Antiobesity drug therapy: An individualized and comprehensive approach

ABSTRACT

Obesity affects 42% of US adults and has a devastating impact on health. Although many patients initially lose weight with diet and exercise, long-term weight loss is difficult to achieve. Pharmacotherapy, as part of a comprehensive plan, can help patients lose weight and avoid regaining it. Choosing an antiobesity drug regimen should be an individualized, shared decision-making process that accounts for patient preferences, comorbidities, and out-of-pocket costs. We review antiobesity drugs and propose an individualized and comprehensive approach to obesity management.

KEY POINTS

- Antiobesity medications as part of a comprehensive plan can help patients achieve lasting obesity control and provide independent health benefits, including decreased cardiovascular risk.
- All patients suffering from obesity should be counseled to adopt a healthful low-calorie diet, exercise regularly, get adequate sleep, and manage stress.
- Antiobesity management plans should include lifestyle counseling, discontinuation of obesity-inducing medications when possible, and, when indicated, weight loss surgery.

Antiobesity medications are significantly underprescribed. Only 2% of US adults eligible for obesity pharmacotherapy receive it. Contributing to this underutilization are inadequate training of prescribers and stigmatization of obesity as resulting from a perceived lack of willpower on the part of the patient. Familiarizing clinicians with the pathophysiology of obesity and helping them provide an individualized and comprehensive plan for their patients is the purpose of this review.
Obesity rates decrease with increasing income: 39% obesity at 130% or less of the federal poverty level vs 31.2% in those at higher than 350% of the federal poverty level. Rates also decrease with college education: 27.8% in college graduates vs 40% in nongraduates.

ADVERSE EFFECTS ON HEALTH
Obesity is a chronic disease characterized by a long-term positive energy balance resulting in excess adiposity. Weight in relation to height (ie, the BMI) and waist circumference are surrogates for measuring adiposity.

Obesity leads to structural abnormalities such as venous stasis and hepatic steatosis, physiologic derangements such as insulin resistance and inflammation, and functional impairments such as gastrointestinal reflux disease, urinary incontinence, osteoarthritis, and disability. Obesity increases the risk of developing more than 200 other chronic diseases and thus is associated with significant rates of morbidity and death.

DRUG THERAPY CAN AID WEIGHT LOSS
Obesity is influenced by genetics, epigenetics, socioeconomic status, access to food and exercise, psychological health, iatrogenic factors, and behavior, and thus it is challenging to treat. Furthermore, biological responses to loss of adipose tissue trigger a decrease in metabolic rate and increase in energy efficiency while inducing hunger and decreasing satiety.

Drug therapy helps patients adhere to lifestyle changes and overcome these responses. Typically, monotherapy leads to a loss of 3% to 8% of total body weight from baseline, and combination therapy can result in even greater loss. Moreover, some antiobesity drugs can provide independent health benefits, such as decreases in blood pressure, harmful lipid levels, waist circumference, insulin resistance, nonalcoholic fatty liver disease, risk of major cardiovascular events, and progression of diabetic kidney disease.

CHOOSING THE RIGHT DRUG
Pharmacotherapy is indicated in patients with a BMI of 30 kg/m² or higher, or 27 kg/m² or higher with obesity-associated complications in whom a healthy low-calorie diet and regular physical activity have failed to achieve a healthy weight. Choosing the right drug regimen involves an individualized, shared decision-making process that accounts for patient preferences, comorbidities, and out-of-pocket costs (Table 1, Table 2).

Tolerability
Adverse effects frequently limit the use of antiobesity medications.

Liraglutide and semaglutide, glucagon-like peptide 1 (GLP-1) receptor agonists that carry a US Food and Drug Administration (FDA) indication for long-term treatment of obesity, are generally well tolerated. (Semaglutide was approved in June 2021.) Gastrointestinal effects are common and include nausea, abdominal cramping, and diarrhea. Liraglutide requires daily injections, and semaglutide requires weekly injections, and although some patients find injections undesirable, they rarely discontinue this therapy because of its mode of administration. Semaglutide is available in an oral formulation, but this is not approved for the treatment of obesity.

