Review: Orlistat, sibutramine, and rimonabant reduce weight in overweight and obese persons

Rucker D, Padwal R, Li SK, Curioni C, Lau DC. **Long term pharmacotherapy for obesity and overweight: updated meta-analysis.** BMJ. 2007;335:1194-9.

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

QUESTION

In overweight or obese persons, what is the long-term efficacy of antiobesity drugs (AODs) for reducing weight and improving health status?

METHODS

Data sources: MEDLINE, EMBASE/Excerpta Medica, Cochrane Controlled Trials Register, and Current Science meta-register of controlled trials (all from December 2002 to 2006); and reference lists.

Study selection and assessment: Randomized, double-blind, placebo-controlled trials (RCTs) that lasted ≥ 1 year, used intention-to-treat analysis, and evaluated the efficacy of AODs on weight, overall mortality, cardiovascular (CV) risk factors, CV morbidity, and CV mortality in overweight or obese participants ≥ 18 years of age. Open-label crossover trials, quasi-RCTs, and abstracts were excluded. Quality assessment of individual studies was based on 9 criteria of the Verhagen Delphi list. 30 RCTs (mean age range 38 to 59 y) met the selection criteria.

Outcomes: Included changes in weight; triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol levels; blood pressure (BP); diabetes; and adverse events.

MAIN RESULTS

Meta-analysis showed that orlistat (OST), sibutramine (SBT), and rimonabant (RMB) reduced weight more than did placebo (Table). Compared with placebo, OST reduced LDL, HDL, and total cholesterol levels and BP; SBT increased HDL cholesterol and BP and reduced triglycerides; and RMB increased HDL cholesterol and reduced triglyceride levels and BP (Table). In participants with diabetes, OST and RMB improved glycemic control (Table). In 1 RCT, OST reduced the incidence of diabetes compared with placebo (hazard ratio 0.63, 95% CI 0.46 to 0.86). OST increased risk for gastrointestinal adverse events; SBT increased risk for insomnia, nausea, dry mouth, and constipation; and RMB increased risk for psychiatric disorders.

CONCLUSION

Orlistat, sibutramine, and rimonabant reduce weight and improve some health measures in overweight and obese persons.

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Comparisons of orlistat, sibutramine, and rimonabant with placebo in overweight or obese participants*

Outcomes at 1 to 4 y	Number of trials (*n*)	Drug	Weighted mean difference (95% CI)
Change in weight (kg)	15 (9833)	Orlistat	−2.87 (−3.21 to −2.53)
	10 (2348)	Sibutramine	−4.16 (−4.73 to −3.59)
	4 (4099)	Rimonabant	−4.67 (−5.26 to −4.07)
Change in LDL cholesterol (mmol/L)	13 (5206)	Orlistat	−0.26 (−0.30 to −0.22)
Change in HDL cholesterol (mmol/L)	11 (4152)	Orlistat	−0.03 (−0.04 to −0.02)
	5 (977)	Sibutramine	0.04 (0.01 to 0.08)
	4 (4050)	Rimonabant	0.10 (0.08 to 0.11)
Change in total cholesterol (mmol/L)	13 (5206)	Orlistat	−0.32 (−0.37 to −0.28)
Change in triglycerides (mmol/L)	4 (785)	Sibutramine	−0.18 (−0.30 to −0.07)
	4 (4049)	Rimonabant	−0.24 (−0.30 to −0.17)
Change in systolic BP (mm Hg)	13 (6965)	Orlistat	−1.52 (−2.19 to −0.86)
	7 (1906)	Sibutramine	1.69 (0.11 to 3.28)
	3 (2273)	Rimonabant	−1.78 (−2.81 to −0.76)
Change in diastolic BP (mm Hg)	12 (8322)	Orlistat	−1.38 (−2.03 to -0.74)
	7 (1906)	Sibutramine	2.42 (1.51 to 3.32)
	3 (2273)	Rimonabant	−1.23 (−1.93 to −0.54)
Change in fasting glucose (mmol/L)	5 (1678)	Orlistat	−1.03 (−1.49 to −0.57)
	1 (1047)	Rimonabant	−0.97 (−1.3 to −0.64)
			Risk difference (CI)
Change in hemoglobin A_{1c} (%)	1 (1047)	Rimonabant	−0.70 (−0.84 to −0.56)
	5 (1678)	Orlistat	−0.38 (−0.59 to −0.18)

*BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; CI defined in Glossary. Weighted mean difference based on a random-effects model.

COMMENTARY

The systematic review by Rucker and colleagues confirms that AODs produce small amounts of weight loss along with an unfortunately high rate of side effects and study attrition. Notably, overall weight loss for all 3 drugs was modest (mean 2.9 to 4.7 kg) and tended to plateau within the first year of each trial.

Both lifestyle interventions (1) and AODs have been proven to reduce weight and improve intermediate metabolic measures in relatively short-term trials. However, maintaining adherence to intensive diet and exercise interventions or AODs has been problematic. Although cohort studies have shown that bariatric surgery reduces chronic disease and overall mortality in patients with severe obesity (2), it is not an ideal solution. Such surgery often produces clinically significant adverse effects and requires life-long adherence and medical management.

Novel interventions that can curb the worldwide obesity epidemic are urgently needed. Since the body has redundant mechanisms to counteract weight loss, multifaceted obesity treatments are needed to target different mechanisms. Clinical trials need to test the additive effect of multiple AODs to maximize weight loss and minimize side effects. This approach would make obesity treatment akin to that of other chronic medical conditions (e.g., diabetes and hypertension).

The clinical utility of these AODs is marginal because of side effects and lack of evidence that their use affects hard outcomes, such as CV events or mortality. Lifestyle change with diet and exercise remain the cornerstone of obesity treatment for most patients. The challenge is to maintain these changes in the long term.

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References

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