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Obesity in adults: Drug therapy

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Literature review current through: **Aug 2023.**
This topic last updated: **Aug 08, 2023.**

INTRODUCTION

A number of medications are approved by the US Food and Drug Administration (FDA) for the treatment of overweight or obesity. It is essential that the medications are used in conjunction with healthy eating, physical activity, and behavior modification, as medication usage without such changes are generally ineffective.

The decision to initiate drug therapy in people considered overweight should be made after consideration of the risks and benefits [1-4], and the goals of drug therapy should be clear. This topic will review drug therapy for initial weight loss and for long term weight loss maintenance in patients with obesity. Other treatments for the management of overweight and obesity are discussed elsewhere. (See "Obesity in adults: Overview of management".)

GOALS OF THERAPY

The goal of any treatment (including drug therapy) for people considered overweight is long-term weight reduction and improvement in overall health [5].

- **Reduce weight and maintain weight loss –** Contemporary clinical trials evaluating the efficacy of anti-obesity medications have demonstrated 5 to 22.5 percent weight loss when added to lifestyle modification [6-9].

  Upon initiation of anti-obesity medication, we communicate several important messages to patients. First, not every drug works for every patient; individual responses vary widely. Second, when the maximal therapeutic effect is achieved, a plateau is reached and weight loss ceases. This does not mean the drug has "stopped" working. It simply means that additional strategies will be required to induce additional weight loss. Finally, when drug therapy is discontinued, weight regain can be expected.

  Achieving and maintaining weight loss is made difficult by many factors, including weight loss-induced changes in energy expenditure and hormonal mediators of appetite, which favor weight regain [10,11]. Therefore, we favor using anti-obesity medications longer term for weight loss maintenance if they are well-tolerated and have yielded clinically meaningful weight loss (>5 percent).

- **Improve health status –** If improvement in one's health is the goal, success may be measured by the degree of weight loss and measurable or perceived improvement in physical function, comorbidities, and/or sense of well-being. Weight loss should exceed 2 kg during the first month of drug therapy (1 pound per week), fall more than 4 to 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 substantially reduce the development of diabetes in those with prediabetes [12-14] and reduce blood pressure and risk factors for cardiovascular disease in patients with cardiovascular risk factors [15,16].

  Improvement in health status after weight loss is an important criterion in the determination of whether to continue drug therapy [17]. (See 'Monitoring' below.)

- **Minimize adverse effects –** The potential benefits of weight loss must be considered in light of the potential risks of drug therapy.

  The longest clinical trial examining the safety and efficacy of pharmacotherapy for weight loss utilized orlistat for four years [12]. Thus, in patients wishing to use anti-obesity medication for longer than four years, the lack of longer-term safety (and efficacy) data should be made known.

OUR APPROACH

Our approach outlined below is based upon the available clinical trial evidence and clinical expertise. Our approach is largely consistent with published guidelines [18,19].

General principles

- **Initial management –** Thorough and compassionate counseling around healthy eating, physical activity, and health-seeking behavior is essential for every patient seeking weight loss, whether these lifestyle changes are used alone or in combination with anti-obesity medication or bariatric surgery. (See "Obesity in adults: Overview of management", section on 'Initial treatment' and "Obesity in adults: Dietary therapy" and "Obesity in adults: Behavioral therapy" and "Obesity in adults: Role of physical activity and exercise".)

- **Approach to underlying comorbidities –** An important component of the initial evaluation is the assessment of weight-related comorbid conditions such as diabetes mellitus, dyslipidemia, hypertension, heart disease, sleep apnea, and symptomatic osteoarthritis. It is important to consider that health complications of excess weight span a wide range of body systems. (See "Obesity in adults: Prevalence, screening, and evaluation", section on 'Evaluation of patients with obesity' and "Overweight and obesity in adults: Health consequences".)

  For patients with specific comorbidities, we prefer a weight-centric approach to chronic disease management, trying, if possible, to select comorbidity treatments that may produce weight loss rather than weight gain [1,20]. Several drugs are well known to produce weight gain and should be avoided if good alternatives are available [21]. Medications used to treat diabetes, depression (table 1), and autoimmune diseases are particularly notorious for causing weight gain. (See "Initial management of hyperglycemia 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".)

Candidates for drug therapy — Candidates for drug therapy include those individuals with a body mass index (BMI) ≥30 kg/m^2, or a BMI of 27 to 29.9 kg/m^2 with weight-related comorbidities, who have not met weight-loss goals (loss of at least 5 percent of total body weight at three to six months) with a comprehensive lifestyle intervention alone.

The decision to initiate drug therapy should be individualized, weighing the risks and benefits of all treatment options (lifestyle, pharmacologic, device, surgical).

Choice of agent — Pharmacologic options for the treatment of obesity include the glucagon-like peptide 1 (GLP-1) receptor agonists semaglutide or liraglutide (by weekly or daily injection, respectively), combination phentermine-extended release topiramate, combination extended-release bupropion-naltrexone, orlistat, phentermine, benzphetamine, phendimetrazine, and diethylpropion (table 2).

In meta-analyses of randomized trials comparing pharmacologic therapy with placebo, all active drug interventions are effective at reducing weight compared with placebo (figure 1) [6,20,22]. Many of the trials in the meta-analyses have serious limitations, however, 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 pharmacologic agent will respond to another.

When a decision has been made to initiate pharmacologic therapy, our approach takes into account patient comorbidities, contraindications, patient preferences, insurance coverage and cost, and potential adverse effects.

- Liraglutide, the first GLP-1 receptor agonist approved for the treatment of obesity, is administered as a once-daily subcutaneous injection. Liraglutide has beneficial effects on glycemia in addition to demonstrated efficacy for weight loss. It may be used in patients with or without diabetes, but it is a preferred drug in patients with type 2 diabetes, and particularly in those with comorbid cardiovascular disease owing to its demonstrated reduction of cardiovascular events in this population.

  Semaglutide, another GLP-1 agonist approved for the treatment of obesity, is administered as a once weekly subcutaneous injection. It has demonstrated efficacy in weight reduction, as well improvement in glycemia and lipids [7,23]. Similar to liraglutide, the FDA-approved dose for type 2 diabetes has also demonstrated cardiovascular benefits, with the exception of individuals with a history of heart failure [24].

  Gastrointestinal side effects (nausea, vomiting), the need for an injection, and insurance coverage/out-of-pocket cost may limit the use of these agents. (See 'GLP-1 receptor agonists' below.)

- Combination phentermine-topiramate (extended release) is an option for males or postmenopausal females with obesity but without uncontrolled hypertension or coronary heart disease, particularly for those who cannot access or tolerate GLP-1 receptor agonist therapy. The efficacy for weight loss of phentermine-extended release topiramate appears to be greater than for orlistat (figure 1), but it may have more side effects (eg, increased heart rate, dose-related increase in the incidence of psychiatric [eg, depression, anxiety] as well as cognitive [eg, disturbance in attention] adverse events). It may be an acceptable

option for a patient with an obesity-related comorbidity who does not have any cardiovascular disease.

