

# Overweight and Obesity Management Strategies

Scott Kahan, MD, MPH

**O**besity is a chronic medical condition that requires a comprehensive approach for successful management. Although all affected patients should receive counseling on nutrition, physical activity, and behavioral changes, those who do not respond to lifestyle interventions may benefit from pharmacotherapy, medical devices, or bariatric surgery. There are many new options for managing obesity that managed care clinicians should consider, including tools, resources, and published guidance to support behavioral counseling and obesity treatment in primary care. This article reviews the standards of care and recommendations for the management of obesity.

In 2013, the American College of Cardiology (ACC), the American Heart Association (AHA), and the Obesity Society (TOS) published a joint guideline that provided evidence-based recommendations for comprehensive lifestyle interventions and a model for managing obesity in primary care.<sup>1</sup> In 2015, additional guidelines focusing on obesity pharmacotherapy were published by the Endocrine Society.<sup>2</sup> A 2013 treatment algorithm created by the American Association of Clinical Endocrinologists (AACE) and a 2016 position statement from the American Diabetes Association (ADA) provided recommendations for managing obesity in patients with or at risk for type 2 diabetes (T2D).<sup>3,4</sup> Since 2012, the FDA has approved 4 new medications for chronic management of obesity – the first medications approved for obesity in nearly 13 years: lorcaserin (Belviq), phentermine-topiramate extended release (ER) (Qsymia), naltrexone-bupropion sustained release (SR) (Contrave), and liraglutide 3.0 mg (Saxenda).<sup>5,9</sup> In 2015, 3 minimally invasive devices for the treatment of obesity were approved, including 2 intragastric balloons (Orbera, ReShape) and an implanted vagal nerve stimulator (Maestro Rechargeable System).<sup>10-12</sup> Bariatric surgery patterns have recently changed, with the use of vertical

## Abstract

Comprehensive lifestyle interventions, including nutrition, physical activity, and behavioral therapy, are the foundation for clinical obesity management. New tools and treatment approaches help clinicians provide these interventions and support weight management in the primary care setting. Escalating treatment, such as using pharmacotherapy, medical devices, or bariatric surgery, are important considerations for appropriate patients who do not respond to lifestyle counseling. This article provides a review of obesity treatment in primary care and managed care settings. Principles of lifestyle changes for weight management, behavioral counseling, and options for pharmacotherapy, medical devices, and bariatric surgery are discussed.

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For author information and disclosures, see end of text.

sleeve gastrectomy (VSG) increasing substantially and laparoscopic adjustable gastric band sharply declining.<sup>13</sup>

### Comprehensive Lifestyle Interventions

Effective communication about obesity between healthcare professionals and patients is an important step toward improved care.<sup>14</sup> A diagnosis of obesity is a strong predictor of receiving counseling and an obesity treatment plan.<sup>14,15</sup> Data from the 2005 to 2008 National Health and Nutritional Examination Survey found that when patients were informed of their overweight or obesity status, they were significantly more likely to desire to lose weight, attempt to lose weight, and lose at least 5% of their body weight, compared with patients who were not informed of their excess weight status.<sup>16,17</sup> Moreover, a systematic review suggests that primary care provider (PCP) involvement in obesity counseling has a positive impact on weight-management behaviors and goals.<sup>18</sup> Since 2003, the US Preventive Services Task Force (USPSTF) has recommended that PCPs screen for obesity by measuring body mass index (BMI); however, just a minority of patients are appropriately screened for obesity, diagnosed with obesity, and documented with this diagnosis in their health records.<sup>19-21</sup> In the 2005 National Ambulatory Medical Care survey, only 29% of patients with obesity received a diagnosis and 18% received weight-reduction counseling.<sup>9</sup> Even patients with severe obesity frequently fail to receive weight-management counseling and support.<sup>22,23</sup>

Obesity can be a sensitive topic, and clinicians may feel unqualified or uncomfortable to initiate discussions. Further, few pharmacists or physicians have formal training in obesity treatment and counseling. A Strategies to Overcome and Prevent (STOP) Obesity Alliance and Harris Interactive survey found that among 290 PCPs, nearly 80% did not have training in obesity,<sup>24</sup> and a review of obesity coverage in the US Medical Licensing Examinations (USMLE) showed few questions pertaining to obesity management or treatment.<sup>25</sup>

