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Review

# Repetitive Transcranial Magnetic Stimulation for Major Depressive Disorder in Older Adults: Systematic Review and Meta-analysis

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## Abstract

**Background:** Major depressive disorder (MDD) in older adults is a serious public health concern. Repetitive transcranial magnetic stimulation (rTMS) is a nonpharmacological intervention approved for MDD treatment in adults, but its value in older adults remains unknown. This study aims to systematically review and meta-analyze evidence of rTMS efficacy in MDD treatment among older adults.

**Methods:** We systematically reviewed the literature for randomized controlled trials (RCTs) and open-label studies assessing rTMS for the treatment of MDD in patients older than 50 years, published until June 2020. Random-effects meta-analyses using standardized mean differences (SMDs) were conducted to assess change in depression severity score (primary outcome), while odds ratios (ORs) were used to assess secondary categorical outcomes (response and remission). Additionally, univariate meta-regression analyses were performed to identify potential predictors of change in depression severity scores.

**Results:** Fourteen RCTs were included in meta-analyses and 26 studies (10 RCTs and 16 open-label studies) in meta-regression. Active rTMS was significantly superior to sham treatment for reduction of severity (SMD = 0.36; 95% CI = 0.13–0.60), as well as response (OR = 3.26; 95% CI = 2.11–5.04) and remission (OR = 4.63; 95% CI = 2.24–9.55). Studies were of moderate to high quality, with funnel plots and Egger's regression test not suggestive of publication bias. In meta-regressions, higher mean age and number of sessions were significantly associated with greater improvement.

**Conclusions:** Our results support that rTMS is an effective, safe, and well-tolerated treatment for MDD in older adults and that it should be considered in the treatment of this vulnerable population.

**Keywords:** Brain stimulation, Depression, Meta-analysis, Meta-regression

Major depressive disorder (MDD) is a serious public health concern across all ages, including older adults. Currently, a high proportion of adults older than 55 years old suffer from MDD or clinically significant depressive symptoms, with estimated 1-month prevalence of 2% and 15%, respectively (1). Moreover, the progressive increase in life expectancy predicts higher absolute numbers of patients with

geriatric depression. Unfortunately, older patients frequently suffer from multiple medical comorbidities and are often poly-medicated and thus have a higher risk of pharmacological adverse effects and drug interactions (2). Consequently, treatment is challenging and treatment-resistant depression occurs at an estimated rate of 28.9/100 person-years (3). Furthermore, across several randomized controlled trials (RCTs) assessing the efficacy of pharmacological treatments for MDD among older adults, effect sizes were smaller for older patients, with the number needed to treat increasing with age from 6 in those younger than 55 years old, to 8 in those from 55 to 65 years old, and 21 in those older than 65 years old (4).

Brain stimulation techniques might be an alternative for the treatment of depression among patients who do not respond or do not tolerate first-line pharmacological alternatives (5). Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation technique whereby an alternating magnetic field, generated by a pulsating electric current, is delivered by a coil placed over the patient's scalp, depolarizing the underlying brain tissue (6) and eliciting functional modifications to the cortical tissue (7). The efficacy of rTMS in the treatment of depression has been demonstrated by several original studies and meta-analyses (8,9).

When compared to other pharmacological and nonpharmacological methods, the safety–tolerability profile of rTMS favors its use in older adults: it is better tolerated when compared to electroconvulsive therapy (ECT) (8) and usually offers fewer side effects than medication. Headache is the most common complaint and seizure the most serious adverse event, albeit very rare (10). Moreover, the method is clearly free from the risk of drug interactions, which is an issue with the use of psychoactive medications in older adults. Finally, contrary to ECT, there are no reports that rTMS might negatively interfere with cognitive function and, rather, there is limited evidence that rTMS may actually have cognitive-enhancing properties (11). However, there have been few trials and no meta-analyses designed to assess the efficacy of rTMS in geriatric depression (12–14). Thus, the aim of this study was to systematically review and analyze the available evidence concerning rTMS efficacy in MDD treatment among older adults.

## Material and Methods

The study methodology was designed according to Cochrane recommendations (15) and PRISMA guidelines (16) and published a priori in a written protocol in the Prospero Platform (registration number PROSPERO: 2017 CRD42017079619).

### Search Strategy

We systematically reviewed the literature in order to identify trials evaluating rTMS efficacy in the treatment of MDD among patients older than 50 years old. Studies were identified through electronic searches in MEDLINE, Web of Science, The Cochrane Library, and Embase databases. We searched from the first RCT of rTMS for depression, published on July 27, 1996 (17) until June 11, 2020, using the following syntax: ("Transcranial stimulation" OR "TMS" OR "Transcranial Magnetic Stimulation" OR "non-invasive brain stimulation" OR "NIBS") AND ("depressive disorder" OR "depression" OR "depressive episode") AND ("elderly" OR "old age" OR "geriatric" OR "late-life"). The resulting studies were independently selected by 2 authors (A.M. and G.C.) in sequential phases of title, abstract, and full-text review, with consensus lists of selected articles at the end of each step. Disagreements were solved by a third researcher (L.V.). For the original studies that were included and reviews, we further inspected the reference lists for additional eligible studies. It was not necessary to contact study authors to assess study eligibility.

