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Glucagon-Like Peptide-1 Receptor Agonists in the Treatment of Obesity

Mojca Jensterle[a, b] Andrej Janež[a, b]

[a]Department of Endocrinology, Diabetes and Metabolic Disease, University Medical Centre Ljubljana, Ljubljana, Slovenia; [b]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

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Obesity · Adolescents · Liraglutide · Semaglutide · Glucagon-like peptide-1

Abstract
Background: Obesity treatment based on glucagon-like peptide-1 receptor agonists (GLP-1 RAs) proved to limit morbidity and mortality in adult population. In children, optimizing lifestyle intervention (LSI) and reducing culpable environmental exposures represent the mainstay strategy for obesity prevention and management. However, there remains a subset of children and adolescents whose obesity is resistant to lifestyle approach. For these poor responders, the need for safe and effective weight-reducing agents is apparent. The purpose of this review is to provide an overview of the efficacy and safety of approved GLP-1 RA in the management of adult and pediatric obesity. ***Summary:*** We presented the main outcomes of clinical trial programs called SCALE and STEP that supported a market authorization approval for liraglutide and semaglutide for the treatment of obesity in adult population. Then, we summarized the studies on the efficacy of GLP-1 RA in pediatric obesity that have been accumulating from 2 larger studies with liraglutide and few other smaller studies with exenatide and liraglutide. The results indicate that GLP-1 RA is safe, tolerable, and effective in reducing weight and also in improving cardiometabolic profile in children with obesity and poor response to LSI alone. At present, liraglutide is the first and so far the only GLP-1 RA that received FDA approval in 2020 for use in children aged 12–17 years with obesity. New trials including semaglutide for pediatric obesity are ongoing. ***Key Messages:*** There is a strong interest in current use and further development of obesity treatments based on glucagon-like peptide-1 (GLP-1) agonism. In adolescents with obesity, who are poor responders to lifestyle approach, the use of GLP-1 RA as an adjunct to LSI is effective and safe. Due to limited experience, a general recommendation is to prioritize long acting over short acting GLP-1 RA because they are approved for the treatment of obesity and have better tolerability, safety, and treatment response effect. In the future research, more high-grade evidence including novel iterations of GLP-1 agonism and long-term follow-ups are needed in pediatric population.

Introduction

The steep increase in the rate of obesity becomes an alarming threat to public health [1]. Overweight affects 30–70% and obesity 10–30% of adults in European Union

karger@karger.com
www.karger.com/hrp

Correspondence to:
Mojca Jensterle, mojca.jensterlesever@kclj.si
Karger

Table 1. Treatment targets based on obesity-related complications in the management of adult patients with obesity

Diagnosis	Weight loss target, %	Expected outcome
Metabolic syndrome	10	Prevention of type 2 diabetes
Type 2 diabetes	5–15	Reduction in glycated hemoglobin; reduction in diabetes medication; diabetes remission if short duration
Dyslipidemia	5–15	Lower triglycerides; increase HDL, decrease LDL
Hypertension	5–15	Lower blood pressure, decrease in medication
NAFLD	10–40	Reduction in intrahepatocellular lipids and inflammation
Polycystic ovary syndrome	5–15	Ovulation; reduction of hirsutism; decrease in androgen levels; increase insulin sensitivity
Sleep apnea	7–11	Decrease apnea/hypopnea index
Asthma	7–8	Improvement of FEV1
Gastroesophageal reflux disease	10 or more	Reduced symptoms

Adopted by Durrer Schutz et al. [15]. NAFLD, nonalcoholic fatty liver disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FEV1, forced expiratory volume in 1 s.

countries. In many European regions, the prevalence has been tripled since 1980 [2]. Moreover, the prevalence of overweight and obesity among children and adolescents has risen dramatically from just 4% in 1975 to just over 18% in 2016. Over 340 million children and adolescents aged 5–19 were overweight or obese in 2016. In 2019, estimated 38.2 million children under the age of 5 years were overweight or obese [2]. The estimation of percentage of obese adolescents becoming overweight/obese adults varied between 24% and 90% [3, 4]. At 2 years of age, severely obese children have only 20% chance of not being obese by the age of 35 years, and by 5 years the chance dropped to 10%. The persistence of elevated risk is striking: a 2-year-old who is obese is more likely to be obese at 35 years of age than an overweight 19-year-old [5]. If current trends continue, more than 1.1 billion individuals will have obesity in 2030, corresponding to almost 2.5 times the number of adults currently living with diabetes [1].

