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Title

Safety, tolerability and nocebo phenomena during repetitive transcranial magnetic stimulation: a systematic review and meta-analysis of placebo-controlled clinical trials.

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Abstract

Background: The methodology used for the application of repetitive transcranial magnetic stimulation (TMS) is such that it may induce a placebo effect. Respectively, adverse events (AEs) can occur when using a placebo, a phenomenon called nocebo. The primary aim of our meta-analysis is to establish the nocebo phenomena during TMS. Safety and tolerability of TMS were also studied.

Methods: After a systematic Medline search for TMS randomized controlled trials (RCTs), we assessed the number of patients reporting at least one AE and the number of discontinuations because of AE in active and sham TMS groups.

Results: Data was extracted from 93 RCTs. The overall pooled estimate of active TMS and placebo treated patients who discontinued treatment because of AEs was 2.5% (95% CI 1.9% - 3.2%) and 2.7% (95% CI 2.0% - 3.5%) respectively. The pooled estimate of active TMS and placebo treated patients experiencing at least one AE was 29.3% (95% CI 19.0% - 22.6%) and 13.6% (95% CI 11.6% - 15.8%) respectively, suggesting that the odds of experiencing an AE is 2.60 times higher (95% CI 1.75 – 3.86) in the active treatment group compared to placebo ($p<0.00001$). The most common AE was headache, followed by dizziness.

Secondary meta-analyses in depression and psychotic disorders showed that the odds of experiencing an AE is 3.98 times higher (95% CI 2.14 – 7.40) and 2.93 times higher (95% CI 1.41 – 6.07), respectively, in the active treatment groups compared to placebo.

Conclusions: TMS is a safe and well-tolerated intervention. Nocebo phenomena do occur during TMS treatment, and should be acknowledged during clinical trial design and daily clinical practice.

Highlights

- TMS is a safe and well-tolerated intervention.
- Serious adverse event during TMS are rare
- Nocebo phenomena do occur during TMS treatment
- Headache is the commonest adverse event during TMS.

INTRODUCTION

Transcranial magnetic stimulation (TMS) is a neurostimulation and neuromodulation technique, based on the principle of electromagnetic induction of an electric field in the brain [1]. The therapeutic utility of repetitive TMS (rTMS) has been demonstrated in a variety of neurological [2] and psychiatric conditions [3] and has already been approved as a treatment for depression and migraines in many countries.

The methodology used for the application of rTMS, such as the presence of auditory and somato-sensory perception, as well as the positioning a TMS coil on the head, can induce a placebo effect in some patients predominantly due to the belief that one is undergoing brain stimulation [4]. The placebo effect, as it is the case with other medical interventions, may add to the effects induced through activation of neural structures and may contribute to the subjective feeling of improvement in some instances [1]. Placebo phenomena during rTMS treatment have been evaluated in various neuropsychiatric disorders, including depression [5, 6] and schizophrenia [7].

Respectively, adverse events (AEs) can occur when using a placebo, a treatment with no active therapeutic effect. This phenomenon is called nocebo and is probably the result of negative expectations by patients that medical treatment will probably harm rather than heal [8, 9]. The fact that AEs are occurring in placebo-treated patients suggests that a part of the AEs reported in patients receiving active treatment is also because of nocebo [10, 11]. Nocebo is associated with lower adherence to the therapeutic interventions, higher rates of treatment withdrawal, as well as significant difficulty in assessing the efficacy and the safety profile of an intervention [12, 13].

The aim of our study was to investigate the frequency and strength of nocebo phenomena in TMS randomized placebo-controlled trials. The AE and dropout rates of patients receiving active TMS and placebo treatment (nocebo AE and nocebo dropout rates) were used as a measure of TMS tolerability and severity of the nocebo effect, respectively.

METHODS

Standard protocol approvals and registrations

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14].

Sham or placebo TMS

In TMS studies, the term “placebo” is often replaced by the term “sham”. For the purposes of this paper the two terms are used interchangeably. Although there are different sham TMS approaches, they can be broadly divided into two groups [15].

The more common approach involves utilising regular active TMS coils. These coils are angled off the head (either at 45° and 90°) such that only one edge remains in contact with the scalp. This reproduces a clicking sound, which is very similar to that of an active TMS pulse. Muscle twitching can also occur [15]. This method, therefore, preserves the somatosensory effects of active TMS, however, it is inherently difficult to determine whether there is any residual neuronal stimulation [15]. It has already been demonstrated that some sham TMS conditions produce substantial cortical stimulation, making it critical to carefully select the sham manipulation for clinical trials [16].

