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ORIGINAL ARTICLE

Liraglutide for weight management: a critical review of the evidence

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Summary

Objective

To review the efficacy, safety, and clinical applicability of liraglutide for weight management from phase III clinical trials.

Methods

A search of the English language literature was performed using PubMed search terms: "liraglutide", "glucagon-like peptide-1 receptor agonist", and "randomized clinical trial". Articles and bibliographies relevant to the subject were reviewed and additional references known to the authors were included.

Results

Five randomized, placebo-controlled trials of liraglutide for weight management were identified. In addition to recommended diet and physical activity, liraglutide consistently resulted in a 4 to 6 kg weight loss, with a greater proportion of patients achieving at least 5 and 10% weight loss compared with placebo. The most common adverse effects were gastrointestinal and primarily occurred early in the treatment course. Comparative data suggest that weight loss with liraglutide is greater than that seen with orlistat or lorcaserin, but slightly less that seen with phentermine/topiramate. Liraglutide 1.8 mg was recently shown to have cardiovascular benefit in a large outcomes trial; applicability of these results for the 3.0 mg formulation in a more diverse weight loss population at high cardiovascular risk is not currently known. Barriers to real-world clinical use as a first-line agent include gastrointestinal side effects, high cost, and need for injection.

Conclusions

Liraglutide helps to induce and sustain weight loss in patients with obesity. Its efficacy is comparable to other available agents but it offers the unique benefit of improved glycemic control. Additional studies are needed to determine its long term efficacy and safety profile.

Keywords: glucagon-like peptide 1 receptor agonist, liraglutide, obesity, pharmacologic therapy, weight loss.

Introduction

Liraglutide is a glucagon like peptide-1 (GLP-1) receptor agonist, marketed as Saxenda® and Victoza®. Victoza® is a 1.8 mg daily subcutaneous injection of liraglutide that was initially approved by the FDA in 2010 as an adjunct therapy to diet and exercise for management of type 2 diabetes (1). Results from clinical trials repeatedly demonstrated the ability of GLP-1 analogs to induce weight loss (2). As a result, liraglutide was also developed as a weight loss agent and its 3.0 mg daily dose has shown encouraging results in multiple phase III clinical trials (see below) (3–8). Saxenda® (liraglutide 3.0 mg daily subcutaneous injection) is the newest FDA approved drug for chronic weight management in patients with obesity or who are overweight with a BMI $\geq$27 kg/m^2 and have a weight related comorbid condition (9).

Liraglutide is a derivative of GLP-1 and shares 97% amino acid sequence homology with its parent molecule (9). GLP-1 is a polypeptide incretin hormone secreted by the L-cells of the gastrointestinal tract in response to nutrients in the lumen. It causes a glucose dependent stimulation of insulin secretion (10), reduction in plasma glucagon concentrations (11), delayed gastric emptying (12), appetite suppression (13,14), and an increase in heart rate (Fig. 1) (15). Appetite suppression and delayed gastric emptying are thought to be responsible for the weight lowering effects of GLP-1 (16). However GLP-1's pharmacokinetic profile has severely limited its therapeutic potential in its natural form. The half-life of native GLP-1, once in the circulation, is less than 2 minutes as it is rapidly degraded by the enzymes dipeptidyl peptidase-IV (DPP-IV) and neutral endopeptidases (NEP) (9,17,18). Therefore, liraglutide was created by substituting arginine for lysine at position 34 in the GLP-1 peptide and adding a palmitic acid chain with a glutamic acid spacer on the lysine residue at position 26 to improve the pharmacokinetic effects (9). Following subcutaneous injection of liraglutide, peak absorption occurs at 11 hours and absolute bioavailability is 55% (9). Liraglutide is highly protein bound (98%) due to the fatty acid chain and has a large volume of distribution. Its half-life in healthy individuals and in those with type 2 diabetes is 13 hours, allowing for once daily subcutaneous administration (19,20). It does not interfere with the cytochrome P450 system and is thought to be eliminated through the liver and kidneys as small peptides (1).

Liraglutide efficacy and safety in phase III clinical trials

Five large scale randomized multicenter phase III trials have been conducted to evaluate the efficacy of liraglutide as a weight loss agent (3–8). Four of these are part of the Satiety and Clinical Adiposity – Liraglutide Evidence in non-diabetic and diabetic individuals (SCALE) program. Pertinent study characteristics, interventions, and efficacy and safety outcomes for the five trials are presented in the Table 1.