As a direct consequence of obesity surge, a substantial cardiometabolic, oncological, psychiatric, and financial burden will continuously expand [6]. In children and adolescents, obesity leads to the increased risk of developing early puberty [7], menstrual irregularities in adolescent girls [8, 9], obstructive sleep apnea [8, 10], and cardiovascular risk factors including prediabetes, type 2 diabetes mellitus, high cholesterol levels, hypertension, nonalcoholic fatty liver disease, and metabolic syndrome [1, 11]. Additionally, obese children and adolescents suffer from psychological issues such as depression, anxiety, poor self-esteem, body image and peer relationships, and eating disorders [12, 13]. An increased all-cause morbidity and mortality, an impaired quality of life and lower national productivity, should characterize obesity as one of the primary efforts to combat the increasing noncommunicable diseases epidemic across lifespan from the early childhood on [14].

Recognition of obesity as a chronic progressive disease by relevant organizations represents an essential first step in advocating for appropriate healthcare management and treatment of people with obesity [2, 14]. The principal goals in obesity management in adults are to prevent complications by trying to keep the patient metabolically healthy, to prevent or treat comorbidities if they are already present, to fight against stigmatization, and to restore well-being, positive body image, and self-esteem. Body weight loss per se is not considered the first priority. The treatment goals should be tailored to the complications. For adults, the predictive weight loss should always also be given as an indicator of what could be achieved to decrease cardiometabolic risks (Table 1) [15].

The identification of such immanent treatment goals tailored to the complications in pediatric population is more challenging. A change in the body mass index (BMI) standard deviation score of at least 0.2 has been suggested to be clinically meaningful in children and adolescents [16–18], yet the data are limited and inconclusive. The US Preventive Service Task Force determined that comprehensive intensive lifestyle therapy resulting in a reduction in the mean BMI standard deviation score with a difference of 0.17 did not lead to associated improvements in cardiometabolic markers [16]. On the other hand, a modest reduction in the BMI standard deviation score differ-

ence of 0.09 with exenatide led to improvements in glucose and cholesterol levels [19]. The specific role of different weight management modalities and the long-term follow-up regarding risk reduction for obesity-related complications should be evaluated to better define clinically meaningful treatment goals in pediatric population.

For prevention and management of pediatric obesity, public health measures optimizing lifestyle intervention (LSI) and reducing culpable environmental exposures are the primary target for governments and societies [20]. However, LSI can often be insufficient in treating obesity. There remains a subset of children and adolescents whose obesity is resistant to lifestyle approach [21]. For these poor responders, the need for safe and effective weight-reducing agents is apparent. Recognition that much of the pathophysiology of obesity involves abnormal satiety and feeding signaling within the brain supports the effective treatment approaches that address central nervous system processes via glucagon-like peptide-1 (GLP-1) agonism [22]. Following the promising results from the adult population with and without type 2 diabetes, the data about the efficacy and safety of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in pediatric obesity have also been accumulating over the past decade. The purpose of this review is to provide an overview of the efficacy and safety of approved GLP-1 RA in the management of adult and pediatric obesity.

Stepwise Approach in the Management of Obesity

Obesity is a chronic and progressive disease; therefore, weight management needs to be continued lifelong [23]. Stepwise approach to obesity treatment includes (1) LSI with behavioral therapy, physical activity, and dietary modification; (2) pharmacotherapy; and (3) bariatric surgery. The decision about the intervention depends on the BMI, waist circumference, comorbidities, and response to previous anti-obesity management [15].

LSI alone is generally associated with moderate weight loss that is gradually regained [22]. It yields many poor responders in adult and pediatric population [16, 17]. Bariatric surgery is characterized as the most effective management, but it comes at a cost of irreversibility, surgery-related complications, and important late complications [1]. Pharmacotherapy can complement lifestyle therapy and bariatric surgery, yet the duration of such intervention remains to be determined.

Maintaining weight loss achieved by any treatment modality is extremely challenging due to adaptation, which is characterized by changes in the levels of appetite-regulating hormones and a decrease in resting metabolic rate [24]. Some studies indicate that even temporary weight loss may have long-term benefits, but the results are insufficient to support short-term anti-obesity interventions [25].

