BMJ Open

Comparative efficacy, cognitive effects and acceptability of electroconvulsive therapies for the treatment of depression: protocol for a systematic review and network meta-analysis

Stevan Nikolin ,[1,2] Kieran Owens,[1] Rohan Francis-Taylor,[1,2] Anna Chaimani,[3] Donel M Martin,[1,2] Michael Bull,[1,2] Harold A Sackeim,[4] Declan M McLoughlin,[5] Pascal Sienaert ,[6] Charles H Kellner,[7] Colleen Loo[1,2]

To cite: Nikolin S, Owens K, Francis-Taylor R, *et al*. Comparative efficacy, cognitive effects and acceptability of electroconvulsive therapies for the treatment of depression: protocol for a systematic review and network meta-analysis. *BMJ Open* 2022;**12**:e068313. doi:10.1136/bmjopen-2022-068313

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-068313).

Received 14 September 2022
Accepted 07 December 2022

For numbered affiliations see end of article.

Correspondence to
Dr Stevan Nikolin;
stevan.nikolin@unsw.edu.au

ABSTRACT

Introduction There have been important advances in the use of electroconvulsive therapy (ECT) to treat major depressive episodes. These include variations to the type of stimulus the brain regions stimulated, and the stimulus parameters (eg, stimulus duration/pulse width). Our aim is to investigate ECT types using a network meta-analysis (NMA) approach and report on comparative treatment efficacy, cognitive side effects and acceptability.

Method We will conduct a systematic review to identify randomised controlled trials that compared two or more ECT protocols to treat depression. This will be done using the following databases: Embase, MEDLINE PubMed, Web of Science, Scopus, PsycINFO, Cochrane CENTRAL and will be supplemented by personal contacts with researchers in the field. All authors will be contacted to provide missing information. Primary outcomes will be symptom severity on a validated continuous clinician-rated scale of depression, cognitive functioning measured using anterograde verbal recall, and acceptability calculated using all-cause drop-outs. Secondary outcomes will include response and remission rates, autobiographical memory following a course of ECT, and anterograde visuospatial recall.

Bayesian random effects hierarchical models will compare ECT types. Additional meta-regressions may be conducted to determine the impact of effect modifiers and patient-specific prognostic factors if sufficient data are available.

Discussion This NMA will facilitate clinician decision making and allow more sophisticated selection of ECT type according to the balance of efficacy, cognitive side effects and acceptability.

Ethics This systematic review and NMA does not require research ethics approval as it will use published aggregate data and will not collect nor disclose individually identifiable participant data.

PROSPERO registration number CRD42022357098.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This network meta-analysis (NMA) will synthesise evidence from randomised controlled trials of electroconvulsive therapy (ECT) reporting on efficacy, cognitive and acceptability outcomes.
⇒ The NMA will investigate the impact of ECT electrode placements (right unilateral, bifrontal and bitemporal), pulse width (ultrabrief and brief) and dosing protocols including those based on seizure titration, fixed doses and formula-based dosing.
⇒ The findings from this study will provide a comprehensive ranking of ECT interventions according to their comparative antidepressant efficacy and cognitive side effect profile to guide clinical treatment decisions.
⇒ The Confidence In Network Meta-Analysis approach will be used to assess the quality of evidence of primary studies and estimate the confidence in the NMA results.
⇒ As a limitation, considering the large parameter space for ECT, there may be insufficient data available to comprehensively assess the impact of all potential prognostic factors and effect modifiers for all outcome measures.

INTRODUCTION

Depression is a prevalent mental illness characterised by a loss of interest in pleasurable activities, or persistent low mood.[1] Global estimates suggest that 3.2% of individuals are currently depressed, and that rates of depression have increased by 27.6% due to the COVID-19 pandemic.[2] In addition to the subjective suffering caused by this mental illness, patients with severe depression represent a collective socioeconomic cost of US$29–US$48 billion in the USA alone,[3] due to increased unemployment, disability and reduced work performance.[4] Over 10% of depressed individuals report suicidal ideation with some intention to act,[5] producing a heightened lifetime risk

of suicide of 3.8%–7.8%.[6] Approximately one-third of patients with depression do not attain remission after multiple adequate courses of evidence-based pharmacotherapy,[7] suggesting that there are limits to standard drug interventions—although novel interventions, including esketamine show promise.[8] Therefore, there is an imperative to apply high-efficacy, non-pharmacological based interventions to treat depression. Electroconvulsive therapy (ECT) is a highly efficacious therapy for clinical depression, including treatment resistant depression and melancholic, psychotic, and bipolar subtypes.[9 10]

ECT involves the administration of a single transcranial electrical pulse train to stimulate the brain and induce a generalised seizure.[10–12] Empirical studies of neurobiological predictors and correlates of response have led to several proposed mechanisms of action, including enhancement of monoaminergic transmission,[13] neurotrophic changes[14–17] and metabolic changes.[18 19] ECT is safe,[20 21] and has been shown to be more effective than pharmacotherapy,[22 23] and other forms of non-invasive brain stimulation,[24] including transcranial magnetic stimulation and transcranial direct current stimulation, for severe and treatment-resistant presentations of depression. Treatment remission rates may be as high as 60%–70%.[25 26] Further, ECT rapidly reduces suicidal ideation,[27–29] death by suicide[30] and significantly improves quality of life.[31]

The efficacy, safety and acceptability of modern ECT practices are the result of several major advances in treatment delivery since the technique's development in the 1930s. Improvements in ECT technique have focused on preserving and improving efficacy while minimising cognitive sequelae such as memory dysfunction, which includes both anterograde (verbal and visual) and retrograde memory side effects.[32 33] While anterograde memory side effects with ECT tend to be more transient and typically resolve within a month following acute treatment, retrograde memory side effects, for example, for autobiographical information, can be more lasting.[34 35] For instance, in the 1980s, ECT stimulus parameters changed from a sine wave to a brief rectangular-wave biphasic stimulus of pulse duration 0.5–2.0 ms, reducing the incidence of cognitive side effects while retaining therapeutic efficacy.[36] More recently, pulse width has been narrowed even further, to 0.25–0.3 ms, giving rise to ultrabrief (UB) pulse ECT.[37–39]

In addition to ECT stimulus parameters, electrode placement on the scalp can also alter efficacy and cognitive outcomes due to changes in the pattern and spatial extent of cortical activation.[40–42] The neural correlates associated with antidepressant response following ECT, and those associated with cognitive side effects, have been demonstrated to be dissociable.[43] This suggests that brain regions responsible for antidepressant effects may be distinct from those that mediate cognitive impairment, and that ECT may be improved by the restriction of electrical currents to the former. For example, bifrontal (BF) ECT has been shown to have similar overall efficacy to bitemporal (BT) ECT, with possibly less cognitive impairment.[40 44 45] Alternative electrode placements and convulsive therapy types that are capable of restricting current pathways while eliciting adequate seizure activity are in development for example, left anterior right temporal electrode placement,[46] focal electrically administered seizure therapy[47 48] and magnetic seizure therapy,[49 50] although large randomised controlled tirals (RCTs) are not yet available to confirm their utility.

