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# 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.

**A**NTIOBESITY MEDICATIONS are significantly underprescribed. Only 2% of US adults eligible for obesity pharmacotherapy receive it.<sup>1</sup> 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.<sup>2,3</sup> 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 ARE HIGH AND GETTING HIGHER

Obesity (body mass index [BMI]  $\geq 30$  kg/m<sup>2</sup>) affects 42.4% of US adults, or more than 107 million people, and 9.2% of US adults have severe obesity (BMI  $\geq 40$  kg/m<sup>2</sup>).<sup>2,4</sup> These rates have increased dramatically since 1999, when 30.5% of Americans were obese and 4.7% were severely obese,<sup>2</sup> and they continue to increase, so that it is now estimated that 51% of US adults will be obese by 2030.<sup>5</sup>

The prevalence of obesity is similar in both sexes, but women are more likely to be severely obese (11.5% vs 6.9%).<sup>4</sup> Young, middle-aged, and older adults all have similar obesity rates. The obesity rate in non-Hispanic Black people is 49.6%, which is higher than in Hispanic people (44.8%), non-Hispanic White people (42.2%), and non-Hispanic Asian people (17.4%). Rates of severe obesity are 13.8% in Black people, 9.3% in non-Hispanic White people, 7.9% in Hispanic people, and 2% in non-Hispanic Asian people.<sup>4</sup>

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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.<sup>6</sup> Rates also decrease with college education: 27.8% in college graduates vs 40% in nongraduates.<sup>6</sup>

### ■ ADVERSE EFFECTS ON HEALTH

Obesity is a chronic disease characterized by a long-term positive energy balance resulting in excess adiposity.<sup>3</sup> 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 gastroesophageal 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.<sup>3</sup>

### ■ 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.<sup>7</sup>

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.<sup>6,7</sup> 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.<sup>1,5,8–11</sup>

### ■ CHOOSING THE RIGHT DRUG

Pharmacotherapy is indicated in patients with a BMI of 30 kg/m<sup>2</sup> or higher, or 27 kg/m<sup>2</sup> or higher with obesity-associated complications in whom a healthy low-calorie diet and regu-

lar physical activity have failed to achieve a healthy weight.<sup>7</sup> 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.

**By 2030,  
51% of US adults  
may be obese**

**TABLE 1**
**Drugs approved for long-term treatment of obesity**

Drug and class	Ideal candidates	Adverse effects	Contraindications <sup>a</sup>	Average wholesale price <sup>b</sup>
<b>Liraglutide</b> <b>Semaglutide</b> (GLP-1 receptor agonist)	Patients with coronary artery disease, prediabetes, and diabetes	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.	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.	Liraglutide \$1,619  Semaglutide \$1,022
<b>Naltrexone-bupropion</b> (opioid receptor antagonist and DNRI)	Patients with depression, those interested in smoking cessation, and those with food addiction and strong cravings	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.	Uncontrolled hypertension, seizures, anorexia, bulimia, drug or alcohol withdrawal, or chronic opioid use.	\$365
<b>Orlistat</b> (lipase inhibitor)	Patients who do not want to take a systemic drug, or patients who eat a moderate- or high-fat diet	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, cholelithiasis, nephrolithiasis.	None, but not recommended for patients with malabsorption (eg, after gastric bypass surgery).	\$108
<b>Phentermine-topiramate ER<sup>c</sup></b> (sympathomimetic amine and GABA receptor modulator)	Patients with chronic migraines	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.	Uncontrolled anxiety or depression, cardiovascular disease, uncontrolled hypertension, hyperthyroidism, glaucoma, and history of substance dependence.	\$239

<sup>a</sup>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.

<sup>b</sup>Lexicomp average wholesale price for 30-day supply of maximum doses as of May 2021.

<sup>c</sup>A controlled substance.