GLP-1 RA for the Treatment of Obesity

GLP-1 agonism with current GLP-1 RA and novel anti-obesity compounds will presumably become a benchmark for future pharmacological anti-obesity treatment. Functionally relevant GLP-1 receptors are present in the pancreas, intestine, and hypothalamus. Most important for the weight-reducing properties is activation of neural pathways causing reductions in appetite-regulating regions in the hypothalamus causing reductions in appetite and food intake and thereby promoting weight loss [26, 27].

Liraglutide was the first long acting GLP-1 RA approved by the Food and Drug Administration (FDA) and European Medicine Agency (EMA) for the treatment of obesity. It proved efficacious in reducing body weight of patients with and without diabetes as well as in children. Further development then focuses on improving efficacy and prolonging effects by some essential structural modifications. With these characteristic features in mind, a new long acting GLP-1 RA, semaglutide, has been developed [28, 29]. Structurally, liraglutide is a polypeptide based on 97% homology to human GLP-1 with a fatty acid side chain attached through a linker molecule [30]. Semaglutide is similar to liraglutide, but with minor changes in the GLP-1 moiety, with 94% homology to human GLP-1 and another fatty acid side chain [30]. The pharmacokinetic properties gained by this modification allow once weekly dosing of semaglutide versus once daily administration of liraglutide [31]. The modification results in greater efficacy that was firstly confirmed in the phase 2 trial in adults with obesity where patients experienced a mean weight loss from baseline of −13.8% compared with −7.8% for liraglutide at week (wk) 52 [32]. In June 2021, injectable semaglutide was approved in the USA by FDA as the latest anti-obesity medication. For both drugs, the recommended doses for weight loss are greater than those for glycemic control: for liraglutide 3.0 versus 1.8 mg and for semaglutide 2.4 mg versus 1.0 mg [1].

Liraglutide

A clinical trial program called SCALE supported a market authorization approval for liraglutide for the

treatment of obesity [33–36]. SCALE trials were conducted to investigate the efficacy and safety of liraglutide 3.0 mg compared with those of a placebo in combination with a reduced-calorie diet and increased physical activity for weight management in overweight or obese patients with or without comorbidities. This series consisted of SCALE-obesity and prediabetes trial of 3,731 overweight or obese patients without evidence of type 2 diabetes mellitus, SCALE-diabetes trial of 846 overweight or obese adults with type 2 diabetes mellitus, SCALE-maintenance trial of 422 overweight or obese adults who had lost ≥5% of initial body weight during a calorie restriction period, and the 3-year assessment of the SCALE-obesity and prediabetes trial of 2,254 overweight or obese patients with prediabetes [33–36].

The mean weight loss was significantly higher in the liraglutide group than in the placebo group (SCALE-obesity and prediabetes, 8.4 kg vs. 2.8 kg; SCALE-diabetes, 6.4 kg vs. 2.2 kg; SCALE-maintenance, additional 6.2% vs. 0.2%, respectively). Significantly more patients in the liraglutide group than in the placebo group achieved at least 5% weight loss from the baseline (SCALE-obesity and prediabetes, 63.2% vs. 27.1%; SCALE-diabetes, 54.3% vs. 21.4%; SCALE-maintenance, 50.5% vs. 21.8%) [33–35]. Moreover, in the SCALE-obesity and prediabetes trial the time to the onset of diabetes was 2.7 times longer with liraglutide than with the placebo [36]. In the SCALE-sleep apnea trial liraglutide reduced the severity of obstructive sleep apnea after 32 wks of treatment [37]. In all SCALE trials, liraglutide resulted in a greater improvement than the placebo in terms of glycemic control, blood pressure, lipid levels, and health-related quality of life in overweight or obese participants [33–36].

The most frequently reported adverse events with liraglutide in SCALE-obesity and prediabetes trial were mild or moderate nausea and diarrhea. Serious events occurred in 6.2% of the patients in the liraglutide group and in 5.0% of the patients in the placebo group [33].

