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INTRODUCTION — Along with diet, exercise, and behavior modification, drug therapy may be a helpful component of treatment for patients who are overweight or obese. The role of drug therapy has been questioned, however, because of concerns about efficacy, safety, and the observation that body weight slows and then plateaus with continued treatment, and most patients regain weight when their weight-loss drugs are stopped.

The decision to initiate drug therapy in overweight subjects should be made only after a careful evaluation of risks and benefits [1,2]. The first step is evaluation of the patient, which should include determination of the body mass index (BMI), the distribution of fat based upon the waist circumference, and investigations for comorbid conditions such as diabetes mellitus, dyslipidemia, hypertension, heart disease, sleep apnea, and symptomatic osteoarthritis. (See "Obesity in adults: Prevalence, screening, and evaluation".)

Anti-obesity drugs can be useful adjuncts to diet and exercise for adults with obesity and a BMI greater than 30 kg/m^2, who have failed to achieve weight loss goals through diet and exercise alone. A trial of drug therapy is also warranted in patients with a BMI of 27 to 29.9 kg/m^2 with comorbidities, or in those in whom gastrointestinal bypass surgery is being considered.

This topic will review drug therapy for weight loss in patients with obesity (table 1). Other treatments are discussed separately. (See "Obesity in adults: Overview of management".)

GOALS OF THERAPY — The goal of any treatment, including drug therapy, for overweight subjects must be realistic.

- The ideal outcome is a return to normal body weight, but this is usually unrealistic. In one study, as an example, subjects were asked about their dream weight, and this was later compared with the actual weight loss achieved; no subject achieved their dream weight and few were happy with the weight loss they achieved [3]. Thus, the clinician and the patient need to come to a mutual understanding of the realities of weight loss.

- Success may be measured by the degree of weight loss and improvement in associated risk factors. Weight loss should exceed 2 kg during the first month of drug therapy (one pound per week), fall more than 5 percent below baseline between three to six months, and remain at this level to be considered effective. A weight loss of 5 to 10 percent can significantly reduce the development of diabetes in those with pre-diabetes [4] and reduce blood pressure and risk factors for cardiovascular disease in higher risk patients [5]. Improvement in baseline risk factors after weight loss is an important criterion in the determination of whether to continue therapy [6].

- In drug trials, weight loss of 10 to 15 percent using both drug and behavioral intervention is considered a very good response, and weight loss exceeding 15 percent is an excellent response. This degree of weight loss generally has substantial benefits, including lowering blood pressure and improving serum lipid concentrations, increasing insulin sensitivity, and reducing hyperglycemia, with reversion to normal glucose

tolerance in some early onset diabetics, and may reduce risk of mortality. However, a drug may produce side effects that can reduce its overall benefits. (See 'Side effects' below and 'Adverse effects' below and 'Safety' below.)

- The maximal duration of published treatment results is four years for orlistat [7]. If patient response is good, using the criteria noted above, and the patient wishes to continue orlistat, this may be considered after acknowledging the lack of longer term data and obtaining the patient's willingness to continue.

- Drug therapy does not cure obesity. Patients with obesity given drugs should be advised that when the maximal therapeutic effect is achieved, weight loss ceases. When drug therapy is discontinued, weight is expected to rise.

- When overweight patients have diabetes, depression, behavioral problems, or cardiovascular disease, it is important to select drugs for these diseases which produce weight loss, rather than weight gain, when benefits in total outweigh risks of adverse effects. Several drugs are well known to produce weight gain and should be avoided if good alternatives are available [1,8]. Although weight loss is always desirable, it must be balanced against other factors (ability to achieve desired glycemic control, other side effects and risks of meds, and expense).

Achieving and maintaining weight loss is made difficult by the reduction in energy expenditure that is associated with weight loss. In one report, as an example, maintenance of body weight at 10 percent below the baseline weight in patients with obesity was associated with an 8 kcal/kg reduction in total energy expenditure (figure 1) [9].

OUR APPROACH

Choice of agent — When the health care provider concludes that treatment for obesity is needed, initiating a comprehensive or multi-component lifestyle program is the first line of approach. If weight loss is unsatisfactory (ie, less than 5 percent below baseline at three to six months), then pharmacologic therapy can be discussed with the patient. The agents with the least side effects are the preferred initial considerations. This would include orlistat and lorcaserin first, with liraglutide and phentermine/topiramate as potential alternatives. If weight loss does not achieve 5 percent or more in six months with one of these agents, it should be discontinued and another tried if that is thought necessary.

In meta-analyses of randomized trials comparing pharmacologic therapy with placebo, all active drug interventions are effective at reducing weight compared with placebo (table 2) [1,10,11]. Many of the trials in the meta-analyses have serious limitations, including short duration of study, high attrition rates, heterogeneity, and inadequate reporting of important clinical outcomes (eg, cardiovascular outcomes) [2]. In addition, there are few head-to-head trials comparing the individual therapies, and it is uncertain whether people who fail to respond to one therapy will in fact respond to another.

Thus, the decision to use pharmacologic therapy should be individualized, weighing the potential benefits with the risks of the agents. The choice of antiobesity drugs is often governed by the comorbidities and relative contraindications present in the individual patient. Our approach outlined below is based upon the available clinical trial evidence and clinical expertise.

- Counsel all overweight (body mass index [BMI] 25 to 29.9 kg/m^2) and patients with obesity (BMI ≥30 kg/m^2) on diet, lifestyle, and goals for weight loss. (See "Obesity in adults: Overview of management" and "Obesity in adults: Dietary therapy" and "Obesity in adults: Behavioral therapy" and "Obesity in adults: Role of physical activity and exercise".)

- Pharmacologic therapy may be offered to those with a BMI >30 kg/m^2 or a BMI of 27 to 29.9 kg/m^2 with comorbidities, who have failed to achieve weight loss goals through diet and exercise alone.

- Pharmacologic options for use in patients include orlistat, lorcaserin, combination phentermine-extended release topiramate (in one capsule), combination bupropion-naltrexone (in one extended-release tablet), liraglutide (daily injection), phentermine, benzphetamine, phendimetrazine, and diethylpropion (table 1). Of these options, we prefer orlistat as initial therapy because of its efficacy and long-term safety record. In particular, we favor orlistat over other pharmacologic options for patients with obesity and dyslipidemia and/or diabetes. However, unpleasant gastrointestinal side effects may limit the use of orlistat for the treatment of obesity and patients need to be counseled carefully about side-effects before beginning this drug.

  Lorcaserin is an alternative option with similar efficacy as orlistat. It appears to have fewer adverse effects than orlistat, although long-term safety data are limited. Like orlistat, it may be used in obese patients with diabetes, hypertension, and/or dyslipidemia. Some patients respond well to lorcaserin, and it is these patients in whom it might be continued. Lorcaserin should be discontinued if patients do not lose 5 percent of their body weight in 12 weeks.

  Liraglutide is an alternative option for overweight or obese patients with type 2 diabetes. However, unpleasant gastrointestinal side effects (nausea, vomiting) and the need for a daily injection may limit the use of this drug in some patients.

  Combination phentermine-extended release topiramate is an option for men or women with obesity without hypertension or coronary heart disease. The efficacy for weight loss of phentermine-extended release topiramate appears to be greater than either orlistat or lorcaserin, but it may have more side effects (eg, increased heart rate, dose-related increase in the incidence of psychiatric [eg, depression, anxiety] and cognitive [eg, disturbance in attention] adverse events). It may be an acceptable option for a patient with an obesity-related comorbidity such as sleep apnea, who does not have any cardiovascular disease. If a patient does not lose 5 percent of body weight after 12 weeks on the highest dose, phentermine-topiramate should be discontinued gradually. The presence of topiramate in this combination may increase risk of fetal malformations and it should thus be used with cause in women of child bearing age, who should have a pregnancy test before its use and monthly thereafter.

  Combination bupropion-naltrexone produces similar weight loss as orlistat and lorcaserin, but it has more side effects and contraindications (table 1). Owing to the uncertainty about cardiovascular effects, we prefer to use orlistat or lorcaserin, rather than bupropion-naltrexone.

  Phentermine, benzphetamine, phendimetrazine, and diethylpropion are only approved for short-term use, have more side effects, and the potential for abuse (table 1). Thus, we suggest not using these drugs for long-term weight loss. If they are prescribed for short-term weight loss, clinicians would serve their patients well by providing them written description of the limits of these drugs so that they may consent to their use.

- For patients with specific comorbidities, we suggest a weight-centric approach to chronic disease management, trying, if possible, to select the drugs to treat the comorbidity that may produce weight loss, rather than weight gain [1]. As an example, for patients with or at high risk for developing diabetes, metformin is a reasonable choice because it does not cause weight gain and may cause weight loss in some [12]. Exenatide, liraglutide, pramlintide, and sodium glucose transport-2 inhibitors are associated with weight loss in patients with type 2 diabetes, whereas sulfonylureas, thiazolidinediones, glinides, and insulin are associated with weight gain, and the dipeptidylpeptidase-4 inhibitors are weight neutral. However, for patients with diabetes, weight loss must be balanced against other factors (ability to achieve desired glycemic control, other side effects and risks of medications, and expense). A drug that results in better

glycemia at the expense of a few more kg of weight gain may still be preferable to more expensive, side-effect laden drugs that do not achieve goal glycemia (table 3). For patients with obesity and depression, we choose antidepressants that are weight neutral or produce weight loss, rather than weight gain (table 4). (See "Initial management of blood glucose in adults with type 2 diabetes mellitus" and "Management of persistent hyperglycemia in type 2 diabetes mellitus" and "Unipolar major depression in adults: Choosing initial treatment".)

- Bariatric surgery should be considered for patients with BMI ≥40 kg/m^2 who have failed diet, exercise, and drug therapy [13]. Individuals with BMI >35 kg/m^2 and comorbidities (hypertension, impaired glucose tolerance, diabetes mellitus, dyslipidemia, sleep apnea), who have failed diet, exercise, and drug therapy, are also potential surgical candidates, assuming that the anticipated benefits outweigh the costs, risks, and side effects of the procedure. Bariatric surgery should be performed at high-volume centers with experienced surgeons. (See "Bariatric operations for management of obesity: Indications and preoperative preparation".)

Our approach is largely consistent with published guidelines [14,15].

The efficacy, dosing, and adverse effects of each drug are described below.

Monitoring — After initiating pharmacologic therapy, we monitor weight loss, blood pressure, heart rate, and side effects on a weekly basis for four weeks, and then monthly for the next three to four months, at which time a decision should be made whether to continue the drug. If patients do not lose 5 percent of body weight after 12 weeks of tolerated maximum-dose therapy, the drug should be tapered and discontinued. Although it is uncertain whether people who fail to respond to one drug will respond to another, this approach can be tried if the patient and clinician believe the benefits outweigh the risks.

Weight loss may cause hypoglycemia in patients taking medication for diabetes, especially insulin or sulfonylureas, and in such patients, self-monitoring of blood glucose (SMBG) should be performed more frequently for safety. SMBG should be performed at least daily in people with type 2 diabetes treated with insulin or sulfonylureas who are started on weight loss medications and during dose titration.

More specific monitoring instructions depend upon the drug initiated. As an example, lorcaserin, phentermine-topiramate, and bupropion-naltrexone may cause neuropsychiatric side effects, and patients taking these drugs should be monitored for depression or suicidal thoughts. Hyperchloremic, non-anion gap metabolic acidosis, and increases in serum creatinine have been reported in patients treated with phentermine-topiramate. Thus, serum electrolytes (including bicarbonate) and creatinine should be measured before and approximately four weeks after initiation of this combination.

