Electroconvulsive therapy for acute affective episodes in people with bipolar disorder

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[Intervention Protocol]

Electroconvulsive therapy for acute affective episodes in people with bipolar disorder

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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 electroconvulsive therapy for an acute affective episode (hypomania, mania, mixed state or depression) in children, adolescents, adults and older people with bipolar disorder.

BACKGROUND

Description of the condition

The definition of the clinical diagnosis of bipolar disorder differs between the main classificatory diagnostic systems, the International Classification of Diseases (ICD) (WHO 1992) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) (APA 2013)). The tenth revision of the ICD (ICD-10) (WHO 1992) defines bipolar disorder as a condition characterised by the occurrence of two or more episodes of depression and either hypomania or mania that are sufficiently severe to cause a change in functioning. Patients with two or more episodes of hypomania or mania, but not depression, are also classified as having bipolar disorder; while patients with recurring depression, but no hypomanic or manic episodes, are not classified as having bipolar disorder. The fifth edition of the DSM (DSM-5) (APA 2013) distinguishes between two types of bipolar disorder: bipolar I disorder, defined by the occurrence of at least one manic episode, but not necessarily any depressive episodes; and bipolar II disorder, defined by the occurrence of at least one hypomanic episode and at least one major depressive episode, in the absence of prior manic episodes.

Depending on the diagnostic system, a depressive episode is characterised by a period of almost daily depressed mood, reduced energy or fatigue, or loss of interest or pleasure in activities, accompanied by other symptoms such as difficulty concentrating, feelings of worthlessness, 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 diagnostic system, a manic or hypomanic episode is characterised by a period of symptoms of abnormally and persistently elevated, expansive or irritable mood and abnormally and persistently increased goal-directed activity or energy, accompanied by other symptoms such as inflated self esteem, decreased need for sleep, pressure to keep talking, flight of ideas or racing thoughts and distractibility; with such symptoms occurring daily, for most of the day (APA 2013; WHO 1992). Manic episodes, in contrast to hypomanic episodes, are characterised by disturbances that are sufficiently severe to cause marked impairment in functioning (APA 2013; WHO 1992). According to ICD-10, a diagnosis of a manic or hypomanic single episode is given to patients fulfilling criteria for a manic or hypomanic episode, respectively, but who do not fulfil criteria for bipolar disorder. ICD-10 additionally specifies a diagnosis of a mixed state characterised by concurring or rapidly shifting manic and depressive symptoms in patients who have previously had at least one other affective episode (hypomania, mania, depression or mixed state) (WHO 1992); in DSM-5, the presence of mixed symptoms is instead acknowledged by assigning a mixed feature specifier to a diagnosis of hypomania, mania or depression (APA 2013). The diagnostic criteria for mixed states thus differ between diagnostic systems, have undergone changes in both diagnostic systems over time, and are surrounded by some controversy (Malhi 2017; Parker 2019).

Depending on the number of criterion symptoms present, their severity and the degree of functional impairment, the severity of the manic, hypomanic and depressive episode can be characterised as mild, moderate or severe (APA 2013; WHO 1992). The presence of specific clinical features, e.g. mixed or psychotic (APA 2013; WHO 1992), as well as anxious, rapid cycling, melancholic, atypical, catatonic or seasonal (APA 2013; WHO 1992), may additionally define the character of the episode.

There is no known pathophysiology underlying bipolar disorder and no objective test to verify the clinical diagnosis of affective episodes or of bipolar disorder.

The lifetime prevalence of bipolar disorder varies among regions and countries. Among eleven middle- to high-income countries, prevalence is estimated at a mean of 0.6% for bipolar I disorder and 0.4% for bipolar II disorder (Merikangas 2011). Bipolar I prevalences range from just above 0% in countries such as Bulgaria and India to 1% in countries such as Mexico and the US (Merikangas 2011). The prevalence of bipolar I and II disorder among older adults specifically, is estimtated to be between 0.5% and 1% (Sajatovic 2015). The prevalence of bipolar I disorder in prepubertal children and adolescents has been estimated at a mean of 0.6% across nine middle to high-income countries, with prevalences ranging from 0% in countries such as Brazil, Ireland and Turkey, to 2% in Mexico and Canada (Van Meter 2019). However, the diagnosis of bipolar disorder and its prevalence in prepubertal children and adolescents has been controversial (Malhi 2020; Parry 2017; Parry 2019; Van Meter 2019a). The prevalence of bipolar disorder appears to be roughly similar between males and females (Diflorio 2010). The World Health Organization (WHO) estimates that 45 million people suffer from bipolar disorder worldwide (WHO 2019). However, as these estimates are based on diagnostic systems with likely low validity in many parts of the world, they should be interpreted with caution (Summerfield 2008).

