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TABLE OF CONTENTS

[Intervention Review]

Magnetic seizure therapy for people with schizophrenia

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ABSTRACT

Background

Schizophrenia is one of the most common and disabling mental disorders. About 20% of people with schizophrenia do not respond to antipsychotics, which are the mainstay of the treatment for schizophrenia today, and need to seek other treatment options. Magnetic seizure therapy (MST) is one of the novel non-invasive brain stimulation techniques that are being investigated in recent years.

Objectives

To evaluate the efficacy and tolerability of MST for people with schizophrenia.

Search methods

On 6 March 2022, we searched the Cochrane Schizophrenia Group's Study-Based Register of Trials which is based on CENTRAL, CINAHL, ClinicalTrials.Gov, Embase, ISRCTN, MEDLINE, PsycINFO, PubMed, and WHO ICTRP.

Selection criteria

All randomised controlled trials (RCTs) comparing MST alone or plus standard care with ECT or any other interventions for people with schizophrenia.

Data collection and analysis

We performed reference screening, study selection, data extraction and risk of bias and quality assessment in duplicate. We calculated the risk ratios (RRs) and their 95% confidence intervals (CIs) for binary outcomes and the mean difference (MD) and their 95% CIs for continuous outcomes. We used the original risk of bias tool for risk of bias assessment and created a Summary of findings table using GRADE.

Main results

We included one four-week study with 79 adults in acute schizophrenia, comparing MST plus standard care to ECT plus standard care in this review. We rated the overall risk of bias as high due to high risk of bias in the domains of selective reporting and other biases (early termination and baseline imbalance) and unclear risk of bias in the domain of blinding of participants and personnel.

We found that MST and ECT may not differ in improving the global state (n = 79, risk ratio (RR) 1.12, 95% confidence interval (CI) 0.73 to 1.70), overall (n = 79, mean difference (MD) -0.20, 95% CI -8.08 to 7.68), the positive symptoms (n = 79, MD 1.40, 95% CI -1.97 to 4.77) and the negative symptoms (n = 79, MD -1.00, 95% CI -3.85 to 1.85) in people with schizophrenia.

We found that MST compared to ECT may cause less delayed memory deficit and less cognitive deterioration (n = 79, number of people with a delayed memory deficit, RR 0.63, 95% CI 0.41 to 0.96; n = 79, mean change in global cognitive function, MD 5.80, 95% CI 0.80 to 10.80), but also may improve more cognitive function (n = 47, number of people with any cognitive improvement, RR 3.30, 95% CI 1.29 to 8.47).

We found that there may be no difference between the two groups in terms of leaving the study early due to any reason (n = 79, RR 2.51, 95% CI 0.73 to 8.59), due to adverse effects (n = 79, RR 3.35, 95% CI 0.39 to 28.64) or due to inefficacy (n = 79, RR 2.52, 95% CI 0.11 to 60.10).

Since all findings were based on one study with high risk of bias and the confidence in the evidence was very low, we were not sure these comparable or favourable effects of MST over ECT were its true effects.

Authors' conclusions

Due to the paucity of data, we cannot draw any conclusion on the efficacy and tolerability of MST for people with schizophrenia. Well-designed RCTs are warranted to answer the question.

PLAIN LANGUAGE SUMMARY

What are the benefits and risks of magnetic seizure therapy for people with schizophrenia?

Key messages

There were too scarce data to evaluate the benefits and risks of magnetic seizure therapy (MST) for people with schizophrenia.

We need more and better studies to look into this.

What is schizophrenia?

Schizophrenia is one of the most common and disabling mental disorders. People with schizophrenia may have difficulties living a normal life due to the illness, which may include distorted beliefs despite reality, hearing voices created by their minds, and having no interest in caring for others or themselves.

Why is this important for people with schizophrenia?

Most people with schizophrenia receive antipsychotic treatments. For those who don't respond well to antipsychotics or wish to use alternative treatments, electroconvulsive therapy (ECT) could be an effective and safe choice. This therapy causes a seizure in an anaesthetised person by electric currents applied to the brain; in this way, psychotic symptoms are improved or relieved. However, ECT has side effects such as temporary memory loss, and confusion after treatments, which limits its use. Magnetic seizure therapy is one of the novel non-invasive brain stimulation techniques, which works like ECT by inducing a seizure, however not with electric currents but with magnetic energy fields, which theoretically would cause less risk of memory loss or confusion after the treatments.

What did we want to find out?

We wanted to know whether MST helps people with schizophrenia.

We were interested in:

- number of people with symptoms improved;

- number of people with impaired cognitive function;

- number of people with clinically important side effects.

What did we do?

We searched for studies that investigated the effect of MST compared to any other treatments for people with schizophrenia.

We compared and summarised the results of the study and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

Main results

We found one short-term randomised controlled trial (RCT) with 79 adults that met the review requirements. It compared MST plus standard care to ECT plus standard care. Our findings were based on very limited data. We found that MST and ECT may be comparable in improving the global state of people with schizophrenia, and in improving the overall, positive and negative symptoms of schizophrenia. MST may cause less delayed memory deficit and less cognitive deterioration and may improve cognitive function compared to ECT. There

may be no difference between the two groups in terms of leaving the study early due to any reason, adverse effects, or inefficacy. We cannot conclude whether MST is helpful or safe for people with schizophrenia based on limited data. Well-designed RCTs are warranted to answer the question.

How up-to-date is this evidence?

The evidence is up-to-date to 06 March 2022.

Summary of findings 1. Magnetic seizure therapy plus standard care compared to electroconvulsive therapy plus standard care for people with schizophrenia

Magnetic seizure therapy plus standard care compared to electroconvulsive therapy plus standard care for people with schizophrenia

Patient or population: people with acute schizophrenia
Setting: inpatient
Intervention: magnetic seizure therapy + standard care
Comparison: electroconvulsive therapy + standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with electroconvulsive therapy	Risk with magnetic seizure therapy				
Global state: clinically important change assessed by: number of participants with a clinical response Study duration: 4 weeks	Study population 472 per 1000	529 per 1000 (345 to 803)	RR 1.12 (0.73 to 1.70)	79 (1 RCT)	⊕⊖⊖⊖ Very low [1,2]	A clinical response was defined as a ≥ 25% reduction from baseline to the endpoint of the PANSS total score.
Cognitive functioning: clinically important change - not measured	-	-	-	-	-	
Adverse effects: clinically important adverse effects assessed by: number of participants with a delayed memory deficit Study duration: 4 weeks	Study population 667 per 1000	420 per 1000 (273 to 640)	RR 0.63 (0.41 to 0.96)	79 (1 RCT)	⊕⊖⊖⊖ Very low [1,3]	A delayed memory deficit was defined as a ≥ 10% decrease from baseline to the endpoint of the RBANS delayed memory score.
Quality of life: clinically important change - not measured	-	-	-	-	-	
Social functioning: clinically important change - not measured	-	-	-	-	-	
Leaving the study early: any reason assessed by: number of dropouts for any reason	Study population 83 per 1000	209 per 1000	RR 2.51 (0.73 to 8.59)	79 (1 RCT)	⊕⊖⊖⊖ Very low [1,2]	

Study duration: 4 weeks		(61 to 716)	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio; **PANSS**: the Positive and Negative Syndrome Scale; **RBANS**: the Repeatable Battery for the Assessment of Neuropsychological Status; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded by two levels: high risk of bias in two domains (selective reporting, other bias) and unclear risk in one domain (blinding of participants and personnel).
[2] Downgraded by two levels: the optimal information size (OIS) was not met and the confidence interval included both appreciable benefit and harm.
[3] Downgraded by one level: OIS was not met.

BACKGROUND

Description of the condition

Schizophrenia is one of the most common mental disorders; its lifetime morbid risk is estimated to be 1% with no gender difference (McGrath 2008). The mean age of onset is about 25 years old (Solmi 2022) with generally earlier onset in men than in women (Ochoa 2012). Clinical presentation is diversified and principal features include positive symptoms (e.g. delusions, hallucinations, disorganised speech), negative symptoms (e.g. affective flattening, alogia, avolition) and cognitive impairment (Tandon 2013). Diagnosis is built on history and mental state examination (Owen 2016) using operationalised criteria from manuals such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) (APA 2013) and the WHO International Classification of Diseases (ICD) (WHO 1992). This psychopathology causes deterioration of functioning over time and is described as a highly disabling condition, which makes it a heavy burden on individuals, families and society. It is the twentieth leading cause of disability worldwide in 2019 according to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019 (GBD 2019).

The main treatment plan for schizophrenia is antipsychotic medications combined with psychosocial interventions and rehabilitation (Lehman 2004; Owen 2016). Antipsychotics remain the mainstay of the treatments for schizophrenia (Owen 2016). However, about 20% of people with schizophrenia do not respond to antipsychotics (Marder 1993; Samara 2019) and need to seek other treatment options. One such treatment is electroconvulsive therapy (ECT). People with schizophrenia receive ECT treatment because of unpleasant side effects and unsatisfactory efficacy of medications, anticipation of or need for rapid response, or personal preference (APA 1990; Tharyan 2005; Weiss 2019).

Major depression is the main indication for ECT in the United States, Australia, and European countries (Chanpattana 2007; Moksnes 2010; Mowla 2015) while schizophrenia is the most common indication in Asia (Chanpattana 2005; Chanpattana 2010). ECT has been widely used in China since its introduction in the 1950s for the treatment of schizophrenia (Tang 2012). The usage rate of ECT for schizophrenia increased over the past decade in China while remaining low and relatively stable in other Asian countries (Xiang 2015). The popularity of ECT in developed countries such as the United States and United Kingdom has declined since concerns about cognitive side effects arose (Allan 2011).

