Liraglutide for Weight Management, Critical Analysis of Efficacy and Side effects in Non diabetic, individuals with obesity: A Comprehensive Systematic Review

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Received: February 2021; Accepted: March 2021; Published: April 1, 2021.
Citation: Sidra Kanwal, Elham Abdullah Nusrullah AlEmadi. Liraglutide for Weight Management, Critical Analysis of Efficacy and Side effects in Non diabetic, individuals with obesity: A Comprehensive Systematic Review. World Family Medicine. 2021; 19(4): 72-83 DOI: 10.5742/MEWFM.2021.94031

Abstract

Objective: Liraglutide is a FDA approved pharmacological option of weight loss with admissible safety profile and generally considered as a safe therapeutic. However, almost all liraglutide based studies always reported a certain number of withdrawals and serious adverse events with its weight management effect. This study was designed to evaluate the efficacy, safety, and use of all doses of liraglutide for weight management in non-diabetic persons with obesity.

Methods: The literature search was performed using Cochrane advanced search using “liraglutide”, non-diabetic, weight loss, obese, and glucagon-like peptide-1 receptor agonist in different combinations. All randomized control trials, relevant to the inclusion criteria were selected for review writing.

Results: Nine randomized controlled trials of all doses of liraglutide for weight management in non-diabetic, obese individuals were identified. Most of the trials were based on liraglutide 3.0 mg, other doses were 1.2, 1.8, and 2.4 mg. All trials concluded that the greater proportion of participants achieved about 5-10% weight loss. Trials carried out with all doses of liraglutide, concluded dose 3.0 had better weight loss outcomes. Reduction of cardiovascular risks was the most reported benefit of liraglutide administration. The common adverse events were gastrointestinal and usually occurred in the early phase of treatment during dose escalation. The only associated concern was serious adverse events such as Pancreatitis, Cancer, Psychiatric Effects linked with all doses of liraglutide, particularly dose 3.0 and associated withdrawals.

Conclusion: All doses of liraglutide are effective in weight loss in non-diabetic, obese individuals; particularly dose 3.0 is the most effective one. Generally, liraglutide is safe for most study participants with minor gastrointestinal adverse events. The only concern is its associated serious adverse events; although, experienced by very few.

Key words: Liraglutide, glucagon-like peptide, weight management, non-diabetic, obese

Introduction

Liraglutide is a unique glucagon-like peptide-1 (GLP-1) with 97% amino acid homology to human endogenous GLP1. GLP1 is a hormone produced by the gastrointestinal L-cells as a nutrient response. It initiates many functions like low blood glucose levels, slow down of gut emptying, suppression of appetite, and increased cardiac rate. Suppression of appetite and delayed gut emptying are considered a weight reduction effect , and make this peptide a choice of weight reduction therapeutic [1, 2]. However, the pharmacokinetic profile of GLP1 is specifically limited to its natural form; the half-life of native GLP1 is less than 2 minutes in blood circulation and is rapidly degraded by other enzymes. Therefore, a modified form was created to increase its shelf life and pharmacokinetic effects. Liraglutide had a modified chemical structure; Lysine is in 34th position by replacing arginine and at 26th position C-16 palmitic acid side chain attached to lysine [1, 3]. This hormone modification induces its slow absorption from the subcutaneous tissues, enhances glucose homeostasis, and reduces body weight by reducing appetite and slowing down stomach emptying process. It is non-degradable by endogenous dipeptidyl peptidase 4 (DPP4) and correctable albumin binding. An additional benefit of extended half-life for up to 13 hours is reducing its intake requirement and required daily consumption of 1 dose only, with absolute bioavailability of 55% [1-3].

It has a dose-dependent dual beneficial effect. Liraglutide is well identified as an important medication in the management of type 2 diabetes mellitus (T2DM) for years as a therapeutic option approved by FDA 2010, and also very well sounded, recommended, and prescribed for obesity, and cardiac efficiency for both diabetic and non-diabetic individuals [2,4].

It is a well-known anti diabetic and anti obese drug. The anti diabetic required dose is 1.8mg however; a higher dose is required for weight reduction. Liraglutide 3.0mg (subcutaneous injection) mg is a well-known dose for chronic weight reduction by FDA approval [2]. Liraglutide 3.0mg for >5% - 15% of weight reduction has been approved in recent years for weight reduction in many countries. High dose human exposure has not yet reported adverse events and tissue deterioration in comparison with low doses. This 3.0 dose is recommended for BMI ≥27 kg/m2 and has positive effect on obesity related co-morbidities like cardiac health [1, 2] or has obesity-related comorbidities. However, it has a possibly high prevalence of gastrointestinal reactions [2]. The licensed dose for glycemic control is up to 1.8 mg daily whereas, the Liraglutide 3.0 mg has been approved as an anti-obesity therapeutic for the non-diabetic population and is widely used in the U.S and the European Union [2].

Obesity is not only a serious health problem but is associated with serious co-morbidities such as diabetes, risk of heart disease, hypertension, hyperlipidemia, stroke, cancer, and even death [4]. Obesity and metabolic disorder have the potential to increase the overall mortality rate by 30% of every increase of 5 kg/m2 of body mass index (BMI). Patients of Obese Class I (BMI 30–35 kg/m2) have reduced survival rate by an average of 2–4 years whereas Obese Class II and III patients may reduce the survival up to 8–10 years. Additionally, Obesity and associated metabolic disorders are a massive economic burden on the healthcare sector. The period between 1980 - 2014 was the major lifestyle modification period with a reported prevalence of more than double cases of obesity [6, 7]. A recent study of 2019 reported the obesity rising trend is three-fold or even more in European countries. They reported that around 50% of the adult population of Europe was obese or overweight. Obesity is now a global epidemic, affecting societies both developing and developed. In association with comorbid conditions, obesity can lead to reducing life quality [8]. Weight reduction is never an easy task for the majority of people. Countless studies, randomized trials of obesity therapeutics, lifestyle modification strategies, and surgical procedures are applied for weight reduction. However, the majority of patients can reduce weight by adapting different strategies but cannot sustain them [8, 9].

