2021

Is liraglutide effective for weight loss in adults who are overweight or obese compared to placebo?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 12, 2020

ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not is liraglutide effective for weight loss in adults who are overweight or obese compared to placebo.

STUDY DESIGN: Review of three double-blind, randomized controlled trials published after 2010.

DATA SOURCES: All three English language, double-blind, randomized controlled trials were found using PubMed. All three RCT's were published in peer reviewed journals.

OUTCOMES MEASURED: The outcome measured was loss of 7% or more of body weight from baseline in the study by Sun et al., and loss of greater than 10% of body weight from baseline in the studies by Pi-Sunyer et al. and Davies et al.

RESULTS: The RCT performed by Davies et al. showed 25.2% of subjects in the liraglutide 3.0mg group lost more than 10% of baseline body weight compared to 6.7% in the placebo group ($p < 0.001$). The RCT performed by Sun et al. showed 54% of subjects in the liraglutide 1.8mg group lost 7% of baseline body weight compared to 4% in the placebo group ($p < 0.001$). The RCT performed by Pi-Sunyer et al. showed 33.1% of subjects in the liraglutide 3.0mg group lost more than 10% of baseline body weight compared to 10.6% in the placebo group ($p < 0.001$).

CONCLUSIONS: The results of all three RCT's included in this review indicate that the use of liraglutide is effective for weight loss in adults. These studies demonstrated that dosages of liraglutide 1.8 mg and 3.0 mg worked in reducing body weight from baseline when compared to placebo. Future studies should include lower dosages of liraglutide to assess the efficacy they have in weight loss.

KEY WORDS: Liraglutide, weight loss

INTRODUCTION

Obesity is considered a national epidemic and more than 70% of American adults are overweight or obese.[1] It is well known that Americans weigh more now than they did in the last decade. In 2016, more than 1.9 billion adults (39%), 18 years and older, were overweight, of these over 650 (13%) million were obese.[2] Being overweight or obese can be caused by high calorie intake, poor diet, lack of physical activity, genetics, underlying medical conditions, or certain medications. A high BMI can be an indicator of high body fatness. If the BMI is 25.0 to < 30, it falls within the overweight range and if the BMI is 30.0 or higher it falls within the obese range. In 2012, 11 million visits, or an annual visit rate of 49 visits per 1000 persons, to physician offices for obesity were made by adults aged 20 and over.[3] Weight loss can prevent or at least slow down major risk factors of obesity that include adverse cardiac events, diabetes, dyslipidemia, sleep-disordered breathing, diastolic dysfunction, joint problems and others, and, by doing this, possibly decrease morbidity and mortality in the long term.[4] All these complications mentioned are a major concern for patients and physician assistants. Physician assistants in the primary and hospital setting will encounter patients that are suffering from the complications of being overweight or obese and; thus, will have to come forth with a plan to help their patients effectively lose weight. Even a modest weight loss of 5 to 10% of the total body weight can produce health benefits, such as improvements in blood pressure, blood cholesterol, and blood sugar.

Obesity not only cost people their health but it comes at a monetary cost as well. It costs the global economy about $2 trillion annually or 2.8% of global GDP.[5] Research suggests that the percentage of U.S. health spending on treatment of obesity related illnesses in adults climbed 29% between 2001 and 2015.[5] Individuals with obesity have 42% higher healthcare costs than

people of normal weight and each 1-point increase in BMI leads to a 4% increase in medical costs and a 7% increase in pharmaceutical costs.[5] The pharmaceutical cost of a one-month supply of liraglutide at the target dose of 3.0 mg per day is approximately $1194.[6] That cost is an out of pocket cost without insurance coverage being applied.

Currently, there are a few options available for weight loss, such as healthy lifestyle changes including heart healthy eating and physical activity, bariatric surgeries including Roux-en-Y gastric bypass, sleeve gastrectomy, and adjustable gastric banding, and FDA approved medications including orlistat, lorcaserin, phentermine-topiramate, and liraglutide.[7] With almost half of American adults making an effort to lose weight, the treatment options mentioned play an effective role in helping them achieve their goals.[8]

Liraglutide may be used as an effective agent in helping adults obtain weight loss. It is a glucagon-like peptide 1 (GLP-1) analog, with 97% homology to human GLP-1 and a therapeutic potential for both obesity and type 2 diabetes owing to its dual benefits on body weight and glycemic control.[9] GLP-1 analogs like liraglutide not only suppress glucagon but they induce satiety which leads to reducing appetite and food intake and; thus, subsequent weight reduction.