Initiating productive conversations about obesity that do not shame or embarrass patients improves the doctor-patient relationship and supports patient weight-management goals.<sup>26,27</sup> One simple strategy to promote positive discussions is to avoid stigmatizing words such as “obese” because these may trigger negative emotional reactions. People-first language, such as referring to a “patient with obesity,” rather than condition-first language (an “obese patient”), is preferred.<sup>28,29</sup> The *American Medical Association Manual of Style* states to avoid labeling (and

thus equating) people with their disabilities or diseases.<sup>30</sup> The STOP Obesity Alliance has created a practical tool called “Why Weight? A guideline to discussing obesity & health with your patients” ([www.whyweightguide.org](http://www.whyweightguide.org)) that helps clinicians start productive conversations about weight management. Another important aspect of providing care for affected patients is ensuring that office equipment can accommodate patients with excess weight and that the office environment is supportive for productive doctor-patient interactions.<sup>28</sup>

Barriers to obesity management, such as lack of tools, training, and time, as well as inadequate reimbursement, are being addressed. Medicare began reimbursing for obesity counseling in primary care in 2011—although reimbursement is limited to services provided by PCPs, not specialists or allied health professionals. Clinicians can be reimbursed for a maximum of 22 visits (15 minutes each) over one year, with reimbursement in the second 6 months contingent on patients achieving at least a 3-kg weight loss.<sup>29</sup> Educational resources to help PCPs acquire obesity counseling and management skills have expanded, as well. A team-based approach with contributions from dietitians, nurse specialists, and obesity specialists, as well as commercial programs, such as Weight Watchers, can extend the reach of a PCP and relieve time pressures on busy clinicians.<sup>31</sup> In addition, productive discussions about obesity do not need to be lengthy to be effective.<sup>28</sup>

Since 2003, the USPSTF has recommended that clinicians offer comprehensive lifestyle interventions to patients with a BMI of 30 kg/m<sup>2</sup> or higher.<sup>19,20</sup> The ACC/AHA/TOS guidelines recommend programs led by trained interventionists that provide at least 14 sessions over 6 months.<sup>32</sup> The ADA recommends at least 16 sessions over 6 months for patients with excess weight and T2D.<sup>3</sup> Additional participation in a comprehensive weight-loss maintenance program or ongoing counseling is recommended in order to minimize weight regain.<sup>3,32</sup> Despite these recommendations and consistent data supporting the benefit of counseling, some studies suggest that weight-related counseling may be declining.<sup>33</sup> Providers should increase the frequency and intensity of counseling for patients with obesity and those at risk for obesity.

Components of behavioral therapy include goal setting, self-monitoring, addressing barriers, problem-solving, positive reinforcement, and ongoing support.<sup>20</sup> Motivational interviewing can improve behavioral counseling in patients who are ambivalent about behavior change and has been shown to improve weight-loss outcomes.<sup>34-36</sup> This technique is a collaborative, patient-

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centered process that focuses on assisting and guiding patients to build internal motivation and supporting personalized problem-solving to achieve behavior change.<sup>28</sup>

The 5 As strategy, initially developed for smoking cessation counseling, has been adapted by several groups for behavioral therapy of obesity.<sup>37-39</sup> The Society of Behavioral Medicine has developed a multidisciplinary 5As model in which the healthcare professional provides brief counseling and arranges additional care for patients with psychosocial issues or comorbid conditions.<sup>29</sup> The components are:

- ◆ **Assess:** Measurement of BMI, identification of comorbid conditions known to interfere with weight loss (depression, sleep disorders, chronic pain, stress, binge eating), and discussion about readiness for change.
- ◆ **Advise:** Counseling about the benefits of weight loss and behavioral changes.
- ◆ **Agree:** Establish weight-loss goals that are specific, measurable, attainable, relevant, and time-based (SMART). Establishing attainable weight-loss goals is important because patients often expect to lose far more weight than is reasonable.<sup>40</sup> Self-monitoring of weight, nutrition, and/or physical activity is a key part of maintaining positive behavioral changes.
- ◆ **Assist:** A problem-solving process in which barriers to achieving weight loss are identified and resolved. Identifying the underlying causes of, and contributors to, weight problems in individual patients can help them achieve weight loss.
- ◆ **Arrange:** Based on assessment of the patient's progress, patients may be referred to more intensive or specialized treatment. Referral options include dietitians, hospital-based programs, behavioral medicine providers, and evidenced-based commercial weight-loss programs.<sup>29</sup>

