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Transcranial magnetic stimulation for the treatment of later-life depression: a scoping review

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Abstract

Objective: Transcranial magnetic stimulation (TMS) is a form of neuromodulation used to treat various neuropsychiatric disorders. The clinical utility of TMS in older adults with depression is less studied. This review was conducted to compile the study findings on the efficacy and adverse effects of TMS in later-life depression to elucidate gaps in the literature and formulate recommendations.

Materials and methods: A search was conducted on PubMed, Scopus and Ovid databases with search terms based on the three domains of our research questions, namely „transcranial magnetic stimulation", „depression", and „later life". All the articles published in English until June 2021 were incorporated and critically appraised after fulfilling inclusion and exclusion criteria.

Results: A total of 643 articles were screened with title and abstract, and 41 were selected for full-text assessment. Finally, 26 articles were included after scrutiny and findings were tabulated. This consisted of 8 randomized controlled trials (RCTs), six open-label, one retrospective study, 4 case series and 7 case reports. Available findings in this area so far are mixed and inconclusive. Level I evidence for the use of TMS in later-life depression is lacking.

Conclusion: Evidence regarding the efficacy of TMS in the treatment of depression in older adults lacks consistency in the outcomes, which warrants an urgent need for systematic review and meta-analysis of RCTs on the use of TMS in later-life depression.

Keywords

Transcranial Magnetic Stimulation, TMS, Later-Life Depression, Treatment

INTRODUCTION

Later-life depression is common psychiatric morbidity in older people. Epidemiological studies suggest that the prevalence of later-life depression is 29% in the European population, with gross variations in regional prevalence (17% to 35%) (Horackova et al., 2019). A systematic review and meta-analysis of 81 studies revealed the prevalence of depression among the older population to be 20% in the Chinese population (Tang et al., 2021). Various factors have been associated with late-life depression, of which the most common are chronic medical conditions, painful medical conditions, cognitive impairments, lack of grip strength and lack of instrumental support (Horackova et al., 2019). It has been seen that there is a close association between later-life depression and suicidal behaviour in older people (Ding and Kennedy, 2021). Supportive care, adequate treatment of depression in older people and the use of newer modalities like neuromodulation may help improve later-life depression, quality of life and risk of suicide (Ding and Kennedy, 2021).

Though pharmacotherapy is the most common mode of treating depression, psychotherapy and neuromodulation techniques like electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) are also used in treating depression. TMS is one of the approved treatment modalities in depression management. TMS has been used in various age groups of patients, including the geriatric population with depression (Cosmo et al., 2021; Somani and Kar, 2019). TMS exerts its action by focal neuromodulation (either by cortical stimulation or inhibition). High frequency repetitive transcranial

magnetic stimulation (HF rTMS) over the left dorsolateral prefrontal cortex (DLPFC) produces an antidepressant effect by producing focal cortical excitation.

Similarly, low frequency repetitive transcranial magnetic stimulation (LF rTMS) over right DLPFC has an antidepressant effect by producing focal cortical inhibition (Kar, 2019; Somani and Kar, 2019). In treating depression, commonly left DLPFC is targeted in most existing research, and the common indication is treatment-resistant depression (Cosmo et al., 2021; Lefaucheur et al., 2020). Initial evidence suggests that there is age-dependent therapeutic efficacy of TMS. With increasing age, the therapeutic efficacy of TMS declines as there is an increase in cortical atrophy, which increases the distance between the skull and cortical surface (Kar, 2019; Pallanti et al., 2012). However, the age-dependent therapeutic efficacy concept is controversial. Milev and others (2009), in their study, found that older adults with medication-resistant depression respond well to HF rTMS over left DLPFC (Milev et al., 2009). In addition, recent research suggests that older patients with depression (both unipolar and bipolar depression) respond to accelerated TMS protocol and tolerate well to the therapy (Desbeaumes Jodoin et al., 2019).

Similarly, deep TMS is effective and well-tolerated among patients with later-life depression, with a remission rate of 40% (versus 15% in the sham comparator group) (Kaster et al., 2018). In addition, a recent systematic review reported that less than 2% of the older adults with depression report serious adverse effects to TMS treatment, and milder side effects like headache are reported in about 7% of the patients (Overvliet et al., 2021). Therefore, TMS is considered a safe therapeutic modality in later life. Furthermore, a recent meta-analysis that included 14 RCTs and 26 studies for meta-regression analysis suggests that active rTMS is effective in reducing the symptom severity of depression significantly in comparison to sham comparators (Valiengo et al., 2022). Similarly, the response rate and remission achieved in the active rTMS group are considerably higher (Valiengo et al., 2022). Likewise, another recent systematic review attempted to measure the response rate to rTMS in geriatric depression and found a gross variability in the response rate of remission (6.75 to 4.3%) (Cappon et al., 2022).

