant patients with OCD.

Treatment Modality and Stimulation Frequencies

In regard to differences in low and HFs of rTMS, results from the extracted studies suggest that, administration of HF (10 Hz) rTMS at 100% or 110% MT over the RDLPFC did not differ from sham rTMS in terms of efficacy in relieving symptoms, reducing clinical severity or improving responses in treatment-resistant OCD[265, 270]. By contrast, another study indicated that low frequency (1 HZ) rTMS delivered to the RDLPFC appeared to be superior to sham rTMS for relieving OCD symptoms and depression in patients with treatment-resistant OCD. Based on the results from the studies in this review, there is no evidence for a statistically significant difference between low or HF rTMS over RDLPFC and LDLPFC for the treatment of OCD.

The different study designs did not contribute to any differences in the treatment outcomes between the sham and active subjects. A study conducted[253, 269] using the double-blind, randomized, sham-controlled trial with the application of low or HF rTMS over the left or right PFC resulted in a significant reduction in YBOCS scores in both sham and active subjects, with no significant statistical difference in the two groups at the end of the treatment intervention. The

results also failed to depict any meaningful therapeutic efficacy in treatment for non-responder OCD patients from either group[254].

Sachdev et al. (2001) compared effects of active HF-RDLPFC rTMS to active HF-LDLPFC rTMS. The evaluation yielded a notable improvement in OCD symptoms in study subjects. Notwithstanding the significant improvement in YBOCS scores for the two arms of the study, it is possible that the positive results were because of the smaller sample size (N = 12) and the absence of a control group. Six years later, the same researchers conducted a similar study that confirmed the assertion of a smaller sample size and the lack of a sham control. Sachdev et al. (2007) in their study with a larger sample size (N = 18) revealed that the active and sham arms of the study did not show any difference in the reduction in OCD symptoms after treatment. These conflicting results indicate that prefrontal high or low frequency rTMS may probably not be effective in the treatment of OCD symptoms.

In contrast to the contradictory results from other studies, most of the trials that presented with major clinically insignificant improvements in OCD symptoms were studies with the targeted brain regions over the SMA with low frequency rTMS[260, 261, 264, 271, 273, 284-288] and the left OFC with LF-rTMS[262, 264, 267]. These studies suggest that rTMS had a specific and significant clinically effective influence on OCD symptoms: specifically in relation to the SMA stimulation site.

Poor study outcomes as witnessed in most of the studies could be partly attributed to differences in stimulation parameters, shorter treatment durations (many used two weeks), the levels of frequencies used and, in some cases, the use of the circular coil, which typically induces less focal current than the figure-8 shape coil. Differences may also be attributed to the choice of left or right prefrontal cortices of targets for stimulations and the severity of the drug resistance of the subjects used for the studies.

Other Factors Affecting Therapeutic Outcomes

Many factors may have accounted for the varied effectiveness of the application of rTMS across the studies and major domains of outcomes. For instance, rTMS treatment protocols and stimulation parameters vary greatly across studies, with poorly-defined intervention protocols. Another factor is the different measurement tools used to evaluate similar outcomes across studies and, therefore, making comparison and evaluation of results difficult. These

inconsistencies also make it difficult to understand which rTMS parameters led to the most significant outcomes and treatment responses. It remains possible that positive outcomes may also be attributed partially to the therapeutic contributions of concurrent medications taken by the subjects, although most subjects have been on these medications for a long time without yielding improvements in their OCD symptoms.

Additionally, the varied clinical significance and effectiveness of rTMS across studies can be partly attributed to factors such as variations in coil type and coil positions, the different cortical targets and the variations in motor thresholds. In the case of the application of rTMS to treat OCD, a majority of the studies applied rTMS to normalize frontal dysfunction associated with OCD symptoms, choosing to stimulate the left/right DLPFC or the SMA. For example, in the case of the cortical target, the SMA was consistently used to relieve subjects of their OCD symptoms with consistent and clinically significant treatment responses noted. Thus, from the data gathered with respect to rTMS in OCD, the SMA may be a promising target region for the application of rTMS to treat the symptoms of OCD in contrast to left or right DLPFC.

Furthermore, an important factor noticed is the evaluation of the longevity and time course effects of rTMS. The majority of studies reviewed evaluated the treatment outcomes of the various interventions immediately after the last session of rTMS with a few months of follow-up. Considering the chronic, debilitating and highly-prevalent nature of mental conditions, evaluating the long-term therapeutic effects of rTMS intervention is of great importance. Therefore, it would be of high clinical significance and research value to estimate the sustainability of treatment effects, and specifically, maintenance strategies following response or remission with rTMS.

Limitations

The authors of this scoping review acknowledge several limitations. First, our search strategy considered only studies published in English. Although every effort was made to identify all relevant studies for this review per our eligibility criteria, we may have missed some relevant studies, especially those published in other languages.

Conclusion

Many of the studies included in this scoping review resulted in conflicting and inconsistent outcomes on the efficacy and utilization of rTMS as a treatment intervention for OCD. This makes it difficult to make definitive conclusions on the clinical usefulness and the appropriate technique for rTMS treatment interventions for OCD. Larger sample sizes for sufficiently-powered and preferably multi-centred sham-controlled trials with the appropriate coil and stimulation parameters, well-defined stimulation targets and a longer treatment duration would be required to clarify the therapeutic effect of rTMS in the treatment of resistant OCD.

Despite the inconsistencies in the literature, the application of rTMS over the SMA and the OFC is promising in efficacy and tolerability compared with other target regions, such as PFC, for the treatment of OCD. Despite the diversity in outcomes and the clinical variability of the studies under review, rTMS appears to be a promising treatment intervention for OCD.

1.5: The Use of Repetitive Transcranial Magnetic Stimulations for the Treatment of Post-Traumatic Stress Disorder: A Scoping Review

Adu, M.K., et al., The Use of Repetitive Transcranial Magnetic Stimulations for the Treatment of Post-Traumatic Stress Disorder: A Scoping Review. Trauma Care, 2022. 2(2). doi.org/10.3390/traumacare2020012. Available at: https://www.mdpi.com/2673-866X/2/2/12

Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive procedure in which brain neural activity is stimulated by the direct application of a magnetic field to the scalp. Despite its wide and ongoing use for the management of psychiatric disorders, the use of rTMS for post-traumatic stress disorder (PTSD) is not well established and evaluated by researchers. This scoping review seeks to explore the relevant literature regarding the use of rTMS as a mode of treatment for PTSD, to map evidence in support of the use of rTMS for PTSD, and recommendations on future clinical and research work. Five databases were searched (MEDLINE, CINAHL, Psych INFO, SCOPUS, and EMBASE) to identify empirical studies and randomized controlled trials aimed at the treatment of PTSD with rTMS. A total of 10 studies were eligible for this review. The search results are up-to-date as of the date of the electronic data search of 20 December 2020. The frequencies applied in the studies ranged from low (1 Hz) to high (10 Hz) at different thresholds. Nine studies reported significant positive outcomes and PTSD symptoms improvement. rTMS was reported as well tolerated with no significant side effects. The application of rTMS for PTSD looks promising despite the diversity in its outcomes and its clinical significance. Studies with well-defined stimulation parameters need to be conducted in the future.

Keywords: repetitive transcranial magnetic stimulation; post-traumatic stress disorders; mental illness

1. Introduction

Post-traumatic stress disorder (PTSD) is a common psychiatric condition that results in significant psychosocial dysfunction and presents through four distinct diagnostic clusters: re-experiencing, avoidance, negative cognitions and mood, and arousal[289, 290]. The prevalence of specific traumatic events varies geographically. Thus, compared to developing countries, developed countries have a greater number of individuals (28 to 90%) with at least an exposure to a traumatic event[291]. Studies suggest that most adults experience some form of traumatic situation at some point in their lives irrespective of their geographical location[291].

About 7% of the population of the United States experience PTSD during their lifetime[292]. Furthermore, 48% to 71% of veterans are exposed to more traumatic situations during their service days, 15% of whom are diagnosed with PTSD[293, 294]. 25–40% of patients with PTSD are expected to recover within a year but the rate of remission for most persons can take longer. The mean duration of symptoms is 6 years across the various trauma types. Symptoms from combat-associated PTSD have a mean duration of 13 years[295, 296]. The treatment of choice for PTSD is psychotherapy and antidepressant medications[297]. Despite receiving these treatments, about 50% of patients continue to experience significant symptoms[298, 299]. This highlights the need to continue therapeutic development research for PTSD and to consider the role of machine-based interventions, such as transcranial magnetic stimulation (TMS).

TMS is a non-invasive neuromodulatory tool that stimulates neural activity by the use of rapidly alternating magnetic fields. TMS operates through Faraday's law of electromagnetic induction, where the rapidly alternating electric current in the stimulating coil placed over the scalp generates a magnetic field that moves across the skull and produces electric currents in the neural tissue underneath[236]. This magnetic field penetrates the skull to stimulate activity in the cortical neurons beneath. The pulse can be delivered in a repeated manner to induce a long-term effect on neural activity[199]. Anthony Berker introduced TMS in 1985 as a safe and painless means of studying the central nervous system to stimulate the motor cortex and to assess human central motor pathways[122].

Repetitive transcranial magnetic stimulation (rTMS) is a new TMS technique that alters brain activity via repeated changes of the coil's magnetic field. The modulation effect is capable of reaching the cortex and subcortical areas and, depending on whether high (>1 Hz) or low (1 Hz) frequency, rTMS can decrease or increase cortical excitability[300, 301]. rTMS has become an

integral research tool in psychiatry treatment as a result of its ability to cause explicit effects on a range of measures of brain function[195, 196]. rTMS is considered a safe and non-invasive treatment modality[118, 129]. rTMS has been evaluated extensively as a major therapeutic tool for several psychiatric disorders, such as bipolar disorders, psychotic disorders, anxiety disorders, obsessive-compulsive disorders and PTSD[220].

The use of rTMS in PTSD was investigated as early as 1998[302]. Studies since then have suggested rTMS as a potentially effective treatment modality for PTSD[303-306]. Consequently, there has been increasing use of rTMS in the treatment of PTSD[307, 308]. However, despite the increasing use of rTMS for the treatment of psychiatric disorders, the therapeutic use of rTMS is still largely in the domain of major depression disorder (MDD)[251]. Much less is known about how rTMS is used in the management of PTSD[309]. This scoping review aims to bridge this gap in the literature.

2. Methods

Study methods have been published in a related paper[310]. In summary, an operationalized search strategy was employed to electronically search five research databases (MEDLINE, CINAHL, Psych INFO, SCOPUS, and EMBASE) using identified keywords and index terms across all the databases to identify evidence-based studies and randomized controlled trials. Keywords included: repetitive transcranial magnetic stimulation, obsessive-compulsive disorder, post-traumatic stress disorders, bipolar disorders, and treatment. This is a larger search strategy involving results for the use of rTMS to treat three major mental disorders (OCD, PTSD, and bipolar disorders) but this paper reports only on and discusses results for PTSD. The related paper reported on the results related to the use of TMS for OCD[310]. The search results are up-to-date as of the date of the electronic data search of 20th December 2020. Table 1.5.1 shows a sample of the search strategy on Medline. Thematic classifications were done by the first reviewer (MA), with decisions analyzed by the second reviewer (EE). Where conflicts in classification existed, the article in question was scrutinized and a consensus was reached between the two reviewers.

Table 1.5.1: Medline search strategy

Search strategy	Results
Exp * stress disorders, post-traumatic/or (PTSD or ((posttraumatic or post-traumatic or combat or war or trauma *) adj1 (stress * or neurosis or neuroses or nightmare *)) or ((traumatic or acute) adj (stress disorder * or stress symptom *)) or shell shock * or shellshock *).mp.	46,596
Exp obsessive-compulsive disorder/ or bipolar disorder/	54,776
(Bipolar or bi-polar or manic-depress * or mania or obsessive-compulsive disorder * or OCD).mp.	10,2961
1 or 2 or 3	14,7991
Transcranial Magnetic Stimulation/	11,653
(Repetitive transcranial magnetic stimulation or rTMS).mp.	5,423
5 or 6	13,372
4 and 7	492

Inclusion and Exclusion Criteria

This study included completed randomized controlled trial (RCT) of rTMS as a treatment intervention for PTSD and open-label trials on PTSD using rTMS as a treatment intervention, full-text articles and studies published in English. Studies involving rTMS as a form of treatment for conditions other than PTSD and studies with rTMS treatment involving PTSD patients but targeting comorbidities, studies with rTMS as combined therapy with pharmacotherapy or any other interventions, systematic reviews, meta-analysis and study protocols, and experiments of rTMS that are not designed for treatment for PTSD were not involved.

Through the search strategy, we identified a total of 2,373 studies from the electronic databases searched. The Covidence software (Melbourne, VIC, Australia) automatically screened and removed 872 studies as duplicates. The remaining items (1501) were screened against the eligibility criteria set by the authors based on the title and abstract only, yielding 182 remaining records for full-text screening. The remaining items were full-text screened by the two reviewers who excluded 172 studies from the records. A total of 10 studies were then eligible for inclusion for this scoping review, as shown in Figure 1.5.1 All studies examined rTMS as a stand-alone

treatment intervention for PTSD, with most of them comparing the use and efficacy of rTMS to sham treatment. The key findings are summarized from the various studies and presented in Table 1.5.2.

Figure 1.5.1: PRISMA flow diagram summarizing search process and results

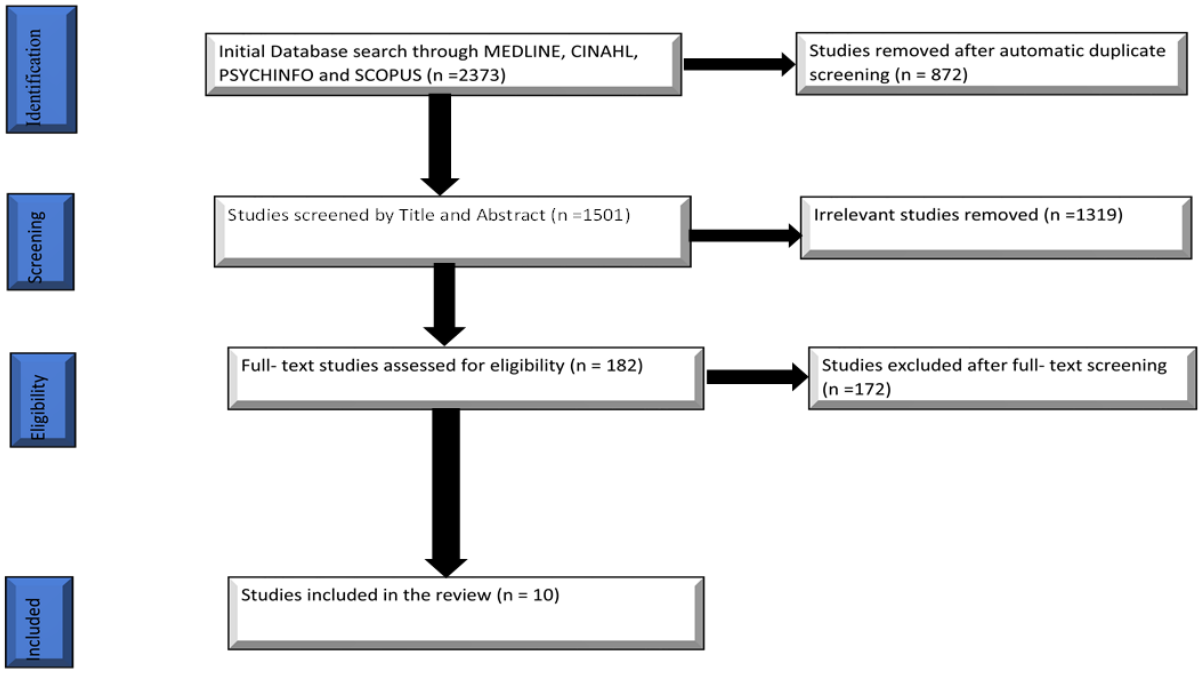


Table 1.5.2: Summary of studies using rTMS for the treatment of PTSD

Author (year)	Country of Origin	Study Design	Number of Participants	Targeted Brain Region	Targeted Symptom	Measurement	Duration	Coil/ rTMS Parameters /Stimulation method	Outcome/Significant Improvements	Assessment and Follow-Up	Conclusion	Side Effects
K. Leong et al. (2020) [311]	Canada	Randomized sham-controlled trial	31 patients	Right - DLPFC	Change in severity of PTSD symptoms	CAPS-IV. GAD-7 PCL-C	2 weeks	Double 70 mm Air Film Coil model 3910-00. 120% RMT. 1-Hz with 2250 pulses over 37.5 min, whereas those assigned to 10-Hz received 3000 pulses over 37.5 min (4-sec stimulation train with 26 s intertrain interval). 2 weeks of daily treatments (10 treatments).	Low-frequency 1-Hz rTMS results in greater improvements in PTSD symptoms relative to sham (Hedges' g = −1.07). but not in the 10-Hz group.	At baseline, at treatment end, and 3-month follow-up.	Low-frequency rTMS is efficacious in the treatment of civilian PTSD.	Suicidal ideation
F.A. Kozel et al. (2019) [312]	USA	A randomized clinical trial	44 patients	Right DLPFC	PTSD and depressive symptoms	CAPS, PCL-5, IPF	6 weeks	110% of MT. 1 Hz rTMS. 40 min for a total of 2400 pulses/session. 10 Hz, rTMS was 4s on and 36 s off for 40 min for a total of 2400 pulses/session.	Although both groups demonstrated significant improvement in PTSD and depression symptoms, a significant advantage for either the 1 Hz or 10 Hz frequency group on any of the scales acquired was not demonstrated. (IPF 1 Hz – (p = 0.075)) and IPF 10 HZ- (p = 0.008)).	After every 5 treatments for the first 30 treatments, at the end of treatment taper, and 1- and 3-month posttreatment follow-ups.	Although both groups demonstrated significant improvement in PTSD and depression symptoms, a significant advantage for either the 1 Hz or 10 Hz frequency group on any of the scales acquired was not demonstrated.	Nil