The process of lifestyle modification mainly includes restricted calorie intake and physical activity; the process is easy to initiate but hard to maintain. Also, lifestyle modification is not recommended in all obese cases, due to its ineffectivity in the long run because in obese cases the body is adapted to lower calorie burn due to lower calorific intake. In these cases of lifestyle modification, high motivation is required to sustain desirable weight change. Studies reported gradual weight re-gain even in highly motivated cases. In other options, bariatric surgery is also adopted but it's an invasive procedure with associated surgical danger. Pharmacological agents were designed to overcome all these concerns of obese individuals. In these cases, product safety is always crucial to give a safe therapeutic option for obese patients [9]. There are very few effective and safe therapeutics available for obesity, especially for long term use with overall healthy effect on other systemic processes including reducing cardiovascular risk [9].

Liraglutide is generally considered a safe anti obese therapeutics and is one of the highly prescribed therapeutics, although, very few clinical studies are available to demonstrate its functionality in weight management of non-diabetic individuals with reported side effects [8]. In the present systemic review, we aimed to evaluate the efficacy of liraglutide in weight management among non-diabetic obese individuals and its reported side effects.

Methodology

Search Scheme, Inclusion and Exclusion Criteria
All randomized controlled trials (RCTs) that evaluated the effect of liraglutide in weight management for non-diabetic obese individuals of all treatment doses were systematically searched by advanced search methodology of "Cochrane Controlled Trials Register database" and "clinical trial.org" with no initial year restriction until October 2020.

Age restriction was imposed and data of adult age group without gender restrictions were included. All possible key words were used for data extraction to ensure all possible data collection. The applied key words were "Liraglutide, obese, non diabetics" OR "Liraglutide, obese, non diabetics, side effects" OR "Liraglutide, obese, non diabetics, adverse" and "Liraglutide, obese, non diabetics, adverse events". No language criteria were imposed but all the included studies were published in English. No database restriction was imposed on Cochrane site extracted data, such as PubMed, Embase, and Medline. The excluded RCTs were i) duplicate studies ii) studies not fulfilling the inclusion criteria, e.g; based on liraglutide administration in diabetic individuals.

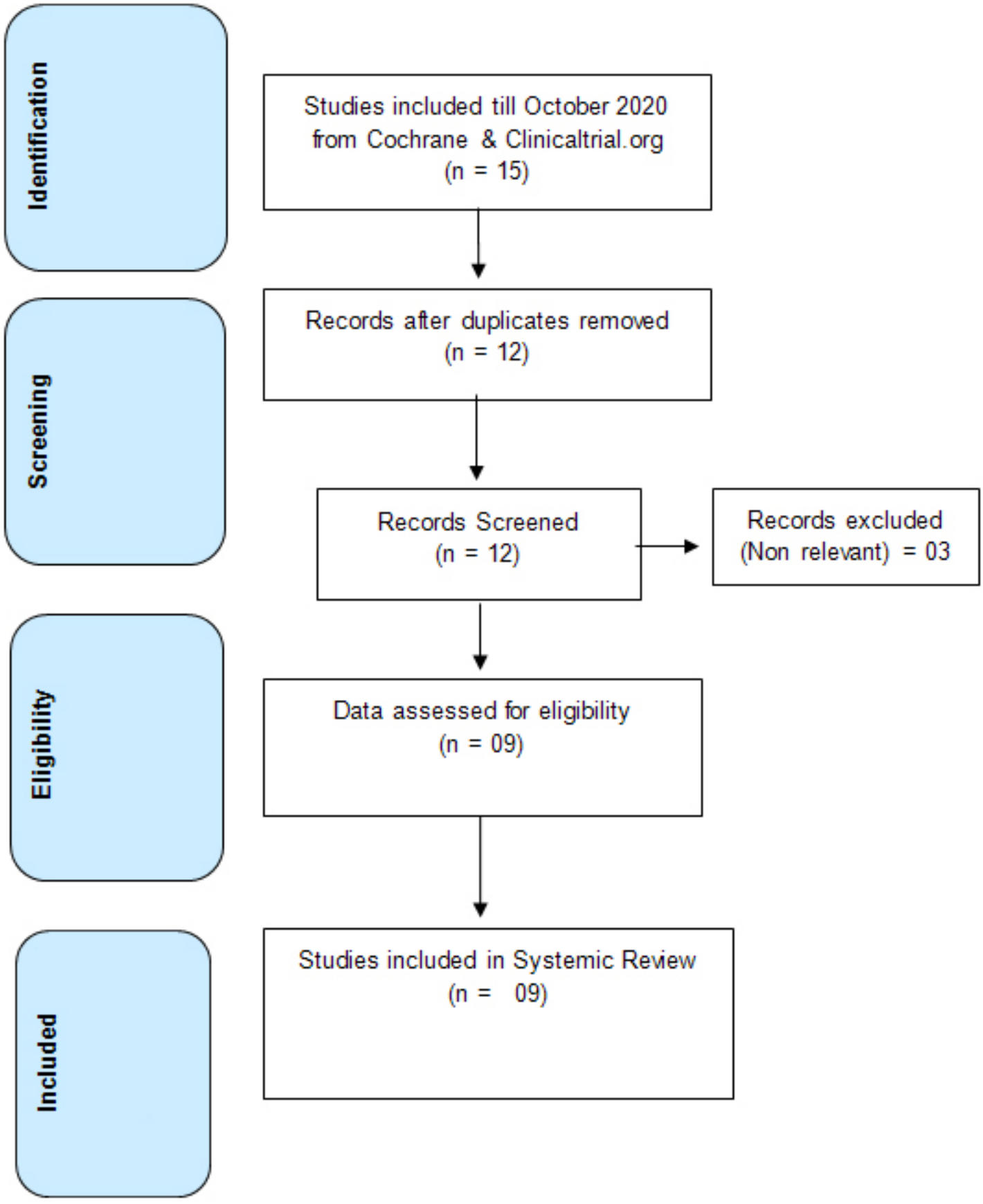
Screening and Selection of Studies
Study titles, and abstracts of retrieved data were evaluated and full text studies were accessed for further evaluation.

