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# POTENTIAL USE OF EXENATIDE FOR THE TREATMENT OF OBESITY

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## Abstract

**a.** Introduction: Obesity is a major worldwide health threat in Western World because of its high incidence and prevalence and its association with metabolic and cardiovascular disease as well as cancer. The reduction of food intake in obese patients can be achieved only transiently (generally for no longer than 6 months), in the absence of concomitant pharmacological therapy. Only bariatric surgery provides a mean to increase satiety and/or decrease nutrients absorption in obese patients, in the long term.

**b.** Areas covered: The available pharmacological treatments for obesity, as well as the pharmacology and mechanisms of action of Exenatide in obese type 2 diabetic patients.

**c.** Expert opinion: Exenatide is a potential new candidate treatment for obesity, possibly in combination with other hormones that increase satiety (leptin) and slow gastric emptying (amylin).

### Keywords

GLP-1 analogues; exenatide; obesity; type 2 diabetes mellitus; medical treatment

## 4) Introduction

Obesity is a worldwide health problem, not only because an increase in its incidence and prevalence, but also because it increases the risk of cardiovascular disease, type 2 diabetes, hypertension, dyslipidemia, obstructive sleep apnea and some cancers, among other health problems. In the US, the prevalence of obesity has increased dramatically in recent decades, data from the National Health and Nutrition Examination Survey reporting that, in 2007–2008, 34% of American adults were obese. In general, obesity appears when energy intake exceeds energy expenditure and most of the therapeutical options to control this problem are focused on these points. There is no question that the first approach in a patient with obesity would be the adjustment on the food intake with a concomitant increase in the physical activity to improve the energy expenditure; however, it is still very difficult to achieve the long-term goals using only these strategies[1], and despite the transcendence of the problem, there are not many pharmacological options available for this issue, many of them have

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several side effects and cannot be used for more than 3 months, their efficacy is modest, with placebo-subtracted weight loss of < 5 kg after 1 year and their efficacy in the long-term is suboptimal, since cessation of the pharmacotherapy results in patients regaining lost weight [2–6].

**a.** *Overview of the market:* At the present time, there are few drugs approved by the FDA to treat obesity. Sibutramine was recently withdrawn from the market due to its association with cardiovascular events. The results of the Sibutramine Cardiovascular Outcome Trial (SCOUT) have been questioned by many, mainly because the increase in nonfatal myocardial infarction and nonfatal stroke was observed only in patients with preexisting cardiovascular disease, highlighting the point that sibutramine should not be used in patients with this clinical characteristic, but perhaps it could be used in patients without any cardiovascular pre-existing condition. The final approval for Rimonabant was denied by the FDA due to its association with mental disorders (mainly depression); there is no doubt that the lack of new and effective pharmacological therapies has contributed to a greater gap between the availability of medical therapy and the steadily rising rates of obesity [3, 4]. Recently, FDA denied the approval to lorcaserin and the combination of phentermine and topiramate, the last due to potential long-term adverse effects (teratogenicity and depression). A combination of bupropion, a dopamine and norepinephrine reuptaker inhibitor, and naltrexone, a narcotic antagonist, are still awaiting for the FDA approval. The available antiobesity drugs approved by the FDA, are: 1) Orlistat, an inhibitor of pancreatic and intestinal lipases, 2) Phentermine, approved for short-term use only, 3) Diethylpropion, which is also approved for short-term use only, 4) Benzphetamine, which is an appetite suppressant that affects central nervous system, and 5) Phendimetrazine, a sympathomimetic amine that also stimulates the central nervous system. With these drugs, patients can achieve a 2–5% of weight loss, and they may have side effects, which highlight the need of new therapeutical options for obesity and the establishment of clear clinical criteria specifying the contraindications and the characteristics of the patients that can make them more susceptible to the side effects of the drug, and then limit the recipients to those in whom a favorable risk-benefit ratio exists maintaining the clinical efficacy regarding weight loss[2, 4–7].

