Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis

The UK ECT Review Group*

Summary

Background We aimed to review published work for the efficacy and safety of electroconvulsive therapy (ECT) with simulated ECT, ECT versus pharmacotherapy, and different forms of ECT for patients with depressive illness.

Methods We designed a systematic overview and meta-analysis of randomised controlled trials and observational studies. We obtained data from the Cochrane Collaboration Depressive Anxiety and Neurosis and Schizophrenia Group Controlled trial registers, Cochrane Controlled Trials register, Biological Abstracts, CINAHL, EMBASE, LILACS, MEDLINE, PsycINFO, and SIGLE, reference lists, and specialist textbooks. Our main outcome measures were depressive symptoms, measures of cognitive function, and mortality.

Findings Meta-analysis of data of short-term efficacy from randomised controlled trials was possible. Real ECT was significantly more effective than simulated ECT (six trials, 256 patients, standardised effect size [SES] –0·91, 95% CI –1·27 to –0·54). Treatment with ECT was significantly more effective than pharmacotherapy (18 trials, 1144 participants, SES –0·80, 95% CI –1·29 to –0·29). Bilateral ECT was more effective than unipolar ECT (22 trials, 1408 participants, SES –0·32, 95% CI –0·46 to –0·19).

Interpretation ECT is an effective short-term treatment for depression, and is probably more effective than drug therapy. Bilateral ECT is moderately more effective than unilateral ECT, and high dose ECT is more effective than low dose.

Introduction Electroconvulsive therapy (ECT) has been used as a treatment for mental disorder since the 1930s. Views on ECT vary, from researchers who consider that it is probably ineffective but certainly causes brain damage, through to those who think it is the most effective treatment available in psychiatry and is completely safe. The substantial geographical variation in rates of use of ECT suggests uncertainty about its efficacy and safety. We did a systematic review and meta-analysis of published work to ascertain the benefits and harms of ECT in the treatment of depression.

Methods We searched scientific and medical databases for properly randomised, unconfounded, controlled trials that compared ECT with no ECT, ECT versus pharmacotherapy, or different forms of ECT, for patients with depressive illness. The primary outcome we used for estimation of the efficacy of ECT was change in symptoms on a continuous depressive symptom scale at the end of the course of ECT. The change in symptoms at 6 months' follow-up was also investigated. We sought data on the immediate and long-term effects of ECT on cognitive functioning (including orientation, retrograde and anterograde memory) and mortality. We identified non-randomised studies investigating mortality after ECT and case-control neuroimaging and post-mortem studies looking at the possibility of structural brain changes after ECT. The search strategy is described in the webappendix (http://image.thelancet.com/extras/02art8375webappendix.pdf).

Two reviewers independently checked search results, and all potentially suitable papers were requested. Paired members of the review team independently extracted data from the identified studies. We assessed the quality of identified randomised trials through the reporting of allocation concealment, masking, loss to follow-up, and length of follow-up. The quality of cohort studies was analysed by consideration of likelihood of measurement bias, handling of confounding factors, number of cases, and loss to follow-up. We judged the quality of case-control studies, including brain-imaging studies, by accounting for likelihood of measurement bias (eg, was the assessment of outcome masked from exposure status?), handling of confounding factors, and number of cases. When randomised trials were available, only this evidence was considered. We resolved any disagreements on quality or data extraction by discussion within the study team.

One primary outcome for assessment of the efficacy of ECT was defined, a priori, to avoid risk of multiple testing or data-driven analyses. When appropriate, data from individual trials was pooled by meta-analysis. Dichotomous data were merged to produce estimates of odds ratios and absolute risk differences. Odds ratios and standardised mean differences were combined with numerical simulation
techniques based on Gibbs sampling. An advantage of this method is that it includes studies that have no events in either or both treatment groups without resorting to crude continuity corrections. Also, the approach does not make the limiting assumption that confidence intervals need to be symmetrical, but rather recognises that it is possible to know more (or less) about the tolerance of an estimate in one direction or the other. Furthermore, the method facilitates meta-regression analyses. We used standard methods for pooling risk differences. In trials in which multiple doses of unilateral ECT were compared with bilateral ECT, the unilateral groups were combined for the analysis, and any possible differences between groups were described qualitatively.

