

Pharmacological Management of Obesity

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Abstract

Introduction: A major pandemic of the 21st-century obesity is in both developed and developing countries, which is increasingly contributing to chronic diseases associated with it and draining economic resources. Despite the overwhelming amount of information regarding obesity and the morbidity and mortality associated with it, the number of obese individuals rise each year. The dangers of being obese are far more alarming than most people realize. Obesity significantly increases the risk of diabetes mellitus, hypertension, coronary artery disease, dyslipidaemia, stroke, gallbladder disease, osteoarthritis, gastroesophageal reflux disease, sleep apnoea, lower back pain, asthma. Obesity is also known to increase the risk of cancers of colon, endometrium, prostate, and breast. Using pharmacotherapy for weight management is consistent in treating obesity as a chronic disease that requires a multi-faceted approach, including behavioral intervention, medical intervention, and dietary change. The current guideline recommends that a person who fails to respond to lifestyle intervention with BMI more than 30 kg/m² with obesity-related comorbidity should opt for weight loss medical treatment.

Aim of the Study: Aim of study is to understand pharmacological intervention of weight loss management.

Methodology: The review is comprehensive research of PUBMED from the year 1998 to 2017.

Conclusion: The benefits of weight reductions are irrefutable, and lifestyle intervention aimed at promoting weight loss remains the cornerstone of the treatment. But despite all most patients are unable to achieve 10kg weight loss targets and maintenance. Thus, pharmacotherapy is one valuable option in weight loss management with growing acceptance to it. Several drugs are approved and currently used, but long-term data on safety and efficacy in cardiovascular conditions remain warranted. Apart from this the health care practitioners should consider the weight effects of pharmacotherapy in management of obesity-related comorbidities with the use of weight-neutral or weight-reducing medication that can complement patient's desire and for healthier lifestyles.

Keywords: Weight Loss Management; Pharmacotherapy

Introduction

Obesity is a chronic disease and necessitates lengthy-term treatment. Health care professionals should be aware of the fundamentals regarding the pharmacotherapy of obesity. The main goal of treatment is not only to reduce weight but also to improve the comorbid conditions associated with obesity such as hyperlipidemia, hyperglycemia and heart disease. The efficacy of current medication used in obesity is limited to 5 - 10% of body weight loss in majority of obese population. Therefore, medication should not be viewed as ultimate treatment but adjunct to bariatric surgery when additional weight loss is required or prevent regain after weight loss surgery [1].

Earlier the only market approved weight loss medicines for long term use by FDA were sibutramine and orlistat. Orlistat remains on the market; however, sibutramine (centrally-acting serotonin-norepinephrine reuptake inhibitor) was unapproved by both European and US regulators in 2019 due its increased risk of non-fatal myocardial infarction and non-fatal stroke associated with patients with cardiovascular condition [2].

The advances in research led to the development of new medication in 2012 such as combination of phentermine and Topamax marketed as Qsymia and lorcaserin marketed as Belviq and liraglutide 3.0 marketed as saxenda in year 2014 [1].

Methodology

We did a systematic search for pharmacologic management of weight loss using PubMed search engine (<http://www.ncbi.nlm.nih.gov/>) and Google Scholar search engine (<https://scholar.google.com>). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: weight loss, pharmacologic management of weight loss, weight management, obesity treatment.

Patients assessment

The first step to assessment includes body mass index (BMI). The patient's weight and height are the parameters used to calculate patient's BMI, which is an indirect measurement of body fat. The second step includes separating patients into different classes. Another assessment includes waist circumference since excessive abdominal fat has been shown to be an increased risk factor for diseases such as waist measurement of more than 40 inches in men and 35 inches in women is associated with an increased risk of type-2 diabetes and hypertension and cardiovascular disease [3].

	BMI kg/m ²	Obesity Class	Disease Risk (Relative to Normal Weight and Waist Circumference)	
			Men ≤ 40 inches and Women ≤ 35 inches	> 40 inches and women > 35 inches
Underweight	< 18.5		-	-
Normal weight	18.5-24.9		-	-
Overweight	25.0-29.9		Increased	High
Obesity	30.0-34.9	I	High	Very High
Obesity	35.0-39.9	II	Very High	Very High
Extreme Obesity	> 40	III	Extremely High	Extremely High

Table 1: Classification of overweight and obesity by body mass index, waist circumference and associated disease risk [3].

