Electroconvulsive therapy for preventing relapse and recurrence in people with depression

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Electroconvulsive therapy for preventing relapse and recurrence in people with depression (Protocol)

Munkholm K, Jørgensen KJ, Paludan-Müller AS

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Electroconvulsive therapy for preventing relapse and recurrence in people with depression

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the benefits and harms of ECT for preventing relapse and recurrence of depression in children, adolescents, adults, and older people with major depressive disorder.
BACKGROUND

Description of the condition

The main classificatory diagnostic systems, the International Classification of Diseases (WHO 1992), and Diagnostic and Statistical Manual of Mental Disorders (APA 2013), define the clinical diagnosis of depression by symptoms that form a syndrome and cause impairment (Malhi 2018). Depending on the diagnostic system, a depressive episode is thus characterised by a period of almost daily depressed mood, reduced energy or fatigue, or loss of interest or pleasure in activities, that is accompanied by other symptoms such as difficulty concentrating, feelings of worthlessness or excessive or inappropriate guilt, hopelessness, recurrent thoughts of death or suicide, changes in appetite or sleep, and psychomotor agitation or retardation (APA 2013; WHO 1992). Depending on the number of criterion symptoms present, their severity and the degree of functional impairment, the severity of the depressive episode may be characterised as mild, moderate, or severe. The presence of certain clinical features may further define the character of the depressive episode, such as psychotic, catatonic, or melancholic.

There is no known pathophysiology underlying depression and no objective test to verify the clinical diagnosis of depression. The reliability of the diagnosis of depression, even in an academic setting, is low (Regier 2013).

The lifetime prevalence of depression varies between regions and countries, and is estimated at a mean of 14.6% among 10 high-income countries that include the USA, Germany, and Japan, and a mean of 11.1% among eight low- to middle-income countries including Ukraine, Mexico, and Colombia (Bromet 2011). The prevalence of depression is higher in women than in men; in the USA, the lifetime prevalence of depression in adult women and men has been estimated at 26.1% and 14.7%, respectively (Hasin 2018), with corresponding lifetime prevalences in England of 24% in women and 13% in men (NHS 2015). The World Health Organization (WHO) estimates that more than 264 million people suffer from depression worldwide (WHO 2020); such estimates, however, should be interpreted with caution, as they are based on diagnostic categories with likely low validity in many parts of the world (Summerfield 2008).

Most individuals with depression do not achieve remission with initial treatment with antidepressants, which is the usual recommended first-line treatment for moderate to severe depression, ideally in combination with psychotherapy (RANZCP 2016; WFSBP 2017). In the largest trial to investigate the effectiveness of antidepressant treatment for depression, designed to mimic clinical practice, approximately a quarter of patients achieved remission, when remission was defined by a total score on the Hamilton Depression Rating Scale (Hamilton 1967), of 7 or lower after a course of treatment with a selective serotonin reuptake inhibitor (SSRI; Kirsch 2018). However, this rate of remission likely overestimates the benefit of the treatment, since as many as half of the patients classified as being in remission using those common criteria do not consider themselves remitted (Zimmerman 2006; Zimmerman 2012), and since other factors, such as spontaneous improvement and placebo effects, may partially or fully explain the improvement observed in individual patients. In situations where patients are not helped by available pharmacological or psychological treatments or develop a more severe course of depression, electroconvulsive therapy (ECT) can be considered as a treatment option (CANTAR 2016; NICE 2009; WFSBP 2013).

A proportion of those who achieve remission or recovery from a depressive episode later develop a further depressive episode. Remission is often described as the absence or near absence of signs and symptoms of depression (Rush 2006), whereas recovery implies an extended period of remission, for example, of at least four months, such that a depressive episode is unlikely to occur in the near future (Rush 2006). Depressive episodes that occur before recovery but after remission is ascertained, are often labelled relapses, and episodes that occur after recovery is ascribed are labelled as recurrences (Rush 2006). The rate of recurrence appears to be higher in clinical samples compared with community samples; one clinical study found that 50% of the participants had a recurrence within 1.5 years of achieving recovery, with similar rates among those treated with antidepressants during the index depressive episode and those who were not (Mueller 1999), while a community study found that 13.2% had a recurrence within five years after their depressive episode (Hardeveeld 2013). For patients treated for an acute depressive episode with ECT, specifically, approximately 80% appear to relapse within six months after achieving remission without subsequent treatment (Sackeim 2001; Van Beusekom 2007). To reduce the risk of relapse and recurrence, treatment with antidepressants or other drugs or treatments, including ECT, are often given for a period of time after the treatment of the acute depressive episode; treatment given until recovery has been attained is usually labelled continuation treatment while treatment beyond that point often is usually labelled maintenance treatment (RANZCP 2015; WFSBP 2013). Even with continued pharmacological treatment, 40% to 60% of people achieving remission after ECT treatment for an acute depressive episode have been found to experience a relapse within six months (Sackeim 2001; Tew 2007). ECT is particularly considered a treatment option for continuation or maintenance treatment in cases where the index acute depressive episode was treated with ECT (APA 2010; CANTAR 2016; RANZCP 2015; WFSBP 2013).

