Clinical Practice Guidelines for the Therapeutic Use of Repetitive Transcranial Magnetic Stimulation in Neuropsychiatric Disorders

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INTRODUCTION

Psychopharmacology and psychotherapy form the mainstay of treatment in psychiatric disorders. Despite advances in both the forms of treatments and their strategies, 20-60% of patients with psychiatric disorders do not respond.[1] This treatment non-response, which is now recognized across the whole range of psychiatric disorders, leads to a greater healthcare burden. Moreover, poor adherence, which is related to the stigma attached to psychopharmacological agents, their side-effect profiles, and poor feasibility in following psychotherapy sessions, contributes to poor treatment outcomes, specifically termed as 'pseudo-resistance'.[1] In the background of this, and also in the wake of technical advances in the field of basic neurosciences, newer forms of treatments have been developed and investigated. One such newer treatment is the use of repetitive transcranial magnetic stimulation (rTMS).

rTMS is a non-invasive, non-convulsive method of brain stimulation first described by Anthony Barker and his colleagues in 1985 and came to be used in clinical settings in the 1990s. It refers to a multisession treatment where magnetic fields induced by recurring TMS pulses stimulate nerve cells in a particular brain region. It has a neuromodulatory effect on neuronal excitability and has been implied to have neuroplastic effects. The development of rTMS as a form of treatment is supported by a large number of clinical studies across psychiatric disorders. Since 2008, the US Food and Drug Administration (FDA) has so far cleared many pieces equipments for the therapeutic use of rTMS as an adjunctive treatment strategy in various conditions [Table 1].[2]

Over the course of the last 2 decades, there has been a significant increase in interest in the use of rTMS, and several forms of rTMS, various protocols, coils, target regions, etc., have been investigated. While high-frequency (>5/10 Hz) and low-frequency (≤1 Hz) stimulations are considered the conventional rTMS forms, patterned rTMS i.e., theta burst stimulation (TBS) and quadri-pulse stimulation (QPS) are the newer forms. Further, there are three sub-forms of TBS– intermittent TBS (iTBS), continuous TBS (cTBS), and intermediate TBS (imTBS). Several protocols- once daily, twice or more daily (also called intensive or accelerated protocols), 3-5/week to once weekly, fortnightly, or even once a month maintenance protocols are being investigated. Further, as many as 50 TMS coil designs are being examined.[3] Moreover, apart from the conventional target sites– dorsolateral prefrontal cortex (DLPFC) and the temporoparietal cortex (TPC), several new brain regions (cerebellum, orbitofrontal cortex (OFC), supplementary motor area (SMA), etc) including bilateral stimulations have been chosen to study the effects of rTMS in various psychiatric disorders.

Table 1: The United States Food and Drug Administration (FDA) approval timeline for rTMS equipment

Year	Equipment	Disorder
2008	Neuronetics (Neurostar)	MDD
2013	Deep TMS (Brainsway)- H1 coil	MDD
2013	eNeura	Migraine
2015	Rapid^2 (Magstim)	MDD
2016	Tonica Elektronik (MagVenture)	MDD
2017	Navigated Brain Therapy (NBT) system (Nexstim)	MDD
2017	Deep TMS (Brainsway)- H7 coil	OCD
2018	Apollo TMS (MAG & More)	MDD
2018	Tonica Elektronik (MagVenture) with TBS	MDD
2020	Neuronetics (Neurostar) with TBS	MDD
2020	Tonica Elektronik (MagVenture)	OCD
2020	Deep TMS (Brainsway)- H4 coil	Smoking cessation
2020	CloudTMS (Soterix Medical)) along with robotic coil positioning/neuronavigation	-
2021	CloudTMS (Soterix Medical)	MDD
2021	Deep TMS (Brainsway)- H1 coil	Anxiety comorbid with MDD

TMS=Transcranial Magnetic Stimulation; TBS=Theta Burst Stimulation; MDD=Major Depressive Disorder; OCD=obsessive compulsive disorder

Given the rising interest among psychiatrists for the use of rTMS in routine clinical practice, increasing availability of TMS equipment, an array of numerous choices in modes of rTMS delivery forms, and increasing literature base for the use of rTMS in several psychiatric disorders,[4] even from India,[5] it is important to develop specific and up-to-date clinical practice guidelines (CPG). The Indian Psychiatric Society (IPS)- CPG for the use of rTMS in various psychiatric disorders intends to synthesize the emerging evidence-based literature and provide expert guidance for bringing consistency in the clinical application of rTMS. While we encourage practitioners to implement evidence-based recommendations, we also deem that the use of rTMS in clinical practice can vary and depends upon the clinician's acumen and experience.

METHODS

Process of forming the CPG for use of rTMS

The IPS-CPG task force delegated a team of five experts for drafting the CPG for use of rTMS. The experts met at IPS state/zonal conferences and via online meetings and developed the recommendations and the draft. The recommendations were informed primarily by an umbrella review of recent meta-analytic studies assessing the role of rTMS in various psychiatric disorders performed by the authors and supplemented by other clinical practice guidelines,[6] evidence-based guidelines, and umbrella reviews[7-9], and consensus or expert recommendations.[10-12] The experts involved in developing the recommendations were also abreast of the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework.

Umbrella review- Search strategy and Inclusion criteria

We performed an umbrella review of meta-analyses that have assessed the efficacy and/or safety of various rTMS protocols in different psychiatric disorders.

We systematically searched the PubMed database until July 15th, 2022 supplemented with manual searches. The search string used was "("rTMS") OR ("theta burst stimulation") OR ("Non-Invasive Brain Stimulation")". We applied the "Meta-Analysis" filter and adjusted the "timeline" to 2018–2022 (i.e. last five years). This resulted in a total of 168 articles, that were further screened for the following inclusion criteria: i) meta-analysis of randomized controlled trials (RCTs), and ii) reporting on efficacy and safety of rTMS (including theta burst stimulation (TBS)) in psychiatric disorders, specifically a) cognitive disorders and dementia; b) substance use disorders; c) schizophrenia; d) depression (including unipolar depression, bipolar depression, peripartum depression, post-stroke depression, post-traumatic brain injury depression, depression associated with Parkinson's disease); e) bipolar disorder; f) anxiety disorders; g) obsessive-compulsive disorder (OCD) and related disorders; h) Post-traumatic stress disorder (PTSD); i) autism spectrum disorder (ASD); j) attention deficit hyperactivity disorder (ADHD); k) eating disorders; l) chronic pain disorders including headache and fibromyalgia; m) insomnia; n) chronic tinnitus; and o) essential tremors. We also included meta-analyses specifically aimed at assessing suicidality, impulsivity, empathy, and borderline personality disorder. The Exclusion criteria we chose were i) study designs other than MA of RCTs, ii) no safety or efficacy data reported, iii) non-English articles. Studies that assessed other (non-invasive brain stimulation (NIBS) together with rTMS, or two conditions together or not having specifically defined a clinical condition and not having provided pooled statistics for rTMS separately for distinct disorders were also excluded.

Finally, 97 meta-analyses were reviewed. Only sham-controlled pooled effect sizes were noted and included for synthesis. A list of references for all the studies is submitted as supplementary material.

CLINICAL PRACTICE GUIDELINES

Who can provide rTMS?

Provision of rTMS sessions can primarily be understood as i) prescribing or advising rTMS treatment and ii) delivering rTMS sessions. This two personnel are termed "TMS physician" and "TMS operator". The "TMS physician" by definition is "a clinician with prescriptive privileges who is knowledgeable about, trained, and credentialed in rTMS"[8]. Moreover, they are essentially required to have an "extensive background in brain physiology that is obtained during residency training in psychiatry, neurology, or neurosurgery", and "a deep understanding about the neurophysiological effects of rTMS".[13] On the other hand, the "TMS operator" needs to be able to "recognize potentially serious changes in a patient's mental status and know when to alert an attending physician" and have been trained in recognizing and effectively responding to seizures.[10,13] Therefore, the "TMS operator" may be any non-medical personnel. However, paramedical staff such as nurses may be preferred when available.

Training for providing rTMS treatment

The Indian Psychiatric Society (IPS) in collaboration with NIMHANS, Bengaluru, and AIIMS New Delhi, has been conducting a series of annual training workshops in this regard. Other institutes such as the Central Institute of Psychiatry, Ranchi, and Kasturba Medical College, Manipal also are providing training in rTMS. In fact, recommendations for training in NIBS have also been put forth and they recommend training not only for clinicians but also for technicians and scientists.[14]

rTMS set-up and the device

An air-conditioned suit with adequate space for the rTMS equipment including the participant sitting arrangement

and space for storage of spare coils is an essential requisite. There should be enough space for the person delivering the sessions. Also, the rTMS suite must have a provision for participant waiting and a washroom. The essential needs for emergency seizure management set-up, including the need for storage of anticonvulsants, and the immediate availability of trained physicians has to be ensured. There has to be a provision for a powerful air conditioning unit to cool the coils, in case cooled coils are not used.

The components of the rTMS device are:

1. Electronic Main Unit
2. Coil (the figure-of-eight coil is most commonly used)
3. Cooling unit and control cable for the cooling unit
4. Power Supply Unit and its cables
5. EMG machine
6. Coil Holder
7. Computer system.

A trolley for the machine and a flexible stand for fixing the coil in the right position near the seating set-up may be acquired. The sitting equipment must preferably be a comfortable recliner chair. The height of its back resting must allow for the coil to be placed for delivering stimulation. Disposable earplugs must be available for participants for each session. A skin marker and a measuring tape will be required for marking the target location.

Sample technical specifications for an rTMS device are given in Table 2.

Table 2: Sample technical specification for TMS

Tools	Specifications
TMS Stimulator (Essential)	At least 50 Hz capacity with burst mode to deliver theta-burst stimulation (basic model will come with 20 Hz capacity without burst mode)
Coils (Essential)	Air or liquid cooled Figure of 8 coils- 2 in number (placebo coil if keen to do research)
Accessories (Essential)	TMS Trolley TMS coil holder (goose neck) TMS chair; a comfortable simplified dental chair UPS/Stabilizer unit
Others (Desirable)	USFDA/CE/ISO certification. Integrated EMG interface/set-up 'Double cone' coils or 'H' coils will be required for stimulation of deeper structures Upgradable to add neuro-navigation for coil position and orientation in future.

TMS=Transcranial Magnetic Stimulation; UPS=uninterruptible power supply; USFDA=United States Food and Drug Administration; CE=Conformité Européenne; ISO=International Organization for Standardization; EMG=electromyography

Patient inclusion and pre-rTMS evaluation

Informed consent has to be taken before the start of rTMS sessions and all the possible side-effects and their probability have to be explained. Along with the psychiatric evaluation, detailed medical, treatment and neurological history have to be taken. Particularly, a history of epilepsy (both in the patient and in the family), significant or recent traumatic brain injury, loss of consciousness, stroke, brain tumor or currently taking medication/s that lowers the seizure threshold should be specifically noted. If any of these are reported to be positive, then the patient has to be informed regarding the risk of a possible rTMS-related seizure, and the patient's risk-benefit ratio has to be determined.[10] It is important to note that participants who have received rTMS sessions safely in the past are at less risk than those receiving rTMS newly.[12] Moreover, the chances of seizures are highest in the first three sessions (62% during the first session and 75% during the first three sessions)[12] and therefore rTMS operators/physicians must exercise high precaution during the initial rTMS sessions.