The primary target for behavior change is to create an energy deficit by addressing caloric intake and energy expenditure.<sup>1</sup> A caloric reduction of 500 to 750 calories per day can achieve weight loss of approximately 1 to 1.5 lb/week in the short term, with the rate of weight loss decreasing asymptotically over time.<sup>41</sup> This typically translates to a rule-of-thumb caloric intake goal of 1200 to 1500 calories/day for women and 1500 to 1800 calories/day for men.<sup>1,3</sup> Clinically meaningful weight loss can occur across a broad range of macronutrient compositions.<sup>19-21</sup> For example, in one study that exam-

ined 4 diets that varied in content of fat (20%-40%), protein (15%-25%), and carbohydrates (35%-65%), there was similar weight loss and no difference in hunger or satiety ratings among the interventions over 2 years. Thus, a key factor of diet choice is patient preference.<sup>1</sup> However, there is a wide inter-individual variation in weight loss between groups, and there is mounting evidence that certain physiologic factors affect responsiveness to different dietary patterns. For example, patients with insulin resistance tend to respond better to either lower carbohydrate or lower glycemic index dietary patterns compared with patients with normal insulin sensitivity.<sup>42-44</sup>

To address energy expenditure, aerobic physical activity on par with at least 30 minutes of brisk walking on most days of the week ( $\geq 150$  minutes/week) is recommended to help achieve an energy deficit. Higher levels of activity, 200 to 300 minutes/week, are recommended over the long term in order to prevent weight regain.<sup>1</sup> Strength and resistance training stimulate muscle production, which improves metabolism. Finding exercises that fit individual limitations, abilities, and preferences and/or supervision by an experienced fitness instructor with a prescribed exercise program can help improve adherence.<sup>22</sup>

Commercial weight-loss programs that have evidence to support their efficacy and safety are an option to provide a comprehensive lifestyle program.<sup>1,3</sup> However, the amount of weight loss that patients can expect to achieve with these programs is likely less than they expect.<sup>45</sup> A recent meta-analysis of 13 randomized controlled trials (RCTs) found that, among the most popular programs, weight loss at one year compared with controls ranged from 2.6% for Weight Watchers to 4.9% for Jenny Craig. Few commercial programs had long-term data available.<sup>46</sup>

Very low calorie diets (<800 kcal/day) are viable options in some patients but should be provided only within the context of a high-intensity lifestyle intervention and close medical monitoring.<sup>3,32</sup> Patients should be supervised by trained practitioners in a medical care setting because rapid weight loss has the potential for medical complications, such as gallstones and electrolyte disturbances.<sup>3,32,47</sup> Total meal replacement with a very low calorie diet over 3 months has the potential to achieve 10% to 15% weight loss, but it may result in substantial weight regain, especially in the absence of a maintenance program.<sup>3</sup> These diets are typically prescribed in medical settings, but several commercial options are also available.<sup>46</sup>

Pharmacists can be actively involved in weight-management counseling,<sup>48</sup> which can include collaboration among physicians, dietitians, and other healthcare pro-

viders, and referring patients to providers for care as needed; monitoring of vital signs; motivational behavioral counseling and education; nutrition and exercise support; and medication monitoring. It is conceivable that active involvement of pharmacists can address some of the gaps identified with PCP obesity management.

### Impact of Weight Loss on Comorbid Conditions

Numerous comorbid conditions are associated with obesity. Expected improvement of a comorbid condition can be a potent motivator for behavioral change and weight loss.<sup>29</sup> As little as 3% sustained body weight loss improves glycemic control, triglycerides, and risk of T2D.<sup>1</sup> Weight loss of 5% to 10% further reduces hyperglycemia and triglycerides, and it improves blood pressure, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol ranges, as well as liver function and fatty liver disease; it also reduces functional limitations, chronic pain, and the need for hypertension, T2D, and lipid medications in most patients.<sup>1,2,32</sup> Many other conditions, such as obstructive sleep apnea and osteoarthritis, along with the risk for several cancers, can also be improved, reversed, or prevented with moderate sustained weight loss.<sup>1,2</sup> T2D is a particularly relevant example.