Description of the intervention

ECT involves the application of electricity to the scalp in order to induce a generalised tonic-clonic seizure (Lisaby 2007). Continuation or maintenance ECT usually involves ECT treatment given once every week to once every three to four weeks after the end of an acute ECT treatment course (Gill 2019), although it may also be considered after a non-ECT acute treatment course, or occasionally less often (RANZCP 2019). Continuation ECT may be considered for the first six months after the end of the acute treatment course, while maintenance ECT occurs after that period (RANZCP 2019). It is considered best practice to administer ECT under anaesthesia together with muscle relaxant medication, so-called modified ECT (CPA 2010; RANZCP 2019; RCPYSCH 2019), methods that were introduced to reduce treatment complications such as pain, panic, and fractures (APA 1978). However, ECT administered without anaesthesia, so-called unmodified ECT, is practised around the world, including parts of Asia, Africa, South America and Europe (Leiknes 2012). In India, the use of unmodified ECT has been prohibited by law (Duffy 2019; Government of India 2017); in reaction to this, professional societies have advocated for the continued use of unmodified ECT in exceptional circumstances, such as when ECT is considered strongly indicated and seizure modification with succinylcholine is not feasible (Andrade 2012).
Different regimens of intravenous sedatives or hypnotics may be used; the evidence regarding whether different types of anaesthetic agents influence the efficacy of ECT for depression is uncertain (Liuha 2014). ECT for severe depression in individuals aged 13 years and older who are considered treatment-resistant (commonly defined as an inadequate response to two or more antidepressants (McIntyre 2014)), or who require a rapid response due to the severity of the condition or a medical condition was reclassified by the US Food and Drug Administration (FDA) from a class III (‘high risk’) device to a class II (‘moderate risk’) device in 2018 (FDA 2018).

ECT is traditionally administered with a ‘brief’ pulse width, defined as pulses of 0.5 to 2.0 milliseconds in duration (CPA 2010; RANZCP 2019; RCPsych 2019). Brief-pulse-wave ECT has been associated with fewer cognitive adverse effects compared with sine-wave ECT (Sackeim 2007), and is the stimulus method recommended in most current guidelines (APA 2001; CPA 2010; RANZCP 2019; RCPsych 2019). The sine-wave stimulus employed by the earliest ECT devices delivered an electrical charge in excess of the amount needed to efficiently elicit a seizure, leading to more frequent or severe cognitive adverse effects compared with brief-pulse ECT (CPA 2010); however, sine-wave ECT continues to be practised around the world (Leiknes 2012). Ultrabrief-pulse-wave ECT (0.25 to 0.3 milliseconds) has been available for the last decade and may be associated with fewer cognitive adverse effects compared with brief-pulse-wave ECT (Loo 2008; Sackeim 2008), although the efficacy may be lower, depending on the electrode placement (Brus 2017; Tor 2015).

Common electrode placements include bitemporal, right unilateral, and bifrontal (Lisanby 2007). Bitemporal ECT is generally considered to involve the highest risk of retrograde amnesia; one guideline recommends that it is not used as the initial form of ECT treatment, unless there are specific reasons to do so (RANZCP 2019). For maintenance treatment, it may be preferable to use the same electrode placement that was used during the acute ECT treatment course (Gill 2019).

The choice of stimulus current dose depends on both electrode placement and pulse width (CPA 2010; RANZCP 2019). In general, higher doses relative to the seizure threshold may be needed when reducing the pulse width in order to achieve a similar effect in acute depressive episodes (Loo 2008). Depending on the pulse width, the recommended dose level for acute depressive episodes is approximately 1.5 times the seizure threshold for bitemporal and bifrontal ECT, and approximately six times the seizure threshold for right unilateral ECT (CPA 2010; RANZCP 2019).

It is generally recommended that the choice of the particular treatment approach be determined by balancing, among other factors, the patient's response to acute ECT treatment, and concerns regarding potential cognitive side effects (RANZCP 2019). However, all electrode placements and stimulus forms appear to be associated with cognitive adverse effects, including a risk of retrograde amnesia (Sackeim 2008; Sackeim 2014).

ECT use varies by country and region, with an estimated 1.5 million people being treated annually worldwide for any indication (Leiknes 2012). ECT is used less often in children and adolescents compared with adults (AACAP 2004), but data regarding ECT use in children and adolescents are scarce. The use of ECT for the prevention of relapses and recurrences, specifically, is unclear.

Given the controversial nature of ECT, special legal restrictions are imposed on its administration in some countries (Leiknes 2012). The administration of ECT under involuntary conditions occurs worldwide, but the extent varies between countries (Leiknes 2012). The United Nations has long called for member states to ban all forced and non-consensual use of ECT (UN 2013; UN 2018), and to reframe and recognise such ECT practices as constituting torture or other cruel, inhuman, or degrading treatment (UN 2018). Several US states have prohibited by law the use of ECT in children and adolescents (Livingston 2018), and Western Australia has prohibited the use of ECT in children under 14 years (GWA 2018). WHO has stated that there is no indication for ECT in minors and that it should therefore be prohibited by legislation (WHO 2005). Some psychiatrists and ECT experts advocate for the continued use of ECT in both prepubertal children and adolescents for certain clinical indications and for the removal of impediments to ECT access in that population (Wachtel 2011).

ECT is recommended in international guidelines as a first-line treatment of acute depressive episodes with certain clinical features, such as psychosis (APA 2010; CANMAT 2016; FPG 2017; RANZCP 2015; WFSBP 2013), and catatonia (APA 2010; CANMAT 2016; RANZCP 2015); when the patient refuses to eat or drink (APA 2010; RANZCP 2015; WFSBP 2013); or when there is a high risk of suicide (APA 2010; CANMAT 2016; RANZCP 2015; WFSBP 2013). Guidelines also recommend ECT as a first-line treatment for treatment-resistant acute depressive episodes (CANMAT 2016; NICE 2009; WFSBP 2013); in patients who have had previous response to ECT (APA 2010; CANMAT 2016; RANZCP 2015; WFSBP 2013); as a first-line treatment for depression in pregnant women when medication is considered contraindicated, especially during the first trimester (WFSBP 2013); in severe depression with certain clinical features and in treatment-resistant depression (CANMAT 2016); and two guidelines suggest ECT as the treatment of choice for severe depression during pregnancy without specifying any particular clinical features or situations (APA 2010; RANZCP 2015).

