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SYSTEMATIC REVIEWS

Role of transcranial magnetic stimulation in the management of trichotillomania: A systematic review

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Abstract

BACKGROUND

Trichotillomania is a challenging to treat psychiatric disorder, with limited evidence for pharmacotherapy. Treatment typically involves medication, cognitive behavioral therapy, and behavioral interventions. Recently, transcranial magnetic stimulation (TMS) has emerged as a potential treatment strategy.

AIM

To assess the role of TMS in treating trichotillomania.

METHODS

A systematic search using specific terms was done in PubMed and Scopus databases for articles published until May 17, 2024, related to trichotillomania and TMS. The search included randomized controlled trials, open-label studies, case series, case reports, and retrospective chart reviews, following the Preferred Items for Systematic Reviews and Meta-Analysis guideline.

RESULTS

We identified 32 articles (6 in PubMed and 26 in Scopus). After removing duplicates and articles that did not meet the selection criteria, we conducted a final analysis of four articles. These included one retrospective study, two case series, and one case study, with a total of 22 patients diagnosed with trichotillomania enrolled across all four studies. The brain areas targeted were the supplementary

motor area (SMA), pre-SMA, and left dorsolateral prefrontal cortex. The studies reported an improvement in the severity of symptoms of trichotillomania in the majority of patients with negligible side effects. Nevertheless, it is important to note that the existing studies are mostly of low to moderate quality.

CONCLUSION
Early evidence suggests repetitive TMS and accelerated continuous theta burst stimulation can help treat trichotillomania adjunctively to other treatments.

Key Words: Neuromodulation; Transcranial magnetic stimulation; Theta burst stimulation; Trichotillomania; Systematic review

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Core Tip: Transcranial magnetic stimulation (TMS) can be a viable treatment option in the management of trichotillomania. The brain areas targeted are supplementary motor area (SMA), pre-SMA, and left dorsolateral prefrontal cortex. TMS is well tolerated with negligible side effects. Maintenance TMS treatment facilitates sustained improvement of symptoms of trichotillomania.

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INTRODUCTION

Trichotillomania is characterized by recurrent hair-pulling and is associated with significant distress[1,2]. A recent meta-analysis involving 30 studies, including 38526 individuals estimated the prevalence of trichotillomania to be 1.14%[2]. When individuals with hair-pulling behaviors are considered, prevalence goes close to 9%[2]. These figures indicate that the prevalence of these disorders is higher than the prevalence of schizophrenia or bipolar affective disorder alone. Trichotillomania and related disorders have a significant health impact and produce enormous psychological distress, which results in impairment of socio-occupational functioning and social embarrassment[3]. Patients with trichotillomania experience extreme shame and guilt[3].

The common age of onset of trichotillomania is the second decade of life (mean age 17.7 years), and 80% of the patients with trichotillomania have comorbid psychiatric illnesses[1]. The common psychiatric comorbidities associated with trichotillomania include anxiety disorders, obsessive-compulsive disorder (OCD), depression, post-traumatic stress disorder, and attention deficit hyperactivity disorder (ADHD)[1]. Several neurobiological changes have been identified in the brains of patients with trichotillomania. Chamberlain *et al*[4] found that patients with trichotillomania have increased cortical thickness in the region of the right inferior frontal gyrus, in contrast to impulsive-compulsive disorders like OCD, ADHD, and gambling disorders (where there is thinning of the cortex). In another neuroimaging study, it is found that during the activities of reward anticipation, there is hyperactivation of the bilateral inferior frontal gyrus in patients with body-focused repetitive disorders like trichotillomania and skin picking disorder[5]. A diffuse tensor imaging study revealed a significant reduction in fractional anisotropy of the anterior cingulate cortex, pre-supplementary motor area (SMA) and temporal cortex[6]. This abnormality of the white matter might be responsible for affective dysregulation, and dysregulation in the formation of motor habit[6]. A recent neuroimaging study found the involvement of inferior temporal gyrus and ventral visual pathways in trichotillomania[7]. Additionally, there is involvement of brain structures like parahippocampal gyrus, fusiform gyrus, cerebellum, as well as inferior parietal lobule during the above-mentioned task [5]. Evidence supports about several shared unique neural mechanisms in the pathogenesis of trichotillomania and OCD [8].