The Diabetes Prevention Program Research Group found that moderate lifestyle intervention led to 7% weight loss over 6 months, with about half this weight loss being maintained over 4 years. The intervention led to 58% decreased progression to T2D compared with placebo and nearly 40% decreased progression to T2D compared with metformin therapy.<sup>49</sup> For every kilogram of weight loss, there was a 16% reduced risk of developing T2D.<sup>50</sup> Moreover, a reduced risk for T2D was maintained for more than a decade, despite much of the weight being regained over time.<sup>51</sup> In a trial that included lifestyle intervention based on the Diabetes Prevention Program combined with an older medication for weight control, orlistat, lifestyle intervention plus medication led to twice the weight loss and a 45% risk reduction for progression to T2D in patients with impaired glucose tolerance compared with lifestyle intervention plus placebo.<sup>52</sup>

### Pharmacotherapy

Pharmacotherapy is indicated as an adjunct to behavioral counseling in patients with a BMI of 30 kg/m<sup>2</sup> or higher and those with a BMI of 27 kg/m<sup>2</sup> or higher with at least 1 obesity-related comorbidity (eg, T2D, hypertension, hyperlipidemia).<sup>2,5-8,53</sup> Similar to treatments for other behavior-related health conditions, such as phar-

macotherapy for hypertension or T2D, the benefits of medication are most often lost if the treatment is discontinued. Thus, patients who respond to treatment, often defined as at least a 5% weight loss after 3 months of treatment, should continue the medication, with goals of continuous weight loss and maintenance of lost weight.<sup>2</sup> For this reason, although short-term medications may be useful in some cases, this article will only review those medications approved by the FDA for long-term use. Five medications are currently approved for long-term obesity treatment; several others are approved for short-term (<12 weeks) use.

### Orlistat

Orlistat is a pancreatic lipase inhibitor that decreases the absorption of ingested fat.<sup>2</sup> The medication is dosed thrice-daily with meals.<sup>53</sup> It was initially approved by the FDA in 1999 and has also since been approved for OTC use at half-dose (60 mg), branded as Alli.<sup>54</sup>

Several studies have shown orlistat to help with weight loss and chronic weight management; of these, the most notable is the XENDOS trial, which showed orlistat plus behavioral counseling led to meaningful weight loss through 4 years of therapy, with approximately twice the weight loss compared with counseling plus placebo. Among 3305 patients randomized to orlistat or placebo, far more patients in the orlistat group completed the trial (52%) compared with the placebo group (34%), and weight loss in the orlistat group at year 1 (10.6 kg) and year 4 (5.8 kg) significantly exceeded placebo (6.2 kg and 3.0 kg, respectively). Similarly, far more subjects taking orlistat lost at least 5% of their body weight at both 1 year (72.8% vs 45.1%) and 4 years (52.8% vs 37.3%) of treatment. As described above, risk of progression to T2D was reduced by 45% in patients with baseline impaired glucose tolerance and 37% overall in the orlistat group compared with the placebo group. Decrease in waist circumference and lipids were also significantly noted.<sup>52</sup>

Patients using orlistat should be counseled on the risk of gastrointestinal (GI) adverse events (AEs), such as diarrhea, flatulence, or other GI complaints, when consuming large amounts of fat while taking the medication. Because orlistat binds to fat-soluble vitamins, patients are at risk for deficiencies; thus, they should be advised on a nutritionally balanced, reduced-fat, and reduced-calorie diet, and they should take a multivitamin that contains fat-soluble vitamins separately from the medication (at bedtime). Orlistat should not be used in patients with cholestasis or chronic malabsorption syndromes. As

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with all obesity medications, orlistat is contraindicated in pregnancy and should be used with caution with lactation. Further warnings include coadministration with cyclosporine, which leads to a decrease in the absorption of cyclosporine and an increased level of urinary oxalate; this may predispose patients to kidney stones.<sup>53</sup>

### Lorcaserin

Lorcaserin is a selective serotonin 2c (5HT-2c) receptor agonist, which specifically stimulates the 5HT-2c receptors in the appetite center of the brain. As opposed to prior serotonin agonists that were used off-label for weight loss, lorcaserin primarily stimulates the 2c subtype rather than other serotonin receptors in the brain and body, thereby leading to fewer AEs. This mechanism of action primarily increases satiety. Treatment with lorcaserin leads to a nearly 8% body weight loss, on average, in patients completing 1 year of treatment, with far more patients achieving clinically meaningful weight loss compared with placebo (66.4% vs 32.1% lost  $\geq$ 5% body weight; 36.2% vs 13.6% lost  $\geq$ 10% body weight).<sup>55</sup> In responders (described below), the average weight loss exceeds 10%.<sup>56</sup> Several intermediate cardiovascular risk factors, including blood pressure, heart rate, lipids, and glycemic control, improve with the weight loss.<sup>55,57</sup> Patients with T2D had 0.9% glycosylated hemoglobin (A1C) improvement, which is more than expected from moderate weight loss alone and on par with many T2D medications.<sup>45,57</sup> In one study, patients with prediabetes and obesity who were treated with lorcaserin had a 38% lower risk of developing T2D than patients treated with placebo.<sup>58</sup>

Patients who respond to lorcaserin usually do so relatively quickly. Therefore, response to treatment should be evaluated 12 weeks after initiation. If patients lose 5% or more weight from baseline, they will likely continue losing weight, so the medication should generally be continued. In contrast, if patients do not lose at least 5% of initial body weight after 12 weeks, then the treatment should generally be discontinued because there is low likelihood of further weight loss.<sup>56</sup> Thus, patients will know relatively quickly whether the medication is worth continuing for the longer term.

