

Review: Several pharmacologic therapies promote modest weight loss

Li Z, Maglione M, Tu W, et al. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med.* 2005;142:532-46.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆☆ Endocrinology ★★★★★☆☆☆

QUESTION

How effective and safe are pharmacologic therapies in the treatment of obesity?

METHODS

Data sources: MEDLINE (to July 2003), the Cochrane Central Register of Controlled Trials, and existing systematic reviews.

Study selection and assessment: Randomized controlled trials that evaluated pharmaceutical agents for weight loss in patients with body mass index ≥ 27 kg/m² and reported ≥ 6 -month weight outcomes. Study quality was assessed using the 5-point Jadad scale (5 = highest quality) and considered study design, method of random assignment, blinding, and withdrawal.

Outcomes: Weight loss and side effects.

MAIN RESULTS

The studies meeting inclusion criteria were 3 existing meta-analyses (39 RCTs) evaluating sibutramine, phentermine, and diethylpropion, and 47 RCTs that evaluated orlistat, bupropion, topiramate, and fluoxetine. All comparisons were with placebo, and most trials had a hypocaloric diet co-intervention. Meta-analyses were done using random effects. Most medications led to modest weight loss compared with placebo; side effects varied by drug (Table).

CONCLUSION

On average, sibutramine, phentermine, orlistat, diethylpropion, bupropion, topiramate, and fluoxetine led to 1 to 7 kg of weight loss by 6 months in obese adults with body mass index ≥ 27 kg/m².

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Medical therapies vs placebo for obesity*

Drug	Number of placebo-controlled RCTs	Follow-up	Weight loss (kg) (95% CI or range)	Commonly reported side effects
Sibutramine	12	16 to 24 wk	-3.4 to -6.0	Increased heart rate (4 beats/min)
	5	44 to 54 wk	-4.5 (-5.3 to -3.6)	
Phentermine	6	2 to 24 wk	-3.6 (-6.0 to -0.6)	Palpitations, tachycardia, increased blood pressure, central nervous system and gastrointestinal effects
Diethylpropion	9	6 to 52 wk	-3.0 (-11.5 to 1.6)	Central nervous system effects, dizziness, headache, insomnia, restlessness, increased blood pressure, palpitations, tachycardia, gastrointestinal effects, rash
Orlistat	12	6 mo	-2.6 (-3.5 to -1.7)	Diarrhea, flatulence, bloating, abdominal pain, dyspepsia
	22	12 mo	-2.9 (-3.5 to -2.3)	
Fluoxetine	7	6 mo	-0.9 to -9.1	Nervousness, sweating, tremors, nausea, vomiting, fatigue, asthenia, hypersomnia, somnolence, insomnia, diarrhea
	6	12 mo	-14.5 to 0.4	
Bupropion	3	6 to 12 mo	-2.8 (-4.5 to -1.1)	Dry mouth
Topiramate (percentage weight loss)	6	6 mo	-6.5% (-8.3 to -4.8)	Paresthesia, taste perversion, central nervous system effects, constipation, dry mouth, upper abdominal symptoms, fatigue

*RCT = randomized controlled trial; CI defined in Glossary. A random-effects model was used.

COMMENTARY

Obesity is a chronic condition resulting from a myriad of factors causing an imbalance of energy intake and expenditure. Although lifestyle changes can result in weight loss for some, many obese patients need more efficacious interventions for weight reduction. The use of pharmacologic and surgical treatments has increased in response to the increasing prevalence of obesity.

Li and colleagues and a Cochrane review on this topic (1) agree that several available medications combined with dietary intervention result in average weight loss of about 3 to 5 kg in excess of placebo with relatively mild short-term side effects.

Although a 5% to 10% weight loss can result in reduced risk for chronic disease (2), Foster and colleagues showed that most patients achieving the degree of weight loss reported with pharmacotherapy by Li and colleagues would be "very disappointed" (3). A group underrepresented in pharmacologic trials, severely obese patients (BMI > 40 kg/m²), may perceive less palliation from a "modest" weight loss.

Large loss to follow-up in trials and in clinical practice may, in part, reflect limitations of medical therapy and complicate the interpretation of trials.

With this in mind, clinicians should appreciate why some patients are enamored with surgical treatments for obesity. Maggard and colleagues noted that although current high-quality data are lacking, a large observational study from Sweden supports the efficacy and probable superiority of surgical treatments for severely obese patients. When considering the large, consistent differences in weight, major comorbid outcomes observed, and low risk for major complications in a large number of patients, they suggest it is more likely that the differences are attributable to surgical treatment and not due to unmeasured variables. Consistent findings from other investigators have been published (4). Still, RCTs are needed to establish causality and to detect small differences (particularly between surgical procedures) in outcomes important to patients, including quality of life and cost-effectiveness.

