



2016

## **Obesity Management: Clinical Review and Update of the Pharmacologic Treatment Options**

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### **Recommended Citation**

Plodkowski, R. A., McGarvey, M. E., Reisinger-Kindle, K., Kramer, B., Nelson, E., Lee, J., & Nguyen, Q. T. (2016). Obesity management: Clinical review and update of the pharmacologic treatment options. *Federal Practitioner*, 33(1), 6-16.

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# Obesity Management: Clinical Review and Update of the Pharmacologic Treatment Options

Raymond A. Plodkowski, MD; Megan E. McGarvey, MD; Keith Reisinger-Kindle; Bradley Kramer; Erik Nelson, DO; Jennifer Lee, DO; and Quang T. Nguyen, DO

The toolbox of medications available for medical weight management is more robust than ever and includes a wide variety of mechanisms of actions and options for patients.

Over the past decade the prevalence of obesity as defined by a body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup> has significantly increased. In the U.S. more than 78 million adults are estimated to be obese.<sup>1</sup> The World Health Organization projects that by 2025 up to half the U.S. population will be obese. Cardiovascular disease (CVD) and diabetes mellitus (DM) are the main comorbid conditions that are complicated by obesity. Initial weight loss of 5% to 10% of total body weight reduces CVD risk factors, prevents or delays the development of type 2 DM (T2DM) and improves the health consequences of obesity.<sup>2</sup>

To date, public health initiatives that have focused on obesity prevention and lifestyle intervention have had marginal success. In recent years, anti-obesity drug therapies have had a limited role in clinical treatment algorithms. In 2013, the American

Medical Association acknowledged obesity as a disease. In turn, this acknowledgement allowed the recognition of anti-obesity drugs as acceptable therapeutic adjuncts to intensive lifestyle intervention that could address the growing obesity epidemic.

In the past, medications for weight reduction were limited. Several that were FDA approved had to be removed from the market due to safety concerns. With few approved options, clinicians often had to resort to off-label use of medications. However, the landscape has changed with 4 new medications gaining recent FDA approval. This review covers older available medications and the newer medications that are now available.

## SYMPATHOMIMETICS

Sympathomimetic drugs have been approved for use as a pharmaco-

logical method to lose weight since 1960. Of the many versions of this drug class that have been available since then, there are 4 major versions available today. These include diethylpropion<sup>3</sup> and benzphetamine,<sup>4</sup> both approved in 1960; phendimetrazine, approved in 1976;<sup>5</sup> phentermine, approved in 1980;<sup>6</sup> and phentermine hydrochloride, approved in 2012.<sup>7</sup> Despite the existence of several other classes of drugs to treat obesity, phentermine remains the most often prescribed weight loss drug in the U.S.<sup>8</sup>

Although the mechanism of action (MOA) of sympathomimetic drugs is not particularly clear, weight loss from these medications is believed to be due to the increase in the release of biogenic amines (mainly norepinephrine, but also possibly dopamine), from storage sites in nerve terminals. It is possible that these drugs slow catecholamine metabolism by inhibiting the actions of monoamine oxidase. The resulting increase in amine availability, particularly in the lateral hypothalamic feeding center, is associated with reduced food intake. Interestingly, injection of these drugs into the ventromedial satiety center does not seem to suppress food intake, and the effects of

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biogenic amines on increasing metabolism does not seem to play a significant role in weight loss in patients on these medications.<sup>9</sup>

Each of these drugs is rapidly absorbed from the gastrointestinal (GI) tract except for phentermine hydrochloride, the newest of the medications in this class. Phentermine hydrochloride is a sublingual tablet that is readily absorbed through the buccal mucosa.<sup>5</sup> All of the drugs in this class are excreted through the kidneys, with varying rates. Each drug's excretion is highly dependent on the pH of the urine—more alkaline conditions result in less excretion and more acidic conditions result in more excretion. As a result, these drugs should be used with caution in patients with renal impairment; however, there are no specific contraindications listed for patients with poor renal function.

The adverse effects (AEs) for this drug class are to be expected from an increase in the release of biogenic amines in the central nervous system (CNS). The most common AEs include palpitations, tremors, restlessness, insomnia, dry mouth, constipation, diaphoresis, changes in libido, and irritability. The more dangerous AEs that have been observed include arrhythmias, hypertension, dependency/abuse, convulsions, acute transient ischemic colitis, and acute urinary retention secondary to increased bladder sphincter tone, transient hyperthyroxemia, and paranoia.<sup>10</sup>

Several contraindications exist for sympathomimetics, including the presence of advanced arteriosclerosis, symptomatic CVD, moderate to severe hypertension, hyperthyroidism, glaucoma, patients in an agitated state, or those with a history of amphetamine abuse. The warnings for prescribers include pulmonary

hypertension and cardiomyopathy secondary to chronic use of sympathomimetics, and valvular heart disease secondary to use of sympathomimetics with additional anorectic agents.

Additional precautions should be considered in those with a history of anxiety/psychosis, those who operate machinery and motor vehicles, and even those with mild hypertension. The data surrounding the effects of sympathomimetics on blood pressure (BP) appears to be conflicting and the relationship does not seem to have been significantly studied in depth to warrant any definitive conclusions. The MOA of this drug class itself is enough to urge caution to prescribers.<sup>11</sup> Special attention should be given to patients with diabetes when using sympathomimetics. A reduction of insulin dose or oral hypoglycemic dose may be necessary in some people with diabetes.