Semaglutide

A market authorization approval for semaglutide for the treatment of obesity was based on a clinical trial program called STEP [38–42]. Four STEP studies have been published, and long-term weight management trial STEP 5 is undergoing [38]. STEP 1 trial consists of 1,961 adults with obesity and overweight without evidence of type 2 diabetes mellitus [39], and STEP 2 of 1,210 adults with overweight or obesity with type 2 diabetes mellitus [40]. STEP 3 is weight management with intensive behavioral therapy trial of 611 overweight or obese adults without type 2 diabetes mellitus [41]. In the sustained weight management trial STEP 4, 902 participants with obesity or overweight, without type 2 diabetes mellitus, were treated for additional 48 wks, assigned in a 2:1 manner to receive continued semaglutide 2.4 mg or placebo after completing a 20-wk run-in period with semaglutide [42]. STEP 1–3 showed a 68-wk mean change in body weight from baseline of −9.8 kg to −17.1 kg (−9.6 to −16%) with semaglutide 2.4 mg and −6.9 kg (−7%) with semaglutide 1 mg compared to −3.1 to −5.9 kg (−2.9 to −5.7%) with placebo [39–41]. STEP 4 showed a 20-wk mean change in body weight from baseline of 11.3 kg (−10.6%) with semaglutide 2.4 mg. A 48-wk change in mean body weight from wk 20 baseline was −7.6 kg (−7.9%) with continued semaglutide compared to +6.8 kg (+6.9%) with shift to placebo [42]. Transient and mild to moderate in severity nausea and diarrhea were the most common adverse events with semaglutide. At present, at least 5 phase 3 trials with semaglutide in adult patients with obesity are ongoing in 2021 [43].

Comparison of GLP-1 RA-Induced Weight Reduction in Patients with and without Diabetes

The challenges of achieving weight reduction in people with type 2 diabetes mellitus as compared with people without diabetes are well known. As predicted, smaller weight losses with both GLP-1 RA have been confirmed in treating patients with than without type 2 diabetes mellitus [33, 39, 40, 44, 45]. The differences in the efficacy of liraglutide and semaglutide in the weight management of patients with and without type 2 diabetes are presented in Table 2.

GLP-1 RA for Pediatric Obesity

At present, the only 2 GLP-1 RA compounds for which pediatric data are available are short acting GLP-1 RA exenatide and liraglutide [46]. The efficacy and safety of subcutaneous liraglutide 3.0 mg as an adjunct to lifestyle therapy for weight management in adolescents with obesity were evaluated in a randomized, double-blind, placebo-controlled, phase 3 trial from 2016 to 2019 [47]. The trial had a 12-wk run-in period, a 56-wk treatment period, and a 26-wk follow-up period without treatment. They enrolled individuals aged 12 to <18 years with obesity and a poor response to lifestyle alone. A total of 125 participants were assigned to the liraglutide group and 126 to the placebo group.

Liraglutide was superior to placebo with regard to the change from baseline in the BMI standard deviation score at wk 56 with an estimated difference −0.22. A reduction

Table 2. Efficacy of liraglutide and semaglutide in the management of adult and pediatric obesity with and without type 2 diabetes

	Liraglutide 1.8 mg, change in BW from BL	Liraglutide 3 mg, change in BW from BL, %	Semaglutide 1 mg, change in BW from BL, %	Semaglutide 2.4 mg, change in BW from BL, %
Adults				
Without diabetes	NA	−8.0[2]	NA	−14.9[6]
With diabetes	−3.1 kg**,[1]	−5.8[3]	−6.9[5]	−9.6[5]
Adolescents				
Without diabetes*	NA	−5.0[4]	NA	NA
With diabetes	No estimated difference versus placebo	NA*	NA	NA

* Adolescents with type 2 diabetes were eligible, but adolescents with type 1 diabetes were excluded. The exact number of participants with type 2 diabetes has not been reported (Kelly et al. [47]). **Data for relative change (%) not reported (Pratley et al. [44]), NA, not available. [1] Pratley et al. [44]. [2] Pi-Sunyer et al. [33]. [3] Garvey et al. [45]. [4] Kelly et al. [47]. [5] Davies et al. [40]. [6] Wilding et al. [39].

in BMI for at least 5% was observed in 43.3% participants in the liraglutide group and in 18.5% of participants in the placebo; reduction in BMI of at least 10% was observed in 33% and 9% of participants, respectively. A greater reduction was observed with liraglutide than with placebo for BMI with estimated difference −4.64 percentage points and for body weight with estimated difference −4.5 kg for absolute change and −5.01% for relative change. After discontinuation, a greater increase in the BMI standard deviation score was observed with liraglutide than with placebo [47].