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Review: Sparse high-quality evidence supports surgery for obesity

Maggard MA, Shugarman LR, Suttorp M, et al. **Meta-analysis: surgical treatment of obesity.** *Ann Intern Med.* 2005;142:547-59.

Clinical impact ratings: Endocrinology ★★★★★☆☆

QUESTION

How effective and safe are surgical treatments for obesity?

METHODS

Data sources: MEDLINE and EMBASE/Excerpta Medica (to July 2003), and existing systematic reviews.

Study selection and assessment: Randomized controlled trials (RCTs), controlled clinical trials, cohort studies, and case series that evaluated surgical treatment of obesity.

Outcomes: Weight loss, mortality, complication rates, and control of major obesity-related comorbid conditions.

MAIN RESULTS

147 studies met the inclusion criteria: 89 reported weight loss results (mean age 38 y, 75% women, baseline body mass index 47 kg/m²), 134 reported mortality rates, and 128 reported complication rates. The analysis focused on the most common currently performed surgical procedures: Roux-en-Y gastric bypass (RYGB) (including open and laparoscopic), vertical-banded gastroplasty (VBG), adjustable gastric banding, and biliopancreatic diversion (including duodenal switch). **Weight loss:** 3 RCTs compared surgery with no surgery. 2 older RCTs favored surgery: 1 RCT from 1984 showed greater weight loss at 24 months with horizontal

gastroplasty plus diet than with diet alone (31 vs 8 kg); 1 RCT from 1979 comparing jejunoileal bypass with medical treatment showed a 37-kg difference favoring surgery at 24 months. 1 RCT available only in abstract form that compared surgery with medical therapy (very-low-calorie diet, pharmacotherapy, and exercise) showed more loss of excess body weight in the surgical group than in the medical group (72% vs 21%, $P < 0.001$). The most recent high-quality evidence was from a large, matched-cohort study, showing greater weight loss at 8 years (20-kg difference) and at 10 years (17-kg difference) with surgery (mostly VBG or adjustable gastric banding) than with non-surgical therapy. Of 5 RCTs comparing surgical procedures, 2 compared RYGB with VBG. Both procedures showed > 30 kg of weight loss at 12 and 36 months, with RYGB showing an additional weight loss of 8 to 9 kg. 2 RCTs showed additional weight loss of 14 and 3 kg at 12 and 36 months, respectively, for VBG compared with laparoscopic adjustable gastric banding; and 1 showed similar weight reductions (≥ 30 kg) with open and laparoscopic RYGB at 12 months. **Mortality:** Among RCTs reporting operative mortality, early (≤ 30 d from the procedure) and late (> 30 d from the procedure) mortality were $\leq 1\%$ for all procedures.

Complications: 5 RCTs comparing RYGB with VBG showed no difference between procedures in rates of adverse events. Studies comparing open with laparoscopic surgery showed reductions in wound complications, major and minor wound infections, and incisional hernias with the laparoscopic approach, but a greater rate of reoperation. **Comorbid conditions:** No RCTs provided results on control of comorbid conditions. A cohort study showed a reduction in hypertension, diabetes, and dyslipidemia in surgically treated patients at 24 months compared with a nonsurgical control group. Reductions in diabetes and dyslipidemia persisted to 10 years. Improvements were also seen for sleep apnea, dyspnea, and chest pain.

CONCLUSION

Evidence, mostly from observational studies, suggests that surgical treatment of obesity is more effective than nonsurgical treatment for weight loss and control of some comorbid conditions in patients with body mass index ≥ 40 kg/m².

Source of funding: Agency for Healthcare Research and Quality.

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COMMENTARY (continued from page 50)

Clinicians should consider many variables before generalizing these data to patient care, as they may not reflect such variables as advancements in surgical techniques, differences in technical skill, refined systems of care (e.g., multidisciplinary bariatric surgery teams), patient age, and the addition of co-interventions (e.g., behavior therapy and support groups). Further research needs to explore the largely unexplained differences in results among many of the weight loss therapy trials. These differences suggest that patient populations with specific barriers to effective weight loss or specific comorbid conditions may respond better to different types of weight loss drugs, combinations of drugs, and co-interventions.

Clinicians should work with patients to define important outcomes, including the magnitude of weight loss, effect on relevant obesity-related comorbid conditions, and cost to identify patients' tolerance of risk for adverse events and to convey the uncertainty about the available evidence.

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