Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials


CRD summary
The authors concluded that reboxetine was ineffective and potentially harmful as an antidepressant in adults with major depressive disorder, when compared with placebo or SSRIs. Published evidence was affected by publication bias. This was a well-conducted review of high-quality trials. The authors' conclusion is likely to be reliable.

Authors' objectives
To evaluate the benefits and harms of reboxetine compared with placebo or selective serotonin reuptake inhibitors (SSRIs) for treatment of acute depression in adults.

Searching
MEDLINE, EMBASE, PsycINFO, BIOSIS Previews and The Cochrane Library were searched to February 2009. There was reference to search terms being reported elsewhere (see Other Publications of Related Interest). Reference lists, clinical trial registries, trial results databases and websites of the European Medicines Agency and US Food and Drug Administration were screened for further trials. Pfizer (drug manufacturer) was contacted for details of unpublished trials and unpublished data from published trials. Authors of responses to the associated health technology assessment report (see Other Publications of Related Interest) were asked to supply details of relevant trials. All languages were considered, provided the English title or abstract indicated potential relevance of the trial.

Study selection
Double-blind randomised controlled trials (RCTs) of adults with major depressive disorder (according to International Classification of Diseases, Diagnostic and Statistical Manual of Mental Disorders or Research Diagnostic Criteria) who received acute treatment (at least six weeks duration) with reboxetine versus placebo or SSRIs were eligible for inclusion in the review. Eligible outcomes were remission and response rates and adverse events (at least one) or withdrawals that arose from adverse events. Definitions of adverse events were taken from the primary studies.

All included trials were sponsored by drug manufacturers. A large proportion of the included data were unpublished. Where reported, mean age of participants ranged from 36 to 46 years and most trials included more women than men. There were differences between trials in terms of trial setting (in-patient, outpatient or both) and baseline severity of depression. Control SSRIs were fluoxetine, imipramine, citalopram and paroxetine; some were considered to be underdosed compared with reboxetine. All included trials used Hamilton Depression Rating Scale; some also used Montgomery-Asberg Depression Rating Scale. All trials defined a reduced response rate as more than 50% from baseline to end of study on the Hamilton scale. Remission was defined as a reduction in Hamilton score to below an end of study threshold (≤10 in most trials). Just under half of the trials were conducted in Europe.

Two reviewers independently selected trials for inclusion in the review. Disagreements were resolved by consensus.

Assessment of study quality
Trial quality was assessed on adequacy of randomisation, allocation concealment, blinding and reporting of complete (non-selective) results. Trials were reported to have a low or high risk of bias.

One reviewer carried out the quality assessment, which was checked by a second reviewer. Disagreements were resolved by consensus.

Data extraction
Where possible, data were extracted to enable calculation of odds ratios (OR) and 95% confidence intervals for the
outcomes of interest.

One reviewer carried out data extraction and this was checked by a second reviewer. Disagreements were resolved by consensus.

**Methods of synthesis**

Where possible, weighted odds ratios and 95% CIs were pooled in a random-effects meta-analysis. Statistical heterogeneity was assessed using the $I^2$ statistic. Where $I^2$ was greater than 50%, a pooled estimate was not calculated and sensitivity analysis (random-effects meta-regression) was conducted to explore possible sources of heterogeneity, which included influence of gender and trial setting. Publication bias was assessed by comparison of effect sizes from published, unpublished and all studies. This analysis was expressed as the ratio of odds ratio (ROR). Any under- or over-estimation of effects were reported as a percentage change.

**Results of the review**

Thirteen RCTs were included in the review (n=4,098). Three trials were placebo-controlled, five were active controlled and five had both placebo and active control. Twelve trials were included in the meta-analysis. Overall methodological quality was considered to be good. Publication bias was considered to be minor.

There were no statistically significant differences between reboxetine and placebo for remission rate or response rate. The latter result followed exclusion of one statistically outlying in-patient trial, which demonstrated that trial setting was likely to be an effect modifier. Heterogeneity was $I^2=49\%$ (remission) and 42\% (response rate).

Reboxetine was associated with a lower remission rate (OR 0.80, 95\% CI 0.67 to 0.96, $I^2=4.6\%$; eight trials) and a lower response rate (OR 0.80, 95\% CI 0.67 to 0.95, $I^2=0\%$; eight trials) compared to SSRIs overall. Similar trends were noted in comparisons with individual SSRIs and with trials that compared reboxetine with both placebo and SSRIs.

Reboxetine was associated with a higher rate of patients with at least one adverse event (OR 2.14, 95\% CI 1.59 to 2.88, $I^2=44\%$; eight trials) and a higher withdrawal rate due to adverse events (OR 2.21, 95\% CI 1.45 to 3.37, $I^2=38.4\%$; eight trials) compared to placebo. There were no statistically significant differences in adverse event rate between reboxetine and SSRIs (overall and individually), but a gender effect was noted in the comparison with fluoxetine. Withdrawal rates were significantly higher with reboxetine compared with fluoxetine (OR 1.79, 95\% CI 1.06 to 3.05, $I^2=19.3\%$; four trials).

For remission and response outcomes, inclusion of unpublished data substantially reversed the reported superiority of reboxetine over placebo and over SSRIs in published trials. Published data was reported to over-estimate the benefits of reboxetine compared to placebo by 99\% to 115\% and when compared to SSRIs by 19\% to 23\%. For adverse events and withdrawals due to adverse events, inclusion of unpublished data similarly reversed the direction of effect, which meant that reboxetine was less favourable than placebo and fluoxetine.

**Authors' conclusions**

Reboxetine was ineffective and potentially harmful as an antidepressant in adults with major depressive disorder. Published evidence was affected by publication bias.

**CRD commentary**

The review question was clear. Inclusion criteria were presented in sufficient detail to be potentially reproducible. The search strategy was extensive in its sourcing of published and unpublished material. A thorough analysis was undertaken to explore the influence of including unpublished data. Attempts were made to minimise language bias. Appropriate criteria were applied to assess the quality of included trials and the results of this were highlighted in this review findings. The review process was carried out with adequate attempts to minimise error and bias. Study details were reported clearly. The chosen method of synthesis was appropriate and included an exploration of heterogeneity.

This was a well-conducted review of high-quality trials. The authors' conclusion is likely to be reliable.
Implications of the review for practice and research

**Practice:** The authors stated that, in their opinion, the contemporary NICE guideline in relation to reboxetine could no longer be upheld.

**Research:** The authors stated an urgent need for mandatory publication of clinical trial data, including data from older agents.

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**Other publications of related interest**
Institute for Quality and Efficiency in Health Care (Bupropion, mirtazapine and reboxetine in the treatment of depression: final report; commission no AO5-20C) (German). 2009.


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