Sjournals
Scientific Journal of Medical Science (2012) 1(1) 1-6

Contents lists available at Sjournals
Scientific Journal of Medical Science
Journal homepage: www.Sjournals.com

Review article

Treatment of obesity: medical managements

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ARTICLE INFO

Article history:
Received 08 June 2012
Accepted 15 July 2012
Available online 17 July 2012

Keywords:
Overweight
Obesity
Body mass index
Weight loss
Pharmacotherapy
Orlistat
Rimonabant
Bariatric surgery

ABSTRACT

Obesity is a very complex illness. It is one of the most prevalent diseases in the western world, its importance lies in the comorbidities that surround it, as well as the predisposition to cardiovascular events and other diseases that reduce life quality and expectancy. There are many factors that contribute to obesity pathogenesis; genetic, psychological, emotional, social factors, among others. Nowadays dietetic measures and changes in lifestyle are the first step in management of obesity. Because in many cases it is not enough for patients to reach their ideal weight, pharmacotherapy must be used to treat obesity and its comorbidities. Several studies have compared various drugs for losing weight, being Orlistat the only one approved by the FDA. In bariatric surgery, many surgical techniques have been developed to try to reach a balance between efficacy and safety. Although it is relatively safe, it has its own risks inherent to the procedure and its complications. It is the most effective measure to improve the global patients' health as it not only helps people to lose weight, but also helps to have a better control of other comorbidities and lower overall mortality.

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1. Introduction

Obesity is defined as a body mass index (BMI) of over 30 kg/m^2, and as an abnormal or excessive fat accumulation that impairs an individual's wellbeing, as a result of an imbalance between energy intake and expenditure (Dodd, 2008). It represents a major threat, given that over the last 30 years, obesity has become an epidemic of great concern among global population. Estimates sustain that; 2.8 million adults die each year because of this condition (Levy *et al.*, 2007; Erlanger *et al*., 2007).

The threats of being either an overweight or obese person are far more dangerous than most of the people can comprehend. Obesity contributes to the development of other morbidities, such as diabetes mellitus, coronary artery disease, hypertension, dyslipidemia, gastroesophageal reflux disease, lower back pain, sleep apnea, asthma and even certain types of cancer (Mechanick *et al.*, 2008). All of these symptoms occur as comorbidities of obesity, making it the fifth leading cause for global deaths.

Obesity is considered a chronic, degenerating and multifactorial disease, involving genetic, environmental and psychological factors. Due to its high yield as a global health crisis, the need for appropriate therapeutic measures becomes increasingly important (Isidro *et al.*, 2009). Significant morbidities initiate in young adulthood, and obesity risk projections for the next thirty years are alarming. In year 2010, over 43 million children under age five were diagnosed as overweight patients worldwide. Obesity in adolescence is associated with severe obesity in adulthood, and as a major preventable disease, different therapeutic approaches must be employed to address this situation (Chen *et al.*, 2007).

Weight loss is the most effective way of treating for both the medical and psychological conditions of obesity along with an improvement on the patients' life quality. Diversity of treatments to accomplish weight loss have been developed over the years with variable grades of success (Isidro *et al.*, 2009). Lifestyle changes, such as dietary restriction, pharmacotherapy and surgery are among the most used therapeutic methods for treating obesity (Aronne *el al.*, 2007). On the present article we will make a special emphasis on the pharmaceutical treatment.

The latest pharmaceutical approaches for obesity target anabolic or catabolic regulatory networks to reduce food intake and increase energy expenditure to promote weight loss. These new pharmaceutical schemes aim to maintain homeostasis by adapting meal size to current energy requirements (Aronne *el al.*, 2007). This article intends to review the existent pharmacological therapies for weight loss, and the mechanisms by which they act, added to the clinical aspects and patients physiological reactions to the administration of this kind of medications,

2. Lifestyle intervention

The most effective way to address a public health matter is by promoting lifestyle modification. In the following years, it is estimated that obese population will shadow those of the malnourished or infected ones, and will pose a major concern to the medical economy worldwide (Aballay *et al.*, 2009). There is great need for the medical society to focus on preventive measures, considering the difficulty to visualize how obesity comorbidities in pandemic proportions will affect global healthcare. Behavioral approach, the promotion of physical activity, and nutritional counsel, each by itself has moderate impact on therapy, whereas additive results are seen when applied in combined strategies (Limbers *et al.*, 2008; Keightley *et al.*, 2011).

