



**Article title:** Liraglutide vs. Lifestyle Intervention in Obesity Treatment: Pros and Cons

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**Keywords:** liraglutide, saxenda, lifestyle changes, weight loss, diet, obesity, GLP-1 receptor agonist

## **Title: Liraglutide vs. Lifestyle Intervention in Obesity Treatment: Pros and Cons**

### **Abstract**

The increasing prevalence of obesity continue to trigger a cascade of other non-communicable medical conditions and further cripple healthcare financial budgets worldwide. This preventable chronic disease is a global public health concern and has been the center of past, present and future research. As an adjunct to lifestyle intervention, the Food and Drug Administration (FDA) has currently approved five anti-obesity medications. However, skepticism surrounding the prescription of medication is presented based on historic concerns of previously withdrawn medication.

Liraglutide is among the newly approved anti-obesity medications and has shown favorable weight loss results. The choice of treatment requires a selective determination based on the specific patient population, existing chronic condition(s) and individual preferences.

The goal of this review is to highlight the advantages and disadvantages of liraglutide use compared to lifestyle intervention in treating obesity. This would help individuals make informed decisions in choosing the most suitable option for treating obesity.

It can be concluded that there is no single-handed approach to combat obesity. Regardless of the chosen option, individuals need to be consistent with behavioral changes and exercise in order to effectively treat and possibly eradicate this global epidemic.

Keywords: liraglutide, saxenda, GLP-1 receptor agonist, lifestyle changes, exercise, weight loss, diet, obesity.

## Introduction

The worldwide prevalence of obesity has nearly tripled from 1975 to 2016<sup>[1]</sup> and projections based on current trends anticipate an estimated 51% of US adults will be obese by 2030<sup>[2],[3]</sup>. According to the World Health Association, overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health. A body mass index of  $\geq 25$  is classified as being overweight and  $\geq 30$  is considered obese<sup>[1]</sup>. The top 10 most obese countries in the world according to 2017 data were United States, Mexico, New Zealand, Hungary, Australia, United Kingdom, Canada, Chile, Finland and Germany (ranked from most to least)<sup>[4]</sup>. Consequently, obesity has become a global pandemic, and is no longer considered a problem predominantly in western countries<sup>[5]</sup>. Obesity is said to cost the EU £81 billion per annum<sup>[6]</sup>, the US 190.2 billion per annum for obesity-related illnesses<sup>[7]</sup> and 24.35 billion Yuan per annum in China<sup>[8]</sup>. Obesity leads to the development of cardiovascular disease, diabetes, musculoskeletal disorders and some cancers<sup>[1]</sup>.

The recommended cornerstone of obesity management is lifestyle intervention. However, many patients do not achieve long lasting benefits because of poor adherence, along with inability of the body to adapt to physiological and neurohormonal changes in response to weight loss<sup>[9]</sup>.

The emergence of glucagon-like peptide-1 (GLP-1) agonist, liraglutide has shown greater body weight loss in overweight and obese adults without diabetes compared to placebo<sup>[5]</sup>. Liraglutide is one of the five main pharmacological therapy options used to treat obesity<sup>[3]</sup>. Recent studies demonstrated reduced energy intake and weight loss, modest relative shift toward fat oxidation and reductions in energy expenditure by calorimetry in obese individuals who used sustained liraglutide treatment of 1.8 or 3 mg daily<sup>[10]</sup>.

Anti-obesity medication like liraglutide is costly and produces adverse outcomes in individuals. Recent withdrawal of lorcaserin (an anti-obesity medication) by the Food and Drug Administration (FDA) due to its suspected increased occurrence of cancer, arouse concern in initiating drug therapy in obese individuals and causes closer scrutiny of the benefits and risks involved with medication use<sup>[11]</sup>.

Treatment of obesity requires selective determination based on specific patient subpopulations, existing chronic condition(s) and individual preferences<sup>[11]</sup>. This article will outline the benefits and risks of liraglutide against lifestyle intervention in treating obesity with the aim of effective application of concepts and possible eradication of obesity. This is a traditional review paper presenting data collected during the last five years.

## Discussion

Highlighted among the causes of a dramatic rise in obesity in both developed and developing countries is genetic predisposition, environmental factors<sup>12</sup> and sedentary lifestyle<sup>5</sup>. The worldwide exponential increase over time<sup>3</sup> and concomitant adverse medical, economic, social and psychological consequences<sup>13</sup> emphasizes the need for effective and safe strategies to treat this chronic medical condition.