Phentermine-topiramate, another FDA-approved drug, is also well tolerated. The combination can achieve higher weight loss at lower doses of each medication, thus lessening the chance of dose-dependent adverse effects. Irritability, insomnia, neuropathy, problems with memory, and changes in taste are the adverse effects most frequently reported. Patients often find soda drinks less appealing, which can help their weight management.

When patients experience severe topiramate-associated effects such as neuropathy, or phentermine-associated effects such as irritability, one can consider prescribing the other medication by itself. Generally, phentermine is very well tolerated, and side effects wane with continued use. However, the clinician may recommend as-needed use for patients who experience significant adverse effects. For example, if a patient tends to eat excessively during the weekends, phentermine can be taken just on weekends.

Phentermine carries a theoretical potential for abuse and addiction, but this concern is not supported in the literature. Topiramate is generally less well tolerated, with frequent neurologic and psychiatric adverse effects.
# TABLE 1

## Drugs approved for long-term treatment of obesity

<table>
<thead>
<tr>
<th>Drug and class</th>
<th>Ideal candidates</th>
<th>Adverse effects</th>
<th>Contraindications(^a)</th>
<th>Average wholesale price(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liraglutide</strong>&lt;br&gt;<strong>Semaglutide</strong>&lt;br&gt;(GLP-1 receptor agonist)</td>
<td>Patients with coronary artery disease, prediabetes, and diabetes</td>
<td>Constipation, diarrhea, nausea, headache, fatigue, and injection site reactions. Serious but rare: increased heart rate, renal impairment, pancreatitis, and suicidal ideation. Potential risk of thyroid C-cell tumor. Semaglutide is associated with an increased incidence of diabetic retinopathy complications, probably attributable to rapid correction of hyperglycemia in patients with diabetes.</td>
<td>Family or personal history of medullary thyroid cancer or multiple endocrine neoplasia type 2. Use with caution in patients with severe chronic kidney disease and history of pancreatitis.</td>
<td>Liraglutide $1,619&lt;br&gt;Semaglutide $1,022</td>
</tr>
<tr>
<td><strong>Naltrexone-bupropion</strong>&lt;br&gt;(opioid receptor antagonist and DNRI)</td>
<td>Patients with depression, those interested in smoking cessation, and those with food addiction and strong cravings</td>
<td>Glaucoma, hepatotoxicity, increase in heart rate and blood pressure, headache, nausea, constipation, vomiting, dry mouth. Serious but rare: suicidal ideation and a lower seizure threshold.</td>
<td>Uncontrolled hypertension, seizures, anorexia, bulimia, drug or alcohol withdrawal, or chronic opioid use.</td>
<td>$365</td>
</tr>
<tr>
<td><strong>Orlistat</strong>&lt;br&gt;(lipase inhibitor)</td>
<td>Patients who do not want to take a systemic drug, or patients who eat a moderate- or high-fat diet</td>
<td>Headaches, flatulence, cramping, fecal incontinence, oily spotting, decreased absorption of medications and fat-soluble vitamins. Gastric disturbances can be reduced by taking with psyllium. Serious but infrequent: liver injury, cholecystitis, nephrolithiasis.</td>
<td>None, but not recommended for patients with malabsorption (eg, after gastric bypass surgery).</td>
<td>$108</td>
</tr>
<tr>
<td><strong>Phentermine-topiramate ER</strong>&lt;br&gt;(sympathomimetic amine and GABA receptor modulator)</td>
<td>Patients with chronic migraines</td>
<td>Increased heart rate, dizziness, neuropathy, insomnia, anxiety, depression, cognitive impairment, and dry mouth. Serious but rare: suicidal ideation, acidosis, hypokalemia, rise in serum creatinine, myopia, or glaucoma. Minimal risk of seizures with rapid discontinuation.</td>
<td>Uncontrolled anxiety or depression, cardiovascular disease, uncontrolled hypertension, hyperthyroidism, glaucoma, and history of substance dependence.</td>
<td>$239</td>
</tr>
</tbody>
</table>

\(^a\) All antiobesity medications are contraindicated in pregnancy. Because of potential teratogenicity of many antiobesity drugs, a pregnancy test should be done before prescribing, and women should be counseled on effective birth control.

