Weighing the Options for Obesity Meds

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In June 2013, the American Medical Association classified obesity as a disease. Since then, several medical societies have published guidelines to help clinicians improve care of affected patients. One avenue is, of course, pharmacologic treatment.

Until recently, there was only one FDA-approved medication for chronic weight loss on the market: orlistat, which was approved in 1999. (Phentermine and diethylpropion are only indicated for short-term use). After a long hiatus, the FDA approved two additional agents (phentermine/topiramate and lorcaserin) in 2012 and another two (liraglutide and bupropion/naltrexone) in 2014.

While clinicians appreciate having options for managing their patients' conditions, in this case, many are overwhelmed by the choices. Most health care providers have not received formal training in obesity management. This column will attempt to fill the information gap in terms of what agents are available and what factors should be assessed before prescribing any of them.

Proviso: Experts claim obesity is a chronic disease, similar to hypertension, and should be managed as such. Although not discussed here, the most important aspect of weight loss and maintenance is lifestyle intervention (diet, exercise, and behavioral modification). It should be emphasized that no medication works by itself; all should be used as an adjunct tool to reinforce adherence to lifestyle changes.[1] Furthermore, patients may be disappointed to learn that without these changes, the weight may return when they cease medication use.

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CASE Deb, age 61, presents to your office for routine follow-up. She has a history of type 2 diabetes, dyslipidemia, hypertension, atrial fibrillation, depression, and chronic back pain due to a herniated disc. Her medications include insulin glargine, glyburide, pioglitazone, atorvastatin, metoprolol, paroxetine, and acetaminophen/hydrocodone.

Her vital signs include a blood pressure of 143/91 mm Hg and a pulse of 93 beats/min. She has a BMI of 37 and a waist circumference of 35 in.

Deb, concerned about her weight, would like to discuss weight-loss options. She has tried three different commercial programs; each time, she was able to lose 30 to 50 lb in three to six months but regained the weight once she stopped the program. She reports excessive appetite as the main reason for her rebound weight gain. Her exercise is limited due to her back pain.

She recently tried OTC orlistat but could not tolerate it due to flatulence and fecal urgency. She reports an incident in which she couldn't reach the bathroom in time.

DISCUSSION

The Endocrine Society's recommended approaches to obesity management include diet, exercise, and behavioral modification for patients with a BMI ≥ 25. The addition of pharmacotherapy can be considered for those with a BMI ≥ 30 or with a BMI ≥ 27 and one or more weight-related comorbidities (eg, diabetes, dyslipidemia, hypertension). This matches the FDA-approved product labeling for chronic weight-loss medications. Bariatric surgery should be considered for patients with a BMI ≥ 40 or with a BMI ≥ 35 and at least one weight-related comorbidity.

Orlistat

Orlistat is available OTC in a 60-mg thrice-daily form. A higher dosage (120 mg tid) is available via prescription. Orlistat decreases fat absorption in the gastroin-

testinal (GI) tract by inhibiting GI lipase. Average weight loss with orlistat is 3% at first and second year, and, when compared with placebo, 2.4% greater at four years.[2]

Orlistat should be prescribed with a multivitamin due to decreased absorption of fat-soluble vitamins. It is contraindicated in patients with malabsorption syndrome and gallbladder disease (> 2% incidence[3]). It can increase cyclosporine exposure, and rare cases of liver failure have been reported. The most common adverse effect is related to steatorrhea. Of the available options, orlistat is the only medication that has no effect on neurohormonal regulation in appetite control and metabolic rate, which may be a limiting factor.

CASE POINT Due to Deb's intolerance of and embarrassment with GI adverse effects, she requests an alternative medication.