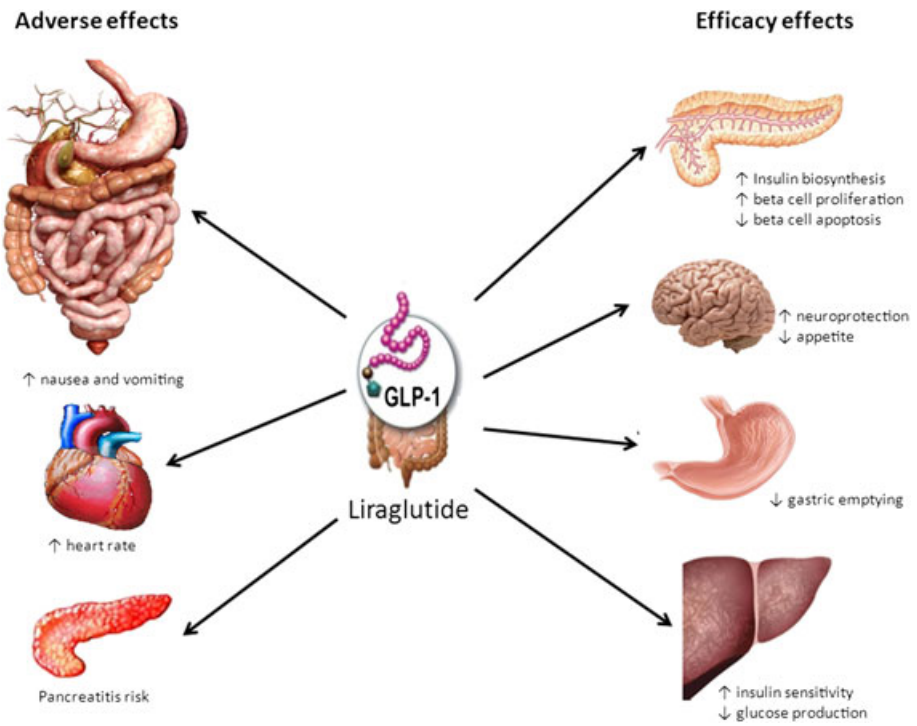

Figure 1 Effects of liraglutide (GLP-1 receptor agonist) – Efficacy and Adverse Effects Liraglutide causes a glucose dependent stimulation of insulin secretion, reduction in plasma glucagon concentrations, delayed gastric emptying, appetite suppression via neuronal pathways, and decreased hepatic glucose production. Adverse effects observed in clinical trials include gastrointestinal symptoms such as nausea and vomiting, risk for pancreatitis, and an increase in heart rate (with unclear clinical significance).

Table 1 Large scale phase III randomized placebo-controlled trials evaluating efficacy and safety profile of liraglutide 3.0 mg

Study	Participant Characteristics	Number randomized	Lifestyle intervention	Placebo-corrected results for Liraglutide 3.0 mg	Adverse events for Liraglutide 3.0 mg	Attrition rate
Astrup et al (3) 2009 Duration: 20 wks	76% women stable body weight, BMI ≥ 30 kg/m^2 and ≤ 40 kg/m^2	Liraglutide 1.2 mg (N = 95) Liraglutide 1.8 mg (N = 90) Liraglutide 2.4 mg (N = 93) Liraglutide 3.0 mg (N = 93) Orlistat (N = 95) Placebo (N = 98)	Dietary deficit of 500 kcal per day and increased physical activity using pedometer	Body weight: -4.4 kg (95% CI: -6.0 to -2.9 kg, $p < 0.0001$ ≥5% body weight loss: 76.1% vs. placebo 29.6% ($p \leq 0.0001$) ≥10% body weight loss: 28.3% vs. placebo 2.0%	Nausea (47.3%) Diarrhea (12.9%) Vomiting (11.8%) Fatigue (10.8%) Gastroenteritis (7.5%)	16.3%
Astrup et al 2-year extension (4) 2012 Duration: 2 yrs (Results censored after year 1)	76% women stable body weight, BMI ≥ 30 kg/m^2 and ≤ 40 kg/m^2	Liraglutide 1.2 mg (N = 95) Liraglutide 1.8 mg (N = 90) Liraglutide 2.4 mg (N = 93) Liraglutide 3.0 mg (N = 93) Orlistat (N = 95) Placebo (N = 98)	Dietary deficit of 500 kcal per day and increased physical activity using pedometer	Body weight: -5.8 kg (95% CI: -8.0 to -3.7 kg, $p \leq 0.001$) ≥5% body weight loss: 73% vs. placebo 28% ($p \leq 0.001$) ≥10% body weight loss: 37% vs. placebo 10% ($p \leq 0.001$)	Nausea (48.4%) Gastroenteritis (23.7%) Influenza (23.7%) Constipation (18.3%) Diarrhea (15.1%) URI (14.0%) Fatigue (14.0%) Vomiting (12.9%) Dyspepsia (8.6%) Upper abdominal pain (5.4%) Insomnia (5.4%)	23.8%
Wadden et al SCALE Maintenance (5) 2013	81% women, stable body weight, BMI ≥ 30 kg/m^2	Liraglutide 3.0 mg (N = 212) Placebo (N = 210)	Dietary deficit of 500 kcal per day and exercise	Body weight: -5.9 kg (95% CI: -7.3 to -4.4 kg, $p < 0.0001$)	Nausea (47.6%) Constipation (26.9%) Diarrhea (17.9%) Vomiting (16.5%)	27.7%