Though the efficacy of depression is well established, it is poorly studied in the geriatric population. Most studies that attempted to investigate the effectiveness of TMS in depression excluded the geriatric population from the study participation. In recent years, innovations in TMS technology and various new forms of TMS (theta-burst stimulation, deep TMS) have been used to manage later-life depression. This study aims at evaluating the existing evidence that measures the efficacy of TMS in later-life depression.

METHODS

Research question

What is the clinical utility of TMS in the treatment of later-life depression?

OBJECTIVES

1. To evaluate the efficacy of TMS in terms of response or remission in later-life depression.

2. To evaluate the frequency and severity of adverse effects caused due to TMS in later-life depression.

With the consensus of all the authors, we used both subject terms and keywords for searching literature based on the three domains of our research questions, namely "transcranial magnetic stimulation" (TMS), "depression", and "late life". Keywords included commonly used synonyms of these three domains. Electronic databases PubMed, Scopus and Ovid, were used to search relevant literature. An advanced search through PubMed was done with search strings – "(transcranial magnetic stimulation[mh] OR TMS[tiab] OR rTMS[tiab] OR dTMS[tiab] OR iTBS[tiab] OR trans-cranial magnetic stimulation[tiab] OR theta-burst stimulation[tiab]) AND (depression[mh] OR depressive[tiab] OR depression[tiab] OR MDD[tiab] OR LLD[tiab]) AND (late-life[tiab] OR geriatric[tiab] OR older[tiab] OR elderly[tiab] OR veteran[tiab] OR veterans[tiab]) NOT (bipolar[tiab])". Same search strings were used for Ovid sans [mh] and [tiab]. A similar search string was optimized to the Scopus database also with minor modifications to suit the search requirements of the database, which resulted in a search string of – ("transcranial magnetic stimulation" OR tms OR rtms OR dtms OR itbs OR "trans-cranial magnetic stimulation" OR "theta burst stimulation" AND depression OR depressive OR depression OR mdd OR lld AND late-life OR geriatric OR older OR elderly OR veteran OR veterans AND NOT

bipolar). All articles were screened from inception to June 2021. Articles were initially screened by two independent reviewers (VKL and BK) using title, abstract and keywords. Evidence was gathered from all relevant systematic reviews and meta-analyses, RCTs, open-label studies, retrospective studies, case series and case reports published in English.

After checking for duplicates, we included only those papers in which patients' primary psychiatric diagnosis was depressive disorders/major depressive disorder and excluded those articles which included bipolar depression, major neurocognitive disorders, or dementia, those where the age of the patient population or the control group was less than 50 years and articles which shared only protocol without outcome specifications. Selected articles were read and analyzed with full text. Additional relevant articles were added from hand searching, going through the references of the selected articles. Data were extracted using a customized Google form which focused on three specific domains: TMS parameters, clinical profile of patient population and outcome. First, the clinical profile of the patient population like mean age, duration of illness, the severity of depression, treatment resistance, ongoing pharmacotherapy and duration of follow-up assessment were ascertained. Second, TMS parameters like type, target site, frequency, number of sessions and pulses per session were extracted and tabulated. Finally, under the outcome domain, we specifically searched for response/ reduction in depression rating scales, remission, and presence and severity of adverse effects.

RESULTS

A total of 26 papers have been found eligible to be included in this scoping review. Of those 26, eight randomized controlled trials (RCT), six open-label studies, one retrospective study, 4 case series and 7 case reports (Figure 1).

