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Magnetic seizure therapy for treatment-resistant depression (Review)

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TABLE OF CONTENTS

[Intervention Review]

Magnetic seizure therapy for treatment-resistant depression

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ABSTRACT

Background

Magnetic seizure therapy (MST) is a potential alternative to electroconvulsive therapy (ECT). Reports to date on use of MST for patients with treatment-resistant depression (TRD) are limited.

Objectives

To evaluate the effects of MST in comparison with sham-MST, antidepressant, and other forms of electric or magnetic treatment for adults with TRD.

Search methods

In March 2020, we searched a wide range of international electronic sources for published, unpublished, and ongoing studies. We handsearched the reference lists of all included studies and relevant systematic reviews and conference proceedings of the Annual Meeting of the American College of Neuropsychopharmacology (ACNP), the Annual Scientific Convention and Meeting, and the Annual Meeting of the European College of Neuropsychopharmacology (ECNP) to identify additional studies.

Selection criteria

All randomised clinical trials (RCTs) focused on MST for adults with TRD.

Data collection and analysis

Two review authors extracted data independently. For binary outcomes, we calculated risk ratios (RRs) and 95% confidence intervals (CIs). For continuous data, we estimated mean differences (MDs) between groups and 95% CIs. We employed a random-effects model for analyses. We assessed risk of bias for included studies and created a 'Summary of findings' table using the GRADE approach. Our main outcomes of interest were symptom severity, cognitive function, suicide, quality of life, social functioning, dropout for any reason, serious adverse events, and adverse events that led to discontinuation of treatment.

Main results

We included three studies (65 participants) comparing MST with ECT. Two studies reported depressive symptoms with the Hamilton Rating Scale for Depression (HAMD). However, in one study, the data were skewed and there was an imbalance in baseline characteristics. Analysis of these two studies showed no clear differences in depressive symptoms between treatment groups (MD 0.71, 95% CI -2.23 to 3.65; 2 studies, 40 participants; very low-certainty evidence). Two studies investigated multiple domains of cognitive function. However most of the outcomes were not measured by validated neuropsychological tests, and many of the data suffered from unbalanced baseline and skewed distribution. Analysis of immediate memory performance measured by the Wechsler Memory Scale showed no clear differences

between treatment groups (MD 0.40, 95% CI -4.16 to 4.96; 1 study, 20 participants; very low-certainty evidence). Analysis of delayed memory performance measured by the Wechsler Memory Scale also showed no clear differences between treatment groups (MD 2.57, 95% CI -2.39 to 7.53; 1 study, 20 participants; very low-certainty evidence). Only one study reported quality of life, but the data were skewed and baseline data were unbalanced across groups. Analysis of quality of life showed no clear differences between treatment groups (MD 14.86, 95% CI -42.26 to 71.98; 1 study, 20 participants; very low-certainty evidence). Only one study reported dropout and adverse events that led to discontinuation of treatment. Analysis of reported data showed no clear differences between treatment groups for this outcome (RR 1.38, 95% CI 0.28 to 6.91; 1 study, 25 participants; very low-certainty evidence). Adverse events occurred in only two participants who received ECT (worsening of preexisting coronary heart disease and a cognitive adverse effect). None of the included studies reported outcomes on suicide and social functioning. No RCTs comparing MST with other treatments were identified.

Authors' conclusions

Evidence regarding effects of MST on patients with TRD is currently insufficient. Our analyses of available data did not reveal clearly different effects between MST and ECT. We are uncertain about these findings because of risk of bias and imprecision of estimates. Large, long, well-designed, and well-reported trials are needed to further examine the effects of MST.

PLAIN LANGUAGE SUMMARY

Is magnetic seizure therapy an effective add-on treatment for people with treatment-resistant depression?

Review question

Whether magnetic seizure therapy (MST) is effective and acceptable to treat treatment-resistant depression (TRD).

Why this is important

More than 30% of patients with depression respond poorly to medicine and psychotherapy. We recognise those people as patients with TRD. They suffer from much higher rates of disability and economic burden compared with non-TRD patients.

Electroconvulsive therapy (ECT) is an important treatment for people with TRD. Nevertheless, ECT is often associated with cognitive adverse effects, such as memory loss. Magnetic seizure therapy (MST) is a potential alternative to ECT with fewer cognitive adverse effects. Therefore, it is important to know how well MST works for treating people with TRD.

What we did

In March 2020, we searched randomised controlled trials (RCTs) for studies of MST for treatment-resistant depression. Participants received different treatments at random. This study design provides the most reliable evidence.

Outcomes included how well treatments worked (improvement in symptom severity, quality of life, and social functioning, as well as in numbers of participants conducting suicides, making suicide attempts, or inflicting self-harm) and whether participants experienced adverse effects (cognitive function, number of dropouts, and number of adverse events).

What we found

We included three studies involving 65 participants. These studies compared MST and ECT with up to 12 treatment sessions in six weeks. Existing evidence did not reveal differences in effectiveness or tolerance between MST and ECT.

However, we are not sure how reliable study results are. All findings are based on only a few studies with a small number of participants. Participants knew which treatment they received. Studies were conducted in a different way from their protocols. Some key information was not reported, such as how participants were allocated to different treatments and whether there were participant dropouts from these studies. All studies were conducted by a single research team in Germany and were funded in part by the manufacturer of an MST device.

Conclusions

Evidence regarding effects of MST on patients with TRD is currently insufficient. Our analyses of available data did not reveal clearly different effects between MST and ECT. Our certainty in the evidence is very low. Large, long, well-designed, well-reported trials are needed to further examine the effects of MST.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings

MST compared with ECT for schizophrenia

Patient or population: patients with schizophrenia

Settings: inpatient or outpatient

Intervention: MST

Comparison: ECT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with ECT	Risk with MST				
MST vs ECT - symptom severity - HAMD (high = poor; short term)	Mean score 8.1	**MD 0.71 higher** (2.23 lower to 3.65 higher)	-	40 (2 RCTs)	⊕⊖⊖⊖ **very low** [a,b]	Baseline data were unbalanced across groups in 1 study
MST vs ECT - cognitive function - immediate memory (high = better; short term)	Mean score 13.8	**MD 0.40 higher** (4.16 lower to 4.96 higher)	-	20 (1 RCT)	⊕⊖⊖⊖ **very low** [a]	-
MST vs ECT - cognitive function - delayed memory (high = better; short term)	Mean score 10.33	**MD 2.57 higher** (2.39 lower to 7.53 higher)	-	20 (1 RCT)	⊕⊖⊖⊖ **very low** [a]	Baseline data were unbalanced across groups
MST vs ECT - suicides, suicide attempts, self-harm	-	-	-	-	-	No study reported on this important outcome
MST vs ECT - quality of life	-	**MD 14.86 higher** (42.26 lower to 71.98 higher)	-	20 (1 RCT)	⊕⊖⊖⊖ **very low** [a]	Baseline data were unbalanced across groups
MST vs ECT - social functioning	-	-	-	-	-	No study reported on this important outcome

MST vs ECT - dropout for any reason (short term)	**167 per 1000**	**230 per 1000**	**RR 1.38** (0.28 to 6.91)	25 (1 RCT)	⊕⊝⊝⊝ **very low** [b]	-
MST vs ECT - serious adverse events	-	-	-	-	-	No study reported on this important outcome
MST vs ECT - adverse events that led to discontinuation of treatment (short term)	**167 per 1000**	**31 per 1000**	**RR 0.19** (0.01 to3.52)	25 (1 RCT)	⊕⊝⊝⊝ **very low** [b]	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; ECT: electroconvulsive therapy; MD: mean difference; MST: magnetic seizure therapy; RCT: randomised controlled trial; RR: risk ratio.

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.

[a]Downgraded three levels for risks of bias (no blinding and funding from an MST device manufacturer) and imprecision (very broad confidence interval that crossed the null) of Kayser 2011.
[b]Downgraded three levels for risks of bias (no blinding and funding from an MST device manufacturer) and imprecision (very broad confidence interval that crossed the null) of Kayser 2017.

BACKGROUND

Description of the condition

Major depressive disorder (MDD) is characterised by depressed mood and loss of interest or pleasure, accompanied by a range of symptoms including weight loss or weight gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or inappropriate guilt, diminished ability to think or concentrate or decide, thoughts of death or suicidal ideation, and suicide attempts (APA 2013). Although antidepressants remain the first-line treatment for depressive disorders (NICE 2010), they generate small to medium effects when compared with placebo (Cipriani 2018; Jakobsen 2017). Typically, we can recognise a situation where people with depressive disorders fail to adequately respond (usually defined by 50% reduction in depressive symptom severity) to multiple trials of adequate antidepressants (in terms of dose, duration, and compliance) as treatment-resistant depression (TRD), but no consensus on this definition has been reached (Trevino 2014).

Globally, depression is a common mental disorder estimated to affect more than 300 million people (WHO 2017). Lifetime prevalence varies across nations, with an estimate of 14.6% in high-income countries and 11.1% in low-income countries (Bromet 2011). Rates of TRD vary from 30% to 60% depending on how the disorder is defined (Vieta 2011).

Noticeable personal, social, and economic morbidity, as well as loss of functioning and productivity, often coexists with depression and leads to substantial demands on service providers (NICE 2010). Depression is also associated with suicide (Kessler 2005), along with increased rates of mortality (Cuijpers 2002). It is the second leading cause of disability globally, and it has contributed 8.1% of all-cause years lived with disability (Vos 2013). Depression contributes substantially to the burden of disease globally, and it ranks third worldwide, eighth in low-income countries, and first in middle-income and high-income countries (Mathers 2008). Compared with people with non-TRD depression, people with TRD experience much higher rates of long-term disability (Rizvi 2014), as well as economic burden (Mrazek 2014).

Description of the intervention

Magnetic seizure therapy (MST) is a potential alternative option to electroconvulsive therapy (ECT). For depression, ECT is effective, possibly even more so than multiple types of antidepressants (UK ECT RG 2003). ECT is considered the last resort for people with depression with antidepressant intolerance, medication resistance, or other difficult-to-treat conditions, and it may serve as life-saving treatment for acute suicide-threatening and catatonic patients (Frederikse 2006). Nevertheless, ECT is often associated with cognitive adverse effects such as anterograde amnesia and postictal disorientation in the short term, along with retrograde amnesia in the long term (Lisanby 2007). The rate of reported persistent memory loss appears to vary between 29% and 55% (Rose 2003).

The hypothesis of using magnetic stimulation to induce therapeutic seizures arose in the mid-1990s (Sackeim 1994). The first successful and deliberate induction of seizures with magnetic pulses was conducted on two *Macaca mulatta* (rhesus macaque) in 2001 (Lisanby 2001a). Results from further animal experiments indicate that MST has a significantly lower impact on cognitive function than is seen with electroconvulsive shock (ECS), the animal equivalent of ECT, and that no significant differences exist between MST and sham in most measures (McClintock 2013; Spellman 2008). No morphological changes or histological lesions were found in postmortem animals that had received MST (Dwork 2009; Dwork 2014).

The first case report of MST in humans was published in 2001, soon after the first MST report on animals (Lisanby 2001b). Since that time, several clinical trials have primarily investigated the feasibility, efficacy, and safety of MST. Lisanby and colleagues provided support for the feasibility of MST for depression and did not find evidence of serious adverse events (Lisanby 2003). Kayser and colleagues pointed out that MST has antidepressant effects comparable with those of ECT (Kayser 2011). Fitzgerald and colleagues claimed that MST has an antidepressant effect with no apparent cognitive adverse effects (Fitzgerald 2013).

Usually, multiple sessions of MST are administered by trained psychiatrists twice or three times a week. Magnetic stimulation is delivered via a twin coil with its midline on the vertex or frontal cortex at 25 Hz to 100 Hz. Given that the seizure threshold is likely to increase as treatment continues as ECT (Sackeim 1999), titration methods are employed to determine the dose of stimulation (100 pulses to 1000 pulses per session). In addition, MST is administered under general anaesthesia.

How the intervention might work

The quest to refine ECT techniques has been impeded by a fundamental limitation - the electrical stimulus. The substantial impedance of the scalp and skull shuts most of the electrical stimulus away from the brain, resulting in widespread stimulation of cortical and subcortical regions (Deng 2011; Rush 1968). In contrast, magnetic pulses, which can pass through the scalp and the skull without resistance, are capable of focusing the stimulus on a specific area of the brain (Deng 2011). Additionally, a magnetic stimulus can reach a depth of only a few centimetres, while electric currents are able to penetrate into deeper structures (Deng 2011). Theoretically, unlike ECT, MST can generate focal stimulation of superficial regions of the cortex, which may give MST the capability of producing comparable therapeutic benefit in the absence of apparent cognitive adverse effects. Indeed, some studies have provided evidence for this superiority of MST (Fitzgerald 2013; Polster 2015).

