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# The multimodal approach to obesity treatment – current pharmacological and surgical methods and lifestyle changes

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**Abstract**

**Introduction**

Obesity is one of the major health problems of today's population and is defined as a body mass index ≥ 30 kg/m2. For a long time, obesity is no longer treated as a result of negligence but as a disease as indicated by the millions of people around the world affected by this condition. It is known that obesity may cause many complications such as type 2 diabetes, cardiovascular disease, osteoarthritis, obstructive sleep, apnoea, and several cancers. The only effective treatment of obesity can be pharmacological or surgical, especially when a years-long attempt to change habits has had no effects.

**Aim of the study**

This review aims to present the current state of knowledge about non-pharmacological and pharmacological obesity treatment methods.

**Materials and methods**

The paper was created based on the Pubmed database. The literature was reviewed using the keywords: ”obesity”, ”obesity treatment”, “ obesity lifestyle changes”, “obesity medications” and ”obesity surgery”.

**The current state of knowledge**

The treatment of obesity requires a multimodal approach to treatment, including the addition of anti-obesity medications or bariatric surgery, or both, to assist people in reaching and sustaining sufficient weight loss to meet treatment goals. Nevertheless, lifestyle interventions are the cornerstone of weight maintenance. The 3 principal components of a comprehensive lifestyle intervention are diet, physical activity, and behavioral therapy. Among available anti-obesity medications include orlistat, phentermine, topiramate, naltrexone, bupropion, liraglutide, and semaglutide.

**Summary**

The key challenge in the treatment of obesity is to maintain the effects obtained with multimodal therapy. Without proper motivation of patients and changes in eating and behavioral habits, it is impossible to achieve optimal results, therefore, in addition to medical interventions, more and more attention should be paid to psychological interventions.

**Keywords:** obesity; obesity treatment; obesity lifestyle changes; obesity medications; obesity surgery

## Introduction

Obesity is one of the major health problems of today's population and is associated with many complications such as type 2 diabetes, cardiovascular disease, osteoarthritis, obstructive sleep apnoea, and several cancers (eg, breast, colorectal, endometrial, ovarian, kidney, liver, gallbladder, gastric cardia, oesophageal, and pancreatic) [1,2]. The epidemic rise of obese people has fuelled the current debate over its classification as a disease [3]. Actually, obesity is recognized as a disease and is listed in the International Classification of Diseases (ICD-10) under number E66.

It is defined as an excess of body fat causing prejudice to health and is usually assessed in clinical practice by the body mass index (BMI), which is expressed as the ratio of body weight in kilograms divided by height in square meters (kg/m2) [4]. A value ≥ 30 kg/m2 indicates a diagnosis of obesity. It has been estimated by the Global Burden of Disease Obesity Collaborators that >603.7 million adult individuals are obese. [2] Furthermore, severe obesity (class III and above), defined by a BMI ≥40 kg/m2, has been reported to reach 7.7% with considerable disparities among ethnic groups [5]. Obesity has a clear effect on overall mortality, which rises by 29% with every 5 kg/m2 increase in BMI. The life expectancy of persons with a BMI in the range of 40–45 kg/m2 is reduced by eight to ten years. This effect is comparable to that of cigarette smoking [6].

Based on epidemiological data, one can conclude how huge the problem is worldwide, and the fight against obesity must no longer be simplified to recommendations in the form of reduced food intake and increased physical activity. We will increasingly turn to pharmacological and surgical methods, which are not without side effects but may be the only effective treatment. Nevertheless, despite these advanced treatment options, lifestyle interventions are the cornerstone of weight maintenance. Therefore, clinical practice guidelines recommend a multimodal approach to treatment, including the addition of anti-obesity medications or bariatric surgery, or both, to assist people in reaching and sustaining sufficient weight loss to meet treatment goals [7].

**Lifestyle changes**

According to Look AHEAD Research Group intensive lifestyle and behavioral interventions can lead to 7–10% mean weight loss over 52 weeks in clinical trials, including in primary care settings [8]. Lifestyle intervention programs within community, clinical, and research settings vary but generally involve a combination of diet, physical activity, and behavioral treatment strategies. These programs often refer to well-researched and reviewed physical activity and dietary guidelines for the management of obesity. However, these programs are often ineffective due to low rates of adherence to recommendations. For lifestyle intervention programs to be successful, it is crucial that individuals adhere as best they can to the recommendations provided [9]. The three principal components of a comprehensive lifestyle intervention are diet, physical activity, and behavioral therapy. Comprehensive interventions are designed to induce a weight loss of approximately 0.5–1 kg per week for the first 12 weeks [10].

