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Chen R, Spencer DC, Weston J, Nolan SJ.
Transcranial magnetic stimulation for the treatment of epilepsy.
Cochrane Database of Systematic Reviews 2016, Issue 8. Art. No.: CD011025.
DOI: 10.1002/14651858.CD011025.pub2.

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[Intervention Review]

Transcranial magnetic stimulation for the treatment of epilepsy

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Editorial group: Cochrane Epilepsy Group.
Publication status and date: New, published in Issue 8, 2016.
Review content assessed as up-to-date: 10 March 2016.

Citation: Chen R, Spencer DC, Weston J, Nolan SJ. Transcranial magnetic stimulation for the treatment of epilepsy. *Cochrane Database of Systematic Reviews* 2016, Issue 8. Art. No.: CD011025. DOI: 10.1002/14651858.CD011025.pub2.

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ABSTRACT

Background

Epilepsy is a highly prevalent neurological condition characterized by repeated unprovoked seizures with various etiologies. Although antiepileptic medications produce clinical improvement in most individuals, nearly a third of individuals have drug-resistant epilepsy that carries significant morbidity and mortality. There remains a need for non-invasive and more effective therapies for this population. Transcranial magnetic stimulation (TMS) uses electromagnetic coils to excite or inhibit neurons, with repetitive pulses at low-frequency producing an inhibitory effect that could conceivably reduce cortical excitability associated with epilepsy.

Objectives

To assess the evidence for the use of TMS in individuals with drug-resistant epilepsy compared with other available treatments in reducing seizure frequency, improving quality of life, reducing epileptiform discharges, antiepileptic medication use, and side-effects.

Search methods

We searched the Cochrane Epilepsy Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO), MEDLINE (Ovid 1946 to 10 March 2016), ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (ICTRP) up to March 2016. We also searched SCOPUS (1823 to June 2014) as a substitute for Embase (but it is no longer necessary to search SCOPUS, because randomized controlled trials (RCTs) and quasi-RCTs in EMBASE are now included in CENTRAL).

Selection criteria

Eligible studies were RCTs that were double-blinded, single-blinded or unblinded, and placebo, no treatment, or active controlled, which used repetitive transcranial magnetic stimulation (rTMS) without restriction of frequency, duration, intensity, or setup (focal or vertex treatment) on patients with drug-resistant epilepsy. The search revealed 274 records from the databases, that after selection provided seven full-text relevant studies for inclusion. Of the seven studies included, five were completed studies with published data and included randomized, blinded trials. The total number of participants in the seven trials was 230.

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Data collection and analysis

We extracted information from each trial including methodological data; participant demographics including baseline seizure frequency, type of epileptic drugs taken; intervention details and intervention groups for comparison; potential biases; and outcomes and time points, primarily change in seizure frequency or responder rates, as well as quality of life and epileptiform discharges, adverse effects, and changes in medication use.

Main results

Two of the seven studies analyzed showed a statistically significant reduction in seizure rate from baseline (72% and 78.9% reduction of seizures per week from the baseline rate, respectively). The other five studies showed no statistically significant difference in seizure frequency following rTMS treatment compared with controls. We were not able to combine the results of the trials in analysis due to differences in the designs of the studies. Four studies evaluated our secondary endpoint of mean number of epileptic discharges, and three of the four showed a statistically significant reduction in discharges. Quality of life was not assessed in any of the studies. Adverse effects were uncommon among the studies and typically involved headache, dizziness, and tinnitus. No significant changes in medication use were found in the trials.

Authors' conclusions

Overall, we judged the quality of evidence for the primary outcomes of this review to be low. There is evidence that rTMS is safe and not associated with any adverse events, but given the variability in technique and outcome reporting that prevented meta-analysis, the evidence for efficacy of rTMS for seizure reduction is still lacking despite reasonable evidence that it is effective at reducing epileptiform discharges.

PLAIN LANGUAGE SUMMARY

Transcranial magnetic stimulation for treatment of epilepsy

Background

Epilepsy is a common neurological disorder that appears in various forms. Many individuals with epilepsy have satisfactory seizure control with the use of antiepileptic medications. Yet, nearly a third of individuals suffer from frequent and uncontrolled seizures despite taking medications, or find that they cannot tolerate the side-effects of those medications. Surgery is an option for some individuals with uncontrolled seizures, but it is invasive and not suitable for all individuals. Therefore, there remains a substantial unmet need for safe, effective therapies for these harder-to-treat epilepsies.

Transcranial magnetic stimulation (TMS) is one of several emerging treatments that can potentially offer individuals a safe and non-invasive alternative to epilepsy surgery. Long used as a research tool to study brain function, TMS has also been studied as a possible treatment for a number of neurological conditions, including epilepsy. This non-surgical and painless treatment uses induced magnetic currents to modulate brain function in order to reduce the tendency to have seizures.

Objective

This review aims to assess the evidence for the use of TMS in individuals with epilepsy compared with other available treatments in reducing seizure frequency, improving quality of life, reducing epileptiform discharges (sharp or spiking abnormalities on brain electrographic testing that suggest underlying brain disturbance or seizure tendency that can be focal, multifocal, or diffuse), antiepileptic medication use, and side-effects.

Methods

The last search for trials for this review was 10 March 2016. We assessed the evidence from seven randomized controlled trials (230 participants) comparing TMS to control treatments ('sham' (placebo)) TMS, antiepileptic medication, and low-frequency TMS). We were not able to combine the results of the trials in analysis due to differences in the designs of the studies; therefore, we have summarized the results of the seven studies narratively.

Results

Some of the trials show that TMS reduces the number of seizures individuals had compared to before the therapy, but other trials did not show any significant differences in seizure frequency. Four trials showed a reduction in epileptiform discharges following TMS

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treatment. None of the studies measured changes in quality of life, and only one trial reported an increase in antiepileptic medication in a single person. Side-effects were not commonly reported; the most frequent side-effect reported was headache (and the majority of individuals completed the treatment with TMS).

Quality of the evidence

Overall, we judged the quality of the evidence in this review for the main outcome of reduction in seizure frequency to be low due to unclear information in the published papers about how the studies were designed and unclear presentation of results. This review provides no information about the effect of TMS on quality of life. It is important that future studies are larger and measure important outcomes, such as the effect of TMS on reducing seizure frequency, improving quality of life, and any side-effects associated with TMS compared with other available treatments.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Repetitive transcranial magnetic stimulation (rTMS) compared with control for epilepsy

Patient or population: adults and children with epilepsy
Settings: outpatients
Intervention: repetitive transcranial magnetic stimulation (rTMS)
Comparison: control treatment (see footnote 1)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)[2]	No. of Participants (studies)	Quality of the evidence (GRADE)[2]	Comments
	Assumed risk	Corresponding risk				
	Control treatment[1]	Repetitive transcranial magnetic stimulation (rTMS)				
Reduction in seizure frequency: the proportion of people with a 50% or greater reduction in seizure frequency following the treatment period	See comment	See comment	Not estimable	99 (3 studies)	⊕⊕◯◯ **low**[3,4]	In one study (Fregni 2006), there was a statistically significant advantage to rTMS compared with sham rTMS, and in the two other studies no statistically significant difference was found between rTMS and sham rTMS (Cantello 2007) or non-focal rTMS (Joo 2007)
Reduction in seizure frequency: the difference in pre- and post-treatment seizure rates	See comment	See comment	Not estimable	215 (7 studies)	⊕⊕◯◯ **low**[3,5]	Three studies reported statistically significant reductions in seizure rates post-treatment in the rTMS group (Fregni 2006; Sun 2012;

						Tergau 2003), while four studies did not find a statistically significant reduction in seizure frequency in the rTMS group (Cantello 2007; Joo 2007; Theodore 2002; Wang 2008) Between-group differences were not reported
Improvement in quality of life: the difference in quality of life scores for participants surveyed before and after treatment	Not reported	Not reported	Not estimable	NA	NA	Quality of life was not reported in any of the included studies

*The basis for the **assumed risk** and the **corresponding risk** are the narrative summaries of the studies contributing to each outcome. A **relative effect** is not estimable as meta-analysis was not performed[2]
CI: Confidence interval; NA: not available

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Control treatments were sham rTMS (placebo), antiepileptic drug treatment, low-intensity rTMS (compared with high-intensity rTMS) and non-focal rTMS (compared with focal rTMS).
[2]Due to variation in study design, interventions, and outcomes measured in the seven studies, we deemed meta-analysis to not be appropriate and we discussed the seven studies narratively in the review. The GRADE judgement for each outcome is based on the characteristics and narrative results of the studies which contribute to each outcome.
[3]Downgraded due to unclear design and methodological information in the included studies (unclear risk of bias).
[4]Downgraded due to imprecision; small number of participants contribute to the outcome.
[5]Presentation of results did not allow for comparisons between rTMS and control, only within rTMS group were pre- and post-treatment seizure rates available.

