A systematic review of treatments for refractory depression in older people
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CRD summary
The authors concluded that there was a paucity of evidence on treatment refractory depression, but half the older people examined responded to additional or alternative pharmacological treatment. Further high-quality research was needed urgently. Given the poor quality of the small evidence base, findings should be interpreted with caution. The recommendations for further high-quality research seem appropriate.

Authors' objectives
To evaluate the role of pharmacological, physical and psychological interventions for the treatment of refractory depression in older people.

Searching
PubMed, Web of Science and Cochrane Database of Systematic Reviews were searched up to August 2010; search terms were reported. Reference lists of included studies were manually searched.

Study selection
Studies of older people (at least 55 years) treated for refractory depression (defined as failure to respond to at least one adequate treatment during the current illness episode in an entire cohort or a separately analysed subgroup) were eligible for inclusion. Studies of patients who had responded to treatment but relapsed early and studies that did not allow data on baseline non-responders to be separately analysed were excluded. Abstracts were excluded. The outcome of interest was response to any treatment.

Included studies were of patients with psychotic or non-psychotic depression. Most studies diagnosed patients based on the Diagnostic and Statistical Manual of Mental Disorders. The mean age of included patients ranged from 65.6 to 77.1 years. Some patients had comorbid conditions, but all studies excluded patients with severe dementia. Definitions for resistant depression varied across studies, but included failure to respond to one or more pharmacological therapies. Response definitions were measured mostly using various cut-off values on the Hamilton Depression Rating Scale or the Montgomery-Asberg Depression Rating Scale. Some patients were resistant to electroconvulsive therapy. The duration of treatment resistance varied considerably. Sixteen active treatments were assessed in the included studies (antidepressants with or without psychological therapy or augmentation). Study duration ranged from two weeks to three years. Half of the studies reported sources of funding and half did not.

The authors did not state how many reviewers screened studies for inclusion.

Assessment of study quality
Two reviewers independently assessed study quality according to Centre for Evidence Based Medicine randomised controlled trial evaluation criteria. Studies were assessed on whether they reported on randomisation, blinding, comparability of groups and baseline, equal study conditions for treatment groups, intention-to-treat analyses and loss to follow-up. Discrepancies were resolved through discussion.

Data extraction
The proportion of patients who responded to treatment or, where appropriate, to a comparator (placebo or control) was extracted, along with mean changes in depression scores (where this was the primary outcome of the study). Response was defined as below a threshold or a reduction of at least 50% in a depression score.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Where at least three studies reported on the same treatment, a fixed-effect model was used to calculate pooled proportions of patients who responded to treatment, along with associated 95% confidence intervals (CIs). Where there was evidence of statistical heterogeneity, a random-effects model was used to pool data. Statistical heterogeneity was
assessed using the $I^2$ statistic. Sensitivity analysis included only randomised trials.

Publication bias was assessed using funnel plots and the Egger test.

**Results of the review**

Fourteen articles (13 studies) were included in the review (390 participants, range six to 93). Three studies were randomised (one double blind, one single blind and one not blinded). One randomised study was placebo controlled and the other two studies compared two active treatments. The 10 non-randomised studies were open label. Most were single-arm studies with no comparison group.

There was evidence of significant statistical heterogeneity among studies ($I^2=72\%$) and a random-effects model was used to pool data. The overall response rate for the 16 active treatments investigated in the studies was 52\% (95\% CI 42 to 62). Similar rates were reported when only randomised trials were assessed, but with slightly wider confidence intervals.

More than three studies (all non-randomised) investigated lithium augmentation and were combined in meta-analysis. The overall response rate was 42\% (95\% CI 21 to 65; five studies, 57 participants).

Treatments were reported to be generally well tolerated. Other findings were reported for individual studies. There was no evidence of significant publication bias.

**Authors' conclusions**

There was a paucity of evidence on treatment refractory depression. In the studies examined, half of the older people with refractory depression responded to the addition of a second pharmacological treatment or change to another antidepressant. Further high-quality research was needed urgently.

**CRD commentary**

The review question was clear and supporting inclusion criteria were stated. Appropriate sources were searched for relevant publications. It was unclear whether language restrictions were applied and there were no apparent attempts appear to locate unpublished data, so potentially relevant data may have been missed. Study quality was assessed using previously published criteria that may not have been the most appropriate tool to assess non-randomised trials. Study quality was performed in duplicate, but it was unclear whether this was also the case for study selection and data extraction, so reviewer error and bias could not be ruled out.

The authors acknowledged the paucity in data and that most of the evidence was based on small open label studies. Indeed, most studies were non-comparative and the meta-analysis assessed only prevalence of response rather than effectiveness of treatments. The authors acknowledged heterogeneity among studies and the short treatment durations. One of the higher-quality studies assessed a treatment that was not licensed for depression at the time. The authors highlighted that it was unclear from the studies whether treatment resistance was due to patients actually being resistant to treatment or whether it was due to non-adherence in taking medication.

Given the paucity of data and limitations of the evidence base, any findings should be interpreted with caution. The authors’ recommendation for further high quality research seems appropriate.

**Implications of the review for practice and research**

**Practice**: The authors stated that half the patients responded to either an additional second treatment or a change to another antidepressant, which indicated that failure to respond to a single antidepressant did not imply lack of response to other treatments.

**Research**: The authors stated an urgent need for high-quality randomised controlled trials to compare treatments in older patients with refractory depression. Trials should include populations with physical and cognitive impairment and assess psychological treatments and electroconvulsive therapy.

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