

# Obesity Epidemic: Pharmaceutical Weight Loss

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## ABSTRACT

Obesity is a chronic disease universally defined as an excess of adipose tissue resulting in body mass index (BMI)  $\geq 30.0$  kg/m<sup>2</sup>. Over the past few years, the concept of prevention has gained increased awareness, thus leading to the development of additional pharmaceutical options for the treatment of obesity since 2012. Treating obesity revolves around an individualized, multi-disciplinary approach with additional focus on a healthy and supportive lifestyle to maintain the weight loss.

**KEYWORDS:** obesity, morbid obesity, overweight, anti-obesity therapies, weight-loss medications

## THE IMPORTANCE OF MEDICAL WEIGHT LOSS

In 2008, the World Health Organization reported that more than 1.4 billion adults were overweight, BMI  $> 25$  kg/m<sup>2</sup>, and more than half a billion were obese.<sup>1</sup> This global epidemic has led to growing concerns, for adults, and for the increased rate in childhood obesity that predisposes them to become obese adults.<sup>1</sup> Prevention is imperative regardless of age.

Initiating lifestyle interventions, including behavioral modifications, diet and exercise are recommended first-line approaches for anyone with a BMI  $\geq 25$  kg/m<sup>2</sup>. Anti-obesity medications have been approved for use in conjunction with the above mentioned lifestyle interventions for patients with a BMI  $\geq 30$  kg/m<sup>2</sup> with no co-morbidities and those with a BMI  $\geq 27$  kg/m<sup>2</sup> with obesity related co-morbidities.<sup>2,3</sup> Weight related co-morbidities include metabolic syndrome, pre-diabetes, type 2 diabetes mellitus, dyslipidemia, hypertension, nonalcoholic fatty liver disease, polycystic ovarian syndrome, female infertility, male hypogonadism, obstructive sleep apnea, asthma/reactive airway disease, osteoarthritis, urinary stress incontinence, gastroesophageal reflux disease and depression.<sup>2</sup>

There have been an increasing number of prominent medical studies displaying the benefits of medical weight loss. The Diabetes Prevention Program Research Group performed a large, randomized clinical trial which displayed a reduction in progression from impaired glucose tolerance to type 2 diabetes mellitus with both metformin and lifestyle changes, focusing on diet and exercise.<sup>4</sup> This study clearly showed that type 2 diabetes mellitus can be prevented or delayed for high-risk patients, such as those who are obese.<sup>4</sup>

## OBESITY THERAPEUTIC INTERVENTIONS

There are now multiple clinical practice guidelines published from various societies endorsing medical weight loss. Recently, the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) published the clinical practice guidelines for comprehensive medical care of patients with obesity.

Currently, there are a total of 6 FDA-approved anti-obesity medications on the market. This is a very exciting time, because since 2012, there have been 4 new agents approved for use by the FDA.

When treating patients with weight-loss medications, as with all medications, it is important to remember that there may be a wide heterogeneity of responses. The goal of obesity medications is to see a 5-10% decrease in weight within the first 6 months of therapy. If there is  $< 5\%$  weight loss in 3–6 months, it is recommended to consider a dose adjustment or discontinue the medication.

## ORLISTAT

Orlistat, also known as Xenical, is a non-systemic, gastric and pancreatic-lipase inhibitor that was approved in 1999. By inhibiting pancreatic lipase, it blocks the absorption of approximately 30% of dietary fat.<sup>6</sup> At 1 year, patients treated with orlistat had a 4.0% decrease in body weight compared to placebo.<sup>2</sup> Several randomized controlled trials, ranging from 2–4 years in duration showed long-term weight reduction, in addition to improvement in blood pressure, insulin resistance and serum cholesterol levels.<sup>7,8</sup> It is dosed three times a day before meals. A co-prescription for fat soluble vitamin supplementation including A, D, E and K is recommended, given the mechanism of inhibiting fat absorption to prevent deficiencies.<sup>6,8</sup>

The main disadvantage is the side effect profile with a higher incidence of unpleasant gastrointestinal adverse effects including abdominal pain, bloating, diarrhea, flatulence, steatorrhea, fecal incontinence and dyspepsia.<sup>7,8</sup> Contraindications to use include chronic malabsorption, cholestasis, oxalate nephrolithiasis, pregnancy, and breastfeeding.<sup>2</sup>

## PHENTERMINE

Phentermine, also known as Adipex-P, is a sympathomimetic that was approved for monotherapy in 1959.<sup>8,9</sup> This is

the most common, inexpensive, anti-obesity medication prescribed in the United States. It is a central, norepinephrine-releasing agent that reduces appetite, which has been approved for short-term use. Aside from the weight loss benefits, it improves total cholesterol and low-density-lipoprotein cholesterol levels.<sup>8</sup>

The main adverse effects are secondary to the stimulant effects, including increased heart rate, palpitations, hypertension, restlessness, agitation, dry mouth, headache and insomnia.<sup>2,3,6</sup> It is prescribed once a day and is given in the morning. Contraindications include heart disease, uncontrolled hypertension, hyperthyroidism, glaucoma, MAO inhibitors, anxiety disorders, seizure disorder, pregnancy, and breastfeeding.<sup>2,3</sup> Currently, there are no long-term clinical trials to demonstrate efficacy past one year.