The pre-rTMS evaluation may be supplemented by the use of tools such as the TMS Adult Safety Screen (TASS)[15] or the screening standard questionnaire for rTMS candidates [Table 3] suggested by Rossi *et al*.[16]

Table 3: Rossi *et al*. (2009)[16] screening standard questionnaire for rTMS candidates

Questions
Do you have epilepsy or have you ever had a convulsion or a seizure?
Have you ever had a fainting spell or syncope? If yes, please describe in which occasion (s)
Have you ever had severe (i.e., followed by loss of consciousness) head trauma?
Do you have any hearing problems or ringing in your ears?
Are you pregnant or is there any chance that you might be?
Do you have metal in the brain/skull (except titanium)? (e.g., splinters, fragments, clips, etc.)
Do you have cochlear implants?
Do you have an implanted neurostimulator? (e.g., DBS, epidural/subdural, VNS)
Do you have a cardiac pacemaker or intracardiac lines or metal in your body?
Do you have a medication infusion device?
Are you taking any medications? (Please list)
Did you ever have a surgical procedures to your spinal cord?
Do you have spinal or ventricular derivations?
Did you ever undergo TMS in the past?
Did you ever undergo MRI in the past?

rTMS=Repetitive Transcranial Magnetic Stimulation; DBS=Deep Brain Stimulation; VNS=Vagal nerve stimulation

Contraindications for the use of rTMS are:

1. Presence of implanted medical devices that is ferromagnetic or magnetic sensitive or any such metal objects in the brain, head, and neck areas.
2. Deep Brain Stimulation (DBS) where subcutaneous leads are placed in the scalp, etc., is also a contraindication, if the coil position is <10 cm away.
3. Any other metallic medical devices such as chips, pumps, pacemakers, cochlear implants, dental implants, permanent piercings, and tattoos containing ferromagnetic containing ink, if the coil position is <10 cm away.

X-rays may be helpful for screening but they cannot determine if the metals are ferromagnetic. Metallic implants

below the head and neck, such as knee or hip prosthesis are considered safe.[12]

Substance in the past week, the day before the treatment sessions must be documented.

Current drugs and their doses, along with the total duration should be documented. Also, any medication changes during the rTMS treatment course must be noted.

Patient preparation

The following may be ensured before commencing the rTMS treatment session:

- Adequate sleep (other than in cases of insomnia) has to be ensured.
- Also, absence of any acute medical emergency including high fever, uncontrolled hypertension and elevated blood pressure, uncontrolled diabetes, and hyperglycaemia, acute headache, acute vertigo/giddiness/dizziness, any fresh scalp/facial injury, etc., has to be ascertained. Also ensure that the patient is cooperative and is not acutely violent, aggressive, and suicidal.
- Use of alcohol, tobacco, or any substance prior to the treatment session must be avoided.

Determining the motor threshold

Determination of the motor threshold (MT) is a must for determining the stimulus intensity of rTMS. Ideally, it has to be measured before every session. However, for the sake of ease the MT and the stimulus intensity that is determined before the start of the first session may be used for all subsequent sessions in the following week. However, in cases where the treatment sessions are lasting more than a week or are given at an interval >1 week, MT (and therefore the stimulus intensity) has to be ascertained again. Also in cases where there are changes in medication doses or heavy intake of alcohol or any other substance 24 hours prior to the rTMS session or if the participant is complaining of headache or scalp/facial pain, MT must be determined again.

MT is defined as the "minimum stimulus intensity that elicits a response in either the abductor pollicis brevis (APB) or the first dorsal interosseous (FDI) on the contralateral side for ≥50% of applied stimuli (usually defined as ≥5 of 10 stimuli administered)"[10] following single-pulse TMS, that is graded from small to high and delivered every 5 seconds. The muscle response may be either determined by the amplitude of the EMG response or by visual observation of finger twitching. Although finger twitching is a more feasible alternative in busy clinical settings, it may be noted that this method yields "significantly higher MTs than EMG of that muscle."[17]

Target location

Apart from the conventional scalp i.e., the "5-cm" and "International 10-20 electroencephalography (EEG)" system-based methods, neuroimaging i.e., magnetic resonance imaging (MRI, both structural & functional, resting & task-based as well as 3D), Single-photon emission computed tomography (SPECT) and positron emission tomography (PET), based methods too have been developed for precise location of target for stimulation.[18] TMS equipment with in-built neuronavigation systems, that utilize the neuroimages have been approved by the FDA.[2] It is suggested that although neuroimaging-based methods are more accurate, the use of the International 10-20 EEG system for the target location is considered a cost-effective alternative.[18]

Safety issues and monitoring

TMS and hearing

Following steps shall be addressed for hearing safety during TMS:[12]

1. Individuals with pre-existing noise-induced hearing loss or receiving simultaneous treatment with ototoxic medications (aminoglycosides) shall undergo risk/benefit considerations.
2. Use of well-fitted hearing protection such as earplugs by patients and TMS operators
3. ENT referral for any complaints of hearing loss, tinnitus, or ear fullness.
4. Patients with Cochlear implants should not undergo TMS.

Safety of TMS in combination with other devices

TMS can be safely employed with devices such as implanted stimulators in the central or peripheral nervous system, cardiac pacemakers, and VNS systems given that the coil is not closer than 10 cm to the electronic components like Implanted pulse generator (IPG) in the neck. An important point to consider is that TMS should start with low intensity and progressively increase to the desired intensity. If overall risk-benefit analysis confers risk, then turning the IPG off during TMS may offer some protection against induced electrode currents. TMS in patients with DBS shall only be carried out if there are concrete scientific or medical reasons and shall be overseen by the institute's ethics committee.[12]

Safety of TMS in combination with drugs

Despite large numbers of patients receiving drugs and TMS in the past decade, no detailed toxicities have arisen from the combination. Moreso, the observed seizure rate is very low despite most of them receiving CNS-activating medications. The situation is very reassuring with the use of traditional stimulation parameters and focal coils. So, currently, no caution shall be entertained. However, documentation of the simultaneous intake of drugs (like clozapine) and additional possible seizure threshold-lowering factors (such as alcohol intake, sleep deprivation, and infection) during the TMS sessions shall be done. All efforts to systematically capture reports of side effects shall be carried out.[12]

TMS safety in special population

Paediatric: The majority of TMS studies continue to be single and paired-pulse studies. The most common side effect reported was a headache. No other serious side effects have been reported. With suitable hearing safety measures, single-pulse and paired-pulse TMS use are safe in children with age two years and older.[12]

Pregnancy: Approximately 100 mV/m of TMS-induced E-field is generated by a figure-of-eight coil (adjacent to the DLPFC) when the coil-uterus distance was 60 cm. This is far less than the safety threshold to stimulate myelinated central and peripheral nerves (800 mV/m). So, it is viable to conclude that rTMS (figure-of-eight coil) has minimal risk for the mother and child.[12]

TMS safety for the operators

Safety issues are seldom addressed for TMS operators, despite being exposed for several hours daily for several years. It is pertinent that the TMS operator should avoid (or minimize) proximity i.e., less than 40 cm distance from the magnetic coil in order to derail exposures. Also, the use of earplugs or earmuffs is mandatory for operators.[12]

TMS safety and protocols intensity

Safety parameters of stimulation defined by Rossi *et al*.[12] needs to be adhered to for conventional protocols. But for parameters exceeding these safety guidelines, the use of neurophysiological monitoring (i.e., the appearance of motor twitches during stimulation as a warning for increased cortical stimulation) needs to be carried out. If any de novo seizure arises, kindly reconsider the protocol of the trial. Also, the scientific community needs to be alerted about the unsafety of any new combination of parameters.[12]

Evidence

It is important to note at the beginning that in all the meta-analyses reviewed for recommendations on efficacy in this document, for all conditions except headache and a small minority of studies for other conditions, rTMS has been used as an adjunct to the treatment as usual.

Evidence- depression

We reviewed 23 meta-analyses for depression [Table 4].

Efficacy of rTMS in major depression (please see Figure 1 for recommendation)

There is strong evidence for a significant positive effect of the use of rTMS for treating acute depression, especially for unipolar depression. The pooled effect sizes for improvement in depression severity range between 0.302 to 0.83. The odds for response (pooled odds ratios (ORs) ranging between 3.26 and 3.64) and remission rates (pooled ORs ranging between 2.45 and 4.63) were significantly higher for the use of rTMS. The strongest evidence was for high-frequency rTMS over the left DLPFC (pooled ORs for response ranging from 3.17 to 3.75).

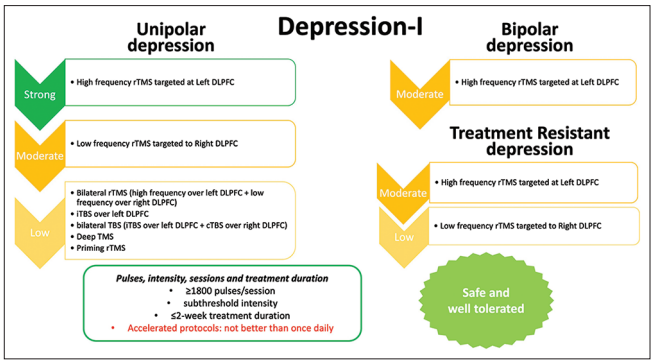

Figure 1: Recommendation A: Depression- I: Unipolar depression, bipolar depression and treatment resistant depression

Two network meta-analyses *[Supplementary Table 1; sl.no. 6 and 10]* compared the odds of response for various rTMS forms. Based on the ORs and narrow confidence intervals, high-frequency rTMS over the left DLPFC has been shown to be superior followed by low-frequency rTMS over the right DLPFC. Bilateral rTMS (high-frequency over left DLPFC + low-frequency over right DLPFC), iTBS over left DLPFC, bilateral TBS (iTBS over left DLPFC + cTBS over right DLPFC), deep TMS and iTBS and priming rTMS have also been found to have a significant positive effect. A meta-analysis focussing on TBS *[Supplementary Table 1; sl.no. 3]* though claims that the effects of iTBS are similar to high-frequency rTMS.

There is moderate positive evidence for the use of rTMS in acute bipolar depression (effect size 0.302, OR for response 2.72), one meta-analysis that compared unipolar and bipolar depression *[Supplementary Table 1; sl.no. 9]* found that the significance was restricted to only unipolar depression and not to bipolar depression. For bipolar depression too, the strongest evidence was for high-frequency rTMS over the left DLPFC (pooled ORs for response 2.17). In fact, in bipolar depression, only high-frequency rTMS over the left DLPFC has been shown to cause significant effects. Bilateral rTMS and low-frequency rTMS over right DLPFC have not been shown to have significant effects.

When only treatment-resistant depression (TRD) cases were considered, rTMS was found to have a significant positive effect. Based on the ORs and narrow confidence intervals, high-frequency rTMS over the left DLPFC followed by low-frequency rTMS over the right DLPFC has been shown to be superior. Bilateral TBS and priming rTMS too showed a significant positive effects. One meta-analysis *[Supplementary Table 1; sl.no. 11]* though showed that both unilateral and bilateral stimulation paradigms did not differ significantly in terms of both response and remission rates.

