World Journal of Psychiatry

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*World J Psychiatr* 2021 August 19; 11(8): 477-490

DOI: 10.5498/wjp.v11.i8.477

ISSN 2220-3206 (online)

META-ANALYSIS

# Hypomanic/manic switch after transcranial magnetic stimulation in mood disorders: A systematic review and meta-analysis

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**Conflict-of-interest statement:** The authors declare no conflicts of interest.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.



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## Abstract

### *BACKGROUND*

Nowadays there is an increasing use of transcranial magnetic stimulation (TMS) both in neurological and psychiatric fields. After Food and Drug Administration approval of TMS for the therapy of treatment-resistant depression, TMS has been widely used in the context of mood disorders (MD). However, growing reports regarding the possibility of developing hypomanic/manic switch (HMS) have generated concern regarding its use in MDs.

### *AIM*

To investigate the actual risk of developing HMS due to TMS in the treatment of MD.

### *METHODS*

We led our research on PubMed, Scopus and Web of Science on March 22, 2020, in accordance to the PRISMA guidelines for systematic review. Only double blind/single blind studies, written in English and focused on the TMS treatment of MD, were included. A meta-analysis of repetitive TMS protocol studies including HMS was conducted using RevMan 5.4 software. The assessment of Risk of Bias was done using Cochrane risk of bias tool. This protocol was registered on PROSPERO with the CRD42020175811 code.

### *RESULTS*

**Manuscript source:** Invited manuscript

**Specialty type:** Psychiatry

**Country/Territory of origin:** Italy

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**Received:** February 16, 2021
**Peer-review started:** February 16, 2021
**First decision:** March 16, 2021
**Revised:** March 24, 2021
**Accepted:** July 20, 2021
**Article in press:** July 20, 2021
**Published online:** August 19, 2021

**P-Reviewer:** Tajiri K
**S-Editor:** Fan JR
**L-Editor:** Filipodia
**P-Editor:** Guo X

Twenty-five studies were included in our meta-analysis: Twenty-one double blind randomized controlled trials (RCT) and four single blind-RCT (no. of subjects involved in active stimulation = 576; no. of subjects involved in sham protocol = 487). The most frequently treated pathology was major depressive episode/major depressive disorder, followed by resistant depression, bipolar depression and other MD. The majority of the studies used a repetitive TMS protocol, and the left dorsolateral prefrontal cortex was the main target area. Side effects were reported in eight studies and HMS (described as greater energy, insomnia, irritability, anxiety, suicidal attempt) in four studies. When comparing active TMS *vs* sham treatment, the risk of developing HMS was not significantly different between conditions.

*CONCLUSION*

Applying the most usual protocols and the appropriate precautionary measures, TMS seems not to be related to HMS development.

**Key Words:** Hypomanic/manic switch; Transcranial magnetic stimulation; Active *vs* sham comparison; Mood disorders; Adverse event; Safety



**Core Tip:** Transcranial magnetic stimulation (TMS) has been widely used in the context of mood disorders. The purpose of this review/meta-analysis was to examine the risk of developing a hypomanic/manic switch (HMS) during active TMS treatment of mood disorders. Twenty-five double blind/single blind studies were included in the quantitative synthesis. When comparing active TMS *vs* sham treatment, we did not find any significant difference in the risk of developing HMS between conditions. So, we can conclude that, applying the appropriate precautionary measures, TMS seems not to be related to HMS development.

**Citation:** Miuli A, Sepede G, Stigliano G, Mosca A, Di Carlo F, d'Andrea G, Lalli A, Spano MC, Pettorruso M, Martinotti G, di Giannantonio M. Hypomanic/manic switch after transcranial magnetic stimulation in mood disorders: A systematic review and meta-analysis. *World J Psychiatr* 2021; 11(8): 477-490
**URL:** https://www.wjgnet.com/2220-3206/full/v11/i8/477.htm
**DOI:** https://dx.doi.org/10.5498/wjp.v11.i8.477

## INTRODUCTION

Non-invasive brain stimulation is a complex of neuromodulation techniques that have a therapeutic effect by stimulating the nervous system[1]. Transcranial magnetic stimulation (TMS) uses the principle of magnetic induction to modulate the neural circuitry[2]. Some electrical currents pass through a coil to induce repetitive magnetic field pulses that, if applied on the scalp, can stimulate target brain regions depolarizing the underlying neurons[3]. Depending on the stimulation frequency, cortical activity can be inhibited [low frequencies (LF) ≤ 1 Hz] or improved [high frequencies (HF) ≥ 5 Hz][4].

There are different protocols based on the number of pulses administrated (single pulses or paired pulses TMS)[5] or specific intervals between trains [like intermittent theta burst stimulation (TBS)[6], but one of the most used protocol is repetitive TMS (rTMS) where the pulses are applied as repetitive stimulation trains set at a specific frequency[4].

The use of rTMS has found an application in the field of substance[7] and non-substance addiction[8] but also in major psychiatric disorders such as post-traumatic stress disorder, schizophrenia and obsessive–compulsive disorder and in suicide[9-12]. It has also been used in the treatment of bipolar disorder, with good results in the treatment of depressive states and controversial results in mania[13]. In particular, TMS was approved by Food and Drug Administration in 2007 as a therapy for the treatment resistant depression (TRD)[14]. The standard protocol used in the treatment

of depression provides 75 trains *per* session for a total of 3000 pulses over about 35 min generated at 120% of resting motor threshold at 10 Hz, train duration of 4 s[14,15].