Continues

Table 1. *Continued*

Study	Participant Characteristics	Number randomized	Lifestyle intervention	Placebo-corrected results for Liraglutide 3.0 mg	Adverse events for Liraglutide 3.0 mg	Attrition rate
Duration: 56 wks	or ≥ 27 kg/m^2 with dyslipidemia or hypertension, lost ≥5 % of the initial body weight in low caloric diet run-in period (4 to 12 weeks)		≥ 150 minutes per week	Body weight: -6.1 % (95% CI: -7.5 to -4.6%, $p < 0.0001$) ≥5% body weight loss: 50.5% vs. placebo 21.8% ($p < 0.0001$) ≥10% body weight loss: 6.1% vs. placebo 6.3% ($p < 0.0001$) Maintenance of ≥ 5% run-in weight loss: 81.4% vs. placebo 48.9% ($p < 0.0001$)		
Pi-Sunyer et al SCALE Obesity and Prediabetes (6) 2015 Duration: 56 wks	78% women, stable body weight, BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 if with dyslipidemia or hypertension	Liraglutide 3.0 mg (N = 2487) Placebo (N = 1244)	Dietary deficit of 500 kcal per day and exercise ≥ 150 minutes per week	Body weight: -5.6 kg (95% CI: -6.0 to -5.1 kg, $p < 0.0001$) Body weight: -5.4 % (95% CI: -5.8 to -5.0%, $p < 0.001$) ≥5% body weight loss: 63.2% vs. placebo 27.1% ($p < 0.001$) ≥10% body weight loss: 33.1% vs. placebo 10.6% ($p < 0.001$)	Nausea (40.2%) Diarrhea (20.9%) Constipation (20.0%) Vomiting (16.3%) Hypoglycemia (11.9%) Decreased appetite (10.8%) Dyspepsia (9.5%)	30.6%
Davies et al SCALE Diabetes (7) 2015 Duration: 56 wks	50% women, stable body weight, BMI ≥ 27 kg/m^2, type 2 diabetes (HbA1c 7.0-10.0%) treated with diet and exercise alone	Liraglutide 3.0 mg (N = 423) Liraglutide 1.8 mg (N = 211) Placebo (N = 212)	Dietary deficit of 500 kcal per day and exercise ≥ 150 minutes per week	Body weight: -4.2 kg Body weight: -4.0 % (95% CI: -5.1 to -2.9%, $p < 0.001$) ≥5% body weight loss: 54.3% vs. placebo 21.4% ($p < 0.001$)	Hypoglycemia (44.5%) Nausea (32.7%) Diarrhea (25.6%) Constipation (16.1%) Vomiting (15.6%) Dyspepsia (11.1%)	25.8%

	or in combination with one to three oral hypoglycemic agents				≥10% body weight loss: 25.2% vs. placebo 6.7% ($p < 0.001$)	Abdominal distension (6.2%) Abdominal pain (6.2%) Arrhythmia (3.8%)	
Blackman et al SCALE Sleep Apnea (8) 2015 Duration: 32 wks	28% women, stable body weight, BMI ≥ 30 kg/m^2, moderate to severe OSA, unwilling or unable to use CPAP	Liraglutide 3.0 mg (N = 180) Placebo (N = 179)	Dietary deficit of 500 kcal per day and exercise ≥ 150 minutes per week	Body weight: -4.9 kg (95% CI: -6.2 to -3.7 kg, $p < 0.0001$) Body weight: -4.2 % (95% CI: -5.2 to -3.1%, $p < 0.0001$) ≥5% body weight loss: 46.4% vs. placebo 18.1% ($p < 0.0001$) ≥10% body weight loss: 22.4% vs. placebo 1.5% ($p < 0.0001$)	Nausea (26.7%) Diarrhea (16.5%) Constipation (11.9%) Dyspepsia (8.5%) Vomiting (7.4%) GERD (5.7%)	23.1%

BMI: body mass index, CI: confidence interval, CPAP: continuous positive airway pressure, GERD: gastroesophageal reflux disease, HBA1c: glycosylated hemoglobin A1c, kcal: kilocalories, OSA: obstructive sleep apnea, URI: upper respiratory tract infection.