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BACKGROUND

Description of the condition

Epilepsy is a highly prevalent neurological disorder affecting an estimated 70 million people worldwide (Ngugi 2010). There are 50 new cases per 100,000 people globally each year and up to 82 new cases per 100,000 people in developing countries (Ngugi 2011). One of the world's oldest recognized conditions, epilepsy affects all age groups and has various presentations and causes. Epilepsy is characterized by repeated unprovoked seizures (episodes of continual discharges of brain activity) and can be considered a consequence of an underlying condition, such as a tumour, or of genetic alterations, brain malformations, infection, intoxication, or another illness (Shorvon 2011). Although antiepileptic medications produce clinical improvement, enabling most individuals to control their seizures, a 2008 study conducted in France estimated that 22.5% of individuals have 'drug-resistant' epilepsy (Picot 2008), leading to increased risks of premature death, injury, psychosocial dysfunction, and a reduced quality of life (Kwan 2011). Individuals whose epilepsy is resistant to medication may pursue alternative therapies including surgery, high-fat, low-carbohydrate diets, and vagus nerve stimulation. Although these other therapies can be quite effective, they have limitations in that the diets have poor adherence and the procedural treatments are invasive and effective only in selected populations. Therefore, there remains a need for non-invasive and more effective therapies.

Description of the intervention

Transcranial magnetic stimulation (TMS) was developed in 1985 in the UK to study and map different areas of brain activity (Kimiskidis 2010). In the study of epilepsy, TMS has been used to probe cortical excitability in various epilepsy syndromes, to assess the effects of antiepileptic drugs on the brain, and to help identify areas of the brain more prone to seizure for surgical removal (Kimiskidis 2010). Once it became known that repeated pulses of TMS could either excite or suppress neural activity for a prolonged period of time, TMS was studied as a potential therapy for a number of neurological and psychiatric conditions, ranging from stroke to depression to amyotrophic lateral sclerosis (Ridding 2007). Recently, studies have looked at TMS as a potential treatment for epilepsy (Kimiskidis 2010). TMS is a procedure that uses magnetic fields to stimulate nerve cells in the brain to improve the symptoms of epilepsy. With TMS, a large electromagnetic coil is placed against the scalp. The electromagnet creates electrical currents that stimulate nerve cells in the region of the brain involved in epilepsy.

How the intervention might work

The prolonged inhibitory effects of TMS are thought to reduce cortical hyperexcitability associated with various epilepsies. Although the exact mechanisms remain a topic of active investigation, emerging evidence suggests TMS can generate either excitatory or inhibitory responses in cortical tissue. A TMS device employs either one or two copper coils, positioned superficial to a site of interest in the brain, to non-invasively produce a brief (100 to 400 μs) magnetic pulse (generating a 1.5 to 2 T magnetic field) to an estimated depth of ~2 cm. This magnetic pulse induces an electrical current in a patch of cortical tissue of a few square centimetres, causing a depolarisation of nearby axons (Reithler 2011). Such local stimulation can even affect distant areas in ways that are poorly understood (Reithler 2011). It has been observed that repetitive pulses of TMS can cause long-lasting effects, persisting for more than one hour after a treatment (Huang 2005). Aside from physical positioning of the device, there is no known way to target particular cell types and various interactions between excitatory and inhibitory processes may occur. However, repetition at higher frequencies generally has an overall excitatory effect while, conversely, low-frequency repetitive pulses have an inhibitory effect on neurons and may suppress the activity related to seizures. Earlier animal studies showed that a single TMS pulse follows a particular time course, producing an initial facilitation or excitation followed by delayed and prolonged suppression (Moliadze 2003). Thus, low-frequency repetitive stimulation has been hypothesized to result in prolonged synaptic depression when each incoming pulse arrives during the late inhibitory phase produced by the previous pulse, however this has not been not proven (Reithler 2011). Other important parameters in the use of TMS include intensity and duration.

Why it is important to do this review

Repetitive transcranial magnetic stimulation (rTMS) is an emerging therapy for epilepsy, a highly prevalent neurological condition for which a significant proportion of individuals do not achieve an adequate response to medications. Drug-resistant epilepsy is associated with reduced quality of life and such individuals often face surgery or other invasive therapies, which carry significant risks. Even individuals responsive to pharmacological therapy may struggle with the possible adverse effects of their medications. In contrast, rTMS is a painless, non-invasive approach that, if effective, could have significant advantages over both antiepileptic drugs and surgical management. This systematic review will clarify the available scientific evidence to help clinicians and individuals assess the safety and effectiveness of this approach for the treatment of epilepsy.

OBJECTIVES

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To assess the evidence for the use of TMS in individuals with drug-resistant epilepsy compared with other available treatments in reducing seizure frequency, improving quality of life, reducing epileptiform discharges, antiepileptic medication use and side-effects.

METHODS

Criteria for considering studies for this review

Types of studies

Eligible studies included:

1. randomized controlled trials (RCTs);
2. double, single or unblinded;
3. placebo/sham-controlled, no treatment or active controlled (e.g. antiepileptic drug treatment).

Types of participants

Any participant of any age, with any type of drug-resistant epilepsy syndrome, which includes unclassified types of epilepsy and post-surgical epilepsy participants.

Types of interventions

Repetitive transcranial magnetic stimulation of any frequency, either single or double-coiled, for any duration and at any intensity added to current therapy or used as single therapy.

Types of outcome measures

Primary outcomes

Reduction in seizure frequency

- The proportion of people with a 50% or greater reduction in seizure frequency following the treatment period.
- The difference in pre- and post-treatment seizure rates.

Improvement in quality of life

- The difference in quality of life scores for participants surveyed before and after treatment.

Secondary outcomes

Reduction in epileptiform discharges

Mean number of epileptiform discharges seen on electroencephalography (EEG) during the period between seizures.

Adverse effects

The proportion of people experiencing any of the following adverse effects that are considered to be common and important potential adverse effects of transcranial magnetic stimulation.

- Behavioral changes
- Cognitive disturbances
- Headache
- Tinnitus
- Pain/discomfort
- Sedation
- Seizures

The proportion of people experiencing the six most common adverse effects, if different from the list above.

Changes in medication requirements

- The proportion of people who required fewer seizure medications after treatment.
- The proportion of people who required more seizure medications after treatment.
- The proportion of people who had no changes to their medication after treatment.

Treatment withdrawal

- The proportion of people withdrawn from the study for any reason.
- The proportion of people withdrawn from the study due to lack of efficacy or adverse effects.

Search methods for identification of studies

Electronic searches

We searched the following databases.

- Cochrane Epilepsy Group Specialized Register (searched 10 March 2016), using the search strategy outlined in Appendix 1.
- Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 2) via the Cochrane Register of Studies Online (CRSO; searched 10 March 2016), using the search strategy outlined in Appendix 2.
- MEDLINE Ovid (1946 to 10 March 2016), using the search strategy outlined in Appendix 3.

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- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 10 March 2016), using the following search strategy: transcranial magnetic stimulation AND epilepsy NOT NCT*.
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 10 March 2016), using the following search strategy: 'transcranial magnetic stimulation' AND epilepsy.

In addition, we searched SCOPUS (1823 to 1 June 2014) as a substitute for Embase, using the search strategy outlined in Appendix 4, but it is no longer necessary to search SCOPUS, because RCTs and quasi-RCTs in Embase are now included in CENTRAL. We did not impose any date or language restrictions.

Searching other resources

We checked the reference lists of retrieved reports for additional reports of relevant studies. We contacted the authors of any conference proceedings to identify any unpublished data and experts in the field to identify any further ongoing trials.

Data collection and analysis

Selection of studies

Two review authors (RC and DS) independently assessed articles for inclusion. Any disagreements were resolved though mutual discussion; failing this, advice from a third party (JW or SN) was sought and a consensus determination was made.

Data extraction and management

We extracted the following information from each trial using a data extraction sheet.

Methodological/trial design

1. Method of randomisation and allocation concealment.
2. Method of blinding.
3. Number of people excluded from reported analyses.
4. Duration of baseline period.
5. Duration of treatment period.

Individual participant/demographic information

1. Total number of participants allocated to each treatment group.
2. Age/gender.
3. Number of participants within each epilepsy type.
4. Seizure frequency during baseline period.
5. Type of background antiepileptic drugs taken.

Intervention

1. Total number of intervention groups and comparisons.
2. Intervention details.
3. Potential biases.

Outcomes

1. Outcomes and time points reported.
2. Definition of outcome.
3. Unit of measurement.

Assessment of risk of bias in included studies

Two review authors (RC and DS) independently assessed the risk of bias for each trial using the Cochrane 'Risk of bias' tool as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We discussed any disagreements and reached a consensus. If an agreement could not be made, a third party opinion (JW or SN) was sought. We rated included studies as high, low or unclear risk of bias on six domains of bias applicable to RCTs: method of randomisation, method of concealing allocation, method of blinding, incomplete outcome data, selective outcome reporting, and other sources of bias.

Measures of treatment effect

We intended to present an overall effect estimate for seizure reduction as a risk ratio. We intended to present an overall effect estimate for the difference in pre- and post-treatment seizure rates and the reduction in the number of epileptiform discharges seen on EEG during the period between seizures as a mean difference. We intended to present overall effect estimates for adverse effects, changes in medication requirements, and withdrawals as risk ratios. We intended to present an overall estimate for the difference in quality of life scores before and after treatment as mean difference (or standardized mean difference if varying quality of life scales were used across studies).