International guidelines recommend that continuation and maintenance treatment with ECT is considered for patients who have responded to ECT for an acute depressive episode (APA 2010; CANMAT 2016; RANZCP 2019). Other international and major guidelines state that the evidence base, while limited, suggests that the use of continuation ECT is more effective than the use of antidepressants alone (WFSBP 2013), or that the evidence is insufficient to provide recommendations regarding the use of continuation or maintenance ECT (NICE 2009).

In children and adolescents, guidelines recommend that ECT is considered during all treatment phases, including continuation and maintenance treatment, in children and adolescents who are not responding to pharmacological or psychotherapeutic treatments (AACAP 2007), and that ECT should specifically be available to pre-adolescent children when “clinically appropriate” (RANZCP 2019). The American Psychiatric Association supports the use of ECT in children and adolescents (APA 2016).

Consensus among some ECT experts is that maintenance ECT is an evidence-based strategy for preventing relapse for patients treated with ECT for an acute depressive episode (Gill 2019), and, by some, considered underused (Petrides 2011).

There are important known harms of ECT (Andreade 2016), which include nausea, headache and myalgia, prolonged seizures, status...
electroconvulsive, and cardiac events such as asystole and myocardial infarction (Andrade 2016; CPA 2010). Unmodified ECT may also be associated with a risk of loosened or broken teeth, joint dislocation, bone fracture, spinal fracture, and muscle or ligament injuries (Andrade 2012). Cognitive impairment has long been recognised as a prominent adverse effect of ECT (APA 1978). Cognitive effects commonly include postictal confusion states and antegrade amnesia; ECT is also associated with retrograde amnesia, including impairment of autobiographical memory (APA 2010; CPA 2010; RANZCP 2019), which can be persistent (APA 2001; Sackeim 2007). Amnesia for autobiographical information is considered to be the most critical adverse cognitive effect of ECT (Sackeim 2014), its intensity depending on the electrode placement and the pulse width (Fraser 2008), although the clinical methods used to assess retrograde amnesia has been a subject of discussion (Sackeim 2014; Semkovska 2014).

Some aspects of the current practice of ECT, whilst varying between countries and regions, are not in alignment with international guidelines. Despite recommendations by several international guidelines to use right unilateral ECT, evidence shows that use of bitemporal ECT is still a common practice (Bjornshauge 2019; Leiknes 2012). Similarly, although discouraged by the WHO and all international guidelines, there is continued use of unmodified ECT (Leiknes 2012).

**How the intervention might work**

Although there are many theories (Michael 2009), the mechanism of action of ECT is unknown. Amongst current hypotheses, the more prominent relate to effects of the generalised seizure, actions on the neuroendocrine system through engagement of structures in the central core of the brain stem, and neurotrophic effects induced by seizure activity in the limbic system (Bolwig 2014).

**Why it is important to do this review**

The two extant systematic reviews of maintenance ECT in depression considered only adults and did not assess the certainty of the evidence (Brown 2014; Elias 2018); one of them did not assess any harms (Brown 2014), and the other included both participants with unipolar and bipolar depression but did not present separate results for patients with depression (Elias 2018).

Given the limitations of extant systematic reviews, a high-quality synthesis of the evidence of the benefits and harms of ECT for preventing relapse and recurrence in children and adults with depression, with a careful assessment of the certainty of the evidence, is needed.

**OBJECTIVES**

To assess the benefits and harms of ECT for preventing relapse and recurrence in children, adolescents, adults, and older people with major depressive disorder.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We will include randomised trials, including cross-over and cluster-randomised trials. We will only include the results from the first randomised period of cross-over trials, as depressive symptoms may be fluctuating, depression can be episodic, and carry-over effects of ECT are likely.

We will not include studies that use inappropriate strategies of allocating interventions, often labelled ‘quasi-randomised’ trials.

We will include studies using a so-called enriched design, in which all randomised participants have received ECT for the treatment of the index acute depressive episode, as well as studies using a non-enriched design, in which the participants did not receive any specific treatment for the index acute depressive episode. As enriched designs may create a selection bias because those participants entering the trial may be more likely to tolerate or experience fewer adverse effects of ECT and because they increase the risk of unblinding of participants assigned to non-ECT treatment, we will explore the effect of including studies with such a design in sensitivity analyses.

**Types of participants**

**Participant characteristics**

We will include participants of both sexes and of all ages.

**Diagnosis**

We will include participants considered to be in remission from major depressive disorder diagnosed using standardised diagnostic criteria including Feighner criteria (Feighner 1972), the International Classification of Diseases 10th revision (ICD-10; WHO 1992), and 11th revision (ICD-11; WHO 2018), as well as the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DSM-III; APA 1980), 4th edition (DSM-IV; APA 1994), and 5th edition (DSM-5; APA 2013). We will also include studies using the International Classification of Diseases 9th revision (ICD-9; WHO 1978), but as it does not employ specific diagnostic criteria, we will make a judgement of whether the description of the inclusion criteria is similar to standardised criteria. We will similarly consider studies using earlier versions of the ICD and the DSM, and explore the influence of including such studies in sensitivity analyses. We will not include studies that use cut-offs on symptom severity scales or studies that use self-rating scales, such as the participant-rated Beck Depression Inventory (BDI; Beck 1961), and the Patient Health Questionnaire (PHQ; Spitzer 1999), to establish the diagnosis of major depressive disorder. We will include participants with any subtype of depression (e.g. chronic, with catatonic features, with melancholic features, with atypical features, and with seasonal pattern). We will not include participants with bipolar depression.