The presence of topiramate in this combination may increase risk of fetal malformations and should thus be used with caution in females of childbearing potential. Such patients should be advised about the teratogenic potential of the medication, counseled to use reliable contraception, and should have a pregnancy test before initiation of therapy and monthly thereafter. (See 'Phentermine-topiramate' below.)

- Orlistat has proven benefits with regard to glycemia, lipids, and blood pressure. There are long-duration trials with orlistat demonstrating its safety profile. Unfortunately, it frequently causes gastrointestinal side effects and is often not tolerated by patients. Due to its limited tolerability, and the established safety and benefits of other available agents such as liraglutide and semaglutide, we no longer consider orlistat to be first-line pharmacotherapy. (See 'Orlistat' below.)

- Combination bupropion-naltrexone (sustained release) produces similar weight loss as orlistat but has more contraindications and may have more side effects (table 2). Owing to the uncertainty about cardiovascular effects, we prefer to use GLP-1 receptor agonist therapy, combination phentermine-topiramate, or orlistat rather than bupropion-naltrexone. (See 'Bupropion-naltrexone' below.)

- Phentermine, benzphetamine, phendimetrazine, and diethylpropion are only approved by the US Food and Drug Administration (FDA) for short-term (ie, 12 weeks) use, have more side effects (table 2), and have potential for abuse. However, some clinicians and their patients choose to use phentermine for longer periods of time, owing to long-term clinical experience with this drug and its low cost. (See 'Sympathomimetic drugs' below.)

Monitoring

- **Weight, vital signs –** After initiating pharmacologic therapy, we monitor weight loss, blood pressure, and heart rate every six weeks. If patients do not lose 4 to 5 percent of body weight after 12 weeks of therapy (at the maximum tolerated dose), the drug should be tapered and discontinued. Although it is uncertain whether those who fail to respond to one drug will respond to another (or to a combination drug), this approach can be tried if the patient and clinician believe the benefits outweigh the risks.

- **Blood sugar in patients with diabetes –** Weight loss may cause hypoglycemia in patients taking medication for diabetes, especially insulin or insulin secretagogues (eg, sulfonylureas, meglitinides), 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 insulin secretagogues during initiation and dose titration of weight loss medications, particularly GLP-1 receptor agonist therapy. In patients with well-controlled diabetes, it may also be advisable to reduce the doses of sulfonylureas or meglitinides during the first four weeks of treatment with any anti-obesity drug and adjust as needed based on blood glucose values.

- **Adverse effects –** We ask about adverse effects during every follow-up visit. More specific monitoring instructions depend upon the drug initiated. As examples:

  - Phentermine-topiramate and bupropion-naltrexone may cause neuropsychiatric side effects, and patients taking these drugs should be monitored for depression or suicidal

thoughts.

- Patients taking liraglutide or semaglutide should be monitored for symptoms of acute pancreatitis and gallbladder disease.
- Hyperchloremic, non-anion gap metabolic acidosis and increases in serum creatinine have been reported in patients treated with phentermine-topiramate because topiramate is a carbonic anhydrase inhibitor. Thus, serum electrolytes (including bicarbonate) and creatinine should be measured before and approximately four weeks after initiation of this combination agent.

GLP-1 RECEPTOR AGONISTS

The incretin peptides (glucagon-like peptide 1 [GLP-1] and glucose-dependent insulinotropic 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. GLP-1 receptor agonists bind to the GLP-1 receptor and stimulate glucose-dependent insulin release from the pancreatic islets. GLP-1 receptor agonists were initially approved for the treatment of type 2 diabetes. One of the mechanisms by which GLP-1 receptor agonists improve glycemia in diabetes is due to their ability to induce weight loss. (See "Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus", section on 'Weight loss'.)

Two GLP-1 receptor agonists have been approved for the treatment of obesity in the United States: semaglutide and liraglutide, both administered by subcutaneous injection. For patients with or without diabetes mellitus, we suggest these agents as preferred first-line pharmacotherapy for the treatment of obesity. For patients with diabetes in particular, the side effects, need for injections, and expense are balanced by improved glycemia and weight loss.

We prefer treatment with semaglutide rather than liraglutide; administration of semaglutide is once weekly rather than once daily, and semaglutide has greater efficacy for weight loss than liraglutide [8] (figure 1). (See 'Efficacy' below.)

Subcutaneous semaglutide — Semaglutide is a long-acting GLP-1 receptor agonist which can be administered subcutaneously once weekly for the treatment of obesity. Semaglutide has demonstrated efficacy in weight loss in trials involving patients with and without type 2 diabetes [7,25,26]. In the United States, both oral and injectable preparations are approved for the treatment of type 2 diabetes, whereas only the injectable form is approved for the treatment of obesity.

For patients considered overweight or with obesity, we treat with semaglutide injections at the maximum dose (2.4 mg weekly) to achieve maximum weight loss. For patients unable to tolerate this dose, lower doses can be used as long as ≥5 percent weight loss is achieved (see 'Dosing' below). In patients who also have type 2 diabetes, glycemic control as well as weight loss should be monitored.

Efficacy — Once-weekly subcutaneous semaglutide has been shown to induce weight loss in individuals considered overweight or with obesity, with or without diabetes. As examples:

- In STEP 1, a randomized controlled trial including 1961 adults without diabetes and a BMI of ≥30 kg/m^2 (or ≥27 with ≥1 weight-related comorbidity), participants were randomly

assigned to 68 weeks of treatment with once-weekly subcutaneous 2.4 mg semaglutide or placebo, plus lifestyle intervention [7]. Mean weight loss was greater in the semaglutide group compared with placebo (-15.3 versus -2.6 kg; estimated treatment difference -12.7 kg, 95% CI -13.7 to -11.7). More participants in the semaglutide group achieved a weight reduction of ≥5 percent (86.4 versus 31.5 percent), ≥10 percent (69.1 versus 12.0 percent), and ≥15 percent (50.5 versus 4.9 percent) compared with placebo. More participants in the semaglutide group discontinued treatment due to gastrointestinal side effects compared with those in the placebo group (4.5 versus 0.8 percent).

Comparing results of the STEP 3 trial (including 611 participants who were overweight or with obesity) with the STEP 1 trial, the addition of a more intensive lifestyle intervention with an initial calorie-restricted diet to semaglutide treatment was not associated with significantly greater weight loss than the less intensive lifestyle intervention [7,27].

- In STEP 2, a similarly designed trial to STEP 1 including over 1200 patients with type 2 diabetes mellitus and obesity, once-weekly semaglutide 1 mg and 2.4 mg were compared with placebo [26]. Both treatment groups lost more weight compared with placebo (6.9 kg [-7 percent]; -9.7 kg [-9.6 percent], and -3.5 kg [-3.4 percent], respectively), but the mean treatment difference was greatest with semaglutide 2.4 mg (-6.21 percent, 95% CI -7.28 to -5.15). (See "Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus", section on 'Weight loss'.)

- Shorter duration of treatment is associated with weight regain. In the STEP 4 trial, participants considered overweight or with obesity were randomly assigned to continue semaglutide treatment or switch to placebo after 20 weeks of initial therapy [28]. Individuals continuing semaglutide continued to lose weight, while those switched to placebo regained weight over the subsequent 48 weeks.

