

## Medical Therapy for the Patient With Obesity

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**A**lthough the prevalence of overweight in the United States during the past decade has been stable and the median body mass index (BMI), at least in women, may have remained constant,<sup>1,2</sup> the prevalence of obesity now exceeds 34% of US adults,<sup>1</sup> and the prevalence of more severe obesity continues to rise at alarming rates. Excessive weight is a problem for children and adolescents, as well.<sup>3</sup> The fundamental problem underlying obesity is a small, but prolonged, positive energy balance, where energy derived from food exceeds energy expended for everyday living.<sup>3,4</sup> Obesity is associated with many illnesses that are related to and may be caused by excess fat.<sup>5</sup> Selection of medications for these associated conditions should take into consideration the effect of the selected drugs on body weight, because obesity is a root cause in most cases.

### Realities in Treating a Patient With Obesity Without Other Problems

One of the key messages for patients with obesity is that when caloric intake is reduced below that needed for daily energy expenditure, there is a predictable rate of weight loss.<sup>6</sup> Men generally lose weight slightly faster than women of similar height and weight on any given diet, because men have more lean body mass and therefore higher energy expenditure. Similarly, older patients have a lower metabolic expenditure and as a rule lose weight more slowly than do younger patients with similar adherence to weight-loss programs. Thus, adherence to any program is an essential component of success.

If obesity is the result of a prolonged small difference between energy intake and energy expenditure, then losing body fat requires reversing this imbalance. According to Guidelines (National Heart, Lung, and Blood Institute Guidelines, 1998, [http://www.nhlbi.nih.gov/guidelines/obesity/ob\\_gdlns.htm](http://www.nhlbi.nih.gov/guidelines/obesity/ob_gdlns.htm)) the use of medication to help patients adhere to lifestyle change is indicated for individuals with  $BMI \geq 27 \text{ kg/m}^2$  and at least 1 comorbid condition and for those with  $BMI \geq 30$ . Unfortunately, the withdrawal of sibutramine from use for treatment of obesity in 2010, and the failure of other drugs reviewed by the US Food and Drug Administration (FDA) to win approval has resulted in a single agent being approved for long-term use in obesity—orlistat. However because many patients with obesity also have comorbidities, such as diabetes mellitus, hypertension, depression, and others, selection of

medications that produce weight loss, and treat the comorbidity, as well, can ameliorate both problems at the same time with the use of approved drugs.

### Treating the Patient With Obesity Who Has 1 or More Comorbidities

Because one third of the American population is classified as obese, it is not unusual for practitioners to deal with patients who are obese and have additional medical problems, often chronic diseases. It is clear that treating the obesity will, in many cases, also deal with the other medical problems. However, there are many barriers to implementing weight management in the office setting, including lack of reimbursement, paucity of medications approved for weight loss, and lack of trained paramedical staff to deliver weight counseling. Thus, in deciding whether to treat the underlying cause (obesity) or the complication(s) (diabetes mellitus, hypertension, depression, and others), the healthcare provider usually takes the path of least resistance and mediates for the complication(s). As outlined below, some medications for chronic diseases associated with obesity produce weight gain, others are weight neutral and some actually produce weight loss. When selecting drugs to treat associated medical problems, the patient may benefit, all other things being equal, from the choice of drugs that also produce weight loss, as opposed to weight gain.<sup>4,7–10</sup> This strategy could be used in dealing with the weight problem of Ms BL that is outlined here.

Ms BL's case is illustrative of the family medicine and internist's challenge. She has class II obesity ( $BMI 35\text{--}39 \text{ kg/m}^2$ ) and glucose, triglyceride, and HDL levels that meet the criteria for metabolic syndrome.<sup>11</sup> In fact, with a hemoglobin A1c  $>6.5\%$ , she meets 1 of the current American Diabetes Association criteria for diagnosis of type 2 diabetes mellitus.<sup>12</sup> All of these signs and symptoms would improve with a weight loss of as little as 5% to 10%.<sup>13–17</sup> Furthermore, snoring suggests sleep apnea, frequently associated with obesity, and it has been demonstrated in diabetic patients that weight loss of 10 kg or more can reduce the episodes of apnea and hypopnea with symptomatic improvement.<sup>18</sup> But Ms BL is already on medications that promote weight gain ( $\beta$ -blocker, escitalopram oxalate) and if her diabetes mellitus is treated with a sulfonylurea, a thiazolidinedione or insulin), further weight gain is assured. Imagine a scenario where she is on

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a weight-neutral medication for hypertension, an antidepressant associated with weight loss (venlafaxine, desvenlafaxine, or bupropion) and on topiramate for migraine prophylaxis. In addition, what if her diabetes mellitus were treated with medications producing weight loss (metformin, exenatide, liraglutide, or pramlintide)? And finally, what would the patient's lipid profile and blood pressure look like if these changes were accompanied by therapeutic lifestyle change, aimed at healthier diet, physical activity, and weight reduction? Therapeutic lifestyle change should be foundational to management of the patient with obesity.