Remission implies that the signs and symptoms of depression are absent or close to it (Rush 2006). We will, in the context of the current review, define remission, based on criteria outlined by Rush and colleagues (Rush 2006), as the absence of depression according to diagnostic criteria for three consecutive weeks or more, during which the patient does not meet diagnostic criteria for depression. Although commonly employed, definitions of remission based on cut-offs on symptom severity scales have been shown to have poor correlation with patients’ experience of being free from depression (Zimmerman 2006). We will also include studies that use such, and other, definitions to establish the presence of remission, as well any duration of remission, and will explore the effect of including such studies in sensitivity analyses.

**Electroconvulsive therapy for preventing relapse and recurrence in people with depression (Protocol)**
Comorbidities
Studies that involve participants with a comorbid psychiatric or physical disorder are eligible for inclusion.

Setting
We will include studies in all settings.

Where studies include subsets of eligible participants, we will only include the study provided separate data are available, either in the study report of through contact with the study authors, from the eligible section of the study population.

Types of interventions
Experimental intervention
The experimental intervention is ECT, meaning the application of electricity to the scalp in order to induce a generalised tonic-clonic seizure.

We will consider both modified (i.e. ECT applied under general anaesthesia and with administration of a muscle-relaxant drug) and unmodified ECT (i.e. ECT applied without anaesthesia). For modified ECT, we will consider any anaesthetic and muscle relaxant.

We will consider ECT delivered with any pulse width (e.g. sine wave, brief pulse, or ultrabrief pulse), electrode placement (e.g. bitemporal, bifrontal, right unilateral), and stimulus dose (e.g. measured as millicoulombs of charge or the dose relative to the dose corresponding to the seizure threshold).

We will consider any treatment schedule (e.g. once weekly or once monthly) or duration of the treatment course (i.e. the total number of times ECT was administered).

Comparator intervention
We will include the following comparators:

- sham ECT (i.e. a procedure similar to ECT, involving anaesthesia with or without muscle relaxant, but without delivery of electricity to the scalp);
- pharmacological treatment, including, but not limited to, antidepressants, antipsychotics, and lithium;
- non-pharmacological treatment, including, but not limited to, interventions such as repetitive transcranial magnetic stimulation, psychotherapy and social interventions;
- no intervention.

Co-interventions
We will include studies regardless of whether ECT was administered as monotherapy or in combination with non-pharmacological or pharmaceutical intervention or as augmentation to another non-pharmacological or pharmaceutical intervention, as long as the combination or augmentation therapy is given equally in the comparator arm.

Types of outcome measures
Primary outcomes
- Relapse or recurrence, measured as the total number of participants who experience a full depressive episode, according to standardised criteria as defined in the Types of participants section above.
- Serious adverse events, defined as the number of participants with at least one medical event that is life-threatening, results in death, disability, or significant loss of function, or causes hospital admission or prolonged hospitalisation (EMA 2002).

Secondary outcomes
- Self-harm and suicide-related events, measured as the number of participants experiencing self-harm and suicide-related events (suicide ideation, suicide attempts, and completed suicide).
- Global functioning assessed using the Sheehan Disability Scale (SDS; Sheehan 1996), the Social Adjustment Scale — Self-report (SAS-SR; Weissman 1976), or the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott 1993), which are amongst the most commonly used scales for assessing functioning in depression (Sheehan 2017). As the scales measure different constructs (Endicott 2009), we will not combine scores across scales but present them separately.
- Retrograde amnesia, including autobiographical information, measured using any relevant instrument (e.g. the Columbia University Autobiographical Memory Interview (CUAMI; McElhiney 1995), the CUAMI short form (CUAMI-SF, McElhiney 2001), an altered version of the CUAMI (Semkovska 2012), or the Kopelman Autobiographical Memory Interview (Kopelman AMI; Kopelman 1989).
- Number of participants with at least one adverse event. We will categorise adverse events according to System Organ Class and Preferred Term per the Medical Dictionary for Regulatory Activities terminology (MedDRA).

Reporting one or more of the outcomes listed here in the study is not an inclusion criterion for the review. Where a published report does not report one of these outcomes, we will access the study protocol and contact the study authors to ascertain whether they measured the outcomes but did not report them. Relevant studies that did not measure these outcomes or did not report the data at all, or not in a useable format, will be included in the review as part of the narrative.

Timing of outcome assessment
We will extract outcomes post-intervention (i.e. at the end of the treatment period) at the time points reported in the studies and group them into short-term (one to three months), medium-term (three to six months) and long-term (six months or longer). Where a study reports more than one time point within one of the prespecified time periods, we will select the latest time point.

Depressive episodes that occur early during the continuation or maintenance treatment are more likely to constitute relapses into the acute index depressive episode rather than representing recurrences of a new depressive episode. It has therefore been suggested that only episodes occurring later than four months (Rush 2006) or even as long as six or 12 months (Ghaemi 2017), after achieving remission should be considered new episodes, rather than relapses, although such a distinction is arbitrary. We will consider the time period of six months or longer for our primary analysis, which will then be more likely to inform on the prevention of new depressive episodes rather than the prevention of relapse into the index acute depressive episode.
Electroconvulsive therapy for preventing relapse and recurrence in people with depression (Protocol)

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Hierarchy of outcome measures
If studies report multiple measures of an eligible outcome, we will include the data based on several factors. If several measures of an outcome are available on the same hierarchy level used in a study, we will prioritise the outcome measures according to the order specified for each of the outcomes above. If several outcome measures on the same scale are available (e.g. multiple subscales of the CUAMI-SF), we will give priority to the outcome measure that is most frequently used across all the included studies. If several analyses are available, we will give priority to an adjusted model (e.g. by baseline measures of an outcome), if appropriately conducted, and use the effect estimates directly.