A study that surveyed patients with bipolar disorder over a period of up to 20 years using retrospective assessments of the occurrence of affective symptoms in each week, found that the patients had some affective symptoms approximately half of the weeks (Judd 2003). Patients with bipolar I disorder appeared to meet criteria for major depression approximately 9% of the weeks, more than three times the frequency of weeks where criteria for a manic episode were met. Patients with bipolar II disorder appeared to meet criteria for major depression approximately 13% of the weeks (Judd 2003).

Many patients with bipolar depression do not recover with initial or secondary pharmacological treatment (Parikh 2010). In situations where the patients' condition is not sufficiently alleviated by available pharmacological or psychological treatments or where patients develop a more severe acute affective episode, electroconvulsive therapy (ECT) is considered a treatment option (APA 2003; Goodwin 2016; Yatham 2018).

Description of the intervention

Electroconvulsive therapy (ECT) involves the application of electricity to the scalp in order to induce a generalised tonic-clonic seizure. ECT for the treatment of depression is usually delivered two to three times per week (Kellner 2012) in a series of six to 12 treatments in total (Lisanby 2007). ECT for acute delirious mania may be delivered daily (Baghai 2008). It is considered best practice to administer ECT under anesthesia together with muscle relaxant medication, as what is termed 'modified' ECT (Enns 2010; RCPSYCH 2019; Weiss 2019). These methods that were introduced to reduce treatment complications such as pain, panic and fractures (APA 1978). However, 'unmodified' ECT, administered without anesthesia, is still being practised around the world, including in 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 some circumstances, i.e. where anesthesia is unavailable and ECT is deemed necessary (Andrade 2012). Different regimens of intravenous sedatives or hypnotics may be used; the evidence is uncertain as to whether different types of anaesthetic agents have an effect on the efficacy of ECT for depression (Lihua 2014) or mania (Kadiyala 2017). ECT for use in catatonia and severe bipolar depression in patients aged 13 years and older, who are considered treatment-resistant 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) in 2018 from a class III ('high risk') device to a class II ('moderate risk') device (FDA 2018); ECT for the treatment of mania is classified as class III.

ECT is traditionally administered with a 'brief' pulse width, defined as pulses of 0.5 to 2.0 milliseconds in duration (Enns 2010; RCPSYCH 2019; Weiss 2019). Brief-pulse wave ECT has been associated with fewer cognitive adverse effects, compared with sine wave ECT (Sackeim 2007) and is the recommended stimulus method by current guidelines (APA 2001; Enns 2010; RCPSYCH 2019; Weiss 2019). The sine-wave stimulus employed by the earliest ECT devices delivered an electrical charge in excess to the amount needed to efficiently elicit a seizure leading to more cognitive adverse effects (Enns 2010); sine wave ECT is, however, still 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). However, it has been suggested to have a smaller effect, depending on the electrode placement (Brus 2017; Tor 2015).

Common electrode placements include bitemporal, right unilateral and bifrontal (Lisanby 2007). Generally, bitemporal ECT is considered to involve the highest risk of retrograde amnesia and is by one guideline (Weiss 2019) recommended not to be used as the initial form of ECT treatment given, unless there are specific reasons to do so. Another guideline, however, states that bitemporal ECT should be preferred for acute mania (Enns 2010).

The choice of stimulus current dose depends in clinical practice on both electrode placement and pulse-width (Enns 2010; Weiss 2019). Generally, higher doses relative to the seizure threshold may be needed when reducing the pulse width, to achieve a similar effect (Loo 2008). Depending on the pulse-width, the recommended dose level is approximately 1.5 times the seizure threshold for bitemporal and bifrontal ECT and approximately six times the seizure threshold for right unilateral ECT (Enns 2010; Weiss 2019).