**Diet**

To lose weight, “energy in” (i.e., dietary energy intake) must be less than “energy out” (i.e., total energy expenditure). Thus, most dietary interventions for weight loss prescribe some form of energy restriction. The most important thing in successfully losing weight is a caloric deficit. The Obesity Guidelines recommend that patients consume a diet designed to induce a deficit of 500–750 kcal/day and a loss of 0.5–1.0 kg/week. This is why women are often prescribed a 1200-1500 kcal diet, while men are prescribed 1500-1800 kcal [11]. The Look AHEAD Research Group recommends a traditional low-fat and low-calorie diet [12]. According to Bales et al., exercise treatments without a diet component typically result in little or no weight loss, while calorie-restricted diets achieve mean reductions in baseline body weight of 5% to almost 10% [13]. Furthermore, in the recently reported CROSSROADS (Calorie Restriction in Overweight SeniorS: Response of Older Adults to a Dieting Study) trial, Ard et al. found that an exercise regimen plus a weight-loss diet was more successful at reducing body fat and improving cardiometabolic risk factors than exercise alone [14]. Greater caloric restriction, with its larger resulting negative energy deficit, is associated with a faster rate of weight reduction in the short term [15]. However, there is not a one-size-fits-all diet for obesity treatment. Adherence to a diet to produce an energy deficit to lose weight and then maintain the loss, regardless of which diet is chosen, is one of the most important factors for obesity treatment. According to Chao et al. there is no convincing evidence that one diet is universally easier to adhere to than another for extended periods, a feature necessary for long-term weight management [16].

**Physical activity**

As for physical activity, 150-180 minutes of aerobic activity is recommended [11]. Aerobic activities include, among others: brisk walking, swimming, cycling, and jogging. Regular aerobic activity is associated with a host of health benefits including improvements in lipid levels, blood pressure, and visceral fat [17]. Physical activity also is associated with improved fitness, which may attenuate the risk of mortality associated with obesity [18]. However, increased physical activity by itself is associated with little weight loss. A study by Wing et al. found that exercise combined with diet only marginally increases weight loss compared to calorie restriction alone after 6 months (-10.3 kg for diet plus exercise vs -9.1 kg for diet only) [19]. Therefore, obese people should increase their physical activity mainly to reduce cardiovascular risk, rather than weight loss itself.

### Behavioral therapy

The Obesity Guidelines recommend that patients be instructed in behavior therapy, which provides a set of strategies and techniques to modify diet and physical activity patterns [11]. The most important thing in behavioral therapy for obese people is to set realistic goals for health behavior change that clearly define the behavior to be modified and how to achieve it. The cornerstone of behavior change is self-monitoring of food and calorie intake, along with recording physical activity and weight [10, 20, 21]. Those people who engage in frequent self-monitoring of eating and weight achieve the largest weight loss [22, 23, 24]. Behavioral treatment also may include motivational interviewing to support patients' commitment to change and cognitive techniques to address maladaptive thinking [25].

## Pharmacological therapies

Obesity treatment guidelines agree that the appropriate approach for weight management should be multidisciplinary, including lifestyle modifications, behavioral therapy, pharmacotherapy, and/or bariatric surgery [26].

### Orlistat

Orlistat has mainly a peripheral effect; it inhibits gastric and pancreatic lipases, thus decreasing dietary fat absorption. When taken three times a day during or up to 1 hour after meals, leads to the excretion of approximately 30% of ingested fat. A study by Wing et al. found that obesity medications approved for long-term use, when prescribed with lifestyle interventions, produce additional weight loss relative to placebo ranging from approximately 3% of initial weight for orlistat. The proportion of patients achieving clinically meaningful (at least 5%) weight loss ranges from 35% to 73% for orlistat [27]. Among the orlistat 120mg trials examined, the percentage of orlistat 120mg-treated participants who achieved clinically meaningful (≥5%) weight loss at 1 year varied from 35–73% and the proportion losing ≥10% varied from 14–41%. At the end of a second year of treatment when a weight-maintenance diet was prescribed, orlistat 120mg-treated participants had lost approximately 3.3 kg (~3.3% of initial weight) more and orlistat 60mg-treated participants had lost approximately 2.5 kg (~2.5% of initial weight) more than those given placebo [28].

### Phentermine-topiramate

Phentermine/topiramate-Extended Release is the first FDA-approved combination drug for obesity, combining low-dose phentermine with a non-standard dose of the

antiepileptic medication topiramate-ER. One of the main studies, EQUIP33 randomized adults without diabetes and with BMI ≥35 kg/m2 to placebo, phentermine/topiramate-ER 3.75/23mg (starting dose), or 15/92mg (top dose). At the top dose, mean 1y weight loss was 10.9% vs. 1.6% of initial weight for placebo. 67% of patients given the top dose lost ≥5% of initial weight and 47% lost ≥10% of initial weight, compared with 17% and 7%, respectively for placebo [29]. In a CONQUER34 study, randomized a higher-risk sample of adults with BMI 27–45 kg/m2 and ≥2 obesity-associated comorbid conditions, to placebo or phentermine/topiramate-ER. One year weight loss was 8.1 kg (7.8%) with the recommended dose and 10.2 kg (9.8%) with the top dose, vs. 1.4 kg (1.2%) with placebo. In addition, 62% (recommended dose) and 70% (top dose) lost ≥5% of initial weight vs. 21% for placebo, with 37%, 48%, and 7% respectively losing ≥10% of initial weight [30].