Data collection and analysis

Selection of studies
Two review authors (KM and ASP-M) will independently screen the titles and abstracts of all the studies identified as a result of the search for potential eligibility, coding them as ‘retrieve’ (eligible or potentially eligible/unclear) or ‘do not retrieve’. We will resolve any disagreements through discussion or by asking the third review author (KJJ) to arbitrate if necessary. We will retrieve the full-text study reports of potentially eligible studies, and two review authors (KM and ASP-M) will independently screen the full texts and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreements through discussion or by consulting a third review author (KJJ) if necessary. We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Page 2021), and ‘Characteristics of excluded studies’ table.

Data extraction and management
We will use an electronic data collection form prepared in Microsoft Excel for study characteristics and outcome data that has been piloted on at least one included study. Two review authors (KM and ASP-M) will independently extract data from the included studies. We will resolve any disagreements by consensus or by involving a third review author (KJJ). We will extract the following study characteristics and outcome data.

- Methods: study design, total duration of study, duration of follow-up, details of any ‘run-in’ period, details of any preceding open-label phase, diagnostic criteria for establishing the acute index depressive episode and for determining remission, number of study centres and location, study setting, and date of study start and completion
- Participants: number randomised, number lost to follow-up/withdrawn with reasons, number analysed for each outcome, mean age, age range, sex, mean severity of depressive symptoms, mean number of previous depressive episodes, diagnostic criteria, clinical specifiers of the index depressive episode (e.g. psychotic, catatonic, or melancholic), number having previously received ECT, inclusion criteria, and exclusion criteria, details on pharmacological and ECT treatment prior to randomisation, method of tapering off potential active treatment with drugs or ECT after randomisation to comparator arm
- Interventions: intervention, comparison, concomitant medications or non-pharmaceutical treatment, ECT device manufacturer, type and dosage of anaesthetic administered, muscle relaxant administered, pulse width, electrode placement, stimulus current dose, frequency of ECT administration (number of times per month), number of total ECTs delivered during treatment course, whether rescue medication (i.e. medication allowed to be administered in the study to treat exacerbation of symptoms or adverse effects) was allowed in study and if so, number of participants using rescue medication
- Outcomes: outcomes specified and collected, and time points reported; any frequency threshold for reporting of adverse events used; whether adverse events were actively monitored (prespecified) or spontaneously reported

Electronic searches
We will search the following databases using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource:

- Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR; all available years);
- Cochrane Central Register of Controlled Trials (CENTRAL; current issue) in the Cochrane Library;
- Ovid MEDLINE (1946 onwards; preliminary search strategy Appendix 1);
- Ovid Embase (1974 onwards);
- Ovid PsycINFO (1806 onwards);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/; all available years);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/; all available years).

We will place no restrictions on date, language, or publication status.

We will not perform a separate search for adverse effects of ECT used for the treatment of depression. For the current review, we will consider adverse effects described in the included studies only. We plan to conduct a separate review of the adverse effects of ECT for acute depressive episodes in which we will include evidence across all potential indications.

We will update the search just before submitting the review to the editorial base.

Searching other resources
We will check reference lists of all included studies, relevant books, and any relevant systematic reviews that we identify for additional references to studies. We will also examine any relevant retraction statements and errata for the included studies. We will also conduct internet searches for relevant grey literature sources such as reports, dissertations, theses, databases and databases of conference abstracts.

We will contact all study authors to obtain the study protocol if it is not otherwise available and any data or information needed to assess eligibility, calculate effect sizes, assess unreported outcomes, and perform risk of bias assessment.

We will also conduct internet searches for relevant grey literature sources such as reports, dissertations, theses, databases and databases of conference abstracts.

We will contact all study authors to obtain the study protocol if it is not otherwise available and any data or information needed to assess eligibility, calculate effect sizes, assess unreported outcomes, and perform risk of bias assessment.
Notes: funding for the study, and conflicts of interest of authors

One review author (KM) will import the data into R (R Core Team 2019). We will double-check that data have been entered correctly by comparing the data presented in the systematic review with the data extraction form.

Assessment of risk of bias in included studies

Two review authors (KM and ASP-M) will independently assess the risk of bias for each study using RoB 2 (Sterne 2019), outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2021a). We plan to use the RoB 2 Microsoft Excel tool to manage the risk of bias assessment (Microsoft Excel 2019; RoB 2 Microsoft Excel tool 2019). We will resolve any disagreements by discussion or by involving the third review author (KJJ). We will assess the risk of bias of a specific result of randomised trials according to the following domains:

- bias arising from the randomisation process;
- bias due to deviations from intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome;
- bias in selection of the reported result.

We will assess the risk of bias of a specific result of cluster-randomised trials using the Cochrane RoB 2 tool for cluster-randomised trials, as outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2021b).

We will assess the risk of bias for the outcomes of the included studies presented in the summary of findings table. For the purposes of this review, we are interested in quantifying the effect of assignment to the interventions at baseline, regardless of whether the interventions are received as intended (the intention-to-treat effect).

We will use the signalling questions in RoB 2 and rate each domain as 'low risk of bias', 'some concerns', or 'high risk of bias'. We will summarise the risk of bias judgements across different studies for each of the domains listed for each outcome. The overall risk of bias within the study for the result is the least favourable assessment across the domains; however, where a study is judged to have some concerns for multiple domains, we will judge the overall risk of bias as high, based on the approach outlined in Table 8.2.b of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2021a).

We will make our consensus decisions for the signalling questions available as supplemental data stored on the Open Science Framework. We will assign supplemental files a digital object identifier (DOI).

Measures of treatment effect

We will analyse dichotomous data as odds ratios (OR) with 95% confidence intervals (CIs) and continuous data as mean difference (MD) or standardised mean difference (SMD) with 95% CIs. We will enter data presented as a scale with a consistent direction of effect. If studies use different scales to measure the same outcome, we will pool the data by calculating the SMD. If studies report the outcome as both an endpoint score and a baseline-to-endpoint change score, we will prioritise endpoint scores, as they may be easier to interpret clinically; if these are not available, we will use the change score from baseline to endpoint. If both the mean and standard deviation (SD) for baseline and change from baseline are available, but not endpoint scores, we will transform these data into endpoint means and estimate the endpoint SD using the formulae in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2021c). We will not pool data using endpoint scores and baseline-to-endpoint change scores when calculating SMDs for the reasons outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2021). We will present results calculated as SMD by re-expressing the data in units of one or more of the instruments used in the included studies, employing an SD calculated as a weighted average across all intervention groups of all studies that used the instrument (Schünemann 2021a).