Description of the intervention

Since the introduction of ECT as a therapeutic method for schizophrenia in 1934, it has played an important role in the treatment for schizophrenia for over 70 years (Eitan 2006). ECT is the only non-pharmacological physical treatment option for schizophrenia approved by the U.S. Food and Drug Administration (FDA) (Weiner 2013). It is also widely used for other psychiatric conditions such as major depressive disorder (MDD), bipolar disorder (BPD), catatonia, and schizoaffective disorder (Owen 2016). Advances in anaesthesiology have greatly improved the safety and tolerability of ECT, however post-ictal confusion, attention deficiency, and transient memory disturbance are often problematic and affect treatment compliance (Holtzheimer 2006; Hoy 2011; Lisanby 2003a). Attempts to improve the efficacy and side effect profile of ECT can be made by using alternative electrode placements, variations in stimulus configuration and focal electrical stimulation. Novel developments such as magnetic seizure therapy (MST) are also used (Eitan 2006; Lisanby 2003b; Loo 2006)

MST is a promising alternative to ECT that, for now, is only used for research purposes. MST is a noninvasive, physical treatment, developed as an improvement over conventional convulsive therapies (Lisanby 2001b). It combines the characteristics of both ECT and repetitive transcranial magnetic stimulation (rTMS). MST generates electromagnetic stimulation by rapidly alternating magnetic fields like rTMS but in a more intensive way (Lisanby 2001b; Lisanby 2002) and induces a seizure to alleviate symptoms (Rau 2007).

MST is conducted under general anaesthesia, requiring short-acting anaesthetics and muscle relaxants (Lisanby 2001b; Tharyan 2005). A twin coil held at the vertex (or sometimes a figure eight coil on the right prefrontal cortex) generates magnetic fields and forms an indirect electric current in the brain, which induces a seizure when it exceeds the individual seizure threshold (Fitzgerald 2013; Hoy 2010; Kayser 2015: Lisanby 2001a; Lisanby 2001b; Noda 2014; Polster 2015). The magnetic seizure threshold is normally titrated at the first treatment session by ascending duration in train (Fitzgerald 2013; Hoy 2011). Electroencephalograms (EEGs) are monitored and rated to ensure the required seizure (Kayser 2015) and precautions should be taken to prevent side effects. Earplugs are required for patients and staff present to prevent tinnitus or potential hearing damage (Fitzgerald 2013) and a bite-block should be used by patients to protect their teeth (Hoy 2011). Session arrangements are basically the same as in an ECT treatment plan, occurring twice a week for a period of five to six weeks (Hoy 2011; Polster 2015).

How the intervention might work

The mechanism of the therapeutic effect of an induced-seizure from brain stimulation is still unclear (Singh 2017). The effect of ECT is affected by impedance of the scalp and skull. Impedance can elevate electrical intensity and influence current distribution which leads to less control over regional stimulation of the brain. The MST device is immune to impedance as it generates electromagnetic signals by rapidly alternating magnetic fields, so is not shunted into the scalp and cerebrospinal fluid and only affects cells to a depth of 2 cm below the scalp (Eitan 2006; Lisanby 2001a). Spherical model tests have shown that MST generates more focal and superficial stimulations than ECT (Deng 2009; Deng 2011). Due to its superficial and confined stimulation field, MST is thought to have less impact on deeper brain structures (Dwork 2004; Dwork 2009). Physiological findings in rhesus monkeys show that MST, compared to electroconvulsive shock (ECS, equivalence to human ECT), triggered remarkably less marked sympathetic and parasympathetic response (Rowny 2009).

EEG data also show that seizure characteristics in neurophysiology are different between a MST-induced seizure and an ECS-induced one. MST and ECS had some cross-over in seizure expression, but MST had less marked expression and post-ictal suppression than ECS (Cycowicz 2008). Further experiments demonstrated a link between ictal expression and cognitive side effects (Cycowicz 2009). Animal studies and human trials have found a positive effect for MST on cognitive functions including less impaired spatial working memory (McClintock 2013), better completion of criteria tasks (Spellman 2008), less acute memory disruption (Polster 2015), and

shorter post-ictal recovery and reorientation times (Kayser 2013) compared to ECS/ECT.

Why it is important to do this review

MST was first used in a study for treating a person with major depression in 2001 (Lisanby 2001a). Since then, an increasing number of studies have examined the antidepressant effect of MST for depression, and the results are promising (Fitzgerald 2013; Hoy 2011; Kayser 2011; Lisanby 2003a) but remain unclear (Mutz 2019). However, for schizophrenia, there is a paucity of evidence. It remains a question whether MST is more or less efficacious than ECT (Allan 2011) or non-convulsive TMS (Holtzheimer 2006) for schizophrenia and whether MST carries additional effects for people with schizophrenia.

Pilot studies showed MST were safe for people with schizophrenia (Jiang 2018; Tang 2017). Also, as it may cause less cognition impairment, MST may be valuable in senior populations (Luber 2013).

To our knowledge, to date there has been no systematic review of RCTs to address the safety and efficacy of MST for schizophrenia, which is important for guiding clinical practice and further development of this novel treatment.

OBJECTIVES

To evaluate the efficacy and tolerability of magnetic seizure therapy (MST) for people with schizophrenia.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials. If a trial was described as 'double-blind' but implied randomisation, we would include such trials in a sensitivity analysis (see Sensitivity analysis). We excluded quasi-randomised studies, such as those allocating by alternate days of the week. Where people were given additional treatments within MST, we would only include data if the adjunct treatment was evenly distributed between groups and it was only the MST that was randomised. There were no restrictions on language or publication status.

Types of participants

Adults, however defined, with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder and delusional disorder, again, by any means of diagnosis.

We were interested in making sure that information was as relevant to the current care of people with schizophrenia as possible, so we clearly highlighted the current clinical state (acute, early post-acute, partial remission, remission) as well as the stage (prodromal, first episode, early illness, persistent) and whether the studies primarily focused on people with particular problems (for example, negative symptoms, treatment-resistant illnesses).

We excluded studies in which the psychotic symptoms were caused by definite physical conditions such as cerebral lesions, hyperthyroidism.

Types of interventions

1. Experimental intervention

Magnetic seizure therapy, however defined, performed under general anaesthesia, inducing a seizure by electromagnetic fields (See Background).

The experimental intervention might be:

1.1 Magnetic seizure therapy; or

1.2 Magnetic seizure therapy + standard care.

2. Comparator intervention

Comparators might be one or combination of:

2.1 Placebo (sham MST) or waiting-list or standard care;

2.2 Antipsychotic medications;

2.3 Electroconvulsive therapy;

2.4 Other physical treatments (e.g. Tai Ji, acupuncture, etc); or

2.5 Psychosocial therapies (e.g. cognitive behavioural therapy, psychoanalysis, art therapy, etc).

Types of outcome measures

We divided outcomes into short term (less than 6 months), medium term (7 to 12 months) and long term (over 1 year).

We reported binary outcomes recording clear and clinically meaningful degrees of change (e.g. global impression of much improved, or more than 50% improvement on a rating scale - as defined within the trials) before any others. Thereafter, we would list other binary outcomes and then those that were continuous.

Primary outcomes

1. Global state

1.1. Clinically important change - as defined by individual studies (e.g. rated by any validated assessment such as the Clinical Global Impression Scale (CGI) (Guy 1976), the Brief Psychiatric Rating Scale (BPRS) (Overall 1962), the Positive and Negative Syndrome Scale (PANSS) (Kay 1986)).(acute phase studies)

1.2 Relapse - as defined by individual studies. (studies that investigated the relapse prevention effect of a treatment in stable schizophrenia)

2. Cognitive functioning

2.1 Clinically important change - as defined by individual studies (e.g. rated by any validated assessment such as the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) (Nuechterlein 2008)

3. Adverse effects

3.1 Clinically important adverse effects

Secondary outcomes

1. Global state

1.1 Any change in global state, as defined by individual studies
1.2 Average endpoint/change score global state scale

2. Cognitive functioning

2.1 Any change in overall cognitive functioning, as defined by each study
2.2 Average endpoint/change score in cognitive functioning rating scale

3. Adverse effects

3.1 General adverse effects

3.1.1 At least one adverse effect
3.1.2 Average endpoint/change scores in adverse-effect scales

3.2 Specific adverse effects

3.2.1 Anticholinergic
3.2.2 Cardiovascular
3.2.3 Central nervous system
3.2.4 Gastrointestinal
3.2.5 Endocrine (e.g. amenorrhoea, galactorrhoea, hyperlipidaemia, hyperglycaemia, hyperinsulinaemia)
3.2.6 Haematology (e.g. haemogram, leukopenia, agranulocytosis/ neutropenia)
3.2.7 Hepatic (e.g. abnormal transaminase, abnormal liver function)
3.2.8 Metabolic
3.2.9 Movement disorders
3.2.10 Various other

4. Mental state

4.1 Overall

4.1.1 Any change in overall mental state, as defined by each study
4.1.2 Average endpoint/change score in total mental state scale

4.2 Positive symptoms

4.2.1 Clinically important change in positive symptoms, as defined by each study
4.2.2 Any change in positive symptoms, as defined by each study
4.2.3 Average endpoint/change score in total positive mental state subscale

4.3 Negative symptoms

4.3.1 Clinically important change in negative symptoms, as defined by each study
4.3.2 Any change in negative symptoms, as defined by each study
4.3.3 Average endpoint/change score in total negative mental state subscale