- In STEP 8, a randomized controlled trial including 338 adults with a BMI of ≥30 kg/m^2 (or ≥27 with ≥1 weight-related comorbidity), participants were randomly assigned to once-weekly subcutaneous semaglutide 2.4 mg (or placebo), or once-daily subcutaneous 3.0 mg liraglutide (or placebo); all groups received counseling on lifestyle modification [8]. At 68 weeks, participants in the semaglutide group lost more weight than the liraglutide group (-15.8 versus -6.4 percent; treatment difference -9.4 percent [95% CI -12.0 to -6.8]). Both active treatment groups lost more weight than placebo groups (pooled placebo group weight change -1.9 percent).

Cardiovascular effects — Semaglutide has been shown to reduce major cardiovascular disease events in adults with type 2 diabetes and established cardiovascular disease or chronic kidney disease, although the dose of semaglutide used was lower than the dose recommended for weight loss (0.5 and 1.0 versus 2.4 mg) [29]. Cardiovascular outcomes with semaglutide are being investigated in people with obesity who do not have diabetes.

Adverse effects and contraindications — As with other GLP-1 receptor agonists, adverse effects are common; the major adverse effects are gastrointestinal, including nausea, diarrhea, and vomiting. In the STEP 1 trial, these adverse effects were generally mild to moderate and, for most patients, improved over time [7].

Semaglutide is contraindicated during pregnancy and in patients with a personal history of pancreatitis or a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B [30]. In addition, for patients taking semaglutide concurrent with insulin or

an insulin secretagogue (eg, a sulfonylurea), blood glucose should be monitored, and a dose reduction in the insulin or the sulfonylurea may be necessary to avoid hypoglycemia. Rare cases of angioedema and anaphylaxis have been reported with semaglutide. Patients with diabetic retinopathy should be monitored for complications [30].

Dosing — Semaglutide is administered subcutaneously in the abdomen, thigh, or upper arm once weekly. The initial dose is 0.25 mg once weekly for four weeks. The dose is increased at four-week intervals (0.5, 1, 1.7, 2.4 mg) to the recommended dose of 2.4 mg once weekly [30]. Patients who cannot tolerate the 2.4 mg dose or have an acceptable weight loss response with the 1.7 mg dose can be maintained on the lower dose. If dose escalation is not tolerated due to side effects (eg, nausea, vomiting), the increase in dose can be delayed by another four weeks. We continue a patient on the maximum tolerated dose if goal weight loss is achieved, although there are limited data on the efficacy of doses lower than the recommended dose in patients without diabetes.

Oral semaglutide — Although the FDA has not approved oral semaglutide for the treatment of obesity, high-dose oral semaglutide also reduces weight in adults with obesity or overweight [31].

In one trial of 667 adults with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 and at least one obesity-related condition, patients who received semaglutide 50 mg were more likely to achieve weight reductions of at least 5, 10, and 20 percent (achieved by 85, 69, and 34 percent of participants, respectively) compared with placebo (26, 12, and 3 percent, respectively), with an odds ratio of 14.7 (95% CI: 9.6-22.6) for achieving 10 percent weight reduction [31]. Mean body weight loss was 15.1 percent with semaglutide 50 mg qd versus 2.4 percent with placebo at week 68. Doses of oral semaglutide that are currently approved for the treatment of diabetes are lower, 3 to 14 mg daily.

Adverse effects and contraindications are similar to those for subcutaneous semaglutide. (See 'Adverse effects and contraindications' above.)

Liraglutide — Liraglutide is a chemically modified version of human GLP-1. It is available in the United States and Europe in a higher dose (3 mg daily) than used in diabetes for the treatment of obesity in 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) [32].

For patients considered overweight or with obesity, we treat with liraglutide at the maximum dose (3 mg daily) to achieve maximum weight loss. For patients unable to tolerate this dose, lower doses can be used as long as ≥4 percent weight loss is achieved by 16 weeks (see 'Dosing and contraindications' below). In patients who also have type 2 diabetes, glycemic control as well as weight loss should be monitored.

Efficacy — 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-based therapies 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, 1.8, 2.4, or 3 mg daily), placebo, and open-label orlistat (120 mg

orally three times daily) in 564 patients (mean BMI 35 kg/m^2), weight loss increased with increasing doses of liraglutide, with mean weight loss ranging from 4.8 to 7.2 kg [33]. 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 two-year extension (with only 50 percent of patients remaining at two years), results were similar [34].

- 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) [35]. In addition, cardiometabolic risk factors, glycated hemoglobin (A1C), and quality of life all improved modestly but significantly.

  The subset of individuals with prediabetes at baseline continued on randomized treatment (liraglutide or placebo) [13]. After 160 weeks, mean weight loss was greater in the liraglutide group (-6.1 versus -1.9 percent), and time to diabetes onset was longer (99 versus 87 weeks). However, only half of the participants completed the study up to week 160.

- 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 in the liraglutide group maintained at least 5 percent weight loss (81.4 compared with 48.9 percent in the placebo group) [36].

Cardiovascular effects — Liraglutide has been shown to reduce major cardiovascular disease events in adults with type 2 diabetes and preexisting cardiovascular disease. The dose of liraglutide used was lower than the dose recommended for weight loss (1.8 versus 3 mg) [37]. Cardiovascular outcomes with liraglutide have not been studied in people with obesity who do not have diabetes.

Adverse events — Gastrointestinal side effects, including nausea and vomiting, are common. In the trials described above, the two highest doses of liraglutide (2.4, 3 mg) 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 compared with 5 to 15 percent with placebo) and vomiting (12 to 16 percent compared with 2 to 4 percent with placebo) [33,35,36]. Thus, weight loss may be due, in part, to gastrointestinal side effects directly or through suppression of appetite.

Other side effects include diarrhea, low blood sugar, and anorexia. Serious but less common side effects include pancreatitis, gallbladder disease, and renal impairment. In one trial, pancreatitis, although rare, occurred more frequently with liraglutide treatment (10 cases in the liraglutide group versus two cases with placebo) [35]. (See "Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus", section on 'Adverse effects'.)

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. In multiple trials, there has been no evidence of these tumors in humans. (See 'Dosing and contraindications' below.)

Dosing and contraindications — 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 is increased at weekly intervals (1.2, 1.8, 2.4, 3 mg) to the recommended dose of 3 mg (table 2) [32]. We consider a slower-dose titration if liraglutide is poorly tolerated (eg nausea, vomiting). In addition, we will continue a patient on the maximum tolerated dose (if less than the goal of 3 mg) if goal weight loss is achieved on that dose. Data demonstrating long-term (>3-year) benefits with regard to sustained weight loss are scant [13]. (See 'Monitoring' above.)

Liraglutide is contraindicated during pregnancy and in patients with a personal history of pancreatitis, or a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B. In addition, for patients taking liraglutide concurrent with insulin or an insulin secretagogue (eg, a sulfonylurea), blood glucose should be monitored, and a dose reduction in the insulin or the sulfonylurea may be necessary to avoid hypoglycemia [38]. (See "Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus", section on 'Contraindications and precautions'.)