The second approach utilises commercially available sham TMS coils. These are coils that resemble regular TMS coils but markedly attenuate the magnetic field and can, therefore, be positioned exactly like the regular TMS coils. These purpose built sham coils mimic regular coils by reproducing the same clicking noises. Although this method ensures no cortical stimulation, the somatosensory effects of regular TMS coils is not replicated. These can be overcome with the use of surface electrodes for electrical stimulation of the skin to reduce such differences [15].

Literature search strategy

A computer-based literature search was conducted on December 11th, 2017 on Medline. The Medical Subject Headings (MeSH) terms that had to be present in the

title and/or the abstract of the papers as well as the filters that were used are detailed in PROSPERO, where the protocol was prospectively registered (registration: CRD42017081824).

Eligibility criteria

We selected the articles that fulfilled the following criteria; (i) were studies testing TMS, (ii) were randomized controlled trials (RCTs), (iii) they included a purely placebo arm, (iv) they involved humans, (v) each treatment arm had at least 10 patients, (vi) withdrawals were reported in detail in each treatment arm, and (vii) they scored a JADAD score of higher than or equal to 3.

The JADAD scale classifies the quality of reports and includes only five items. Each item has to be answered with either a yes (scoring 1 point) or a no (scoring 0 points). The items are as follows: (i) Was the study described as randomized?, (ii) Was the study described as double blind?, (iii) Was there a description of withdrawals and dropouts?, (iv) Was the method of randomisation described in the paper and was appropriate? and (v) Was the method of blinding described and was appropriate? [17].

Data extraction

Data was extracted from each study in a structured coding scene using Excel and included information on article identification, year of publication, total number of subjects, disease where TMS was tested, number of placebo-treated subjects, number of placebo-treated subjects who dropped out because of AEs, number of female subjects treated with placebo, mean age of placebo-treated subjects, number of TMS-treated subjects, number of TMS-treated subjects who dropped out because of AEs, number of female subjects treated with TMS, mean age of TMS-treated subjects, number of sessions, motor threshold percentage, frequency of stimulation, sham TMS approach (angled coil (45° versus 90°) or shielded coil) and country. Where reported, we also extracted information on number of placebo-treated subjects who experienced at least one AE, number of TMS-treated subjects who experienced at least one AE and the nature of AEs. On all occasions patients had to be on stable treatment regimens of any medical condition (i.e. comorbidities) before entering the

RCT. We calculated the nocebo AE rates or dropout rates for each group by pooling the percentage of placebo-treated or TMS-treated patients respectively, who had at least one AE or dropped out because of AE.

Statistical analyses

A database was developed using IBM SPSS Statistics (version 23.0 for Mac). Frequencies and descriptive statistics were examined for each variable. The outcomes of interest were the proportion of patients treated with TMS and placebo who experienced AEs, and the proportion of patients treated with TMS and placebo who dropped out of the study because of any AE.

The meta-analysis was conducted using the RevMan programme (Review Manager, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) as suggested by the Cochrane Collaboration Group.

Heterogeneity between studies was assessed using the I^2 statistic. Data were analysed using a random effects model.

The nocebo dropout and nocebo AE rates among patients treated with different characteristics of sham procedures (angled or shielded) and different coil positioning method (45° or 90°), were examined using the chi-square test

Correlations between percentages and the characteristics of the treatment protocol were examined using Spearman's correlations.

A value of $p<0.05$ was considered to be statistically significant. The bonferroni correction was used in multiple comparisons.

Data availability

All extracted data can be shared following a reasonable request to the corresponding author.

RESULTS

The process of the article selection is presented in Figure 1. From the 302 articles retrieved, 93 placebo controlled RCTs were included in the meta-analysis (Supplement 1). These studies were published between 1999 and 2017 and they involved 2290 TMS-treated and 1854 placebo-treated patients. The majority of TMS studies were conducted in patients whose principal diagnosis was depression (28.0% of the studies), followed by psychotic disorders (19.4%) that were grouped together (i.e. schizophrenia and schizoaffective disorder), stroke (12.9%), Parkinson's disease (7.5%) and pain (6.5%). The main characteristics of the studies and their populations are presented in Table 1. Detailed characteristics and breakdown of JADAD scores per study are provided (Supplements 2 and 3 respectively).

