Authors' objectives
To investigate further the efficacy of fenfluramine and dexfenfluramine in the treatment of obesity over time, and to identify all those aspects that could influence this efficacy.

Searching
MEDLINE (from January 1966 to June 1999), EMBASE (from January 1982 to June 1999) and IDIS (January 1966 to July 1999) were searched using a combination of the following keywords: 'fenfluramine', 'dexfenfluramine', 'dextrofenfluramine', 'd-fenfluramine', 'obesity', 'double-blind' and 'clinical trial'. The bibliographies of selected articles and general reviews were checked, and the manufacturer was contacted for further trials.

Study selection
Study designs of evaluations included in the review
Only double-blind, randomised placebo-controlled trials were included in the review.

Specific interventions included in the review
Comparisons of fenfluramine or dexfenfluramine with placebo were eligible for inclusion in the review. In the included studies, the doses of fenfluramine and dexfenfluramine were 60 and 30 mg/day, respectively, with the exception of two studies in which the doses were 80 and 60 mg/day, respectively.

Participants included in the review
Individuals requiring treatment for obesity. No definition of obesity was included in the review.

Outcomes assessed in the review
Studies were included in the review if they provided data on the difference between the study groups in terms of the absolute weight loss (kg lost), with the standard error or standard deviation of these values or the possibility of obtaining them.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
All trials included in the review were double-blind, randomised and placebo-controlled. No further formal quality assessment of the identified trials was performed. The quality of the identified trials was not formally assessed.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The categories of data extracted from the included studies were: bibliographic details, country, sample size, and the difference between the active and placebo groups in terms of the absolute weight loss at various time points.

Methods of synthesis
How were the studies combined?
The trials of both fenfluramine and dexfenfluramine were combined in a meta-analysis using mean values weighted by
the inverse of the variance. The association between the difference of the mean values of weight loss in the experimental and placebo groups, and different predictive variables of efficacy was studied by weighted linear regression. This analysis was only performed for the studies that provided 3-month follow-up data, since these studies were the only ones with sufficient data. Publication bias was investigated using the file drawer method and with a funnel plot.

**How were differences between studies investigated?**

Heterogeneity of the included studies was tested using the numeric Q-based method and the Galbraith plot. After 1 month of treatment (12 studies), the difference in weight loss between the active and placebo groups was 1.16 kg (95% confidence interval, CI: 0.85, 1.47; Q=13.51, p=0.26).

**Results of the review**

Twenty-five trials (n=1,393) were included in the review. The size of the study populations ranged from 17 to 822 participants.

After 2 months’ treatment (10 studies), the difference in weight loss between the active and placebo groups was 2.76 kg (95% CI: 2.22, 3.31; Q=3.92, p=0.86) after the removal of one study that rendered the heterogeneity statistically significant.

After 3 months’ treatment (19 studies), the difference in weight loss between the active and placebo groups was 3.72 kg (95% CI: 3.29, 4.16; Q=9.93, p=0.93). There was some indication of possible publication bias, which might have led to a lower effect estimate.

After 6 months’ treatment (5 studies), the difference in weight loss between the active and placebo groups was 3.10 kg (95% CI: 1.99, 4.20) after the removal of one study that had rendered the heterogeneity statistically significant(Q=8.18, p=0.09).

After 12 months’ treatment (2 studies), the difference in weight loss between the active and placebo groups was 2.67 kg (95% CI: 1.37, 3.98; Q=0.00, p=0.99).

There was no statistical association between the additional weight loss (compared with placebo) and baseline weight, baseline body mass index or other variables tested. Those studies with higher weight loss in the placebo group also attained proportionately more weight loss in the active treatment group; for studies in which the weight losses in the placebo group were greater than 3.5 kg and less than 3.5 kg, respectively, the effect joint estimators were 4.04 kg (95% CI: 3.42, 4.66) and 3.42 kg (95% CI: 3.13, 4.21).

**Authors’ conclusions**

Obese individuals treated with fenfluramine or dexfenfluramine achieved overall weight losses significantly higher than obese patients treated with placebo. From the data obtained, the maximum effect was observed at 3 months from the beginning of treatment when the drug-treated patients achieved a weight loss 3.7 kg higher than placebo. Following this maximum effect, the weight differences reached between the placebo group patients and drug-treated patients decreased over time.

**CRD commentary**

This review addressed an appropriate question using well-defined inclusion criteria. The search was thorough and publication bias was investigated. The validity of the trials was not formally assessed; however, as only double-blind, randomised placebo-controlled trials were eligible for inclusion, the overall quality of the included studies was likely to be good. The level of detail of the individual studies in the review was limited, with no information on patient demography or the actual weight losses. The meta-analysis was appropriate, statistical heterogeneity was tested, and the results of such testing were incorporated into the review.

The authors’ conclusions are supported by the findings of this review.
Implications of the review for practice and research
Practice: The authors state that, on the basis of the efficacy data, treatment lasting longer than 3 months would not be justified.

Research: The authors state ‘A better knowledge of the magnitude of the effects and the way in which they change with time, subject of this meta-analysis, would be of interest to understand the way fenfluramine and dexfenfluramine act’.

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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.