Data extraction and management:
One author was responsible for data extraction and evaluation with appropriate broad-spectrum search words to cover the inclusion criteria. An advanced search of the Cochrane library and clinicaltrial.org was used. Data without year restriction till October 2020 were extracted. Data extraction from all provided data sources was included without any language barriers or other limitations. Data extraction was done twice. All included studies were downloaded as complete articles by manual search to analyze complete study.

Study Outcome
To analyze weight loss by all doses of liraglutide in obese, non-diabetic individuals, and its associated adverse events

Quality assessment of extracted data
Cochrane guideline, Risk of bias was followed for data extraction and data was extracted twice with the same search words in a different time frame to get the same results to avoid any risk of bias [10].

Summary of Study Selection Process



PRISMA flow diagram, Preferred Reporting Items for Systematic Review and Meta-Analysis
RCT: Randomized Control Trial
Data base: Cochrane Central Register of Controlled Trials (CENTRAL)

Table 1: Overview of Selected Studies

Author, year, & Reference No	Country	Study participants allocated (n)/ Study participants completed	liraglutide group (n)	placebo group	liraglutide dose	Age (year)	Gender (%)	BMI	Duration	Study Design	Statistical analysis	% withdrawal due to Adverse Effects
Astrup A, et al. 2009 [11]	19 clinical research centers in eight countries across Europe	472/564	_	79/98	_	18–65	Both	30–40 kg/m²	20 weeks	double-blind, placebo-controlled	Analysis of covariance	Liraglutide 1.2 mg: 4 (4·2%) Liraglutide 1.8 mg: 5 (5·6%) Liraglutide 2.4 mg: 9 (9·7%) Liraglutide 3.0 mg: 5 (5·4%)
			85/95	_	1·2 mg							
			74/90	_	1·8 mg							
			73/93	_	2·4 mg							
			82/93	_	3·0 mg							
			79/95	_	Orlistat 120 mg ×3							
Astrup A, et al. 2012 [12]	19 clinical research centers in eight countries across Europe	365 completed 1 year, 268 completed 2 years	(An extension of reference 11, Results examined after year 1)			18–65	Both	30–40 kg/m²	2 years	double-blind, placebo-controlled	Analysis of covariance	Liraglutide 1.2 mg: 17 (18%) Liraglutide 1.8 mg: 20 (22%) Liraglutide 2.4 mg: 27 (29%) Liraglutide 3.0 mg: 18 (19%)
Janssen Research & Development, LLC [13]	Belgium, Canada, Poland, Sweden, United Kingdom, United States	444	_	57/60	_	18 - 70	Both	greater than or equal to (>=) 35	26 weeks	Randomized Double blind control trial	Difference of least square (LS) Means and Difference of LS Means,	None
			_	59/59	JNJ-6456511 15.0 mg				26 weeks			
			_	104/118	JNJ-6456511 17.4 mg				26 weeks			
			_	109/118	JNJ-6456511 1 10.0 mg				26 weeks			
			115/119	_	3·0 mg							

Adam B, 2016 et al. [14]	40 sites in the USA and Canada	359	180	179	3.0 mg	mean age 48.6 years	males 71.9%	39.1 kg/m2	32 weeks	Randomized, double-blind trial	Analysis of covariance	12%
Xavier Pi-S. et al. 2015 [15]	Europe, North America, South America, Asia, Africa, and Australia	3731 patients	2487 (61.2% prediabetics*)	1244	3.0 mg	> 18	Female: 78.7% Male: 21.3 %	38.3±6.4 ;	56-week	double-blind trial	Analysis of covariance	246 (9.9%)
Robert SA, et al. 2015 [16]	Malaysia	42	21	21	1.8 mg	mean age: 34 ± 9 years		35.9 ± 4.2 kg/m2	12 weeks	randomized, prospective, controlled trial	t-test analysis, Two-tailed p value	0%
Wadden TA, et al. 2013 [17]	US and Canada	305/422	159/212	146/210	3.0 mg	> 18	Men 16%, Women 84%,	BMI≥30kg/m	56 weeks	randomized, double-blind, placebo controlled trial	Analysis of covariance	18 (8.5%)
J van Can et al. 2014 [18]	The Netherlands	44/49 (crossover study)	_	30		18–75	Both	30–40 kg m 2	5 weeks	Single-center, randomized, placebo-controlled, double-blind, two-period incomplete crossover trial.	Statistical analysis of all secondary end points was two-sided and on a 5% significance level	1 (2.2%)
			30		1.8 mg							
			30	_	3.0 mg							
Chien-An Chou et al. 2020 [4]	Taiwan	46	28	_	0.6 mg	41.5	Both	35.2 kg/m2	12 weeks	single center study	x2-test, and y U-test for continuous variables	Not reported
			18		1.2 mg	35.5	Both					

Results and Discussion

A randomized, double-blind, placebo-controlled study of 19 European clinical research centers [11] – 20 weeks trial

An extensive study was designed more than a decade ago with 564 participants; participants were randomly allocated to receive liraglutide treatment of 20-weeks duration. The dose wise participant detail was explained in Table 1. The study participants were randomly assigned to liraglutide 1.2, 1.8, 2.4 or 3.0 mg of n= 95, 90, 93, 93 respectively, and placebo n=98 by one daily, evening subcutaneous injectable administration. The starting dose was 0.6mg daily and escalated weekly. The comparator group (n=95) received orlistat capsules 3X120 mg, orally. Out of 564, 472 (84%) were completed the trial, 03 participants were also excluded from 1•2 mg, 2•4 mg, and 3•0 mg liraglutide doses due to baseline data missing of body weight, 3 due to noncompliance of criteria, 12 had week 20 missing assessment, 7 with treatment compliance concerns, and 01 due to drug dispensing error. The liraglutide group (all doses) reported significant weight loss from 4•8 to 7•2 kg. About 224 (61%) of liraglutide group participants lost > 5% of their body weight, liraglutide 3•0 mg significantly reduced >5% body weight in comparison with orlistat. The adverse events frequency was higher with a high dose of liraglutide. Liraglutide1•8 mg, 2•4 mg, and 3•0 mg reported more adverse events than liraglutide 1•2 mg, placebo, and orlistat. About 10% participants from each treatment group experienced adverse events. Gastrointestinal events, Nausea, Constipation, Diarrhea, and vomiting were the most common ones. Most events were transient, mild, or moderate. The frequency of events increased with dose intensity. More than 80% of nausea complaints, and 50% of vomiting episodes were reported in the first 4 weeks of treatment during dose adjustment. Eight individuals withdrew from the study due to nausea and five because of vomiting. Nine participants had serious adverse episodes. Psychiatric events like insomnia, depressed mood, and nervousness were more often reported in 6 individuals of liraglutide 2•4 mg. Depression and anxiety were reported by 2 individuals in each group.