Dropout rates in placebo and TMS groups

The overall pooled estimate of the percentage of placebo treated patients who withdrew from treatment was 9.4% (95% CI 8.1% - 10.9%). The pooled estimate of the percentage of placebo treated patients who withdrew from treatment because of AEs was 2.7% (95% CI 2.0% - 3.5%).

The pooled estimate of the percentage of TMS treated patients who withdrew from treatment was 9.1% (95% CI 7.9% - 10.3%). The pooled estimate of the percentage of TMS treated patients who withdrew treatment because of AEs was 2.5% (95% CI 1.9% - 3.2%).

Figure 2a shows that the odds of dropping out because of an adverse event did not differ between the placebo and TMS treatment arms (Odds Ratio 0.91, 95% CI 0.60 – 1.38, p=0.66). The heterogeneity in reporting withdrawals because of AEs and experiencing at least one AE was minimal (I^2 = 0%), which rendered pooling studies together appropriate. The symmetry of funnel plot (figure 2b) only suggest a small possibility of publication bias and a small study effect.

Adverse event rates in placebo and TMS groups

Fifty-seven studies reported in detail the exact number of patients experiencing at least one AE in both study groups. The pooled estimate of the percentage of placebo treated patients with at least one AE was 13.6% (95% CI 11.6% - 15.8%), in comparison to 29.3% (95% CI 19.0% - 22.6%) for TMS treated patients.

As illustrated in Figure 3a, the odds of experiencing an adverse event was 2.60 times higher (95% CI 1.75 – 3.86) in the active treatment group compared to placebo ($p<0.00001$) (Figure 3a).

Heterogeneity in reporting AEs was moderate ($I^2 = 49\%$), which rendered pooling studies together appropriate. The symmetry of funnel plot (figure 3b) only suggest a small possibility of publication bias and a small study effect.

Nature of AE in placebo and TMS groups

The most commonly reported AE in both groups were discomfort at the stimulation site / headache (10.1% (95% CI 8.4% - 12.0%) for placebo treated patient versus 19.7% (95% CI 17.7% - 21.9%) for active TMS treated patients. The second commonest AE in both groups was dizziness (1.8% (95% CI 1.1% -2.8%) for placebo treated versus 2.8% (95% CI 2.0% - 3.8%) for active TMS treated patients. Occurrence of seizures during treatment was extremely rare (0.2% in the placebo group and 0.1% in the active treatment group).

As illustrated in the forest plot (Figure 4) the odds of experiencing discomfort/headache was 2.19 times higher (95% CI 1.52 – 3.14) in the active treatment group compared to placebo ($p<0.0001$). The odds of experiencing dizziness did not differ significantly between the active TMS and the placebo arms (Odds Ratio 1.47, 95% CI 0.82 – 2.64, $p=0.20$).

<u>Determinants of AE in placebo and TMS groups</u>

Correlations between AE rate and withdrawal rate because of AE and various parameters including treatment protocol, study characteristics and demographics are summarized in Table 2. After adjusting for multiple comparisons, the only statistically

significant correlation observed was between age and AE rate in the group of patients treated with active TMS; the higher the age, the smaller the AE rate (spearman's rho -0.470, p<0.001).

Also, as the number of patients in the active TMS group experiencing AEs increased, the number of patients in the placebo group also experiencing AEs increased (Spearman's rho 0.646, p<0.001). Similarly, the higher the number of patients in the active TMS groups that were withdrawing because of AE was, the higher the number of patients in the placebo groups that were withdrawing because of AE was (Spearman's rho 0.660, p<0.001).

No differences were observed in the nocebo dropout rate between the patients who received placebo treatment with an angled TMS coil in comparison to the patients that received placebo treatment with a shielded TMS coil (2.4% versus 3.1%, p=0.332). However the nocebo AE rate was higher in the patients who received placebo treatment with an angled TMS coil in comparison to the patients that received placebo treatment with a shielded TMS coil (16.8% versus 10.5%, p=0.002).

When comparing the nocebo dropout rate between the angled TMS coil at 45° in comparison to the angled TMS coil at 90°, no differences were observed (3.4% versus 2.8%, p=0.699). However, the nocebo AE rate was higher in the patients who received placebo treatment with an angled TMS coil at 45° in comparison to the patients that received placebo treatment with an angled TMS coil at 90° (15.6% versus 7.1%, p<0.001).

