35 - 29.35 Weight Loss Drugs

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are difficult, if not impossible, to overcome through diet and exercise alone. For these reasons, it may be necessary to use prescription medications to facilitate weight loss. In this section, drugs used to manage obesity are categorized in two ways: (1) drugs

approved by the U.S. Food and Drug Administration (FDA) as diet pills; and (2) drugs with primary indications other than weight loss but produce weight loss as a side effect. DRUGS WITH U.S. FOOD AND DRUG ADMINISTRATION APPROVAL FOR WEIGHT LOSS All of the drugs approved by the FDA as weight loss agents are specifically indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m2 or greater (obese) or 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia. Phentermine Phentermine hydrochloride (Adipex-P) is a sympathomimetic amine with pharmacological activity similar to the amphetamines. It is indicated as a short-term adjunct in a regimen of weight reduction, but in fact, many patients use the drug for extended periods. As with all sympathomimetics, contraindications include advanced arteriosclerosis, cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, agitated states, and glaucoma. The drug should be prescribed with caution to patients with a history of drug abuse. Hypertensive crises may result if phentermine is used during or within 14 days following the administration of monoamine oxidase inhibitors (MAOIs). Insulin requirements in diabetes mellitus may be altered in association with the use of phentermine hydrochloride and the concomitant dietary regimen. Phentermine hydrochloride may decrease the hypotensive effect of guanethidine. Phentermine is pregnancy Category X and thus contraindicated during pregnancy. Studies have not been performed with phentermine hydrochloride to determine the potential for carcinogenesis, mutagenesis, or impairment of fertility. Phentermine should be taken on an empty stomach, once daily, prior to breakfast. Tablets may be broken or cut in half but should not be crushed. To avoid disrupting normal sleep patterns, it should be dosed early in the day. If taking more than one dose a day, the last dose should be taken approximately 4 to 6 hours prior to going to bed. The recommended dose of phentermine may be different for different patients. Adults under age 60 taking phentermine using 15- to 37.5-mg capsules should take them once per day before breakfast or 1 to 2 hours after breakfast. Those using 15- to 37.5-mg tablets should take them once per day before breakfast or 1 to 2 hours after breakfast. Instead of taking it once a day, some patients may take 15 to 37.5 mg in divided doses a half hour before meals. An oral resin formulation is available in 15- and 30-mg capsules, which should be taken once per day before breakfast.

Phentermine/Topiramate Extended Release (Qsymia) This drug is a combination of phentermine and topiramate (Topamax). The phentermine/topiramate combination was approved by the FDA in 2012 as an extended-release formulation. Both active agents in this formulation are associated with weight loss through separate mechanisms. Adverse events associated with the use of this drug may include, but are not limited to, paresthesia, dizziness, dysgeusia, insomnia, constipation, dry mouth, kidney stones, metabolic acidosis, and secondary angle closure glaucoma. Use of this drug is associated with a fivefold increased risk of infants with cleft palate and is classified as pregnancy Category X. As a result, it can only be prescribed by clinicians who have been certified in the use of this drug. It is available as a tablet and should be administered once daily in the morning with or without food. Avoid dosing with the drug in the evening due to the possibility of insomnia. The recommended dose is as follows: Start treatment with 3.75 mg/23 mg