Fryml et al. (2019 [313]	USA	A prospective, randomized, double-blinded, active sham-controlled design	12 patients	Left or right DLPFC	Mood and PTSD symptoms	CAPS, HDRS, PCL-C	5 weeks	Figure-eight solid core coil at 120% MT, 10 Hz, 5-second train duration, and 10-second intertrain interval for 30 min (6000 pulses) weekly for 5 weeks (30,000 stimuli).	Results from this study suggest that delivering rTMS to PTSD patients while they simultaneously receive PE is feasible.	Baseline and weekly throughout the treatment	The study demonstrates the safety and feasibility of rTMS delivery to PTSD patients.	Nil
F.A. Kozel et al. (2018) [314]	USA	A randomized clinical trial	103 patients	Right - DLPFC	Reduction in symptoms of PTSD	CAPS, QIDS, SCID, SC-Q	12 weeks	Double 70 mm Air Cooled Coil 110% MT at 1 Hz rTMS for 30 min for a total of 1800 pulses.	Improved symptom reduction in combat veterans with PTSD. $t\ (df \geq 325) \leq -2.01$, $p \leq 0.023$, one-tailed and $t(df \geq 303) \leq -2.14$, $p \leq 0.017$, one-tailed, respectively.	Baseline repeated session-5, session-9,1-month post-treatment, 3- and 6-months post-treatment.	Combining CPT with rTMS led to improved symptom reduction in combat veterans with PTSD.	Head aches
M.-J. Ahmadizadeh,M. Rezaei (2018) [315]	Iran	A randomized controlled study	384 males patients	Bilateral DLPFC and right DLPFC (F4),	PTSD symptoms	SCID, PCL-M	4 weeks	70 mm figure-eight stimulation coil (air film coil). 100% MT. HF, 20 Hz rTMS Duration: 2 s Inter-train interval: 28 s Total train: 30 for bilateral Total pulse per session: 1200 for 15 min.	Significant PTSD symptom reductions in the bilateral group compared to the sham group in session five and endpoint. (Effect of time: Wilks' Lambda = 0.22, $F_{(2,45)} = 81.50$, $p = 0.0001$).	Baseline and after each session.	Findings suggest that bilateral and unilateral right rTMS are superior to sham rTMS but do not support the hypothesis that bilateral rTMS is more effective than unilateral high-frequency right-sided rTMS.	Head ache

D.H. Nam, et al. (2013) [316]	Korea	A double-blind, sham-controlled study	18 patients	Right-PFC	Re-experiencing symptoms of PTSD	CAPS, SCID	3 weeks	A figure-of-8 coil 100% MT total, 18,000 pulses 3 weeks of 1 Hz for 20 minutes per weekday (for a total of 15 days).	The study showed low-frequency rTMS to be an effective and tolerable option for the treatment of PTSD. Treatment group effect ($df = 1$, $F = 2.36$, $p = 0.147$).	Baseline and at 2, 4, and 8 weeks	The study showed low-frequency rTMS to be an effective and tolerable option for the treatment of PTSD.	Head ache, Dizzi ness
B.V. Watts et al. (2012) [317]	USA	A sham-controlled study	20 patients	Right - DLPFC	Changes in symptom measures	CAPS, BDI, STAI, BNCE	10 days	A figure-of-eight (MCB) 70 coil 90% MT. 1 Hz 20 minutes per day. Each 1-minute cycle consisted of a 20-second stimulation train with a 40-second intertrain interval.	Statistically and clinically significant improvements in core PTSD symptoms CAPS ($p = 0.009$) and PCL ($p = 0.0002$) and depressive symptoms compared with sham treatments. ($p = 0.03$)	At baseline, after 10 rTMS sessions, 1 month after the last session, and 2 months after the last session.	This blinded sham-controlled trial supports the efficacy of 10 sessions of right DLPRC rTMS delivered at 1 Hz for the treatment of PTSD symptoms.	Nil
Boggio et al. (2010) [308]	USA	Double-blind, placebo-controlled phase II trial,	30 patients	L-DLPFC and right DLPFC	PTSD symptoms	PCL-5 HRSD HAMA	2 weeks	Figure-8 coil, 20 Hz at 80% MT 10 TMS, 1600 pulses per session, 5 days per week for 2 weeks.	Results show that both active conditions—20 Hz rTMS of left and right DLPFC—induced a significant decrease in PTSD symptoms.	Baseline, at day 5, at day 10, at day 24, at day 38, at day 66, and day 94 (12 weeks after treatment).	Results support the notion that modulation of the prefrontal cortex can alleviate the core symptoms of PTSD and suggest that high-frequency rTMS of R-DLPFC might be the optimal treatment strategy.	Nil

E.A. Osuch et al. (2009) [318]	USA	Double-blind, sham-controlled crossover design	9 patients	R-DLPFC	Exaggerated reactions individuals have in response to reminders of the traumatic event	CAPS, HDRS	2 weeks	Figure-8 shaped water-cooled coil. 100% MT. 1 Hz. total of 36,000 stimuli in each condition 20 rTMS sessions. 3 sessions per wk and no more than 5 per wk. Each for 30 min. 2 weeks interval between first and second conditions.	Reduction of the exaggerated reactions individuals have in response to reminders of the traumatic event or other stimuli through fear extinction. CAPS ($p = 0.87$) HDRS ($p = 0.92$)	At baseline (within 3 days before the first condition); on the final day of the first condition; on the day before the onset of the second condition; and on the last day of the second condition.	Reduction of the exaggerated reactions individuals have in response to reminders of the traumatic event or other stimuli through fear extinction.	Nil
Cohen et al. (2004) [319]	Israel	A double-blind, placebo-controlled study	24 patients	Right-DLPFC	Reexperiencing, avoidance	HDRS, PCL-C	2 weeks	Circular coil with a 9-cm diameter. (1 Hz) or (10 Hz) rTMS at 80% MT 20 minutes per days. 10 daily sessions over 2 weeks.	10 daily sessions of 10-Hz rTMS at 80% MT over the right DLPFC has therapeutic effects on PTSD patients active 10-Hz rTMS was significantly different from the sham ($p < 0.01$) and 1-Hz ($p < 0.002$) treatments.	Before TMS (baseline), at day 5, at day 10, and day 24 (14 days after the intervention).	Trial suggests that in PTSD patients,10 daily sessions of right dorsolateral prefrontal rTMS at a frequency of 10 Hz have greater therapeutic effects than slow-frequency or sham stimulation.	Head ache

MT = motor threshold; SMA = supplementary motor area; Y-BOCS = Yale–Brown obsessive-compulsive scale; Ham-D–24 = Hamilton Rating Scale for Depression–24-item; BDI–II, DLPFC = dorsal lateral prefrontal cortex; OFC = orbitofrontal cortex; RMT = resting motor threshold; CGI-I = Clinical Global Impression; HAMA = Hamilton Anxiety Rating Scale; HRSD = Hamilton Rating Scale for Depression; YMRS = Young Mania Rating Scale; GAF = Global Assessment of Functioning; MCCB = MATRICS Consensus Cognitive Battery; QIDS = Quick Inventory of Depressive Symptomatology; CAPS = Clinician-Administered PTSD Scale; BNCE = Brief Neurobehavioural Cognitive Examination; STAI = State-Trait Anxiety Inventory; SC-Q = Self-Administered Comorbidity Questionnaire; SCID = Structured Clinical Interview for DSM-IV; IPF = Inventory of Psychosocial Functioning; BRMAS = Bech–Rafaelsen mania scale; CRSD= circadian rhythm sleep disorder; SCL-90-R = Symptom Checklist-90-Revised.

3. Results

Of the 10 studies on rTMS application and treatment included in this review, six (60%) were conducted in the United States. Iran, the Republic of Korea, Canada, and Israel, all had one paper, representing (10%) each. This suggests that studies on rTMS treatment in PTSD are not widely and evenly conducted across geographical regions. All 10 studies applied the randomized controlled trial method but of different formats and forms, such as parallel, double-blind, open labels, and with single, two, or, four arms. The sample size for the various trials ranged from (n = 9 to n = 384). The participants were all patients diagnosed with PTSD.

3.1. Outcome Measures

A wide range of scales was used to measure positive symptoms and reduction in symptoms scales including, PCL-C, PCL-5, CAPS, and HDRS. Safety outcomes included adverse event reporting, neurocognitive assessments, and vital signs assessments.

3.2. Frequency, Intensity of Stimulation, Duration of Treatment, and Brain Target

The frequency of rTMS ranged from as low as 1 Hz to 20 Hz. The majority of the studies (6 out of 10) applied the 1 Hz frequency. The intensity of stimulation reviewed ranged from 80% to 120% motor threshold. The duration of active rTMS treatments ranged from 2 weeks to 12 weeks. Regarding the number of magnetic pulses given per treatment session, the range varied from 1,200 pulses up to 36,000 pulses. The studies were heterogeneous in terms of features of clinical variability, such as the severity of PTSD symptoms and duration of sickness. Of the 10 studies included, seven used 70 mm figure-8 shaped coils, one study utilized the 9 cm circular coil design, and two studies used the double 70 mm air cooled coil. In eight of the ten studies extracted, the site of rTMS stimulation was targeted at the right-DLPFC[311, 315-321], and the remaining two studies sought to compare the efficacy of the right-DLPFC and the left-DLPFC[308, 313].

3.3. Results

Nine of the ten studies reported significant positive outcomes and significant PTSD symptoms improvement. One study that sought to evaluate the effectiveness between low and high frequencies failed to identify any superiority of one over the other. rTMS application was

reported as well tolerated with no significant side effects, although there were a few reports of mild side effects, such as mild headache, dizziness, and scalp pain, across the studies.

4. Discussion

This review found that rTMS may be a clinically efficacious treatment modality for patients diagnosed with PTSD. There were consistent significant improvements in the condition of subjects across the studies despite the diverse nature of the outcomes. Many factors may have accounted for the differences in the effectiveness of rTMS application across the major domains. For example, rTMS treatment protocols and stimulation parameters vary across studies, with poorly defined application protocols. Again, the different measuring tools used for the evaluation of similar outcomes across studies make comparison and evaluation of results difficult. It also makes it difficult to identify which rTMS application protocols led to the most significant treatment response. However, due to the differences in the presentation of patients' conditions in terms of severity and duration of illness, it may be unrealistic to identify a single or even a standardized rTMS protocol that works for studies of the different conditions even if they target similar or the same symptoms[244]. An essential aspect of rTMS as identified in this review is its versatility, giving its application room for study-specific protocols addressing different symptoms and still resulting in potentially positive outcomes.

Although data suggest that rTMS may have some therapeutic effect in managing PTSD[322], data mostly present without information about maintenance treatment or long-term outcomes[323]. The possible effect of rTMS may be through stimulation of the prefrontal cortex, especially the ventromedial aspects, hence inhibiting the hyperactive amygdala and the overactive sympathetic system, which in turn may explain the reduction of hyperarousal symptoms in PTSD[322, 323].

4.1. Targeted Brain Regions of rTMS

According to neurobiological and imaging studies, post-traumatic stress disorder is characterized by a dysregulated fear response and a hyperactive amygdala. The regions involved in the modulation of the amygdala, thus, the medial prefrontal cortex and hippocampus, have a reduced activity to fear cues in functional magnetic resonance imaging studies[324]. Considering the pathophysiology of PTSD, neuromodulation of prefrontal structures using rTMS has been

hypothesized by many studies to have potential effects in the treatment of patients with PTSD[322, 325]. Some studies have also suggested that rTMS induced significant changes in a monoamine receptor in the cerebral cortex, and has a substantial and rapid effect on the monoamine neurotransmitters system[315, 322]. Studies evaluating the use and efficacy of rTMS as a treatment intervention for PTSD are still accumulating and evolving[305]. In eight of the ten studies extracted, rTMS stimulation targeted the right DLPFC[311, 315-321], and the remaining two studies sought to compare the efficacy of the right DLPFC and the left DLPFC[308, 313] . In a double-blind placebo-controlled study[317], the efficacy of a right-sided low-frequency rTMS to sham treatment in 20 patients diagnosed with PTSD found clinically significant improvements in PTSD symptoms and depressive symptoms compared with sham treatments. Although the improvement of depression symptoms by rTMS improves PTSD symptoms, the majority of rTMS studies have sought to stimulate the R-PFC for PTSD versus L-PFC commonly targeted in MDD[320, 321].

Another open-label and prospective trial, involving nine subjects conducted over the R-DLPFC[326] with treatment lasting for 4 weeks reported that right prefrontal rapid TMS is safe and efficacious in the treatment of PTSD. Similar studies of rTMS[312, 316, 318, 319, 327] applied over the R-DLPFC included in the study, all suggested the safety and efficacy of rTMS for the treatment of PTSD. Boggio et al. (2012), evaluated the clinical significance of right versus left PFC stimulation with high frequency (20 Hz) rTMS involving 30 subjects diagnosed with PTSD. Although the study significantly improved symptoms of PTSD as measured on PCL in both right and left DLPFC treatment against the sham treatments, R-DLPFC had a significant edge over the L-DLPFC at the post-treatment follow up. These results affirm the assertion that modulation of the prefrontal cortex can minimize the core symptoms of PTSD and suggest that high-frequency rTMS of R-DLPFC might be the optimal treatment strategy.

In their study, Ahmadizadeh et al.[315] summarized that both bilateral and unilateral rTMS are safe and effective treatments for patients with PTSD as they are superior to sham rTMS but they do not support the hypothesis that bilateral rTMS is more clinically significant and effective than unilateral high-frequency right-sided rTMS.

4.2. Effects of High and Low Frequencies

The pattern drawn from the reviewed studies suggests there is no significant advantage in high versus low frequencies as both 1-Hz and 10-Hz protocols over L-DLPFC or R-DLPFC appear effective, safe, and tolerable to participants.

4.3. Tolerability/Side Effects of rTMS

The overall importance of any treatment intervention must acknowledge its efficacy as well as any safety and tolerability issues. rTMS is generally noted in the literature as tolerable, with minimal or no major side effects on patients. Data from this review suggest the application was generally highly tolerated with minimal side effects, such as mild headache, dizziness, localized scalp pain, and, at times, stimulation of facial nerves during the administration of rTMS.

