Case Presentation

An obese, 55-year-old man with metabolic syndrome meeting all 5 of the Adult Treatment Plan III National Cholesterol Education Program criteria, including hypertension, type 2 diabetes mellitus, atherogenic dyslipidemia with low high-density lipoprotein cholesterol, elevated triglycerides, and abdominal obesity with a high waist circumference, is having trouble losing weight on his own through lifestyle intervention. He has hired a personal trainer and is working out 3 times a week but has lost no weight. He enjoys eating out with his wife or his business associates 3 to 4 times per week. This is where he reports consuming most of his excess calories in both food and alcohol. He takes 7 medications to control his obesity-related comorbidities. These include: Atenolol 50 mg once per day, valsartan 80 mg once per day, glipizide 5 mg twice per day, pioglitazone 30 mg once per day, metformin 500 mg twice per day, atorvastatin 40 mg once per day, and insulin glargine 20 U nightly. Anthropometrics and laboratory data include a weight of 264 lbs, height 5 feet 10 inches, body mass index (BMI) 38 kg/m², waist circumference 47 inches, blood pressure 150/95 mmHg, hemoglobin A1c 7.2%, fasting blood glucose 150 to 175 mg/dL, total cholesterol 220 mg/dL, triglycerides 300 mg/dL, low-density lipoprotein cholesterol 130 mg/dL, and high-density lipoprotein cholesterol 40 mg/dL.

The 2013 guidelines encourage the provider to help patients lose weight with lifestyle modification. Adding a low-calorie diet to his exercise routine would be an important first step to enhance lifestyle modification. Another important step for the provider would be to evaluate the medical regimen to determine if there are any medications that might exacerbate weight gain, and to consider alternatives.

If diet, exercise, and antiobesity agents do not achieve weight loss and weight maintenance, he is a candidate for bariatric surgery, based on the presence of type 2 diabetes mellitus and BMI 35 to 40 kg/m². The 2013 American Heart Association/American College of Cardiology/The Obesity Society guidelines acknowledge the National Institutes of Health guidelines for bariatric surgery, which recommend a BMI ≥ 40 kg/m² or >35 with at least 1 serious comorbidity, such as type 2 diabetes mellitus, coronary artery disease, sleep apnea, or hypertension.

American Association of Clinical Endocrinologists diabetes management guidelines recommend avoiding hypoglycemia and weight gain while administering diabetes medications to those with prediabetes and type 2 diabetes mellitus and to enhance lifestyle modification. The medications to titrate downward to avoid hypoglycemia while undergoing weight loss with a diet include the antihyperglycemic agents insulin, glipizide, and pioglitazone. These medications should be slowly reduced based on blood glucose, one at a time, using an organized plan.
discussed with the patient. Blood glucose fingersticks should be checked by the patient 3 times per day during this process. As blood glucose declines toward 100 mg/dL, medications should be decreased to prevent hypoglycemia. These changes can be facilitated by consultation with an endocrinologist or obesity medicine specialist. However, an example of a down titration regimen would be either halving or cutting the medication by one-third the dose, 1 medication at a time, until each medication is stopped. The first medication in this patient’s list to decrease would be the insulin, because it is an injectable agent and least appealing to patients.

During down titration, metformin can be maximized to 1000 mg twice a day, and a gluconolike peptide-1 agonist, like liraglutide or exenatide, could be added, based on American Association of Clinical Endocrinologists guidelines.6 Canagliflozin or dapagliflozin, sodium-glucose cotransporter-2 inhibitors, can also be considered. All these drugs have been associated with weight loss while ameliorating blood glucose and hemoglobin A1c.

The provider should counsel the patient to continue down titration of antihyperglycemic medications that cause weight gain until most or all have been stopped based on blood glucose values during the weight loss period. In cases where type 2 diabetes mellitus has been present for more than several years, the severity of diabetes mellitus is high, or both occur, it may not be possible to stop all hypoglycemic medications. The blood glucose values will guide the provider and the patient.

This patient should also be weaned off atenolol, if possible, replacing it with another agent, such as a thiazide diuretic, angiotensin-converting enzyme inhibitor, or angiotensin receptor blockers. β-blocking agents may cause weight gain and should not be considered first-line agents for hypertension in the setting of obesity and type 2 diabetes mellitus.

Should weight loss plateau following these changes, obesity pharmacotherapy such as lorcaserin or the phentermine/topiramate combination can be added.