The choice of the particular treatment approach is recommended to be informed by the balancing of the need for speed of response, the urgency of the clinical situation, the patient's previous response and concern regarding potential cognitive side-effects (Weiss 2019). All electrode placements and stimulus forms, however, appear to be associated with cognitive adverse effects, including a risk of retrograde amnesia (Sackeim 2008; Sackeim 2014).

The use of ECT varies by country and region, with an estimated total of 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 (Ghaziuddin 2004), but data regarding the use in children and adolescents is scarce.

Given its controversial nature, special legal restrictions are, in some countries, imposed on the administration of ECT (Leiknes 2012). The administration of ECT under involuntary conditions occurs worldwide but the extent varies among 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 recognize such ECT practices as constituting torture or other cruel, inhuman or degrading treatment (UN 2018). Several US states have by law prohibited the use of ECT in children and adolescents (Livingston 2018) and in Australia, the state of Western Australia has prohibited the use of ECT in children under age 14 years (GWA 2018). The 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).

Multiple clinical guidelines recommend that ECT should be considered for the treatment of bipolar depression (APA 2003; Fountoulakis 2017; Goodwin 2016; Grunze 2010; Malhi 2015; Yatham 2018), particularly for treatment-refractory patients (APA 2003; Goodwin 2016; Yatham 2018) and patients for whom a rapid response is needed, such as those with severe depression with acute suicidal risk (APA 2003; Goodwin 2016; Yatham 2018), as well as catatonic (APA 2003; Yatham 2018) or psychotic features (APA 2003; Goodwin 2016; Grunze 2010; Malhi 2015; Yatham 2018). Guidelines also recommend to consider ECT for the treatment of acute manic episodes (APA 2003; Fountoulakis 2017; Goodwin 2016; Grunze 2009; Malhi 2015; NICE 2014; Yatham 2018), especially in treatment-refractory cases (APA 2003; Goodwin 2016; Grunze 2009; Malhi 2015; NICE 2014), cases where the condition is considered potentially life-threatening in patients with catatonic features (Malhi 2015; NICE 2014), or in cases with a prolonged or severe episode (NICE 2014). Guidelines also recommend (APA 2003; Grunze 2018; Malhi 2015) to consider ECT for the treatment of refractory mixed episodes.

Several guidelines specifically recommend that ECT should be considered for the treatment of acute affective episodes of bipolar disorder during pregnancy (APA 2003; Fountoulakis 2017; Goodwin 2016; Grunze 2009).

In children and adolescents, guidelines recommend that ECT should be considered for the treatment of depressive episodes (Birmaher 2007; Gautam 2019) and manic episodes (Birmaher 2007) that do not respond to medication therapies. The American Psychiatric Association supports the use of ECT in children and adolescents (APA 2016).

There are known harms of ECT treatment (Andrade 2016), including nausea, headache, muscle pain, prolonged seizures, status epilepticus, and cardiac events such as asystole and myocardial infarction (Andrade 2016; Enns 2010). In addition to these harms, unmodified ECT is associated with a risk of loosened or broken teeth, joint dislocation, bone fracture, spinal fracture, and muscle or ligament injuries (Andrade 2012). Cognitive impairment is recognised as a prominent adverse effect of ECT (APA 1978), commonly including confusion states following the seizure and anterograde amnesia (loss of the ability to create new memories). ECT is also associated with retrograde amnesia, the loss of memory for events that occurred or information that was learned in the past, including impairment of autobiographical memory,

the personal representation of one's past (APA 2010; Enns 2010; Weiss 2019); this amnesia may be persistent (APA 2001; Sackeim 2007). Amnesia for autobiographical information is thus considered the most critical adverse cognitive effect of ECT (Sackeim 2014). Its intensity seemingly depends on the electrode placement and the pulse width (Fraser 2008). The clinical methods used to assess retrograde amnesia, however, have been a subject of discussion (Sackeim 2014; Semkovska 2014).

How the intervention might work

Although there are many theories on the mechanism of action of ECT across the conditions for which it is used, it is unknown (Michael 2009). Among 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 and neurotrophic effects induced by seizure activity in the limbic system (Bolwig 2011).