4.4. Limitations

This scoping review has several limitations. First, our search strategy considered only studies published in English. Secondly, although we tried to identify all necessary studies per our eligibility criteria, we may have missed some relevant studies, with special emphasis on those published in other languages. Notwithstanding these limitations, the therapeutic potential of rTMS for treating PTSD as evidenced from the studies appears robust.

5. Conclusion

In summary, the review of these ten studies suggests that rTMS may be effective as a treatment for symptoms of PTSD. The study found significant heterogeneity concerning the sites and intensity of stimulation as well as the outcomes of rTMS use in PTSD management. Findings suggest that the application of rTMS to the right DLPFC may be more effective than left DLPFC. There seems to be no significant advantage in high versus low frequency; and rTMS was generally well tolerated. Both 1-Hz and 10-Hz protocols over L-DLPFC or R-DLPFC appeared acceptable to participants. The treatment is generally well tolerated with mild side effects.

Despite limitations and concerns, the field of therapeutics in PTSD is progressing toward the use of innovative treatment approaches, such as rTMS. Though the data from the 10 studies reviewed are diverse in terms of their outcomes and clinical viability, there is enough evidence to show

that rTMS is a promising treatment intervention in PTSD. However, a definitive conclusion of the clinical effectiveness of rTMS and its long-term treatment outcomes and use in maintenance treatment in PTSD is yet to be established. More studies, particularly systematic reviews of RCTs with well-defined stimulation parameters, must be conducted with large sample sizes to evaluate the true effect of rTMS in PTSD. It will be appropriate for researchers to find a robust and refined methodology that includes the risk of bias assessment, quantitative analysis, and evaluation of the reliability of findings across different outcomes by the use of the Grading of Recommendations Assessment, Development, and Evaluation, which is applied in many major guidelines and is being considered a universal standard method of providing a transparent and authentic estimate of evidence.

1.6: The Use of Internet-Based Cognitive Behavioural Therapy (iCBT) in Treatment-resistant Depression: General Review.

Medard Kofi Adu, Reham Shalaby, Adegboyega Sapara, and Vincent Israel Opoku Agyapong.

Abstract

Background: According to the World Health Organization (WHO), major depression disorder (MDD) is the leading cause of disability, globally and the fourth leading cause of total global burden of disease in 1990. Over 34 million cases of MDD remain untreated annually in the United States and Europe. These data reflect the importance of treatments that reduce current depressive symptoms and minimize the rate of relapse. Internet-based treatment interventions such as iCBT have been proposed in the literature as one of the major means to help close the treatment gap that exists for most psychiatric conditions, including treatment-resistant depression (TRD).

Objectives: This review aims to explore the literature regarding the use of iCBT in TRD and to gather evidence in support of the effectiveness of iCBT in the management of the same. **Methods**: This study was designed as a general review. We aimed to examine the literature covering iCBT in TRD, regarding the origin and progression of the technology and effectiveness/efficacy of iCBT in TRD. AN electronic data search was conducted in five databases (MEDLINE, CINAHL, Psych INFO, SCOPUS, and EMBASE) using all identified keywords and index terms across all the databases to identify evidence-based studies. We included the individual studies as well as meta-analyses or reviews written in English. In **conclusion**, the reviewed studies demonstrate that iCBT serves as a vehicle for innovation and holds promise as a means to widen access to evidence-based psychological treatment. Within the past decades, internet interventions and iCBT have experienced considerable advancement in their operations by providing a variety of techniques and protocols that seem to be efficacious and effective for the management of depressive disorders.

Key words: Internet-based cognitive behavioural therapy; major depressive disorder; treatment resistant depression; mental health; treatment

Introduction

Major depressive disorder (MDD) is a common psychiatric condition and a major public health issue that impacts heavily on individuals, society and public healthcare systems of the world[115]. Thus, according to the World Health Organization(WHO), MDD is the leading cause of disability globally[328] and the fourth leading cause of total global burden of disease in 1990[328]. Depression remains one of the leading causes of disability-adjusted life years (DALY) globally, accounting for 4.46% of total DALYs in 2000[329]. Over 34 million cases of MDD remain untreated annually in the United States and Europe according to data from the WHO[330]. These data reflect the importance of treatments that reduce current depressive symptoms and minimize the rate of relapse.

Many barriers hinder access to treatment for psychiatric conditions; hence, the wide treatment gap that has emerged. These barriers include the cost of treatment, perceived stigma of seeking treatment, the long wait lists, limited availability of therapeutic interventions, and inadequate healthcare personnel[73]. These factors notwithstanding, computerized and internet-based treatment interventions proposed in the literature are one of the major means to help close the treatment gap that exists for most psychiatric conditions, including depression. One such intervention is internet-based cognitive behavioural therapy (iCBT) for the treatment of resistant depression(TRD) [331].

Despite pharmacotherapy being a key component of standardized treatments for MDD, treatment resistance remains a significant problem in the field of depression[332]. The definition of TRD is sparse in the literature but it is commonly explained as the failure of an MDD patient to respond adequately to two or more types of pharmacotherapies[333]. According to the data, about one-third of MDD patients become nonresponsive to pharmacotherapy [333]. In another study, 50-60% of MDD patients fail to respond to antidepressant therapy[17]. Therefore, the management of TRD has become a major concern for healthcare providers and the healthcare system, who try to find appropriate and integrated treatment approaches to manage individuals, aiming to close the treatment gap that exists for TRD along with its socioeconomic burden on the individual and society[334]. Additionally, it became essential for research and policy to evaluate and look out for well-tailored remote delivery means, such as the internet-based psychological treatment interventions that proved significant efficacy and an appropriate mode of delivery[334].

Advanced information technology has greatly influenced how communication and interactions among individuals globally are patterned[335]. The use of computers and the internet in clinical practice has also increased rapidly. These technological advances have therefore dominated practices in clinical psychiatry and psychology[336, 337]. They are highly accessible and have websites that provide information regarding mental health conditions, diagnostic criteria, and assessment techniques[338-340]. One key internet intervention is the use of smartphones in data collection[341] which additionally has helped to disseminate therapeutic interventions for people with mental health concerns, such as stress and resistant depression, who would otherwise have limited access to these interventions in times of need[342, 343].

Methodology

This study was designed as a general review of the literature. We examined the literature covering iCBT in TRD regarding the origin and progression of the technology, effectiveness/efficacy of iCBT in TRD, examples for software and platforms incorporated in this technology, accessibility, economic implications, iCBT during the COVID-19 pandemic, transdiagnostic and tailored iCBT, downsides and challenges, and future implications of the technology.

We visited five databases, MEDLINE, CINAHL, Psych INFO, SCOPUS, and EMBASE, using all identified keywords and index terms to identify evidence-based studies examining iCBT in TRD. We included individual studies as well as meta-analyses or reviews. For the clinical outcome of iCBT, the studies covered focused on the reviews or meta-analyses that reported on the clinical effectiveness/efficacy of iCBT (+/- effect size), while considering related individual studies for the rest of the topic. Included studies were limited to those written in English.

iCBT Overview

Focusing on cognitive-behavioural therapy (CBT), this first psychotherapeutic intervention was developed and offered as part of routine care practice in the 1960s[344, 345]. Since its development and evaluation, CBT has grown rapidly, and emerged as one of the most frequent and extensively studied interventions compared to other forms of psychotherapy[346]. Although several kinds of psychotherapy are deemed effective in treating depressive disorders[347], CBT is believed to have a solid empirical base with a large number of control studies compared to

other psychotherapies[347]. A large body of studies attests to the efficacy and effectiveness of CBT in reducing symptoms and rates of relapses in depressive disorders[346, 348]. CBT is presented in many forms but the dominant kind is individual or group face-to-face therapy[73]. Similarly, iCBT interventions in children and adolescents have been found to be effective and significant in reducing depressive symptoms. In a general population study of young people, there were small positive effects for depression (SMD −0.15, 95% CI −0.26 to −0.03; N = 1280).[349].

Despite this, the development of the internet-based form of CBT (iCBT) coupled with the rapid rise in internet access globally, have grown the potential to transform positively the scope of the psychological, behavioural, and mental healthcare system[73].

iCBT can be administered with or without guidance. With assistance, iCBT was found to take less therapist time than individual face-to-face CBT[350]. The assistant can be a therapist or a technician. While the technician uses scripts to coach, the therapist can provide clinical advice or send out brief motivational messages and reminders to the patient[350]. In guided iCBT, the guidance can be given while the program is in session or outside the session and can also be by telephone[351].

Older forms of iCBT were presented in the forms of internet-based self-help books and psychoeducational materials but the current versions have more interactive content with quality graphical representations and audios visuals, and are in different languages to reach a wide range of audiences[352]. The different varieties of iCBT usually require computerized software platforms through which the interventions can be administered[353]. In guided iCBT, the interactions between patients and therapists on these software channels come in the form of assessment instruments and treatment materials. The content of the interventions is delivered in the form of videos, audio, and text messages[354]. Unguided iCBT does not involve a therapist since it depends primarily on computerized platforms or software provided to the customers, who can navigate the material themselves following a timeline scheduled modules[355].

Examples of Software/Platforms Used in iCBT

Several forms of iCBT programs were identified in the literature for managing depression. For example, the UK-developed cognitive-behavioural Beating the Blues (BTB)[72]. The BTB is made up of eight unique online cognitive modules on depression, each of which takes about 50

minutes to complete. Each module in BTB is accompanied by a home assignment after completion[71, 72].

MindBeacon provides care that is accessible anytime through any digital device of choice. MindBeacon is committed to evidence-based care, and was developed by experts with knowledge in CBT[356]. This digital platform is designed to address the mental health needs of its users while helping them to build psychological resilience[356]. This iCBT platform has embedded in its protocol a licensed therapist who is knowledgeable in the mental health needs of their clients, and helps them to develop protocols that best suit their needs. Patients may also send a message to the therapist when the they need help or clarity in any of the assigned protocols, even from home[356].

MoodGYM was developed in Australia. It is an interactive, self-assisted book that leads a patient to learn and practise skills that can help to prevent and manage symptoms of depression and anxiety. MoodGYM consists of five unique modules. The modules targeted the relationship between thoughts and emotions, identifying cognitive distortions and negative thoughts, techniques to adjust negative thoughts, assertiveness and self-esteem training, behavioural activation, and problem-solving[357]. This platform also comes with a personalized workbook, which consists of assessments and easy access to quizzes and diaries[357].

Accessibility and Economic Values of iCBT

I-CBT has numerous benefits for its management of major depressive disorders compared to conventional face-to-face contact treatment. As noted in the literature, a major reason for people suffering from mental health conditions is not receiving adequate treatment due to their inability to access care[330].

Additionally, unlike traditional face-to-face care, iCBT does not require any strict insurance policy for users to access the various platforms to engage in the treatment interventions[358]. These software interventions come with relatively small fees and, at times, can be accessed free of charge. Overall, iCBT is deemed a cost-effective intervention despite limited data backing this assertion[358, 359]. The common and critical issue of perceived stigma is also adequately dealt with in the case of iCBT, specifically self-assisted iCBT where patients feel confident and safe to receive care in their homes while protecting their privacy, hence increasing the number of patients receiving care[73]. With the advent of internet-based interventions such as iCBT,

patients who would have had difficulty accessing treatment due to the limited resources can conveniently receive treatment in their homes or any place they have internet connectivity. Thus, as more patient receive care through this medium, patient wait time within healthcare facilities are reduced, which eventually helps reduce the problem of the treatment gap for depression and helps raise the functional capacity of the healthcare system[73].

Furthermore, an essential aspect of web-based interventions is their positive influence on clinical research[360]. Studies involving psychotherapy in randomized control trials are often deemed expensive as opposed to research conducted online[359]. Thus, studies examining web-based services such as iCBT may be less costly and conducted over a short period. Compared to traditional clinical trials, the recruitment process of such web-based services is quite easy and faster since they are not geographically bound[361]. Again, with the use of validated instruments, web-based interventions can accrue more self-reported data from participants. With online interventions, the actual time spent on each client is less (average of about 10 minutes) compared to about 45-minute weekly sessions of conventional face-to-face treatment research[361]. Diagnostic procedures are mostly conducted online through structured interviews, which can save the long wait times reported for traditional face-to-face procedures. Furthermore, online platforms can be accessed without concerns about limited space; this can significantly help increase the delivery of therapeutic content to the patients without having to use a therapy room[73].

Evidence of Therapeutic Effect of iCBT in TRD

The last few decades have seen a steady growth of evidence in support of the therapeutic benefits of iCBT in managing depression[362, 363]. Users of these interventions and the therapists involved can afford to select these modalities out of the many different but comparable helpful psychotherapeutic treatment interventions for TRD[363]. Following our search criteria, we found only two meta-analyses that examined the iCBT effectiveness in TRD management. iCBT, according to the two meta-analyses, is effective in reducing depression symptoms compared to conventional treatment methods[351, 364]. The studies found a small-to-moderate post-treatment effect size (g= .36) and (d = .56)[351, 364] favouring iCBT over control groups regarding improving depressive symptoms[365]. In addition to the projection of iCBT to reduce treatment gaps for mental health conditions[366], internet-based interventions for depression add

additional prospects for the wide dissemination of evidence-informed psychotherapeutic interventions to the global space[367]. Most of these standardized and highly structured web-based interventions follow the design and principles of iCBT[368].

In this regard, a systematic review and meta-analysis study conducted by Richards and Richardson evaluated the overall effectiveness of internet-based interventions in the management of depression[365]. They further examined the impact of support on attrition rates and clinical outcomes, revealing the overall significant efficacy and effectiveness of iCBT in depression. However, the attrition rate was quite high, particularly in the self-assisted iCBT(74%) group compared to therapist-guided iCBT(28%)[365]. This may imply that, to sustain patients' engagement and reduce the rate of dropout in iCBT interventions, some assistance seems important. Consistent with other iCBT studies, Twomey and O'Reilly in their meta-analysis also garnered evidence in support of the effectiveness of self-assisted cognitive behavioural therapy program (MoodGYM) for depression in an adult population by evaluating 11 studies producing results with a small effect size (g = 0.36, 95% confidence interval: 0.17–0.56; I2 = 78%)[369].

Transdiagnostic and Tailored iCBT

Considering that anxiety is a major comorbidity of MDD, transdiagnostic iCBT interventions have been developed and found efficacious in reducing the symptoms of comorbid anxiety and depression within the same program[370]. Furthermore, specialized iCBT interventions have been designed and made fit to target the distinct characteristic features or symptoms of every individual patient. For instance, a study was conducted on MDD patients characterized by different comorbidities. The participants were tested with a standard, all-purpose iCBT protocol against a tailored iCBT technique that took into account the symptoms of each participant. Thus, participants in the tailored iCBT intervention who presented with a considerable amount of worry aside from the usual depression symptoms were received an iCBT module that focused on worry in addition to the modules that addressed their depressive symptoms [371]. Despite both tailored and standard iCBT arms of the study producing significant symptoms improvements in depression and anxiety, subset analyses suggested that participants with higher pre-treatment major depression scores benefited immensely from the tailored intervention[371].

Influence of the COVID-19 Pandemic on iCBT

In the face of adversities, such as severe outbreaks of infectious diseases including the COVID-19 pandemic, several health measures were proposed, such as the imposition of mass quarantines[372], self-isolation, and social distancing[373], aimed at protecting the population and mitigating the impact of the infection. Inadvertently, these factors collectively increased the existing treatment gap for people with mental health concerns[374]. During the COVID-19 pandemic, there was an increased need for mental healthcare as a result of the economic hardship, stress, and grief brought on by the public health restrictions and the devasting nature of the pandemic itself. The situation called for an immediate solution to care and, hence, accelerate the pace of adopting the technology of internet-based interventions, such as iCBT when face-to-face treatment methods were limited and, in some instances, inaccessible[352]. More clinicians quickly moved from in-person visits to telehealth and more clients with depression and resistant-depression concerns logged onto iCBT treatment platforms for their mental health needs[352]. Thus, internet-based interventions became a cost-effective and accessible alternative means to render mental health care and psychotherapy the conventional means of care delivery were limited. Plenty of evidence in the literature supports internet-based treatment interventions and iCBT, especially for the management of depression and anxiety disorders during natural disasters and pandemics[375].