To investigate the possibility of an interaction between dose and electrode position, we did a meta-regression of trials that allocated participants to multiple electrode placements and electrical doses. We based analyses on intention-to-treat data when these data were obtainable. Otherwise we used the researchers’ analysis, in which individuals included have actually received the course of treatment that they were allocated to. The main protocol-defined patients’ subgroups were identified by clinical or demographic factors: psychotic depression, retarded depression, the effect of age, treatment resistance, sex, and severity of depression at entry into the trial. Funnel plots were inspected to assess the presence of publication bias.

**Role of the funding source**

The UK Department of Health, which funded this review, had no role in design of the protocol, in collection, analysis or interpretation of data, in writing of the report, or in the decision to submit the report for publication.

**Results**

Of 624 reports obtained from the search, 73 randomised trials met the inclusion criteria for this review. Several trials...
resulted in multiple publications: a complete list is available from the authors. The quality of reporting of the trials was poor; only two described the method of allocation concealment and most were small. Most, however, used some form of masking of the outcome assessor to limit the effect of ascertainment bias. Visual inspection of funnel plots did not suggest the presence of publication bias.

ECT versus simulated ECT

ECT versus simulated (sham) ECT trials (webtable 1; http://image.thelancet.com/extras/02art8375webtable1.pdf) allow estimation of the specific effect of the electrical stimulus and resulting shock, because patients allocated to a simulated condition receive all the other components of the ECT procedure (including anaesthetic).

Six trials presenting data of 256 patients were available. In five of these, participants received ECT twice a week, and in the remaining trial, three times per week. In four trials, position of the electrodes was reported, with one trial using unilateral placement. Bilateral electrode placement was used in two trials, and in another both unilateral and bilateral electrode placement. The waveform of ECT was described in two trials: sinewave was used in both.

Depressive symptoms—Real ECT was significantly more effective than simulated ECT (figure 1). This result translates to a mean difference in the Hamilton depression rating score (HDRS) of 9.7 (95% CI 5.7 to 13.5) in favour of real ECT. In only one trial were depression ratings scores reported at 6 months after the end of ECT, and a non-significant two-point difference in final HDRS was noted (95% CI –2.7 to 6.7) in favour of the simulated group.

Cognitive functioning—Only one trial provided data on cognitive functioning. In the Northwick Park trial, patients treated with real ECT were better able to retrieve remote memories than were those treated with simulated ECT but had more word recognition errors immediately after treatment. At 6 months, no significant difference was noted between patients treated with real ECT and those treated with simulated ECT on measures of subjective memory impairments, new learning, and remote memory.

Other outcomes—Premature discontinuation from trials happened for patients receiving ECT and simulated ECT, though no significant difference was noted between treatment groups (figure 2). Expressed as risk difference, no significant difference was seen (risk difference –0.003, 95% CI –0.060 to 0.060). No deaths were reported.

ECT versus pharmacotherapy

18 trials (total 1144 participants) comparing ECT with drug therapy were included in the analysis (webtable 2;
### Table

<table>
<thead>
<tr>
<th>Trial</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacSweeney 1975</td>
<td>0.923 (0.011–78.426)</td>
</tr>
<tr>
<td>Robin 1962</td>
<td>0.214 (0.004–2.683)</td>
</tr>
<tr>
<td>Gangadhar 1982</td>
<td>1.970 (0.295–15.338)</td>
</tr>
<tr>
<td>Stanley 1962</td>
<td>1.389 (0.252–8.107)</td>
</tr>
<tr>
<td>Herrington 1974</td>
<td>0.500 (0.008–10.493)</td>
</tr>
<tr>
<td>Greenblatt 1964</td>
<td>0.620 (0.146–2.022)</td>
</tr>
</tbody>
</table>