The observed reduction in the BMI standard deviation score with liraglutide (−0.22) was greater than differences observed in trials of lifestyle therapy conducted by the US Preventive Service Task Force (−0.17) [16] and in an overview of Cochrane reviews (−0.13) [17]. When compared with adults, the treatment difference in body weight observed with liraglutide was similar to the treatment effect observed in the corresponding trial of liraglutide in adults despite some differences in the weight loss trajectory [33]. The weight regain seen in the 26-wk follow-up period was also in line with observations from placebo-controlled trials of liraglutide 3.0 mg in adults [33, 36].

More participants in the liraglutide group had gastrointestinal adverse events (64.8% vs. 36.5%) and adverse events that led to discontinuation of the trial treatment (10.4% vs. 0%). Few participants in either group had serious adverse events (2.4% vs. 5 [4%]). During the 26-wk follow-up period, additional serious adverse events occurred in 1 participant who had received liraglutide (1 event) and 4 participants who had received placebo (5 events). Events related to psychiatric disorders occurred in 13 participants (10.4%) in the liraglutide group and in 18 participants (14.3%) in the placebo. There were no clinically relevant differences between treatment groups with respect to results on mental health questionnaires. However, 1 suicide occurred in the liraglutide group approximately 340 days after the initiation of treatment and 2 participants (1 per treatment group) reported a suicide attempt during the 26-wk follow-up period. The site investigators deemed these 3 events as unlikely to be related to the trial treatment. More hypoglycemic episodes occurred with liraglutide than with placebo (26 vs. 18); none was deemed as severe according to the American Diabetes Association-International Society for Paediatric and Adolescent Diabetes classifications. There were no apparent differences between treatment groups in growth or pubertal development [47].

Adverse events that led to discontinuation of the trial treatment occurred in 13 participants in the liraglutide group (10.4%) and none in the placebo group ($p < 0.001$). In 10 participants, discontinuation was due to gastrointestinal events. Adherence was relatively high >80%, as compared with many previous trials involving adolescents with obesity (approximately 70%) [17, 48]. However, the proportion of samples obtained for pharmacokinetics analysis that had liraglutide concentrations below the lower limit of quantifications increased towered the end of the treatment period.

In summary, in adolescents with obesity, liraglutide 3.0 g as an adjunct to lifestyle therapy led to a greater reduction in the BMI than placebo. The higher frequency of gastrointestinal adverse events observed with liraglutide suggests that this treatment may not be suitable for all patients [47].

Another larger study that assessed whether liraglutide 1.8 mg added to metformin with or without basal insulin treatment is safe and effective was conducted in youth

with type 2 diabetes from 2012 to 2018 [49]. The weight reduction was reported but not characterized as primary or secondary outcome. Patients who were 10 to <17 years of age were randomly assigned, in a 1:1 ratio, to receive subcutaneous liraglutide or placebo for a 26-wk double-blind period, followed by a 26-wk open-label extension period. Inclusion criteria were a BMI greater than the 85th percentile and a glycated hemoglobin level between 7.0 and 11.0% if the patients were being treated with diet and exercise alone or between 6.5 and 11.0% if they were being treated with metformin with or without insulin. All the patients received metformin during the trial. The primary end point was the change in the glycated hemoglobin level after 26 wks. Secondary end points included the change in fasting plasma glucose level. Safety was assessed throughout the course of the trial. Of 135 patients who underwent randomization, 134 received at least one dose of liraglutide (66 patients) or placebo (68 patients) [49].

The 26-wk analysis of the primary efficacy end point and the mean glycated hemoglobin level had decreased by 0.64 percentage points with liraglutide and increased by 0.42 percentage points with placebo; the difference increased to −1.30% by 52 wks. The fasting plasma glucose level had decreased at both time points in the liraglutide group but had increased in the placebo group. Very low-density lipoprotein cholesterol levels were decreased more with liraglutide than with placebo at wk 26, as were triglyceride levels, but no differences were apparent at wk 52 [49].

In contrast to these metabolic parameters, the statistical superiority of liraglutide to placebo in lowering the BMI *Z* score was not shown; the estimated treatment difference at wk 26 was −0.05, which subsequently increased at wk 52 to −0.18. Similarly, mean body weight decreased in both groups at wk 26 (−2.3 kg with liraglutide and −0.99 kg with placebo) but was maintained only with liraglutide at wk 52 (−1.91 kg with liraglutide vs. 0.87 kg with placebo) [49]. Notably, this study was not designed to assess the anti-obesity effectiveness of liraglutide. A comparative trial between liraglutide of higher dosage versus metformin in obese adolescents without any other background antidiabetic therapy is needed to properly evaluate the superiority of weight loss potential of liraglutide as compared with metformin.

