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Obesity and Related Sequelae: Are Medications the Answer?

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Obesity, and its related morbidities, is a major health concern worldwide.[1] In the U.S., approximately 69% of people are overweight and 35% of these are obese.[2] Oregon fares better than the national average but the numbers are still alarming: 60% of the adult population is overweight and 26% of these are obese.[3] Obesity is linked with many chronic diseases and staggeringly high medical costs.[4] Obesity increases the risk of several health conditions including type 2 diabetes mellitus (T2DM), cardiovascular diseases, stroke, and some cancers.[4,5] Relative to the non-obese weight population, persons with obesity incur 46% greater inpatient costs and an 80% increase in prescription medications costs.[4] In 2008, costs associated with obesity and its complications cost $147 billion nationwide.[4]

Definitions of Overweight, Obesity, and Weight Loss Success

The International Obesity Task Force defines obesity as a body mass index (BMI) of 30 kg/m^2 or greater.[1] The U.S. Food and Drug Administration (FDA) subdivides obesity into 3 classes based on BMI: class I (30.0-34.9 kg/m^2), class II (35.0-39.9 kg/m^2), and class III ($\geq$40 kg/m^2).[6,7] Industry guidance for obesity treatment by the FDA considers treatments to be effective if: 1) there is a statistically significant difference in mean weight loss of 5% or more between the drug and placebo, or 2) at least 35% of subjects lose at least 5% body weight and the difference in weight loss between the drug and placebo is statistically significant.[6]

Treatment Modalities for Obesity

An increasing number of treatment options are available for obese patients unable to successfully lose weight and keep weight off with behavioral interventions alone. Bariatric surgery can lead to body weight reductions of 30-40% as well as a reduction in obesity-related comorbidities.[5] Historically, bariatric surgery was reserved for patients with extreme obesity (BMI ≥40 kg/m^2 or ≥35 kg/m^2 with comorbidities), but recent research has led to FDA approval of bypass surgery for an expanded subset of the population (BMI ≥35 kg/m^2 or ≥30 kg/m^2 with at least one obesity-related comorbidity).[1,5,11] Nevertheless, surgery is expensive, and not without risks, so there is continued interest in less invasive treatment options; medications are an attractive option for clinicians and patients looking for weight loss aids that are simple to administer and minimally invasive.

Weight Loss Medication History

Sympathomimetic agents were some of the first available weight loss medications.[9] However, many formerly approved sympathomimetics were removed from the market due to increased risk for cardiac events and other adverse effects.[9] Two sympathomimetics, phentermine and diethylpropion, are still approved, but their use is limited to less than 12 weeks and both carry safety concerns for abuse potential and risk for cardiovascular events.[5,8] Serotonergic agents also act centrally but reduce appetite by affecting other neurotransmitters.[8] Two serotonergic medications, fenfluramine and dexfenfluramine, were removed from the market due to pulmonary hypertension and risk for cardiovascular events.[10] Orlistat is a peripherally-acting medication for long-term use that prevents uptake of fatty substances through the gastrointestinal tract but is minimally effective and associated with gastrointestinal adverse effects.[1,8] Besides orlistat, long-term health outcomes data are still not available and there is no evidence these drugs decrease morbidity outcomes associated with obesity.

Guideline Recommendations

Current guidelines recommend behavioral and lifestyle interventions as first-line treatment for weight loss in obese patients.[1,4,5,7,8,11] If comprehensive lifestyle changes fail to promote durable weight loss, the American Association of Clinical Endocrinologists, The Obesity Society, the American Society for Metabolic & Bariatric Surgery, the American Heart Association, and the American College of Cardiology all recommend bariatric surgery over pharmacologic agents.[4,11] Bariatric surgery demonstrates greater weight loss, improved durability of weight loss, and improved surrogate markers of metabolic disease as compared to weight loss drugs.[4,11] The Canadian Task Force on Preventive Health Care advises practitioners to not routinely prescribe medications for weight loss due to unfavorable harms and unknown long-term benefit.[7] The World Gastroenterology Organization and the Endocrine Society also suggest reserving these drugs for patients who cannot lose weight by lifestyle interventions alone, with both organizations acknowledging that these drugs are only modestly effective.[1,8] Finally, a 2015 Institute for Clinical and Economic Review report calls into question the utility and safety of all weight loss drugs.[5]

Current FDA-Approved Medications for Weight Loss

Four weight loss drugs have gained popularity in recent years.[5] These drugs are approved for adults with a BMI of 30 kg/m^2 or more, or a BMI of 27 kg/m^2 or more with an obesity-associated comorbidity.[5,8] In general, patients on a weight loss drug should be monitored every 3 months, and the drug should be discontinued if there is less than 5% weight loss or an adverse event occurs.[8]

Lorcaserin (Belviq®)

Lorcaserin is a selective serotonin 2c agonist previously reviewed in the December 2012 newsletter.[10] Lorcaserin was approved based on 3 placebo-controlled trials, each about one year in duration.[10] Combined data (n=6139) demonstrated a modest percent reduction in body weight compared to placebo (-4.5 to -5.8% vs. -1.5 to -2.8%, p<0.001).[5] It is still unknown whether this modest reduction is sustained over time and whether use of the drug improves comorbidities associated with obesity.[10] Lorcaserin is also associated with a number of adverse effects and precautions such as adverse psychiatric effects, headache, dizziness, and nausea.[10]