DRUGS THAT ALTER FAT DIGESTION

Orlistat — For initial therapy of patients with obesity who are candidates for pharmacologic therapy, we suggest orlistat, given its excellent cardiovascular safety profile and beneficial effects on serum total and low-density lipoprotein (LDL) cholesterol concentrations. Orlistat alters fat digestion by inhibiting pancreatic lipases [16]. Thus, fat is not completely hydrolyzed and fecal fat excretion is increased. In normal subjects eating a diet that contains 30 percent fat, orlistat causes a dose-dependent increase in fecal fat excretion that peaks when approximately 30 percent of ingested fat is not digested.

Orlistat, available for the long-term treatment of obesity, is provided in 120 mg capsules. The recommended dose is 120 mg three times daily. A lower dose (60 mg) over-the-counter version is approved and available in some countries, including the United States. Two of the 60 mg over-the-counter capsules are the same as one of the 120 mg capsules. We typically advise patients to take a multivitamin at bedtime because orlistat may decrease the absorption of fat soluble vitamins. (See 'Side effects' below.)

Pharmacology — Less than 1 percent of an oral dose of orlistat is absorbed. What little is absorbed is degraded into two major metabolites. Orlistat does not alter the pharmacokinetics of digoxin, phenytoin, warfarin, glyburide, oral contraceptives, alcohol, furosemide, captopril, nifedipine, or atenolol. However, absorption of fat-soluble vitamins may be decreased by orlistat. For patients taking warfarin, a decrease in vitamin K may necessitate a reduction in the dose of warfarin [17].

Efficacy — The efficacy of orlistat in facilitating weight loss has been demonstrated in several randomized trials and in meta-analyses [7,10,18-28]. In a meta-analysis of 12 trials that included patients with and without diabetes and reported data with 12-month outcomes, patients randomly assigned to orlistat plus a behavioral intervention lost 5 to 10 kg (8 percent of baseline weight) compared with 3 to 6 kg in the control group (placebo plus behavioral intervention), for a mean placebo-subtracted difference of 3 kg (95% CI -3.9 to -2.0 kg) [28]. Weight loss was maintained with up to 24 to 36 months of orlistat treatment [28]. In another meta-analysis, orlistat was equally effective in Caucasians and ethnic minority groups [27].

In one of the longest trials, 3304 overweight patients, 21 percent of whom had impaired glucose tolerance, were randomly assigned to placebo or orlistat [7]. During the first year, weight loss was greater in the orlistat-treated group (11 percent compared with 6 percent below baseline in the placebo-treated group) (figure 2). Over the remaining three years of the trial, there was a small regain in weight, such that by the end of four years, the orlistat-treated patients were 6.9 percent below baseline compared with 4.1 percent for those receiving placebo. There was a 37 percent reduction in the conversion of patients from impaired glucose tolerance to diabetes, essentially all of which occurred in the patients with impaired glucose tolerance at enrollment into the trial. In other trials in patients with diabetes, orlistat resulted in significantly more weight loss and decrease in hemoglobin glycated hemoglobin (A1C) at one year than placebo [23-25].

In a subsequent trial published after the meta-analyses (146 obese patients [mean body mass index {BMI} 39.3]), the combination of orlistat and a low fat diet (<30 percent of daily energy) resulted in similar weight loss (approximately 9 percent) as a low-carbohydrate ketogenic diet (initially <20 g carbohydrate/day) [29].

In summary, many clinical trials have demonstrated that initial weight loss is greater and that weight regain is slowed by orlistat, as compared with lifestyle/placebo.

Other beneficial effects — In hypertensive patients, orlistat improves blood pressure, as illustrated by the findings of a meta-analysis of four trials comparing orlistat with placebo in hypertensive, obese patients [30]. There was a significant reduction in systolic and diastolic blood pressure (weighted mean difference -2.5 and -1.9 mmHg, respectively). Patients taking orlistat also lost significantly more weight (weighted mean difference -3.7 kg).

In addition, orlistat improves some serum lipid values more than can be explained by weight reduction alone (figure 3) [19]. In a multicenter trial, as an example, serum total and LDL cholesterol concentrations decreased by 4 to 11 and 5 to 10 percent, respectively, in subjects treated with a weight-maintaining diet plus 30 to 360 mg of orlistat per day for eight weeks [31]. These decreases were probably related to fecal fat loss. Others have reported a reduction in postprandial triglyceridemia associated with orlistat therapy [32].

Side effects — The predominant side effects of orlistat therapy are gastrointestinal, including intestinal borborygmi and cramps, flatus, fecal incontinence, oily spotting, and flatus with discharge [25]. In a meta-analysis of nine clinical trials, these side effects occurred at frequency rates of 15 to 30 percent [33], and tended to occur early and to subside as patients learned how to avoid these problems by avoiding high fat diets and sticking to the recommended intake of no more than 30 percent fat. There was no evidence of an increased risk of gallstones, renal stones, or cardiovascular or central nervous system events.

Absorption of vitamins A and E and beta-carotene may be slightly reduced in some studies of patients receiving orlistat. In the meta-analysis noted above, levels of fat-soluble vitamins (A, D, E, K) and beta-carotene were lowered by orlistat therapy, with vitamin D the most frequently affected [33]. It is advisable to give vitamin supplements to patients treated with this drug. Orlistat does not seem to affect the absorption of other drugs, with the exception of cyclosporine.

Severe liver injury has been reported rarely with the use of orlistat [34]. A US Food and Drug Administration (FDA) review identified 13 reports of severe liver injury, 12 of which occurred outside of the United States. Over the 10-year period of the review, an estimated 40 million people worldwide used orlistat. A causal relationship has not been established. In a population-based study using the United Kingdom Clinical Practice Research Datalink, the incidence of acute liver injury from orlistat use similarly increased (approximately doubled) during the 90 days before and 30 days after the start of treatment compared with background incidence [35]. These data suggest that the association is not causal. Nevertheless, patients who take orlistat should contact their health care provider if itching, jaundice, pale color stools, or anorexia develop.

Oxalate-induced acute kidney injury has also been reported in orlistat users [36-38]. Malabsorption syndromes are a risk factor for calcium oxalate stones (see "Risk factors for calcium stones in adults"). Similarly, fat malabsorption induced by orlistat may result in the binding of enteric calcium. When less calcium is available in the intestinal lumen to bind oxalate, intestinal oxalate absorption and urinary oxalate excretion increase. Free oxalate can be deposited in the renal parenchyma, resulting in acute kidney injury. Orlistat should not be used in patients with a history of calcium oxalate stones.

SEROTONIN AGONISTS

Lorcaserin — In 2012, the United States Food and Drug Administration (FDA) approved lorcaserin as an addition to a reduced-calorie diet and exercise for patients who are obese (body mass index [BMI] ≥30 kg/m^2) or overweight (≥27 kg/m^2) with at least one medical comorbidity, such as type 2 diabetes, hypertension, high cholesterol, or sleep apnea [39,40]. Lorcaserin appears to have similar efficacy as and fewer adverse effects than orlistat, although long-term safety data are limited. (See 'Adverse effects' below.)

Serotonin reduces food intake in animals and human beings, and thus agonists to appropriate serotonin receptors are potentially valuable drugs. Lorcaserin is a selective agonist of the serotonin 2C receptor. It activates central serotonin 2C receptors with a functional selectivity of approximately 15 and 100 times over that for serotonin receptors 2A and 2B, respectively. It reduces appetite and thereby reduces body weight in men and women [41-43]. Nonselective serotonergic agonists, such as fenfluramine and dexfenfluramine, also enhanced weight loss in clinical trials. However, they increased the risk of serotonin-associated cardiac valvular disease, thought to occur through activation of serotonin receptor 2B. Due to its selective agonism of serotonin receptor 2C, lorcaserin theoretically should not have similar cardiac effects. However, there are few long-term data.

Efficacy — The efficacy of lorcaserin appears similar to that of orlistat (mean difference in weight loss between active and placebo treated groups approximately 3 to 4 kg) and perhaps slightly less than that of phentermine-topiramate and sibutramine (no longer available in most countries).

In one of the longer randomized trials, 3182 obese adults (BMI 36) were randomly assigned to lorcaserin (10 mg) or placebo twice daily for one year, followed by a one year extension period [42]. All subjects participated in a lifestyle modification program that included nutritional and exercise counseling. After one year, the proportion of patients with a reduction in baseline body weight of 5 percent or more was greater in patients in the lorcaserin group (47.5 versus 20.3 percent). Approximately 50 percent of participants remained in the trial during year two. The patients in the placebo group continued to receive placebo, whereas the patients in the lorcaserin group were randomly reassigned to receive lorcaserin or placebo. Among patients who received lorcaserin during year

one and successfully lost 5 percent or more of their baseline body weight, a greater proportion of patients who received lorcaserin than placebo during year two maintained the weight loss (67.9 versus 50.3 percent). Those participants who were reassigned to placebo gained back weight during year two. At the end of the trial, their mean body weight was similar to those who had received placebo for two years.

In addition to weight loss, lorcaserin had beneficial effects on surrogate markers of cardiovascular and diabetes risk, including slight but significant decreases in systolic and diastolic blood pressures, heart rate, total and low-density lipoprotein (LDL) cholesterol, c-reactive protein, fibrinogen, fasting glucose and insulin levels.

Similar findings were reported in other trials, as illustrated by the following:

- In a one-year randomized trial in 4008 patients, a significantly greater proportion of patients assigned to lorcaserin (10 mg twice daily or once daily) compared with placebo lost at least 5 percent of baseline body weight (47.2, 40, and 25 percent, respectively) [43]. The mean change in weight from baseline was -5.8, -4.7, and -2.9 kg, respectively.

- In another one-year trial, 604 patients with type 2 diabetes were randomly assigned to lorcaserin (10 mg once daily or twice daily) or placebo [44]. The majority of patients were treated with metformin, a sulfonylurea, or both. Patients treated with exenatide, pramlintide, or insulin were excluded from participation in this study. After one year, more patients lost ≥5 percent of their body weight with lorcaserin compared with placebo (44.7, 37.5, and 16.1 percent, respectively). There was also a significant reduction in glycated hemoglobin (-1.0, -0.9, and -0.4 percentage points, respectively) and fasting blood glucose (-28.4, -27.4, and -11.9 mg/dL [1.58, 1.52, and 0.66 mmol/L], respectively) in the lorcaserin compared with placebo group.

All of the trials described above were limited by a high dropout rate, which ranged from 35 to 50 percent. These levels of "dropouts" would invalidate most other clinical trials. In addition, slightly more than 50 percent of patients taking lorcaserin for one year did not lose 5 percent of their baseline body weight.

Adverse effects — Adverse effects of lorcaserin were generally mild and included headache, upper respiratory infections, nasopharyngitis, dizziness, and nausea, occurring in 18, 14.8, 13.4, 8, and 7.5 percent of patients, respectively [42]. Headaches, nausea, back pain, and nasopharyngitis, in particular, occurred with greater frequency than with placebo [44]. In patients with type 2 diabetes on oral agents, lorcaserin-induced weight loss may increase the risk of symptomatic hypoglycemia, necessitating a reduction in dose of diabetes medications [44]. In two of the trials, there was no significant increase in the incidence of serotonin-associated valvulopathy (as assessed by echocardiography at week 52) [42,43]. In the smaller trial of lorcaserin in patients with type 2 diabetes, the incidence of valvulopathy at week 52 was 2.9 and 0.5 percent in the lorcaserin and placebo groups, respectively [44]. The total number of events was small, reducing the precision of the analysis. Neuropsychiatric side effects were not significantly increased in any of the trials.

