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Perspective

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The FDA's Assessment of Two Drugs for Chronic Weight Management

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Owing to a complex interplay among genetic, environmental, and cultural factors, obesity has reached epidemic proportions in the United States. The adverse health consequences of obesity are manifold, potentially involving all major organ systems and contributing to reduced quality of life. The goal of all obesity therapies is negative energy balance. Drugs have long been used in an attempt to achieve this goal.

However, numerous once-promising weight-loss drugs have been abandoned because of serious toxic effects: aminorex (which caused pulmonary hypertension), fenfluramine and dexfenfluramine (valvulopathy), phenylpropanolamine (stroke), rimonabant (suicidal ideation and behavior), and most recently sibutramine (myocardial infarction and stroke). The removal of sibutramine from the market left orlistat as the only prescription drug approved for the long-term treatment of obesity.

It was with this troubled history and the undeniable need for effective, safe weight-loss drugs in mind that we at the Food and Drug Administration (FDA) recently approved two new drugs as adjuncts to a reduced-calorie diet and increased physical activity for chronic weight management in adults who are obese (defined as having a body-mass index [BMI; the weight in kilograms divided by the square of the height in meters] of ≥30) or overweight (BMI ≥27) with at least one weight-related coexisting condition.

Belviq (lorcaserin, Arena Pharmaceuticals) is a selective agonist of the serotonin (5-hydroxytryptamine) 2C (5-HT_{2C}) receptor.[1] Qsymia (phentermine plus extended-release topiramate, Vivus) is a fixed-dose combination of the sympathomimetic amine phentermine, which is an anorectic agent, and the antiepileptic drug topiramate.[2] Both medications reduce appetite and, in some people, induce a negative energy balance.

In 1-year placebo-controlled clinical trials in which all participants received instruction in lifestyle modification, lorcaserin and phentermine–topiramate met one or both of the FDA criteria for clinically meaningful weight loss (see table).[3] Moreover, as compared with the administration of placebo, drug treatment was gen-

Weight-Loss Efficacy of Lorcaserin (Belviq) and Phentermine plus Extended-Release Topiramate (Qsymia) at 1 Year.*

Drug, Study, and Treatment	Mean Percentage Change in Body Weight (Mean Efficacy Criterion)	Proportion of Patients Losing ≥5% of Body Weight (Categorical Efficacy Criterion)
Belviq†		
Studies 1 and 2 combined		
10 mg BID	−5.8	47
Placebo	−2.5	23
Study 3		
10 mg BID	−4.5	38
Placebo	−1.5	16
Qsymia‡		
Study 1		
15 mg/92 mg	−10.9	67
Placebo	−1.6	17
Study 2		
7.5 mg/46 mg	−7.8	62
15 mg/92 mg	−9.8	70
Placebo	−1.2	21

* The mean efficacy criterion was a statistically significant difference in mean weight loss of at least 5% between the active-drug and placebo groups. The categorical efficacy criterion included the loss of at least 5% of baseline body weight in at least 35% of participants in the active-drug group; such weight loss in approximately double the proportion of participants in the active-drug group as in the placebo group; and a significant difference between the groups. BID denotes twice daily.

† In Belviq studies 1 and 2, participants had a BMI of 27 to 45 and did not have type 2 diabetes mellitus, and in Belviq study 3, participants had a BMI of 27 or higher with inadequately controlled type 2 diabetes mellitus.

‡ In Qsymia study 1, participants had a BMI of 35 or higher and did not have type 2 diabetes mellitus, and in Qsymia study 2, participants had a BMI of 27 to 45 (no lower limit for BMI in patients with type 2 diabetes mellitus) and had two or more obesity-related coexisting conditions (elevated blood pressure, hypertriglyceridemia, elevated fasting glucose levels, or increased waist circumference). For Qsymia, the first value in the dose information is for the dose of phentermine, and the second is for the dose of extended-release topiramate.

erally associated with numerically more favorable changes in cardiometabolic and anthropometric parameters (e.g., blood pressure, high-density lipoprotein cholesterol levels, and waist circumference). Both drugs also improved glycated hemoglobin levels in overweight and obese participants with type 2 diabetes.

Initially, some potentially serious safety concerns about lorcaserin were identified; these included an increased incidence of multiple tumor types in rats, among them mammary and brain tumors, and a numerical imbalance in the incidence of FDA-defined valvulopathy — that is, either moderate or worse mitral-valve regurgitation or mild or worse aortic-valve regurgitation. Concern about the potential of lorcaserin to increase the risk of breast cancer in humans diminished after the data on mammary tumors in rats were readjudicated by a panel of five independent pathologists who, with near unanimity, categorized fewer tumors as malignant than the initial readings had. A clinical study, demonstrating that only a small fraction of the administered dose of lorcaserin enters the central nervous system, indicated that there was a large margin of safety in humans and allayed concern about brain tumors.