\(^b\) Lexicomp average wholesale price for 30-day supply of maximum doses as of May 2021.

\(^c\) A controlled substance.

DNRI = dopamine-norepinephrine reuptake inhibitor; ER = extended release; GABA = gamma aminobutyric acid; GLP-1 = glucagon-like protein-1.
Naltrexone-bupropion, another FDA-approved option, is usually well tolerated, with constipation, headaches, irritability, anxiety, and insomnia being commonly reported. These can be ameliorated by reducing doses, eg, skipping the afternoon dose to reduce sleep disturbance. A stool softener or coprescription with metformin can be considered to promote more regular bowel movements.

Lisdexamfetamine, FDA-approved for treating binge-eating disorder but not obesity per se, has very infrequent side effects. It
has potential for abuse and dependence, but whether this actually occurs in patients taking it for binge-eating disorder is not well established.

**Metformin**, a diabetes drug frequently used off-label to treat obesity, is also well tolerated. Its most common adverse effects include abdominal pain, nausea, and diarrhea. These are lessened when using extended-release formulations and when taken with meals. Dose reduction is often required to manage adverse effects.

**Orlistat**, FDA-approved for treating obesity, is poorly tolerated, with abdominal pain, nausea, bloating, flatulence, and diarrhea being very common and bothersome effects. Gastric disturbances can be reduced when this drug is taken with psyllium.

### COST

Antiobesity drugs are not frequently covered by insurance, and their cost limits patients’ choices.

**Most expensive**

- **Liraglutide and semaglutide.** Liraglutide, average wholesale price (30-day supply of maximum dose) $1,619, and semaglutide (average wholesale price $1,022) are the most expensive choices, have no generic alternatives, and are often not covered by insurance. Lower doses are more affordable. These drugs are usually covered by insurance when prescribed for diabetes, but when prescribed for this indication, the doses are lower and thus there is less effect on weight loss.

- **Lisdexamfetamine,** average wholesale price $402, has no generic alternative but is often covered by insurance when prescribed for binge-eating disorder.

**Most affordable**

- **Metformin,** average wholesale price $5, is an economical option available in generic form and covered by insurance. Phentermine and topiramate are also affordable at less than $10 per month, and bupropion is another affordable option.

Very frequently, manufacturers offer customer-assistance programs, but these programs often exclude patients with Medicaid and Medicare insurance.

### EFFICACY IN WEIGHT LOSS

Semaglutide is the most effective agent. Phentermine-topiramate, naltrexone-bupropion, liraglutide, lisdexamfetamine, and pramlintide are also associated with a high percentage of total body weight loss. Orlistat, topiramate alone, metformin, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors are associated with a more modest weight loss. Further, orlistat is effective only in those who consume a moderate- or high-fat diet. Table 3 lists percentages of total body weight loss observed in randomized controlled trials of the various drugs. Of note, not all available dosages of the medications today were included in
**TABLE 3**