OBJECTIVE

The objective of this systematic review is to determine whether or not is liraglutide effective for weight loss in adults who are overweight or obese compared to placebo.

METHODS

The criteria used for the selection of the three studies included adults. The three studies in this review were found by searching the PubMed database. The keywords used for this search were “liraglutide” and “weight loss”. The three articles were chosen for this review because they proved relevant to the clinical question and the outcomes were measured by Patient-Oriented

Evidence that Matters. The inclusion criteria included randomized controlled trial, clinical trial, studies published after 2010, humans, and English language. Exclusion criteria included studies published earlier than 2010. The three studies that were selected were double-blind, randomized controlled trials comparing liraglutide to placebo. All three studies were published in the English language in peer-reviewed journals from 2013 to 2015. The statistics used included RBI, ABI, NNT, and p-values.

The intervention evaluated in the Sun et al. study was once-daily subcutaneous injections of liraglutide 1.8 mg compared to placebo. The interventions evaluated in Pi-Sunyer et al. and Davies et al. studies were once-daily subcutaneous injections of liraglutide 3.0 mg compared to placebo.

Table 1. Demographics and Characteristics of Included Studies

Study	Type	#Pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Davies (2015)	Double blind RCT	846	≥ 18	Adults aged ≥18 with a stable body weight, BMI of ≥27 kg/m^2, diagnosed with type 2 diabetes treated with diet and exercise alone or in combination with 1-3 oral hypoglycemic agents	Treatment w/ any antidiabetic drug other than metformin w/in last 3 mos., obesity from other endocrinologic d/o, surgical treatment for obesity, current participation in wt. loss program, diet attempts using herbal supplements, history of MEN type 2 or medullary thyroid carcinoma, cancer, suicidal ideation, behavior or attempt	218	Received liraglutide subcutaneously once daily. Starting dose= 0.6mg, tittered by 0.6 mg weekly to dose of 3.0mg
Sun (2013)	Double blind RCT	68	40-70	Men and women, age 40-70 years, BMI of 27-40 kg/m^2 with prediabetes & required to have a stable weight (< 5% reported change) in the previous 3 months	DM2, use of meds that can affect carb metabolism or promote wt. loss, gallstones, hx of pancreatitis, medullary carcinoma, family hx of medullary carcinoma or MEN type 2, and known cardiac, liver, or kidney disease	17	Received liraglutide subcutaneously once daily. Starting dose= 0.6mg, tittered by 0.6mg weekly to max dose of 1.8mg
Pi-Sunyer (2015)	Double blind RCT	3731	≥ 18	Adults aged ≥18, stable body weight, BMI of at least 30 kg/m^2 or a BMI of at least 27 kg/m^2 if they had treated or untreated dyslipidemia or hypertension	DM1 or DM2, meds that cause clinically significant weight gain/loss, previous bariatric surgery, hx of pancreatitis, hx of psychiatric d/o, hx of MEN type 2 or familial medullary thyroid carcinoma	895	Received liraglutide 3.0mg subcutaneously once daily

OUTCOMES MEASURED

The outcome measured in all three studies was percentage of body weight lost from baseline. In the Sun et al. study the outcome measured was loss of greater than or equal to 7% of body weight from baseline. The subjects were weighed at baseline and then at the completion of the 14 week treatment.[10] In the Pi-Sunyer et al. and Davies et al. studies the outcome measured was loss of greater than 10% of body weight from baseline. In the Pi-Sunyer et al. study subjects were evaluated every 2 weeks until week 8, then every 4 weeks until week 44, and then again at weeks 50, 56, 58, 60, 64, 68, and 70.[11] In the Davies et al. study body weight was measured at every visit to week 68.[9] The bodyweight in all three studies was measured in kilograms.