Issues of Concern about the Efficacy of iCBT

Internet-based therapeutic modalities, like other interventions, post their own risk and limitations to users although most of these negative effects go unnoticed. In the case of iCBT, the negative consequences have been evaluated and documented in the literature[376]. Assessment of current iCBT platforms indicates a seemingly ill-equipped software that may not have the capacity to identify or deal with clinical crises, such as suicidality[73]. These web-based software platforms are unlike conventional face-to-face therapy where the therapist could identify suicidal ideations and swiftly recommend an alternative treatment to curb the crisis.

An important aspect of internet-based interventions such as iCBT is its ability to reach a wide variety of people with depression concerns who normally would have had difficulty receiving treatment. However, an earlier concern about the iCBT intervention is its high attrition rate. Data report that the dropout rate in unguided iCBT is greater than that of guided iCBT, (72%) versus

(26%), respectively[365]. This notwithstanding, iCBT interventions, in their attempt to increase treatment patronage and reduce the attrition rate, usually integrate administrative support teams including therapists into the service to increase participants' engagement. For instance, in one study, researchers utilized brief weekly phone calls and emails from research assistants to respond to and give feedback to users on issues or concerns related to the content of the intervention[377].

Aside from the positive outcomes of iCBT and web-based interventions that support their therapeutic efficacy for the management of depression, the literature proposes major unanswered questions that need critical evaluation to ascertain the true efficacy of these interventions, especially while considering the proper dissemination of these treatment modalities for TRD in clinical settings[378]. The queries include the transferability of interpersonal therapeutic protocols from conventional to computerized treatments, raising concerns regarding patients' adherence to treatment and possible clinical outcomes. Though it may be concluded that, to obtain good clinical outcomes compared to face-to-face CBT, iCBT interventions need to incorporate some level of therapist assistance. The standard of therapeutic relationships and individual support are not clearly stated in the research related to the iCBT interventions[362]. Thus, no clear road map defines the role of the therapeutic relationship between the client and therapist in iCBT. This may be due to the limited number of studies targeting this valid outcome despite the evidence of the usefulness of this therapeutic working alliance in traditional face-to-face psychotherapeutic interventions[379].

Some valid developer concerns raised in literature concern the privacy of patients while accessing and interacting online platforms. Since vital health information could be shared by patients while accessing iCBT, it is recommended that developers of the web-based platforms put measures in place to regulate and safeguard the health-related information of their users[380]. Another downside of iCBT applications is that they provide a limited data regarding the characteristics of individuals who can use and benefit from their application. Although studies have explored this area in research, only a handful of consistent findings have been identified in the literature[381, 382]. Additionally, the probable negative outcomes or risks that may be posed to the users of internet-based interventions, especially iCBT, are mostly ignored and not evaluated in the literature on psychological treatment interventions[383].

Conclusions

ICBT and other forms of internet-based therapeutic interventions serve as vehicles for innovation, and hold promise to widen access to evidence-based psychological treatment. Within the past decades, the field of internet interventions and iCBT has experienced considerable advancement by providing a variety of techniques and protocols that seem to be both efficacious and effective in managing depressive disorders. This psychotherapeutic approach seems to guarantee increased access, improved outcomes, and a reduction in the high cost of treatment for depression. However, it is difficult to foretell how technology will advance and be integrated into clinical use in the future due to the dynamics of everyday life circumstances.

Future Directives

Future narratives on the effective implementation strategies of web-based interventions for managing TRD should also consider issues on specific predictors and impediments of their usage that can be addressed in future studies and practices. Furthermore, a conscious effort should be made by inventors and researchers to update healthcare providers with current information and evidence-based technological advances in the field of psychological treatments for TRD, such as internet-based and smartphone-delivered interventions, including iCBT, to educate their clients and enable them to make informed choices about appropriate and easily accessible forms of support that meet their individual treatment needs.

CHAPTER 2: Protocol and methodology

The methodological details are provided in the following section with respect to the published protocol for the main study in this thesis as:

Repetitive Transcranial Magnetic Stimulation with and Without Internet-Delivered Cognitive-Behavioral Therapy for the Treatment of Resistant Depression: Protocol for Patient-Centered Randomized Controlled Pilot.

Abou El-Magd, R. M., Obuobi-Donkor, G., **Adu, M. K.,** Lachowski, C., Duddumpudi, S., Lawal, M. A., . . . Agyapong, V. I. O. (2020). Repetitive Transcranial Magnetic Stimulation with and Without Internet-Delivered Cognitive-Behavioral Therapy for the Treatment of Resistant Depression: Protocol for Patient-Centered Randomized Controlled Pilot Trial. JMIR Res Protoc, 9(10), e18843. doi:10.2196/18843

Available at: https://www.researchprotocols.org/2020/10/e18843/

Abstract

Background

Major depression is a severe, disabling, and potentially lethal clinical disorder. Only about half of patients respond to an initial course of antidepressant pharmacotherapy. At least 15% of patients with major depressive disorder (MDD) remain refractory to any treatment intervention. By the time a patient has experienced three definitive treatment failures, the likelihood of achieving remission with the fourth treatment option is below 10%. Repetitive transcranial magnetic stimulation (rTMS) is a treatment option for patients with MDD who are refractory to antidepressant treatment. It is not known if adding internet-delivered cognitive-behavioural therapy (iCBT) enhances patients' response to rTMS treatments.

Objective

This study will evaluate the initial comparative clinical effectiveness of rTMS with and without iCBT as an innovative patient-centred intervention for the treatment of participants diagnosed with treatment-resistant depression (TRD).

Method

This study is a prospective, two-arm randomized controlled trial. In total, 100 participants diagnosed with resistant depression at a psychiatric care clinic in Edmonton, Alberta, Canada, will be randomized to one of two conditions: (1) enrollment in rTMS sessions alone and (2) enrollment in rTMS sessions plus iCBT. Participants in each group will complete evaluation measures (e.g., recovery, general symptomatology, and functional outcomes) at baseline, 1 month, 3 months, and 6 months. The primary outcome measure will be the mean change to scores on the Hamilton Depression Rating Scale. Patient service utilization data and clinician-rated measures will also be used to gauge patient progress. Patient data will be analyzed with descriptive statistics, repeated measures, and correlational analyses.

Results

We expect the results of the study to be available in 24 months. We hypothesize that participants enrolled in the study who receive rTMS plus iCBT will achieve superior outcomes than participants who receive rTMS alone.

Conclusion

The concomitant application of psychotherapy with rTMS has not been investigated. We hope this project will provide a concrete base of data to evaluate the practical application and efficacy of using a novel combination of these two treatment modalities (rTMS plus iCBT).

Trial Registration

ClinicalTrials.gov NCT0423965; https://clinicaltrials.gov/ct2/show/NCT04239651

International Registered Report Identifier (IRRID) PRR1-10.2196/18843

Keywords: repetitive transcranial magnetic stimulation, internet-delivered cognitive-behavioral therapy, treatment of resistant depression, cognitive-behavioral therapy, depression

Introduction

Background and Rationale

Major depression is a severe, disabling, and potentially lethal clinical disorder[384-386]. Although a wide variety of pharmaceutical agents are available as treatments, only about half of patients respond to an initial course of antidepressant pharmacotherapy[22, 387]. For these patients, the current standard of care involves an empirical series of treatment attempts, typically using medication switches, antidepressant combinations or adjunctive therapy with mood stabilizers, benzodiazepines, atypical antipsychotics, or other agents[388]. The adverse event burden and tolerability of some of these more complex interventions are not trivial and are a significant factor that hinders patient adherence to treatment[389]. Similarly, although increasing evidence shows that at least some atypical antipsychotics are effective as adjuncts to antidepressants, the potential for side effects, including weight gain and dyslipidemia, warrants both caution and careful clinical management.

It has been conservatively estimated that at least 15% of all patients with major depressive disorder (MDD) remain refractory to any treatment intervention[387, 388]. Although a complicated relationship exists between disease chronicity and ineffective treatment[390], clinical evidence suggests that the higher the number of treatment failures, the lower the likelihood of good treatment response to subsequent interventions[22, 391]. The results of the STAR*D study are the most vivid example of this clinical phenomenon[28, 392-397]. In that work, there was an increased likelihood of reduced response with each successive treatment failure. For example, after the first treatment attempt, about 30% of patients remitted. By the time a patient had experienced three definitive treatment failures, the likelihood of achieving remission with the fourth treatment fell below 10%. Poor treatment adherence and high discontinuation rates represent a major challenge, particularly for pharmacotherapy. Strategies for enhancing adherence include patient education and supported self-management as well as the use of collaborative care systems by practitioners. Treatment adherence should be discussed at an early stage and monitored frequently in a collaborative manner. A weak therapeutic alliance predicts poorer treatment adherence[398]. These facts underline the clinical urgency for physicians to identify treatment-resistant patients as early as possible so that alternative treatments with proven efficacies may be offered sooner. In turn, this will result in superior treatment outcomes.

Technology and the internet have dramatically changed medicine. According to Statistics Canada, 83% of Canadians had internet access in 2012, and more than 70% use the internet daily; in addition, 62% were smartphone users[398]. E–mental health refers to the use of computers, internet, and mobile devices for mental health information and care provision[399]. E–mental health apps are now widely available for information, screening, assessment and monitoring, interactive self-management, psychotherapy, and social support. Clinicians should be aware of the benefits and potential harms to using and recommending e–mental health apps, and that few have good-quality evidence of effectiveness[399-401]. Meta-analyses and reviews of computer-based psychological treatment for the treatment of MDD, whether delivered over the internet or as a stand-alone program, demonstrate convincing support for these treatment modalities[365, 402-407]. Internet- and computer-delivered cognitive behavioural therapy (iCBT) can also be helpful in relapse prevention[408].

In 2009, the Canadian Network for Mood and Anxiety Treatments (CANMAT), a not-for-profit scientific and educational organization, published a revision of evidence-based clinical guidelines for the treatment of depressive disorders[409]. CANMAT updated these guidelines in 2016 to reflect new evidence [410-415]. These updated CANMAT guidelines cover a variety of treatments, including psychological treatments in general and cognitive-behavioural therapy (CBT) in particular, as well as pharmacological treatments, neurostimulation, and complementary and alternative medicine (CAM) treatments. Choosing a first-line treatment remains a collaborative decision between patient and clinician. However, there continues to be greater evidence and clinical experience with traditional treatments (psychotherapy and pharmacotherapy) and few studies directly comparing these with neurostimulation or CAM treatments. In addition, many studies of neurostimulation include populations of patients who have failed at least one treatment. Therefore, first-line psychological and/or pharmacological treatments should usually be considered before neurostimulation or CAM treatments[398, 411-415].

Neurostimulation, also referred to as neuromodulation, is an expanding area of research and clinical interest, driven in part by the increasing knowledge base on the neurocircuitry of depression[416]. Most of these neurostimulation treatments have been studied and are used in patients with TRD who have failed to respond to standard treatments[413]. However, no studies examined the effect of rTMS plus iCBT compared to rTMS alone. Our study seeks assess the

initial comparative clinical effectiveness of rTMS treatments when used with and without iCBT in a patient population where an improvement in treatment effects is much needed.

Repetitive Transcranial Magnetic Stimulation

rTMS uses powerful (1.0-2.5 Tesla) focused magnetic field pulses to induce electrical currents in neural tissue noninvasively via an inductor coil placed on the scalp. Therapeutic rTMS is usually delivered by a trained technician or nurse under physician supervision. Unlike electroconvulsive therapy (ECT), no anesthesia is required. The therapeutic mechanism of rTMS is still under investigation, with mechanisms proposed at molecular, cellular, and network levels[417]. Standard protocols deliver rTMS once daily, five days/week. Stimulation three times/week has been reported as similarly effective, albeit with slower improvement and a similar number of sessions required overall[241]. "Accelerated" protocols with multiple daily sessions (2-10/day) are being explored to complete the course more rapidly[418, 419]. Repeated rTMS sessions can exert therapeutic effects lasting several months[413]. Clinical trials and naturalistic studies have found maximal effects at 26-28 sessions[207, 420]. Clinical experience concurs in suggesting 20 sessions before declaring treatment failure, with extension to 25-30 sessions if improvements occur[413].

More than 30 systematic reviews and meta-analyses have been conducted on rTMS in depression, with most studies involving participants with some degree of treatment resistance (i.e., having failed at least one or two antidepressant trials). Overall, rTMS is considered a first-line treatment for MDD for participants who have failed at least one antidepressant treatment. Both high-frequency (10 Hz) rTMS of the left dorsolateral prefrontal cortex (DLPFC) and low-frequency (1 Hz) rTMS of the right DLPFC have demonstrated efficacy in numerous meta-analyses[108, 421-423], with no differences in outcomes between them[421]. Hence, both high-frequency left DLPFC and low-frequency right DLPFC are first-line rTMS protocol recommendations.

The efficacy of rTMS is established in patients with TRD defined by stringent criteria[424]. The most recent meta-analysis of high-frequency left DLPFC rTMS for TRD (23 trials, n=1156) illustrated significant efficacy of rTMS over sham, with a weighted mean difference of 2.31 and an effect size of 0.33[425]. In addition, randomized controlled trials (RCTs) with adequate sessions (20-30) and treatment durations of four weeks or more achieved 40%-55% response and

25%-35% remission rates; and a real-world effectiveness study reported 58% response and 37% remission rates[420]. Similarly, for low-frequency right DLPFC rTMS, a meta-analysis (8 trials, n=263) revealed that patients who received the treatment had superior remission rates than sham (35% versus 10%, respectively, P<.001)[426]. Maintenance treatment is essential to prevent relapse following successful rTMS sessions. One study (n=204) reported median relapse time at 120 days, with relapse rates of 25%, 40%, 57%, and 77% at 2, 3, 4, and 6 months, respectively[427]. In another study (n=257), maintenance rTMS sessions were needed over 12 months for sustained remission in 71% of rTMS remitters and response in 63% of rTMS responders[428]. Moreover, a study found that, without maintenance, 38% of rTMS responders relapsed within 24 weeks at a mean of 109 days post-treatment[429]. With reintroduction of rTMS as needed, 73% met response criteria and 60% met remission criteria at 24 weeks[429]. Various rTMS maintenance schedules have been proposed[430, 431], yet insufficient evidence supports any particular schedule of maintenance sessions.

Cognitive-Behavioural Therapy

Cognitive-behavioural therapy is an evidence-based, structured, intensive, time-limited, symptom-focused form of psychotherapy recommended for the treatment of major depression and anxiety disorders[432]. Internet-delivered CBT (iCBT) is structured CBT delivered via the internet. CBT helps people become aware of how certain negative automatic thoughts, attitudes, expectations, and beliefs contribute to feelings of sadness and anxiety. Specifically, “people undergoing CBT learn how their thinking patterns, which may have developed to deal with difficult or painful experiences and negatively affect their behaviour, can be identified and changed to reduce unhappiness”[433].

Barriers to conventional face-to-face treatment include stigmas around seeking help in person, geography (distance from a healthcare professional), time, and cost. Increasingly, there is a desire to pursue internet delivery as an option to increase access to treatment[434].

iCBT consists of structured modules with clearly defined goals, and delivered via the internet[433]. Although there are many types of iCBT programs, each is a goal-oriented session that typically consists of 8-12 modules and can be guided or unguided[433]. iCBT programs are made available by computer, smartphone or tablet for a fee[433]. With unguided iCBT, participants are informed of a website through which they can participate in an self-directed

program. Guided iCBT involves support from a regulated health professional (e.g., social worker, psychologist, psychotherapist, occupational therapist, nurse or physician). In guided iCBT, people complete modules and communicate their progress via email, text messages or telephoneto a regulated health care professional[433].