Dosing and contraindications — The recommended dose of lorcaserin is 10 mg twice daily, taken with or without food, and there is no need for a titration period. The response to therapy should be evaluated by week 12. Lorcaserin should be discontinued if patients do not lose 5 percent of body weight in 12 weeks [40]. No dose adjustment is required in patients with mild renal (creatinine clearance 50 to 80 mL/min) or mild to moderate hepatic (Child-Pugh score 5 to 6 and 7 to 9, respectively) impairment.

Lorcaserin should not be used in individuals with creatinine clearance <30 mL/min. It is contraindicated during pregnancy. In addition, lorcaserin should not be used with other serotonergic drugs (eg, selective serotonin reuptake inhibitors, selective serotonin-norepinephrine reuptake inhibitors, bupropion, tricyclic antidepressants, and monamine oxidase inhibitors) because of the theoretical potential for serotonin syndrome (see "Serotonin

syndrome (serotonin toxicity)"). Lorcaserin inhibits CYP 2D6-dependent metabolism, and can therefore increase exposure of drugs that are CYP 2D6 substrates (eg, dextromethorphan).

SYMPATHOMIMETIC DRUGS — The noradrenergic sympathomimetic drugs:

- Stimulate the release of norepinephrine or inhibit its reuptake into nerve terminals (phentermine, diethylpropion, benzphetamine, phendimetrazine)
- Block norepinephrine and serotonin reuptake (sibutramine - now withdrawn from the market)
- Directly act upon adrenergic receptors (phenylpropanolamine - now withdrawn from the market)
- May increase blood pressure

Sympathomimetic drugs reduce food intake by causing early satiety. The currently available sympathomimetic drugs (phentermine, diethylpropion, benzphetamine, and phendimetrazine) are only approved for the short-term (up to 12 weeks) treatment of obesity. Although phentermine is the most widely prescribed weight loss drug, we suggest **not** using sympathomimetic drugs because of their potential side effects, potential for abuse, and limited duration of use. They are contraindicated in patients with coronary heart disease, hypertension, hyperthyroidism, or in patients with a history of drug abuse.

Phentermine in combination with topiramate is reviewed separately below. (See 'Combination drugs' below.)

Pharmacology — All of the sympathomimetic drugs are rapidly absorbed after oral administration, and peak plasma concentrations are reached within one to two hours [45]. Their plasma half-lives are short, except for the active metabolites of sibutramine (which is the only drug in this group that has active metabolites). All the drugs in this class are metabolized to inactive products in the liver. The major route of elimination is via the kidneys.

Phentermine and diethylpropion are Schedule IV drugs, a regulatory classification suggesting potential for abuse, although the actual potential is low. Benzphetamine and phendimetrazine are Schedule III drugs. These drugs are approved only for short-term administration, which is widely interpreted as up to 12 weeks. They have been used in combination with other drugs. (See 'Combination drugs' below.)

Efficacy — Phentermine, as a single agent, is the most often prescribed drug for weight loss in the United States. Because phentermine was approved in 1959 for short term use for weight loss, there is only one 36-week trial from that period [46]. In this trial, both continuous and intermittent administration of phentermine led to more weight loss than placebo (net weight loss 7.4 kg) (figure 4) [46]. Shorter-term trials from Korea support the efficacy of phentermine. As examples:

- In one trial, 68 obese adults were randomly assigned to receive phentermine (37.5 mg) or placebo once daily [47]. After 12 weeks, weight reduction was greater in patients receiving phentermine (-7.2 versus -1.9 kg with placebo).

- In another trial evaluating a controlled release form of phentermine, 74 obese adults with diabetes, hypertension, or dyslipidemia were randomly assigned to phentermine diffuse-controlled release (30 mg) or placebo daily [48]. After 12 weeks, patients in the active treatment arm lost significantly more weight (-8.1 versus -1.7 kg with placebo).

In other trials of up to 25 weeks duration, net weight loss with diethylpropion compared with placebo ranged from 1 to 10 kg [49].

Safety — All sympathomimetic drugs can increase heart rate, blood pressure, and cause insomnia, dry mouth, constipation, and nervousness. In the clinical trials of sibutramine, systolic and diastolic blood pressure increased on average by 1 to 3 mmHg (including patients with hypertension controlled with a calcium-channel blocker with or without concomitant thiazide treatment) [50], and pulse increased by approximately four to five

beats per minute. In a trial of sibutramine or placebo in over 10,000 patients with or at high risk for cardiovascular disease, 92 percent of whom did not meet current labeling criteria, sibutramine was associated with a higher risk of nonfatal myocardial infarction (4.1 versus 3.2 percent, hazard ratio [HR] 1.28, 95% CI 1.04-1.57) and nonfatal stroke (2.6 versus 1.9 percent, HR 1.36, 95% 1.04-1.77) [51-54]. Based upon this information, the European Medicines Agency suspended the marketing of sibutramine across the European Union [53]. In 2010, the US Food and Drug Administration (FDA) and Health Canada also removed sibutramine from the market [55,56].

Phenylpropanolamine was also removed from the market because of a small but significant risk of hemorrhagic stroke in women [57].

Ephedrine is a sympathomimetic amine with a prolonged duration of action, increased peripheral actions, and decreased central actions on adrenergic receptors. Ephedra and ephedra alkaloids (Ma Huang) are a group of ephedrine-like molecules found in plants. Ephedrine stimulates weight loss at least in part by increasing thermogenesis and by reducing food intake. Because of safety concerns, ephedrine with or without caffeine and the ephedra alkaloids are not approved for treatment of obesity and have been removed from the market [58-60].

ANTIDEPRESSANTS — Drugs used to treat depression can increase body weight, be weight neutral, or reduce weight. When efficacy is equivalent, it is important for the clinician to select antidepressant drugs that are weight neutral or cause weight loss (table 4). (See "Unipolar major depression in adults: Choosing initial treatment".)

Bupropion — Bupropion is a drug approved for the treatment of depression and for the use in prevention of weight gain when trying to stop smoking [61]. It is a relative of diethylpropion, an approved drug for treating obesity (see 'Sympathomimetic drugs' above). It probably acts through modulating the action of norepinephrine [61]. In a six-month trial of bupropion SR (300 or 400 mg/day) versus placebo with a six-month blinded extension where all patients received active medication, both doses of bupropion produced significantly more weight loss than placebo (7.2, 10.1, and 5.0 percent loss of initial body weight for bupropion 300 mg, 400 mg, and placebo, respectively) [62]. During the six-month extension, the weight loss was largely maintained. (See "Atypical antidepressants: Pharmacology, administration, and side effects", section on 'Bupropion'.)

Bupropion used in combination with naltrexone is reviewed below. (See 'Combination drugs' below.)

ANTIEPILEPTIC DRUGS — Some antiepileptic drugs cause weight gain, others are weight neutral, and a few produce weight loss. When efficacy is equivalent, it is important for the clinician to select antiepileptic drugs that are weight neutral or cause weight loss (table 4).

Topiramate — Topiramate is approved for use as an antiepileptic and for the treatment of migraine. In clinical studies, its use was associated with weight loss, prompting evaluation of its efficacy and safety as an anti-obesity agent [63-65].

In a six-month dose-ranging trial, topiramate produced a net weight loss versus placebo of 3.7 kg (2.17 to 5.23 kg). In a meta-analysis of six trials, the average six-month weight loss was 6.51 percent (4.77 to 8.25 percent) with a placebo effect of about 2 percent [10]. Significant side effects of topiramate included paresthesias, somnolence, and difficulty concentrating. Topiramate has also been associated with metabolic acidosis. We do not recommend its use as a single agent for the management of obesity at this time. (See "Antiseizure drugs: Mechanism of action, pharmacology, and adverse effects", section on 'Topiramate'.)

Topiramate used in combination with phentermine is reviewed below. (See 'Combination drugs' below.)

Zonisamide — Zonisamide is an antiepileptic drug that has serotonergic and dopaminergic activity in addition to inhibiting sodium and calcium channels. Weight loss was noted in clinical trials for the treatment of epilepsy, prompting a trial for obesity. A one-year trial investigated its use in 225 obese individuals (mean body mass index [BMI] 37.6 kg/m^2) who followed a calorie-restricted diet and were randomly assigned to zonisamide (200 or 400 mg/day) or placebo [66]. The high dose zonisamide group lost significantly more weight than the placebo group (mean weight loss 7.3 versus 4.0 kg). Weight loss in the low dose zonisamide group (4.4 kg) was similar to placebo. Side effects (gastrointestinal, central nervous system, and psychiatric adverse events) occurred more commonly with zonisamide than with placebo. We do not recommend its use for the management of obesity at this time. (See "Antiseizure drugs: Mechanism of action, pharmacology, and adverse effects".)

DIABETES DRUGS

Metformin — Metformin is a biguanide that is approved for the treatment of diabetes mellitus, a disease that is exacerbated by obesity and weight gain. In one trial of patients with obesity and the metabolic syndrome, patients receiving metformin lost significantly more weight (1 to 2 kg) than the placebo group [67].

After a mean follow-up of 2.8 years in the Diabetes Prevention Program for patients with impaired glucose tolerance, average weight loss was 0.1, 2.1, and 5.6 kg in the placebo, metformin, and lifestyle-intervention groups, respectively [68]. In a follow-up study, the modest weight loss with metformin was maintained during the 10-year observation period [4]. The weight loss was directly related to the level of adherence. Individuals with high adherence lost about 3.1 kg, whereas those who stopped taking it were comparable in weight to the placebo group [12]. Although metformin does not produce enough weight loss (5 percent) to qualify as a "weight-loss drug," it would appear to be a very useful choice for overweight individuals at high risk for diabetes. As opposed to most weight loss studies with duration <1 year, the Diabetes Prevention Program had essentially no loss to follow-up in almost three years, making its results much more credible and less vulnerable to bias. Metformin is discussed in detail elsewhere. (See "Prevention of type 2 diabetes mellitus", section on 'Metformin' and "Initial management of blood glucose in adults with type 2 diabetes mellitus" and "Metformin in the treatment of adults with type 2 diabetes mellitus".)

Pramlintide — Amylin (also known as islet amyloid polypeptide) is a peptide hormone secreted by pancreatic beta cells in conjunction with insulin in response to nutrient stimuli (see "Pathogenesis of type 2 diabetes mellitus"). Pramlintide is a synthetic analog of human amylin that slows gastric emptying, reduces postprandial rises in blood glucose concentrations, and improves glycated hemoglobin (A1C) concentrations in patients with type 1 and type 2 diabetes. It must be given by subcutaneous injection. Pramlintide for the treatment of diabetes is discussed in detail elsewhere. (See "Amylin analogs for the treatment of diabetes mellitus", section on 'Pramlintide'.)

Unlike insulin and many other diabetes medications, pramlintide is associated with modest weight loss. In a meta-analysis of eight randomized trials, pramlintide reduced weight compared with placebo (mean difference -2.57 and -2.27 kg, in patients with and without diabetes, respectively) [69]. In one of the larger trials, 651 patients with type 1 diabetes were randomly assigned to placebo or subcutaneous pramlintide, in addition to their usual insulin therapy [70]. Weight decreased 0.4 kg in the pramlintide group and increased by 0.8 kg in the placebo group [70]. In other trials of pramlintide in obese patients with or without diabetes, small but significant reductions in body weight have been reported [71-74].