Approved medication for weight reduction

Orlistat

Orlistat, approved in 1999, is marketed as Xenical (Alli). The weight loss mechanism of orlistat by inhibiting gastrointestinal lipase, thereby decreasing the absorption of fat from gastrointestinal tract. The dose of 120 mg thrice a day will decrease fat absorption by 30%. This is effective in inhibiting the digestion of fat in solid foods as opposed to liquids. In lower dose of 60mg thrice daily (Alli) is approved over the counter drugs [4].

Efficacy, metabolic profile and side effects

Efficacy of orlistat is supported in several trails as weight loss and weight maintenance drugs. According to some studies, orlistat is proven to lower the weight more significantly in first year of treatment and fewer regained weight for second year than placebo. Subjects taking medicine had lower serum levels of vitamin D, E, and B-carotene, which was treated additionally by multivitamin supplementation. Apart from promoting weight loss, this drug has been shown to improve insulin sensitivity, and lower serum glucose levels, improved glycaemic control, reduction in total cholesterol, LDL cholesterol, triglyceride levels, and apolipoprotein B were also noted [5-7].

The side effects include:

- Fatty/oily stool
- Fecal urgency
- Oily spotting
- Increased defecation

- Fecal incontinence
- Flatus with discharge
- Oily evacuation
- Liver injury.

These are the main reason for discontinuation of therapy. The symptoms are mild to moderate. Psyllium intake (psyllium mucilloid, natural fiber) decreased this GI event [8].

Phentermine/topiramate

Qsymia (trade name) is controlled release; a single-tablet combination of phentermine plus topiramate was approved by FDA in 2012 for a long term treatment of obesity in adults with body mass index ≥ 30 kg/m² or with a BMI ≥ 27 kg/m² with at least one associated comorbidity. The mechanism of weight loss by phentermine is based on by its increasing release of norepinephrine and reducing its uptake in hypothalamic nuclei, leading to decrease in food intake as well as acting on adrenergic agonist that activates the sympathetic nervous system and increases resting expenditure [9].

Topiramate is a drug used for epilepsy and migraine prophylaxis tends to reduce body weight by promoting taste aversion and decreasing caloric intake. Phentermine-topiramate is available in 4 doses: 3.75/23 mg (starting dose), 7.5/46 mg (lowest treatment dose), 11.25/69 mg or 15/92 mg (maximum treatment dose) [10].

Efficacy, metabolic profile and side effects

A multiple phase 1, 2 and 3 studies have evaluated the efficacy and safety of phentermine/topiramate combination therapy. There is improvement in systolic and diastolic blood pressure, triglyceride levels, and greater increase in HDL was seen in patients treated with phentermine plus topiramate compared with placebo in two phase 3 trials. Improvement in fasting glucose and insulin levels was also seen with reduction in progression of type-2 diabetes in two treatment groups. Phentermine-topiramate combination is not recommended for patients with cardiac history, coronary heart disease, and uncontrolled hypertension. The drug also possesses risk of cleft lip/palate in infants when exposed in first trimester of pregnancy. Contraindicated in patients with hyperthyroidism, glaucoma, and patients on monoamine oxidase inhibitors within 14 days. Risk of acidosis and renal stones are increased by topiramate [11-13].

The side effects include [1]:

- Paraesthesia
- Dizziness
- Dry mouth
- Constipation
- Dysgeusia
- Insomnia
- Anxiety.

Lorcaserin

Lorcaserin markets as Belviq is a selective serotonin receptor agonist which was approved by FDA in year 2012 for long-term treatment for obesity in adults with BMI ≥ 30 kg/m² or with a BMI ≥ 27 kg/m² with at least one weight-related comorbidity and has 15 - 100 fold selectively of the central serotonin 5-HT_{2C} receptor over the 5-HT_{2A} and 5-HT_{2B} receptors. Thus, it reduces appetite by binding to 5-HT_{2C} receptors on anorexigenic proopiomelanocortin (POMC) neurons in hypothalamus. Lorcaserin comes in 10 mg tablet to be taken twice daily and once-daily 20 mg XR tablet [14,15].

Efficacy, metabolic profile and side effects

In a phase 3 trial, a group assigned to lorcaserin 10 mg twice daily showed an average placebo-subtracted weight loss of 3.1%. The study shows significant improvements in HbA1c, total cholesterol, blood pressure, triglycerides, and heart in lorcaserin vs. placebo group [8,16].

Side effects are:

- Headache
- Dizziness
- Fatigue

- Nausea
- Dry mouth
- Constipation
- Serotonin syndrome
- Patient with monoamine oxidase inhibitor.