### Selection Criteria

We included RCTs and open-label studies assessing rTMS for the treatment of MDD in patients older than 50 years old. MDD was considered as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-III or later) or its equivalent in the International Classification of Diseases. Studies including patients with a wider age range were only considered if it was possible to extract data for patients older than 50 years old from the published manuscript. Articles in English, Mandarin Chinese, Spanish, French, or Portuguese were considered. Studies were excluded if they did not provide efficacy data regarding depression severity scores (mean and standard deviation [SD] or standard error [SE]) nor data regarding response and remission rates. Case reports or case series with less than 3 individuals were also excluded.

### Data Extraction

Data were extracted independently by 2 authors (A.M. and L.V. or G.C.) using the text, tables, and/or figures, and discrepancies were solved through consensus. When necessary, a third researcher was consulted (G.C. or L.V.). The following variables were extracted: (a) metadata (authorship, publication date); (b) demographics (sample size, age, sex); (c) depression characteristics (scales, interviews, and checklists used for depression diagnosis and severity assessment, depression scores at baseline and after intervention, age of onset, episode duration, use of antidepressants, use of ECT, refractoriness); (d) rTMS protocol characteristics (angle and size of the coil, treatment intensity according to % of motor threshold [MT], frequency, interval between trains, number of sessions, trains and pulses, stimulation location, treatment method, ie, add-on or monotherapy); (e) study methodology (study type, randomization protocol, sham method, blinding assessment, number of dropouts). Whenever studies did not specifically report the number of participants who did not complete the protocol, dropouts were assumed to be zero. The quality of each RCT was independently assessed by 2 authors (A.M. and L.V. or G.C.) using the Physiotherapy Evidence Database (PEDro) scale (18).

The primary outcome was defined as the change in depression severity scores after rTMS or sham treatment (continuous outcome) and secondary outcomes were defined as response or remission rates (categorical outcomes). Whenever available, Hamilton Depression Rating Scale (HDRS) was chosen as the reference for all outcomes. If measures were reported at more than one time point after treatment, the primary endpoint was considered to be the first measure after the end of rTMS or sham induction treatment. Most studies did not report a change in severity scores after treatment, but rather severity data for pre- and posttreatment. Thus, mean severity change was calculated as the difference between mean pre- and posttreatment severity, and SD was calculated using the following formula:

$$S_{\text{diff}} = \sqrt{(s1^2 + s2^2 - 2 \times r \times s1 \times s2)}$$

where $s1$ stands for pretreatment SD and $s2$ for posttreatment SD. When it was not reported, the $r$ coefficient was assumed to be 0.5, according to previous reports (19).

### Statistical Analysis

Analyses were performed using StataCorp. 2017 (Stata Statistical Software: Release 15; StataCorp LP, College Station, TX), Review Manager Version 5.3, and Comprehensive Meta-analysis Version 3. Meta-analyses were conducted using controlled studies only. For the primary outcome, the mean change of depression severity from baseline was compared between the active treatment and the control intervention groups, considering the respective SDs and group sample sizes. Hedges' *g* was used as a measure of effect size for the primary outcome, while for the secondary outcomes, odds ratio (OR) was used. Due to considerable heterogeneity in study methodology, namely differences in HDRS versions and heterogeneous populations characteristics, the random-effects model of DerSimonian and Laird (20) was used to calculate standardized mean differences (SMDs; for the primary outcome) or pooled OR (for secondary outcomes), with pooled SD and 95% confidence intervals (95% CIs), weighted by sample size. Heterogeneity was evaluated with the $I^2$ (greater than 30% considered for heterogeneity) and the $\chi^2$ test ($p < .10$ considered for heterogeneity) (15), while inspection of funnel plots and Egger's regression tests were used for assessment of publication bias.

To assess the impact of individual studies on each meta-analysis, sensitivity analyses were performed by manually excluding each of the included studies. Further sensitivity analyses were conducted to test the effect of excluding studies with younger participants (mean age younger than 60 years old), with less severe baseline depression severity (mean score less than 40% of maximum scale score), late posttreatment assessment of depression severity (1 week or more after finishing rTMS), with TMS used as an add-on treatment, with low stimulation intensity (less than 100% MT), low stimulation frequency (no more than 5 Hz), low number of sessions (10 sessions or less), and low number of pulses per session (less than 1 200), including right-sided rTMS stimulation (right or bilateral dorsolateral prefrontal cortex [DLPFC] stimulation) or with low study quality (PEDro score less than 5). Sensitivity analyses according to resistance to treatment were not possible to perform due to high heterogeneity in the definition of treatment-resistance levels. To avoid excessive loss of statistical power, sensitivity analyses were only performed when at least two thirds of studies in the original analyses were available for analysis, as defined a priori.

The active arms of controlled studies were analyzed jointly with open-label, noncontrolled studies, in univariate meta-regression analyses, to identify variables that could be associated with the change in depression severity scores among those treated with active rTMS. Difference between baseline and posttreatment HDRS was used to calculate SMD and Hedges' *g*. Only variables with a minimum of 10 studies available were explored. The following continuous variables were tested as potential predictors: mean age, percentage of females, baseline severity score (% of total), age of onset (years), and episode duration (months). Due to their nature and/or distribution, other variables were tested as discrete predictors: rTMS treatment intensity (less than 100% MT vs 100% MT or more), rTMS treatment frequency (10 Hz or less vs more than 10 Hz), number of treatment sessions (less than 15 vs 15 or more), number of stimulation trains per session (less than 20 vs 20 or more), interval between stimulation trains (30 seconds or less vs more than 30 seconds), and total number of pulses per session (1 250 or less vs more than 1 250). Discrete variables were binarized according to their median value. Again, resistance to treatment was not tested as a potential predictor due to heterogeneity in the definition of treatment-resistance levels. When appropriate, and if at least 20 studies were available, bivariate meta-regression analyses were performed to explore potential confounders for univariate analyses.