Exenatide — The incretin peptides (glucagon-like polypeptide-1 [GLP-1] and glucose-insulin polypeptide, also called gastric inhibitory polypeptide [GIP]) are gastrointestinal peptides that stimulate glucose-dependent insulin secretion. GLP-1 also inhibits glucagon release and gastric emptying. Exenatide, a long-acting synthetic peptide that is a GLP-1 receptor agonist, is available for adjunctive therapy for patients with type 2 diabetes who are inadequately controlled on oral agents. The drug is administered subcutaneously twice daily. Dose-dependent weight loss has been reported in trials of exenatide in patients with type 2 diabetes not well controlled on oral

agents. These exenatide trials are discussed in detail elsewhere. (See "Glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes mellitus", section on 'Exenatide twice daily'.)

Liraglutide — Liraglutide, another long-acting GLP-1 analog, is an option for overweight or obese patients with type 2 diabetes. It is available for use in the United States and Europe for the treatment of type 2 diabetes at a dose of 1.8 mg once daily and at a higher dose (3 mg daily) for the treatment of adults with body mass index (BMI) ≥30 kg/m^2 or ≥27 kg/m^2 with at least one weight-related morbidity (eg, hypertension, type 2 diabetes, dyslipidemia) [75].

In diabetes trials, liraglutide (1.8 or 3 mg daily) was associated with a significant reduction in weight (2 to 4 kg) when compared with placebo or glimepiride. (See "Glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes mellitus", section on 'Weight loss'.)

Weight loss has also been reported in patients without diabetes who received liraglutide. As examples:

- In a 20-week randomized trial comparing liraglutide (administered subcutaneously in one of four daily doses, 1.2 to 3 mg), placebo, and open-label orlistat (120 mg orally three times daily) in 564 patients (mean BMI 35), weight loss increased with increasing doses of liraglutide, with mean weight loss ranging from 4.8 to 7.2 kg [76]. Patients randomly assigned to any dose of liraglutide lost significantly more weight than those assigned to placebo, in whom the mean weight loss was 2.8 kg. Patients taking the two highest doses of liraglutide (2.4 and 3.0 mg) lost significantly more weight than those assigned to orlistat (6.3, 7.2, and 4.1 kg, respectively).

- In a 56-week trial comparing liraglutide 3 mg once daily with placebo injection in 3731 patients who had a BMI of ≥30 kg/m^2 or ≥27 kg/m^2 with dyslipidemia and/or hypertension, mean weight loss was significantly greater in the liraglutide group (-8.0 versus -2.6 kg with placebo) [77]. In addition, cardiometabolic risk factors, A1C, and quality of life all improved modestly, but significantly. Gastrointestinal side effects, including nausea, vomiting, and diarrhea, occurred at least transiently in at least 40 percent of the liraglutide-treated group and were the most common reason for withdrawal (6.4 percent). Pancreatitis, although rare, was associated with liraglutide treatment (10 cases in the liraglutide group versus 1 case in the control).

- In a 56-week trial comparing liraglutide 3 mg once daily with placebo injection in 422 patients with BMI ≥30 kg/m^2 or ≥27 kg/m^2 with dyslipidemia and/or hypertension (but not type 2 diabetes) who lost ≥5 percent of their initial body weight with diet and exercise during a 4 to 12-week pretrial run-in, a greater proportion of patients maintained weight loss in the liraglutide group (81.4 compared with 48.9 percent in the in the placebo group) [78].

The two highest doses of liraglutide are higher than those previously assessed for the treatment of diabetes, and a greater proportion of patients taking these doses reported nausea (37 to 47 percent) and vomiting (12 to 16 percent) [76-78]. Thus, weight loss may be due, in part, to gastrointestinal side effects. Other side effects include diarrhea, low blood sugar, and anorexia. Serious but less common side effects include pancreatitis, gallbladder disease, renal impairment, and suicidal thoughts. In rodent studies, liraglutide was associated with benign and malignant thyroid C-cell tumors. It is unclear whether any effect is present in humans because humans have far fewer C-cells than rats, and expression of the GLP-1 receptor in human C-cells is very low. Nevertheless, liraglutide is not recommended for use in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B [75]. (See "Glucagon-like peptide-1 receptor agonists for the treatment of type 2 diabetes mellitus", section on 'Precautions and adverse effects'.)

Liraglutide is administered subcutaneously in the abdomen, thigh, or upper arm once daily. The initial dose is 0.6 mg daily for one week. The dose can be increased at weekly intervals (1.2, 1.8, 2.4 mg) to the

recommended dose of 3 mg. If after 16 weeks a patient has not lost at least 4 percent of baseline body weight, liraglutide should be discontinued, as it is unlikely the patient will achieve clinically meaningful weight loss with continued treatment [75]. Data demonstrating long-term (>1 year) benefits with regard to sustained weight loss are scant.

HORMONES — Although injections of human chorionic gonadotropin (hCG) have been advertised to aid in weight loss, clinical trials fail to support this claim. Oral or sublingual diet drops of hCG are also available and are touted to have the same benefits as injectable hCG. Among the values claimed for this treatment are loss of one to two pounds daily, absence of hunger, and maintenance of muscle tone. Several randomized trials have shown that the hCG diet is **not** more effective than placebo in the treatment of obesity [79,80]. An integral component of the hCG diet is adherence to a very low calorie diet (500 kcal/day). Adherence to a very low calorie diet (200 to 800 kcal/day) results in short-term weight loss. The addition of hCG has not been shown to provide any additional effect. Thus, hCG should **not** be used for the treatment of obesity. In addition, very low calorie diets have not been shown to be superior to conventional diets for long-term weight loss. (See "Obesity in adults: Dietary therapy", section on 'Very-low-calorie diets'.)

COMBINATION DRUGS — Because the regulation of food intake is controlled by several pathways, it has been hypothesized that combining two drugs with different mechanisms of action could improve efficacy (and tolerability if used in lower doses) compared with single drug therapy.

Phentermine-topiramate — In 2012, the US Food and Drug Administration (FDA) approved a preparation of phentermine and extended-release topiramate (in one capsule) for adults with a body mass index ≥30 kg/m^2 or with a body mass index (BMI) ≥27 kg/m^2 with at least one weight-related comorbidity (eg, hypertension, diabetes, dyslipidemia) [81]. We do not recommend phentermine-topiramate for patients with cardiovascular disease (hypertension or coronary heart disease) or in pregnant women. Phentermine-topiramate may be considered for obese postmenopausal women and men without cardiovascular disease, particularly those who do not tolerate orlistat or lorcaserin.

This combination has been shown to enhance weight loss in the first year of use, as illustrated by the following trials:

- A combination of controlled-release phentermine-topiramate (7.5/46 mg or 15/92 mg) was compared with placebo in 2487 adults with BMI of 27 to 45 kg/m^2 and two or more comorbidities [82]. After one year, mean weight loss was greater in those assigned to active treatment (8 to 10 versus 1.4 kg with placebo [8 to 10 percent versus 1.2 percent of baseline bodyweight]). Only 61 percent of participants completed one year of treatment, again calling the results into question.

  In a 52-week extension of the above trial (78 percent of eligible subjects participating), mean total weight loss (from baseline to 108 weeks) was significantly better than placebo (9.6, 10.9, and 2.1 kg [9.3, 10.5, and 1.8 percent of baseline bodyweight] for low dose, high dose, and placebo, respectively) [83]. Of note, phentermine-topiramate was less effective in increasing weight loss in the second year of use, although most individuals were able to maintain the weight they lost in year one. In those subjects who were able to participate in the second year of the trial, the therapy was well tolerated.

- In another trial, men and women with BMI ≥35 kg/m^2 were randomly assigned to controlled release phentermine-topiramate (3.75/23 mg or 15/92 mg) or placebo [84]. After 56 weeks, mean weight loss was greater in the active treatment groups (mean reduction 6, 12.6, and 1.9 kg [5.1, 10.9, and 1.6 percent of baseline bodyweight]). Among those assigned to active treatment, 45 to 67 percent lost at least 5 percent of baseline weight compared with 17 percent of placebo patients.

The most common adverse events in these trials were dry mouth (13 to 21 versus 2 percent), constipation (15 to 17 versus 6 percent), and paraesthesia (14 to 21 versus 2 percent) [82,84]. There was a dose-related increase in the incidence of psychiatric (eg, depression, anxiety) and cognitive (eg, disturbance in attention) adverse events in the active treatment group. Although blood pressure improved slightly with active therapy, there was an increase in heart rate (0.6 to 1.6 beats/min) compared with placebo.

Combination phentermine-topiramate is contraindicated during pregnancy because of an increased risk of orofacial clefts in infants exposed to the combination drug during the first trimester of pregnancy. Women of child-bearing age should have a pregnancy test before starting this drug and monthly thereafter. It is also contraindicated in patients with hyperthyroidism, glaucoma, and in patients who have taken monoamine oxidase inhibitors within 14 days. Because topiramate can produce renal stones, this combination preparation should be used cautiously in patients with a history of renal stones.

Clinicians who prescribe phentermine-topiramate are encouraged to enroll in a Risk Evaluation and Mitigation Strategy (REMS), which includes an online or print formal training module detailing safety information [85]. Pharmacies that dispense the drug require certification, which involves identifying a representative to oversee the REMS program, and providing patients with a medication guide and brochure each time the drug is dispensed, detailing the risks of birth defects. The initial dose of phentermine-topiramate is 3.75/23 mg for 14 days, followed by 7.5/46 mg thereafter. If after 12 weeks a 3 percent loss in baseline bodyweight is not achieved, the dose can be increased to 11.25/69 mg for 14 days, and then to 15/92 mg daily [86]. If an individual does not lose 5 percent of body weight after 12 weeks on the highest dose, phentermine-topiramate should be discontinued gradually, as abrupt withdrawal of topiramate can cause seizures [86].

Use of phentermine and topiramate individually is reviewed elsewhere. (See 'Sympathomimetic drugs' above and 'Topiramate' above.)

Bupropion-naltrexone — We do not suggest combination bupropion-naltrexone as first-line pharmacologic therapy. It could be prescribed for the obese smoker who desires pharmacologic therapy for smoking cessation and obesity. However, it is unclear from the available literature whether naltrexone adds anything to the bupropion effect (see 'Bupropion' above). Owing to the uncertainty about cardiovascular effects, we prefer to use orlistat or lorcaserin. Combination bupropion-naltrexone appears to have similar efficacy as, but more adverse effects than, lorcaserin (table 1).

The combination of bupropion-naltrexone was approved by the FDA in September 2014 as an adjunct to diet and exercise in patients with BMI ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of at least one weight-related comorbidity [87]. Bupropion is a drug available for the treatment of depression and for use in prevention of weight gain during smoking cessation. Naltrexone is an opioid-receptor antagonist used to treat alcohol and opioid dependence. (See "Atypical antidepressants: Pharmacology, administration, and side effects", section on 'Bupropion' and "Pharmacotherapy for smoking cessation in adults", section on 'Bupropion' and "Pharmacotherapy for alcohol use disorder", section on 'Oral naltrexone' and "Pharmacotherapy for opioid use disorder", section on 'Naltrexone'.)

Efficacy — Compared with placebo, the combination of bupropion-naltrexone has been shown to reduce weight by approximately 4 to 5 percent [88-92]. As an example, in a randomized trial of bupropion and naltrexone (varying doses) versus double placebo, weight loss was greater in those assigned to active treatment (mean change in body weight -5 to 6 percent versus -1.3 percent) [88]. Only 50 percent of participants completed 56 weeks of treatment.