Lorcaserin is classified as a schedule IV substance.<sup>5</sup> Dosing is 10 mg twice-daily and does not require titration. The most common AEs are headache, dizziness, fatigue, nausea, dry mouth, and constipation. In some patients, hypoglycemia may occur when concomitantly taken with blood sugar-lowering agents for diabetes. Lorcaserin is contraindicated during pregnancy and lactation. Caution

is necessary if patients are being treated with serotonergic or anti-dopaminergic medications, which can, rarely, precipitate serotonin syndrome or neuroleptic malignant syndrome. Other warnings include caution in patients with valvular heart disease, congestive heart failure, or psychiatric disorders and those at risk for priapism.<sup>5</sup>

### Phentermine-topiramate ER

The combination of phentermine and topiramate takes advantage of the additive weight loss effects of these 2 agents.<sup>7</sup> Phentermine, a sympathomimetic amine, has been approved for short-term weight loss since 1959; by itself, it decreases appetite and leads to short-term weight loss. Topiramate, which has multiple mechanisms of action, is approved for migraine and seizure prevention. On average, topiramate leads to relatively little weight loss by itself. Together, however, these medications lead to impressive weight loss at low doses.

In the SEQUEL trial, a 2-year evaluation of phentermine-topiramate ER versus placebo, patients treated with the medication lost approximately 10% of body weight, on average, compared with less than 2% weight loss in the placebo group. Patients treated with the medication also had improved cardiometabolic markers, including reduced blood pressure and lipids, and many were able to decrease or discontinue blood pressure or T2D medications. Moreover, progression to T2D was reduced by 76% compared with placebo in patients treated with the high dose of the medication.<sup>59</sup>

In the EQUIP trial, patients with severe obesity (BMI  $\geq$ 35 kg/m<sup>2</sup>) who completed one year of treatment with phentermine-topiramate ER 15/92 lost 14.4% of body weight compared with 2.1% in the placebo group; 83.5% lost at least 5% of body weight, compared with 25.5% in the placebo group, and 67.7% lost at least 10% of body weight compared with 13.0% of those completing placebo treatment.<sup>60</sup> Sub-analysis in patients with extreme obesity (BMI  $>$ 45 kg/m<sup>2</sup>), a population that is rarely studied for nonsurgical weight-loss interventions, showed even greater benefits, with more than 50% of patients who completed the trial losing more than 15% of initial body weight and 28% of patients losing more than 20% of initial body weight.<sup>61</sup>

Notably, the maximum approved dose of phentermine is 37.5 mg and the maximum approved dose of topiramate is 400 mg; therefore, the doses of each medication in this combination treatment are quite low and well-tolerated.<sup>7</sup> Treatment is initiated at 3.75 mg phentermine/23 mg topiramate ER and escalated to

7.5/46 mg after 2 weeks. Responses should be evaluated after 12 weeks at this dose, and treatment should either be escalated to a higher dose or discontinued if patients do not achieve at least a 3% weight loss. The most common AEs are paresthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth. These are usually mild and transient; about 3% of patients on the lower doses and 9% of the patients on the highest dose discontinue the medication due to an AE.<sup>7</sup>

Phentermine-topiramate ER is classified as a schedule IV substance.<sup>7</sup> It is contraindicated during pregnancy and lactation. However, because topiramate is a known teratogen (which can cause cleft lip/palate), pregnancy should be ruled out before starting the medication, and women of childbearing age should use contraception and have monthly pregnancy testing during use (as stipulated by the product's risk evaluation and mitigation strategy). Other contraindications include glaucoma, use of monoamine oxidase (MAO) inhibitor medications, and hyperthyroidism. Additionally, warnings for this medication include a risk for mood disorders, suicidal thoughts, hypoglycemia in patients on some diabetes medications, cognitive impairment, metabolic acidosis, and sleep difficulty. If discontinuation is necessary, patients treated with the highest dose (15/92 mg) require tapering by taking the dose every other day for 1 week before discontinuing; patients taking other doses can discontinue the medication without weaning.<sup>7</sup>