If the patient is placed on phentermine/topiramate combination, blood pressure should be monitored carefully because it is already elevated. Alternatively, lorcaserin can be considered. For those on selective serotonin reuptake inhibitors, lorcaserin is relatively contraindicated owing to the risk of serotonin syndrome. This warning also pertains to the use of serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, triptans, bupropion, dextromethorphan, and St John’s Wort.

This case is a good starting point to discuss the American Heart Association/American College of Cardiology/The Obesity Society update of the earlier National Institutes of Health/National Heart, Lung, and Blood Institute Obesity guidelines (Obesity 1),7 recently Food and Drug Administration–approved antiobesity medications, and the newest bariatric surgery option, the sleeve gastrectomy.

First, the new American Heart Association/American College of Cardiology/The Obesity Society guidelines (Obesity 2) were released in 2013 and focus on diets, behavioral approaches, and surgical options for obesity.8

There are 5 recommendations (Table 1). The first recommendation helps the provider identify patients who need to lose weight and uses BMI as a first step to assess health risks. The waist circumference should also be measured, because it is a risk factor.

The second recommendation advises the provider to counsel patients who need to lose weight on lifestyle changes and how much weight is needed for health benefit. As little as 3% to 5% weight loss can reap benefits in terms of lowering lipids, hemoglobin A1c, and cardiovascular risk. More weight loss will produce greater benefits.

The third recommendation was developed after an investigation of the literature concerning diets of differing macronutrient content for weight loss. The conclusion after investigating the literature was that there is no ideal diet for weight loss and that the diet that seems most befitting the patient should be the one to prescribe, whether a low-carbohydrate, low-fat, Mediterranean style, or other low-calorie diet. The evidence is clear that it is the reduction of the caloric content of the diet that matters for weight loss.

The fourth recommendation was based on the literature on behavioral interventions for weight loss, which concluded that a high-intensity intervention of ≥14 sessions over 6 months led by a trained interventionist delivered the best results for weight loss. Interventions should last at least ≥1 year to be successful long term.

The fifth recommendation reiterated the indications for pharmacotherapy for obesity (BMI >30 or 27–30 with a comorbidity) from Obesity 1; no other mention was made in Obesity 2 regarding the various pharmaeutic options because there was very little in the literature on the new drugs available at the time.8

Based on these 5 recommendations, the first steps in treating our patient would be to provide diet and behavior counseling by a trained interventionist with or without pharmacotherapy. This should last at least 6 months before considering surgery.

Current medications that are Food and Drug Administration approved for obesity prescription as of the end of 2014 (Table 2) include phentermine/topiramate, naltrexone/bupropion, lorcaserin, phentermine (short-term), orlistat, and liraglutide.9–12 Orlistat is also available over the counter at half the prescription dose. Initial options include any of these long-term, with the exception of phentermine. Phentermine was approved for use as an antiobesity agent in 1959 for short-term use and, therefore, should be used for only 3 months at a time. Long-term options include phentermine/topiramate, which is dosed initially at 3.75 mg phentermine/23 mg topiramate once per day for 2 weeks, and then escalated to the most commonly used dose of 7.5 mg phentermine/46 mg topiramate once per
day. If a weight loss plateau is reached, there are two further doses that can be prescribed: 11.25 mg phentermine /69 mg topiramate and 15 mg phentermine /92 mg topiramate. This medication can be prescribed to this patient, but his blood pressure should be monitored closely, because it is not adequately controlled with his medications at the time of the visit. Naltrexone/bupropion is initially dosed at 8 mg/90 mg per day and is slowly titrated upward weekly until the maximum dose is reached at 2 pills twice per day (32 mg/360 mg). Blood pressure should be closely monitored with this preparation as well. Lorcaserin is dosed at 10 mg twice per day and has not been shown to elevate blood pressure. Liraglutide is initially dosed at 0.6 mg subcutaneous injection once a day and increased weekly in increments of 0.6 mg/d until a maintenance dose of 3 mg once a day is reached. In this patient’s case, there is no clear choice, and the decision regarding choice of drug should be made by talking to the patient about the benefits and risk of each drug.

A surgical option is possible for this patient because he meets the BMI criteria for surgery. Obesity 2 is clear in advising health providers to counsel patients who meet surgical criteria and have failed

more conservative obesity treatments that surgery is an available option for weight loss and weight maintenance. This patient meets criteria, because he has a BMI of 38 and has type 2 diabetes mellitus, hypertension, and elevated lipids that are related to obesity.

This patient was placed on a diet and behavioral program for 3 months while preparing for surgery, and phentermine/topiramate was added at the 1-month visit. He was evaluated for bariatric surgery, and he and his surgeon opted for the sleeve gastrectomy after a 7% preoperative weight loss goal was achieved with diet, a behavioral program, and phentermine/topiramate.