Unit of analysis issues

Seizure reduction may be reported using different measures in trials. In this event, we sought data from study authors in order to obtain data suitable to be combined in meta-analysis. The unit of analysis in all included studies was the individual.

If future updates of this review include studies with units of analysis other than the individual (e.g. cluster-randomized studies), we will implement the methods described in Chapter 16.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We included two cross-over studies in the review. We would have liked to have analysed the results of these studies via paired analyses, taking account of the correlated structure of the treatment groups (Elbourne 2002), however insufficient data were presented in the publications for such an analysis and we have narratively presented the results of the studies.

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Dealing with missing data

We sought missing data from study authors. We intended to carry out intention-to-treat, best-case, and worst-case analyses in order to account for any missing data (see Data synthesis for details). We intended to present all analyses in the main report.

Assessment of heterogeneity

We intended to assess clinical heterogeneity by comparing important participant and intervention factors among trials including: age, seizure type, duration of epilepsy, number and type of antiepileptic drugs taken at time of randomisation, study methods, loss to follow-up, and missing data. We intended to examine statistical heterogeneity using a Chi^2 test for heterogeneity and the I^2 statistic. Providing no significant heterogeneity is present ($P > 0.1$), we intended to employ a fixed-effect meta-analysis. In the event heterogeneity is found to be present, we intended to carry out a random-effects analysis and present both results in the main report.

Assessment of reporting biases

We assessed the included studies for reporting biases using the Cochrane 'Risk of bias' tool. In the event outcome reporting bias was suspected, we investigated this using the ORBIT classification system (Kirkham 2010). We requested all protocols from study authors to enable a comparison between a list of a priori listed outcomes and what was reported in the matching papers. We intended to examine publication bias via asymmetry of funnel plots if ten or more trials had been combined. However, as insufficient studies were included in the review, we made an informal assessment by identifying certain aspects of each study, including sponsors of the research and research teams involved.

Data synthesis

We were not able to perform meta-analysis of the included studies in this review due to variation in study design, interventions, and outcomes measured.

However, for future updates of the review, if further studies are included and meta-analysis is possible, we intend to employ a fixed-effect meta-analysis to synthesise data, or in the case that substantial heterogeneity is present, a random-effects method (see Assessment of heterogeneity). Comparisons we expect to carry out include:

1. intervention group versus control on seizure reduction;
2. intervention group versus control on reduction in epileptiform discharges;
3. intervention group versus control on adverse effects;
4. intervention group versus control on treatment withdrawal.

We will stratify each comparison by type of control group (e.g. placebo, other active treatment, no treatment) to enable appropriate combination of study data.

Our preferred effect estimate is a risk ratio. For all outcomes, except adverse effects, we will use 95% confidence intervals. For individual adverse effects we will use 99% confidence intervals to make allowance for multiple testing.

All analyses will include all participants in the treatment group to which they were allocated. For the efficacy outcome of seizure reduction we intend to employ three analyses as follows.

1. Primary (intention-to-treat) analysis: participants not completing follow-up or with inadequate seizure data were assumed non-responders. To test the effect of this assumption, we employed the following sensitivity analyses.
2. Worst-case analysis: participants not completing follow-up or with inadequate seizure data were assumed non-responders in the magnetic stimulation group, and responders in the control group.
3. Best-case analysis: participants not completing follow-up or with inadequate seizure data were assumed responders in the magnetic stimulation group and non-responders in the control group.

'Summary of findings' and quality of the evidence (GRADE)

In a post-hoc change from the protocol, we have added a 'Summary of findings' table to the review (Summary of findings for the main comparison), reporting the primary outcomes of the review (reduction in seizure frequency and quality of life).

We determined the quality of evidence using the GRADE considerations of study limitations, consistency of effect, imprecision, indirectness, and publication bias (Atkins 2004).

We downgraded evidence by one level if we considered the limitation serious and two levels if considered very serious. Under the GRADE approach, evidence may also be upgraded if a large treatment effect is demonstrated with no obvious biases or if a dose-response effect exists.

Subgroup analysis and investigation of heterogeneity

If further studies are included in the update of this review and meta-analysis is possible, we intend to carry out subgroup analysis of any variable trial and participant characteristics (e.g. cross-over compared to parallel trial design, adults compared to children, epilepsy types etc.) to explore heterogeneity, if this is found.

Sensitivity analysis

If further studies are included in the update of this review and meta-analysis is possible, we intend to carry out sensitivity analysis if deemed appropriate, including the sensitivity analysis described in Data synthesis to account for the presence of missing data. If peculiarities were found between studies with regards to quality, characteristics of participants, interventions and/or outcomes, we would conduct a sensitivity analysis to explore these differences.

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RESULTS

Description of studies

Results of the search

The search revealed 274 records from the databases outlined in Electronic searches. After we removed duplicates (92), we screened the remaining 182 records for eligibility. We excluded 173 studies at this point due to irrelevance and one study was an ongoing study (NCT01745952). This left eight full-text articles to be assessed, of which we included seven in the review (Cantello 2007; Fregni 2006; Joo 2007; Sun 2012; Tergau 2003; Theodore 2002; Wang 2008), and excluded one due to study design (NCT00382707); see Included studies and Excluded studies for further information. Due to variation in study design, interventions, and outcomes measured in the seven studies, we deemed meta-analysis to not be appropriate and we have discussed the seven studies narratively within the review, see Figure 1 for further information.

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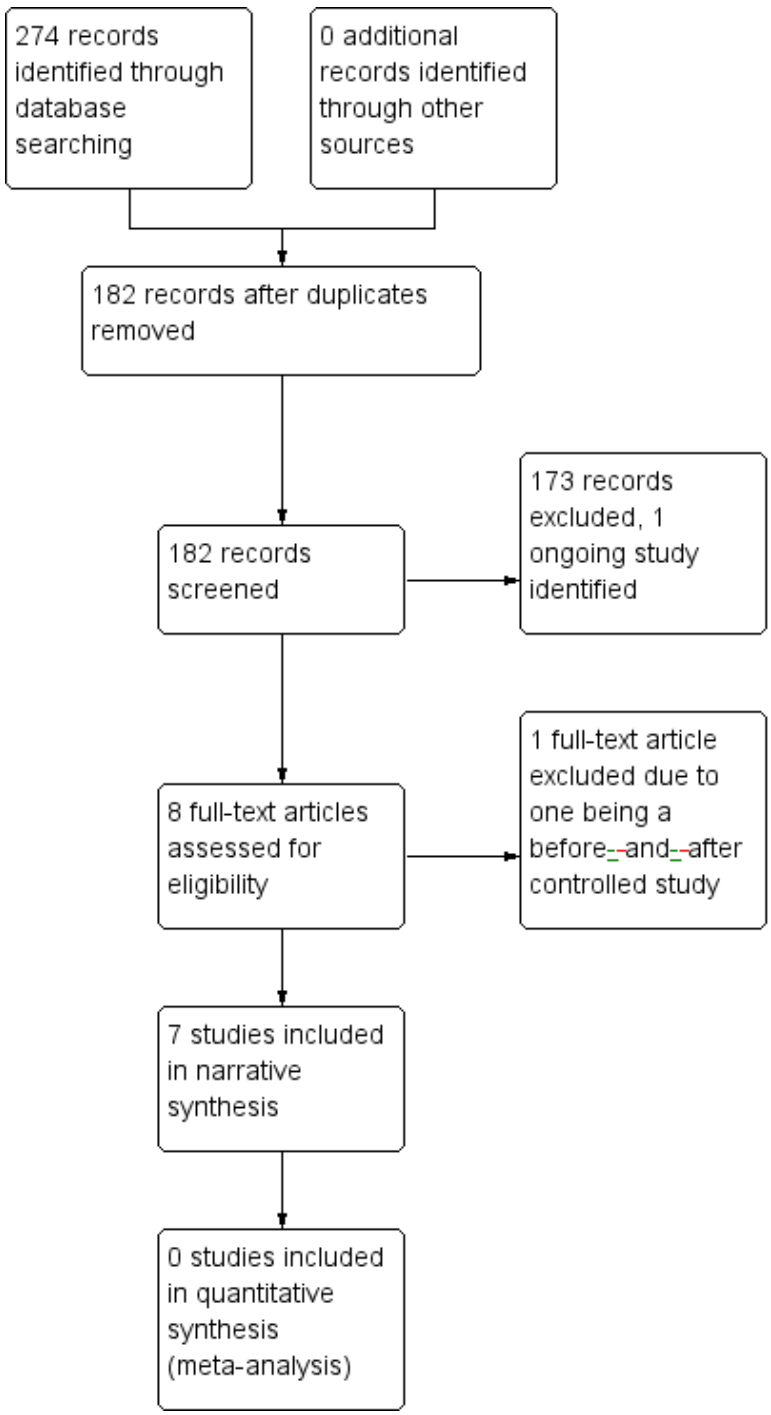
Figure 1. Study flow diagram.



