A metaanalysis of clinical trials comparing moclobemide with selective serotonin reuptake inhibitors for the treatment of major depressive disorder

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CRD summary
The authors concluded that moclobemide and selective serotonin re-uptake inhibitors do not differ in their overall effectiveness in the treatment of major depressive disorder, but they do differ with respect to side-effects. The authors' conclusions reflect the evidence presented. However, given the methodological weaknesses in the review process, the reliability of their conclusions is unclear.

Authors' objectives
To compare response rates among patients with major depressive disorder (MDD) who have been treated with either moclobemide or selective serotonin re-uptake inhibitors (SSRIs).

Searching
MEDLINE, EMBASE and the Cochrane Library were searched; the keywords were reported. There were no limits on publication dates and no language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies comparing moclobemide with at least one SSRI for the treatment of acute-phase MDD were eligible for inclusion. The included studies assessed moclobemide compared with fluvoxamine, fluoxetine, sertraline or paroxetine. The duration of treatment ranged from 4 to 16 weeks. None of the studies included a placebo group.

Participants included in the review
Studies of patients being treated for acute-phase MDD were eligible for inclusion. Studies that reported only on the treatment of patients with bipolar disorder, dysthymic disorder, minor depressive disorder or seasonal affective disorder were excluded from the review. Studies of patients with psychotic features or patients with active alcohol or substance abuse disorders were also excluded from the review. In the included studies, MDD diagnosis was based on the American Psychiatric Association's DSM-III or DSM-III-R criteria.

Outcomes assessed in the review
Studies that measured response rates to treatment using either the Hamilton Depressive Rating Scale (HDRS) or the Montgomery-Asberg Depression Rating Scale, and defined response as a 50% or greater decrease in depression severity from baseline to end point, were eligible for inclusion. With the exception of one study, the included studies used the HDRS. Secondary outcomes included overall discontinuation rates, rates of discontinuation due to adverse events and inefficacy, and the rates for five adverse events (nausea, fatigue or somnolence, insomnia, anxiety and headaches).

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for inclusion. Any disagreements were resolved by the involvement of a third person not involved in the meta-analysis. The authors reported that there were no disagreements between authors' choices relating to study selection.

Assessment of study quality
The authors did not state that they assessed validity.
Data extraction
Data were extracted for response rates, overall discontinuation rates, rates of discontinuation due to adverse events and rates of discontinuation due to inefficacy, and relative risks (RRs) and 95% confidence intervals (CIs) were calculated. The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
A meta-analysis was conducted by pooling the estimates of response rates for moclobemide and SSRI treatment groups in a random-effects model, using the methods of DerSimonian and Laird. A random-effects model was also used to compare all secondary outcome measures. Publication bias was assessed using a funnel plot and Egger's test.

How were differences between studies investigated?
A chi-squared test was used to test for statistical heterogeneity in the meta-analyses. A meta-regression was used to examine the impact of mean moclobemide dosage on response rate RR.

Results of the review
Twelve RCTs (n=1,207) were included; the numbers of patients ranged from 40 to 209. All of the included studies were sponsored by the manufacturer of moclobemide.

Response rates.
There were no statistically significant differences in response rates between moclobemide and SSRI treatment groups; the pooled RR was 1.08 (95% CI: 0.92, 1.26, p=0.314). There were no statistically significant relationships between the mean moclobemide dosage and the RR of response rates. There was no evidence of statistical heterogeneity among the included studies (p=0.958).

Discontinuation rates.
There were no statistically significant between-group differences in overall discontinuation rates, discontinuation rates due to adverse events, or discontinuation rates due to lack of efficacy.

Side-effects.
SSRI treatment was associated with higher rates of nausea (RR 0.6, 95% CI: 0.5, 0.8, p=0.001), headaches (RR 0.6, 95% CI: 0.5, 0.8, p=0.001) and treatment-emergent anxiety (RR 0.5, 95% CI: 0.2, 0.9, p=0.029) when compared with treatment with moclobemide. There were no statistically significant between-group differences in rates of fatigue and somnolence, nor in rates of insomnia.

There was no evidence of publication bias (p=0.643).

Authors' conclusions
The results suggested that moclobemide and SSRIs do not differ in their overall efficacy in the treatment of MDD, but they do differ with respect to side-effects.

CRD commentary
The inclusion and exclusion criteria were clearly stated, although the authors did not provide a rational for the adverse events they focused on. Several databases were searched but specific attempts to locate unpublished studies were not made, therefore relevant studies might have been missed. There was no evidence of publication bias. The authors made some attempts to minimise bias and error by carrying out the study selection process in duplicate. However, the absence of a formal validity assessment means that the reliability of the included studies is unclear. The authors did not report on the conduct of the data extraction, therefore there is the potential for reviewer error and bias.
Statistical heterogeneity was assessed only for the primary outcome, and it is therefore unclear whether it was appropriate to pool studies for the other outcomes. The information provided on individual study characteristics was very limited, which makes it difficult to assess the extent of clinical heterogeneity and the generalisability of the findings: for example, drug doses and participant characteristics were not reported. The authors' comments in their discussion suggest that the population was fairly heterogeneous. The authors' conclusions reflect the evidence presented. However, not all SSRIs were included in the study and so the results are not generalisable to all SSRIs. In addition, due to methodological weaknesses in the review process, the reliability of the conclusions is unclear.

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

Practice: The authors stated that decisions about the treatment of MDD with moclobemide or an SSRI cannot be based on overall differential efficacy, nor on overall differential tolerability. There appears to be differences in the side-effect profiles of the two treatment regimes.

Research: The authors did not state any implications for further research.

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