DUAL-ACTING GLP-1 AND GIP RECEPTOR AGONISTS

Treatment of obesity with a dual-acting glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (also called gastric inhibitory polypeptide [GIP]) receptor agonist may be more effective than "traditional" GLP-1 receptor agonists in achieving weight loss. However, this is not approved by the US Food and Drug Administration (FDA) for the treatment of obesity. (See 'GLP-1 receptor agonists' above.)

Tirzepatide is a novel GLP-1 and GIP receptor agonist administered by once-weekly subcutaneous injection [39]. It is effective in the treatment of obesity in patients with and without diabetes mellitus [9] (see "Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus", section on 'Weight loss'). As examples:

- In an open-label trial including over 1800 patients with diabetes, once-weekly tirzepatide (in varying doses) was compared with semaglutide 1 mg [40]. At 40 weeks, reduction in body weight with all doses of tirzepatide was greater compared with semaglutide (5, 10, and 15 mg of tirzepatide; -7.6, -9.3, and -11.2 kg, respectively: 1 mg of semaglutide; -5.7 kg). Of note, no participants received semaglutide of 2.4 mg once weekly, which is the recommended dose for treatment of obesity. (See 'Dosing' above.)

- In a multicenter trial of 938 adults with type 2 diabetes and BMI of 27 mg/kg^2 or greater, participants randomized to once-weekly tirzepatide (10 mg or 15 mg) were more likely to meet weight reduction thresholds of 5 percent (79 to 83 percent versus 33 percent with placebo) and 20 percent (22 to 31 percent versus 1 percent with placebo) [41].

- In a double-blind placebo-controlled randomized trial including over 2500 adults with obesity (but without diabetes), tirzepatide once weekly was compared with placebo [9]. At 72 weeks, reduction in body weight at all tirzepatide doses (5, 10, and 15 mg) was greater compared with placebo (-16.1, -22.2, and -23.6 kg, respectively, versus -2.4 kg).

In studies, the most frequently reported adverse effects of tirzepatide were nausea, diarrhea, and constipation, and these were generally more frequent at increased doses [9,40].

DRUGS THAT ALTER FAT DIGESTION

Orlistat — Orlistat alters fat digestion by inhibiting pancreatic lipases. Thus, fat is not completely hydrolyzed, and fecal fat excretion is increased. In normal individuals eating a diet that contains 30 percent fat, orlistat causes a dose-dependent increase in fecal fat excretion, inhibiting the absorption of approximately 25 to 30 percent of calories ingested as fat.

Although orlistat has demonstrated long term safety and efficacy in weight loss, it is less effective than glucagon-like peptide 1 (GLP-1) agonist therapy and combination phentermine-topiramate (figure 1), and it is often poorly tolerated due to gastrointestinal side effects. (See 'Adverse effects' below.)

Efficacy — The efficacy of orlistat in facilitating weight loss has been demonstrated in several randomized trials and in meta-analyses [12,42-53]. 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) [53]. Weight loss was maintained with up to 24 to 36 months of orlistat treatment. In another meta-analysis, orlistat was equally effective among all ethnic groups [52].

In one of the longest trials, 3304 people considered overweight, 21 percent of whom had impaired glucose tolerance, were randomly assigned to placebo or orlistat [12]. During the first year, weight loss was greater in the orlistat-treated group (11 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. After four years, the cumulative incidence of diabetes was lower in the orlistat group (6.2 versus 9 percent). In other trials in patients with diabetes, orlistat resulted in significantly more weight loss and reductions in glycated hemoglobin (A1C) at one year than placebo [48-50].

In a subsequent trial published after the meta-analyses (146 patients with obesity [mean body mass index (BMI) 39.3 kg/m^2]), 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 per day) [54]. The latter study highlights the fact that people can still lose weight on orlistat when complying with a low-fat diet despite the drug being a fat-absorption blocker. Further, side effects of the medication may be lessened with this diet-drug combination.

Cardiovascular effects — In hypertensive patients, orlistat improves blood pressure (likely due to weight loss), as illustrated by the findings of a meta-analysis of four trials comparing orlistat with placebo in patients with obesity and hypertension [16]. 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 [44]. In a multicenter trial, as an example, serum total and low-density lipoprotein (LDL) cholesterol concentrations decreased by 4 to 11 and 5 to 10 percent,

respectively, in patients treated with a weight-maintaining diet plus 30 to 360 mg of orlistat per day for eight weeks [55]. These decreases were probably related to fecal fat loss. Others have reported a reduction in postprandial hypertriglyceridemia associated with orlistat therapy [56].

Adverse effects

- **Gastrointestinal** – The predominant side effects of orlistat therapy are gastrointestinal, including intestinal borborygmi and cramps, flatus, fecal incontinence, oily spotting, and flatus with discharge [50]. In a meta-analysis of nine clinical trials, these side effects occurred at frequency rates of 15 to 30 percent [57] 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.

  Severe liver injury has been reported rarely with the use of orlistat [58]. 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 [59]. 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.

- **Absorption of fat-soluble vitamins –** In the meta-analysis described 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 [57].

  Orlistat does not seem to affect the absorption of other drugs, with the exception of cyclosporine. However, for patients taking warfarin, a decrease in vitamin K may necessitate a reduction in the dose of warfarin [60].

- **Kidney –** Oxalate-induced acute kidney injury has also been reported in orlistat users [61-63]. Malabsorption syndromes are a risk factor for calcium oxalate stones (see "Kidney stones in adults: Epidemiology and risk factors"). 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.

Dosing and contraindications — Orlistat, available for the long-term treatment of obesity, is provided in 120 mg capsules. The recommended dose is 120 mg three times daily (table 2). 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 'Adverse effects' above.)

Orlistat should not be used during pregnancy or in patients with chronic malabsorption, cholestasis, or a history of calcium oxalate stones.

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 (BMI) ≥30 kg/m^2 or with a BMI ≥27 kg/m^2 with at least one weight-related comorbidity (eg, hypertension, diabetes, dyslipidemia) [64]. Phentermine-topiramate is not recommended for patients with known cardiovascular disease (hypertension or coronary heart disease), but it is an appropriate agent for individuals with obesity who do not have cardiovascular disease and for whom glucagon-like peptide 1 (GLP-1) therapy is not appropriate, accessible, or tolerated. The efficacy and safety of combining generic phentermine with generic topiramate for weight loss (each taken individually) has not yet been established, although this is commonly done to reduce patients' out-of-pocket costs.

Efficacy — 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 [65]. 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 body weight]). Only 61 percent of participants completed one year of treatment.

  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 body weight] for low dose, high dose, and placebo, respectively) [14]. Of note, phentermine-topiramate was less effective for weight loss in the second year of use, although most individuals were able to maintain the weight they lost in year 1. In those subjects who were able to participate in the second year of the trial, the therapy was well tolerated.

- In another trial, patients with BMI ≥35 kg/m^2 were randomly assigned to controlled-release phentermine-topiramate (3.75/23 mg or 15/92 mg) or placebo [66]. 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 body weight]). 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.

Adverse effects — 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 paresthesia (14 to 21 versus 2 percent) [65,66]. 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.