#### **Naltrexone-bupropion SR**

Like phentermine-topiramate ER, the combination of naltrexone and bupropion leads to much greater weight loss than either agent alone.<sup>6</sup> Bupropion, a dopamine and norepinephrine reuptake inhibitor, was initially approved by the FDA in 1989 for the treatment of depression; more recently, it was approved for smoking cessation. By itself, bupropion leads to little weight loss. Naltrexone, an opioid receptor antagonist that has long been used for the treatment of addictions, leads to little weight loss on its own, as well. The combination, however, leads to impressive weight loss, especially when combined with intensive lifestyle counseling.<sup>62</sup> Subjectively, patients generally describe feeling diminished appetite and fewer cravings.<sup>63,64</sup>

In clinical trials, weight loss in subjects who completed 1 year of treatment with naltrexone-bupropion SR was approximately 8.2% of baseline body weight compared with 1.4% with placebo, and several cardiometabolic parameters improved, including lipids and glycemic parameters.<sup>65</sup>

When combined with intensive lifestyle intervention, naltrexone-bupropion SR use led to a 12% weight loss compared with 7% weight loss in the counseling plus placebo group.<sup>66</sup> Patients with T2D completing 1 year of treatment lost about 6% of body weight and had significantly improved glycemic control, including lowering of A1C by 0.6%, compared with 0.1% with placebo.<sup>67</sup> Measures of food cravings were also improved across the clinical trials, which may be related to the effects of naltrexone and/or bupropion in the mesocorticolimbic dopamine system and other brain areas related to reward-driven behaviors.<sup>63</sup>

To best tolerate naltrexone-bupropion SR, treatment is initiated with 1 tablet (8 mg naltrexone/90 mg bupropion) daily for the first week, followed by weekly escalation to a target dose of 4 tablets (32/360 mg), administered as 2 tablets twice-daily, by week 4.<sup>6</sup> Response should be evaluated after 12 weeks on the target dose (which is typically 16 weeks from initiation, accounting for the titration schedule). Treatment should be stopped if patients do not achieve at least 5% weight loss. The most common AEs are nausea, constipation, diarrhea, headache, and vomiting. In most cases, these AEs occur within the first few days or weeks of therapy and, in most cases, resolve soon thereafter.<sup>58</sup> The most common cause of treatment discontinuation was nausea (6%). There is a warning of suicidal thoughts in patients younger than 24 who are taking antidepressants, including bupropion, which also applies to naltrexone-bupropion SR. Other contraindications include uncontrolled hypertension, seizure disorders, chronic opioid pain medication use, and MAO inhibitor use. Naltrexone-bupropion SR is contraindicated in pregnancy and lactation.<sup>6</sup>

#### **Liraglutide 3.0 mg**

Liraglutide 3.0 mg, the most recently approved medication for chronic weight management, was studied and approved for a primary indication of obesity treatment in December 2014.<sup>8</sup> Liraglutide is a glucagon-like peptide-1 receptor agonist that was initially approved in 2010 for T2D treatment, at a maximum dose of 1.8 mg. It has multiple central and peripheral actions that may promote weight loss; the primary effect on weight is believed to be decreased appetite and increased satiety through direct stimulation of the appetite center of the brain.<sup>68</sup> Unlike the other medications described here, liraglutide requires injectable administration, through a small needle delivered subcutaneously to the abdomen, arm, or thigh.<sup>8</sup>

The clinical trials for liraglutide 3.0 mg included both weight loss and weight maintenance studies. In the stud-

ies focusing on weight loss, treatment with liraglutide led to approximately 9% weight loss compared with 3% with placebo in patients completing 1 year of treatment. Nearly two-thirds of patients treated with liraglutide 3.0 mg lost at least 5% of initial body weight, compared with less than one-third in the placebo group, and nearly 15% lost at least 15% of body weight, which approaches the weight loss of some bariatric surgery procedures.<sup>69,70</sup> In patients with prediabetes at baseline, 71% treated with liraglutide no longer had prediabetes at the end of year 1 compared with 37% in the placebo group. At 3 years out, there was nearly an 80% decreased progression to T2D compared with placebo.<sup>71</sup> In a unique trial assessing weight maintenance, subjects initially engaged in a medically monitored diet and lost approximately 6% of body weight within 12 weeks. They were then randomized to either liraglutide 3.0 mg or placebo and followed for one year to evaluate how well they maintained the weight loss. Whereas the placebo group mostly maintained their weight, on average, subjects in the liraglutide group lost an additional 6% of body weight and were much less likely to regain lost weight.<sup>70</sup>

