density. Diets containing low-energy-dense foods have been shown to control hunger and thus to result in decreased caloric intake and weight loss.

Occasionally, very low-calorie diets (VLCDs) are prescribed as a form of aggressive dietary therapy. The primary purpose of a VLCD is to promote a rapid and significant (13- to 23-kg) short-term weight loss over a 3- to 6-month period. The proprietary formulas designed for this purpose typically supply ≤800 kcal, 50–80 g of protein, and 100% of the recommended daily intake for vitamins and minerals. According to a review by the National Task Force on the Prevention and Treatment of Obesity, indications for initiating a VLCD include the involvement of well-motivated individuals who are moderately to severely obese (BMI, >30 kg/m^2), have failed at more conservative approaches to weight loss, and have a medical condition that would be immediately improved with rapid weight loss. These conditions include poorly controlled type 2 diabetes, hypertriglyceridemia, obstructive sleep apnea, and symptomatic peripheral edema. The risk for gallstone formation increases exponentially at rates of weight loss >1.5 kg/week (3.3 lb/week). Prophylaxis against gallstone formation with ursodeoxycholic acid (600 mg/d) is effective in reducing this risk. Because of the need for close metabolic monitoring, VLCDs usually are prescribed by physicians specializing in obesity care.

Physical Activity Therapy Although exercise alone is only moderately effective for weight loss, the combination of dietary modification and exercise is the most effective behavioral approach for the treatment of obesity. The most important role of exercise appears to be in the maintenance of the weight loss. The 2008 Physical Activity Guidelines for Americans (*www.health.gov/paguidelines*) recommend that adults should engage in 150 min of moderate-intensity or 75 min a week of vigorous-intensity aerobic physical activity per week, performed in episodes of at least 10 min and preferably spread throughout the week. Focusing on simple ways to add physical activity into the normal daily routine through leisure activities, travel, and domestic work should be suggested. Examples include walking, using the stairs, doing housework and yard work, and engaging in sports. Asking the patient to wear a pedometer or accelerometer to monitor total accumulation of steps or kcal expended as part of the activities of daily living is a useful strategy. Step counts are highly correlated with activity level. Studies have demonstrated that lifestyle activities are as effective as structured exercise programs for improving cardiorespiratory fitness and weight loss. A high level of physical activity (>300 min of moderate-intensity activity per week) is often needed to lose weight and sustain weight loss. These exercise recommendations are daunting to most patients and need to be implemented gradually. Consultation with an exercise physiologist or personal trainer may be helpful.

Behavioral Therapy Cognitive behavioral therapy is used to help change and reinforce new dietary and physical activity behaviors. Strategies include self-monitoring techniques (e.g., journaling, weighing, and measuring food and activity); stress management; stimulus control (e.g., using smaller plates, not eating in front of the television or in the car); social support; problem solving; and cognitive restructuring to help patients develop more positive and realistic thoughts about themselves. When recommending any behavioral lifestyle change, the patient should be asked to identify what, when, where, and how the behavioral change will be performed. The patient should keep a record of the anticipated behavioral change so that progress can be reviewed at the next office visit. Because these techniques are time-consuming to implement, their supervision is often undertaken by ancillary office staff, such as a nurse-clinician or registered dietitian.

PHARMACOTHERAPY

Adjuvant pharmacologic treatments should be considered for patients with a BMI ≥30 kg/m^2 or—for patients who have concomitant obesity-related diseases and for whom dietary and physical activity therapy has not been successful—a BMI ≥27 kg/m^2. When an antiobesity medication is prescribed, patients should be actively engaged in a lifestyle program that provides the strategies and skills needed to use the drug effectively, since such support increases total weight loss.

Medications for obesity have traditionally fallen into two major categories: appetite suppressants (*anorexiants*) and gastrointestinal fat blockers. Appetite-suppressing medications have primarily targeted three monoamine receptor systems in the hypothalamus: noradrenergic, dopaminergic, and serotonergic receptors. Two new appetite suppressants were approved by the U.S. Food and Drug Administration (FDA) in 2012: lorcaserin and phentermine/topiramate (PHEN/TPM) extended release. Gastrointestinal fat blockers reduce the absorption of selective macronutrients, such as fat, from the gastrointestinal tract.

Centrally Acting Anorexiant Medications Anorexiants affect *satiety* (the absence of hunger after eating) and hunger (the biologic sensation that prompts eating). By increasing satiety and decreasing hunger, these agents help patients reduce caloric intake without a sense of deprivation. The target site for the actions of anorexiants is the ventromedial and lateral hypothalamic regions in the central nervous system **(Chap. 415e)**. The biologic effect of these agents on appetite regulation is produced by augmentation of the neurotransmission of three monoamines: norepinephrine; serotonin (5-hydroxytryptamine, or 5-HT); and, to a lesser degree, dopamine. The classic sympathomimetic adrenergic agents (benzphetamine, phendimetrazine, diethylpropion, mazindol, and phentermine) function by stimulating norepinephrine release or by blocking its reuptake. Among the anorexiants, phentermine has been the most commonly prescribed; there is limited long-term data on its effectiveness. A 2002 review of six randomized, placebo-controlled trials of phentermine for weight control found that patients lost 0.6–6.0 additional kilograms of weight over 2–24 weeks of treatment. The most common side effects of the amphetamine-derived anorexiants are restlessness, insomnia, dry mouth, constipation, and increased blood pressure and heart rate.

PHEN/TPM is a combination drug that contains a catecholamine releaser (phentermine) and an anticonvulsant (topiramate). Topiramate is approved by the FDA as an anticonvulsant for the treatment of epilepsy and for the prophylaxis of migraine headaches. Weight loss was identified as an unintended side effect of topiramate during clinical trials for epilepsy. The mechanism responsible for weight loss is uncertain but is thought to be mediated through the drug's modulation of γ-aminobutyric acid receptors, inhibition of carbonic anhydrase, and antagonism of glutamate. PHEN/TPM has undergone two 1-year pivotal randomized, placebo-controlled, double-blind trials of efficacy and safety: EQUIP and CONQUER. In a third study, SEQUEL, 78% of CONQUER participants continued to receive their blinded treatment for an additional year. All participants received diet and exercise counseling. Participant numbers, eligibility, characteristics, and weight loss outcomes are displayed in **Table 416-6**. Intention-to-treat 1-year placebo-subtracted weight loss for the PHEN/TPM 15-mg/92-mg dose was 9.3% and 8.6%, respectively, in the EQUIP and CONQUER trials. Clinical and statistical dose-dependent improvements were seen in selected cardiovascular and metabolic outcome measurements that were related to the weight loss. The most common adverse events experienced by the drug-randomized group were paresthesias, dry mouth, constipation, dysgeusia, and insomnia. Because of an increased risk of congenital fetal oral-cleft formation from topiramate, the FDA approval of PHEN/TPM stipulated a Risk Evaluation and Mitigation Strategies requirement to educate prescribers about the need for active birth control among women of childbearing age and a contraindication for use during pregnancy.

Lorcaserin is a selective 5-HT2C receptor agonist with a functional selectivity ~15 times that of 5-HT2A receptors and 100 times that of 5-HT2B receptors. This selectivity is important, since the drug-induced valvulopathy documented with two other serotonergic agents that were removed from the market—fenfluramine