Table 4: Meta-analyses on the effect of rTMS in depression

Article (See supplementary table 1 for full list of references)	Total no of Studies	Age group	Depression type	rTMS type	Reduction in severity	Response	Remission
Valiengo *et al*. 2022	26	>50	MDD	Any rTMS	SMD 0.36 (0.13-0.60)	OR 3.26 (2.11-5.04	OR 4.63 (2.24-9.55)
Voigt *et al*. 2021	10	>18	MDD	Any TBS	NA	RR 2.4 (1.27-4.55)	NA
Chu *et al*. 2020	10	16-75	MDD	Any TBS	SMD 0.38 (0.29-0.48)	OR 3.64 (1.61-8.23)	2.45 (1.11-5.42)
Nguyen *et al*. 2021	14	Adult	Bipolar Depression	Conventional rTMS	NA	OR 2.72 (1.44-5.14) overall; 2.57 (1.17-5.66) for HF-LDLPFC	-
Tee and Au 2020	8	Adult	Bipolar Depression	Conventional rTMS	SMD 0.302 (0.055-0.548)	RD 0.104 (0.018-0.190)	Trend 0.074 (-0.003-0.151)
Mutz *et al*. 2019	53	Adult	Any Depression	Any rTMS	SMD 0.83 (0.66-1.00)	OR 6.02 (2.21-16.38) for pTMS, 4.92 (2.93-8.25) for BL rTMS, 4.44 (1.47-13.41) for BL TBS, 3.65 (2.13-6.24) for LF-RDLPFC, 3.20 (1.45-7.08) for iTBS, 3.17 (2.29-4.37) for HF-LDLPFC.	5.21 (2.64-10.29) for LFR; 4.55 (1.39,14.91) for pTMS; 3.30 (1.38,7.90) for TBS; 2.77 (0.47,16.35) BL TBS; 2.67 (1.79,4.00) HFLDLPFC; 2.21 (0.95,5.18) for dTMS; 1.65 (0.46,5.98) for aTMS; 1.59 (0.52,4.81) for sTMS; 1.02 (0.17,6.02) for LF-LDLPFC; 0.51 (0.06,4.24) for cTBS
Mutz *et al*. 2018	56	Adult	Both unipolar and bipolar depression	Any rTMS	Hedge's g 0.72 (0.46-0.99) for HF-LDLPFC, 0.29 (0.03-0.55) for deepTMS	OR 3.75 (2.44-5.75) for HF-LDLPFC, 7.44 (2.06-26.83) for LF-RDLPFC, 3.68 1.66-8.13) for BL TMS, 1.69 (1.003-2.85) for deepTMS, 4.70 (1.14-19.38) for iTBS	OR 2.52 (1.62-3.89) for HF-LDLPFC, 14.10 (2.79-71.42) for LF-RDLPFC, 2.24 (1.24-4.06) for deep TMS; 3.05 (0.87-10.67) for BL-rTMS
Sonmez *et al*. 2019	8	Any	Any depression	accelerated rTMS & TBS	Hedge's g 1.27 (0.902-1.637)	Accelerated TMS over left DLPFC was not associated with a statistically significantly higher rate of response compared to sham. OR 3.12 (0.98-9.97)	-
Hyde *et al*. 2022	46	Any	Unipolar (42) & Bipolar (4)	Any rTMS	SMD 0.44 (0.31-0.56) over all; 0.60 (0.42-0.78) significant for unipolar depression; 0.20 (0.11-0.52) not significant for bipolar depression	-	-
Li *et al*. 2021	49	Any	TRD	Any rTMS	-	RR 5.00 (1.11-22.44) for Bilateral theta burst stimulation, 2.97 (1.20-7.39) for priming TMS, 2.62 (1.56-4.39) for LF-RDLPFC, 2.18 (1.52-3.13) for HF-LDLPFC, 3.08 (1.78-5.31) for BL rTMS	-
Sehatzadeh *et al*. 2019	23	Any	TRD	Unilateral (19) vs. bilateral (4)	WMD 3.36 (1.85-4.88) for UL; 2.67 (0.83-4.51) for BL	25.1% for UL; 25.4 for BL	16.0% for UL; 16.6% for BL
Shen *et al*. 2022	a	Any	Poststoke depression	Any rTMS	SMD 4.92 (2.69-7.15) for immediate effects, 7.21 (3.50-10.92) for longterm effects	-	-

Contd...

Table 4: Contd...

Article (See supplementary table 1 for full list of references)	Total no of Studies	Age group	Depression type	rTMS type	Reduction in severity	Response	Remission
Shao *et al*. 2021	7	Any	Poststoke depression	Any rTMS	SMD 1.15 (0.69-1.62)	-	OR 3.46 (1.68-7.12)
Liu *et al*. 2019	17	Any	Poststoke depression	HF-rTMS	SMD 1.01 (0.66-1.36)	OR 3.31 (2.25-4.88)	OR 2.72 (1.69-4.38)
Liang *et al*. 2022	34	Any	Poststoke depression	HF and LF rTMS	SMD 1.44 (1.03-1.86) for LF augment;	-	-
Deng *et al*. 2017	5	Any	Poststoke depression	Any rTMS	SMD 1.43 (1.06 to 1.79)	OR 5.26 (2.17-12.5)	OR 4.72 (1.29 to 17.24)
Lee *et al*. 2021	5	Any	Peripartum depression	Any rTMS	SMD 1.394 (0.944-1.843)	-	-
Liu *et al*. 2020	10	Any	Peripartum depression	Any rTMS	SMD 0.65 (0.31-0.98)	OR 1.47 (0.99-2.17) Not significant	OR 1.83 (1.05-3.18)
Peng *et al*. 2020	14	Any	Postpartum depression	Any rTMS	SMD 1.02 (0.66-1.37)	-	-
Tsai *et al*. 2021	5	Any	post TBI depression	Any rTMS	SMD 1.03 (0.20-1.86) over all; 0.98 (0.04-1.92) for LDLPFC	-	-
Chen *et al*. 2021	12	Any	Parkinson's depression	Any rTMS	SMD 0.62 (0.28-0.96) vs sham	-	-
Li *et al*. 2020	8	Any	Parkinson's depression	Any rTMS	SMD 0.80 (0.31-1.29) over all; 1.64 (0.20-3.09) for LDLPFC; 1.03 (0.41-1.66) for HF rTMS; 0.74 (0.83-2.31) vs. fluoxetine	-	-
Hai-Jiao *et al*. 2020l	6	Any	Parkinson's depression	Any rTMS	SMD 0.86 (0.43-1.29) for sham	-	-

rTMS=repetitive transcranial magnetic stimulation; MDD=Major depressive disorder; TRD=Treatment resistant depression; TBI=traumatic brain injury; TBS=theta burst stimulation; iTBS=intermittent theta burst stimulation; cTBS=continuous theta burst stimulation; HF=high frequency; LF=low frequency; SMD=standardized mean difference; WMD=weighted mean difference; LDLPFC=left dorsolateral prefrontal cortex; UL=unilateral; BL=bilateral; OR=odds ratio; RR=relative risk; RD=relative difference; pTMS=priming transcranial magnetic stimulation; dTMS=deep transcranial magnetic stimulation; aTMS=accelerated transcranial magnetic stimulation; sTMS=synchronized transcranial magnetic stimulation; NA=not available

There is clear evidence that in TRD, response to rTMS was better when it is added as an augment to antidepressants rather than stand-alone.

Accelerated rTMS (including accelerated TBS) paradigm targeted over left DLPFC was not found to be associated with significant response, in a meta-analysis focussing on accelerated protocols *[Supplementary Table 1; sl.no. 8]*. Although the more recent, Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) protocol,[19] a high dose- accelerated (10 daily sessions for 5 days), resting-state functional connectivity functional MRI-guided iTBS, has shown to have 86.4% remission rates in patients with treatment-resistant depression, such protocols remain to be tested in controlled studies.

One meta-analysis focussing on unilateral and bilateral stimulation paradigms (both conventional and TBS) *[Supplementary Table 1; sl.no. 11]* find that only the frequency of stimulation could predict the treatment outcome, while the intensity of stimulation, train duration and a number of treatment sessions did not. However, a meta-analysis involving only TBS studies find that ≥1800 pulses/session, subthreshold intensity, and ≤2-week treatment duration predict higher response rates *[Supplementary Table 1; sl.no. 3]*. One meta-analysis focussing on MDD patients aged >50 years found higher age and number of sessions predicted greater response *[Supplementary Table 1; sl.no. 1]*.

Which device/coil is better?

The efficacy and acceptability of 3 stimulation devices (NeuroStar, MagPro, and Magstim) for depressive disorders were not significantly different. The response rates, all-cause discontinuation, or remission rates among the devices ($P = 0.12$, $P = 0.84$, and $P = 0.07$, respectively) were comparable *[Supplementary Table 1; sl.no. 24]*. The comparison between H1 and F8 coils showed a larger reduction in depression severity in H1-coil vs. F8-coil studies and a trend towards higher remission rates in F8-coil vs. H1-coils. However, authors deem these differences are not clinically-relevant as they were based on a low volume of studies and were not placebo-controlled *[Supplementary Table 1; sl.no. 25]*.

How does rTMS fare compared to other non-invasive brain stimulation strategies?

In the comparisons between two active treatments, bitemporal ECT was associated with higher response than

high-frequency left rTMS, continuous theta burst stimulation and deep transcranial magnetic stimulation. High dose right unilateral ECT was associated with a higher response than continuous theta burst stimulation *[Supplementary Table 1; sl.no. 6]*. In TRD, BL-rTMS was found to be more effective than deep brain stimulation. BL-rTMS was more acceptable than bitemporal ECT. Priming TMS was more acceptable than BT-ECT *[Supplementary Table 1; sl.no. 10]*.

How sustained is the antidepressant response to rTMS?

Among initial responders, 66.5 (57.1-74.8)% sustained response in the 3rd month, 52.9 (40.3-65)% in the 6th month, and 46.3 (32.6-60.7)% in the 12th month. The further higher proportion of women, as well as receipt of maintenance treatment, predicted higher responder rates at specific time points. This meta-analysis, which included 19 studies, showed the absence of major bias *[Supplementary Table 1; sl.no. 26]*.

Maintenance rTMS for MDD

The evidence base for maintenance rTMS for relapse prevention in MDD is still accumulating and not enough for making specific recommendations. However, it has shown a promise for effectively reducing or preventing the relapses in treatment-resistant MDD patients when scheduled along with rTMS treatment during acute phases.[20]

How much is the placebo effect of rTMS treatment in depression?

A meta-analysis of randomized controlled trials (RCTs) involving participants with MDD on this issue showed a large placebo response (g = 0.8 (0.65-0.95). This was regardless of the modality of intervention and was directly associated with depression improvement in the active group, and inversely associated with higher levels of treatment-resistant depression. Most of these studies had low to unclear risk of bias *[Supplementary Table 1; sl.no. 27]*. Recently, 34 neuroimaging studies of placebo effects were meta-analyzed and showed that the placebo effects are associated with activation in the left dorsolateral prefrontal cortex and left sub-genual anterior cingulate cortex (sgACC)/ventral striatum *[Supplementary Table 1; sl.no. 28]*.

Safety of TMS for MDD

A meta-analysis including 53 sham-controlled trials found no increased risk of either serious adverse events or drop-outs due to an adverse event [see Table 5]. However, there is a significantly greater risk of non-serious adverse events (mild and transient) following rTMS treatment for depression *[Supplementary Table 1; sl.no. 29]*.

Specifically, a Hypomanic/manic switch with rTMS treatment was assessed in a recent meta-analysis of 25 clinical trials where the majority of the studies targeted the left dorsolateral prefrontal cortex. The hypomanic switch was described in 4 studies. Overall, the results suggest that rTMS protocols for the treatment of depression are not related to affective switch *[Supplementary Table 1; sl.no. 30]*.

Combined rTMS and psychosocial interventions

Seventeen studies that combined NIBS and psychosocial interventions were meta-analyzed *[Supplementary Table 1; sl.no. 31]*. Three out of four of these studies using rTMS (2-HF-L and 1-LF-R) as NIBS modality were analyzed. rTMS combined with psychosocial intervention had no significant effect in alleviating depressive symptoms when compared with sham rTMS plus psychosocial intervention (SMD 0.31 (0.76-1.38)). These three studies though included patients where depression was a secondary outcome variable (these included cases of TBI, post-stroke, and fibromyalgia).

rTMS for suicidality

A meta-analysis of 10 RCTs showed that rTMS significantly reduced suicidal ideation (Hedges' g 0.390 (0.193 to 0.588) and severity of depressive symptoms (Hedges' g 0.698 (0.372-1.023) in patients with major mental disorders. A subgroup analysis in this meta-analysis found that rTMS reduced suicidal ideation among patients with non-treatment-resistant depression (non-TRD) but not in those with TRD. rTMS as a combination therapy and more than 10 sessions had a larger effect *[Supplementary Table 1; sl.no. 32]*. Another meta-analysis included only TRD (unipolar as well as bipolar) patients from 16 studies. It found that the reductions in suicidal ideation were not significant (g 0.158 (0.078-0.393) in RCTs. However, uncontrolled trials showed a significant decrease in suicidal ideation scores (g 0.692 (0.463-0.922) *[Supplementary Table 1; sl.no. 33]*. Godi *et al*. (2021),[21] in a systematic review showed that high-frequency rTMS at the left dorsolateral prefrontal cortex as an adjunct to the antidepressant medication has the highest evidence for reducing suicidal behavior in treatment-resistant depression.