4.4 Aggressive symptoms/agitation

4.4.1 Clinically important change in aggressive symptoms/ agitation, as defined by each of the studies
4.4.2 Any change in aggressive symptoms/agitation, as defined by each study
4.4.3 Average endpoint/change score in aggressive symptoms/ agitation scale

4.5 Depressive symptoms

4.5.1 Clinically important change in depressive symptoms, as defined by each of the studies

4.5.2 Any change in depressive symptoms, as defined by each study
4.5.3 Average endpoint/change score in depressive symptoms scale

4.6 Anxiety symptoms

4.6.1 Clinically important change in anxiety symptoms, as defined by each study
4.6.2 Any change in anxiety symptoms, as defined by each study
4.6.3 Average endpoint/change score in anxiety symptoms scale

5. Quality of life

5.1 Clinically important change in quality of life, as defined by each study
5.2. Any change in quality of life, as defined by each study
5.3 Average endpoint/change score in quality of life scale

6. Satisfaction

6.1. Any change in quality of life (patient or carers), as defined by each study
6.2 Average endpoint/change score in quality of life scale (patient or carers)

7. Service use

7.1 Hospital admission
7.2 Duration of hospital stay
7.3 Readmission
7.4 Contact with psychiatric services (binary or continuous measures)

8. Social functioning

8.1 Clinically important change in social functioning, as defined by each study
8.2 Any change in social functioning, as defined by each study
8.3 Average endpoint/change score in social functioning scale
8.4 Imprisonment (police contact and arrest)
8.5 Employment status (employed/unemployed)
8.6 Accommodation status
8.7 Alcohol use
8.8 Illicit drug use
8.9 Occurrence of violent incidents (to self, others or property)

9. Leaving the study early

9.1 Any reason
9.2 Due to adverse effect
9.3 Due to inefficacy

10. Economic

10.1 Direct costs
10.2 Indirect costs
10.3 Cost-effectiveness

Search methods for identification of studies

Electronic searches

On 3 July 2017, 27 August 2019, 10 February 2021, and 06 March 2022, the information specialist searched the register using the following search strategy.

(*Magnetic Seizure Therapy*) in Intervention Field of STUDY

In such a study-based register, searching on the major concept retrieves all the synonyms and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics (Shokraneh 2017). This allows rapid and accurate searches that reduce waste in the next steps of systematic reviewing (Shokraneh 2019).

Following the methods from Cochrane (Lefebvre 2021), the Information Specialist compiles this register from systematic searches of major resources and their monthly updates (unless otherwise specified).

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library
- MEDLINE
- Embase
- Allied and Complementary Medicine (AMED)
- BIOSIS
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)
- PsycINFO
- PubMed
- US National Institute of Health Ongoing Trials Register (ClinicalTrials.gov)
- World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp)
- ProQuest Dissertations and Theses A&I and its quarterly update

The register also includes handsearches and conference proceedings (see Group's website). It does not place any limitations on language, date, document type or publication status.

Searching other resources

1. Reference searching

We searched the references of relevant reviews and studies and inspected the reference lists.

2. Personal contact

We contacted authors of the included study. We contacted experts of the field and manufacturers including Magstim in the UK and MagVenture A/S in Denmark for information regarding unpublished or ongoing trials. No additional eligible studies were identified.

Data collection and analysis

Selection of studies

Two review authors, HW and XC, independently examined the reports obtained from the searches. We planned to contact the authors of the eligible study/studies for clarification if it was not possible to resolve disagreement by discussion.

Data extraction and management

1. Extraction

Review authors HW and XC extracted data independently in duplicate. We planned to extract data presented only in graphs and figures whenever possible, but would have included these data only if two review authors independently had the same result. If studies were multicentre, where possible, we planned to extract data relevant to each. If necessary, we planned to contact authors through an open-ended request in order to obtain missing information or for clarification. With any remaining problems, a third review author would have been involved to clarify issues and we would have documented these final decisions.

2. Management

2.1 Forms

We extracted data onto standard, simple forms.

2.2 Scale-derived data

We included continuous data from rating scales only if:
a) the psychometric properties of the measuring instrument had been described in a peer-reviewed journal (Marshall 2000);
b) the measuring instrument had not been written or modified by one of the trialists for that particular trial; and
c) the instrument was a global assessment of an area of functioning and not subscores which are not, in themselves, validated or shown to be reliable. However, we would include subscores of scales if these were validated or if these were predefined in a scale such as the positive symptom, negative symptom and general symptom scores of the Positive and Negative Syndrome Scale (PANSS, Kay 1986).

Ideally the measuring instrument should either be i. a self-report or ii. completed by an independent rater or relative (not the therapist). We, however, realise that this is not often reported clearly.

2.3 Endpoint versus change data

There are advantages of both endpoint and change data. Change data can remove a component of between-person variability from the analysis. On the other hand calculation of change needs two assessments (baseline and endpoint) which can be difficult in unstable and difficult-to-measure conditions such as schizophrenia. We have decided to primarily use endpoint data, and only use change data if the former are not available. If necessary, we would combine endpoint and change data in the analysis. This procedure is possible when using mean differences (MDs) (Deeks 2020) and also when using standardised mean differences (SMDs). Although theoretically the combination of change and endpoint data when SMDs are used can be problematic, meta-epidemiological research has shown that on average no major over- or underestimations can be expected (Da Costa 2013).

2.4 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we applied the following check to relevant continuous data before inclusion.

For endpoint data from studies including fewer than 200 participants, we calculated the observed mean minus the lowest possible value of the scale and divided this by the standard deviation (Higgins 2020).

For example, in a scale that has the possible lowest values higher than 0 (such as the Positive and Negative Syndrome Scale (PANSS), which can have values from 30 to 210 (Kay 1986)), we subtracted the minimum score (in this case, 30) from the observed mean, and then divided by the standard deviation. In a scale that has 0 as

the minimum possible score, we divided the observed mean by the standard deviation.

For this calculation, we checked the original publication of the scales referenced in the studies, in order to understand if they could have a lowest possible score different from 0, and the adjustment described above was needed or not.

If this ratio obtained is lower than one, it strongly suggests that the data are skewed. If it is higher than one but less than two, there is a suggestion that the data are skewed; if the ratio is larger than two, it is less likely that they are skewed (Altman 1996).

Where there is suggestion of skewness (ratio < than 2), we planned to exclude the relevant studies in a sensitivity analysis to check if they had an impact on the results (see Sensitivity analysis for further details).

Skewed results were nevertheless reported in Additional tables.

We would have entered all relevant data from studies of more than 200 participants in the analysis irrespective of the above rules, because skewed data pose less of a problem in large studies. We would also enter all relevant change data as, when continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed.

2.5 Common measure

To facilitate comparison between trials we intended, if necessary, to convert variables that can be reported in different metrics, such as days in hospital (mean days per year, per week or per month) to a common metric (e.g. mean days per month).

2.6 Conversion of continuous to binary

Where possible, we would make efforts to convert outcome measures to dichotomous data. This could be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It is generally assumed that, if there is a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS, Overall 1962) or the PANSS (Kay 1986), this could be considered as a clinically significant response (Leucht 2005a; Leucht 2005b). If data based on these thresholds were not available, we would use the primary cut-off presented by the original authors, because the exact cut-off is not as important in a meta-analysis using risk ratios or odds ratios as effect sizes (Furukawa 2010).

2.7 Direction of effect in graphs

We planned to report the direction of effect in graphs.

Assessment of risk of bias in included studies

Again, review authors HW and XC worked independently to assess risk of bias by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b), risk of bias tool 1. This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias in domains such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

We agreed on the final assessments of risk of bias of the included study and noted the level of risk of bias in the text of the review, the Summary of findings table and figures.

Measures of treatment effect

1. Binary data

For binary outcomes, we calculated a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI). It has been shown that RRs are more intuitive (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as RRs by clinicians (Deeks 2000). The number needed to treat for an additional beneficial/harmful outcome (NNTB/NNTH) statistic with its CIs is intuitively attractive to clinicians but is problematic both in its accurate calculation in meta-analyses and interpretation (Hutton 2009). For binary data presented in the Summary of findings 1, where possible, we calculated illustrative comparative risks.

2. Continuous data

For continuous outcomes, we estimated the MD between groups. We preferred not to calculate standardised effect size measures (SMD). However, if scales were different yet of considerable similarity, we would presume there was a small difference in measurement, and we would calculate the SMD. It should be noted that the SMD can be transformed to the MD by using the formula MD = SMD x Standard Deviation of the scale of interest (Higgins 2020).

Unit of analysis issues

1. Cluster trials

Analysis and pooling of data from cluster trials poses problems. Firstly, authors often fail to account for intraclass correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby P values are spuriously low, CIs unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997; Gulliford 1999).

Where clustering had been incorporated into the analysis of primary studies, we would have presented these data as if from a non-cluster-randomised study, but adjust for the clustering effect.

Where clustering was not accounted for in primary studies, we would have presented data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. We would have sought to contact first authors of studies to obtain intra-class correlation coefficients (ICCs) for their clustered data and to adjust for this by using accepted methods (Gulliford 1999).

We had been advised that the binary data, as presented in a report, should be divided by a 'design effect'. This was calculated using the mean number of participants per cluster (m) and the ICC [Design effect = 1 + (m - 1) * ICC] (Donner 2002). If the ICC was not reported, we would have assumed it to be 0.1 (Ukoumunne 1999).

If cluster studies had been appropriately analysed taking into account ICCs and relevant data documented in the report by study authors, synthesis with other studies would have been possible using the generic inverse variance technique.