## Results

### Search Results

After excluding duplicates, a total of 876 articles were found, 749 retrieved from literature search and 127 additional articles from reference screening. Of these, 839 articles were excluded as per predefined criteria, resulting in 37 articles eligible for inclusion in our systematic review, 17 RCT (13,14,21–35) and 20 open-label clinical trials (36–55) (Figure 1).

### Studies Synthesis

From the 37 studies, a total of 1 028 patients received active or sham TMS (728 and 300, respectively) at baseline. Of those, 43 patients did not complete treatment (3.9% of those receiving active rTMS and 5% in sham arms of RCTs). At baseline, 555 were female (54.9%) and the mean age was 63.5 (*SD* 5.6) years. Most studies assessed depression severity using a version of the HDRS, with the exception of 3 studies that used the Montgomery–Asberg Depression Rating Scale (50,54,55), one that used Beck Depression Inventory (52), and one that used the Inventory of Depressive Symptomatology Self Report (38).

Considering only the 17 RCTs, there were 633 patients at baseline (333 in the active and 300 in the sham groups), 598 of whom completed treatment (313 in the active and 285 in the sham groups). At baseline, 50.9% were female, and the mean age across studies was 60.4 (*SD* 4.96) years (Supplementary Table 1). With the exception of 2 studies (23,34), all RCTs were of moderate to high quality, scoring 7 or more on the PEDro scale, with an average total PEDro score of 7.7 (*SD* 1.6) across all studies (Supplementary Table 2). Regarding

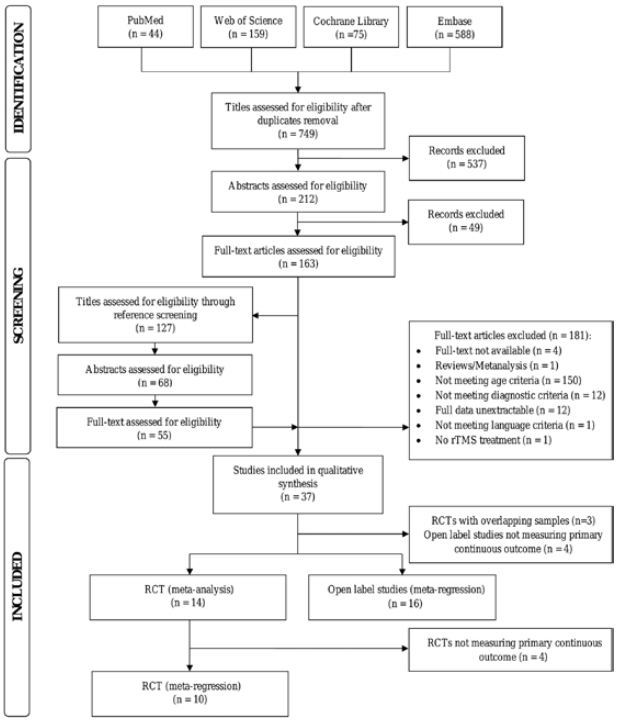


**Figure 1.** PRISMA flow diagram for study selection. RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation.

the 20 open-label studies, there were 395 patients at baseline, 387 of whom completed treatment. At baseline, 59.3% were female, and the mean age was 65.04 (*SD* 5.43) years (Supplementary Table 3). Most trials did not systematically report comorbid medical conditions, cognitive impairment, or psychotic symptoms. The majority of studies, both RCTs and open-label, tested high-frequency and high-intensity rTMS delivered with a figure-of-eight coil to the left dorsolateral prefrontal cortex, but there was significant variability in the protocols tested (Supplementary Tables 4 and 5). The effects of treatment on mean depression severity and rates of response and remission, presented in Tables 1 and 2, are fully analyzed in the meta-analysis and meta-regression sections.

### Meta-analysis

While 17 RCTs were identified (13,14,21–35), not all were included in meta-analyses. Tenev et al. (34) performed a follow-up to Jorge et al. (28) and was thus excluded. Similarly, because Goldberger et al. (26) and Trevizol et al. (35) performed a subanalysis of older patients included in the work of Blumberger et al. (24), only the study of Goldberger et al. was included. In both cases, those excluded from the meta-analysis were the studies with less available data. Whenever appropriate and possible, studies were also divided for analysis purposes. Because Goldberger et al. evaluated 2 different stimulation locations, bilateral and unilateral, it was divided into Goldberger BL and Goldberger UL, respectively, compared to the same sham rTMS group. Similarly, Jorge et al. (28) included 2 substudies testing different protocols (1 200 pulses per treatment session across 10 treatment days, or 1 800 pulses per treatment session across 15 treatment days) and they were divided into Jorge 1 and Jorge 2, respectively, each with a distinct sham rTMS group.