Only diethylpropion is pregnancy category B, whereas the others drugs in this class are pregnancy category X. It has been demonstrated that diethylpropion and benzphetamine are secreted into breastmilk; insufficient data exist to suggest whether or not phentermine and phendimetrazine are present in breastmilk. All drugs in this class should be used in caution with breastfeeding mothers.

Although all 4 drugs are registered as controlled substances, benzphetamine and phendimetrazine are schedule III and phentermine and diethylpropion are schedule IV, despite evidence suggesting the potential for abuse to be extremely low.<sup>12,13</sup> Phentermine has been approved for adults aged > 18 years, phendimetrazine has been approved for those aged > 17 years, diethylpropion has been approved for those aged > 16 years, and benzphetamine has been approved for those aged > 12 years.

There is a wealth of literature surrounding the effectiveness of this drug class for weight loss. One of the longest trials of phentermine was recently conducted as part of the initial component of a FDA study for the newly approved topiramate-phentermine combination. Weight loss at 6 months in the phentermine-only group was significantly higher at -5.8% compared with -1.5% with the placebo group in the last observation carried forward-Intent to treat (LOCF-ITT) analysis.<sup>14</sup> Similarly, a long-term study looking at diethylpropion examined the use of diethylpropion for up to a year vs placebo. Participants administered diethylpropion lost a mean 9.8% of original weight vs 3.7% in the placebo group in the first 6 months alone.<sup>15</sup>

Several meta-analyses and review papers have been authored that examine and analyze the published data on this drug class overall and comparatively within this class. Haddock and colleagues in 2002 reviewed the numerous clinical trials associated with each drug in this class, in addition to several other classes, and found that although each drug demonstrated a significant advantage vs placebo in weight loss, there was not a specific drug that was significantly superior to any of the others.<sup>16</sup>

These results seem to be in relative agreement with additional studies like that published by Suplicy and colleagues, which demonstrated that several sympathomimetics were better than placebo in weight loss, and that there was little difference between the specific drugs in the class.<sup>17</sup> However, it should be noted that as highlighted in a review by Ioannides-Demos and colleagues in 2005, the vast majority of studies that had been performed on this drug class focused on short-term use (< 16 weeks) and none of the

**Table 1. Clinical Trial Results on Pharmacologic Obesity Treatment Options**

Generic Name	Bupropion/ Naltrexone		Liraglutide		Lorcaserin		Orlistat		Phentermine/ Topiramate	
	Maintenance Dose	16 mg/180 mg bid	3 mg qd		10 mg bid		120 mg tid		7.5 mg/46 mg qd	
	Medication	Control	Medication	Control	Medication	Control	Medication	Control	Medication	Control
Age, y	44.4	43.7	45.2	45.0	43.8	43.7	43.2	41.6	51.1	51.2
Gender (% female)	85	85	78.7	78.1	80.5	78.0	79	78	70.0	70.0
Baseline weight, kg	99.7	99.5	106.2	106.2	100.1	100.5	100.5	101.8	102.6	103.3
Baseline waist circumference, cm	108.8	110.0	115.0	114.5	108.9	110.2	n/a	n/a	112.6	113.4
Baseline BMI	36.1	36.2	38.3	38.3	36.0	35.9	36.0	36.1	36.2	36.7
Completers weight loss, %	-8.0	-1.9	-9.2	-3.5	-7.9	-4.0	-8.78	-4.26	-9.6	-1.6
LOCF weight loss, %	-6.1	-1.4	-8.0	-2.6	-5.8	-2.8	-7.94	-4.14	-8.1	-1.4
≥ 5% LOCF weight loss, %	48	16	63.2	27.1	47.2	25.0	50.5	30.7	62	21
≥ 10% LOCF weight loss, %	25	7	33.1	10.6	22.6	9.7	28.6	11.3	37	7

Abbreviations: BMI, body mass index; LOCF, last observation carried forward.

sympathomimetics listed here have been approved for long-term use.<sup>18</sup>

### ORLISTAT

Orlistat 120 mg was approved in 1999 as a reversible inhibitor of GI lipases that specifically reduced the absorption of dietary fat due to the inhibition of triglyceride hydrolysis.<sup>19</sup> Orlistat was later approved in 2007 for release in a reduced dosage form (60 mg) for over-the-counter sales.<sup>20</sup>

Orlistat forms a covalent bond with the active serine residue site of gastric and pancreatic lipases in the lumen of the stomach and small intestine. The inhibition of these enzymes causes dietary fat to remain undigested as triglycerides, which cannot be converted to absorbable

free fatty acids and monoglycerides, leading to decreased calorie absorption. Orlistat is not systemically absorbed and is eliminated mainly through feces. Some metabolism occurs in the GI wall.<sup>21</sup>

Orlistat is most known for its GI AEs. Because it is most active in the lumen of the GI system and reduces the absorption of triglycerides, many AEs are related to malabsorption. The most common issues 1 year after starting the drug were oily spotting (26.6% vs 1.3% placebo); flatus with discharge (23.9% vs 1.4% placebo); fecal urgency (22.1% vs 6.7% placebo); fatty/oily stool (20% vs 2.9% placebo); increased defecation (10.8% vs 4.1% placebo); and fecal incontinence (7.7% vs

0.9% placebo) (Table 1). Most of these AEs were greatly reduced after taking the drug for 2 years. Orlistat also has more serious AEs noted, including abdominal pain/discomfort; nausea; infectious diarrhea; rectal pain/discomfort; tooth disorder; gingival disorder; vomiting; upper respiratory infection; lower respiratory infection; ear, nose and throat symptoms; back pain; arthritis; myalgia; joint disorders; tendonitis; headache; dizziness; fatigue; sleep disorders; rash; dry skin; menstrual irregularity; vaginitis; urinary tract infection; and psychiatric disorders, although these did not differ markedly from placebo.