RESULTS

In all three studies subjects were randomly chosen to receive treatment to lose bodyweight. The Davies et al. study focused on overweight or obese adults aged 18 years and older over a 56 week trial. Eligible subjects were randomly assigned, in a 2:1 ratio, to receive once daily subcutaneous injections of liraglutide at a starting dose of 0.6 mg that was increased in increments of 0.6 mg weekly over 4 weeks to the treatment dose.[9] This trial used a modified intent-to-treat analysis and subjects were selected based on inclusion/exclusion criteria noted in Table 1 of which 423 were randomized to liraglutide and 212 to placebo; however, 324 subjects in the liraglutide group and 140 subjects in the placebo group completed the 56 week trial.[9] At the conclusion of the trial, from a mean baseline body weight of 105.7 kg for liraglutide 3.0 mg and 106.5 kg for placebo mean weight losses of 6.0% (6.4 kg) and 2.0% (2.2 kg) were seen.[9] In the liraglutide group, 25.2% of subjects lost more than 10% of their body weight compared to 6.7% of subjects in the placebo group (Table 2).[9] Between groups, there was a statistically significant difference, with $p < 0.001$ (Table 2).[9] The estimated treatment difference was 18.5%

[95% CI, 12.7% to 24.4%].[9] This study was presented in dichotomous form and the relative benefit increase was 2.761, the absolute benefit increase was 0.185, and the number needed to treat was 6. Adverse events seen with liraglutide during this study included gastrointestinal disorders.

The Sun et al. study compared liraglutide to placebo in adults with a BMI of 27-40 kg/m^2 aged 40-70 years over a 14 week trial. Subjects were block-randomized by sex and BMI (<31 vs. ≥31 kg/m^2) to receive a starting dose of liraglutide 0.6 mg once daily by subcutaneous injection; the dose was titrated by 0.6 mg weekly to a maximum dose of 1.8 mg or placebo once daily by subcutaneous injection.[10] Sixty-nine individuals qualified for the study based on the inclusion/exclusion criteria noted in Table 1 of which one withdrew from the study before randomization.[10] Eleven out of 35 individuals assigned to liraglutide discontinued participation in the study compared with 6 out of 33 assigned to placebo (P = 0.26); 8 out of 11 individuals using liraglutide discontinued participation due to adverse events compared with none assigned to placebo (P = 0.009).[10] Adverse events included intolerable gastrointestinal side effects (n = 3), injection site reaction (n = 2), pneumonia (n = 1), gallstone (n = 1), and fall (n = 1).[10] Thus, 24 subjects were randomized to the liraglutide group and 27 subjects assigned to the placebo group. All subjects tolerated the 1.8 mg dose except two liraglutide subjects who required a dose reduction down to 1.2 and 0.6 mg, respectively, and one placebo subject who required a dose reduction down to 1.2 mg.[10] At the end of the study it was evaluated that subjects randomized to the liraglutide group lost twice as much weight as those assigned to the placebo group (6.8 vs 3.3 kg; P < 0.001).[10] In the liraglutide group, 54% of subjects lost greater than or equal to 7% of baseline body weight compared to 4% of subjects in the placebo group (Table 2.)[10] Between the groups, there was a statistically significant difference, with p < 0.001 (Table 2).[10] The estimated

treatment difference was -6.8 kg [95% CI, -7.8kg to -5.9kg].[10] This study was presented in dichotomous form and the relative benefit increase was 12.5, the absolute benefit increase was 0.5, and the number of patients who need to be treated to achieve one additional good outcome was 2 (Table 3). This study found adverse effects from liraglutide related to the gastrointestinal system.

The Pi-Sunyer et al. study focused on adults with a BMI of 30 kg/m^2 or higher or 27 kg/m^2 or higher if they had treated or untreated dyslipidemia or hypertension aged 18 years or older over a 56 week trial. Eligible subjects were randomly assigned, in a 2:1 ratio, to receive once daily subcutaneous injections of liraglutide, starting at a dose of 0.6 mg with weekly 0.6 mg increments to 3.0 mg, or placebo.[11] A total of 3731 patients were selected based on the inclusion/exclusion criteria noted in Table 1 of which 2487 were randomized to liraglutide and 1244 to placebo. In the liraglutide group, 246 of 2487 (9.9%) withdrew due to adverse events compared to 47 of 1244 (3.8%) in the placebo group; 23 of 2487 (0.9%) in the liraglutide withdrew due to ineffective therapy compared to 36 of 1244 (2.9%); other subjects withdrew their consent.[11] Thus, a total of 1789 patients (71.9%) in the liraglutide group, as compared with 801 patients (64.4%) in the placebo group, completed 56 weeks of treatment.[11] At the end of the study, subjects in the liraglutide group lost a mean of 8.0 ± 6.7% (8.4 ± 7.3 kg) of body weight compared to 2.6 ± 5.7% (2.8 ± 6.5 kg) in the placebo group.[11] In the liraglutide group, 33.1% of subjects lost more than 10% of their body weight compared to 10.6% of subjects in the placebo group (Table 2).[11] Between groups, there was a statistically significant difference, with $p < 0.001$ (Table 2).[11] The estimated treatment difference was -5.6 kg [95% CI, -6.0 to -5.1].[11] This study was also presented in dichotomous form and the relative benefit increase was 2.123, the absolute benefit increase was 0.225, and the number needed to treat was 5. Adverse events were more