**Ms BL** is a 54-year-old white woman who comes in for progressive weight gain.

**Medical History:** hypertension, hyperlipidemia, migraine headaches, and depression.

**Current Problem:** Her diet is high in carbohydrate and salt. She has a "very big" appetite, and she craves bread and pasta. She has made numerous attempts to lose weight through Weight Watchers and LA Weight Loss. She is exercising ≈60 minutes per week, mostly walking outside.

**Medications:** She takes the antidepressant escitalopram oxalate (Lexapro) 20 mg once daily and the β-blocker/diuretic bisoprolol (Ziac) 5 mg once daily.

**Review of Systems:** She snores while sleeping.

**Family History:** Mother with diabetes mellitus.

**Social History:** Widowed, no children. She works in the human resources department.

**Physical Examination:** Obese, white female in no acute distress. Vital signs: blood pressure, 146/88 mm Hg; P, 76; weight, 242 pounds; height, 68.4 inches; BMI, 38.2; obesity class II. The remainder of the physical examination was within normal limits.

**Laboratory Evaluation:** Random glucose, 104 mg/dL; potassium, 4.1 mEq; creatinine, 0.8 mg/dL; aspartate aminotransferase (serum glutamic oxaloacetic transaminase), 16 IU; alanine aminotransferase (serum glutamic pyruvate transaminase), 20 IU; hemoglobin A1c, 6.9%; triglycerides, 159 mg/dL; total cholesterol, 187 mg/dL; low-density lipoprotein cholesterol, 111 mg/dL; high-density lipoprotein cholesterol, 44 mg/dL; high-sensitivity C-reactive protein, 3.20 g/L (nl <1.0).

This case illustrates that it is possible for physicians to take weight-centric approaches to chronic disease management in their choice of medicating for chronic diseases, and to amplify the results of attempts at therapeutic lifestyle change by prescribing in ways that help, not hinder, patients' intentions to achieve weight loss and healthier lifestyles. This is a critically important approach for patients with obesity who have chronic diseases, because it is an approach that addresses the root cause. To undertake weight-centric chronic disease management, an understanding of how drugs can impact body weight is necessary. We will review the state of the art regarding available medications and their impact on body weight.<sup>4,7–10</sup>

## Medications in the Treatment of the Patient With Obesity

### Mechanisms Underlying Drug Therapy for Obesity

Currently, available medications to help treat the patient with obesity work either in the brain or on the gut.<sup>4,19</sup> A number of neurotransmitter systems, including monoamines, amino acids, and neuropeptides, are involved in modulating food intake. Serotonin 5-HT<sub>2C</sub> receptors modulate fat and caloric intake. Mice that cannot express the 5-HT<sub>2C</sub> receptor are obese and have increased food intake. Lorcaserin, a drug in clinical trial, works directly on serotonin-2C receptors in the brain. These receptors may work through modulation of downstream melanocortin-4 receptors.<sup>20</sup> Sibutramine blocks serotonin and norepinephrine reuptake.<sup>12</sup>

α<sub>1</sub>-Receptors also modulate feeding. Some α<sub>1</sub>-receptor agonist drugs that are used to treat hypertension produce weight gain, indicating that this receptor is clinically important. In contrast, stimulation of α<sub>2</sub>-receptors increases food intake, and a polymorphism in the α<sub>2a</sub>-adrenoceptor is associated with reduced metabolic rate in humans. Activation of β<sub>2</sub>-receptors in the brain reduces food intake and β-blocker drugs can increase body weight.<sup>19</sup>

Other drugs act in the periphery. Blockade of intestinal lipase with orlistat will produce weight loss, both because ≈30% of ingested fat is not absorbed, and because orlistat-treated patients avoid high-fat meals and snacks. Glucagon-like peptide-1 released from intestinal L cells acts on the pancreas and brain to reduce food intake. Amylin is secreted from the pancreas and can reduce food intake.

### Drugs Approved by the FDA for Treating the Patient With Obesity

Although several drugs are currently approved in the United States to treat patients with obesity, only one (orlistat) is approved for long-term use (Table 1).

### Sympathomimetic Drugs

The sympathomimetic drugs, benzphetamine, diethylpropion, phendimetrazine, and phentermine, are grouped together because they act like norepinephrine and were tested before 1975. Phentermine and diethylpropion are classified by the US Drug Enforcement Agency as schedule IV drugs; benzphetamine and phendimetrazine are schedule III drugs. This regulatory classification indicates the government's belief that these drugs have the potential for abuse, although this potential appears to be very low.<sup>19</sup> Phentermine and diethylpropion are approved for only a few weeks, which usually is interpreted as up to 12 weeks.