DNRI = dopamine-norepinephrine reuptake inhibitor; ER = extended release; GABA = gamma aminobutyric acid; GLP-1 = glucagon-like protein-1

TABLE 2

## Other drugs used for treating obesity

Drug and class	Ideal candidates	Side effects	Contraindications <sup>a</sup>	Average wholesale price <sup>b</sup>
<b>Lisdexamfetamine<sup>c</sup></b> (amphetamine prodrug)	Patients with attention deficit hyperactivity disorder	Insomnia, irritability, anxiety, dry mouth, increased heart rate and blood pressure. Controlled substance with theoretical potential for abuse and dependence.	None, but we recommend against using in patients with cardiovascular disease.	\$402
<b>Phentermine<sup>d</sup></b> (sympathomimetic amine)	N/A	Headaches, increased blood pressure and heart rate, irritability, insomnia, constipation, diarrhea, impotence, dizziness. Controlled substance with theoretical potential for abuse and dependence. Serious but rare: pulmonary hypertension, valvular disease.	Uncontrolled anxiety and hypertension, cardiovascular disease, hyperparathyroidism, glaucoma, and history of drug dependence.	\$21.30
<b>Topiramate<sup>e</sup></b> (GABA receptor modulator)	Patients with chronic migraines	Insomnia, xerostomia, constipation, paresthesias, dizziness, anxiety, depression, drowsiness, language and memory impairments. Very rare: seizures with rapid discontinuation.	Hyperthyroidism, glaucoma.	\$10
<b>Metformin<sup>e,f</sup></b> (biguanide)	Patients with diabetes and prediabetes	Diarrhea, nausea, abdominal pain. Serious but rare: lactic acidosis.	Severe chronic kidney disease.	\$5
<b>Pramlintide<sup>e,f</sup></b> (amylin analogue)	Patients with type 1 or type 2 diabetes	Hypoglycemia, headaches, nausea, vomiting.	Gastroparesis and hypoglycemic unawareness.	\$694
<b>SGLT-2 inhibitors<sup>e,f</sup></b>	Patients with type 2 diabetes, hypertension, heart failure, cardiovascular disease, diabetic kidney disease	Genitourinary infections, hypovolemia, increased low-density lipoprotein cholesterol, and hyperkalemia. Serious but rare: diabetic ketoacidosis, bone fractures, amputations, Fournier gangrene.	Severe chronic kidney disease and ketogenic diet (concern for euglycemic ketoacidosis).	\$600–\$700

<sup>a</sup> All antiobesity medications are contraindicated in pregnancy except for metformin in patients with diabetes. Because of the potential teratogenic effect of many antiobesity medications, a pregnancy test should be obtained before prescribing, and women should be counseled on effective birth control.

<sup>b</sup> Lexicomp average wholesale price for 30-day supply of maximum doses as of May 2021.

<sup>c</sup> Approved for treatment of binge-eating disorder.

<sup>d</sup> Approved for short-term use; however, it is often prescribed long-term in US states where this regulation is not strictly enforced.

<sup>e</sup> Off-label use.

<sup>f</sup> Occasionally prescribed for patients who do not have diabetes or another US Food and Drug Administration indication for their use; however, this is not our practice.

GABA = gamma aminobutyric acid; SGLT-2 = sodium-glucose cotransporter-2

**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 distur-

bance. 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

Antioesity 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.

Depending on insurance coverage, other GLP-1 receptor agonists may be more suitable for patients with diabetes and obesity.

### Intermediate cost

**Naltrexone-bupropion**, average wholesale price \$365, has no generic option and is not usually covered by insurance. However, its individual components are available as generic formulations and can be prescribed separately at much lower cost (average wholesale price \$50 for naltrexone 25 mg plus bupropion XL 300 mg). Bupropion can also be prescribed alone for obesity management and is usually covered by insurance (average wholesale price \$16.50).

**Phentermine-topiramate**, average wholesale price \$239, has no generic formulation and is usually not covered by insurance. Its in-

dividual components are available generically and can be prescribed separately, in combination or individually (average wholesale price \$21.30 for phentermine 18.75 mg plus topiramate 100 mg).

Despite the listed prices, both phentermine and topiramate can be bought very inexpensively at certain retailers at less than \$10 per month. Phentermine-topiramate can be used alternatively with phentermine alone to reduce overall costs.

Phentermine is FDA-approved for short-term use only—3 months of therapy with 6 months between courses. This is not strictly enforced in all US states. Phentermine is the most commonly prescribed antioesity drug in the United States.<sup>5</sup>

**Orlistat**, average wholesale price \$108, has no generic formulation and often is not covered by insurance. It is available over the counter at a lower dose.