Other adverse events were General disorders and administration-site conditions like fatigue, Gastroenteritis, Nasopharyngitis, Injury, poisoning, and procedural complications, Metabolism and nutrition disorders, Musculoskeletal and connective-tissue disorders, Nervous system disorders, Headache, Skin and subcutaneous-tissue disorders. No case of pancreatitis was reported over the 20 week trial in any of the liraglutide group.

Weight loss was significantly seen in liraglutide 2•4 mg and 3•0 mg in comparison with placebo and orlistat. The mean weight loss of liraglutide 3.0mg was 7.2kg, 76% of participants reported >5% weight loss, and significantly around 30% participants lost >10% of body weight. This weight loss shared a valuable contribution to cardiovascular health. Pre diabetic rate was also significantly decreased in liraglutide 2.4 and 3.0 mg.

A randomized, double-blind, placebo-controlled study of 19 European clinical research centers [12] – 2-year trial

Three hundred ninety-eight individuals agreed to a 2-year treatment extension from which 268 (67%) completed it. The starting dose was 0.6mg daily and escalated weekly. The comparator group received orlistat capsules 3X120 mg, exactly for 2 years. After 20 weeks of initial assessment, participants consented for a 1-year extension with the switching of liraglutide dose to 2.4 mg for liraglutide or placebo-administered participants. One year trial reported the dose 3.0mg as the most favorable and effective. Adverse events were mostly gastrointestinal, of mild to moderate severity, and 51 participants withdrew due to adverse events.

The serious adverse events in each individual and withdrawal due to liraglutide 3.0 mg were cholelithiasis, and acute pancreatitis after 299 days, anaphylactic reaction after 692 days, and atrial fibrillation after 707 days. Liraglutide 1.8mg, serious adverse events and withdrawal was reported because of Breast cancer after 465 days and prostate cancer after 94 days of therapeutic administration. Liraglutide 2.4 mg reported intestinal adenocarcinoma after 410 days, uterine leiomyoma after 219 days.

This 2 year study concluded Liraglutide as a sustainable therapeutic in weight reduction, well-tolerated, and beneficial for cardiovascular health.

Safety and Efficacy Evaluation of obesity drugs including Liraglutide in nondiabetic, severely obese individuals [13]

This 26 week randomized study was started with 474 participants and completed with 444. The study was categorized into 5 groups including double-blind placebo, JNJ-64565111 5.0 mg, JNJ-64565111 7.4 mg, JNJ-64565111 10.0 mg, and open-label Liraglutide 3.0 mg. The starting dose of Liraglutide was 0.6mg/per day, and titrated gradually to 1.2, 1.8, 2.4, and 3.0 till week 5 and then continued to 3.0 mg dose till week 26. The defined outcome was ≥ 5% reduction of body weight which was awaited.

The 119 reported adverse events associated with liraglutide 3.0mg were seen in 81 individuals, mostly minor to moderate, included gastrointestinal disorders, general disorders, and infections. The serious adverse events associated with mortality risk were seen in 4 (3.36%) individuals. Those reported were Myocardial Infarction, acute pancreatitis, Biliary Colic, Cholelithiasis, and major depression.

Effect of liraglutide 3.0 mg in obese individuals having moderate or severe obstructive sleep apnea [14]

A randomized double-blind control trial with liraglutide 3.0 mg was designed in 359 nondiabetic, obese individuals having moderate or severe obstructive sleep apnea. The primary outcome was an improvement in apnea-hypopnea index (AHI) and also it evaluated the weight loss by 32 weeks

of liraglutide 3.0mg administration. The starting dose of liraglutide was 0.6 mg/day and increased weekly to 3.0mg, and then maintained for 28 weeks. This study reported significantly greater improvement in AHI as compared to placebo. Weight reduction was also significantly seen in the liraglutide group i.e. 46.3% participants lost more than 5% of their body weight. A noteworthy improvement was also reported in Glycemic control and cardiometabolic indices.

Out of 359, 276 completed the study, 134 (74%) from liraglutide group and 142 (79%) from placebo.

More individuals reported adverse events with the liraglutide group i.e. 80.1%, Liraglutide group also had a higher withdrawal rate due to adverse events than placebo 12% vs. 3%. Gastrointestinal mild to moderate adverse events were the most common. Serious adverse events were Angina pectoris, Anxiety, Cholelithiasis, Coronary revascularization, Dehydration, Depression-suicidal, Oropharyngeal swelling, Pneumonia, Procedural pain, Sinus arrest, Sleep apnea syndrome, and Spinal fracture. This study concluded liraglutide 3.0mg is a significantly superior therapeutic than placebo or lifestyle modification alone, and pronounced weight loss resulted in AHI reduction, improved cardiovascular health, and improved systolic blood pressure.