One of the most serious AEs reported was fulminate hepatic failure,

though this AE is rare. Thirteen cases of liver injury were reported with the 120-mg prescription dose of orlistat and 1 case report in the U.S. involved the 60-mg over-the-counter dosage of orlistat.<sup>21,22</sup> The FDA suggests that patients talk to their physicians about risks of liver failure, and that physicians should educate their patients about signs and symptoms of liver failure so that patients can stop taking orlistat and seek immediate medical help if symptoms occur.

One of the first published trials was the European Multicentre Orlistat Study Group, which included 743 participants with BMI between 28 kg/m<sup>2</sup> and 47 kg/m<sup>2</sup> from 15 different European centers. To test adherence, a 4-week single blind placebo lead-in was started with a hypocaloric diet. The first stage was completed by 688 patients who then proceeded to the double blind randomized control trial portion with a hypocaloric diet. From the start of lead-in to the end of year 1, the orlistat group weight decreased 10.2% (10.3 kg) vs 6.1% (6.1 kg) in the placebo group. The placebo subtracted difference between the groups was 3.9 kg ( $P < .001$ ).<sup>23</sup>

A U.S.-based randomized double-blind placebo-controlled multicenter study included 796 obese patients with BMI between 30 kg/m<sup>2</sup> and 44 kg/m<sup>2</sup>. Patients were assigned to 1 of 3 groups: placebo, orlistat 60 mg 3 times daily, or orlistat 120 mg 3 times daily. All groups were given a reduced energy diet. Patients in the orlistat 120 mg group lost significantly more weight than did the placebo group, -8.78% vs -4.26% respectively in year 1 in the completer analysis ( $P = .001$ ). More participants who were treated with orlistat 120 mg lost 5% or more of their initial weight in year 1 compared with placebo, 50.5% vs 30.7% respectively ( $P < .001$ ).<sup>24</sup>

In the XENDOS study the primary outcome measurement was time to onset of T2DM. Eligible participants were aged 30 to 60 years, with a BMI > 30 kg/m<sup>2</sup>. All patients had a 75-g oral glucose tolerance test and were required to have normal glucose tolerance or impaired glucose tolerance, but not T2DM. The double-blind randomized controlled trial included 3,305 subjects and compared a group taking 120 mg orlistat 3 times daily vs placebo. All patients were prescribed a reduced-calorie diet (800 kcal/d deficit) containing 30% of calories from fat. Patients were also encouraged to walk at least 1 kilometer daily in addition to their usual physical activity. Incidence of T2DM after 4 years was 6.2% in the orlistat group and 9.0% in the placebo group, reflecting a 37.3% risk reduction in the orlistat group ( $P = .0032$ ).<sup>25,26</sup>

### LORCASERIN

In 2012, lorcaserin HCl was FDA approved as a schedule IV drug for use as a weight loss medication as an adjunct to a reduced-calorie diet and increased physical activity. Lorcaserin is thought to act on 5-hydroxytryptamine-2c (5HT2c) receptors on the pro-opiomelanocortin (POMC) neurons in the arcuate nucleus, causing release of alpha-melanocortin-stimulating hormone (alpha-MSH), which in turn acts on melanocortin-4 receptors in the paraventricular nucleus to suppress appetite. At the maximum suggested dose of 10 mg twice daily, lorcaserin binds with 15 to 100 times greater affinity to 5HT2c receptors compared with 5HT2a and 5HT2b receptors respectively.

Indications for lorcaserin include patients with BMI  $\geq 30$  kg/m<sup>2</sup> or  $\geq 27$  kg/m<sup>2</sup> or greater with a weight-related comorbid condition such as hypertension, dyslipidemia, cardio-

vascular disease, impaired glucose tolerance, or sleep apnea.

The efficacy of lorcaserin for weight loss has been evaluated in 3 separate trials. The trials were randomized, double blinded and placebo controlled. The BLOOM trial, which included 3,182 patients with a mean BMI of 36.2 kg/m<sup>2</sup>, evaluated the efficacy of lorcaserin as a weight loss adjunct.<sup>27</sup> Patients with pre-existing valvular disease, uncontrolled hypertension, or a major psychiatric condition were excluded. After initial randomization, patients were assigned to receive either lorcaserin 10 mg twice daily or a placebo. The primary endpoint was a 5% weight reduction from baseline by the end of 2 years. At 1 year, 47.5% of patients in the lorcaserin group and 20.3% in the placebo group had lost  $\geq 5\%$  of their body weight ( $P < .001$ ). The average loss for the lorcaserin group was  $5.8 \pm 0.2$  kg and  $2.2 \pm 0.1$  kg for the placebo group at 1 year ( $P < .001$ ).

