

Novel Serotonergic Pharmaceutical Agent Leads to Weight Loss

Smith S, Weissman N, Anderson C, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med* 2010;363:245–56.

Study Overview

Objective. To determine whether a selective serotonin 2C receptor agonist reduces body weight.

Design. Randomized, double-blind, placebo-controlled trial.

Setting and participants. 3182 patients aged 18 to 65 years who had a body mass index (BMI) of 30 to 45 kg/m² or BMI of 27 to 30 kg/m² with at least 1 comorbid condition (hypertension, cardiovascular disease, dyslipidemia, impaired glucose tolerance, or sleep apnea). Exclusions included moderate or greater mitral regurgitation, mild or greater aortic regurgitation, diabetes, hypertension, pregnancy or breast-feeding, and depression or other major psychiatric disease within 2 years of randomization. The study was conducted in 98 academic and private clinical sites from 2006 to 2009.

Intervention. Subjects received, in a 1:1 ratio, either lorcaserin 10 mg or placebo twice daily for the first year. Subjects who remained in the trial at the end of year 1 were eligible for participation in year 2, with subjects previously on placebo maintained on the same treatment and subjects on lorcaserin randomized to continue lorcaserin or placebo in a 2:1 ratio. All subjects in the study received a behavioral counseling intervention provided at weeks 2 and 4 and then monthly throughout the course of the study, with a goal of compelling subjects to exercise moderately for 30 minutes daily and to reduce daily caloric intake by 600 kcal.

Main outcome measures. End of year 1—proportion of patients with a body weight reduction of 5% or more, proportion with a body weight reduction of 10% or more, and change in weight from baseline; year 2—proportion of patients with body weight reduction of 5% at year 1 who maintained the reduction by the end of year 2. Secondary endpoints included changes in lipids, glycemic variables, waist circumference, BMI, blood pressure, inflammatory markers, and quality of life.

Main results. The average age of subjects was 43.8 and 44.4 years in the lorcaserin and placebo arms, respectively. More than two-thirds of subjects in each arm were women and approximately two-thirds were white. Mean BMI was 36.2 kg/m² in both arms. Only 55.4% in the lorcaserin arm and 45.1% in the placebo arm completed year 1; 7.1% and 6.7% discontinued the study because of adverse events. Of patients who completed year 1, 72.6% completed year 2 with similar drop-out rates among groups. At the end of year 1, 47.5% of those in the lorcaserin arm lost 5% or more of their baseline body weight compared with 20.3% in the placebo arm ($P < 0.001$), and 22.6% in the lorcaserin arm lost 10% or more of their body weight compared with 7.7% in the placebo arm ($P < 0.001$). The average weight loss was 5.8 kg compared with 2.2 kg for the placebo group. Among patients taking lorcaserin who had a 5% or more weight loss by year 1, 67.9% maintained that weight loss if they remained on lorcaserin compared with 50.3% of those switched to

Outcomes Research in Review SECTION EDITORS

Ashish K. Jha, MD, MPH
Brigham and Women's Hospital
Boston, MA

Ula Hwang, MD, MPH
Mount Sinai School of Medicine
New York, NY

Nirav R. Shah, MD, MPH
New York University School of Medicine
New York, NY

Mark W. Friedberg, MD, MPP
Brigham and Women's Hospital
Boston, MA

Maya Vijayaraghavan, MD
University of California, San Francisco
San Francisco, CA

Asaf Bitton, MD
Brigham and Women's Hospital
Boston, MA

Jason P. Block, MD, MPH
Brigham and Women's Hospital
Boston, MA

placebo ($P < 0.001$). The patients receiving lorcaserin for 2 years had more weight loss at the end of 2 years than any other group. For secondary endpoint analyses at the end of year 1, patients taking lorcaserin had significant decreases in BMI, waist circumference, fasting glucose, insulin, HbA1c levels, inflammatory markers and insulin resistance compared with those taking placebo. Lipid levels were lower in the lorcaserin group at year 1 but had increased by year 2. Blood pressure was lower in the lorcaserin group at both year 1 and year 2, and quality of life was higher. The incidence of psychiatric disease and valvulopathy were equivalent in both arms; headache and dizziness were more common in the lorcaserin arm.

Conclusion. Lorcaserin was associated with significant weight loss compared with placebo.