The effect of MST on brain glucose metabolism in depression has been investigated by positron emission tomography/computed tomography (PET/CT) (Hoy 2013). Hoy 2013 found increased relative glucose metabolism (relative to whole-brain glucose uptakes) in basal ganglia, orbitofrontal cortex, medial frontal cortex, and dorsolateral prefrontal cortex. There was a trend toward differences in brain activation between responders and non-responders in the ventral anterior cingulate. Another study identifying the metabolic impact of MST on the brain of receivers via PET scans revealed increased glucose metabolism in the frontal cortex bilaterally and decreased glucose metabolism in the left striatum (Kayser 2015). Given the dysfunction of glucose metabolism in TRD (Li 2015; Martinot 2011), modulation of glucose metabolism may result from the therapeutic effect of MST for TRD.

Why it is important to do this review

Almost two decades after the first published reports of MST for people with depressive disorders, information regarding its efficacy and safety remains insufficient. All published research is limited by the small number of participants and the early-stage study design. Thus, high-quality evidence about the benefits and harms of MST is needed. As reflected by trial registrations in the International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov, many researchers and clinicians have recognised the potential of MST as an effective treatment for TRD with minimal cognitive effect. A considerable number of high-quality studies exploring the antidepressant effects of MST are anticipated in the coming decade. Meanwhile, it is important to reflect on research that has been performed in this area, limitations of these data, and implications for future research. Therefore, synthesis of available evidence from up-to-date, reliable, relevant, and critical trials is another best way to meet this demand. This approach may help clinicians and practitioners to make a decision about whether to offer people with difficult-to-treat depression MST as an alternative treatment to ECT. However, no up-to-date systematic reviews have specifically assessed the effectiveness of MST.

We conducted this review according to the corresponding published protocol and reported any deviations from it in the Differences between protocol and review section of the systematic review.

OBJECTIVES

To evaluate the effects of MST in comparison with sham-MST, antidepressant, and other forms of electric or magnetic treatment for adults with TRD.

METHODS

Criteria for considering studies for this review

Types of studies

We searched for randomised controlled trials (RCTs) including cross-over RCTs (all participants receive all interventions, but the order in which they receive the interventions is randomised) and cluster-RCTs (groups or clusters of individuals rather than individuals themselves are randomised). We excluded quasi-RCTs (with participants allocated to different forms of care in a way that is not truly random, such as by date of birth, day of the week, or medical record number).

Types of participants

Participant characteristics

We included participants with TRD of both sexes, of any ethnicity, aged 18 years and older.

Diagnosis

TRD was defined in this review as a primary diagnosis of a major depressive episode according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV; APA 1994), the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision (DSM-IV-TR; APA 2000), the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM-5; APA 2013), the *International Classification of Diseases*, 10th Revision (ICD-10; WHO 1992), and the *Chinese Classification of Mental Disorders* (CCMD-3; CSP 2001), with no response or only partial response to at least four weeks of one or more antidepressants at recommended doses. Both unipolar depression and bipolar depression were included. We excluded patients who were resistant to psychological treatments or to other non-pharmacological treatments.

Comorbidities

We included patients with comorbid non-psychotic mental health disorders and somatic illness as long as the comorbidity was not the focus of the study.

Setting

We placed no restrictions on the setting of studies.

Types of interventions

Experimental interventions

- MST (i.e. magnetic induction of cerebral seizure activity after intravenous induction of brief general anaesthesia and pre-administration of a skeletal muscle relaxant drug). We placed no restrictions on the number or strength of doses

Comparator interventions

- 'Sham-MST' or 'simulated-MST' (i.e. general anaesthesia without administration of magnetic stimuli)
- ECT (i.e. electric induction of cerebral seizure activity with or without brief general anaesthesia)
- Any type of antidepressant, regardless of its category, with or without antipsychotics
- Other forms of electric or magnetic treatment, such as repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS)

Types of outcome measures

Studies that met the above inclusion criteria were included regardless of whether they reported on the following outcomes.

Primary outcomes

- Symptom severity
  - The primary outcome measure for assessing benefit was symptom severity, determined from the following validated psychometric scales
    - Continuous symptom scales, such as the Hamilton Rating Scale for Depression (HAMD) (Hamilton 1960), the Montgomery–Äsberg Depression Rating Scale (MADRS) (Montgomery 1979), the Clinical Global Inventory (CGI) (Guy 1976; Spearing 1997), and the Beck Depression Inventory (BDI) (Beck 1961), which were analysed as continuous variables
    - Global state: clinically significant response in depressive symptoms (i.e. response or non-response) as defined by studies (short term). For trials in which dichotomous outcome data were available, we summarised these as the number of people who experienced those outcomes in each comparison group and the total number in each group, and we analysed them as dichotomous variables
- Cognitive function

- The primary outcome measure for assessing harm was cognitive function. Outcome measures of interest were changes in test scores and in rate of cognitive recovery by means of validated neuropsychological tests from baseline to follow-up periods after completion of treatment. These included (but were not limited to):
  - Montreal Cognitive Assessment (MoCA);
  - Repeatable Battery for Assessment of Neuropsychological Status (RBANS); and
  - Cogstate computerised cognitive tests.

Secondary outcomes

- Suicides, suicide attempts, and self-harm
  - Suicides, measured as a dichotomous outcome (suicide versus no suicide)
  - Suicide attempts, measured as a dichotomous outcome (suicide attempt versus no suicide attempt)
  - Episodes of self-harm, measured as a dichotomous outcome (episodes of self-harm versus no episodes of self-harm)
- Quality of life
  - Assessed by validated measures such as the Wisconsin Quality of Life Index (W-QLI; Becker 1993), along with the World Health Organization Quality of Life (WHOQOL; WHO 1998)
- Social functioning
  - Measured by the Social Adaptation Self-evaluation Scale (SASS; Bosc 1997), or as defined by trialists (e.g. time to return to work or time to resume normal activities)
- Dropout for any reason
  - Number of participants who dropped out during the trial as a proportion of the total number of randomised participants
- Serious adverse events
  - We defined serious adverse events as medical events that were life-threatening or that resulted in death, disability, or significant loss of function, and that caused hospital admission or prolonged hospitalisation (e.g. cause-specific mortality, cerebral haemorrhage). These were measured as dichotomous outcomes
- Adverse events that led to discontinuation of treatment, measured as a dichotomous outcome

Timing of outcome assessment

We categorised outcomes as short term (up to six months from the beginning of treatment), medium term (6 to 12 months) or long term (longer than 12 months). Short-term assessment was our primary time frame. If a study reported more than one time point within one of the pre-specified time frames, we selected the latest time point (e.g. measures at nine months rather than those at seven months).

Hierarchy of outcome measures

If several continuous primary outcome measures were available, we used results from the HAMD. If results from the HAMD were not available, we used results from the BDI. However, if results from neither of the two were available, we used results from the MADRS.

Search methods for identification of studies

To reduce publication and retrieval bias, we searched across a number of different resources; we did not restrict the search by date, language, or publication status.

Electronic searches

A Cochrane Information Specialist searched the following databases and trial registers (2 March 2020) (search strategies are listed in Appendix 1).

- Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 3), in the Cochrane Library (searched 2 March 2020).
- Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR) (all available years).
- MEDLINE ALL, Ovid (1946 to 28 February 2020).
- Embase Ovid (1974 to 28 February 2020).
- PsycINFO Ovid (1806 to February Week 4 2020).
- Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to 2 March 2020).
- Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (1990 to 2 March 2020).
- ClinicalTrials.gov (www.clinicaltrials.gov) (all available years).
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/) (all available years).

Chinese databases

We conducted complementary searches of the following Chinese biomedical databases, using the terms ("难治", "治疗抵抗", "顽固性", "抑郁症", "抑郁障碍", "情感障碍", "磁抽搐", "磁痉挛").

- Chongqing VIP Database (VIP).
- Wanfang Database.
- China Hospital Knowledge Database (CHKD).
- Chinese Biology Medicine Database (SINOMED).

Grey literature

A Cochrane Information Specialist searched Proquest's Dissertation and Thesis database (PQDT), the Open Access Theses and Dissertations database (OATD), the DART Europe e-theses Portal, the Networked Digital Library of Theses and Dissertations (NDLTD), and OpenGrey (2 March 2020).

Searching other resources

We checked the reference lists of all included studies and relevant systematic reviews to identify additional studies missed by the original electronic searches (e.g. unpublished, in-press citations).

We handsearched conference proceedings of the Annual Meeting of the American College of Neuropsychopharmacology (ACNP), the Annual Scientific Convention and Meeting, and the Annual Meeting of the European College of Neuropsychopharmacology (ECNP).

We contacted trialists and subject experts to request information on unpublished or ongoing studies or to request additional trial data.

Data collection and analysis

Selection of studies

Two review authors (CZ, JJ) independently performed the first assessment of titles and abstracts for all literature generated by electronic database searches for relevance. We removed obviously irrelevant reports and retrieved the full texts of the remaining literature. These two review authors independently assessed the full-text manuscripts against inclusion criteria. As necessary, a third review author (WL) acted as an arbitrator to resolve disagreements that could not be resolved through discussion by the two review authors. If usable data were included but were not presented in the published manuscript of a study, we contacted study authors directly to request further information. Review authors were not blinded to articles' authorship, journals, and institutions. We recorded reasons for exclusion in the Characteristics of excluded studies table. At each time point, we detailed the numbers of studies selected in a PRISMA flow diagram.

When studies had multiple publications, we collated reports of the same study, so that each study, rather than each report, was the unit of interest for the review, and we gave such studies a single identifier with multiple references.

Data extraction and management

Two review authors (CZ, JJ) independently extracted data from studies using a data extraction form, which was piloted on at least one trial included in the review. We extracted the following study characteristics.

- Methods: study design, total duration of study, number of study centres and locations, study settings, withdrawals, date of study.
- Participants: number, mean age, age range, gender, course of disease, severity of condition, diagnostic criteria, inclusion criteria, exclusion criteria, co-morbid conditions.
- Interventions: MST (coil placement, frequency, dose, number of sessions), ECT (electrode placement, pulse width, dose, number of sessions), concomitant medications, concomitant psychosocial interventions, excluded medications.
- Outcomes: primary and secondary outcomes specified and collected, time points reported, whether outcome data were reported in a usable way.
- Notes: funding for trial, notable conflicts of interest of trial authors.

As necessary, a third review author acted as an arbitrator to resolve disagreements that could not be resolved through discussion by the two review authors. We presented these in the Characteristics of included studies table.

Main comparisons

We made the following main comparisons.

- MST versus sham-MST or simulated-MST.
- MST versus ECT.
- MST versus antidepressants.
- MST versus other forms of electric or magnetic treatment.

Assessment of risk of bias in included studies

Two review authors (CZ, JJ) independently assessed the methodological bias of each trial according to the criteria in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Review authors were not blind to authorship nor to the source of papers. When inadequate details were provided, we attempted to contact authors of the trial to obtain further information. We settled any disagreements by consensus with involvement of a third review author.

We assessed risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We judged each potential source of bias as having high, low, or unclear risk and provided a supporting quotation from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes when necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality might be very different than for a participant-reported pain scale). When information on risk of bias relates to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for studies that contributed to that outcome.

Measures of treatment effect

We analysed continuous data using mean differences (MDs) if studies used the same scales, and we used standardised mean differences (SMDs) if studies used different scales, with 95% confidence intervals (CIs). We converted multiple categorical variables into dichotomous outcomes and calculated risk ratios (RRs) and 95% CIs for individual studies. We used Review Manager 5 for data analysis (Review Manager 2014).

Unit of analysis issues

Cluster-randomised trials

We included cluster-randomised trials only if the following information was available.

- Number of clusters randomised to each intervention group or mean number of each cluster (M).
- Outcome data ignoring cluster design for the total number of participants (e.g. number or proportion of participants with events), means, and standard deviations (SDs).
- Intracluster (or intraclass) correlation coefficient (ICC) as provided or estimated.

An approximately correct analysis proceeded as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Section 16.3.4; Higgins 2011). The effective sample size of a single

intervention group in a cluster-randomised trial was its original sample size divided by the 'design effect', which was 1 + (M – 1) ICC.