Table 5: Adverse events with rTMS

Serious adverse event			No-serious adverse event				Drop out due to adverse event		
Active group	Sham group	OR (95%CI; *P*)	Type	Active group	Sham group	Pooled OR	Active group	Sham group	OR (95%CI; *P*)
0.9%	1.5%	0.67 (0.29-1.55;0.35)	Headaches	22.6%	16.2%	1.48 (1.15-1.91;0.002)	3.3%	2.3%	1.30 (0.78-2.16;0.31)
			discomfort	10.9%	5.0%	1.98 (1.22-3.21;0.006)			
			Pain at stimulation site	23.8%	5.2%	8.09 (4.71-13.90;<.001)			

rTMS=repetitive transcranial magnetic stimulation; OR=odds ratio; CI=confidence interval; *P*=significance

Suicidality has been assessed as a secondary outcome variable in most of the trials considered for the meta-analyses and excluded acutely suicidal patients. Acutely suicidal patients have been considered in some studies using accelerated rTMS, but with a lack of positive evidence. Essentially, therefore, with the evidence so far, we do not recommend rTMS for acutely suicidal patients.

Efficacy of rTMS in peripartum depression (please see Figure 2 for recommendation)

Evidence [see Table 4] suggests that rTMS has a significant positive effect on peripartum depression. The pooled effect sizes range between 0.65 and 1.39. However, one meta-analysis has found that the OR for remission rates (i.e. 1.83) but not for response rates is significant for the use of rTMS in peripartum depression. Pooled effect sizes for the use of high-frequency rTMS over the left DLPFC were greater than those for low-frequency rTMS over the right DLPFC. The treatment was deemed safe for both mothers and fetuses/infants.

Efficacy of rTMS in post-stroke depression (please see Figure 2 for recommendation)

There is strong evidence for a significant positive effect for the use of rTMS for treating post-stroke depression, both for immediate as well as long-term effects [see Table 4]. The pooled effect sizes for improvement in depression severity range between 1.01 to 4.92. The odds for response (pooled odds ratios (ORs) ranging between 3.31 and 5.26) and remission rates (pooled ORs ranging between 2.72 and 4.72) were significantly higher for the use of rTMS. The most evidence was for high-frequency rTMS over the left DLPFC. There is some evidence that rTMS for post-stroke depression may be more effective in Asian than the North American population; those receiving high-frequency rTMS are more prone to headaches; and that high-frequency rTMS combined with antidepressants may be more effective. rTMS though had no significant effect on cognitive function recovery in post-stroke depression patients.

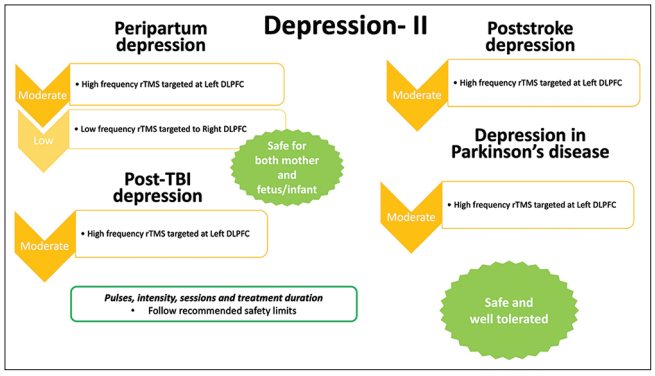

Figure 2: Recommendation B: Depression- II: Peripartum depression, post-stroke depression, post traumatic brain injury (TBI) depression and depression in Parkinson's disease

Efficacy of rTMS in post-traumatic brain injury depression (please see Figure 2 for recommendation)

One meta-analysis [see Table 4; *Supplementary Table 1; sl.no. 20*] assessed the efficacy of rTMS in post-traumatic brain injury (TBI) depression and found that it has a significant positive effect (pooled effect size 1.03). The effect was significant for high-frequency rTMS over the left DLPFC (pooled effect size 0.98). However, these effects were short-lasting and they dissipated at a 1-month follow-up.

Efficacy of rTMS in depression associated with Parkinson's disease (please see Figure 2 for recommendation)

There is strong evidence for a moderate effect of the use of rTMS for treating depression associated with Parkinson's disease [see Table 4]. The pooled effect sizes for improvement in depression severity range between 0.62 to 0.86. The effect was significant only for high-frequency rTMS (pooled effect size 1.03) and over the left DLPFC (pooled effect size 1.64). The antidepressant effects of rTMS were found to be greater than fluoxetine (pooled effect size 0.74) and found to be statistically compared to when SSRIs were used alone. Age, disease duration, number of pulses, and session durations were shown to influence the efficacy of rTMS on depression associated with Parkinson's disease.

Evidence- bipolar mania (please see Figure 3 for recommendation)

A meta-analysis *[Supplementary Table 1; sl.no. 5]* included 3 RCTs of patients with bipolar mania receiving HF-R rTMS, of which only one study reported improvement with rTMS compared to sham. The sham-controlled improvements were not significant (SMD 0.298 (−0.77- 1.37)). Two of the three RCTs included adults and one included adolescent patients. All three studies used high-frequency rTMS targeting the right DLPFC.

Evidence- anxiety disorders (please see Figure 3 for recommendation)

We reviewed four meta-analyses. One of them *[Supplementary Table 1; sl.no. 35]* analyzed other forms of NIBS combined with rTMS and did not provide separate pooled statistics for rTMS, therefore was not considered for synthesis. Evidence [see Table 6] suggests that rTMS has a significant positive effect on the treatment of generalized anxiety disorder. The pooled effect sizes range between 1.45 and 1.87. Moreover, depression associated with a generalized anxiety disorder also shows significant improvement (SMD 1.65). However, rTMS was not found to be effective in the treatment of the panic disorder. Evidence in this regard has been shown to be homogenous.

Among the rTMS forms, both conventional rTMS and TBS have been used. The most commonly used stimulation paradigm is low-frequency rTMS targeted to the right DLPFC. High-frequency rTMS has also been used to target the right DLPFC. A few studies have targeted left DLPFC using iTBS.

Evidence- obsessive-compulsive disorder (OCD) and Tourette syndrome

There is moderately positive evidence for use of rTMS (10 to 30 sessions; 1 to 12 weeks) for treating OCD (Pooled SMDs for YBOCS scores range from .501 to 0.79) [see Table 7]. Both high and low-frequency protocols have been equally effective than sham stimulation. There are 3 preferred target sites for stimulation i.e., low-frequency right DLPFC (most effective), high-frequency bilateral DLPFC, and low-frequency supplementary motor area (SMA). High-frequency bilateral DLPFC (SMD: 1.52) and low-frequency right DLPFC (SMD:.83) stimulations have reported the most global improvements. Effects of stimulation are evident earliest by 2 weeks of stimulation and would have short-lasting effects (till 4 weeks). Maximum robust effects were found with 800 to 1200 pulses per session. TBS was found to be ineffective, though data is insufficient. There is inconclusive as well as insufficient evidence with respect to the effect of deep TMS in OCD *[Supplementary Table 1; sl.no. 39*]. Common adverse effects reported were headache, concentration difficulties, scalp pain, sedation, weakness, fatigue, fainting, and facial nerve stimulation. There were no major side effects reported and no difference between dropout rates for active vs sham rTMS.

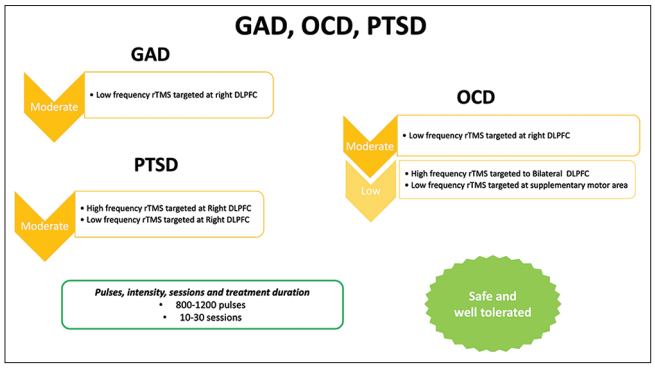

Figure 3: Recommendation C: Generalized Anxiety Disorder (GAD), Obsessive Compulsive Disorder (OCD) and Post Traumatic Stress Disorder (PTSD)

We reviewed one meta-analysis, which included 8 RCTs and open-label trials *[Supplementary Table 1; sl.no. 43]*, and found that rTMS improves tics severity (SMD:.61) but not when controlled for placebo response in Tourette's disorder.

Table 6: Meta-analyses for rTMS in anxiety disorders

Study (See supplementary Table 1 for full list of references)	Diagnosis	Number of studies included	rTMS forms	Pooled Effect size
Cox *et al*. 2022	Generalized anxiety disorder & Panic disorders	13	Any rTMS	SMD 1.45 for anxiety in GAD; SMD 1.65 for depression in GAD; anxiety and panic severity did not improve in PD
Parikh *et al*. 2022	Generalized anxiety disorder	6	Any rTMS	SMD 1.857 (1.494-2.219)
Hyde *et al*. 2022	Generalized anxiety disorder	5	Any rTMS	SMD 1.8 (1.0-2.6)

rTMS=repetitive transcranial magnetic stimulation; SMD=standardized mean difference; GAD=generalized anxiety disorder; PD=panic disorder

Table 7: Meta-analyses for rTMS in obsessive compulsive disorder (OCD)

Article (See supplementary table 1 for full list of references)	Total no of Studies	rTMS type	Reduction in severity	Predictors of response
Hyde *et al*. 2022	26	Any rTMS	−0.66 (−0.91 to−0.41)	BLDLPFC, LF-RDLPFC and LF-SMA sessions were superior to sham.
Fitzsimmons *et al*. 2022	21	Any rTMS	Hedges' g = -0.502 [95% CI = -0.708, -0.296	Network Meta-analysis: LF pre-SMA, HF-LDLPFC, and LF-RDLPFC were all efficacious . LF- RDLPFC was ranked highest in terms of efficacy. 10 TO 30 sessions; 1 to 6 weeks
Liang *et al*. 2021	22	Any rTMS	LF-RDLPFC (MD=6.34 (2.12-10.42)); LF-SMA-(MD=4.18 (0.83-7.62)); HF-LDLPFC (MD=3.75 (1.04-6.81));	LF-RDLPFC was most effective All LF-RDLPFC, LF-SMA and HF-LDLPFC were more effective than sham rTMS.
Perera *et al*., 2021	26	Any rTMS	YBOCS scores (Hedges' g=0.77, 95% CI=0.41, 1.14; *P*<0.0001	The largest significant effect size=BL-DLPFC; HF and LF rTMS showed comparable effects; highest improvements with 800 pulses per session; highest improvement within 2 weeks and effects lasting till 4 weeks
Rehn *et al*. 2018	18	Any rTMS	Hedge's g of 0.79 (95% CI=0.43-1.15, *P*<0.001	LF rTMS was more effective than HFrTMS. The effectiveness of rTMS was also greater at 12 weeks follow-up than at 4 weeks; TBS: Ineffective
Gao *et al*. 2022	NA	Any rTMS	NA	Both high-frequency and the low-frequency stimulation showed significantly positive effects, with no statistical difference. Targeting the DLPFC showed significant improvements over sham stimulation, but no such improvement was found in the SMA

rTMS=repetitive transcranial magnetic stimulation; TBS=theta burst stimulation; SMD=standardized mean difference; CI=confidence intervals; *P*=significance; MD=mean difference; YBOCS-Yale Brown obsessive compulsive scale; LDLPFC=left dorsolateral prefrontal cortex; RDLPFC=right dorsolateral prefrontal cortex; BLDLPFC=bilateral dorsolateral prefrontal cortex; SMA=supplementary motor area; HF=high frequency; LF=low frequency

Younger age and bilateral supplementary motor area stimulation predicted a better treatment effect.

