Discontinuation due to adverse events in randomized trials of orlistat, sibutramine and rimonabant: a meta-analysis

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CRD summary
This review concluded that there was heterogeneity between the drugs in risk rates for drop-out due to adverse effects and underlying causes. The low number needed to harm for rimonabant was of concern. The conclusion reflected the results of the review and appears likely to be reliable.

Authors' objectives
To assess drop-out rates due to adverse effect in trials of patients using orlistat, sibutramine or rimonabant.

The authors stated that rimonabant had not been licensed in USA and was recently withdrawn in in the European Union after European Medicine Agency concluded that the benefits no longer exceeded the harms.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1990 to May 2008. Search terms were reported. Searches were limited to English-language publications. The authors searched reference lists of included articles and systematic reviews published previously.

Study selection
Randomised controlled trials (RCTs) of 12 to 24 months duration that studied the effects of clinically licensed doses of orlistat (360mg\textsuperscript{d\textsuperscript{-1}}), sibutramine (10 to 15mg\textsuperscript{d\textsuperscript{-1}}) or rimonabant (20mg\textsuperscript{d\textsuperscript{-1}}) were eligible for inclusion in the review. Eligible studies were placebo controlled. Studies were excluded if they evaluated weight maintenance after weight loss.

Drop-out rates (discontinuation) and reasons for drop-out were the primary outcomes. Mean age of included studies ranged from 41 to 59 years. Mean body mass index ranged from 33kgm\textsuperscript{-2} to 38kgm\textsuperscript{-2}. Patients were predominantly white women. Patients were diagnosed with various weight-related diseases. Most included trials were in populations considered to be high risk. Included patients also underwent a variety of behavioural treatments (diet, exercise, counselling)

Two reviewers assessed the studies for inclusion. Differences were resolved by a third reviewer.

Assessment of study quality
Trial quality assessment was conducted using the Verhagen Delphi list. Criteria were: description of randomisation; concealment allocation; baseline comparability; eligibility criteria; blinding; outcomes; and intention-to-treat analysis.

Two reviewers independently performed quality assessment. Differences were resolved by a third reviewer.

Data extraction
Data were extracted on drop-out rates measured by risk ratio (RR), risk difference (RD), 95% confidence intervals (CI) and reason for drop-out. Overall attrition data and the type of adverse event were extracted. When treatments were not significantly different, they were presented without CI. In studies where both groups had zero events, 0.5 was added to cells in 2x2 table to calculate risk ratio.

Two reviewers independently extracted data. Disagreements were resolved by discussion.

Methods of synthesis
A random-effects model was used to calculate pooled risk ratios and risk differences, and number needed to harm, with
95% CIs. Statistical heterogeneity between trials was calculated using the $I^2$ statistic; reasons for heterogeneity were explored if $I^2$ exceeded 50% or was statistically significant. In the absence of heterogeneity, a fixed-effect model was used to pool results.

Sensitivity analyses were used to assess impact of study quality. Funnel plots and Egger's test were used to assess publication bias.

**Results of the review**

Twenty eight RCTs (n=13,457) were included in the meta-analysis: 16 (n=7,038) studies of orlistat; seven (n=1,475) studies of sibutramine; and five studies (n=4,944) of rimonabant. Twenty two studies reported funding from a drug manufacturer.

Most studies were of a similar quality. All studies were intention-to-treat, all studies specified eligibility criteria and treatment groups were comparable at baseline. Most studies did not report randomisation process or allocation concealment. Three studies did not report whether they were double blinded. Follow up was 12 to 18 months.

Overall median drop out rates were high and similar: 30% for orlistat; 34% for sibutramine; and 39% for rimonabant. Adverse effects drop-out rates were more heterogeneous and were higher for drug treatments than controls: 7.1% for orlistat (4% for placebo); 9.3% for sibutramine (8.9% for placebo); and 15% for rimonabant (7.2% for placebo).

Patients who took rimonabant and orlistat had a significantly increased risk of drop out due to adverse effects compared to controls (RR 2.00, 95% CI 1.66 to 2.41 and RD 0.07, 95% CI 0.05 to 0.09 for rimonabant and RR 1.59, 95% CI 1.21 to 2.08 and RD 0.03, 95% CI 0.01 to 0.04 for orlistat). Sibutramine did not increase risk. No significant heterogeneity was found between the trials. Number needed to harm was 14 (95% CI 11 to 19) for rimonabant, 39 (95% CI 25 to 83) for orlistat and 500 (not significant) for sibutramine, which indicated that rimonabant was the greatest clinical risk. The most common reasons for withdrawal were patient request, adverse effects and poor compliance. The most common adverse effects that led to withdrawal were gastrointestinal for orlistat (40%) and psychiatric for rimonabant (47%). No results were presented for adverse effects for sibutramine.

Sensitivity analysis indicated that exclusion of poor-quality studies (studies without double blinding) did not significantly effect the results. No publication bias was detected.

**Authors' conclusions**

High attrition rates were found overall in both drug and control groups. Available weight-loss drugs differed markedly regarding risk of drop-out due to adverse effects and cause of adverse effect. The low number needed to harm for rimonabant was of concern.

**CRD commentary**

This review addressed a clear research question supported by clear inclusion criteria. Relevant sources were searched to locate the included studies. There was no apparent search for unpublished material and so relevant trials may have been missed, but no publication bias was found. Only English-language publications were included, which introduced a risk of language bias. Relevant criteria were used to examine study quality. Sensitivity analysis was used to determine the effect of poor-quality studies on the pooled results. Adequate steps were taken throughout the review process to minimise errors and bias. Statistical heterogeneity was assessed and appropriate methods were used to pool results. This review was generally well conducted. There were limited trials (four) and no data on drop-out rates due to adverse effects reported for sibutramine. The authors' conclusion reflected the results of the review and appears likely to be reliable.

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

**Practice:** The authors stated that the low number needed to harm for rimonabant indicated cause for clinical concern. The synthesis was performed predominantly on white middle-aged females and the results may not be applicable to other groups.

**Research:** The authors stated that head-to-head trials for all three drugs would improve validity of comparisons.
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