2. Cross-over trials

A major concern of cross-over trials is the carry-over effect. This occurs if an effect (e.g. pharmacological, physiological or

psychological) of the treatment in the first phase is carried over to the second phase. As a consequence, on entry to the second phase, the participants can differ systematically from their initial state despite a wash-out phase. For the same reason, cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both effects are very likely in severe mental illness, we would have only used data of the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involves more than two treatment arms, if relevant, we would have presented the additional treatment arms in comparisons. If data were binary we would have simply added these and combined them within the two-by-two table. If data were continuous, we would have combined data following the formula in section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Where the additional treatment arms were not relevant, we would have not reproduced these data. We would list all treatment arms in the Characteristics of included studies table, even if they were not used in the review.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2009). If, for any particular outcome, more than 50% of data were unaccounted for, we would have not reproduced these data or used them within analyses. If, however, more than 50% of those in one arm of a study were lost, but the total loss was less than 50%, we would have addressed this within the Summary of findings 1 by down-rating quality. Finally, we would also have downgraded quality within the Summary of findings 1 should loss have been 25% to 50% in total.

2. Binary

In the case where attrition for a binary outcome was between 0% and 50% and where these data were not clearly described, we would have presented data on a 'once-randomised-always-analyse' basis (an intention-to-treat (ITT) analysis). Those leaving the study early would be all assumed to have the same rates of negative outcome as those who completed. We would have used the rate of those who stayed in the study - in that particular arm of the trial - and applied this also to those who did not. We would have undertaken a sensitivity analysis testing how prone the primary outcomes were to change when data only from people who completed the study to that point were compared to the ITT analysis using the above assumptions.

3. Continuous

3.1 Attrition

We would have reproduced and used data where attrition for a continuous outcome was between 0% and 50%, and data only from people who completed the study to that point would have been reported.

3.2 Standard deviations (SDs)

If SDs were not reported, we would have first tried to obtain the missing values from the authors. If not available, where there were missing measures of variance for continuous data, but an exact standard error (SE) and CIs available for group means, and either P value or t value available for differences in mean, we would have calculated them according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a): when only the SE is reported, SDs are calculated by the formula SD = SE * square root (n). Chapters 7.7.3 and 16.1.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a) present detailed formulae for estimating SDs from P values, t or F values, CIs, ranges or other statistics. If these formulae did not apply, we would have calculated the SDs according to a validated imputation method which was based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus to lose information. We nevertheless would have examined the validity of the imputations in a sensitivity analysis excluding imputed values.

3.3 Assumptions about participants who left the trials early or were lost to follow-up

Various methods are available to account for participants who left the trials early or were lost to follow-up. Some trials just present the results of study completers, others use the method of last-observation-carried-forward (LOCF), while more recently, methods such as multiple imputation or mixed effects models for repeated measurements (MMRM) have become more of a standard. While the latter methods seem somewhat better than LOCF (Leon 2006), we feel that the high percentage of participants leaving the studies early and differences in the reasons for leaving the studies early between groups is often the core problem in randomised schizophrenia trials. Therefore, we do not exclude studies based on the statistical approach used. However, we would have preferably used the more sophisticated approaches, e.g. we would prefer MMRM or multiple imputation to LOCF and we would have only presented completer analyses if some kind of ITT data were not available at all. Moreover, we planned to address this issue in the item 'incomplete outcome data' of the Risk of bias tool.

Assessment of heterogeneity

1. Clinical heterogeneity

We would have considered all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We would have simply inspected all studies for clearly outlying people or situations which we had not predicted would arise and discussed such situations or participant groups.

2. Methodological heterogeneity

We would have considered all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We would have simply inspected all studies for clearly outlying methods which we had not predicted would arise and discussed any such methodological outliers.

3. Statistical heterogeneity

3.1 Visual inspection

We would have visually inspected graphs to investigate the possibility of statistical heterogeneity.

3.2 Employing the I^2 statistic

We would have investigated heterogeneity between studies by considering the I^2 method alongside the Chi^2 P value. The I^2 provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 depends on: i. magnitude and direction of effects, and ii. strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a CI for I^2). We would have interpreted an I^2 estimate greater than or equal to around 50%, accompanied by a statistically significant Chi^2 statistic, as evidence of substantial levels of heterogeneity (section 9.5.2 *Cochrane Handbook for Systematic Reviews of Interventions)* (Deeks 2011). When substantial levels of heterogeneity were found in the primary outcome, we would have explored reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These were described in section 10.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011).

1. Protocol versus full study

We would have compared outcomes in the protocol and in the published report. If the protocol was not available, we would have compared outcomes listed in the methods section of the trial report with actual reported results.

2. Funnel plot

We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We only use funnel plots for outcomes where there are at least ten studies or more.

Data synthesis

We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model. It puts added weight onto small studies which often are the most biased ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. We used fixed-effect models for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes

We planned to perform subgroup analyses on dose or frequency of MST, type and shape of coils, and placement of coils if enough data were gathered.

2. Investigation of heterogeneity

We would have reported heterogeneity if inconsistency was high. First, we would have investigated whether data had been entered correctly. Second, if data were correct, we would visually inspect the graph and we would successively remove studies outside the company of the rest to see if homogeneity was restored. For this review, we had decided that, should this occur with data contributing to the summary finding of no more than around 10% of the total weighting, we would have presented data. If not, we would not pool these data and would discuss any issues. We know of no supporting research for this 10% cut-off but are investigating use of prediction intervals as an alternative to this unsatisfactory state.

When unanticipated clinical or methodological heterogeneity were obvious, we would have simply stated hypotheses regarding these for future reviews or versions of this review. We do not anticipate undertaking analyses relating to these.

Sensitivity analysis

If there were substantial differences in the direction or precision of effect estimates in any of the sensitivity analyses listed below, we would not add data from the lower-quality studies to the results of the higher-quality trials, but would present these data within a subcategory. If their inclusion did not result in a substantive difference, they would remain in the analyses.

1. Implication of randomisation

If trials were described in some way as to imply randomisation, for the primary outcomes, we would pool data from the implied trials with trials that were clearly randomised.

2. Assumptions for lost binary data

Where assumptions had to be made regarding people lost to follow-up (see Dealing with missing data), we would have compared the findings of the primary outcomes when we used our assumption compared with completer data only. If there was a substantial difference, we would report results and discuss them but continue to employ our assumption.

3. Risk of bias

We would have analysed the effects of excluding trials that were at high risk of bias across one or more of the domains (see Assessment of risk of bias in included studies) for the meta-analysis of the primary outcome.

4. Imputed values

We would have also undertaken a sensitivity analysis to assess the effects of including data from trials where we used imputed values for ICC in calculating the design effect in cluster-randomised trials.

Where imputation were made regarding missing SDs (see Dealing with missing data), we would undertake a sensitivity analysis testing how prone results were to change when 'completer' data only were compared to the imputed data. If there was a substantial difference, we would report results and discuss them but continue to employ our imputation.

5. Fixed-effect and random-effects models

We would have also synthesised data for the primary outcome using a random-effects model to evaluate whether this altered the significance of the results, when compared with the use of a fixed-effect model.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to interpret findings (Schünemann 2020) and exported data from our review using GRADEpro to create the Summary of findings 1. Summary of findings tables provide outcome-specific information concerning the overall certainty of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes that we rated as important to patient care and decision-making. We selected the following main outcomes for inclusion in the Summary of findings 1 (these outcomes were assessed at the study endpoint).

- Global state: clinically important change, as defined by individual studies (acute-phase studies);
- Global state: relapse (relapse-prevention studies);
- Cognitive functioning: clinically important change, as defined by individual studies;
- Adverse effects: clinically important adverse effects;
- Quality of life: clinically important change, as defined by individual studies;
- Social functioning: clinically important change in social functioning, as defined by each study;
- Leaving the study early: for any reason.

If data were not available for these prespecified outcomes but were available for ones that were similar, we would present the closest outcome to the prespecified one in the table but take this into account when grading the finding.