Evidence- Post-traumatic stress disorder (PTSD) (please see Figure 3 for recommendation)

We reviewed three meta-analyses. Evidence [see Table 8] suggests that rTMS has a significant positive effect on the treatment of post-traumatic stress disorder. The pooled effect sizes range between 0.68 and 1.16. Both high-frequency rTMS and low-frequency rTMS targeted at the right DLPFC show significant improvements, without significant differences between them.

Evidence- Schizophrenia (please see Figure 4 for recommendation)

Efficacy of rTMS in auditory hallucinations

There is moderate positive evidence for use of rTMS (4 to 40 sessions delivered till 8 weeks) for treating resistant auditory hallucinations (AH) (Pooled SMDs range from .24 to 0.51) [see Table 9]. Low-frequency (LF) rTMS

Table 8: Meta-analyses for rTMS in post-traumatic stress disorder (PTSD)

Study (See Supplementary Table 1 for full list of references)	Number of studies	rTMS forms	Outcome measure	Pooled Effect size
McGirr *et al*. 2022	10	Any rTMS	PTSD symptoms	SMD 0.70 (0.22 to 1.18) for LF-RDLPFC and 0.71 (0.11-1.31) for HF-RDLPFC
Kan *et al*. 2020	11	Any rTMS	PTSD symptoms	SMD 0.975 (0.58-1.37) overall; 1.16 (0.50-1.82) for excitatory (4 HF-RDLPFC, 2 HF-LDLPFC, 1 dTMS at MPFC, 1 HF-LDLPFC); 0.68 (0.32-1.04) for inhibitory (all LF-RDLPFC); no significant difference between HF-RDLPFC and LF-R DLPFC
Hyde *et al*. 2022	8	Any rTMS	PTSD symptoms	SMD 1.03 (0.45-1.61)

rTMS=repetitive transcranial magnetic stimulation; PTSD=post-traumatic stress disorder; SMD=standardized mean difference; LDLPFC=left dorsolateral prefrontal cortex; RDLPFC=right dorsolateral prefrontal cortex; MPFC=medial prefrontal cortex; HF=high frequency; LF=low frequency; dTMS=deep transcranial magnetic stimulation

Table 9: Meta-analyses on the effect of rTMS in schizophrenia

Article (See Supplementary Table 1 for full list of references)	Total no of studies	Symptom group/ outcome	rTMS type	Reduction in severity	Predictors of response	Adverse events
Guttesen *et al*. 2021	27	Medication resistant auditory verbal hallucinations	Any rTMS	Cohen D SMD -0.24 (-0.61 to 0.13) (one month)	not reported	OR: 6.39 [3.13, 13.05] (headache) OR: 16.60 [4.24, 65.09 (facial twitching); 60 dropouts (OR: 1.00, 3.17], *P*=0.05)
Sloan *et al*. 2021	9	Working Memory: Accuracy/ Speed	HF rTMS to LDLPFC	Accuracy: Hedges' g=0.112, CI95:−0.082, 0.305, = 0.257; Speed: Hedges' g=0.233, CI95: −0.212, 0.678, *P*=0.305)	reported; no predictor varaibles found	not reported
Li *et al*. 2020	11	Auditory Hallucinations	LF rTMS to RTPC	Cohen D SMD -0.27, 95%CI = -0.51 to -0.03	not reported	not reported
Siskind *et al*. 2019	3	clozapine refractrory schizophrenia	LF & HF rTMS	No benefit PS/NS/Composite	no predictors found on sensitivity analyses	headache (no difference in active/placebo)
Aleman *et al*. 2018	19	NS	Any rTMS	Cohen D SMD: 0.64 (0.32-0.96)	Studied; HF rTMS to LDLPFC containing more than 7500 stimuli per week at an intensity of >100% motor threshold, may be more effective than other protocols. The treatment may be more effective in younger patients with a shorter duration of illness.	not reported
Kennedy *et al*. 2018	30	Composite Hallucinations/ PANSS-P/N/ Total	Any rTMS	Hallucinations (Hedge's g=0.51, *P*<0.001); NS: (Hedge's g=0.49, *P*=0.01)	not reported	not reported
Osoegawa *et al*. 2018	31	NS	Any rTMS	Hedges' g=0.19 (0.07-0.32)	not reported	not reported
Hyde *et al*. 2022	59	PANSS-PS/ NS/Total scores	Any rTMS	NS SMD: −0.49 (−0.73 to−0.26); Total scores SMD: −0.50 (−0.66-−0.33)	For NS, HF-LDLPFC was superior to sham	not reported

rTMS=repetitive transcranial magnetic stimulation; NS=negative symptoms; PS=positive symptoms; PANSS=positive and negative syndrome scale; SMD=standardized mean difference; LDLPFC=left dorsolateral prefrontal cortex; RTPC=right temporo-parietal cortex; HF=high frequency; LF=low frequency

stimulation at left temporoparietal cortices (T3P3) is the preferred site.

Efficacy of rTMS in negative symptoms (NS)

There is moderate to large positive evidence for use of rTMS for treating NS in schizophrenia (SMD:.49 to. 64) [Table 9]. High-frequency (HF) stimulation to left DLPFC and more than 10 sessions were found to be superior to sham. Stimulation protocols containing more than 7500 stimuli per week at an intensity of >100% motor threshold, may be more effective than other protocols.

Efficacy of rTMS in cognitive dysfunction

rTMS has been shown to have minimal efficacy of active over sham in improving attention, processing speed, executive functioning, and working memory.

Efficacy of rTMS in clozapine refractory schizophrenia

We reviewed one meta-analysis *[Supplementary Table 1; sl.no. 49]* that included 3 RTCs employing rTMS as an augmentation strategy in clozapine refractory schizophrenia. It was found that the effects of rTMS were not significant for either positive symptoms, NS, or cognition in schizophrenia.

Evidence- Substance use disorders (please see Figure 5 for recommendation)

We reviewed six meta-analyses. Two of them *[Supplementary Table 1; sl.no. 53 and 54*] assessed other NIBS together with rTMS and did not provide pooled statistics either for rTMS or for substance use disorders, separately, therefore were not considered for synthesis. Evidence [see Table 10] suggests that high frequency rTMS targeted at left DLPFC, respectively) and high-frequency deep TMS targeted over bilateral DLPFC has a significant positive effect on reducing cigarette smoking frequency (pooled effect size 1.22 (0.66-1.77), 0.77 (0.34-1.20), reducing craving in general in substance use disorders (pooled effect size 0.62 (0.35-0.89)), also in nicotine (pooled effect size 0.47 (0.12-0.82) and illicit drug dependence (pooled effect size 0.81 (0.37-1.24). High-frequency rTMS targeted at left

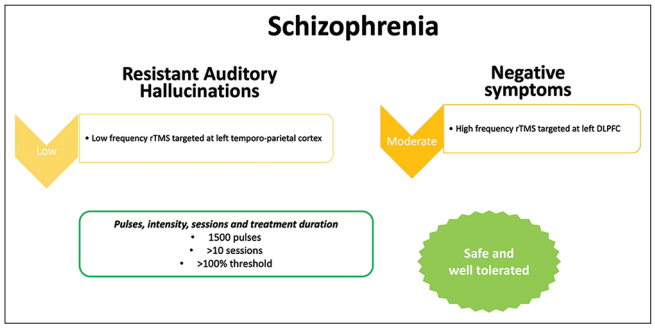

Figure 4: Recommendation D: Schizophrenia: Resistant auditory hallucinations and negative symptoms

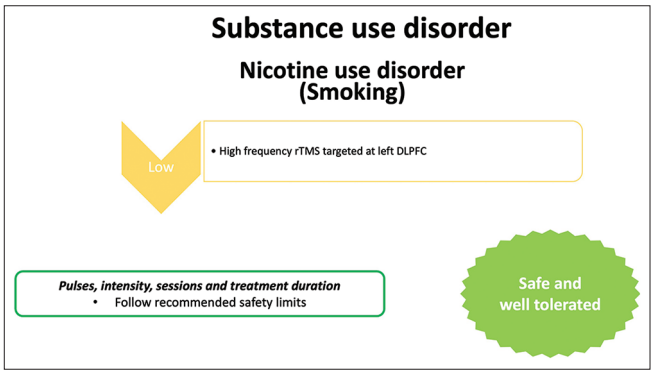

Figure 5: Recommendation E: Substance Use Disorder: Smoking Cessation

Table 10: Meta-analyses for rTMS in substance use disorders

Study (See supplementary table 1 for full list of references)	Diagnosis/condition	Number of studies	rTMS forms	Outcome measure	Pooled Effect size	Other remarks
Tseng *et al*. 2022	Cigarette smoking	12	Any rTMS	Cigarette smoking frequency	SMD 1.22 (0.66-1.77) for HF-LDLPFC rTMS; 0.77 (0.34-1.20) for HF deep TMS over BL DLPFC	No study was associated with improvement in craving and overall severity of nicotine dependence.
Mostafavi *et al*. 2020	Alcohol use disorder	5	Any rTMS	Alcohol craving	Not significant SMD 0.07 (-0.27-0.40)	All targeting RDLPFC
Zhang *et al*. 2019	Nicotine, Alcohol, Cannabis, Cocaine, Methamphetamine, Opioid use disorders	19	Any rTMS	Craving Substance consumption	SMD 0.62 (0.35-0.89) for HF-LDLPFC for all substances; 0.47 (0.12-0.82) for HF-LDLPFC for nicotine; 0.81 (0.37-1.24) for HF-LDLPFC for illicit drugs SMD 0.77 (0.03-1.53) for HF-LDLPFC for nicotine/cocaine; 1.16 (0.68-1.64) for BL DLPFC and Insula deep TMS for nicotine/alcohol	Not significant for other forms
Hyde *et al*. 2022	Substance use disorders in general	4	Any rTMS	Symptoms of SUDs	SMD 1.46 (0.42-3.35) not significant	

rTMS=repetitive transcranial magnetic stimulation; SUD=substance use disorders; SMD=standardized mean difference; LDLPFC=left dorsolateral prefrontal cortex; RDLPFC=right dorsolateral prefrontal cortex; HF=high frequency; LF=low frequency

DLPFC and deep TMS targeted to B/L DLPFC and insula also have been found to reduce substance consumption for nicotine/cocaine (pooled effect size 0.77 (0.03-1.53)) and nicotine/alcohol (pooled effect size 1.16 (0.68-1.64)). Apart from the positive evidence for high-frequency rTMS targeted at left DLPFC to reduce symptoms of a tobacco use disorder, both craving and consumption amounts, none of the other evidence is consistent.

Evidence- Eating disorders

We reviewed three meta-analyses for eating disorders. All three of them *[Supplementary Table 1; sl.no. 53, 54, and 58]* did not provide effect sizes separately for eating disorders and for rTMS (they included persons with drug addiction and overeating together, and rTMS and other NIBS together). One study also included sub-clinical and clinical eating disorders together *[Supplementary Table 1; sl.no. 58]*. No recommendation could therefore be drawn.

Evidence- Neurodevelopmental disorders- Autism spectrum disorder and attention deficit hyperactivity disorder

We found one meta-analysis *[Supplementary Table 1; sl.no. 59]* for attention deficit hyperactivity disorder (ADHD) and two meta-analyses *[Supplementary Table 1; sl.no. 60 and 61]* for autism spectrum disorders (ASD). The meta-analysis for ADHD included all NIBS studies on both adults and children with ADHD, and did not include any rTMS study for the quantitative synthesis. Therefore, no conclusions are drawn from it.

