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Reviews

Pharmacotherapy for the management of obesity



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ABSTRACT

In the last 30 years, obesity has rapidly increased and obesity-related comorbidities have surged. Once considered to be a problem only in developed nations, obesity has become a global epidemic. Consequently, the costs associated with managing overweight and obesity worldwide are astronomical. The objective of this mini-review is to provide an overview of current options available for obesity management, with a focus on anti-obesity pharmacotherapies. The impact of weight loss on improving obesity-related comorbidities and risk factors has been well documented. Although established clinical guidelines suggest comprehensive lifestyle modification to induce weight loss, many patients do not respond to lifestyle interventions and may not qualify for bariatric surgery. For these patients, pharmacotherapy may serve as a therapeutic option. Several anti-obesity pharmacotherapies, such as phentermine, are indicated for short-term use and are not required to demonstrate clinically meaningful weight loss (i.e., $\geq 5\%$). For long-term weight management, the FDA has approved 5 agents so far—orlistat, lorcaserin, phentermine/topiramate, naltrexone/bupropion, and liraglutide. These drugs have shown efficacy in enabling patients to achieve clinically meaningful weight loss and improving cardiometabolic parameters. Healthcare practitioners can help alleviate the obesity epidemic by tailoring these pharmacotherapies based on individual needs, comorbidities, and associated drug safety concerns.

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1. Introduction

Obesity is currently one of the most critical public health problems because of its severe physiological and economic implications [1]. Recently, the National Health and Nutrition Examination Survey estimated that in 2011–2012 more than two-thirds (68.5%) of adults in the US were either overweight

or obese (body mass index [BMI] ≥ 25 kg/m²), with 34.9% classified as obese (BMI ≥ 30 kg/m²) and 6.4% classified as extremely obese (BMI ≥ 40 kg/m²) [2]. Once considered to be a problem limited to developed countries, obesity has now transformed into a global epidemic [3]. The World Health Organization reported that, in 2014, more than 1.9 billion adults (39%) worldwide were overweight and over 600 million

Abbreviations: ACC, American College of Cardiology; AE, adverse event; AHA, American Heart Association; BID, twice daily; BLOOM, Behavioral Modification and Lorcaserin for Overweight and Obesity Management; BLOOM-DM, Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus; BLOSSOM, Behavioral Modification and Lorcaserin Second Study for Obesity Management; BMI, body mass index; BMOD, intensive behavioral modification; COR, Contrave Obesity Research; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; POMC, pro-opiomelanocortin; QD, once daily; REMS, risk evaluation and mitigation strategy; SCALE, Satiety and Clinical Adiposity – Liraglutide Evidence in Nondiabetic and Diabetic Individuals; T2DM, type 2 diabetes mellitus; TID, three times daily; TOS, The Obesity Society; XENDOS, XENical in the Prevention of Diabetes in Obese Subjects.

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adults (13%) were obese [3]. Strikingly, the rate of overweight and obesity has more than doubled since 1980, from 857 million (1980) to 2.1 billion people in 2013 [4].

Obesity is linked with various non-communicable diseases such as hypertension, dyslipidemia, type 2 diabetes mellitus (T2DM), coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, respiratory problems, as well as chronic liver disorders like nonalcoholic fatty liver disease and its most severe subset, nonalcoholic steatohepatitis [3,5,6]. Obesity has also been associated with increased mortality from cardiovascular disease and most cancers, including liver cancers [5–7]. In 2013, the American Medical Association officially recognized obesity as a disease to draw attention to this problem and facilitate obesity treatment and prevention strategies [8].

Besides its public health implications, the economic burden associated with obesity is staggering. Use of prescription medications to treat obesity-related comorbidities is rising because comorbidities such as hypertension, hypercholesterolemia, and diabetes increase with weight [9]. For example, use of antihypertensives, lipid-lowering agents, analgesics, antidepressants, proton pump inhibitors, thyroid medications, diabetes medications, and bronchodilators is greater among obese adults [9]. In 2011, it was projected that, by 2030, there will be an additional 65 million obese adults in the US, resulting in 6–8 million additional cases of diabetes, 5–6.8 million additional cases of heart disease and stroke, and 400,000–500,000 additional cases of cancer. The cost associated with the rise in these diseases is estimated at \$48–\$66 billion a year [10]. Globally, obesity is estimated to account for 0.7%–2.8% of total healthcare expenditures, and the combination of overweight and obesity is estimated to account for 9.1% of total healthcare expenditures [11].