The clinical decision of which ECT protocol to pursue must be made with an understanding of the risks and benefits associated with the choice of electrical dose, stimulus parameters (eg, pulse width) and electrode placement (eg, bilateral or unilateral). Considering that approximately one million patients receive ECT for the treatment of mental disorders each year globally,[51] or between 0.11 and 0.50 individuals per 10 000,[52–54] it is vital that clinicians have access to the information needed to make an appropriate evidence-based selection of ECT parameters. However, variability in methodology and findings between studies make this choice difficult, and have contributed, in part, to significant global variations in ECT practices.[52]

One means of addressing this issue is to conduct multiple head-to-head RCTs comparing all interventions of interest, including more recent stimulus parameters and seizure induction methods. Such an endeavour, however, is unlikely to eventuate due to the number of possible pairwise comparisons between all treatment variations. An alternative solution is to leverage the available direct, as well as indirect, comparisons in the current ECT literature using a network meta-analysis (NMA).[55] An NMA allows for comparisons of different interventions, even though they may not have been examined in head-to-head RCTs. Moreover, an NMA can be used to facilitate clinical decision making by ranking ECT interventions across a range of clinical outcomes, including their comparative antidepressant efficacy and cognitive side effect profile. Although prior NMAs have confirmed the overall safety and efficacy of ECT relative to other interventions,[24 56–59] they have not investigated crucial differences between treatments according to electrode placement, pulse-width and dosing protocol.

Objectives

The aim of this systematic review and NMA is to inform and facilitate clinical practice decisions by comparing and ranking ECT types for the acute treatment of depression. ECT types will be compared according to three outcomes obtained from the acute post-treatment period:

1. Efficacy of the treatment to reduce depressive symptomatology.
2. Cognitive functioning, including the severity and pattern of any cognitive dysfunction.
3. Acceptability operationalised as the all-cause drop-out rate.

METHODS

The methodology of this NMA will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statements for NMAs.[60] This protocol has been prepared according to the recommendations of Cochrane.[61] This review does not require ethics approval.

Eligibility criteria

Types of studies

The systematic review will identify and include RCTs of at least two eligible ECT interventions under investigation for the acute treatment of depression, including unipolar and bipolar disorders. Trials may be double-blind, single-blind or unblinded. Studies without blinding will not be excluded because most modern ECT RCTs compare active interventions. For cross-over trials, we will extract data from before crossover.

Exclusion criteria include: (1) naturalistic observations of mood and cognitive outcomes following ECT; (2) investigations using ECT for the primary treatment of neuropsychiatric conditions other than a major depressive episode, for example, schizophrenia; (3) and finally, we will exclude the use of historical and now outmoded sine wave forms due to evidence of deleterious neurocognitive effects and subsequent decline in popularity for clinical use.[35 62]

Types of participants

Studies investigating adult patients aged 18 years and older will be included in the review, including patients diagnosed with either unipolar or bipolar depression experiencing a major depressive episode. Diagnoses must have been made using standardised diagnostic criteria, such as the Feighner criteria,[63] Research Diagnostic Criteria,[64] Diagnostic Statistical Manual (any version),[1] or the International Statistical Classification of Diseases and Related Health Problems. Comorbidities and secondary diagnoses of other neuropsychiatric disorders will not be considered as exclusion criteria.

Types of interventions

We will include RCTs of head-to-head comparisons, as well as studies with a sham-controlled trial arm. Nodes in the NMA will be defined using a combination of electrode placement, pulse width and dose (see figure 1 for a network plot of included ECT types).

Electrode placements include right unilateral (RUL), BF and BT. Left unilateral (LUL) electrode placements are infrequently used in clinical practice, although a recent narrative review has suggested comparable antidepressant and antipsychotic effects to RUL and BF placements.[65] Considering the lack of adequately powered RCTs of LUL in the literature, this montage is not included as a node in the NMA. If sufficient studies are identified during the systematic review, LUL will be included as a node.

Pulse width will be dichotomised as either UB for values <0.5 ms, and brief for values ≥0.5 ms but ≤2 ms. Appropriate dosing of the ECT stimulus is known to impact treatment outcomes.[66 67] In recent years, studies have suggested that ECT should optimally be delivered as a multiple of the patient's individual seizure threshold (ST).[68 69] Importantly, adequate dosing relative to ST differs between ECT types. For example, efficacy for brief-pulse RUL ECT delivered at six times ST does not differ from BT ECT given at 1.5–2.5-times ST.[26 38 70 71] Similarly, UB-RUL ECT delivered eight times ST has shown comparable efficacy to brief-pulse RUL ECT given at five times ST.[72] To ensure consistency across comparisons, the adequate dose range relative to ST will, therefore, be specified according to electrode placement. BF and BT placements will be categorised as low dose for values ≤1.5× ST, as moderate dose for values >1.5× ST and ≤3.0× ST, and as high dose for values >3.0× ST. Given the wider range of studied values, RUL will be categorised as low dose for values ≤3.0× ST, as moderate dose for values >3.0× ST and <5.0× ST, and as high dose for values ≥5.0× ST.[73]

Fixed or formula-based dosing protocols,[74] which remain in widespread use globally,[75] will be included as separate nodes for each of the available placements (BF, BT and RUL). However, we are conscious that substantial heterogeneity may arise within nodes for fixed and formula-based dosing protocols, due to differences in the choice of fixed charge or the specific dosing algorithm in use between studies, as well as due to the limited number of RCTs adopting these methods. We aim to reduce heterogeneity in treatment nodes to limit the possibility of inconsistency within network loops and improve precision of effect effects.[60] Therefore, depending on the inconsistency and quantity of data available for these nodes, they may be excluded from NMA analyses.

If an included study examined multiple ECT types, only data from those defined as nodes will be extracted. In instances where a study reports participant switching between ECT types, for example, to improve efficacy or reduce adverse events, we will correspond with the study authors and obtain data strictly prior to any change in ECT type. During the literature review if new treatment interventions are identified the study investigators will decide whether to include them as a node in the NMA through consensus. The working group will ensure that participants within the identified studies meeting inclusion criteria would have an equal likelihood, in theory, of being randomly allocated to any of the interventions included as nodes in the final NMA. That is, it is feasible to conceive of a multi-arm trial consisting of all included ECT types, such that they can be jointly randomisable.

Outcome measures

Primary outcomes

Antidepressant efficacy: symptom severity (continuous outcome)

Depression severity scores will be extracted using the total score on the Montgomery Asberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale (HDRS).