RESULTS

Description of studies

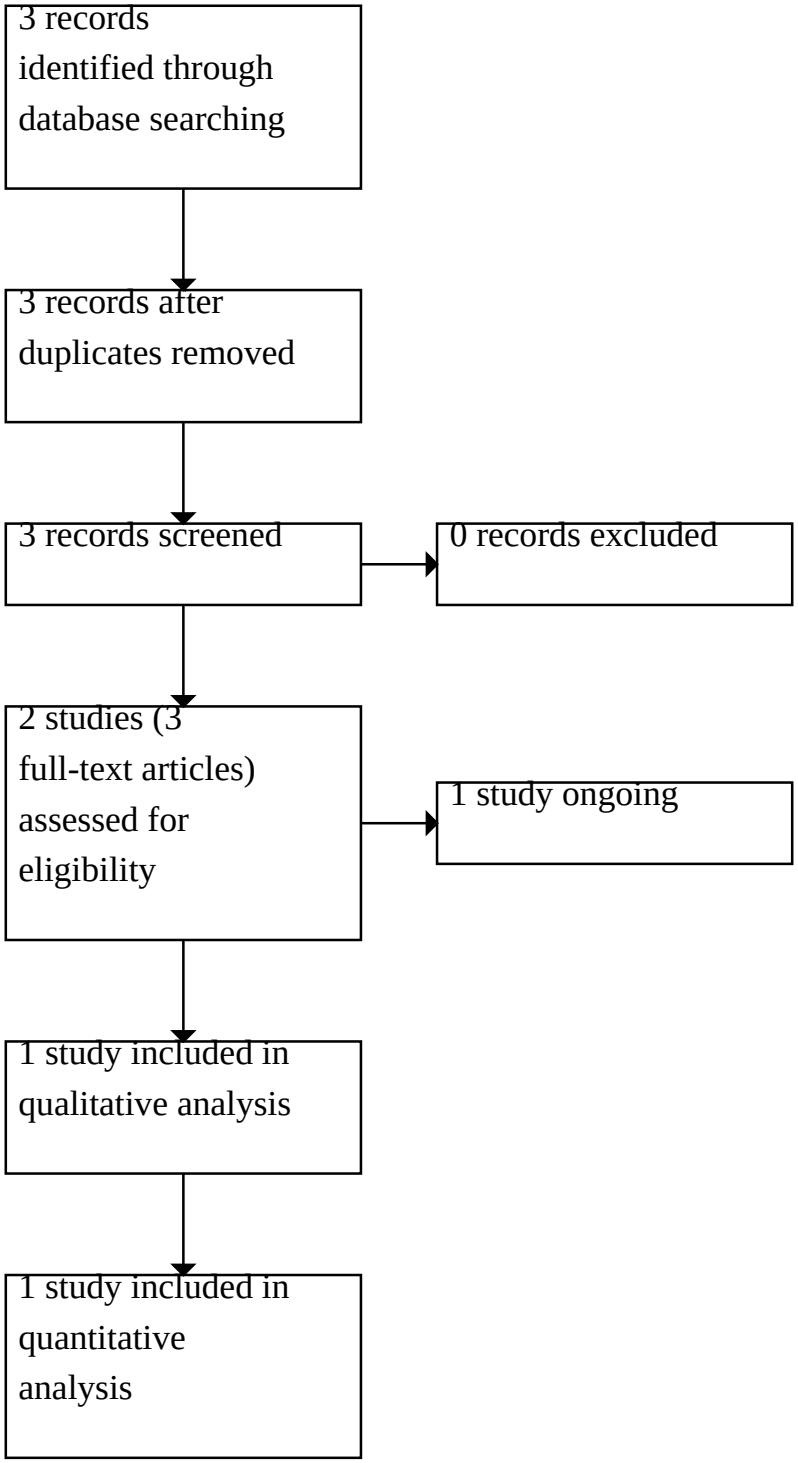
For detailed description of studies, see Characteristics of included studies and Characteristics of ongoing studies tables.

Results of the search

The Information Specialist searched the Cochrane Schizophrenia Group register of trials and retrieved two studies (3 reports). We included one study (2 reports) in our review and one ongoing study. There were no studies awaiting classification.

See also Figure 1.

Figure 1.



Included studies

We identified one eligible study (Jiang 2021). See also Characteristics of included studies.

1. Design and duration

The included study was a four-week double-blind RCT.

2. Participants

Participants had a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The mean age of participants in the MST group was 31 years and 34 years in the ECT group. Twenty-four of 43 and 22 of 36 were females in the MST and the ECT group, respectively. Nineteen of them were clozapine-resistant. All completers were on atypical antipsychotics. The participants were acutely ill. The baseline mean total PANSS score was 92.3 (SD 13.0) in the MST group and 99.1 (SD 11.6) in the ECT group.

3. Size

Ninety-three participants were assessed for eligibility and 79 were included.

4. Setting

All participants were inpatients in settings in China.

5. Interventions

The study compared MST plus standard care to ECT plus standard care. Session schedules were kept the same for both interventions and consisted of ten sessions, three sessions per week for the first fortnight and two for the second fortnight. Participants were under general anaesthesia with intravenous etomidate and propofol. Intravenous succinylcholine was used as a muscle relaxant and intravenous atropine was used to reduce airway secretions. Standard care was defined as participants continuing their usual antipsychotic medication treatments.

5.1 Magnetic seizure therapy

MST was administered at 50 Hz and 100% output. The pulse width was 370 µs, and the peak intensity of the magnetic field was 4.2 Tesla. The duration was titrated for each participant according to the induced seizure quality. The maximum duration was 20 seconds. When no seizures were generated, an extra stimulation lasting for 20 seconds was administered immediately. Magnetic stimulation was delivered via a twin coil with its midline on the vertex.

5.2 Electroconvulsive therapy

Bitemporal ECT was administered. The pulse width of the electrical stimulus was set to 0.5 ms. The energy used was tailored to each participant according to their age and the induced seizure quality. The maximum dosage was 100%. If no seizures were induced, the maximum dosage was administered immediately.

6. Outcomes

6.1 General

The study provided data for the following primary outcomes and secondary outcomes:

- Global state: clinically important change - number of participants with a clinical response. A clinical response was defined as a ≥ 25% reduction in the PANSS total score from baseline to the endpoint (improvement);
- Adverse effects: clinically important adverse effects - number of participants with a delayed memory deficit. A delayed memory deficit was defined as a ≥ 10% decrease in the RBANS delayed memory score from baseline to the endpoint;
- Cognitive functioning: any change - number of participants with improvement. An improvement was defined as any increase of RBANS total index from baseline to the endpoint;
- Cognitive functioning: change scores of RBANS total index from baseline to the endpoint;
- Mental state (overall): change scores of PANSS total score from baseline to the endpoint;
- Mental state (positive symptoms): change scores of PANSS positive subscale from baseline to the endpoint;
- Mental state (negative symptoms): change scores of PANSS negative subscale from baseline to the endpoint;
- Leaving the study early: any reason; due to adverse effect; due to inefficacy.

6.2 Outcome scales providing useable data

Clinically important change was measured by the Positive and Negative Syndrome Scale (PANSS) (Kay 1986). PANSS is a clinician-rated scale that contains 30 items. Three subscales, positive scale (7 items), negative scale (7 items) and general psychopathology scale (16 items) are rated on a seven-point Likert scale (1 to 7). Higher scores indicate worse performance. The PANSS total score is the sum of three subscales, ranging from 30 to 210.

Cognitive functioning was measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph 1998). RBANS generates 12 subtests which form five index scores (immediate memory, visuospatial/constructional, language, attention and delayed memory) and a total scale index score (range from 40 to 160) (Karantzoulis 2013). The scores are age-adjusted. Higher scores indicate better cognitive functioning.

7. Funding

The study was not funded by industrial companies but by public institutions.

Excluded studies

We did not exclude any studies from the search.

Ongoing studies

We identified one ongoing study (NCT02926976). See also Characteristics of ongoing studies.

Awaiting assessment

There was no study awaiting assessment.

Risk of bias in included studies

See also Figure 2, Figure 3 and Characteristics of included studies

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

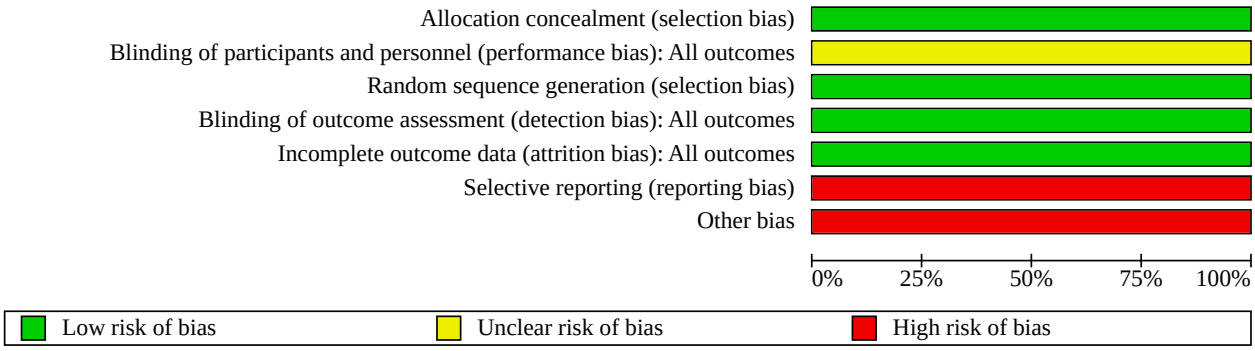
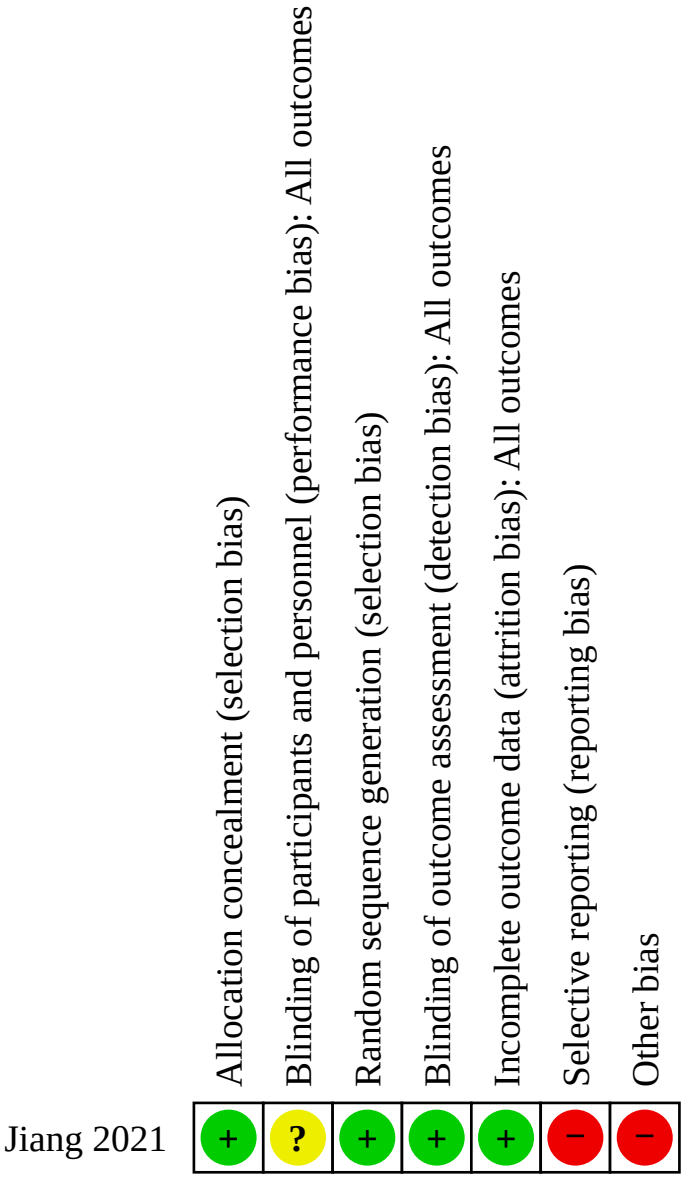


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The study used a computer-generated random sequence by an independent biostatistician, and the numbers were concealed in opaque envelopes; therefore, we considered the selection bias to be of low risk.