### Lifestyle intervention : Overview and pros

The recommended cornerstone of treating obesity is lifestyle intervention, which requires a multimodal approach in order to achieve clinically meaningful weight loss of 5-10% within six months, according to various professional guidelines in the US, Europe and other parts of the world<sup>[9]</sup>. Clinically significant weight loss achieved through this means can result in reduced risk of type 2 diabetes mellitus, cardiovascular disease and obstructive sleep apnea<sup>[6]</sup>. This intense, highly structured plan involves dietary changes through the prescription of a calorie-reduced diet, increased physical activity or exercise and behavior modification. The behavioral component which seeks to encourage adherence to dietary and physical recommendations<sup>[9]</sup>, incorporates at least 14 in-person sessions within six months<sup>[13]</sup>, self-monitoring of diet and physical activity, routine weight checks, behavioral contracts, goal setting and strict limit of eat out locations, also known as stimulus control<sup>[9]</sup>. Maintaining these efforts over a long time can be challenging<sup>[11]</sup> and some authors consider weight lost through lifestyle intervention as limited due to weight regain in most patients after 12 months<sup>[14]</sup>. However, studies have shown maintenance of weight loss over long periods of time in a considerable number of individuals. The Weight Loss Maintenance trial revealed maintenance of 4kg and 3kg weight loss after two and five years of follow up, respectively. These were participants who initially lost 8kg over a six-month period. Additionally,  $\geq 5\%$  of weight lost after two years was maintained in 35% of participants who were involved in a four-month weight loss intervention program. The Diabetes Prevention Outcome Study showed that after 15 years, 40% of the participants who had achieved clinically significant weight loss in one year, were able to maintain at least 5% of weight loss. It was noted that these participants were part of the intensive lifestyle group in this study<sup>[15]</sup>. It has been shown that comprehensive lifestyle intervention which involves daily weight checks and portion-controlled foods, promote effective weight loss for both short and long term. Additionally, face-to-face counseling is proven more effective than “not in-person means” through telephone-based sessions and electronic treatments<sup>[9]</sup>. Successful individuals in weight loss maintenance were characterized as those who obtained substantial weight loss during initial treatment, those who achieved their self-determined weight loss goal, those involved in active lifestyle and those involved in leisure time activities. Noteworthy, is the fact that these individuals did not skip breakfast, ate at regular intervals and maintained healthy, low-fat diets. They experienced less psychological and emotional instability, along with reduced binge eating and weight cycling<sup>[16]</sup>. Studies have noted improvement in cardiovascular health through lifestyle interventions including moderate exercise and diet. In fact, participants in a four-month

program of either a low-calorie diet or exercise revealed reductions in adipose tissue, systolic, diastolic and mean arterial pressures and lower total and low-density lipoprotein cholesterol profiles compared to control group<sup>[17]</sup>.

Lifestyle intervention in obesity treatment can be accomplished and leads to an improvement in physical, psychological, physiological and overall quality of life once strict adherence to intense, highly structured guidelines are executed and maintained.

The study discussing in-person behavioral sessions is a systematic review which comprised of 12 studies with a total of 1,862 participants. All other studies discussed were narrative review publications. As a result, the systematic review study provides less risk of bias and a higher quality assessment score compared to the narrative review publications.

#### Lifestyle intervention: Cons

Effective weight loss involves partnership between a highly motivated patient and a team of skilled professionals including psychiatrist, psychologist, physical and exercise therapist, dietitian, physician, and subspecialist(s) based on patient's existing comorbid condition(s)<sup>[5]</sup>. Also, generally a higher level of physical activity is required for weight maintenance<sup>[9]</sup>. Undoubtedly, self-discipline and persistence are key in order to accomplish these goals<sup>[5]</sup>. Consequently, lack of adherence to a strict comprehensive lifestyle intervention most commonly results in unattained long-lasting weight loss results<sup>[9]</sup>. A study which compiled 8,222 articles stated that demographic, social and physical environmental determinants were not predictive of weight loss maintenance. In fact, behavioral and cognitive determinants that promote reduced energy intake, increased energy expenditure and monitoring of this balance, strongly predict weight loss maintenance<sup>[16]</sup>. Literature has also highlighted that poorly maintained weight loss despite adherence to lifestyle intervention is possibly due to genetic predisposition<sup>[18]</sup> and the difficulty of the human body to adapt to the physiological and neurohormonal changes associated with weight loss<sup>[9]</sup>.