commonly seen in subjects in the liraglutide group that consisted of gastrointestinal effects.

Table 2. Percentage of Bodyweight Lost and p-value by Study

Study	Liraglutide	Placebo	P-value
Davies et al.	25.2% lost >10% weight	6.7% lost >10% weight	<0.001
Sun et al.	54% lost ≥7% weight	4% lost ≥7% weight	<0.001
Pi-Sunyer et al.	33.1% lost >10% weight	10.6% lost >10% weight	<0.001

Table 3. Calculations for Treatment by Study

Study	CER	EER	RBI	ABI	NNT
Davies et al.	0.067	0.252	2.761	0.185	6
Sun et al.	0.04	0.54	12.5	0.5	2
Pi-Sunyer et al.	0.106	0.331	2.123	0.225	5

DISCUSSION

Based on these three studies, liraglutide is effective at lowering body weight and is, in fact, superior to placebo. Not only did liraglutide reduce bodyweight, it was effective in improving insulin resistance, systolic blood pressure, glucose and triglyceride levels according to the Sun et al. study. One flaw with this particular study, though, was the short duration of the trial which only lasted 14 weeks. Another flaw of the Sun et al. study was the small sample size along with 31% of subjects discontinuing participation from the liraglutide group. Pi-Sunyer et al. found liraglutide to be effective in reducing bodyweight along with decreasing waist circumference and inflammatory markers. The limitation with this study was the use of last-observation-carried-forward imputation in the analyses.[11] All three studies had limitations that, most likely, affected the amount of weight lost by advising the subjects to exercise and diet. The Sun et al. study instructed the subjects to eat a moderate carbohydrate diet with 43% carbohydrate, 42% fat (< 7 saturated fat) and 15% protein and to decrease total caloric intake by 500 kcal/day.[10] In the Pi-Sunyer et al. study both groups received counseling on lifestyle

modification.[11] In the Davies et al. study the subjects were encouraged to follow a diet containing a maximum of 30% fat, 50% carbohydrate, with a 500 kcal/day reduction and an exercise program that involved > 150 min/week of brisk walking.[9]

To continue, even though all three studies proved liraglutide to be effective at reducing bodyweight, it comes with a host of adverse events, contraindications, and warnings on use. Some of the contradictions of liraglutide include a personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2, hypersensitivity to liraglutide or any product components, and pregnancy.[12] The FDA has listed the following warnings with the use of liraglutide thyroid C-cell tumors, acute pancreatitis, acute gallbladder disease, serious hypoglycemia which can occur with the concurrent use of sulfonylurea, heart rate increase, renal impairment, hypersensitivity reactions, such as anaphylactic reactions and angioedema, suicidal behavior and ideation.[12] The FDA states the most common adverse reactions, reported in greater than or equal to 5% are: nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain, and increased lipase, which has also been observed in all three of the studies.

CONCLUSION

The three studies in this review provide enough evidence to prove that liraglutide is effective for weight loss in adults who are overweight or obese compared to placebo. Irrespective of the dose used, it was shown that liraglutide reduced bodyweight from baseline. Due to the adverse event profile of liraglutide, long term studies should assess the risk-benefit ratio, which may lead to future studies assessing the effectiveness of low dose liraglutide on weight loss for adults who have had adverse events from the higher dose. Also, future studies should include a

broader age range to include children that are overweight or obese. Finally, future studies should be conducted on subjects that are barred from exercise and diet to assess the full potential of liraglutide and its effectiveness on weight reduction.

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