Regarding the meta-analysis of the primary outcome, we found an overall effect size of 0.36 (95% CI = 0.13–0.6) across the 10 studies reporting these data, demonstrating a statistically significant improvement in HDRS with active rTMS when compared to sham. Secondary categorical outcomes were also statistically significant, favoring active rTMS for both response rates in 13 studies (active group: 28.13 ± 24.34%, sham group: 11.67 ± 18.35, mean ± *SD*; OR = 3.26, 95% CI = 2.11–5.04) and remission rates in 7 studies (active group: 24.29 ± 22.99, sham group: 6.25 ± 11.57, mean ± *SD*; OR = 4.63, 95% CI = 2.24–9.55; Figure 2). Heterogeneity was not significant for any of these meta-analyses (HDRS change: $I^2$ = 28%, $p$ = .17; response: $I^2$ = 0%, $p$ = .6; remission: $I^2$ = 0%, $p$ = .73). Analysis of funnel plots revealed a symmetrical distribution, and the Egger's tests were not significant ($p$s > .31), which is not suggestive of publication bias (Supplementary Figure 1). In a meta-analysis of dropout rates, these were similar between sham and active groups across all studies (OR = 1.06; 95% CI = 0.25–4.52), with only 2 studies reporting total dropouts rates higher than 10%, balanced between active and sham groups (24,31) (Supplementary Figure 2). For this meta-analysis, there was also no evidence of publication bias ($p$ = .17, Egger's test). Severe adverse effects were not reported in any of the included studies.

Regarding sensitivity analyses, removing individual trials did not suggest that any study was responsible for the observed results. Excluding studies with younger participants, less severe baseline depression severity, late posttreatment assessment of depression severity, low rTMS stimulation intensity, low rTMS stimulation frequency, low number of rTMS sessions, including right-sided rTMS stimulation, or with low study quality did not affect statistical significance for the primary and both of the secondary outcomes. Only when excluding studies with a low number of pulses per session (less than 1 200) did the meta-analysis for the primary outcome lose significance, albeit only at a borderline level (Supplementary Table 6).

### Meta-regression

For univariate meta-regression analyses, assessing the association of covariates with the primary outcome, we considered data from the active arm of each RCT as well as from open-label trials, including a total of 10 RCTs and 16 open-label studies where primary outcome was reported. We found that mean age ($p$ = .02) and total number of sessions ($p$ = .003), but not any of the remaining variables, were significantly associated with improvement in depression severity scores (Table 3). These findings were maintained after exclusion of the work of Pallanti et al. (49), an open-label study that, contrary to the remaining studies, targeted the right, rather than the left, DLPFC.

Because age has been associated with a decreased, rather than increased, response to rTMS (56), we further explored this finding performing bivariate meta-regression analyses, to identify potential confounders of the effect of age. The statistically significant effect of age was lost in all bivariate analyses, namely those with sex, baseline depression severity, intensity, frequency, number of pulses or trains per session, and interval between trains and number of sessions. However, in these bivariate analyses, the variable number of sessions retained significance ($p$ = .01), with a significant interaction factor ($p$ = .01; Supplementary Table 7). To further explore potential confounders of the effects of age, we divided studies into 2 groups according to the mean age of study participants, defined according to the median split of mean age per study (65.15 years old). We then compared the remaining covariates between the 2 groups and found a significant difference in the mean number of sessions (26.7% performing ≥15 sessions for studies with younger patients vs 80% for studies with older patients; $p$ = .003, Pearson chi-square), but not for any of the remaining covariates.

## Discussion

In this systematic review and meta-analysis, we found that, among older adult patients, rTMS has efficacy in the treatment of major depression, as shown by significantly more symptom reduction, as well as higher response and remission rates, when comparing active to sham treatment. Importantly, analyses of funnel plots and the Egger's regression interception test were not suggestive of publication bias. Additionally, none of the studies reported severe side effects of treatment, with an overall low dropout rate (4.2%), that did not differ between sham and active treatment groups, indicating high acceptability of rTMS in this population. While several studies have suggested that rTMS is less effective in older patients (56), others have considered that age cannot be considered a consistent predictor of rTMS antidepressant effect in adult samples (57). To the best of our knowledge, this is the first meta-analysis of rTMS efficacy in old-age depression, with results that support the efficacy and tolerability of rTMS in older depressed patients. Efficacy and tolerability of rTMS were previously described for the general adult population in previous trials (58) as well as meta-analyses (5,59).

While our main conclusion was consistent across different efficacy outcomes, revealing the robustness of our findings, several factors may contribute toward the differential antidepressant effect of rTMS among older depressed patients. We initially used sensitivity analyses of our meta-analysis results to address this question and