### Figure 4

**Effect of ECT versus pharmacotherapy on withdrawal from trial**

http://image.thelancet.com/extras/02art8375webtable2.pdf

In five trials, bilateral ECT was used, and unilateral ECT was implemented in two. Frequency of ECT applications was twice a week in four studies and three times a week in five. In five trials, patients were treated with tricyclic antidepressants at doses of 75–150 mg of imipramine or 150 mg of amitriptyline. Tryptophan was used in two trials at doses of 3 g and 6–8 g. The remaining trials used paroxetine 40–50 mg, lithium 800 mg, combination phenelzine 15–45 mg and amitriptyline 100 mg, phenelzine 15–60 mg, imipramine 150 mg or phenelzine 45 mg, or a tricyclic antidepressant or monoamine oxidase inhibitor. Only four trials explicitly required patients to have failed to respond to at least one antidepressant drug before being considered for randomisation to (typically) different drug therapy or ECT. Treatment was for various durations, with three trials reporting end of treatment results at 3 weeks, one study at 3–5 weeks, four at 4 weeks, one at 5 weeks, and one at 12 weeks. In one trial, treatment was continued for four to eight episodes of ECT (about 2–4 weeks).

### Depressive symptoms

Treatment with ECT was significantly more effective than pharmacotherapy (figure 3), translating to a mean difference of 5–2 points (95% CI 1·4 to 8·9) on the HDRS.

### Cognitive functioning

Two trials measured cognitive functioning at the end of the course of ECT, comparing patients treated with drugs with those treated with ECT. One trial reported no significant difference between patients treated with ECT and those treated with drug therapy, and another that more patients treated with ECT had discontinuations in the pharmacotherapy arm only. One trial reported a death in each group.

### Bilateral versus unilateral electrode placement

28 trials comparing patients treated with bilateral or unilateral ECT were identified (1408 participants, webtable 3; http://image.thelancet.com/extras/02art8375webtable3.pdf). Data could be obtained from 22 of these trials to calculate a standardised pooled effect size. In these 22 studies, various electrode placements were used for both unilateral and bilateral ECT. Two studies reported bitemporal electrode placement, two used bifrontal placement, and one bifrontotemporal placement. In three trials, either dominant or non-dominant unilateral placements were reported, and the remaining studies—where described—used non-dominant or right unilateral placement. Three types of unilateral placement were used: D'Elia, Lancaster, and Raotma.

### Patients were treated for various durations, and with different frequencies and electrical doses. Duration of course of treatment was defined in only eight trials: 2 weeks at two doses per week, 6 weeks at two per week, 2 weeks at three per week, 6 weeks at two per week, up to 7 weeks at three per week, four treatments, six treatments, and ten treatments. In two trials, use of a fixed dose of ECT was reported, and in four, a titrated dose was used.

### Depressive symptoms

Bilateral ECT was more effective than unipolar ECT (figure 5), translating to a 3·6 point (95% CI 2·2–5·2) change in depression score in favour of bilateral ECT. Year of publication, which might indicate the confounding effects of improved antidepressant therapy over time, had no effect on outcome (SES –0·05, 95% CI –0·34 to 0·23, in favour of publication before median year).

Two trials reported that high-dose unilateral ECT might be as effective as bilateral ECT, but it could cause fewer adverse cognitive effects. The results of the meta-regression investigating the relation between dose and electrode placement are shown below. 6-month follow-up data were unavailable.

### Cognitive functioning

Six trials reported that time to recovery of orientation was longer for patients treated with bilateral ECT compared with unilateral ECT. In four trials, results from testing of retrograde memory within a week of the end of a course of ECT were reported.
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weeks, maximum of eight actual treatments, and maximum of 4 weeks’ treatment.

Depressive symptoms—No difference between ECT twice a week and three times a week, or between once a week and three times a week, was noted (figure 6). No long-term outcomes were reported.

Other outcomes—Discontinuations were reported in two trials, which were similar for both groups. One trial reported a death due to suicide.

Cognitive functioning—One trial reported no difference in time to reorientation in patients treated three times a week compared with those treated twice a week. Four randomised trials measured cognitive functioning at the end of a course of ECT. Overall, more frequent ECT led to more cognitive impairment.