We will describe skewed data using medians and interquartile ranges narratively.

Unit of analysis issues

Cross-over trials

For cross-over trials, we will only consider results for the calculation of summary statistics when data for the first randomised period can be extracted.

Cluster-randomised trials

For cluster-randomised trials, we will analyse results using the generic inverse-variance approach and the effect estimates and standard errors reported in the trial provided the analyses appropriately accounted for the cluster design. If these data are not available, we will multiply the standard error of the effect estimate by the square root of the design effect and analyse results using the generic inverse-variance method (Higgins 2021b).

Trials with multiple treatment groups

For studies with multiple arms, we will combine the treatment arms using the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2021b), if they can be regarded as providing subtypes of the same treatment and their effect can therefore be considered similar (e.g. different doses within the range of approved dosages). When this is not the case, we will treat each arm as a separate group and will divide the sample size of the placebo arm between the treatment arms whilst leaving the mean and SD unchanged for continuous outcomes, and split the events evenly amongst intervention groups for dichotomous variables.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when relevant (e.g. when a study is identified as abstract only) and will document details regarding the correspondence. Where possible, we will calculate missing SDs using other data from the study, such as CIs, based on methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2021). Where this is not possible, we will report the study narratively and discuss its impact in the overall assessment of results.

Dichotomous outcomes

For participants for whom data are available but were excluded from the analyses because of protocol non-adherence, we will...
attempt to obtain the data from the original study report or by directly contacting study investigators. Where data can be obtained for non-adherent participants, we will apply an intention-to-treat analysis, in which the total of the excluded participants is added to the denominator and the number with events is added to the numerator of the arm to which they were randomised. We will consider the exclusion of ineligible participants who are mistakenly randomised to be appropriate only if information about ineligibility was available at randomisation and those making the decision regarding exclusion were blind to allocation; otherwise, we will treat those participants similarly to non-adherent participants.

For participants with missing dichotomous outcome data, we will follow the methods proposed by Higgins and colleagues to assess the potential impact of missing data on the results (Higgins 2008). We will conduct an available-case analysis as a reference. For our primary analysis, we will conduct an imputed-case analysis, in which we will impute missing data according to reasons for missingness. We will specify the categorisation of reasons based on a pilot assessment of the study methods in a few included studies, in advance of seeing the data. We will consider the uncertainty of the imputed data when calculating standard errors so that these are not inappropriately reduced, and weight the studies accordingly, using the methods outlined by Higgins and colleagues (Higgins 2008). When the primary meta-analysis suggests an important effect, we will conduct several sensitivity analyses to assess the risk of bias associated with missing participant data. We will first calculate best-case and worst-case scenarios, to provide the most extreme limits on the effect estimates compatible with the data. Next, we will conduct several analyses by selecting informative missing odds ratios for the two groups that cover more realistic situations (Higgins 2008), based on, amongst other factors, information about the reasons for missing data. Lastly, we will evaluate the effects of missing participants on the weights awarded to the studies using the method by Gamble and Hollis (Gamble 2005).

Continuous outcomes

For participants with missing continuous outcome data, we will follow the methods proposed by Ebrahim and colleagues to assess the potential impact of missing data on the results (Ebrahim 2013). This will involve conducting an initial available-case analysis as our primary analysis and subsequent sensitivity analyses in which we will make progressively more stringent assumptions about results for participants with missing data. This will permit an assessment of the extent that results change with the sensitivity analyses, and, in turn, how risk of bias as a result of missing data may increase. We will assume in these analyses that the reasons for missing data, and the participants with missing data, were similar across studies. We will use five sources of data reflecting observed mean scores in the participants followed up (i.e. the best and worst mean score of the intervention group and control group across included studies, respectively, and the mean score of the control arm of the same study). We will then use these data in four progressively more stringent imputation strategies (Ebrahim 2013). For studies in which authors do not report missing participant data rates, we will use the median missing participant data rate from the remaining studies and perform a sensitivity analysis employing a missing participant data rate of zero in both arms. If only the total missing participant data are reported, we will assume that missing data were equally distributed in both arms. If the individual study handled missing participant data and reported imputed analyses only, we will use the imputed results for the meta-analysis (Ebrahim 2013). If the authors reported both the imputed analysis and the complete-case analysis, we will apply our approach to the study’s available-case analysis. When studies used different measures for assessing the same outcome, we will choose a reference measurement instrument and convert the scores from different instruments to the units of the reference instrument (Ebrahim 2014).

Assessment of heterogeneity

We will use the I² statistic to quantify inconsistency among the studies in each analysis (Higgins 2003). We will also consider the P value from the Chi² test. We will consider an I² statistic estimate equal to or greater than 50% accompanied by a statistically significant Chi² test (P < 0.1) as indication of substantial heterogeneity (Deeks 2021). In the case of substantial heterogeneity, we will report it and explore possible causes by prespecified subgroup analysis.

Furthermore, we will inspect forest plots visually to consider the direction and magnitude of effects and the degree of overlap between CIs.

Assessment of reporting biases

We will attempt to retrieve the protocols of the included studies and compare the outcomes in the protocol with those in the published report. If we cannot retrieve the protocol, we will compare the outcomes in the methods section of the report with the reported results.

