Appetite suppressants and valvular heart disease: a systematic review

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Authors' objectives
To assess the risk of valvular heart disease with appetite suppressants.

Searching
MEDLINE (from 1966 to September 2001) and EMBASE (from 1980 to September 2001) were searched using keywords for the interventions ('phentermine' or 'fenfluramine' or 'dexfenfluramine'), the outcome measures and the study types. The search strategies were provided in the text. Relevant studies were identified through a combination of electronic searches and manual checks of the reference lists from previous review papers. Studies reported in any language were considered. Full journal publications were included; abstracts, letters, review articles and case reports were excluded.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with placebo or no treatment control groups, and observational studies evaluating the risk of valvulopathy, were eligible for inclusion in the review. The studies had to include at least 10 participants. Crossover studies were excluded.

Specific interventions included in the review
Studies that addressed the use of appetite suppressants for the treatment of obesity, for at least one month, were eligible for inclusion in the review. The appetite suppressant drugs in the included studies were fenfluramine (40 to 160 mg/day), dexfenfluramine (10 to 80 mg/day), phentermine (30 mg/day), and phentermine-fenfluramine (30-60 mg/day). These were taken over a mean duration of 17 weeks (range: 4 to 60).

Participants included in the review
Adult, obese patients treated with appetite suppressants were eligible for inclusion in the review. The mean age of the study participants was 43 years, and 77% were female.

Outcomes assessed in the review
Reports of echocardiographically detectable valvulopathy were of interest. In particular, those that met the U.S. Food and Drug Administration (FDA) case definitions, i.e. aortic regurgitation of mild or greater severity (FDA AR) and mitral regurgitation (FDA MR) of mild or greater severity, were assessed in the review.

How were decisions on the relevance of primary studies made?
All potentially relevant studies were checked independently by the reviewers using a predetermined protocol to determine eligibility for inclusion. The reports were not made anonymous before assessment. Any discrepancies were resolved by discussion. A list of excluded studies is available from the authors.

Assessment of study quality
The quality of the RCTs was assessed on the basis of criteria such as concealment of allocation sequence, blinding and the reporting of withdrawals. Methods for patient selection and blinding of the outcome assessors were evaluated for observational studies. Judgements were made independently by the reviewers using a predetermined protocol. The reports were not made anonymous. Any discrepancies were resolved by discussion.

Data extraction
The data were extracted independently by the reviewers using a predetermined protocol. The study authors were contacted when specific aspects of the published data required clarification. The reports were not made anonymous.
Any discrepancies were resolved by discussion.

Data were extracted on: the numbers and severity of any valvular lesions; participants; blinding; type of control; drug exposure; nature of the follow-up; and the methods or criteria used in diagnosing valvulopathy.

Methods of synthesis
How were the studies combined?
The data were combined statistically in a meta-analysis. For the controlled studies, pooled relative risk ratios (RRs) were calculated using a fixed-effect model. The number-needed-to-harm (NNH) was calculated, along with 95% confidence intervals (CIs), by applying the calculated RR ratio to the pooled control event rate.

In the uncontrolled studies, the numbers of patients with valvulopathy were summed to calculate the overall rate from the total number of patients who underwent echocardiography.

How were differences between studies investigated?
Heterogeneity was investigated using a chi-squared test.

Results of the review
Seventy-one studies were included in the review: 57 RCTs (n=5,159) and 14 echocardiographic studies, of which 7 were cohort-controlled studies (n=5,200) and 7 were uncontrolled (n=1,279).

Only one case of valvular heart disease for an intervention participant was noted among the 41 RCTs that reported adverse effects. This was mitral regurgitation, and was judged to be due to myocardial infarction rather than drug therapy. However, echocardiography was not routinely performed in any of the RCTs.

Of the 7 cohort-controlled echocardiographic studies that evaluated the risk of valvulopathy in 5,200 obese individuals, FDA AR was found in 9.7% of those taking appetite suppressants and in 3.5% of controls. The pooled RR for FDA AR was 2.82 (95% CI: 2.20, 3.61, P<0.00001) with a NNH of 16 (95% CI: 11, 24). Data on severe aortic regurgitation was reported in 6 studies, with a pooled rate of 7 out of 3,045 (0.23%) in the exposed group, and 4 out of 1,825 (0.22%) in the control group. Following the removal of one study, to take account of the significant heterogeneity found in the analysis of FDA AR (chi-squared 16.0, P=0.01), the RR for FDA AR was 2.32 (95% CI: 1.79, 3.01, P<0.00001) with a NNH of 20 (95% CI: 13, 33).

FDA MR was much less common than FDA AR. It was found in 2.9% of those taking appetite suppressants and in 1.9% of controls. The pooled RR ratio for FDA MR was 1.55 (95% CI: 1.06, 2.25, P=0.02) with a NNH of 99 (95% CI: 44, 909). There was no evidence of significant heterogeneity.

Of the 7 uncontrolled echocardiographic surveys, a total of 236 (18%) FDA AR cases and 58 (5%) FDA MR cases were detected in the 1,279 patients evaluated. The FDA AR rates ranged from 6 to 29%. This suggested that more than 1 in 5 patients taking appetite suppressants were at risk of developing valvulopathy.

Authors' conclusions
Patients treated with appetite suppressants are at significantly increased risk of developing valvular heart disease. However, the risk of valvulopathy found was much lower than that suggested by initial, less methodologically rigorous studies.

CRD commentary
The review question was clear. The study selection criteria were stated clearly, but were not adhered to in the case of the outcomes: echocardiography was not routinely performed in the RCTs. The literature review seemed reasonably comprehensive, and no language restrictions were applied. The range of statistical tests carried out seemed appropriate for the data analysis undertaken, and there was ample presentation and discussion of the review's findings.
The authors' conclusions seem appropriate in the light of the data they present from the cohort-controlled and uncontrolled echocardiographic studies. However, this seems to discount evidence from the 57 RCTs, which found no cases of valvulopathy attributable to appetite suppressants, and did not perform echocardiography routinely.

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

Practice: The authors state that patients treated with appetite suppressants are at significantly increased risk of developing valvular heart disease. However, the risk of valvulopathy found was much lower than that suggested by initial, less methodologically rigorous studies. The authors state further that despite withdrawal by regulatory authorities, sizeable numbers of people may still be consuming appetite suppressants from other sources, such as unlicensed prescriptions or Chinese herbal preparations. Therefore, safety information from this analysis continues to be relevant, both to slimmers who are still trying for a cure and to medical practitioners who may become involved in their care.

Research: The authors state that judgements on drug safety should be backed by evidence from high-quality sources. The effects of multiple variables require individual patient data.

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