Cross-over trials

To avoid any carry-over effects, we included in the synthesis only data from the first active treatment phase.

Studies with multiple treatment groups

In the case of trials with more than one treatment arm, we included only relevant treatment arms and listed other treatment arms in the Characteristics of included studies table. If a study involved multiple relevant treatment arms (e.g. different magnetic field frequencies), we tried to combine them into a single group. We summarised dichotomous outcomes data across groups and continuous outcomes into a single sample size, with mean and SD, according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Section 7.7.3.8; Higgins 2011). If multiple relevant treatment arms could not be combined (e.g. ECT and drugs as comparators), we divided the sample size of the shared group so that the two arms could be treated as independent comparisons.

Dealing with missing data

We contacted investigators or study sponsors to obtain missing outcome data when possible. We excluded a trial from the analysis if its outcome was missing for more than 40% of participants (Xia 2009). If SDs were unavailable from trial authors, we calculated missing SDs from reported standard errors, P values, or CIs when possible using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Sections 7.7.3.2 and 7.7.3.3; Higgins 2011). We used no other methods to impute missing values.

We contacted study authors to obtain individual participant data when only a subset of participants (e.g. due to age or diagnosis) would be eligible. We employed the strategy that we used to deal with missing data (i.e. we excluded a trial if less than 60% of participants were eligible).

Assessment of heterogeneity

We assessed heterogeneity of results across included studies using the I^2 statistic (which provided an estimate of the percentage of inconsistency thought to be due to heterogeneity, with 30% to 60% representing moderate heterogeneity, 50% to 90% substantial heterogeneity, and 75% to 100% considerable heterogeneity (Higgins 2011), and we used the Chi^2 statistic. If the I^2 statistic was greater than 50% or the P value for Chi^2 was less than 0.10, we considered the results substantially heterogeneous (Higgins 2011).

We visually inspected study characteristics and participant characteristics of all included studies along with data from individual studies to explore the possibility of heterogeneity.

Assessment of reporting biases

We attempted to identify reporting bias by recording both trial outcomes planned in the protocol and outcomes actually reported. If there were discrepancies, we tried to obtain data on missing outcomes from authors of the study. We prepared funnel plots to assess reporting biases when 10 or more trials were included. Nevertheless, it must be noted that asymmetry in funnel plots could be caused by other methodological or sample size issues as well.

Data synthesis

We used the random-effects model to calculate RRs for dichotomous outcomes and MDs or SMDs for continuous outcomes for analyses after considering potential heterogeneity in conducting trials and administering the intervention. The random-effects method incorporated the assumption that different studies were estimating different intervention effects; therefore, it was more conservative than the fixed-effect model. However, the random-effects model had the disadvantage of adding extra weight to small sample size trials, which often were most biased (Higgins 2011). As a consequence, we used the fixed-effect model in the sensitivity analysis to assess the robustness of findings. If there were differences between the two models, we discussed what might be driving the difference (e.g. small-study effect). In addition, if data were considerably heterogeneous ($I^2 \geq 75\%$) (Higgins 2011), particularly if there was inconsistency in the direction of effect and no clear reasons for heterogeneity were evident, we did not undertake a meta-analysis. We presented the final data in descriptive form.

Subgroup analysis and investigation of heterogeneity

We performed the following subgroup analyses for primary outcomes (symptom severity and cognitive function).

- High-dose MST (magnetic frequency 100 Hz or greater) versus low-dose MST (magnetic frequency < 100 Hz): considerable efforts have been made toward development of MST with higher magnetic frequency (Hoy 2011). However, it is unclear whether high-dose MST is superior to low-dose MST.
- Long course (more than 12 sessions) versus short course (12 sessions or fewer): the number of treatments was expected to affect outcomes, and there was no consensus on treatment schedules for MST; this led to a broad range of numbers of treatments in trials (Hoy 2011).
- Differences in the definition of TRD (e.g. failure to respond to one, two, or three antidepressant agents): there was no consensus on the definition of TRD, and this was expected to affect outcomes.
- Unipolar versus bipolar depression: due to differences in the pathology of unipolar and bipolar depression (Cuellar 2005), and due to potential influence on treatment response of seizure therapies (Medda 2009), we performed this subgroup analysis when possible.

Sensitivity analysis

We performed the following sensitivity analyses for primary outcomes (symptom severity and cognitive function) to examine the robustness of the effect size.

- Risk of bias: as risk of bias was a potential factor of influence on outcomes, we used overall risk of bias as a marker and excluded trials we judged as having high overall risk of bias (Higgins 2011). We rated studies with high overall risk of bias if any domains of the risk of bias tool were rated to be at high risk of bias.

Summary of findings and assessment of the certainty of the evidence

As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Section 11.5 and Section 12.2; Higgins 2011), we employed GRADEprofiler to prepare the 'Summary of findings'

table (GRADEpro GDT 2015), and we used the GRADE approach to assess the certainty of a body of evidence (Langendam 2013). We justified all decisions to downgrade the certainty of studies by using footnotes, and we made comments to aid readers' understanding of the review when necessary.

We included the following details in the 'Summary of findings' table.

- Participants or population: adults of either gender with a primary diagnosis of unipolar depression based on validated criteria and with no response or only partial response to at least four weeks of one or more antidepressants at recommended doses.
- Settings: inpatient or outpatient clinical units/services.
- Intervention: MST, high dose or low dose, and long course or short course.
- Comparison: sham-MST or simulated-MST, ECT, antidepressants, and other forms of electric or magnetic treatment.

We assessed the following short-term outcomes for the 'certainty' criteria.

- Continuous outcome measures for symptom severity.
- Categorical outcome measures for symptom severity.
- Cognitive function.
- Quality of life.
- Social functioning.
- Dropout for any reason.
- Adverse events leading to discontinuation of treatment.

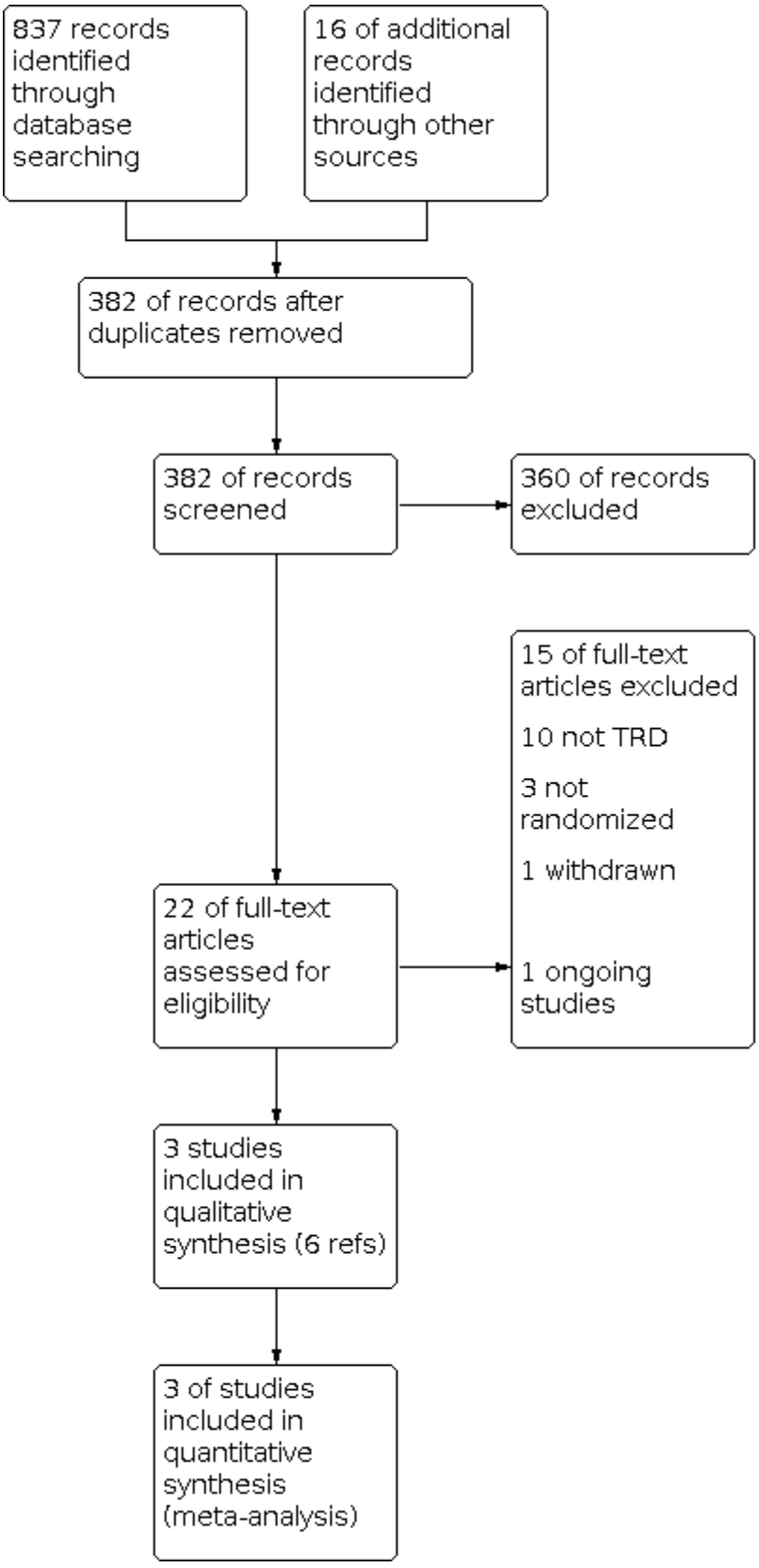
RESULTS

Description of studies

Results of the search

An electronic search of English language databases run 2 March 2020 yielded 837 records, and after deduplication, 374 records remained. In addition, an electronic search of Chinese language databases and other resources run 23 March 2020 revealed seven and nine possibly relevant references, respectively. After removing eight duplicates, we screened 382 titles and abstracts, of which we deemed 360 to be irrelevant. Following retrieval and inspection of 22 full-text reports, we excluded 15 of them. From the remaining seven references, we included three studies (six references), one of which we identified as an ongoing study. See Figure 1 for details.

Figure 1. Study flow diagram.



Included studies

Through our search, we identified three studies (Kayser 2011; Kayser 2017; Polster 2015), along with one ongoing study (NCT03191058), as eligible for inclusion in this review. We noted that although Kayser 2011 and Polster 2015 share the same registration code (NCT00770783), the dates of these two studies did not overlap and the design of these studies differed in some respects. Therefore, we treated Kayser 2011 and Polster 2015 as two different studies instead of as two reports of the same study. Please see Characteristics of included studies and Characteristics of ongoing studies for detailed information.

Design

All included studies were single-site open-label parallel randomised controlled trials conducted by a single research team at University Hospital Bonn. None of these studies described the study setting. Kayser 2011 and Kayser 2017 were two-arm trials comparing MST and ECT, and Polster 2015 was a three-arm trial with an additional healthy control arm.

Follow-up for both studies was short term (six weeks for Kayser 2011, five to six weeks for Polster 2015, and four to six weeks for Kayser 2017). Kayser 2011 was conducted from July 2006 to November 2008, and Polster 2015 from June 2009 to December 2012. Kayser 2017 started in February and was completed in June of 2011.

One study reported that five participants withdrew and provided detailed reasons (Kayser 2017); these participants were not included in the statistical analyses of this study. The other two studies did not report withdrawal information (Kayser 2011; Polster 2015).

Participants

Recruitment criteria

All three included studies diagnosed a major depressive episode using DSM-IV. Although Polster 2015 included affective disorders, eventually only patients with unipolar depression were recruited. On the other hand, Kayser 2011 and Kayser 2017 recruited patients with unipolar or bipolar depression, but only major depressive disorder was described in the diagnostic criteria of Kayser 2011. All studies employed a Thase and Rush stage 2 TRD definition as failure to respond to at least two different antidepressants during the current depressive episode.

Kayser 2011 and Polster 2015 included only patients with a minimum score of 20 on HAMD-28 and a clinical indication of MST/ECT. Polster 2015 also required the absence of former ECT treatments for patients with MST.

All three studies excluded patients with a diagnosis of other psychiatric, cognitive, or neurological disorders; those at high risk for anaesthesia (e.g. cardiac disease, injury); and those with magnetic material in the head or in implanted medical devices. Kayser 2011 further excluded patients with psychotic depression. In addition, Kayser 2011 and Polster 2015 excluded patients with signs of a cognitive disorder. Polster 2015 and Kayser 2017 excluded pregnant women. Patients with nicotine dependence were not excluded from Polster 2015.