**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.<sup>10–29</sup> Of note, not all available dosages of the medications today were included in

Obesity is multifactorial and thus is difficult to treat with lifestyle modifications alone



TABLE 3

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

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

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 m<sup>2</sup>).

**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 lra-

glutide 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 ( $\geq 5\%$  total body weight loss at 3 months), safe, and tolerable, it should be continued indefinitely.<sup>7,30</sup> 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

Multiple agents or combination agents, off-label and on-label, are sometimes required for clinically significant weight loss

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.<sup>1,7</sup>

For contraception, oral contraceptive pills and intrauterine devices should be considered over medroxyprogesterone acetate.<sup>1</sup>

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.<sup>1,7</sup> Analogue insulins are recommended over human insulin.<sup>31</sup>

When treating patients with chronic inflammatory diseases, disease-modifying antirheumatics 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 though lifestyle changes and who meet one of the following criteria<sup>1,30</sup>:

- BMI 40 kg/m<sup>2</sup> or greater
- BMI 35 kg/m<sup>2</sup> or greater, with obesity-associated complications
- BMI 30 kg/m<sup>2</sup> 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.<sup>32</sup> Weight loss surgery also achieves superior glycemic control and reduction of cardiovascular risk factors in patients with diabetes and obesity.<sup>30</sup> However, despite its effectiveness and safety, only 0.5% of eligible patients receive this treatment.<sup>33</sup> 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.<sup>33</sup>

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.

**Weight loss surgery can result in superior glycemic control and reduction of cardiovascular risk factors in patients with diabetes and obesity**