The role of the left dorsolateral prefrontal cortex (LDLPFC) in the pathophysiology of depression has been widely demonstrated with numerous evidences from functional imaging[16]. TMS, stimulating the DLPFC, is able to increase the neuronal excitability and to induce growth of the new connections having an antidepressant effect[17], both as a single treatment and as an add-on to antidepressants[18]. Some evidence, in fact, suggests that it may increase or decrease the neural excitability producing lasting changes in the efficiency of the synaptic transmission known as long-term potentiation and long-term depression[3,19].

When provided within recommended guidelines[20], rTMS is a very safe and well-tolerated technique both in the elderly[21] and in children[22] and has shown a favorable profile compared to antidepressant medications[23,24].

The most common side effects of TMS are headache, neck pain and local pain during the treatment at the site of stimulation[25]. The serious side effects are typically uncommon: Those reported were seizures, noted in less than 1% of healthy subjects and in patients with neurological morbidities and/or epilepsy[20,26], and hearing impairment, preventable with adequate protection[27]. Another potential side effect of TMS is the development of hypomanic/manic switch (HMS)[24,28].

HMS is one of the most critical events in bipolar disorder, affecting the severity of illness and being associated with an increased risk of suicide[29]. It can be linked to antidepressant treatments, and therefore antidepressants should be associated with mood stabilizers in bipolar patients[30]. Following the Diagnostic and Statistical Manual of Mental Disorders-5 criteria, hypomanic symptoms subsiding after stopping the antidepressants are called "antidepressant-induced hypomania", otherwise the episode can be defined as a true HMS[31,32].

During TMS treatment, cases of HMS were described in some reports[33,34], but to date the risk of TMS-induced HMS has not been yet extensively reported.

The purpose of this study was therefore to examine the actual risk of developing HMS due to TMS in the treatment of mood disorders, providing both qualitative and quantitative synthesis.

## MATERIALS AND METHODS

The statistical methods of this study were reviewed by Gianna Sepede (GSe), who has qualified experience in Biomedical Statistics, Systematic Reviews and Meta-analysis.

Our systematic review was conducted to study the risk of developing HMS in a population of patients with mood disorders. We led our research on PubMed, Scopus and Web of Science (WoS) on March 22, 2020 using the following search strategy: (1) PubMed: (TMS OR Transcranial Magnetic Stimulation) AND (side effect OR adverse event) AND (depression OR manic OR bipolar OR hypomanic OR switch) NOT review NOT (animal OR rat OR mouse); (2) Scopus: [TITLE-ABS-KEY (tms) OR TITLE-ABS-KEY (transcranial AND magnetic AND stimulation) AND TITLE-ABS-KEY (side AND effect) OR TITLE-ABS-KEY (adverse AND event) AND TITLE-ABS-KEY (depression) OR TITLE-ABS-KEY (manic) OR TITLE-ABS-KEY (bipolar) OR TITLE-ABS-KEY (hypomanic) OR TITLE-ABS-KEY (switch) AND NOT TITLE-ABS-KEY (review) AND NOT TITLE-ABS-KEY (animal) OR TITLE-ABS-KEY (rat) OR TITLE-ABS-KEY (mouse)]; and (3) WoS: [(TMS OR Transcranial Magnetic Stimulation) AND (side effect OR adverse event) AND (depression OR manic OR bipolar OR hypomanic OR switch) NOT review NOT (animal OR rat OR mouse)]

All the procedures are in accordance with the PRISMA guidelines for systematic review[35]. Exclusion criteria, both for the first and the second phase of the screening, were: (1) Non-original research (*e.g.*, review, commentary, editorial, book chapter); (2) Non full-text article (*e.g.*, meeting abstract); (3) Language other than English; (4) Animal/*in vitro* studies; (5) Non double blind randomized controlled trial (DB-RCT) or single blind-RCT (SB-RCT) design; (6) Use of other neuromodulation techniques (*e.g.*, tDCS, MST); (7) Treatment of other conditions unrelated to mood disorders and (8) Data not reported.

We found 702 articles (PubMed = 80; Scopus = 338; WoS = 284). After removing the duplicates (No = 239), we screened 463 records and, of all these, 80 were non-original articles (review, meta-analysis, commentary, letter to the editor without data available), 267 were not related to the focus of the review (animal/*in vitro* studies, no DB-RCT or SB-RCT design, open label study, no sham comparison, no mood disorder treated, no TMS treatment), and 23 were not written in English. Out of 93 articles

assessed for eligibility, 46 were case report/series, 19 were not relevant to the subject (no DB-RCT or SB-RCT design, open label study, no sham comparison, no mood disorder treated, no TMS treatment) and three articles were not available. Twenty-five articles, finally, were taken into consideration for qualitative synthesis.

The process was conducted individually by AM, GS and Amo, creating an Excel database. For doubtful cases, the eligibility was discussed with GM, MP or MdG. These research methods were approved by PROSPERO (CRD42020175811 identification code). The method is summarized in Figure 1.

### Risk of bias

The assessment of risk of bias was measured independently by AM, GS and AMo using the Cochrane risk of bias tool (Figure 2)[36]. This result was discussed with GSe and evaluated by MP, GM and MdG.

### Quantitative analysis

The main outcome was to calculate the risk of developing HMS with TMS therapy in a population with mood disorders, so an active *vs* sham treatment comparison was conducted. The meta-analysis was performed using Review Manager Software v 5.4 [37]. Provided that HMS is an uncommon side effect and in order to include the studies with an event frequency of zero, a risk difference (RD) and not a risk ratio was applied[38,39].

The RD of the HSM for each individual article was calculated and, therefore, computed together obtaining a Fixed Effect with 95% confidence interval (CI). Statistical significance was set for values of $P < 0.05$.