Characteristics of included participants

Each eligible paper reported 20 patients, 10 of whom received MST, with the other 10 receiving ECT. Kayser 2011 and Kayser 2017 recruited patients from 18 to 65 years of age, and Polster 2015 recruited patients from 18 to 69 years of age. None of the studies reported significant differences in age. However, the mean age of participants who received MST in Kayser 2011, Polster 2015, and Kayser 2017 was below 50 years (48.80, 43.7, and 45 years, respectively), but the mean age of participants who received MST was 50 years or over (52.8, 54.7, and 55 years, respectively). All studies included males and females. The proportion of female participants who received MST and ECT was 60% and 70% in Kayser 2011, 30% and 60% in Polster 2015, and 30% and 40% in Kayser 2017, respectively.

Both Kayser 2011 and Polster 2015 reported the duration of current depressive episodes. In Kayser 2011, mean duration was 6.01 years and 3.5 years for MST and ECT, respectively, and in Polster 2015, mean duration was 4.1 years for MST and 3.1 years for ECT. In addition, Kayser 2011 reported the mean number of lifetime episodes, with 6.10 for MST and 6.7 for ECT. Kayser 2017 did not provide information regarding the course of disease.

All three studies reported baseline depressive symptom severity; Kayser 2011 also reported baseline anxiety and quality of life. All three studies claimed that baseline clinical characteristics were balanced between treatment groups. However, in Kayser 2011, we observed that patients who received MST had more severe depression (Analysis 1.1), and poorer quality of life (Analysis 1.12) and cognitive function (Analysis 1.11) compared to those who received ECT. None of these studies provided information on comorbid conditions.

Interventions

All studies implemented MST using vertex placement of twin coils and pulse frequency of 100 Hz. Polster 2015 delivered magnetic pulse by seizure threshold (up to 600 pulses in a train), Kayser 2011 by three times seizure threshold (up to 600 pulses in a train), and Kayser 2017 by six times seizure threshold (up to 800 pulses in a train).

Most participants in the active control group of all studies received right unilateral ECT, except one participant in Kayser 2017, who received bifrontotemporal ECT. These studies administered brief-pulse electric current of 0.5 ms at different intensities: Kayser 2011 at three times seizure threshold, Polster 2015 at seizure threshold for the first treatment session and at six times seizure threshold for the following sessions, and Kayser 2017 at six times seizure threshold for right unilateral ECT and at three times seizure threshold for bifrontotemporal ECT.

The total number of MST/ECT sessions for each patient was 12 in Kayser 2011, 10 to 12 in Polster 2015, and 8 to 12 in Kayser 2017. Neither Polster 2015 nor Kayser 2017 provided information on how the number of treatment sessions was determined nor on mean treatment sessions.

All included studies kept concomitant antidepressants stable from one month before the start of treatment to the end of the study. In Kayser 2011, 90% of participants received certain types of psychotherapy, but no details were provided. The other two studies did not report information regarding concomitant

psychosocial interventions. None of the eligible studies excluded any medications.

Outcomes

Included studies reported symptom severity, cognitive functions, quality of life, dropouts, and adverse events that led to discontinuation of treatment. None of these studies reported suicides, suicide attempts, self-harm, social functioning, or serious adverse events.

Kayser 2011 and Kayser 2017 reported symptom severity before and after all treatments. Kayser 2011 employed HAMD, MADRS, BDI, and the Hamilton Anxiety Scale (HAMA; Hamilton 1959), and Kayser 2017 used only HAMD.

Kayser 2011 and Polster 2015 reported cognitive function. Kayser 2011 employed neuropsychological assessments four hours after 1, 4, 8, and 12 treatments, which measured general intellectual ability, language, processing speed, executive function, learning, and memory. Polster 2015 used a learning model comprising immediate, delayed, and cued recall on two treatment days and on two treatment-free days within two weeks after the start of treatment.

Only Kayser 2011 reported quality of life before and after all treatments, as measured by the 90-Item Symptom Checklist (SCL-90; Franke 1995). Only Kayser 2017 reported dropouts with adverse events that led to dropout.

Kayser 2011 reported other outcomes including recovery and reorientation time, subjective side effects, and seizure characteristics. In addition, Kayser 2017 reported seizure features.

Conflicts of interest

It is notable that all included studies were funded in part by MagVenture A/S for the MST device. All trial authors stated that MagVenture A/S had no influence on design or conduct of the study; on collection, management, analysis, and interpretation of data; nor on preparation, review, or approval of the manuscript.

Excluded studies

In total, we excluded 15 references (14 studies) at full-text screening for reasons detailed in Characteristics of excluded studies.

Risk of bias in included studies

Full details of the risk of bias for included studies are provided under Characteristics of included studies. Graphical representations of overall risk of bias in included studies are presented for each risk of bias item (Figure 2) and for each study (Figure 3). Given the small number of included studies, no formal assessment of reporting bias via a funnel plot was undertaken.

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

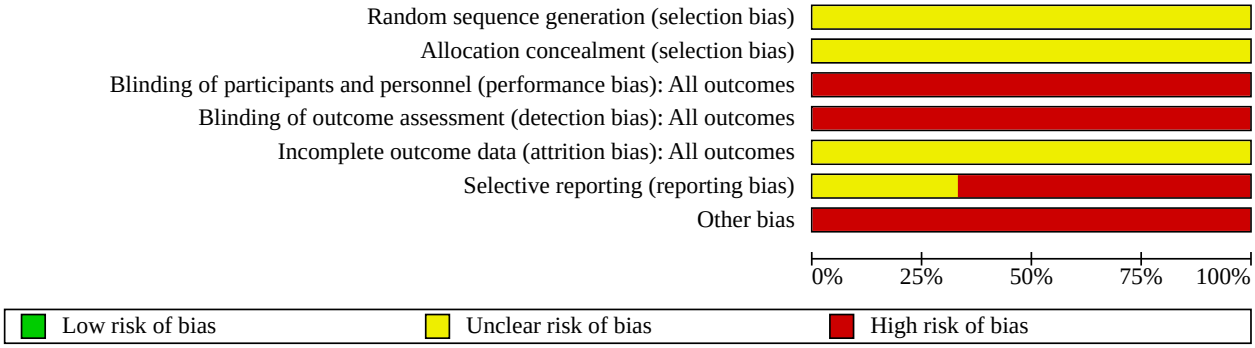
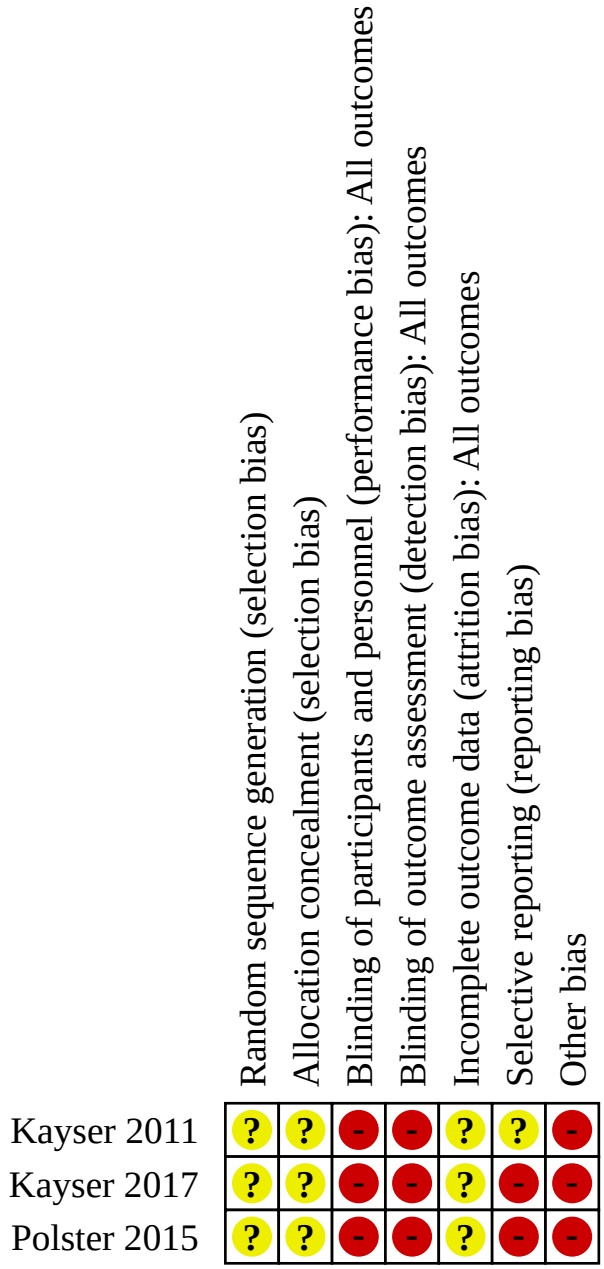


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

All included studies described themselves as randomised. Two studies did not provide any information on how the randomisation sequence was generated (Kayser 2011; Polster 2015). One study claimed use of a randomised block design, although its protocol described the study as case-control (Kayser 2017). As a consequence, we rated all included studies as having unclear risk of bias for random sequence generation.

Allocation concealment

None of the included studies described allocation concealment; therefore we rated all studies as having unclear risk of selection bias.

Blinding

Performance bias (blinding of participants and those delivering the intervention)

All included studies stated that blindness for participants and psychiatrists who administered treatments was impossible due to distinct differences between MST and ECT, for example, the use of a coil and the loud clicking noise of the MST device. Therefore, we rated all studies as having high risk of performance bias.

Detection bias (blinding of outcome assessors)

None of the included studies blinded outcome assessors to treatment allocation. In Kayser 2011, blinding was not possible due to the necessary presence of an assessing psychologist at the time of treatment, in one case for organisational reasons (Polster 2015); in the other case, the reason was not provided (Kayser 2017). Therefore, we rated all three studies as having high risk of detection bias.

Incomplete outcome data

The attrition rate was 20% in Kayser 2017 and was similar across treatments (three patients in the MST group versus two patients in the ECT group). It is noted that reasons for discontinuing the study were entirely different. All three patients receiving MST withdrew because of an MST device defect, and both patients receiving ECT withdrew because of adverse events. On the other hand, attrition was not reported in the other two studies (Kayser 2011; Polster 2015). As a consequence, we rated all three studies as having unclear risk of attrition bias.

Selective reporting

None of the included studies reported outcomes in strict accordance with their protocols. The protocols of Kayser 2011 and Polster 2015 specified HAMD and MADRS as outcomes. Nevertheless, Kayser 2011 reported HAMD, MADRS, BDI, HAMA, SCL-90, neuropsychological assessments, recovery and reorientation times, subjective side effects, and seizure characteristics, and Polster 2015 reported memory performance. Kayser 2017 reported HAMD and seizure features but its protocol specified recovery time as the only outcome. Kayser 2011 was rated as having unclear risk of reporting bias because the primary outcome (antidepressive response) but not all secondary outcomes were pre-specified. However, we rated Polster 2015 and Kayser 2017 as having high risk because none of the reported outcomes was pre-specified in the protocols.

Other potential sources of bias

All three included studies were funded in part by MagVenture A/S, a manufacturer of the MST device. Although study authors stated that sponsors were not involved in the design or conduct of the study; in collection, management, analysis, or interpretation of data; nor in preparation, review, or approval of the manuscript, we still cannot rule out the potential influence of the MST manufacturer on the results; hence we rated these studies as having high risk.

Effects of interventions

See: **Summary of findings 1** Summary of findings

Comparison 1. MST versus sham-MST or simulated-MST

None of the included studies compared MST with sham-MST or simulated-MST.

Comparison 2. MST versus ECT

Symptom severity - continuous outcome (primary)

Kayser 2011 and Kayser 2017 reported HAMD. Analysis of included data showed no clear differences between treatment groups for this outcome (mean difference (MD) 0.71, 95% confidence interval (CI) -2.23 to 3.65; 2 studies, 40 participants; Analysis 1.1). It is noted that in Kayser 2011, follow-up data were skewed and baseline data were unbalanced across groups (30.7 ± 5.03 for MST versus 25.8 ± 2.62 for ECT).

Symptom severity - global state (primary)

None of the included studies reported outcomes related to global state.