**Weight loss in randomized, double-blind, placebo-controlled trials**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Patients</th>
<th>Dose</th>
<th>% TBWL vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide(^{10})</td>
<td>Diabetes, body mass index (BMI) ≥ 27 kg/m(^2)</td>
<td>1.8 mg</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.0 mg</td>
<td>4.0</td>
</tr>
<tr>
<td>Liraglutide(^{11})</td>
<td>Prediabetes, BMI ≥ 30 or ≥ 27 with hypertension or dyslipidemia</td>
<td>3.0 mg</td>
<td>5.4</td>
</tr>
<tr>
<td>Liraglutide(^{12})</td>
<td>No diabetes, BMI ≥ 30 or ≥ 27 with hypertension or dyslipidemia, who lost ≥ 5% total body weight with a low-calorie diet</td>
<td>3.0 mg</td>
<td>6.0</td>
</tr>
<tr>
<td>Naltrexone-bupropion(^{13})</td>
<td>Diabetes, BMI ≥ 27</td>
<td>32/360 mg</td>
<td>3.2</td>
</tr>
<tr>
<td>Naltrexone-bupropion(^{14})</td>
<td>No diabetes, BMI ≥ 30 or ≥ 27 with hypertension or dyslipidemia</td>
<td>16/360 mg</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32/360 mg</td>
<td>4.8</td>
</tr>
<tr>
<td>Naltrexone-bupropion(^{15})</td>
<td>No diabetes, BMI ≥ 30 or ≥ 27 with hypertension or dyslipidemia</td>
<td>32/360 mg</td>
<td>5.2</td>
</tr>
<tr>
<td>Naltrexone-bupropion(^{16})</td>
<td>No diabetes, BMI ≥ 30 or ≥ 27 with hypertension or dyslipidemia</td>
<td>32/360 mg</td>
<td>4.2</td>
</tr>
<tr>
<td>Orlistat(^{17})</td>
<td>BMI 30–43</td>
<td>120 mg TID</td>
<td>3.0</td>
</tr>
<tr>
<td>Orlistat(^{18})</td>
<td>BMI 30–44</td>
<td>120 mg TID</td>
<td>3.7</td>
</tr>
<tr>
<td>Orlistat(^{19})</td>
<td>Type 2 diabetes, clinically stable on oral sulfonylureas, BMI 28–40</td>
<td>120 mg TID</td>
<td>1.9</td>
</tr>
<tr>
<td>Phentermine-topiramate ER(^{20})</td>
<td>No diabetes, BMI ≥ 35, blood pressure ≤ 140/90 mm Hg</td>
<td>3.75/23 mg</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15/92 mg</td>
<td>9.3</td>
</tr>
<tr>
<td>Phentermine-topiramate ER(^{21})</td>
<td>BMI 27–45 with at least 2 of the following: hypertension, dyslipidemia, diabetes, prediabetes, abdominal obesity</td>
<td>7.5/46 mg</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15/92 mg</td>
<td>10.8</td>
</tr>
<tr>
<td>Phentermine-topiramate ER(^{22})</td>
<td>BMI 27–45 with at least 2 of the following: hypertension, dyslipidemia, diabetes, prediabetes, abdominal obesity</td>
<td>7.5/46 mg</td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15/92 mg</td>
<td>8.5</td>
</tr>
<tr>
<td>Phentermine-topiramate ER(^{23})</td>
<td>BMI 30–45</td>
<td>7.5/46 mg</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15/92 mg</td>
<td>7.5</td>
</tr>
<tr>
<td>Lisdexamfetamine(^{24})</td>
<td>Adults with binge eating disorder, BMI 25–45</td>
<td>30 mg</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 mg</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70 mg</td>
<td>5.3</td>
</tr>
<tr>
<td>Phentermine(^{25})</td>
<td>BMI 30–45</td>
<td>7.5 mg</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 mg</td>
<td>4.4</td>
</tr>
<tr>
<td>Topiramate(^{26})</td>
<td>BMI 30–45</td>
<td>46 mg</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>92 mg</td>
<td>4.7</td>
</tr>
<tr>
<td>Metformin(^{27})</td>
<td>No diabetes, BMI ≥ 24 (≥ 22 in Asian Americans), elevated fasting glucose or impaired glucose tolerance</td>
<td>850 mg BID</td>
<td>2.3</td>
</tr>
<tr>
<td>Pramlintide(^{28})</td>
<td>No diabetes, BMI 30–50</td>
<td>120 μg TID</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>360 μg TID</td>
<td>6.8</td>
</tr>
<tr>
<td>Canagliflozin(^{29})</td>
<td>No diabetes, BMI 27–50</td>
<td>50 mg</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>300 mg</td>
<td>1.4</td>
</tr>
<tr>
<td>Semaglutide(^{30})</td>
<td>No diabetes, BMI ≥ 30, or ≥ 27 with at least 1 obesity-associated comorbidity</td>
<td>2.4 mg/week</td>
<td>12.4</td>
</tr>
<tr>
<td>Semaglutide(^{31})</td>
<td>Diabetes, BMI ≥ 27</td>
<td>2.4 mg/week</td>
<td>6.2</td>
</tr>
</tbody>
</table>