Why it is important to do this review

Existing systematic reviews of ECT for bipolar disorder have considered only acute depressive episodes in adults, not manic or mixed episodes, and compared ECT with only sham ECT (i.e. a procedure similar to ECT, involving anesthesia with or without muscle relaxant, but without delivery of electricity); or repetitive transcranial magnetic stimulation (rTMS) (Chen 2017; Mutz 2018; Mutz 2019; Ren 2014) and not other treatment modalities such as antidepressants. rTMS involves the induction of electrical currents using focused magnetic field pulses via a coil placed against the scalp, which can be administered without the requirement of anesthesia (Hallett 2007), and is also a recommended treatment option for patients with bipolar depression, whose condition is not sufficiently helped by initial treatment (Yatham 2018). Only one systematic review of ECT in patients with bipolar disorder used GRADE to assess the certainty of the evidence, and this was only in the context of rTMS with ECT as the comparator; the certainty was assessed as moderate (Ren 2014). There is no Cochrane Review of ECT for acute affective episodes in patients with bipolar disorder.

Beyond guidelines and systematic reviews, many clinicians and ECT experts consider ECT to be a very effective treatment for both bipolar depression (Kellner 2015; Kellner 2020), mania (Kellner 2015; Kellner 2020; Sackeim 2017) and mixed states (Kellner 2015), often citing remission rates in observational studies (Jensen 2018; Sackeim 2017). Large placebo responses, however, have been observed in sham-controlled ECT studies (Rasmussen 2009), and for this and other reasons, there is the risk that observational studies may overestimate the benefits of ECT.

Some aspects of the current practice of ECT, whilst varying considerably among countries and regions, are not in alignment with international guidelines. Thus, despite recommendations to use unilateral ECT by several international guidelines, evidence shows it is still common practice to use bilateral ECT (Bjornshauge 2019; Leiknes 2012). Similarly, although discouraged by the WHO and major international guidelines, there is continued use of unmodified ECT in some countries (Leiknes 2012).

Given the limitations of existing systematic reviews, a comprehensive synthesis is needed of the evidence of the benefits and harms of ECT for acute affective episodes (hypomania, mania, depression or mixed state) in children and adults with bipolar disorder, with a careful assessment of the certainty of the evidence.

OBJECTIVES

To assess the benefits and harms of electroconvulsive therapy for an acute affective episode (hypomania, mania, mixed state or depression) in children, adolescents, adults and older people with bipolar disorder.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized trials, including cross-over trials and cluster-randomised trials. For cross-over trials, only the results from the first randomized period will be included, as affective symptoms may be fluctuating and as carry-over effects of ECT are likely.

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

Types of participants

Participant characteristics

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

Diagnosis

We will include participants diagnosed with bipolar disorder in an acute affective episode (hypomania, mania, mixed state or depression), using standardized diagnostic criteria, including the Feighner criteria (Feighner 1972) the ICD-10 (WHO 1992) and the ICD's 11th revision (ICD-11) (WHO 2018), as well as DSM criteria from its third edition (DSM-III) (APA 1980), fourth edition (DSM-IV) (APA 1994) and DSM-5 (APA 2013). We will also include studies using the ICD's ninth revision (ICD-9) (WHO 1978), but as this revision did not employ specific diagnostic criteria, we will make individual judgements for each study, as to whether the description of the inclusion criteria is similar to later standardized criteria. We will similarly consider studies using earlier versions of the ICD and the DSM, exploring the influence of including such studies in sensitivity analyses. We will not include studies that establish the diagnosis by using cut-offs on a symptom severity scale; 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).

We will include participants with bipolar I or bipolar II disorder as well as participants with a diagnosis of a single manic episode.

We will include participants with any subtype of acute affective episode (e.g. chronic, with catatonic features, with melancholic features, with atypical features, and with seasonal pattern).

We will categorise participants as being in depressive, hypomanic, manic or mixed states. We will categorise participants as being in a mixed state if they are described or diagnosed as in a depressive, manic or hypomanic state with mixed features, or if they are described or diagnosed as being in a mixed state.

Comorbidities

Trials involving participants with a comorbid psychiatric or physical disorder are eligible for inclusion.

Setting

We will include studies conducted in all settings.