Lorcaserin

Lorcaserin is a selective serotonin 2C receptor agonist that reduces appetite by affecting anorexigenic pro-opiomelanocortin (POMC) neurons in the hypothalamus. Of note, lorcaserin "selects" the 2C receptor instead of 2A and 2B; 2B receptors are found in both aortic and mitral valves, which may explain the association between fenfluramine/phentermine (commonly known as "fen/phen" and withdrawn from the market in 1997) and possible cardiac valvulopathy. (Fenfluramine is an amphetamine derivative that nonselectively stimulates serotonin release and inhibits reuptake.)

Lorcaserin comes in a 10-mg twice-daily dosage. In studies, patients taking lorcaserin had an average weight loss of 3.3% more than those taking placebo at one year; weight loss was maintained through the second year for those who continued on medication. However, those who stopped the medication at one year had regained their weight by the two-year mark.[4]

It is recommended that the medication be discontinued if patients don't achieve a loss of more than 5% of body weight by 12 weeks.

In a study that enrolled diabetic patients, lorcaserin also demonstrated a 0.9% reduction in A1C, which is similar to or even better than some oral antidiabetic medications.[4] However, since the manufacturer was not planning for an antidiabetic indication, A1C was only a secondary endpoint. The reduction is most likely due to decreased caloric intake and weight loss.

The most common adverse effects of lorcaserin include headache, dizziness, and fatigue. The discontinuation rate due to intolerance was 8.6%, compared to 6.7% with placebo.[5]

Although this was not observed in clinical studies, coadministration of lorcaserin (a serotonin receptor agonist) with other serotonergic or antidopaminergic agents can theoretically cause serotonin syndrome or neuroleptic malignant syndrome–like reactions. Caution is therefore advisable when prescribing these agents. The package insert carries a warning for cardiac valvulopathy due to fen/phen's history and a lack of long-term cardiovascular safety data.

CASE POINT Deb is taking paroxetine (an SSRI) for her depression. Since you are concerned about serotonin syndrome, you decide to keep exploring options. Checking the package insert for phentermine/topiramate, you learn that it does not have a potential adverse reaction related to co-administration with SSRIs.

Phentermine/Topiramate

Phentermine, a sympathomimetic medication, was approved for short-term (12-week) use for weight loss in the 1960s. Topiramate, an antiseizure and migraine prophylactic medication, enhances appetite suppression—although the exact mechanism of action is unknown.[1]

Four once-daily doses are available: 3.75/23 mg, 7.5/46 mg, 11.25/69 mg, and 15/92 mg. Dosing starts with 3.75/23 mg for two weeks, then increases to 7.5/46 mg. If a loss of 5% or more of body weight is achieved, the patient can continue the dosage; if not, it can be increased to 11.25/69 mg for two weeks and then to 15/92 mg. The average weight loss for mid and maximum dose was 6.6% and 8.6% greater than placebo at one year.[5]

Commonly reported adverse effects include paraesthesia, dysgeusia (distortion of sense of taste), dizziness, insomnia, constipation, and dry mouth. Due to phentermine's sympathomimetic action, mild increases in heart rate and blood pressure were reported. The Endocrine Society recommends against the use of phentermine in patients with uncontrolled hypertension and a history of heart disease.[1]

Weight loss is generally not recommended during pregnancy, and all weight loss medications are classified as category X for pregnancy. Strict caution is ad-

vised with this particular agent, as topiramate has known teratogenicity and therefore comes with a Risk Evaluation Mitigation Strategy. Patients must be advised to use appropriate contraception while taking topiramate, and a pregnancy test should be performed before medication commencement and monthly thereafter.

Abrupt cessation of topiramate can cause seizure. When taking the 15/92-mg dosage, the patient should reduce to one tablet every other day for at least one week before discontinuation.

CASE POINT Deb's blood pressure is still not at goal. This, along with her history of atrial fibrillation and high pulse, prompts you to consider another option.

Bupropion/Naltrexone

Bupropion, a widely used antidepressant, inhibits the uptake of norepinephrine and dopamine and thereby blocks the reward pathway that various foods can induce. Naltrexone, an opioid antagonist, blocks the opioid pathway and can be helpful in enhancing weight loss.