We used $I^2$ to calculate the heterogeneity of the studies: $I^2 < 30\%$ low heterogeneity; $30\% < I^2 < 60\%$ moderate heterogeneity; $60\% < I^2 < 75\%$ substantial heterogeneity; $I^2 > 75\%$ high heterogeneity[40].

In case of heterogeneous results, a meta-analysis *per* categorical variable level was performed to evaluate the influence of categorical moderators on study outcomes. The final result is shown in the Forest Plot.

In order to assess potential publication bias, a funnel plot of study effect sizes was visually inspected for asymmetry (Figure 3).

## RESULTS

All the characteristics of the included articles are described in Table 1.

We obtained a total of 25 studies for our systematic review. Following our inclusion and exclusion criteria all of them were DB-RCTs except for four SB-RCTs[41-44].

Among the included studies, the most frequently treated pathology was major depressive episode (No = 10)[42,44-52] followed by resistant depression (No = 5)[43,44,53-55], bipolar depression (No = 4)[41,43,44,56], major depressive disorder (No = 3)[57-59] and other mood disorders (No = 6)[60-65].

We found four studies allowing the use of antidepressants: Fluoxetine[49], paroxetine[46], amitriptyline[48] and not specified molecules (tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors) [45].

The majority of the studies had LDLPFC as the main target area (No = 19)[41,42,44-53,56-60,62,64], although other areas have been stimulated, in particular: Right DLPFC (RDLPFC; No = 4)[44,53,55,65], bilateral (LDLPFC and RDLPFC; No = 4)[43,54,55,63] and other area (No = 1)[42], specifically the anterior cingulate.

The most used coil was the figure eight coil (No = 16)[41-49,51,53-56,59-63,65]. Other coils used were the double cone coil (No = 1)[42] and the H1 coil (No = 3)[52,58,64]. The number of studies where the type of coil was not specified were two[50,57].

The duration of the treatment also differed greatly in our sample: Most of our sample received 2 wk of acute treatment (No = 10)[41,43-47,49,51,59,61]. Other durations of acute treatment were 3 wk (No = 3)[42,54,56], 4 wk (No = 4)[48,52,58,65], 5 wk (No = 2)[50,63], 6 wk (No = 3)[53,55,64], only 1 wk (No = 2)[57,60] and less than 1 wk in just one study[62].

About the TMS technique used, most have used a rTMS protocol (No = 23)[41-55,57,59-63,65]. Other protocols were TBS at 50 Hz (No = 2)[56,59] and deep TMS (dTMS) at 18 Hz (No = 2)[58,64].