**Table 1.** Clinical Outcomes of Randomized Controlled Trials

| Study | Age (years) Mean (*SD*) Active \| Sham | HDRS Version | Baseline Depression Severity Mean (*SD*) Score Active | Baseline Depression Severity Mean (*SD*) Score Sham | Final Depression Severity Mean (*SD*) Score Active | Final Depression Severity Mean (*SD*) Score Sham | Response % Patients Active | Response % Patients Sham | Remission % Patients Active | Remission % Patients Sham | Dropouts *N* Patients Active | Dropouts *N* Patients Sham |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baeken (2013) | 57.6 (4.28) \| 56.4 (6.0) | HDRS-17 | 26.9 (9.0) | 28.3 (10.1) | 21.33 (9.0) | 25.6 (11.1) | 16.7 | 14.3 | — | — | 1 | 0 |
| Berman (2000) | 55.3 (6.7) \| 56 (8.4) | HDRS-25 | 34.7 (12.2) | 34.5 (12.0) | 15.7 (9.6) | 46.5 (2.1) | 33.3 | 0 | — | — | 0 | 0 |
| Blumberger (2011)—UL[†1] | — | HDRS-17 | — | — | — | — | — | — | 0 | 25 | 1 | 1 |
| Blumberger (2011)—BL[*,†1] | — | HDRS-17 | — | — | — | — | — | — | 66.7 | 25 | 2 | 1 |
| Blumberger (2017) | — | HDRS-24 | — | — | — | — | — | — | 40 | 14.8 | 0 | 0 |
| Boutros (2002) | 55 (5.2) \| 55.7 (4.8) | HDRS-25 | 40.3 (11.8) | 35.5 (4.9) | 27.5 (17.2) | 26 (16.3) | 66.7 | 40 | — | — | 0 | 1 |
| Goldberger (2016)—UL[†1] | 66.1 (8.5) \| 64.1 (3.7) | HDRS-17 | 26.5 (3.4) | 24.5 (3.5) | 22 (ER) | 17.8 (5.9) | 0 | 16.7 | 0 | 0 | 0 | 0 |
| Goldberger (2016)—BL[*,†1] | 66.8 (5.8) \| 64.1 (3.7) | HDRS-17 | 24.6 (4.2) | 24.5 (3.5) | 14.1 (9.3) | 17.8 (5.9) | 45 | 16.7 | 40 | 0 | 0 | 0 |
| Herwig (2003) | 54.2 (3.6) \| 57.3 (2.2) | HDRS-21 | — | — | — | — | 50 | 0 | — | — | 0 | 0 |
| Jorge (2008)—1 | 62.9 (7.2) \| 62.1 (8.5 | HDRS-17 | 19.5 (5.8) | 19.9 (5.4) | 15.6 (-) | 15.7 (-) | 33.3 | 6.7 | 13.3 | 6.7 | 0 | 0 |
| Jorge (2008)—2[†2] | 64.3 (9.4) \| 66.1 (11) | HDRS-17 | 18.4 (3.4) | 17.6 (5.6) | 11.4 (-) | 14.8 (-) | 39.4 | 6.9 | 27.3 | 3.4 | 0 | 0 |
| Kaster (2018) | 65 (5.5) \| 65.4 (5.5) | HDRS-24 | 25.8 (4.0) | 27.6 (4.1) | 14.8 (3) | 17.6 (3) | 55 | 18.5 | 50 | 14.8 | 5 | 0 |
| Kristic (2014) | 57.7 (2.0) \| 55 (2.8) | HDRS-24 | — | — | — | — | 33.3 | 0 | 16.7 | 0 | 0 | 0 |
| Manes (2001) | 60.5 (3.4) \| 60.9 (2) | HDRS | 22.7 (5.2) | 22.7 (7.1) | 13.7 (5.4) | 16.2 (8.5) | 30 | 30 | — | — | 0 | 0 |
| Mosimann (2004) | 62.9 (12.0) \| 64.4 (12.5) | HDRS-21 | — | — | — | — | 0 | 0 | — | — | 0 | 0 |
| Narushima (2010) | 63.4 (8.4) \| 61.5 (8.3) | HDRS-17 | 16.5 (5.0) | 16.8 (6.3) | 11.3 (4.4) | 13 (5.3) | 43.7 | 9.1 | 34.4 | 0 | 11 | 11 |
| Qin (2017) | 70.0 (6.0) \| 69.4 (6.0) | HDRS-24 | 33.8 (5.2) | 33.5 (6.7) | 18.8 (5.7) | 22.3 (5.6) | 79.5 | 53.1 | — | — | 2 | 0 |
| Tenev (2009)[†2] | 64.5 (8.9) \| 63.3 (8.6) | HDRS-17 | 18.7 (2.9) | 17.6 (4.6) | — | — | 39.4 | 6.9 | — | — | 0 | 0 |
| Trevizol (2019)—UL[†1] | 66.1 (8.5) \| 64.1 (3.7) | HDRS-17 | — | — | — | — | 0 | 16.7 | 0 | 0 | 2 | 1 |
| Trevizol (2019)—BL[*,†1] | 66.8 (5.8) \| 64.1 (3.7) | HDRS-17 | — | — | — | — | 45 | 16.7 | 40 | 0 | 1 | 1 |
| Xie (2015) | 65.3 (5.1) \| 64.7 (4.2) | HDRS-17 | 21.1 (2.9) | 20.6 (2.6) | 14.6 (3.2) | 14.4 (3.1) | 17.1 | 15.4 | 2.8 | 3.8 | 1 | 3 |

*Note:* BL = bilateral; ER = error; HDRS = Hamilton Depression Rating Scale; SD = standard deviation; UL = unilateral.

*The sham group is the same as in UL.

[†]Overlapping samples: (1) Goldberger et al. and Trevizol et al. performed a subanalysis of older patients included in the work of Blumberger et al. and (2) Tenev et al. performed a follow-up to the work of Jorge et al.