Two review authors (KM and ASP-M) will independently assess the risk of reporting biases using the preliminary Risk Of Bias due to Missing Evidence (ROB-ME) tool (Page 2020). We will resolve disagreements through discussion or, if necessary, by involving a third review author (KJJ).

Following the ROB-ME guidance, we will construct an outcome matrix and then assess the within-study and across-studies non-reporting bias using the signalling questions and algorithm outlined in the ROB-ME tool.

We will present the assessment of risk of reporting biases in a table along with a brief justification for each judgment. We will display studies with missing results in forest plots as proposed in the ROB-ME guidance.

If we are able to pool more than 10 studies, we will create and examine a funnel plot to explore possible small study biases for the primary outcomes. We will also use Egger’s test for funnel plot asymmetry provided we can include 10 or more studies in the meta-analysis and studies are not similar in size (Egger 1997).

Data synthesis

We will assess heterogeneity by comparing participants, interventions, and outcomes between the included studies. In the case of considerable methodological and clinical heterogeneity, we will not pool the data but will describe them separately and report the clinical diversity of the studies.

If the treatments, participants, and the underlying clinical question are similar enough for a meta-analysis to be considered meaningful, we will undertake meta-analyses. Since we expect that there will be heterogeneity between studies, we will use the
random-effects model for pooling studies, regardless of the degree of statistical heterogeneity. We will use the Hartung-Knapp-Sidik-Jonkman method for estimating the between-study variance, as it results in more adequate type I error rates than the often-used DerSimonian and Laird approach, especially in situations when the number of studies is small (IntHout 2014; Langan 2018), which we expect to be the case. In the case of dichotomous outcomes where a high proportion of the studies in the meta-analysis observe no events in one or more study arms, we will consider other methods (Deeks 2021; Erhaimou 2018). When event rates are below 1%, the groups are balanced, and the effects are small, we will thus employ Peto’s method; if these conditions are not met, we will employ the Mantel-Haenszel odds ratio method without continuity correction. We will conduct sensitivity analyses employing a range of alternative models to assess the robustness of the results, using Peto’s method, the Mantel-Haenszel odds ratio with and without continuity correction, inverse-variance odds ratio with continuity correction, and arcsine difference (Rucker 2009).

We will furthermore calculate the prediction interval to provide a better appreciation of the uncertainty around the effect estimate (Borenstein 2017), which may be particularly relevant when between-study heterogeneity is high (IntHout 2014). As prediction intervals are strongly based on the assumption of a normal distribution for the effects across studies, and can therefore be problematic when the number of studies is small, we will only calculate them provided there are 10 or more studies and no clear funnel plot asymmetry.

We will include all eligible studies regardless of their risk of bias for the primary analysis. We will explore the influence of including studies judged as having a high risk of bias or as some concerns in sensitivity analyses.

We will perform all analyses using the freely available software R (R Core Team 2019).

Main comparison
We will make the following main comparisons.

- ECT versus sham-ECT
- ECT versus pharmacological treatment
- ECT versus non-pharmacological treatment
- ECT versus no treatment

Subgroup analysis and investigation of heterogeneity
We plan to carry out the following subgroup analyses for any outcomes with substantial heterogeneity.

- Psychotic features of the index acute depressive episode. Observational evidence indicates that ECT may be more effective in patients with acute depressive episodes with psychotic features compared with patients without psychotic features (Heijnen 2019; Kellner 2020; Van Diermen 2018); the effect of ECT for the prevention of relapse or recurrence may therefore differ depending on the presence of psychotic features during the index depressive episode. We will categorise studies according to whether they included some, only or no participants with an index acute depressive episode with psychotic features.

- Age of participants. Observational evidence indicates the ECT may be more effective in elderly patients with acute depressive episodes, compared with younger patients (Kellner 2020; Van Diermen 2018). Due to differences in brain development between children and adolescents, and adults, the effects of ECT, including adverse effects, may be different for children and adolescents compared with adult and elderly patients. We will categorise the studies according to whether the mean age of the participants was below 18 years, older than 18 years and below 65 years, and 65 years and older.

- Method of ECT delivery. Modified, compared with unmodified ECT, may be associated with increased risk of adverse events such as broken teeth, joint dislocation and bone fracture (Andrade 2012). Also, using an anaesthetic as is the case with modified ECT may moderate the effect of the treatment, although the effect of the specific anaesthetic regimen is uncertain (Lihu 2014). We will categorise the studies according to whether they used modified or unmodified ECT.

- Electrode placement and pulse width. Observational evidence indicates that electrode placement and pulse width moderate the effect of ECT and the risk of adverse events (Lisanby 2007). We will categorise studies according to the stimulation method (e.g. brief-pulse bilateral, ultrabrief-pulse right unilateral).

- Treatment schedule. Observational evidence indicates that the effect of ECT and cognitive adverse effects are moderated by the frequency with which the treatment is administered (Gangadhar 2010). We will assess the impact of the mean number of administrations of ECT per month in meta-regression.

Any additional analysis will be reported post hoc. We will compare subgroups using a formal statistical test for subgroup differences. We will undertake subgroup analysis provided 10 or more studies are available for each characteristic modelled and covariates are reasonably evenly distributed across studies. Given the risk of type I errors due to multiple testing issues, we will interpret findings from subgroup analysis conservatively.

Sensitivity analysis
We plan to carry out the following sensitivity analyses to test whether key methodological factors or decisions have affected the main result.

- Imputation of missing data using any method. We will analyse the impact of imputing data as described in Dealing with missing data.

- Diagnostic criteria for index acute depressive episode. We will remove studies that used non-operationalised criteria to diagnose participants with depression.

- Criteria for establishing the presence of remission. We will remove studies that used cut-offs on symptom-severity scales or a period of less than three weeks in which diagnostic criteria for depression was not fulfilled, for establishing the presence of remission.

