TECHNICAL COMMENTARY

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Electroconvulsive therapy

Introduction

Electroconvulsive therapy (ECT) involves the delivery of an electrical stimulus to the brain via electrodes placed either bilaterally or unilaterally to elicit a generalized seizure. Seizure thresholds vary between people and are affected by factors such as medication, age and sex. Thresholds may be estimated by applying a patient profile average or they may be empirically determined, e.g., in an initial titration session, the dose is increased gradually until a seizure eventuates. ECT's efficacy and safety are affected by a number of factors such as where electrodes are placed, the frequency of treatment, the degree to which the stimulus dose exceeds the seizure threshold and the dose and duration of concurrent medication.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, the most recent and/or comprehensive review was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomized controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found three systematic reviews that met our inclusion criteria[3-5].

- High quality evidence suggests a small effect of greater response to ECT treatment in people with bipolar depression compared to people with major depression (77% vs. 74% responded), although this difference was not significant in treatment-resistant patients. Moderate to high quality evidence suggests fewer number of sessions are required for bipolar depression. There were no differences in remission rates.
- High quality evidence suggests longer duration of depressive episode and non-

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response to medication are associated with medium effects of poorer response to ECT treatment.

- Moderate quality evidence suggests comorbid psychotic features may be associated with a small effect of poorer response to ECT treatment and increasing age may be associated with a small effect of better response to ECT treatment.

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Bahji A, Hawken ER, Sepehry AA, Cabrera CA, Vazquez G

ECT beyond unipolar major depression: systematic review and meta-analysis of electroconvulsive therapy in bipolar depression

Acta Psychiatrica Scandinavica 2019; 139: 214-26

View review abstract online

Comparison	**Effectiveness of ECT for bipolar depression vs. major depression.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) suggests a small effect of greater response to ECT treatment for bipolar depression compared to major depression. Moderate to high quality evidence (inconsistent) suggests fewer number of sessions are required for bipolar depression. There were no differences in remission rates.**

Response

Small effects showed response rates were greater and quicker in bipolar depression;

Response rate: 17 studies, N = 2,247, rate = 77.1% vs. 74.2%, OR = 0.73, N = 95%CI 0.56 to 0.95, $p = 0.02$, $I^2 = 0\%$

Number of sessions required: 15 studies, N = 2,184, SMD = -0.23, 95%CI -0.44 to -0.023, $p = 0.03$, $I^2 = 65\%$

There were no moderating effects of diagnostic tool, study design (prospective vs. retrospective), medication status, age, and sex.

Remission

There were no differences in remission rates (52.3% in both groups);

15 studies, N = 2,152, OR = 0.91, 95%CI 0.65 to 1.26, $p = 0.56$, $I^2 = 46\%$

There were no moderating effects of diagnostic tool, study design (prospective vs. retrospective), medication status, age, and sex.

Risks	Not reported
Consistency in results‡	Consistent for response rate only.
Precision in results§	Precise for response and number of sessions.
Directness of results‖	Direct

Fornaro M, Carvalho AF, Fusco A, Anastasia A, Solmi M, Berk M, Sim K, Vieta E, de Bartolomeis A

The concept and management of acute episodes of treatment-resistant bipolar disorder: a systematic review and exploratory meta-analysis of randomized controlled trials

Journal of Affective Disorders 2020; 276: 970-83

View review abstract online

Comparison	**ECT for people with treatment-resistant bipolar depression vs. treatment-resistant unipolar depression.**
Summary of evidence	**Moderate quality evidence (small to medium-sized sample, consistent, imprecise, direct) finds no differences in depression symptoms between bipolar and unipolar depression after bifrontal ECT.**
Symptoms	
There were no differences in depression symptoms between bipolar and unipolar depression after bifrontal ECT; 3 RCTs, N = 176, OR = 0.919, 95%CI 0.44 to 1.92, p = 0.822, I^2 = 14%	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Haq AU, Sitzmann AF, Goldman ML, Maixner DF, Mickey BJ

Response of depression to electroconvulsive therapy: A meta-analysis of clinical predictors

Journal of Clinical Psychiatry 2015; 76: 1374-84

View review abstract online

Comparison	**Predictors of treatment response following ECT treatment (6-14 treatments) either via prospective or retrospective analysis.** **Note: this meta-analysis included people with major depression**

	or bipolar disorder.
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) suggests longer duration of depressive episode and non-response to medication are associated with medium effects of poorer response to ECT treatment.** **Moderate quality evidence (possible publication bias) suggests comorbid psychotic features may be associated with a small effect of poorer response to ECT treatment and increasing age may be associated with a small effect of better response to ECT treatment.**
Predictors of treatment response	
A medium-sized, significant effect of poorer response to ECT treatment with longer duration of depressive episode; 7 studies, N = 702, SMD = -0.427, 95%CI -0.662 to -0.192, p = 0.0004, I^2 = 35%, p = 0.16 *A medium-sized, significant effect of poorer response to ECT treatment with non-response to medication;* 11 studies, N = 1,175, OR = 0.574, 95%CI 0.401 to 0.821, p = 0.002, I^2 = 35%, p = 0.12 *A small, trend effect of poorer response to ECT treatment with comorbid psychotic features (analysis with two outliers removed);* 15 studies, N = 2,251, OR = 1.342, 95%CI 0.968 to 1.860, p = 0.08, I^2 = 37%, p = 0.07 Authors report possible publication bias. *A small, significant effect of better response to ECT treatment with increasing age (analysis with one outlier removed);* 9 studies, N = 1,713, SMD = 0.244, 95%CI 0.124 to 0.363, p = 0.00006, I^2 = 0.06%, p = 0.38 Authors report only low-dose ECT was associated with this effect. Authors report possible publication bias. Authors report no differences in treatment response according to; diagnosis (bipolar vs. unipolar depression), number of previous depressive episodes, sex, age of onset, presence of melancholic features, baseline symptom severity, number of treatments, or study design.	
Risks	Not reported
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

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Explanation of acronyms

CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), SMD = standardized mean difference, vs. = versus

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results, publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[6].

† Different effect measures are reported by different reviews.

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, an RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. An RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[7]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large treatment effect[6].

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years

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denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed[8].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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