MoodGYM is the iCBT program that will be used in this study. It aims to help participants identify and overcome emotional problems and demonstrate how patients can develop good coping skills for good mental health. It is a modular program developed by the Centre for Mental Health Research at the Australian National University[435]. Each module explores topics including: why someone feels the way they do, changing the way they think, changing "warped" thoughts, knowing what makes an individual upset, assertiveness, and interpersonal skills training[435]. Once registered, individuals work through a series of modules or workbooks, which can be undertaken piecemeal depending on the time available. Many studies have demonstrated the effectiveness of MoodGYM for MDD and anxiety in both outpatients and inpatients in different clinical settings[69, 364, 400, 402, 436-442]. In addition, it is effective for mitigating burnout, depression, and suicidality among healthcare students and professionals[443].

Objectives

The goal of this project is to evaluate the initial comparative clinical effectiveness of rTMS treatments when used with and without iCBT. Due to the limited availability of data in this area, another goal is to generate effect size data for these interventions, which will help inform sample size and power calculations for a full randomized clinical trial. Patient outcomes are organized according to recovery variables (e.g., recovery and stigma), functional variables (quality of life and employment), symptom variables (psychological symptoms and overall outcomes), and service variables (eg, health service utilization, cost, and satisfaction).

Methods

Ethics and Dissemination

The study will be conducted per the Declaration of Helsinki (Hong Kong Amendment) and the Canadian guidelines for Good Clinical Practice. All participants will provide informed consent before inclusion. The results will be disseminated at several levels, including participants,

practitioners, academics/researchers, and healthcare organizations. The study will be a prospective, parallel design, two-arm, rater-blinded randomized controlled pilot trial with a recruitment period of 12 months. It will involve active treatment for six weeks and an observation period of six months for each participant. An overview of the timeline for the project is in Table 1. The research will be carried out in an addiction and mental health clinic in a large, sociodemographically diverse city in Western Canada (Edmonton, Alberta).

Table 2.1: Gantt chart timeline.

Milestones	Year 1				Year 2	
	Q1	Q2	Q3	Q4	Q1	Q2
Milestone 1: Recruiting and training of trainee in psychiatry, setting up of infrastructure for iCBT[a]						
1.1. Advertising and recruitment of a trainee in psychiatry to support the research/evaluation of the project component, apply rTMS[b,] and facilitate iCBT.	✓					
Milestone 2: The recruitment of study participants						
2.1. Recruitment, baseline assessment, and randomization		✓	✓			
2.2. Assignment into one of the two arms of the study		✓	✓			
2.3. Delivery of iCBT and rTMS to participants		✓	✓	✓		
Milestone 3: Follow-up assessment of study participants						
3.1. Follow-up assessments of individual study participants				✓	✓	
3.2. Follow-up satisfaction survey of participants, all groups				✓	✓	
Milestone 4: Data compilation, data analysis, and preparation of reports, publications, and presentations						
4.1. Data compilation		✓	✓	✓	✓	✓
4.2. Data analysis		✓	✓	✓	✓	✓
4.3. Preparation of reports, publications, and presentations						✓

Inclusion Criteria

Study participants must meet the following:

- Aged 18-65 years
- Suffering from a major depressive episode based on Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 criteria and having failed two or more standard antidepressant treatments during the current episode.
- Hamilton Depression Rating Scale (17-HAM-D) score of 10 or more.
- May be on psychotropic medications, including antidepressants, antipsychotics, benzodiazepines, and anticonvulsants.
- Have a good understanding of the English language with fair computer/internet skills, and able and willing to provide informed consent.

Exclusion Criteria

The exclusion criteria for this study are the folowing:

Diagnosis with the following conditions (current unless otherwise stated):

- A neurological disorder, including a history of seizures, cerebrovascular disease, primary or secondary tumours in the central nervous system, stroke, cerebral aneurysm, movement disorder or any lifetime history of loss of consciousness due to a head injury.
- Any current Axis 1 psychotic disorder (including substance-induced psychosis, psychotic disorder due to a medical condition or major depression with psychotic features) as defined by the Mini-International Neuropsychiatric Interview[444] at the screening visit.
- Any current Axis II personality disorder that would interfere with participation in the study or might affect cognition and ability to participate meaningfully as well as mental retardation identified through medical history or by the investigator.
- A current amnestic disorder, dementia or delirium as defined by a Montreal Cognitive Assessment score of ≤16 or any other neurological or mental disease that might affect cognition or the ability to participate meaningfully in CBT.
- Participation in any drug or device clinical trial in the six weeks (42 days) prior to the screening visit and/or participation in another clinical trial for the duration of the study.
- Pregnancy/breastfeeding.

- Discovery and/or the sudden appearance of any condition or circumstance from the above list that, in the opinion of the investigator, has the potential to prevent study completion and/or to have a confounding effect on outcome assessments.

The rTMS-trained healthcare practitioners' team will determine a participant's eligibility for the rTMS treatments. Once the individual has been accepted into the rTMS program, a member of our research team will introduce the study to them, give them a copy of the information leaflet, and ask if they would also be interested in enrolling in our study. The recruitment and an informed consent process will involve a face-to-face meeting with the participant during the week of their rTMS eligibility assessment, which occurs one week before beginning the rTMS sessions. Participants can withdraw from the study at any time without providing a reason. To withdraw, participants can contact the research coordinator to let them know. If participants leave the study, we will not collect new health information about them, and they may ask the research coordinator to withdraw any data we have already collected from them before data analysis and dissemination.

Interventions

Participants will be randomly assigned to receive rTMS alone or rTMS plus iCBT. Participants in both arms of the study will attend an introductory visit to introduce the rTMS system to them and learn the procedure that will be carried out in each visit. Participants will be asked to complete standard questionnaires as part of their participation in the rTMS program. A week before the start of rTMS sessions, participants will be invited into the clinic for motor threshold (MT) assessments, which are important for selection of stimulation intensities for each patient, and assessment for inclusion in the study. MT is roughly a measure of the TMS intensity necessary to evoke a peripheral motor response. These assessments will be done by the rTMS team, which includes healthcare practitioners trained on how to assess and use rTMS. Each assessment will take 3-5 minutes, and the total time will be 35-45 minutes. The timeline for visits will be the same for all participants. All participants will receive 30 sessions of rTMS treatments over 6 weeks as predetermined by Alberta Health Services' Strategic Clinical Network for Addiction and Mental Health. In addition, participants in the rTMS plus iCBT arm will be assisted in registering for the iCBT program (MoodGYM) and to receive unique login information. They will be assisted in participating in 12 one-hour sessions of iCBT at the clinic

followed by rTMS treatments on the same day. These in-clinic iCBT sessions will be scheduled at about three-day intervals (ideally Tuesdays and Thursdays) so that participants receive two iCBT sessions each week. These in-clinic iCBT sessions are necessary to avoid poor treatment adherence and high discontinuation rates, as conducting these sessions by themselves at home may present a major challenge for patients with TRD. Participants will also be encouraged to continue with iCBT treatments on their own at home, outside the sessions delivered in the clinic. The personal information relating to the MoodGYM website that will be collected consists of age group, gender, email address, password, answers to secret questions, and the information the participants submit when using the MoodGYM website (including quizzes, workbooks, and diaries). In addition, the following information about participants' usage of the MoodGYM website will be collected using transient cookies: participants' browser's internet address, the date and time the site was visited, the pages that were accessed and the documents that were downloaded, the type of browser used, the number of bookmarks created, the last viewed date, the time of visit, and details about participant's subscription excluding credit card details. MoodGYM has its own privacy policy that controls the personal information obtained from all participants under their respective User Data profile. There is no risk that a participant's diagnosis could be exposed to the public should a breach at MoodGYM occur.

All participants will be followed for 6 months and encouraged to continue to receive whatever community clinic/program treatments or supports are part of their usual care.

Sample Size

Consistent with the idea that this is a pilot study with no established effect size data available to aid in power and sample size calculations, the research will use data elicited from participants who can be enrolled within existing operational resources. This method is acceptable for pilot studies involving novel interventions, and has been described by Haynes et al[445] as using "the participants I can get." Therefore, the study will be limited to a sample size of 100, with about 50 participants recruited into each arm of the study. Patients with TRD are vulnerable to severe depressive attacks, and it can reasonably be expected that only a small number of eligible participants will enroll in and complete the study.

Results

We hypothesize that participants enrolled in the rTMS plus iCBT treatment arm of the study will achieve superior outcomes than participants enrolled in the rTMS alone arm of the study on each outcome measure used.

Outcomes

Outcome measures and time points are detailed in Table 2 and follow from the aim and objectives of the study. All measures (except patient experience questionnaire, interviews, and data extraction) are objective measures with published information regarding reliability and validity. The Hamilton Depression Rating Scale (HAM-D)[23, 446] will be the primary outcome, and all other measures will be secondary outcomes. These measures include: Columbia Suicide Severity Rating Scale (CSSRS)[447, 448], Young Mania Rating Scale (YMRS)[449], Quick Inventory of Depressive Symptomatology Self Report-16 (QIDS SR-16)[450], Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER; edited for rTMS)[451], Patient Rated Inventory of Side Effects (PRISE)[452], EuroQoL 5-Dimension 5-Level (EQ-5D-5L)[453, 454], and World Health Organization Disability Assessment 2.0 (WHODAS 2.0)[455]. The primary outcome measure will be the mean change in the scores on the Hamilton Depression Rating Scale. Patient service utilization data and clinician-rated measures will also be used to gauge patient progress. Patient data will be analyzed with descriptive statistics, repeated measures, and correlational analyses. All quantitative data will be analyzed using SPSS (Version 26; IBM Corp)[456].

Table 2. 2: Client-oriented outcome measures

Outcome measures			Time points assessed			
Variable type and construct	Tool	Rater	Baseline	1 month	3 months	6 months
Symptom variables						
Depression	Hamilton Depression Rating Scale (HAM-D)	Clinician	✓	✓	✓	✓

Depression	Quick Inventory of Depressive Symptomatology Self Report-16 (QIDS SR-16)	Client	✓	✓	✓	✓
Suicidal ideation	Columbia Suicide Severity Rating Scale (CSSRS)	Clinician	✓	✓	✓	✓
Mania	Young Mania Rating Scale (YMRS)	Clinician	✓	✓	✓	✓
Functional variables						
Side effects	Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER; edited for rTMS)	Client	✓	✓	✓	✓
Side effects	Patient Rated Inventory of Side Effects (PRISE)	Client	✓	✓	✓	✓
Disability measures	World Health Organization Disability Assessment 2.0 (WHODAS 2.0)	Client	✓	✓	✓	✓
Quality of life	EuroQoL 5-Dimension 5-Level (EQ-5D-5L)	Client	✓	✓		

Randomization and Blinding

A simple randomization technique will be used based on a single sequence of random assignments. A computer-generated Excel sheet (Microsoft Corp) will be used for simple randomization of subjects. Randomization will be stratified using permuted blocks to ensure balance (1:1) between the two follow-up treatment groups. The randomization codes will be transmitted by an independent statistician via text message directly to a researcher's password-protected phone line with a secure online backup. This will commence as soon as participants sign the consent forms.

As it will not be possible for participants to be blinded, treatment allocation will be made explicit to them as soon as randomization is concluded. Primary outcome assessors will be blinded to treatment group allocation by not involving them in discussions about study participants and not

granting them access to the database that contains the randomization code. After data collection is complete, all data will undergo a blind review to finalize the planned analysis.

Follow-up Assessment

At 1, 3, and 6 months, a blinded researcher will contact all study participants and help them complete a range of assessment tools relating to the primary and secondary outcome measures. They will be offered the opportunity to complete the assessments face-to-face or over the phone. Qualitative data collection will be in the form of a patient experience questionnaire and a focus group workshop, which will be conducted at 3 and 6 months. At 6 months, data related to each person's clinic/program attendance rates and utilization of health services will be compiled from administrative records by the blinded researcher.

Patient and Public Involvement

This study was designed to address the clinical urgency to identify and respond to early evidence of treatment resistance using treatments that have proven efficacy in these more difficult-to-treat psychiatric patients. The study is designed as patient-oriented research with the active involvement of a patient representative who will be a coauthor of the study protocol. Our randomized trial offers participants the opportunity to provide feedback regarding the burden of the intervention through a focus group workshop involving a cross-section of participants from the two arms of the study.

Ethics and Dissemination

The study will be conducted per the Declaration of Helsinki (Hong Kong Amendment) and Good Clinical Practice (Canadian Guidelines). Written informed consent will be obtained from each participant. The study has received ethical clearance from the Health Ethics Research Board of the University of Alberta (Pro00094208). The study is registered with ClinicalTrials.gov (registration number NCT04239651; preresult). The study results, expected 18 months after commencement of recruitment, will be disseminated at several levels, including participants, practitioners, academics/researchers, and healthcare organizations.

The investigator's team will plan an organizational engagement strategy to advance discussions about practicability and effectiveness before the conclusion of the trial. This will help ensure the

findings are a relevant part of decision-making processes as they emerge. This may facilitate the planning of a more extensive study that is endorsed at leadership and operational levels so that the potential benefits of the interventions can reach participants in a timelier fashion.

Discussion

Overview

The results of the study will provide the data required to evaluate the initial effectiveness of rTMS plus iCBT for patients diagnosed with resistant depression. The majority of RCTs support the efficacy of rTMS for major depression. The data collected on rTMS is significant only as a single intervention. The concomitant application of psychotherapy with rTMS has not been investigated previously. We hope this project will provide a concrete base of data to evaluate the practical application and efficacy of using a novel combination of these two treatment modalities (rTMS plus iCBT). To our knowledge, no clinical trials have applied these two new treatment interventions together before. Due to the limited availability of data in this specific area, another aim is to generate effect size data for these interventions, which will help in sample size and power calculations for a full randomized clinical trial.

Strengths of this Study

The strengths of this study include the following:

Randomization of participants will ensure that participants in the two treatment arms have somewhat similar psychiatric morbidity at baseline.

Blinding of primary outcome assessors for the primary outcome measures will ensure the elimination of bias in outcome measures.

Limitation of this Study

The limitations of this study include the following:

The small sample size may reduce the study power, which will limit the ability of the study to detect differences in outcome measures between participants in the two treatment arms.

Possible variability in concomitant treatments (medication and/or psychotherapy) being received by patients outside the rTMS clinic as well as the differing lengths of treatment time between the two arms of the study could have confounding effects on the outcomes of our interventions.

Chapter 3: This chapter represents the main results of the study included in this thesis. Apparent Lack of Benefit of Combining Repetitive Transcranial Magnetic Stimulation with Internet-Delivered Cognitive Behaviour Therapy for the Treatment of Resistant Depression: Patient-centred Randomized Controlled Pilot Trial.

Medard K Adu, Reham Shalaby, Ejemai Eboreime, Adegboyega O Sapara, Mobolaji Lawal, Corina Chew, Shelley Daubert, Liana Urichuck, Shireen Surood, Daniel Li, Mark Snaterse , Mike Mach, Pierre Chue, Andrew J. Greenshaw, Vincent I O Agyapong

ABSTRACT

Background: Treatment-resistant depression (TRD) is considered one of the major clinical challenges in psychiatry. An estimated 44% of patients with major depression disorder (MDD) do not respond to two consecutive antidepressant therapies, and 33% do not respond to up to four antidepressants. Over 15% of all patients with MDD remain refractory to any treatment intervention. rTMS is considered a treatment option for patients with TRD. Likewise, iCBT is evidence-based, symptom-focused psychotherapy recommended for the treatment of TRD.

Objective: This study aims to evaluate the initial comparative clinical effectiveness of rTMS treatment with and without iCBT as an innovative intervention for participants diagnosed with TRD.

Methods: This study is a prospective, two-arm randomized controlled trial. Overall, 78 participants diagnosed with TRD were randomized to one of two treatment interventions: rTMS sessions alone and rTMS sessions plus iCBT. Participants in each group w completed evaluation measures at baseline, and six weeks (discharge) from treatment. The primary outcome measure was baseline to six weeks change in mean score for the 17-item Hamilton depression rating scale (HAMD-17). Secondary outcomes included mean baseline to six-week changes in the Columbia suicide severity rating scale (CSSRS) for the rate of suicidal ideations, the QIDS-SR16 for subjective depression, and the EQ-5D-5L to assess the quality of health in participants.