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

Types of interventions

Experimental intervention

ECT, meaning the application of electricity to the scalp in order to induce a generalised tonic-clonic seizure.

We will consider both modified ECT (i.e. ECT applied under general anesthesia and with administration of a muscle relaxant drug) and unmodified ECT (i.e. ECT applied without anesthesia). For modified ECT, we will include studies using 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 milicoulombs of charge, or the dose corresponding to the seizure threshold).

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

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);
- pharmacological treatment, including, but not limited to, antidepressants, antipsychotics, anticonvulsants and lithium;
- non-pharmacological treatment, including, but not limited to, interventions such psychotherapy, social interventions and other types of brain stimulation (e.g. rTMS) ; and
- no intervention.

Co-interventions

We will include studies regardless of whether ECT was administered as monotherapy, or in combination with a non-pharmaceutical or pharmaceutical intervention or as augmentation to another non-pharmaceutical or pharmaceutical intervention.

Types of outcome measures

Primary outcomes

Efficacy

- **Depressive episodes:** depression symptom scores at the time of assessment (or if these are not available, the change scores from baseline) on a standardized observer-based rating scale (e.g. the Hamilton Depression Rating Scale (HAMD) (Hamilton 1967) (any version), the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery 1979), the Bipolar Depression Rating Scale (BDRS) (Berk 2007) or other). Although several depression severity rating scales have important limitations, including a lack of unidimensionality and longitudinal invariance (Bagby 2004; Chang 2009; Fried 2016) they are considered the gold standard in assessing the severity of depression. We will include scales regardless of these limitations and discuss the results in the context of the limitations.
- **Manic or hypomanic episodes:** mania symptom scores at the time of assessment (or if these are not available, the change scores from baseline) on a standardized observer-based rating scale (e.g. the Young Mania Rating Scale (YMRS) (Young 1978), the Bech-Rafaelsen Mania Scale (MAS) (Bech 2002) or other. As there are psychometric limitations of mania symptom rating scales (Licht 1997; Prisciandaro 2016), we will discuss the results in the context of these limitations.
- **Mixed episodes:** depression symptom scores at the time of assessment (or if these are not available, the change scores from baseline) on a standardized observer-based rating scale (e.g. depression or mania symptom scales as above or the Cavanagh Scale (Cavanagh 2009)). We will include assess both depressive, manic and mixed symptom scores and report these separately. As above, we will discuss the results in the context of the limitations of the scales used.

Harms

- Serious adverse events, defined as the number of participants with at least one medical events that is life-threatening, results in death, disability or significant loss of function, causes hospital admission or prolonged hospitalisation (EMA 2002).

Secondary outcomes

- Remission, adapted from the definition concerning depression by Rush and colleagues (Rush 2006), measured as the total number of participants who achieved remission, defined as the absence of depression, hypomania, mania or mixed state, respectively, according to diagnostic criteria for three consecutive weeks, during which each week the patient does not meet diagnostic criteria for any such affective states. We will also consider patient reported remission, meaning the absence of any affective state for three consecutive weeks, during which each week the participant does not consider him- or herself in an affective state. We will explore the effect of including different studies with different definitions of remission in sensitivity analysis. We will not consider definitions of remission based on cut-offs on symptom severity scales, as these have been shown to have poor correlation with patients' experience of being free from depression (Zimmerman 2006) and potentially also from other affective states. We will explore the influence of including studies in which remission was assessed by observers, not participants, in sensitivity analysis.
- Patient reported outcome measures of depression symptom burden (e.g. Becks Depression Inventory (BDI) (Beck 1961), Major Depression Inventory (MDI) (Bech 2001), SCL-10 (Bech 2018) and WHO-5 (Bech 2018) or mania symptom burden (e.g. the Altman Self-Rating Mania Scale (ASRM) (Altman 1997)).
- Global functioning assessed using the Sheehan Disability Scale (SDS) (Sheehan 1996), the Social Adjustment Scale – Self-report (SAS-SR) (Weissman 1976) or the Q-LES-Q (Endicott 1993),

which are among 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 the scales but present them separately.

- 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).
- 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 (e,g. nausea, headache, muscle pain or prolonged seizures). We will categorise adverse events at the System Organ Class and Preferred Term level per the Medical Dictionary for Regulatory Activities terminology (MedDRA).