NN8022-1807 – The first phase III clinical trial

The first major phase III trial to study liraglutide was conducted in patients with body mass index (BMI) between 30 kg/m^2 and 40 kg/m^2 in eight European countries (3). The trial compared the effects of four different doses of liraglutide (1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg, injected subcutaneously once daily) with placebo (once daily subcutaneous injection) and an open-label active comparator, orlistat (120 mg three times a day orally) (3). Individuals with type 1 or 2 diabetes, major medical problems, drug induced obesity, those using other weight lowering pharmacotherapy, those enrolled in a clinical weight control study over the past 3 months, and recipients of bariatric surgery were excluded (3). The trial consisted of a screening visit, a 2 week single-blind placebo run-in period, a 4 week dose titration period followed by a 16 week constant dose period (3). All participants were prescribed a lifestyle intervention during the treatment period (including the 2 week run-in phase) to include a 500 kcal per day energy deficit diet (based on estimated 24 hour energy expenditure) and counseling on increased physical activity using pedometers. The primary endpoint was change in body weight among the intention-to-treat (ITT) population at the end of 20 weeks (3).

The estimated mean weight loss in the ITT population was significantly greater with all doses of liraglutide as compared with placebo (4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg for liraglutide 1.2 mg, 1.8 mg, 2.8 mg, and 3.0 mg, respectively vs. 2.8 kg for placebo; $p < 0.01$ for all doses). (3) Participants receiving 2.4 mg and 3.0 mg liraglutide lost significantly more weight than those receiving orlistat (6.3 kg and 7.2 kg vs. 4.1 kg, $p < 0.01$ for both). Also participants in the liraglutide 3.0 mg group had significantly improved mean physical function score and mean self-esteem score coupled with lower rates of prediabetes after completing the trial as compared to both placebo and orlistat. There were no significant differences in withdrawal rates between liraglutide and placebo treated groups. The overall frequency of adverse effects was higher with liraglutide 1.8 mg, 2.4 mg, and 3.0 mg as compared with placebo, orlistat, and liraglutide 1.2 mg. The most common adverse events with liraglutide 3.0 mg were nausea and vomiting, occurring nine and six times more frequently than placebo, respectively. 80% of the nausea events and 50% of the vomiting events occurred during the first 4 weeks of the trial. Psychiatric disorders were slightly more frequent and mean pulse rate was slightly increased with liraglutide treatment as compared to placebo and orlistat. The result of this trial brought forward the potential utility of liraglutide as a long-term weight loss agent.

Two year extension data from this initial trial concerning the long-term efficacy, safety and tolerability of liraglutide was subsequently published (4). Of the 564 patients enrolled in the trial, 398 (71%) entered the extension. Investigators and participants were unblinded to the treatment assignment at 1 year and participants were switched to liraglutide 2.4 mg and subsequently to the 3.0 mg dose between weeks 70 and 96. For the ITT population with last-observation-carried-forward (LOCF) imputation, placebo-corrected mean weight loss for liraglutide 3.0 mg was 5.8 kg at the end of first year. Prediabetes and metabolic syndrome prevalence were also significantly reduced as compared to placebo with liraglutide 3.0 mg ($p < 0.01$ for both). No new adverse events were observed in the extension period. The results of this trial highlighted the potential of liraglutide 3.0 mg as a sustainable weight loss agent and sparked interest in evaluating its effects in larger populations and in patients with obesity related comorbid conditions.

The SCALE Program – SCALE Maintenance trial

The SCALE Maintenance trial was a randomized, double-blind, placebo-controlled trial conducted in patients with a BMI $\geq$ 30 kg/m^2 or $\geq$27 kg/m^2 with a weight-related comorbid condition designed to determine the efficacy of liraglutide for weight maintenance (5). To qualify for randomization participants had to lose at least 5% of their initial body weight in a 4 to 12 week low calorie diet run-in period. Participants were randomized in a 1:1 ratio to receive liraglutide 3.0 mg or placebo. Dosing was started at 0.6 mg per day and increased weekly by 0.6 mg through a 4-week dose escalation period to the 3.0 mg dose. Individuals with type 1 or 2 diabetes, fasting plasma glucose (FPG) equal to or greater than 126 mg/dL at run-in, on medications causing weight loss/gain or GLP-1 analogs; history of bariatric surgery, idiopathic acute or chronic pancreatitis, major depressive disorder or other severe psychiatric illness or clinically active significant cardiovascular disease were excluded. All participants were prescribed a lifestyle intervention during the entire treatment. The primary endpoints at 56 weeks were change in body weight and proportion of participants that lost at least 5% body weight from randomization; and proportion maintaining the greater than 5% reduction in body weight achieved in the run-in period.