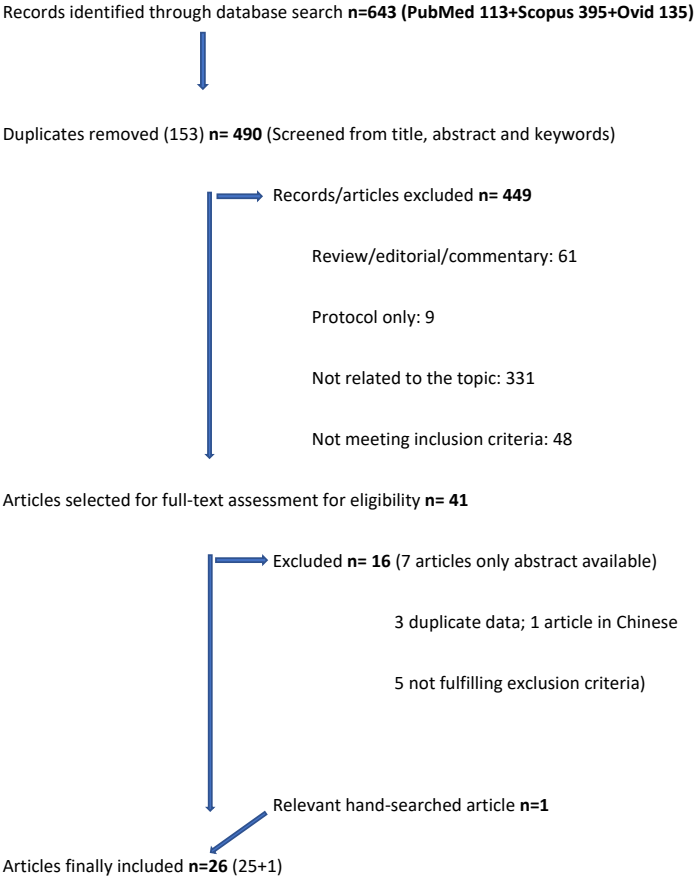

Figure 1: Flow diagram showing a selection of articles.

[8 RCTs, six open-label, one retrospective, 4 case series and 7 case reports]

Treatment resistance was present in all the reported cases and study populations. In the majority of the papers, TMS has been added as an adjunct to ongoing pharmacotherapy or started along with pharmacotherapy (Dai et al., 2020), and in a few, rTMS was the only therapeutic modality which was given (Jorge et al., 2008; Manes et al., 2001). Summary of these RCTs, open-label and retrospective studies along with case series with a sample size of at least 10, have been tabulated in Table 1.

Table 1*: Summary of studies on TMS in later-life depression.

Study	TMS parameters	Study design	Follow-up duration	Outcome	Adverse effects
(Dai et al., 2020)	**Type**: HF-rTMS **Frequency**: 10Hz **Site**: Left PFC **Pulses**: 800 **Sessions**: 20	RCT double-blind; N=103 (active group- 48, sham comparator (control) group-55) **Tools**: HAMD, SIOSS.	Four weeks	After two weeks, HAMD reduction rate ≥26% was higher in the rTMS group After four weeks, the effective rate was higher in the rTMS group versus the sham comparator (control) rTMS group. Lower SIOSS score, was noted in the rTMS group. Active rTMS exhibited rapid onset and an enhanced effect. **Drop out**: 2 dropped out in active group and 2 in sham comparator (control) due to poor tolerance to noise	Dizziness, Nausea, chest discomfort (5) Nausea, dryness of mouth (3) Headache (4) **SAE**: Nil
(Zhao et al., 2019)	**Type**: HF-rTMS, **Frequency**: 10 Hz **Site**: Left DLPFC, **Pulses**: 1200 **Sessions**: 20	RCT; N= 88 (29-rTMS group, 29- control group not receiving rTMS, 30 healthy volunteers receiving rTMS) Tools: HAMD24; S. BDNF, IL-8, TNF-α levels were also measured	Four weeks	HAMD-24 scores decreased in the rTMS group compared with the control group. Levels of BDNF, IL-18, and TNF- α were unaffected by rTMS in the healthy individuals. BDNF levels gradually increased with treatment with rTMS, and IL-18 and TNF- α levels decreased in patients with refractory depression. **Drop out**: None	None reported **SAE**: Nil
(Trevizol et al., 2019)	B/L Sequential: Type: 1Hz in Right DLPFC followed by 10 Hz in left DLPFC Pulses: 750-1500 U/L HFL: Type: HF-rTMS (10Hz) on left DLPFC Pulses: 1450-2100 Sessions: 15 for remitters additional 15 for non-remitters	RCT, double blind; N= 43 (Sham comparator (control)-12, HFL- 11, B/L rTMS-20) Tools: HAMD	6 weeks	B/L rTMS showed greater improvement compared to U/L and sham comparator (control), with no difference between U/L and sham comparator (control). **Drop out**: 4 (3- lack of response, 1- poor tolerance)	Insomnia (1) and headache (1) in HFL group **SAE**: Nil
(Kaster et al., 2018)	**Type**: Deep TMS, **Frequency**: 18 Hz **Site**: B/L DLPFC and VLPFC, with greater intensity and penetration of the left hemisphere **Pulses**: 6012 **Sessions**: 20	RCT double-blind; N= 58 (active-30, sham comparator (control)-28) Tools: HAM D, SSI, HRQoL, BSI, RBANS, DKEFS-CWI, DKEFS-TMT	Four weeks	Higher rate of remission, response in participants receiving active deep rTMS compared to sham comparator (control) rTMS. No difference in the effect of time between active and sham comparator (control) rTMS on any cognitive function. **Drop out**: 5 with H1 coil; did not continue (1), symptoms worsened (1), discomfort (1), reasons unrelated to TMS(2) 2 with H1L coil; seizure (1), pain at the site (1) 1 due to pain at the stimulation site in sham comparator (control) group	In the active group Headache (14), Pain at the stimulation site (4), Nasopharyngitis (1), Aphthous ulcer (1), Corneal abrasion (1), Dermatitis (1), Sinusitis (1), Nausea (1), **SAE**: Seizure 1 day after the 10th session with H1L coil; Nil with H1 coil
(Yesavage, Fairchild, Mi, Biswas, Davis-Karim, Phibbs, Forman, Thase, Williams, Etkin, O'Hara, Georgette, Beale, Huang, Noda, George, et al., 2018)	**Type**: HF-rTMS, **Frequency**: 10 Hz **Site**: Left PFC, **Pulses**: 400 **Sessions**: 30, 6 additional for those who had remission	RCT, double blind; N=164 (Active-81, sham comparator (control)-83) Tools: HAM D, MADRS, BDI, BSI, CSSRS, CAPS	24 weeks	Clinically significant improvement in depressive symptoms; there was no evidence of difference in remission rates between active and sham comparator (control) treatments. No significant effect of treatment on PTSD symptoms, suicidality and quality of life. **Drop out**: 39 (21 in active group, 18 in sham comparator (control) group)	Nasopharyngitis (8 in both), depression (8: active, 3: sham comparator (control)), fall (3 active, 7 sham comparator (control)), headache (15 active, 16 sham comparator (control)) **SAE**: Suicidal ideation (3 active, four sham comparator (control))