Initiation of treatment includes weekly titration by 0.6 mg/week over 5 weeks, to the target dose of 3.0 mg. Response to treatment should be evaluated after 12 weeks and treatment should be stopped if patients do not achieve at least 4% weight loss. The most common AEs include nausea and gastrointestinal complaints. Hypoglycemia may also occur, particularly in patients on antidiabetic medications, and may be severe in patients concomitantly treated with sulfonylureas or insulin. This medication should not be used in patients with history of medullary thyroid carcinoma, multiple endocrine neoplasia type 2, or acute pancreatitis. Liraglutide 3.0 mg is contraindicated in pregnancy and lactation.<sup>8</sup>

### Considerations for Long-term Use

Obesity is a chronic, likely lifelong, medical condition. Regardless of treatment modality, most patients require long-term treatment and monitoring. In pharmacotherapy, the FDA has approved the newer medications for long-term use, and the standard of care is to continue treatment, as long as patients are receiving benefit. It should be noted that most available medications have been studied for 2 years only (although liraglutide has positive 3-year data and orlistat has positive 4-year data).<sup>52,72</sup> Although many intermediate cardiovascular risk factors are improved by use of these medications, long-term cardiovascular safety has not yet been established. The FDA

has requested noninferiority cardiovascular outcomes trials for each newly approved medication. Long-term data on liraglutide (based on treatment with the 1.8-mg dose, which is approved for diabetes but not obesity) is expected to be published in mid-2016; a preliminary report suggests a sizable cardiovascular benefit.<sup>73</sup> The trials for lorcaserin and naltrexone-bupropion SR are under way, and the trial for phentermine-topiramate ER is still in negotiations with the FDA.<sup>67,74-76</sup> Until the trials are completed, we cannot be certain that treatment with these medications induces a mortality benefit (although few medications in any class have RCT-proven long-term mortality benefits).

### Bariatric Surgery and Medical Devices

Several bariatric surgeries and 5 minimally invasive medical devices are used for the treatment of severe obesity. Bariatric surgery is indicated for patients with BMI of 40 kg/m<sup>2</sup> or higher or for patients with a BMI of 35 kg/m<sup>2</sup> or higher with at least 1 obesity-related comorbidity who have failed conservative treatment.<sup>2,3,32</sup> The most common bariatric surgeries are VSG and Roux-en-Y gastric bypass (RYGB).<sup>77</sup> Long-term data on bariatric surgery are impressive, with average 2-year weight losses of 25% and 32% of body weight for VSG and RYGB, respectively. Additionally, the majority of patients show improvement or resolution in numerous comorbid conditions, including T2D, hypertension, sleep apnea, hyperlipidemia, and others.<sup>78,79</sup> Several studies have shown long-term mortality improvements, as well.<sup>79,80</sup> Perioperative complications with bariatric surgeries in experienced surgical teams have declined and are similar to those seen with other common abdominal surgeries.<sup>81</sup> Because these procedures have been well-documented elsewhere, this discussion will focus on the newly approved medical devices.

In 2015, 3 medical devices were approved by the FDA in addition to the 2 adjustable gastric band devices that have been FDA-approved since 2001. Of the newer options, 2 are variations of the space-occupying gastric balloon and primarily intended to restrict gastric volume, although they may also result in neurohormonal effects.<sup>10,12</sup> The neurohormonal effects occur via cholecystokinin, which delays gastric emptying, causes pyloric constriction, and increases gastric vagal efferent activity; this leads to increased satiety.<sup>82,83</sup>

The Orbera balloon (previously known as the BioEnterics IntraGastric Balloon), approved in August 2015, is a single, spherical silicone device filled with 400 to 700 mL of saline.<sup>10</sup> The device remains in the stomach for

up to 6 months and is then removed endoscopically. A meta-analysis of nearly 4000 patients showed weight losses in the range of 10% to 15% of initial body weight, with relatively few complications, and many studies showed improvements in blood pressure, fasting glucose, A1C, and lipids. Early removal of the balloon was required in 4.2% of patients; fewer than 1% developed severe complications, such as bowel obstruction or perforation.<sup>84-86</sup> Outcomes improve significantly when use of the balloon is combined with ongoing dietary and lifestyle modification counseling.<sup>87</sup> Orbera has also shown durability of weight loss after balloon removal and has been studied for repeated use after removal of the initial balloon.<sup>88,89</sup>