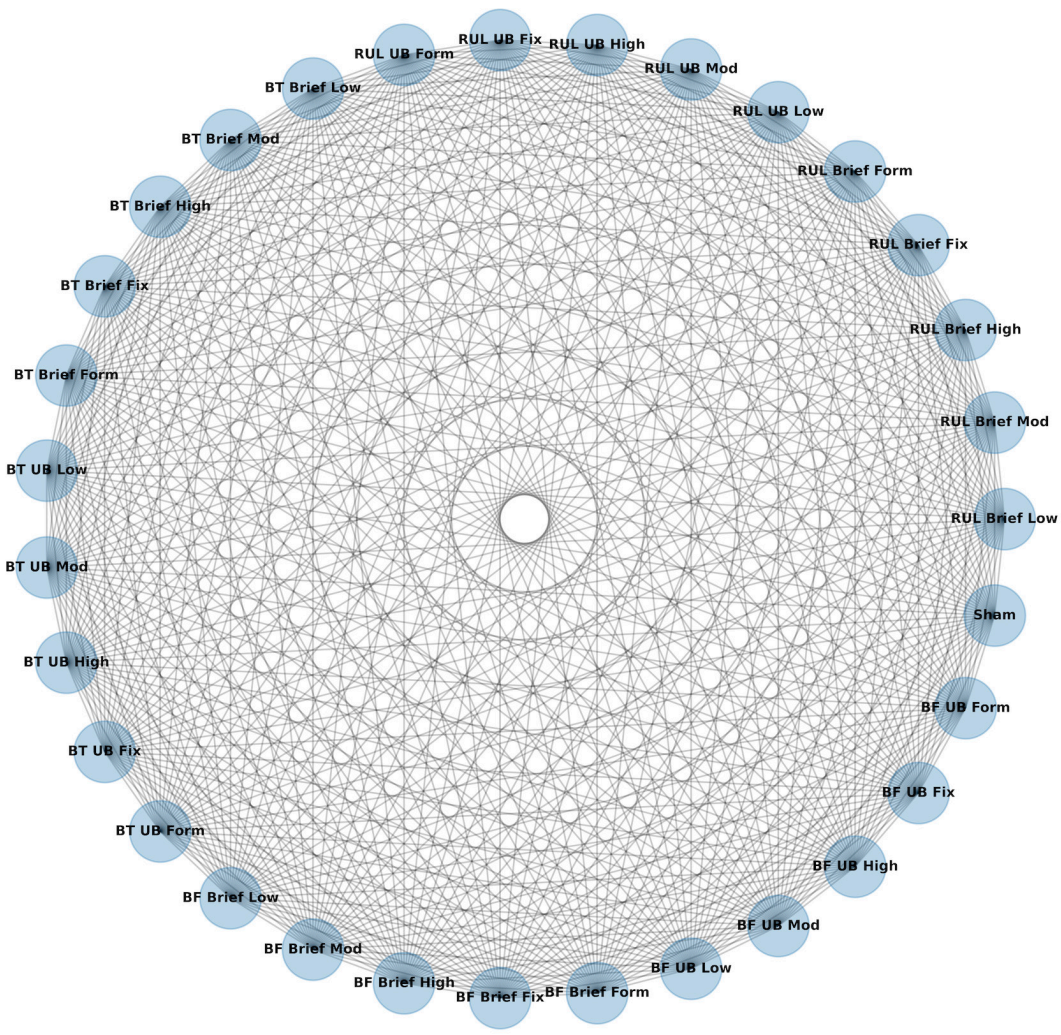

Figure 1 Provisional network plot of electroconvulsive therapy nodes. BF, bifrontal; BT, bitemporal; Fix, fixed; Form, formula; Mod, moderate; RUL, right unilateral; UB, ultrabrief.

If these are not reported, other standardised observer-rated scales for depression may be used. Group means and SD will be extracted at baseline and the primary study end point. When end point scores are not reported but change scores are, we will use the latter.

Cognitive functioning: anterograde verbal recall

The primary outcome for effects of ECT on cognitive functioning in patients with MDD will be a standardised neuropsychological measure of anterograde verbal recall. This was chosen as verbal recall is commonly most affected in the immediate period after a course of ECT,[34 76] despite such effects generally being transient. Verbal recall will be measured using scores obtained from standardised neuropsychological tests such as the Rey Auditory Verbal Learning Test, Buschke Selective Reminding Test, Verbal Learning and Memory Test, the Hopkins Verbal Learning Test or others.

Acceptability

The proportion of patients exiting the study for any reason from baseline to the end of the course of treatment (ie, all-cause drop-out rate). If sufficient data are available, we will perform an additional analysis of drop-outs due specifically to tolerability in receiving the intervention.

Secondary outcomes

Antidepressant efficacy: response rate

The proportion of responders to ECT for the treatment of depression will be used as a secondary measure of efficacy. Response will be defined as an improvement of at least 50% in depression scores from baseline to study end point on a standardised observer-rated scale for depression. The MADRS and HDRS will be used as primary sources to determine response. However, if these are not reported, other standardised observer-rated scale for depression may be used. The number of patients meeting response criteria, and the number of non-responders, will be extracted.

Antidepressant efficacy: remission rate

Remission will be defined as a reduction in depression scores below a scale-specific threshold on a standardised scale of depression. A depression score less than 10 will be

considered remission using the MADRS,[77] less than 8 on the HDRS 17-item scale, and less than 11 on the 24-item HDRS scale.[78] If other standardised observer-rated scales of depression are used, the scale-specific threshold for remission will be used, if defined. If undefined then, where possible, a validated conversion of remission threshold from HDRS or MADRS (whichever is available) will be performed.[79 80] The total number of patients who experienced a remission of depressive symptoms between baseline and study end point will be extracted for each study.

Cognitive functioning: autobiographical memory

Retrograde autobiographical memory impairments are the most durable side effects of ECT[34] and are associated with the greatest concern from patients. Notwithstanding, unlike standardised neuropsychological tests, measures of retrograde autobiographical memory have greater variability in their respective outcomes, which increases heterogeneity when collating results from different studies. For this reason, anterograde verbal recall was prioritised as a primary cognitive outcome. Retrograde autobiographical memory changes after ECT will be obtained from the Autobiographical Memory Interview (AMI), the AMI-Short Form, or a similar standardised scale.

Cognitive functioning: anterograde visuospatial recall

Visuospatial recall will be assessed as a secondary cognitive outcome using assessments of delayed visuospatial recall (eg, Brief Visuospatial Memory Test) or complex figure tasks (eg, Medical College of Georgia Complex Figure) extracted from baseline and the study end point.

