

# IS ELECTROCONVULSIVE THERAPY ANY MORE EFFECTIVE THAN SIMULATED ELECTROCONVULSIVE THERAPY IN TREATMENT-RESISTANT DEPRESSION?

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## SUMMARY

**Background:** Electroconvulsive therapy (ECT) fell out of favour towards the end of the 20<sup>th</sup> century with the advent of effective and well-tolerated antidepressants. It is now experiencing somewhat of a 'renaissance' in England, with an 11 percent increase in the number of ECT treatments carried out in 2015-16 compared with 2012-13, which represents approximately 2,000 additional treatments.

**Aims:** This paper seeks to examine clinical trials comparing the efficacy of real ECT with simulated ECT in treatment-resistant depression (TRD) to determine whether the resurgence of ECT in recent years is justified.

**Methods:** A PubMed search was performed to identify clinical trials comparing real ECT with simulated ECT. 6 trials met the inclusion criteria. These were then analysed, and their methodology assessed.

**Results:** 5 out of the 6 trials found real ECT to have a greater antidepressant effect than simulated ECT. The trial that showed no significant difference used a unilateral electrode placement. Analysis revealed significant weaknesses in the trials.

**Conclusions:** There is clear evidence that real ECT has a greater antidepressant effect than simulated ECT when a bilateral electrode placement is used, despite the weaknesses identified in the trials. Continued use of ECT to treat TRD in England and other countries should be encouraged. Further research is needed to better understand its mechanism of action and refine the techniques used.

**Key words:** electroconvulsive therapy – simulated – depression - ECT

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## INTRODUCTION

Electroconvulsive therapy (ECT) is a controversial treatment in psychiatry and is sometimes viewed unfavourably by both members of the medical profession and the public. The Royal College of Psychiatrists states on its website: "It has been suggested that ECT works not because of the fit, but because of all the other things – like the extra attention, support and the anaesthetic – that happen to someone who has it." This commonly held view has been a barrier to its use in treatment-resistant depression (TRD).

To determine if the electrical stimulus applied to a patient during ECT has an antidepressant effect, clinical trials comparing simulated ECT with real ECT have been carried out. In simulated ECT, the patient receives the same medical treatment as a patient undergoing real ECT, but the electrical stimulus is not applied. In all the clinical trials identified in this paper, the medical treatment included the use of a muscle relaxant and general anaesthesia. This is termed 'modified ECT' and is preferable for safety reasons.

The main use of ECT in the West is in the treatment of TRD. TRD is defined as depression with an unsatisfactory response to two adequate trials of two different classes of antidepressant. Inherent difficulties exist in conducting a clinical trial for this indication and in interpreting results. First, variation in the drugs between patients makes them less comparable. The drugs used vary between patients because of differences in the side effects experienced and how effective they are for that

patient, which makes a bespoke drug regime necessary. A good trial design must balance the needs of the patient with the need for comparable groups of patients with regards to medication. Ideally all the patients would be on identical drugs or none at all throughout the whole study. In the trials discussed, a common theme is difficulty in interpreting the data due to differences in the drugs prescribed between patients.

Second, ECT is often considered a last resort, which places a limit on the sample size that can be achieved in a single trial. The National Institute for Health and Care Excellence (NICE) guidelines (2009) advise "Consider ECT for acute treatment of severe depression that is life-threatening and when a rapid response is required, or when other treatments have failed." In practice, this means that trial participants can only be recruited from a very limited pool of patients. This means that the differences observed between real ECT and simulated ECT groups may be due to low statistical power.

Finally, the severity of TRD means that ethical considerations preclude further trials of this sort from being approved, as ECT is now believed to be an effective treatment. This is especially important due to the risks of general anaesthesia itself, which is now required for safety reasons.

## METHODS

A PubMed search was carried out to identify clinical trials (using the clinical trials filter) which compared the efficacy of real ECT and simulated ECT using the key

words 'electroconvulsive therapy' AND 'simulated' AND 'depression'. After removing a duplication, 17 results were returned. The inclusion criteria were:

- Original clinical trial (2);
- Comparing efficacy between real and simulated ECT as the main aim (8);
- Indication of TRD (1).

Numbers in brackets indicate papers that did not meet each of the stated inclusion criteria.

After applying the inclusion criteria, 6 trials were identified for further analysis.

## RESULTS

Six clinical trials met the inclusion criteria. Table 1 outlines the methods and findings of the six trials. Four of these trials compared bilateral ECT with simulated ECT and one compared unilateral ECT with simulated ECT. The final trial (Brandon et al. 1985) had two experimental groups, comparing right unilateral ECT, bilateral ECT and simulated ECT.

