Antidepressant pharmacotherapy failure and response to subsequent electroconvulsive therapy: a meta-analysis
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CRD summary
Remission rates after electroconvulsive therapy treatment for major depressive disorder were significantly higher in patients without previous pharmacotherapy failure compared with medication-resistant patients. Electroconvulsive therapy also appeared to be effective for severely depressed patients. Limitations in the review process and reliance on observational studies imply that the authors' conclusions should be treated with caution.

Authors' objectives
To evaluate the effect of previous antidepressant pharmacotherapy failure on the efficacy of electroconvulsive therapy for major depressive disorder.

Searching
PubMed was searched to June 2009 for publications in English; search terms were reported. Bibliographies of retrieved articles were handsearched.

Study selection
Prospective cohort studies of patients treated with electroconvulsive therapy (ECT) for major depressive disorder were eligible for inclusion. Participants had to be diagnosed with major depression using accepted diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM) third edition (DSM-III-R), fourth edition (DSM-IV) or Research Diagnostic Criteria. Outcomes had to be reported using a valid depression rating scale such as Hamilton Rating Scale for Depression (HAM-D) or Montgomery-Asberg Depression Rating Scale. Eligible patients could be diagnosed with major depression with or without psychotic features. Patients had to discontinue antidepressant drugs at least three days before and during the course of ECT. Adequacy of both antidepressant and antipsychotic treatment for psychotic patients was assessed and, therefore, criteria for patients with psychotic depression and nonpsychotic depression differed. Medication resistance was defined using the Antidepressant Treatment History Form (ATHF) developed in 1990 by the Columbia University Group. The primary outcome was remission rate defined as a score of 7 or less on the 17-item HAM-D, 10 or less on the 24-item HAM-D or 8 or less on the Montgomery-Asberg Depression Rating Scale (with a preference in that order if more than one scale was reported), which was felt to be more appropriate than response rate since most patients show some benefit in HAM-D after ECT. Studies were excluded if they did not address medication resistance or remission rates and if they focused on relapse or continuation therapy after successful ECT.

Four of the seven studies were carried out by the same group in New York; two of these studies included bipolar depressive patients. In two studies a minority of patients had psychotic features. In one study almost 50% of patients had psychotic features. One study was only of patients with non-psychotic depression. In two of the three non-New York studies almost 50% of patients had psychotic features; the third study excluded patients with psychotic depression. In three studies a substantial number of patients received a less effective form of ECT (right unilateral ECT) now considered to require a higher dose and patients were allowed to use lorazepam during the ECT course, which could reduce the effectiveness of the ECT therapy. Two of the same three studies allowed concurrent use of haloperidol during the ECT course, which was considered unlikely to interfere with the efficacy of the ECT. Diagnosis in these three studies was made using DSM-IV criteria and diagnosis was made using the Research Diagnostic Criteria in the four New York studies. Two of the three non-New York studies used the 17-item HAM-D to measure remission rate. All other studies used the 24-item HAM-D.

The authors did not state how many reviewers performed study selection.

Assessment of study quality
Methodological quality was assessed by three reviewers who used an assessment form designed by the Dutch Institute.
for Healthcare Improvement for cohort studies to assess the adequacy of the cohort definition, selection bias, blinded outcome assessment, confounders, prognostic factors and clinical outcomes.

**Data extraction**
Remission rates were extracted for patients with and without previous pharmacotherapy failure and used to calculate differences expressed as odds ratios with 95% confidence intervals (CI).

The authors did not report how many reviewers performed data extraction.

**Methods of synthesis**
Odds ratios (ORs) were pooled using a Mantel-Haenszel fixed-effect model. Between-study heterogeneity was determined using the Cochrane Q and I² statistics. An adjusted pooled analysis was performed using weighted odds ratios.

**Results of the review**
Seven prospective cohort studies were identified (958 participants, range 53 to 328). The total number of patients with previous pharmacotherapy failure was 585 and 373 patients were not medication resistant.

Overall remission rates after ECT were 48.0% for patients with previous pharmacotherapy failure and 64.9% for patients without previous pharmacotherapy failure. There was a significant increase in remission rate for patients without previous pharmacotherapy failure versus those with previous pharmacotherapy failure (OR 0.58, 95% CI 0.44 to 0.75, I²=34.1%; seven studies). After weighting, the adjusted pooled odds ratio was similar (OR 0.52, 95% CI 0.39 to 0.69). Only four individual studies showed a significant effect and all four of these were carried out by the same group.

**Authors' conclusions**
The efficacy of ECT was significantly superior in patients without previous pharmacotherapy failure compared with medication-resistant patients. ECT seemed to be an effective treatment for severely depressed patients as well as for patients with previous pharmacotherapy failure.

**CRD commentary**
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Only one relevant database was searched for published studies in English and it appeared that unpublished studies were not considered; therefore, some relevant studies may have been missed. The authors may have identified potentially relevant studies without using the search strategy and included one of these in the review. Study quality was assessed using suitable criteria, but few relevant details were reported. Validity assessment was carried out with efforts to reduce error and bias; it was unclear whether this applied to other aspects of the review process.

Some relevant study details were reported, but no details of patient age and gender were provided. Statistical heterogeneity was assessed. The statistical method used for the meta-analysis seemed appropriate, but there were reservations about the appropriateness of combining the results considering heterogeneity in symptoms and lack of patient data. No subgroup analyses were performed. The authors noted that patients with psychotic depression were known to respond better to ECT and so the proportion of those patients in a study would affect the overall results.

Potential limitations in the review process, uncertainties about the quality of included studies (all the studies were observational studies and these have their own biases) and the limited number of studies identified mean the authors’ conclusions should be treated with caution.

**Implications of the review for practice and research**
**Practice:** The authors stated that optimal administration of ECT was very important, especially in medication-resistant patients. Bilateral ECT should be considered without concomitant medication with benzodiazepines and the ECT course should be continued for as long as the patient improved.
Research: The authors did not state any implications for research.

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