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Included studies

We included seven randomized controlled trials (RCTs) that compared repetitive transcranial magnetic stimulation (rTMS) with active or placebo controls (Cantello 2007; Fregni 2006; Joo 2007; Sun 2012; Tergau 2003; Theodore 2002; Wang 2008). Three studies were placebo controlled (Cantello 2007; Fregni 2006; Theodore 2002), one study compared transcranial magnetic stimulation (TMS) of different intensities (Sun 2012), one study compared TMS of different intensities with placebo (Tergau 2003), one study compared focal to non-focal application of TMS (Joo 2007), and one study compared TMS with antiepileptic drug treatment (Wang 2008).

All recruited participants had drug-resistant epilepsy of varying definitions across studies; generally defined as at least one complex partial or secondarily generalized seizure per month (but most required 3 or more seizures per week) and an unchanging drug regimen of at least two antiepileptic medications. All used standard figure-8 coils to deliver rTMS, although sham methods differed.

Cantello 2007 presented an Italian multi-center, cross-over trial that was a randomized, double-blind, sham-controlled trial, with a pre-treatment period of 12 weeks, five days of active treatment, and a follow-up evaluation period of six weeks. Forty-three participants were randomized to either active first or placebo first treatment with six weeks of follow-up after each treatment phase (active or sham). Active rTMS was administered twice daily for five days using two circular coils of 500 stimuli at 0.3 Hz, separated by a 30-second interval at an intensity of 100% of resting motor threshold (RMT).

Fregni 2006 published a randomized, double-blind, sham-controlled trial in Brazil with a baseline period of four weeks, five days of active treatment, and a post-treatment evaluation period of eight weeks. Twenty-one participants were randomized to active (n = 12) and sham (n = 9) treatment arms. For the treatment group, the participants received either focal rTMS, based on the known location of abnormalities on their electroencephalography (EEG), or at midline (CZ site) if there were diffuse EEG abnormalities. They were administered rTMS for 20 minutes a day for five days at settings of 1 Hz, 1200 pulses, at 70% of RMT intensity.

Joo 2007 presented results from their Korean study, which was a randomized, double-blind, but not placebo controlled study. They used a baseline surveillance period of eight weeks, five days of active treatment, and a post-treatment evaluation period of eight weeks. Thirty-five subjects with focal, non-focal, or multifocal epilepsy were randomized into one of four subgroups (F-1500, F-3000, NF-1500, NF-3000) to either receive focal or non-focal rTMS for five days, delivering a total of either 1500 (50 minutes) or 3000 pulses (100 minutes) a day, at an intensity of 100% of RMT, 0.5 Hz frequency. The participants were assessed with daily symptom logs before the treatment period and at eight weeks post-stimulation.

Sun 2012 presented a Chinese randomized, single-blind, non-placebo controlled study with a baseline evaluation period of four weeks, two weeks of active treatment and eight weeks of clinical follow-up. Sixty participants were randomized to one of two treatment arms: high-intensity rTMS at 90% of RMT (n = 31) and low-intensity rTMS at 20% RMT (n = 29). rTMS was delivered three times a day for two weeks to the focal epileptic zone best reflected on EEG with 500 stimuli at 0.5 Hz, separated by a 600-second interval.

Tergau 2003 presented an interim analysis of a randomized, multi-center, cross-over study conducted over three centers in Germany with three treatment arms; placebo stimulation, 0.333 Hz stimulation and 1 Hz stimulation. Baseline period was three months, treatment periods were five days followed by a four week observation period. All three treatment periods were separated by at least eight weeks. Treatment was delivered unifocally for all three arms, with 1000 pulses each day (500 monopolar pulses with clockwise current direction followed directly by 500 pulses in anticlockwise direction). Data were available for 17 participants in the interim analysis who had received all three treatments.

Theodore 2002 published a randomized, double-blind, placebo controlled trial conducted at the National Institutes of Health, with a baseline evaluation of eight weeks, one week of active treatment, and a post-treatment follow-up period of eight weeks. Their study randomized 24 participants with localization-related drug-resistant epilepsy into active (n = 12) and placebo (n = 12) treatment arms. rTMS was administered at an intensity of 120% RMT at 1 HZ frequency, for 15 minutes, twice a day, for one week.

Wang 2008 presented a randomized, open-label, antiepileptic drug controlled trial at a single center in China. Fifteen participants were randomized to 1 Hz TMS at 90% RMT threshold, simulation frequency of 500 times, once a day for seven days and 15 participants were randomized to 600 mg to 800 mg oral carbamazepine per day for at least 60 days. Outcomes were measured 30 days after treatment with TMS.

Excluded studies

We only excluded one study from the review after full-text evaluation (NCT00382707). This was due to the study design, as the trial was a controlled before-and-after study, and not a RCT.

Risk of bias in included studies

Two review authors (RC and DS) independently made an assessment of the risk of bias for each trial using the Cochrane 'Risk of bias' tool as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements were

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discussed and resolved by consensus or discussion with a third review author (JW or SN). We assessed six domains for each trial: allocation concealment, randomization method, blinding, completeness of data, selective outcome reporting, and other bias. Notable risks of bias are highlighted as follows. We considered Wang 2008, a randomized but open-label study, to be at high risk of detection bias, as outcome assessors were not blinded. We deemed Tergau 2003, an interim analysis, to be at high risk for attrition bias due to incomplete outcome data and unclear risk of performance bias, since blinding was not described. We found Joo 2007 to have a high risk of reporting bias as no primary or secondary outcomes were defined in their methods section. The majority of studies showed unclear risk of selection bias when the allocation concealment method was not specified. More detailed findings for each study are summarized below in the 'Risk of bias' tables and in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