(phentermine/topiramate extended release) daily for 14 days; after 14 days increase the recommended dose to 7.5 mg/46 mg once daily. Evaluate weight loss after 12 weeks of treatment 7.5 mg/46 mg. If at least 3 percent of baseline body weight has not been lost on 7.5 mg/46 mg, discontinue the drug or escalate the dose. To escalate the dose, increase to 11.25 mg/69 mg daily for 14 days; followed by dosing 15 mg/92 mg daily. Evaluate weight loss following dose escalation to 15 mg/92 mg after an additional 12 weeks of treatment. If at least 5 percent of baseline body weight has not been lost on 15 mg/92 mg, discontinue the medication gradually. Phendimetrazine (Bontril PDM Adipost, Phendiet, Statobex) Phendimetrazine is a sympathomimetic amine that is closely related to the amphetamines. It is classified by the Drug Enforcement Agency (DEA) as a Schedule III controlled substance. Overall prescribing of this agent is limited. The most commonly used formulation is the 105-mg extended-release capsule, which approximates the action of three 35-mg immediate-release doses taken at 4-hour intervals. The average half-life of elimination when studied under controlled conditions is about 3.7 hours for both the extendedrelease and immediate-release forms. The absorption half-life of the drug from the immediate-release 35-mg phendimetrazine tablets is appreciably more rapid than the absorption rate of the drug from the extended-release formulation. The major route of elimination is via the kidneys, where most of the drug and metabolites are excreted. Phendimetrazine contraindications are similar to those of phentermine. They include history of cardiovascular disease (e.g., coronary artery disease, stroke, arrhythmias, congestive heart failure, uncontrolled hypertension, pulmonary hypertension); use during or within 14 days following the administration of MAOIs; hyperthyroidism; glaucoma; agitated states; history of drug abuse; pregnancy; nursing; use in combination with other anorectic agents or central nervous system (CNS) stimulants;

and known hypersensitivity or idiosyncratic reactions to sympathomimetics. Given the lack of systematic research, phendimetrazine should not be used in combination with over-the-counter preparations and herbal products that claim to promote weight loss. Phendimetrazine tartrate is considered pregnancy Category X and is contraindicated during pregnancy because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm. Studies with phendimetrazine tartrate sustained release have not been performed to evaluate carcinogenic potential, mutagenic potential, or effects on fertility. Interactions may occur with MAOIs, alcohol, insulin, and oral hypoglycemic agents. Phendimetrazine may decrease the hypotensive effect of adrenergic neuron blocking drugs. The effectiveness and the safety of phendimetrazine in pediatric patients have not been established. It is not recommended in patients less than 17 years of age. Adverse reactions reported with phendimetrazine include sweating, flushing, tremor, insomnia, agitation, dizziness, headache, psychosis, and blurred vision. Elevated blood pressure, palpitations, and tachycardia are common. Gastrointestinal side effects include dry mouth, nausea, stomach pain, diarrhea, and constipation. Genitourinary side effects include frequency, dysuria, and changes in libido. Phendimetrazine tartrate is related chemically and pharmacologically to the amphetamines. Amphetamines and related stimulant drugs have been extensively abused, and the possibility of abuse of phendimetrazine should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Acute overdose with phendimetrazine may manifest itself by restlessness, confusion, belligerence, hallucinations, and panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include tachycardia, arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Poisoning may result in convulsions, coma, and death. The management of acute overdose is largely symptomatic. It includes lavage

and sedation with a barbiturate. If hypertension is marked, the use of a nitrate or rapid-acting α-receptor–blocking agent should be considered. Diethylpropion (Tenuate) Diethylpropion preceded its analog, the antidepressant drug bupropion (Wellbutrin). Diethylpropion comes in two formulations: a 25-mg tablet and a 75-mg extended-release tablet (Tenuate Dospan). It is usually taken three times a day, 1 hour before meals (regular tablets), or once a day in midmorning (extended-release tablets). The extendedrelease tablets should be swallowed whole, never crushed, chewed, or cut. The maximum daily dose is 75 mg. Side effects include dry mouth, unpleasant taste, restlessness, anxiety, dizziness, depression, tremors, upset stomach, vomiting, and increased urination. Side effects that warrant medical attention include tachycardia, palpitations, blurred vision, skin rash, itching, difficulty breathing, chest pain, fainting, swelling of the ankles or feet, fever,