Of the 551 participants that entered the run-in, 422 (77%) lost more than 5% of the screening body weight and were randomized to liraglutide 3.0 mg or placebo. The liraglutide group had significantly greater decrease in body weight than placebo (6.2% versus 0.2%,

$p < 0.0001$). A significantly greater proportion of liraglutide-treated patients achieved at least a 5% weight loss (50.5% versus 21.8%), at least 10% weight loss (26.1% versus 6.3%) and maintained the 5% weight loss achieved during the run-in (81.4% versus 48.9%) than placebo-treated patients ($p < 0.0001$ for all). Treatment with liraglutide was associated with significant improvements in glycosylated hemoglobin A1c (HbA1c) and FPG. The most common adverse events in the liraglutide group were gastrointestinal distress. Most of these were mild to moderate in severity; nausea was transient and mainly occurred in the first four weeks of the trial, coinciding with dose escalation. Withdrawal rates from adverse events were the same between liraglutide and placebo. However, 11 out of 18 withdrawals due to adverse events in the liraglutide group were due to gastrointestinal adverse events but no withdrawals from the placebo group were due to gastrointestinal symptoms. Participants in the liraglutide group experienced symptomatic hypoglycemia more frequently than the placebo group (5.2% vs. 2.4%), but none of the events was classified as severe and the difference was not statistically significant. It is important to note that it is uncommon for patients without diabetes who are not taking other medications known to cause hypoglycemia to develop hypoglycemia from liraglutide alone. This study also had a better than average withdrawal rate, with 75% of liraglutide- and 69.5% of placebo-treated participants completing the 56-weeks trial, as compared with other obesity medication studies which typically have withdrawal rates in the 35-50% range by 1 year. Overall, the SCALE maintenance trial showed that liraglutide could be useful in maintaining weight loss in patients that are able to lose clinical significant weight through intensive lifestyle modifications.

SCALE Obesity and Prediabetes trial

The SCALE Obesity and Prediabetes trial was a large, randomized, double-blind, placebo-controlled trial conducted over a period of three years (56 week initial study period followed by a 2-year extension in patients with prediabetes at baseline) designed to test the hypothesis that liraglutide can achieve significant weight loss in a large and diverse patient population living across the world (6). Individuals with a BMI $\geq$30 kg/m^2 or $\geq$27 kg/m^2 with treated or untreated dyslipidemia or hypertension were randomized in a 2:1 ratio to receive once daily subcutaneous liraglutide 3.0 mg injections or placebo. The dosing regimen was similar to prior trials and both groups received counseling on lifestyle modifications. Patients meeting exclusion criteria of SCALE maintenance trial and those with a personal or family history of multiple endocrine neoplasia 2 (MEN 2) or familial medullary thyroid carcinoma (MTC) were excluded. At week 56, the co-primary end points were change in body weight from baseline, proportion of participants losing at least 5% body weight, and proportion of participants losing at least 10% body weight from randomization.

The data reported below pertains to results from the initial 56 week period of the trial. Patients randomized to liraglutide had a significantly greater reduction in the mean body weight (8.0% versus 2.6%, $p < 0.001$). The liraglutide group had a greater proportion of patients who lost at least 5% (63.2% versus 27.1%) and 10% (33.1% versus 10.6%) of the initial body weight as compared with placebo ($p < 0.001$ for both). The liraglutide group had a significant decrease in the mean BMI, waist circumference, HbA1c, FPG, fasting insulin, systolic and diastolic blood pressures as compared with placebo ($p < 0.001$ for all). The pulse rate was noted to be slightly higher in the liraglutide group as compared with placebo (~2-3 beats per minute, $p < 0.001$). There was a significant improvement in the fasting lipid profile in the liraglutide treated group as well. The incidence of neoplasms was similar in both groups and no clinically relevant differences in mental health assessments were noted.

The effect of liraglutide in reducing the risk of type 2 diabetes in patients with pre-existing prediabetes in this trial over a three-year period was recently reported (21). At week 160, 1.8% patients treated with liraglutide 3.0 mg developed type 2 diabetes as compared with 6.2% in the placebo group. The risk of developing type 2 diabetes was reduced by 79% with liraglutide (hazard ratio 0.21, $p < 0.0001$) and the estimated time to onset of type 2 diabetes over 160 weeks was 2.7 times longer with liraglutide than with placebo (95% confidence interval: 1.9 to 3.9) (21). The results of this trial confirmed the applicability of liraglutide as a weight loss agent that improves various cardio-metabolic parameters and delays the onset of type 2 diabetes.

SCALE Diabetes trial

The SCALE Diabetes trial was a randomized, double-blind, placebo-controlled, parallel-group trial designed to evaluate liraglutide's efficacy in patients with type 2 diabetes (7). It was conducted over 56 weeks with a 12-week off-drug follow-up period (7). Individuals with a BMI of at least 27 kg/m^2 and type 2 diabetes (HbA1c 7.0 to 10.0%) were screened for randomization. Of the 1361 participants screened for eligibility, 846 were randomized in a 2:1:1 ratio to liraglutide 3.0 mg, liraglutide 1.8 mg and placebo groups. Dosing regimen followed standard protocol and all participants were encouraged to follow lifestyle interventions throughout the duration of the trial.