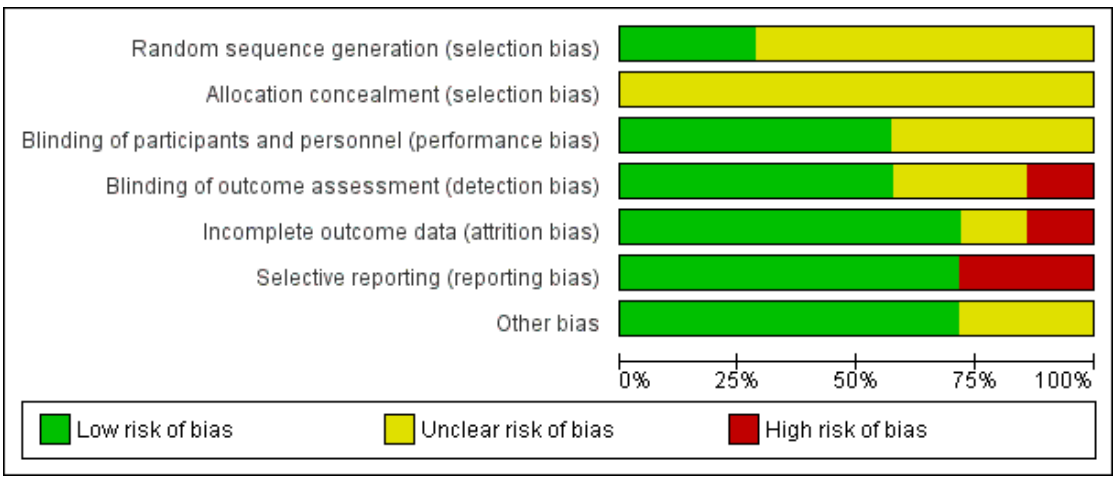

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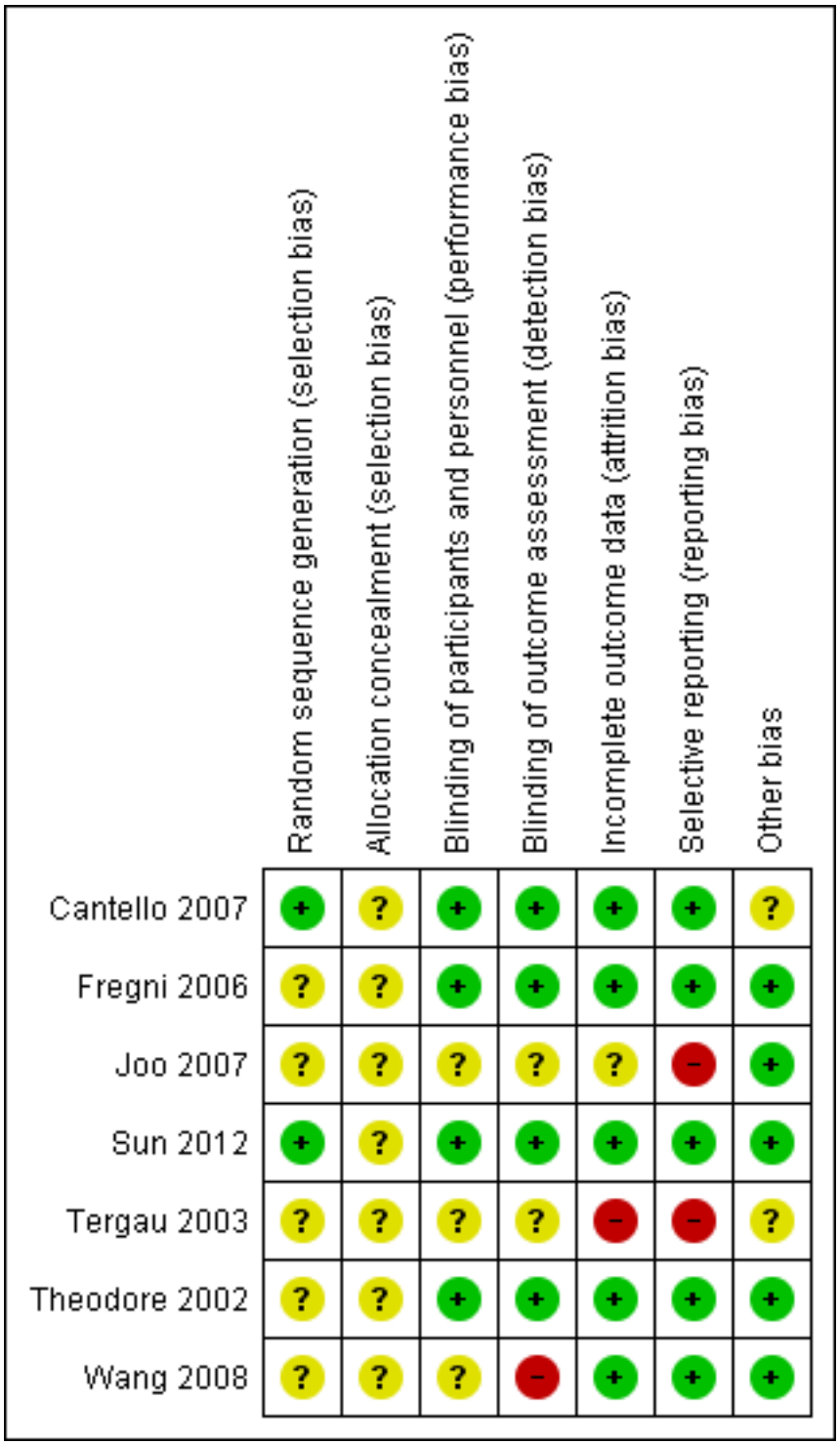
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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Allocation

Two studies described adequate methods of generating random sequences (computer-assisted generation of random sequence) and we judged them to be at low risk of bias (Cantello 2007; Sun 2012). Three studies described that studies were 'randomized' but no information was provided on methods of generating random sequences (Tergau 2003; Theodore 2002; Wang 2008), and one study reported that a "randomization code" was used but with no details of how the code was generated (Joo 2007). We judged these four studies to be at unclear risk of bias. One study stated that the 'order of entrance' into the trial was used as well as computer-generated randomization blocks (Fregni 2006). It is unclear exactly how the 'order of entrance' was taken into account in the randomization and whether this could have led to a predictable randomisation sequence, and so we judged this study to be at unclear risk of selection bias.

None of the studies reported how allocation was concealed and so we judged all seven studies to be at unclear risk of bias.

Blinding

Five of the seven studies were described as "double-blind" (Cantello 2007; Fregni 2006; Joo 2007; Sun 2012; Theodore 2002). In four of the five studies, only the investigator(s) responsible for initiating rTMS treatment were not blinded; participants, all other personnel and outcome assessors were blinded and so we judged these four studies to be at low risk of performance and detection bias (Cantello 2007; Fregni 2006; Sun 2012; Theodore 2002). In the other study (Joo 2007), only blinding of the EEG reader was described; it was unclear if participants and other personnel and outcome assessors were blinded and so we judged this study to be at unclear risk of performance and detection bias.

In Tergau 2003, blinding of interventions was not mentioned, even though a 'placebo stimulation' was used; we judged this study to be at unclear risk of performance and detection bias.

Wang 2008 randomized participants to TMS or drug treatment and so blinding or participants and personnel would not be possible by design; it is unclear how this design may have influenced outcomes and so we judged this study to be at unclear risk of performance bias. Blinding of outcome assessors in a trial of this design would be possible, however it appears that outcome assessors were not blinded and so we judged this study to be at high risk of detection bias.

Incomplete outcome data

In five studies there were no apparent missing data, study attrition was reported (if any withdrawals occurred from the study), and an intention-to-treat (ITT) approach to analysis was used and so we judged these five studies to be at low risk of attrition bias (Cantello 2007; Fregni 2006; Sun 2012; Theodore 2002; Wang 2008).

In one study there were no apparent missing data and no withdrawals from treatment reported, but ITT analysis is not specified and so we judged this study to be at unclear risk of attrition bias (Joo 2007).

In Tergau 2003, an interim analysis is presented for 17 participants out of 28 randomized (5 participants were yet to complete the study and 6 had dropped out). An ITT approach was not used to analysis and it was unclear when participants dropped out and how many of the cross-over arms had been completed. We judged this study to be at high risk of attrition bias.

Selective reporting

Study protocols were not available for any of the included studies and so we made a judgement regarding selective reporting bias based on study publications alone. In five studies, all primary and secondary outcomes stated in the methods section were reported in the results and all expected outcomes were reported and so we judged these studies to be at low risk of reporting bias (Cantello 2007; Fregni 2006; Sun 2012; Theodore 2002; Wang 2008).

In two studies (Joo 2007; Tergau 2003), no primary or secondary outcomes were specified in the methods section and so we judged that the results of these studies were at high risk of selective reporting bias.

Other potential sources of bias

In five studies, we did not identify any other sources of bias and so we judged these studies to be at low risk of bias (Fregni 2006; Joo 2007; Sun 2012; Theodore 2002; Wang 2008).

In the two included cross-over studies (Cantello 2007; Tergau 2003), the carryover effect was not formally assessed but the observation period of six weeks and eight weeks, respectively, between treatments is likely to be a sufficient "washout period". However, it was not stated in either of these studies how many participants were randomized to each treatment arm first and whether these randomized groups were balanced for clinical demographics at baseline. Furthermore, for Tergau 2003, it is unclear how a three-arm cross-over trial design was to be implemented and so we judged these studies to be at unclear risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Repetitive transcranial magnetic stimulation (rTMS) compared with control for epilepsy

Due to variation in study design, interventions, and outcomes measured in the seven studies, we deemed meta-analysis to not be

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appropriate and we discussed the seven studies narratively within the review. See Summary of findings for the main comparison for a summary of the quality of evidence for the primary outcomes of the review.

Primary outcomes

Reduction in seizure frequency

The proportion of people with a 50% or greater reduction in seizure frequency following the treatment period

Three studies reported on this primary outcome. Only Fregni 2006 reported a statistically significant and high responder rate of 10 out of 12 participants in their intervention arm experiencing > 50% reduction in seizures (including 3 participants who were seizure-free) compared with zero responders in the sham procedure group. The proportion of responders was not statistically different between the intervention and sham arms in Cantello 2007. For example, four weeks after treatment, 9/43 and 3/43 participants in the active and sham procedure groups, respectively, exhibited a 50% reduction of seizures, but this was not a statistically significant difference. Joo 2007 also reported no statistically significant difference in responder rates, but compared only focal versus non-focal use of TMS without a placebo control. The other four studies did not report on this outcome.

The difference in pre- and post-treatment seizure rates

All seven of the studies reported on this primary outcome, however generally within-treatment group results were reported rather than comparisons between treatment groups. Fregni 2006 showed a statistically significant reduction of seizure frequency by 72% of baseline after two weeks of treatment that continued (53% at 4 weeks, 58% at 8 weeks) in the active treated group. There was no significant change in seizure frequency in the sham treated group. Sun 2012 also reported a statistically significant 78.9% reduction of seizure frequency from baseline (8.9 to 1.8 seizures per week) in the high-intensity treatment group. There was no significant change in frequency after treatment in the low-intensity treatment group. The study did not have a placebo control group. In Theodore 2002, there was no significant reduction in seizure frequency in either the active or placebo groups, although a trend was reported. The study by Tergau 2003 showed no significant reduction of seizure frequency in the two intervention groups (0.333 Hz and 1.0 Hz) compared with placebo overall. However, there was a statistically significant, approximately 40% reduction in seizure frequency two weeks following intervention when compared with baseline. This difference was not significant when compared with placebo. Similarly, Joo 2007, Cantello 2007, and Wang 2008 reported no significant reduction in seizure frequency in either treatment group.

Improvement in quality of life

The difference in quality of life scores for participants surveyed before and after treatment

None of the studies reported on this primary outcome.

Secondary outcomes

Reduction in epileptiform discharges

Mean number of epileptiform discharges seen on electroencephalography (EEG) during the period between seizures

Four of the studies reported on this secondary outcome. Fregni 2006 reported a statistically significant reduction of epileptiform discharges in the active treatment group of 31% immediately after the five-day treatment and 16% at four weeks prior to washing out. There was no significant change in number of epileptiform discharges in the sham group. Sun 2012 reported a significant reduction of epileptiform discharges to 65.8% in the first 24 hours in the high-intensity treatment group, whereas the number of epileptiform discharges did not change from baseline in the low-intensity treatment group. In Cantello 2007, the mean reduction in number of epileptiform discharges was not statistically significant. In Joo 2007, epileptiform discharges were significantly reduced by 54.9% after rTMS treatment in all groups combined. In Theodore 2002, Wang 2008, and Tergau 2003, the mean number of epileptiform discharges were not studied. Two of the studies reported a responder rate based on epileptiform discharges. For example, Cantello 2007 reported a statistically significant decrease in epileptiform discharges by 50% or more from baseline in one-third of the participants receiving rTMS versus less than 5% of those receiving sham treatment. Wang 2008 noted there were significantly fewer participants with epileptiform discharges after treatment with rTMS (27% of participants) than in the drug-only group (73% of participants), compared with 100% with such discharges at baseline.