Five out of the six trials found real ECT to have a greater antidepressant effect than simulated ECT. The trial in which no significant difference was seen used unilateral electrode placement rather than bilateral electrode placement (Lambourn & Gill 1978).

In the Freeman trial (Freeman et al. 1978), the simulated ECT group received two simulated treatments in week 1, followed by real treatments twice-weekly from week 2. The real ECT group received real treatments twice-weekly from the start. As such, the simulated group were 'delayed' by 1 week and two real treatments. After two treatments, the real ECT group were significantly less depressed than the simulated group by all measures other than the Beck self-rating depression scale. After this time, the simulated ECT group caught up with the real ECT group such that there was no significant difference in depression scores after the final treatment. The mean number of treatments for the simulated group was 7.15 (including the two simulated treatments) and 6.0 for the real ECT group, suggesting that factors other than the electrical stimulus had a part to play in the recovery of the patients.

Lambourn and Gill found no benefit of real ECT over simulated ECT in terms of improvement in symptoms, as measured by the Hamilton rating scale for depression. Unilateral electrode placement is used, rather than bilateral electrode placement. At the time of the study (1978), it may not have been fully understood that the efficacy of unilateral ECT is strongly dose-related, which could explain the absence of a significant difference.

In the Northwick Park trial (Johnstone et al. 1980), a statistically significant advantage was found in the Hamilton scores over the 4-week treatment period, but not the Leeds and nurses' rating scales. Additionally, the advantage was not maintained at the 1- and 6-month

follow-ups. The medications prescribed after the treatment period were similar between the groups, so it is hard to attribute the loss of effect to differential treatment. The authors concluded that the antidepressant effect of real ECT is short-lived.

West and colleagues (1981) conducted another trial which showed real bilateral ECT to be significantly superior to simulated ECT, although it was limited in its sample size (just 11 patients per group). A crossover phase, where 10 of the 11 in the simulated group then had real ECT, showed these patients improved too.

The Leicestershire trial (Brandon et al. 1984) had the advantage of a large sample size (n=95 intended to treat and n=77 completers included in the analysis). At the 2-week and 4-week assessments (where the results were comparable due to cessation of antidepressant therapy), there was a significant advantage in the real ECT group compared to the simulated ECT group. At the 12- and 28-week assessments, there was no significant difference between the groups. The disappearance of this difference could be attributed to the unrestricted use of drugs in the follow-up period. In addition, those in the simulated group were more likely to be prescribed a course of real ECT in the follow-up period (20 out of 34 versus 17 out of 43;  $p=0.04$ ) and additional courses had a greater number of treatments for those in the simulated group compared to the real group (6.77 versus 5.24 treatments).

Gregory and colleagues (1985) carried out another trial, but this time comparing bilateral ECT, unilateral ECT and simulated ECT. Whilst five patients received additional drugs unique to them during the treatment period, the drugs used are clearly stated (the research team decided that it was unethical to stop these). Their results are statistically significant during the treatment period, finding bilateral ECT and unilateral ECT to be more effective than simulated ECT, and bilateral ECT having the fastest speed of response.

## DISCUSSION

Whilst most of the trials provide support for real ECT, differences exist in the use of medications during the trials and the treatment prescribed after the ECT course. Differences in the anaesthetic and other medications used as part of the procedure make the studies less comparable. In four of the trials, antidepressant drugs were either stopped or standardised during the treatment period. In the Freeman trial, however, patients were allowed to continue taking their antidepressant drugs throughout the study, which is a weakness in their methodology. In the Gregory trial, five out of sixty-nine patients received additional drugs in the treatment period, but this was due to ethical considerations, rather than poor trial design.

In the Freeman trial, had the simulated treatments been of equivalent effect to the real treatments, it would be reasonable to assume that the simulated group would

