Long-term changes in blood pressure following orlistat and sibutramine treatment: a meta-analysis

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CRD summary
This review of 22 trials concluded that sibutramine caused significant elevations in diastolic blood pressure especially amongst diabetics but orlistat did not. There were major methodological limitations of the included trials and important potential biases in the conduct and interpretation of the synthesis. The review conclusions are unreliable but the recommendation for further research is well founded.

Authors' objectives
To assess the comparative effects of orlistat and sibutramine on systolic and diastolic blood pressure.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1990 to February 2009. Search terms were reported. Reference lists of relevant primary studies and previously published systematic reviews were handsearched for additional studies. Searches were restricted to studies in English.

Study selection
Studies/study arms were included if they were placebo controlled RCTs of 12 month duration or randomised head-to-head studies that compared orlistat and sibutramine regardless of duration. Only studies that used licensed doses for clinical use (orlistat 360mg d$^{-1}$, sibutramine 10 to 15mg d$^{-1}$) and reported blood pressure were eligible.

Trial populations were variable but most studies recruited higher risk patients (e.g. patients with diabetes, hypertension and other cardiovascular risk factors). All used some kind of diet and exercise regimen in combination with either placebo or active drug. Patient demographics were similar across trials consisting predominantly of white female patients with mean age ranging from 42 to 59 years and body mass index ranging from 32 to 39kg m$^{-2}$. Head-to-head comparisons were of shorter duration than placebo comparisons.

Two reviewers independently assessed eligibility with reference to a third to resolve discrepancies.

Assessment of study quality
The Verhagen Delphi nine point list was used to assess known potential biases associated with randomised controlled trials

Two reviewers independently assessed trial validity with discrepancies resolved by reference to a third person.

Data extraction
Data on mean and standard deviation for change from baseline in systolic and diastolic blood pressure (mmHg) were extracted with sample sizes. Where standard deviations were unreported or ambiguous they were calculated or inferred making standard assumptions (appendix 1).

Data were extracted by two independent reviewers with reference to a third to resolve any discrepancies.

Methods of synthesis
Weighted mean differences (WMD) were pooled using DerSimonian and Laird random-effects models. Heterogeneity was measured using I$^2$ and explored using subgroups based on patients with and without diabetes. Funnel plots and Egger tests were used to assess publication bias. Sensitivity analyses based on study quality were also performed.

Results of the review
Twelve placebo controlled trials of orlistat (5,540 patients), six of sibutramine (1495) and four head-to-head comparisons (348) were eligible. The authors reported that the trials were generally of similar quality and that attrition
was an important limitation. There was some attrition in all trials with rates often unbalanced and up to 54% of patients dropped out. Randomisation procedures and allocation concealment were unclear as they were poorly reported in the primary literature.

Compared with placebo, orlistat significantly reduced both systolic (WMD -1.9 mmHg, 95% CI -2.7 to -1.1 mmHg) and diastolic blood pressure (WMD -1.5 mmHg, 95% CI -2.2 to -0.8 mmHg). Sibutramine illustrated no significant difference for systolic blood pressure (WMD 0.5 mmHg, 95% CI -1.1 to 2.1 mmHg) but significantly elevated diastolic blood pressure (WMD 1.7 mmHg, 95% CI 0.7 to 2.6 mmHg). Effect magnitudes were small.

Effect estimates from direct head-to-head comparisons were also small, non significant and less precise than placebo treatment comparisons. Interaction tests were not presented for diabetes subgroups, but 95% confidence intervals overlapped substantially suggesting no difference between subgroups. There was no substantial heterogeneity in any of the analyses except diastolic blood pressure for the orlistat-placebo comparison.

**Authors' conclusions**

Sibutramine caused significant elevations in diastolic but not systolic blood pressure. Elevation of diastolic blood pressure with sibutramine was higher in patients with diabetes than those without; orlistat had no impact on this subgroup. Head-to-head comparisons suggested that the drugs did not differ but these studies were small and of short duration.

**CRD commentary**

Methods utilised to identify, select and assess study quality were all appropriate to minimise potential biases. Attrition bias was present to some extent in all trials and may have had a profound effect on the results given its magnitude and differential impact on comparators. Data extraction and analysis were largely appropriate although failure to present interaction tests substantially devalued the subgroup analysis and interpretation of the results does not sufficiently consider uncertainty.

Overlapping confidence intervals suggested that there was no clear difference between subgroups despite the difference in estimates of effect. Effect magnitudes were small so statistically significant results may not have clinical significance even across high-risk populations. Substantial clinical heterogeneity, particularly with respect to concomitant diet and exercise, along with informal use of direct and indirect comparison in conjunction, all add to uncertainty regarding the reliability of the conclusions.

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

**Practice**: The authors stated that blood pressure should be monitored carefully during sibutramine treatment especially with diabetic patients.

**Research**: The authors stated that further head-to-head studies were required to directly establish the relative effects of orlistat and sibutramine.

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