**Table 2.** Clinical Outcomes of Open-Label Studies

| Study | Age (years) Mean (*SD*) | HDRS Version | Baseline Depression Severity Mean (*SD*) Score | Final Depression Severity Mean (*SD*) Score | Response % Patients | Remission % Patients | Dropouts *N* Patients |
|---|---|---|---|---|---|---|---|
| Charnsil (2012) | 56.4 (2.41) | HDRS-17 | 13.2 (1.3) | 7.2 (2.49) | — | 40 | 0 |
| Ciobanu (2013) | 74.5 (6) | HDRS-21 | 18.47 (1.96) | 9.13 (2.9) | 46.7 | — | 0 |
| Conelea (2017) | 66 (5.5) | IDS-SR | 45.1 (10.7) | 26.7 (14.7) | 45.3 | 26.7 | 0 |
| Cristancho (2019) | 66.4 (3) | MADRS | 27.72 (8.21) | 15.91 (10.05) | 36.4 | 36.4 | 1 |
| Dardenne (2018) | 73.9 (5.7) | HDRS-17 | 22.6 (4.1) | 12 (9.11) | 40 | 20 | 0 |
| Fabre (2004) | 67.9 (6.7) | HDRS-17 | 24.3 (6.3) | 19.26 (8.4) | 45.5 | — | 0 |
| Garcia-Toro (2006) | 65.17 (7.39) | HDRS-21 | — | — | 16.7 | — | 0 |
| George (1997) | 57.33 (5.86) | HDRS-21 | 28 (1) | 23.33 (4.04) | — | — | 0 |
| Godfrey (2020) | — | MADRS | — | — | 50 | — | 0 |
| Grunhaus (2002) | — | HDRS-17 | — | — | 41.2 | — | 0 |
| Januel (2004) | 67 (9.64) | HDRS | 23.67 (1.52) | 7.33 (2.3) | — | — | 0 |
| Motttaghy (2002) | 56.43 (6.55) | HDRS-28 | 34.14 (5.37) | 27.71 (11.09) | 14.3 | — | 0 |
| Nadeau (2002) | 66 (7.55) | HDRS-24 | 22 (9.54) | 20.67 (6.11) | 100 | — | 1 |
| Padberg (1999)—fast | 69.2 (8.17) | HDRS-21 | 31 (10.34) | 28.85 (10.45) | — | — | 0 |
| Padberg (1999)—slow | 58.33 (2.52) | HDRS-21 | 24.67 (9.45) | 21 (6.24) | — | — | 0 |
| Padberg (2002)—100% MT | 52.1 (4.6) | HDRS-21 | 23.6 (1.9) | 16.71 (2.45) | 30 | 20 | 0 |
| Padberg (2002)—90% MT | 60.3 (4.1) | HDRS-21 | 21.9 (1.8) | 19.1 (2.8) | 20 | 10 | 0 |
| Pallanti (2012) | 67.22 (4.22) | HDRS | 24.8 (5.2) | 12.75 (5.53) | 47.2 | — | 0 |
| Pridmore (1999) | 68.89 (7.37) | MADRS | 41.78 (7.61) | 25.89 (15.73) | 55.6 | 55.6 | 0 |
| Sayar (2013) | 66.57 (5.77) | HDRS-17 | 21.94 (5.12) | 11.28 (4.56) | 58.5 | 29.2 | 5 |
| Tendler (2017) | 59.25 (6.24) | BDI | 25.75 (9.91) | 19 (16.09) | 33.3 | 33.3 | 1 |
| Zhang (2019) | 72 (-) | HDRS-17 | — | — | 77 | 36 | 0 |

*Note:* BDI = Beck Depression Inventory; HDRS = Hamilton Depression Rating Scale; IDS-SR = Inventory of Depressive Symptomatology Self Report; MADRS = Montgomery–Asberg Depression Rating Scale; MT = motor threshold; SD = standard deviation.

did not find an individual study or specific variable that significantly influenced the results. However, not all sensitivity analyses were possible, due to excessive loss of statistical power (ie, when less than two thirds of the original studies remained for the sensitivity analysis) in several cases. In any case, it is important to note that, when excluding trials with the youngest mean patient age, results maintained statistical significance, suggesting that studies with younger patients are not responsible for the overall effects of the meta-analyses.

To more adequately explore potential predictors of clinical response of rTMS among older individuals, we performed univariate meta-regression analyses, revealing that increased age and increased number of sessions were associated with greater clinical improvement. As mentioned above, age has previously been argued to be a negative predictor of clinical improvement (56). In an article assessing the impact of age in response to rTMS treatment, Pallanti et al. suggested that the association between age and antidepressant response could be explained by issues concerning the presence of prefrontal cortical atrophy, age-related alterations in neuroplasticity, or a combination of both. Concerning neuroplasticity, previous studies demonstrated that a greater prefrontal skull–cortex distance predicts a worse response to rTMS treatment (60), supporting proposals for higher stimulation intensities to stimulate the cortex in older patients (12). Regarding the latter, evidence suggests that decreased neural plasticity is associated with changes of neurotrophic factors, Brain-Derived Neurotrophic Factor, in particular, could have an important role in depression pathophysiology (61). Furthermore, enhancement of neurotrophic factor signaling has been associated with antidepressant response not only after medication (62), but also following rTMS (63). Older individuals have been shown to have less neural plasticity (64), which could further contribute toward altered responses to rTMS, and the age-related decline in clinical antidepressant response proposed previously. However, in a meta-analysis assessing TMS to treat MDD in the general adult population, Allan et al. (57) did not find an association between age and clinical response. On the other hand, our results suggest that, among older adults, higher age could actually predict a better, rather than worse, response to treatment. For the remaining variables tested as potential predictors of rTMS response, meta-regression analyses were not significant. Some of these variables have been identified as predictors of response in previous rTMS studies, such as sex or treatment resistance (56,65,66). We hypothesize that our meta-regression may be underpowered for at least some of these variables, a common limitation in such analyses (67).