The BLOSSOM trial was a 1-year study of 4,008 patients aged 18 to 65 years. The trial evaluated the effects of lorcaserin on body weight, CVD risk factors, and safety in obese and overweight patients.<sup>28</sup> Patients were randomized in a 2:1:2 ratio to receive lorcaserin 10 mg twice daily, lorcaserin 10 mg once daily, or placebo. The primary endpoint was the proportion of patients achieving at least 5% reduction in body weight. Completer analysis showed weight reduction in the placebo group was 4.0% and 7.9% in the lorcaserin group ( $P < .001$ ). In the modified intent-to-treat/last observation carried forward analysis (MITT/LOCF), a statistically significant 47.2% of patients receiving lorcaserin 10 mg twice daily and 40.2% of patients receiving lorcaserin 10 mg once daily lost at least 5% of baseline body weight; compared with

**Table 2. Recent FDA-Approved Pharmacologic Obesity Treatments**

Drug (Brand)	Mode of Action	Maintenance Dose	Weight Loss vs Placebo, %	Significant Adverse Event vs Placebo	Discontinuation Rate vs Placebo, %	Renal or Hepatic Dose Adjustment
Naltrexone/ Bupropion (Contrave)	Opioid receptor antagonist/ Aminoketone antidepressant	16 mg/180 mg BID	8.1 vs. 1.6	Nausea: 28.9% vs 5.3% Constipation: 19.1% vs. 7.1% Headache: 17.5% vs. 8.7%	24% vs. 13.8%	No dose adjustment
Liraglutide (Saxenda)	GLP-1 receptor agonist	3 mg	9.2 vs. 3.0	Nausea: 39.3% vs. 13.8% Diarrhea: 20.9% vs. 9.9% Constipation: 19.4% vs. 8.5%	9.9% vs. 3.8%	Use with caution in moderate to severe renal impairment or hepatic impairment
Locaserin (Belviq)	Serotonin 2C receptor agonist	10 mg BID	5.8 vs 2.8	Nausea: 9.4% vs. 7.9% Back pain: 11.7% vs. 7.9% Headache: 14.5% vs. 7.1%	22.1% vs. 37.9%	Use with caution in moderate to severe renal impairment or hepatic impairment
Orlistat (Xenical)	Gastrointestinal lipase Inhibitor	120 mg TID	7.9 vs 4.2	Oily spotting: 26.6% vs. 1.3% Flatus with discharge: 23.9% vs 1.4% Fecal urgency: 22.1% vs. 6.7%	8% vs. 4%	No dose adjustment
Phentermine/ Topiramate (Qsymia)	Sympathomimetic/ Unknown	7.5 mg/46 mg	8.0 vs 1.6	Constipation: 16.3% vs. 7.1% Paresthesia: 13.7% vs. 2.6% Dry mouth: 13.7% vs. 2.2%	11.6% vs 8.4%	Use with caution in moderate to severe renal impairment or hepatic impairment

25% of patients receiving placebo ( $P < .001$ ). Weight loss of at least 10% was achieved by 22.6% of patients receiving lorcaserin 10 mg twice daily, and 17.4% of patients receiving 10 mg daily compared with 9.7% of patients in the placebo group ( $P < .001$ ).

The most common AEs noted were headache, nausea, and dizziness. Echocardiographic evidence of valvulopathy occurred in 2% of patients taking lorcaserin 10 mg twice

daily and those taking the placebo. Lorcaserin administered in conjunction with a diet and exercise program was associated with an overall reduction in baseline BMI when compared with placebo over the year.

The BLOOM-DM study evaluated efficacy and safety of lorcaserin for weight loss in 604 patients with T2DM over the course of 1 year.<sup>29</sup> Patients had a hemoglobin A<sub>1c</sub> (A<sub>1c</sub>) of 7% to 10% and were treated with

metformin, a sulfonylurea, or both. The primary endpoint was a 5% weight reduction from baseline at the end of 1 year. Patients were randomized into 3 groups: 1 group received lorcaserin 10 mg twice daily, 1 group took lorcaserin 10 mg daily, and 1 group received the placebo. A statistically significant 37.5% of patients taking lorcaserin 10 mg twice daily achieved > 5% body weight reduction, compared with 44.7% in the lorcase-

rin 10 mg daily group, and 16.1% in the placebo group. Overall reductions in  $A_{1c}$  and fasting glucose were observed in both lorcaserin groups taking as compared with placebo. Patient  $A_{1c}$  decreased  $0.9 \pm 0.06$  with lorcaserin 10 mg bid,  $1.0 \pm 0.09$  with lorcaserin 10 mg qd, and  $0.4 \pm 0.06$  with the placebo ( $P < .001$ ). Fasting glucose in the lorcaserin bid, lorcaserin qd, and placebo groups decreased  $27.4 \pm 2.5$  mg/dL,  $28.4 \pm 3.8$  mg/dL, and  $11.9 \pm 2.5$  mg/dL, respectively ( $P < .001$ ). Symptomatic hypoglycemia occurred in 7.4% of patients on lorcaserin bid, 10.5% on lorcaserin qd, and 6.3% on placebo. Headache, back pain, nasopharyngitis, and nausea were among the most commonly reported AEs.

As lorcaserin is a serotonergic agonist, potential interactions exist when used with other medications affecting serotonin. Most notably, serotonin syndrome and neuroleptic malignant syndrome-like reactions may occur. Because of this, it is recommended to avoid selective serotonin re-uptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors, tricyclic antidepressants, bupropion, triptans, monoamine oxidase inhibitors, lithium, dextromethorphan, and dopamine agonists. Lorcaserin seems to be safe in those patient populations with mild hepatic as well as mild renal impairment; however, it is not recommended for those with severe renal impairment. Given the multiple enzymatic pathways used to metabolize lorcaserin, there is a low probability for cytochrome drug interactions. Safety has not been well evaluated in patients aged  $< 18$  years and those that are pregnant (pregnancy category X).