Adverse effects

Seven of 43 participants in Cantello 2007 experienced adverse effects without a significant difference between active and sham treatments, with dizziness and headache reported most frequently.

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Sun 2012 had two participants who experienced mild adverse effects such as headache and tinnitus in the high-intensity group. Theodore 2002 reported rare adverse effects, with one patient reporting mild discomfort and another patient withdrawing after having a seizure during treatment (but then had 80% decrease in seizure frequency 2 weeks after treatment). In Joo 2007, five of 35 participants complained of a mild and transient headache during and immediately after rTMS. Several participants had a mild headache and one had insomnia in the Fregni 2006 group, with no significant difference between the intervention and sham groups. Five of 15 participants in the rTMS group experienced headache in the Wang 2008 study compared with none in the placebo group. Tergau 2003 reported no significant side-effects of rTMS.

Changes in medication requirements

The proportion of people who required fewer seizure medications after treatment

None of the studies reported on this outcome.

The proportion of people who required more seizure medications after treatment

Only one study reported on this outcome. One out of nine participants after sham treatment compared with 0 of the active treatment participants required an increase in medication in the Fregni 2006 study.

The proportion of people who had no changes to their medication after treatment

None of the studies reported on this outcome.

Treatment withdrawal

The proportion of people withdrawn from the study for any reason

Six of the studies reported on this outcome. Cantello 2007, Fregni 2006, and Joo 2007 reported no withdrawals in any of their participants. Sun 2012 had no withdrawals in the high-intensity treatment group, but two out of 29 participants were lost to follow-up in the low-intensity treatment group. In Theodore 2002, one of 12 active participants developed an unrelated medical condition (cancer of the colon) and was not included in the eight-week analysis. Another active participant did not complete the full week of stimulation due to having had a seizure during stimulation. One control participant did not keep evaluable seizure calendars for the post-treatment period and had reported a seizure frequency eight times the population mean during baseline and was not included in the analysis. In Tergau 2003, out of 28 patients enrolled, five are yet to complete the study and six were dropped from analysis without a reason given. Treatment withdrawal was not reported by Wang 2008.

The proportion of people withdrawn from the study due to lack of efficacy or adverse effects

Withdrawals were reported as above and were rare. The only instance when withdrawal was noted to be due to an adverse effect was in one of 12 active participants in Theodore 2002 after experiencing a seizure during stimulation.

DISCUSSION

Summary of main results

Of the seven studies included in the review, five were completed and published studies, and included randomized, blinded trials (Cantello 2007; Fregni 2006; Joo 2007; Sun 2012; Theodore 2002). Two of the studies showed a statistically significant reduction in seizure rate from baseline (72% and 78.9% reduction of seizures per week from the baseline rate, respectively) (Fregni 2006 and Sun 2012). Three randomized, blinded trials showed no statistically significant difference in seizure frequency following rTMS treatment compared with controls (Cantello 2007; Joo 2007; Theodore 2002). Across studies, seizure frequency and seizure rates were reported by different measures, time points, and techniques which precluded comparison between groups.

The other studies reviewed included Wang 2008, which was an open-label study which showed no significant effect of intervention, and Tergau 2003, an interim analysis. There was a trend towards response reported in Tergau 2003 at two weeks after repetitive transcranial magnetic stimulation (rTMS) with the 0.333 Hz stimulation subgroup with a 40% reduction in seizure frequency compared with baseline that failed to reach significance when compared with the placebo group. Of the three studies that reported on the proportion of responders (Cantello 2007; Fregni 2006; Joo 2007), only Fregni 2006 showed a significant high responder rate of 10 out of 12 active participants experiencing > 50% reduction in seizure frequency compared with zero responders in the sham procedure group.

Of the seven studies reviewed, four evaluated our secondary endpoint of change in mean number of epileptic discharges. Fregni 2006, Sun 2012, and Joo 2007 demonstrated a statistically significant reduction in epileptiform discharges. In Cantello 2007, there was no difference in the mean reduction in number of epileptiform discharges, but it did show a statistically significant decrease in

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epileptiform discharges by 50% in more active participants compared with sham. Similarly, Wang 2008 showed significantly fewer participants with any epileptiform discharges after treatment than in controls.

Quality of life was not assessed in any of the studies. Adverse effects were uncommon among the studies and typically involved headache, dizziness, and tinnitus, with one patient experiencing a seizure during treatment. Changes in medication requirements was only reported in one study, which found no significant need to increase medications in patients after active rTMS. Treatment withdrawal was well reported and was uncommon among the studies. Only one patient reportedly withdrew from further rTMS due to adverse effects and that was because of a seizure.

Overall completeness and applicability of evidence

Overall, we reviewed seven studies, including 230 randomized participants. One study, Tergau 2003, was only an interim analysis of a study that was never completed; the rest were completed published studies. In most studies, partial/focal epilepsy with or without secondary generalization was more common than diffuse or multifocal epilepsies. In all studies, participants had drug-resistant epilepsy, and typically, were either not good surgical candidates or had declined surgery. Although the inclusion criteria required a minimum of one to three seizures per week at baseline (depending on the study) despite medication, the average number of baseline seizures in the participants were generally greater than 10 per week in most studies, suggesting these were truly drug-resistant participants. Thus, the participants studied likely do represent a clinically relevant population, making the results applicable.

Quality of the evidence

The reviewed studies had a substantial amount of methodological variability, and details regarding design were not reported in sufficient detail in many studies to make an accurate assessment of study quality.

The study of Theodore 2002 leaves open the possibility of a mild treatment effect. A trend towards positive effect was noted, but the study was only powered to detect a large (70%) reduction in seizures, making a type II error possible. Their subgroup analysis showed that focal cortical epilepsies may respond better to rTMS. Joo 2007 also reported a trend in their focal stimulation, long duration treatment subgroup with 30.6% reduction (P = 0.059) from baseline seizure frequency. Their study measured seizure frequency by averaging over eight weeks before and after intervention, and did not report discrete data points, making it difficult to evaluate whether a potential shorter-lived initial effect was masked by averaging seizure frequency over such a long period.

Three studies were placebo controlled, where others compared focal to non-focal application of rTMS or application of rTMS at different intensities or durations. Even between the placebo controlled studies, differing parameters of frequency (0.3, 0.5, or 1 Hz), intervals, duration (between 500 to 3000 stimuli, daily for five to seven days in most trials, except Sun 2012 which had 14-day treatment), and intensity (low of 20% resting motor threshold (RMT) to high of 120% RMT and one study that used a fixed high-intensity) were found. We noted that the low-intensity treatment arm in the Sun 2012 study could serve as a de-facto placebo control group given that the level of stimulation at that intensity would be unlikely to be effective and indeed did not result in a statistically significant treatment effect in their study.

Because of this high degree of variability in study design, we were not able to synthesize results in meta-analysis. We therefore presented a discussion of the results in narrative text. Overall, we judged quality of the evidence for the primary outcomes of this review to be low due to the limited and methodologically unclear information available. Of the seven studies included, two studies did show a significant effect, whereas five did not. Given that the variability of study design and techniques and reported parameters precluded meta-analysis, this narrative review cannot refute a beneficial effect of rTMS on seizure reduction, though strong supportive and comparative evidence for efficacy is still lacking.

Potential biases in the review process

Our searches were comprehensive, including searches of unpublished literature and ongoing studies; we hope to include the identified ongoing study in future updates of the review (NCT01745952). There is a possibility our searches may have missed relevant studies, however we believe this to be unlikely.

Given the extent of variability in the design of the included studies, we felt performing a meta-analysis of study results would be inappropriate and that a narrative review, although less informative and concise than a meta analysis, would provide more reliable and appropriate interpretations of the results and conclusions drawn from this review.

Agreements and disagreements with other studies or reviews

A prior systematic review of 11 studies by Hsu 2011 found a small but significant effect of low-frequency rTMS on medically intractable epilepsy. However, the effect was based on first measurement after the intervention despite differences in technique and outcome reporting within each study. The present study found that no appropriate meta-analysis can be done due to the wide variability of technique and also time points reported in each study, as the first measurement could be at one day, two weeks, or eight weeks after treatment with demonstrable differences in

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effect within individual study parameters. Moreover, the prior systematic review included additional open-label, non-randomized studies where all patients received the intervention. The present review included only randomized studies comparing intervention and control cohorts.