Cognitive function (primary)

Kayser 2011 and Polster 2015 investigated multiple domains of cognitive function. However, these investigators did not employ validated neuropsychological tests, except the memory test based on the Wechsler Memory Scale (Kayser 2011; Wechsler 1997), nor did they provide details of tests used to measured cognitive changes. In addition, many of the data showed unbalanced baseline and skewed distribution. As a consequence, we presented the results of these invalid tests as 'other data' (Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 1.5; Analysis 1.6; Analysis 1.7; Analysis 1.8; Analysis 1.9). Analysis of outcomes for immediate memory revealed no clear differences between treatment groups (MD 0.40, 95% CI -4.16 to 4.96; 1 study, 20 participants; Analysis 1.10). Analysis of outcomes for delayed memory also revealed no clear differences between treatment groups (MD 2.57, 95% CI -2.39 to 7.53; 1 study, 20 participants; Analysis 1.11). It is noted that follow-up data for delayed memory were skewed and baseline data were unbalanced across groups (8.7 ± 4.32 for MST versus 10.4 ± 6.93 for ECT).

Suicides, suicide attempts, and self-harm

None of the included studies reported outcomes related to suicides, suicide attempts, or self-harm.

Quality of life

Only Kayser 2011 measured quality of life, and analysis showed no clear differences between treatment groups (MD 14.86, 95% CI -42.26 to 71.98; 1 study, 20 participants; Analysis 1.12). It was noted that follow-up data were skewed and baseline data were unbalanced across groups (133.78 ± 59.47 for MST versus 102.1 ± 58.06 for ECT).

Social functioning

None of the included studies reported outcomes related to social functioning.

Dropout for any reason

Only Kayser 2017 reported dropout, and analysis showed no clear differences between treatment groups (risk ratio (RR) 1.38, 95% CI 0.28 to 6.91; 1 study, 25 participants; Analysis 1.13).

Serious adverse events

None of the included studies reported serious adverse events.

Adverse events that led to discontinuation of treatment

Only Kayser 2017 reported adverse events that led to discontinuation of treatment, which occurred in only two participants who received ECT. One participant who received ECT discontinued the study because of worsening of preexisting coronary heart disease, and the other experienced cognitive decline. Analysis of reported data showed no clear differences between treatment groups for this outcome (RR 0.19, 95% CI 0.01 to 3.52; 1 study, 25 participants; Analysis 1.14).

Comparison 3. MST versus antidepressants

None of the included studies compared MST with antidepressants.

Comparison 4. MST versus other forms of electric or magnetic treatment

None of the included studies compared MST with other forms of electric or magnetic treatment.

Subgroup analyses

Studies were too few for pre-planned subgroup analyses to be conducted.

Sensitivity analysis

Studies were too few for pre-planned sensitivity analyses to be conducted.

DISCUSSION

This review identified only three randomised controlled trials (RCTs) comparing magnetic seizure therapy (MST) with electroconvulsive therapy (ECT). Review authors found no studies that described other comparators.

Summary of main results

We have summarised the main findings of this review in one key table (Summary of findings 1).

Symptom severity

Although two studies compared short-term changes in depressive symptom following MST versus ECT, no data synthesis (combining results from different studies and providing a quantitative estimate of overall effect) was performed due to skewed data and unbalanced baseline characteristics in one of the studies. These studies provided no evidence of a difference in depressive symptoms at the end of all treatment sessions, with very low-quality estimates. Sample size was very small (n = 20 for each study), and there was imprecision in the estimates; therefore our confidence in these findings is very limited. No eligible studies reported global state, which is a missed opportunity, as such a finding would have been of interest and of value for future updates, as more data become available.

Cognitive function

Although two studies compared short-term changes in various domains of cognitive function with MST and ECR, data synthesis could not be performed due to the invalidity of most tasks used in both studies. Analysis revealed no evidence of differences in immediate memory nor in delayed memory at the end of all treatment sessions, with very low-quality estimates. Sample size was very small (n = 20), and there was imprecision in the estimates; therefore our confidence in these findings is very limited.

Suicides, suicide attempts, and self-harm

No eligible studies reported this outcome, which is a missed opportunity, as such a finding would have been of interest and of value for future updates, as more data become available.

Quality of life

Only one study compared short-term changes in quality of life following MST versus ECT. Analysis revealed no evidence of a difference in this outcome at the end of all treatment sessions, with very low-quality estimates. In addition, sample size was very small (n = 20), and there was imprecision in the estimates. As a consequence, our confidence in these findings is very limited.

Social functioning

No eligible studies reported this outcome, which is a missed opportunity, as such a finding would have been of interest and value for future updates, as more data become available.

Dropout for any reason

Only one study compared short-term dropout following MST versus ECT. This study found no evidence of a difference in this outcome at the end of all treatment sessions, with very low-quality estimates. Sample size was very small (n = 25), and there was imprecision in the estimates; therefore our confidence in these findings is very limited.

Adverse events that led to discontinuation of treatment

Only one study reported short-term adverse events that led to discontinuation of treatment. Two participants who received ECT discontinued the study (due to worsening of preexisting coronary heart disease and cognitive adverse effects, respectively), but no serious adverse events occurred in participants who received MST. Sample size was very small (n = 25); therefore our confidence in these findings is very limited.

Overall completeness and applicability of evidence

Despite our comprehensive search, we identified only a small body of evidence. This systematic review included three studies, and pooling of data from these studies was not possible due to skewed data, unbalanced baseline characteristics, and invalidity of measures. Included studies reported only short-term outcomes; therefore, medium- and long-term effects of MST remain unknown. In addition, none of these studies provided information related to suicides, suicide attempts, self-harm, or social functioning. In summary, reporting was incomplete.

Findings from this review are applicable to adults with treatment-resistant depression (TRD). Included studies recruited participants of both genders with mean age between 40 and 50 years. Definitions

of TRD were consistent between studies (i.e. failure to respond to at least two treatments from different treatment categories during the current major depressive episode). In terms of severity of depression, mean scores on the Hamilton Rating Scale for Depression (HAMD) equated to moderate depression. One trial was conducted in an inpatient setting, and the other two trials did not report study setting. Eight to twelve sessions of MST were administered at 100 Hz with coil placement on the vertex over a course of four to six weeks. In all trials, MST was added-on to antidepressants. All studies were conducted by a single research team at a single site in Bonn, Germany. Therefore, findings may reflect limited generalisability to other age groups (children, adolescents, and the elderly), other definitions of TRD, patients with more severe depressive symptoms, other settings, other MST parameters, MST sole treatment, and other countries.

Quality of the evidence

All studies were judged to be at high or unclear risk of bias for study design. The three included studies were threatened by risks of bias due to lack of information about how randomisation was undertaken and then concealed, or due to inconsistency with the protocol. None of the included studies blinded or reported outcomes in strict accordance with their protocols. Moreover, two of the three studies did not report attrition. All eligible studies for inclusion were funded in part by the manufacturer of an MST device. All three studies were conducted by a single research team, and data pooling was limited due to the small number of included studies. However, studies with usable data presented obvious imprecision, as very wide confidence intervals that crossed the null were shown in the forest plots. Studies included in this review were applicable to the aims of our review in terms of comparisons of interest, as well as target populations, types of interventions, comparators, and methods of outcome determination. However, the quality of presented evidence was very low, so all results should be treated with considerable caution.

Potential biases in the review process

To avoid introducing our own bias to this review, we strictly followed Cochrane methods for conducting reviews and reported all available processes, methods, and data transparently, so they can be checked if needed. We would welcome any comments or additional data that would improve this review.

Agreements and disagreements with other studies or reviews

To the best of our knowledge, this is the only systematic review of MST for TRD. One study systematically reviewed MST for unipolar or bipolar depression, regardless of whether treatment resistance was presented (Cretaz 2015). That review also included Kayser 2011 and Polster 2015. Although no data pooling was performed, review authors found a better cognitive profile than with ECT. Direct comparison of MST and ECT did not reveal a significantly different antidepressant effect; nevertheless, the remission rate of MST (15% to 30%) was far below rates reported in most ECT studies (50% to 70%). It is noted that the small number of included studies, the inclusion of non-randomised studies, the mixture of participants with different diagnoses and severity, the variety of MST parameters, and severe heterogeneity have reduced the certainty of review conclusions.

AUTHORS' CONCLUSIONS

Implications for practice

Currently, no clear evidence is available for or against MST as treatment for patients with TRD. This intervention is still an experimental treatment. If this therapy is considered by clinicians, they should inform patients of the experimental nature of the treatment and should explain the details to patients in a transparent way, so they can make an informed decision.

Implications for research

Given that research is insufficient to show whether MST is effective for TRD, further research is needed to address this question. All RCTs should report the standards required by CONSORT (an evidence-based, minimum set of recommendations for reporting randomised trials; www.consortstatement.org). To be more specific, methods of randomisation and allocation concealment, along with attrition with corresponding reasons, should be reported. Studies should be conducted and outcomes reported according to the protocol. A double-masked approach should be taken to reduce detection and performance bias. Studies with a large sample size can improve precision; validated tests are essential to determine the true cognitive effects. Exploration of effects of MST on suicide and social functioning will enhance our understanding of this novel treatment. It is important that future researchers seek to evaluate longer-term outcomes. Separate reports of unipolar and bipolar TRD may help reduce heterogeneity. Comparators other than ECT may further reveal the effects of MST. In addition, current reports of MST are limited geographically. Therefore, research should be conducted in non-Western countries with a clear description of location provided for local healthcare users, healthcare providers, and policymakers.

On the other hand, people with TRD could help generate much more evidence by taking part in good evaluative studies while making participation contingent on release of all trial data to the public. For policymakers, additional high-quality and long-term studies that explore effects, safety, and costs of this novel intervention will prove useful.

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Disclaimer: the views and opinions expressed herein are those of the review authors and do not necessarily reflect those of the NIHR, the NHS, nor the Department of Health and Social Care.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Kayser 2011

Study characteristics	
Methods	**Study design:** open-label, parallel, randomised
	Total duration of study: 6 weeks
	Number of study centres and locations: 1, University Hospital, Bonn, Germany.
	Study setting: inpatient
	Withdrawals: no information

Kayser 2011 *(Continued)*

	Dates of study: July 2006 to November 2008
Participants	**Number:** 10 for MST (8 MDD, 1 BPI, 1 BPII); 10 for ECT (8 MDD, 2 BPII) **Mean age (SD), age range:** 48.80 (8.35) for MST; 52.8 (11.43) for ECT; no information on range **Gender:** 6 females for MST; 7 females for ECT **Course of disease** Current episodes, years (SD): 6.01 (10.42) for MST; 3.5 (4.12) for ECT Number of lifetime episodes (SD): 6.10 (7.56) for MST; 6.7 (7.8) for ECT **Severity of condition** MADRS (SD): MST 31.2 (6); ECT 26.3 (3.83) HAMD-28 (SD): MST 30.7 (5.03); ECT 25.8 (2.62) BDI (SD): MST 36.5 (10.96); ECT 31.8 (12.97) HAMA (SD): MST 22.4 (4.38); ECT 17.7 (4.79) SCL-90 (SD): MST 133.78 (59.47); ECT 102.1 (58.06) **Diagnostic criteria** • Major depressive disorder in a current major depressive episode diagnosed according to DSM-IV • TRD defined as failure to respond to at least 2 treatments from different treatment categories during the current major depressive episode **Inclusion criteria** • 18 to 65 years old • HAMD ≥ 20 • Convulsive therapy clinically indicated • No psychotic depression **Exclusion criteria** • Secondary diagnosis, or signs, of delirium, dementia, amnesia, or other cognitive disorders and/or diagnosis of non-affective psychotic disorder • Alcohol or substance dependence within previous 12 months or abuse within previous 6 months • Diagnosis of clinically relevant cardiac disease, injury, disease of central nervous system • Magnetic material in the head or implanted medical device (i.e. cardiac pacemaker, vagus nerve stimulator, medical pump) **Co-morbid conditions:** no information
Interventions	**MST** (coil placement, frequency, dose, number of sessions) • Centre of the twin coil was placed at the vertex • 100 Hz • At the beginning of each trial, we treated with 100, 200, 300, etc., pulses in train (reflecting approximately 3× seizure threshold in ECT); afterwards, we chose stimulation depending on the seizure threshold up to 600 pulses in a train. MST seizure threshold was defined as the minimum number of pulses required to induce a tonic-clonic seizure • 12 sessions **ECT** (electrode placement, pulse width, dose, number of sessions) • Right unilateral

Kayser 2011 *(Continued)*

- 0.5 ms
- 3× seizure threshold
- 12 sessions

Concomitant medications: antidepressant medication was kept stable for 1 month (± 5 days) before treatment and was not stopped or changed during treatment