Most of the data on these drugs come from short-term trials. Phentermine is a long-established sympathomimetic drug approved for the short-term treatment of obesity in 1968. It is a scheduled drug, meaning that the US Drug Enforcement Agency has concluded that this drug carries risk for habituation or addiction. One of the longest of the clinical trials of drugs in this group lasted 36 weeks and compared placebo treatment with continuous phentermine or intermittent phentermine.<sup>19,21</sup> Both continuous and intermittent phentermine therapy produced more weight loss than did placebo. Patients treated intermittently had a slowing of weight loss

**Table 1. Drugs Approved by the FDA That Produce Weight Loss**

Generic Name	Trade Names	Usual Dose	Comments
Long-term treatment of obesity (12 mo)			
Orlistat	Xenical	120 mg TID	May have gastrointestinal side effects
Short-term treatment of obesity(12 wk)			
Diethylpropion*			Sympathomimetic drugs; approved for use for only a short time
Tablets	Tenuate	25 mg TID	
Extended release	Tenuate	75 mg in morning	
Phentermine HCl*			
Capsules	Phentridol	15–37.5 mg in the morning	
	Teramine		
	Adipex-P		
Tablets	Tetramine		
	Adipex-P		
Extended release	Ionamin	15 or 30 mg/d in the morning	
Benzphetamine†	Didrex	25–150 mg/d in single or divided doses	
Phendimetrazine†			
Capsules, extended release	Adipost	105 mg once daily	
	Bontril		
	Melfial		
	Prelu-2		
	X-trozine		
Tablets	Bontril	35 mg 2–3 times a day	
	Obezine		

FDA indicates US Food and Drug Administration.

\*Drug Enforcement Agency Schedule IV.

†Drug Enforcement Agency Schedule III.

Adapted from Bray.<sup>4</sup>

during the periods when the drug was withdrawn and lost weight more rapidly when the drug was started again (Figure). There was no difference in weight loss with continuous or intermittent treatment.

Weight loss with phentermine and diethylpropion persists for the duration of treatment, suggesting that tolerance, defined as requiring more drug to maintain the same effect, does not develop, although patients stop losing weight at a lower plateau. If tolerance were to develop, the drugs would be expected to lose their effectiveness, and patients would require increased amounts of the drug to maintain weight loss. This does not occur. Both medications are available in generic forms and are therefore relatively inexpensive.

In 1 survey of bariatric physicians, use of sympathomimetic amines was more frequent than sibutramine or orlistat and they were often used for longer than approved by the FDA.<sup>22</sup> However, prescribers should be aware of the local and federal regulations governing prescribing limits and the lack of long term clinical trial data for phentermine.

#### *Safety of Sympathomimetic Drugs*

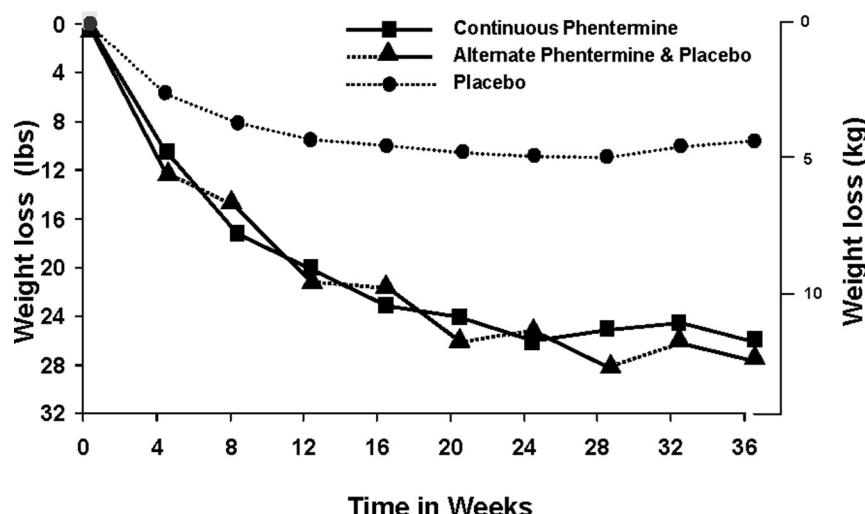
Sympathomimetic drugs produce insomnia, dry mouth, asthenia, and constipation. They are scheduled by the US Drug Enforcement Agency, suggesting the Agency's view that they

may be abused. Sympathomimetic drugs can also increase blood pressure. If a physician decides to use any of these drugs >3 months in succession, it would be appropriate to obtain written informed consent from the patient and to consider an intermittent therapy approach.