Blinding

The authors of the study made efforts to blind the participants by identical procedures and room settings prior to treatments. However, due to the nature of the interventions, the treating clinicians were not blinded from the first session. As a result, we considered the risk of performance bias to be unclear.

The outcomes were rated by independent assessors who were blinded to the interventions. We rated the risk of detection bias to be low.

Incomplete outcome data

Ten per cent (8 in 79 participants) dropped out of the study. Authors of the study conducted intention-to-treat (ITT) analysis and used 'the worst-case scenario' to impute missing data. Reasons for dropouts were reported. We considered the risk of attrition bias to be low.

Selective reporting

There was no protocol for the study. Outcomes listed in the trial register (www.clinicaltrials.gov/ct2/show/study/NCT02746965) were reported. However, data at multiple time points were planned. Due to early termination of the study, only data at four weeks were reported. We rated the risk of reporting bias to be high.

Other potential sources of bias

The study was terminated early due to coil malfunction and there was baseline imbalance between two groups. Participants in the ECT group had more severe symptoms than participants in the MST group. As a result, we rated the risk of other bias as high.

Effects of interventions

See: **Summary of findings 1** Magnetic seizure therapy plus standard care compared to electroconvulsive therapy plus standard care for people with schizophrenia

Only one study (n = 79) was included in this review. It was short term (4 weeks study duration) and examined adults with schizophrenia.

MST plus standard care verus ECT plus standard care

Primary outcomes

1. Global state: clinically important change

1.1 Number of participants with clinical response

A clinical response was defined as a ≥ 25% reduction from baseline to the endpoint of the PANSS total score.

We found very low certainty of evidence that there was no difference between groups (n = 79, RR 1.12, 95% CI 0.73 to 1.70, Analysis 1.1).

2. Cognitive functioning: clinically important change

No data were available.

3. Adverse effects: clinically important adverse effects

3.1 Number of participants with a delayed memory deficit

A delayed memory deficit was defined as a ≥ 10% decrease from baseline to the endpoint of the RBANS delayed memory score.

We found very low certainty of evidence that there was a favourable effect for MST compared to ECT (n = 79, RR 0.63, 95% CI 0.41 to 0.96, Analysis 1.2).

Secondary outcomes

1. Global state: any change in global state or average endpoint/change score of global state scale

No data were available.

2. Cognitive functioning

2.1 Any change of overall cognitive functioning: number of participants with improvement.

An improvement was defined as any increase of RBANS total index from baseline to the endpoint.

We found very low certainty of evidence that there was a favourable effect for MST compared to ECT (n = 47, RR 3.30, 95% CI 1.29 to 8.47, Analysis 1.3).

2.2 Average change score from baseline to endpoint of RBANS total index (high = good)

We found very low certainty of evidence that there was a favourable effect for MST compared to ECT (n = 79, MD 5.80, 95% CI 0.80 to 10.80, Analysis 1.4).

3. Adverse effects

No data were available.

4. Mental state

4.1 Overall: average change score from baseline to endpoint of PANSS total (high = poor)

We found very low certainty of evidence that there was no difference between groups (n = 79, MD -0.20, 95% CI -8.08 to 7.68, Analysis 1.5).

4.2 Positive symptoms: average change score from baseline to endpoint of PANSS positive subscale (high = poor)

We found very low certainty of evidence that there was no difference between groups (n = 79, MD 1.40, 95% CI -1.97 to 4.77, Analysis 1.6).

4.3 Negative symptoms: average change score from baseline to endpoint of PANSS negative subscale (high = poor)

We found very low certainty of evidence that there was no difference between groups (n = 79, MD -1.00, 95% CI -3.85 to 1.85, Analysis 1.7).

5. Quality of life

No data were available.

6. Satisfaction

No data were available.

7. Service use

No data were available.

8. Social functioning

No data were available.

9. Leaving the study early

9.1 Any reason

We found very low certainty of evidence that there was no difference between groups (n = 79, RR 2.51, 95% CI 0.73 to 8.59, Analysis 1.8).

9.2 Due to adverse effect

We found very low certainty of evidence that there was no difference between groups (n = 79, RR 3.35, 95% CI 0.39 to 28.64, Analysis 1.9).

9.3 Due to inefficacy

We found very low certainty of evidence that there was no difference between groups (n = 79, RR 2.52, 95% CI 0.11 to 60.10, Analysis 1.10).

10. Economic

No data were available.

Subgroup analysis

There were not enough data for the prespecified subgroups.

Sensitivity analysis

Prespecified sensitivity analyses were not conducted as there were insufficient data.

DISCUSSION

Summary of main results

We included only one short-term study with 79 participants which compared MST plus standard care with ECT plus standard care. Data were very limited. The overall risk of bias of the study was high. We rated the following domains as having low risk of bias: random sequence generation, allocation concealment, blinding of outcome assessment, and incomplete outcome data; unclear risk of bias in the domain, blinding of participants and personnel; and high risk of bias in the domains selective reporting and other bias (baseline imbalance and early termination due to technical problems of the MST machine).

We found that MST and ECT may be comparable in improving the global state of adults with schizophrenia, and in improving overall, positive and negative symptoms. We found that MST may cause less delayed memory deficit and less cognitive deterioration and improve cognitive function compared to ECT. There may be no difference between the two groups in terms of leaving the study early due to any reason, adverse effect, or inefficacy.

Since all the findings were based on very low certainty of evidence, we were not sure these comparable or favourable effects of MST over ECT were its true effects.

Overall completeness and applicability of evidence

There were too few data to address the review question. The very limited data were only about adults with acute schizophrenia in a short-term setting. There were no data on median and long-term effects of MST and no information about subgroups, such as first-episode schizophrenia, or vulnerable populations (elderly, children). From the available evidence, cognitive function and adverse effects were not adequately assessed and there were no data about quality of life, satisfaction, service use, social functioning and economic outcomes.

Current findings are at most preliminary and cannot be applied directly to clinical practice. RCTs are warranted to investigate the effect of the novel intervention MST for people with schizophrenia.

Quality of the evidence

Results for three outcomes in the SoF table were available, i.e. clinically important change in global state; clinically important change in cognitive functioning; and leaving the study early due to any reason. We downgraded the certainty of the evidence by two levels for high RoB and by one to two levels for imprecision because of small sample size and the CIs including appreciable benefit and harm. We assessed the overall certainty of the evidence to be very low for all outcomes using GRADE.

Potential biases in the review process

We have used the Cochrane Schizophrenia Group's study-based trial register to identify eligible studies. We also contacted experts in the fields and manufacture companies to look for additional unpublished studies or data. However, we retrieved very limited RCT data relevant to this review. We restricted the inclusion criteria to RCTs to ensure quality of the evidence and avoid risk of bias, so data from other types of studies, such as non-randomised or observational studies were not assessed and summarised in this review.

Three study authors, including the lead author and the principal investigator of the included study were co-authors of the current review. We have taken measures to prevent bias by excluding them from screening and selection of studies, data extraction and assessment of risk of bias and the quality of the evidence.

Agreements and disagreements with other studies or reviews

One systematic review (Zhang 2021) synthesised two single-armed self-controlled studies and found low certainty of evidence that MST improved psychotic symptoms but with a high discontinuation rate. It also reported inconsistent evidence regarding cognitive adverse effects of MST. The review resonated with our findings that currently there was a lack of high-quality evidence investigating the effect of MST for people with schizophrenia.

AUTHORS' CONCLUSIONS

Implications for practice

MST as novel non-invasive brain stimulation was developed to be an alternative to current treatment options for schizophrenia. However, no recommendations for this new therapy can be given before a proper assessment is available. Data were too scarce to draw any useful conclusions for people with schizophrenia, clinicians, and policy-makers. MST has been more often investigated in people with depression but, unfortunately, there is still insufficient information on its efficacy and tolerability in such a group of people (Jiang 2021), underscoring the overall limited evidence we have about MST. Those who wish to use MST should bear the unknown risk in mind. Cautions should be taken before application.

Implications for research

There is a significant lack of evidence in this field. Preliminary findings showed MST could have good efficacy and result in minimal cognitive impairment for acute treatment in depression (Cretaz 2015; Daskalakis 2020; Mutz 2019). However, the findings lacked not only precision but also consistency, similar to the findings of the evidence in people with schizophrenia. More

investigation is needed to answer the question with certainty, and emphasis should be put on cognitive function evaluation with regard to the side effects profile.