The number of patients who reported adverse events was similar in the 2 groups (56 [84.8%] with liraglutide and 55 [80.9%] with placebo), but the overall rates of adverse events and gastrointestinal adverse events were higher with liraglutide [49]. The data on the efficacy of GLP-1 RA in pediatric obesity have been accumulating also from few other smaller studies with exenatide and liraglutide [46]. The recent systematic review and meta-analysis [46] included both large studies that are summarized in the previous paragraphs [47, 49] and 7 other studies that were smaller in size and shorter in duration [50–55]. The 3 trials explored exenatide [51, 52, 54], and other 6 trials applied liraglutide [47, 49, 50, 53, 55, 56]. They are summarized in Table 3.

In total, meta-analysis included data from 574 children and adolescents, 302 of which received a GLP-1 RA. The mean age across all included participants was 14.15 years, with a slight female predominance. Mean weights of participants at baseline ranged from 71.5 kg to 124 kg, with BMI ranging from 33.9 to 43 kg/m^2 and BMI *Z* score from 2.9 to 3.9 [46]. Although all studies included children with obesity or severe obesity, only 3 of the studies exclusively included participants with type 2 diabetes or prediabetes [49, 55, 56].

The review and meta-analysis assessed whether GLP-1 RAs reduce weight or BMI and improve cardiometabolic profile, defined as improvement in glycated hemoglobin, lipid profile, or blood pressure in children with obesity when compared with placebo or no intervention in a randomized controlled trial. As a secondary aim, the meta-analysis sought to determine if GLP-1 RAs were associated with increased gastrointestinal side effects, pancreatitis, and altered liver function in the same population [46].

The results revealed GLP-1 RAs to be effective in reducing weight, the glycated hemoglobin, and blood pressure in children and adolescents with obesity or severe obesity. In addition, this weight-reducing effect appears to be boostered by concurrent LSI. In contrast to what has been established in adult populations, there was no difference noted in the efficacy of liraglutide and exenatide in this population [57]. However, based on the data from adult population, the use of liraglutide over exenatide should be prioritized for the treatment of obesity, because liraglutide has better tolerability, safety, and treatment response effect. Finally, apart from increased rates of minor GI-related symptoms such as nausea, no serious adverse events were noted [46].

The Current Position of GLP-1 RA for the Weight Management

Adult Population

GLP-1 RA for overweight and obesity should be used only as an adjunct to lifestyle therapy and not alone aiming to produce greater weight loss and weight loss main-

Table 3. Efficacy of GLP-1 RAs in children and adolescents with obesity

Studies (author)	Intervention	Control	*N*	Mean age at baseline, years (SD)	Mean weight at baseline, kg	Weight mean difference, kg	BMI mean difference, kg/m^2	BMI *Z* score mean difference
Kelly et al. [52]	13 wk Exenatide 10 μg BID + LSI	Placebo + LSI	11	12.7 (2.1)	93.8	−3.9	−1.71	NA
Kelly et al. [51]	13 wk Exenatide 10 μg BID	Placebo	26	15.2 (1.8)	124	−0.3	−1.13	NA
Danne et al. [53]	5 wk Liraglutide 3 mg QD	Placebo	21	14.9 (1.3)	105.5	−0.3	NA	−0.02
Mastrandrea et al. [50]	8 wk Liraglutide 3 mg QD	Placebo	24	9.9 (1.1)	71.5	−1.5	NA	−0.28
Kelly et al. [47]	56 wk Liraglutide 3 mg QD + LSI	Placebo + LSI	251	14.6 (1.6)	100.8	−4.5	−1.58	−0.22
Weghuber et al. [54]	26 wk Exenatide 2 mg per week	Placebo	44	14.4 (2.3)	104.4	−3	−0.83	−0.09
Tamborlane et al. [49]	26 wk double blind +26 wk OLE Liraglutide 1.8 QD + met	Placebo + met	134	14.6 (1.7)	91.5	−1.31	NA	−0.18
Zhou et al. [56]	3 mo Liraglutide 1.3 QD + LSI	LSI	42	11.16 (2.2)	NA	NA	−1.2	NA

N, number of participants; mo, month; QD, quaque die (means once a day); BID, bis in die (twice a day); OLE, open-label extension; NA, not available.

tenance compared with lifestyle therapy alone [58]. Pharmacotherapy is suitable for adult patients with BMI >30 kg/m^2 or with BMI >27 kg/m^2 with comorbidities. There are responders and nonresponders to the anti-obesity drugs. A 5% weight loss in nondiabetic patients and >3% weight loss in diabetic patients should be achieved after 3-month treatment. If this is not the case, the anti-obesity drug should be interrupted. Weight loss drugs should not be used in pregnancy, lactation, and childhood [15].