#### *Orlistat*

Orlistat is the only drug approved by the FDA for long-term treatment of obesity. It is also approved at a lower dose as an over-the-counter preparation. Orlistat is a potent and selective inhibitor of pancreatic lipase that reduces intestinal digestion of fat.<sup>4</sup> It is available as a prescription drug (120 mg TID before meals), and at 60 mg as an over-the-counter preparation. A number of long-term clinical trials with orlistat have been published by using patients with uncomplicated obesity and patients with obesity and diabetes mellitus. A 4-year double-blind, randomized, placebo-controlled trial with orlistat in 3304 overweight patients, 21% of whom had impaired glucose tolerance,<sup>23</sup> achieved a weight loss during the first year of >11% below baseline in the orlistat-treated group compared with 6% below baseline in the placebo-treated group. Over the remaining 3 years of the trial, there was a small regain in weight, such that by the end of 4 years, the orlistat-treated patients were 6.9% below baseline in compar-

## Weight Loss with Continuous and Intermittent Phentermine



**Figure.** Weight loss over 36 weeks with phentermine given continuously or intermittently. Adapted from Munro et al<sup>21</sup> with permission of the publisher. Copyright © BMJ Publishing Group Ltd, 1968.

ison with 4.1% for those receiving placebo. There was a reduction of 37% in the conversion of patients from impaired glucose tolerance to diabetes mellitus.

Orlistat has also been studied in adolescents. In 539 adolescents, orlistat 120 mg TID decreased BMI by  $0.55 \text{ kg/m}^2$  in the drug-treated group in comparison with an increase of  $+0.31 \text{ kg/m}^2$  in the placebo group.<sup>24</sup> In a meta-analysis of trials with orlistat, the weighted mean weight loss in the placebo group was  $-2.40 \pm 6.99 \text{ kg}$ , and the weight loss in those treated with orlistat was  $-5.70 \pm 7.28 \text{ kg}$  for a net effect of  $-2.87$  (95% CI,  $-3.21$  to  $-2.53$ ).<sup>25</sup>

### Safety of Orlistat

Orlistat is not absorbed to any significant degree, and its side effects are thus related to the blockade of triglyceride digestion in the intestine.<sup>19</sup> Fecal fat loss and related gastrointestinal symptoms are common initially, but they subside as patients learn to use the drug. Orlistat can cause small but significant decreases in fat-soluble vitamins. Levels usually remain within the normal range, but a few patients may need vitamin supplementation. Because it is clinically challenging to tell which patients need vitamins, it is wise to provide a multivitamin routinely with instructions to take it before bedtime. Orlistat does not seem to affect the absorption of other drugs, with the exception of acyclovir. Rare cases of severe liver injury have been reported with the use of orlistat, only 1 of which occurred in the United States, and 13 elsewhere over 10 years, at a time when an estimated 40 million people took orlistat. A causal relationship has not been established, but patients who take orlistat should contact their healthcare provider if itching, jaundice, pale-color stools, or anorexia develop.

### Treatment of the Diabetic Patient Who Is Obese

The epidemic of diabetes mellitus is following closely on the heels of the obesity epidemic. The rate of developing diabetes mellitus can clearly be slowed by weight loss,<sup>13–15,26</sup> and this is the first line of treatment. There is growing interest in the

ability of weight loss to reverse diabetes mellitus, and this has been demonstrated in association with various surgical procedures.<sup>26</sup> However, over the long term, weight loss may not prevent the eventual development of diabetes mellitus in at-risk people and may not prevent relapse in all of those who experienced diabetes mellitus reversal with weight loss, presumably due to the gradual decompensation of the pancreatic  $\beta$ -cells. Then, antidiabetic treatment of the patient is required. Table 2 lists the antidiabetic drugs that are available to treat obesity. Insulin produces a weight gain that ranges from 1.8 to  $6.6 \text{ kg}$ .<sup>7</sup> Two widely used sulfonylurea drugs (glipizide and glibenclamide) also produce weight gain in most studies that ranges from  $-0.3$  to  $4.0 \text{ kg}$ ,<sup>7</sup> and this is also true for the thiazolidinediones (rosiglitazone and pioglitazone), which lead to weight gains of 0.18 to  $1.5 \text{ kg}$ .<sup>7</sup> Other drugs are weight neutral or cause weight loss. Metformin has been in use the longest and, in clinical trials, has been shown to reduce the rate of conversion of high-risk individuals with impaired glucose tolerance to frank diabetes mellitus. Weight loss with this drug, in 1 study, was  $2.7 \text{ kg}$  in the first year.<sup>13</sup>

### Metformin

Metformin is a biguanide that is approved by the FDA for the treatment of diabetes mellitus and has a good safety profile. This drug reduces hepatic glucose production, decreases

**Table 2. Categorization of Antidiabetic Drugs by Their Effects on Body Weight**

Produce Weight Loss	Are Weight Neutral	Produce Weight Gain
Metformin	Dipeptidyl peptidase-4 inhibitors (DPP-4)	Insulin
Pramlintide	Acarbose	Sulfonylureas*
Exenatide	Miglitol	Glitazides
Liraglutide	Bromocriptine	Thiazolidinediones†

\*Glipizide, glimepiride, glibenclamide, chlorpropamide.