Results: The majority of the participants were female 50(64.1%), aged ≥40 39(50.0%), and had college/university education 54(73.0%). After adjusting for the baseline scores, the study failed to find a significant difference in the changes in mean scores for participants from baseline to six weeks between the two interventions under study on HAMD-17 scale; $F(1, 53) = 0.15$, $p = 0.70$, partial eta squared = 0.003, CSSRS; $F(1, 56) = 0.04$ $p = 0.85$, partial eta squared = .001, QIDS-SR16 scale; $F(1, 53) = 0.04$ $p = 0.61$, partial eta squared = 0.005, and EQ-5D-VAS; $F(1,51) = 0.46$ $p = 0.50$, partial eta squared = .009. However, there was a significant reduction in means scores at week six compared to baseline scores for the combined study population on HAMD-17 scale (42%), CSSRS (41%), QIDS-SR16 scale (35%), and EQ-VAS scale (62%).

Conclusion: This study did not find combined treatment of TRD with rTMS + iCBT(unguided) superior to treatment with rTMS alone. Our findings do not support the use of combined treatment of rTMS + iCBT to manage TRD disorders.

Keywords: Repetitive transcranial magnetic stimulation (rTMS), treatment-resistant depression (TRD), internet-based cognitive behavioral therapy (iCBT), MoodGYM, and major depression disorder (MDD)

INTRODUCTION

Treatment-resistant depression (TRD) is a major clinical feature of patients treated for major depression disorder (MDD). TRD is considered a major clinical challenge in psychiatry. It is estimated that 44% of MDD patients do not respond to two consecutive antidepressant therapies, and 33% do not respond to four antidepressants[28]. Despite high TRD frequency, it seems that the concept is poorly understood[457]. Thus, a clear consensus for a standard definition for TRD is missing in the literature [22], leading to many misdiagnoses and inadequacies in the treatment of patients considered treatment-resistant in MDD[15]. Although researchers have used a variety of criteria to define TRD[458], a common agreement is that a person with MDD is "resistant", based on no adequate response to at least two trials of antidepressants from different pharmacological classes despite a well-managed treatment protocol[459]. The determination of resistance is only confirmed after the patient has been evaluated to ascertain the accuracy of diagnosis, adequate dosing, treatment adherence, and whether the worsening of the patient's condition is influenced by other confounding factors, such as coexisting medical or psychiatric disorders[460].

The prognosis of TRD seems bleak, as it is characterized by a profound worsening of the quality of life, a greater rate of mortality, decreased productivity, more hospitalizations, higher individual and community-related healthcare costs, and higher rates of suicidal ideation. [461-463]. About 30% of TRD patients attempt suicide at least once in their lifetime[463, 464]twice the rate of suicide attempts in nontreatment resistant MDD patients (estimated between 8.4%[465] and 15.9%[466]), and about 15 times higher than the rate estimated for the entire European population[465, 467]. Considering the high suicide risk of TRD patients, it is of utmost importance to evaluate whether specific treatments might impact the rate of suicidal ideation in this cohort of patients. Despite the rapid growth of the variety of treatment choices for TRD, the condition represents a domain of unmet therapeutic need. Few psychopharmacological agents have been approved for the management of TRD and, overall, treatment outcomes remain poor[468]. Regarding antidepressant treatments for TRD, their efficacy is comparable between classes. Thus, the choice of any particular antidepressant medication is determined by the evaluation of side effects, history of treatment response in the patient and relatives and, to some extent, the cost of medication[460].

Amid uncertainty in the management of TRD due to the limited evidence-based optimal pharmacologic and psychotherapeutic interventions for TRD[135, 136], repetitive transcranial magnetic stimulation (rTMS) has been considered an essential investigational treatment technique, fit for purpose[137]. Several randomized controlled studies on rTMS have focusing on TRD patients, however, most of these investigated effects in treatment of a combination of drug-resistant patients, and did not strictly evaluate the effectiveness of rTMS in patients with TRD[469].

rTMS is non-invasive focal brain stimulation considered an essential technique in neuropsychiatry treatment due to its ability to produce direct effects on a range of measures of brain function[195, 196]. rTMS has been greatly studied as a major technique in many psychiatric disorders and deemed a brain-system-based neuromodulation treatment, based on its focus on the direct target of the neural circuitry of disorders[237]. High frequency (≥1 Hz) and low frequency ((≤1 Hz) methods are the two major forms of rTMS techniques applied in clinical practice. While the high frequency rTMS is believed to produce a highly stimulating effect on the cerebral cortex, the low frequency is thought to produce an inhibitory effect[125, 470]. More importantly, at a time when researchers are struggling to find a much better treatment for resistant depression, rTMS has earned a place in the management of depressive disorders globally, and more research is being conducted to evaluate it. Study findings indicate asymmetry in the functioning of patients diagnosed with MDD[130]. Therefore, researchers have to apply an inhibitory rTMS stimulation (low frequency) to the right dorsolateral prefrontal cortex (DLPFC) and excitatory stimulation (high frequency) to the left DLPFC in TRD patients[131].

Cognitive-behavioural therapy (CBT) is another treatment option that has a proven empirical base for the management of TRD[347]. However, CBT comes with a major challenge of access and dissemination, which is partly due to the insufficient number of trained therapists [471]. Digital technology interventions are emphasized by experts in psychiatry as a major means to transform the delivery of healthcare[472, 473]. There has been a sharp recent increase in the use of web-based technologies in support of the application of cognitive behavioural therapy [69, 474], and studies have been conducted to demonstrate the efficacy of internet-based CBT (iCBT) in TRD[440]. The literature on therapist-supported iCBT trials for depression indicates a significant and stable clinical effect on MDD[475]. iCBT interventions, administered with or without therapist assistance, are typically referred to as guided and unguided iCBT, respectively.

Unguided iCBT is considered more affordable and more accessible than guided iCBT but results indicate that therapist assistance generally leads to better outcomes[476]. iCBT uses web-based software programs to deliver these interventions.[353]. Interactions on these software platforms are provided as assessment instruments and treatment materials delivered in the form of videos, audio, and text messages[354].

Several programs for iCBT are identified in the literature for the management of depression, including the UK-developed cognitive-behavioural Beating the Blues (BTB)[72]. The BTB consists of 8 person-centred online cognitive modules on depression that takes up to 50 minutes to complete. [71, 72]. MoodGYM is a popular internet-based iCBT platform developed in Australia, consisting of an interactive self-guided book that leads a patient to learn and practise skills that help to prevent and manage symptoms of depression and anxiety. MoodGYM comprises five unique modules targeted to the relationship between thoughts and emotions, identifying cognitive distortions and negative thoughts, techniques to adjust negative thoughts, assertiveness and self-esteem training, behavioural activation, and problem-solving[357]. MoodGYM helps identify negative thoughts, and teaches practical strategies for managing the negative thoughts and beliefs to reduce dysfunctional thinking of MDD patients. Several studies have attested to the efficacy of MoodGYM for MDD for outpatients and inpatients in clinical settings[68, 69, 400, 436-438]. According to the World Health Organization (WHO), it is an international priority to increase the coverage of interventions and evidence-based treatments for TRD globally[477]. In addition, rTMS is considered a treatment option for patients with TRD who are refractory to antidepressant treatment, while iCBT is an evidence-based, symptom-focused psychotherapy recommended for the treatment of TRD. It is not known if adding unguided iCBT will enhance patients' responses to rTMS treatments. This project was designed to evaluate the initial comparative clinical effectiveness of rTMS treatments with and without unguided iCBT in TRD patients as an alternative to current pharmacological and other treatment options.

METHODS

Study Design

This study is a two-arm parallel design, rater-blinded randomized controlled pilot trail. The study was conducted at the Addiction and Mental Health clinic, 108th Street Building, and at the

Alberta Day Hospital's rTMS clinic in Edmonton, Alberta. Participants were recruited and randomized into one of two treatment interventions under study (rTMS alone and rTMS plus unguided iCBT) to receive active treatment for six weeks. Assessment measures were conducted at baseline and six weeks (discharge) for all participants.

Institutional Review Board Approval

The study protocol[478] received ethical clearance from the Health Ethics Research Board of the University of Alberta (Pro00094208), and was registered with clinicaltrials.gov: (registration number: NCT04239651; pre-result). The study was conducted per the Declaration of Helsinki (Hong Kong Amendment) [479] and Good Clinical Practice (Canadian Guidelines). Written informed consent was obtained from each study participant.

Inclusion and Exclusion Criteria

To be eligible for the study, participants had a diagnosis of TRD [6] and met the general criteria for receipt of publicly-funded rTMS treatment in the Edmonton locations, between 18 and 65 years, with a good understanding of the English language, with access to a computer with internet, have fair computer/internet skills (thus, the ability to navigate the moodGYM program on a computer with ease), and be able and willing to provide informed consent. Determination of eligibility for the rTMS treatment was assessed by the rTMS-trained personnel (M.L. and D.L.) at the study sites. Patients not meeting all these inclusion criteria were excluded from the study.

Recruitment Procedures

After a patient was evaluated and found to be eligible for rTMS treatment, a research team member (MA) introduced the study to them with the aid of an information leaflet that contained brief details about the study protocol, answering any questions before aiding them to sign a consent form. The process of recruitment and obtaining consent was completed within the rTMS eligibility assessment week, a week before initial rTMS administration to the participant. Once recruited, the patient was assigned a study identification number - passed to an independent statistician for randomized group allocation. Participants in both arms of the study were educated on the protocol for the study. Participants were informed of the routine activities that take place

during each visit to the rTMS clinic. As part of their participation, participants were pre-informed about the completion of standard questionnaires at baseline and six weeks (discharge).

Randomization and Blinding

The participants were block randomized into the rTMS alone group or the rTMS + iCBT group. with randomization codes secured on a password-protected computer. Primary outcome assessors were blinded to treatment group allocation by not involving them in discussions about study participants and not granting them access to the secured database that contained the randomization codes.

Intervention

All participants were scheduled to receive 30 sessions of rTMS over six weeks. In addition, participants recruited to the combined treatment intervention group (rTMS + iCBT) were guided to enroll into the iCBT program (MoodGYM). With the aid of their unique login information, these participants were enabled to participate in 12 one-hour sessions of iCBT over six weeks. The MoodGYM sessions were scheduled at least twice a week at three days intervals (preferably Tuesdays and Thursdays). Participants completed a 1-hour session of iCBT in their homes each night before the rTMS session or an hour before the rTMS session on the same day. Participants within the rTMS + iCBT arm of the study were sent reminders via text messaging on the days and times of their 1-hour sessions of iCBT and also encouraged to assess the MoodGYM program even outside the scheduled periods at their convenience.

Sample Size Calculation

Consistent with the idea that this is a pilot study, with no established effect size data available to assist in power and sample size calculations, the researchers used data from participants who could be enrolled within the existing operational resources. This method is acceptable for pilot studies involving novel interventions, and has been described by Haynes et al. as using ‘the participants I can get’[445]. In this way, the study was limited to a sample size of 80, with 40 participants recruited into each arm.

Data Collection

Social demographics including gender, age, the educational level attained, and clinical characteristic information were routinely collected for all patients at baseline and six weeks for patients receiving rTMS at the two sites. Clinical variables were collected at pre rTMS treatment (baseline) and post rTMS treatment (six-weeks) using the 17-item Hamilton Depression Scale (HAMD) [23], which is used to quantify depression symptom severity in patients diagnosed with MDD, the Columbia Suicide Severity Rating Scale (CSSRS), which is used to screen and evaluate a person's level of suicidal ideations [447], the self-reported 16 items Quick Inventory Depression Scale (QIDS-SR16), which is used to evaluate the nine diagnostic symptoms domain of the DSM-IV [480], and the EQ-5D-5L, which is used to assess quality of overall health status [481]. The HAMD has strong psychometric properties[482], including internal reliability evaluated by the Cronbach's alpha statistic [483] of ≥ 0.70, which is deemed sufficient reliability [484]. Ratings on the HAMD are determined on a semi-structured clinical interview, producing the highest score of 52. Eight of the 17 items are rated on a 5-point scale of 0-4 (0=absent, 1=doubtful or mild, 2=mild to moderate, 3=moderate to severe, 4=very severe) and the remaining nine on a 3point scale of 0-2 (0=absent, 1=doubtful or mild, 2=clearly present). The ratings are based on the individual rater's clinical judgment; both severity and frequency of the symptoms are taken into account[485]. The total scores of 0–7 are considered as normal, 8–16 suggest mild depression, 17–23 moderate depression, and scores over 24 are indicative of severe depression; the maximum score being 52 on the 17-point scale[486].

The screen version of CSSRS is made up of 6 questions. Users are tasked to respond "Yes" or "No" to whether they have thought about suicide, have acted or plan to act, or whether they attempted suicide or plan to attempt suicide. Each of the 6 questions evaluates a different component of the respondent's suicide ideation severity and behaviour. This measuring tool is scored as Low, Moderate, or High risk, depending on positive answers (Yes) to the various questions. Once a respondent answers positive (Yes) to Question 2, he/she is instructed to respond to Questions 3-5. If the respondent answers "No" to Question 2, they may skip to Question 6. Responding "Yes" to any of the 6 items may imply a need for referral to a mental healthcare professional but responding "Yes" to questions 4, 5 or 6 indicates high risk. This scale has a wide evidence base and is supported by SAMHSA, the CDC, the FDA, the NIH, the WHO, and many other credible institutions. There is a good internal consistency for the CSSRS

intensity of ideation subscale, with Cronbach's alpha values ranging between 0.73 and 0.93. [447]. The questions on the scale include 1: wish to be dead, 2: non-specific suicidal thoughts. 3-5: more specific suicidal thoughts and intent to act, and 6: suicidal behaviour over the respondent's lifetime and past three months.

QIDS-SR16 has an internal scale consistency of (coefficient $\alpha = 0.86$)[487], and is a valid depression screening instrument for patients in different age categories[488, 489]. Three domains (sleep, appetite/weight, and restlessness/agitation) are scored based on the highest score obtained on two or more questions. The remaining domains are each scored on a single item. All items are scored from 0 to 3 and greater scores reflect severe psychopathology. The total scores on this scale range from 0 – to 27. A score of ≤ 5 indicates no depression, 6 to 10 represents mild depression, 11 to 15 indicates moderate depression, 16 to 20 indicates severe depression, and a total score greater than 21 reflects a very severe depression[450].

The EQ-5D-5L consists of the EQ-5D descriptive system and the EQ visual analog scale. The descriptive system is made up of five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression[481]. Each dimension consists of five levels (no problems, slight problems, moderate problems, severe problems, and extreme problems). The combined score from the five dimensions indicates the quality of health of the patient. The patient's self-rated quality of health is recorded on a vertical visual analog scale (EQ-VAS) from 0 to 100, with 100 representing the best health you can imagine and 0 representing the worst health you can imagine. This can be used as a quantitative measure of health outcomes that reflect the patient's judgment [481, 490]. The EQ-5D-5L has adequate psychometric properties in patients with major depression. Reliability of EQ-5D-5L per calculation using Cronbach's alpha coefficient was 0.77, which is superior to the minimum acceptable value of 0.70. Regarding convergent and discriminant validity, there are high correlations between the PHQ-9 and the EQ-5D-5L index and the anxiety/depression dimension (−0.52 and 0.56, respectively). For known-groups validity, patients with a greater level of depression and those with poorer general health have significantly lower scores on the EQ-5D-5L ($p < 0.001$)[491].

Primary Outcome Measure

The primary outcome measure was the mean change in the HAMD-17 from baseline to six weeks for the intervention and control groups.

Secondary Outcome Measures

Secondary outcomes included changes in mean scores from baseline to six weeks on the CSSRS, the QIDS-SR16, and the EQ-VAS for the intervention and control groups. Other secondary outcomes include differences in the prevalence of the clinical conditions measured by the HAMD, CSSRS, the QIDS-SR16 and the EQ-5D-5L between the two interventions (rTMS alone and rTMS + iCBT) at discharge (six weeks).