Liraglutide 3.0mg in Weight Management [15]

A 56-week double-blind trial was designed with 3,731 participants, 2,487 for liraglutide 3.0 mg with lifestyle modification and 1,244 for placebo plus lifestyle intervention, negative for type 2 diabetes with 27-30 BMI. The evaluation was done every 2 weeks till week 8, then on every 4 weeks evaluation until weeks 50, 56, 58, 60, 64, 68, and 70. A total of 71.9% (n=1789) of liraglutide group individuals and 64.4% (n=801) of the placebo group completed the 56 weeks study. A large number of liraglutide group individuals withdrew due to adverse events i.e. 246 of 2,487 (9.9%) participants, and 23 of 2,487 (0.9%) due to ineffective therapy. 264 participants out of 2,487 (10.6%) withdrew their consent. After 56 weeks of evaluation, liraglutide individuals lost body weight of 8.4±7.3 kg and maintained it throughout the 56 weeks of assessment. 63.2% of patients lost around 5% of their weight, and 92% of the total liraglutide group reportedly lost body weight. Other glycemic, cardiometabolic variables and quality of life parameters were significantly improved in the liraglutide group.

Adverse events are also linked with liraglutide group; mild to moderate gastrointestinal adverse effects were the most reported and the leading cause of trial withdrawal (n=159), and included Nausea, Vomiting, Diarrhea, Constipation, Dyspepsia, Upper abdominal pain, Abdominal pain, Nasopharyngitis, Upper respiratory tract infection, Sinusitis, Influenza, Headache, Dizziness, Decreased appetite, back pain, Arthralgia, Injection-site hematoma, fatigue. The incidence of serious adverse events was also reportedly high in the liraglutide group including cholelithiasis, cholecystitis, Osteoarthritis, Intervertebral disc protrusion, Acute Pancreatitis, Breast cancer, Back pain, Uterine leiomyoma, and Cellulitis. An unusual representation of Spontaneous hypoglycemia was also identified in 32 of 2,481 of the liraglutide group. The indifferent unexpected results were greater weight loss reported in individuals with gallbladder related adverse events in comparison with mean weight reduction in total participants. Three participants died during the study, 1 from the liraglutide group due to cardiomegaly and 2 from the placebo group due to pulmonary fibrosis and cardiorespiratory arrest.

This study reported the similar effects of liraglutide administration with prediabetes and nondiabetic individuals with significant improvement in metabolic control also. This is an exception study and was included because of comparative conclusion of liraglutide administration in prediabetes and nondiabetic individuals.

Three months liraglutide 1.8mg treatment in obese, in non-diabetic, binge eating individuals [16]

Forty-two obese binge eater individuals were randomly categorized: 21 participants in liraglutide 1.8mg group, plus exercise, and diet; twenty one individuals in the control group – exercise and diet only, for 3 months. The assessment was done on 1, 6, and 12 week intervals. Liraglutide receiving participants reportedly had marked reduction in Binge Eating Scale (BES) from 20 to 11, weight from 94.54 ± 18.14 kg to 90.14 ± 19.70 kg, BMI from 36.15 ± 3.84 kg/m2 to 34.40 ± 4.77 kg/m2, and waist circumference from 103.9 ± 13.7 cm to 100.2 ± 14.0 cm. Overall 50% of liraglutide individuals resulted in 5% of weight reduction which also reduces cardiovascular risks. This study used Ghrelin testing as a hunger indicator which was significantly increased and ultimately reduced body weight. No adverse effects were reported in this pilot study.

Weight maintenance randomized study with liraglutide [17]

The study was conducted with 422 participants, with 40% drop out. Initially, 675 participants were screened; 551 were taken up for low-calorie diet - LCD and encouraged to reduce ≥5% of initial weight loss during 4-12 weeks duration. Immediately after ≥5% of weight loss participants were randomly allocated to liraglutide 3.0 mg daily in a 1:1 ratio of n = 212 and placebo group n = 210. Liraglutide dose initially started with 0.6 mg and escalated between 4-5 weeks and continued with 3.0 mg till 56 weeks. 53 participants were withdrawn from the liraglutide group and 64 from the placebo. 18 participants from each group were withdrawn due to adverse events. Results were significantly positive ; the liraglutide group reduced a further 6.2% (mean) body weight. 81.4% of liraglutide participants reduced ≥5% of body weight and 26.1% lost ≥10% of their body weight.

In terms of safety 91.5 vs. 88.6% of liraglutide and placebo group participants respectively reported adverse events, with more frequency of events in the liraglutide group.

Six out of eighteen withdrawals experienced serious events i.e. ischemic colitis, worsening cholelithiasis, ovarian cancer, papillary thyroid carcinoma, and bilateral breast cancer in the liraglutide group. Eleven withdrawals were

due to the most common gastrointestinal adverse events. This study also concluded liraglutide as well-tolerated and contributes well in terms of meaningful weight loss with improvement in cardiovascular risk factors.

Effects of liraglutide on metabolic activities in obese, non-diabetic adults [18]

This study was defined as the mechanism of weight loss in obese, non-diabetic individuals by Liraglutide. The first and second treatment phase was of 5 weeks with a 6-8 weeks wash off period. This was a single-institutional, randomized, double-blind placebo-controlled, crossover trial with Liraglutide 1.8 mg, 3.0 mg, and placebo per day. Out of 62 screened individuals, 42 were enrolled in the study. Weight loss was reported as a secondary outcome and the weight loss mechanism was the primary one. The 5 week mean weight loss was reported as 2.1kg and 2.5 kg with liraglutide 1.8 mg and 3.0 mg respectively. Five participants withdrew from the study, 2 because of adverse events of toe thrombosis and tooth infection.

Liraglutide 1.8mg and 3.0mg both were reported as well tolerated. The reported adverse events were 90% with liraglutide 1.8 mg and 94% of liraglutide 3.0 mg, mostly gastrointestinal complaints of nausea and decreased appetite.

Low-dose liraglutide assessment in weight control among obese, non-diabetics [4]

A small scale study was conducted with 46 participants who were administered liraglutide 0.6 or 1.2 mg daily for 12 weeks. Liraglutide 1.2 mg showed better outcome with 44.4% patients with weight reduction in comparison with liraglutide 0.6mg where 32.1% patients showed weight reduction. Young age was reported as a positive factor in weight reduction, and even a low dose of liraglutide can help in weight reduction. Adverse events were not reported in this study.