### rTMS protocols

Based on the Hz set, the sample can be divided between those who have used LF

**Table 1 Characteristics of the studies included in the systematic review**

| Ref. | Population (No total, No male, No subgroups, age ± SD of the subgroups) | Type of treatment | Protocol (type, Hz, No pulses/session, RMT, coil type, target area, treatment duration) | Mood Disorder Sub-type | Reported adverse events (yes, no, NS) | HMS (No tot) | Drop out due to HMS |
|---|---|---|---|---|---|---|---|
| Trevizol *et al* [53], 2019-A | Active TMS, No = 20, age = 66.8 ± 5.8 (M = 13). Sham = 12, age = 64.1 ± 3.7 (M = 3) | Only TMS | rTMS, 1 Hz, 465 impulse/session, 120% RMT, B-65 figure-8 coil, RDLPFC, 15 session AND rTMS, 10 Hz, 750 impulse/session, 120% RMT, B-65figure-8 coil, LDLPFC, 15 session | Late-life TRD | No (light and not worth mentioning) | 0 | no |
| Trevizol *et al* [53], 2019-B | Active TMS, No = 11, age = 66.1 ± 8.5 (M = 4). Sham = 12, age = 64.1 ± 3.7 (M = 3) | Only TMS | rTMS, 10 Hz, 1450 impulse/session, 120% RMT, B-65 figure-8 coil, LDLPFC, 15 session | Late-life TRD | Yes (TMS, No = 2; SHAM, No = 0) | 1 | no |
| Rao *et al*[65], 2019 | Active TMS, No = 13, age = 39.8 ± 14.2 (M = 5). Sham = 17, age = 40.2 ± 14.6 (M = 11) | Only TMS | rTMS, 1 Hz, 12000 impulse/session, 110% RMT, B-65 figure-8 coil, RDLPFC, 20 session | MDE after traumatic Brain Injury | No (light and not worth mentioning) | 0 | no |
| Matsuda *et al* [64], 2020 | Active TMS, No = 20, age = 43.4 ± 5.5 (M = 18). Sham = 20, age = 45.2 ± 7 (M = 19) | Only TMS | dTMS, 18 Hz, 1980 impulse/session, 120% RMT, H1 coil, LDLPFC, 30 session | Depression NS | No (light and not worth mentioning) | 0 | no |
| Li *et al*[59], 2020-A | Active TMS, No = 35, age = 47.1 ± 13.8 (M = 11). Sham = 35, age = 47.1 ± 12.4 (M = 11) | Only TMS | rTMS, 10 Hz, 1600 impulse/session, 100% RMT, figure-8 coil, LDLPFC, 10 session | Recurrent major depression | Yes (TMS, No = 12; SHAM, No = 8) | 0 | no |
| Li *et al*[59], 2020-B | Active TMS, No = 35, age = 47.1 ± 14.2 (M = 12). Sham = 35, age = 47.1 ± 12.4 (M = 11) | Only TMS | piTMS, 50 Hz, 1800 impulse/session, 80% RMT, figure-8 coil, LDLPFC, 10 session | Recurrent major depression | Yes (TMS, No = 9; SHAM, No = 8) | 0 | no |
| Bulteau *et al* [56], 2019 | Active TMS, No = 12, age = 52.7 (M = 5). Sham = 14, age = 53.1 (M = 10) | Only TMS | iTBS, 50 Hz, 990 impulse/session, 80% RMT, figure-8 coil, LDLPFC, 15 session | BD | No | 0 | no |
| Siddiqi *et al* [63], 2019 | Active TMS, No = 9, age = 43 ± 13 (M = 7). Sham = 6, age = 50 ± 18 (M = 4) | Only TMS | Bilateral rTMS, 10 Hz, 4000 impulse/session, 120% RMT, B-65 figure-8 coil., LDLPFC, 25 session AND Bilateral rTMS, 1 Hz, 1000 impulse/session, 120% RMT, B-65figure-8 coil, RDLPFC, 25 session | MDE after traumatic Brain Injury | Yes (TMS, No = 9; SHAM, No = 0) | 0 | no |
| Kaster *et al* [52], 2018 | Active TMS, No = 25, age = 65.0 ± 5.5 (M = 17). Sham=27, age = 65.4 ± 5.5 (M = 15) | Only TMS | rTMS, 18 Hz, 6012 impulse/session, 120% RMT, H1 coil, LDLPFC, 20 session | Late-life MDE | No (light and not worth mentioning) | 1 | no |
| Xie *et al*[57], 2015 | Active TMS, No = 35, age=65.3 ± 5.1 (M = 12). Sham = 26, age = 64.7 ± 4.2 (M = 8) | rTMS + shuganjieyu | rTMS, 10 Hz, NS impulse/session, 30% RMT, B-65NS coil, LDLPFC, 5 session | MDD | Yes (TMS, No = 14; SHAM, No = 13) | 0 | no |
| Levkovitz *et al* [58], 2015 | Active TMS, No = 101, age = 45.1 ± 11.7 (M = 53). Sham = 111, age = 47.6 ± 11.6 (M = 58) | Only TMS | dTMS, 18 Hz, 1980 impulse/session, 120% RMT, H1 coil, LDLPFC, 20 session | MDD | No (light and not worth mentioning) | 0 | no |
| Kreuzer *et al* [42], 2015-A | Active TMS, No = 13, age = 43.5 ± 10.3 (M = 8). Sham = 12, age = 43.8 ± 10.5 (M = 4) | Only TMS | rTMS, 10 Hz, 2000 impulse/session, 110% RMT, B-65 double cone coil, Anterior Cingulate, 15 session | MDE | Yes (TMS, No = 7; SHAM, No = 8) | 0 | no |
| Kreuzer *et al* [42], 2015-B | Active TMS, No = 15, age = 46.1 ± 9.5 (M = 7). Sham = 12, age = 43.8 ± 10.5 (M = 4) | Only TMS | rTMS, 10 Hz, 2000 impulse/session, 110% RMT, B-65 figure-8 coil., LDLPFC, 15 session | MDE | Yes (TMS, No = 4; SHAM, No = 8) | 0 | no |
| George *et al* [62], 2014 | Active TMS, No = 20, age=38.7 ± 15 (M = 18). Sham = 21, age = 46.1 ± 15.9 (M = 17) | Only TMS | rTMS, 10 Hz, 6000 impulse/session, 120% RMT, B-65 figure-8 coil., LDLPFC, 9 session | MDE | Yes (TMS, No = 7; SHAM, No = 6) | 0 | no |