**Table 1.** A Comparison of Studies Investigating Simulated ECT and Real ECT

| Study                 | Blinding and Randomisation   | Intervention and patient treatment   | Metrics  | Results summary  | Conclusion stated   |
|-----------------------|--|--|--|--|---|
| Freeman et al. 1978   | Not blinded: ECT doctor, anaesthetist and ECT nurse. Other clinicians and assessors were blinded. Random allocation. | N=20 for real and simulated groups. The real group received bilateral ECT twice weekly from week one. The simulated group received simulated ECT twice in week one followed by twice weekly real bilateral ECT from week two. Identical anaesthesia used. Patients were allowed to continue pharmacotherapy.     | HRSD, visual analogue scale, Wakefield and Beck self-rating depression scales.   | After two treatments, greater improvement in real group by all measures except the Beck score (no significant difference). Subsequent 'catch-up' so there are no significant differences after the final treatment. Mean total number of treatments was 6.0 for real and 7.15 for simulated. | "The results show that ECT is clearly superior to simulated ECT."   |
| Lambourn & Gill 1978  | Assessor was blinded, as was the referring doctor. A constrained random procedure based on age and sex.              | N=16 for real and simulated groups. The real group received brief pulse unilateral ECT three times a week for two weeks. The simulated group received the same treatment except no electrical stimulus was applied. Psychotropic drugs were discontinued during the treatment period except for benzodiazepines. | HRSD, global assessment of improvement by the referring doctor one day after the six treatments, days in hospital and treatment received in the one-month follow-up. | No significant difference between the two groups in terms of improvement in Hamilton score. 5 patients failed to improve at all from the treatment (4 of which were from the simulated group). Six patients did not complete the one-month follow-up.  | "... the effectiveness of unilateral brief pulse ECT... is due in large part to the attendant procedures associated with the administration of an anaesthetic and the mystique associated with an unusual form of treatment." |
| Johnstone et al. 1980 | Not blinded: anaesthetist and ECT doctor. All other parties blinded. Random allocation.                              | N=70 overall (Assume N=35 for each group). 62 completers. Real ECT group received 8 real bilateral ECT treatments over 4 weeks. Control group received 8 simulated procedures. Antidepressants stopped for treatment period.   | HRSD, Leeds rating scale and nurses' rating scale. Present State Examination.  | Significant results established for the HRSD, but not the Leeds or nurses' rating scales. No difference at the one month and 6-month follow-up between the groups.   | "... our findings suggest that the antidepressant effects of repeated electrically induced convulsions are of relatively short duration."   |

**Table 1.** Continued

| Study               | Blinding and Randomisation   | Intervention and patient treatment  | Metrics  | Results summary  | Conclusion stated   |
|---------------------|--|---|--|--|---|
| West et al. 1981    | Patients and assessors were blinded. Random allocation.                                | N=11 for real and simulated groups. Bilateral ECT used twice weekly for three weeks. Simulated group received simulated procedures. All received 50 mg Amitriptyline at night. No other medications were prescribed.  | Visual analogue scale, nurses' rating scale and Beck Depression Inventory.   | Significant improvement by all measures for the real group, but not the simulated group. 10 patients entered the crossover phase (all from the simulated group) and there was a significant improvement in all measures.   | "In this study, electric convulsion therapy was shown to be an excellent treatment of severe depressive illness. The question of further treatment after the initial study was not investigated."   |
| Brandon et al. 1984 | Extensive efforts to ensure blinding were carried out. Random allocation.              | N=53 for real ECT and N=42 for simulated ECT. Real group given bilateral ECT twice weekly. Maximum of eight treatments over 4 weeks. Control group received simulated procedures. Only anxiolytics were prescribed during the trial. After the trial, antidepressants were prescribed freely. | A comprehensive rating package including the HRSD at the initial interview. Then assessment at 2 weeks, 4 weeks, 12 weeks (one month after last treatment) and 26 weeks (6 months after last treatment). | N=77 for analysis. The real ECT group showed greater improvement at the 2-week and 4-week assessments. This difference was not maintained at 12 and 28 weeks. 11 out of 43 real ECT patients did not need all eight treatments, compared to just 2 out of 34 simulated ECT patients. | "We believe that our data indicate that electroconvulsive therapy is an effective and rapidly acting treatment for severe depressive illness and that its use should be favoured in patients at risk of suicide because of the rapidity of response." |
| Gregory et al. 1985 | Assessors and clinicians responsible for the patients were blinded. Random allocation. | N=23 for each group. Patients were randomly allocated to receive either bilateral ECT, right unilateral ECT or simulated ECT twice weekly for three weeks. Small doses of benzodiazepines given during the study and 5 patients received additional drugs during the study.                   | A comprehensive rating package (including the HRSD and MADRS) initially. MADRS after every two treatments and a final assessment to include the MADRS, PSE, PIRS and HRSD.                               | Bilateral and unilateral ECT were both significantly better than simulated ECT, using either MADRS, HRSD or PIRS scores, or percentage change scores. Differences were not maintained after treatment. Speed of onset was slower for unilateral ECT compared to bilateral ECT.       | "... the passage of electricity is an important part of the ECT procedure. Both bilateral and unilateral ECT are highly effective, but unilateral requires more treatments, and the speed of response is probably slower."                            |

require the same total number of treatments as the real ECT group to achieve the same improvement in symptoms. However, the simulated ECT group required 7.15 treatments, whilst the real ECT group required only 6.0. This indicates that the electrical stimulus provided an antidepressant effect, but also that improvement was not solely due to the electrical stimulus (in which case a full 2 additional treatments would be required).

In the Northwick Park trial (Johnstone et al. 1980), a statistically significant advantage of real ECT over simulated ECT was found with the Hamilton rating scale, but not the nurses' rating scale or the Leeds rating scale. This discrepancy was largely neglected in the results and discussion, which makes drawing a confident conclusion from this trial difficult.