To assess the effect of MST, studies with a longer duration are needed, as well as studies of people with stable schizophrenia for a relapse prevention purpose.

The only included study was terminated due to coil malfunction, which leads to the question whether MST is cost-effective. To assess whether MST is a good alternative to other treatment options, an economic assessment is necessary for inclusion in future studies.

Regardless of the limited data, current evidence could not exclude the potential for MST to be a promising treatment alternative that may have desirable efficacy and a benign side effect profile for people with schizophrenia. Well-designed RCTs are needed to inform clinical practice about the efficacy and tolerability of MST in people with schizophrenia. The optimal information size should be met to provide good precision and efforts should be made to undertake blinding to avoid bias. However, due to the nature of MST, it is difficult to conduct such RCTs. Good reporting is also essential to allow adequate evaluation of the evidence. The CONSORT Statement (available at www.consort-statement.org) should be complied with.

ACKNOWLEDGEMENTS

The Cochrane Schizophrenia Group Editorial Base situated between the University of Melbourne, Australia, the Technical University of Munich, Germany, and the University of Nottingham, UK, produces and maintains standard text for use in the Methods section of their reviews. We have used this text as the basis of what appears here and adapted it as required.

Editorial and peer-reviewer contributions:

Cochrane Schizophrenia supported the authors in the development of this review.

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Mahesh Jayaram, University of Melbourne
- Handling Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Spyridon Siafis, Technical University of Munich
- Copy Editor (copy-editing and production): Anne Lethaby
- Information Specialist (search strategy and search results): Farhad Shokraneh, Systematic Review Consultants
- Peer-reviewers* (clinical/content review, provided comments and recommended an editorial decision): Liam Kennedy, St Vincent's University Hospital, Gamze Erzin, Dışkapı Training and Research Hospital
- The previous Cochrane Schizophrenia Group editorial base also supported this work: Co-ordinating Editor, Clive Adams (before 2020), Managing Editor, Claire Irving (before 2020), Assistant Managing Editor, Ghazaleh Aali, University College London (before April 2021)

*Peer-reviewers provided peer-review comments on this article, but they were not otherwise involved in the editorial process or decision-making for this article.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Jiang 2021

Study characteristics	
Methods	Allocation: randomised, computer-generated random sequence Blinding: double-masking (participants, outcome assessors) Duration: 4 weeks Design: parallel Location: single-centre, China Setting: inpatients
Participants	Diagnosis: schizophrenia (DSM-5); clinically indicated convulsive therapy, for the treatment of severe psychomotor excitement or retardation, suicide attempts, highly aggressive behaviours, pharmacotherapy intolerance, and ineffectiveness of antipsychotics (total or partial lack of response to previous treatment using at least one antipsychotic at adequate doses and periods), as assessed by two attending doctors; PANSS score ≥ 60 Sample size: N = 79, data of 71 completers were reported Gender: 33 male, 46 female Age: 18–55 years old; MST group mean age: 31 years old, ECT group mean age: 34 years old History: mean duration of illness: 8 years; clozapine-resistant participants: 24% of all completers were on atypical antipsychotics; 11 of them also took benzodiazapines.
Interventions	Participants were randomised to either of the two intervention groups: 1. MST + SC (N = 43) MST was administered at 50 Hz and 100% output. The pulse width was 370 μs, and the peak intensity of the magnetic field was 4.2 Tesla. A titration method was employed to determine the duration of the magnetic stimulation; the duration began at 4 s and was increased by 4 s in each subsequent session up to a maximum of 20 s (i.e. 200–1000 pulses per session). If the seizure quality was poor (seizure duration < 15 s) in a certain session, the increment of the stimulation duration was 8 s during the next session. If no seizures were generated, an extra stimulation lasting for 20 s was administered immediately. Magnetic stimulation was delivered via a twin coil with its midline on the vertex. Participants continued to receive their routine antipsychotic medications. 2. ECT + SC (N = 36) The pulse width of the electrical stimulus was set to 0.5 ms. The energy used in the first session was set according to patient's age, and the percent energy used in the following sessions was increased by 5%. If the seizure was inadequate (seizure duration < 25 s), the maximum dosage was administered in the subsequent session. If no seizures were induced, the maximum dosage was administered immediately. Bitemporal ECT was administered. Participants continued to receive their routine antipsychotic medications. Ten sessions of MST/ECT over 4 weeks, with three sessions per week the first fortnight and two sessions per week the second fortnight. General anaesthesia with intravenous etomidate (0.21 to 0.3 mg/kg) and propofol (1.82 to 2.44 mg/kg) were used for both interventions. Intravenous succinylcholine (1 mg/kg) was used as a muscle relaxant, and intravenous atropine (0.5 mg) was used to reduce airway secretions. EEGs were recorded during MST and ECT.
Outcomes	Primary outcomes Global state: clinically important change - number of participants with clinical response. A clinical response was defined as a ≥ 25% reduction from baseline to the endpoint of the PANSS total score.

Jiang 2021 *(Continued)*

	Adverse effects: clinically important adverse effects - number of participants with a delayed memory deficit. A delayed memory deficit was defined as a ≥ 10% decrease from baseline to the endpoint of the RBANS delayed memory score. Secondary outcomes: Cognitive functioning: any change of overall cognitive functioning - number of participants with improvement. An improvement was defined as any increase of RBANS total index from baseline to the endpoint. Cognitive functioning: average change score from baseline to endpoint of RBANS total index (high = good) Mental state: Overall: average change of PANSS total (high = poor) Positive symptoms: average change of PANSS positive subscale (high = poor) Negative symptoms: average change of PANSS negative subscale (high = poor) Leaving the study early: any reason; due to adverse effects; due to inefficacy
Notes	The study was supported by grants from the Shanghai Hospital Development Center (SHDC12014111 to CL), the Science and Technology Commission of Shanghai Municipality (13dz2260500 to CL, 14411961400 to JW, and 17411969900 to DL), Shanghai Municipal Commission of Health and Family Planning (201740042 to YJ), National Natural Science Foundation of China (81971251 to JW), and the SHSMU-ION Research Centre for Brain Disorders (to CL). The study authors declared that the supporters had no role in the design, analysis, interpretation, or publication of this study. The study was terminated early because of coil malfunction.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	"Each subject received a number within a concealed opaque envelope indicating their randomisation assignment. The treatment code was provided to the treating clinician following the baseline assessment, but prior to the first treatment session."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"All procedures prior to treatment and the room setup were made identical to ensure the blinding of patients (e.g. presence of both ECT and MST equipment)." The authors of the study made efforts to implement blinding, however, due to the nature of the interventions, the treating clinicians were not blinded from the first session.
Random sequence generation (selection bias)	Low risk	"A random sequence of allocation with a ratio of 1:1 was generated using SAS 9.3 (SAS Institute Inc., USA) by an independent biostatistician who had no access to information on the study subjects".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Clinical and cognitive assessments were conducted by a trained psychiatrist who was blinded to the treatment group".
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 of 79 participants dropped out. ITT analysis was undertaken and "the worse-case scenario was used to impute missing data". Reasons for dropouts were reported.
Selective reporting (reporting bias)	High risk	Data at multiple time points were planned. Due to early termination of the study, only data at 4 weeks were reported.

Jiang 2021 *(Continued)*

Other bias	High risk	Baseline imbalance, terminated early due to coil malfunction

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECT: electroconvulsive therapy
EEG: electroencephalogram
MCI: mild cognitive impairment
MST: magnetic seizure therapy
PANSS: Positive and Negative Syndrome Scale
RBANS: Repeatable Battery for the Assessment of Neuropsychological Status
SC: standard care

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

NCT02926976

Study name	NCT02926976
Methods	Randomised, parallel assignment, double-blind
Participants	Treatment-resistant schizophrenia, 18 years to 60 years (adult), all sexes
Interventions	Experimental: Magnetic seizure therapy + clozapine; Active comparator: risperidone + clozapine; Active comparator: aripiprazole + clozapine; Active comparator: sodium valproate + clozapine; Active comparator: clozapine; Active comparator: modified electroconvulsive therapy + clozapine.
Outcomes	Primary outcome: change from baseline in PANSS Secondary outcomes: change from baseline in CGI, SAS, AIMS
Starting date	
Contact information	Dr. Dengtang Liu, erliu110@126.com
Notes	The study authors are analysing their data and will share the data with us after publication.