Study Withdrawals due to adverse events

Gastrointestinal disorders are the most common associated adverse events with liraglutide administration. Most adverse events are self-limiting and occur mostly in the first 4-5 weeks during dose escalation, and large scale data reported these as insignificant [21, 22]. A lesser percentage of serious adverse events were reported throughout the studies. Although, these serious events are less in number participants refused to continue the study which lead to withdrawal. Figure 1, presents the overall withdrawals of all included studies among all doses of liraglutide.

Serious adverse events are always a concern associated with liraglutide consumption including pancreatitis and cancer. Although, the numbers are few they are crucial due to the nature of their severity [23]. Figure 2 (page 82) gives a comprehensive picture of all included studies and reported serious adverse events.

Serious Adverse events due to Liraglutide Administration

Serious adverse events were reported among almost all selected studies; however, these numbers are insufficient statistically but crucial to address [11-18]. These adverse events were the unpredicted medical occurrence due to liraglutide administration of all doses. A study of Alves et al. evaluated acute pancreatitis and cancer as adverse effects, a decade ago among liraglutide administered individuals [23].

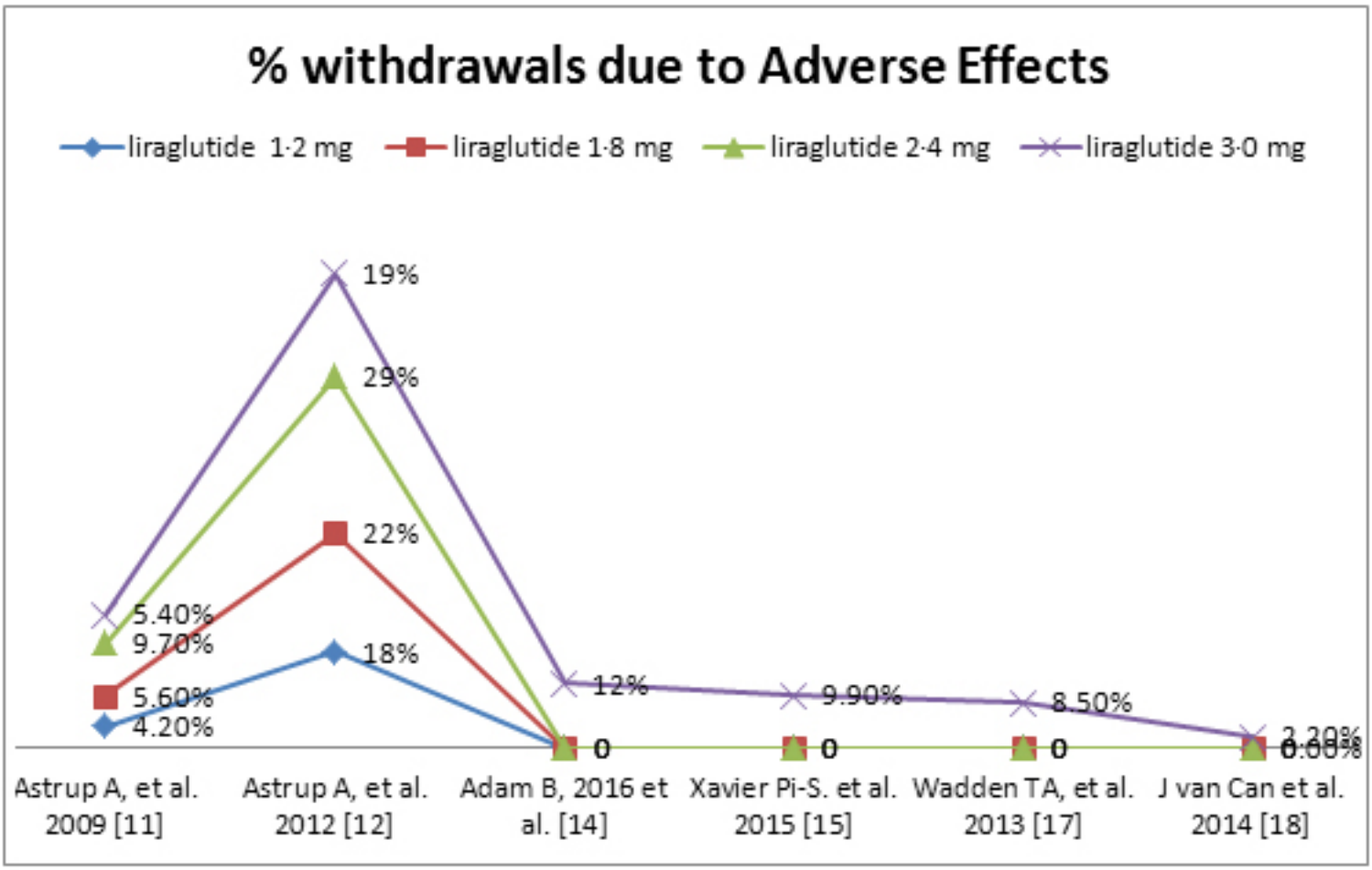
Obesity, Liraglutide, and comparative therapeutics

There are many forms of obesity treatments like life style modification and non-pharmacological ones, which are also helpful in weight loss but the process is slow with a low success outcome. Regaining obesity is another concern with these options [19]. There are five weight loss therapeutics available that are approved by the FDA, including orlistat, which was approved in 1997, lorcaserin, and phentermine/topiramate approved in 2012, and naltrexone/bupropion combination, and Liraglutide 3.0mg approved by the FDA in 2014 [3, 20]. Only 1 study did a comparative analysis of different doses of Liraglutide, placebo, and orlistat and reported liraglutide as more effective for weight reduction in almost all doses as compared to orlistat in a 20 week trial [11]. An extension of this study also reported liraglutide 3.0mg as more effective in weight reduction than orlistat [12]. Adverse events were reportedly more seen in the liraglutide group than orlistat [11, 12]. Another, interesting finding was that, the participants who did not experience gastrointestinal disorders like nausea and vomiting, experienced more weight loss, the mechanism of this needs to be explored [21].