Comorbidities are common with trichotillomania. The common psychiatric comorbidities associated with trichotillomania are: (1) Anxiety disorders; (2) depression; (3) OCD; (4) ADHD; (5) panic disorder; (6) post-traumatic stress disorder; (7) substance use disorder; and (8) eating disorders[3]. Skin picking disorder is also commonly found to be comorbid with trichotillomania[3].

To date, there is no treatment that has been approved by the US Food and Drug Administration for the treatment of trichotillomania[9-11]. Various pharmacological and psychological/behavioral interventions are conventionally used in the treatment of trichotillomania. However, the mainstay of treatment remains psychotherapy and behavior therapy like habit reversal therapy[12,13]. Among the pharmacological treatment, serotonergic agents and tricyclic antidepressants such as clomipramine are commonly used in the management of trichotillomania, although N-acetyl cysteine, lamotrigine, olanzapine, naltrexone, and inositol are also used with some efficacy[12,14]. However, a recent Cochrane systematic review reported inconclusive evidence concerning the roles of different psychotropic agents in the treatment of trichotillomania and the existing studies are mostly of poor quality[15]. Despite trials of pharmacotherapy and psychotherapy, the treatment of trichotillomania remains challenging as many patients do not respond well to these therapies. Therefore,

Table 1 Characteristics of the included studies

Ref.	Title of the article	Journal name	Country	Type of study	Level of evidence
Chaudhary *et al* [18], 2024	Accelerated Continuous Theta Burst Stimulation in the Treatment of Trichotillomania: A Comprehensive Case Study From Acute Intervention to Maintenance Phase	*The Journal of ECT*	India	Case report	IV
Di Ponzio *et al* [19], 2023	rTMS investigation of resistant Obsessive-Compulsive Related Disorders: Efficacy of targeting the reward system	*Frontiers in Psychiatry*	Italy	Retrospective study	III
Aydin *et al*[17], 2020	Repetitive Transcranial Magnetic Stimulation for Treatment of Trichotillomania: Case Series	*Clinical Psychopharmacology and Neuroscience*	Turkey	Case series	IV
Kar *et al*[21], 2020	Successful treatment of trichotillomania with repetitive transcranial magnetic stimulation: A report of two cases with review of literature	*Asian Journal of Psychiatry*	India	Case series	IV

researchers explored other possible treatment avenues for trichotillomania. As trichotillomania is an OCD spectrum disorder and shares a lot of neurobiological similarities with OCD, possibly the targets of neuromodulation in OCD may also be useful in the management of trichotillomania.

Neuromodulation techniques such as repetitive transcranial magnetic stimulation (rTMS)[16], transcranial direct current stimulation (tDCS), and electroconvulsive therapy (ECT) have been used in the management of trichotillomania in the recent decade[17-21]. The existing evidence is mostly limited to case studies. Neuromodulation treatment is a rapidly evolving field and evidence regarding the safety and efficacy of the above-mentioned neuromodulation techniques are well-established in various psychiatric disorders. However, a limited number of studies have discussed the scope and relevance of neuromodulation techniques in trichotillomania. Of the existing studies that discuss about the relevance of neuromodulation in trichotillomania, most have used TMS. TMS uses repetitively generated magnetic stimuli that modulate the neuronal activity of a focal group of neurons in the superficial cortical region (at the site of placement of the TMS coil). The underlying cortical neuronal activity following TMS application depends on the nature of TMS stimuli. High-frequency (> 5Hz) rTMS, and intermittent theta burst stimulation (a form of patterned TMS) produces underlying cortical stimulation whereas, low-frequency rTMS and continuous theta burst stimulation produces underlying cortical inhibition[22-25]. No systematic review has explored the relevance of TMS in the management of trichotillomania. This is the first systematic review that attempted to analyze the role of TMS in the management of trichotillomania.

