Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials

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CRD summary
This review concluded that, although rimonabant produced greater weight loss after 1 year than placebo, it increased the risk of psychiatric adverse events (mood disorders and anxiety). These conclusions are likely to be reliable, and the authors' recommendations for further research into the safety of rimonabant and careful monitoring of patients appear appropriate.

Authors' objectives
To assess the efficacy and safety of rimonabant, a weight-loss drug.

Searching
MEDLINE (from the mid-1950s), EMBASE (from 1980), Web of Science (from 1945-54), Scopus (from 1966) and the Cochrane Library were searched up to November 2006; the search terms were stated. The reference lists of review articles and included studies were also checked. There were no language restrictions.

Study selection
Study designs of evaluations included in the review
To be eligible, studies had to be double-blind, randomised placebo-controlled trials. All trials in the review were multicentre.

Specific interventions included in the review
Studies were of the drug rimonabant (Acomplia, Sanofi-Aventis). All of the included trials were sponsored by the manufacturer. The length of the trials varied from 12 to 24 months. In all trials, after a weight maintenance diet of 4 weeks, patients who were compliant with dietary instruction and able to cope with therapy were assigned to placebo, rimonabant 5 mg/day or rimonabant 20 mg/day.

Participants included in the review
To be eligible, studies needed to be of overweight or obese patients with a body mass index (BMI) of at least 30 kg/m2, or 27 kg/m2 or greater plus one or more obesity-related co-morbidities. The proportion of women in the trials ranged from 52 to 81%, and the mean age ranged from 44.7 to 55.4 years. The mean BMI ranged from 33.9 (standard deviation, SD=3.4) kg/m2 to 37.3 (SD=6.3) kg/m2. The proportion of participants suffering from metabolic syndrome ranged from 33 to 78%.

Outcomes assessed in the review
To be eligible, studies needed to assess weight loss as an outcome. Efficacy outcomes were the difference in mean weight change between groups and the number of individuals achieving at least a 10% reduction in weight. Other outcomes assessed included depression and anxiety, as measured on the Hospital Anxiety and Depression Scale (HADS).

How were decisions on the relevance of primary studies made?
Two reviewers selected studies for the review.

Assessment of study quality
Two reviewers independently assessed trials using the Jadad instrument, which scores randomisation, blinding and withdrawals. Any disagreements were resolved by consensus.

Data extraction
Two reviewers extracted the data from studies in the review. All analyses were based on data reported as intention-to-
treat. If a study contained phases for both weight loss and weight maintenance, the authors included only data from the weight loss phase. Mean differences were calculated for the mean weight change, standardised mean differences (SMDs) for the HADS score, and odds ratios (ORs) for dichotomous outcomes. Exact methods were used to calculate confidence intervals (CIs) for the ORs, owing to small numbers of events.

Methods of synthesis
How were the studies combined?
The studies were combined by meta-analysis using a random-effects model; SAS software was used. Numbers-needed-to-treat and to-harm were calculated from pooled ORs.

How were differences between studies investigated?
The hypothesis of statistical homogeneity was tested using the Q-test statistic and I-squared values. Clinical heterogeneity was investigated using meta-regression techniques.

Results of the review
Four randomised controlled trials (4,105 patients) were included in the review.

All four included trials were in the Rimonabant in Obesity (RIO) programme, which investigated the efficacy and safety of rimonabant for the treatment of obesity, diabetes and metabolic disorders in overweight and obese individuals. All were found to be of a high quality (about 5 on the Jadad scale). There was no evidence of a difference in the likelihood of completing a year’s treatment between rimonabant (59%) and placebo (58%) groups (OR 1.12, 95% CI: 0.99, 1.28).

Compared with placebo, rimonabant resulted in a greater weight loss of 4.7 kg (95% CI: 4.1, 5.3). Although all studies reported greater weight reductions with rimonabant than with placebo, there was evidence of heterogeneity regarding the magnitude of weight loss (I-squared 62.2%). Individuals receiving rimonabant were more likely to achieve at least a 10% weight loss (OR 5.1, 95% CI: 3.6, 7.3); there was also moderate heterogeneity for this outcome (I-squared 57.3%).

There was no significant difference between rimonabant and placebo in relation to depression, as measured on the HADS scale. However, the increase in anxiety score was significantly greater in the rimonabant group than in the placebo group (SMD 0.18, 95% CI: 0.07, 0.28); there was no evidence of heterogeneity (I-squared 0%).

Adverse events were more likely in the rimonabant group than in the placebo group; there was no evidence of heterogeneity between the studies. Patients receiving 20 mg/day rimonabant were more likely to report adverse events than those in the placebo group (OR 1.4, 95% CI: 1.1, 1.6). Serious adverse events were also more frequent in the rimonabant group than in the placebo group (OR 1.4, 95: CI: 1.2, 2.0), and patients were more likely to discontinue treatment due to depressive mood disorders (OR 2.5, 95% CI: 1.2, 5.1) and more likely to leave due to anxiety (OR 3.0, 95% CI: 1.1, 8.4).

The results of the meta-regression suggested that high concentrations of triglyceride at baseline might predict those who would suffer from depression on rimonabant, and that elderly people (unspecified) might be more likely than younger patients to have serious adverse events during treatment with rimonabant.

Authors’ conclusions
Although rimonabant produced greater weight loss after 1 year than placebo, it increased the risk of psychiatric adverse events (i.e. mood disorders and anxiety).

CRD commentary
This review had clear inclusion criteria. A range of resources were searched with no language restrictions. The methods used to assess quality and extract the data were documented, but full details of the quality assessment were not reported for each study, although the authors did state that the studies were all rated as high quality. Details of the software used for the meta-analyses were reported, but not the actual method used (fixed or random), although the results appear consistent with random-effects models. The meta-analysis methods appear appropriate. However, since the meta-regression was based on only 4 studies and numerical results were not reported, these results should be treated with
caution. The conclusions are likely to be reliable but it should be acknowledged that they are based on only 4 studies, all of which were sponsored by the manufacturer of rimonabant. The authors' recommendations for further research and monitoring of practice appear appropriate.

**Implications of the review for practice and research**
Practice: The authors advised that, as the patients in trials were not suffering from depression at baseline, the risk of severe adverse events in clinical practice might actually be higher. They recommended that physicians remain alert to these adverse events.

Research: The authors suggested that the association between high triglyceride concentrations at baseline and the development of depression needs to be investigated, as does the link between older age and serious adverse events with rimonabant. The authors recommended an individual patient data meta-analysis to investigate safety concerns with rimonabant and to assess whether psychiatric adverse events are associated with the magnitude of weight loss.

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**Other publications of related interest**
This additional published commentary may also be of interest.


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**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract
contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.