In analyses to identify potential confounders of the association between age and treatment response, we found that the impact of age on clinical improvement was dependent on studies with older patients also applying a higher number of sessions. Findings regarding the number of sessions are consistent with a meta-analysis for the general adult population, including 30 RCTs and more than 1 700 patients, where the mean effect size for rTMS was found to be higher with more treatment sessions (68). These findings are supportive across adult patients with major depression, including older patients, rTMS treatments should be delivered for a sufficient number of days prior to assessments and decisions regarding efficacy. Importantly, this is consistent with the most recent Canadian Network for Mood and Anxiety Treatments guidelines for the treatment of major depression, recommending a minimum of 20 rTMS sessions (69).

We believe our study has important implications for clinical practice regarding rTMS for the treatment of depression. As mentioned previously, rTMS has been shown to be an effective and safe treatment strategy in MDD, which is not associated with drug

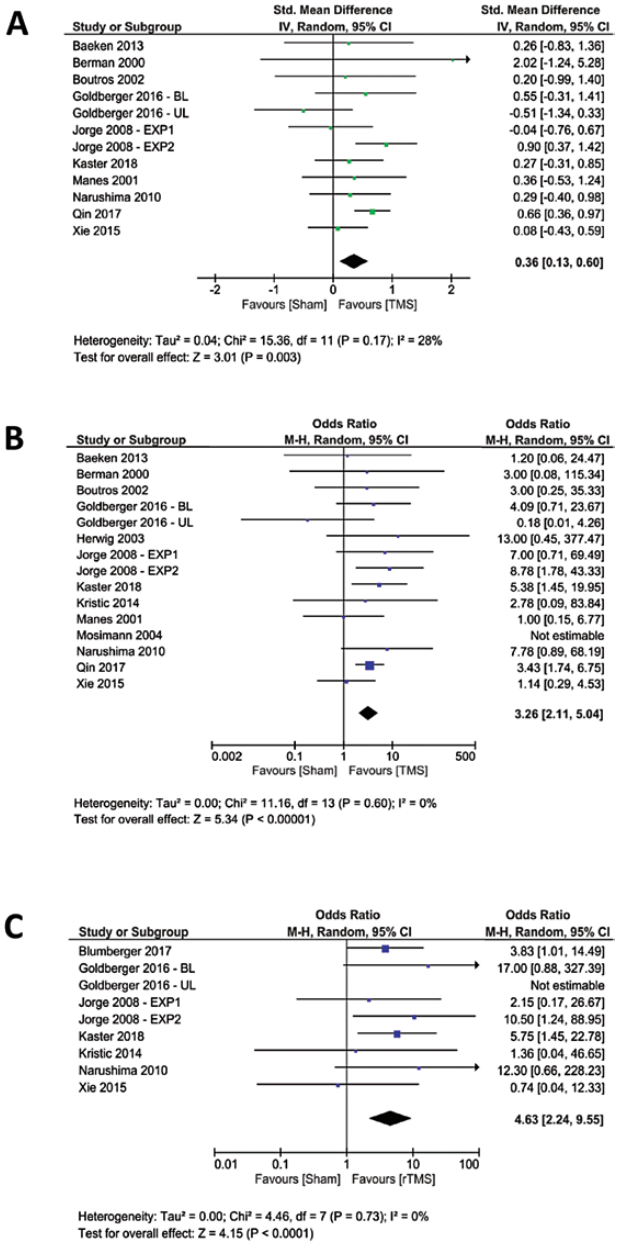


**Figure 2.** Forest plots for primary and secondary outcomes. Forest plots for meta-analyses comparing between active and sham rTMS regarding (A) mean change of depression severity from baseline (primary outcome), (B) response rate, and (C) remission rate (secondary outcomes). BL = bilateral; CI = confidence interval; UL = unilateral.

interactions or severe side effects (5). This treatment modality thus has several potential advantages in vulnerable populations, such as older patients, that have a higher risk of adverse effects from medication, poly-medication, and comorbid conditions (2). Here, we have, for the first time, provided a quantitative summary of the best available evidence regarding the use of rTMS to treat depression in older patients, showing that this is an effective and safe alternative, and should be considered as a valid treatment option for this population. Furthermore, our analyses support that in older adults, the number of treatment sessions is a potential predictor of treatment response, such that any conclusions regarding treatment efficacy or inefficacy should only be considered after a sufficiently long treatment course. It is important to highlight that our results refer to the induction course only, as we have always considered the first outcome measure after the end of acute rTMS cycle. Consequently, our analyses do not inform about long-term or maintenance effect of rTMS in older adults.