In selecting the optimal weight loss medication for each patient, clinicians should consider differences in efficacy, side effects, cautions, and warnings that characterize medications approved for chronic management of obesity, as well as the presence of weight-related complications and medical history; these factors are the basis for individualized weight loss pharmacotherapy; a generalizable hierarchical algorithm for medication preferences that would be applicable to all patients cannot currently be scientifically justified [58].

Pediatric Population

In children, obesity prevention and lifestyle weight management interventions, including instructive exercise and nutritional education, promotion of healthy options, and behavioral counseling, represent the mainstay of obesity management [46]. Rather than treating obesity in isolation as an individual problem, it is crucial to approach this problem by focusing on the family unit [59].

Although these interventions can be highly effective in certain individuals in the correct setting, they have their clear limitations and may benefit from adjunctive approaches or therapies [46]. Bariatric surgery is offered to adolescents only when they have severe obesity, and it is performed infrequently [60, 61].

Liraglutide is the first and so far the only class of GLP-1 RA, received FDA approval for use in children aged 12–17 years with obesity (weight >60 kg and BMI of >30 kg/m^2 in accordance with international standards 10/≥95th percentile) in 2020. At present, EMA has not approved any pharmacotherapeutic agents for obesity in pediatric patients.

Currently, a double-blind placebo-controlled phase 3 trial is ongoing to evaluate the efficacy and safety of liraglutide 3.0 mg on weight management in children with obesity aged 6–12 years (Clinicaltrials.gov ID: NCT04775082). Also, there are a phase 2 trial evaluating the efficacy of the use of liraglutide in adolescents (12–20 years) with obesity after sleeve gastrectomy (Clinicaltri-

als.gov ID: NCT04883346) and a double-blind placebo-controlled phase 3 trial evaluating the efficacy and safety of semaglutide 2.4 mg once weekly in the management of adolescents with overweight and obesity (Clinicaltrials.gov ID: NCT04102189).

Conclusion

There is a strong interest in current use and further development of obesity treatments based on GLP-1 agonism, which have proved to limit morbidity and mortality in adult population. In children, obesity prevention and LSI within the family unit represent the mainstay of anti-obesity management.

Currently, pediatricians have little to offer to the patients who are resistant to lifestyle approach. The accumulating data indicate that GLP-1 RA is safe and modestly effective in reducing weight and in improving cardiometabolic profile in children with obesity and poor response to LSI alone. Due to limited experience, a general recommendation is to prioritize long acting over short acting GLP-1 RA because they are approved for the treatment of obesity and have better tolerability, safety, and treatment response effect. New trials gathering pediatric data are ongoing, including long acting GLP-1 RA semaglutide.

To fulfill the gaps in our knowledge for use of these agents in the pediatric population, more high-grade evidence for GLP-1 RA anti-obesity use in larger pediatric population and the assessment of long-term potential of such intervention in the prevention of obesity-related complications are needed. Since it seems difficult to convince adolescents without diabetes to take subcutaneous injection for a modest weight loss, the data from real-life setting are also warranted.

Conflict of Interest Statement

M.J. has given lectures, received honoraria, and participated in conferences and advisory boards sponsored by pharmaceutical companies including Amgen, Eli Lilly, Merck Sharp & Dohme (MSD), Novo Nordisk, Novartis, and Servier. Andrej Janež has served as a consultant and is on Speakers Bureaus for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Medtronic, and Sanofi. None of the above had any role in this article, which has been written independently, without any financial or professional help, and reflects only the authors' opinion, without any role of the industry.

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Author Contributions

A.J. and M.J. performed conceptualization; M.J. wrote and drafted the preparation; A.J. and M.J. wrote, reviewed, and edited; all authors have read and agreed to the published version of the manuscript.

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