Study	TMS parameters	Study design	Follow-up duration	Outcome	Adverse effects
(XIE et al., 2015)	**Type**: HF-rTMS, **Frequency**: 10 Hz **Site**: Left DLPFC, **Pulses**: not mentioned **Sessions**: 20	RCT, double-blind; N= 65 Experiment group:36 rTMS with shuganjieyu (Chinese herbal medicine) Control group: 29 shuganjieyu with mock-rTMS Tools: HAMD	Six weeks	At the end of the trial the two groups had similar efficacy. **Drop out**: 3 (1: diagnosis revised, 2: early hospital discharge)	Dry mouth (2 in active, 3 in control), headaches or discomfort in the head (3 in active, 2 in control), dizziness (2 in active, 4 in control), constipation (3 in active, 1 in control), nausea (3 in active), sweating (1 in active), poor appetite (1 in active and 1 in control), stuffy nose, diarrhoea (1) **SAE**: Nil
(Jorge et al., 2008)	**Type**: HF-rTMS, **Frequency**: 10 Hz Experiment 1: left DLPFC, 1200 pulses,10 sessions (TCD-12k group); Experiment 2: Left PFC 1200 pulses, 15 sessions (TCD-18k)	RCT, double-blind; N=92 Experiment 1: active-15, sham comparator (control)-15 Experiment 2: active 33, sham comparator (control)-29 Tools: HAMD17	Three weeks	Both the experiments resulted in a greater response rate, remission rate and greater decrease in HAM-D score in the active rTMS group than sham comparator (control) group. Older age and smaller frontal gray matter volumes were associated with a poorer response to rTMS. No dropouts due to adverse effects. **Drop out**: 5; before stimulation (4 voluntarily, one drug abuse)	Local pain (3), headache (19), local discomfort (13) and anxiety (2) SAE: Nil
(Mosimann et al., 2004)	**Type**: HF-rTMS, **Frequency**: 20 Hz **Site**: Left DLPFC, **Pulses**: 1600 **Sessions**: 10	RCT, Double blind; N= 24 (Active-15, sham comparator (control)-9) Tools: HAM D, Visual analogue depression scale, BDI	Two weeks	Improvement in depressive symptoms after ten stimulations but no significant within-group effects. The two groups did not differ with respect to response rate. **Drop out**: None	Nausea (1 in active, 2 in the sham comparator (control), headache (2 in sham comparator (control)), toothache (1 in active), dizziness (1 in sham comparator (control), conjunctivitis (1 in active), metallic taste (1 in active), crying (2 in active) **SAE**: Suicidal ideation (1 in active)
(Cristancho et al., 2020)	**Type**: Theta-burst stimulation, **Frequency**: 50 Hz repeated at 5 Hz **Site**: B/L DLPFC, **Pulses**: 1200 **Sessions**: 20	Open-label; N=13 Tools: MADRS, FLANKER test, DCCS MADRS, Flanker Inhibitory Control and attention test	4 weeks	All the test scores significantly improved from baseline to treatment end. **Drop out**: 1 withdrew before stimulation, 1 due to low tolerance.	Twitching in facial muscles (11), headache (10), stimulation discomfort (4) **SAE**: Nil
(Leblhuber et al., 2019)	**Type**: HF-rTMS, **Frequency**: 3 Hz **Site**: B/L PFC, **Pulses**: Not mentioned **Sessions**: 10	Open label; N= 29 (Active-19, sham comparator (control)-10) Tools: HAMD 17, levels of phenylalanine, neopterin, Kyn/Trp ratio also measured	2 weeks	Improvement in depressive symptoms after active rTMS than sham comparator (control). Decrease in phenylalanine concentration in patients receiving active rTMS, no effect on rest of the biomarkers. **Drop out**: None	Not reported
(Dardenne et al., 2018)	**Type**: HF-rTMS, **Frequency**: 20 Hz **Site**: Left DLPFC, **Pulses**:1560 **Sessions**: 20	Open label; N= 10 **Tools**: HAMD, BDI.	4 days	There was improvement in HAM-D and BDI scores except for 1. 4 were responders of whom 2 were remitters. **Drop out**: None	local discomfort (1), headache (4) **SAE**: Nil
(Fabre, Galinowski, Oppenheim, Gallarda, Meder, Montigny, et al., 2004)	**Type**: HF-rTMS, **Frequency**: 10 Hz **Site**: Left PFC, **Pulses**: 1600 **Sessions**: 10	Open label; N=11 **Tools**: HAM D, GDS	2 weeks	5 out of 11 resistant patients were responders. Improvement in HAMD, verbal fluency and visuospatial memory. No cognitive deterioration. **Drop out**: None	Not mentioned.
(Manes et al., 2001)	**Type**: HF-rTMS, **Frequency**: 20 Hz **Site**: not mentioned **Pulses**: 800 **Sessions**: 5	Open label; N= 20 (Active-10, sham comparator (control)-10) **Tools**: HAMD	1 week	No significant differences in HAM-D scores either before or after treatment at 7 days follow-up in both groups. **Drop out**: None	Local pain (5) Headache (4) Local discomfort (8) Anxiety (1) **SAE**: Nil

