THERAPEUTICS

# Review: Fluoxetine, orlistat, and sibutramine modestly reduce weight in type 2 diabetes

Norris SL, Zhang X, Avenell A, et al. **Efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes mellitus: a meta-analysis.** Arch Intern Med. 2004;164:1395-404.

## QUESTION

In patients with type 2 diabetes mellitus, what is the efficacy of pharmacotherapy for weight loss?

## METHODS

**Data sources:** Studies were identified by searching MEDLINE (1966 to September 2002), EMBASE/Excerpta Medica (1974 to September 2002), CINAHL (1982 to September 2002), Web of Science (1981 to September 2002), Biosis (1970 to September 2002), International Pharmaceutical Abstracts (1970 to September 2002), the Cochrane Library (Issue 3, 2002), the Cochrane Register of Controlled Trials (Issue 3, 2002), key journals, and bibliographies of relevant studies; and by contacting experts and drug manufacturers.

**Study selection and assessment:** Published and unpublished studies in any language were selected if they used pharmacotherapy as the primary strategy for weight loss in patients ≥ 18 years of age with type 2 diabetes and had weight as an outcome. The drugs evaluated were centrally acting appetite suppressants, drugs with a peripheral effect on appetite, drugs that affect nutrient partitioning, and drugs that increase thermogenesis. Drugs that have been withdrawn from the U.S. market or are not available in the United States, investigational drugs and dietary supplements, and metformin and acarbose were excluded. Studies were assessed for quality, including method of randomization, allocation concealment, blinding, intention-to-treat analysis, and attrition.

**Outcomes:** Changes in weight and glycated hemoglobin levels.

## MAIN RESULTS

Of 59 studies that met the inclusion criteria, 14 randomized placebo-controlled trials ($n$ = 2231) had sufficient data for meta-analysis: 6 of fluoxetine ($n$ = 296, mean age 55 y, 51% women, follow-up 8 to 52 wk), 4 of orlistat ($n$ = 1475, mean age 55 y, 52% women, follow-up 52 to 57 wk), and 4 of sibutramine ($n$ = 460, mean age 53 y, 59% follow-up 12 to 26 wk). Compared with placebo, fluoxetine, orlistat, and sibutramine led to modest reductions in weight; and fluoxetine and orlistat led to modest reductions in glycated hemoglobin (Table).

## CONCLUSION

In patients with type 2 diabetes mellitus, fluoxetine, orlistat, and sibutramine modestly reduce weight and fluoxetine and orlistat improve blood sugar control.

*Source of funding: Centers for Disease Control and Prevention.*

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**Pharmacotherapy for weight reduction in type 2 diabetes***

| Comparisons | Outcomes | Follow-up | Number of trials ($n$) | Weighted mean difference (95% CI) |
|---|---|---|---|---|
| Fluoxetine vs placebo | Weight (kg) | 8 to 16 wk | 5 (192) | –3.4 (–5.2 to –1.7) |
| | Weight (kg) | 24 to 30 wk | 4 (97) | –5.1 (–6.9 to –3.3) |
| | GHb | 8 to 16 wk | 4 (145) | –1.0% (–1.5 to –0.4) |
| | GHb | 24 to 30 wk | 4 (97) | –1.0% (–1.4 to –0.6) |
| Orlistat vs placebo | Weight (kg) | 52 to 57 wk | 3 (818) | –2.6 (–3.2 to –2.1) |
| | GHb | 52 to 57 wk | 4 (904) | –0.4% (–0.5 to –0.3) |
| Sibutramine vs placebo | Weight (kg) | 12 to 26 wk | 4 (391) | –4.5 (–7.2 to –1.8) |
| | GHb | 12 to 26 wk | 4 (368) | –0.7% (–1.9 to 0.5)† |

*GHb = glycated hemoglobin. CI defined in Glossary; data were pooled using a random-effects model. Differences favor the active drug.
†Not significant.

## COMMENTARY

Padwal and colleagues have systematically reviewed the effectiveness and safety of approved antiobesity medications in clinical trials that lasted for ≥ 1 year for which the results were available by the end of 2002. Norris and colleagues have done a meta-analysis of studies reported before September 2002 that examined the efficacy of pharmacotherapy for weight loss over 8 to 57 weeks in adults with type 2 diabetes. Norris and colleagues also report the limited data describing the effects of fluoxetine. More research is needed before the clinical usefulness of this agent can be established. The authors of both reviews conclude that available licensed therapies (e.g., sibutramine and orlistat) help induce weight loss. Although of shorter duration, trials of sibutramine suggest that the magnitude of weight reduction is similar to that seen with orlistat.

A number of important questions need to be addressed before advocating widespread use of pharmacologic treatments for weight reduction. Norris and colleagues attempted to obtain results of unpublished studies of weight loss treatments but were unable to identify whether publication bias had occurred. It is difficult to infer whether some patients might respond better to certain weight loss therapies because sampling frames, the method of recruitment, and selection of participants are rarely described. Attrition is an important issue in weight loss studies because patients who do not achieve their goal weight often do not return for follow-up.

The safety of pharmacologic interventions also needs to be considered. Orlistat treatment has been associated with lower levels of fat-soluble vitamins in plasma. Sibutramine is a similar compound to dexfenfluramine, which has been associated with pulmonary hypertension and valvular heart disease. In the studies reviewed, these serious side effects were not identified. Common side effects were dry mouth, constipation, and insomnia and more rarely palpitations and increased blood pressure. However, sibutramine is contraindicated in persons with coronary artery disease, congestive heart failure, arrhythmias, stroke, or inadequately controlled hypertension or those receiving psychiatric medications. These restrictions limit its usefulness in clinical practice.