2.1. Psychological assessment

Behavioral weight loss programs rely on a thorough examination of antecedents, behaviors, and consequences (—ABC model). These programs include self-monitoring, goal setting, stimulus control, cognitive strategies, social support, and reinforcement. A psychological strategy focuses on permitting individuals to realize how their eating habits, activity patterns, environmental settings, and social stressors affect their weight management (Levy *et al.*, 2007). Relapse prevention is another important aspect of behavioral therapy. Group counseling has proved major effectiveness in this subject compared to individual assessment. Behavior modification can facilitate patient compliance in accompanying therapeutic approaches, improving overall results (Keightley *et al.*, 2011).

2.2. Physical activity

Sedentary lifestyle predisposes to weight gain and obesity. Physical activity is important in weight management. Few studies correlate accelerated exercise programs with a greater decrease in weight (Hainer *et al*., 2008). Supportive environments such as active transportation have been recommended, arguing that populations that live within walkable distances of their daily activities are more physically fit than those who are accustomed to public transportation or vehicle utilization. Walking can be a major source of activity to start with, given that most of the time comorbidities like arthritis-related joint pain make exercise a burden to obese patients. In general, weight loss programs encounter faster results when structured physical activity is combined with the other key components of therapy like dietary restriction (Poortinga *et al.*, 2011).

3. Pharmacotherapy

Pharmacotherapy is the generally the last resource of a weight loss program. Measurement of the body mass index (BMI) provides a tool that aids to decide if anti-obesity drugs should be included in a patient's therapy. Pharmacotherapy is indicated in people with BMI ≥27 kg/m^2 and risk factors for type 2 diabetes mellitus, dyslipidemia, hypertension or cardiovascular diseases (Neff *et al*., 2007); while patients with BMI of 30 kg/m^2 should consider pharmacotherapy even when they don't have comorbidities but only after lifestyle modification attempts have failed for 6 months or reached the plateau, as well as when there's an urge for weight loss (Halford, 2006). The selection of the pharmaceutical agent depends on the patient's physiognomies. Diverse approaches can be considered in this matter, each with different drugs that will have distinct effects on the patient (Halford, 2006).

3.1. Reduction of energy reabsorption

Pharmacologic therapy can be offered to obese patients who have been unsuccessful to accomplish their weight loss objectives through diet and exercise alone. Medications used for weight loss can be separated into 2 classes—appetite suppressants and lipase inhibitors—on the basis of their mechanisms of action (Table 1). The main drug intended to reduce energy reabsorption is Orlistat. An important factor in weight gain is the amount of fat that is being consumed. This drug interacts based on its principle as an enzyme that inhibits the hydrolization of triglycerides into fatty acids and monoglycerides by binding to pancreatic lipase (Hollander *et al*., 1998). The FDA in The United States and Europe approved it in 1998, and it is the only drug that has not been removed from the market (Ballinger *et al.*, 2002). To be effective, it must be accompanied with exercise and diet. Studies have shown a fat absorption reduction by 30% causing gastrointestinal effects that include: fat-soluble vitamins deficiency (vitamins A, D, E and K), oily stools, increased defecation, fecal incontinence, flatus discharge and abdominal pain (Filippatos *et al*., 2008).

Orlistat would be indicated in an obese patient with high blood pressure, insulin resistance and high serum lipid levels, since significant improvements have been demonstrated in a long-term therapy, from 2 to 4 years, with a 120 mg doses three times daily (Ballinger *et al*., 2002; *Hsieh et al.*, 2005).

3.2. Reduction of appetite/ induction of satiety

The neurological structures involved in appetite control are closely related, forming a complex brain network. These include the hypothalamus, the limbic system, the brainstem, the hippocampus, and some elements of the neo-cortex. Some neurotransmitters, as well as neuropeptides and hormones, play an important role to produce satiety (Berthoud *et al*., 2004). The main biogenic amines that have been associated with a decrease of food intake in the Central Nervous System are serotonin 5-HT2C and noradrenergic α1 and β2 receptor activation (Lam *et al*., 2008). *Tesofensine* acts on these receptors as a dopamine, norepinephrine and serotonin reuptake inhibitor. It is on phase III of clinical testing (Aronne *et al.*, 2007).The gastrointestinal tract plays an important part on signaling to the brain the feeling of satiety. Enteroendocrine cells, located on the gut, are responsible for the sensing of nutrients like carbohydrates, fatty acids and small peptides. These cells, when stimulated, release satiation-inducing peptides that include: glucagon, cholecystokinin (CCK), bombesin, GLP-1, peptide YY (PYY), GLP-2, apolipoprotein A-IV, amylin, somatostatin and enterostatin. This information is sensed and integrated by the hypothalamus (Berthoud, 2004). One drug that was taken out of the market because of its adverse effects that included depression, anxiety and other psychological symptoms is *Rimonabant* (Scheen *et al*., 2006). This drug acts on the endocannabinoid system and blocks the CB1 receptors, which are located both on the CNS and on the gastrointestinal tract, and reduces satiation (Bray, 2008). To avoid adverse effects, numerous companies are trying

to produce a similar drug that is specific for peripheral tissue and does not cross the blood brain barrier by making it more lipophilic (Hampp *et al*., 2008).