The major contributors to unattained clinically meaningful weight loss and maintenance are poor adherence (behavior and physical activity) to recommended guidelines and genetic influence. Table 1 summarizes the advantages and disadvantages of lifestyle intervention in obesity treatment.

The study discussing the compilation of 8,222 articles is a systematic review and all other studies discussed were narrative review publications. Thus, this data has less risk of bias and a higher quality assessment score compared to the narrative review publications discussed.

#### Liraglutide: GLP-1 agonist pros

Liraglutide, at a dose of 3mg which is administered as a daily subcutaneous injection, was approved by the FDA in 2014 for long-term weight management in adults<sup>[11],[19]</sup> and in 2020 for treatment of obesity in children 12-17 years old<sup>[19]</sup>. This new generation anti-

obesity medication is a glucagon-like peptide-1 (GLP-1) agonist, and was initially approved for the treatment of type 2 diabetes mellitus in 2010 at a dose of 1.8mg daily<sup>[11]</sup>. As a GLP-1 receptor agonist, liraglutide has metabolic effects which include glucose-dependent stimulation of insulin secretion, decreased gastric emptying<sup>[20]</sup> due to direct action on the hypothalamus<sup>[21]</sup>, inhibition of food intake<sup>[20]</sup> resulting in weight loss<sup>[10]</sup>, increased natriuresis and diuresis<sup>[20]</sup>, and a modest relative shift toward fat oxidation, thereby improving lipid metabolism<sup>[10]</sup>. In addition to lowering both systolic and diastolic blood pressure and total cholesterol, GLP-1 agonists have shown to promote an average weight loss of 2.9 kg when compared to placebo. Among the main cardioprotective effects of GLP-1 agonists is improved coronary blood flow, left ventricular ejection fraction, myocardial contractility, cardiac output and endothelial function<sup>[21]</sup>.

An increased visceral fat can lead to GLP-1 resistance. Studies have shown that moderate and high intensity acute exercise, increase GLP-1 levels in healthy obese individuals compared to controls. In fact, GLP-1 levels were reportedly increased in overweight/obese individuals who underwent a 12-week supervised chronic exercise program. It was concluded that exercise potentiates the effect on GLP-1 receptor agonists treatment by ameliorating GLP-1 resistance<sup>[22]</sup>.

Pharmacotherapy is recommended by most current guidelines to be used as the second-line treatment for obesity. It has been reported that when used as an adjunct to lifestyle modification, clinically meaningful weight loss is more likely anticipated<sup>[6]</sup>. The results of three main randomized control trials (RCTs) – the SCALE Obesity and Prediabetes, the SCALE Diabetes and the SCALE Maintenance, formed the basis of approval for liraglutide use in obesity management<sup>[11]</sup>. In the SCALE Obesity and Prediabetes trial, a weight loss of 8% was seen in the liraglutide group after 56 weeks, compared to 2.6% in the placebo group. Additionally, 63.2% and 33.1% of the participants in the liraglutide group obtained weight loss of  $\geq 5\%$  and  $\geq 10\%$  respectively, compared to 27.1% and 10.6% in the placebo group<sup>[23]</sup>. Also, there was better improvement of blood pressure, lipid profiles and A1c levels in the liraglutide group<sup>[11]</sup>. The SCALE Maintenance trial assessed weight maintenance in non-diabetic participants who lost  $\geq 5\%$  of body weight during a four to 12 week low-calorie diet run-in period<sup>[24]</sup>. Individuals in the liraglutide group lost an additional 6.1% body weight compared to 0.2% in the placebo group. Diet, exercise and weight counseling was given to all participants during the trial<sup>[25]</sup>. Overall, the trial revealed that liraglutide could be used in maintaining weight loss in patients who initially achieved  $\geq 5\%$  weight loss through intensive lifestyle modifications<sup>[24]</sup>. In addition to weight loss, liraglutide has been noted to promote neuronal survival and reduce apoptosis and oxidative stress in the brain. This arouses implications in neurological recovery after cerebral ischemia<sup>[26]</sup> and for learning and memory<sup>[20]</sup>.

Liraglutide as a GLP-1 agonist has shown to produce favorable metabolic effects which lead to weight loss and improved lipid metabolism, and provide cardioprotective and neuroprotective properties.

All studies discussed provided information from narrative review publications. Hence, there is a high risk of bias and the quality assessment score is low.