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|---|---|---|---|---|---|---|---|
| Lingeswaran [51], 2011 | Active TMS, No = 9, age = 34 ± 10.5 (M = 3). Sham = 14, age = 37.26 ± 11.8 NS (M = 6) | Only TMS | rTMS, 10 Hz, 500 impulse/session, 100% RMT, B-65 figure-8 coil, LDLPFC, 10 session | MDE | No | 0 | no |
| Pallanti *et al* [54], 2010-A | Active TMS, No = 20, age=47.6 ± 12.33, (M = 9). Sham = 20, age = 47.85 ± 9.12 (M = 8) | Only TMS | Bilateral rTMS, 1 Hz, 420 impulse/session, 110% RMT, B-65 figure-8 coil., RDLPFC, 15 session AND rTMS, 10 Hz, 1000 impulse/session, 100% RMT, B-65 figure-8 coil., LDLPFC, 15 session | TRD | No (light and not worth mentioning) | 0 | no |
| Pallanti *et al* [54], 2010-B | Active TMS, No = 20, age = 51.2 ± 12.33, (M = 8). Sham = 20, age = 47.85 ± 9.12 (M = 8) | TMS + placebo | rTMS, 1 Hz, 420 impulse/session, 110% RMT, B-65 figure-8 coil., RDLPFC, 15 session | TRD | No (light and not worth mentioning) | 0 | no |
| Fitzgerald[55], 2008 | Active TMS, No = 30, age = 45.7 ± 10.8 (M = 10). Sham = 28, age = 44.8 ± 11.4 (M = 15) | Only TMS | LF rTMS, 1 Hz, 900 impulse/session, 110% RMT, B-65 figure-8 coil., rDLPFC, 10 session | Depression NS | No (light and not worth mentioning) | 0 | no |
| Fitzgerald *et al* [44], 2007 | Active TMS, No = 25, age = 46.8 ± 10.7 (M = 10). Sham = 25, age = 43.7 ± 10.2 (M = 9) | Only TMS | Bilateral rTMS, 10 Hz, 750 impulse/session, 100% RMT, B-65 figure-8 coil., LDLPFC, 30 session AND Bilateral rTMS, 1 Hz, 420 impulse/session, 110% RMT, B-65 figure-8 coil., RDLPFC, 30 session | TRD | No (light and not worth mentioning) | 0 | no |
| O'Reardon *et al*[50], 2007 | Active TMS, No = 155, age = 47.9 ± 11 (M = 69). Sham = 146, age = 48.7 ± 10.6 (M = 72) | Only TMS | rTMS, 10 Hz, 3000 impulse/session, 120% NS coil, LDLPFC, 25 session | MDE | No (light and not worth mentioning) | 0 | no |
| Fitzgerald *et al* [43], 2006 | Active TMS, No = 25, age = 46.8 ± 10.7 (M = 10). Sham = 25, age = 43.7 ± 10.2 (M = 9) | Only TMS | Bilateral rTMS, 10 Hz, 750 impulse/session, 100% RMT, B-65 figure-8 coil., LDLPFC, 30 session AND Bilateral rTMS, 1 Hz, 420 impulse/session, 110% RMT, B-65figure-8 coil., RDLPFC, 30 session | TRD | No (light and not worth mentioning) | 0 | no |
| Rumi *et al*[48], 2005 | Active TMS, No = 22, age = 39.3 ± 12.8 (M = 3). Sham = 24, age = 38.9 ± 8.8 (M = 4) | TMS + Amitriptyline | rTMS, 5 Hz, 1250 impulse/session, 120% RMT, B-65 figure-8 coil, LDLPFC, 20 session | MDE | No (light and not worth mentioning) | 0 | no |
| Boggio *et al* [49], 2005 | Active TMS, No = NS, age = NS (M = NS). Sham = NS, age = NS, (M = NS) | TMS + fluoxetine+ placebo | rTMS, 15 Hz, 3000 impulse/session, 110% RMT, B-65figure-8 coil, LDLPFC, 10 session | MDE in Parkinson's disease | No | 0 | 0 |
| Poulet *et al* [46], 2004 | Active TMS, No = NS, age=NS (M = NS). Sham = NS, age = NS (M = NS) | TMS + paroxetine | rTMS, 10 Hz, 400 impulse/session, 80% RMT, B-65 figure-8 coil, LDLPFC, 10 session | MDE | No | 0 | no |
| Mosimann *et al* [47], 2004 | Active TMS, No = 15, age = 60 ± 13.4 (M = 10). Sham = 9, age = 64.4 ± 13 (M = 5) | Only TMS | rTMS, 20 Hz, 1600 impulse/session, 100% RMT, B-65 figure-8 coil, LDLPFC, 10 session | MDE | Yes (TMS, No = 7; SHAM, No = 5) | 1 | no |
| Hansen *et al* [45], 2004 | Active TMS, No = 6, age = 42.5 (M = 4). Sham = 7, age = 46, (M = 5) | TMS + antidepressant | rTMS, 10 Hz, 2000 impulse/session, 90% RMT, B-65 figure-8 coil, LDLPFC, 10 session | MDE | No | 0 | no |
| Nahas *et al* [41], 2003 | Active TMS, No = 11, age = 42.4 ± 7.3 (M = 4). Sham = 12, age = 43.4 ± 9.3 (M = 5) | Only TMS | rTMS, 5 Hz, 1600 impulse/session, 110% RMT, B-65 figure-8 coil, LDLPFC, 10 session | BD | No (light and not worth mentioning) | | no |
| Fitzgerald *et al* [66], 2003-A | Active TMS, No = 20, age = 42.4 ± 9.8 (M = 12). Sham = 20, age = 49C.15 ± 14.243 (M = 9) | Only TMS | rTMS, 1 Hz, 300 impulse/session, 100% RMT, B-65 figure-8 coil, RDLPFC, 10 session | BD,MDE, TRD | No (light and not worth mentioning) | 0 | no |
| Fitzgerald *et al* [66], 2003-B | Active TMS, No = 20, age = 45.55 ± 11.49 (M = 13). Sham = 20, age = 49.15 ± 14.243 (M = 9) | Only TMS | rTMS, 10 Hz, 1000 impulse/session, 100% RMT, B-65 figure-8 coil., LDLPFC, 10 session | BD,MDE, TRD | No (light and not worth mentioning) | 1 | no |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Pascual-Leone *et al*[60], 1996 | Active TMS, No = 17, age = 48.6 ± NS (M = 6). Sham = 17, age = 48.6 ± NS (M = 6) | Only TMS | rTMS, 10 Hz, 2000 impulse/session, 90% RMT, B-65 figure-8 coil, LDLPFC, 5 session | Psychotic depression | Yes (TMS, No = 7; SHAM, No = 7) | 0 | no |

SD: Standard deviation; RMT: Resting motor thresholds; HMS: Hypomanic/manic switch; TMS: Transcranial magnetic stimulation; rTMS: Repetitive TMS; RDLPFC: Right dorsolateral prefrontal cortex; LDLPFC: Left dorsolateral prefrontal cortex; TRD: Treatment resistant depression; MDE: Major depressive episode; dTMS: Deep TMS; piTBS: Prolonged intermittent theta burst stimulation; iTBS: Intermittent theta-burst stimulation; BD: Bipolar depression; MDD: Major depressive disorder.