Dosing and contraindications — 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 body weight is not achieved, the dose can be increased to 11.25/69 mg for 14 days and then to 15/92

mg daily (table 2) [67]. If an individual does not lose 5 percent of body weight after 12 weeks on the highest dose, phentermine-topiramate should be discontinued gradually, tapering the dose over at least one week using every-other-day dosing, as abrupt withdrawal of topiramate can cause seizures [67]. (See 'Monitoring' above.)

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. Females of childbearing age should have a pregnancy test before starting this drug and monthly thereafter. It is also contraindicated in patients with hyperthyroidism or 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 [68]. 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 congenital anomalies.

Use of phentermine monotherapy is reviewed below. (See 'Sympathomimetic drugs' below.)

Bupropion-naltrexone — 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 [69].

Bupropion is a dopamine-reuptake inhibitor used for the treatment of depression and smoking cessation. Naltrexone is an opioid-receptor antagonist used to treat alcohol and opioid dependence. The rationale for their combination comes from animal studies in which combination therapy utilized bupropion's ability to stimulate hypothalamic pro-opiomelanocortin (POMC) neurons while simultaneously blocking opioid-mediated pro-opiomelanocortin autoinhibition with naltrexone [70]. Additional preclinical data indicated synergism of these drugs in midbrain dopamine areas to reduce food intake [71]. (See "Atypical antidepressants: Pharmacology, administration, and side effects", section on 'Bupropion' and "Pharmacotherapy for smoking cessation in adults", section on 'Bupropion' and "Opioid use disorder: Pharmacologic management", section on 'Naltrexone: Opioid antagonist' and "Measurement of ACTH, CRH, and other hypothalamic and pituitary peptides", section on 'Other POMC-derived peptides'.)

Combination bupropion-naltrexone is not generally used as first-line pharmacologic therapy due to uncertainty about cardiovascular safety (see 'Cardiovascular effects' below) but may be considered for patients in whom GLP-1 agonist therapy is not appropriate, accessible, or tolerated.

Bupropion-naltrexone could, however, be a reasonable option for an individual who smokes, has obesity, and desires pharmacologic therapy for the treatment of both. In addition, the combination may have a benefit for people with excess caloric consumption from drinking alcohol given naltrexone's standalone indication for the treatment of alcohol use disorder. Nevertheless, bupropion/naltrexone should be avoided in people who are at risk from alcohol withdrawal and seizures due to the potential for bupropion to lower the seizure threshold.

Efficacy — Compared with placebo, the combination of bupropion-naltrexone has been shown to reduce weight by approximately 4 to 5 percent [72-76]. As an example, in a randomized trial of naltrexone (varying doses) and bupropion versus placebo, weight loss was greater in those assigned to active treatment (mean change in body weight -5 to 6 percent versus -1.3 percent) [72]. 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 bupropion-naltrexone compared with placebo group [72,73]. Other adverse effects included insomnia, vomiting, dizziness, and dry mouth, occurring in 7 to 10 percent [72,73].

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. However, in a pooled analysis of five trials including 2500 adults taking bupropion-naltrexone, there was no difference in depression or suicidality compared with placebo [77].

Cardiovascular effects — The cardiovascular safety of bupropion-naltrexone has not been established [78]. A randomized trial designed to assess cardiovascular outcomes of bupropion-naltrexone compared with placebo in 8910 patients who were overweight or with obesity at increased cardiovascular risk was terminated early, due to public release of confidential interim data by the sponsor [79]. 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 endpoints. 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 (table 2). (See 'Monitoring' above.)

Dose adjustment or avoidance is recommended in patients with renal or hepatic impairment, depending upon the severity [80].

Contraindications include pregnancy, uncontrolled hypertension, seizure disorder, eating disorder, use of other bupropion-containing products, chronic opioid use, severe hepatic dysfunction, and use within 14 days of taking monamine oxidase inhibitors.

SYMPATHOMIMETIC DRUGS

The available sympathomimetic drugs (phentermine, diethylpropion, benzphetamine, and phendimetrazine) are only approved by the US Food and Drug Administration (FDA) for the short-term (up to 12 weeks) treatment of obesity because of their potential side effects, potential for abuse, limited duration of use, and regulatory surveillance. They are contraindicated in patients with coronary heart disease, uncontrolled hypertension, hyperthyroidism, or in patients with a history of drug abuse (table 2). Nevertheless, generic phentermine (as a single agent) remains the most widely prescribed weight loss drug, and the observed rate of abuse with this drug is low. Some UpToDate experts use phentermine long term in selected patients, whereas other UpToDate experts would not.

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

Pharmacology — All of the sympathomimetic drugs are rapidly absorbed after oral administration, and peak plasma concentrations are reached within one to two hours [81]. 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.

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])
- May increase blood pressure

Sympathomimetic drugs reduce food intake by causing early satiety.

Phentermine and diethylpropion are Schedule IV drugs, a regulatory classification suggesting potential for abuse, although the actual observed rate is very 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' above.)

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 [82]. In this trial, both continuous and intermittent administration of phentermine led to more weight loss than placebo (net weight loss 7.4 kg) [82]. Shorter-term trials from Korea support the efficacy of phentermine. As examples:

- In one trial, 68 adults with obesity were randomly assigned to receive phentermine (37.5 mg) or placebo once daily [83]. 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 adults with obesity and diabetes, hypertension, or dyslipidemia were randomly assigned to phentermine diffuse-controlled release (30 mg) or placebo daily [84]. 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 [85].

Adverse effects — All sympathomimetic drugs can increase heart rate and 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) [86], and pulse increased by approximately 4 to 5 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) [87-90]. Based upon this information, the European Medicines Agency suspended the marketing of sibutramine across the European Union [89]. In 2010, the FDA and Health Canada also removed sibutramine from the market [91,92].

Phenylpropanolamine was also removed from the market because of a small but significant risk of hemorrhagic stroke in females [93]. Sibutramine can still be found illicitly in dietary supplements marketed for weight loss. (See 'Therapies not recommended' below.)

THERAPIES NOT RECOMMENDED

The following therapies are poorly substantiated or with limited data, and some have concern for adverse effects.

- Lorcaserin – In February 2020, the US Food and Drug Administration (FDA) asked the manufacturer of lorcaserin to voluntarily withdraw lorcaserin from the United States market because of clinical trial data showing an increased occurrence of cancer [94,95]. In a randomized trial including 12,000 patients followed for five years, more patients taking lorcaserin developed malignancies (including colorectal, pancreatic, and lung cancers) compared with those taking placebo (7.7 versus 7.1 percent of patients). Clinicians should stop prescribing lorcaserin, and patients should stop taking it. The FDA has not recommended any special or intensified cancer screening beyond age-appropriate screening for individuals who have taken lorcaserin.

- **Dietary supplements** – Clinicians should caution patients against the use of weight-loss dietary supplements and should monitor those who choose to use them. Over-the-counter dietary supplements are widely used by individuals attempting to lose weight, but evidence to support their efficacy and safety is limited. Dietary supplements for weight loss are reviewed in detail elsewhere. (See "High-risk dietary supplements: Patient evaluation and counseling".)

  - **Safety** – FDA laboratory tests have revealed the presence of sibutramine, fenproporex, fluoxetine, bumetanide, furosemide, phenytoin, cetilistat, and phenolphthalein in weight loss products being sold over the counter [96] (table 3). 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 female Brazilian immigrants were using these drugs while living in the United States; two-thirds reported adverse effects [97].