The sleeve gastrectomy was chosen because of the simplicity of the procedure in comparison with the gastric bypass (partial gastrectomy versus gastrectomy plus bypass of a portion of small intestine). The sleeve gastrectomy, roux-en-y gastric bypass, and laparoscopic adjustable gastric band are the most commonly performed bariatric procedures in the United States. These procedures can produce 20% to 35% total body weight loss that is sustained at 2 years. Ten-year follow-up data show some weight regain of ≈7%, but the majority of patients keep most of the weight off. In addition, most comorbidities resolve or improve out to 10 years, with the exception of hypertension.

In the end, this patient was able to achieve a total weight loss of 40 lbs, or nearly 15% of his baseline weight, with diet, exercise, and phentermine/topiramate in the 3 months while being evaluated for surgery. He opted to hold off on surgery and maintain the weight loss with the changes in his medications, a reduced calorie diet, and exercise. He was weaned completely off the insulin, sulfonylurea, and thiazolenedione, and he has a hemoglobin A1c of 5.9% on metformin 1000 mg twice per day, liraglutide 1.8 mg once per day, and canagliflozin 100 mg twice per day. His blood pressure is under good control, with a smaller dose of valsartan at 40 mg once per day after weaning off atenolol. He is currently still taking a statin.

For this patient, medical treatment has been successful. He has made lifestyle changes that are consistent with those seen in successful weight loss and maintenance patients enrolled in the Weight Loss Registry. Patients who keep a ≥10% weight loss for longer than 2 to 5 years as seen in the Weight Loss Registry generally weigh themselves almost every day, eat a low-calorie diet, exercise to expend the equivalent of ≥2500 kcal/wk, and eat breakfast daily. This patient could also have achieved substantial weight reduction and weight maintenance from the sleeve gastrectomy. The choice between a sleeve gastrectomy and the roux-en-y gastric bypass is a decision that should be made during the discussion between the surgical team and the patient. Obesity 2 guidelines concluded that there was insufficient evidence in the literature to compare weight loss, complications, and other outcomes between the roux-en-y gastric bypass and the sleeve gastrectomy. However, large databases generally confirm that the most weight loss results from the roux-en-y gastric bypass, then the sleeve gastrectomy, with the least weight loss from the laparoscopic adjustable gastric band. The most commonly performed surgical procedures in the United States (the roux-en-y gastric bypass and the sleeve gastrectomy) have a higher success rate, with most patients maintaining weight loss for 5 years or more. This is in contrast to the other procedures, where weight regain is common after 2 years. The benefits of the sleeve gastrectomy include lower complications and a faster recovery time, which is important for patients who are at high risk for complications. The roux-en-y gastric bypass, on the other hand, has a higher success rate in terms of weight loss, but it also has a higher risk of complications. It is important to note that the decision-making process should be individualized and based on the patient’s medical history, lifestyle, and personal preferences.
Table 2. Pharmacotherapy for Obesity in the United States. December 2014