Dose of electrical stimulus

Seven trials containing results for 342 patients were identified (webtable 5; http://image.thelancet.com/extras/02art8375webtable5.pdf). For the analysis, dose was classified as high and low. In two trials by one group of investigators, the lower dose was reported as 2.5 J and the higher dose was fixed at 40 mC. One trial compared doses of 7–10 J with 40–55 J; in another, treatment titrated to seizure threshold was compared with a fixed dose of 240 mC. Doses of 50% above seizure threshold were compared with either 150% or 500% above seizure threshold in one study, and in another, threshold was compared with 2.5× threshold.

Depressive symptoms—Treatment with a high dose of ECT led to a greater reduction in depressive symptoms or mean change in HDRS of 4.1 points (95% CI 2.4–5.9) in favour of the high dose group (figure 7). Meta-regression analysis, investigating whether the effect of dose was affected by electrode placement, did not note a significant interaction (coefficient 0.175; 95% CI –0.329 to 0.679, in favour of bilateral placement). This result suggests that high dose led to a larger effect in bilateral rather than unilateral ECT, but the effect was not significant. No long-term outcomes were reported.

Cognitive functioning—Patients treated with high-dose unilateral ECT took longer to regain orientation than did those treated with low-dose unilateral ECT. Five trials measured cognitive functioning at the end of a course of ECT. Personal memory was no worse in patients treated with high-dose ECT than in those treated with low-dose ECT, but there was some indication of impairments in anterograde memory in the high-dose group. Findings on the mini-mental state examination (MMSE) were inconsistent.

Stimulus wave form

Eight trials containing results for 296 patients were included (webtable 6; http://image.thelancet.com/extras/02art8375webtable6.pdf). This analysis compared brief pulse with sinewave for electrical stimulation. Bilateral and unilateral placements were used in two trials, and in the remaining studies only bilateral placement was used. Of those trials reporting frequency of administration, ECT twice a week was given in one trial and three times a week in another.

Depressive symptoms—No significant difference between brief pulse and sinewave ECT was noted (figure 8). This finding translates to a mean change in HDRS of 4.2 points (95% CI –2.1 to 10.5). 6-month follow-up data were unavailable.
Cognitive functioning—Results of one trial showed that patients receiving brief pulse ECT recovered more quickly and had better recall of word associates learned shortly before the treatments than did those receiving sinewave ECT.34 Two other trials reported no differences.62,73 In one trial, no significant difference was seen at 6 months post treatment in overall self-rating of memory between patients treated with brief pulse and sinewave ECT.62

Other outcomes—No data were available on discontinuations and no deaths were reported.

Observational studies of mortality secondary to ECT
Four non-randomised cohort studies comparing mortality rates in patients contemporaneously treated with ECT with those not treated with ECT were identified (webtable 7; http://image.thelancet.com/extras/02art8375webtable7.pdf).78–81 Of these, three reported lower overall mortality in patients treated with ECT78–80 and one showed no difference.81

Observational studies of structural brain changes after ECT
Three studies compared ventricular/brain ratios (VBR) on CT scans of patients treated with ECT with those who had...
RCTs were identified which specifically investigated the confidence with which results can be used to lend support for efficacy in older patients. For example, despite the reputation of ECT for safety, the effect of adjunctive treatment during ECT, and studies were identified.

Results would be likely to change materially if a few neutral numbers of trial participants were frequently low, and the mind when interpreting the findings, because the total sample of primary studies. Our search was comprehensive, but several tentative conclusions can be drawn. First, the cognitive impairments associated with ECT treated a cohort of elderly depressed patients with MRI, and a strong association between age and severity of white-matter lesions, but no association with previous ECT, was reported.84

Discussion

Although many of the trials are old, and most were small, the randomised evidence consistently shows that, in the short-term (ie, at the end of a course of treatment), ECT is an effective treatment for adult patients with depressive disorders—as measured by symptom rating scales—and without substantial comorbidity. Despite the considerable heterogeneity in doses and methods of administration between trials, the evidence on the key comparisons of ECT with drug treatments and between different forms of ECT is also reasonably consistent. ECT is probably more effective than drug therapy. Bilateral ECT is moderately more effective than unilateral ECT, and high dose ECT is more effective than low dose.