†Pioglitazone, rosiglitazone.

intestinal glucose absorption from the gastrointestinal tract, and enhances insulin sensitivity. One mechanism for the reduction in hepatic glucose production by metformin may depend on the phosphorylation of a nuclear binding protein (cAMP response element-binding binding protein at Ser436, AMP-activated protein kinase). This disrupts a number of other signals, including a master transcription factor, peroxisome proliferator-activated receptor- $\gamma$  coactivator 1A, which in turn leads to the suppression of hepatic glucose output.<sup>27</sup>

Most of the clinical literature on metformin deals with its use in treatment and prevention of diabetes mellitus.<sup>28-30</sup> Only a relatively few studies have focused on weight loss with metformin.<sup>14,19,31</sup> In 1 French trial called BIGPRO, metformin was compared with placebo in a 1-year multicenter study involving 324 middle-aged patients with upper-body adiposity and the insulin resistance syndrome (metabolic syndrome). The patients treated with metformin lost significantly more weight (1–2 kg) than members of the placebo group, and the study concluded that metformin may have a role in the primary prevention of type 2 diabetes mellitus.<sup>32,33</sup> In a meta-analysis of weight loss in 3 studies with metformin, Avenell et al<sup>34</sup> reported a nonsignificant weight loss at 12 months of –1.09 kg (95% CI, –2.29 to 0.11 kg). A meta-analysis of 3 studies with metformin in children and adolescents also found a nonsignificant loss of body weight (–0.17 kg, 95% CI, –0.62 to 0.28).<sup>31</sup>

The longest and best study of metformin on body weight comes from the Diabetes Prevention Program.<sup>13,14</sup> During the first 2.8 years of the double-blind, placebo-controlled trial, the metformin-treated group lost 2.9 kg (–2.5%) of their body weight versus –0.42 kg in the placebo group ( $P<0.001$ ). The degree of weight loss was related to the adherence to metformin. Those who were the most adherent lost –3.5 kg at 2 years in comparison with a small weight gain of 0.5 kg in those who were assigned to, but never took, metformin. This differential weight loss persisted throughout the 8 years of follow-up with highly adherent patients remaining 3 to 4 kg below baseline, and those who were not adherent were no different from the placebo group.<sup>14</sup>

Metformin has been used to reduce weight gain in people treated with antipsychotic drugs. In a systematic review, Bushe et al<sup>35</sup> found that metformin may have some value in reducing or preventing weight gain and change in metabolic parameters during treatment with antipsychotic medications.

### **Pramlintide**

Pramlintide is a modified form of amylin, a peptide secreted from the  $\beta$ -cell of the pancreas along with insulin. Pramlintide has been approved by the FDA for treatment of diabetes mellitus and in clinical trials produced weight loss. Leptin is a secretory product, primarily from adipocytes, that can act as a negative feedback signal to the brain and inhibit food intake. In clinical trials, leptin produced disappointing weight loss.<sup>36</sup> The combination of leptin with pramlintide, however, produced additive weight loss in a 6-month clinical trial, which may offer promise for the future,<sup>37</sup> although further studies have not been undertaken.

### **Exenatide**

Exenatide (Exendin-4) is a 39-amino-acid peptide that is produced in the salivary gland of the Gila monster lizard. It has 53% homology with glucagon-like peptide-1 (GLP-1), but it has a much longer half-life. Exenatide has been approved by the FDA for treatment of patients with type 2 diabetes who disease is inadequately controlled while being treated with either metformin or sulfonylureas. In human beings, exenatide reduces fasting and postprandial glucose levels, slows gastric emptying, and decreases food intake by 19%.<sup>38</sup> A systematic review of incretin therapy in type 2 diabetes mellitus<sup>39</sup> showed a weight loss of –2.37 kg for all GLP-1 analogues versus control, –1.44 for exenatide versus placebo injection, and –4.76 for exenatide versus insulin (which often leads to weight gain). A 24-week multicenter randomized placebo-controlled clinical trial of exenatide enrolled patients with poorly controlled diabetes with either metformin or sulfonylurea with a hemoglobin A1c between 6.6% and 10.0% and a BMI between 25.0 and 39.9 kg/m<sup>2</sup>. The decrease in caloric intake by exenatide (378±58 kcal/d), although lower, was not significantly different from placebo (295±58 kcal/d) and may reflect the difficulty to getting accurate estimates of food intake from food records. Weight loss was significantly greater and hemoglobin A1c and blood pressure were reduced more in the exenatide-treated patients.<sup>40</sup> The side effects of exenatide in humans are headache, nausea, and vomiting that are lessened by gradual dose escalation.<sup>41</sup> The interesting feature of this weight loss is that it occurred without prescribing lifestyle modification, diet, or exercise. A 26-week randomized control trial of exenatide produced a –2.3 kg weight loss in comparison with a gain of 1.8 kg in the group receiving the glargine form of insulin.<sup>42</sup>