Commentary

The search for the magic bullet for obesity, in pill form, marches on. The history of pharmaceutical agents for obesity has thus far been grim. Plagued by adverse effects, most medications that have emerged have been eventually removed from the market [1]. Fenfluramine and dexfenfluramine, which promote the release of serotonin and function as appetite suppressants, caused valvulopathy and were removed from the market in 1997. Rimonibant, a cannabinoid receptor antagonist, was never approved in the United States because of an association with severe psychiatric sequelae, and it was withdrawn from the market in Europe after an initial approval. Sibutramine, a serotonin and norepinephrine reuptake inhibitor, is the most recent antiobesity drug in the sights of regulators and has been removed from the European market after evidence for an association with nonfatal myocardial infarctions and stroke emerged in a large 6-year trial. Investigations about its safety are ongoing in the United States [2].

With this history, skepticism rightly meets the release of any new obesity medication, such as will be the case with lorcaserin, a serotonergic agent with high selective affinity for central serotonin receptors, which are active in appetite stimulation and not involved in the development of valvulopathy. This study by Smith et al is the first phase III trial of this drug and documented the efficacy of lorcaserin in promoting weight loss for the duration of a 2-year trial. All subjects in the study received an intensive behavioral intervention in addition to lorcaserin or placebo. Those subjects taking lorcaserin lost an average of 5.8 kg by 1 year, with nearly one-half losing 5% of their baseline body weight, compared with 2.2 kg of weight loss and 20% losing 5% of baseline body weight in the placebo arm. Two-thirds of those subjects who lost at least 5% of their baseline body weight while on lorcaserin maintained their weight loss through

2 years if they remained on lorcaserin, compared with only 50% who maintained their loss if they were switched to placebo for year 2. By the end of year 2, only those assigned to take lorcaserin for the full 2 years had a lower body weight than the placebo arm.

These results are impressive, and the metabolic benefits of the reductions in body weight were manifested in lower blood pressure, cholesterol, glycemic measures, and inflammatory markers. Yet concerns remain about this trial and the long-term potential of lorcaserin. In the trial, funded by the manufacturer of lorcaserin, the drop-out rate was incredibly high, with 45% and 55% of subjects dropping out of the lorcaserin and placebo arms, respectively. Another 25% of subjects remaining in the trial for year 2 dropped out by the end of second year. By using an intention-to-treat analysis, this drop-out rate biases results toward finding no effect and increases the confidence in the estimates for the effect of lorcaserin. The per protocol analysis, which measured the weight loss among those adhering to therapy, found an average weight loss of 8.1 kg compared with 3.3 kg for placebo. However, the high drop-out rate does raise questions about the tolerability of this medication among subjects, even with relatively benign adverse effects.

A further limitation was the use of a method of analysis whereby the last observation was carried forward (LOCF) for those subjects who dropped out. This method assumes that the weight of the final assessment was the weight that was achieved at the end of the measurement period, an assumption that is far from realistic for a weight trial. Most subjects who stop a treatment for obesity are likely to return to their baseline weight rather than maintain whatever weight they achieved at the point of stopping therapy. Investigators did use several sensitivity analyses to overcome this limitation, but the potential for overestimating the benefit of lorcaserin in the case of LOCF is real.

Most concerning is the uncertainty about the long-term safety of this novel medication. Several of the obesity drugs that later proved to be harmful were found to be safe in initial studies, and only large-scale trials or post-marketing surveillance revealed their risks. Sibutramine is the prime example of this. Studies have shown long-term benefit for sibutramine without adverse effects [3], yet the recently completed 6-year trial did find harm. This not to say that lorcaserin will face a similar fate, but the promising initial results should be viewed skeptically until longer-term data are available. This study found no increased risk of valvulopathy with lorcaserin, a major concern with any serotonergic agent; however, the study was underpowered somewhat to find a small increase in the risk of valvulopathy. Another reason for skepticism arises from the unsurprising return toward baseline weight for those subjects who lost weight on lorcaserin in the first year but were randomized to placebo during the second year.

The concept of using a medication for short-term treatment of obesity should be viewed similarly to the brief use of anti-hypertensive medications for the control of blood pressure. If medications are a useful therapy for obesity, then their use should be maintained rather than be temporary. Because of the need for long-term or even lifelong therapy with a medication, the scrutiny must be all the more intense. Yanovski [4] identifies other reasons for extra scrutiny for weight loss medications, including the likely use of these medications by nonobese people for off-label weight loss.

The early results for lorcaserin are good. Whether these promising findings are matched by long-term safety has yet to be determined.

Applications for Clinical Practice

Lorcaserin might be a useful pharmacotherapy for weight loss when used in conjunction with an intensive behavioral program. The medication has not yet been approved for use,

and long-term data on safety are still needed before its use could be widely recommended.

—Review by Jason P. Block, MD, MPH

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