In addition, 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 [98]. The use of *Garcinia cambogia* has been associated with hepatic failure [99,100].

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 [101-103].

- **Efficacy –** Conclusions from a 2015 review of available dietary supplements were as follows [104]:

  - Green tea [105], *Garcinia cambogia* (hydroxycitric acid) [106], conjugated linoleic acid, and chitosan were ineffective for weight loss, and their use should be discouraged.

  - Efficacy and safety data were unclear for chromium, *Gambisan*, *Hoodia gordonii*, and *Cynanchum auriculatum*.

  - 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 [107]. 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.

  - 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 [108].

- **Human chorionic gonadotropin –** 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 1 to 2 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 [109,110]. An integral component of the hCG diet is adherence to a very-low-calorie diet (500 kcal/day), which has been recognized to result in short-term weight loss simply from caloric restriction, with no added benefit from hCG. 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'.)

- **Calcium –** While epidemiologic data suggested that calcium supplementation might be associated with weight loss [111], a meta-analysis of randomized trials evaluating the effect of calcium (through supplementation or dairy food intake) on body weight reported no significant effect of calcium on weight loss [112].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Obesity in adults".)

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: Losing weight (Beyond the Basics)" and "Patient education: Weight loss surgery and procedures (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **General approach to the management of individuals with obesity**
  - All patients considered overweight (body mass index [BMI] ≥25 kg/m^2) or with obesity (BMI ≥30 kg/m^2) should receive counseling on diet, lifestyle, and goals for weight loss. (See 'General principles' above and "Obesity in adults: Overview of management".)
  - For patients with specific comorbidities (eg, depression, diabetes), we prefer 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 (table 1). (See 'General principles' above.)
- **Candidates for pharmacotherapy –** Candidates for drug therapy include individuals with a BMI ≥30 kg/m^2, or a BMI of 27 to 29.9 kg/m^2 with comorbidities, who have not met weight loss goals (weight loss of at least 5 percent of total body weight at three to six months) with a comprehensive lifestyle intervention. The decision to initiate drug therapy should be individualized and made only after evaluation of risks and benefits of all treatment options. (See 'Candidates for drug therapy' above.)

- **Choice of agent –** Our choice of anti-obesity drug depends upon patient comorbidities but also takes into account patient preferences, adverse effects, and insurance coverage and cost (see 'Choice of agent' above):

  - **GLP-1 agonist therapy –** For patients who are overweight or with obesity in whom pharmacologic therapy is warranted for further weight reduction, we suggest using a glucagon-like peptide 1 (GLP-1) receptor agonist rather than other agents as first-line treatment (**Grade 2C**). We prefer treatment with semaglutide rather than liraglutide; administration of semaglutide is once weekly rather than once daily, and semaglutide has greater efficacy than liraglutide. (See 'GLP-1 receptor agonists' above.)

  - **Other pharmacotherapy options –** If there is an inadequate response to initial therapy with a (GLP-1) agonist, or it is not accessible or tolerated, and treatment with a different drug is considered, we switch to another agent (table 2 and figure 1). Options include:

    - Combination phentermine-topiramate (see 'Phentermine-topiramate' above)
    - Orlistat (see 'Orlistat' above)
    - Combination bupropion-naltrexone (see 'Bupropion-naltrexone' above)
    - Phentermine (See 'Sympathomimetic drugs' above.)

    The choice of agent largely depends on patient comorbidities and contraindications (table 2).

- **Alternative options for patients who do not respond to pharmacotherapy –** For patients who do not have an adequate response to pharmacotherapy, bariatric surgery is an option for those who meet surgical criteria. (See 'Monitoring' above and "Obesity in adults: Overview of management", section on 'Bariatric surgery' and "Bariatric surgery for management of obesity: Indications and preoperative preparation", section on 'Indications'.)

- **Dietary supplements not recommended –** We recommend **against** using dietary supplements marketed for weight loss (**Grade 1B**), owing to low-quality evidence of efficacy and concern for potential adverse effects (table 3). (See 'Therapies not recommended' above and "High-risk dietary supplements: Patient evaluation and counseling", section on 'Weight loss supplements'.)

ACKNOWLEDGMENT — The UpToDate editorial staff acknowledges George Bray, MD, who contributed to an earlier version of this topic review.

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Topic 5376 Version 82.0

GRAPHICS

Categorization of certain medications by their effects on body weight[1]

Produce weight loss
Antiseizure medications: topiramate, zonisamide, lamotrigine
Antidepressants: bupropion, venlafaxine, desvenlafaxine
Antipsychotics: ziprasidone
Attention deficit hyperactivity disorder medications: eg, methylphenidate, amphetamine, dextroamphetamine[2,3]
Are weight neutral
Antipsychotics: haloperidol, aripiprazole
Produce weight gain
Antidepressants: monoamine oxidase inhibitors, tricyclic antidepressants (nortriptyline, amitriptyline, doxepin), paroxetine, citalopram, escitalopram, imipramine, mirtazapine
Antipsychotics: thioridazine, olanzapine, risperidone, clozapine, quetiapine
Diabetes medications: eg, insulin, sulfonylureas, thiazolidinediones, meglitinides
Glucocorticoids: eg, prednisone
Hormonal agents: especially progestins, eg, medroxyprogesterone
Antiseizure medications: eg, divalproex
Neurologic and mood-stabilizing agents: eg, lithium, carbamazepine, gabapentin, valproate
Antihistamines: cyproheptadine
Alpha blockers: especially terazosin
Beta blockers: especially propranolol

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Adapted from: Bray GA, Ryan DH. Medical therapy for the patient with obesity. Circulation 2012; 125:1695.

Graphic 85807 Version 9.0

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 3 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.
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, followed by 7.5 mg phentermine/46 mg topiramate daily for 12 weeks. Then titrate based upon response: 11.25 mg phentermine/69 mg topiramate daily for 14 days, and then to a maximum dose of 15 mg phentermine/92 mg topiramate once daily.	C-IV (due to phentermine component)	Dry mouth, taste disturbance, constipation, paraesthesias, depression, anxiety, elevated heart rate, cognitive disturbances, insomnia (higher dose). 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 2 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 1 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: 1 tablet (8 mg naltrexone/90 mg bupropion) once daily.	Not a controlled substance	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth.

