How does lorcaserin facilitate weight loss and who will benefit?

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**Pharmacotherapy for obesity, as an adjunct to targeted behavioural modifications, can facilitate weight loss. Previous serotonergic candidates have been withdrawn due to undesirable cardiovascular effects. A new study in a large sample of high-risk patients shows lorcaserin has no greater increase in cardiovascular problems than placebo. What does this mean for personalised pharmacotherapy for obesity?**

*Refers to* Bohula E. A. et al. Cardiovascular Safety of Lorcaserin in Overweight or Obese Patients. *N Engl J Med*http://dx.doi.org/10.1038/10.1056/NEJMoa1808721 (2018).

During the last 40 years the incidence of obesity has reached pandemic status across the developed and developing world1. This is a global, major public health concern, as obesity is associated with increases in mortality of many causes, and often coexists with several health complications such as type 2 diabetes mellitus, various cancers and cardiovascular diseases2. The need for safe and effective weight management solutions is therefore urgent. Principle components of obesity management are that we make adjustments to our eating behaviour and increase our daily activity such that we can attain a negative energy balance to enable weight loss3. However, these lifestyle changes can be extremely difficult for individuals to follow, especially if we consider that eating behaviour and daily activity are shaped by lifelong learning. Thus, behaviour change requires persistent exertion from the individual.

We have been seeking to produce effective drugs for weight-management to assist with behaviour modification since the late 1950s, and lorcaserin, although not new (several weight-loss clinical trials using lorcaserin have been published since 2010), is the newest in a long line of serotonergic drugs for weight-management. Other serotonergic drugs (such as sibutramine and fenfluramine), which had an affinity for the 5HT2A or 5HT2B receptor subtypes, have all previously been withdrawn following concerns over their psychological and cardiovascular side effects4. Unlike other serotonergic drugs, lorcaserin is selective for the 5HT2C receptor subtype, which is proposed to underscore its effects on eating behaviour (reduced hunger via action on POMC neurons) and safety. Previous studies and meta-analyses have suggested that lorcaserin is generally well tolerated and improves the likelihood of achieving 5% weight-loss relative to placebo at 12 months (OR3.10, 95% CI 2.38–4.05)5. While, lorcaserin has been FDA approved since 2012, it has yet to receive European Medicines Agency (EMA) approval, and researchers have urged longer term clinical and pharmacovigilance studies to inform long-term efficacy and safety of lorcaserin.

In a new study by Erin A. Bohula and colleagues6 the authors set out to observe what is considered to be the ‘holy grail’ for weight-loss medication; assist weight-loss without precipitating or increasing cardiac issues. A total of 12,000 patients with atherosclerotic cardiovascular disease, or multiple cardiovascular risk factors, who had a BMI of >27 were randomly selected to either receive placebo (n = 6000) or lorcaserin (10mg two times a day, n = 6000). The study lasted for a total of ~40 months, at which point >2000 patients had discontinued medication in each condition (a rate of 12% per year for lorcaserin and 12.7% per year for placebo) — although discontinuation was unrelated to adverse events. At 12 months 38.7% of participants taking lorcaserin achieved 5% weight loss, compared with 17.4% of participants in the placebo group. A total of 14.6% of the participants taking lorcaserin and 4.8% of individuals in the placebo group achieved 10% weight loss and both comparisons were statistically significant.

The primary outcomes in this study were to assess cardiovascular safety of lorcaserin (non-inferiority compared to placebo) based on a composite measure of cardiovascular death, myocardial infarction and stroke, at an interim analysis. If non-inferiority was observed, the trial progressed to a superiority (or efficacy) analysis for lorcaserin on a composite of extended major cardiovascular events (to include major events from non-inferiority analysis as well as heart failure, hospitalisation for angina, and coronary revascularisation) over the >3 year period. The authors reported non-inferiority of lorcaserin in terms of cardiovascular safety, but that superiority was not observed.

A key finding of this paper is that it suggests that patients can be maintained on lorcaserin treatment for at least 3 years without an increased incidence of cardiovascular problems relative to placebo. This is a longer time period than that usually assessed in safety and efficacy studies of pharmacotherapies for obesity. The present study was conducted in a large sample of 12,000 patients across a number of sites within 8 countries. Given the seemingly impressive safety profile of lorcaserin, one would imagine this would gain favourable opinion for risk-benefit analysis from EMA, providing it considers the drug to demonstrate added benefit to sustained weight-loss approaches.

The paper by Bohula and colleagues goes some way to establishing the safety profile of lorcaserin, but we must not overlook the fact that that its effects on weight-loss are modest. Of the current sample, 61.3% of the participants did not meet the clinically meaningful weight-loss target of 5% at 12 months (incidentally weight loss plateaued after 12 months). It could be argued that weight-loss drugs will probably show reduced efficacy in samples of patients with co-morbidities, such as that presented here. However, meta-analysis5 across studies that included populations without co-morbidities suggest a median 49% of patients successfully achieve 5% weight-loss with lorcaserin. Either way, this means that a large portion of the wider population that will not respond to this treatment. If we consider that lorcarserin is one of several candidate drugs for weight loss, each of which has a distinct pharmacology (in this case targeting 5HT2C receptors), then presumably each drug will have distinct behavioural manifestations. We are at a juncture in the research with pharmaceutical treatments for weight-loss where we need to start to properly characterise the effects of drugs on eating behaviour, and neural mechanisms that belie weak satiety signalling, high-reward motivated eating, or poorly controlled responses to food stimuli in our environment.

Clearly, clinical response to weight-loss drugs varies a great deal. Future research should begin to characterise sub-populations who respond well to pharmacotherapy. In our 2017 review7, we proposed a methodological platform for assessing drug action on various psychological mechanisms (satiety, reward and inhibitory control), which underpin eating behaviour. Appropriate mechanistic behavioural profiling of weight-loss drugs can inform future prescribing decisions about how to best tailor pharmacotherapy for specific problem obesogenic behaviours.

The results reported by Bohula and colleagues are very encouraging in terms of profiling the safety of lorcaserin, and might provide prescribers with a valuable safe tool in the fight against obesity. However, we still need to fully elucidate the behavioural response of this drug to observe who, and how it can aid weight loss.

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**Competing interests**

J.C.G.H declares associations with Astra Zeneca, American Beverage Association, Bristol Meyers Squibb, Novo Nordisk and Orexigen. C.A.R declares no competing interests.

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