Adverse events include headache, dizziness, fatigue, nausea, and dry mouth. Other notable AEs include nasopharyngitis and URI. Hypoglycemia appeared to be more common in

patients with DM taking lorcaserin. Cognitive impairment and psychiatric disorders including euphoria and hallucinations were also reported. Notably, valvular heart disease has been reported in patients who take medications with 5HT2b activity. In a 1-year clinical trial, a small number of patients were found to develop valvular regurgitation. Furthermore, bradycardia, priapism, leucopenia, elevated prolactin, and pulmonary hypertension have also been observed. Caution is recommended if symptoms of any of the aforementioned conditions are noticed.

### QSYMIA

The schedule IV controlled substance Qsymia (Vivus, Mountain View, CA) is a combination of phentermine, an anorexigenic agent, and topiramate extended-release, an antiepileptic drug. In July of 2012 it was approved for chronic weight management as an addition to a reduced-calorie diet and exercise. The drug is approved for adults with a BMI  $\geq 30$  kg/m<sup>2</sup> or adults with a BMI  $\geq 27$  kg/m<sup>2</sup> who have at least 1 weight-related condition such as hypertension, T2DM, or dyslipidemia.<sup>30</sup>

In 1996 topiramate was approved by the FDA for the treatment of seizure disorders and was also approved for migraine prophylaxis in 2004. In patients who were treated with topiramate for seizure disorders and migraines, weight loss and a reduction in visceral body fat has been observed.<sup>31</sup> The precise MOA of topiramate in regards to weight loss is not fully understood. It may be due to its effects on both appetite suppression and satiety enhancement. Topiramate exhibits a combination of properties including modulatory effects on sodium channels, enhancement of GABA-activated chloride channels, inhibition of excitatory

neurotransmission through actions on kainite and AMPA receptors, and inhibition of carbonic anhydrase (CA) isoenzymes in particular CA II and IV.<sup>14</sup>

The combination of phentermine and topiramate is a once-daily formulation that is designed to provide an immediate release of phentermine and a delayed release of topiramate, allowing a peak exposure of the phentermine in the morning and a peak concentration of topiramate in the evening. It should be taken in the morning in order to avoid the possibility of insomnia that can occur if taken in the evening. It can be taken with or without food. The recommended dose is as follows: Start treatment with Qsymia 3.75 mg/23 mg extended-release daily for 14 days; after 14 days increase to the recommended dose of Qsymia 7.5 mg/46 mg once daily.

Weight loss should be evaluated after 12 weeks at the higher dose. If at least 3% of baseline body weight has not been lost at that time, discontinue or escalate the dose. To escalate the dose: Increase to Qsymia 11.25 mg/69 mg daily for 14 days; followed by Qsymia 15 mg/92 mg daily. Evaluate weight loss following dose escalation to Qsymia 15 mg/92 mg after an additional 12 weeks of treatment. If at least 5% of baseline body weight has not been lost on Qsymia 15 mg/92 mg, discontinue as directed. It is important not to suddenly discontinue, as this may cause seizures. Patients should be slowly titrated off the medication.

In vitro studies of phentermine and topiramate indicate that these drugs are not likely to cause clinically significant interactions with drugs using the cytochrome P450 enzyme pathways, or those involved in plasma protein binding displacement; however there is evi-



dence suggesting that ethinyl estradiol levels may be decreased by 16%, thus raising a concern about the possibility of decreased contraceptive efficacy.<sup>31</sup> In patients with moderate (creatinine clearance  $\geq 30$  mL/min to  $< 50$  mL/min) and severe renal dysfunction ( $< 30$  mL/min), the maximum dose of should not exceed 7.5 mg/46 mg.

Qsymia was evaluated in 3 phase 3 trials for its long-term efficacy and safety. In all trials, diet and lifestyle counseling were provided for all patients. The first of these studies was OB-301, a 28-week confirmatory trial with a factorial design involving 7 treatment arms, tested 2 fixed-dose Qsymia combinations—regular dose (7.5 mg/46 mg) and maximum dose (15 mg/92 mg)—as well as regular and maximum doses of the individual constituent drugs vs placebo.<sup>32</sup> The study randomized 756 obese patients with a BMI range of 30 kg/m<sup>2</sup> to 45 kg/m<sup>2</sup> to 1 of the 7 treatment arms for 28 weeks. Patients treated with maximum-dose Qsymia achieved an average weight change of -9.0%, vs -1.5% with placebo ( $P < .0001$ ). Weight change with regular-dose Qsymia was -8.2%. Weight changes with monotherapies were: -6.1% with topiramate 92 mg, -4.9% with topiramate 46 mg, -5.8% with phentermine 15 mg, and -5.2% with phentermine 7.5 mg.

OB-302 was a 56-week trial that randomized 1,267 morbidly obese patients with a BMI  $\geq 35$  kg/m<sup>2</sup> without significant comorbidities to low-dose Qsymia (3.7 mg/23 mg), maximum-dose Qsymia (15 mg/92 mg), or placebo.<sup>33</sup> At baseline, the mean BMI for the entire study cohort was 42 kg/m<sup>2</sup>. Mean weight changes were -1.6% with placebo, -5.1% with low-dose Qsymia, and -10.9% with maximum-dose Qsymia. The proportions of patients achieving  $\geq 5\%$

weight loss were: 17% with placebo, 45% with low-dose Qsymia, and 67% with maximum-dose Qsymia.