MATERIALS AND METHODS

Methodology

A systematic search was done by using the search terms: (trichotillomania) AND ((TMS) OR (rTMS) OR (transcranial magnetic stimulation) OR ((transcranial magnetic stimulation))). The databases searched are PubMed and Scopus. All articles published from inception up to May 17, 2024 were included. To be included in this systematic review, the article had to be either a randomized controlled trial (RCT), open-label study, case series, case report, or retrospective chart review. The articles were extracted to RAYYAN software and screened by two investigators (Joshi M and Agrawal A) keeping the blinding on. Subsequently, a third investigator (Kar SK) evaluated the extracted articles, and through mutual discussion final selection of the articles was made. An additional search was done from the prominent journals focusing on neuromodulation (*Brain Stimulation*, *The Journal of ECT*, and *Neuromodulation*: *Technology at the Neural Interface*). Extraction of data in a given format was done by an independent investigator (Kumari B). The risk of bias assessment was done by using the Joanna Briggs Institute (JBI) critical appraisal tools[26] by two blinded investigators (Joseph R and Chatterjee S) independently and was finally sorted through mutual discussion. As this systematic review included one retrospective cohort study, two case series and one case report, the risk of bias assessment was done by applying specific tools for critical appraisal.

RESULTS

We found 32 hits (6 in PubMed and 26 in Scopus). Six duplicate articles were removed after the initial screening and subsequent screening of the title and abstract resulted in the exclusion of 21 more articles (Figure 1). Articles were excluded for multiple reasons (which were not mutually exclusive). Major reasons for exclusion were: wrong publication type (n = 21), wrong study design (n = 15), wrong outcomes (n = 14), wrong population (n = 11), and wrong intervention type (n = 4). A total of five articles were initially included; however, one[27] more article was excluded after a detailed evaluation of the whole article (as the article discussed biological markers, neuroimaging changes, and pathophysiological models in OCD and related disorders). The final analysis was done on four selected articles, which included one retrospective study, two case series and one case study (Table 1)[17-19,21]. A total of 22 patients diagnosed with trichotil-