### **Liraglutide**

Liraglutide is another GLP-1 agonist that has a 97% homology to GLP-1. This molecular change extends the circulating half-life from 1 to 2 minutes to 13 hours. Liraglutide reduces body weight. In a 20-week multicenter European clinical trial, Astrup et al<sup>43</sup> reported that daily injections of liraglutide at 1.2, 1.8, 2.4, or 3.0 mg produced weight losses of –4.8, –5.5, –6.3, and –7.2 kg, respectively, in comparison with –2.8 kg in the placebo-treated group and –4.1 kg in the orlistat-treated comparator group. In the group treated with 3.0 mg/d, 76% achieved a >5% weight loss in comparison with 30% in the placebo group. Blood pressure was significantly reduced, but there was no change in lipids. The prevalence of prediabetes mellitus was reduced by liraglutide. In a head-to-head comparison, liraglutide and exenatide produced similar amounts of weight loss (–3.24 kg with liraglutide versus –2.87 kg with exenatide). In patients with poorly controlled type 2 diabetes mellitus on maximally tolerated doses of metformin and/or sulfonylurea, liraglutide reduced mean hemoglobin A1c significantly more than did exenatide (–1.12% versus –0.79%).<sup>44</sup> Liraglutide has been approved by the European Medicines Agency and the FDA for the treatment of diabetes mellitus at a dose up to 1.8 mg/d. Although this dose is lower than the top dose used by Astrup et al,<sup>43</sup> it would be a good choice for the diabetic patient with obesity.

**Table 3. Categorization of Neurobehavioral Drugs by Their Effects on Body Weight**

Produce Weight Loss	Are Weight Neutral	Produce Weight Gain
Bupropion	Haloperidol	Tricyclic antidepressants*
Venlafaxine	Aripiprazole	Monoamine oxidase inhibitors
Desvenlafaxine		Paroxetine
Topiramate		Escitalopram
Zonisamide		Lithium
Lamotrigine		Olanzapine
Ziprasidone		Clozapine
Topiramate		Risperidone
		Carbamazepine
		Valproate
		Divalproex
		Mirtazapine

\*Nortriptyline, amitriptyline, doxepin.

### Treatment of the Patient With Neurobehavioral Disorders and Obesity

This category includes patients with obesity who are depressed, who have migraine symptoms, and who need antipsychotic drugs. Some of the approved drugs in this class produce weight gain, and others are associated with weight loss (Table 3). One option for the health provider is to change to an effective medication that produces weight loss from one that produces weight gain. The magnitude of weight gain ranges from 1.2 to 5.8 kg for valproate, 4.0 kg for lithium, 2.1 to 2.3 for risperidone, 2.8 to 7.1 kg for olanzapine, and 4.2 to 9.9 kg for clozapine for the drugs in the weight gain column.<sup>7</sup> This degree of weight gain can make continuation of treatment more difficult, and the use of weight neutral or the alternatives that produce weight loss, particularly for the individual who is obese and overweight, is good clinical practice.

#### Bupropion

Bupropion is an approved drug for treatment of depression and to help patients stop smoking. It reduces food intake by acting on adrenergic and dopaminergic receptors in the hypothalamus.

Bupropion is a norepinephrine and dopamine reuptake inhibitor that is approved for the treatment of depression and for smoking cessation. These neurotransmitters are involved in the regulation of food intake. Gadde and colleagues<sup>45</sup> reported a clinical trial in which 50 individuals with obesity were randomly assigned to bupropion or placebo for 8 weeks with a blinded extension for responders to 24 weeks. The dose of bupropion was increased to a maximum of 200 mg BID in conjunction with a calorie-restricted diet. After 8 weeks, the 18 patients in the bupropion group who remained in the study had lost -6.2% of body weight in comparison with -1.6% loss for the 13 patients in the placebo group who were still in the study ( $P<0.0001$ ). After 24 weeks, the 14 responders to bupropion lost -12.9% of initial body weight, of which 75% was fat loss as determined by DEXA.<sup>45</sup>

**Table 4. Categorization of Commonly Used Drugs That Affect Blood Pressure or Cholesterol by Their Effects on Body Weight**

Produce Weight Loss	Are Weight Neutral	Produce Weight Gain
	Selective $\beta_1$ -receptor agonists	Some $\beta_1$ -receptor agonists*
	Angiotensin converting enzyme inhibitors	Some $\alpha_2$ -receptor antagonists
	Angiotensin receptor blockers	
	Nicotinic acid	
	Statins	

\*Atenolol, metoprolol, propranolol.