Adverse events in placebo and TMS groups per disease

There were a sufficient number of RCTs to allow for secondary meta-analyses in depression and psychotic disorders, including calculation of odds ratios. Pooled data in other disease groups are summarized in Table 3.

Depression

The active TMS dropout rate because of AEs was 3.2% (95% CI 2.0% - 4.8%) and the nocebo dropout rate was 2.2% (95% CI 1.2% - 3.8%). The active TMS AE rate was 35.2% (95% CI 30.6% - 40.0%) and the nocebo AE rate was 12.2% (95% CI 8.9% - 16.3%).

The chance of dropping out because of an adverse event did not differ between the placebo and the TMS treatment arms (Odds Ratio 1.70, 95% CI 0.78 – 3.73, p=0.18), but the chance of experiencing an adverse event was 3.98 times higher (95% CI 2.14 – 7.40) in the active treatment group compared to placebo (p<0.00001)

Psychotic disorders

The active TMS dropout rate because of AEs was 2.3% (95% CI 1.1% - 4.2%) and the nocebo dropout rate was 3.9% (95% CI 2.0% - 6.7%). The active TMS AE rate was 34.0% (95% CI 28.7% - 39.5%) and the nocebo AE rate was 16.6% (95% CI 11.7% - 22.5%).

The chance of dropping out because of an adverse event did not differ between the placebo and the TMS treatment arms (Odds Ratio 0.53, 95% CI 0.21 – 1.33, p=0.18), however the chance of experiencing an adverse event was 2.93 times higher (95% CI 1.41– 6.07) in the active treatment group compared to placebo (p=0.004).

DISCUSSION

Our meta-analysis included randomized placebo-controlled TMS trials in various neurological and psychiatric conditions. Our findings suggest that TMS is a well-tolerated intervention as the rate of dropouts because of AEs is small and does not differ significantly between treatment with sham or active TMS (2.7% and 2.5% respectively).

Serious AE were extremely rare and in particular the prevalence of seizures was extremely low, not differing between the active TMS and the placebo groups. Only one patient receiving active TMS had a seizure during one of the trials [18]. The patient suffered from depression and no cause for the seizure was identified [18]. Only two patients receiving sham TMS have been reported to had a seizure; one was a patient with alcohol dependence who discontinued the benzodiazepines for the purposes of the study and, therefore, the seizure was considered to be related to this [19], and one patient suffered from depression and no cause for the seizure was identified [20].

We were able to perform secondary analyses looking separately into the RCTs where TMS or placebo were used in depression and psychotic disorders. In depression, the nocebo AE rate in TMS RCTs was 12.2% and the nocebo dropout rate was 2.2%. These figures are significantly lower compared to the respective figures of nocebo rates in pharmacological RCTs of depression, where the pooled estimates are 44.7% and 4.5% respectively [9]. This finding suggests that nocebo depends on the method of treatment. Nocebo phenomena in pharmacological RCTs of psychotic disorders – to our knowledge – have not yet been described.

One of the major determinants of nocebo, if not the most important, is the uncertainty of treatment action, which pervades all clinical trials, and particularly brain diseases' trials [21]. Whether nocebo phenomena depend on the underlying disease or on the actual treatment remains debatable. On one hand, nocebo varies significantly among neurological conditions [22 - 32]. Moreover, Zaccara et al, showed that nocebo rates in RCTs may be affected by the clinical condition for which the experimental drug is given [33]. For example, placebo-treated patients in pain RCTs where anticonvulsants

are used have significantly higher proportions of intolerable AEs leading to drug withdrawal compared to placebo-treated patients in epilepsy RCTs where anticonvulsants are used [33]. On the other hand, the nature of nocebo AEs experienced might depend on the active drug [27, 34]. This has been demonstrated, in anti-migraine RCTs, where anorexia and memory difficulties, which are typical AEs of anticonvulsants, were present only in the placebo arm of anticonvulsants trials. This suggests that the AEs in placebo arms of clinical trials of anti-migraine medications might depend on the adverse events of the active medication against which the placebo is compared, which is in accordance with the expectation theory of placebo and nocebo effects [34]. In TMS RCTs, the nature of AE and the AE and dropout rates did not differ between diseases (where secondary meta-analyses where performed).