Study selection

Two researchers will independently conduct searches in the previously mentioned databases using the terms: [Depression (MeSH Terms) OR Depression (All Fields) OR Depress* (All Fields) OR Melancholia (All Fields) OR 'Bipolar disorder' (All Fields) OR 'Bipolar spectrum' (All Fields)] AND ['Electroconvulsive therapy' (MeSH Terms) OR 'Electroconvulsive shock' OR 'Electroconvulsive shock therapy' OR 'Electroshock therapy' OR Electroconvulsive OR ECT]. They will sequentially review article titles, abstracts and full-text articles to determine whether studies meet eligibility criteria. Any disagreements will be resolved through consensus. If necessary, authors of disputed studies will be contacted for clarification.

Data extraction

Information sources

Embase, MEDLINE, PubMed, Web of Science databases are recommended to obtain adequate coverage of search terms for a systematic review, and so will be used for the present review.[81] In addition to the databases listed above, the search will also include Scopus, PsycINFO and the Cochrane Central Register of Controlled Trials (CENTRAL).

Reference lists of studies meeting inclusion criteria, and of prior systematic reviews examining therapeutic efficacy and cognitive impairments associated with ECT, will also be examined to locate additional relevant trials.

Data collection and management

First or corresponding authors from studies identified during the systematic review will be contacted by email and asked to provide additional information using our data extraction form. Aggregate data will be extracted from the included studies' manuscripts or supplementary materials. Additionally, we will check for data on public repositories, such as the National Institute of Mental Health Data Archive. A structured data extraction form will be used to obtain qualitative and quantitative data from all included studies. This form will collect information regarding study characteristics including, lead author, publication year, study title, study link (eg, DOI), country where the majority of data collection occurred, study type (eg, cross-over or parallel design); participant demographics including, sample size, gender, age, proportion with psychotic depression, proportion with bipolar depression, and treatment resistance; intervention details including ECT device, pulse width, number of convulsive therapy treatments, treatment frequency (ie, number of treatments per week), dosage as proportion of ST, electrode placement and anaesthetic used; and outcome measures including depression rating scale, baseline depression score, end of acute phase treatment depression score, response and remission rates, drop-outs, cognitive scale/s used for verbal recall, visuospatial recall, and retrograde autobiographical memory, baseline cognition score, and end of acute phase treatment cognition score.

Continuous outcomes

Means and SD will be extracted for ECT types included in prespecified NMA nodes. If these values are not reported, authors will be contacted to supply any missing information. If needed, 95% CIs, SEs of the mean, manuscript figures and other approaches will be used to estimate SD.

Dichotomous outcomes

Dichotomous outcomes, such as response and remission rates and all-cause drop-outs will be the secondary outcome measures for antidepressant efficacy and acceptability. These will be examined in addition to continuous outcomes because they are commonly reported in studies of depression and therefore allow easier generalisability to other treatment modalities, for example, antidepressant medications. For measures of antidepressant efficacy, patients that drop-out will conservatively be labelled as non-responders and non-remitters, unless explicitly stated as otherwise in the study manuscript. An NMA of pharmacological treatments for depression used a similar rationale to include dichotomous outcomes as a variable of interest.[82]

Length of a trial

There is no consensus regarding the length and session frequency of an adequate course of acute phase ECT treatment. For the purposes of this NMA, we will consider an acute phase of treatment as a protocol of 2–3 sessions of ECT per week and a minimum of six sessions based on findings suggesting that the majority of patients experience a response to treatment by this stage.[83] Data will be extracted from the primary endpoint as defined by the study, using the earliest assessment ≤7 days after the final ECT session and excluding assessments performed immediately after ECT during emergence from anaesthesia.

Risk of bias assessment within individual studies

Once the search is complete, independent raters will evaluate the risk of bias of included studies using the Cochrane tool.[84] This assesses several methodological criteria, including: (1) random sequence generation (selection bias); (2) allocation concealment; (3) blinding of participants and study personnel rating antidepressant efficacy and cognitive outcomes (performance bias), though blinding of study treaters may not be possible when comparing ECT montages; (4) blinding of study personnel rating antidepressant efficacy and cognitive outcome assessments (detection bias); (5) incomplete outcome data (attrition bias); (6) selective outcome reporting (reporting bias) and (7) other bias. Each study's overall risk of bias will be summarised using a label of low, high or unclear using the methodology described in the Cochrane Collaboration Handbook.

Risk of bias assessment across studies

Primary and secondary outcomes will be examined for small-study effects through visual inspection of contour-enhanced funnel plots,[85] and statistical methods such as the Harbord-Egger bias test of asymmetry,[86] if more than 10 studies are available. This will be repeated for each comparison between included ECT interventions. Lack of significance on the Harbord-Egger bias test will not be interpreted as indicative of lack of bias but will be reported as no evidence of bias. Evidence of bias will be incorporated into the interpretation of the results. Comparison-adjusted funnel plots of the entire network will be used to assess the presence of small-study effects.[87] Small-study effects will be assumed to be in the direction of exaggerated outcomes. If funnel plot asymmetry is detected, we will perform network meta-regression models to test whether small studies systematically tend to favour specific interventions.[87]

Reporting bias

Unpublished studies alter the effect size of meta-analyses, generally in the direction of reduced effects,[88] though not in all cases.[89] Clinical trials registries, including ClinicalTrials.gov and the European Union Clinical Trials Register, will be searched to identify unpublished studies. If any are identified, study authors will be contacted to obtain access to outcomes of interest, thereby minimising the risk of publication bias. This approach can significantly increase the number of studies included in the analysis, though may not necessarily lead to a qualitative change in the interpretation of results.[90]

Transitivity

Transitivity is the assumption that the interventions included in the analysis do not differ with respect to the distribution of effect modifiers (ie, variables associated with treatment outcomes). To check the transitivity assumption additional sensitivity, subgroup and meta-regression analyses will be conducted to confirm the robustness of findings. If the distribution of effect modifiers is balanced across comparisons, we will conclude that there is insufficient evidence of intransitivity, not that there is evidence against intransitivity. If intransitivity is identified within an outcome measure, we will not proceed with statistical analysis for that outcome.

Summary measures

Clinical and demographic information

A table containing clinical and demographic data extracted from included studies will be provided in a supplementary document.

Network geometry

For each outcome, a network graph will be reported showing all included studies in the NMA. Nodes and edges will be scaled according to the number of participants, and the number of trials, respectively.