In the trial by Gregory and colleagues, the data analysis is not entirely clear with regards to withdrawals. In the figure, the 'number on whom complete data available' is given as a higher number than the number of participants minus the withdrawals, so some of the withdrawals had been included in the analysis. This ambiguity reduces the credibility of the paper. In contrast, the Leicestershire trial (Brandon et al. 1984), which found real ECT to be significantly better than simulated ECT, had the advantages of a large sample size and complete cessation of antidepressant drugs during the treatment period.

The two main rating scales used to measure the severity of depression are the Hamilton Rating Scale for Depression (HRSD; Hamilton 1960) and the Montgomery Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg 1979). Whilst the HRSD is the most commonly used measure of depression, it has clear weaknesses. Critics of Hamilton's scale argue that heterogeneity exists within the rating descriptors (i.e. the items do not measure a single symptom), the reliability of the scale is poor, it is insensitive to change (thus reducing the apparent efficacy of treatments used in clinical trials), and it provides no justification for the differential weighting of items (some items score a maximum of 4, whereas others score a maximum of 2) (Bagby et al. 2004). Whilst this is not the focus of this discussion, it is important to realise that many of the trials discussed above rely on this scale which has significant shortcomings.

## CONCLUSION

When evaluating each of these trials in turn, it is apparent that weaknesses exist in all of them. However, in many cases these weaknesses arise because of the difficult nature of conducting a well-designed trial for this indication, as described in the introduction. Five out of the six trials demonstrated an advantage of real ECT over simulated ECT. The trial by Lambourn and Gill used only unilateral ECT, which may not have been administered effectively due to a low charge being used. Unfortunately, undertaking further clinical trials of this

type would be very difficult owing to contemporary ethical considerations, making further analysis of existing trials necessary. The data itself consistently shows an advantage of bilateral ECT over simulated ECT. On balance, it can be reasonably concluded that real ECT is superior to simulated ECT in terms of alleviating TRD, despite the weaknesses identified. Thus, the electrical stimulus does have an antidepressant effect and the improvement in depressive symptoms is not solely due to the placebo effect or increased medical attention.

It is therefore prudent to encourage further research into the mechanism of action of ECT and refining the techniques used (such as the electrode placement and the properties of the electrical stimulus). Its continued and increasing clinical use in England and elsewhere is justified and it remains a valuable treatment in combating TRD.

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## References

1. Bagby RM, Ryder AG, Schuller DR & Marshall MB: *The Hamilton Depression Rating Scale: Has the Gold Standard Become a Lead Weight?* *American Journal of Psychiatry* 2004; 161:2163-2177
2. Barnes R: *Information about ECT (Electro-convulsive therapy)*. Royal College of Psychiatrists, 2015. Retrieved from <https://www.rcpsych.ac.uk/healthinformation/treatmentsandwellbeing/ect.aspx>
3. Brandon S, Cowley P, McDonald C, Neville P, Palmer R & Wellstood-Eason S: *Electroconvulsive therapy: results in depressive illness from the Leicestershire trial*. *British Medical Journal (Clinical Research Edition)* 1984; 288:22-25
4. Davis N & Duncan P: *Electroconvulsive therapy on the rise again in England*. *The Guardian*, 17<sup>th</sup> April 2017. Retrieved from <https://www.theguardian.com/society/2017/apr/17/electroconvulsive-therapy-on-rise-england-ect-nhs>
5. Freeman CPL, Basson JV & Crichton A: *Double-Blind Controlled Trial of Electroconvulsive Therapy (E.C.T.) and Simulated E.C.T. in Depressive Illness*. *The Lancet* 1978; 311:738-740
6. Gregory S, Shawcross CR & Gill D: *The Nottingham ECT Study*. *British Journal of Psychiatry* 1985; 146:520-524
7. Johnstone EC, Lawler P, Stevens M, Deakin JFW, Frith CD, Mcpherson K & Crow TJ: *The Northwick Park Electroconvulsive Therapy Trial*. *The Lancet* 1980; 316:1317-1320
8. Lambourn J & Gill D: *A Controlled Comparison of Simulated and Real ECT*. *British Journal of Psychiatry* 1978; 133:514-519

9. NICE: *Depression in adults: recognition and management. Clinical guideline, 2009. CG90. 1.10.4 Electroconvulsive therapy (ECT). Retrieved from <https://www.nice.org.uk/guidance/cg90/chapter/1-Guidance#step-4-complex-and-severe-depression>*
10. West ED: *Electric convulsion therapy in depression: a double-blind controlled trial. British Medical Journal (Clinical Research Edition) 1981; 282:355-357*

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