- Statistical methods for summarising rare dichotomous outcomes. We will perform meta-analysis using different methods for pooling studies when assessing rare outcomes as described in Data synthesis.

- The influence of imputing SDs. We will remove studies for which we have imputed missing SDs based on the SD of similar studies.
Cochrane Database of Systematic Reviews

- Risk of bias. We will remove studies for which we have judged the overall risk of bias as some concerns or high risk.
- Enriched design. We will remove studies that used an enriched design.

**Reaching conclusions**

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice, and our implications for research will suggest priorities for future research and outline the remaining uncertainties in the area.

**Summary of findings and assessment of the certainty of the evidence**

We will create a summary of findings table using the following outcomes.

- Relapse or recurrence
- Serious adverse events
- Self-harm and suicide-related events
- Global functioning
- Retrograde amnesia
- Number of participants with at least one adverse event

We will prioritise the presentation of outcomes assessed at six months or longer. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes. We will use the methods and recommendations described in Chapter 14 of the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann 2021), employing GRADEpro GDT software. We will use the ROB-ME assessment to inform the assessment of publication bias, downgrading one level for all syntheses rated as ‘some concerns’ or ‘high risk of bias’. We will use overall risk of bias to inform GRADE. We will create a separate summary of findings table for each comparison (ECT versus sham-ECT; ECT versus pharmacological treatment; ECT versus non-pharmacological treatment; ECT versus no treatment). We will justify all decisions to downgrade the certainty of the evidence using footnotes and make comments to aid the reader’s understanding of the review where necessary.

Two review authors (KM and ASP-M) will independently make judgements about the certainty of the evidence, with any disagreements resolved by discussion or by involving a third review author (KJJ). We will justify and document our Judgements, and incorporate them into the reporting of results for each outcome.

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- Sign-off Editor (final editorial decision): Nick Meader, CCMD, Centre for Reviews and Dissemination, University of York
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Jessica Hendon, CCMD, Centre for Reviews and Dissemination, University of York
- Information Specialist (search strategy guidance, provided editorial guidance to authors, edited the article): Sarah Dawson, CCMD and University of Bristol
- Peer-reviewers (provided comments and recommended an editorial decision): Theodoros A. Filippou, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece (consumer review); Lindsay Robertson, CCMD, Centre for Reviews and Dissemination, University of York (methods review).
- An additional peer reviewer provided clinical and content peer review, but chose not to be publicly acknowledged.
- Copy Editor (copy-editing and production): Denise Mitchell

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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, National Health Service (NHS), or the Department of Health and Social Care.
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GWA 2018
Electroconvulsive therapy for preventing relapse and recurrence in people with depression (Protocol)

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McElhiney 1995

McElhiney 2001

McIntyre 2014

MedDRA

Michael 2009

Microsoft Excel 2019 [Computer program]

Mueller 1999

NHS 2015

NICE 2009

Page 2020

Page 2021

Petrides 2011

RANZCP 2015

RANZCP 2018

R Core Team 2019 [Computer program]

RCPsych 2019

Regier 2013

RoB 2 Microsoft Excel tool 2019

**Rush 2006**

**Sackeim 2001**

**Sackeim 2007**

**Sackeim 2008**

**Sackeim 2014**

**Schünemann 2021**

**Schünemann 2021a**

**Semkovska 2012**

**Semkovska 2014**

**Sheehan 1996**

**Sheehan 2017**

**Spitzer 1999**

**Sterne 2019**

**Summerfield 2008**

**Tew 2007**

**Tor 2015**

**UN 2013**

**UN 2018**

**Van Beusekom 2007**

**Van Diermen 2018**

**Wachtel 2011**


**Weissman 1976**


**WFSBP 2013**


**WFSBP 2017**


**WHO 1978**


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**APPENDICES**

**Appendix 1. Preliminary MEDLINE (Ovid) search strategy**

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 onwards> search strategy:

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1 Electroconvulsive Therapy/
2 (ECT or ((electroconvuls* or electr* convuls*) adj2 (intervention? or treatment? or therap*))) or ((electroshock* or electr* shock*) adj2 (intervention? or treatment? or therap*)).mp.
3 (1 or 2)
4 Depression/
5 exp Depressive Disorder/
6 (depression? or depressive? or depressed or MDD or TRD or affective disorder* or affective symptom? or mental).mp.
7 (4 or 5 or 6)
8 (3 and 7)
9 randomized controlled trial.pt.
10 controlled clinical trial.pt.
11 single-blind method or /double-blind method/ or random allocation/
12 (randomized or randomised or random ly).mp.
13 (RCT or “at random” or (random* adj3 (administ* or allocat* or assign* or class* or cluster or crossover or cross-over or control* or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or substitut* or treat*))).ti,ab,kf.
14 (placebo or sham or simulat*).mp.
15 trial.ti,ab,kf.
16 (control* adj3 group*).ab.
17 (control* and (trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,kf,hw.

Electroconvulsive therapy for preventing relapse and recurrence in people with depression (Protocol)

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**WHO 1992**


**WHO 2005**


**WHO 2018**


**WHO 2020**


**Zimmerman 2006**


**Zimmerman 2012**

18 ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,kf.
19 or/9-18
20 exp animals/ not humans.sh.
21 (19 not 20)
22 (8 and 21) (1289 records retrieved as of 18 Sept 2020)

CONTRIBUTIONS OF AUTHORS

Klaus Munkholm: conceptualisation, methodology, writing; original draft, writing; review and editing, supervision
Karsten Juhl Jørgensen: methodology, writing; review and editing
Asger Sand Paludan-Müller: methodology, writing; review and editing

DECLARATIONS OF INTEREST

Klaus Munkholm: no conflicts of interest
Karsten Juhl Jørgensen: no conflicts of interest
Asger Sand Paludan-Müller: no conflicts of interest

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