CONQUER was the largest of the phase 3 trials. It randomized 2,487 overweight or obese patients with a BMI of 27 kg/m<sup>2</sup> to 45 kg/m<sup>2</sup> and  $\geq 2$  obesity-related comorbidities (hypertension, dyslipidemia, T2DM, prediabetes or abdominal obesity) to receive a placebo, regular-dose Qsymia, or maximum-dose Qsymia for 56 weeks.<sup>34</sup> In the completer population, mean weight changes in the placebo, regular dose Qsymia, and maximum-dose Qsymia groups were -1.6%, -9.6% ( $P < .0001$ ), and -12.4% ( $P < .0001$ ); and weight loss of  $\geq 5\%$  was achieved by 21%, 62%, and 70%, respectively. Relative to placebo, there were greater reductions in systolic BP, triglycerides, and fasting insulin with both doses of Qsymia.

Patients should not take Qsymia if they are pregnant, planning to become pregnant, or become pregnant during Qsymia treatment as there is an increased risk of birth defects, namely cleft lip and cleft palate. Women who can become pregnant should have a negative pregnancy test before taking Qsymia and every month while on the medication. They should use effective birth control consistently while taking Qsymia.

Qsymia is contraindicated in patients with glaucoma and patients who have hyperthyroidism. Qsymia can cause an increase in resting heart rate and regular monitoring of resting heart rate is recommended, especially in patients with cardiac or cerebrovascular disease. It has not been studied in patients with recent or unstable cardiac or cerebrovascular disease and therefore use is not recommended.

Qsymia can cause mood disorders such as anxiety and depression

and can increase the risk of suicidal thoughts. Patients should be monitored for worsening depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior. It is not recommended in patients with a history of suicidal attempts or active suicidal ideation. Qsymia can cause cognitive dysfunction. It can cause confusion, problems with concentration, attention, memory, or speech. Patients should be cautioned about operating automobiles and hazardous machinery.

Normal anion gap hyperchloremic metabolic acidosis has been reported in patients treated with Qsymia. If this does develop and persists, consideration should be given to either reduce the dose or discontinue Qsymia.

Weight loss may increase the risk of hypoglycemia in patients with T2DM treated with insulin and/or insulin secretagogues (eg, sulfonylureas). Qsymia has not been studied in combination with insulin. A reduction in the dose of antidiabetic medications, which are nonglucose dependent, should be considered to reduce the risk of hypoglycemia.

The most common AEs in controlled clinical studies ( $\geq 5\%$  and at least 1.5 times placebo) included paraesthesia in the hands, arms, feet or face, dizziness, dysgeusia, insomnia, constipation, and dry mouth.

## CONTRAIVE

In 2014, the FDA approved Contrave (Takeda, Deerfield, IL) as treatment option for chronic weight management in addition to reduced-calorie diet and physical activity. The combination of naltrexone hydrochloride and bupropion hydrochloride was originally introduced for the treatment of opioid addiction and later expanded to include the treatment of alcoholism. The antidepressant bu-

propion was approved in the U.S. in 1989. It is structurally different from all other marketed antidepressants (ie, tricyclics, tetracyclics, and SSRIs), but closely resembles the structure of diethylpropion, an appetite depressant with minimal CNS effects.<sup>35</sup>

This drug is approved for adults with BMI  $\geq 30$  kg/m<sup>2</sup> and for adults with BMI  $\geq 27$  kg/m<sup>2</sup> with at least 1 weight-related risk factors such as hypertension, T2DM, or dyslipidemia. It should be used as an adjunct to diet and exercise and is not approved for use for depression even though it contains bupropion.

Naltrexone is a pure opioid antagonist with high affinity to  $\mu$ -opioid receptor, which is implicated in eating behavior. Naltrexone is rapidly and nearly completely absorbed from the GI tract after oral administration. The time to peak plasma concentration is about 1 hour. Naltrexone is well absorbed but first pass extraction and metabolism by the liver decreases oral bioavailability to between 5% to 40%. Primary elimination of naltrexone and its metabolites is renal excretion.

Bupropion is a weak inhibitor of neuronal reuptake of dopamine and norepinephrine. This drug is used to treat depression and seasonal affective disorder, and aid in smoking cessation. Bupropion is absorbed rapidly after oral administration, but the absolute oral bioavailability of bupropion is not known because an IV preparation is not available. The time to peak plasma concentrations of bupropion is within 2 hours of oral administration. Bupropion is extensively metabolized by the liver to multiple metabolites. Primary elimination of bupropion is urinary excretion. However, hepatic and renal impairment may affect the elimination of bupropion and its metabolites. Patients with hepatic or renal impairment should use a reduced dosage.

Combination therapy has been found to have complementary actions on CNS to reduce food intake. They are believed to dampen CNS reward pathways, taking away the compulsive feeding behavior and pleasure of feeding, ultimately leading to weight loss. Bupropion stimulates hypothalamic pro-opiomelanocortin neurons (POMC), which results in reduced food intake and increased energy expenditure. Naltrexone blocks opioid-receptor mediated POMC auto-inhibition, blocks the increase in dopamine in nucleus accumbens that occurs when eating, and acting synergistically with bupropion in augmenting POMC firing.

The COR-I and COR-II trials compared Contrave to diet and exercise in patients who did not have DM. The COR-Diabetes trial included the same study design but focused on patients with DM. In all the studies the participants had a 4-week titration to Contrave (naltrexone 8 mg/bupropion 90 mg) to decrease nausea. The first week dosing was 1 tablet in the morning and 1 tablet in the evening. In week 3, patients took 2 tablets in the morning and 1 tablet in the evening. The final titration step was 2 tablets in the morning and 2 tablets in the evening.