sore throat, chills, and painful urination. Diethylpropion is classified pregnancy Category B and has a low abuse potential. It is listed as a Schedule IV drug by the DEA. Orlistat (Xenical, Alli) Orlistat interferes with the absorption of dietary fats, causing reduced caloric intake. It works by inhibiting gastric and pancreatic lipases, the enzymes that break down triglycerides in the intestine. When lipase activity is blocked, triglycerides from the diet are not hydrolyzed into absorbable free fatty acids and are excreted undigested instead. Only trace amounts of orlistat are absorbed systemically; it is almost entirely eliminated through the feces. The effectiveness of orlistat in promoting weight loss is definite, though modest. When used as part of weight loss program, between 30 and 50 percent of patients can expect a 5 percent or greater decrease in body mass. About 20 percent achieve at least a 10 percent decrease in body mass. After orlistat is stopped, up to a third of people gain the weight they lose. Among the benefits of orlistat treatment are a decrease in blood pressure and a reduced risk of developing type 2 diabetes. The most common subjective side effects of orlistat are gastrointestinal related, and include steatorrhea, flatulence, fecal incontinence, and frequent or urgent bowel movements. To minimize these effects, foods with high fat content should be avoided; a low-fat, reduced calorie diet is advisable. Ironically, orlistat can be used with high-fat content diets to treat constipation that results from treatment with some psychotropic drugs, such as the tricyclic antidepressants. Side effects are most severe when beginning therapy and may decrease in frequency with time. Hepatic and renal injuries are potentially serious side effects of orlistat use. In 2010, new safety information about rare cases of severe liver injury was added to the product label of orlistat. The rate of acute kidney injury is more common among orlistat users than nonusers. It should be used with caution in patients with impaired liver function and renal function, as well as those with an obstructed bile duct and pancreatic disease. Orlistat is contraindicated in malabsorption syndromes, hypersensitivity to orlistat, reduced gallbladder function, and in pregnancy and breast-feeding. Orlistat is rated pregnancy Category X. Absorption of fat-soluble vitamins and other fat-soluble nutrients is inhibited by the use of orlistat. Multivitamin supplements that contain vitamins A, D, E, K, as well as βcarotene should be taken once a day, preferably at bedtime. Orlistat can reduce plasma levels of the immunosuppressant cyclosporine (Sandimmune), so the two drugs should therefore not be administered concomitantly. Orlistat can also impair absorption of the antiarrhythmic amiodarone (Nexterone). At the standard prescription dose of 120 mg three times daily before meals, orlistat prevents approximately 30 percent of dietary fat from being absorbed. Higher doses have not been shown to produce more pronounced effects. An over-the-counter formulation of orlistat (Alli) is available as 60-mg capsules—half the dosage of prescription orlistat.

Lorcaserin (Belviq) This drug is awaiting approval by the FDA because it appears to have hallucinogenic potential. The exact mechanism of action of lorcaserin is not known, but it most likely decreases food consumption and promotes satiety through selective activation of 5-HT2C receptors on neurons in the hypothalamus. The effect of multiple oral doses of lorcaserin 15 mg and 40 mg once daily on QTc interval has been evaluated in healthy subjects. The largest placebo adjusted, baselinecorrected QTc based on individual correction method (QTcI) was below 10 milliseconds, the threshold for regulatory concern. Lorcaserin is absorbed from the gastrointestinal tract, with peak plasma concentration occurring 1.5 to 2 hours after oral dosing. The absolute bioavailability of lorcaserin has not been determined. Lorcaserin has a plasma half-life of approximately 11 hours; steady state is reached within 3 days after twice daily dosing, and accumulation is estimated to be approximately 70 percent. Lorcaserin can be administered with or without food. Lorcaserin hydrochloride is moderately bound (approximately 70 percent) to human plasma proteins. It is extensively metabolized in the liver by multiple enzymatic pathways, and the metabolites are excreted in the urine. Lorcaserin and its metabolites are not cleared by hemodialysis. It is not recommended for patients with severe renal impairment (creatinine clearance less than 30 mL per minute) or patients with end-stage renal disease. The half-life of lorcaserin is prolonged by 59 percent to 19 hours in patients with moderate hepatic impairment. Lorcaserin exposure (area under the curve) is approximately 22 and 30 percent higher in patients with mild and moderate hepatic impairment, respectively. Dose adjustment is not required for patients with mild to moderate hepatic impairment. No dosage adjustment based on gender is necessary because it did not meaningfully affect the pharmacokinetics of lorcaserin. No dosage adjustment is required based on age alone. Lorcaserin significantly inhibits CYP2D6-mediated metabolism. DRUGS WITHOUT U.S. FOOD AND DRUG ADMINISTRATION APPROVAL FOR WEIGHT LOSS Topiramate Topiramate and zonisamide (Zonegran) are discussed more fully in Section 29.6, but are mentioned here because both agents can have a substantial effect on weight loss. Topiramate is approved as an antiepileptic drug and for prevention in adults of migraine headaches. The degree of weight loss associated with topiramate may be comparable to the weight loss that other FDA-approved antiobesity drugs induce. Small studies and extensive anecdotal reports indicate that topiramate can help to offset