Treatment effects

Mean effect sizes, 95% credible intervals (CrIs) and 95% predictive intervals (PrIs) will be reported. The 95% PrI indicates the range within which a treatment effect is to be expected, with 95% probability, if a new trial were to be conducted comparing a specific pair of treatments, and is generally more conservative than the 95% CrI.[91]

Statistical analysis and model implementation

Bayesian random effects NMAs will be conducted using rjags,[92] and nmjags,[93] which will run on open-source R software (R Foundation for Statistical Computing). Random effects models do not assume a priori that the true treatment effect is the same between studies and thus provide a more conservative estimate of outcomes. Markov Chain Monte Carlo (MCMC) methods will be implemented to fit the model and obtain posterior distributions of summary treatment effects, thereby allowing estimation of rank probabilities. For each model, the first 50 000 iterations will be discarded as the burn-in period to achieve convergence, and the subsequent 100 000 iterations will be used to fit the data. Convergence will be assessed via inspection of MCMC history plots, as well by using the Brooks Gelman-Rubin diagnostic tool and the potential scale reduction factor statistic representing the ratio of between-chain to interchain variability.[94 95] Model fit will be quantified using the deviance information criterion.[96] Non-informative or vague priors will be used for

the overall mean effect and between-study SD.[97] Multiarm trials will be incorporated into the NMA by substituting the random effects distribution with a multivariate normal distribution of intervention effects, thus statistically accounting for the covariate structure between arms of the same trial.[98]

Rank order analysis

To facilitate clinical decision making, we will place the included interventions into a treatment hierarchy for the primary outcomes of efficacy and cognitive functioning using surface under the cumulative ranking (SUCRA) curve analyses.[99] A SUCRA value of 100% indicates that a treatment is certain to outperform other treatments included in the NMA, whereas a value of 0% indicates it will be the worst. Additionally, posterior probabilities obtained from the Bayesian NMA model can also be used to rank ECT types, with higher posterior values indicating a higher likelihood that the intervention is a better performer.

Missing data

Outcomes of patients who leave the trial early are often imputed. The most common approach is last observation carried forward[100]; however, other methods may include interpolation, the group mean at the time of drop-out, prediction of missing data using regression, and matching (using values from similar cases). The type of imputation used will be reflected in the risk of bias assessment. Where possible, study authors will be contacted and asked to provide more information.

Assessment of heterogeneity

Residual heterogeneity will be calculated using τ^2, and 95% PrI will be used to investigate the impact of heterogeneity. Standard pairwise meta-analyses and forest plots will be generated for all possible pairwise node comparisons to check that there is no relevant heterogeneity between trials. A random effects model will be used as it produces a more conservative estimate of heterogeneity. A high level of heterogeneity may indicate that pooling of studies within that comparison is unadvisable.

Assessment of inconsistency

Within the context of NMAs, inconsistency is a statistical term that refers to the discrepancy between direct effects (ie, direct comparison between nodes) and indirect effects (ie, indirect comparisons between nodes via at least one additional node). Both local and global tests will be used to examine network inconsistency. For the local test, we will conduct a preliminary assessment using the loop-specific approach.[101] Subsequently, a node-splitting method called Separating Indirect from Direct Evidence[102 103] will be used, focusing on the subset of nodes highlighted in the loop-specific method as showing a difference between indirect and direct forms of evidence, if any. Finally, we will use a design-by-treatment interaction/inconsistency model, similar to a goodness-of-fit-test,[104–106] as a global measure to assess whether the network as a whole demonstrates any inconsistency.

Non-significance on either local or global tests of inconsistency will not be interpreted as proof of absence of inconsistency, but rather as a lack of evidence of statistical difference between direct and indirect treatment effects.[107]

In the event that we detect statistically significant inconsistency we will investigate potential underlying causes. This will include inspection of the data for extraction errors as well as an exploration of effect modifiers identified a priori as possible sources for differences between direct and indirect comparisons. These effect modifiers are described in further detail in the Additional analyses section. Finally, if inconsistency cannot be resolved, we will consider avoiding synthesis of the problematic network loop.

Additional analyses

Sensitivity analyses

Studies with a high risk of bias will be excluded as part of sensitivity analyses to check the robustness of the model.

To further explore heterogeneity between studies, we will perform subgroup and meta-regression analyses on the following variables, if reported in a sufficient number of studies.

Subgroup and meta-regression analyses

Exploratory analyses will investigate the influence of gender, as well as the type of depression, including psychotic versus non-psychotic depression, as well as bipolar versus unipolar disorder, on outcome measures. These variables will be assessed by including the proportion of participants in a specified reference category (eg, percentage of bipolar participants) for each included study in the NMA model. Regarding acceptability outcomes, measured using all-cause drop-out rates, if sufficient data are available, we will perform an additional analysis of drop-outs occurring specifically due to tolerability issues arising during the treatment course.

Additional meta-regression analyses will be used for continuous variables, including age at the time of ECT treatment, baseline depression severity, baseline measures of cognitive functioning and treatment resistance defined as the average number of failed courses of antidepressants given at an adequate therapeutic dosage in the current episode.

Quality assessment of all comparisons in the network

The open-source software package CINeMA (Confidence In Network Meta-Analysis) will be used to assess the quality of evidence contributing to network estimates of primary and secondary outcomes,[108] and, in so doing, estimate the confidence in the NMA results. CINeMA is similar to the GRADE methodological framework and considers six domains to evaluate the confidence in the NMA findings. These domains are within-study bias,

across-studies bias, indirectness, imprecision, heterogeneity and incoherence.

Patient and public involvement

No patients or public representatives were involved in the design of the NMA protocol.

DISCUSSION

Limitations

Though dropouts will be well documented, psychological test batteries and cognitive adverse events experienced during the treatment course are not expected to be consistently reported. Therefore, it may not be possible to conduct a full assessment of cognitive outcomes as outlined in the protocol.

Due to the large parameter space for ECT, and the subsequent variability in treatment protocols observed in the literature, there may be insufficient data available to comprehensively assess the impact of all potential prognostic factors and effect modifiers for all outcome measures. Where there is insufficient data to perform additional analyses, this will be transparently reported.

Finally, the aim of this NMA is to investigate immediate outcomes of efficacy, cognitive effects and acceptability following ECT. Of equivalent concern is the longevity of efficacy outcomes in the months and years following successful treatment, as well as the persistence of cognitive side effects. However, these issues are beyond the scope of the present analysis and will require separate study.

Strengths

Despite the limitations listed above, we hope this study will be a valuable clinical tool. This NMA will determine the factors that influence efficacy, cognitive effects and patient acceptability of ECT. Ranking of treatments according to these outcomes will facilitate clinical decision making when determining the appropriate convulsive therapy type to prescribe for patients.

Author affiliations
[1]Department of Psychiatry, University of New South Wales, Sydney, New South Wales, Australia
[2]Black Dog Institute, Randwick, New South Wales, Australia
[3]Research Center of Epidemiology (CRESS-UMR1153), INSERM, INRA, Universite de Paris, Paris, France
[4]Department of Psychiatry, Columbia University, New York, New York, USA
[5]Department of Psychiatry, Trinity College Dublin, Dublin, Ireland
[6]Department of Neurosciences, KU Leuven Psychiatric University Hospital KU Leuven, Leuven, Belgium
[7]Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, South Carolina, USA

Twitter Stevan Nikolin @NikolinStevan

Acknowledgements We are grateful to Brendan Mauch and Sereibanndith Seang for conducting a preliminary review of the ECT literature to establish the feasibility of this NMA.