The exclusion criteria were similar to the SCALE obesity and prediabetes trial. The co-primary endpoints were relative change in body weight and the proportion of participants losing at least 5% and 10% of randomization body weight.

Patients in the liraglutide 3.0 mg, liraglutide 1.8 mg and placebo groups had a mean weight loss of 6.0% (6.4 kg), 4.7% (5.0 kg) and 2.0% (2.2 kg) respectively, at the end of 56 weeks. The weight loss with both liraglutide doses was significantly more than placebo ($p < 0.001$). The proportion of participants who lost 5% or more body weight was significantly higher with liraglutide 3.0 mg (54.3%) than placebo (21.4%, $p < 0.001$). This was also true for proportion of participants who lost at least 10% body weight (25.2% with liraglutide 3.0 mg and 6.7% with placebo, $p < 0.001$). Mean weight loss and proportion of patients losing at least 5% or 10% body weight were significantly lower with 1.8 mg dose of liraglutide dose than 3.0 mg, but comparison between the two doses were not controlled for multiplicity. Mean waist circumference, BMI, systolic blood pressure, HbA1c, FPG, postprandial glucose increment; glucagon and proinsulin levels were significantly lower with liraglutide 3.0 mg than placebo ($p < 0.001$). Also the proportion of patients achieving the target HbA1c (below 7.0%) was significantly greater with liraglutide 3.0 mg than placebo (69.2% vs. 27.2%, $p < 0.001$). Similar to previous trials, gastrointestinal side effects were the most common AEs in the liraglutide 3.0 mg group. Notably, hypoglycemic episodes, as per the American Diabetes Association classification (22), were more frequent in the liraglutide 3.0 mg group than placebo (44.5% vs. 27.4%). The mean pulse rate increase was significantly higher with both liraglutide doses than placebo ($p < 0.001$) with cardiac arrhythmias being more frequent with liraglutide 3.0 mg than placebo. The rate of gallbladder related adverse events was low across groups as well but it was higher with liraglutide 3.0 mg. No cases of acute pancreatitis or MTC were reported in the liraglutide 3.0 mg group. The SCALE diabetes trial highlighted that liraglutide is an effective weight loss agent in patients with type 2 diabetes, who form a large subset of individuals that can benefit from pharmacotherapy for obesity.

SCALE Sleep Apnea trial

The SCALE Sleep Apnea trial was a 32-week randomized, double-blind, placebo-controlled trial conducted in the United States and Canada (8). Individuals with a diagnosis of moderate or severe obstructive sleep apnea by polysomnogram who were unwilling or unable to use continuous positive airway pressure (CPAP) treatment and had a BMI ≥ 30 kg/m^2 were randomized in a 1:1 ratio to receive once daily subcutaneous liraglutide 3.0 mg injections or placebo. Dosing followed standard protocol and both groups received counseling on lifestyle modifications. Individuals with diabetes were excluded. A sleep study was performed at screening, at 12 weeks, and at the end of the trial at 32 weeks. The primary endpoint was change in the apnea-hypopnea index (AHI). Secondary outcomes included changes in body weight and glycemic control. Patients randomized to liraglutide 3.0 mg group had a significantly greater reduction in the mean body weight (5.7% versus 1.6%), had a greater proportion of patients who lost at least 5% (46.3% versus 18.5%) and 10% (23.4% versus 1.7%) of the initial body weight as compared to placebo ($p < 0.0001$ for all three). Liraglutide 3.0 mg group had a significant reduction in AHI as compared to placebo (12.2 events per hour vs. 6.1 events per hour, $p = 0.015$). Mean HbA1c and systolic blood pressure were significantly lowered in the liraglutide group ($p < 0.0001$). Similar to previous trials most of the adverse events in the liraglutide group were

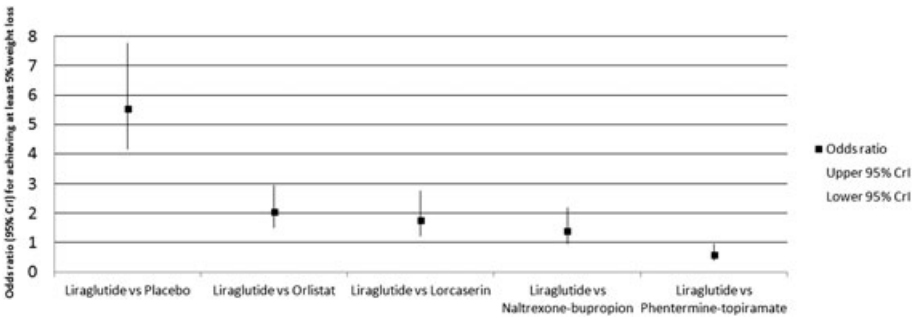

Figure 2 The odds ratios and 95% credible intervals (CrI) for achieving at least 5% weight loss at one year in phase III clinical trials for liraglutide as compared with placebo and other FDA approved long-term weight loss agents. (Modified from the network meta-analysis by Khera et al.) (27)