This device has also been studied as a bridge to gastric bypass surgery. In 1 trial, preliminary treatment with the Orbera balloon led to decreased bariatric operative time, improved weight loss, and fewer AEs compared with patients who underwent gastric bypass without prior Orbera treatment.<sup>90</sup>

Orbera is approved for short-term use in patients with a BMI of 30 to 40 kg/m<sup>2</sup> in the presence of at least 1 obesity-associated comorbid condition. It is indicated in patients without previous gastric surgery who do not have active gastric disease (eg, gastritis, ulcers, hiatal hernia); patients should avoid using nonsteroidal anti-inflammatory drugs (NSAIDs) or other gastric irritants during the course of treatment. Nausea and vomiting are the most common AEs; however, they can be managed with antiemetic and antispasmodic medications. Patients should be instructed to eat slowly and thoroughly chew their food to minimize complications.<sup>90</sup>

The ReShape dual balloon device, approved in July 2015, uses 2 connected balloons, filled with 750 to 900 mL of saline, to displace gastric volume and increase satiety.<sup>12</sup> In the REDUCE trial, which included 326 patients with obesity and at least 1 comorbid condition, subjects treated with ReShape who completed the trial lost twice as much weight as completers who received a sham control (7.6%/15.9 lbs vs 3.6%/7.8 lbs, respectively).<sup>91</sup> As expected, several risk factors and comorbid conditions improved, including blood pressure, A1C, and lipids, and treated patients experienced significant improvements in quality of life domains.

Treatment was generally successful and well tolerated. Among 265 balloon insertions, there were 1 failure and 2 replacement procedures, and 24 patients required early retrieval due to non-ulcer intolerance. The most common AEs include nausea, vomiting, and abdominal pain or discomfort. Gastric ulcers may occur, as well.<sup>91</sup> In another clinical trial that evaluated durability of lost weight,

98% of weight lost at the time of balloon removal was maintained at 6 months.<sup>92</sup> Also, like Orbera, ReShape is approved for short-term use in patients with a BMI of 30 to 40 kg/m<sup>2</sup> in the presence of at least 1 obesity-associated comorbid condition and is indicated in patients without previous gastric surgery who do not have active gastric disease (eg, gastritis, ulcers, hiatal hernia); patients should avoid using NSAIDs or other gastric irritants during the course of treatment.<sup>12</sup> An improvement that may be seen with the next generation of gastric balloon devices includes the ability for placement by swallowing rather than endoscopic insertion.<sup>93</sup>

The Maestro Rechargeable System is an electrical neurostimulator that blocks vagus nerve activity between the stomach and the brain. It consists of a surgically implanted, rechargeable electrical pulse generator and 2 wire electrodes that are placed in contact with the vagus nerve trunks near the junction of the stomach and esophagus. The neurostimulator intermittently blocks vagus nerve conduction, thereby affecting stomach emptying and satiety signals to the brain.<sup>11</sup> The ReCharge clinical trial evaluated the effectiveness and safety of this vagal nerve blockade therapy. Among 162 subjects receiving the active device and 77 receiving a sham control device, treatment with the active device led to greater weight loss than the sham control (9.2% vs 6.0% weight loss). There are few AEs, with the most common being heartburn, dyspepsia, and abdominal pain.<sup>94</sup> This device is approved in patients who have failed conservative weight-loss attempts and who either have a BMI of 40 to 45 kg/m<sup>2</sup> or a BMI of 35 to 39.9 kg/m<sup>2</sup> with at least 1 obesity-associated comorbid condition.<sup>11</sup>

## Conclusion

Prevention of obesity is paramount. However, when obesity develops, various clinical treatment modalities should be available to improve weight and minimize comorbid conditions. Lifestyle interventions and counseling are the cornerstones of treatment. When possible, more frequent and intensive multidisciplinary interaction, ideally with a range of clinical providers such as pharmacists, physicians, nurses, dietitians, psychologists, and obesity medicine specialists, leads to greater improvements than less intensive or less frequent counseling. In patients who do not sufficiently respond to lifestyle intervention alone, pharmacotherapy, medical devices, and/or bariatric surgery should be considered. With new tools and the development of multidisciplinary models to provide lifestyle interventions in primary care and

managed care, pharmacists and prescribers can expect their patients to be more successful in achieving realistic weight loss and improvements in comorbid conditions.

**Author affiliation:** Strategies to Overcome and Prevent (STOP) Obesity Alliance, George Washington University, and National Center for Weight and Wellness, Washington, DC.

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**Address correspondence to:** kahan@gwu.edu.

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