Liraglutide and microbiota

With this extensive literature review, we found that the most reported adverse events of liraglutide in all selected studies reported a similar declaration of adverse events reporting and gastrointestinal adverse events were the most common ones. statement. Reporting of liraglutide and its impact on gut microbiota is a much less reported field. A decade ago, seminal studies based on liraglutide administration reported the alteration of gut microbial ecology with increase of Akkermansia muciniphila both in type 2 diabetes mellitus and non-diabetic individuals [24, 25]. Then it was finally concluded by research that liraglutide is responsible for disturbing gut microbial balance [25]. There is no clue to link this alteration of gut ecology with the most common adverse events of liraglutide “gastrointestinally”, future studies need to explore this area.

Figure 1: Overall Presentation of liraglutide withdrawals among selected studies due to serious adverse events



Conclusion

Obesity is a multifactorial complex disease influenced by genetic and environmental factors and pharmacological or therapeutic options plays a significant role in weight loss with minimal side effects. Liraglutide is reported as a safe, well tolerated therapeutic in all included studies with significantly improved cardiovascular health status.

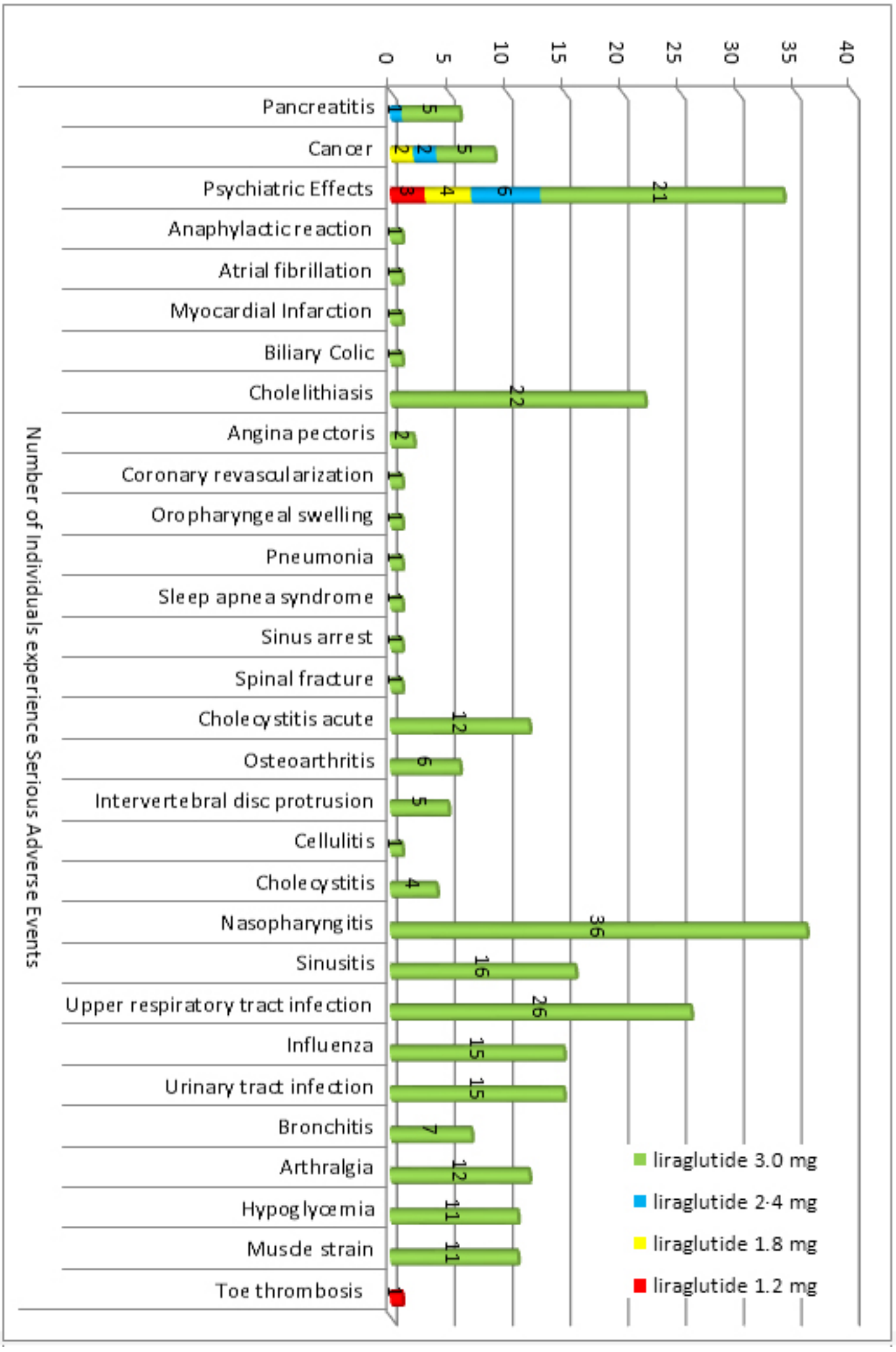
Scientific studies and trials have shown liraglutide as an effective weight reducing therapeutic with limited adverse events both in diabetic and non diabetic individuals.

We need to identify the drug mechanism precisely to know the alteration in the human body in response to liraglutide administration, starting from the most common to serious adverse eventsas well as to identify the connection of more weight loss in individuals with absence of gastrointestinal weight loss [21]. The serious adverse events including pancreatitis, and cancer are also daunting and a specific study participant group can bear the liraglutide administration consequences [23]. Also, studies on related mortality due to severe adverse events in response to liraglutide administration are also suggested. This will help to design safer therapeutics with possibly no serious adverse effects.