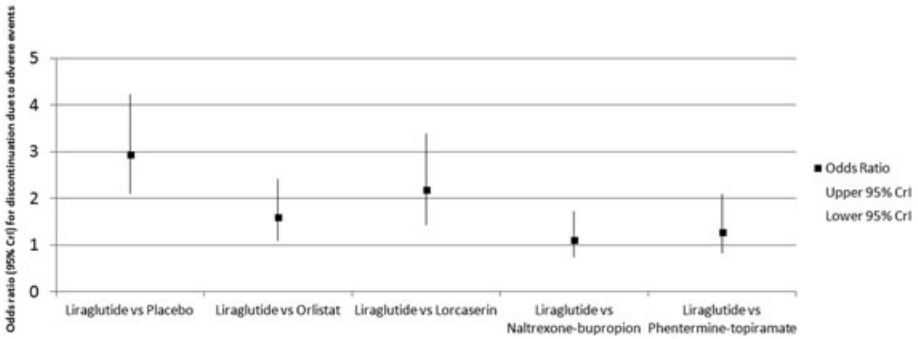

Figure 3 The odds ratios and 95% credible intervals (CrI) for drug discontinuation at one year in phase III clinical trials due to adverse effects for liraglutide as compared with placebo and other FDA approved long-term weight loss agents. (Modified from the network meta-analysis by Khera et al.) (27)

gastrointestinal and occurred more frequently with liraglutide compared with placebo.

Safety outcomes

Overall, liraglutide 3.0 mg is a well-tolerated long-term weight loss agent. The most common AEs (prevalence greater than 5%) are nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, dyspepsia, fatigue, dizziness, abdominal pain, and increased lipase (9). Gastrointestinal intolerability is common and in clinical trials was noted to be the most common reason for drug discontinuation in patients with adverse events. Liraglutide should be used cautiously in patients with impaired kidney or liver function (9) but has been shown to be safe and did not affect kidney function in patients with moderate renal impairment (estimated glomerular filtration rate 30-59 ml/min/1.73 m^2) (23). Patients starting liraglutide should be cautioned about the risks of acute pancreatitis, acute gallbladder disease, serious hypoglycemia, heart rate increase, hypersensitivity reactions and suicidal behavior. Also, it is marketed with a black box warning about the risk of medullary thyroid carcinoma as it has been shown to cause thyroid C-cell tumors in rats and mice; however, with the evidence to date including over 6000 patients, no increased risk for MTC has been observed in humans (9). Nevertheless, liraglutide is contraindicated in patients with a personal or family history of MTC or MEN (9). Liraglutide is also contraindicated in pregnancy and is not recommended in nursing mothers, children, patients taking insulin or other GLP-1 agonists (9). Finally, although liraglutide (as well as other GLP-1 agonists) increase heart rate to a small degree (24), the clinical meaningfulness of this change is not known and it does not appear to adversely affect cardiovascular outcomes at the 1.8 mg dose (see discussion of LEADER trial below).

Liraglutide and cardiovascular outcomes – LEADER trial

Over the last decade, the US FDA has mandated that pharmaceutical companies demonstrate that any new drug for diabetes does not increase the risk of cardiovascular events. The primary endpoint is usually a non-inferiority comparison to placebo, often with a pre-specified caveat that should non-inferiority be met, a test for superiority would subsequently be conducted. The FDA Guidance issued in 2008 (25) requires a pre-approval upper bound of the two-sided 95% confidence interval for major adverse cardiovascular events of less than 1.80 and post-approval upper bound of less than 1.30. In this context, the cardiovascular effects of liraglutide added to standard therapy in patients with type 2 diabetes were recently reported (26).

In a large, multicenter, double blind trial, 9340 patients with type 2 diabetes and high cardiovascular risk were randomized to receive liraglutide 1.8 mg daily or placebo and followed for 3.8 years. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary outcome occurred in significantly fewer patients in the liraglutide group (13.0%) than in the placebo group (14.9%), HR 0.87, 95% CI 0.78 to 0.97); $p < 0.001$ for noninferiority and $p = 0.01$ for superiority). There were fewer deaths overall (HR 0.85, 95% CI 0.74 to 0.97) and fewer cardiovascular deaths (HR 0.78, 95% CI 0.66 to 0.93) in the liraglutide treated group compared with placebo. Importantly, there was no signal for increased hospitalization for heart failure in the liraglutide group and

adverse events were similar to those seen in prior trials. This seminal study was performed using the dose approved for type 2 diabetes treatment (1.8 mg) and further cardiovascular outcomes studies may be warranted using the 3.0 mg dose in a more diverse population of overweight and obese patients at high cardiovascular risk. These studies would further help to inform the clinical applicability of liraglutide for weight management. If findings are consistent in this patient population, liraglutide would be the first medication approved for weight management to demonstrate a cardiovascular, and possibly mortality, benefit.