Study	TMS parameters	Study design	Follow-up duration	Outcome	Adverse effects
(Sayar et al., 2013)	Type: HF-rTMS, Frequency: 25 Hz Site: Left PFC, Pulses:1000 Sessions: 18	Case series prospective; N=65 Tools: HAMD	3 weeks	58.46% of the study group demonstrated significant mood improvement. Drop out: None	Not reported
(Dardenne et al., 2018)	Type: HF-rTMS, Frequency: 20 Hz Site: Left DLPFC, Pulses:1560 Sessions: 20	Open label; N= 10 Tools: HAMD, BDI.	4 days	There was improvement in HAM-D and BDI scores except for 1. 4 were responders of whom 2 were remitters. Drop out: None	local discomfort (1), headache (4) SAE: Nil

*Case series reporting up to 3 cases and single-case reports have not been included in the table, but are mentioned in the result description.

Abbreviations: DLPFC: dorsolateral prefrontal cortex; VLPFC: ventrolateral prefrontal cortex; HF: high frequency, B/L: bilateral; U/L: unilateral; HAM D: Hamilton Depression Rating Scale; SSI: Scale for Suicidal Ideation; HRQoL: Health-Related Quality of Life; BSI: Brief Symptom Inventory anxiety subscale; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; DKEFS-CWI: Delis–Kaplan Executive Function System ColoUr Word Interference; DKEFS-TMT: trail making test; BSI: Beck Scale for Suicide Ideation; CAPS: Clinician-Administered PTSD Scale for DSM-IV; CSSRS: Columbia Suicide Severity Rating Scale; Flanker test: Flanker Inhibitory Control and Attention Test; DCCS: Dimensional Sort Card Test; SIOSS: Self Rating Idea of Suicide Scale; MADRS: Montgomery Asberg Depression Scale; QIDS-SR: Quick Inventory of Depressive symptoms – self-report; BDI: Beck's Depression Inventory; GDS: Geriatric Depression Scale; Phe/ Tyr: phenylalanine to tyrosine ratio; Kyn/Trp: kynurenine to tryptophan ratio; SAE: serious adverse effect.

