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The Future of Newer Obesity Medications

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Obesity has become a major health crisis in the United States. The 2009-2010 Centers for Disease Control (CDC) report stated that over 1/3 of the adult population was considered obese.[1] In the state of Oregon, about 60% of the adult population is considered overweight or obese, and in 2006, medical costs related to obesity were over 1.6 billion for the state.[2] Many chronic diseases, such as hypertension, type 2 diabetes, and hyperlipidemia can result from being obese. The high prevalence of obesity has led to the development and approval of many weight loss medications to assist in weight loss and prevent long-term morbidity and mortality. However, due to limited efficacy along with intolerable and serious side effects, most have been removed from the market. Two new centrally acting obesity medications were approved for long-term weight loss in the summer of 2012: lorcaserin hydrochloride (Belviq®) and phentermine/topiramate controlled-release (Qsymia®). The question now remains, will these medications help put an end to the health crisis, or will they be pulled from the market like their predecessors?

Obesity Guidelines

Currently, the World Gastroenterology Organization (WGO) Global Guidelines recommend diet, exercise, and behavioral modifications as first-line treatment steps to losing weight.[3] If weight loss is not achieved, medications can be added on depending on patient's body mass index (BMI) and co-morbidities. Patients who are overweight (BMI 25.0-29.9 kg/m^2) or fit into obesity class I (BMI 30.0-34.9 kg/m^2) with co-morbidities present are considered candidates for weight loss medications, along with patients who are in the class II (BMI 35.0-39.9) or class III (BMI ≥40) obesity category with or without co-morbidities. Bariatric surgery is only recommended as a last resort for obese individuals with a BMI ≥40 or BMI ≥35 with co-morbid conditions, including diabetes.

According to the 2007 Food and Drug Administration (FDA) Industry Guidance for Obesity Treatment, a product can be considered effective for weight management after one year of treatment if either of the following occurs: 1) the difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant, or 2) if the proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, weight loss is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant.[4] Attrition rates in studies evaluating weight loss medications are generally high, averaging above 30% and are, in part, a function of weight loss.[5] Under the Oregon Health Plan, medical treatment of obesity is limited to intensive counseling on nutrition and exercise, provided by health care professionals. Pharmaceutical agents are not covered services for the treatment of obesity.

Past and Present: Weight Loss Medications

Currently, there are several short-term (generally 12 weeks or less) weight loss medications available on the market, such as phentermine. Orlistat is the only medication available for long-term use (generally a year or longer). Orlistat has a peripheral mechanism of action, blocking fat absorption from the gut and, in combination with lifestyle modifications, has been shown in clinical trials to cause a ≥5% reduction in baseline body weight at one year.[6,7] In 2010, safety concerns surfaced about orlistat causing rare cases of severe liver injury, and in 2012, case reports of oxalate nephrolithiasis and oxalate nephropathy with renal failure led to the release of a new warning.[8,9] The long-term weight loss medication, sibutramine, was pulled off the market by the FDA in October 2010 due to the safety concerns identified in outcomes from the Sibutramine Cardiovascular Outcomes Trial (SCOUT), which demonstrated a 16% increase in the risk of major adverse cardiovascular events (hazard ratio [HR] for nonfatal myocardial infarction, 1.28; 95% CI 1.04, 1.57; p-value=0.02; HR for nonfatal stroke, 1.36; 95% CI 1.04, 1.77; p-value=0.03).[10] The difference in mean percent change in body weight between sibutramine and placebo was 3.5%. Additionally, two serotonergic weight loss medications, flenfluramine and dexfenfluramine, were pulled off the market in the 1990's because use was linked to pulmonary hypertension and cardiac valvulopathy.[11, 12]

Lorcaserin

Lorcaserin, a selective serotonin 2c agonist thought to decrease appetite and increase satiety, was approved by the FDA in June 2012 for adults with a BMI of 30 kg/m^2 or greater or with a BMI of 27-30 kg/m^2 and at least one co-morbid condition.[14] The serotonin 2c selectivity is assumed to reduce the risk for cardiac valvulopathy.[12]