Comparison of Liraglutide with other weight loss agents

Currently there are four other FDA approved long-term weight loss agents – orlistat, lorcaserin, and fixed-dose combinations of phentermine/topiramate and naltrexone/bupropion. All the above mentioned FDA approved weight lowering agents have been shown to cause clinically significant weight loss of at least 5% of initial body weight when used as an adjunct to lifestyle interventions. However, the degree of weight loss over a period of 1 year is variable. A recent network meta-analysis comparing the effectiveness of these five medications demonstrated that liraglutide was one of two medications associated with the highest odds of achieving at least 5% weight loss as compared with placebo (27). Liraglutide had higher odds of achieving at least 5% weight loss at one year in clinical trials, than with lorcaserin or orlistat, similar odds as compared with naltrexone/bupropion, and slightly lower odds as compared with phentermine/topiramate (Fig. 2). In clinical trials the odds of discontinuation of liraglutide due to adverse events were similar as compared with phentermine/topiramate and naltrexone/bupropion but were higher when compared with lorcaserin, orlistat, or placebo (Fig. 3). It should be noted that attrition rates are typically high in trials of obesity medications and the magnitude of efficacy seen in randomized trial data may not always be generalizable to the "real world" setting.

Guidelines from the American Heart Association/-American College of Cardiology/The Obesity Society recommend using a multifactorial approach to manage obesity (28). This includes initiation of comprehensive lifestyle intervention programs and pharmacotherapy in individuals with BMI $\geq$30 kg/m^2 or $\geq$27 kg/m^2 with comorbid conditions like type 2 diabetes, hypertension, dyslipidemia, or obstructive sleep apnea if lifestyle modification alone is not effective (29). Liraglutide may be a particularly effective choice among obese patients with type 2 diabetes, and can be considered for those at high risk for cardiovascular disease given a beneficial signal in cardiovascular outcomes seen in the 1.8 mg formulation in a diabetes population; however the effects of the 3.0 mg formulation on cardiovascular morbidity and mortality have not been established. It is important to note that the safety and efficacy of co-administration of liraglutide with other weight loss agents has not been studied and it is not known whether the effects may be synergistic or if side effects would limit concomitant use. Further studies of pharmacological combination therapies may be warranted.

Additional important considerations in the application of liraglutide to clinical weight management in the context of currently available agents include its high cost, injectable delivery system, and requirement for dose titration. Saxenda debuted on the US market at a cost of approximately $1000/month, significantly more than the other available agents, and many commercial insurances have yet to include it (or some other newer weight loss agents) as part of their coverage plans. Among clinically available weight loss medications, liraglutide is the only injectable agent, which may limit is "real-word" applicability. Although patients with established type 2 diabetes on insulin therapy may be comfortable with injection, Saxenda is not labeled for use with insulin, and therefore patients eligible for treatment may be injection-naïve and less likely to use it. In addition to its injectable delivery, the dose must be titrated up on a weekly basis starting from 0.6 mg per day in weekly intervals of 0.6 mg, taking 5 weeks to achieve the maintenance dose of 3.0 mg daily. If a dose is missed for $>$72 hours, patients are instructed to resume dosing at 0.6 mg daily and restart the titration schedule (in order to reduce gastrointestinal side effects). Whether or not these perceived barriers will influence the "real world" adoption of liraglutide for weight management remains to be seen.

Conclusion

Liraglutide has been shown to be effective at inducing and sustaining weight loss in a population of obese patients including those with hypertension, dyslipidemia, type 2 diabetes and obstructive sleep apnea. Comparative data suggest that weight loss with liraglutide is greater than that seen with orlistat or lorcaserin, but slightly less than weight loss seen with phentermine/topiramate combination treatment. In addition, discontinuation due to adverse effects (primarily gastrointestinal) is highest for liraglutide and naltrexone/bupropion and lowest for lorcaserin. The higher rates of discontinuation for liraglutide compared

with some other obesity medications due to adverse effects may limit its use in some patient populations. Also, liraglutide is an injectable medication with a high monthly cost. However, it offers the unique benefit of improved glycemic control and its relatively few contraindications as compared with other weight loss agents make it an attractive option for patients, especially with comorbid type 2 diabetes or cardiovascular disease. Additional studies are needed to determine its long term outcomes, including its effects on cardiovascular morbidity and mortality, in a large and diverse population with varying races/ethnicities, for a weight loss indication. For now, liraglutide remains another important option in the physician's toolkit to combat the growing obesity epidemic in the United States and abroad.

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Conflict of interest

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