	Week 2: 1 tablet twice daily. Week 3: 2 tablets in morning and one tablet in evening. Week 4: 2 tablets twice daily. Maximum daily dose: 4 tablets (32 mg naltrexone/360 mg bupropion).		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 agonists approved for long-term use			
Liraglutide	Initial: 0.6 mg subcutaneously daily. Increase at weekly intervals (1.2, 1.8, 2.4, 3 mg) until recommended dose of 3 mg daily. If increased dose is not tolerated, consider delaying dose escalation by an additional week.[◇]	Not controlled substances	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. Causes a modest delay of gastric emptying. 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%) and other anti-diabetic medications as needed to prevent potentially severe hypoglycemia. 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. For semaglutide, monitor patients with diabetic retinopathy for eye complications.
Semaglutide	Initial: 0.25 mg subcutaneously once weekly. Increase dose at 4-week intervals (0.5, 1, 1.7, 2.4 mg) until recommended dose of 2.4 mg weekly. If increased dose is not tolerated, consider delaying dose escalation by 4 weeks.[§]		
Noradrenergic sympathomimetic drugs approved for short-term use			
Benzphetamine	Initial: 25 mg once daily; may titrate up to 25 to 50 mg one	C-III	Applies to all sympathomimetic agents:

	to 3 times daily. Maximum dose: 50 mg 3 times daily.		▪ Due to their side effects and potential for abuse, we suggest **not** prescribing sympathomimetics for weight loss. ▪ If prescribed, limit to short-term (≤12 weeks) use. ▪ Adverse effects include increase in heart rate, blood pressure, insomnia, dry mouth, constipation, nervousness. ▪ 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. ▪ Contraindicated in patients with a history of CVD, hyperthyroidism, glaucoma, MAO inhibitor-therapy, agitated states, pregnancy, or breast feeding.
Diethylpropion	Immediate release: 25 mg 3 times daily, 1 hour before meals. Controlled release: 75 mg every morning.	C-IV	
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. Immediate release (Lomaira): 8 mg 3 times daily before meals.	C-IV	
Phendimetrazine	Immediate release: 17.5 to 35 mg 2 or 3 times daily, 1 hour before meals. Maximum dose: 70 mg 3 times daily. Sustained release: 105 mg daily in the morning.	C-III	

Dosing in this table is for adults with normal kidney and liver function. Patients are reevaluated after 12 weeks on the maximum tolerated dose of a weight loss drug to determine efficacy.

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% after 16 weeks or 3 mg/day is not tolerated, discontinue use. Labeling in the European Union recommends discontinuation of use if weight loss is not ≥5% after 12 weeks of 3 mg/day.

§ According to United States labeling, if 2.4 mg/week is not tolerated, discontinue use.

Courtesy of authors.

With additional data from:

1. *The US National Library of Medicine DailyMed website. Availablet at: https://dailymed.nlm.nih.gov/dailymed/ (Accessed October 8, 2014).*

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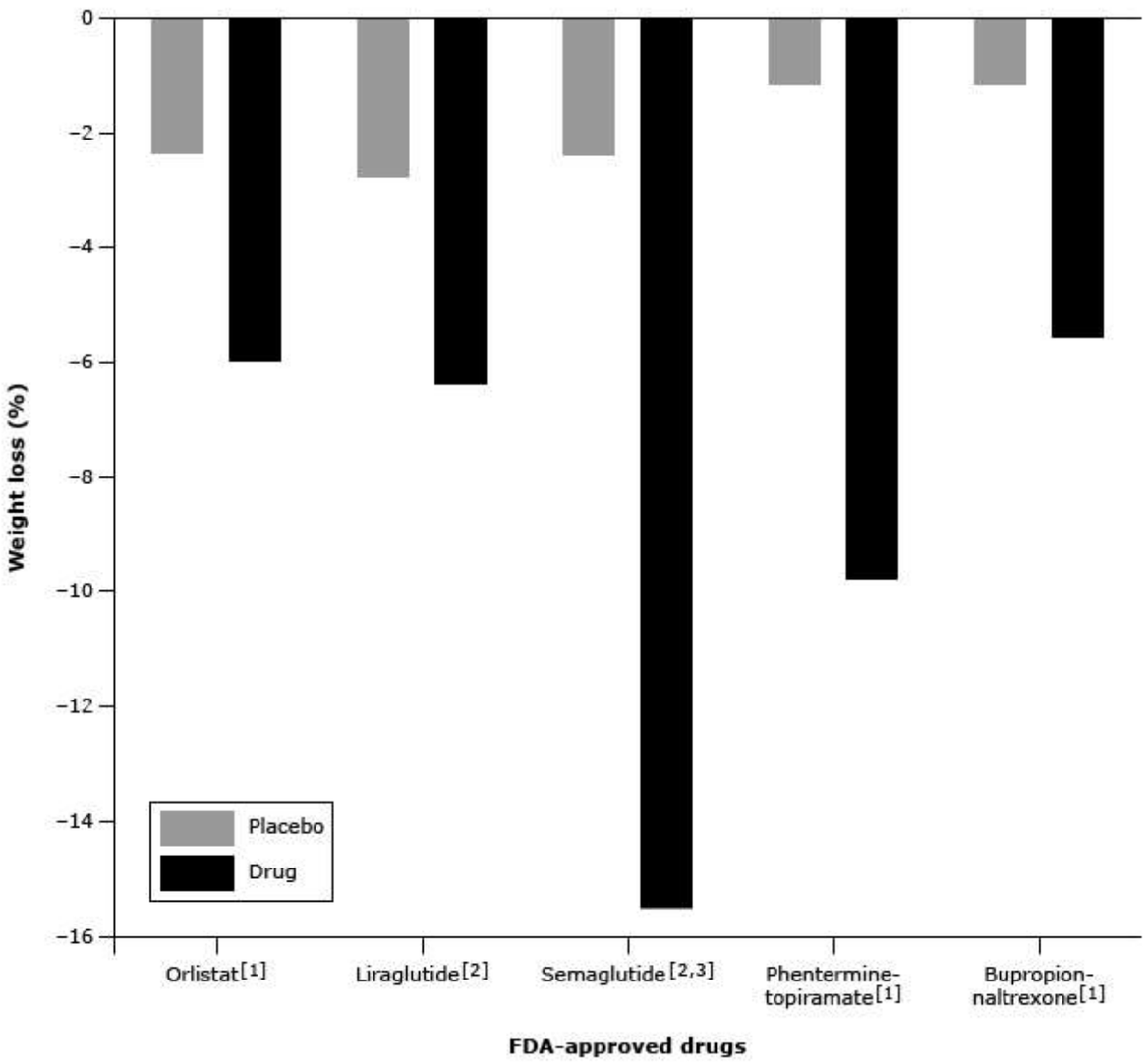
Graphic 86204 Version 21.0

Weight loss outcomes with FDA-approved medications



Weight loss reflects results at 52 weeks, except for semaglutide and liraglutide, which reflect weight loss at 68 weeks.

FDA: US Food and Drug Administration.

Courtesy of George A Bray, MD.

Data from:

1. *Khera R, Murad MH, Chandar AK, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: A systematic review and meta-analysis. JAMA 2016; 315:2424.*
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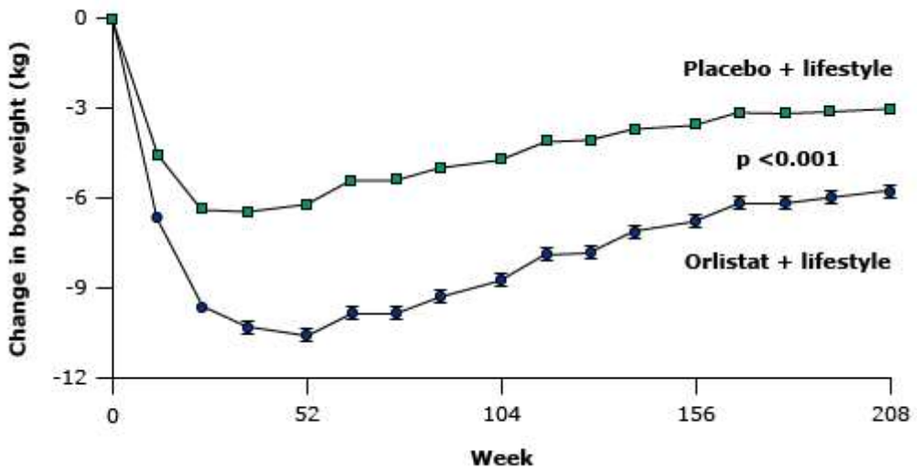
Graphic 115096 Version 5.0

Weight loss with orlistat



Weight loss (means ± SEM) during four years of treatment with orlistat plus lifestyle changes or placebo plus lifestyle changes in obese patients.