Interestingly, the type of sham plays a role in the nocebo AE rates as angled coils lead to higher nocebo rates of AE. This possibly relates to the fact that the coil is not shielded, meaning that the produced magnetic field can be sufficient enough to cause a mild degree of brain stimulation [15]. Therefore, in TMS RCTs the use of shielded TMS coils producing a similar acoustic and somatosensory effect through other means (such as the use of surface electrodes) is better as it would avoid a residual brain stimulation that is likely occurring when angled active coils are used. Moreover, the higher the AE and dropout rates was reported in the active TMS groups, the higher the AE and dropout rates was reported in the placebo groups. A possible explanation for this observation is that different information might be given to the participants in different trials, highlighting the likely AEs of treatment and thereby increasing the likelihood of their occurrence.

Limitations

Our results should be interpreted with some caution given the limitations of our study design.

Firstly, although our measures of nocebo were calculated from the trial drop-outs designated as treatment-related, and the AEs that were classified as treatment-related, the inherent difficulty in attribution of non-specific symptoms has to be recognized as a potential source of bias. Secondly, nocebo severity is an indirect

estimation using dropout rate as a proxy measure. Thirdly, our literature search strategy was limited to the Medline database, which means that we may have missed studies that were unpublished or published only on other databases. Finally, we were able to perform secondary analyses only in depression and psychotic disorders' trials and therefore, whether the nocebo AE and nocebo dropout rates differ amongst other diseases where TMS has been tried, remains to be determined. However, the overall AE and dropout rates does not differ when looking separately at the pooled rates in depression and psychotic disorders, which account for half of the studies used for the primary analysis.

Conclusions

TMS is a safe and well-tolerated intervention. Nocebo phenomena do occur during TMS treatment, and should be acknowledged during clinical trial design and daily clinical practice.

Source of finding

None

Acknowledgments

This is a summary of independent research carried out at the NIHR Sheffield Biomedical Research Centre (Translational Neuroscience). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

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Conflict of interest

All authors report no disclosures related to the context of this article.

CAPTIONS

Table 1. Descriptive characteristics of studies included in the analysis

Table 2. Correlations between percentage of patients experience at least one adverse event (AE) or withdrawing because of AE and various parameters (TMS characteristics, study characteristics, demographics). After adjusting for multiple comparisons (n=14), level of statistical significance is set at $p<0.0036$). * Statistically significant correlation, after having adjusted for multiple comparisons.

Table 3. Nocebo adverse event (AE) and dropout rates per disease where TMS was studied.

Figure 1. PRISMA chart

Figure 2a. Forest plot showing that the odds of dropping out because of an adverse event did not differ between the placebo and TMS treatment arms

Figure 2b. Respective funnel plot

Figure 3a. Forest plot showing that the odds of experiencing an adverse event is higher in the TMS arm.

Figure 3b. Respective funnel plot

Figure 4. Forest plot showing that the odds of experiencing headache/discomfort is higher in the TMS arm.

Supplement 1. Studies included in this meta-analysis

Supplement 2. Study characteristics per study

Supplement 3. Breakdown of total JADAD score per study

APPENDIX 1

Author's name	Affiliations	Contribution
Panagiotis Zis	Academic Department of Neurosciences, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK Medical School, University of Cyprus, Nicosia, Cyprus	Study concept, drafting/revising the manuscript, data collection, statistical analysis, accepts responsibility for conduct of research and final approval.
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Daniel Blackburn	Sheffield Institute for Translational Neuroscience, Sheffield, UK	Drafting/revising the manuscript, accepts responsibility for conduct of research and final approval.
Annalena Venneri	Sheffield Institute for Translational Neuroscience, Sheffield, UK	Drafting/revising the manuscript, accepts responsibility for conduct of research and final approval.
Stamatina Iliodromiti	School of medicine, University of Glasgow, Glasgow, UK	Drafting/revising the manuscript, statistical analysis accepts responsibility for conduct of research and final approval.
Dimos-Dimitrios Mitsikostas	1st Neurology Department, Aeginition Hospital, National and Kapodistrian University, Athens, Greece	Drafting/revising the manuscript, accepts responsibility for conduct of research and final approval.
Ptolemaios G Sarrigiannis	Academic Department of Neurosciences, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK	Drafting/revising the manuscript, accepts responsibility for conduct of research and final approval.

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