Although mean weight loss was greater with combination therapy than with placebo, mean reductions in blood pressure and heart rate were significantly greater in the placebo group (-2.1/2.8 versus 0.2/-0.4 mmHg and -0.1 versus 1.5 beats per minute).

Adverse effects — In clinical trials, nausea (30 versus 5 percent), headache (14 versus 9 percent), and constipation (15 versus 6 percent) occurred more frequently in the naltrexone-bupropion compared with placebo group [88,89]. Other adverse effects included insomnia, vomiting, dizziness, and dry mouth, occurring in 7 to 10 percent [88,89].

Because bupropion-naltrexone can raise blood pressure and heart rate, the FDA is requiring post-marketing studies to evaluate cardiovascular outcomes and the effect of the combination on cardiac conduction. (See 'Cardiovascular effects' below.)

Because it contains bupropion, the FDA recommends warning young adults (18 to 24 years) of the risk of becoming suicidal during initial treatment of psychiatric disorders with any antidepressant. The warning also notes that there have been serious neuropsychiatric events reported in patients taking bupropion for smoking cessation.

Cardiovascular effects — The cardiovascular safety of bupropion-naltrexone has not been established [93]. A randomized trial designed to assess cardiovascular outcomes of bupropion-naltrexone compared with placebo in 8910 overweight or obese patients at increased cardiovascular risk was terminated early, due to public release of confidential interim data by the sponsor [94]. In interim analyses performed after 25 and 50 percent of planned events, the primary outcome (time to first major adverse cardiovascular event) had occurred in 0.8 versus 1.3 percent of patients in the placebo group (hazard ratio [HR] 0.59, 95% CI 0.39-0.90) and in 2.0 versus 2.3 percent (HR 0.88, 95% CI 0.57-1.34), respectively. The final analysis was performed with 64 percent of originally planned end points. The primary outcome occurred in 2.7 versus 2.8 percent (HR 0.95, 95% CI 0.65-1.38). As more data were accumulated after the first interim analysis, the active treatment group experienced more adverse cardiovascular events, as evidenced by increasing point estimates. Because the trial was terminated early, it is unclear how to interpret this data, and the cardiovascular safety remains unknown.

Dosing and contraindications — The initial dose is one tablet (8 mg of naltrexone and 90 mg of bupropion) daily. After one week, the dose is increased to one tablet twice daily, and by week four, to two tablets twice daily. If after 12 weeks the patient has not lost at least 5 percent of baseline body weight, the drug should be discontinued because benefit is unlikely.

Contraindications include uncontrolled hypertension, seizure disorder, eating disorder, use of other bupropion-containing products, chronic opioid use, and use within 14 days of taking monamine oxidase inhibitors (table 1).

DIETARY SUPPLEMENTS — Over-the-counter dietary supplements are widely used by individuals attempting to lose weight, but evidence to support their efficacy and safety are limited. Examples of dietary supplements include ephedra (described above, no longer available), green tea, chromium, chitosan, and guar gum.

Guar gum preparations derived from the Indian cluster bean have been promoted as weight reduction agents. The presumed mechanism of action is an increase in the viscosity of gastric contents, leading to a feeling of postprandial fullness. However, in a meta-analysis of 20 clinical trials, guar gum was not effective for weight loss and caused adverse events such as abdominal pain, flatulence, and diarrhea [95].

Conclusions from a 2004 review of available dietary supplements were as follows [96]:

- Chitosan [97] and guar gum were ineffective for weight loss, and their use should be discouraged.
- Evidence and safety data were unclear for chromium, ginseng, glucomannan, green tea, hydroxycitric acid [98], L-carnitine, psyllium, pyruvate supplements, St. John's wort, and conjugated linoleic acid.

In a 2012 meta-analysis of trials comparing green tea preparations with a control in overweight adults or adults with obesity, green tea did not significantly affect weight loss or maintenance of weight loss [99].

In a 2013 meta-analysis of nine trials comparing chromium picolinate with placebo in overweight adults or adults with obesity, the mean difference in weight after 12 to 16 weeks was -1.1 kg, favoring chromium picolinate [100]. There was no evidence of a dose effect. The meta-analysis was limited by the poor quality of the included trials and the absence of safety data. Given the limited evidence, we do not suggest chromium as a dietary supplement for the treatment of obesity.

Hoodia gordonii, a dietary supplement derived from a desert plant in South Africa, is marketed and sold as an appetite suppressant. However, its efficacy and safety have not been established in clinical trials [101].

Safety issues are a concern with dietary supplements. In addition to the problems with ephedra outlined above, a study of two weight loss preparations containing bitter orange (*Citrus aurantium*), a botanical source of synephrine, showed a non-dose related increase in heart rate and blood pressure; the cardiovascular effects were postulated to relate to caffeine and other stimulants in the multicomponent formulations [102].

Clinicians should caution patients about use of weight loss formulations and should monitor those who choose to use these supplements.

Compounded diet pills — Two compounded dietary supplements imported from Brazil, Emagrece Sim (also known as the Brazilian diet pill) and Herbathin dietary supplement, have been shown to contain prescription drugs, including amphetamines, benzodiazepines, and fluoxetine. In one report, 18 percent of Brazilian immigrant women were using these drugs while living in the United States; two-thirds reported adverse effects [103]. The US Food and Drug Administration (FDA) has issued a warning against their use [104].

Calcium — While epidemiologic data suggested that calcium supplementation might be associated with weight loss [105], a randomized, clinical trial of 100 pre- and postmenopausal women with obesity undergoing a weight reduction program (with or without calcium supplementation 1000 mg/day), reported no significant effect of calcium on body fat or weight loss [106]. Subsequent larger trials confirmed a lack of effect of calcium supplementation on weight [107,108].

EXPERIMENTAL DRUGS

Peptides — There are several peptides that result in weight loss, either by a reduction in food intake or by increasing energy expenditure. None are currently approved by the US Food and Drug Administration (FDA).

Leptin — Leptin is a peptide produced primarily in adipose tissue. Absence of leptin is associated with massive obesity in mice (ob/ob) and in humans [109]. In mice and rare humans with leptin deficiency, administration of physiological doses of leptin decreases food intake and causes weight loss [110]. In contrast, db/db mice and fatty rats, which have genetic defects in the leptin receptor and are also obese, do not respond to leptin. (See "Physiology of leptin" and "Pathogenesis of obesity".)

Adults with obesity have leptin resistance, based upon the fact that they have high serum leptin concentrations. In a study of 47 women and men with obesity given placebo or varying doses of recombinant human leptin for 24 weeks (and advised to eat 500 kcal less than requirement each day), there was a weakly dose-dependent decrease in body weight, ranging from -1.3 kg in the placebo group to -1.4 kg in the 0.03 mg/kg group to -7.1 kg in the 0.30 mg/kg group [111]. These results suggest that leptin resistance can be overcome with high doses of leptin, but whether the effect can be sustained is not known. One small study suggests that leptin therapy may prevent regaining weight after significant weight loss by preventing the weight loss-associated decrease in energy expenditure [112].

Leptin therapy is effective in some patients with lipodystrophy. (See "Lipodystrophic syndromes".)

Peptide YY — The gut hormone peptide YY (PYY) suppresses appetite and decreases food intake. This was illustrated in a trial of obese and lean adults receiving short-term intravenous PYY administration. Appetite and caloric intake decreased by approximately 30 percent in both groups, suggesting that PYY might be a useful therapy for weight loss [113].

However, in a 12-week trial of 133 patients with obesity who were randomly assigned to intranasal PYY (200 or 600 mcg three times daily before meals) or placebo, in conjunction with diet and exercise, weight loss was similar in the placebo and 200 mcg PYY groups (2.8 and 3.7 kg, respectively) [114]. Weight loss could not be assessed in the 600 mcg PYY group because 60 percent of patients dropped out due to nausea and vomiting. (See "Pancreatic polypeptide, peptide YY, and neuropeptide Y".)

Oxyntomodulin — Oxyntomodulin is a peptide produced in L-cells of the gastrointestinal (GI) track from the proglucagon gene product. When self-administered three times a day, 30 minutes before meals in obese volunteers, the group (n = 14) treated with oxyntomodulin lost 2.3±0.4 kg compared with 0.5±0.5 kg in those treated with placebo. Food intake was reduced by 250 kcal (35±9 percent) in the last meal [115].

Melanocortin-4 receptor agonists — The hypothalamic melanocortin system appears to play an important role in the control of body weight. As an example, intranasal administration of the melanocortin sequence MSH/ACTH4-10 to normal-weight subjects for six weeks decreased body fat by 1.7 kg [116]. However, in a study of 23 overweight men, the same compound administered for 12 weeks did not induce any significant decrease in body weight or body fat when compared with placebo [117].

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Weight loss treatments (The Basics)")
- Beyond the Basics topics (see "Patient education: Weight loss treatments (Beyond the Basics)" and "Patient education: Weight loss surgery and procedures (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

Diet and lifestyle

- All patients who are overweight (body mass index [BMI] ≥25 kg/m^2) or obese (BMI ≥30 kg/m^2) should receive counseling on diet, lifestyle, and goals for weight loss. (See "Obesity in adults: Overview of management".)

Pharmacotherapy

- For individuals with a BMI >30 kg/m^2 or a BMI of 27 to 29.9 kg/m^2 with comorbidities, who have failed to achieve weight loss goals through diet and exercise alone, we suggest pharmacologic therapy be added to diet and exercise (**Grade 2B**). (See 'Our approach' above.)

- For patients with obesity, we suggest orlistat as first-line pharmacologic therapy, given its excellent cardiovascular safety profile and beneficial effects on serum total and low-density lipoprotein (LDL) cholesterol concentrations (table 1) (**Grade 2B**). (See 'Our approach' above and 'Orlistat' above.)

  Treatment guidelines suggest up to two years of treatment. In the United States, the US Food and Drug Administration (FDA) has approved orlistat for four years of use. However, if the patient has done well with weight loss/weight maintenance without adverse effects and wants to continue the drugs, we think it is reasonable to continue with an "informed consent" arrangement if both patient and clinician agree.

  Lorcaserin is an alternative option for those who cannot tolerate orlistat. However, there are few long-term safety data beyond two years. Lorcaserin should be discontinued if a patient does not lose 5 percent of body weight in 12 weeks. (See 'Lorcaserin' above.)

  Combination phentermine-topiramate is also an option for men or postmenopausal women with obesity but without hypertension or coronary heart disease. For women of child-bearing potential, a pregnancy test is required before initiating therapy and monthly thereafter since this combination can produce fetal anomalies. If a patient does not lose 5 percent of body weight after 12 weeks on the highest dose, phentermine-topiramate should be discontinued gradually. (See 'Phentermine-topiramate' above.)

  Combination bupropion-naltrexone is also an option for patients with obesity who cannot tolerate orlistat or lorcaserin. It produces similar weight loss as orlistat and lorcaserin, but it has more side effects and contraindications (table 1). If a patient does not lose 5 percent of body weight after 12 weeks on the highest dose, bupropion-naltrexone should be discontinued. (See 'Bupropion-naltrexone' above.)

- For patients with type 2 diabetes, in addition to lifestyle modifications, we suggest initial therapy with metformin both for glycemic control and for modest weight reduction (**Grade 2B**). We suggest orlistat if further weight reduction is needed (**Grade 2B**). (See 'Our approach' above and "Initial management of blood glucose in adults with type 2 diabetes mellitus", section on 'Initial pharmacologic therapy'.)