Of the two meta-analyses on ASD [see Table 11], one quantitatively synthesized studies on the effects on various symptom domains, and the other one exclusively focussed on adverse events associated with rTMS in ASD. Moderate improvements were reported in the domains of repetitive and restricted behavior (pooled effect size 0.50) and social behavior deficits (pooled effect size 0.47). One of the included studies did report that the effects on social behavior deficits persisted till one month after the rTMS sessions. There is a large variability in the stimulation parameters, especially the intensity and the target location in the included studies. This makes suggesting specific recommendations for the use of rTMS in ASD difficult. The reported adverse effects were all mild and transient. Commonest of them are irritability, facial discomfort, and headaches.

Evidence- Dementia and mild cognitive impairment (MCI) (please see Figure 6 for recommendation)

We reviewed 12 meta-analyses on the effects of rTMS in patients with dementia (all articles were focussed on Alzheimer's dementia) or MCI. One of them, which did not assess global cognition, was not included for synthesis; this study assessed only individual cognitive functions- attention and executive function; both of which were found not to improve with rTMS *[Supplementary Table 1; sl.no. 73]*. The synthesis of the other 11 studies is shown in Table 12. Evidence suggests that rTMS has a significant positive effect in the management of dementia- for both cognitive functions (pooled effect sizes ranged between 0.42 and 1.14) and neuropsychiatric/behavioral and psychological symptoms (pooled effect sizes ranged between 0.47 and 0.82). While all studies favor high-frequency rTMS targeted at left or bilateral DLPFC, for both cognitive functions and neuropsychiatric symptoms, low-frequency rTMS targeted at right DLPFC has also been suggested in some analyses. Subgroup analyses showed improvements in sub-domains of cognition, specifically memory, language, and executive functions with high-frequency rTMS. Treatment with high-frequency rTMS shows improvement in global cognition in both the short-term and also long-term.

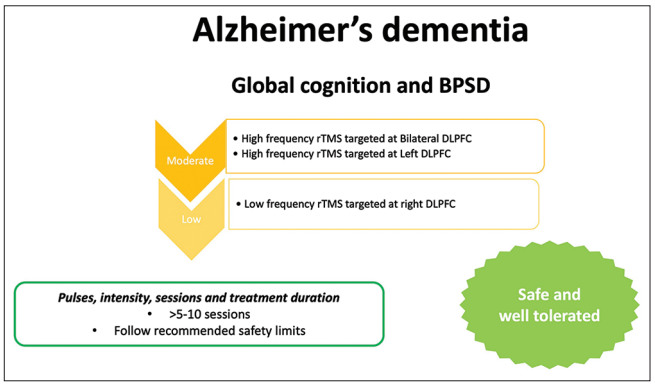

Figure 6: Recommendation F: Alzheimer's Dementia: Global cognition and Behavioral and Psychological Symptoms of Dementia (BPSD)

Table 11: Meta-analyses for rTMS in autism spectrum disorder (ASD)

Study (See supplementary Table 1 for full list of references)	Year	Number of studies	rTMS forms	Outcome measure	Pooled Effect size
Barahona-Corrêa *et al*.	2018	5 (only controlled studies)	Any rTMS	Repetitive and restricted behaviour Social behaviour deficits irritability	SMD 0.50 (0.16-0.85) SMD 0.47 (0.04-0.98) not significant SMD 0.30 (-0.72-1.32)
Huashuang *et al*.	2022	11	Any rTMS	Adverse events	Overall AEs: 25% (18-33%); headache: 10% (3-19%); facial discomfort: 15% (4-29%); irritability 21% (8-37%); pain at the application site: 6% (0-19%); headedness or dizziness: 8% (0-23%)

rTMS=repetitive transcranial magnetic stimulation; ASD=autism spectrum disorders; SMD=standardized mean difference; AEs=adverse effects

Table 12: Meta-analyses for rTMS in dementia

Study (See supplementary table 1 for full list of references)	Year	Number of studies	Condition	rTMS forms	Outcome	Pooled effect size	Remarks
Teselink *et al*.	2021	19	AD, MCI	Any rTMS	Global cognition Neuro-psychiatric symptoms	SMD 1.13 (0.44-1.82) SMD 0.78 (0.03-1.53)	These effects restricted were to rTMS and to patients with AD but not MCI. Younger populations show significantly more improvement.
Wang *et al*.	2021	28	AD, MCI	Any rTMS	Cognition	NA	LF-RDLPFC, HF-LDLPFC significantly improve the memory. HF-LDLPFC, RDLPFC, BLDLPFC significantly improve the language. HF-LDLPFC improve the executive function Multiple sessions of rTMS with 80% to 100% significantly better
Chu *et al*.	2021	27	AD, MCI	Any rTMS	Global cognition	SMD 1.08 (0.37-1.79) for HF-LDLPFC and short term; 1.65 (0.80-2.50) HF-LDLPFC-1 month; no improvements with LF-RDLPFC; HF rTMS had both short-term (1.50, 0.61-2.40) and long-lasting (1.71, 0.86-2.56) positive effects in only AD. not MCI	For short term & 1 month for HF-LDLPFC- Memory (0.72;0.52), working memory (0.32, 0.68). HF-LDLPFC ranked as the best intervention
Chou *et al*.	2020	17	AD, MCI	Any rTMS	Global cognition	SMD 0.77 (0.574-0.967); both MCI (0.91) and AD (0.75) were significant. Both short term (0.71) and long term (0.71) significant.	HF-LDLPFC (0.68) and LF-RDLPFC (1.53) significant for memory; HF-rIFG improved executive functions. No serious adverse events, only one study reported dropout due to adverse events
Wang *et al*.	2020	15	AD	Any rTMS	Cognition	SMD 0.42 (0.18-0.67)	Stimualtion at multiple sites (0.47), >10 sessions (0.59), HF (20 Hz) stimulation (0.41), cotherapy with cognitive training (0.55) and mild-moderate cognitive impairement (0.45) showed significant improvements
Lin *et al*.	2019	12	AD	Any rTMS	Cognition	SMD 0.60 (0.35-0.85)	Stimualtion at multiple sites (0.86), >5 sessions (2.77) showed significant improvement. Combined CT was not found significantly different
Dong *et al*.	2018	5	AD	Any rTMS	Cognition	MD 3.65 (1.48-5.82) FOR HF-LDLPFC	Significant improvments in global impression with HF-LDLPFC also (0.79). NS for mood, functional performance and LF. Adverse effects mild and few
Zhang *et al*.	2021	12	MCI	Any rTMS	Cognition	SMD 0.83 (0.48-0.97)	HF stimulation, multiple sites (i.e. BLDLPFC), and >10 sessions produced higher improvements
Cheng *et al*.	2018	7	MCI, Probable AD, AD	Any rTMS	Cognition	SMD 0.48 (0.12-0.84)	High-frequency rTMS showed more benefit and mild-moderate AD were more benefitted. Concurrent cognition enhancement drugs (0.66), cognitive training (0.94) and stimulation at multiple sites (0.94) produced greater effect.
Wang *et al*.	2020	7	AD	Any rTMS	BPSD	SMD 0.47 (0.16-0.79) immediately after treatment; 0.57 (0.18-0.96)	HF at BL or LDLPFC
Vacas *et al*.	2019	2	AD	Any rTMS	BPSD	SMD 0.58 (0.14-1.02)	HF at BL or LDLPFC

rTMS=repetitive transcranial magnetic stimulation; AD=Alzheimer's Dementia; MCI=mild cognitive impairment; BPSD=behavioural and psychological symptoms of dementia; SMD=standardized mean difference; MD=mean difference; LDLPFC=left dorsolateral prefrontal cortex; RDLPFC=right dorsolateral prefrontal cortex; BL=bilateral; BLDLPFC=bilateral dorsolateral prefrontal cortex; rIFG=right Inferior Frontal Gyrus; HF=high frequency; LF=low frequency; CT=cognitive therapy; NS=not significant

Studies including both Alzheimer's Dementia (AD) and MCI found that the positive effects were restricted to only AD. Younger age, multiple sites, more sessions (>5-10), concurrent cognitive training or cognitive enhancers, and

mild-moderate severity of cognitive impairment have been found as possible factors involved in a greater response.

Evidence- Cognitive function in other psychiatric disorders

We reviewed two meta-analyses [Table 13] that assessed the effect of rTMS on cognitive functioning in various psychiatric disorders- depression, schizophrenia, and substance use disorders. rTMS has been found to have a significant effect on working memory improvement only in substance use disorders. One meta-analysis, which specifically examined the effects of rTMS on executive function with advancing age, found that the effects of rTMS on executive functions are not greater as age advances, but found that the benefits in executive functions are positively related to improvement in depression *[Supplementary Table 1; sl.no. 74]*. Two meta-analyses (that investigated the effects of rTMS for cognitive enhancement in healthy participants were not included in the synthesis *[Supplementary Table 1; sl.no. 75 and 76]*.

Evidence- Insomnia (please see Figure 7 for recommendation)

We reviewed three meta-analyses. Evidence from sham-controlled studies [see Table 14] suggests that rTMS has a significant positive effect in the treatment of insomnia, rated on the standard instrument- the Pittsburgh Sleep Quality Index (PSQI). The pooled effect sizes range between 1.44 and 3.94. The pooled effect sizes for all seven subscales of PSQI– sleep quality (1.28), sleep latency (1.34), sleep time (0.70), sleep efficiency (0.67), sleep disturbance (1.35), hypnotic usage (1.57) and daytime dysfunction (1.13) suggested significant improvements. Similarly, except for non-REM 2, pooled effect sizes for all 8 polysomnography (PSG) parameters – sleep efficiency (0.57), sleep onset latency (0.95), total sleep time (0.49), wakefulness after sleep onset (0.65), non-REM 1 (0.68), non-REM 3 (0.49) and REM sleep (0.77) suggested significant improvements. It has been noted that improvement in sleep parameters increases significantly with treatment duration (from 10 days to 30 days) too. It has also been shown that the significant improvements in insomnia with rTMS persist even at 1-4 weeks follow-up (pooled effect size 3.41). The majority of these studies have used low-frequency rTMS targeted at the right DLPFC. Therefore, low-frequency rTMS targeted at the right DLPFC is suggested for the treatment of insomnia.

Evidence- Migraine (please see Figure 7 for recommendation)

Three meta-analyses were reviewed. One of them did not report effect sizes for rTMS, separately and therefore not used for synthesis *[Supplementary Table 1; sl.no. 80]*. The other two studies [see Table 15] provided evidence for a significant reduction in the number of 'migraine days', especially with high-frequency rTMS targeted at the primary motor cortex. There was inconsistent evidence for the use of high-frequency rTMS targeted at the left prefrontal cortex in the treatment of migraine. There was evidence that the response for chronic migraine and episodic migraine were similar.