Nevertheless, our findings should be interpreted considering the limitations of the study design. First, methodological heterogeneity between studies could affect the robustness of our conclusions. However, this problem was, at least in part, addressed by estimation of effect sizes with a random-effects model that is more conservative and considers heterogeneity. Another limitation was the relatively low number of RCTs ($n$ = 14) and total number of participants ($n$ = 633) included in meta-analyses. While the number of included studies and the robustness of our findings could have been improved with searches of gray literature, findings were nevertheless significant and consistent across the 3 meta-analyses. Furthermore, meta-analyses were consistent with results of one large RCT (32) and robust to exclusion of this study, as well as of several other individual medium-sized trials (23,28,29,31,33,34). Nevertheless, it is important to underline that the effect size for our primary outcome (0.36) is considered to be a medium effect in the context of gerontology research (70). Additionally, the included studies did not use scores assessing subjective clinically meaningful changes, such as the Minimum Clinically Important Difference, which would contribute to determine whether the observed change in HDRS score was associated with clinically significant effects. Notwithstanding, the main limitation resulting from the low number of studies was that reduced statistical power limited the flexibility in conducting sensitivity analyses according to the categorization of several relevant variables. Given this limitation, and to provide additional statistical power in meta-regression, open-label studies were also included in a total of 16 additional trials and 306 additional patients. However, the use of only active treatment groups and open-label studies in meta-regression does not account for the potential contribution of placebo effect, which could confound meta-regression results. Nevertheless, nonexperimental clinical practice also does not distinguish between placebo and active effects, and the results of our meta-regression may thus be useful and relevant for clinical settings, regarding both patient selection and choice of the treatment protocol.

Finally, the mean age across studies of just older than 60 years is relatively low for studies of geriatric populations, potentially limiting the generalizability of findings to older patients. However, in sensitivity analyses for the primary and secondary outcomes, meta-analyses conserved statistical significance when excluding studies with mean participant age younger than 60 years old, supporting generalizability to the geriatric population. Additional sensitivity analyses, removing studies with a mean age younger than 65 years old, were not considered due to the exclusion of a large number of studies, as defined a priori (ie, less than two thirds of studies in the original analyses remained). Furthermore, while none of the included studies defined a maximum age limit among the inclusion criteria, the average age was younger than 75 years in all studies. Among RCTs (Supplementary Table 1), the study with the oldest mean age was the work of Qin et al. (69.7 years old) [32] while for open-label studies (Supplementary Table 3) it was of Ciobanu et al. (74.5 years old) [37]. Thus, generalizability of our results to the oldest of old patients with depression may be limited.

Although approved for the treatment of depression in adults who have not responded to one antidepressant trial, without age restriction, to date there is no specific recommendation regarding rTMS

**Table 3.** Meta-regression Results

| Variables* | Number of Studies | With All Studies | | | Without the Study of Pallanti et al. | | |
|---|---|---|---|---|---|---|---|
| | | Coefficient | *SE* | *p* | Coefficient | *SE* | *p* |
| Age (years) | **30** | **−0.07** | **0.03** | **.02** | **−0.07** | **0.03** | **.03** |
| % Female | 30 | −0.005 | 0.01 | .56 | −0.004 | 0.01 | .58 |
| % Baseline HDRS | 26 | 0.03 | 0.02 | .1 | 0.03 | 0.02 | .1 |
| Age of onset (years) | 10 | 0.01 | 0.02 | .51 | 0.01 | 0.02 | .51 |
| Episode duration (months) | 10 | 0.001 | 0.007 | .94 | 0.001 | 0.01 | .94 |
| Intensity (% motor threshold) | 29 | −0.36 | 0.34 | .28 | −0.32 | 0.35 | .35 |
| Number of sessions | **30** | **−0.83** | **0.28** | **.003** | **−0.8** | **0.29** | **.01** |
| Frequency (Hz) | 26 | 0.15 | 0.39 | .7 | 0.1 | 0.4 | .81 |
| Number of pulses | 23 | 0.15 | 0.43 | .73 | 0.06 | 0.45 | .89 |
| Number of trains | 22 | −0.004 | 0.42 | .99 | −0.24 | 0.44 | .58 |
| Interval between trains | 20 | 0.03 | 0.43 | .95 | −0.07 | 0.52 | .89 |

*Note:* HDRS = Hamilton Depression Rating Scale; SE = standard error. In bold are highlighted the meta-regression results of the variables that were significant at p <.05.
*Age, % female, % baseline Hamilton Depression Rating Scale (HDRS), age of onset, and episode duration are continuous variables, the remaining are binary variables.

use for the treatment of MDD in older people. We believe the results presented here are an important contribution to support the use of rTMS for the treatment of MDD in older adults.

## Conclusions

After reviewing the best available evidence, we have found that rTMS is an effective, safe, and well-tolerated treatment for MDD in older patients and thus should be considered for the treatment of this vulnerable population. Additionally, we found that among older depressed patients, older mean age and a higher number of sessions were associated with greater clinical improvement. In the future, large multicentre clinical trials should be conducted in this field to optimize rTMS in this specific population and understand, among others, the durability of rTMS response, as well as the role of maintenance treatment in prolonging clinical improvement.

## Supplementary Material

Supplementary data are available at The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences online.

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## Conflict of Interest

A.J.O.-M. was the national coordinator for Portugal of a noninterventional study (EDMS-ERI-143085581, 4.0) to characterize a Treatment-Resistant Depression Cohort in Europe, sponsored by Janssen-Cilag, Ltd (2019–2020), is the recipient of a grant from Schuhfried GmBH for norming and validation of cognitive tests, and is the national coordinator for Portugal of trials of psilocybin therapy for treatment-resistant depression, sponsored by Compass Pathways, Ltd (EudraCT number 2017-003288-36 and 2020-001348-25), and of esketamine for treatment-resistant depression, sponsored by Janssen-Cilag, Ltd (EudraCT NUMBER: 2019-002992-33). A.R.B. receives in-kind support from MagVenture and Flow Neuroscience. All the remaining authors have no conflicts of interest to declare.

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