This combination comes in an 8/90-mg tablet. The suggested titration regimen is to start with one tablet per day and increase by one tablet every week, up to the maximum dosage of two tablets twice a day. Average weight loss was 3.1% greater than placebo at one year with the maximum dosage. An A1C reduction of 0.6% was seen in diabetic patients.[6] It is recommended to stop the medication and seek an alternative treatment option if > 5% loss of body weight is not achieved by 12 weeks.

GI adverse effects (eg, nausea and vomiting) are common; these can be reduced with a slower titration regimen or by prescribing a maximum of one tablet twice daily (instead of two). Every antidepressant carries suicidal risk, and caution is advised with their use. Bupropion can also lower the seizure threshold, and it is contraindicated for patients with seizure disorder. It is also contraindicated in patients who are undergoing abrupt cessation of alcohol, benzodiazepines, or barbiturates. It can increase pulse and blood pressure during early titration; regular blood pressure monitoring is warranted.

CASE POINT Due to Deb's opioid usage and uncontrolled hypertension, you discuss a final option that was recently approved for weight loss.

Liraglutide

This glucagon-like peptide-1 (GLP1) receptor agonist affects the brain to suppress/control appetite, slows down gastric emptying, and induces early satiety. A 3-mg dosage was approved in December 2014, but 0.6-, 1.2-, and 1.8-mg dosages have been available since 2010 for patients with type 2 diabetes.

Average weight loss was 4.5% greater than placebo at one year.[7] If < 4% weight loss is achieved by 16 weeks, consider using an alternative agent.

The most common adverse effect is GI upset, which could be related to the mechanism of action (slower gastric emptying). Although self-reported GI upset was high (39%), the actual discontinuation rate was low (2.9% for nausea, 1.7% for vomiting, and 1.4% for diarrhea).[3]

This adverse effect could, in certain contexts, be considered "wanted," since it discourages overeating or eating too quickly. My clinical pearl is to tell patients taking liraglutide that they are "trapped" and have to eat smaller portions and eat more slowly or they will be more prone to GI effects. With this strategy, we can encourage portion control and responsibility for behavior. (Please note that this is my experience with the diabetic dosage of liraglutide; I do not have any clinical experience with the obesity dosage, which was not clinically available at the time of writing.)

Both branded versions of liraglutide carry a black-box warning for thyroid C-cell tumors, which were observed in rodents but unproven in humans. The medication is contraindicated in patients with medullary thyroid cancer or with multiple endocrine neoplasia 2 syndrome. Increased rates of acute pancreatitis, cholecystitis, and cholelithiasis were seen in studies, and caution is advised.

A WORD ABOUT MEDS THAT CAUSE WEIGHT GAIN

The Endocrine Society has published a list of medications that can influence weight gain, along with suggestions for alternative agents that are either weight neutral or promote weight loss.

Note that our case patient, Deb, is taking insulin, a sulfonylurea (glyburide), and thiazolidinedione (pioglitazone) for diabetes—all of which can promote weight gain. Guidelines suggest choosing metformin, DPP4 inhibitors, GLP1 agonists, amylin analog, and SGLT2 inhibitors instead when weight gain is a major concern.[1]

Guidelines also suggest using ACE inhibitors, angiotensin receptor blockers, and calcium channel blockers instead of β-

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blockers as firstline antihypertensive therapy for diabetic patients.[1] Adequate blood pressure and lipid control are imperative in diabetes management.

CASE POINT Deb would need better hypertension control before she considers weight-loss medication. Since she is also taking paroxetine, which among SSRIs is associated with greatest weight gain, a changed to fluoxetine or sertraline should be considered.[2]

CONCLUSION

There are now five medications approved by the FDA for chronic weight loss, with more to come. Agents with different mechanisms of action give us options to help obese patients and hopefully reduce and prevent obesity-related complications. It is important for clinicians to be competent in managing obesity, especially since we live in an era in which the disease is considered pandemic. **CR**

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