<table>
<thead>
<tr>
<th>Drug (Generic)</th>
<th>Dosage</th>
<th>Mechanism of Action</th>
<th>Weight Loss Above Diet and Lifestyle</th>
<th>Duration of Clinical Studies</th>
<th>FDA Drug Approval Date</th>
<th>Common Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine resin</td>
<td>Adipex P (37.5 mg)</td>
<td>Norepinephrine-releasing agent</td>
<td>Mean Weight Loss (%) or kg*; Duration of Clinical Studies</td>
<td>1960s</td>
<td></td>
<td>Headache, Elevated BP, Elevated HR, Insomnia, Dry mouth, Constipation, Anxiety</td>
<td>Anxiety disorders (agitated states), History of heart disease, Uncontrolled hypertension, Seizure, MAOIs, Pregnancy and breastfeeding, Hyperthyroidism, Glaucoma, History of drug abuse, Sympathomimetic amines</td>
</tr>
<tr>
<td></td>
<td>37.5 mg/d</td>
<td></td>
<td>3.6 kg (7.9 lb)</td>
<td>2–24 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ionamin (30 mg)</td>
<td>Norepinephrine-releasing agent</td>
<td>30–37.5 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30–37.5 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phentermine resin</td>
<td>Adipex P (37.5 mg)</td>
<td>Norepinephrine-releasing agent</td>
<td>Mean Weight Loss (%) or kg*; Duration of Clinical Studies</td>
<td>1960s</td>
<td></td>
<td>Headache, Elevated BP, Elevated HR, Insomnia, Dry mouth, Constipation, Anxiety</td>
<td>Anxiety disorders (agitated states), History of heart disease, Uncontrolled hypertension, Seizure, MAOIs, Pregnancy and breastfeeding, Hyperthyroidism, Glaucoma, History of drug abuse, Sympathomimetic amines</td>
</tr>
<tr>
<td></td>
<td>37.5 mg/d</td>
<td></td>
<td>3.6 kg (7.9 lb)</td>
<td>2–24 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ionamin (30 mg)</td>
<td>Norepinephrine-releasing agent</td>
<td>30–37.5 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30–37.5 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>Tenuate (75 mg)</td>
<td>Norepinephrine-releasing agents</td>
<td>3.0 kg (6.6 lb)</td>
<td>6–52 wk</td>
<td>1960s</td>
<td>See Phentermine resin</td>
<td>See Phentermine resin</td>
</tr>
<tr>
<td></td>
<td>75 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic weight management</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide</td>
<td>3.0 mg injectable</td>
<td>GLP-1 agonist</td>
<td>5.8 kg (12.8 lb)</td>
<td>1 y</td>
<td>2014</td>
<td>Nausea</td>
<td>Medullary thyroid cancer history</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorcaserin (10 mg)</td>
<td>10 mg twice a day</td>
<td>5HT2c receptor agonist</td>
<td>3.6 kg (7.9 lb), 3.6%</td>
<td>1 y</td>
<td>2012</td>
<td>Headache</td>
<td>Pregnancy and breastfeeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naltrexone/bupropion (NB)</td>
<td>32 mg/360 mg</td>
<td>Reuptake inhibitor of dopamine and norepinephrine (B) and opioid antagonist (N)</td>
<td>4.8%</td>
<td>2014</td>
<td></td>
<td>Nausea</td>
<td>Use with caution: SSRI, Dizziness, SNRI/MAOI, Fatigue, St John’s wort, Constipation, Triptans, Buproprion, Dextromethorphan, Uncontrolled hypertension, seizure disorders</td>
</tr>
</tbody>
</table>

(Continued)
gastrectomy) are successful in producing and maintaining weight losses of 25% to 32% of initial body weight chiefly by altering the gut hormone milieu responsible for influencing appetite and satiety at the level of the hypothalamus.\footnote{17}

**Summary and Recommendations**

Patients with obesity and metabolic syndrome on multiple medications for each condition should be managed with intensive behavioral therapy, including changes in diet and physical activity. Evaluate medications to determine if any may exacerbate weight gain and obesity. A dietary and exercise prescription combined with a plan to wean off medications that enhance weight gain is appropriate. Alternative medications should be weight neutral or those that may cause weight loss. A meta-analysis and guidelines on using commonly prescribed medications that cause weight gain and weight loss were published by the Endocrine Society.\footnote{10} If these initial low-risk steps do not produce weight loss, weight loss medications can be considered. If BMI is >40 kg/m\(^2\) or >35 with comorbidities, bariatric surgery should be considered and discussed with the patient.

**Disclosures**

Dr. Apovian reports personal fees from Merck, Johnson & Johnson, Arena, Nutrisystem, Scientific Intake, Novo Nordisk,
EnteroMedics, and Zafgen; grants and personal fees from Amylin, Sanofi-Aventis, Orexigen, and Takeda; grants from Aspire Bariatrics, GI Dynamics, and Myos; and has an ownership interest in Science-Smart LLC outside the submitted work. Dr. Aronne has participated in advisory boards/acted as a consultant for Amylin Pharmaceuticals, Ethicon Endo-Surgery Inc., GlaxoSmithKline Consumer Healthcare LP, Novo Nordisk, Orexigen Therapeutics, Inc., VIVUS Inc., Takeda Pharmaceuticals, Jamieson Laboratories, Pfizer, Inc., Healthcare Research Consulting Group, Marwood Group, Eisai, Inc., Rhythm, Johnson & Johnson, GI Dynamics, GLG and Myos Corp., and has ownership interest in Cardiometabolic Support Network, LLC, MYOS Corporation, and BMIQ.

References
The 2013 American Heart Association/American College of Cardiology/The Obesity Society Guideline for the Management of Overweight and Obesity in Adults: What Is New About Diet, Drugs, and Surgery for Obesity?

Caroline M. Apovian and Louis J. Aronne

_Circulation_. 2015;132:1586-1591
doi: 10.1161/CIRCULATIONAHA.114.010772

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/132/16/1586

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/