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

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 eight weeks) and long-term (longer than eight weeks).

As guidelines commonly recommend that treatment consists of six to 12 ECT treatments that are generally administered two to three times per week (Lisanby 2007; Weiss 2019), we will consider the time period of one to eight weeks for our primary analysis. Where a study reports more than one time point within one of the prespecified time periods, we will select the latest time point. We will also extract outcomes measured post-treatment (i.e. after the end of the treatment period) and categorise these outcomes as short-term (up to six months post-treatment), medium-term (six to 12 months post-treatment) and long-term (longer than 12 months post-treatment) as knowledge about benefits and harms beyond the treatment period are likely to be important to patients. We recognise that such outcomes can be biased due to differences arising between groups in the treatment and care received after the treatment period and will discuss the results accordingly.

Hierarchy of outcome measures

If studies report multiple measures of an eligible outcome, we will include the data based on several considerations. 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 HAMD) 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. baseline measures of an outcome), if appropriately conducted, and use the effect estimates directly.

Search methods for identification of studies

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) (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).

Additionally, we will search regulatory data from the US Food and Drug Administration (FDA) (www.fda.gov).

We will not perform a separate search for adverse effects of ECT used for the treatment of acute affective episodes in bipolar disorder. 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 in which we will include evidence across all potential indications.

Searching other resources

We will check reference lists of all included studies, relevant books and any relevant systematic reviews identified for additional references to trials. 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 to obtain any data or information needed in order to assess eligibility, calculate effect sizes, assess unreported outcomes and perform 'Risk of bias' assessments.

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 we identify as a result of the search for eligibility and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there are any disagreements, we will seek to resolve the issue through discussion or, if necessary, a third review author (KJJ) will be asked to arbitrate. We will retrieve the full-text study reports of potentially eligible studies; two review authors (KM and ASP-M) will independently screen the full-text reports and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required,

by consulting a third review author (KJJ). 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 (Liberati 2009) and a 'Characteristics of excluded studies' table.

Data extraction and management

We will use an electronic data collection form for study characteristics and outcome data piloted on at least one study included in the review. Two review authors (KM and ASP-M) will independently extract data from the included studies. We will resolve 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, number of study centres and location, study setting, and date of study start and completion.
- Participants: N randomized, N lost to follow-up/withdrawn with reasons, N analyzed for each outcome, mean age, age range, sex, mean severity of depression and mania, mean duration of the current affective episode, mean number of previous affective episodes, diagnostic criteria, clinical specifiers (e.g. psychotic, catatonic or melancholic), N having previously received ECT, inclusion criteria, and exclusion criteria.
- 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 (N times per week), N total ECT delivered, whether rescue medication 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 (pre-specified) or spontaneously reported.
- Notes: funding for the trial, and notable 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 is 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 version 2 of the Cochrane 'Risk of bias' tool (RoB 2) (Sterne 2019), outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a). We plan to use the RoB 2 Microsoft Excel tool to manage the 'Risk of bias' assessment (RoB 2 Microsoft Excel tool 2019). We will resolve any disagreements by discussion or by involving a third author (KJJ). We will assess the risk of bias of a specific results of randomized trials according to the following domains:

- bias arising from the randomization process;
- bias due to deviations from intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome; and
- 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 Chapter 8 of the *Cochrane Handbook* (Higgins 2019a).

We will assess the risk of bias for the outcomes of the included trials presented in the 'Summary of findings' table. For the purpose 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 the RoB 2 tool 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 trial for the result is the least favourable assessment across the domains of bias; however, where a trial is judged to have some concerns for multiple domains we will judge the overall risk of bias as high following the approach outlined in Table 8.2.b of the *Cochrane Handbook* (Higgins 2019a).

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

Measures of treatment effect

We will analyze dichotomous data as odds ratios (OR) with 95% confidence intervals (CIs) and continuous data as mean difference (MD), and as a standardized mean difference (SMD) with 95% CIs when outcomes are measured on different scales. We will enter data presented as a scale with a consistent direction of effect. 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 Chapter 6 of the *Cochrane Handbook* (Higgins 2019b). We will not pool data using endpoint scores and baseline-to-endpoint change scores when calculating SMDs for reasons outlined in Chapter 10 of the *Cochrane Handbook* (Deeks 2019). Results calculated as SMD will be presented 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.