AUTHORS' CONCLUSIONS

Implications for practice

There is evidence that repetitive transcranial magnetic stimulation (rTMS) is safe and effective at reducing epileptiform discharges on electroencephalography (EEG). Narrative review of currently available studies included two studies that showed a significant effect on seizure frequency and five studies that did not show significant effect. Given the variability in technique and outcome reporting that prevented meta-analysis, more definitive evidence for the efficacy of rTMS for seizure reduction in focal drug-resistant epilepsies is still lacking.

Implications for research

The use of rTMS is still a relatively new therapy for seizures, and future studies should aim to scientifically establish a standard technique for its application. There is some evidence that focal epilepsies with imaging findings may be more amenable to treatment with rTMS and further randomized trials are needed to assess its efficacy for drug-resistant epilepsies. It is important that future trials are of sufficient duration and adequately powered in sample size to inform longer-term outcomes of efficacy (seizure reduction), quality of life, and any adverse effects related to rTMS treatment.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cantello 2007

Methods	Randomized, double-blind, placebo controlled, cross-over trial 2 treatment arms: 1 placebo first, 1 rTMS first Pre-randomization baseline period: 12 weeks Treatment period: twice daily for 5 days in each arm Follow-up evaluation period: 6 weeks after each treatment or placebo phase for observation of effect Total study duration: 14 weeks
Participants	A multi-center study in Italy 43 people randomized. 26 participants were male and 17 were female. Mean age 36.9 years (SD 13 years) All with drug-resistant epilepsy (treated with 2-4 AEDs and experiencing 3 or more seizures per week), majority were partial epilepsy Not stated how many participants were randomized to each treatment arm (placebo first or rTMS first)
Interventions	Sham procedure treatment followed by active rTMS or active rTMS followed by sham treatment Treatment parameters: two circular coils of 500 stimuli at 0.3 Hz, separated by a 30-s interval at an intensity of 100% of RMT, placed at the vertex regardless of type of epilepsy
Outcomes	The proportion of people with a 50% or greater reduction in seizure frequency following the treatment period Change in seizure frequency per week post-treatment Mean number of ED seen on EEG during the period between seizures (during and after the rTMS cycle) Proportion of people experiencing adverse events and withdrawals from treatment
Notes	This trial differs from the others because of its cross-over design (carryover effect is not formally assessed but the observation period of 6 weeks between treatments is likely to be a sufficient "washout period", and that rTMS was placed at the vertex regardless of type of epilepsy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The study used computer-assisted randomization to initial active treatment or sham treatment
Allocation concealment (selection bias)	Unclear risk	The allocation concealment method was not specified

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Cantello 2007 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	The same apparatus and 'noise' was used to blind participants and personnel. Only the investigator initiating the treatment was not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor was blinded to intervention group of participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study attrition was reported, and no missing data
Selective reporting (reporting bias)	Low risk	Study protocols not available. Primary and secondary outcomes stated in methods section were reported in results, all expected outcomes reported
Other bias	Unclear risk	Observation period of 6 weeks between treatments is likely to be a sufficient "washout period" in this cross-over study Not stated how many participants were randomized to each treatment arm (placebo first or rTMS first) and whether these randomized groups were balanced for clinical demographics at baseline

Fregni 2006

Methods	Randomized, double-blind, sham-controlled parallel design trial 2 treatment arms: active rTMS versus sham rTMS Baseline observation period: 4 weeks Follow-up period: 8 weeks
Participants	Single-center study in Brazil 21 participants were randomized (12 to active rTMS, 9 to sham rTMS) All had drug-resistant epilepsy, with a mean frequency of seizures greater than 10 per month despite 2 or more AEDs, majority had focal epilepsy compared with generalized epilepsy Participants either had refused surgery or were poor surgical candidates 12 participants female, 9 male participants. Mean age 21.9 years (SD 8.1 years)
Interventions	Treatment period: once a day for 5 consecutive days Treatment parameters: 1 Hz frequency, fixed intensity of 70% of max stimulator output, for duration of 20 minutes

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Fregni 2006 (*Continued*)

Outcomes	The proportion of people with a 50% or greater reduction in seizure frequency following the treatment period Change in seizure frequency per week post-treatment Mean number of EDs in the EEG Proportion of people experiencing adverse events and withdrawals from treatment Proportion of people who required a change in seizure medication
Notes	The design of this study was different from the others due to its use of a fixed intensity rather than adjusted to resting motor threshold

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization was performed using the order of entrance in the study and a randomization table previously generated by a computer using randomization blocks of seven (for each seven participants, three were randomized to sham and four to active rTMS) to minimize the risk for unbalanced group sizes." Unclear how the 'order of entrance' was taken into account in the randomization and whether this could have lead to a predictable randomization sequence
Allocation concealment (selection bias)	Unclear risk	The allocation concealment method was not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and study personnel blinded except for those delivering therapy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor was blinded to intervention group of participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data and study attrition reported
Selective reporting (reporting bias)	Low risk	Study protocols not available. Primary and secondary outcomes stated in methods section were reported in results, all expected outcomes reported
Other bias	Low risk	Appears free of other sources of bias

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Joo 2007

Methods	Randomized, double-blind, non-placebo controlled parallel design trial 4 treatment arms: focal rTMS for 3000 pulses (n = 8), focal rTMS for 1500 pulses (n = 10); non-focal rTMS for 3000 pulses (n = 8), and non-focal rTMS for 1500 pulses (n = 9) Baseline period: 8 weeks Follow-up period: 8 weeks
Participants	Single-center South Korean study 35 subjects with focal, non-focal, or multifocal epilepsy drug-resistant to medications (range 2-7 AEDs). 18 male participants, 17 female participants Mean age 25 years (range 18-46 years). Mean seizure frequency 9.1 per week
Interventions	Focal (over epileptogenic zone) or non-focal (at vertex) rTMS for 1500 or 3000 pulses Treatment period: once a day for 5 consecutive days Treatment parameters: 0.5 Hz frequency, 100% RMT intensity, 50 min duration
Outcomes	The proportion of people with a 50% or greater reduction in seizure frequency following the treatment period Change in seizure frequency per week post-treatment Percentage reduction interictal spikes Proportion of people experiencing adverse events
Notes	The design of this study was different from the others due to no placebo control arm; four active treatment arms

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Use of "randomization code" - no further information reported to assess if the code was likely to be predictable
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Only blinding of the EEG reader is specified. Blinding of participants is not stated, but they all received active therapy
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Only blinding of the EEG reader is specified, unclear if other outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No apparent issues with missing data and no withdrawals from treatment reported, but ITT analysis is not specified

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Joo 2007 (*Continued*)

Selective reporting (reporting bias)	High risk	Outcomes are not adequately specified in the methods section (no primary or secondary outcomes defined)
Other bias	Low risk	No other sources of bias identified

Sun 2012

Methods	Randomized, single-blind, non-placebo controlled parallel design study Baseline evaluation period: 4 weeks Follow-up period: 8 weeks 2 treatment arms: high-intensity rTMS at 90% of RMT (n = 31) and low-intensity rTMS at 20% RMT (n = 29)
Participants	60 participants randomized. Mean age 20.5 years (SD 7 years). 41 male participants, 19 female participants Various types of epilepsies but majority were partial epilepsy with or without secondary generalization 20 participants had previously undergone surgical resection which failed to control the seizures
Interventions	Treatment period: 2 weeks rTMS was delivered 3 times a day for 2 weeks to the focal epileptic zone best reflected on EEG with 500 stimuli at 0.5 Hz, separated by a 600-s interval
Outcomes	Change in seizure frequency per week post-treatment Proportion of people experiencing adverse events and withdrawals from the study Effect of rTMS on interical ED at 60 minutes
Notes	The design of this study was different from the others due to no placebo control arm; four active treatment arms

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence numbers generated by computer-assisted randomization program
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and study personnel blinded except for those delivering therapy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor was blinded to intervention group of participants

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Sun 2012 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of missing data, and study attrition reported. ITT analysis used
Selective reporting (reporting bias)	Low risk	Study protocols not available. Primary and secondary outcomes stated in methods section were reported in results, all expected outcomes reported
Other bias	Low risk	No other sources of bias identified

Tergau 2003

Methods	Randomized, placebo and active controlled cross-over trial 3 treatment arms: placebo stimulation first, 0.333 Hz stimulation first, 1 Hz stimulation first Baseline period: 3 months Follow-up period: 4 weeks observation and treatment periods separated by at least 8 weeks
Participants	Multi-center study across 3 centers in Germany Results for 17 randomized participants presented. Mean age 29 years (SD 10 years) Participants included had any type of medically intractable epilepsy and at least two seizures per week on average during three month baseline period
Interventions	Treatment period: 5 days Treatment with 1000 pulses each day (500 monopolar pulses with clockwise current direction followed directly by 500 pulses in anticlockwise direction). Treatment delivered "unifocally"
Outcomes	Change in seizure frequency per week post-treatment Proportion of people experiencing adverse events and withdrawals from the study
Notes	At the time of study publication 28 participants had been enrolled, 5 participants had yet to complete and six had dropped out of the study (reasons stated). Carryover effect is not formally assessed but the observation period of at least 8 weeks between treatments is likely to be a sufficient "washout period"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study is described as randomized, no further information given
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not described

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Tergau 2003 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	method of placebo stimulation described, but not stated who was blinded, if anyone
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	method of placebo stimulation described, but not stated who was blinded, if anyone
Incomplete outcome data (attrition bias) All outcomes	High risk	Data presented for 17 participants out of 28 randomised, ITT approach not used to analysis. Unclear how many of the crossover arms were completed by the participants who dropped out
Selective reporting (reporting bias)	High risk	Study protocol not available, Outcomes are not adequately specified in the methods section (no primary or secondary outcomes defined)
Other bias	Unclear risk	Period of at least 8 weeks between treatments is likely to be a sufficient "washout period" in this cross-over study Not stated how many participants were randomised to each treatment arm (placebo first, 0.333Hz first or 1Hz first) and whether these randomised groups were balanced for clinical demographics at baseline. Unclear how a three arm crossover trial design was to be implemented (i.e. a second randomisation after first arm?)