weight gain associated with selective serotonin reuptake inhibitors (SSRIs) and secondgeneration antipsychotic drugs. Its impact on body weight may be due to its effects on both appetite suppression and satiety enhancement. These may be the result of a combination of pharmacological effects including augmenting γ-aminobutyric acid (GABA) activity, modulation of voltage-gated ion channels, inhibition of excitatory glutamate receptors, or inhibition of carbonic anhydrase. The duration and dosage of treatment affect the weight loss benefits of topiramate. Weight loss is higher when the drug is prescribed at doses of 100 to 200 mg per day for more than a month compared with less than a month. In a large study it was shown that compared to those who took placebo, topiramate-treated patients were seven times more likely to lose more than 10 percent of their body weight. In clinical practice, many patients experience weight loss at a starting dose of 25 mg per day. The most common side effects of topiramate are paresthesias, typically around the mouth, impaired taste (taste perversion), and psychomotor disturbances, including slowed cognition and reduced physical movements. Concentration and memory impairment, often characterized by word finding and name recall problems, is often reported. Some patients may experience emotional lability and mood changes. Medical side effects include increased risk of kidney stones and acute-angle closure glaucoma. Patients should report any change in visual

acuity. Those with a history of kidney stones should be instructed to drink adequate amounts of fluid. Topiramate is available as 25-, 50- 100-, and 200-mg tablets and as 15-, 25-, and 50mg capsules. Zonisamide Zonisamide is a sulfonamide-related drug, similar in many ways to topiramate. Its exact mechanism of action is not known. Like topiramate, it can cause cognitive problems, but the incidence is lower than that with topiramate. Zonisamide has been assigned to pregnancy Category C. Animal studies have revealed evidence of teratogenicity. Fetal abnormalities or embryo-fetal deaths have been reported in animal tests at zonisamide dosage and maternal plasma levels similar to, or lower than, human therapeutic levels. Therefore, use of this drug in human pregnancy may expose the fetus to significant risk. The most common side effects include drowsiness, loss of appetite, dizziness, headache, nausea, and agitation or irritability. Zonisamide has also been associated with hypohidrosis. There is a 2 to 4 percent risk of kidney stones. Other drugs known to provoke stones, such as topiramate or acetazolamide (Diamox), should not be combined with zonisamide. Serious, but rare, adverse drug reactions include Stevens-Johnson syndrome, toxic epidermal necrolysis, and metabolic acidosis. Typical dosing for weight loss has not been established. Generally, zonisamide is started at 100 mg at night for 2 weeks, and increased by 100 mg daily every 2 weeks to a target dose of 200 to 600 mg per day in one or two daily doses.