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

Unit of analysis issues

Cross-over trials

For cross-over studies, we will only consider results for the calculation of summary statistics when we can extract data for the first randomized period.

Cluster-randomised trials

For cluster-randomised trials, we will analyze results using the generic inverse-variance approach and the effect estimates and standard errors reported in the study, 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 analyze results using the generic inverse-variance method (Higgins 2019c).

Studies with multiple treatment groups

For studies with multiple arms, we will combine the treatment arms using the methods outlined in Chapter 6 of the *Cochrane Handbook* (Higgins 2019b) 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 among intervention groups for dichotomous variables.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data when relevant (e.g. when a study is identified as abstract only) and document details regarding the correspondence. Where possible, we will calculate missing SDs using other data from the trial, such as CIs, based on methods outlined in Chapter 6 of the *Cochrane Handbook* (Higgins 2019b). 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 is available, but who were excluded from the analyses because of protocol non-adherence, we will try obtain the data from the original trial report or by directly contacting trial investigators. Where data cannot 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 randomized. We will consider the exclusion of ineligible participants who are mistakenly randomized to be appropriate only if information about ineligibility was available at randomization 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 (Higgins 2008) to assess the potential impact of missing data on the results. We will conduct an available-case analysis (ACA) as a reference. For our primary analysis, we will conduct an imputed case analysis (ICA), in which we will impute missing data according to reasons for missingness (ICA-r). 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 take the uncertainty of the imputed data into account when calculating standard errors, so that these are not inappropriately reduced, and weight the studies accordingly, using the methods outlined in 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. First, we will 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, among 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 (Ebrahim 2013) to assess the potential impact of missing data on the results. The method involves conducting an initial ACA 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 allows for 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. In these analyses, we will assume 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 trials, respectively, and the mean score of the control arm of the same trial). We will then use these data in four progressively more stringent imputation strategies (Ebrahim 2013). For trials in which authors do not report missing participant data rates, we will use the median missing participant data rate from the remaining trials and perform a sensitivity analysis, using a missing participant data rate of zero in both arms. If only the total missing participant data is reported, we will assume that missing data was equally distributed in both arms. If the individual trial 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 trial's ACA. When different measures were used across trials 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 assess heterogeneity by comparing characteristics of 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 narratively.

We will use the I^2 statistic to quantify heterogeneity among the trials in each analysis. We will also consider the P value from the Chi^2 test. We will consider an I^2 estimate equal to or greater than 50% accompanied by a statistically significant Chi^2 test ($P < 0.1$) as indication of substantial heterogeneity (Deeks 2019). If we identify substantial heterogeneity we will report it and explore possible causes through our prespecified subgroup analysis.

Additionally, we will inspect forest plots visually to consider the direction and magnitude of effects and the degree of overlap among 95% CIs.

Assessment of reporting biases

We will attempt to retrieve the protocols of the included trials 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 (ROB-ME 2020). Disagreements will be resolved through discussion or, if necessary, by involving a third review author (KJJ)

Following the ROB-ME guidance, we will construct an outcome matrix and will 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 trials, 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

If the treatments, participants and the underlying clinical question are similar enough for it to be considered meaningful, we will undertake meta-analyses. Since we expect that there will be heterogeneity among 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); we expect this be will the case. For dichotomous outcomes where a high proportion of the studies in the meta-analysis report no events in one or more study arms, we will consider other methods (Deeks 2019; Efthimiou 2018). Where event rates are below 1%, the groups are balanced and the effects are small, we will employ Peto's method; if these conditions are not met, we will employ the Mantel-Haenszel odds ratio method without continuity correction (Deeks 2019). We will conduct sensitivity analyses using 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 also calculate the prediction interval to provide a better appreciation of the uncertainty around the effect estimate (Borenstein 2017), which may be particularly relevant when the 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 there are few studies, we will only calculate them where there are 10 or more studies and no clear funnel plot asymmetry.

For the primary analysis, we will include all eligible studies, regardless of their risk of bias. We will explore the influence of including studies judged as '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 for each affective state (depression, hypomania, mania and mixed state).

- 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.