Findings of small-case series and single-case reports are being summarised here. Januel and colleagues (2004) reported 3 cases of treatment-resistant depression that received 10 Hz rTMS as add-on therapy. With 16 sessions, they reduced the Hamilton Depression Rating Scale (HDRS) scores from 23.67 ± 1.52 to 7.33 ± 2.30 at four-week follow-up, reporting no adverse effects (Januel et al., 2004). Another series of 2 cases which received 1 Hz rTMS over the right frontal cortex also reported remission after receiving 30 sessions of 1,600 pulses each at the end of 6 weeks with no side effects (Caulfield et al., 2017). Chatterjee and colleagues (2020) have reported remission with well-tolerated 12 daily sessions of intermittent theta-burst stimulation given on left DLPFC with no recurrence at six months follow-up (Chatterjee et al., 2020). There is another report of accelerated intermittent theta-burst stimulation to left DLPFC given in a 66-year-old female who achieved a quick response with no side effects (Konstantinou et al., 2020). Thanks and colleagues (2020) have reported safe administration of 15 sessions of adjuvant 1 Hz rTMS over the right DLPFC in a 60-year-old male who had recurrent antidepressant-induced hyponatremic seizures with the patient reaching remission and maintaining it in the next one and a half years (Thanki et al., 2020). A team of researchers from Brazil have reported sustained remission for up to five months in a 60-year-old male following 20 sessions of 10 Hz rTMS over bilateral dorsomedial PFC rTMS (DMPFC). However, local discomfort and headache were reported as adverse effects that subsided with minimal intervention (Sender et al., 2017). Philip and Carpenter (2013) have published the development of hypomanic symptoms following six sessions of five Hz rTMS over left DLPFC with 3,000 pulses per session in a 52-year-old woman, which was severe enough to stop the further sessions. The patient had a history of hypomanic symptoms previously induced by electroconvulsive therapy (ECT)(Philip and Carpenter, 2013). Posterior vitreous detachment and retinal tear have been reported in a 60-year-old woman who received 11 sessions of 1 Hz rTMS over right DLPFC, due to which further sessions had to be aborted (Kung et al., 2011). Similar side effects are also reported by Marafon and colleagues (2019). They administered 25 sessions of theta-burst stimulation to bilateral DLPFC over five weeks in a 50-year-old female, which resulted in the cessation of further sessions (Marafon et al., 2020). Treatment resistance to pharmacotherapy was present in all the patients. The table 1 summarises the major findings of the studies.

DISCUSSION

Despite portraying advancing age as one of the predictors of a poor response to TMS in various studies (Pallanti et al., 2012)depressive syndromes often affect people with chronic medical illnesses, cognitive impairment, and disability, which can worsen the outcomes of other medical disorders and promote disability. Repetitive magnetic transcranial stimulation (rTMS, it's use in later-life depression has gained phenomenal interest over the years. The concept of later-life depression itself has different connotations, but generally speaking, depression that occurs on or after the age of 65 years without any prior episode of depression is known as later-life depression. Interestingly, some authors have also

included bipolar depression under the rubric of later-life depression (Overvliet et al., 2021; Sabesan et al., 2015)repetitive transcranial magnetic stimulation (rTMS.

However, for the purpose of this review, we have remained conservative in defining later-life depression and have excluded bipolar depression, considering the different etiology and pathophysiology from later-life depression. This review is the first of its kind to focus exclusively on TMS in later-life depression with a systematic protocol and not any other forms of neuromodulation, therefore making it unique and precise compared to the earlier reviews (Gálvez et al., 2015; Iriarte and George, 2018).

We have included all available literature including single-case reports, as they significantly contribute to the understanding of the safety profile and the adverse effect of these novel techniques.

The majority of studies have included TMS as an adjunct to the ongoing pharmacotherapy and treatment resistance has been uniform in all the reported cases and study population (Dai et al., 2020). However, a few studies have included rTMS as the only therapeutic modality (Jorge et al., 2008; Manes et al., 2001). Interestingly, we could not find any level Ia/Ib evidence (systematic review with homogeneity of RCTs or large individual RCT with narrow confidence interval) for the use of TMS in later-life depression and therefore the current review summarises best possible evidence for the utility of TMS in later-life depression.

