TABLE 416-6 CLINICAL TRIALS FOR WEIGHT LOSS MEDICATIONS[a]

	Lorcaserin		PHEN/TPM[d]	
	BLOOM[b]	BLOSSOM[c]	EQUIP	CONQUER
No. of participants (ITT-LOCF)	3182	4008	1230	2448
Age (years)	18–65	18–65	≥35	27–45
BMI (kg/m^2)	27–45	27–45	18–70	18–70
Comorbid conditions (cardiovascular and metabolic)	≥1	≥1	≥1	≥2
Mean weight loss (%) with treatment vs. placebo	5.8 vs. 2.2	4.8 vs. 2.8	11 vs. 1.6	10.4 vs. 1.8
Placebo-subtracted weight loss (%)	3.6	3.0	9.3	8.6
Categorical change in 5% weight loss with treatment vs. placebo	47.5 vs. 20.3	47.2 vs. 25	67 vs. 17	70 vs. 21
Completion rate (%)	Lorcaserin, 55.4; placebo, 45.1	55.5	59.9	62

[a]Table shows a comparison of two 1-year prospective, randomized, double-blind trials of lorcaserin (BLOOM and BLOSSOM) and phentermine-topiramate extended release (EQUIP and CONQUER). [b]Lorcaserin dose: 10 mg bid. [c]Lorcaserin dose: 10 mg bid or qd. [d]Phentermine-topiramate extended release dose: 15 mg/92 mg.

Abbreviations: BMI, body mass index (see Table 416-1); ITT-LOCF, intention to treat, last observation carried forward; PHEN/TPM, phentermine-topiramate extended release.

and dexfenfluramine—was due to activation of the 5-HT2B receptors expressed on cardiac valvular interstitial cells. By activating the 5-HT2C receptor, lorcaserin is thought to decrease food intake through the pro-opiomelanocortin system of neurons.

Lorcaserin has undergone two randomized, placebo-controlled, double-blind trials for efficacy and safety. Participants were randomized to receive lorcaserin (10 mg bid) or placebo in the BLOOM study and to receive lorcaserin (10 mg bid or qd) or placebo in the BLOSSOM study. All participants received diet and exercise counseling. Participant numbers, eligibility, characteristics, and weight loss outcomes are displayed in Table 416-6. Overweight or obese subjects had at least one coexisting condition (hypertension, dyslipidemia, cardiovascular disease, impaired glucose tolerance, or sleep apnea)—medical conditions that are commonly seen in the office setting. Intention-to-treat 1-year placebo-subtracted weight loss was 3.6% and 3.0%, respectively, in the BLOOM and BLOSSOM trials. Echocardiography was performed at the screening visit and at scheduled time points over the course of the studies. There was no difference in the development of FDA-defined valvulopathy between drug-treated and placebo-treated participants at 1 year or 2 years. Modest statistical improvements consistent with the weight loss were seen in selected cardiovascular and metabolic outcome measurements. The most common adverse events experienced by the drug group were headache, dizziness, and nausea.

In approving both PHEN/TPM and lorcaserin, the FDA introduced a new provision with important clinical relevance: a prescription trial period to assess effectiveness. Response to both medications should be assessed after 3 months of treatment. For lorcaserin, the medication should be discontinued if the patient has not lost at least 5% of body weight by that point. For PHEN/TPM, if the patient has not lost at least 3% of body weight at 3 months, the clinician can either escalate the dose and reassess progress at 6 months or discontinue treatment entirely.

Peripherally Acting Medications Orlistat (Xenical™) is a synthetic hydrogenated derivative of a naturally occurring lipase inhibitor, lipostatin, that is produced by the mold *Streptomyces toxytricini*. This drug is a potent, slowly reversible inhibitor of pancreatic, gastric, and carboxylester lipases and phospholipase A_2, which are required for the hydrolysis of dietary fat into fatty acids and monoacylglycerols. Orlistat acts in the lumen of the stomach and small intestine by forming a covalent bond with the active site of these lipases. Taken at a therapeutic dose of 120 mg tid, orlistat blocks the digestion and absorption of ~30% of dietary fat. After discontinuation of the drug, fecal fat content usually returns to normal within 48–72 h.

Multiple randomized, double-blind, placebo-controlled studies have shown that, after 1 year, orlistat produces a weight loss of ~9–10%, whereas placebo recipients have a 4–6% weight loss. Because orlistat is minimally (<1%) absorbed from the gastrointestinal tract, it has no systemic side effects. The drug's tolerability is related to the malabsorption of dietary fat and the subsequent passage of fat in the feces. Adverse gastrointestinal effects, including flatus with discharge, fecal urgency, fatty/oily stool, and increased defecation, are reported in at least 10% of orlistat-treated patients. These side effects generally are experienced early, diminish as patients control their dietary fat intake, and only infrequently cause patients to withdraw from clinical trials. When taken concomitantly, psyllium mucilloid is helpful in controlling orlistat-induced gastrointestinal side effects. Because serum concentrations of the fat-soluble vitamins D and E and β-carotene may be reduced by orlistat treatment, vitamin supplements are recommended to prevent potential deficiencies. Orlistat was approved for over-the-counter use in 2007.

Antiobesity Drugs in Development Two additional medications are currently in development. Bupropion and naltrexone (Contrave™)—a dopamine and norepinephrine reuptake inhibitor and an opioid receptor antagonist, respectively—are theoretically combined to dampen the motivation/reinforcement that food brings (dopamine effect) and the pleasure/palatability of eating (opioid effect). In the COR-1 randomized, double-blind, placebo-controlled trial, 1742 enrolled participants, who were 18–65 years of age and had BMIs of 30–45 kg/m^2, were randomized to receive naltrexone (16 mg/d) plus bupropion (360 mg/d), naltrexone (32 mg/d) plus bupropion (360 mg/d), or placebo. Mean change in body weight for the three groups was 5.0%, 6.1%, and 1.3%, respectively. The most common adverse events were nausea, headache, constipation, dizziness, vomiting, and dry mouth. However, the FDA rejected the drug in 2011 because of cardiovascular concerns and concluded that a large-scale study of the long-term cardiovascular effects of naltrexone would be needed before approval could be considered.

Liraglutide, a glucagon-like peptide 1 receptor agonist currently approved for the treatment of type 2 diabetes, has independent weight loss effects via hypothalamic neural activation causing appetite suppression. In a double-blind, placebo-controlled trial, 564 adults with BMIs of 30–40 kg/m^2 were randomized to receive once-daily SC liraglutide (1.2, 1.8, 2.4, or 3.0 mg), placebo, or open-label orlistat (120 mg tid) for 1 year. The liraglutide and placebo recipients were switched to 2.4 mg of liraglutide during the second year and then to 3.0 mg for an additional year. One-year placebo-subtracted mean weight loss was 5.8 kg for liraglutide and 3.8 kg more than those on orlistat. The most common side effects were nausea, vomiting, and change in bowel habits.