Both orlistat and sibutramine are associated with improved cardiovascular risk factors. However, it is not known whether treatment with these agents reduces risk for cardiovascular events. Since the work of Padwal and colleagues and Norris and colleagues, 1 other important study in this field has been published. A 4-year, double-blind, randomized, prospective trial of 3305 persons with BMI ≥ 30 kg/m$^2$ who were randomized to lifestyle intervention plus either orlistat, 120 mg 3 times daily, or placebo showed that orlistat treatment combined with lifestyle

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# Review: Orlistat and sibutramine are modestly effective for weight loss at 1 year

Padwal R, Li SK, Lau DC. **Long-term pharmacotherapy for obesity and overweight.** Cochrane Database Syst Rev. 2004;(3):CD004094.

## QUESTION

What is the effectiveness of antiobesity medications in trials with ≥ 1-year follow-up?

## METHODS

**Data sources:** MEDLINE (1966 to December 2002), EMBASE/Excerpta Medica (1980 to December 2002), the Cochrane Controlled Trials Register (Issue 3, 2002), the Current Controlled Trials metaRegister of Controlled Trials (December 2002), bibliographies of relevant studies, and contact with experts and manufacturers.

**Study selection and assessment:** Studies in any language were selected if they were randomized controlled trials (RCTs) of approved antiobesity agents for weight loss or weight maintenance in adults (age ≥ 18 y) with body mass index (BMI) ≥ 30 kg/m$^2$ or ≥ 27 kg/m$^2$ plus ≥ 1 obesity-related comorbid condition (e.g., coronary artery disease, stroke, type 2 diabetes, heart failure, dyslipidemia, hypertension, reproductive or gastrointestinal cancer, gallstones, fatty liver disease, osteoarthritis, and sleep apnea), had blinding of patients and health care providers, included a placebo group or compared ≥ 2 antiobesity drugs, used an intention-to-treat analysis, and had ≥ 1 year follow-up. Studies of off-label therapy; drugs with high addiction potential that preclude long-term use; or investigational, herbal, or alternative compounds were excluded. Study quality assessment included method of randomization, allocation concealment, blinding, intention-to treat analysis, and attrition.

**Outcome:** Weight loss at 1 year.

## MAIN RESULTS

Only trials of orlistat and sibutramine met the selection criteria. 16 RCTs (11 of orlistat and 5 of sibutramine) were included. 14 RCTs (11 of orlistat and 3 of sibutramine) were weight loss trials in which drug therapy was used in conjunction with a weight loss diet for 1 year. 2 RCTs of sibutramine were weight maintenance trials with 12- to 18-month follow-up.

11 weight loss trials ($n$ = 6021, mean age 49 y, 71% women, mean BMI 35.7 kg/m$^2$) used standard doses of orlistat (120 mg, 3 times/d). 3 weight loss trials ($n$ = 929, mean age 47 y, 80% women, mean BMI 33.4 kg/m$^2$) used sibutramine, 10 to 20 mg/d. Patients who received orlistat had a 2.7-kg (95% CI 2.3 to 3.1 kg; 11 RCTs) greater weight loss (2.9%, CI 2.3 to 3.4; 10 RCTs) than patients who received placebo, and sibutramine-group patients had a 4.3-kg (CI 3.6 to 4.9 kg; 3 RCTs) greater weight loss (4.6%, CI 3.8 to 5.4; 3 RCTs) than placebo-group patients. More orlistat- and sibutramine-group patients achieved a 5% and 10% weight loss than did placebo-group patients (Table).

2 sibutramine weight maintenance trials ($n$ = 627, mean age 49 y, 83% women, mean BMI 37 kg/m$^2$) used a 10-mg/d dose of sibutramine. Results from these 2 trials were not pooled, but both showed greater weight loss in participants who received sibutramine than in those who received placebo.

## CONCLUSION

Orlistat and sibutramine are modestly effective for weight loss at 1 year.

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**Orlistat (Orl) or sibutramine (Sib) vs placebo for weight loss at 1 year***

| Outcomes | Number of trials | Weighted event rates | | | RBI (95% CI) | NNT (CI) |
|---|---|---|---|---|---|---|
| | | Orl | Sib | Placebo | | |
| 5% weight loss | 11 | 52% | — | 31% | 75% (53 to 100) | 5 (5 to 6) |
| | 3 | — | 49% | 15% | 256% (132 to 446) | 3 (3 to 4) |
| 10% weight loss | 10 | 25% | — | 13% | 93% (66 to 125) | 9 (7 to 13) |
| | 3 | — | 20% | 5% | 345% (168 to 639) | 7 (4 to 25) |

*Abbreviations defined in Glossary; weighted event rates, RBI, NNT, and CI calculated from data in article using a random-effects model.

## COMMENTARY

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changes reduced incident diabetes by 37% (1). It is uncertain if treatment with drugs, such as orlistat or sibutramine, is associated with weight cycling, which appears to adversely affect cardiovascular risk factors.

Although orlistat and sibutramine undoubtedly produce weight loss, the effect is modest and is less than can be achieved with intensive lifestyle interventions. Combining increased physical activity and calorie restriction has been shown to reduce the risk for incident diabetes by as much as 58% in 2 similar studies (2, 3). Lifestyle interventions have been poorly studied but are the preferred treatment option for most individuals, although many persons who are overweight or obese are unable to undertake or adhere to intensive lifestyle interventions, especially over the longer term. Until effective methods of obesity prevention are introduced, a role for pharmacologic treatment of obesity remains. Further research is required to establish cost-effectiveness and to identify subgroups of patients who are most likely to benefit from different approaches to weight loss.

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