

COMMENTARY

Lorcaserin: Making headway

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ABSTRACT

Obesity is a global problem which has reached epidemic proportions. Obesity is morbidly associated with metabolic syndrome, type-2 diabetes, cardiovascular disease and increased cancer risk. There is an alarming increase in the incidence of obesity in young children which puts them at a greater risk for developing diseases at a much earlier age. Obesity also imposes a heavy burden on the healthcare system. Lorcaserin, a novel anti-obesity drug, is a selective agonist to 5-HT_{2C} receptors thereby reducing food intake and promoting weight loss. Lorcaserin has 15-times and 100-times higher selectivity for the 5-HT_{2C} receptor compared to the 5-HT_{2A} and 5-HT_{2B} receptors, respectively.

Keywords: *Obesity, novel therapies, lorcaserin, weight loss*

Introduction

Obesity is a global problem which has reached epidemic proportions. Obesity is morbidly associated with metabolic syndrome, type-2 diabetes, cardiovascular disease and increased cancer risk. There is an alarming increase in the incidence of obesity in young children which puts them at a greater risk for developing diseases at a much earlier age. Obesity also imposes a heavy burden on the healthcare system.

Effective intervention for the treatment of obesity is bariatric surgery which involves invasive procedures and carries significant risks.¹ Reducing calorie intake and leading an active lifestyle through regular exercise although is the best alternative but to achieve significant results takes motivation and commitment over a long time course. Anti-obesity drugs are thus an important intervention as a short term treatment option to patients who are morbidly obese with complications and have restricted abilities to perform physical activity. Current anti-obesity drugs approved by United States Food and Drug Administration (USFDA) include phentermine, phentermine/topiramate (Qsymia) and lorcaserin.^{2,3}

Obesity and the serotonin system

Serotonin has a pivotal role in the satiety and control of food intake. Various serotonin/5-hydroxytryptamine (5-HT) receptors have been identified and of these, 5-HT₂ subfamily is a target for many anti-obesity drugs. 5-HT₂ receptor subfamily includes 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}. 5-HT_{2C} receptors are exclusively located in the central nervous system and are involved in the suppression of appetite. This vital role in appetite control makes 5-HT_{2C} as a

promising anti-obesity target. However, due to highly conserved amino acid sequence between the 5-HT₂ receptor subfamily, developing highly 5-HT_{2C} selective drugs has been a challenging task. Non-selective 5-HT drugs have been shown to reduce body weight but had serious side effects owing to their activation of 5-HT_{2A} and 5-HT_{2B} receptors.⁴

Lorcaserin – the new entrant

Lorcaserin, a novel anti-obesity drug, was approved by FDA in June 2012⁵, marketed by Arena Pharmaceuticals (San Diego, CA) under the trade name Belviq. Chemically lorcaserin is [(1R)-8-chloro-1-methyl-2, 3, 4, 5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate] and is a selective agonist to 5-HT_{2C} receptors thereby reducing food intake and promoting weight loss.^{6,7} Lorcaserin has 15-times and 100-times higher selectivity for the 5-HT_{2C} receptor compared to the 5-HT_{2A} and 5-HT_{2B} receptors, respectively.⁸

Lorcaserin is prescribed along with a low-calorie diet and regular physical activity for obese patients who have Body Mass Index (BMI) of 30 kg/m² or overweight patients with BMI of 27-30 kg/m² and also have one of the obesity related conditions such as type-2 diabetes, high cholesterol or hypertension.

Lorcaserin – the evidence

Three clinical trials have been published so far evaluating the efficacy and safety of lorcaserin for weight loss in obese population: Behavioral modification and lorcaserin for overweight and obesity management (BLOOM), behavioral modification and

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lorcaserin for overweight and obesity management in patients of diabetes mellitus type 2 (BLOOM DM) and behavioral modification and lorcaserin second study for obesity management (BLOSSOM).⁹⁻¹¹ For the BLOOM and BLOSSOM trials, obese or overweight patients were randomized to receive either placebo or lorcaserin 10 mg twice daily for 52 weeks. BLOOM-DM had a similar study design but involved obese patients with type 2 diabetes. These 3 clinical trials demonstrated effective weight loss of ≥ 5 -10% in lorcaserin treated obese patients compared to placebo and also demonstrated a positive outcome on glycated hemoglobin levels, fasting blood glucose, decrease in blood pressure and BMI along with weight loss in obese patients with type-2 diabetes. Meta-analysis of pooled data from five clinical trials show that lorcaserin caused a modest reduction in the body weight but also caused significant side effects including headache, dizziness, nausea, upper respiratory tract infections and nasopharyngitis.¹² FDA-defined mitral regurgitation (valvulopathy) side effect also developed in 2.7 % of lorcaserin treated patients compared to 2.3% in placebo treated patients although statistically not significant.⁹ Other adverse side effects include depression and serotonin syndrome, when lorcaserin is used in combination with other serotonergic drugs such as serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, antipsychotics to name a few.

Concluding remarks

Obesity is a growing health concern across the globe. FDA approval of lorcaserin is a significantly exciting step towards the treatment of obesity. However, large randomised clinical trials in comparison with other anti-obesity drugs are needed to address the benefit to risk ratio for the use of lorcaserin.

Conflict of interest

Dr. Gershome is an editorial advisory board member of *Diabetes*.

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