The impact of weight loss on alleviating obesity-related comorbidities and risk factors has been well documented [5,12–14]. Moderate weight loss has been shown to improve cardiovascular health and reduce the incidence of diabetes. Sustained weight loss of as little as 3%–5% of body weight may result in clinically meaningful health benefits such as improved glycemic and lipid parameters [5]. Current guidelines from the American Heart Association/American College of Cardiology/The Obesity Society (AHA/ACC/TOS) suggest using a multifactorial approach in the treatment of obesity, with comprehensive lifestyle modification as the foundation for weight loss, and using adjunctive anti-obesity pharmacotherapy and/or bariatric surgery when appropriate [5].

The objective of this paper is to review the current options available for the management of obesity in adults, with a focus on anti-obesity pharmacotherapy.

2. Obesity Management Options

The potencies of treatment options for the management of obesity—including behavior/lifestyle interventions, pharmacotherapy, and bariatric surgery—generally increase in proportion to their risk and cost [15]. In this review, all treatment options for the management of chronic obesity in accordance with AHA/ACC/TOS and the Endocrine Society Clinical

Practice Guidelines will be discussed [5,16], with detailed coverage of all currently approved long-term, anti-obesity pharmacotherapies.

2.1. Behavior/Lifestyle Modification

Lifestyle modification—a combination of diet, physical activity, and behavioral strategies such as keeping records or setting goals—is central to weight management [17]. Current guidelines suggest the use of comprehensive lifestyle modification as the first-line treatment for obesity, with a recommended initial weight loss of 5%–10% of body weight within the first 6 months [5]. It is recommended that patients attempt to achieve an energy deduction of ≥ 500 kcal/day by means of physical activity, reduction in caloric intake, or both based on patients' preferences and health status [5]. Pharmacological and surgical approaches to weight loss are recommended to be used as adjuncts to lifestyle modification in appropriate patients [16].

2.2. Bariatric Surgery

On the opposite end of the obesity-management spectrum, bariatric surgery may be a treatment option for patients with extreme obesity (BMI ≥ 40 kg/m² or BMI ≥ 35 kg/m² with comorbidities) who are motivated to lose weight but have not responded to lifestyle modification with or without pharmacotherapies [5,15]. Despite definite improvements in obesity- and weight-related outcomes with bariatric surgery, it is an invasive procedure with both short- and long-term risks, and patients need to be monitored for several years post-surgery [5].

There are 3 major types of bariatric surgery procedures: laparoscopic adjustable gastric banding, where a small band is placed around the upper stomach; sleeve gastrectomy, where a large portion of stomach is removed; and gastric bypass surgery, where a part of the stomach is directly connected to the intestine, bypassing a major portion of the stomach and a section of the duodenum [15]. There is currently a lack of evidence for or against recommending bariatric surgery for patients with BMI < 35 kg/m² [5].

More recently, a first-of-its-kind medical device (the Maestro Rechargeable System) that can be surgically implanted in the abdomen has also been approved for the treatment of obesity. The device is thought to target the nerve pathway between the brain and the stomach that controls hunger [18].

3. Pharmacotherapy

Pharmacotherapy can be a viable option for patients with overweight or obesity who may not qualify for surgery [16]. In general, pharmacotherapy is recommended for use as an adjunctive treatment to lifestyle modification. Pharmacotherapies may help enhance adherence to lifestyle modifications and make it easier for patients who have difficulty starting out with physical activities [16].

Several clinical studies have shown that pharmacotherapy with lifestyle intervention is superior to lifestyle intervention alone in achieving clinically meaningful weight loss ($\geq 5\%$

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