  Liraglutide is an alternative option for overweight or obese patients with type 2 diabetes. However, unpleasant gastrointestinal side effects (nausea, vomiting) and the need for a daily injection may limit the use of this drug in some patients. (See 'Liraglutide' above.)

- For patients with obesity who are candidates for long-term pharmacotherapy for weight loss, we suggest **not** using sympathomimetic drugs (phentermine, diethylpropion, benzphetamine, and phendimetrazine) because of their potential for abuse (**Grade 2B**). (See 'Sympathomimetic drugs' above.)

Bariatric surgery

- For patients with BMI ≥40 kg/m^2 who have failed diet, exercise, and drug therapy, we suggest bariatric surgery (**Grade 2B**). Individuals with BMI >35 kg/m^2 with obesity-related comorbidities (hypertension, impaired glucose tolerance, diabetes mellitus, dyslipidemia, sleep apnea) who have failed diet, exercise, and drug therapy are also potential surgical candidates, assuming that the anticipated benefits outweigh the costs, risks, and side effects of the procedure. (See "Bariatric operations for management of obesity: Indications and preoperative preparation".)

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Topic 5376 Version 38.0

Drugs available as adjuncts to diet and exercise for treatment of obesity

Generic name	Usual dosing (adults)	US DEA schedule	Adverse effects and precautions*
Pancreatic lipase inhibitor approved for long-term use			
Orlistat	120 mg three times daily with fat-containing meals. A reduced dose of 60 mg¶ is an option for patients who do not tolerate 120 mg.	Not a controlled substance	Cramps, flatulence, fecal incontinence, oily spotting, absorption of fat-soluble vitamins may be reduced. Rarely reported: severe liver injury, oxalate-kidney injury. Contraindicated during pregnancy.
Serotinin-2C receptor agonist approved for long-term use			
Lorcaserin	10 mg twice daily; re-evaluate after 12 weeks.	C-IV	Headache, dizziness, nausea, dry mouth, constipation (non-diabetic patients). Hypoglycemia, headache, back pain, cough (diabetic patients). Avoid in patients with severe hepatic or renal insufficiency (CrCl <30 mL/min). Preferably avoid use with other serotoninergic agents (including most antidepressants, triptan anti-migraine medications, 5HT3-antagonist antiemetics, tramadol, dextromethorphan, and some muscle relaxants) due to risk of serotonin toxicity. Neuropsychiatric side effects and valvulopathy were not significantly increased in clinical trials, but few long-term safety data are available. Contraindicated with ergot derivatives (eg, ergotamine) and during pregnancy. May cause psychic dependence and/or euphoria at higher than recommended doses. Possible increase in cancer risk based on murine model data.
Combination of phentermine-topiramate approved for long-term use			
Phentermine-topiramate	Initial: 3.75 mg phentermine/23 mg topiramate once daily in the morning for 14 days. Then titrate based upon response: 7.5 mg phentermine/46 mg	C-IV (due to phentermine component)	Dry mouth, taste disturbance, constipation, paraesthesias, depression, anxiety, elevated heart rate, cognitive disturbances, insomnia (higher dose).

	topiramate daily for 12 weeks, then 11.25 mg phentermine/69 mg topiramate daily for 14 days. Maximum dose: 15 mg phentermine/92 mg topiramate daily; re-evaluate after 12 weeks.		Abuse potential due to phentermine component. Topiramate is teratogenic (increased risk of oral cleft defects, T1); negative pregnancy test prior to and during treatment and two forms of contraception necessary for women of child-bearing potential. Actions of topiramate component include inhibition of carbonic anhydrase; rarely metabolic acidosis and kidney stones may result from renal bicarbonate loss. Maximum dose with moderate hepatic or renal impairment (CrCl <50 mL/min) 7.5 mg phentermine/46 mg topiramate once daily. Upon discontinuation, tapering of dose over at least one week using every other day dosing is recommended. Contraindicated during pregnancy, hyperthyroidism, glaucoma, patients taking MAO inhibitors.
Combination of bupropion-naltrexone approved for long-term use			
Bupropion-naltrexone	Week 1: One tablet (8 mg naltrexone/90 mg bupropion) once daily. Week 2: One tablet twice daily. Week 3: Two tablets in morning and one tablet in evening. Week 4: Two tablets twice daily. Maximum daily dose: Four tablets (32 mg naltrexone/360 mg bupropion); re-evaluate after 12 weeks.	Not a controlled substance	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth. Transient increase in blood pressure (1 to 2 mmHg on average) during initial 12 weeks of treatment; heart rate may also be increased. Contraindicated in patients with uncontrolled hypertension, seizure disorder, eating disorder, use of other bupropion-containing products, chronic opioid use, use within 14 days of MAO inhibitors, pregnancy, or breastfeeding.[Δ]
GLP-1 agonist approved for long-term use			
Liraglutide	Initial: 0.6 mg subcutaneously daily. Increase at weekly intervals (1.2, 1.8, 2.4 mg) until recommended dose of 3 mg daily; re-evaluate after 16 weeks.[◇]	Not a controlled substance	Nausea, vomiting, diarrhea, constipation, hypoglycemia in patients with T2DM (more common if used in conjunction with diabetes medications known to cause hypoglycemia), injection site reactions, increased lipase, increased heart rate. Rarely

			reported: pancreatitis, gallbladder disease, renal impairment, suicidal thoughts. Advise patients to avoid dehydration in relation to GI side effects. Monitor blood glucose in diabetic patients and adjust co-administered sulfonylureas (eg, reduce dose by 50 percent) and other anti-diabetic medications as needed to prevent potentially severe hypoglycemia. Causes a modest delay of gastric emptying. Use is not recommended in severe renal impairment (CrCl <30 mL/min), severe hepatic impairment, or children/adolescents ≤18 years and adults ≥75 years; safety and efficacy data are lacking. Possible increase in thyroid cancer risk based on murine model data. Contraindicated in pregnancy and in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B.
Noradrenergic sympathomimetic drugs approved for short-term use			
Benzphetamine	Initial: 25 mg once daily; may titrate up to 25 to 50 mg one to three times daily. Maximum dose: 50 mg three times daily.	C-III	Applies to all sympathomimetic agents: Due to their side effects and potential for abuse, we suggest **not** prescribing sympathomimetics for weight loss.
Diethylpropion	Immediate release: 25 mg three times daily before meals. Controlled release: 75 mg every morning.	C-IV	If prescribed, limit to short-term (≤12 weeks) use. Adverse effects include increase in heart rate, blood pressure, insomnia, dry mouth, constipation, nervousness.
Phentermine	Immediate release: 15 to 37.5 mg daily or divided twice-daily. Orally disintegrating tablet (ODT): 15 to 37.5 mg once daily in the morning.	C-IV	Abuse potential due to amphetamine-like effects. May counteract effect of blood pressure medications. Avoid in patients with heart disease, poorly controlled hypertension, pulmonary hypertension, or history of addiction or drug abuse.
Phendimetrazine	Immediate release: 17.5 to 35 mg two or three times daily, one hour before meals.	C-III	

	Maximum dose: 70 mg three times daily. Sustained release: 105 mg daily in the morning.		Contraindicated in patients with a history of CVD, hyperthyroidism, glaucoma, MAO inhibitor-therapy, agitated states, pregnancy, or breast feeding.

CrCl: creatinine clearance; CVD: cardiovascular disease (arrhythmias, congestive heart failure, coronary artery disease, stroke, uncontrolled hypertension); GI: gastrointestinal; GLP-1: glucagon-like peptide 1; MAO inhibitors: monamine oxidase inhibitors; T1: first trimester pregnancy; T2DM: type 2 diabetes mellitus; US DEA: United States Drug Enforcement Agency; FDA: US Food and Drug Administration.

* Applies to all drugs except orlistat: May increase risk of hypoglycemia in type 2 diabetics. For additional information on potential interactions of anti-obesity drugs with other medications, use Lexi-Interact program included with UpToDate.

¶ Orlistat 60 mg is available without a prescription in the United States and some other countries.

Δ FDA recommends warning young adults (age 18 to 24 years) of the risk of becoming suicidal during initial treatment of psychiatric disorders with any antidepressant.

◇ According to United States labeling, if weight loss is not ≥4 percent after 16 weeks or 3 mg/week is not tolerated, discontinue use. Labeling in the European Union recommends discontinuation of use if weight loss is not ≥5 percent after 12 weeks of 3 mg/week.

Courtesy of authors.

With additional data from:

1. dailymed.nlm.nih.gov/dailymed/index.cfm *(Accessed October 8, 2014).*
2. *Kim GW, Lin JE, Blomain ES, Waldman SA. Antiobesity pharmacotherapy: new drugs and emerging targets. Clin Pharmacol Ther 2014; 95:1.*

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The Long-Term Management of Obesity with Continuing Pharmacotherapy

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Abstract

Objective: Long-term, possibly lifetime, use of medications for the management of obesity may be thought to be similar to the use of pharmacotherapy for other chronic diseases such as hypertension or diabetes. Because there have been no systematic studies of this extended use, the experience of eight patients who have used obesity medications in a sustaining manner was studied.

Research Methods and Procedures: The clinical characteristics of eight adult patients, each of whom has experience with long-term (more than 10 years) use of medications for weight loss and weight maintenance, were studied.

Results: The clinical experience of these eight patients was analyzed. Each chose to sustain the use of weight management medications for more than 10 years because of perceived benefit, comfort, and the absence of significant side effects. There has been no evidence of the development of tolerance, addiction, or misuse and no adverse events related to the medication. The beneficial effects of the medication have not diminished with time.

Discussion: The clinical characteristics of eight patients, each of whom has used obesity pharmacotherapy for more than 10 years, are described. The experience of these eight individuals cannot be generalized to the entire population of overweight or obese patients. It does suggest, however, that some patients respond successfully to this form of therapy and that they will derive value from it for the management of this disease. Efforts should be made to identify these patients, and consideration should be given to the use of chronic medications for the continuing management of obesity.

Introduction

The search for useful pharmacotherapeutic agents for the management of obesity has been complicated by a series of therapeutic disasters. Dinitrophenol, thyroid, digitalis, amphetamines, and fenfluramine have successively cast a pall on the use of medications for weight management. Nevertheless, the recognition that eating and body weight are highly regulated biological phenomena, that obesity is a disease in which the regulation is dysfunctional, and that behavioral methods alone have limited effectiveness in enabling patients to achieve and sustain weight loss lead inescapably to the question of whether there should be some role for continuing use of medications in managing this disease.

It is very difficult to assess the usefulness of long-term pharmacotherapy. Individual anecdotal case reports are not useful for studying the problem; therapeutic recommendations cannot be based on the experience of one individual. No studies have documented the long-term safety of antiobesity medications for more than 2 years. The issue of whether any medication can or should be used as continuing, perhaps life-long, therapy cannot be resolved with standard clinical trials.

Because it may not be possible to do formal studies of very long-term use, there should be some value in examining the experience of individual patients who have utilized these medications in this form, particularly if a large number of patients with a similar clinical intervention can be assembled for a single assessment of their characteristics. The editors of the *British Medical Journal* have noted that "... case reports expose clinical issues that would otherwise escape attention" (1). A series of case reports can direct consideration to a pattern of similar events that have significant clinical importance. This analysis does not have the power of a clinical trial; it is merely a potentially useful clinical observation.

Eight patients are described here, each of whom has used weight loss medications for more than 10 years.