In a study with uncomplicated and nondepressed people with obesity, 327 patients were randomly assigned to bupropion 300 mg/d, bupropion 400 mg/d, or placebo in equal proportions. All patients were prescribed a hypocaloric diet that included the use of liquid meal replacements. At 24 weeks, 69% of those randomly assigned remained in the study, and body weight was reduced by -5.0%, -7.2%, and 10.1% for the placebo, bupropion 300 mg, and bupropion 400 mg groups, respectively ( $P<0.0001$ ). The placebo group was randomly assigned to the 300-mg or 400-mg group at 24 weeks, and the trial was extended to week 48. By the end of the trial, the dropout rate was 41%, and the weight losses in the bupropion 300 mg and bupropion 400 mg groups were -6.2% and -7.2% of initial body weight, respectively.<sup>46</sup>

#### Topiramate

Topiramate is an anticonvulsant drug that is approved for use in certain types of epilepsy and for the treatment of migraine headache. It was shown to reduce food intake, but was not developed clinically because of the side effects at the doses selected for trial. Topiramate was found to induce weight loss in clinical trials for epilepsy treatment. Weight losses of -3.9% of initial weight at 3 months and -7.3% of initial weight at 1 year were seen. In a 6-month, placebo-controlled, dose-ranging study,<sup>47</sup> 385 patients were randomly assigned to 5 groups: topiramate at 64 mg/d, 96 mg/d, 192 mg/d, or 384 mg/d, or placebo. These doses were gradually increased over 12 weeks and were tapered off in a similar manner at the end of the trial. Weight loss from baseline to 24 weeks was -5.0%, -4.8%, -6.3%, -6.3%, and -2.6%, in the 5 groups, respectively. The most frequent adverse events were paresthesias (tingling or prickly feelings in skin), somnolence, and difficulty with concentration, memory, and attention.

### Treatment of the Patient With Cardiovascular Disease and Obesity

Cardiovascular disorders are the most common cause of death in the United States.<sup>48</sup> The past decades have seen substantial reductions in the rate of heart attack and death in the US population. A number of drugs are used to treat hypertension and other cardiovascular diseases. Although some of them can increase body weight (Table 4). Among the antihypertensive drugs, some  $\beta$ -adrenergic blockers increase weight, but other more selective ones do not. The  $\alpha_2$ -adrenergic

blockers may also be associated with a small amount of weight gain.

### Drugs Reviewed in 2010 by FDA Advisory Panels

#### *Combination of Topiramate and Phentermine*

Some of the side effects of topiramate appear to be reduced when it is combined with phentermine. This pairing has been tried in clinical trials in 1 of 3 combinations: 3.75, 7.5, or 15 mg of phentermine combined, respectively, with 23, 46, or 92 mg of topiramate. This drug combination was reviewed by a panel at the FDA in 2010. The Advisory Panel voted against approval of the drug because of concerns about side effects. Additional evaluation is underway. A clinical trial with this combination included individuals with 3 or more comorbidities (diabetes mellitus, impaired fasting glucose, hypertension, dyslipidemia, and elevated waist circumference) and BMI 27 to 45 kg/m<sup>2</sup>.<sup>49</sup> The LEARN Manual provided the behavioral program for this trial. Two doses of topiramate and phentermine were used (mid and high dose) against a placebo. At the start, the medication was titrated over 4 weeks to reduce side effects from topiramate. A total of 2487 patients were randomly assigned, 994 to placebo, 498 to the mid dose, and 995 to the higher dose. At 56 weeks, weight loss was -1.4 kg, -8.1 kg, and -10.2 kg for those assigned to placebo, mid dose, and high dose. The percentage of those losing >5% was 21%, 62%, and 70% for placebo, mid dose, and higher dose, respectively. The percentage losing greater than 10% was 7%, 37% and 48% for the same groups, respectively.<sup>49</sup> At the end of 1 year, there was significant improvement in all risk factors in the high-dose group, and all but diastolic blood pressure and LDL-cholesterol in the middle dose group. The most common adverse events were dry mouth, paraesthesia, constipation, insomnia, dizziness, and dysgeusia. As for depression and anxiety, 4% patients assigned to placebo, 4% to phentermine 7.5 mg plus topiramate 46.0 mg, and 7% to phentermine 15.0 mg plus topiramate 92.0 mg had depression-related adverse events; and 3%, 5%, and 8%, respectively, had anxiety-related adverse events.