Exploratory Outcomes

An exploratory outcome was the overall change in mean scores on the HAMD-17, The CSSRS) the QIDS-SR16, and the EQ-VAS from baseline to six weeks for all participants in the study.

Statistical Analysis

We completed data analysis following an intention-to-treat basis with (39) patients in the rTMS alone group and (39) patients in the rTMS plus iCBT group. Data were analyzed using the statistical package for social sciences SPSS version 25 (IBM Corporation, 2011) [57]. Descriptive data for baseline parameters were presented using frequencies and percentages among the two intervention groups and compared by Chi Square/Fischer Exact tests for categorical variables and the independent sample t-test for continuous variables. Differences in effectiveness of the two interventions was assessed using one-way between-groups analysis of covariance (ANCOVA) analysis, comparing the changes in mean scores from baseline to six weeks on the HAMD-17, CSSRS, QIDS-SR16, and EQ-VAS scales between the two interventions groups while controlling for their respective baseline scores. Four models were run for each outcome scale. The independent variables consisted of the type of intervention (rTMS alone and rTMS plus iCBT), while the scores on the HAM-D-17, CSSRS, QID-SR16, or EQ-VAS scales at six weeks were considered the dependent variables for each analysis. Baseline scores on the respective scales were used as the covariates in the analyses. Preliminary checks were conducted to ensure there was no violation of the assumptions of normality, linearity, homogeneity of variance, homogeneity of regression slopes or reliable measurement of the variate. For participants with missing data in the six weeks, the last observation (baseline/ interim measures) was imputed before performing sensitivity analyses of covariance to explore

the impact of imputation of data loss on HAMD-17, CSSRS, QIDS-SR16, and EQ-VAS scores at six weeks.

Chi-square/Fischer Exact tests were utilized to compare the prevalence of clinician-rated MDD using the HAMD scale of two categories with a cut-off score of 10, suicidal ideations using the CSSRS scale of two categories, patient self-rated MDD using the QIDS-SR16 scale of two categories, and quality of health using the EQ-5D-5L five subscales between the two intervention groups at six weeks and for the overall sample, between prevalence at baseline and six weeks for each variable.

Chi-squared/Fisher's Exact tests and where necessary, *post hoc* analysis was also used to compare categorical scores on the EQ-5D-5L scale related to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression for the two groups We reported corresponding z-scores, adjusted residuals, and p-values.

Additionally, a paired t-test was used to examine the changes in baseline and six weeks mean scores on the HAM D, CSSRS, QIDS-SR16, and EQ-VAS for participants who completed the instruments at both time points.

Frequencies and percentages were used for reporting categorical variables, while mean scores, confidence intervals, and effect sizes were used when reporting on continuous variables. There was no imputation for missing data, and the total numbers reported represent the total responses recorded for each variable. The two-tailed α-level criterion for statistical significance was set at $P \leq .05$.

Results

The study realized a total of 78 participants, with 39 recruited into each of the two treatment interventions (rTMS alone and rTMS with iCBT). Figure 3.1 is the study flow chart.

Figure 3.1: Study flow chart

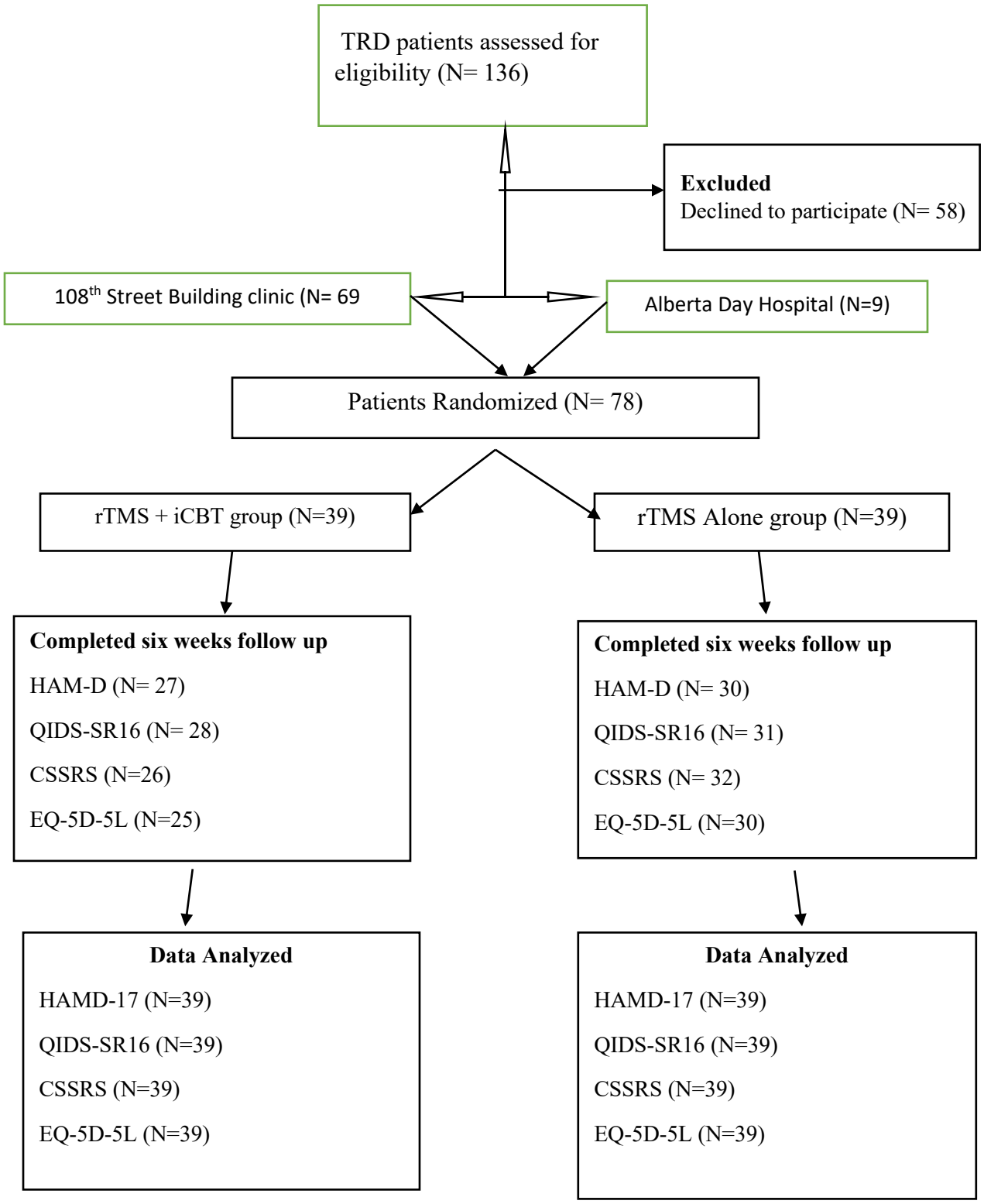


Table 3.1 provides the baseline distribution of sociodemographic and clinical characteristics of the two study groups. The data presented in Table 1 show that the majority of participants were females 50(64.1%), aged ≥40 39(50.0%), and had college/university education 54(73.0%). Regarding the clinical characteristics at baseline, the prevalence of clinician-rated likely MDD was 36(51.4%) by contrast patient-rated likely MDD was 64(90.1%), and presence of suicidal ideation was 52(71.2%). There were no statistically significant differences between the two intervention groups at baseline with respect to mean scores on the HAMD the C-SSRS QIDS-SR16 and the EQ-VAS.

Table 3.1: Baseline distribution of sociodemographic and clinical characteristics between the two study groups at baseline

Variables	rTMS N= 39	iCBT+ rTMS N= 39	**Total**	**Chi Square /t test**	**P-value**
Gender					
Male	17(43.6%)	11(28.2%)	28(35.9%)	$\chi^2(1) = 2.01$	.24
Female	22(56.4%)	28(71.8%)	50(64.1%)		
Age (Years)					
≤25	3(7.7%)	3(7.7)	6(7.7%)		
26-40	19(48.7%)	14(35.9%)	33(42.3%)	1.47*	.54
>40	17(43.6%)	22(56.4%)	39(50.0%)		
Educational level					
Elementary	1(2.8%)	1(2.8%)	2(2.7%)		
High school	8(22.2%)	10(26.3%)	18(24.3%)	0.43*	.89
College/University	27(75.0%)	27(71.1%)	54(73.0%)		
MDD at baseline					
At most, mild depression	18(54.5%)	16(43.2%)	34(48.8%)	$\chi^2(1) = 0.89$	.47
Moderate to severe depression	15(45.5%)	21(56.8%)	36(51.4%)		
Suicidal ideation at baseline					
No suicidal ideation	14 (40.0)	7 (18.4)	21 (28.8)	$\chi^2(1) = 4.14$	.07
Present suicidal ideation	21 (60.0)	31 (81.6)	52 (71.2)		
Subjective depression at baseline (QIDS)					
At most, mild depression	4(11.8)	3(8.1)	7(9.9)	$\chi^2(1) = 0.27$	.70
Moderate to severe depression	30(88.2)	34(91.9)	64(90.1)		
EQ-5D-5L at baseline					
Mobility:					
No problems walking	22(64.7)	28(75.7)	50(70.4)		
Slight problems walking	8(23.5)	2(5.4)	10(14.1)		
Moderate problems walking	3(8.8)	5(13.5)	8(11.3)	5.01*	0.15
Severe problems walking	1(2.9)	2(5.4)	3(4.2)		
Unable to walk					

Self-care: No problems washing/dressing Slight problems washing/dressing Moderate problems washing/dressing Severe problems washing/dressing Unable to wash/dress	 18(52.9) 10(29.4) 5(14.7) 1(2.9)	 21(56.8) 5(13.5) 7(18.9) 4(10.8)	 39(54.9) 15(21.1) 12(16.9) 5(7.0)	3.91	.27
Usual activities No problems doing usual activities Slight problems doing usual activities Moderate problems doing usual activities Severe problems doing usual activities Unable to do usual activities	 7(20.6) 7(20.6) 12(35.3) 7(20.6) 1(2.9)	 2(5.4) 9(24.3) 9(24.3) 15(40.5) 2(5.4)	 9(12.7) 16(22.5) 21(29.6) 22(31.0) 3(4.2)	6.51*	.15
Pain/discomfort No pain or discomfort Slight pain or discomfort Moderate pain or discomfort Severe pain or discomfort Extreme pain or discomfort	 13(38.2) 6(17.6) 10(29.4) 4(11.8) 1(2.9)	 7(18.9) 14(37.8) 11(29.7) 5(13.5) 0(0.0)	 20(28.2) 20(28.2) 21(29.6) 9(12.7) 1(1.4)	5.95*	.17
Anxiety/depression Not anxious or depressed Slightly anxious or depressed Moderately anxious or depressed Severely anxious or depressed Extremely anxious or depressed	 1(2.9) 4(11.8) 13(38.2) 10(29.4) 6(17.6)	 1(2.7) 0(0.0) 13(35.1) 18(48.6) 5(13.5)	 2(2.8) 4(5.6) 26(36.6) 28(39.4) 11(15.5)	6.22*	.15
Total score HAM D at baseline Mean score (SD)	N= 33 15.73 (6.03)	N= 37 17.43 (4.79)	-	t(68)=1.32	.19
Total score CSSRS baseline Mean score (SD)	N= 35 1.57 (1.70)	N= 38 1.79 (1.44)	-	t(71)=0.59	.56
Total score QIDS baseline Mean score (SD)	N= 34 16.62(4.59)	N= 37 17.59(4.15)	-	t(69)=0.94	.35
EQ-VAS at baseline Mean score (SD)	N= 33 47.48 (18.42)	N= 37 45.27 (18.36)	- -	 t(68)= 0.50	 .62

* Fisher Exact test was applied

Primary Outcome Measures

To compare the effectiveness of the treatment interventions (rTMS alone and rTMS plus iCBT) for the management of TRD among participants, ANCOVA was conducted as shown in Table 2. Regarding the HAMD scale, after controlling for the baseline scores, the results revealed no significant differences between the two treatment intervention groups at six weeks, (F (1, 53) = 0.15, p = 0.70, partial eta squared = 0.003). After data imputation, there remain no significant

difference in the mean changes in HAMD scores from baseline to six weeks between the intervention and control groups (p> 0.05). There was a relationship between the baseline intervention score and six weeks intervention score on the HAM-D scale evidenced by the partial eta squared value of 0.11.

Secondary Outcome Measures

ANCOVA analysis was performed on data gathered from the CSSRS scale to assess differences in the change mean scores from baseline to six weeks in suicidal ideation between the study groups (rTMS alone and rTMS plus iCBT). After controlling for baseline scores, no significant differences were found between the two study groups at six weeks on the CSSR scale, (F (1, 56) = 0.04 p = 0.85, partial eta squared = .001) as shown in Table 3.2. There was a relationship between the baseline intervention score and six weeks intervention score on the CSSRS scale evidenced by a partial eta squared value of 0.36.

ANCOVA was also performed on data from the QIDS-SR16 scale to assess differences in the change mean scores from baseline to six weeks for self-rated depression between the study groups (rTMS alone and rTMS plus iCBT). After controlling for baseline scores, the analysis revealed no significant differences between groups at six weeks on the QIDS-SR16 scale, (F (1, 53) = 0.04 p = 0.61, partial eta squared = 0.005) as shown in Table 3.2. There was a relationship between the baseline intervention score and six weeks intervention score on the QIDS-16 scale evidenced by a partial eta squared value of 0.28. ANCOVA analysis of EQ-VAS data was conducted to assess differences in the change mean scores from baseline to six weeks for the quality of health between the two study groups. Controlling for baseline scores, the results indicated no significant difference between groups at six weeks on the EQ-VAS, (F (1,51) = 0.46 p = 0.50, partial eta squared = .009) as displayed in Table 3.2.

After data imputation, there remain no significant difference in the mean changes in CSSRS, QIDS-SR16, and EQ-VAS scores from baseline to six weeks between the intervention and control groups (p> 0.05).

Table 3.2: Descriptive mean scores of outcome measures and ANCOVA test parameters for the rTMS and rTMS + iCBT groups

Measure	Descriptive				ANCOVA parameters		
	Baseline, mean (SD)		Discharge, means (SD)		F value (df)	p-value	Partial eta
	rTMS	rTMS+iCBT	rTMS	rTMS+iCBT			
HAM-D-17	15.73(6.03)	17.43(4.79)	8.89(5.83)	9.97(7.03)	0.15(1)	0.70	0.003
CSSRS	1.57 (1.70)	1.79 (1.44)	0.96(1.45)	1.03(1.11)	0.04(1)	0.85	0.001
QIDS-16	16.62(4.59)	17.59(4.15)	10.08(4.36)	11.34(5.72)	0.26(1)	0.61	0.005
EQ-VAS	65.80(17.06)	59.76(21.72)	64.42 (18.13)	60.90 (21.45)	0.46(1)	0.50	0.009

Table 3.3 illustrates the differences in the prevalence of the clinical conditions between the two interventions (rTMS alone and rTMS + iCBT) at discharge (six weeks). Overall, there was no significant difference between the two intervention groups on all measured scales. The Chi-square/ Fischer exact values ranged from 0.51 to 2.95, while the *p*-values ranged from 0.20 to 0.91.