Concomitant psychosocial interventions: 90% of participants received psychotherapy

Excluded medications: no information

Outcomes

Primary and secondary outcomes specified and collected

- Specified
  - HAMD-28 (primary)
  - MADRS
- Collected
  - HAMD-28
  - MADRS
  - BDI
  - HAMA
  - SCL-90
  - Neuropsychological assessments (general intellectual ability, language, processing speed, executive function, learning, and memory)
  - Recovery and reorientation times
  - Subjective side effects
  - Seizure characteristics (motor activity, EEG activity, EEG latency)

Time points reported

- Before and after 12 treatments for clinical measures
- After 1, 4, 8, and 12 treatments for neuropsychological measures
- Average of all treatments for seizure and orientation measures
- After 12 treatments for subjective side effects

Outcome data reported in a usable way: yes

Notes

Funded in part by MagVenture A/S

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but no information given about how the sequence was generated.
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Described as open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Described as open-label

Kayser 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	Unclear risk	Protocol specified HAMD and MADRS as outcomes. However, studies reported HAMD, MADRS, BDI, HAMA, SCL-90, neuropsychological assessments, recovery and reorientation times, subjective side effects, and seizure characteristics
Other bias	High risk	The study is funded in part by a manufacturer of MST devices

Kayser 2017

Study characteristics	
Methods	**Study design:** open-label, parallel, randomised **Total duration of study:** 4 to 6 weeks **Number of study centres and locations:** 1, University Hospital, Bonn, Germany. **Study setting:** no information **Withdrawals:** 5 patients discontinued the study for different reasons: 3 because of MST device defect, 1 because of cognitive adverse effect during ECT, and 1 because of worsening of preexisting coronary heart disease during ECT **Dates of study:** February to June 2011
Participants	**Number:** 10 for MST (8 MDD, 2 BPII); 10 for ECT (9 MDD, 1 BPI) **Mean age (SD), age range:** 45 (14) for MST; 55 (12) for ECT; no information on range **Gender:** 3 females for MST; 4 females for ECT **Course of disease:** no information **Severity of condition:** HAMD-28 26.1 (4) for MST; 28.4 (4) for ECT **Diagnostic criteria** • MDD, BPI, and BPII according to DSM-IV • TRD defined as failure of 2 different antidepressants (given > 5 weeks at maximum recommended or tolerated dose) during current depressive episode according to Thase and Rush stage 2 definition **Inclusion criteria** • TRD • 18 to 65 years old **Exclusion criteria** • Pregnancy • Younger than 18 years • Other psychiatric, cognitive, or neurological disorder • At high risk for anaesthesia • Magnetisable material in the head, cardiac pacemaker, vagus nerve stimulator, or any medical pump **Co-morbid conditions:** no information

Kayser 2017 *(Continued)*

Interventions	**MST** (coil placement, frequency, dose, number of sessions) • Twin coil containing 2 individual round coils positioned over Cz according to the international 10-20 system • 100 Hz • 6 times seizure threshold up to 800 pulses in a train • 8 to 12 sessions **ECT** (electrode placement, pulse width, dose, number of sessions) • Right unilateral for 9 participants; bifrontotemporal for 1 • 0.5 ms • 6× seizure threshold for right unilateral; 3× seizure threshold for bifrontotemporal • 8 to 12 sessions **Concomitant medications:** psychotropic medication was stable for a minimum of 4 weeks before MST/ECT treatments and remained unchanged during the study **Concomitant psychosocial interventions:** no information **Excluded medications:** no information

Outcomes	**Primary and secondary outcomes specified and collected**
	• Specified
	  ○ Recovery time
	• Collected
	  ○ HAMD
	  ○ Seizure features (polyspike wave duration and polyspike wave amplitude in tonic phase, slow wave duration and slow wave amplitude in clonic phase, postictal suppression in termination phase, and regularity and stereotypy of global pattern)
	Time points reported
	• Before and after all treatments for HAMD
	• Average of all treatments for seizure features
	Outcome data reported in a usable way: yes

Notes	Funded in part by MagVenture A/S

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Protocol described the study as a case-control trial. However, paper claims "the patients were randomized to ECT or MST using a randomized block design, with a block size of 5 patients"
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Described as open-label
Blinding of outcome assessment (detection bias)	High risk	Described as open-label

Kayser 2017 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition rates were similar (3 for MST vs 2 for ECT), however, for different reasons (MST device defect vs adverse effects). As-treated analysis was done
Selective reporting (reporting bias)	High risk	Protocol specified recovery time as the only outcome. However, study reported HAMD and seizure features
Other bias	High risk	The study is funded in part by a manufacturer of MST devices

Polster 2015

Study characteristics	
Methods	**Study design:** open-label, parallel, randomised **Total duration of study:** 5 to 6 weeks **Number of study centres and locations:** 1, University Hospital, Bonn, Germany. **Study setting:** no information **Withdrawals:** no information **Dates of study:** June 2009 to December 2012
Participants	**Number:** 10 for MST; 10 for ECT; 10 healthy controls **Mean age (SD), age range:** 43.7 (11) for MST; 54.7 (13) for ECT; no information on range **Gender:** 3 females in MST; 6 females in ECT; 6 females in healthy controls **Course of disease: current episode, years (SD):** 4.1 (4) for MST; 3.1 (3) for ECT **Severity of condition** • HAMD-28 (SD) 25.3 (7) for MST; 23.2 (8) for ECT • BDI (SD) 27.7 (8) for MST; 24.3 (11) for ECT **Diagnostic criteria** • Affective disorder with current major depressive episode diagnosed according to DSM-IV • TRD defined as stage 2 of resistance according to Thase and Rush for patients who are unresponsive to 2 different antidepressant treatments of adequate length and dosage during a current episode of depression **Inclusion criteria** • 18 to 69 years old • Clinical indication for MST/ECT • Minimum score of 20 on HAMD-28 • Absence of former ECT treatments for patients with MST • Not pregnant **Exclusion criteria** • Diagnosis of cognitive disorder or signs of dementia, delirium, amnesia, or non-affective psychotic disorders

Polster 2015 *(Continued)*

- Alcohol or substance dependence within previous 12 months or substance-related addiction within past 6 months (except nicotine)
- Anaesthesiologically relevant cardiac disease
- Any head injury relevant to MST/ECT
- Other disease of the central nervous system
- Implanted medical device and magnetic material in the head or body

Co-morbid conditions: no information

Interventions	**MST** (coil placement, frequency, dose, number of sessions) • Centre of the twin coil was placed at the vertex • 100 Hz • Ascending titration was done with 100, 200, 300, etc,, pulses in train upon the first trial. Minimum number of pulses required to activate a tonic-clonic seizure defined the individual seizure threshold. For subsequent trials, seizures were induced by stimulation seizure threshold • 10 to 12 sessions **ECT** (electrode placement, pulse width, dose, number of sessions) • Right unilateral • 0.5 ms • Ascending titration determined seizure threshold during first treatment. Following stimulations were performed at 5-fold over seizure threshold • 10 to 12 sessions **Concomitant medications:** antidepressant medication was kept stable 1 month before and during the entire course of treatment **Concomitant psychosocial interventions:** no information **Excluded medications:** no information

Outcomes	**Primary and secondary outcomes specified and collected**
	• Specified
	  ◦ HAMD-28 (primary)
	  ◦ MADRS
	• Collected
	  ◦ Learning model based on reciting of memorised word lists
	Time points reported
	• HAMD-28 and BDI at baseline (2 weeks before treatment)
	• Memorised words 2 hours before and after 2 treatment-free days and 2 treatment days (2 weeks within start of treatments)
	Outcome data reported in a usable way: yes; extracted from figures

Notes	Funded in part by MagVenture A/S

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but no information given about how the sequence was generated

Polster 2015 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	High risk	Described as open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Described as open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	High risk	Protocol specified HAMD and MADRS as outcomes. However, study reported memory performance
Other bias	High risk	The study is funded in part by a manufacturer of MST devices

BDI: Beck Depression Inventory.
BP: bipolar disorder.
BPI: bipolar disorder I.
BPII: bipolar disorder II.
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.
ECT: electroconvulsive therapy.
EEG: electroencephalogram.
HAMA: Hamilton Anxiety Rating Scale.
HAMD: Hamilton Rating Scale for Depression.
MADRS: Montgomery-Äsberg Depression Rating Scale.
MDD: major depressive disorder.
MST: magnetic seizure therapy.
SCL-90: Symptom Checklist-90.
SD: standard deviation.
TRD: treatment-resistant depression.

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

Study	Reason for exclusion
Atluri 2018	Not randomised
Backhouse 2017	Not randomised
ChiCTR-ONN-17010740	Not TRD
Deng 2013	Not TRD
Farzan 2017	Not randomised
Fitzgerald 2018	Not TRD
Lisanby 2003	Not TRD
Ly 2017	Not TRD

Study	Reason for exclusion
NCT00488748	Not TRD
NCT00973934	Not TRD
NCT01748708	Withdrawn
NCT01869374	Not TRD
NCT03641300	Not TRD
NCT04080778	Not TRD

TRD: treatment-resistant depression.

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

NCT03191058

Study name	Confirmatory Efficacy and Safety Trial of Magnetic Seizure Therapy for Depression (CREST-MST)
Methods	**Study design:** double-blind, parallel, randomised **Total duration of study:** 7 weeks **Number of study centres and locations:** 2; University of Texas Southwestern Medical Center, United States; Temerty Centre for Therapeutic Brain Intervention, Centre for Addiction and Mental Health, Canada. **Study setting:** inpatients and outpatients **Dates of study:** June 26, 2018 -
Participants	**Number:** 260 participants **Age:**18 years and older **Gender:** all **Course of disease:** no information **Severity of condition:** baseline HAMD-24 score ≥ 21 **Diagnostic criteria:** non-psychotic MDD, MINI-6.0 **Inclusion criteria** • Voluntary and competent to consent to treatment and research procedures according to ECT/MST attending psychiatrist • MINI International Neuropsychiatric Interview Version 6 (MINI-6.0) diagnosis of non-psychotic MDD • 18 years of age or older • Baseline HAMD-24 score ≥ 21 • Considered appropriate to receive convulsive therapy as assessed by ECT attending psychiatrist and consultant anaesthesiologist • Agreeable to keeping current antidepressant treatment constant during the intervention • Likely able to adhere to intervention schedule • Meeting MST safety criteria

NCT03191058 *(Continued)*

- If a woman of child-bearing potential, willing to provide a negative pregnancy test with agreement not to become pregnant during trial participation

Exclusion criteria

- History of MINI diagnosis of substance dependence or abuse within past 3 months
- Concomitant major unstable medical illness
- Pregnant or intending to get pregnant during the study
- MINI diagnosis of any primary psychotic disorder
- MINI diagnosis of obsessive-compulsive disorder, or post-traumatic stress disorder deemed to be primary and causing more functional impairment than depressive disorder
- Probable dementia based on study investigator assessment
- Any significant neurological disorder or condition likely to be associated with increased intracranial pressure or a space-occupying brain lesion (e.g. cerebral aneurysm)
- Medical condition, medication, or laboratory abnormality that could cause a major depressive episode or significant cognitive impairment in the opinion of the investigator (e.g. hypothyroidism with low TSH, rheumatoid arthritis requiring high-dose prednisone, Cushing's disease)
- Intracranial implant (e.g. aneurysm clips, shunts, stimulators, cochlear implants, electrodes) or any other metal object within or near the head, excluding the mouth, that cannot be safely removed
- Requiring a benzodiazepine with dose > lorazepam 2 mg/d or equivalent, or any anticonvulsant, due to the potential of these medications to limit efficacy of both MST and ECT
- Unable to communicate in English fluently enough to complete neuropsychological tests
- Non-correctable clinically significant sensory impairment (i.e. cannot hear or see well enough to complete neuropsychological tests)

Co-morbid conditions: no information

Interventions

MST (coil placement, frequency, dose, number of sessions)

- Twin coil over frontal cortex in midline position
- 100 Hz
- MST determination of seizure threshold will be done using 100% machine output applied at 100 Hz at progressively escalating train durations, commencing at 2 seconds and increasing by 2 seconds with each subsequent stimulation until an adequate seizure is produced. During subsequent sessions, 1 stimulation will be delivered using a train duration that is 4 seconds longer than the train duration at threshold (with maximum train duration of 10 seconds)
- Up to 21 sessions

ECT (electrode placement, pulse width, dose, number of sessions)

- Right unilateral
- Ultra-brief
- No information
- Up to 21 sessions

Concomitant medications: no information

Concomitant psychosocial interventions: no information

Excluded medications: benzodiazepine with dose > lorazepam 2 mg/d or equivalent or any anticonvulsant

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Outcomes

Primary and secondary outcomes

- HAMD-24 (primary)
- Autobiographical memory test (primary)
- Scale for suicidal ideation

NCT03191058 *(Continued)*	**Time points reported:** before and after all treatments
Starting date	26 June 2018
Contact information	Z. Jeffrey J Daskalakis, MD, PhD; Centre for Addiction and Mental Health
Notes	Sponsor: University of Texas Southwestern Medical Center

ECT: electroconvulsive therapy.
HAMD: Hamilton Rating Scale for Depression.
MDD: major depressive disorder.
MST: magnetic seizure therapy.
TSH: thyroid-stimulating hormone.