BID = twice a day; ER = extended release; TID = three times a day; TBWL = total body weight loss
the trials, and all studies included lifestyle modifications in addition to pharmacotherapy.

■ IN PATIENTS WITH DIABETES

Weight loss can help patients improve glycemic control, and certain diabetes drugs have the added benefit of helping patients lose weight.

GLP-1 receptor agonists and SGLT-2 inhibitors are great choices for patients with high BMI and diabetes, as they lower hemoglobin A1C and carry a low risk of hypoglycemia. Some agents—liraglutide, semaglutide, dulaglutide, empagliflozin, canagliflozin, and dapagliflozin—offer cardiovascular benefits in these already high-risk patients. Use is limited by high copays. Further, most of the GLP-1 drugs are injectable and have frequent adverse gastric effects. Semaglutide is an ideal choice because it has been shown to produce more weight loss than others in this category, requires only weekly injection, and is the only GLP-1 receptor agonist available in oral formulation.

SGLT-2 inhibitors are usually well tolerated, with frequency of urination being the most commonly reported adverse effect. Urinary tract and vaginal infections are also common in these patients, who are already at risk for infection. Canagliflozin should likely be avoided in patients with known or suspected peripheral artery disease, as it is associated with a modest yet higher risk of amputations. Some studies have shown canagliflozin to be associated with a higher incidence of fractures, making other SGLT-2 inhibitors potentially more suitable for those with osteoporosis or frequent falls.

Metformin is a more affordable option that promotes weight loss, lowers hemoglobin A1C, and has low potential for hypoglycemia. However, metformin has not been shown to provide additional cardiovascular benefits. Metformin should be avoided in patients with severe chronic kidney disease (glomerular filtration rate < 30 mL/min/1.73 m²).

Pramlintide is FDA-approved for type 1 and type 2 diabetes, but its use is limited by multiple daily injections and a tendency to cause hypoglycemia.

GLP-1 receptor analogues (other than liraglutide and semaglutide), SGLT-2 inhibitors, and pramlintide are sometimes prescribed for weight loss in patients without diabetes or another FDA-approved indication. This is not our practice.

Orlistat and naltrexone-bupropion can also be considered in this group since they have been shown to improve insulin sensitivity.

■ IN PATIENTS WITH CARDIOVASCULAR DISEASE

Several antiobesity drugs have shown a positive impact on cardiometabolic risk factors such as blood pressure, waist circumference, insulin sensitivity, and lipid profile. These drugs include liraglutide, semaglutide, naltrexone-bupropion, and orlistat. Naltrexone-bupropion is contraindicated in patients with uncontrolled hypertension but is a suitable choice for this patient group once blood pressure control is established.

Phentermine-topiramate has also been shown to improve cardiometabolic markers, but due to its stimulant effect on the heart, it should be avoided in patients with known or suspected coronary artery disease, to avoid infarction. Lisdexamfetamine should similarly be avoided in these patients. In patients at high risk for cardiovascular disease, such as those with multiple metabolic comorbidities, smoking history, and family history of coronary artery disease, a thorough history and examination should be performed before prescribing stimulants.