- Depression with psychotic features. Observational evidence indicates that ECT may be more effective in patients with depression with psychotic features compared with patients without psychotic features (Heijnen 2019; Kellner 2020; van Diermen 2018). We will categorise studies, across all affective states, according to whether the inclusion criteria included participants with psychotic features, or did not.
- Age of participants. Observational evidence indicates the ECT may be more effective in elderly patients with depression, 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 in 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 delivery of ECT. Unmodified ECT, compared with modified ECT, may be associated with increased risk of adverse events, such as broken teeth, joint dislocation and bone fracture (Andrade 2012). In addition, 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 (Lihua 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, particularly cognitive adverse effects (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 week in meta-regression.

Any additional analysis will be reported as post-hoc. We will compare subgroups using a formal statistical test for subgroup differences. We will undertake subgroup analysis provided ten or more studies are available for each characteristic modelled and covariates distribution across studies is reasonably even. 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 affected the main result.

- Imputation of missing data using any method. We will analyze the impact of imputing data as described in Dealing with missing data.
- Diagnostic criteria. We will remove studies that used non-operationalised criteria to diagnose participants.
- Diagnostic criteria: We will remove studies that included participants with a diagnosis of single manic or hypomanic episode.
- 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 SDs of similar studies.
- Risk of bias. We will remove studies for which we have judged the overall risk of bias as 'some concerns' or 'high risk'.

Summary of findings and assessment of the certainty of the evidence

We will create 'Summary of findings' tables using the following outcomes.

- Rater-based symptom scores.
- Serious adverse events.
- Patient-reported measure of symptom severity.
- Global functioning.
- Self-harm and suicide-related events.
- Retrograde amnesia.
- The number of participants with at least one adverse event.

We will prioritise the presentation of outcomes assessed at one to eight weeks; outcomes assessed after eight weeks will not be presented in our 'Summary of findings' tables. 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 which contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in Chapter 14 of the *Cochrane Handbook* (Schünemann 2019), using GRADEpro software (GRADEpro GDT 2015). We will use the 'overall risk of bias' across studies to inform our GRADE judgements for each outcome. Each comparison (ECT versus sham ECT, ECT versus pharmacological treatment, ECT versus non-pharmacological treatment and ECT versus no treatment) will be displayed in a separate 'Summary of findings' table. We will justify all decisions to downgrade the certainty of the evidence using footnotes and where necessary, we will make comments to aid readers' understanding of the review.

Judgements about the certainty of the evidence will be made by two review authors (KM and ASP-M) working independently, with disagreements resolved by discussion or involving a third review author (KJJ). Judgements will be justified, documented and incorporated into reporting of results for each outcome.

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 what the remaining uncertainties are in the area.

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APPENDICES

Appendix 1. MEDLINE Search

Ovid MEDLINE(R) ALL <1946 to September 30, 2021>

1 Electroconvulsive Therapy/ 13539
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. 19339
3 (1 or 2) 19339
4 "bipolar and related disorders"/ or bipolar disorder/ 42434
5 Mania/ 144
6 ((bipolar adj5 (acute* or affective or disorder* or depress* or episode? or mixed)) or BD-NOS or BDNOS or mania* or manic* or hypomani*).ti,ab,kf. 51242
7 ((mixed adj (episode? or state?)) or rapid cycling).ti,ab,kf. 3285
8 or/4-7 63439
9 (3 and 8) 1893
10 randomized controlled trial.pt. 545248
11 controlled clinical trial.pt. 94436
12 double-blind method/ or random allocation/ or single-blind method/ 292903
13 (randomized or randomised or randomly).mp. 1179867
14 (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 subsitut* or treat*))).ti,ab,kf. 627515
15 (placebo or sham or simulat*).mp. 1042477
16 trial.ti,ab,kf. 672071
17 (control* adj3 group*).ab. 588335
18 (control* and (trial or study or group*) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,kf,hw. 28940
19 ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,kf. 184456
20 or/10-19 2813668
21 exp animals/ not humans.sh. 4892740
22 (20 not 21) 2429317
23 (9 and 22) 256

WHAT'S NEW

Date	Event	Description
20 October 2021	Amended	Corrected link to Appendix 1

HISTORY

Protocol first published: Issue 10, 2021

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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