Evidence- Fibromyalgia and chronic pain (please see Figure 7 for recommendation)

Three meta-analyses for fibromyalgia and two for other chronic pain syndromes were reviewed [Table 16]. It was found that high-frequency rTMS targeted at the primary motor cortex was significantly effective for reducing pain intensity (pooled effect sizes ranged between 0.35 to 0.49), both immediately and also till 4 weeks post-intervention. Fibromyalgia-related impact on quality of life also showed improvement with rTMS, especially between 5-12 weeks. High-frequency rTMS targeted at the left prefrontal cortex was not found to be effective. For other chronic pain syndromes, we reviewed two meta-analyses [Table 16]. While, one reported that high-frequency rTMS targeted at the primary motor cortex and iTBS at the cerebellum

Table 13: Meta-analyses for rTMS for cognitive functions in various psychiatric disorders

Study (See Supplementary Table 1 for full list of references)	Year	Cognitive function	Depression (number of studies)	Schizophrenia (number of studies)	Substance use disorders (number of studies)
Hyde *et al*.	2022	Attention	Not significant (3)	Not significant (3)	-
		Executive functions	Not significant (8)	Not significant (5)	-
		Processing speed	Not significant (7)	Not significant (5)	-
		Working memory	Not significant (7)	Not significant (10)	SMD 0.66 (0.55-1.87)
Begemann *et al*.	2020	Working memory	Not significant (11)	Not significant (9)	

rTMS=repetitive transcranial magnetic stimulation; SMD=standardized mean difference

Table 14: Meta-analyses for rTMS in insomnia

Study (See supplementary table 1 for full list of references)	Year	Number of studies	Condition	rTMS form	Outcome	Pooled effect size
Sun *et al*.	2021	13	Insomnia	Any rTMS	PSQI total score	SMD 2.31 (1.66-2.95)
Jiang *et al*.	2019	9	Primary Insomnia	Any rTMS	PSQI total score	SMD 1.44 (1.26-1.63)
Ma *et al*.	2021	23	Insomnia	Any rTMS	PSQI total score	SMD 3.94 (3.16-4.73)

rTMS=repetitive transcranial magnetic stimulation; SMD=standardized mean difference; PSQI=Pittsburgh Sleep Quality Index

Table 15: Meta-analyses for rTMS for migraine

Study (See supplementary table 1 for full list of references)	Year	Number of trials	rTMS form	Outcome	Pooled effect size	Remarks
Cheng *et al*.	2022	19	Any rTMS	Migraine days	MD 8.7 (2.95-14.45) for HF-LMC; 6.28 (1.08-11.47) for HF-LFC	Chronic migraine and episodic migraine similar results
Moisset *et al*.	2020	5	Any rTMS	Migraine days	SMD 0.533 (0.126-0.940) for HF-LMC; not significant for HF-LFC	

rTMS=repetitive transcranial magnetic stimulation; SMD=standardized mean difference; MD=mean difference; LMC=left motor cortex; LFC=left frontal cortex; HF=high frequency

Table 16: Meta-analyses for rTMS for fibromyalgia and chronic pain

Study (See supplementary table 1 for full list of references)	Year	Number of studies	Condition	rTMS form	Outcome	Pooled effect size	Remarks
Toh *et al*.	2022	11	Fibromyalgia	Any rTMS	Pain intensity	SMD 0.35 (0.08-0.62)	HF - LMC was best (0.57 (0.23-0.91). Quality of life also showed significant improvement (0.51 (0.23-0.78)
Choo *et al*.	2022	10	Fibromyalgia	Any rTMS	Pain intensity	NA	HF-LMC had significant effect immediately and also 1-4 weeks. Quality of life improved at 5-12 weeks. HF-LFC not effective
Sun *et al*.	2022	14	Fibromyalgia	Any rTMS	Pain intensity	SMD 0.49 (0.13-0.86)	Fibromyalgia impact (Quality of life) also improved significant (0.50 (0.25-0.75)
Cardenas-Rojas *et al*.	2020	2	Chronic regional pain syndrome (arm), cervical dystonia	rTMS and Exercise	Pain intensity	SMD 0.76 (0.11-1.41)	one study HF-LMC and another cerebellar iTBS
O'Connel *et al*.	2018	27	Chronic pain	Any rTMS	Pain intensity	SMD 0.22 (0.16-0.29) not significant	Low quality of evidence; Quality of Life (0-1 week) SMD 10.80 (6.55-15.04)

rTMS=repetitive transcranial magnetic stimulation; iTBS=intermittent theta burst stimulation; SMD=standardized mean difference; LMC=left motor cortex; LFC=left frontal cortex; HF=high frequency; NA=not available

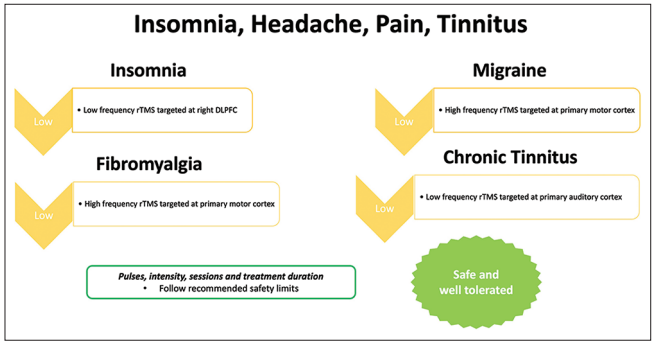

Figure 7: Recommendation G: Insomnia, Migraine, Fibromyalgia and Chronic Tinnitus

significantly improved pain intensity (SMD 0.76) in patients with chronic regional pain syndrome (arm), cervical dystonia, the other one found that the effectiveness was not significant in other chronic pain syndromes.

Evidence- Chronic tinnitus (please see Figure 7 for recommendation)

We reviewed 5 meta-analyses for the use of rTMS in chronic tinnitus [Table 17]. Short term i.e., at 2 and 6 months, and not immediately, the tinnitus severity was shown to reduce significantly with rTMS (pooled effect sizes ranged between 0.42 and 0.79. Tinnitus-related disability (tinnitus handicap) also showed improvements (pooled mean differences ranged between 8.81 to 8.52). The most common modality used was low-frequency rTMS targeted at the primary auditory cortex, which was found to be better than other sites too. Moreover, it was found that stimulation of bilateral auditory cortices, compared to left-alone, and priming paradigms would lead to greater effects. The rTMS sessions were found to be well tolerated in this population.

Evidence- Essential tremors

One meta-analysis *[Supplementary Table 1; sl.no. 91].* that included 8 studies, of which 7 were rTMS, showed a significant positive effect of rTMS on essential tremors (SMD 0.61 (0.42-0.79)). The rTMS form was either low-frequency rTMS or cTBS targeted at the cerebellum (right or BL posterior cerebellum) or pre-supplementary motor area or left the motor area.

Evidence- Others

One meta-analysis showed that there is a lack of positive evidence for the effects of rTMS on impulsivity *[Supplementary Table 1; sl.no. 94*]. A meta-analysis *[Supplementary Table 1; sl.no. 95]* synthesizing evidence for brain stimulation interventions in borderline personality disorder found no randomized controlled trials assessing the effects of rTMS. Albeit in healthy participants, rTMS was found to have small but significant effects on various aspects of empathy *[Supplementary Table 1; sl.no. 96]*.

Table 17: Meta-analyses for rTMS for chronic tinnitus

Study (See supplementary table 1 for full list of references)	Year	Number of studies	rTMS forms	Outcome	Pooled effect sizes	Remarks
Yin *et al*.	2021	12	Any rTMS	Tinnitus handicap-short term	MD 7.05 (2.44-11.65); Was significant at 1 (MD 6.81) and 6 months (MD 7.01) not for immediate	Majority studies used LF-rTMS to Left auditory cortex. No significant impact on tinnitus score and depression
Lefebvre-Demers *et al*.	2021	28	Any rTMS	Tinnitus severity	SMD 0.45 (0.24-0.66) immediate; 0.42 (0.15-0.68) 1 week to 6 months)	Auditory cortex better than others (0.35)
Liang *et al*.	2020	29	Any rTMS	Tinnitus handicap	MD 7.92 (1.66-14.18) for 1 week; 8.52 (4.55-12.49) for 1 month; 6.53 (1.66-11.41) for 6 months	NA
				Tinnitus severity	MD 8.54 (1.52-15.56) for only 1 week, not for long term	
Dong *et al*.	2020	10	LF rTMS	Tinnitus handicap, severity, loudness	None were significant	Well tolerated but not effective
Chen *et al*.	2020	13	Any rTMS	Tinnitus severity	SMD 0.79 (0.01-1.57) for cTBS on BL AC; 0.70 (0.02-1.38) BL (i.e. HF LFC+LF BL AC)	BL better than UL AC, priming superior to non-priming

rTMS=repetitive transcranial magnetic stimulation; cTBS=continuous theta burst stimulation; SMD=standardized mean difference; MD=mean difference; AC=auditory cortex; LFC=left frontal cortex; HF=high frequency; LF=low frequency; UL=unilateral; BL=bilateral; NA=not available

We found no meta-analyses for dissociative (and conversion; psychogenic non-epileptic seizures) disorders. Recently, studies are using many newer forms of rTMS i.e., deep TMS (dTMS), prolonged iTBS (piTBS), synchronized TBS (sTBS), along with priming TBS (pTBS) and accelerated TMS (aTMS),[22] and are targeting many alternate brain areas such as cerebellum for schizophrenia,[23] orbitofrontal cortex for OCD,[24], etc. The meta-analyses we included do not systematically review many of these studies.

Indian evidence

A very recent meta-analysis[25] conducted on 52 Indian studies investigating the safety and efficacy of rTMS in various neuropsychiatric disorders suggested a significant positive effect for all outcomes, with moderate to large effect sizes, at both end of treatment as well as at follow-up compared to pre-intervention scores for groups that received active rTMS. However, rTMS was not found to be effective for any outcome in the series of "active vs sham-controlled" meta-analyses, except for migraine (headache severity and frequency) and craving in alcohol dependence. Many studies had a significant risk of bias and the two conditions that showed positive sham-controlled evidence lost significance in sensitivity analysis. Also, significant heterogeneity was seen. Indian evidence however suggests that serious adverse events with rTMS were rare. The frequency of occurrence of both seizures and the affective switch was <0.5%. Headache and scalp pain were the common non-serious adverse events reported with the use of rTMS.

EVIDENCE- SUMMARY

There are many other psychiatric disorders where rTMS has been used, but there is insufficient evidence. The figure below shows disorders where there are sufficient and positive disorders, and those having either insufficient evidence for the rTMS or the evidence is not significant or significantly lower, compared to sham stimulation. It is important to note that rTMS is to be used as an adjunct to other conventional treatments.

Table 18 shows the list of all indications and recommendations for rTMS in the treatment of various psychiatric disorders. Also see Figure 8 for list of indications i.e., conditions with available positive evidence, and conditions where there is insufficient evidence.

Limitations

The strategy we chose i.e., umbrella review of meta-analyses, in formulating the clinical recommendations is constrained by certain limitations. While the extant available information is limited, selective reporting of outcomes often overlooks negative evidence and tends to provide positive biased evidence.[26] Further, regional variations may be missed in such an approach. Moreover, the umbrella review we conducted was a qualitative one and we did not conduct quantitative analyses and therefore pose an important limitation. The recommendations we make, although primarily based on this overview, they were supplemented by existing guidelines and recommendations and, the meta-analysis of Indian evidence. Although informed regarding the GRADE framework, we could not follow the suggested methodology of grading the evidence and therefore our recommendations might have been influenced by subjectivity, to an extent.