Bupropion/naltrexone

The combination drug of bupropion and naltrexone is marketed as Contrave and was approved by the FDA in 2014. The primary mechanism of action is as reuptake inhibitor of dopamine and norepinephrine that activated central melanocortin pathways. The other component is opioid receptor antagonist that diminishes the auto-inhibitory feedback loop on neurons activated by bupropion thus allowing for sustained weight loss. The tablets contain 8 mg of naltrexone HCl and 90 mg of bupropion HCl. The recommended starting dose is 1 tablet daily and increasing by 1 tablet each week until a total dose of 2 tabs twice daily is reached (total 32 mg naltrexone/360 mg bupropion) [17].

In all the Contrave Obesity Research (COR) trials, secondary cardiovascular endpoints were met, such as statistically significant greater improvements in waist circumference (WC), visceral fat, HDL cholesterol, and triglyceride levels in the participants treated with the naltrexone 32 mg/bupropion 360 mg dose compared with placebo group. Participants with diabetes in the COR-Diabetes trial using bupropion/naltrexone also showed a greater 0.6% reduction in HbA1c from baseline, compared to a 0.1% reduction in placebo. Bupropion/naltrexone is contraindicated in patients with uncontrolled hypertension, history of seizures, bulimia or anorexia nervosa, narcotics for pain control [18,19].

Side effects:

- Nausea
- Vomiting
- Constipation
- Headache
- Dizziness
- Insomnia
- Dry mouth
- Interaction with MAO inhibitors

Liraglutide

Liraglutide is marketed as Saxenda (3.0 mg) and approved by the FDA in year 2014. It is Glucagon-like Peptide 1 (GLP-1) receptor agonist that has been used for type 2 diabetes in doses up to 1.8 mg. In a short-term study of obese individuals without diabetes demonstrated that liraglutide 3.0 mg/day suppressed acute food intake, subjective hunger, and delayed gastric emptying. Conversely, energy expenditure in subjects treated with liraglutide 3.0 mg/day decreased, even when corrected for weight loss, which was probably reflective of metabolic adaptation to weight loss. Side effects mostly include gastrointestinal symptoms such as nausea, vomiting and abdominal pain. It was also known to develop pancreatitis and gallstone among individuals [20,21].

Although liraglutide treatment improved the blood pressure and lipids, it was found to increase heart rate by 2.0/min. Animal studies showing an association with medullary thyroid cancer have led to FDA label warnings with liraglutide. A personal or a family history of medullary thyroid carcinoma or multiple endocrine neoplasia types 2 (MEN 2) is considered a contraindication for treatment with this medication even though the relevance of this observation to humans has not been determined [22].

Investigational therapies

Rimonabant

Marketed as Acomplia. As a growing population with increased number of cases with obesity, there is wide demand for researchers to develop and examine new safe and effective treatment options. This led to development of new medication rimonabant (Sanofi-Aventis). It is selective cannabinoid-1 receptor antagonist. In CNS, endocannabinoids release and stimulate appetite, lipogenesis, and fat accumulation in periphery. This drug works to block these effects of endocannabinoids [23].

Taranabant

Since the rimonabant was not approved by FDA, a drug with a similar mechanism of action, which is a cannabinoid-1 receptor antagonist, was studied in 3 trials, file for FDA approval; in October 2008, however, the company canceled further investigation into this experimental obesity drug. At more effective dosages, side effects increased excessively [23].

Tesofensine

Another agent showing potential as a drug in obesity therapy and has shown a promising result for weight loss and distinguishes from rimonabant and taranabant by the mechanism of action. The serotonin-noradrenaline-dopamine reuptake inhibitor works mainly as an appetite suppressant [23].

Conclusion

The health care providers must be more diligent in recognizing and treating patients with weight management problems since obesity is increasing day by day and has worsening effects on population suffering. Obesity is a major risk factor for several morbid chronic diseases and makes the individual prone to some more. The treatment starts with an appropriate assessment of patients' weight, changes in lifestyle, diet modification, and regular exercise. If traditional methods are not successful, surgical and pharmacological options are considered. Orlistat is considered as long term therapy and phentermine as short-term and are FDA approved along with lorcaserin, bupropion, liraglutide, used in combination with other drugs for effective result. Rimonabant, Taranabant, and Tesofensine are the newly developed drugs but unfortunately not FDA approved due to its certain drawbacks. Thus, with proper drug selection, advent of new drugs, and multifaceted approach to achieve weight loss in population, it is hoped that obesity and chronic disease associated with it will decline.

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