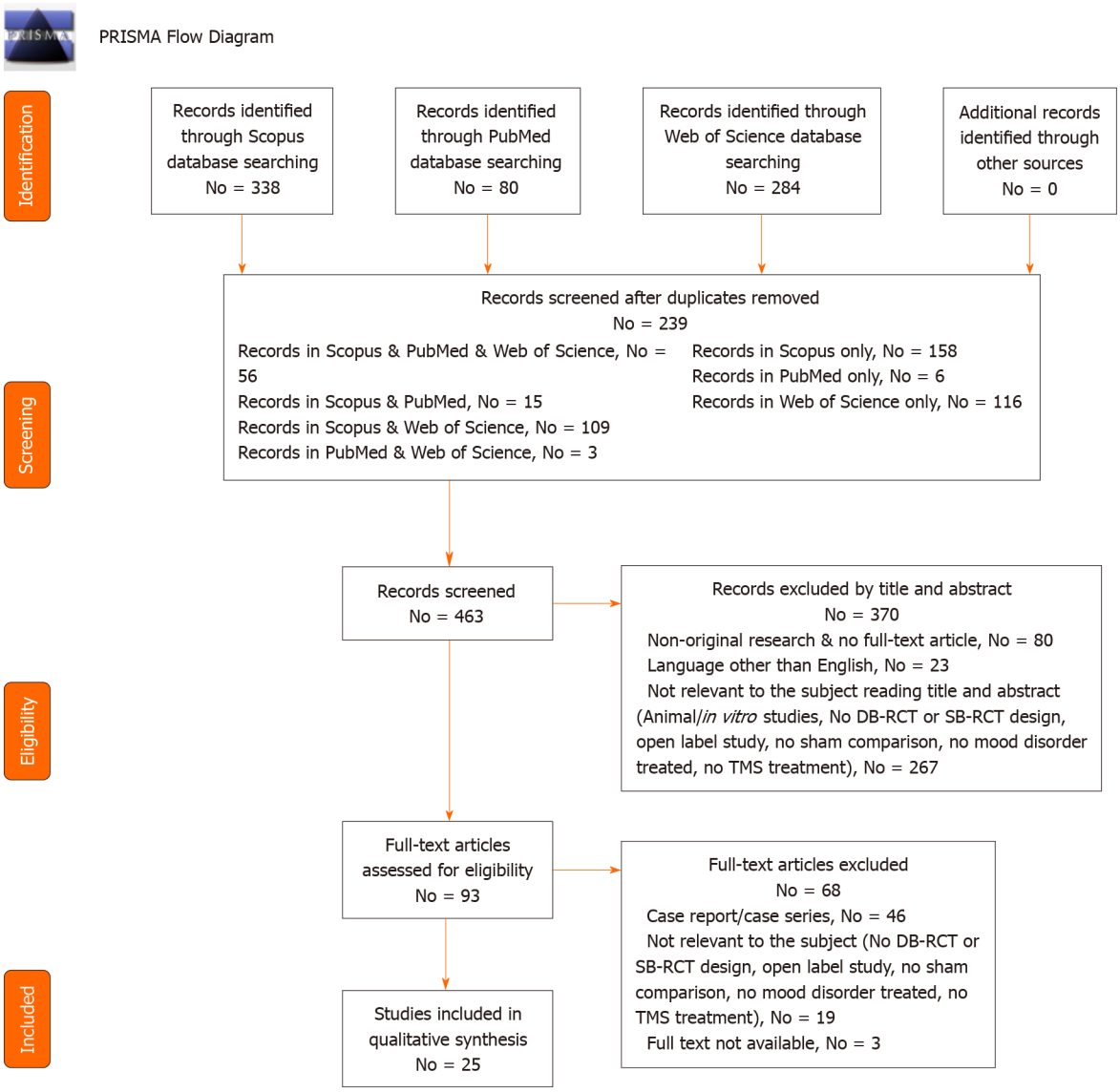


**Figure 1 PRISMA flow diagram: Studies included in qualitative and quantitative synthesis.** DB-RCT: Double blind randomized controlled trials; SB-RCT: Single blind randomized controlled trials.

treatment at 1 Hz (No = 7)[44,53-55,61,63,65] and those who have used a HF treatment (No = 21) divided in 5 Hz (No = 2)[41,48], 10 Hz (No = 15)[42-46,50,51,53-55,57,59,60,62,63], 15 Hz (No = 1)[49] and 20 Hz (No = 1)[47].

The number of pulses/session was very heterogeneous, more frequently 2000 pulses/session (No = 3)[42,45,60] and 3000 pulses/session (No = 2)[49,50].

### *Side effects*

Only eight studies reported at least one side effect[42,47,53,59,60,62,63]. HMSs (described as greater energy, insomnia, irritability, anxiety and suicidal attempt in bipolar patients), were present in four studies[44,47,52,53] and, in particular, once in the sham group and three times in the active group. Only one episode of HMS was