### QSYMIA (PHENTERMINE/TOPIRAMATE)

Qsymia is a fixed dose, combination of phentermine immediate-release and topiramate extended-release. This is a synergistic combination that was approved in 2012. Topiramate functions as a GABA receptor modulator that further adds to the appetite suppressant effect by modulation of the voltage-gated sodium ion channels.<sup>8</sup> This combination therapy was found to produce significant, dose-related weight loss. At 1 year, patients treated with qsymia had an 8.6 - 9.3% decrease in total body weight compared to placebo on high dose and 6.6% decrease on the lower, recommended treatment dose.<sup>2</sup> There were also sustained improvements in both cardiovascular and metabolic variables, including hyperglycemia, hypertension, hyperlipidemia and a reduction in progression to type 2 diabetes mellitus.<sup>9</sup>

Adverse effects are consistent with the adverse effects of the two medications individually including headache, insomnia, constipation, paresthesia, dizziness, dysgeusia, nasopharyngitis, anxiety, depression, concentration, memory impairments and decreased bicarbonate.<sup>2,9</sup> It is also recommended to be taken in the morning to prevent the phentermine stimulatory effects. Contraindications include hyperthyroidism, acute angle-closure glaucoma, concomitant MAO inhibitor, pregnancy and breastfeeding. Topiramate is teratogenic; all females of childbearing age are required to have a pregnancy test before and every month during use.<sup>2,9</sup> In patients with a history of seizures or epilepsy, topiramate has been associated with seizures, therefore, it is advised to taper off of this medication and avoid abrupt discontinuation.

### BELVIQ (LORCASERIN)

Belviq, also known as lorcaserin, is a selective serotonin (5-HT<sub>2c</sub>) receptor agonist that was approved for weight loss in 2012. 5-HT<sub>2c</sub> has a role in food intake and its activation results in increased satiety.<sup>8,10</sup> At 1 year, patients treated with belviq had 3.0-3.6% decrease in total body weight compared

to placebo.<sup>2</sup> Belviq is dosed twice a day and more recently as extended release, once a day formulation has become available called Belviq XR.

It has a fairly favorable side effect profile and is generally well tolerated. Adverse effects include headache, nausea, diarrhea, constipation, dizziness, fatigue, xerostomia, dry eye, hypoglycemia, headache, back pain and cough.<sup>8,10</sup> It was also associated with improvements in hyperlipidemia, insulin resistance, levels of inflammatory markers and hypertension.<sup>10</sup> Contraindications include the use of other serotonergic drugs due to concern for serotonin syndrome, pregnancy and breastfeeding.<sup>2</sup>

### CONTRAVE

Contrave, a combination of naltrexone and bupropion extended release, was approved in 2014. Naltrexone is a non-selective opioid receptor antagonist and bupropion is an inhibitor of dopamine and norepinephrine transporters. Together, the two medications in combination revealed a synergistic effect by producing a greater reduction in food intake and appetite regulation, thought to involve the food reward mechanism.<sup>8</sup> At 1 year, patients treated with Contrave had a 4.2–5.2% decrease in total body weight compared to placebo.<sup>2</sup>

Adverse effects are consistent with the known adverse effects of the two medications individually, including nausea, vomiting, constipation, headache, insomnia, diarrhea, dizziness, anxiety and xerostomia.<sup>2,11</sup> Contraindications include uncontrolled hypertension, seizure disorder, tachyarrhythmia, severe depression, chronic opioid use, concomitant use of MAO inhibitors, anorexia or bulimia nervosa, drug or alcohol withdrawal, liver failure, narrow angle glaucoma, pregnancy and breastfeeding.<sup>2,8,11</sup> It is recommended to discontinue this medication gradually and avoid abrupt cessation given the lowered seizure threshold associated with bupropion.

### SAXENDA (LIRAGLUTIDE)

Saxenda, also known as liraglutide, is the only long-acting, daily, injectable therapy approved for medical weight loss. It is a glucagon-like peptide-1 (GLP-1) receptor agonist that was approved in 2014. It previously was approved at a lower dose by the FDA for treatment of type 2 diabetes mellitus, known as Victoza. The mechanism of delaying gastric emptying and agonist effects on GLP-1 receptors in the brain have been implicated in decreasing appetite thereby decreasing caloric intake.<sup>8,12</sup> At 1 year, patients treated with saxenda had a 5.6 % decrease in total body weight compared to placebo.<sup>2</sup> It has also been shown to improve fasting and postprandial glycemia, beta-cell function, insulin sensitivity and delayed onset of type 2 diabetes mellitus.<sup>12</sup> This is the most expensive medication on the market, costing approximately \$1100 monthly if the employer has not opted into coverage which has limited its use.

Adverse effects include nausea, vomiting, diarrhea, constipation, headache, increased heart rate, dyspepsia and hypoglycemia. Contraindications for use include gastroparesis, pancreatitis, personal or family history of medullary thyroid cancer, acute gallbladder disease, pregnancy and breastfeeding.<sup>2,3,12</sup> The dose of this medication is titrated based on tolerability of adverse effects. Thyroid C-cell tumors have been reported in rodents only; however, the FDA has required a boxed warning of contraindication for patients who have a personal or family history of medullary thyroid cancer or those with multiple endocrine neoplasia syndrome type 2 (MEN 2). The significance in humans is unclear and ongoing post-marketing evaluations are planned to evaluate the incidence of medullary thyroid cancer and the potential risk of breast cancer.<sup>8,12</sup>

## CONCLUSION

The CDC estimates that each year at least 2.8 million people die secondary to being overweight or obese. Both awareness and prevention is the cornerstone of treatment for this disease. Obesity medications have proven to be a favorable, additional therapeutic intervention to complement diet, behavior modifications, physical activity and bariatric surgery. Hopefully, continued awareness, dedication and research will bring more options for providers and patients to treat obesity.

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## Disclosures

None

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