Contributors SN conceived the study. SN, RF-T and KO, drafted the manuscript. SN, KO, RF-T, AC, DoMM, MB, HAS, DeMM, PS, CHK and CL, critically revised the protocol manuscript. All authors approved the final version of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests HAS serves as a scientific advisor to Cerebral Therapeutics, Holmusk Technologies, LivaNova, Neurolief, Neuronetics, Parow Entheobiosciences and SigmaStim (formerly MECTA Corporation); he receives honoraria and royalties from Elsevier and Oxford University Press; he is the inventor on non-remunerative US patents for Focal Electrically Administered Seizure Therapy (FEAST), titration in the current domain in ECT, and ECT devices with current adjustment, each held by SigmaStim; and he is the originator of magnetic seizure therapy. DoMM has received travel support from Miyuki Giken, speaker's honorarium from Lundbeck and consultancy fees from Duncan Pharmaceuticals, all unrelated to the current work. DeMM, has received speaker's honoraria from MECTA and Otsuka and an honorarium from Janssen for participating in an esketamine advisory board meeting. All of these were unrelated to the current work. CHK, receives royalties from Cambridge University Press for Handbook of ECT, fees from UpToDate for ECT topics, and fees from Northwell Health for teaching in an ECT course. CL has received speaker's honoraria from MECTA, an honorarium from Janssen for participating in an esketamine advisory board meeting, and fees from Wesley Hospital and South Eastern Sydney Local Health District for teaching ECT courses. These were unrelated to the current work. The other authors declare no competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Stevan Nikolin http://orcid.org/0000-0003-4440-9273
Pascal Sienaert http://orcid.org/0000-0002-0650-415X

REFERENCES

1 American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®) American Psychiatric Pub; 2013.
2 COVID-19 Mental Disorders Collaborators. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *Lancet* 2021;398:1700–12.
3 Mrazek DA, Hornberger JC, Altar CA, *et al*. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996-2013. *Psychiatr Serv* 2014;65:977–87.
4 Birnbaum HG, Kessler RC, Kelley D, *et al*. Employer burden of mild, moderate, and severe major depressive disorder: mental health services utilization and costs, and work performance. *Depress Anxiety* 2010;27:78–89.
5 Substance Abuse and Mental Health Services Administration,. Key substance use and mental health indicators in the United States: Results from the 2018 National Survey on Drug Use and Health (HHS Publication No. PEP19-5068, NSDUH Series H-54). Rockville, MD Center for Behavioral Health Statistics and Quality. Substance Abuse and Mental Health Services Administration; 2019. https://www.samhsa.gov/data/
6 Nordentoft M, Mortensen PB, Pedersen CB. Absolute risk of suicide after first hospital contact in mental disorder. *Arch Gen Psychiatry* 2011;68:1058–64.
7 Rush AJ, Trivedi MH, Wisniewski SR, *et al*. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 2006;163:1905–17.
8 Popova V, Daly EJ, Trivedi M, *et al*. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. *Am J Psychiatry* 2019;176:428–38.
9 American Psychiatric Association. *The practice of electroconvulsive therapy: recommendations for treatment, training, and privileging (a*