The COR-1 study was a 56-week randomized, double-blind, placebo-controlled study. It compared Contrave 32 mg naltrexone/360 mg bupropion (NB32/360) with an active placebo of diet and exercise.<sup>36</sup> To be included adults must be aged 18 to 65 years with a BMI 30 kg/m<sup>2</sup> to 45 kg/m<sup>2</sup> or a BMI 27 kg/m<sup>2</sup> to 45 kg/m<sup>2</sup> with dyslipidemia or hypertension. Patients were instructed on a hypocaloric diet that was a 500 kcal per day deficit based on World Health Organization algorithm for calculating metabolic rate and they were urged to

increase physical activity.

The completer population results showed 8.0% weight loss in the NB32/360 group and 1.9% weight loss in the placebo group ( $P < .001$ ). For the NB32/360 and placebo groups, weight loss of  $\geq 5\%$  was achieved by 48% and 16% ( $P < .001$ ), respectively; and weight loss of  $\geq 10\%$  by 25% and 7% ( $P < .001$ ), respectively. The most common AE was nausea—29.8% with NB32/360 vs 5.3% with placebo. Nausea generally occurred early and then diminished and the discontinuation rate from nausea was significantly lower (6.3%) than the overall reported nausea rates.

Contrave was also studied in patients with T2DM. The COR-Diabetes Trial was a 56-week randomized, double blind, placebo-controlled study. The trial compared Contrave 32 mg naltrexone/360 mg bupropion (NB32/360) with an active placebo of diet and exercise.<sup>37</sup> Inclusion criteria for the trial were patients aged 18 to 70 years with T2DM and a BMI from 27 kg/m<sup>2</sup> to 45 kg/m<sup>2</sup>, A<sub>1c</sub> between 7% and 10%, and fasting blood glucose  $< 270$  mg/dL. Participants either were not taking a DM medication or were on stable doses of oral antidiabetes drugs  $\geq 3$  months prior to randomization. Patients were placed on a 500 kcal hypocaloric diet and advised to increase physical activity.

The results showed 5.0% weight loss in the NB32/360 group and 1.8% weight loss in the placebo group ( $P < .001$ ). Weight loss of  $\geq 5\%$  and  $\geq 10\%$  was achieved by 44.5% and 18.5% of the NB32/360 group, respectively, and 18.9% and 5.7%, respectively ( $P < .001$ ) of the placebo group. The NB32/360 and placebo showed a reduction of A<sub>1c</sub> of 0.6% and 0.1% respectively ( $P < .001$ ). The most common AE was nausea (42.3% with NB32/360 vs 7.1% with placebo). Nausea generally occurred

early and then diminished and the discontinuation rate from nausea was significantly lower (9.6%) than the overall reported nausea rates.<sup>37</sup>

Due to potential nausea caused by naltrexone, Contrave should be titrated over 4 weeks as described earlier. At maintenance dose, patients should be evaluated after 12 weeks to determine treatment benefits. If a patient has not lost at least 5% of baseline body weight, Contrave should be discontinued, because it would be unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment. Contrave should not be taken with high-fat meals that may result in significant increase in bupropion and naltrexone systemic exposure.

Since Contrave contains the antidepressant bupropion, it has a boxed warning similar to other antidepressants in its class of increased risk of suicidal thoughts and behaviors, especially in children, adolescents, and young adults.<sup>38</sup> Contrave can lower the seizure threshold; therefore it should not be used in people with a seizure disorder. It can also raise BP and heart rate; however the clinical significance of hypertension and elevated heart rate observed with Contrave treatment is unclear. Blood pressure rose on average by 1 point during the first 8 weeks of treatment and then returned to baseline.<sup>38</sup> The heart rate also increased by about 1.7 beats per minute.<sup>38</sup> Patients with uncontrolled hypertension should avoid Contrave.

Contrave should not be taken with products contain bupropion or naltrexone. It should not be taken by patient who are regularly taking opioids or who are opioid dependent, or who are experiencing opiate withdrawal. Pregnant women should also avoid Contrave. In patients with renal impairment the maximum dose

is 1 tablet twice a day and in patients with hepatic impairment the maximum dose is 1 tablet a day.

## LIRAGLUTIDE

Liraglutide is the newest weight loss medication to be approved by the FDA for chronic weight management as an adjunct to a reduced calorie diet and increased physical activity in adult patients with BMI  $\geq 30$  kg/m<sup>2</sup> or  $\geq 27$  kg/m<sup>2</sup> with hypertension, diabetes, or dyslipidemia. The recommended dose of liraglutide is 3 mg daily. The initial dose is 0.6 mg daily for the first week, then titrated up by 0.6 each week for 4 weeks, until reaching 3 mg daily.

Liraglutide is an acylated human glucagon-like peptide-1 (GLP-1) receptor agonist, which are expressed in the brain and is involved in the control of appetite. It is also found in the beta cells of the pancreas, where GLP-1 receptors stimulate insulin release in response to elevated blood glucose concentrations and suppress glucagon secretion. Endogenous GLP-1 has a half-life of 1.5 to 2 minutes due to degradation by the DDP-4 enzyme, but liraglutide is stable against degradation by peptidases and has a half-life of 13 hours.

Liraglutide was studied in a 56-week randomized, double-blind, placebo-controlled trial, which compared liraglutide 3 mg with an active placebo of diet and physical activity.<sup>39</sup> Inclusion criteria were adults aged  $\geq 18$  years old with a BMI 30 kg/m<sup>2</sup> to 45 kg/m<sup>2</sup> or BMI 27 kg/m<sup>2</sup> to 45 kg/m<sup>2</sup> with dyslipidemia and/or hypertension. Both groups received lifestyle modification counseling. Patients were excluded if they had DM.