#### *Combination of Bupropion and Naltrexone*

As noted above, bupropion reduces food intake by acting on adrenergic and dopaminergic receptors in the hypothalamus. Naltrexone is an opioid receptor antagonist with minimal effect on weight loss on its own. The rationale for combining bupropion with naltrexone is that naltrexone might block inhibitory influences of opioid receptors activated by the  $\beta$ -endorphin that is released in the hypothalamus and stimulates feeding, while allowing  $\alpha$ -melanocyte-stimulating hormone which reduces food intake to inhibit food intake.<sup>50</sup> With this rationale, the combination of bupropion and naltrexone were tested to validate the concept and then to show long-term effects. Bupropion was used at a dose of 360 mg/d, halfway between the doses described earlier. Naltrexone has been tested at 16, 32, and 48 mg/d in a dose-ranging study, but the later trials have used in doses of 32 and 48 mg/d.

The clinical program designed to establish the use of this combination consists of 4 main trials, called Contrave Obesity Research or COR trials. COR-I used both 16 and 32 mg

of naltrexone with 360 mg/d of bupropion; COR II used a single 32-mg dose of naltrexone with 360 mg of bupropion, with rerandomization to 32 mg/d or 48 mg/d of naltrexone + bupropion for nonresponders at week 28. The other 2 trials are COR-diabetes and COR-BMod that examine the effect of the drug combination in diabetics and for maintenance of weight loss. Contrave is the name of the combination of bupropion and naltrexone. This drug combination was reviewed by a FDA Advisory Panel in December 2010, and the Panel recommended approval. The letter from the FDA indicated that a preapproval trial of drug safety would be required. The company is currently reviewing options for potential uses of this combination.

In a 52-week multicenter randomized, placebo-controlled trial, the participants were predominantly younger women whose body weight was nearly 100 kg.<sup>50</sup> The combination of bupropion (360 mg) and naltrexone at 16 or 32 mg produced a greater weight loss and decrease in waist circumference than placebo. The decrease in blood triglycerides, HDL-cholesterol, glucose, and insulin improved with the degree of weight loss. Only with weight losses of >10% did blood pressure and pulse show a significant decrease. Nausea, constipation, and headache were among the more prominent side effects. There was no evidence of increased suicidal thoughts. The failure of blood pressure to fall until there was significant weight loss is a concern, and approval of the drug will probably hinge on a cardiovascular outcomes study, either pre- or postmarketing.

#### *Lorcaserin*

Lorcaserin has been evaluated in clinical trials, including 1 large study<sup>52</sup> that demonstrated modest weight loss and acceptable tolerability and toxicity. However, when reviewed by the FDA Advisory Panel in 2010, it was revealed that preclinical toxicology studies in animals showed increased risk for several types of tumors. The company is evaluating the data and ways in which it might answer the FDA concerns.

### Drugs in Clinical Trial

#### *Liraglutide*

This drug has already been discussed, but, in this context, it should be noted that the company is conducting multicenter clinical trials with the anticipation of filing a New Drug application with the FDA for its use in treatment of obesity.

#### *Tesofensine*

Tesofensine is a multiamine reuptake inhibitor, in many ways similar to sibutramine, which was withdrawn from the market for treating obesity in 2010. In one 6-month clinical trial this drug produced dose-related weight loss with the highest dose producing >10% weight loss.<sup>53</sup> However, as with sibutramine, there were demonstrated increases in blood pressure and pulse that will be problematic, and there has been no further clinical investigation of this compound.

### Conclusions

Medications are useful in treatment of the patient with obesity because they can reinforce behavioral intentions that lead to lifestyle change. At present, only 1 drug is approved for

long-term treatment of patients with obesity, and the current approach to medicating the patient with obesity is usually to wait until a comorbidity has developed and to medicate for control of the comorbidity. Although there are medications under consideration by the FDA for a weight loss indication, it is still possible, today, to adopt a weight-centric approach to chronic disease management. This strategy has inherent appeal; obesity is the root cause of many chronic diseases. Physicians should adopt an attitude in their prescribing of, first, doing no harm, ie, avoiding medications that promote weight gain. Second, when possible, medications that promote weight loss should be prescribed. Although the future points to use of combinations of medications for weight management and evaluation of antidiabetic drugs for weight loss indication, it is time for physicians to engage weight-centric management in their prescribing.

### Disclosures

Dr Bray is an occasional consultant to Takeda Global Research and a Nutrition Advisory Board member of Herbalife. Dr Ryan has served for the past 20 years as a paid advisor to many industrial entities that make medications or provide commercial products for weight loss. She has not accepted remuneration for these activities since January 2008. Previous paid affiliations include Abbott, Ajinomoto, Amylin, Arena, GSK, Merck, Novo Nordisk, Orexigen, NutriSystem, Sanofi-aventis, Shionogi, Takeda, Vivus, and Weight Watchers. She received income from speaking engagements in the past 12 months from Cleveland Clinic Educational Foundation, American Gastroenterology Association, American Association for the Advancement of Science, Medical Exchange International, Cardiometabolic Health Congress, and Medical Foundation of Spain.

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