CONCLUSION

This CPG for the use of rTMS in psychiatry highlights its usefulness across various psychiatric disorders and conditions. We provide an overview of the latest and emerging evidence in this regard for the safe and effective application of rTMS. We also mention the basic aspects of

Table 18: Indications and recommendations for rTMS in treatment of various psychiatric disorders

Disorder/Condition	Mode	Target	Recommendation	FDA
Depression Acute/Unipolar	HF	Left DLPFC	Strong	Yes
	LF	Right DLPFC	Moderate	
	Bilateral (HF to Left and LF to Right DLPFC)		Low	
	iTBS	Left DLPFC		
	Bilateral (iTBS to Left and cTBS to Right DLPFC)			
	Deep 'H1' HF	Left DLPFC		
	Priming (HF followed by LF)	Right DLPFC		
Bipolar depression	HF	Left DLPFC	Moderate	Yes
Treatment resistant depression	HF	Left DLPFC	Moderate	Yes
	LF	Right DLPFC	Low	Yes
Peripartum depression	HF	Left DLPFC	Moderate	No
	LF	Right DLPFC	Low	
Post-stroke depression	HF	Left DLPFC	Moderate	No
Depression in Parkinson's Disease	HF	Left DLPFC	Moderate	No
Generalized Anxiety Disorder	LF	Right DLPFC	Moderate	No
Obsessive Compulsive Disorder	LF	Right DLPFC	Moderate	Yes
	HF	Bilateral DLPFC	Low	
	LF	SMA	Low	No
Post-Traumatic Stress Disorder	HF	Right DLPFC	Moderate	No
	LF	Right DLPFC		No
Schizophrenia- Auditory Hallucinations	LF	Left TPC (TPJ + STG)	Low	No
Schizophrenia- Negative symptoms	HF	Left DLPFC	Moderate	No
Nicotine Use Disorder (Smoking Cessation)	HF	Left DLPFC	Low	No
Alzheimer's Dementia	HF	Bilateral DLPFC	Moderate	No
	HF	Left DLPFC		No
	LF	Right DLPFC	Low	No
Insomnia	LF	Right DLPFC	Low	
Migraine	HF	Primary Motor Cortex	Low	
Fibromyalgia	HF	Primary Motor Cortex	Low	
Chronic Tinnitus	LF	Primary Auditory Cortex	Low	

rTMS=repetitive transcranial magnetic stimulation; iTBS=intermittent theta burst stimulation; cTBS=continuous theta burst stimulation; HF=high frequency; LF=low frequency; DLPFC=dorsolateral prefrontal cortex; TPC=temporoparietal cortex; TPJ=temporoparietal junction; STG=superior temporal gyrus; FDA=Food and Drug Administration

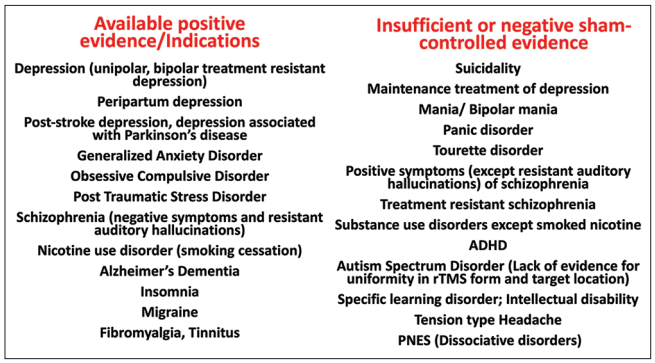

Figure 8: Recommendation H: List of neuropsychiatric conditions with available positive evidence/indications and insufficient or negative sham controlled evidence

rTMS set-up, delivery, and monitoring of rTMS sessions. The evidence for the use of rTMS still emerging and is not thorough. So far, recommendations for its use are only in certain clinical situations. More research is required for preparing comprehensive algorithms for the implementation the use of rTMS across different disorders, especially in various phases of illnesses, various sub-samples, etc., and also in terms of specific rTMS protocols in terms of the number of pulses, trains, sessions, for each of the disorders. Perhaps, there is no sufficient evidence with respect to stimulation with what number of sessions to be considered for a patient to be termed non-responder for a particular outcome. There is meager evidence in terms of rTMS effects in comorbid conditions such as depression with OCD, schizophrenia with OCD, etc. Evidence with respect to alternate target sites for depression, OCD, schizophrenia, and other conditions has begun accumulating, but is not sufficient for quantitative synthesis.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: List of all meta-analyses included for umbrella review

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Valiengo L, Maia A, Cotovio G, Gordon PC, Brunoni AR, Forlenza OV, Oliveira-Maia AJ.	Repetitive Transcranial Magnetic Stimulation for Major Depressive Disorder in Older Adults: Systematic Review and Meta-analysis	J Gerontol A Biol Sci Med Sci. 2022 Apr 1;77 (4):851-860. doi: 10.1093/gerona/glab235.
Voigt JD, Leuchter AF, Carpenter LL.	Theta burst stimulation for the acute treatment of major depressive disorder: A systematic review and meta-analysis	Transl Psychiatry. 2021 May 28;11 (1):330. doi: 10.1038/s41398-021-01441-4.
Chu HT, Cheng CM, Liang CS, Chang WH, Juan CH, Huang YZ, Jeng JS, Bai YM, Tsai SJ, Chen MH, Li CT.	Efficacy and tolerability of theta-burst stimulation for major depression: A systematic review and meta-analysis	Prog Neuropsychopharmacol Biol Psychiatry. 2021 Mar 2;106:110168. doi: 10.1016/j.pnpbp. 2020.110168. Epub 2020 Nov 7.
Nguyen TD, Hieronymus F, Lorentzen R, McGirr A, Østergaard SD.	The efficacy of repetitive transcranial magnetic stimulation (rTMS) for bipolar depression: A systematic review and meta-analysis	J Affect Disord. 2021 Jan 15;279:250-255. doi: 10.1016/j.jad. 2020.10.013. Epub 2020 Oct 8.
Tee MMK, Au CH.	A Systematic Review and Meta-Analysis of Randomized Sham-Controlled Trials of Repetitive Transcranial Magnetic Stimulation for Bipolar Disorder	Psychiatr Q. 2020 Dec; 91 (4):1225-1247. doi: 10.1007/s11126-020-09822-6.
Mutz J, Vipulananthan V, Carter B, Hurlemann R, Fu CHY, Young AH.	Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis	BMJ. 2019 Mar 27;364:l1079. doi: 10.1136/bmj. l1079.
Mutz J, Edgcumbe DR, Brunoni AR, Fu CHY.	Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: A systematic review and meta-analysis of randomised sham-controlled trials	Neurosci Biobehav Rev. 2018 Sep; 92:291-303. doi: 10.1016/j.neubiorev. 2018.05.015. Epub 2018 May 12.
Sonmez AI, Camsari DD, Nandakumar AL, Voort JLV, Kung S, Lewis CP, Croarkin PE.	Accelerated TMS for Depression: A systematic review and meta-analysis	Psychiatry Res. 2019 Mar; 273:770-781. doi: 10.1016/j.psychres. 2018.12.041. Epub 2018 Dec 7.
Hyde J, Carr H, Kelley N, Seneviratne R, Reed C, Parlatini V, Garner M, Solmi M, Rosson S, Cortese S, Brandt V.	Efficacy of neurostimulation across mental disorders: systematic review and meta-analysis of 208 randomized controlled trials	Mol Psychiatry. 2022 Jun; 27 (6):2709-2719. doi: 10.1038/s41380-022-01524-8. Epub 2022 Apr 1.
Li H, Cui L, Li J, Liu Y, Chen Y.	Comparative efficacy and acceptability of neuromodulation procedures in the treatment of treatment-resistant depression: a network meta-analysis of randomized controlled trials	J Affect Disord. 2021 May 15;287:115-124. doi: 10.1016/j.jad. 2021.03.019. Epub 2021 Mar 11.
Sehatzadeh S, Daskalakis ZJ, Yap B, Tu HA, Palimaka S, Bowen JM, O'Reilly DJ.	Unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression: a meta-analysis of randomized controlled trials over 2 decades	J Psychiatry Neurosci. 2019 May 1;44 (3):151-163. doi: 10.1503/jpn. 180056.
Shen Y, Cai Z, Liu F, Zhang Z, Ni G.	Repetitive Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation as Treatment of Poststroke Depression: A Systematic Review and Meta-Analysis	Neurologist. 2022 Jul 1;27 (4):177-182. doi: 10.1097/NRL.0000000000000416.
Shao D, Zhao ZN, Zhang YQ, Zhou XY, Zhao LB, Dong M, Xu FH, Xiang YJ, Luo HY.	Efficacy of repetitive transcranial magnetic stimulation for post-stroke depression: a systematic review and meta-analysis of randomized clinical trials	Braz J Med Biol Res. 2021 Jan 15;54 (3):e10010. doi: 10.1590/1414-431X202010010. eCollection 2021.
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Peng L, Fu C, Xiong F, Zhang Q, Liang Z, Chen L, He C, Wei Q.	Effects of repetitive transcranial magnetic stimulation on depression symptoms and cognitive function in treating patients with postpartum depression: A systematic review and meta-analysis of randomized controlled trials	Psychiatry Res. 2020 Aug; 290:113124. doi: 10.1016/j.psychres. 2020.113124. Epub 2020 May 29.

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Tsai PY, Chen YC, Wang JY, Chung KH, Lai CH.	Effect of repetitive transcranial magnetic stimulation on depression and cognition in individuals with traumatic brain injury: a systematic review and meta-analysis	Sci Rep. 2021 Aug 20;11 (1):16940. doi: 10.1038/s41598-021-95838-2.
Chen J, He P, Zhang Y, Gao Y, Qiu Y, Li Y, Zhang Q, Wang L, Huang Z, Zhao J, Nie K, Wang L.	Non-pharmacological treatment for Parkinson disease patients with depression: a meta-analysis of repetitive transcranial magnetic stimulation and cognitive-behavioral treatment	Int J Neurosci. 2021 Apr; 131 (4):411-424. doi: 10.1080/00207454.2020.1744591. Epub 2020 Apr 7.
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Liang K, Li H, Bu X, Li X, Cao L, Liu J, Gao Y, Li B, Qiu C, Bao W, Zhang S, Hu X, Xing H, Gong Q, Huang X.	Efficacy and tolerability of repetitive transcranial magnetic stimulation for the treatment of obsessive-compulsive disorder in adults: a systematic review and network meta-analysis	Transl Psychiatry. 2021 May 28;11 (1):332. doi: 10.1038/s41398-021-01453-0.
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Song S, Zilverstand A, Gui W, Li HJ, Zhou X.	Effects of single-session versus multi-session non-invasive brain stimulation on craving and consumption in individuals with drug addiction, eating disorders or obesity: A meta-analysis	Brain Stimul. 2019 May-Jun; 12 (3):606-618. doi: 10.1016/j.brs. 2018.12.975. Epub 2018 Dec 27.
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Zhang JJQ, Fong KNK, Ouyang RG, Siu AMH, Kranz GS.	Effects of repetitive transcranial magnetic stimulation (rTMS) on craving and substance consumption in patients with substance dependence: a systematic review and meta-analysis	Addiction. 2019 Dec; 114 (12):2137-2149. doi: 10.1111/add. 14753. Epub 2019 Aug 16.
Xu K, Yi P, Liu J, Ren J, Zhang Q, Yu L, Yang Y, Wang Y, Ma L, Zhang Y, Li X.	Non-invasive brain stimulation interventions for treating Clinical and Sub-clinical eating disorders: A meta-analysis of randomized controlled trials and nonrandomized studies	Psychiatry Res. 2022 Jul; 313:114592. doi: 10.1016/j.psychres. 2022.114592. Epub 2022 May 1.
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Teselink J, Bawa KK, Koo GK, Sankhe K, Liu CS, Rapoport M, Oh P, Marzolini S, Gallagher D, Swardfager W, Herrmann N, Lanctôt KL.	Efficacy of non-invasive brain stimulation on global cognition and neuropsychiatric symptoms in Alzheimer's disease and mild cognitive impairment: A meta-analysis and systematic review	Ageing Res Rev. 2021 Dec; 72:101499. doi: 10.1016/j.arr. 2021.101499. Epub 2021 Oct 23.
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Chu CS, Li CT, Brunoni AR, Yang FC, Tseng PT, Tu YK, Stubbs B, Carvalho AF, Thompson T, Rajji TK, Yeh TC, Tsai CK, Chen TY, Li DJ, Hsu CW, Wu YC, Yu CL, Liang CS.	Cognitive effects and acceptability of non-invasive brain stimulation on Alzheimer's disease and mild cognitive impairment: a component network meta-analysis	J Neurol Neurosurg Psychiatry. 2021 Feb; 92 (2):195-203. doi: 10.1136/jnnp-2020-323870. Epub 2020 Oct 28.
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Supplementary Table 1: Contd...

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