DATA AND ANALYSES

Comparison 1. MST vs ECT

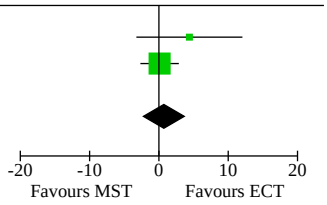
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 MST vs ECT - symptom severity - HAMD - random effects	2	40	Mean Difference (IV, Random, 95% CI)	0.71 [-2.23, 3.65]
1.2 MST vs ECT - cognitive functions - abstract questions - invalidated tests	1		Other data	No numeric data
1.3 MST vs ECT - cognitive function - delayed memory - invalidated tests	2		Other data	No numeric data
1.4 MST vs ECT - cognitive function - immediate memory - invalidated tests	2		Other data	No numeric data
1.5 MST vs ECT - cognitive function - neglect - invalidated tests	1		Other data	No numeric data
1.6 MST vs ECT - cognitive function - spatial - invalidated tests	1		Other data	No numeric data
1.7 MST vs ECT - cognitive function - verbal fluency - invalidated tests	1		Other data	No numeric data
1.8 MST vs ECT - cognitive function - verbal learning and memory - invalidated tests	1		Other data	No numeric data
1.9 MST vs. ECT - cognitive functions - visual spatial learning and memory - invalidated tests	1		Other data	No numeric data
1.10 MST vs. ECT - cognitive functions - immediate memory - random effect	1	20	Mean Difference (IV, Random, 95% CI)	0.40 [-4.16, 4.96]
1.11 MST vs ECT - cognitive function - delayed memory - random effects	1	20	Mean Difference (IV, Random, 95% CI)	2.57 [-2.39, 7.53]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.12 MST vs ECT - quality of life - random effects	1	20	Mean Difference (IV, Random, 95% CI)	14.86 [-42.26, 71.98]
1.13 MST vs ECT - dropout for any reason - random effects	1	25	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.28, 6.91]
1.14 MST vs ECT - adverse events that led to discontinuation of treatment - random effects	1	25	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.01, 3.52]

Analysis 1.1. Comparison 1: MST vs ECT, Outcome 1: MST vs ECT - symptom severity - HAMD - random effects

	MST			ECT				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Kayser 2011	18.3	9.63	10	13.9	7.72	10	14.2%	4.40 [-3.25 , 12.05]	
Kayser 2017	7.2	2	10	7.1	4	10	85.8%	0.10 [-2.67 , 2.87]	
Total (95% CI)			**20**			**20**	**100.0%**	**0.71 [-2.23 , 3.65]**	

Heterogeneity: Tau² = 0.63; Chi² = 1.07, df = 1 (P = 0.30); I² = 7%
Test for overall effect: Z = 0.47 (P = 0.64)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: MST vs ECT, Outcome 2: MST vs ECT - cognitive functions - abstract questions - invalidated tests

MST vs ECT - cognitive functions - abstract questions - invalidated tests

Study	Treatment	Baseline Mean	Baseline SD	Post - treatment Mean	Post - treatment SD	n
Kayser 2011	MST	4.5	0.85	4.5	0.85	10
	ECT	4.2	1.03	3.8	1.4	10

Analysis 1.3. Comparison 1: MST vs ECT, Outcome 3: MST vs ECT - cognitive function - delayed memory - invalidated tests

MST vs ECT - cognitive function - delayed memory - invalidated tests

Study	Treatment	Mean	SD	n
Kayser 2011	MST	2.7	2.11	10
	ECT	1.7	1.95	10
Polster 2015	MST	0.508	0.228	10
	ECT	0.226	0.178	10

Analysis 1.4. Comparison 1: MST vs ECT, Outcome 4: MST vs ECT - cognitive function - immediate memory - invalidated tests

MST vs ECT - cognitive function - immediate memory - invalidated tests

Study	Treatment	Mean	SD	n
Kayser 2011	MST	6.9	1.37	10
	ECT	6.4	2.17	10
Polster 2015	MST	20.4	6.2	10

	ECT	14.3	5.8	10

Analysis 1.5. Comparison 1: MST vs ECT, Outcome 5: MST vs ECT - cognitive function - neglect - invalidated tests

MST vs ECT - cognitive function - neglect - invalidated tests

Study	Sub-test	Treatment	Baseline Mean	Baseline SD	Post - treatment Mean	Post - treatment SD	n
Kayser 2011	geometric forms	MST	54.4	10.29	52	10.5	10
		ECT	68.4	20.89	69.5	19.95	10
	letters	MST	68.5	17.35	63.6	13.48	10
		ECT	96.4	58.73	72.5	22.4	10
	nongeometric forms	MST	101	20.63	87.9	15.1	10
		ECT	146.6	76.4	84.9	30.66	10

Analysis 1.6. Comparison 1: MST vs ECT, Outcome 6: MST vs ECT - cognitive function - spatial - invalidated tests

MST vs ECT - cognitive function - spatial - invalidated tests

Study	Treatment	Baseline Mean	Baseline SD	Post - treatment Mean	Post - treatment SD	n
Kayser 2011	MST	4.3	1.06	4.8	0.63	10
	ECT	4	0.82	4.7	0.67	10

Analysis 1.7. Comparison 1: MST vs ECT, Outcome 7: MST vs ECT - cognitive function - verbal fluency - invalidated tests

MST vs ECT - cognitive function - verbal fluency - invalidated tests

Study	Sub-test	Treatment	Baseline Mean	Baseline SD	Post - treatment Mean	Post - treatment SD	n
Kayser 2011	semantic categorial	MST	32.6	5.78	26.45	8.49	10
		ECT	31.1	8.58	22.2	8.28	10
	formal lexical	MST	18.5	6.17	15.1	7.4	10
		ECT	16.5	9.22	11.2	4.69	10

Analysis 1.8. Comparison 1: MST vs ECT, Outcome 8: MST vs ECT - cognitive function - verbal learning and memory - invalidated tests

MST vs ECT - cognitive function - verbal learning and memory - invalidated tests

Study	sub-test	Treatment	Baseline Mean	Baseline SD	Post - treatment Mean	Post - treatment SD	n
Kayser 2011	immediate recall	MST	6.4	1.51	6.9	1.37	10
		ECT	6	2.4	6.4	2.17	10
	immediate recognition	MST	13.8	1.14	13.3	1.83	10
		ECT	13.1	4.65	13.2	2.44	10
	delayed recall	MST	3.8	1.93	2.7	2.11	10
		ECT	2.4	1.71	1.7	1.95	10
	delayed recognition	MST	12.4	2.22	12.05	1.42	10
		ECT	11.5	3.57	12.3	2.26	10

Analysis 1.9. Comparison 1: MST vs ECT, Outcome 9: MST vs. ECT - cognitive functions - visual spatial learning and memory - invalidated tests

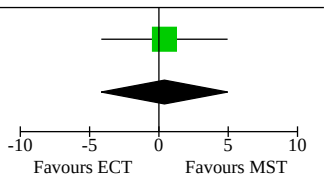
MST vs. ECT - cognitive functions - visual spatial learning and memory - invalidated tests

Study	sub-test	Treatment	Baseline Mean	Baseline SD	Post - treatment Mean	Post - treatment SD	n
Kayser 2011	immediate recognition	MST	6.6	1.08	6.45	1.54	10
		ECT	6.4	1.96	4.6	2.41	10
	delayed recognition	MST	5.7	1.57	4.65	1.92	10
		ECT	5.5	1.9	3.5	2.22	10

Analysis 1.10. Comparison 1: MST vs ECT, Outcome 10: MST vs. ECT - cognitive functions - immediate memory - random effect

Study or Subgroup	MST Mean	MST SD	MST Total	ECT Mean	ECT SD	ECT Total	Weight	Mean Difference IV, Random, 95% CI
Kayser 2011	14.2	4.1	10	13.8	6.1	10	100.0%	0.40 [-4.16 , 4.96]
Total (95% CI)			**10**			**10**	**100.0%**	**0.40 [-4.16 , 4.96]**

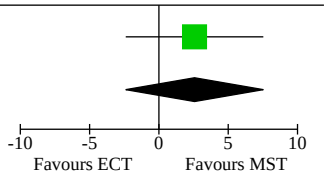
Heterogeneity: Not applicable
Test for overall effect: Z = 0.17 (P = 0.86)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: MST vs ECT, Outcome 11: MST vs ECT - cognitive function - delayed memory - random effects

Study or Subgroup	MST Mean	MST SD	MST Total	ECT Mean	ECT SD	ECT Total	Weight	Mean Difference IV, Random, 95% CI
Kayser 2011	12.9	5.51	10	10.33	5.81	10	100.0%	2.57 [-2.39 , 7.53]
Total (95% CI)			**10**			**10**	**100.0%**	**2.57 [-2.39 , 7.53]**

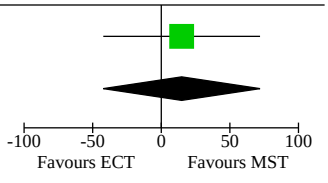
Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: MST vs ECT, Outcome 12: MST vs ECT - quality of life - random effects

Study or Subgroup	MST Mean	MST SD	MST Total	ECT Mean	ECT SD	ECT Total	Weight	Mean Difference IV, Random, 95% CI
Kayser 2011	87.56	64.84	10	72.7	65.5	10	100.0%	14.86 [-42.26 , 71.98]
Total (95% CI)			**10**			**10**	**100.0%**	**14.86 [-42.26 , 71.98]**

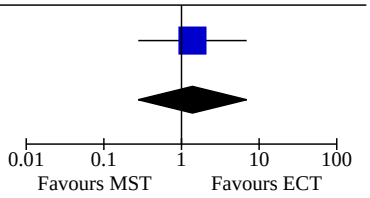
Heterogeneity: Not applicable
Test for overall effect: Z = 0.51 (P = 0.61)
Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1: MST vs ECT, Outcome 13: MST vs ECT - dropout for any reason - random effects

Study or Subgroup	MST Events	MST Total	ECT Events	ECT Total	Weight	Risk Ratio M-H, Random, 95% CI
Kayser 2017	3	13	2	12	100.0%	1.38 [0.28 , 6.91]
Total (95% CI)		**13**		**12**	**100.0%**	**1.38 [0.28 , 6.91]**
Total events:	3		2			

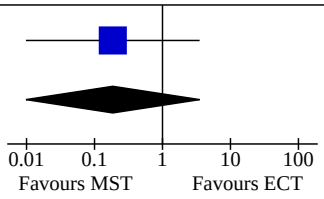
Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1: MST vs ECT, Outcome 14: MST vs ECT - adverse events that led to discontinuation of treatment - random effects

Study or Subgroup	MST Events	MST Total	ECT Events	ECT Total	Weight	Risk Ratio M-H, Random, 95% CI
Kayser 2017	0	13	2	12	100.0%	0.19 [0.01 , 3.52]
Total (95% CI)		**13**		**12**	**100.0%**	**0.19 [0.01 , 3.52]**
Total events:	0		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.12 (P = 0.26)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search strategies

Database	Search date	No. records retrieved	After deduplication
MEDLINE Ovid	02/03/2020	103	103
Embase Ovid	02/03/2020	194	86
PsycINFO Ovid	02/03/2020	78	18
CENTRAL Wiley	02/03/2020	98	67
WoS Science Citation Index Clarivate Analytics	02/03/2020	164	54

(Continued)