High frequency repetitive transcranial magnetic stimulation (HF-rTMS)

Out of the 8 included RCTs in this review, 6 have used HF-rTMS as an active intervention and most of them have used 10 Hz frequency. Interestingly, all the studies have demonstrated clinically significant reduction on depression rating scales following the intervention with variable differences between the active and sham (control) TMS groups. Yesavage and colleagues (2018) reported clinically significant improvement in both rTMS and sham groups with no difference between the groups and concluded the results to be reflection of the close clinical surveillance, monitoring of concomitant medication, and regular interaction with clinic staff in the treatment-resistant population (Yesavage, Fairchild, Mi, Biswas, Davis-Karim, Phibbs, Forman, Thase, Williams, Etkin, O'Hara, Georgette, Beale, Huang, Noda and George, 2018). Among the available studies, this study has a maximum follow-up period of 24 weeks. Contrary to this, Dai and colleagues have reported rTMS with routine drug therapy exhibiting quicker and enhanced improvement in clinical symptoms in older people with treatment-resistant depression. However, authors have asserted the need for assessment of the long-term therapeutic effect (Dai et al., 2020). Furthermore, another RCT which has focused specifically on later-life depression with vascular cause, has reported HF-rTMS to be superior to sham comparators when given alone without psychotropics. Interestingly, a higher dose was found to be superior in the study. The old age and smaller frontal grey matter volumes were demonstrated to have a poorer response to rTMS (Jorge et al., 2008). However, this is the only study which has evaluated the predictors of this response. Xie and colleagues studied the effect of rTMS with Chinese herbal medicines and noticed stepwise improvement in both the groups, but there was no significant difference between the active or sham (control) rTMS groups (Xie et al., 2015)five days a week for 4 weeks. Blinded raters used the Hamilton Rating Scale for Depression (HAMD-17. Further, Zhao and colleagues lacked control using sham rTMS in a study and Mosimann and colleagues had a modest sample size of 24 in a RCT (Mosimann et al., 2004; Zhao et al., 2019). Most of the studies have demonstrated mild to moderate adverse effect with a minimal need for intervention with HF-rTMS. However, a few studies lacks systematic evaluation of the side effects (Fabre, Galinowski, Oppenheim, Gallarda, Meder, De Montigny, et al., 2004; Zhao et al., 2019)this promising and non invasive therapeutic tool seems to be better tolerated than electroconvulsive therapy.Vascular depression is a subtype of late-life depression, associated with cerebrovascular disease and means a poorer response to antidepressant treatment. We employed rTMS over the left prefrontal cortex in 11 patients with late-onset resistant vascular depression. The primary purpose of this two-week open study was to examine antidepressant efficacy of rTMS in vascular depression. The secondary aim was to evaluate cognitive effects of rTMS in our sample. METHODS: Clinical status, as measured with the Hamilton Depression Rating Scale (HDRS. Moreover, studies on predictors of treatment response and tolerability of adverse effects are lacking in the literature. Side effects like suicidal ideations have been reported in the literature, but other serious side effects including

seizures have not been reported.

Deep transcranial magnetic stimulation (dTMS)

The only available study on the effectiveness of dTMS in later-life depression has reported a higher rate of remission and response rate in participants receiving active deep rTMS compared to the control group who received sham rTMS. The authors have reported a 'number needed to treat (NNT; average number of patients needed to be treated to prevent one additional bad outcome) of 4 but the findings have not been replicated. In terms of limitations, the study had a low power and high confidence interval. Moreover, poor tolerability of H1L coil (helmet coil that stimulates specifically over left DLPFC) was reported in the study which was used initially in 6 participants as one participant had seizure after the 10th session. However, H1 coil was used for subsequent participants and was well tolerated (Kaster et al., 2018).

Combination paradigms

Trevizol and colleagues have studied the effectiveness of bilateral sequential rTMS in comparison to unilateral and sham comparator groups in 43 participants and reported a greater improvement in the bilateral sequential rTMS group. Serious adverse effects were not reported (Trevizol et al., 2019)along with medical comorbidities and polypharmacy. Together with the limited data on managing treatment-resistant depression in older adults, there is a need for investigating the efficacy of non-pharmacological treatment strategies. Repetitive transcranial magnetic stimulation (rTMS. However, modest sample size in the study limits its ability to draw a conclusion on its clinical utility. In another study, improvement in depressive symptoms was reported when 3 Hz rTMS was given bilaterally on the prefrontal cortex in small open-label pilot studies, which demand future RCTs to confirm these results (Leblhuber et al., 2019).

Theta-burst stimulation (TBS)

An open-label study with modest sample of 13 has given positive results demanding further research on the utility of TBS in later-life depression. Side effects like headache and discomfort at the site of stimulation were higher than the adult population. However, serious side effects were not reported (Cristancho et al., 2020). Interestingly, serious side effect like retinal tear with posterior vitreous detachment has been reported in a single case report (Marafon et al., 2020). Considering the low number of the population having received TBS, it demands further elaboration to ensure safety profile of this type of TMS.