In the trial, 3,731 participants enrolled, 2,487 in the liraglutide group and 1,244 in the placebo group; 78.7% of the participants were female and the average age

was 45 years. Subjects in the liraglutide group had a weekly titration regimen. The starting dose at week 1 was 0.6 mg, week 2 was 1.2 mg, week 3 was 1.8 mg, week 4 was 2.4 mg, and week 5 was 3.0 mg.

The completer population showed 9.2% weight loss in the liraglutide group and 3.0% weight loss in the control group.<sup>39</sup> Weight loss of  $\geq 5\%$  was seen in 63.2% and 27.1% of the liraglutide and placebo groups, respectively. Weight loss rates of  $\geq 10\%$  was seen by 33.1% and 10.6%, respectively. The most common AEs were nausea, diarrhea, and constipation. Nausea generally occurred early during the titration period and then diminished.

A second clinically relevant study was performed with liraglutide. Often patients are able to lose weight with diet and exercise and then plateau. This study examined participants who lost 5% percent of their initial body weight and then were randomized to liraglutide or placebo.<sup>40</sup> Key inclusion criteria were people aged  $\geq 18$  years old with a BMI 30 kg/m<sup>2</sup> to 45 kg/m<sup>2</sup> or BMI 27 kg/m<sup>2</sup> to 45 kg/m<sup>2</sup> with dyslipidemia and/or hypertension. In order to be randomized, participants were required to lose at least 5% of their initial body weight on a 1,200 kcal to 1,400 kcal diet with increased physical activity during a 4 to 12 week run-in period.

Four hundred twenty-two participants were enrolled, 212 in the liraglutide group and 210 in the placebo group. Most of the participants were female (81%). The average BMI in the study was 35.6 kg/m<sup>2</sup>. Subjects in the liraglutide group had a weekly titration regimen.

After an average weight loss of 6% using a low calorie diet and increased physical activity the participants were randomized to continue diet and increased activity alone (placebo)

or with liraglutide. At week 56 the results showed an additional 6.2% weight loss in the liraglutide group and 0.2% weight gain in the placebo group. The liraglutide group had a greater number of participants with  $\geq 5\%$  weight loss compared to placebo, 50.5% vs 21.8% ( $P < .0001$ ).<sup>40</sup> In the pooled data set from the registration trials the 3 most common GI AEs were nausea, diarrhea, and constipation occurring in 39.3%, 20.9%, and 19.4% of participants respectively. Discontinuation due to nausea for liraglutide was 2.9%.<sup>41</sup>

Clinicians should be aware that medications that can cause hypoglycemia such as sulfonylureas and insulin must be tapered as patients lose weight with liraglutide. Documented symptomatic hypoglycemia in patients with T2DM and with sulfonylurea background therapy was 43.6% with liraglutide vs 27.3% with placebo.

In the setting of renal impairment, patients treated with GLP-1 receptor agonists, including liraglutide, have had reports of acute renal failure and worsening of chronic renal failure usually associated with nausea, vomiting, diarrhea, or dehydration. Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in rats and mice. It is unknown whether liraglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans. As the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined liraglutide is contraindicated in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2.

Acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with liraglutide in postmarketing reports. After ini-

tiation of liraglutide, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, liraglutide should promptly be discontinued.

## CONCLUSION

The treatment of obesity and overweight with comorbidities has always been a challenge. In the past there were few FDA-approved drugs and many drugs had to be used off-label. The toolbox of medications available for medical weight management is more robust than ever. The medications have different MOAs and can be used in a variety of patients. There are differences in the classes and some are controlled substances. Phentermine, lorcaserin, and Qsymia (phentermine/topiramate) are controlled substances whereas orlistat, naltrexone/bupropion and liraglutide are not. Other differences exist including duration of use. The sympathomimetic drugs have a limited window of use whereas orlistat, Qsymia (phentermine/topiramate), lorcaserin, naltrexone/bupropion, and liraglutide do not.

The medications that are available have a wide variety of MOAs. Therefore, if a patient fails one medication, then it is very reasonable to try a medication with a different MOA. In addition, there is the potential for weight regain when weight reduction medications are discontinued. As people lose weight their metabolic rate decreases about 15 kcal per pound of weight reduction.<sup>42</sup>

Another challenge of using these medications is managing patient expectations. The current metric used for FDA approval is a 5% weight loss that is greater in the study group compared with the diet and physi-

cal activity active control. However, many clinicians and patients do not find this weight reduction amount consistent with their expectations. In addition weight loss trajectory may also be too slow for patients and cause early discontinuation. Therefore, patient education and a discussion of reasonable expectations for weight reduction medications are necessary.

Clinicians must acknowledge that there are limitations to the use of these medications. Newer agents do have a higher cost and insurance reimbursement is somewhat limited. However, they offer the opportunity to prevent more expensive, protracted conditions such as diabetes and cardiovascular disease. In summary, clinicians now have a wider variety of medication options to be used with dietary and lifestyle changes in order to improve health and prevent chronic diseases. ●

## Author disclosures

Dr. Nguyen is affiliated with the Takeda Speakers Bureau and Janssen Pharmaceuticals Speakers Bureau. Dr. Plodkowski is affiliated with the Takeda Pharmaceuticals Speakers Bureau and the Novo Nordisk Speakers Bureau. The remaining authors report no actual or potential conflicts of interest.

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adverse effects—before administering pharmacologic therapy to patients.

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