Theodore 2002

Methods	Randomized, double-blind, placebo controlled, parallel design trial 2 treatment arms: active rTMS (n = 12) and sham rTMS (n = 12) Baseline period: 8 weeks Follow-up period: 8 weeks
Participants	Single-center National Institute of Health 24 participants were randomized (13 female, 11 male). Mean age 40 years (SD 14 years) Participants either had localization related or secondary generalized epilepsy that was resistant to medications (at least one CPS or secondary GTCS per week on stable AEDs over 8-week baseline)
Interventions	Treatment period: 1 week Treatment parameters: focal rTMS administered at 1 Hz for 15 minutes twice a day, at 120% RMT

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Theodore 2002 (*Continued*)

Outcomes	Change in seizure frequency per week post-treatment Proportion of people experiencing adverse events and withdrawals from the study
Notes	Authors cited their post-hoc analysis that the study was underpowered to detect less than a 70% reduction in seizure frequency at 2 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study is described as randomized, no further information given
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and assessment team blinded; only treatment team unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessment team blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No significant issues with missing data. Study attrition reported
Selective reporting (reporting bias)	Low risk	Study protocols not available. Primary outcome measure described in methods and reported in results. Secondary measures less clearly stated in methods, but authors make limited claims based on these secondary results
Other bias	Low risk	No additional sources of bias identified

Wang 2008

Methods	Randomized, open-label, AED controlled parallel design study 2 treatment arms: TMS plus carbamazepine (n = 15) and "drug treatment" (n = 15) Baseline period: not stated Follow-up period: 30 days
Participants	Single-center study in China 30 participants randomized (15 to TMS group and 15 to AED group) TMS group: mean age 27.9 years (SD 4.1 years), 10 males, 5 females. AED group: mean age 27.6 years (SD 3.9 years), 9 males, 6 females Participants with temporal lobe epilepsy and epileptiform discharges were enrolled

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Wang 2008 (*Continued*)

Interventions	Treatment period: 7 days (for TMS group), 60 days for AED group 1 Hz TMS at 90% RMT threshold, simulation frequency of 500 times, once a day for 7 days. Drug treatment group received 600-800 mg oral carbamazepine per day for at least 60 days	
Outcomes	Change in seizure frequency per week post-treatment Positive rate of epileptiform charges reported Proportion of people experiencing adverse events	
Notes	Imbalance in treatment time across the intervention groups	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study is described as randomized, no further information given
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open label study (cannot be blinded due to design), unclear if outcomes were influenced
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label study, outcome assessors not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of missing data, no withdrawals from the study. ITT analysis used
Selective reporting (reporting bias)	Low risk	Study protocols not available. Primary and secondary outcomes stated in methods section were reported in results, all expected outcomes reported
Other bias	Low risk	No additional sources of bias identified

Abbreviations
AED: antiepileptic drug
CPS: complex partial seizure
ED: epileptiform discharges
EEG: electroencephalogram
GTCS: generalized tonic clonic seizure
Hz: hertz
ITT: intention-to-treat
RMT: resting motor threshold

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rTMS: repetitive transcranial magnetic stimulation
SD: standard deviation
TMS: transcranial magnetic stimulation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
NCT00382707	Before-and-after controlled study

Characteristics of ongoing studies *[ordered by study ID]*

NCT01745952

Trial name or title	Multimodal image-guided repetitive transcranial magnetic stimulation (rTMS) in the treatment of refractory partial epilepsy
Methods	Randomized intervention study, double-blind
Participants	Participants with drug-resistant unifocal neocortical epilepsy
Interventions	rTMS versus sham rTMS
Outcomes	1) 50% responder rate 2) Percentage of seizure reduction 3) Alteration of brain activation as measured by FDG-PET 4) Difference in seizure reduction using different coil types 5) Quality of life 6) Adverse events
Starting date	Nov 2012
Contact information	L. Seynaeve, W. Van Paesschen
Notes	Authors contacted for more information, no response received

FDG-PET: fluorine-18-fluorodeoxyglucose positron emission tomography
rTMS: repetitive transcranial magnetic stimulation

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DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Epilepsy Specialized Register search strategy

This was used for the most recent update of the searches.
#1 transcranial magnetic stimulation
#2 >01/06/2014:CRSCREATED AND INREGISTER
#3 #1 AND #2

Appendix 2. CENTRAL via CRSO search strategy

This was used for the most recent update of the searches.
#1 MESH DESCRIPTOR Transcranial Magnetic Stimulation EXPLODE ALL TREES
#2 ("transcranial magnetic stimulation"):TI,AB,KY
#3 #1 OR #2
#4 (epilep* OR seizure* OR convuls*):TI,AB,KY
#5 MESH DESCRIPTOR Epilepsy EXPLODE ALL TREES
#6 MESH DESCRIPTOR Seizures EXPLODE ALL TREES
#7 #4 OR #5 OR #6
#8 #3 AND #7
#9 * NOT INMEDLINE AND 31/05/2014 TO 29/02/2016:DL
#10 #8 AND #9

Appendix 3. MEDLINE search strategy

This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials (Lefebvre 2011). This was used for the most recent update of the searches.
1. exp Transcranial Magnetic Stimulation/
2. transcranial magnetic stimulation.tw.
3. 1 or 2
4. exp Epilepsy/
5. exp Seizures/
6. (epilep$ or seizure$ or convuls$).tw.
7. 4 or 5 or 6
8. exp Pre-Eclampsia/ or exp Eclampsia/
9. 7 not 8
10. (randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or placebo or randomly).ab.
11. clinical trials as topic.sh.
12. trial.ti.
13. 10 or 11 or 12
14. exp animals/ not humans.sh.
15. 13 not 14
16. 3 and 9 and 15
17. remove duplicates from 16

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18. limit 17 to ed=20140601-20160310

Appendix 4. SCOPUS search strategy

(TITLE-ABS-KEY("Transcranial Magnetic Stimulation")) and ((TITLE-ABS-KEY(epilep* OR "infantile spasm" OR seizure OR convuls* OR (syndrome W/2 (aicardi OR angelman OR doose OR dravet OR janz OR jeavons OR "landau kleffner" OR "lennox gastaut" OR ohtahara OR panayiotopoulos OR rasmussen OR rett OR "sturge weber" OR tassinari OR "unverricht lundborg" OR west)) OR "ring chromosome 20" OR "R20" OR "myoclonic encephalopathy" OR "pyridoxine dependency") AND NOT (TITLE(*eclampsia) OR INDEXTERMS(*eclampsia))) OR (TITLE-ABS-KEY(lafora* W/4 (disease OR epilep*)) AND NOT (TITLE(dog OR canine) OR INDEXTERMS(dog OR canine)))) and (TITLE((randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR "parallel group" OR crossover OR "cross over" OR cluster OR "head to head") PRE/2 (trial OR method OR procedure OR study)) OR ABS((randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR "parallel group" OR crossover OR "cross over" OR cluster OR "head to head") PRE/2 (trial OR method OR procedure OR study)))

CONTRIBUTIONS OF AUTHORS

RC, DS and JW wrote the Review protocol. All authors were responsible for carrying out the Review methods and writing up the Review. RC is responsible for updating the finished Review.

DECLARATIONS OF INTEREST

RC has no declarations of interest

DS has no declarations of interest

SJN has no declarations of interest

JW has no declarations of interest

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK.

This review was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure Grant funding to the Epilepsy Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service (NHS) or the Department of Health.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Addition to 'Types of intervention' that interventions will be included if 'added to current therapy or used as single therapy.'

Measure of treatment effect for 'quality of life' specified as mean difference (or standardized mean difference) depending on outcome scaled used.

Additional information added to 'Unit of analysis' section to specify methods to be used to analyse cluster-randomized trials and cross-over trials.

In a post-hoc change from protocol, we have added a 'Summary of findings' table to the Review (Summary of findings for the main comparison), reporting the primary outcomes of the review (reduction in seizure frequency and quality of life).

NOTES

Jennifer Pulman (author of the protocol) is now Jennifer Weston.

INDEX TERMS

Medical Subject Headings (MeSH)

*Transcranial Magnetic Stimulation [adverse effects]; Drug Resistant Epilepsy [physiopathology; *therapy]; Electroencephalography; Randomized Controlled Trials as Topic

MeSH check words

Humans

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