Clinical Material

Patients

Patient 1 (female, 52 years old, Table 1) has participated in our weight management program intermittently since 1977 (age 26). Her initial weight was 177 lb (80.5 kg, BMI = 32.4). With repeated effort, she was able to lose weight, but each time she was unable to sustain the weight loss. She reached a maximum weight of 192 lb (87.3 kg, BMI = 35.2). In 1993, she lost weight once again but gradually started to regain her lost weight. She then started phentermine to assist in the maintenance of her weight loss. She maintained her weight thereafter at <145 lb (65.9 kg, BMI <26.6). She regularly uses 15 to 30 mg of phentermine (usually 15 mg) >90% of the time. She occasionally misses a dose but notes more difficulty with eating when she does this. She briefly added fenfluramine and briefly substituted sibutramine, neither of which was helpful.

Table 1. Patient characteristics and medications used

							Weight (kg)			
Patient (gender)	**Age 2004**	**Date/age started current medicines**	**Years of continuous use**	**Consistency of use**	**Medication used**	**Significant side effects**	**Maximum lifetime**	**Start medicines**	**Most recent**	**ΔWe**
1 (female)	52	1994/43	10	>80%	Phentermine	None	87	63	65	
2 (male)	71	1964/31	40	>90%	Phentermine	Sleep *	98	93	84	
					Orlistat	Mood *				
3 (female)	77	1992/65	12	>99%	Phentermine	None	81	70	60	

Patient (gender)	Age 2004	Date/age started current medicines	Years of continuous use	Consistency of use	Medication used	Significant side effects	Weight (kg)			ΔWe
							Maximum lifetime	Start medicines	Most recent	
4 (male)	63	1993/52	11	>95%	Phentermine	None	93	93	89	
5 (female)	55	1971/32	23	>99%	Diethylpropion	None	100	64	68	
6 (male)	61	1970/27	34	>99%	Phentermine	None	101	85	101	
7 (male)	62	1994/51	10	50% to 60%	Phentermine	Dysuria †	114	89	83	
8 (male)	37	1993/26	11	>90%	Phentermine	None	136	97	109	

							Weight (kg)			
Patient (gender)	Age 2004	Date/age started current medicines	Years of continuous use	Consistency of use	Medication used	Significant side effects	Maximum lifetime	Start medicines	Most recent	ΔWe

* Does not affect use of medication.

† Limits use of medication.

‡ Used within the past 10 years.

§ Remote use; (more than 10 years since used).

Patient 2 (male, 71 years old) weighed 215 lb (97.7 kg, BMI = 31.4) at age 17 in 1950. In about 1964, at age 31, he weighed about 205 to 210 lb (93.2 to 95.5 kg). He started medications for weight management and used either diethylpropion or mazindol at different times thereafter. These were helpful in enabling him to lose weight and maintain his weight below 190 lb (86.4 kg, BMI < 27.7). He discontinued his medications when his physician died in 1988 and had more difficulty controlling his weight until he was seen in our program in 1992. He then started using phentermine when he weighed 193.25 lb (87.8 kg, BMI = 28.2). He continued using phentermine about 90% to 95% of the time and has maintained his weight below 185 lb (84.1 kg, BMI <27.0) since. He has added fenfluramine and substituted sibutramine, each without any additional value. He uses orlistat, with benefit, irregularly. He noted persistent, but tolerable, sleep and mood disturbances with diethylpropion and mazindol but no significant side effects with phentermine. In 2003 he had a resection of his prostate for prostatic hypertrophy and was found to have a small carcinoma of his prostate.

Patient 3 (female, 77 years old) lost weight deliberately at age 24 and used dextroamphetamine for weight control from the ages of about 28 to 38 years old. In 1981 at age 54, she was first seen in our program and weighed 177 lb (80.5 kg, BMI = 32.2). She lost weight, but over the next 10 years slowly regained about 75% of what she had lost and lost weight once again. In 1992, when she weighed ~155 lb (70.5 kg, BMI = 28.4), she started fenfluramine and phentermine but soon discontinued the fenfluramine. Initially, she used the phentermine inconsistently but then stabilized her pattern and rarely missed a dose thereafter. She lost ~20 lb (9.1 kg), regained a small amount, and stabilized her weight thereafter in the range of 140 to 150 lb (63.6 to 68.2 kg). She had mild and inconsistent blood pressure elevation that was controlled with hydrochlorothiazide and amlodipine. In 2003, at age 76, when she weighed 134 lb (60.9 kg, BMI = 24.4), she had a small cerebrovascular accident with full recovery and no sequelae. With great reluctance, she discontinued her use of phentermine. Six months later, her weight remained stable.

Patient 4 (male, 63 years old) weighed 196 lb (89.1 kg, BMI = 29.0) in 1986. He lost ~45 lb (20.5 kg) and was able to sustain most of that weight loss for ~3 to 4 years. He eventually regained his lost weight and reached a maximum weight of 205 lb (93.2 kg, BMI = 30.3). In 1993, he started phentermine and reached a weight of 195 lb (88.6 kg, BMI = 28.9) in the ensuing 10 years. He takes the medication continuously, rarely misses a dose, has never taken a holiday to test its effectiveness, and has never tried any other weight control medications. He had mild hypertension which resolved completely with this small weight loss.

Patient 5 (female, 55 years old) weighed 220 lb (100 kg, BMI = 35.0) in 1974. She lost ~80 lb (36.4 kg) but, with two pregnancies, controlled her weight irregularly during the next 5 years. In 1979, she was started on diethylpropion and, with few exceptions, has continued this medication for the ensuing 25 years. She has briefly tried other medications but has not found them to be helpful. She was first seen in our program in 1994 at which time she weighed 170 lb (77.3 kg, BMI = 27.1). She was continued on diethylpropion and lost ~35 lb (15.9 kg). Her weight has since fluctuated between 135 and 170 lb (61.4 to 77.3 kg). She uses 75 mg a day of diethylpropion and rarely misses a dose. Her most recent weight, in 2003, was 150 lb (68.2 kg, BMI = 23.7).

Patient 6 (male, 61 years old) weighed 222 lb (100.9 kg, BMI = 32.8) in 1969. After a modest weight loss, he started using phentermine to assist in the management of his weight. His weight since has fluctuated between 195 and 223 lb (88.6 to 101.4 kg). Although he has not been able to sustain any net weight loss, he is comfortable that the use of the medication has enabled him to avoid gaining additional weight. At times when he discontinued the medication, he had increased difficulty with careful eating and the maintenance of his current, albeit elevated, weight. He now rarely misses regular use of the phentermine. He briefly tried adding fenfluramine but found that it contributed little to his control with phentermine alone.

Patient 7 (male, 62 years old) was first seen as a patient for weight management in 1979. He then weighed 232 lb (105.4 kg; BMI = 30.7) but had previously reached a maximum weight of ~250 lb (113.6 kg, BMI = 33.1). During the following 15 years, he lost and regained significant amounts of weight eight times. In 1994, he successfully lost weight and started using phentermine for the final 10 kg of this weight loss effort. He continues to use this medication to assist in the maintenance of his lost weight. He uses it intermittently (~50% to 60% of the time) because of uncomfortable symptoms of dysuria, urinary hesitancy, and nocturia. With this as-needed approach to the use of phentermine, he has been able (with two brief exceptions) to keep his weight below 215 lb (97.7 kg, BMI = 28.4). He has used methylphenidate for the management of attention deficit disorder. He does not use methylphenidate and phentermine simultaneously. His most recent weight, in 2003, was 181.5 lb (82.5 kg, BMI = 24.0).

Patient 8 (male, 36 years old) weighed over 300 lb (136.4 kg, BMI > 43.1) in 1990 and 266.25 lb (121 kg, BMI = 38.3) when he started our program in 1993. He lost 49 lb (22.3 kg). He then started phentermine to assist in his efforts to maintain his weight loss. He has used phentermine continuously during the ensuing 10 years. He also used fenfluramine ~three to five times a week for ~3 to 4 years without significant additional benefit but discontinued this in ~1996. He used fluoxetine in 1995 and then bupropion in 1995 to 1996 for depression. His blood pressure has occasionally been slightly elevated but is usually normal. He takes the phentermine on most days. All of his recorded weights have been between 210 and 240 lb (95.5 to 109 kg, BMI = 30.2 to 34.5) in the past 10 years.

Results

Six of the eight patients used phentermine as the primary therapeutic agent. A seventh initially used diethylpropion or mazindol and now uses phentermine. One has used diethylpropion regularly (Table 1). The patients studied here occasionally used medications other than phentermine or diethylpropion, testing their effectiveness and tolerability, but all of the patients returned to the one medication that they have found to be most helpful. Many patients who use weight control medications do so intermittently or use them occasionally on an as-needed basis. Although this has been tested by most of these patients, intermittent use has not been the pattern, and all of the patients eventually settled into a pattern of using the medications in a relatively continuous way. Six of the patients used their medication >90% of the time of use.

There have been no complications associated with this long-term use and no significant adverse effects. This is reassuring considering the often-expressed concerns of many clinicians that side effects would be intolerable with continuing use. One patient limits his use because of dysuria. It should not be surprising, however, that these patients have not had significant side effects; those patients with medication-associated adverse events would not likely have continued to use the medications for this many years. No abnormal laboratory tests attributable to the medications have appeared. Blood pressure elevations have not occurred. Patients with pre-existing hypertension tended to normalize their blood pressure with weight loss. In none of these patients has there been an increase in blood pressure that could be temporally associated with the use of these medications. Anticipated adverse events (agitation, insomnia, nervousness, etc.) have not occurred and have not been more troublesome with the passage of time. The reverse appears to have been more common; start-up side effects tended to diminish, rather than increase, with time. None of the patients has had any evidence of dependency or addiction. There also has been no pattern of progressive decreased effectiveness and none of these patients has regularly, or even occasionally, increased the dose beyond ordinary therapeutic standards.

Seven of the eight patients were participants in a comprehensive weight management program with individual medical care, nutrition classes and counseling, behavior therapy, exercise therapy, psychoeducational groups, and psychotherapy. They used these support services variably, some quite extensively and some less so. All patients tended to decrease their use of these services as their weight stabilized. With long-term use, they were seen individually about every 3 to 12 months.

It is not possible to assess to what extent the usefulness of the medication can be associated with the comprehensive support services and if similar results could be obtained by an individual primary care physician working alone. In all cases, patients tended to use the support services more frequently when they were losing weight and then relied entirely on their relationship with the physician alone for the continuing use of the medication for the maintenance of their weight loss.

Some patients used the medication initially to help lose weight; some, initially, to maintain their weight. All ultimately used the medications to sustain their weight loss or to maintain a stable weight. One patient who had lost weight but did not sustain this weight loss was weight stable; he used the medication to avoid further weight gain. The effectiveness of this approach was verified for him by his reliable observation of weight gain when the medication's effectiveness was tested by discontinuing its use.

Seven of the eight patients tested their use of their medication by episodes of discontinuing its use (taking a holiday), adjusting their dose, or trying alternate medications. All eventually abandoned these trials and settled with stable dose and schedule with a single drug.

Discussion

Many studies that have considered the long-term management of obesity have noted the relative ineffectiveness of current procedures and the need for continuing efforts to cope with the chronicity and intractability of its control. The issue of the long-term use of medications has been considered, but studies of this issue have been limited. Glazer (**2**) has reviewed all long-term, placebo-controlled trials of obesity pharmacotherapy lasting >36 weeks. He focused particularly on the possibility of valvulopathy with this therapy. His review, although not sufficient to meet the standards of a meta-analysis, does, nevertheless, suggest the safety and efficacy of the available medications. Padwal et al. (**3**,**4**) have conducted a meta-analysis of randomized, controlled, double-blind, weight loss and weight maintenance trials that lasted more than 1 year. The only

medications for which adequate studies have been done that meet their inclusion criteria for a meta-analysis are orlistat and sibutramine. Both drugs appear modestly effective in promoting weight loss.