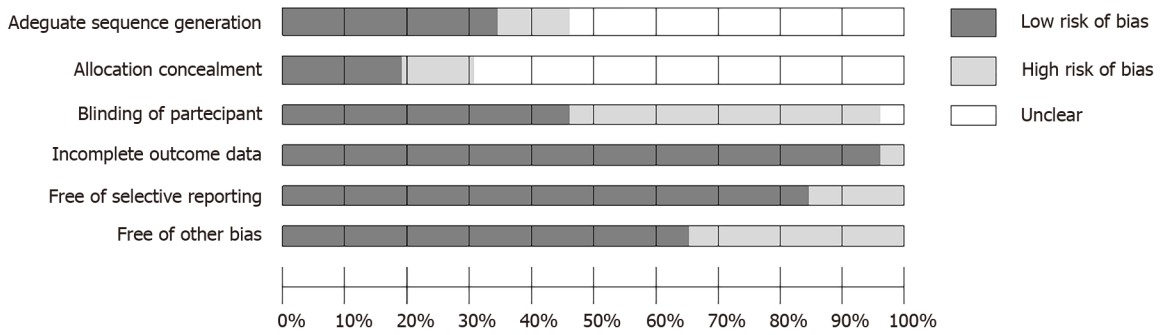


**Figure 2 Risk of bias assessment.**

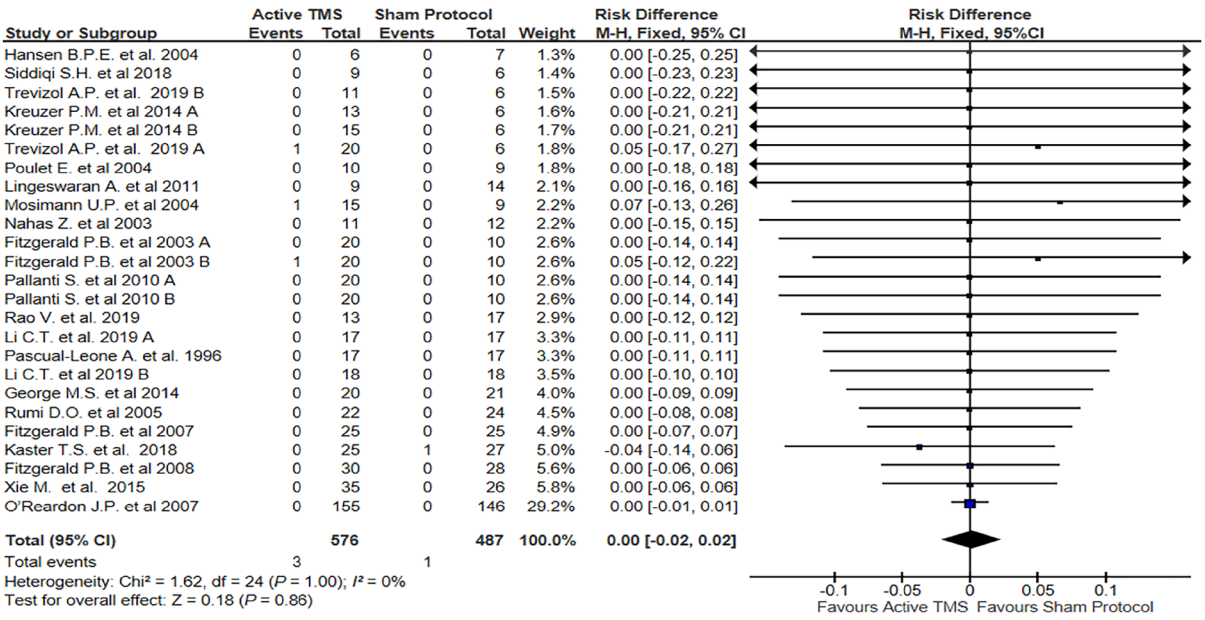


**Figure 3 Forest plot: Risk to develop a hypomanic/manic switch after a transcranial magnetic stimulation protocol.** TMS: Transcranial magnetic stimulation.

specifically reported[66], after stopping taking a mood stabilizer and after the end of the rTMS treatment. No drop-outs due to HMSs were reported. None of the studies that used antidepressants in addition to TMS treatment reported the onset of HMS[45,46,48,49].

### *Risk of bias*

The results of the risk of bias assessment reveal a good quality of the reported data, as evidenced by the items "*Incomplete Outcome Data*" and "*Free of Selective Report*". However, only a few of the included studies accurately indicated the blinding method and the allocation concealment (Figure 2).

### *Meta-analysis of rTMS protocols*

The meta-analysis of the 25 studies included (No. of subjects involved in active stimulation = 576; No. of subjects involved in sham protocol = 487), showed no significant results about the risk of developing HMS after TMS stimulation (RD = 0.00; 95%CI = -0.02-0.02; $P$ = 1.00; $I^2$ = 0%) for a fixed effect.

The inspection of the funnel plot of the RD of the included studies (Fixed Effect) suggested a symmetry of the studies, showing the same concentration of studies on the left and on the right of the mean RD (Figure 4).