**Naltrexone-bupropion**

A proprietary formulation of naltrexone-SR 32mg plus bupropion-SR 360 mg, was recommended for FDA approval as an anti-obesity agent in December 2010. Three randomized controlled trials called Contrave Obesity Research trials (COR-1,69 n=1742; COR-II,70 n= 1,496; and COR-BMOD,71 n= 793) suggest efficacy: ~4–5 kg more weight loss with naltrexone-SR plus bupropion-SR 32/360mg than with placebo at 1 year, and with 48–66%, versus 16–42% of placebo-treated participants, losing ≥5% of initial body weight and 25–42%, versus 6–20%, losing ≥10% of initial body weight at 1 year, varying with intensity of the lifestyle intervention [31, 32, 33].

**Liraglutide & Semaglutide**

The Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RA), injectable incretins approved for the treatment of type 2 diabetes, are known to produce weight loss. Glucagon-like peptide receptor (GLP1-R) agonists, Liraglutide and Semaglutide, act centrally by decreasing appetite, and peripherally, on the pancreas by increasing insulin secretion and on the gastro-intestinal tract leading to decreased intestinal motility and delayed gastric emptying [34]. A meta-analysis of the effect of GLP-1RA on body weight found a placebo-subtracted weight reduction of approximately 3% at 6 to 12 months [35]. Other studies in obese patients without diabetes have found additional weight loss relative to placebo at 6 to 12 months of 3.5 to 5.8 kg [36, 37]. A recently completed phase 3 trial evaluating liraglutide 3.0mg/d vs. placebo for weight maintenance in 422 non-diabetic overweight and obese patients (72% retention) who successfully lost ≥5% initial weight during a 4–12 week dietary run-in, found

that weight decreased an additional 6.2% in the active treatment group over the ensuing 56 weeks, a placebo subtracted-difference of −6.1%. Both groups received face-to-face lifestyle counseling throughout the trial. Those on the drug were more likely to both maintain their initial weight loss (81 vs. 49%) and to lose ≥5% (51 vs. 22%) or ≥10% (26 vs. 6%) additional weight than those taking a placebo during follow-up, suggesting a potential role for liraglutide in augmenting weight loss or ameliorating regain after initial weight loss achieved through lifestyle intervention [38].

**Surgical treatment**

Obesity can be treated with conservative or surgical treatments. There are degrees of obesity and also comorbidities [type 2 diabetes mellitus (T2DM)], arterial hypertension, dyslipidemia, cardiovascular disease, sleep apnea–hypopnea syndrome, and cancer, among others] in which it has been demonstrated that the benefit of conservative medical treatment is very limited compared to a surgical intervention, which constitutes the usual clinical practice [39]. Nowadays, the American Society for Metabolic and Bariatric Surgery (ASMBS) recommends metabolic surgery should be offered as an option for suitable individuals with a BMI of 30–34.9 kg/m2 and obesity-related comorbidities (especially T2DM), who have not achieved substantial, durable weight loss and comorbidity improvement with reasonable nonsurgical methods [40, 41]. The recommended age of the patient would be between 18 and 65 years. Outside of this range, it would be necessary to individualize each case.

Preoperative weight loss of 5–10% is recommended as it presents intra/perioperative advantages, a shorter hospital stay, and greater adherence to life changes [39].

**Conclusions**

Despite progress in the treatment of obesity, treatment results are still unsatisfactory. The key challenge in the treatment of obesity is to maintain the effects obtained with multimodal therapy. Without proper motivation of the treated people and changes in eating or behavioral habits, it is impossible to achieve optimal results, therefore, in addition to medical interventions, more and more attention should be paid to psychological interventions.

**Author contributions**

Conceptualization: LJ, KJ, LL; methodology: LJ, LŁ, KK, NM; software: LŁ, KJ, KS, NM; check: LŁ, LJ, KK, LL, KK; formal analysis: KI, KK, LL, KK; investigation: KI, KM, NM, KS; resources: KI,; data storage: L£, LJ, KI; writing - rough preparation: LŁ, LJ, KM, KI;

writing - review and editing: KI, LŁ; visualization: LJ, KK, KJ, NM, KS; supervision: LJ; project administration: LJ ; All authors have read and agreed with the published version of the manuscript.

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