The weight-loss drugs fenfluramine and dexfenfluramine were removed from the market in 1997 because of an association with cardiac valvulopathy. Subsequent research indicated that the drugs' activation of serotonin 2B (5-HT_{2B}) receptors on cardiac interstitial cells was most likely the mechanism responsible for the valvulopathy.[4] On the basis of echocardiographic data from more than 5200 participants who received lorcaserin or placebo for up to 1 year, the relative risk of FDA-defined valvulopathy in lorcaserin-treated participants, as compared with those who received placebo, was 1.16 (95% confidence interval, 0.81 to 1.67). Considered in isolation, the 16% increase in the relative risk of valvulopathy, although not statistically significant, was of some concern. However, data from in vitro receptor assays indicated that lorcaserin has much greater selectivity for the 5-HT_{2C} receptor than for the 5-HT_{2B} receptor and would not, at the clinically recommended dose, be expected to activate the 5-HT_{2B} receptor. Therefore, on the basis of these and other data, the FDA concluded that it is unlikely that lorcaserin increases the risk of valvulopathy in humans.

Potentially serious safety concerns regarding phentermine plus extended-release topiramate included teratogenicity and elevations in resting heart rate. Preliminary data suggesting that women who received topiramate during pregnancy were more likely to have infants born with an

orofacial cleft were corroborated by additional pharmacoepidemiologic study.[5] Accordingly, the approval of phentermine–topiramate required a risk evaluation and mitigation strategy (REMS). The REMS includes a medication guide, a patient brochure, and a formal training program for prescribers, all of which inform patients and prescribers of the teratogenic risk and stress the need for women of reproductive potential to use effective forms of contraception. The REMS also permits only specially certified pharmacies to dispense phentermine–topiramate. This component will enhance the distribution of informational materials to patients and maximize prescriber training.

Treatment with phentermine–topiramate at doses of 7.5 mg/46 mg and 15 mg/92 mg was associated with mean increases in heart rate of 0.6 bpm and 1.6 bpm, respectively, as compared with placebo. However, study participants treated with these doses had greater mean reductions in blood pressure than did the participants given placebo. Consequently, the combination medication was associated with numerically greater reductions in the rate–pressure product — an index of myocardial oxygen consumption — than was placebo. Taking into account the magnitude of weight loss and the favorable changes in blood pressure, the FDA concluded that the benefit–risk balance was positive and supported the approval of phentermine plus extended-release topiramate. The drug's labeling recommends regular heart-rate monitoring and recommends against use in patients with recent or unstable cardiac or cerebrovascular disease, since its use in these patients has not been studied.

In addition to the safety concerns outlined above, lorcaserin may increase the risk of psychiatric, cognitive, and serotonergic adverse effects. Phentermine–topiramate may increase the risk of metabolic acidosis, glaucoma, and psychiatric and cognitive adverse effects.

The FDA acknowledges that there is more to learn about these drugs. To ensure that the relevant data are obtained, the agency is requiring that the manufacturers conduct a number of postapproval clinical trials. One requirement for both drugs is a rigorous assessment of long-term cardiovascular safety in overweight and obese patients.

The FDA is aware of concern about the off-label use of lorcaserin and phentermine–topiramate by consumers who want to lose a few pounds for cosmetic reasons. Because these drugs are associated with potentially serious risks and are intended to be taken long-term, it is important that their use be limited to patients for whom they are indicated. Moreover, prescribers and patients should adhere to the recommendations in the labels regarding patients' initial weight-loss response to treatment. On the basis of the FDA analyses of the clinical trial data, it was determined that if after 12 weeks of treatment with lorcaserin a patient has not lost at least 5% of the baseline body weight, use of the drug should be discontinued, since it is unlikely that the patient will achieve meaningful weight loss with continued treatment. Similarly, if after 12 weeks of treatment with phentermine–topiramate at the 7.5 mg/46 mg dose, a patient has not lost at least 3% of the baseline weight, either the drug should be discontinued or the dose increased. If the latter option is chosen and the patient does not lose at least 5% of the baseline weight during an additional 12 weeks of treatment, the drug should be discontinued, because the patient is unlikely to achieve meaningful weight loss with continued treatment.

As with any newly marketed drugs, there may be yet-unknown benefits and risks associated with lorcaserin and phentermine–topiramate. However, on the basis of available data, the FDA determined that these two drugs have favorable benefit–risk profiles for chronic weight management in some obese and overweight patients.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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