Approval was based on three fair quality, randomized, placebo-controlled phase III clinical trials that studied the medication adjunctively with a reduced calorie diet and exercise for chronic weight management in non-diabetics (BLOOM and BLOSSOM) and in the diabetic population (BLOOM-DM).[12,15,16] The majority of the subjects in all of the trials were white women in their mid-40's to 50's that were relatively healthy, reducing the generalizability to the overall population. All patients were asked to participate in 30 minutes of exercise daily and reduce their caloric intake by 600 kcal/day, which are potential confounding variables.

All three trials resulted in a statistically significant weight loss of ≥5% and ≥10% for both doses compared to placebo. The combined data from BLOOM and BLOSSOM (n=6139) demonstrated that 10 mg of lorcaserin twice daily resulted in 47.1% of non-diabetic patients experiencing a weight reduction of ≥5% from baseline, which was statistically significantly greater than placebo (relative risk [RR] 2.09; 95% CI 1.94, 2.26; p-value<0.0001) with an absolute risk reduction (ARR) of 25% and a number needed-to-treat (NNT) of 4.[12,16] In diabetic patients (BLOOM-DM; n=499), 37.5% of patients experienced a weight reduction of ≥5% from baseline (RR 2.32; 95% CI 1.67, 2.38; p-value<0.0001). These results met the second FDA criteria for approval. However, there was only a 3% mean difference in weight loss between lorcaserin and placebo in diabetic patients and 3.3% in nondiabetic patients, not meeting the other FDA approval criteria for demonstrating minimal clinical efficacy.

In BLOOM-DM, mean hemoglobin A1c (a measure of glycemic control) decreased from baseline significantly more in the lorcaserin 10 mg twice-daily group as compared to placebo (-1.0% vs. -0.5%; p-value<0.001).[15] Antihyperglycemic medications could be dose-adjusted after the twelfth week of the BLOOM-DM trial though, so it remains unknown if the hemoglobin A1c reduction was solely due to weight loss from lorcaserin or as a result of medication adjustments.

The clinical trials did not demonstrate a significant difference in FDA-defined valvulopathy between lorcaserin and placebo (pooled RR 1.16; 95% CI 0.81, 1.67).[12,16] However, they were not powered to evaluate the effect on long-term cardiovascular outcomes. The most common adverse effects reported in the trials were headache, upper respiratory infection, nausea, dizziness, and fatigue. In addition, lorcaserin may increase the risk of psychiatric, cognitive, and serotonergic adverse events.

Phentermine/Topiramate

A fixed dose combination of phentermine and topiramate was approved by the FDA in July 2012 for adults with a BMI of 30 kg/m^2 or greater or a BMI of 27-30 kg/m^2 with at least one co-morbid condition. The mechanism of action is unclear at this time, but the combination is thought to reduce appetite and

food consumption through norepinephrine release (phentermine), and augment the activity of gamma-aminobutyrate and inhibit carbonic anhydrase (topiramate). The approved doses of phentermine/topiramate are 7.5mg/46mg and 15mg/92mg with two tapering doses of 3.75mg/23mg and 11.25mg/69mg. Dose adjustment is necessary in moderate to severe renal impairment and in moderate hepatic impairment. It is not recommended for children under 18 and should be used with caution in adults over 65 due to minimal data in both populations. Phentermine/topiramate was approved with a risk evaluation and mitigation strategy (REMS) informing prescribers and female patients of the risk of birth defects and the importance of pregnancy prevention.

Approval was based on two fair to good quality, randomized, double-blind, placebo-controlled phase III clinical trials (EQUIP and CONQUER) that studied varying doses of the medication compared to placebo for chronic weight management for 56 weeks.[17,18] All study participants were asked to reduce their caloric intake by 500 kcal/day and initiate an exercise routine. A double-blind extension study (SEQUEL) was completed following CONQUER, which assessed efficacy and safety of phentermine/topiramate for a total of 108 weeks in the most adherent patients from CONQUER.[19] EQUIP included obesity class II and III patients (BMI ≥35 kg/m^2), while CONQUER and SEQUEL included overweight and obesity class I through III patients (BMI ≥27 kg/m$^{2)}$ with one or more co-morbidities. Unlike lorcaserin, this medication met both of the FDA efficacy criteria endpoints.