Phentermine/Topiramate (Qsymia®)

Phentermine/topiramate was also reviewed in the December 2012 newsletter.[10] Drug approval was based on two 56-week placebo-controlled trials that demonstrated a moderate reduction in body weight with both the high (15/92 mg) and low (7.5/46 mg) doses as compared to placebo (-10.9% and -5.1%, respectively vs. -1.6%, p<0.0001 for all comparisons). It is unknown whether this weight reduction is sustained over time and there is insufficient evidence that the drug improves comorbidities associated with obesity.[10] The agents are also associated with a number of adverse effects and precautions, such increased heart rate, paresthesias, and anxiety.[10]

Naltrexone/Bupropion (Contrave®)

Bupropion is an antidepressant that inhibits dopamine and norepinephrine reuptake and may promote satiety. Naltrexone augments the appetite suppressant effects of bupropion.[5,8] Approval for naltrexone/bupropion was based on four 56-week randomized, placebo-controlled trials (n=4468).[12-15] Results revealed statistically significant weight loss compared to placebo (-5.0 to -9.3% vs. -1.2 to -5.1%).[12-15] The proportion of patients who lost more than 5% and 10% of body weight with naltrexone/bupropion was significantly higher than with placebo (52% and 28%, respectively, vs. 24% and 10% with placebo).[12-15]

Only one trial reported the impact of naltrexone/bupropion on an obesity-related comorbidy.[12] The trial studied the effect of the drug combination on A1C in patients with T2DM and found a higher percentage of patients who took naltrexone/bupropion achieved an A1C of less than 7% compared with placebo (44.1% vs. 26.3%; p<0.001).[12] The Light Study was another highly

anticipated designed to assess the impact of naltrexone/bupropion on cardiovascular events.[16] However, amidst much controversy the study was suddenly halted. Interim analysis indicated that naltrexone/bupropion did not offer any protection from cardiovascular events.[16] In fact, more patients on naltrexone/bupropion experienced cardiovascular events than patients on placebo (55 vs. 43 events, respectively).[16] The manufacturer warns of potential for increased heart rate and blood pressure with use.[17]

Common adverse effects associated with bupropion/naltrexone include nausea, vomiting, headache, constipation, dizziness and dry mouth.[17] Adverse events were reported in 83-90% of patients in clinical trials and between 20-30% of patients stopped the drug early due to an adverse event.[12-15] There is a black boxed warning for the drug combination because of increased risk of suicidal behaviors and neuropsychiatric reactions observed in patients who use bupropion.[17] Other contraindications include seizure disorders and uncontrolled hypertension.[17]

Liraglutide (Saxenda®)

Liraglutide is an injectable glucagon-like peptide-1 agonist approved for T2DM that can promote satiety.[8] The FDA approved liraglutide for weight loss based on three 56-week randomized, placebo- and active-controlled trials with up to 2 years of follow-up.[18-20] Data from these 3 trials (n=4999) demonstrated statistically significant weight loss compared to placebo or orlistat (-6 to -8% vs. -2.4 to -2.9%, respectively).[18-20] The proportion of patients who lost more than 5% and 10% of body weight with liraglutide was significantly higher than with placebo or orlistat (63-73% and 26-27% respectively with liraglutide, vs. 27-28% and 6-11% with placebo and 44% and 14% with orlistat).[18-20] Not surprisingly, liraglutide delayed the diagnosis of T2DM in nondiabetics and reduced the onset of pre-diabetes versus placebo at week 56 (30.8% vs. 67.3%; p<0.001).[18,21]

Common adverse effects include nausea, vomiting, diarrhea, constipation, and headache.[22] Adverse events were reported in 80-96% of patients in clinical trials and between 8-10% of patients stopped the medication early due to an adverse event.[18-20] Liraglutide may interact with other medications by slowing the rate and extent of gastric emptying.[22] The long-term safety data of liraglutide has not been established; concerns about thyroid tumors observed in animal models led the FDA to issue a black boxed warning.[22] Users of liraglutide may also be at increased risk for pancreatitis, pancreatic cancer and immunogenicity-related events.[22]

Discussion & Conclusions

The primary goals of weight loss are improved health outcomes. Bariatric surgery has demonstrated superior health outcomes as compared to weight loss drugs and is covered by the Oregon Health Plan (OHP) in patients with a BMI of 35 or greater.[23] Even though some weight loss drugs have been on the market for several years, none have demonstrated a reduction in obesity-related comorbidities, such as cardiovascular events, nor have they been shown to improve daily functioning, symptom-relief, or quality of life.[5,16] In addition, currently available weight loss drugs are associated with multiple adverse effects and several safety warnings.[5,10] Most medical societies do not consider the benefits of weight loss medications to exceed the potential harms[4,5,7,11] and use of a drug for weight loss is not covered by OHP.[23] Current recommendations for treatment of obesity continue to be diet and physical activity, as well as bariatric procedures in certain populations.[4,5,7,11]

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