Table1
List of anti-obesity drugs, their mechanism of action and side effects.

Bupropion Function: Appetite suppressant: mechanism unknown. Side Effects: Paresthesia, insomnia, central nervous system effects.
Diethylpropion Function: Appetite suppressant: sympathomimetic amine. Side Effects: Palpitations, tachycardia, insomnia, gastrointestinal.
Fluoxetine Function: Appetite suppressant: selective serotonin reuptake inhibitor. Side Effects: Agitation, nervousness, gastrointestinal.
Orlistat Function: Lipase inhibitor: decreased absorption of fat. Side Effects: Diarrhea, flatulence, bloating, abdominal pain, dyspepsia.
Phentermine Function: Appetite suppressant: sympathomimetic amine. Side Effects: Cardiovascular, gastrointestinal.
Sertraline Function: Appetite suppressant: selective serotonin reuptake inhibitor. Side Effects: Agitation, nervousness, gastrointestinal.
Sibutramine Function: Appetite suppressant: norepinephrine and serotonin reuptake inhibitor. Side Effects: Increases in heart rate and blood pressure, nervousness, insomnia.
Topiramate Function: Mechanism unknown. Side Effects: Paresthesia, changes in taste.
Zonisamide Function: Mechanism unknown. Side Effects: Somnolence, dizziness, nausea.

3.3. Reduction of fat mass

Other investigational drugs are focused on increasing energy expenditure or reducing adipose tissue. This groups include β3-adrenergic receptors, selective thyroid hormone receptor subtype β-agonists, growth hormone analogues, 11-β-Hydroxysteroid dehydrogenase type 1 inhibitors, sirtuin 1 activators, diazoxide, inhibitors of angiogenesis and TGR5 agonists (Nakamura *et al*., 2000). Some of them, like the selective thyroid hormones mimetic, have not even passed beyond the phase I of clinical trials because of its adverse effects and lack of significant weight loss. Others only lack of efficacy, like GH analogues, β3-adrenergic receptors and possibly,

diazoxide. The ones that have not been put into clinical trials but are thought to have potential are Sitrulin 1, which oxidizes adipocytes and mobilizes fatty acids; TGR5, which increases energy expenditure and reduces diet related obesity. The angiogenesis inhibitors take advantage of the highly vascularized adipose tissue.

3.4. Bariatric surgery

Bariatric surgery is a method for losing weight that contributes with multiple benefits to the patients' well-being; reduces overall morbidity and mortality, improves carbohydrate and lipid metabolism, among others. It has also been demonstrated that bariatric surgery reduces treatment costs, as it helps to better control, or even cure, other comorbidities such as Diabetes Mellitus, Hypertension, Hyperlipidemia and Obstructive sleep apnea (Buchwald *et al*., 2004). Regarding surgery's safety, it has been reported a procedure-related mortality of less than 1% in some studies (LABS Consortium *et al*., 2009), turning bariatric surgery an effective and relatively safe treatment for losing weight in obesity. However, surgery is not recommended for everyone, as there has been established specific indications for bariatric procedures (Table 2) (NIH conference, 1991).

Table 2
Indications for surgical treatment of obesity

Candidate patients for bariatric surgery should:
• Have a BMI over 40 kg/m^2
• Have a BMI over 35 kg/m^2 and also serious comorbidities related to obesity (Diabetes Mellitus, Hypertension, Severe Joint Disease, Obstructive Sleep Apnea)
• Have previously failed with other non-surgical measures to lose weight (nutritional, behavioral, and exercise changes)
• Have an acceptable surgical risk

* BMI: Body Mass Index

4. Conclusion

Obesity is an underestimated disease by the people who suffer it. It is a public health issue throughout the Western world. It is an epidemic of global impact to the micro and macro economy, as it always is associated with other comorbidities that complicate its treatment, reduce expectancy of life of patients and increases costs. Several metabolic and mechanic complications derive from obesity, such as glucose intolerance, hypertension, sleep apnea, joint pain, among others. Many risk factors are associated with the development of obesity, such as family history of overweight in first degree relatives, sedentarism, inadequate eating habits, and other factors, being most of them from environmental origin. Hence, they are target of therapeutic intervention.

It is essential to have a multi-disciplinary approach to these patients, including a screening of psychological issues, which are present in many of the obese people, as well as nutritional counseling as a first step in the management of obesity. Other treatments (pharmacological and surgical) have specific indications, which aim at reducing complications derived from the disease itself and from the comorbidities associated, increasing life quality and reducing mortality.

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