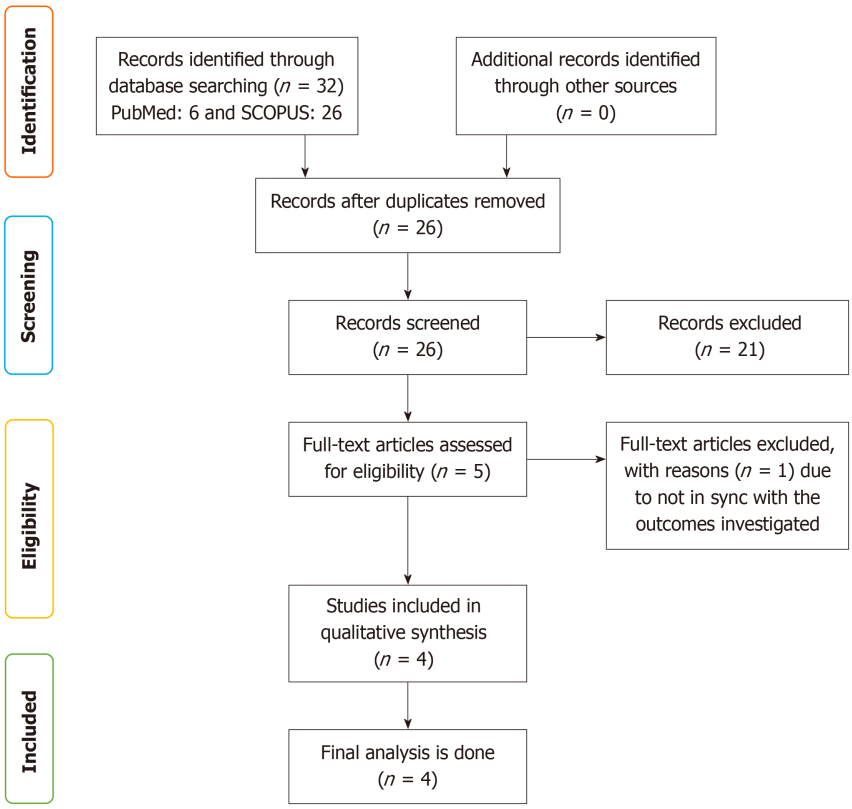


Figure 1 Preferred Items for Systematic Reviews and Meta-Analysis flow diagram describing the studies.

lomania were enrolled in these four studies (Table 2)[17-19,21]. In all the cases, TMS was being used as an add-on treatment modality to ongoing pharmacotherapy with or without psychotherapy. The brain areas targeted in managing trichotillomania were the SMA, pre-SMA, and left dorsolateral prefrontal cortex. Out of the four included studies, one study used accelerated continuous theta burst stimulation, one used high-frequency rTMS, and the other two used low-frequency rTMS (Table 3)[17-19,21]. On risk of bias assessment, only one study scored a JBI quality score of ≥ 70% [28], hence was of good quality and the other three were of moderate to low quality (Table 4, 5 and 6)[17-19,21].

DISCUSSION

Neuromodulation, like TMS, is a less-studied treatment modality to manage trichotillomania. To date, only four published articles discussed the efficacy/effectiveness of TMS in trichotillomania, of which three were case reports/series. Con-sidering the publications available in PubMed and Scopus until the week 3 of May 2024, the first reports of the use of TMS in management of trichotillomania were published in March 2020, by Kar *et al*[21] in the *Asian Journal of Psychiatry*. In November, 2020 another case series was published by Aydin *et al*[17], on five females with trichotillomania. The first observational study (retrospective database review) involving 41 patients, of whom, 14 had trichotillomania, and the rest had hoarding disorder or skin picking disorder, was published in 2022 by Di Ponzio *et al*[19]. A case study that used theta burst stimulation in an accelerated fashion for the first time in the management of trichotillomania was published in March 2024[18]. A total of 22 patients with trichotillomania received TMS treatment, of which only two were males (as part of the study of Di Ponzio *et al*[19]) and the remaining 20 were females[17,18,21]. Although some evidence suggests no gender difference in the prevalence of trichotillomania[1], most studies reported that females had a higher prevalence of trichotillomania than males had (odds ratio = 2.23), which involved hair-pulling with noticeable hair loss [2].

SMA and pre-SMA are commonly targeted in the management of trichotillomania[17,18,21]. Another study that used tDCS in the management of trichotillomania also targeted SMA as the target of neuromodulation[16]. As SMA and pre-SMA are commonly targeted in the management of OCD[29,30] and there is commonality in the neurobiology and phenomenology of OCD and trichotillomania[8,31,32], this probably tempts researchers to target these areas for focal neuromodulation. An inhibitory protocol is exclusively used for the management of trichotillomania targeting SMA and pre-SMA[16-18,21] as hyperactivity of these areas is consistently reported in OCD and related repetitive behavioral disorders.

The studies reported improvement in the severity of symptoms of trichotillomania in most patients with negligible side effects[17-19,21]. One study also considered maintenance accelerated continuous theta burst stimulation in the management of trichotillomania, with improvement of symptoms[18].