task force report of the American psychiatric association. American Psychiatric Pub, 2008.
10 Espinoza RT, Kellner CH. Electroconvulsive therapy. *N Engl J Med* 2022;386:667–72.
11 National Institute for Health and Care Excellence. Depression in adults: treatment and management British Psychological Society; 2022.
12 Kirov G, Jauhar S, Sienaert P, *et al*. Electroconvulsive therapy for depression: 80 years of progress. *Br J Psychiatry* 2021;219:594–7.
13 Baldinger P, Lotan A, Frey R, *et al*. Neurotransmitters and electroconvulsive therapy. *J Ect* 2014;30:116–21.
14 van Buel EM, Patas K, Peters M, *et al*. Immune and neurotrophin stimulation by electroconvulsive therapy: is some inflammation needed after all? *Transl Psychiatry* 2015;5:e609.
15 Schloesser RJ, Orvoen S, Jimenez DV, *et al*. Antidepressant-like effects of electroconvulsive seizures require adult neurogenesis in a neuroendocrine model of depression. *Brain Stimul* 2015;8:862–7.
16 Chang AD, Vaidya PV, Retzbach EP, *et al*. Narp mediates antidepressant-like effects of electroconvulsive seizures. *Neuropsychopharmacology* 2018;43:1088–98.
17 Ousdal OT, Argyelan M, Narr KL, *et al*. Brain changes induced by electroconvulsive therapy are broadly distributed. *Biol Psychiatry* 2020;87:451–61.
18 Perrin JS, Merz S, Bennett DM, *et al*. Electroconvulsive therapy reduces frontal cortical connectivity in severe depressive disorder. *Proc Natl Acad Sci U S A* 2012;109:5464–8.
19 van Waarde JA, Scholte HS, van Oudheusden LJB, *et al*. A functional MRI marker may predict the outcome of electroconvulsive therapy in severe and treatment-resistant depression. *Mol Psychiatry* 2015;20:609–14.
20 Fink M. ECT has proved effective in treating depression. *Nature* 2000;403:826.
21 Kaster TS, Vigod SN, Gomes T, *et al*. Risk of serious medical events in patients with depression treated with electroconvulsive therapy: a propensity score-matched, retrospective cohort study. *Lancet Psychiatry* 2021;8:686–95.
22 UK ECT Review Group. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet* 2003;361:799-808.
23 Heijnen WT, Birkenhäger TK, Wierdsma AI, *et al*. Antidepressant pharmacotherapy failure and response to subsequent electroconvulsive therapy: a meta-analysis. *J Clin Psychopharmacol* 2010;30:616–9.
24 Mutz J, Vipulananthan V, Carter B, *et al*. Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis. *BMJ* 2019;364:l1079.
25 O'Connor MK, Knapp R, Husain M, *et al*. The influence of age on the response of major depression to electroconvulsive therapy: a C.O.R.E. Report. *Am J Geriatr Psychiatry* 2001;9:382–90.
26 Sackeim HA, Dillingham EM, Prudic J, *et al*. Effect of concomitant pharmacotherapy on electroconvulsive therapy outcomes: short-term efficacy and adverse effects. *Arch Gen Psychiatry* 2009;66:729–37.
27 Fink M, Kellner CH, McCall WV. The role of ECT in suicide prevention. *J Ect* 2014;30:5–9.
28 Rönnqvist I, Nilsson FK, Nordenskjöld A. Electroconvulsive therapy and the risk of suicide in hospitalized patients with major depressive disorder. *JAMA Netw Open* 2021;4:e2116589.
29 Sienaert P, Brus O, Lambrichts S, *et al*. Suicidal ideation and ECT, ECT and suicidal ideation: a register study. *Acta Psychiatr Scand* 2022;146:74–84.
30 Kaster TS, Blumberger DM, Gomes T, *et al*. Risk of suicide death following electroconvulsive therapy treatment for depression: a propensity score-weighted, retrospective cohort study in Canada. *Lancet Psychiatry* 2022;9:435–46.
31 McCall WV, Reboussin D, Prudic J, *et al*. Poor health-related quality of life prior to ECT in depressed patients normalizes with sustained remission after ECT. *J Affect Disord* 2013;147:107–11.
32 Ingram A, Saling MM, Schweitzer I. Cognitive side effects of brief pulse electroconvulsive therapy: a review. *J Ect* 2008;24:3–9.
33 Spaans H-P, Verwijk E, Comijs HC, *et al*. Efficacy and cognitive side effects after brief pulse and ultrabrief pulse right unilateral electroconvulsive therapy for major depression: a randomized, double-blind, controlled study. *J Clin Psychiatry* 2013;74:e1029–36.
34 Landry M, Moreno A, Patry S, *et al*. Current practices of electroconvulsive therapy in mental disorders: a systematic review and meta-analysis of short and long-term cognitive effects. *J Ect* 2021;37:119–27.
35 Sackeim HA, Prudic J, Fuller R, *et al*. The cognitive effects of electroconvulsive therapy in community settings. *Neuropsychopharmacology* 2007;32:244–54.
36 Carney MW, Rogan PA, Sebastian J, *et al*. A controlled comparative trial of unilateral and bilateral sinusoidal and pulse E.C.T. in endogenous depression. *PDM* 1976;7(9-12)8:77–9.
37 Loo CK, Sainsbury K, Sheehan P, *et al*. A comparison of RUL ultrabrief pulse (0.3 MS) ECT and standard RUL ECT. *Int J Neuropsychopharmacol* 2008;11:883–90.
38 Sackeim HA, Prudic J, Nobler MS, *et al*. Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *Brain Stimul* 2008;1:71–83.
39 Tor P-C, Bautovich A, Wang M-J, *et al*. A systematic review and meta-analysis of brief versus ultrabrief right unilateral electroconvulsive therapy for depression. *J Clin Psychiatry* 2015;76:e1092–8.
40 Kellner CH, Knapp R, Husain MM, *et al*. Bifrontal, bitemporal and right unilateral electrode placement in ECT: randomised trial. *Br J Psychiatry* 2010;196:226–34.
41 Bai S, Loo C, Al Abed A, *et al*. A computational model of direct brain excitation induced by electroconvulsive therapy: comparison among three conventional electrode placements. *Brain Stimul* 2012;5:408–21.
42 Lee WH, Deng Z-D, Kim T-S, *et al*. Regional electric field induced by electroconvulsive therapy in a realistic finite element head model: influence of white matter anisotropic conductivity. *Neuroimage* 2012;59:2110–23.
43 Nobler MS, Sackeim HA. Neurobiological correlates of the cognitive side effects of electroconvulsive therapy. *J Ect* 2008;24:40–5.
44 Dunne RA, McLoughlin DM. Systematic review and meta-analysis of bifrontal electroconvulsive therapy versus bilateral and unilateral electroconvulsive therapy in depression. *World J Biol Psychiatry* 2012;13:248–58.
45 Bailine SH, Rifkin A, Kayne E, *et al*. Comparison of bifrontal and bitemporal ECT for major depression. *Am J Psychiatry* 2000;157:121–3.
46 Swartz CM, Nelson AI. Rational electroconvulsive therapy electrode placement. *Psychiatry* 2005;2:37.
47 Nahas Z, Short B, Burns C, *et al*. A feasibility study of a new method for electrically producing seizures in man: focal electrically administered seizure therapy [FEAST]. *Brain Stimul* 2013;6:403–8.
48 Sahlem GL, McCall WV, Short EB, *et al*. A two-site, open-label, non-randomized trial comparing focal electrically-administered seizure therapy (feast) and right unilateral ultrabrief pulse electroconvulsive therapy (RUL-UBP ECT). *Brain Stimul* 2020;13:1416–25.
49 Lisanby SH. Update on magnetic seizure therapy: a novel form of convulsive therapy. *J Ect* 2002;18:182–8.
50 Lisanby SH, Schlaepfer TE, Fisch HU, *et al*. Magnetic seizure therapy of major depression. *Arch Gen Psychiatry* 2001;58:303–5.
51 Prudic J, Olfson M, Sackeim HA. Electro-convulsive therapy practices in the community. *Psychol Med* 2001;31:929–34.
52 Leiknes KA, Jarosh-von Schweder L, Høie B. Contemporary use and practice of electroconvulsive therapy worldwide. *Brain Behav* 2012;2:283–344.
53 Wilkinson ST, Agbese E, Leslie DL, *et al*. Identifying recipients of electroconvulsive therapy: data from privately insured Americans. *Psychiatr Serv* 2018;69:542–8.
54 Luccarelli J, Henry ME, McCoy TH. Demographics of patients receiving electroconvulsive therapy based on state-mandated reporting data. *J Ect* 2020;36:229–33.
55 Lumley T. Network meta-analysis for indirect treatment comparisons. *Stat Med* 2002;21:2313–24.
56 Chen J-J, Zhao L-B, Liu Y-Y, *et al*. Comparative efficacy and acceptability of electroconvulsive therapy versus repetitive transcranial magnetic stimulation for major depression: a systematic review and multiple-treatments meta-analysis. *Behav Brain Res* 2017;320:30–6.
57 Zhou D, Zhou X, Lin Q, *et al*. Nonpharmacological interventions for relapse prevention in unipolar depression: a network meta-analysis. *J Affect Disord* 2021;282:1255–62.
58 Li H, Cui L, Li J, *et al*. Comparative efficacy and acceptability of neuromodulation procedures in the treatment of treatment-resistant depression: a network meta-analysis of randomized controlled trials. *J Affect Disord* 2021;287:115–24.
59 Papadimitropoulou K, Vossen C, Karabis A, *et al*. Comparative efficacy and tolerability of pharmacological and somatic interventions in adult patients with treatment-resistant depression: a systematic review and network meta-analysis. *Curr Med Res Opin* 2017;33:701–11.
60 Hutton B, Salanti G, Caldwell DM, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating

network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777–84.
61 Chaimani A, Caldwell DM, Li T, *et al*. Additional considerations are required when preparing a protocol for a systematic review with multiple interventions. *J Clin Epidemiol* 2017;83:65–74.
62 Weiner RD, Rogers HJ, Davidson JR, *et al*. Effects of stimulus parameters on cognitive side effects. *Ann N Y Acad Sci* 1986;462:315–25.
63 Feighner JP, Robins E, Guze SB, *et al*. Diagnostic criteria for use in psychiatric research. *Arch Gen Psychiatry* 1972;26:57–63.
64 Spitzer RL, Endicott J, Robins E. Research diagnostic criteria: rationale and reliability. *Arch Gen Psychiatry* 1978;35:773–82.
65 Kellner CH, Farber KG, Chen XR, *et al*. A systematic review of left unilateral electroconvulsive therapy. *Acta Psychiatr Scand* 2017;136:166–76.
66 McCall WV, Reboussin DM, Weiner RD, *et al*. Titrated moderately suprathreshold vs fixed high-dose right unilateral electroconvulsive therapy: acute antidepressant and cognitive effects. *Arch Gen Psychiatry* 2000;57:438–44.
67 O'Neill-Kerr A, Yassin A, Rogers S, *et al*. Switching from age-based stimulus dosing to dose titration protocols in electroconvulsive therapy: empirical evidence for better patient outcomes with lower peak and cumulative energy doses. *J Ect* 2017;33:181–4.
68 Coffey CE, Lucke J, Weiner RD, *et al*. Seizure threshold in electroconvulsive therapy: I. initial seizure threshold. *Biol Psychiatry* 1995;37:713–20.
69 Sackeim HA, Prudic J, Devanand DP, *et al*. Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *N Engl J Med* 1993;328:839–46.
70 Sackeim HA, Prudic J, Devanand DP, *et al*. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch Gen Psychiatry* 2000;57:425–34.
71 Kolshus E, Jelovac A, McLoughlin DM. Bitemporal V. high-dose right unilateral electroconvulsive therapy for depression: a systematic review and meta-analysis of randomized controlled trials. *Psychol Med* 2017;47:518–30.
72 Loo CK, Katalinic N, Smith DJ, *et al*. A randomized controlled trial of brief and ultrabrief pulse right unilateral electroconvulsive therapy. *Int J Neuropsychopharmacol* 2015;18.
73 Weiss A, Hussain S, Ng B, *et al*. Royal Australian and New Zealand College of psychiatrists professional practice guidelines for the administration of electroconvulsive therapy. *Aust N Z J Psychiatry* 2019;53:609–23.
74 Bennett DM, Perrin JS, Currie J, *et al*. A comparison of ECT dosing methods using a clinical sample. *J Affect Disord* 2012;141:222–6.
75 Gazdag G, Dragasek J, Takács R, *et al*. Use of electroconvulsive therapy in central-eastern European countries: an overview. *Psychiatr Danub* 2017;29:136–40.
76 Semkovska M, McLoughlin DM. Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. *Biol Psychiatry* 2010;68:568–77.
77 Zimmerman M, Chelminski I, Posternak M. A review of studies of the Montgomery-Asberg depression rating scale in controls: implications for the definition of remission in treatment studies of depression. *Int Clin Psychopharmacol* 2004;19:1–7.
78 Frank E, Prien RF, Jarrett RB, *et al*. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry* 1991;48:851–5.
79 Leucht S, Fennema H, Engel RR, *et al*. Translating the HAM-D into the MADRS and vice versa with equipercentile linking. *J Affect Disord* 2018;226:326–31.
80 Rush AJ, Trivedi MH, Ibrahim HM, *et al*. The 16-Item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry* 2003;54:573–83.
81 Bramer WM, Rethlefsen ML, Kleijnen J, *et al*. Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. *Syst Rev* 2017;6:245.
82 Cipriani A, Furukawa TA, Salanti G, *et al*. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 2018;391:1357–66.
83 Husain MM, John Rush A, Fink M, *et al*. Speed of response and remission in major depressive disorder with acute electroconvulsive therapy (ECT): a Consortium for research in ECT (core) report. *J Clin Psychiatry* 2004;65:19907.
84 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
85 Peters JL, Sutton AJ, Jones DR, *et al*. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol* 2008;61:991–6.
86 Harbord RM, Egger M, Sterne JAC. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med* 2006;25:3443–57.
87 Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. *Res Synth Methods* 2012;3:161–76.
88 Hart B, Lundh A, Bero L. Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses. *BMJ* 2012;344:d7202.
89 Schmucker CM, Blümle A, Schell LK, *et al*. Systematic review finds that study data not published in full text articles have unclear impact on meta-analyses results in medical research. *PLoS One* 2017;12:e0176210.
90 Baudard M, Yavchitz A, Ravaud P, *et al*. Impact of searching clinical trial registries in systematic reviews of pharmaceutical treatments: methodological systematic review and reanalysis of meta-analyses. *BMJ* 2017;356:j448.
91 Higgins JPT, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J R Stat Soc Ser A Stat Soc* 2009;172:137–59.
92 Plummer M. *rjags: Bayesian graphical models using MCMC. R package version 4-12*. Statistical software, 2021.
93 Salanti G, Schwarzer G. *nmajags: R functions to run Bayesian network meta-analysis with JAGS version 0.1-0*. Statistical software, 2022.
94 Brooks SP, Gelman A. General methods for monitoring convergence of iterative simulations. *J Comput Graph* 1998;7:434–55. doi:10.1080/10618600.1998.10474787
95 Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. *Statistical Science* 1992;7:457–72.
96 Spiegelhalter DJ, Best NG, Carlin BP, *et al*. The deviance information criterion: 12 years on. *J R Stat Soc B* 2014;76:485–93.
97 Bodnar O, Link A, Arendacká B, *et al*. Bayesian estimation in random effects meta-analysis using a non-informative prior. *Stat Med* 2017;36:378–99.
98 Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004;23:3105–24.
99 Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64:163–71.
100 Spineli LM, Pandis N, Salanti G. Reporting and handling missing outcome data in mental health: a systematic review of Cochrane systematic reviews and meta-analyses. *Res Synth Methods* 2015;6:175–87.
101 Bucher HC, Guyatt GH, Griffith LE, *et al*. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997;50:683–91.
102 Higgins J. Identifying and addressing inconsistency in network meta-analysis. In: *Cochrane comparing multiple interventions methods group Oxford training event*, 2013.
103 van Valkenhoef G, Dias S, Ades AE, *et al*. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. *Res Synth Methods* 2016;7:80–93.
104 Higgins JPT, Jackson D, Barrett JK, *et al*. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012;3:98–110.
105 Jackson D, Barrett JK, Rice S, *et al*. A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. *Stat Med* 2014;33:3639–54.
106 White IR, Barrett JK, Jackson D, *et al*. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods* 2012;3:111–25.
107 Cipriani A, Higgins JPT, Geddes JR, *et al*. Conceptual and technical challenges in network meta-analysis. *Ann Intern Med* 2013;159:130–7.
108 CINeMA. *Confidence in Network Meta-Analysis [Software]*. Institute of Social and Preventive Medicine, University of Bern, 2017. Available: cinema.ispm.ch