Low frequency repetitive transcranial magnetic stimulation (LF-rTMS)

Effectiveness and tolerability of LF-rTMS in adults with depression has been demonstrated superior to HF-rTMS (Berlim et al., 2013). However, it remains unexplored in later-life depression. There is a case report which has described the beneficial effects in an elderly with hyponatremic seizures making him un-suitable for HF-rTMS (Thanki et al., 2020). Moreover, retinal tear with posterior vitreous detachment and hypomania have also been reported in a case report (Philip and Carpenter, 2013). The occurrence of these adverse effects by chance cannot be overlooked, and there is a need to explore further with methodologically sound prospective studies in the future.

Consensus recommendation for clinical application of TMS in depression has recommended that HF-rTMS to be avoided in patients with risk of seizure-like past stroke and dyselectrolytemia making LF-rTMS more suitable for use in elderlies as elderly are prone to develop these conditions more frequently in comparison to adults(McClintock et al., 2018). Therefore, its need of hour to utilize and optimize LF-rTMS in terms of the number of pulses per session, train parameters or its use in combination with other novel paradigms like priming in later-life depression.

Gaps in literature

From the available results of this scoping review, it is clear that there is no level 1 evidence for the use of TMS in later-life depression. There have been one systematic review (Cappon et al., 2022) and one meta-analysis (Valiengo et al., 2022) as well as multicentric RCTs related to use of TMS in later-life depression.

However, the systematic review included bipolar depression also, making the patient population heterogenous. The meta-analysis included studies with a wider age range and comparison group including the younger adult population, again making the patient population heterogenous. These issues were taken care of in this current scoping review by excluding studies with bipolar depression

patients and age specified as 50 years and above.

There are sparse methodologically sound individual RCTs on TMS use in later-life depression, and available RCTs have not been replicated. The available RCTs with relatively good sample sizes significantly vary in terms of their stimulus parameters, number of sessions, and the combination of therapies. Therefore, they lack consistent findings in intervention and outcomes. Maximum studies have used High-frequency rTMS over left DLPFC comparing it with sham, which is found to be beneficial. However, only one study has compared two different protocols of unilateral and bilateral rTMS (Trevizol et al., 2019)along with medical comorbidities and polypharmacy. Together with the limited data on managing treatment-resistant depression in older adults, there is a need for investigating the efficacy of non-pharmacological treatment strategies. Repetitive transcranial magnetic stimulation (rTMS. Small sample sizes again limited the generalisability of findings.

Moreover, long-term follow-up studies are significantly lacking in the literature. Occurrence of rare but serious side effects like retinal tear and posterior vitreous detachment warrants clinicians to monitor closely the visual complaints, if any, during the course of treatment with TMS, especially in older people. Furthermore, the available data on TMS in later-life depression is not enough to estimate the number needed to treat (NNT) and number needed to harm (NNH) as of now.

RECOMMENDATIONS

Based on the review and analysis of the findings, the following recommendations are made:

1. There is a need for an exclusive systematic review and meta-analysis of RCTs alone on the use of TMS in later-life depression, excluding bipolarity which can yield NNT and NNH. The age group of 60 years and above is recommended as the majority of studies have defined 60 years and above as later life. Although we included even single case reports for the purpose of being comprehensive, including only RCTs for the meta-analysis will help in strengthening the evidence base

2. There is scope for systematically assessing predictors of the response to TMS, which can have high translational value.

3. Comparing the different types of protocols, unilateral versus bilateral or low frequency versus high-frequency rTMS, can also yield results that are translatable to therapeutics. The protocol with relative superiority can be used for assessing the efficacy through large multi-centric RCTs as well as long-term follow-up studies that can help build the existing evidence base.

4. The side effect profile of TMS in older people seems to be varying to some extent which opens avenues for developing a separate TMS side effect checklist for older people.

STRENGTH AND LIMITATIONS

For the purpose of this review, we have followed a systematic protocol to search for the studies and were able to elicit gaps in the literature regarding effectiveness, safety profile and tolerability of TMS in later-life depression. We have included articles published in English only. We did not search the grey literature, which include unpublished studies, theses and conference presentations. This review shows a considerable increase in the number of studies relevant to the topic in the last few years.

As the literature is constantly increasing, an exclusive systematic review and meta-analysis of RCTs is essential.

CONCLUSIONS

Level I evidence for the use of TMS in later-life depression is mixed and inconclusive. Considering the lack of clarity and inconsistency, there is a need for large multicenter RCTs as well as systematic reviews and meta-analyses of RCTs on the use of TMS in later-life depression, which will help to build the evidence base.

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