Table 2 Characteristics of participants

Ref.	Sample size	Psychiatric morbidities	Concurrent treatment		Past treatment		Outcome scale	Results	Side effects	Conclusion
			Psychotropics (mg/d)	Psychotherapy	Psychotropics (mg/d)	Psychotherapy				
Chaudhary *et al* [18], 2024	1	Not mentioned	Fluoxetine 80 mg, Aripiprazole 2 mg	Not mentioned	Yes (details not mentioned)	Not mentioned	YBOCS, MGH-HPS, and CGI-I	56% and 80% reduction in YBOCS and MGH-HPS scores, respectively. CGI-I scores improved from moderately worse to moderately efficacious. After 6 sessions of maintenance acTBS over 6 weeks, improvement was sustained	NR	First case report for acute and maintenance acTBS which was well tolerated and effects sustained
Di Ponzio *et al*[19], 2023	14	7 major depressive disorder, 2 ADHD, 4 GAD, 1 bipolar disorder	Selective serotonin reuptake inhibitors: Fluoxetine equivalent of 30 mg	None	Yes (details not mentioned)	Cortical bone trajectory	MGH-HPS and SDQ	Mean percentage of improvement was 58.2% in MGH-HPS and 17.1% in SDQ. No significant reduction after 1 month follow-up. Linear regression analysis indicated no age effect between pre- and post-intervention. Worsening of MGH-HPS scores was at follow-up in older age group	NR	Positive outcomes suggest implic-ations for reward circuits, which are usually used for addictions. This is consistent with the emerging view that obsessive-compulsive and related disorders are behavioral addictions. Worsening of MGH-HPS scores at follow-up in the older age group indicates reduced plasticity in elderly
Aydin *et al*[17], 2020	5	Case 1 ADHD; Case 2 none; Case 3 none; Case 4 GAD; Case 5 bipolar type II, obsessive-compulsive disorder, alcohol abuse, specific phobia	Case 1 Methyl-phenidate 36 mg; Case 2 no psycho-tropics; Case 3 Fluoxetine 80 mg; Case 4 Fluoxetine 20 mg; Case 5 Sertraline 100 mg, Aripiprazole 5 mg, Quetiapine 150 mg	None in all cases	Case 1 Fluoxetine 20 mg; Case 2 Escitalopram 20 mg; Case 3 Fluoxetine 80 mg, N-acetyl cystine 1200 mg; Case 4 no; Case 5 no	Yes in case 1 and case 3	MGH-HPS, Beck's anxiety inventory, Beck's depression inventory	Three patients had substantial benefit (100%, 75%, and 70% improvement in MGH-HSP), one patient had 33% improvement. The last patient experienced a mild increase in the severity	Transient flashes in eye for 2-3 session in one case	Repetitive transcranial magnetic stimulation was effective in 3 of 5 patients. One was a partial responder, and the other nonresponder might have been due to multiple comorbidities that

										acted as confounding factors
Kar *et al*[21], 2020	2	Not mentioned	Case 1 Escitalopram 30 mg; Case 2 Sertraline 200 mg	Habit reversal therapy	Not mentioned	Not mentioned	MGH-HPS	Reduction of 66.6% and 73.6% in both cases, respectively. Case 1 sustained benefits for 6 weeks, while case 2 was maintained well for 2 months then experienced worsening which improved with psychotherapy for 6 months	NR	Reduction in symptom severity and therapy was well tolerated

ADHD: Attention deficit hyperactivity disorder; acTBS: Accelerated continuous theta burst stimulation; CGI-I: Clinical global impression improvement; GAD: Generalized anxiety disorder; MGH-HPS: Massachusetts General Hospital Hair Pulling Scale; NR: None reported; SDQ: Symptoms of depression questionnaire; YBOCS: Yale-Brown Obsessive-Compulsive Scale.

Table 3 Parameters of protocols used

Ref.	Type of TMS intervention	Target area	Frequency (Hz)	Resting motor threshold (%)	Total no. of pulses	No. of sessions per day	Total no. of sessions	Duration of treatment (week)	Maintenance TMS
Chaudhary *et al* [18], 2024	Accelerated continuous theta burst stimulation	SMA	Not mentioned	Not mentioned	900	2 (15 min apart)	20	Not mentioned	Yes (6 > 6 weeks)
Di Ponzio *et al*[19], 2023	High frequency rTMS	Left dorsolateral prefrontal cortex	15	100	2400	1	24	4	No
Aydin *et al*[17], 2020	LF rTMS	Pre-SMA	1	100	1200	1	15	3	No
Kar *et al*[21], 2020	LF rTMS	SMA	1	Not mentioned	1200	1	20	4	No

LF: Low frequency; rTMS: Repetitive transcranial magnetic stimulation; SMA: Supplementary motor area; TMS: Transcranial magnetic stimulation.