WoS CPCI - Science Clarivate Analytics	02/03/2020	45	5
ProQuest Dissertations & Theses A&I	02/03/2020	13	13
Open Access Theses and Dissertations	02/03/2020	13	2
DART-Europe E-theses Portal	02/03/2020	0	0
Networked Digital Library of Theses and Dissertations (NDLTD)	02/03/2020	2	0
OpenGrey	02/03/2020	0	0
ClinicalTrials.gov	02/03/2020	39	18
WHO ICTRP	02/03/2020	57	1
CCMDCTR	02/03/2020	31	7
Total		**837**	**374**

Cochrane Central Register of Controlled Trials (CENTRAL)
via Wiley http://onlinelibrary.wiley.com/
Issue 3 of 12, March 2020
Searched on: 2 March 2020
Records retrieved: 98
#1 MST 743
#2 "magnetic seizure" or "seizure therapy" or "magnetic therapy" 179
#3 (#1 or #2) 882
#4 MeSH descriptor: [Depressive Disorder, Treatment-Resistant] this term only 385
#5 affective next disorder* or depress* or TRD 102273
#6 (#4 or #5) 102273
#7 (#3 and #6) 119
#8 (#3 and #6) in Trials 98

****

Cochrane Specialised Register (CCMDCTR)
Searched on: 2 March 2020 (register current to June 2016 only)
Records retrieved: 31
(“magnetic seizure therapy” or “magnetic therapy” or MST:ab)

Detaials of the CCMDCTR are available at: https://cmd.cochrane.org/specialised-register

****

MEDLINE(R) ALL
via Ovid http://ovidsp.ovid.com/
1946 to February 28, 2020
Searched on: 2nd March 2020
Records retrieved: 103
1 Depressive Disorder, Treatment-Resistant/ (1179)
2 (depress* adj3 (refractory* or resistan* or relaps* or recurr* or chronic* or persist* or sever*)).ti,ab,kf. (36531)
3 (depress* and ((antidepress* or anti-depress* or SSRI* or SNRI* or (serotonin adj3 (uptake or reuptake or re-uptake)) or medication* or psychotropic* or treatment* or respon*) adj2 fail*)).ti,ab,kf. (1641)

4 (depress* and ((antidepress* or anti-depress* or SSRI* or SNRI* or (serotonin adj3 (uptake or reuptake or re-uptake)) or psychotropic* or medication* or treatment*) adj2 (no respon* or "not respon*" or nonrespon* or non-respon* or unrespon*))).ti,ab,kf. (680)
5 (depress* and (augment* or potentiat*)).mp. (16064)
6 TRD.ab. (1474)
7 or/1-6 (53595)
8 (magnetic seizure or seizure therapy or magnetic therapy).ti,ab,kf. (354)
9 MST.ab. (4909)
10 8 or 9 (5183)
11 7 and 10 (83)
12 magnetic seizure therapy.ti. (60)
13 11 or 12 (117)
14 exp animals/ not humans.sh. (4673607)
15 13 not 14 (103)

****

Embase
via Ovid http://ovidsp.ovid.com/
1974 to 2020 February 28
Searched on: 2nd March 2020
Records retrieved: 194
1 treatment resistant depression/ (2955)
2 (depress* adj3 (refractory* or resistan* or relaps* or recurr* or chronic* or persist* or sever*)).ti,ab,kw. (52586)
3 (depress* and ((antidepress* or anti-depress* or SSRI* or SNRI* or (serotonin adj3 (uptake or reuptake or re-uptake)) or medication* or psychotropic* or treatment* or respon*) adj2 fail*)).ti,ab,kw. (2660)
4 (depress* and ((antidepress* or anti-depress* or SSRI* or SNRI* or (serotonin adj3 (uptake or reuptake or re-uptake)) or psychotropic* or medication* or treatment*) adj2 (no respon* or "not respon*" or nonrespon* or non-respon* or unrespon*))).ti,ab,kw. (1028)
5 (depress* and (augment* or potentiat*)).mp. (25268)
6 TRD.ab. (2433)
7 or/1-6 (79542)
8 (magnetic seizure or seizure therapy or magnetic therapy).ti,ab,kw. (553)
9 MST.ab. (7462)
10 8 or 9 (7865)
11 7 and 10 (161)
12 magnetic seizure therapy.ti. (105)
13 11 or 12 (208)
14 (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) not (human/ or normal human/ or human cell/) (6414426)
15 13 not 14 (194)

****

PsycINFO
via Ovid http://ovidsp.ovid.com/
1806 to February Week 4 2020
Searched on: 2nd March 2020
Records retrieved: 78
1 treatment resistant depression/ (2273)
2 (depress* adj3 (refractory* or resistan* or relaps* or recurr* or chronic* or persist* or sever*)).ti,ab,id. (29296)
3 (depress* and ((antidepress* or anti-depress* or SSRI* or SNRI* or (serotonin adj3 (uptake or reuptake or re-uptake)) or medication* or psychotropic* or treatment* or respon*) adj2 fail*)).ti,ab,id. (1195)
4 (depress* and ((antidepress* or anti-depress* or SSRI* or SNRI* or (serotonin adj3 (uptake or reuptake or re-uptake)) or psychotropic* or medication* or treatment*) adj2 (no respon* or "not respon*" or nonrespon* or non-respon* or unrespon*))).ti,ab,id. (574)
5 (depress* and (augment* or potentiat*)).mp. (6991)
6 TRD.ab. (732)
7 or/1-6 (36315)
8 (magnetic seizure or seizure therapy or magnetic therapy).ti,ab,id. (148)
9 MST.ab. (1241)
10 8 or 9 (1312)
11 7 and 10 (62)
12 magnetic seizure therapy.ti. (46)
13 11 or 12 (86)
14 exp animals/ or animal models/ (357091)
15 13 not 14 (78)

****

Science Citation Index Expanded
via Web of Science, Clarivate Analytics https://clarivate.com/webofsciencegroup/
Searched on: 2nd March 2020
Records retrieved: 164
12 164 (#11 OR #10)
11 111 (#9 AND #6)
10 96 TI="magnetic seizure therapy"
9 7,940 (#8 OR #7)
8 7,669 TS=MST
7 355 TS=("magnetic seizure" or "seizure therapy" or "magnetic therapy")
6 54,669 (#5 OR #4 OR #3 OR #2 OR #1)
5 1,725 TS=TRD
4 16,812 TS=(depress* AND (augment* or potentiat*))
3 1,108 TS=(depress* AND ((antidepress* or anti-depress* or SSRI* or SNRI* or (serotonin NEAR/3 (uptake or reuptake or re-uptake)) or psychotropic* or medication* or treatment*) NEAR/2 ("no respon*" or "not respon*" or nonrespon* or non-respon* or unrespon*)))
2 1,795 TS=(depress* AND ((antidepress* or anti-depress* or SSRI* or SNRI* or (serotonin NEAR/3 (uptake or reuptake or re-uptake)) or medication* or psychotropic* or treatment* or respon*) NEAR/2 fail*))
1 37,142 TS=(depress* near/3 (refractory* or resistan* or relaps* or recurr* or chronic* or persist* or sever*))
Conference Proceedings Citation Index - Science (CPCI-SCI)
via Web of Science, Clarivate Analytics https://clarivate.com/webofsciencegroup/
Searched on: 2nd March 2020
Records retrieved: 45
12 45#11 OR #10
11 22#9 AND #6
10 36TI="magnetic seizure therapy"
9 2,106#8 OR #7
8 2,030TS=MST
7 92TS=("magnetic seizure" or "seizure therapy" or "magnetic therapy")
6 4,043 (#5 OR #4 OR #3 OR #2 OR #1)
5 311TS=TRD
4 915TS=(depress* AND (augment* or potentiat*))
3 71TS=(depress* AND ((antidepress* or anti-depress* or SSRI* or SNRI* or (serotonin NEAR/3 (uptake or reuptake or re-uptake)) or psychotropic* or medication* or treatment*) NEAR/2 ("no respon*" or "not respon*" or nonrespon* or non-respon* or unrespon*)))
2 109TS=(depress* AND ((antidepress* or anti-depress* or SSRI* or SNRI* or (serotonin NEAR/3 (uptake or reuptake or re-uptake)) or medication* or psychotropic* or treatment* or respon*) NEAR/2 fail*))
1 2,897TS=(depress* near/3 (refractory* or resistan* or relaps* or recurr* or chronic* or persist* or sever*))

****

Grey Literature Search

ProQuest Dissertations & Theses A&I
via ProQuest https://www.proquest.com/
Searched on: 2 March 2020
Records retrieved: 13

S1	(TI,AB,SU,IF(depress*) AND TI,AB,SU,IF(refractory* OR resistan* OR relaps* OR recurr* OR chronic* OR persist* OR sever* OR fail* OR "no respon*" OR "not respon*" OR nonrespon* OR non-respon* OR unrespon* OR augment* OR potentiat*)) OR TRD	ProQuest Dissertations & Theses A&I	31537
S2	TI,AB,SU,IF("magnetic seizure" OR "seizure therapy" OR "magnetic therapy" OR MST)	ProQuest Dissertations & Theses A&I	878
S3	((TI,AB,SU,IF(depress*) AND TI,AB,SU,IF(refractory* OR resistan* OR relaps* OR recurr* OR chronic* OR persist* OR sever* OR fail* OR "no respon*" OR "not respon*" OR nonrespon* OR non-respon* OR unrespon* OR augment* OR potentiat*))	ProQuest Dissertations & Theses A&I	13

(Continued)

	OR TRD) AND TI,AB,SU,IF("magnetic seizure" OR "seizure therapy" OR "magnetic therapy" OR MST)	These databases are searched for part of your query.	
S4	TI("magnetic seizure therapy")	ProQuest Dissertations & Theses A&I	4
S5	(((TI,AB,SU,IF(depress*) AND TI,AB,SU,IF(refractory* OR resistan* OR relaps* OR recurr* OR chronic* OR persist* OR sever* OR fail* OR "no respon*" OR "not respon*" OR nonrespon* OR non-respon* OR unrespon* OR augment* OR potentiat*)) OR TRD) AND TI,AB,SU,IF("magnetic seizure" OR "seizure therapy" OR "magnetic therapy" OR MST)) OR TI("magnetic seizure therapy")	ProQuest Dissertations & Theses A&I These databases are searched for part of your query.	13

Open Access Theses and Dissertations
https://oatd.org/
Searched on: 2 March 2020
Records retrieved: 13

7	title:("magnetic seizure therapy")	5
6	("seizure therapy") AND (TRD)	2
5	("seizure therapy") AND (depressive)	1
4	("seizure therapy") AND (depression)	5
3	("magnetic therapy") AND (TRD)	0
2	("magnetic therapy") AND (depressive)	0
1	("magnetic therapy") AND (depression)	0

DART-Europe E-theses Portal
http://www.dart-europe.eu/basic-search.php
Searched on: 2 March 2020
Records retrieved: 0
1. Depress* AND (“magnetic therapy” OR “seizure therapy”) – 3 – browsed - none relevant
2. “magnetic seizure therapy” – 0
Networked Digital Library of Theses and Dissertations (NDLTD)
http://search.ndltd.org/index.php
Searched on: 2nd March 2020
Records retrieved: 2
title:"magnetic seizure therapy" – 1
(depression OR depressive OR TRD) AND "seizure therapy" – 1
(depression OR depressive OR TRD) AND "magnetic therapy" – 0
OpenGrey
http://www.opengrey.eu/
Searched on: 2nd March 2020
Records retrieved: 0
Magnetic seizure therapy – 0
“Seizure therapy” AND depress* - 0

"seizure therapy" AND TRD – 0
“magnetic therapy” AND depress* - 0
“magnetic therapy” AND TRD - 0

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HISTORY

Protocol first published: Issue 1, 2020

CONTRIBUTIONS OF AUTHORS

All review authors participated in preparation of this review.

DECLARATIONS OF INTEREST

JJ: none.
CZ: none.
CL: none.
ZC: none.
XC: none.
HW: none.
WL: none.
JW: none.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Due to mixed populations of bipolar and unipolar depression in most current studies, we did not exclude participants with a diagnosis of bipolar disorder. We plan to explore the different effects of MST on bipolar and unipolar TRD by conducting subgroup analyses when possible.

INDEX TERMS

Medical Subject Headings (MeSH)

Antidepressive Agents [therapeutic use]; Bias; Cognition; Depression [diagnosis] [drug therapy] [*therapy]; Drug Resistance; Electroconvulsive Therapy; Magnetic Field Therapy [adverse effects] [*methods]; Quality of Life; Randomized Controlled Trials as Topic; Schizophrenia [therapy]; Symptom Assessment

MeSH check words

Adult; Aged; Female; Humans; Male; Middle Aged; Young Adult