

## Systematic review

# Obesity medications reduce total body weight by 3–9% compared with placebo, when combined with lifestyle changes

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Commentary on: Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. *JAMA* 2014;**311**:74–86.

## Implications for practice and research

- Unless delivered in an intensive manner, lifestyle therapies generally do not yield significant and sustainable weight loss for most obese patients.
- Pharmacotherapy aimed at weight loss, when used prudently and in consideration of individual benefit-to-risk balance, could be a useful addition to lifestyle interventions.

## Context

Obesity is associated with numerous complications, notably type 2 diabetes, hypertension, coronary artery disease and obstructive sleep apnoea. Weight loss of 5–10%, if maintained for 2 years or more, can lead to significant improvements in these comorbidities, especially type 2 diabetes.<sup>1</sup> Mild-to-moderate-intensity lifestyle interventions often do not achieve clinically significant and sustained weight loss for obese patients. Pharmacotherapy is recommended as an adjunct to lifestyle therapies for achieving weight loss in patients with a body mass index (BMI) of  $\geq 30$  kg/m<sup>2</sup>, and in patients with weight-related comorbidities and a BMI of  $\geq 27$  kg/m<sup>2</sup>.

## Methods

Yanovski and Yanovski conducted a systematic and clinical review. Their systematic review involved a search of published literature for randomised controlled trials (RCTs), systematic reviews and meta-analyses examining effects after 1 year of medications currently approved by the Food and Drug Administration (FDA) for weight loss. The findings of the search were then tabulated with clinical interpretation. No synthesis of data into a single quantitative estimate or a summary effect size took place so this was not a meta-analysis.

## Findings

Twenty RCTs (15 with orlistat, 3 with lorcaserin and 2 with phentermine plus topiramate) and a meta-analysis (of lorcaserin) were included in the systematic review. The review found that, among the three antiobesity

pharmacotherapies currently approved for long-term use, the single-drug therapies orlistat and lorcaserin achieved approximately 3% greater weight loss than placebo after 1 year, whereas the combination of phentermine and topiramate appeared the most effective, with a placebo-subtracted weight loss of nearly 9% for the highest dose. All three medications demonstrated greater improvements relative to placebo in certain surrogate measures of cardiovascular and metabolic risks. However, lorcaserin and phentermine plus topiramate are undergoing postmarketing cardiovascular surveillance risk trials required by the FDA.

## Commentary

A wide range of designs and methods that limit the findings and interpretations from systematic reviews and meta-analyses are employed in the conduct of RCTs of antiobesity medications. Such methodological limitations include inadequate enrolment of men and minorities, exclusion of patients taking antidepressants, exclusion of patients with common comorbidities, lack of follow-up after discontinuation of treatment, high dropout rates, disputable imputation methods for missing data, and wide variability in the type and intensity of ancillary lifestyle intervention.<sup>2</sup> When placebo response (weight loss achieved with lifestyle intervention) is 1% in one trial and 5% in another, comparison of placebo-subtracted weight loss from these trials is untenable. As the FDA's yardstick for efficacy is 5% greater weight loss with the investigational drug relative to placebo at 1 year, sponsors whose primary goal is to win marketing approval are often driven to design studies aimed at keeping the placebo response at the bare minimum.

To reduce the noise of heterogeneity among trials, the authors limited inclusion to RCTs of minimum 1-year duration with at least 50 participants per group at baseline and retention of 50% or higher. Efficacy numbers were derived from intention-to-treat (ITT) analysis as published in papers. Although ITT, by definition, implies that the analysis included all randomised patients, sponsors of antiobesity drug trials rarely adhere to this definition and various qualifications are used to exclude many patients from the primary analysis.

In clinical practice, antiobesity drugs may be less effective than in clinical trial settings because very few patients continue taking antiobesity drugs for long periods, due to lack of adequate health insurance coverage for these drugs, higher expectations that often do not match the observed efficacy and adverse effects. In contrast, patients participating in clinical trials do not have out-of-pocket expenses, they receive some degree of diet counselling, and there is structure and monitoring in the form of monthly visits. Even so, several clinical trials have documented that weight benefits disappear after weight loss medication is discontinued.

Although head-to-head trials are lacking, the combination therapy of phentermine and topiramate appears to be the most effective of the approved pharmacotherapy choices. However, its tolerability is limited by psychiatric and cognitive adverse effects, while there are concerns about a slight increase in heart rate observed in clinical trials. In addition, due to its teratogenic risk, women of childbearing age must be enrolled in a risk evaluation and mitigation programme. Lorcaserin, although less effective for weight loss, appears to be fairly well-tolerated; however, safety data in patients taking antidepressants are lacking, and for a new chemical entity, there may be unknown risks after hundreds of thousands of patients are exposed.

Nevertheless, pharmacotherapy, which seems to bridge the gap between lifestyle therapies and invasive and anatomy-altering surgeries, remains a valuable option in the toolbox of clinicians for managing weight in select patients.

**Competing interests** In the past 3 years, KMG has received research funding from Amylin, Eisai, Medical University of South Carolina and Vivus, and held equity (not currently) in Orexigen.



### References

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