References

1. Anirban M, Soumyabrata RC, Debmalya S, Bhattacharjee K. Liraglutide - Indian Experience. Indian J Endocrinol Metab. 2018;22(6):818-826. doi:10.4103/ijem.IJEM_187_18
2. Almarshad F. Short-term monotherapy with Liraglutide for weight management: A case study. J Family Med Prim Care. 2019;8(5):1804-1806. doi:10.4103/jfmpc.jfmpc_213_19
3. Mehta A, Marso SP, Neeland IJ. Liraglutide for weight management: a critical review of the evidence. Obes Sci Pract. 2017 Mar;3(1):3-14. doi: 10.1002/osp4.84. Epub 2016 Dec 19. PMID: 28392927; PMCID: PMC5358074.
4. Chien-An C, Shu-Fen C. Evaluation of the efficacy of low-dose liraglutide in weight control among Taiwanese non-diabetes patients. J Diabetes Investig 2020 11(6).
5. Verma A. Non-diabetic use of liraglutide. Indian J Endocrinol Metab. 2012;16(5):864-865. doi:10.4103/2230-8210.100698
6. Marcio CM, Maria Edna de M. The burden of obesity in the current world and the new treatments available: focus on liraglutide 3.0 mg. Mancini and de Melo Diabetol Metab Syndr (2017) 9:44 DOI 10.1186/s13098-017-0242-0
7. St. Onge, E., Miller, S.A. and Motycka, C. (2016) Liraglutide (Saxenda®) as a Treatment for Obesity. Food and Nutrition Sciences, 7, 227-235. http://dx.doi.org/10.4236/fns.2016.74024
8. Zhang P, Liu Y, Ren Y, Bai J, Zhang G, Cui Y. The efficacy and safety of liraglutide in the obese, non-diabetic individuals: a systematic review and meta-analysis. Afr Health Sci. 2019;19(3):2591-2599. doi:10.4314/ahs.v19i3.35

Figure 2: Serious Adverse events reported among selected studies due to Liraglutide Administration



9. Millar K, Poole R. Current drugs for weight loss. Pract Diabetics 2016; 33(7): 229-232. https://doi.org/10.1002/pdi.2044
10. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928
11. Astrup A, Rössner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, Madsen J, Rasmussen MF, Lean ME; NN8022-1807 Study Group. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet. 2009 Nov 7;374(9701):1606-16. doi: 10.1016/S0140-6736(09)61375-1. Epub 2009 Oct 23. Erratum in: Lancet. 2010 Mar 20;375(9719):984. PMID: 19853906.
12. Astrup A, Carraro R, Finer N, Harper A, Kunesova M, Lean ME, Niskanen L, Rasmussen MF, Rissanen A, Rössner S, Savolainen MJ, Van Gaal L; NN8022-1807 Investigators. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int J Obes (Lond). 2012 Jun;36(6):843-54. doi: 10.1038/ijo.2011.158. Epub 2011 Aug 16. Erratum in: Int J Obes (Lond). 2012 Jun;36(6):890. Erratum in: Int J Obes (Lond). 2013 Feb;37(2):322. PMID: 21844879; PMCID: PMC3374073.
13. A Study to Evaluate the Safety and Efficacy of JNJ-64565111 in Non-diabetic Severely Obese Participants. ClinicalTrials.gov Identifier: NCT03486392
14. Blackman A, Foster GD, Zammit G, Rosenberg R, Aronne L, Wadden T, Claudius B, Jensen CB, Mignot E. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. Int J Obes (Lond). 2016 Aug;40(8):1310-9. doi: 10.1038/ijo.2016.52. Epub 2016 Mar 23. PMID: 27005405; PMCID: PMC4973216.
15. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DC, le Roux CW, Violante Ortiz R, Jensen CB, Wilding JP; SCALE Obesity and Prediabetes NN8022-1839 Study Group. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. N Engl J Med. 2015 Jul 2;373(1):11-22. doi: 10.1056/NEJMoa1411892. PMID: 26132939.
16. Robert SA, Rohana AG, Shah SA, Chinna K, Wan Mohamud WN, Kamaruddin NA. Improvement in binge eating in non-diabetic obese individuals after 3 months of treatment with liraglutide - A pilot study. Obes Res Clin Pract. 2015 May-Jun;9(3):301-4. doi: 10.1016/j.orcp.2015.03.005. Epub 2015 Apr 11. PMID: 25870084.
17. Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, Aronne L; NN8022-1923 Investigators. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes (Lond). 2013 Nov;37(11):1443-51. doi: 10.1038/ijo.2013.120. Epub 2013 Jul 1. Erratum in: Int J Obes (Lond). 2013 Nov;37(11):1514. Erratum in: Int J Obes (Lond). 2015 Jan;39(1):187. PMID: 23812094.
18. van Can J, Sloth B, Jensen CB, Flint A, Blaak EE, Saris WH. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. Int J Obes (Lond). 2014 Jun;38(6):784-93. doi: 10.1038/ijo.2013.162. Epub 2013 Sep 3. PMID: 23999198; PMCID: PMC4052428.
19. Marcio CM, Maria E de M. The burden of obesity in the current world and the new treatments available: focus on liraglutide 3.0 mg. Mancini and de Melo Diabetol Metab Syndr 2017; 9:44. DOI 10.1186/s13098-017-0242-0
20. Lubomíra F. Weight Loss Pharmacotherapy of Obese Non-Diabetic and Type 2 Diabetic Patients. J Obes Weight Loss Ther; 2015 5:5 http://dx.doi.org/10.4172/2165-7904.1000277
21. Lean MEJ, Carraro R, Finer N, et al. Tolerability of nausea and vomiting and associations with weight loss in a randomized trial of liraglutide in obese, non-diabetic adults. Int J Obes 2014; 38: 689–697.
22. Gillani SMR, Singh BM. The use of GLP-1 agonist therapy, liraglutide, is associated with significant weight loss in morbidly obese people without diabetes. Br J Diab Vasc Dis 2015; 15(2): 61– 4.
23. Carlos A, Francisco BM, Ana FM. A meta-analysis of serious adverse events reported with exenatide and liraglutide: Acute pancreatitis and cancer. Diabet Res and Clin Prac 2012; 98(2): 271-284
24. Qin J, Li Y, Cai Z, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature 2012;490:55–60.
25. Cani PD. Human gut microbiome: hopes, threats and promises. Gut. 2018 Sep;67(9):1716-1725. doi: 10.1136/gutjnl-2018-316723. Epub 2018 Jun 22. PMID: 29934437; PMCID: PMC6109275.