Graphic 55426 Version 6.0

Pre-workout and weight loss supplements

Supplement category	Agent name	Alternative name(s) listed on supplement label	Proposed mechanism of activity	Potentia eff
Pre-workout and weight loss supplements	Caffeine	Caffeine source (eg, black tea, cola nut, green tea, guarana, yerba mate)	Increases levels of 3'5' cyclic AMP by inhibiting phosphodiesterase CNS stimulant which increases medullary respiratory center sensitivity to carbon dioxide, stimulates central inspiratory drive, and improves skeletal (including diaphragmatic) muscle contractility	Palpitations, anxiety/agita GI upset[1], c dependence
	Yohimbine	Yohimbe, *Corynanthe johimbe*, coryanthe yohimbe, 11-hydroxy yohimbine	Blocks presynaptic alpha-2-adrenergic receptors, resulting in increased cholinergic and decreased adrenergic tone	GI distress, ta anxiety/agita hypertensior
	Rauwolscine	*Rauwolfia vomitoria*, yohimbe, alpha-yohimbine	Alpha-2-adrenergic receptor blocker	Hypotension
	Higenamine	*Aconitum carmichaelii*, *Nandina domestica*, *Tinospora crispa*, *Aconitum japonicum*, demethylcoclaurine, norcoclaurine	Beta-agonist activity with chronotropic and inotropic properties	Tachycardia, cardiac dema for significan effects[4,5]
	DMAA (1,3-DMAA)	1,3-dimethylamylamine, Geranium extract, *Pelargonium graveolens*, dimethylpentylamine, pentylamine, Geranamine, Forthane, 2-amino-4-methylhexane, methylhexanamine, methylhexamine	Peripheral sympathomimetic activity	Tachycardia, hemorrhagic death[6-9]
	DMBA (1,3-DMBA)	1,3-dimethylbutylamine, 2-amino-4-methylpentane citrate, AMP citrate, 1,3-dimethylbutylamine citrate, 4-amino-2-pentanamine, Pentergy, 4-AMP, pouchong tea, Amperall	Peripheral sympathomimetic activity	Tachycardia, hypertensior
	Octodrine	DHMA, 1,5-dimethylhexylamine, 6-	Peripheral sympathomimetic	Increased blo and cardiac c

		methyl-2-heptanamine, *Aconitum kusnezoffii*, 2-amino-isoheptane, Aconite extract, *Rauwolfia vomitoria*, Halostachine	activity	stimulation[1
	BMPEA	Beta-methylphenethylamine, *Acacia rigidula*, *Vachellia rigidula*, blackbrush, blackbush, chaparro prieto	Amphetamine analog; peripheral sympathomimetic activity	Increased blo and cardiac c
	Phenpromethamine	DHMA, 6-methyl-2-heptanamine, phenylpropylmethylamine, Vonedrine	Sympathomimetic activity; alpha-adrenergic agonist	Increased blo and cardiac c
	Oxilofrine	Methylsynephrine, p-hydroxyephedrine, oxyephedrine, 4-HMP, Halostachine	Ephedrine analog; sympathomimetic amine	Hypertensior cardiac dema vomiting, agi tachycardia, pain[15,16]
	Deterenol	Isopropylnorsynephrine, isopropylnorsynephrine HCl, N-iso-propylnorsynephrine HCl and isopropyloctopamine, Betafrine, Halostachine	Beta-agonist; sympathomimetic activity	Flushing, anx heart rate, hy nausea, vom vision[14,15,17
	DEPEA	Dendrobium orchid extract, *Dendrobium nobile*, Dendrobe Noble	Methamphetamine analog; presumed sympathomimetic activity (no animal or human studies)	Hypertensior cardiac dema
	1,4-DMAA	1,4-dimethylamylamine, DHMA, 6-methyl-2-heptanamine, *Aconitum kusnezoffii*, 2-amino-isoheptane, *Rauwolfia vomitoria*, Halostachine	Sympathomimetic activity	Increased blo and pulse[12]
Supplements exclusively for weight loss	Sibutramine	¶	Noradrenergic sympathomimetic agent; blocks norepinephrine and serotonin reuptake	Increased blo pulse and inc nonfatal MI a stroke[19,20]; anxiety, insor
	2,4-dinitrophenol	DNP, "turmeric powder," Sulfo Black, Nitro Kleenup, Caswell No. 392[21]	Uncouples mitochondrial oxidative phosphorylation[21]	Acute toxicity tachycardia, nausea, vom jaundice Less commor Taste disturb change, arth status chang kidney impai seizures, dea Chronic expo associated w agranulocyto

				neuritis, cata lesions, cardi
	Phenolphthalein	¶	Laxative	Carcinogenic models[24]
	Benzodiazepines (ie, diazepam)	¶	GABA agonist	CNS depressi drowsiness, a driving, confu weakness, ph dependence/
	SSRIs (ie, fluoxetine)	¶	Inhibits serotonin reuptake by CNS neurons	Sexual dysfu abnormal dre
	Diuretics (eg, furosemide, bumetanide)	¶	Loop diuretics which inhibit reabsorption of sodium and chloride in kidney	Orthostatic h hypovolemia acute kidney loss, tinnitus Hyperkalemi metabolic aci

Testing of dietary supplements often reveals drugs not declared on labeling, labeled drugs/herbs not detected in the product, inaccurate quantities, and adulteration with prescription and experimental drugs. In addition, doses contained in supplements may far exceed pharmaceutical quantities, increasing the risks of adverse effects. For review of health risks and an approach to patient counseling, refer to UpToDate topic reviews of high-risk dietary supplements and performance enhancing drugs and hormones in sport.

PDE: phosphodiesterase inhibitor; GABA: gamma-aminobutyric acid; GI: gastrointestinal; CNS: central nervous system; CBD: cannabidiol; THC: delta-9-tetrahydrocannabinol; SARMs: selective androgen receptor modulators; SERMs: selective estrogen receptor modulator; DMAA: 1,3-dimethylamylamine; 1,4-DMAA: 1,4-dimethylamylamine; DMBA: dimethylbutylamine; BMPEA: beta-methylphenethylamine; DEPEA: diethylphenethylamine; MI: myocardial infarction; SSRIs: selective serotonin reuptake inhibitors.

* Based upon animal studies; no human data available.

¶ Typically not declared/listed on supplement label.

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Contributor Disclosures

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