Many reports of short-term interventions of any sort are dismissed with suggestions that this kind of intervention offers little therapeutic benefit for the patient. The U.S. National Task Force on Prevention and Treatment of Obesity (**5**) has noted that: "... obesity responds poorly to short-term interventions" and that "... there is little justification for the short-term use of anorexiant medications." Participants in Weintraub's landmark study of phentermine and fenfluramine (**6**) "... had difficulty maintaining their weight loss without the anorexiant medications. Despite long periods of time at weights much lower than baseline, permanent resetting of the weight control mechanisms could not be demonstrated."

The studies that have been done suggest that all of the currently available medications help some (but not all) patients lose a modest amount of weight (usually not >10% to 15% of their initial weight) during an initial 6 months of therapy. Continuing weight loss beyond that time is uncommon (**7**). This phenomenon of no further weight loss after about 6 months has been interpreted by some to be related to the ineffectiveness of the drug or the development of a tolerance to its therapeutic potency (**8**). Alternatively, this stabilization of weight loss may be thought to be similar to the effect of medications for other chronic diseases such as hypertension or hypercholesterolemia, the development of a therapeutic equilibrium. In this instance, the balance is maintained between the sustaining impact of the pharmacotherapy and the evolution of a series of counterregulatory mechanisms that defend body weight and protect the patient from starvation. This same phenomenon is similar in form, if not in magnitude, to the use of medications for hypertension, diabetes, and hypercholesterolemia.

Even a modest amount of weight loss is more readily sustained if the medications are continued than if they are stopped (**6**,**7**). Medications for obesity seem to be most effective if they are continued indefinitely, unless the weight is regained or significant side effects develop (**7**,**9**,**10**,**11**). In the absence of any better understanding of the mechanisms of the disease of obesity that will enable us to repair the dysfunctional settings of the eating regulation and body weight set-points, it seems possible that lifelong treatment may be necessary. The criterion for continuous use should be the clinical measure of its effectiveness, rather than a simple standard of duration of use.

What is obvious is that any pharmacotherapeutic intervention has no sustaining impact if the medication is discontinued. It appears that nothing about the mechanism of drug action permanently modifies the underlying metabolic abnormality. No drug cures the disease. The medication may continue to be helpful only if it is used in a continuous way. The short-term use of medications appears to be equivalent to the short-term use of medications for diabetes or hypertension. However, phentermine, the single most commonly prescribed drug for obesity treatment in the U.S. (**12**), is approved for "short-term" (12 weeks) use only. Its long-term use is not approved by Federal regulatory authorities in the United States.

Many other medical problems are managed with the continuing use of pharmacotherapy. There is no expectation that we will cure hypertension, hyperlipemia, or diabetes with medications. Rather, medications are used to establish control and to sustain that control. That concept, using medications to help manage rather than to resolve a medical problem, and using medications to sustain control, seems somehow to have been ignored in the management of obesity. There are a number of possible reasons for this therapeutic omission.

- There is a cultural conviction that medications are inappropriate for obesity management. Many health professionals believe that eating is entirely a matter of choice and that losing weight depends simply on choosing to eat less.
- The history of the use of medications for obesity has been clouded by therapeutic complications, and many thoughtful physicians are fearful of being involved in another.

- Patients and medical personnel often have a view that the purpose of weight management is to lose weight. Once weight has been lost, by any method, there is a persistent belief that the issue has been resolved and little attention, and certainly no pharmacotherapy, is directed at the maintenance of weight loss.
- There is a fear that because medications have been approved by regulatory agencies for short-term use only, they would not be continuously effective.
- Because problems with abuse, dependency, and addiction occurred with previously used medications (amphetamines), there is a concern that these issues would arise with pharmacologically similar weight management drugs.
- There is concern that medications, which might be useful for morbid obesity, would be used carelessly, and at too great a risk, by patients with mild forms of this disease.
- Despite the recognition that some patients have derived continuing benefits from the long-term use of medications, others slowly regain their weight despite the medications. This has created the belief that weight gain is inescapable, regardless of any pharmacotherapy.
- Medical training, to the extent that it addresses the problem of obesity in any manner, tends to discourage the continuous use of any medication for weight management.

The primary medication used by the patients reported in this paper is phentermine, although two used diethylpropion, one initially and the other continuously. Other medications which have been available for many years are used less frequently in the U.S. Long-term use of amphetamine and its analogues is considered inappropriate because of concerns about dependency and abuse. Fenfluramine was little used until the publication by Weintraub et al. (**13**) in 1992 of their studies of the long-term use of the fenfluramine-phentermine combination. It was withdrawn from the market (along with its analog, dexfenfluramine) in 1997 for safety reasons. Phenylpropanolamine and the caffeine/ephedrine combinations have, until recently, been available in the U.S. without a physician's prescription. It is probable that any long-term use would not have involved physicians; therefore, its use could have passed without systematic note or study. Phendimetrazine and mazindol have not been used frequently in continuing management. The use of phendimetrazine has been limited by its classification as a category II controlled substance. Mazindol, no longer sold in the U.S., has had limited use, in some part because of its high cost. Sibutramine and orlistat, which seem to be effective and have been studied more extensively and for longer times than the others, have been available only for the past 5 years.

Long-term measures of effectiveness are difficult to assess. Control (nonmedication) patients were not studied here, but sufficient long-term experience has established that most patients are not ordinarily able to sustain their weight loss. Clearly, the patients studied here have self-selected this particular therapeutic format and have been successful with its use. Patients who do not respond well, or who have adverse effects, would not be expected to continue its use. It is not possible, by studying the experience of these patients, to establish any generalizations about the usefulness of this approach. Rather, it is important to demonstrate that some patients will find this form of therapy useful and that some consideration should be given to the identification of these patients and the use of long-term pharmacotherapy for them.

Some of the current medications for the treatment of obesity have been available for >30 years, but systematic long-term studies of their utility have not been published. This is, in fact, true for most medications. There is no realistic way that long-duration (more than 2 years) studies for this category of medication can be blinded and placebo-controlled. Efficacy of long-term use of any medication depends on other assessments; collection (usually by pharmaceutical manufacturers or government agencies) of adverse events and the clinical assessment of whether or not the

drug in question sustains its therapeutic usefulness. It is obviously true that we will require 10 years to establish the safety and efficacy of 10 years of treatment with any pharmacotherapy for any medical problem.

Although this generalizable pharmacotherapeutic dilemma seems obvious, medications for the treatment of obesity seem to have been held to a higher standard of proof of efficacy than medications for other therapeutic categories. This seems, in part, to be related to many factors:

- the complications observed with previously used obesity medications;
- the relatively small therapeutic effect that these medications have (usually the loss of <10% to 15% of the patient's initial weight);
- the patient's and the physician's belief that 10% to 15% weight loss is therapeutically insignificant for patients with substantial obesity and the belief that this magnitude of weight loss is insufficient to justify the use of medications; and
- the long-standing cultural perception that obesity is a trivial problem, that it is caused by the patient's willful misconduct, that it should be easily treated by the patient's behavior change, and that, therefore, no pharmacotherapeutic risk is tolerable.

Given these beliefs, the long-term use of medications for weight management has often been dismissed as therapeutically inappropriate. Moreover, there is an additional cultural bias which directs most therapeutic efforts to weight loss, rather than to the maintenance of weight loss. From this naturally derives an astonishingly naive view that once the patient has completed weight loss, any medication can (or should) be discontinued. This therapeutic misunderstanding would be intolerable for the control and sustaining management of comparable chronic medical problems such as diabetes, hypertension, or hypercholesterolemia.

Individual physicians who have prescribed medications in a continuous form note that their patients use them intermittently (perhaps systematically, as on weekends or when traveling) or on an as-needed basis, when they start to regain after a period of some weight stability. As-needed use of medications, particularly if by patient choice, is a common therapeutic option for many medical problems; arthritis, asthma, anxiety, and chronic pain are obvious examples. It is very likely that there is a useful role for this approach for long-term weight management as well. Most of the patients studied here have tried this kind of medication use, but all have settled down to a relatively stable and continuous pattern of use. Missed doses are usually inadvertent, not deliberate.

Similarly, many of these patients have tried alternate medications and/or have tried a combination of medications. This combination use is limited because there are relatively few current therapeutic options, the use of many therapeutic combinations may be pharmacologically contraindicated, and the cost of multiple medications (particularly in the U.S. without insurance reimbursement) is substantial. One of these patients currently uses orlistat advantageously with phentermine. The pattern of switching among therapeutic options or combination therapy has not evolved with these patients.

Many evaluations of the use of weight management medications have noted the very low incidence of addiction, dependence, abuse. or inappropriate use (**14**,**15**). Although caution, vigilance, and patient monitoring are clearly necessary for continuous use of these medications, the nonabusive patterns in these patients and the noteworthy absence of side effects are therapeutically reassuring.

Although in all cases the medications were prescribed to help patients lose weight or maintain weight loss, one patient has been unable to sustain the weight loss and has used the medication successfully to maintain a controlled and stable, albeit moderately elevated, weight. This invariably raises the question of prevention of weight gain and the substantial difficulty in establishing if any medication is truly helpful for this purpose. It may

be possible to justify this prevention use in a patient with a BMI >30 but it raises the awkward problem of how medical professionals can cope with the problem of mildly overweight patients. All physicians have encountered the patient who is only slightly overweight, who has no evidence of an eating disorder, but who struggles to avoid gaining weight because of a bad family history and the evolving characteristics of the metabolic syndrome. Both the physician and the patient recognize the ominous prognosis; all patients who are substantially obese were, at one time, merely a little overweight. Surely the issue of continuous medication will be raised in the consideration of the management of these patients, but nothing in the analysis of the experience of these long-term patients addresses the appropriateness of prevention, particularly for patients who are mildly overweight.

It is noteworthy also that many of these patients lost weight without medications and did not use the medications primarily to lose weight. Perhaps a neglected role for the medications can be for the greater and more intractable task of weight maintenance, rather than for the often more accessible problem of weight loss. It may be that the possibility and opportunity for medications for maintenance will be greater than their role in weight loss. Weintraub et al. (**14**), in their papers on the use of phentermine and fenfluramine, addressed the concept of long-term use of weight management medications and the effectiveness of medications for this purpose. Their studies emphasized the consideration of the continuous management of obesity as a chronic disease. It is regrettable that this concept has not been systematically evaluated with additional studies.

It is likely that more medications will be available in the next decade. Some consideration must be given to the important question of their potential efficacy for long-term use.

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References

Related content

Citing Literature

Weight loss with various medications

Drug	Length of trial	
Phentermine	13 weeks	-6.4 kg
Diethylpropion	18 weeks	-6.5 kg
Mazindol	11 weeks	-5.7 kg
Orlistat	≥1 year	-5.3 kg
Fluoxetine	24 weeks	-4.8 kg
Bupropion	24 weeks	-8.0 kg
Exenatide	24 weeks	-2.9 kg
Liraglutide	24 weeks	-2.8 kg
Metformin	1 year	-2.8 kg
Sibutramine	≥1 year	-6.4 kg
Lorcaserin	1 year	-5.8 kg
Phen/topiramate	≥1 year	-10.2 kg
Buprop/naltrex	≥1 year	-6.1 kg

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