Metformin (Glucophage) Metformin is a medication for type 2 diabetes mellitus. Its actions include reduction of hepatic glucose production, reduced intestinal glucose absorption, increased insulin sensitivity, and improved peripheral glucose uptake and regulation. It does not increase insulin secretion. When used as an adjunct to second-generation antipsychotics, it has consistently been shown to reduce body weight and waist circumference. Metformin probably has the best evidence of therapeutic benefit for the treatment of antipsychotic drug–induced metabolic syndrome. In several studies, metformin has been shown to attenuate or reverse some of the weight gain induced by antipsychotics. The degree of effect on body weight compares favorably with the effect of other treatment options that are approved for weight reduction. The weight loss effect of adjunctive metformin appears to be stronger in drug-naive patients treated with second-generation antipsychotic medications. This effect is most evident for those being treated with clozapine (Clozaril) and olanzapine (Zyprexa). Based on the existing evidence, if weight gain occurs after second-generation antipsychotic initiation, despite lifestyle intervention, metformin should be considered. Common side effects include nausea, vomiting, abdominal pain, and loss of appetite. Gastrointestinal side effects can be mitigated by dividing the dose, taking the drug after meals, or using delayed-release formulations. One serious treatment risk is that of lactic acidosis. This side effect is more common in those with reduced renal function. Although very rare (approximately 9 in 100,000 persons per year), it has a 50 percent mortality rate. Alcohol use along with metformin can increase the risk of acidosis. Renal function monitoring and alcohol avoidance are important. The weight loss effects of metformin are also evident in chronically ill patients with schizophrenia. Long-term use of metformin appears to be safe and effective. There is no clearly established dose range for metformin when used as an adjunct for weight loss. In most reports, the usual dose ranged from 500 to 2,000 mg per day. The maximum dose used in treating diabetes is 850 mg three times daily. Patients usually start with a low dose to see how the drug affects them. Metformin is available in 500-, 850-, and 1,000-mg tablets, all now generic. Metformin SR (slow release) or XR (extended release) is available in 500- and 750-mg strengths. These formulations are intended to reduce gastrointestinal side effects and to increase patient compliance by reducing pill burden. Amphetamine Amphetamine is a psychostimulant approved for the treatment of

attentiondeficit/hyperactivity disorder and narcolepsy. It has the effect of reducing appetite and has been used off label for that purpose for many years. Some of the drugs discussed above have amphetamine-like properties, which account for their effectiveness.

Amphetamines and other psychostimulants are discussed fully in Section 29.30. REFERENCES Adan RA. Mechanisms underlying current and future anti-obesity drugs. Trend Neurosci. 2013;36(2):133–140. Astrup A, Carraro R, Finer N, Harper A, Kunesova M, Lean MEJ, Niskanen L, Rasmussen MF, Rissanen A, Rössner S, Savolainen MJ, Van Gaal L, NN8022-1807 Investigators. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int J Obes. 2012;36(6):843–854. Colman E, Golden J, Roberts M, Egan A, Weaver J, Rosebraugh C. The FDA's assessment of two drugs for chronic weight management. N Engl J Med. 2012;367(17):1577–1579. Garvey WT. New tools for weight-loss therapy enable a more robust medical model for obesity treatment: Rationale for a complications-centric approach. Endocr Pract. 2013;19(5):864–874. Hampl JS, Lehmann J, Fielder EG. How United States newspapers framed weight-loss drugs. J Acad Nutr Diet. 2013;113(9):A20. Kelly AS, Metzig AM, Rudser KD, Fitch AK, Fox CK, Nathan BM, Deering MM, Schwartz BL, Abuzzahab MJ, Gandrud LM, Moran A, Billington CJ, Schwarzenberg SJ. Exenatide as a weight-loss therapy in extreme pediatric obesity: A randomized, controlled pilot study. Obesity. 2012;20(2):364–370. O'Neil PM, Smith SR, Weissman NJ, Fidler MC, Sanchez M, Zhang J, Brian Raether, Anderson CM, Shanahan WR. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: The BLOOM-DM study. Obesity. 2012;20(7):1426–1436. Suplicy H, Boguszewski CL, dos Santos CMC, de Figueiredo MD, Cunha DR, Radominski R. A comparative study of five centrally acting drugs on the pharmacological treatment of obesity. Int J Obes. 2014:1–7. Vilsbøll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: Systematic review and meta-analyses of randomised controlled trials. BMJ. 2012;344.

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