■ ONCE A DRUG IS CHosen, FOLLOW-UP IS ESSENTIAL

Once a medication is chosen, patients should be evaluated for weight loss and adverse effects at least monthly for the first 3 months, then at least every 3 months. If the medication is effective (≥ 5% total body weight loss at 3 months), safe, and tolerable, it should be continued indefinitely. Multiple or combination agents, off-label and on-label, are sometimes required for clinically significant weight loss.

■ BEYOND DRUG THERAPY

All patients suffering from obesity should be counseled to adopt a healthful low-calorie
diet, exercise regularly, get adequate sleep, and manage stress.

The clinician should also eliminate or replace the patient’s current obesity-inducing medications with more favorable ones whenever appropriate. For example, the clinician may consider bupropion instead of paroxetine, amitriptyline, nortriptyline, or mirtazapine in patients with depression or anxiety. Second-generation antihistamines can be prescribed instead of first-generation ones.

Beta-blocker use should be limited to those with an indication (such as an arrhythmia). When beta-blockers are indicated, carvedilol and nebivolol are associated with less weight gain.\(^1\,7\)

For contraception, oral contraceptive pills and intrauterine devices should be considered over medroxyprogesterone acetate.\(^1\)

In treating patients with diabetes, metformin, pramlintide, SGLT-2 inhibitors, and GLP-1 receptor agonists should be considered, as they promote weight loss. Thiazolidinediones, sulfonylureas, and insulin can cause patients to gain weight, and thus should be limited to those with specific indications (such as insulin for type 1 diabetes mellitus), those unable to tolerate or afford preferred medications, or those whose blood glucose remains uncontrolled. Basal insulin is more favorable than preprandial or biphasic insulin.\(^1\,7\) Analogue insulins are recommended over human insulin.\(^3\,1\)

When treating patients with chronic inflammatory diseases, disease-modifying anti-inflammatory and biologics are preferred over steroids in patients who tolerate them and are able to afford them.

Bariatric weight loss surgery is indicated in patients who have not achieved a healthy weight through lifestyle changes and who meet one of the following criteria\(^1\,3\,8\):

- BMI 40 kg/m\(^2\) or greater
- BMI 35 kg/m\(^2\) or greater, with obesity-associated complications
- BMI 30 kg/m\(^2\) or greater in patients with diabetes.

A substantial body of evidence has demonstrated that weight loss surgery is more effective in promoting long-term weight loss and in improving associated comorbid conditions than intensive lifestyle modifications and pharmacotherapy.\(^1\) Weight loss surgery also achieves superior glycemic control and reduction of cardiovascular risk factors in patients with diabetes and obesity.\(^3\,0\) However, despite its effectiveness and safety, only 0.5% of eligible patients receive this treatment.\(^3\,1\) The reasons behind this underutilization are not fully understood but likely include an overestimation of the surgical risks and an underestimation of the potential benefits by primary providers, who in turn fail to make an initial recommendation.\(^3\,3\)

Another potential barrier is a lack of knowledge by primary providers regarding bariatric surgery options and qualifying patient characteristics. Lastly, underutilization may also be due to variable coverage for bariatric surgery across insurances.

■ TAKE-HOME POINTS

- Obesity, a chronic disease with devastating health consequences, is exceedingly prevalent and affects certain groups disproportionately, including women, non-Hispanic Blacks, and people with lower education and income.
- The prevalence of obesity has increased in the past 20 years, and it is expected to worsen.
- Obesity is multifactorial and thus difficult to treat with lifestyle modifications alone.
- Pharmacotherapy, as part of a comprehensive plan, can help patients achieve meaningful and lasting obesity control. It can also provide independent health benefits, including decreased cardiovascular risk.
- Despite its benefits, antiobesity drug therapy is significantly underutilized.
- Choosing a drug for weight loss should be an individualized, shared decision-making process that accounts for patients’ preferences, comorbidities, and out-of-pocket expenses.
- A comprehensive antiobesity management plan should also include lifestyle counseling, discontinuation of obesity-inducing medications when possible, and weight loss surgery, when indicated.

■ DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.
REFERENCES


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