**b.** *Introduction to the compound:* Exendin-4 is a naturally occurring peptide identified in the saliva of the Gila monster and it has a 53% homology with the human GLP-1 amino acid sequence. The human GLP-1 is rapidly degraded by dipeptidyl peptidase IV (DPP IV), and exenatide, a synthetic version of exendin-4, exhibits prolonged kinetics due to resistance to proteoIytic degradation by DPP IV; it is an incretin mimetic and exhibits glucoregulatory effects similar to those of human GLP-1. Exenatide, is approved by the FDA to improve glycemic control in patients with type 2 diabetes, due to its multiple effects: increase of glucose-dependent insulin secretion, inhibition of glucagon release by the alpha cells, delay of the gastric emptying and appetite suppression. In obese patients, although somehow controversial, it has been reported that the GLP-1 secretion may be reduced, and it is improved after weight loss[8–11]. The mechanism by which obesity reduces GLP-1 secretion is not very well known, but may be related to the insulin resistance associated with weight gain, and to an increase in the circulatory levels of carbohydrates and fatty acids[12–14]. Of course, this could be irrelevant when given a compound that increases the levels of GLP-1 to pharmacological levels. One of the important effects of exenatide is its capability to suppress appetite and by consequence causing weight loss. It is not completely understood how exenatide causes an anorectic response, since the regulation of feeding and energy balance involves hormonal and neural inputs and is quite complex. Exenatide reduces food

intake in rodents following either central of peripheral administration, and repeated or chronic exposure reduces body weight, apparently, this effect is mediated via central GLP-1 receptors but could be also influenced by the exenatide-induced nausea and the delay in gastric emptying[15–20]. In type 2 diabetic patients exenatide causes weight-loss in a range between ≃ 2 to 6 kg and the patients that continued the therapy up to 3 years maintained this weight loss[21–33].

**c.** *Chemistry:* Exenatide is a 39-amino acid peptide

**d.** *Pharmacodynamics, pharmacokinetics and metabolism:* Exenatide has a relatively short half-life of 2.4 hours and is detectable in plasma within 15 minutes of administration and is still detectable 15 hours after a single subcutaneous injection >0.2mcg/kg. It is important to mention that there is another preparation of this drug, exenatide once weekly, which is approved for glycemic control in type 2 diabetic patients in the EU and it is under review by the FDA[34–36]. The predominant route of elimination is via glomerular filtration with subsequent proteolytic degradation; consequently, exenatide is not recommended for use in patients with severe renal impairment[37]. The most common side effect of exenatide is nausea (3–51%). Nausea was transient in clinical trials, disappearing after 8 weeks, and therefore appeared not to have a causal relationship with reductions in weight, which were sustained for the duration of the treatment. There has been a discussion between clinicians on the potential association of exenatide with pancreatitis, however, most of the studies have failed to find such association.[38–40] A characteristic of exenatide is that between 27 – 49% of the patients in clinical trials of 24–30 weeks developed antibodies, although apparently it does not affect its pharmacological effects[21,41].

**e.** *Clinical efficacy:* Due to its nature and origin, more of the clinical trials with exenatide have been performed in patients with type 2 diabetes. As a monotherapy, exenatide achieved a reduction in body weight of 3 kg, after 24 weeks of treatment, in naïve type 2 diabetic patients[32]. In uncontrolled type 2 diabetic patients with metformin and/or sulphoniyureas, the addition of exenatide for a period varying from 3 to 18 months has achieved a weight reduction of 1.6 to 5.3 kg [21–31, 33, 42]. In patients continuing treatment for up to 3 years it has been reported a sustained weight loss of 5.3 – 5.7 kg has been reported[23, 43]. However, during a 3-months off-drug period, body weight slightly trended to increase with a final reduction of around 4.0 kg[43]. When combined with a lifestyle modification program, exenatide treatment can achieve a body weight reduction of 6.16 kg, greater than 3.97 kg which was achieved with the lifestyle modification program + placebo[43]. It is important to mention that besides the improvement in glycemic control and weight reduction, exenatide has been shown to reduce blood pressure, body fat mass, including visceral fat, while lean body mass is not altered, and an improvement in the profile of circulating cardiovascular biomarkers[44]. There are few studies in patients without type 2 diabetes. The first study was performed in 60 overweight (BMI >27), insulin resistance women with polycystic ovary syndrome (PCOS); patients were randomized to one of three treatments: metformin 2000mg/day, exenatide 10μg BID or the combination of metformin + exenatide. After 24 weeks of treatment, the two groups with exenatide showed a decrease of 3.2 to 6.0 kg of body weight, besides the improvement on metabolic parameters. The most common side effects reported in this study were nausea (27%), vomiting (7%) and headache (2%), and although 30% of the patients did not complete the study protocol, it was not due to the adverse effects[45]. The second study was performed in 152 obese subjects, randomized to placebo or exenatide 10 μg during 24 weeks; exenatide-treated subjects lost 5.1kg from baseline versus 1.6 kg with placebo, and 77% of