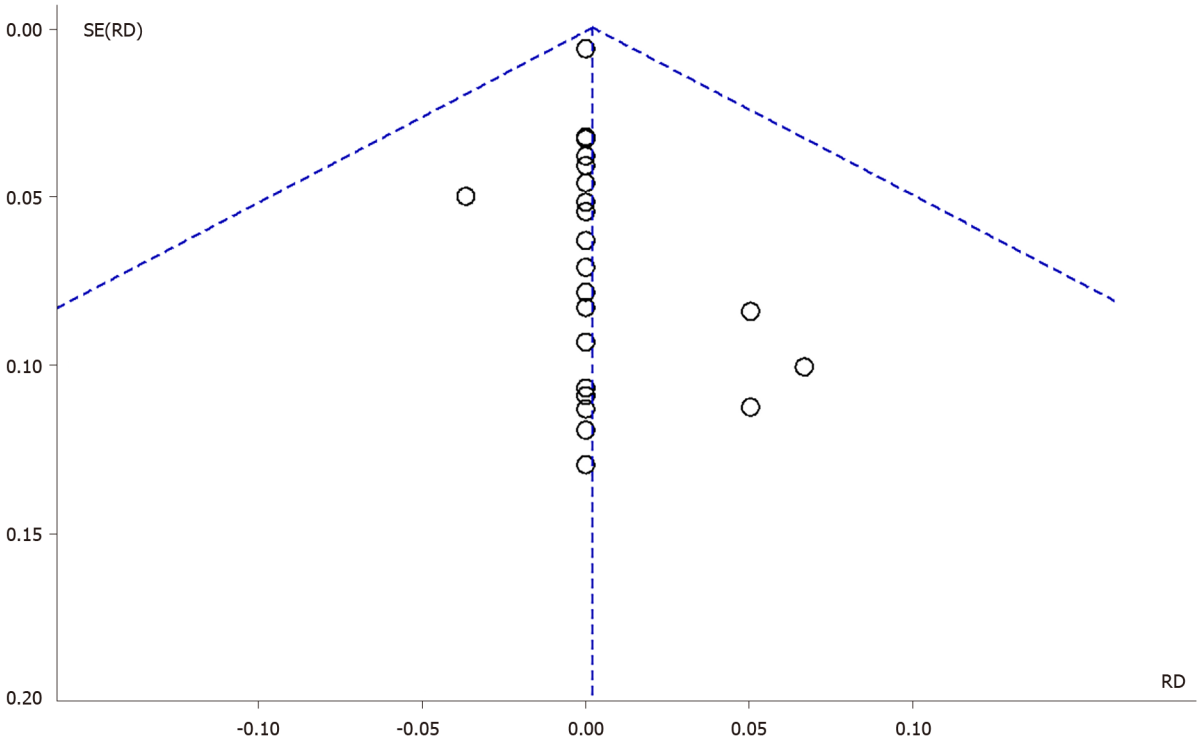


**Figure 4 Funnel plot for publication bias.** RD: Risk difference.

## DISCUSSION

The mechanisms underlying HMSs in mood disorders are complex and still unknown, even if a main role of increased levels of dopamine and/or norepinephrine and of seasonal changes of neural activity were suggested[67]. Antidepressant treatments are well known triggers for HMSs, especially in bipolar disorders[68]. Due to its increasing use in the treatment of mood disorders, the same concern has been voiced about the safety of TMS. In particular, in a previous meta-analysis on the topic, it was hypothesized that HMS was induced by a too intensive treatment with TMS and an incorrect diagnosis of unipolar depression[69]. However, the most recent scientific literature regarding the use of TMS in mood disorders seems to deny the hypomanic effect of TMS. Nowadays, in fact, several TMS treatments (rTMS and TBS in particular) [6,70] are increasingly used not only for the therapy of TRD but also for the treatment of mood disorders in general, including bipolar disorders[71]. However, a critical role on the onset of HMS is probably played by the concomitant use of high-dosage antidepressant treatments[72,73], pointing out the importance of a deep and accurate anamnesis.

In our systematic review focused on RCTs using TMS to treat mood disorders, we found that only 4/25 studies reported a HMS as an adverse event, and the difference between sham and active treatment was not significant.

The most used protocol was rTMS, set at 10 Hz (16/25 studies), 120% RTM (9/25 studies) with a variable number of pulses (the most common included the 2,000 pulses/session present in 3/26 studies). The most investigated brain area was the DLPFC, (24/25 studies); only one study examined the AC with a deep-brain stimulation technique. However, in the context of the DLPFC, lateralization to the right seems preferred in the context of a LF stimulation (all eight studies in question stimulate the RDLPFC) while the left one in the context of a HF (all of the remaining 17 studies stimulate the LDLPFC). The application of the most widely used research protocols could therefore be a useful method to avoid the genesis of HMSs.

Another aspect highlighted by our results is the absence of drop-outs due to HMS. Considering the severity of HMS symptomatology, the absence of drop-outs is a further indication of the TMS safety in the treatment of MD.

## CONCLUSION

Considering the still not understood and complex mechanisms underlying the development of HMS, from the results of our systematic review of the literature and from our meta-analysis (although in the context of a statistical non-significance), it seems clear that by applying the most usual protocols of rTMS and TBS and applying, where necessary, the appropriate precautionary measures (for example going on with mood stabilizers) TMS can be considered a safe technique also in the context of mood disorders.

## ARTICLE HIGHLIGHTS

### *Research background*

One of the most innovative and most investigated non-invasive brain stimulation techniques is Transcranial Magnetic Stimulation (TMS). This device has received Food and Drug Administration approval for the treatment of various neurological (headache) and psychiatric (treatment resistant depression) disorders. Several studies have been conducted to find new applications of TMS in conditions that do not respond or partially respond to standard psychopharmacological therapies.

### *Research motivation*

TMS is an increasingly used technique in the neurological and psychiatric fields. One of the greatest concerns about its use is the possibility of developing severe side effects such as hypomanic/manic switches (HMS).

### *Research objectives*

The aim of this meta-analysis is to quantify the risk of developing HMS after treatment with TMS in mood disorders and to evaluate the drop-out rate due to that adverse event.

### *Research methods*

The search was conducted using PubMed, Scopus and Web of Science databases on March 22, 2020. All procedures were registered on PROSPERO and performed according to the PRISMA guidelines. Only double blind/single blind articles, written in English were included. RevMan 5.4 Software for Windows was used to perform the meta-analysis.

### *Research results*

Of the 25 eligible studies, only four HMSs were described. No dropouts were reported due to symptoms severity.

### *Research conclusions*

Our data confirm that, by applying appropriate psychopharmacological and anamnestic precautions, TMS is a safe technique for treating mood disorders.

### *Research perspectives*

Greater uniformity of protocols, their online registration and the timely reporting of side effects on scientific papers could guarantee a more accurate analysis of the health risks induced by TMS in future meta-analyses.

## ACKNOWLEDGEMENTS

We would like to thank Alessia Di Ferdinando for kindly reviewing the language and Gianluca Mancusi for his precious help in the revision of references.

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