EQUIP demonstrated significantly more patients achieving a weight loss ≥5% of baseline body weight for phentermine/topiramate 15mg/92mg and 3.75 mg/23mg compared to placebo (74.4%, 51.1%, and 24.8% respectively; p-value<0.0001 for all comparisons).[17] Mean percent change in weight loss was also significantly greater with high and low dose phentermine/topiramate compared to placebo (-10.9%, -5.1%, and -1.6%, respectively; p-value<0.0001 for all comparisons). There was a statistically significant difference in withdrawals due to adverse events between the high dose of phentermine/topiramate 15mg/92mg and placebo (16% vs. 8.4%; RR 1.91 95% CI 1.33, 2.76; p-value<0.001). [17] The higher dose of phentermine/topiramate had more significant adverse events than the titration dose and placebo; the most common events (p-values<0.0001) included paresthesia, dry mouth, constipation, dysgeusia, depression, irritability, anxiety, and concentration and attention impairment. [17]

The CONQUER trial compared the higher dose of phentermine/topiramate 15mg/92mg and lower dose of 7.5mg/46mg to placebo. In the intention-to-treat analysis, the change in body weight at 56-weeks was greater in the higher and lower dose groups compared to placebo (least square mean -9.8%, -7.8%, and -1.2%, respectively; p-value<0.0001).[18] The proportion of patients achieving at least 5% weight loss was 70% (RR 3.36; 95% CI 2.98, 3.80), 62% (RR 2.98; 95% CI 2.59, 3.41), and 21% (p-value<0.0001 for all comparisons to placebo) for phentermine/topiramate 15mg/92mg, 7.5mg/46mg versus placebo, respectively. There was no statistically significant difference in serious adverse events, but there was again a statistically significant difference in withdrawal rate between the high dose and placebo (19% vs. 9% for 15mg/92mg vs. placebo; RR 2.16; 95% CI 1.70, 2.78; p-value<0.0001). [18]

In the extension trial (SEQUEL), participants continued to receive the original treatment to which they were randomly assigned during the CONQUER study.[19] Further participation into SEQUEL was optional, potentially biasing toward inclusion of only subjects with positive outcomes. There continued to be a significantly greater mean percentage change from baseline body weight for both the high dose and the medium dose compared to placebo (-10.5%, -9.4%, and -1.8%, respectively). [19] The proportion of patients achieving at least 5% weight loss was 79.7% (RR 2.70; 95% CI 2.22, 3.27), 74.3% (RR 2.51; 95% CI 2.02, 3.07), and 28.9% (p-value<0.0001 for all comparisons to placebo). [19] The incidence of individual adverse events was lower in the second year (weeks 56-108) than in the first year (weeks 0-56). There was a reduction seen in blood pressure that was accompanied by a mean increase in heart rate of 1.7 beats per minute with the 15mg/92mg dose. The long-term clinical significance of this is unknown.

Summary

Newer weight loss medications are currently being developed to try to meet the market demand for a new pivotal weight loss drug. A variety of centrally acting mechanisms and polytherapies are being explored. The treatment of obesity with centrally acting drugs is an area of continued debate regarding whether the benefits justify the risks. To date, no clinical outcome study has been performed to demonstrate that long-term treatment with anti-obesity drugs has a positive effect on morbidity and mortality.

Phentermine/topiramate and lorcaserin were associated with greater weight loss compared to placebo. Phentermine/topiramate was associated with a higher incidence of medical events related to psychiatric, cognitive, and cardiac disorders compared to lorcaserin. It remains unknown if these new agents will demonstrate long-term effectiveness with tolerable harms in the general population.

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