the subjects with exenatide and prediabetes had normal glucose tolerance at the end of the study. The most common side effects were nausea (25%) and diarrhea (14%)[46]. The third study was an open trial performed in 10 patients with metabolic syndrome who received exenatide 5 μg twice daily for 1 month. There was a 3.7 kg weight loss after the treatment and most of the patients improved also in other metabolic parameters; the most frequent adverse events were satiety (70%), anorexia (60%), diarrhea (40%) and headache (30%)[47]. The last study was not performed with exenatide, but with liraglutide, a GLP-1 incretin mimetic with a 97% of similarity to the human GLP-1. In this study, 564 patients with a BMI between 30–40 were randomly assigned to different liraglutide doses (1.2–3.0mg), placebo or orlistat. The estimated mean weight loss in the intention-to-treat population from randomization to week 20 was significantly higher with liraglutide (all doses, from 4.8 to 7.2 kg) than with placebo, and was dose dependent. Most of the patients treated with liraglutide had also beneficial effects on metabolic and cardiovascular profile, and the most frequent adverse effect were nausea and vomiting, which were also dose dependent[48]. Another peptide that has also a regulatory effect on appetite is amylin; amylin is a peptide hormone with glucose-regulatory and anorectic effects, it is stored in the pancreatic beta cell and it is physiologically cosecreted with insulin in response to food ingestion. Amylin acts in the hindbrain are postrema and central nucleus of the amygdale to reduce food intake, by acting as a satiety signal[49–50]. Clinical studies have shown that pramlitide, a synthetic form of amylin currently approved in the United States for the treatment of type 1 or type 2 diabetes, leads to a reduction in food intake and body weight in obese humans, with or without diabetes[51]. In a phase IIa, 24-week study, pramlitide causes a weight loss of 8.4%, as a monotherapy, and this effect could be maintained up to 52 weeks[52].

## 5) Conclusion

The current global epidemic of obesity is one of the most important challenges to our times. In addition to lifestyle modifications, it is important to have new therapies effective to treat, and possible prevent, obesity. Our current therapeutic armamentarium for obesity are limited, by the side effects, the efficacy and the recent withdrawal from the market of rimonabant and sibutramine. The role of GLP-1 receptor agonist on the appetite suppression makes exenatide a potential new candidate therapy in obese patients without type 2 diabetes; there is abundant evidence that exogenous administration of GLP-1 receptor agonist induces weight loss, and besides this, GLP-1 receptor agonists have beneficial effects on several cardiometabolic risk markers (glycemia, insulin resistance, lipid profile, blood pressure) which could give an extra benefit to the patient, since these abnormalities are associated to the presence of obesity. Future prospective studies are needed to address the questions that all the weight-loss drugs must clarify: efficacy, durability of the effect, profile of the patients who would receive the highest benefit with the lowest risk of side effects and complications.

## 6) Expert opinion

**a.** *What, if any, improvement does the drug hold over the other therapies?:* The advantage of exenatide over the actual approved drugs for obesity is that exenatide provides a persistent and continuous long-term reduction in the weight plus the fact that exenatide is not associated to cardiovascular or neurological side effects. Additionally, exenatide may improve many of the metabolic disorders present in obesity, which could be reflected in a lower rate of cardiovascular complications.

**b.** *What, if any, impact is this drug likely to have on current treatment strategies?:* Exenatide could be used in many patients that have contraindications or intolerance to actual therapies.

**c.** *How likely are physicians to prescribe the drug?:* There is no doubt that the route of administration could be a disadvantage for exenatide, since there is still a general resistance, in patients and physicians, to the use of injectable therapies; however, many obese patients could be potential candidates to exenatide, which would give one more tool to the physicians to fight against the obesity epidemic.

**d.** *What data is still needed?:* Prospective studies in obese non-diabetic patients are needed, to reaffirm the capability of the drug to maintain the weight reduction and to identify the profile of the patients who would receive the best benefit without the risk of side effects or complications of the treatment. In particular, more mechanistic and prospective data are needed to clarify the role of exenatide on the potential association with pancreatitis.

**e.** *Where is drug likely to be in 5 years time?:* Exenatide could be approved to be used in obese patients, specifying the selection criteria for the patients who would receive the drug.

## 7) Drug summary box

| **Drug name** | **Exenatide** |
|---|---|
| Phase | Phase II |
| Indication | Type 2 diabetes |
| Route of administration | Subcutaneous |
| Dosing | 5μg twice a day for one month to improve/test tolerability and then increasing to 10 μg twice a day based on clinical response. |
| Chemical structure | 39-amino acid peptide with a 53% homology to human GLP-1 |
| Clinical trials | Most of the clinical trials have shown a suppressive effect on appetite with a reduction of 3–6 kg of weight and improvement in metabolic and cardiovascular risk factors in non-diabetic patients. |

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