## REFERENCES

- Velazquez A, Apovian CM. Updates on obesity pharmacotherapy. *Ann N Y Acad Sci* 2018; 1411(1):106–119. doi:10.1111/nyas.13542
- United States Census Bureau. Quick Facts United States. Accessed March 25, 2021. [www.census.gov/quickfacts/fact/table/US/PST045219](http://www.census.gov/quickfacts/fact/table/US/PST045219)
- Jastreboff AM, Kotz CM, Kahan S, Kelly AS, Heymsfield SB. Obesity as a disease: the Obesity Society 2018 position statement. *Obesity* 2019; 27(1):7–9. doi:10.1002/oby.22378
- Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. *NCHS Data Brief* 2020 Feb;(360):1–8. <https://www.cdc.gov/nchs/data/data-briefs/db360-h.pdf>
- Bersoux S, Byun TH, Chaliki SS, Poole KG. Pharmacotherapy for obesity: what you need to know. *Cleve Clin J Med* 2017; 84(12):951–958. doi:10.3949/ccjm.84a.1609
- Ogden CL, Fakhouri TH, Carroll MD, et al. Prevalence of obesity among adults, by household income and education — United States, 2011–2014. *MMWR Morb Mortal Wkly Rep* 2017; 66(50):1369–1373. doi:10.15585/mmwr.mm6650a1
- Apovian CM, Aronne LJ, Bessen DH, et al. Endocrine Society. Pharmacological management of obesity: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2015; 100(2):342–362. doi:10.1210/jc.2014-3415
- Srivastava G, Apovian CM. Current pharmacotherapy for obesity. *Nature Reviews Endocrinol* 2018; 14(1):12–24. doi:10.1038/nrendo.2017.122
- Crawford AR, Alamuddin N, Amaro A. Cardiometabolic effects of anti-obesity pharmacotherapy. *Curr Atheroscler Rep* 2018; 20(4):18. doi:10.1007/s11883-018-0719-9
- Wilding JPH, Batterham RL, Calanna S. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med* 2021; 384(11):989. doi:10.1056/NEJMoa2032183
- Davies M, Færch L, Jeppesen OK. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet* 2021;397(10278): 971–984. doi:10.1016/S0140-6736(21)00213-0
- Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. *JAMA* 2015; 314(7):687–699. doi:10.1001/jama.2015.9676
- Pi-Sunyer X, Astrump A, Fujioka K, et al; SCALE Obesity and Prediabetes NN8022-1839 Study Group. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med* 2015; 373(1):11–22. doi:10.1056/NEJMoa141189
- Wadden TA, Hollander P, Klein S, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes (Lond)* 2013; 37(11):1443–1451. doi:10.1038/ijo.2013.120
- Hollander P, Gupta AK, Plodkowski R, et al; COR-Diabetes Study Group. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. *Diabetes Care* 2013; 36(12):4022–4029. doi:10.2337/dc13-0234. Erratum in: *Diabetes Care* 2014; 37(2):587.
- Greenway FL, Fujioka K, Plodkowski RA, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicenter, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2010; 376(9741):595–605. doi:10.1016/S0140-6736(10)60888-4
- Apovian CM, Aronne L, Rubino D, et al; COR-II Study Group. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity (Silver Spring, MD)* 2013; 21(5):935–943. doi:10.1002/oby.20309
- Wadden TA, Foreyt JP, Foster GD, et al. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity (Silver Spring, MD)* 2011; 19(1):110–120. doi:10.1038/oby.2010.147
- Davidson MH, Hauptman J, DiGirolamo M, et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. *JAMA* 1999; 281(3):235–242. doi:10.1001/jama.281.3.235
- Hauptman J, Lucas C, Boldrin MN, Collins H, Segal KR. Orlistat in the long-term treatment of obesity in primary care settings. *Arch Fam Med* 2000; 9(2):160–167. doi:10.1001/archfam.9.2.160
- Hollander PA, Elbein SC, Hirsch IB, et al. Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. *Diabetes Care* 1998; 21(8):1288–1294. doi:10.2337/diacare.21.8.1288
- Allison DB, Gadde KM, Garvey WT, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity (Silver Spring, MD)* 2012; 20(2):330–342. doi:10.1038/oby.2011.330
- Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011; 377(9774):1341–1352. doi:10.1016/S0140-6736(11)60205-5. Erratum in: *Lancet* 2011; 377(9776):1494.
- Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUENCE): a randomized, placebo-controlled, phase 3 extension study. *Am J Clin Nutr* 2012; 95(2):297–308. doi:10.3945/ajcn.111.024927
- Aronne LJ, Wadden TA, Peterson C, Winslow D, Odeh S, Gadde KM. Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. *Obesity* 2013; 21(11):2163–2171. doi:10.1002/oby.20584
- McElroy SL, Hudson JI, Mitchell JE, et al. Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge-eating disorder: a randomized clinical trial. *JAMA Psychiatry* 2015; 72(3):235–246. doi:10.1001/jamapsychiatry.2014.2162
- Diabetes Prevention Program Research Group 1. Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. *Diabetes Care* 2012; 35(4):731–737. doi:10.2337/dc11-1299
- Smith SR, Aronne LJ, Burns CM, et al. Sustained weight loss following 12-month pramlintide treatment as an adjunct to lifestyle intervention in obesity. *Diabetes Care* 2008; 31(9):1816–1823. doi:10.2337/dc08-0029
- Bays HE, Weinstein R, Law G, Canavatchel W. Canagliflozin: effects in overweight and obese subjects without diabetes mellitus. *Obesity (Silver Spring, MD)* 2014; 22(4):1042–1049. doi:10.1002/oby.20663
- American Diabetes Association. 8. Obesity management for the treatment of type 2 diabetes: standards of medical care in diabetes—2020. *Diabetes Care* 2020; 43(suppl 1):S89–S97. doi:10.2337/dc20-S008
- American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2020. *Diabetes Care* 2020; 43(suppl 1): S98–S110. doi:10.2337/dc20-S009
- Sudlow AC, le Roux CW, Pournaras DJ. Review of advances in anti-obesity pharmacotherapy: implications for a multimodal treatment approach with metabolic surgery. *Obes Surg* 2019; 29(12):4095–4104. doi:10.1007/s11695-019-04206-7
- Campos GM, Khoraki J, Browning MG, Pessoa BM, Mazzini GS, Wolfe L. Changes in utilization of bariatric surgery in the United States from 1993 to 2016. *Ann Surg* 2020; 271(2):201–209. doi:10.1097/SLA.0000000000003554

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