The existing evidence is mostly limited to case reports/series or retrospective studies on a small sample. There was no RCT on TMS in trichotillomania. The existing studies were mostly of low to moderate quality. Hence, there is a need for extensive research, particularly RCTs, to substantiate the evidence for TMS treatment of trichotillomania.

A major limitation of this systematic review was the small number of studies and the heterogeneity among the studies in terms of the protocols used, sites targeted, number of sessions used, and the presence of comorbidity. Further research is required for better understanding about the efficacy and safety of TMS in trichotillomania.

Table 4 Risk of bias assessment of cohort study on Joanna Briggs Institute critical appraisal tool

Ref.	Were the two groups similar and recruited from the same population	Were the exposures measured similarly to assign people to both exposed and unexposed groups	Was the exposure measured in a valid and reliable way	Were confounding factors identified	Were strategies to deal with confounding factors stated	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)	Were the outcomes measured in a valid and reliable way	Was the follow up time reported and sufficient to be long enough for outcomes to occur	Was follow up complete, and if not, were the reasons to loss to follow up described and explored	Were strategies to address incomplete follow up utilized	Was appropriate statistical analysis used	Score
Di Ponzio *et al* [19], 2023	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	No	Yes	73%

Table 5 Risk of bias assessment of case series on Joanna Briggs Institute critical appraisal tool

Ref.	Were there clear criteria for inclusion in the case series	Was the condition measured in a standard, reliable way for all participants included in the case series	Were valid methods used for identification of the condition for all participants included in the case series	Did the case series have consecutive inclusion of participants	Did the case series have complete inclusion of participants	Was there clear reporting of the demographics of the participants in the study	Was there clear reporting of clinical information of the participants	Were the outcomes or follow up results of cases clearly reported	Was there clear reporting of the presenting site(s)/clinic(s) demographic information	Was statistical analysis appropriate	Score
Kar *et al*[21], 2020	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	Unclear	NA	30%
Aydin *et al* [17], 2020	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Unclear	NA	40%

CONCLUSION

Trichotillomania is a difficult-to-treat mental illness, with limited evidence for pharmacotherapy. Preliminary evidence supports the beneficial role of rTMS and accelerated continuous theta burst stimulation in managing trichotillomania as an add-on treatment modality. There is a need for further research and more clinical trials in larger groups of patients with trichotillomania to establish the evidence.

Table 6 Risk of bias assessment of case reports on Joanna Briggs Institute critical appraisal tool

Ref.	Were patient's demographic characteristics clearly described	Was patient's history clearly described and presented as a timeline	Was current clinical condition of the patient on presentation clearly described	Were diagnostic tests or assessment methods and results clearly described	Was interventions or treatment procedure clearly described	Was post-intervention clinical condition clearly described	Were adverse events or unanticipated events identified and described	Does the case report provide takeaway lessons	Score
Chaudhary *et al*[18], 2024	Unclear	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	63%

FOOTNOTES

Author contributions: Kar SK was responsible for conceptualization; Kar SK and Kumari B were responsible for manuscript writing; Kar SK, Joshi M, and Agrawal A were responsible for the literature search; Kumari B was responsible for tabulation and data extraction; Joseph R and Chatterjee S were responsible for risk of bias assessment; Kar SK, Kumari B, Joseph R, Chatterjee S, Joshi M, and Agrawal A were responsible for revision and editing of the manuscript; all of the authors read and approved the final version of the manuscript to be published.

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