The Leicestershire ECT trial85 compared ECT with simulated ECT in an unselected group of patients who had been referred for inpatient ECT. This trial did not meet the inclusion criteria for this review because 43 patients had non-depressive diagnoses and we only included trials in depressed patients.87 However, the results of the Leicester trial qualitatively accord with those of the included trials.

There is less randomised evidence that the short-term benefits are maintained in the long term. Non-randomised studies suggest that relapse rates are high after acute response to ECT.88 Continuation drug therapy with antidepressants could be an effective preventive strategy, although this area was beyond the scope of this review.

Although ECT is sometimes thought to be a life-saving treatment, there is no direct evidence that ECT prevents suicide: as an effective treatment for severe depression, it is possible that it does.

Any differences between ECT and drug therapy might not be attributable to the stimulus or shock alone, but could be due to other components of the ECT procedures (including anaesthetic and nursing care).

A serious potential source of bias in any systematic review is failure to retrieve a comprehensive and unbiased sample of primary studies. Our search was comprehensive, and funnel plots did not suggest the presence of publication bias in any of the studies in this review. However, the possibility cannot be excluded and needs to be borne in mind when interpreting the findings, because the total numbers of trial participants were frequently low, and the results would be likely to change materially if a few neutral studies were identified.

The effects of different anaesthetic agents on efficacy and safety, the effect of adjunctive treatment during ECT, and the effectiveness of maintenance drug therapy after successful treatment with ECT are outside the scope of this review. We were unable to investigate subgroup effects because data were too limited to allow this to be done reliably. For example, despite the reputation of ECT for efficacy in older patients, elderly people tend to be underrepresented in trials, which limits the confidence with which results can be used to lend support to clinical practice in this subgroup. Similarly, no RCTs were identified which specifically investigated the efficacy of ECT in women with psychiatric symptoms associated with pregnancy or recent childbirth, and again, such patients did not seem to be well represented in the trials.

Data on cognitive functioning were far from comprehensive, but several tentative conclusions can be drawn. First, the cognitive impairments associated with ECT treated a cohort of elderly depressed patients with MRI, and a strong association between age and severity of white-matter lesions, but no association with previous ECT, was reported.84
to keep side-effects to a minimum. It is clear that any attempt to simplify our findings to one strategy for all clinical situations (one size fits all) will be unhelpful. Thus, it is not possible to recommend the exclusive routine use of either unilateral or bilateral ECT because it is likely that specific clinical circumstances may need one or the other. Equally, dose titration may be useful in minimisation of electrical dose, but it will be unnecessary where a maximum clinical effect is judged imperative.

To make ECT maximally effective, keep side-effects to a minimum, and tailor the treatment to an individual patient, it needs to be administered in a service in which the staff keep up-to-date with emerging evidence, have the necessary practical skills to deliver the appropriate treatment, and can provide information to the patient about the risks and benefits of ECT. At present, repeated audits of ECT services across the UK find that the standards of ECT are poor. For example, an audit reported that only a third of ECT clinics met the standards of the Royal College of Psychiatrists. Just 16% of consultants attended their ECT clinic every week, and only 6% had session time for ECT duties. Only about a third of clinics had clear policies to help guide junior doctors to administer ECT effectively.

In conclusion, there is a reasonable evidence base for the use of ECT. It does not rest simply on anecdote, habit, and tradition. The trials that have been done reflect concerns that were uppermost at the time. In the 1970s, this concern was efficacy of electroshock per se, more recently it has been dose and site of shock administration. ECT remains an important treatment option for the management of severe depression.

**Contributors**

S Caremy managed the search process, wrote the protocol, extracted and analysed data, and wrote the report. P Cowen wrote the protocol, interpreted findings, and wrote the report. K Dearthness designed the search strategy and wrote the report. J Eastaugh wrote the protocol, extracted and analysed data, and wrote the report. N Freemantle had overall responsibility for statistical aspects of the review, wrote the protocol, extracted and analysed data, and drafted the report. G Goodwin, A Harvey, H Lester, and R Rogers wrote the protocol, extracted data, interpreted findings, and wrote the report. A Scott wrote the protocol, interpreted findings, and wrote the report. A Tomlin designed the search strategy and wrote the report.

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**Conflict of interest statement**

None declared.

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