### Liraglutide cons and contraindications

The application of liraglutide in achieving clinically significant weight loss, as an adjunct to lifestyle modification is beneficial. However, it is often discontinued due to high cost<sup>[12],[6]</sup>, the requirement for subcutaneous injection and concerns regarding its side effects<sup>[6]</sup>. Liraglutide needs to be monitored closely upon commencement of treatment to evaluate its safety and efficacy<sup>[12]</sup>. If clinically significant weight loss of at least 5% is not achieved within the first three to four months of treatment, the medication is discontinued as this is the only consistent predictor of further successful weight loss with continued treatment<sup>[9]</sup>. Data from five randomized controlled studies of at least 12 weeks reveal the most commonly reported adverse effect of liraglutide use was gastrointestinal in nature<sup>[27]</sup> – nausea (25%), vomiting (12.2%), diarrhea (11.6%), constipation (11%) and dyspepsia (6.4%)<sup>[23]</sup>. Though some studies revealed these adverse effects were mild and transient<sup>[28],[24],[2]</sup>, studies from a meta-analysis revealed that among all FDA approved anti-obesity medications, liraglutide had the highest discontinuation rate as a result of its side effects<sup>[23]</sup>. 9.8% of participants in the liraglutide group discontinued treatment compared to 4.3% in the placebo group because of an adverse event<sup>[28]</sup>. Liraglutide is given at a starting dose of 0.6mg and increased with increments of 0.6mg until a maximum dose of 3mg is achieved in an attempt to ameliorate adverse effects<sup>[23]</sup>. Other reported adverse effects related to liraglutide use include hypoglycemia, headache, decreased appetite, abdominal pain, and increased lipase activity and heart rate. Addition of liraglutide treatment in a patient using a sulfonylurea or long-lasting insulin increases the risk of hypoglycemia<sup>[21]</sup>. Acute pancreatitis, chest pain and bronchitis<sup>[5]</sup> and increased incidence of symptomatic gall stones<sup>[12]</sup> suspectedly due to delayed gall bladder emptying<sup>[29]</sup> were among the more serious adverse effects<sup>[5]</sup>. Pooled studies revealed a 7% increase in mean level of amylase and 31% increase for lipase activity in patients treated with liraglutide versus placebo during a 56-week course. These values were shown to normalize after discontinuation of medication<sup>[30]</sup>. Additionally, literature have highlighted weight regain upon cessation of anti-obesity medication after maximal therapeutic effect is achieved and some weight regain also after continuation of medication for more than one year<sup>[9]</sup>.

Liraglutide should not be used in patients with severe gastrointestinal disease such as gastroparesis and inflammatory bowel disease<sup>[21]</sup>, severe renal insufficiency, hepatic insufficiency, past history of pancreatitis or major depression, pregnancy<sup>[12]</sup>, and patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2<sup>[23]</sup>. The INR levels in patients on warfarin should be monitored closely if GLP-1 analog such as liraglutide is added as it may alter the absorption of warfarin due to delayed gastric emptying<sup>[21]</sup>.

Liraglutide use in obesity treatment presents some challenges due to cost, its requirement of a daily injection, and concerns regarding reported side effects and contraindications. These findings are summarized in Table 2.

The study discussing the most common adverse effects (gastrointestinal symptoms) from liraglutide use, was compiled from a systematic review publication. This data therefore provides the lowest risk of bias and highest quality assessment score compared to data provided from the randomized control trial (RCT) study and narrative review publications. The RCT study provided data in relation to delayed gall bladder emptying which leads to gall stones. This study involved human subjects and the data has a lower risk of bias and a higher quality assessment score compared to the remaining narrative review publications discussed.

## **Conclusion**

The increasing prevalence of obesity continue to trigger a cascade of other non-communicable medical conditions and further cripple healthcare financial budgets worldwide. This preventable chronic disease has become a global health concern. Thus, being knowledgeable of ways in which obesity can be best treated, is imperative. Recognizing the advantages and disadvantages of lifestyle intervention compared to liraglutide use helps individuals make informed decisions in choosing the most suitable option for treating obesity. There is no single-handed approach to combat obesity. Individual responses vary widely and the specific means of treatment is based on individual preferences, tolerance and existing comorbid condition(s).

Lifestyle intervention remains the cornerstone of obesity treatment and is advisably used with medication to produce a more favorable response. The use of medication is costly and does present adverse effects which vary among individuals. Regardless of the chosen option, it is important that individuals be consistent with changed behavioral patterns and exercise in order to effectively treat and possibly eradicate obesity. This paper is a traditional review compilation of studies done in the last five years. It does not involve a significant data which reflect low risk of bias and high quality of assessment scores. It is recommended that a systematic review of topic be done involving updated randomized control trial studies.

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