Table 3.3: Distribution of the prevalence of the clinical characteristics between the two study groups at discharge

Measures	**rTMS N (%)**	**iCBT + rTMS N (%)**	**Total**	**Chi Square /Fischer Exact**	**P-value**
MDD at discharge	N=27	N= 30			
At most, mild depression	24 (88.9)	25 (83.3)	49 (86.0)	*	.71
Moderate to severe depression	3 (11.1)	5 (16.7)	8 (14.0)		
Suicidal ideation at discharge	N=28	N= 31			
No suicidal ideation	16 (57.1)	12 (38.7)	28 (47.5)	2.01	.20
Present suicidal ideation	12 (42.9)	19 (61.3)	31 (52.5)		
Likely depression at discharge (QIDS)	N= 26	N= 32			
At most, mild depression	13 (50.0)	19 (59.4)	32 (55.2)	0.51	.60
Moderate to severe depression	13 (50.0)	13 (40.6)	26 (44.8)		
EQ-5D-5L at discharge					
Mobility:					
No problems walking	17 (65.4)	23 (74.2)	40 (70.2)		
Slight problems walking	7 (26.9)	5 (16.1)	12 (21.1)		
Moderate problems walking	1 (3.8)	1 (3.2)	2 (3.5)	1.48*	.81
Severe problems walking	1 (3.8)	2 (6.5)	3 (5.3)		

Unable to walk	0 (0.0)	0 (0.0)	0 (0.0)		
Self-care:					
No problems washing/dressing	17(65.4)	19(61.3)	36(63.2)		
Slight problems washing/dressing	7(26.9)	8(25.8)	15(26.3)		
Moderate problems washing/dressing	1(3.8)	3(9.7)	4(7.0)	0.98	.91
Severe problems washing/dressing	1(3.8)	1(3.2)	2(3.5)		
Unable to wash/dress					
Usual activities					
No problems doing usual activities	7(26.9)	4(12.9)	11(19.3)		
Slight problems doing usual activities	9(34.6)	15(48.4)	24(42.1)		
Moderate problems doing usual	6(23.1)	6(19.4)	12(21.1)	2.66	.67
activities	3(11.5)	5(16.1)	8(14.0)		
Severe problems doing usual activities	1(3.8)	1(3.2)	2(3.5)		
Unable to do usual activities					
Pain/discomfort					
No pain or discomfort	12(46.2)	13(41.9)	25(43.9)		
Slight pain or discomfort	7(26.9)	9(29.0)	16(28.1)		
Moderate pain or discomfort	6(23.1)	6(19.4)	12(21.1)	1.83*	.87
Severe pain or discomfort	0(0.0)	2(6.5)	2(3.5)		
Extreme pain or discomfort	1(3.8)	1(3.2)	2(3.5)		
Anxiety/depression					
Not anxious or depressed	4(15.4)	4(12.9)	8(14.0)		
Slightly anxious or depressed	6(23.1)	11(35.5)	17(29.8)		
Moderately anxious or depressed	10(38.5)	8(25.8)	18(31.6)	2.95*	.59
Severely anxious or depressed	5(19.2)	8(25.8)	13(22.8)		
Extremely anxious or depressed	1(3.8)	0(0.0)	1(1.8)		

Exploratory outcomes

Table 3.4 demonstrates the changes in study measures from baseline to discharge (six weeks) for all participants who completed both baseline and six weeks scales. The data in table 3.4 suggest that the mean scores of the HAMD-17 at baseline (M=16.25, SD = 5.29) and six weeks (M = 9.45, SD =6.44); t (68) = 7.46, P= .001), CSSRS at baseline ((M =1.69, SD = 1.59) and six weeks (M = 1.00, SD = 1.27); t (71) = 4.06, P= .001), QIDS-SR16 at baseline ((M =16.79, SD =4.45) and six weeks (M = 10.88, SD =5.22); t (69) = 9.45, P= .001), and EQ-VAS at baseline ((M =47.67, SD =18.45) and six weeks (M = 62.56 , SD = 19.75); t (69) = 6.31, P = .001) scales were significantly lower at six weeks than the baseline mean scores. This indicates an overall improvement in the severity of depressive symptoms, suicidal ideations, subjective depression symptoms, and the quality of health, regardless of the type of intervention. The effect size as measured by Cohen's d for HAM-D-17, CSSRS, QIDS-SR16, and EQ-5D-5L were (1.15, 0.48, 1.23, and 0.78), respectively.

From table 3.4, our results revealed a significant reduction in the mean score of all measured scales after week six compared to the baseline scores (HAM-D (42%), CSSRS (41%), QIDS-SR16 (35%), and EQ-VAS (62%))

Table 3.4: Comparison of the baseline and six-week mean scores on the HAMD-17, CSSRS, QIDS, and EQ-VAS scales for study participants who completed both the baseline and sixth-week scales (N=76)

Measure	Responses, n	Scores			Mean difference (95% CI)	*P*-value	*t* value	Effect size (Cohen d)
		Baseline score, mean (SD)	Six-week score, mean (SD)	Change from baseline, %				
HAMD	56	16.25(5.29)	9.45(6.44)	41.8	6.80(4.98 - 8.63)	< .001	7.46	1.15
CSSRS	59	1.69 (1.59)	1.00(1.27)	40.8	0.69(0.35 - 1.04)	< .00	4.06	0.48
QIDS	56	16.79(4.45)	10.88(5.22)	35.2	5.91(4.66 – 7.16)	<.001	9.45	1.23
EQ-VAS	54	47.67 (18.45)	62.56 (19.75)	61.56	14.89 (-19.62) – (-10.16)	< .001	6.31	0.78

Similar to previous results, the data in table 3.5 indicate statistically significant reductions in the prevalence of depression in participants after the six-week assessment compared to the baseline assessment with MDD (33.9%), suicidal ideation (18.7%), and subjective depression (41.1%). Regarding the EQ-5D-5L scale, there were four subscales: mobility, self-care, usual activity, and pain/discomfort that did not show a statistically significant association between baseline and discharge values (*P*= 0.194. *P*= 0.252, *P*= 0.221, *P*= 0.315), respectively. However, for the anxiety/depression subscale (Table 3.5), *post hoc* analysis using adjusted residuals indicated that baseline proportions (20%) of the respondents who reported 'Extremely anxious or depressed' were significantly reduced at six weeks (discharge) (3.6%) (z = 2, p= .046).

Table 3.5: Comparison of the baseline and six-week prevalence of major depressive disorder, suicidal ideations, subjective depression, and the quality of health for all study participants

Condition	Prevalence, n/total responses (%)	Change in prevalence (the sixth week	χ^2 (df)	*P*-value

			from baseline), %		
	Baseline	Sixth week			
MDD clinical diagnosis	27/56 (48.2)	8/56 (14.3)	- 33.9	15.00(1)	< 0.001
Suicidal ideations	42/59 (71.2)	31/59 (52.5)	- 18.7	4.35 (1)	0.004
Subjective depression (QIDS-16)	49/56 (87.5)	26/56 (46.4)	- 41.1	21.35(1)	< 0.001
EQ-5D-5L					
Mobility:					
No problems walking	41/55 (74.5)	39/55(70.9)	-3.6		
Slight problems walking	6/55 (10.9)	12/55(21.8)	10.9	4.72	0.194
Moderate problems walking	5/55 (9.1)	1/55 (1.8)	-7.3	(1)	
Severe problems walking	3/55 (5.5)	3/55 (5.5)	0.0		
Unable to walk					
Self-care:					
No problems washing/dressing	32/55 (58.2)	35/55(63.6)	5.4		
Slight problems washing/dressing	11/55 (20.0)	14/55 (25.5)	5.5		
Moderate problems washing/dressing	11/55 (20.0)	4/55 (7.3)	-12.7	4.09	0.252
Severe problems washing/dressing	1/55 (1.8)	2/55 (3.6)	1.8	(1)	
Unable to wash/dress					
Usual activities					
No problems doing usual activities	8/55 (14.5)	11/55(20.0)	5.5		
Slight problems doing usual activities	14/55 (25.5)	23/55 (41.8)	16.3		
Moderate problems doing usual activities	16/55 (29.1)	11/55 (20.0)	-9.1	5.72	0.221
Severe problems doing usual activities	15/55 (27.3)	8/55 (14.5)	-12.8	(1)	
Unable to do usual activities	2/55 (3.6)	2/55 (3.6)	0.0		
Pain/discomfort					
No pain or discomfort	15/55 (27.3)	24/55 (43.6)	16.3		
Slight pain or discomfort	18/55 (32.7)	16/55 (29.1)	-3.6		
Moderate pain or discomfort	16/55 (29.1)	11/55 (20.0)	-9.1	4.74	0.315
Severe pain or discomfort	5/55 (9.1)	2/55 (3.6)	-5.5	(1)	
Extreme pain or discomfort	1/55 (1.8)	2/55 (3.6)	1.8		
Anxiety/depression					
Not anxious or depressed	2/55 (3.6)	7/55 (12.7)	9.1		
Slightly anxious or depressed	3/55 (5.5)	16/55 (29.1)	23.6		
Moderately anxious or depressed	18/55 (32.7)	18/55 (32.7)	0.0	21.8	<
Severely anxious or depressed	21/55 (38.2	13/55 (23.6)	-14.6	9(1)	0.001
Extremely anxious or depressed	11/55 (20.0)	1/55 (3.6)	-16.6		

Discussion

Principal Findings

This study failed to establish a significant difference between outcomes for the two interventions under study (rTMS alone and rTMS plus iCBT) regarding the improvement of MDD symptoms,

suicidal ideations, subjective depression symptoms, and the quality of health on all scales. However, in the exploratory analysis, there was a significant improvement in all participants regarding depressive symptoms, suicidal ideations, subjective depression, and the quality of health from baseline after being on the intervention for six weeks.

In the wake of a global search for better, safer, and more cost-effective management of TRD, many treatment alternatives to the traditional psychopharmacology have been introduced into the therapeutic space of psychiatric healthcare, including rTMS and CBT. Many studies have been conducted concerning the actual efficacy of these interventions in TRD separately[137, 141, 142, 371, 492]. Although results support the efficacy of these interventions, data concerning their combined efficacy is lacking in the literature. To the best of our knowledge, the concomitant application of internet delivered psychotherapy (iCBT) with rTMS has not been studied before, and this study is the first of its kind. Therefore, the results generated in this study provide a concrete basis for further evaluating the practical application and efficacy of using a novel combination of these two treatment modalities (rTMS plus iCBT) with a larger sample size and target population of different characteristics.

Our study yielded some interesting outcomes regarding the changes in the clinician- as well as the self-evaluated severity and prevalence of depression, suicidal ideations, and quality of health in the TRD patients under study. Overall, there was a significant improvement observed at six weeks (discharge) in participants' mean scores on HAM-D-17 (41.8%), CSSRS (40.8%), QIDS-SR16 (35.2%), and EQ-5D-5L (61.56) from the baseline scores. This suggests that, overall, the treatment intervention was effective in reducing the depressive symptoms, and suicidal symptoms, and improving the quality of health in the TRD patients with high to moderate effect sizes (1.15, 0.48, 1.23, and 0.78), respectively. With regard to prevalence, our results demonstrated statistically significant reductions in the prevalence of major depression disorder as well as suicidal symptoms and improved quality of health in all participants at the week six assessment compared to the baseline assessment. (33.9%, 18.7%, and 41.1%), respectively.

While there were significant improvements in the symptoms of depression, suicidal ideations, and in the quality of health of all participants at week six, this study failed to demonstrate a significant difference between the two interventions (rTMS alone and rTMS plus iCBT). Thus, after controlling for the baseline scores, the results revealed no significant differences between the two treatment intervention groups at six weeks on the 17-item HAM-D ($p = 0.70$), the CSSR

scale (p = 0.85, QIDS-SR16 (p = 0.61), and EQ-5D-5L (p = 0.50). This implies that there is no added value in adding iCBT as an adjunctive treatment with rTMS for the treatment of TRD.

The present findings should, of course, be interpreted cautiously, given that unguided iCBT rather than guided iCBT was used in this study.

Interpreting Findings against the Literature

Contrary to the findings in this study, an RCT to assess the superiority of the combination strategy of rTMS and bright light therapy (BLT) over rTMS treatment alone in reducing depressive symptoms in TRD reported significant improvement in the depressive symptoms of participants in the rTMS plus BLT group recorded on the 17-item HAMD compared to the rTMS alone group [153]. The possible explanation for this may be that, unlike unguided iCBT in our study, BLT could enhance and accelerate the antidepressant effect of rTMS in treating TRD patients by acting as a rapid antidepressant tool involving several pathways through the circadian rhythm regulation and in a non-circadian rhythm dependent manner.

However, even though this study failed to find an additive value for iCBT to rTMS regarding the management of TRD symptoms, it does not invalidate the full use and therapeutic efficacy of iCBT in the management of TRD as there is evidence that supports the use of iCBT for the management of depression and resistant depression [68, 69, 362, 363, 365, 437, 493], with claims of efficacy equivalent to that of CBT delivered by trained personnel[68, 362]

The failure of a combination of rTMS and unguided iCBT in our study may be attributed to differences in the effectiveness of unguided iCBT versus guided iCBT. Enough evidence in the literature supports the effectiveness of guided iCBT over unguided iCBT[364, 365]. A meta-analysis conducted in this regard found the therapist-guided iCBT demonstrated a greater symptom reduction (d = 0.61) than unguided (d = 0.25)[364]. The reasons, according to the researchers, were attributed to the added motivation received from the assistance of the therapist and compliance influenced by the guided interventions. In another meta-analysis of 19 RCTs, the researchers again found superior effects of guided iCBT (therapist support, d=0.78; administrative support, d=0.58) compared to unguided iCBT (d=0.36) for the management of depression[365]. Thus, unguided iCBT interventions seem to result in more modest outcomes and higher dropout rates compared to therapist-guided iCBT interventions.

Furthermore, geographical differences may also account for the modest outcomes of unguided iCBT delivered through the MoodGYM platform to Canadian patients. Thus, cultural references

in the use of this internet-based intervention platform may be more familiar to individuals living in Australia where it was developed than North America and Europe; hence, the demonstration of large effect sizes for MoodGYM RCTs conducted in Australia (g = 0.73, 95% CI: 0.19–1.27) versus the small effect sizes displayed for RCTs conducted in Europe (g = 0.17, 95% CI: 0.04–0.30)[369]. Again, Australia is well known for its expertise in the development of computer-based psychotherapeutic interventions, with excellent infrastructure relating to the administration of these interventions [494]. Therefore, the possibility that the superiority of effectiveness within RCTs conducted in Australia is somehow attributed to the greater acceptance of iCBT especially MoodGYM in this population.

In summary, the present study is highly informative given that it is the first of its kind. However, the study did not find the combined treatment of rTMS + iCBT(unguided) superior over rTMS alone over short-term effects. Hence, we can accept the null hypothesis as our findings found no statistical differences between the two treatment interventions under study in terms of their MDD symptoms, suicidal ideations, subjective MDD symptoms, and health status. This result thus does not support the use of combined treatment of rTMS + unguided iCBT for the management of TRD disorders.

Strengths of this Study

Randomization of participants ensured a balanced distribution of different characteristics of participants between the two treatment arms at baseline. Primary outcome assessors were blinded to treatment group allocation by not involving them in discussions about study participants and not granting them access to the secured database which contained the randomization codes. After data collection was completed, all data underwent a blind review to finalize the planned analysis. Blinding of the primary outcome assessors for the primary outcome measures ensured the elimination of bias in outcome measures.

Limitations

This study has several limitations that need to be considered when interpreting the findings. First, the sample size of study participants who completed both the baseline and six-week assessments was small. Thus, the small sample size might have impacted the study power, which limited the ability of the study to detect differences in outcome measures between participants in the two

treatment arms at discharge. Therefore, our results may not be generalizable to the general population and should be interpreted with caution. Secondly, since the study employed self-guided iCBT, participants were encouraged to conduct the iCBT sessions on their own in their homes. While the research team used continual reminders via text messaging about the iCBT sessions to participants, there was no direct supervision and, hence, the participants' adherence to the protocols of "MoodGYM" cannot be guaranteed. Thirdly, the possible variability in concomitant treatments (medication and/or psychotherapy) outside the rTMS clinic being received by patients as well as the variability in the time to be spent by patients in the two arms of the study could have had some level of confounding effects on the outcomes of our interventions.

Conclusion

This study failed to demonstrate a significant difference regarding the management of MDD symptoms, subjective MDD, suicidal ideations, and the quality of health between rTMS alone and rTMS plus unguided iCBT on all scales. Many factors may have accounted for the lack of significant differences in our intervention groups. To address these factors, future studies need to investigate the cross-cultural factors that may influence the effectiveness of iCBT interventions in North America if delivered by the MoodGYM program. It is recommended that future studies on the combination of rTMS+ unguided iCBT be run on a large sample size and for longer in patients with TRD. This may provide evidence to support the implementation and upscaling of the concomitant application of these interventions in a way that fits the needs of the targeted population.

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