AIMS: Abnormal Involuntary Movement Scale
CGI: Clinical Global Impression
PANSS: Positive and Negative Syndrome Scale
SAS: Simpson-Angus Scale

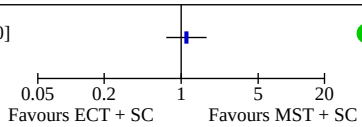
DATA AND ANALYSES

Comparison 1. Magnetic seizure therapy plus standard care verus electroconvulsive therapy plus standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Global state: clinically important change - number of participants with clinical response	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.2 Adverse effects: clinically important adverse effects - number of participants with a delayed memory deficit	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.3 Cognitive functioning: any change - number of participants with improvement	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.4 Cognitive functioning: average change score from baseline to endpoint of RBANS total index (high = good)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.5 Mental state-Overall: average change score from baseline to endpoint of PANSS total (high = poor)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6 Mental state-Positive symptoms: average change score from baseline to endpoint of PANSS positive subscale (high = poor)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7 Mental state-Negative symptoms: change scores of PANSS negative subscale (high = poor)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8 Leaving the study early: any reason	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.9 Leaving the study early: due to adverse effect	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.10 Leaving the study early: due to inefficacy	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Magnetic seizure therapy plus standard care verus electroconvulsive therapy plus standard care, Outcome 1: Global state: clinically important change - number of participants with clinical response

Study or Subgroup	MST + SC Events	MST + SC Total	ECT + SC Events	ECT + SC Total	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Jiang 2021 (1)	24	43	18	36	1.12 [0.73 , 1.70]	+ ? + + + − −



Footnotes

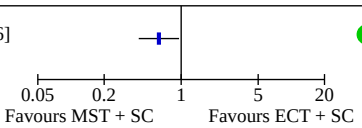
(1) A clinical response was defined as a ≥ 25% reduction from baseline to the endpoint of the total PANSS score

Risk of bias legend

(A) Allocation concealment (selection bias)
(B) Blinding of participants and personnel (performance bias)
(C) Random sequence generation (selection bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: Magnetic seizure therapy plus standard care verus electroconvulsive therapy plus standard care, Outcome 2: Adverse effects: clinically important adverse effects - number of participants with a delayed memory deficit

Study or Subgroup	MST + SC Events	MST + SC Total	ECT + SC Events	ECT + SC Total	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Jiang 2021 (1)	18	43	24	36	0.63 [0.41 , 0.96]	+ ? + + + − −



Footnotes

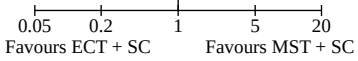
(1) a delayed memory deficit was defined as a ≥ 10% reduction in the RBANS delayed memory score

Risk of bias legend

(A) Allocation concealment (selection bias)
(B) Blinding of participants and personnel (performance bias)
(C) Random sequence generation (selection bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: Magnetic seizure therapy plus standard care verus electroconvulsive therapy plus standard care, Outcome 3: Cognitive functioning: any change - number of participants with improvement

Study or Subgroup	MST + SC Events	MST + SC Total	ECT + SC Events	ECT + SC Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Jiang 2021 (1)	15	25	4	22	3.30 [1.29 , 8.47]		+ ? + + + − −



Footnotes

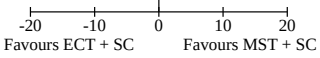
(1) An improvement was defined as any increase of RBANS total index from baseline to the endpoint

Risk of bias legend

(A) Allocation concealment (selection bias)
(B) Blinding of participants and personnel (performance bias)
(C) Random sequence generation (selection bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.4. Comparison 1: Magnetic seizure therapy plus standard care verus electroconvulsive therapy plus standard care, Outcome 4: Cognitive functioning: average change score from baseline to endpoint of RBANS total index (high = good)

Study or Subgroup	MST + SC Mean	MST + SC SD	MST + SC Total	ECT + SC Mean	ECT + SC SD	ECT + SC Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F G
Jiang 2021	0	13.3	43	-5.8	9.3	36	5.80 [0.80 , 10.80]		+ ? + + + − −



Risk of bias legend

(A) Allocation concealment (selection bias)
(B) Blinding of participants and personnel (performance bias)
(C) Random sequence generation (selection bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.5. Comparison 1: Magnetic seizure therapy plus standard care verus electroconvulsive therapy plus standard care, Outcome 5: Mental state-Overall: average change score from baseline to endpoint of PANSS total (high = poor)

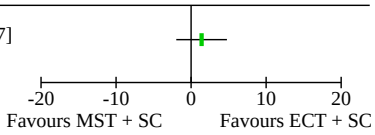
Study or Subgroup	MST + SC Mean	MST + SC SD	MST + SC Total	ECT + SC Mean	ECT + SC SD	ECT + SC Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F G
Jiang 2021	-23.3	16.9	43	-23.1	18.5	36	-0.20 [-8.08 , 7.68]		+ ? + + + − −

Risk of bias legend

(A) Allocation concealment (selection bias)
(B) Blinding of participants and personnel (performance bias)
(C) Random sequence generation (selection bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

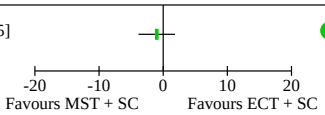
Analysis 1.6. Comparison 1: Magnetic seizure therapy plus standard care verus electroconvulsive therapy plus standard care, Outcome 6: Mental state-Positive symptoms: average change score from baseline to endpoint of PANSS positive subscale (high = poor)

Study or Subgroup	MST + SC Mean	MST + SC SD	MST + SC Total	ECT + SC Mean	ECT + SC SD	ECT + SC Total	Mean Difference IV, Fixed, 95% CI
Jiang 2021	-9.8	8.3	43	-11.2	7	36	1.40 [-1.97 , 4.77]



Analysis 1.7. Comparison 1: Magnetic seizure therapy plus standard care verus electroconvulsive therapy plus standard care, Outcome 7: Mental state-Negative symptoms: change scores of PANSS negative subscale (high = poor)

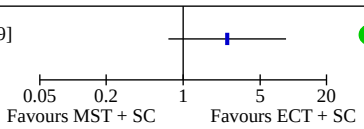
Study or Subgroup	MST + SC Mean	MST + SC SD	MST + SC Total	ECT + SC Mean	ECT + SC SD	ECT + SC Total	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F	G
Jiang 2021	-2.1	6.7	43	-1.1	6.2	36	-1.00 [-3.85 , 1.85]	+	?	+	+	+	−	−



Risk of bias legend
(A) Allocation concealment (selection bias)
(B) Blinding of participants and personnel (performance bias)
(C) Random sequence generation (selection bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.8. Comparison 1: Magnetic seizure therapy plus standard care verus electroconvulsive therapy plus standard care, Outcome 8: Leaving the study early: any reason

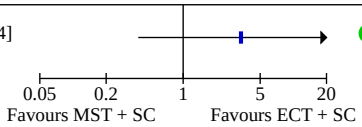
Study or Subgroup	MST + SC Events	MST + SC Total	ECT + SC Events	ECT + SC Total	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F	G
Jiang 2021	9	43	3	36	2.51 [0.73 , 8.59]	+	?	+	+	+	−	−



Risk of bias legend
(A) Allocation concealment (selection bias)
(B) Blinding of participants and personnel (performance bias)
(C) Random sequence generation (selection bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.9. Comparison 1: Magnetic seizure therapy plus standard care verus electroconvulsive therapy plus standard care, Outcome 9: Leaving the study early: due to adverse effect

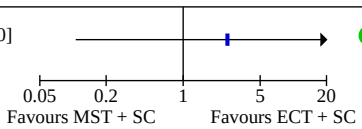
Study or Subgroup	MST + SC Events	MST + SC Total	ECT + SC Events	ECT + SC Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Jiang 2021	4	43	1	36	3.35 [0.39 , 28.64]		+ ? + + + − −



Risk of bias legend
(A) Allocation concealment (selection bias)
(B) Blinding of participants and personnel (performance bias)
(C) Random sequence generation (selection bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.10. Comparison 1: Magnetic seizure therapy plus standard care verus electroconvulsive therapy plus standard care, Outcome 10: Leaving the study early: due to inefficacy

Study or Subgroup	MST + SC Events	MST + SC Total	ECT + SC Events	ECT + SC Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Jiang 2021	1	43	0	36	2.52 [0.11 , 60.10]		+ ? + + + − −



Risk of bias legend
(A) Allocation concealment (selection bias)
(B) Blinding of participants and personnel (performance bias)
(C) Random sequence generation (selection bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

HISTORY

Protocol first published: Issue 6, 2017

CONTRIBUTIONS OF AUTHORS

HW: design of the review, study screening, data extraction, risk of bias assessment, quality assessment, data analyses, interpreting results, writing up the review

JJ: revising the review, providing additional data for analysis

XC: study screening, data extraction, risk of bias assessment, quality assessment

JW: revising the review, supervision

CL: conceiving and coordinating the review, revising the review, supervision

DECLARATIONS OF INTEREST

HW: was the Managing Editor of Cochrane Schizophrenia Group and was not involved in any editorial process of this review.

JJ: participated in the included study; he was excluded from data extraction, risk of bias assessment and quality assessment of this study.

XC: none known

JW: participated in the included study; he was excluded from data extraction, risk of bias assessment and quality assessment of this study.

CL: is an Editor of Cochrane Schizophrenia Group and was not involved in any editorial process of this review. CL is the PI of the included study; he was excluded from data extraction, risk of bias assessment and quality assessment of this study.

SOURCES OF SUPPORT

Internal sources

- Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, China

  The employer of review authors JJ, JW, XC and CL
- Freistaat Bayern, Germany

  The employer of review author HW
- National Institute for Health and Care Research (NIHR), UK

  Provided funding for Cochrane Schizophrenia Group

External sources

- NSFC-DFG project, China

  Project Number (82161138021)
- Program for Outstanding Academic Leader of Shanghai, China

  Project Number (041)
- Shanghai Clinical Research Center for Mental Health , China

  Project Number (19MC1911100)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have updated some content in the background and revised the wording of the method sections to avoid confusion.

We aimed to include all eligible RCTs investigating the effects of MST for people with schizophrenia, in any clinical state. For this reason, we planned to evaluate two different primary outcomes for global state, i.e. clinically important change and relapse. We clarified in the review that clinically important change was to be measured for acute-phase studies (in people with acute exacerbations of schizophrenia) and relapse for relapse-prevention studies (in people with stable schizophrenia). In the current review, only one acute study was included and the outcome, clinically important change, was assessed for the primary outcome.

We did not involve a third author to randomly re-inspect 20% of the abstract screening and 20% of the full-text selection and re-extract 10% of the data to insure reliability since only one study was included and data were limited.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antipsychotic Agents [adverse effects]; Memory Disorders; *Schizophrenia [drug therapy]

MeSH check words

Adult; Humans