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MINI REVIEW

Semaglutide as Treatment for Obesity in Adolescents

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Abstract

Background: Semaglutide was recently approved to treat obesity in adolescents.

Main objective: To provide a critical appraisal of semaglutide as anti-obesity agent in adolescents.

Methods: Pubmed search up to May 19, 2023. Search terms were obesity, semaglutide, safety, phentermine/topiramate, liraglutide, dulaglutide, exenatide. Clinical trials, prospective and observational studies were included.

Results: The STEP TEENS was a double blind, randomized trial that evaluated semaglutide 2.4 mg/week in addition to lifestyle changes in 201 adolescents (62% women) with obesity with mean body mass index (BMI) 37.0 kg/m2. After 68 weeks, difference between semaglutide and placebo in reduction of BMI (the primary outcome) was -16.7% (95% CI, -20.3 to -13.2). Corresponding difference in weight loss was -17.7 kg (95% CI, -21.8 to -13.7). Proportions of subjects who had ≥5% weight loss at 68 weeks were 73% and 18% with semaglutide and placebo groups, respectively. In the semaglutide group, reduction in BMI was evident (>5%) after 3 months, reached a nadir in 52-58 weeks then plateaued. Overall, the safety profile of semaglutide in adolescents mimics that in adults, except for higher incidence of gall bladder disease, and allergic reactions (rash and urticaria) in adolescents. Premature discontinuation of treatment due to adverse effects occurred in 5% of semaglutide-treated patients compared with 4% of placebo-treated subjects.

Conclusions: Semaglutide is a promising addition to pharmacological therapy of obesity in adolescents. Further studies are needed to demonstrate its long-term efficacy and safety, particularly in various ethnic minorities and in patients with concomitant type 2 diabetes..

Key Words: *Obesity; Semaglutide; Phentermine/Topiramate; Weight loss; Safety*

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Introduction

Data from the National Health and Nutrition Examination Survey (NHANES) showed increased prevalence of obesity (defined as BMI for age ≥ 95th percentile) and severe obesity (BMI for age ≥120% of the 95th percentile) among adolescents aged 12 to 19 years [1]. From 1999-2000 to 2017-2018, obesity in this age group increased from 16.0% (95% CI, 14.5%-17.6%) to 20.9% (95% CI, 18.5%-23.5%) and severe obesity from 5.3% (95% CI, 4.4%-6.4%) to 7.6% (95% CI, 6.1%-9.4%) (P for trend <0.001) [1]. These incremental rates were primarily driven by increases in obesity in Blacks and Mexican American youth [1]. Obesity in such young age may have grave health consequences later in life. In a prospective cohort US study of mean follow-up of 35 years, hazard ratio for a fatal cardiovascular (CV) event in adulthood increased by 44% per unit increase in the z score of BMI at the ages of 3 to 19 years [2]. The increased risk was independent of gender and race (Blacks vs Whites/Others) [2]. In a national study from Israel, there was a graded increase in the risk of death in both genders from CV causes and all causes that started among participants between 50th to 74th percentiles of BMI [3]. Unfortunately, pharmacological therapy of obesity in adolescents is of limited efficacy and tolerability. For instance, orlistat (120 mg tid) was approved by the Federal Drug Administration (FDA) to treat obesity at age older than 12 years. In a randomized trial including adolescents aged 12-16 years, mean weight paradoxically increased 0.53 kg with orlistat and 3.14 kg with placebo after 54 weeks [4]. Moreover, frequency of gastrointestinal adverse effects occurred in 9-50% in the orlistat group compared with 1-13% in the placebo group [4]. The glucagon-like peptide-1 receptor (GLP-1) agonist, semaglutide 2.4 mg/weekly, already approved to treat obesity in adults, has shown similar success as weight loss promoting agent in adolescents [5,6]. In June 2022, The FDA approved phentermine/topiramate extended-release (Qsymia) for treating obesity in adolescents (ages 12-17) based on its acceptable efficacy and safety [7,8]. More recently, in December 2022, the FDA approved semaglutide 2.4 mg (Wegovy) for treatment of weight loss in adolescents aged 12 years and older [9]. In fact, despite the lack of head to head trials, available data suggest that semaglutide is more effective than phentermine/topiramate in promoting weight loss in adolescents (Table 1). The main purpose of this article is to provide appraisal of semaglutide as a new promising drug for treatment of obesity in adolescents.

Semaglutide for Treatment of Adolescents with Obesity

The STEP TEENS trial was a double-blind, randomized, placebo-controlled multinational study [5] (Table 1). The primary end point was the percentage change in BMI from baseline to week 68 [5]. After a 12-week lifestyle intervention phase, a total of 201 adolescents, 12 to <18 years-old, underwent randomization in 2:1 ratio to receive once-weekly subcutaneous semaglutide 2.4 mg (n=134) or placebo (n=67) with continuation of lifestyle changes to the trial end. The starting dose of semaglutide was 0.25 mg/week to be escalated gradually over 16 weeks to reach the target dose of 2.4 mg/week. At week 68, the mean change in BMI was -16.1% and 0.6% in the semaglutide and placebo groups, respectively, with an estimated difference -16.7% (95% CI, -20.3 to -13.2, P < 0.001) [5]. Semaglutide-treated individuals lost a mean weight of -15.3 kg compared to a weight gain of 2.4 kg with placebo, difference being -17.7 (95% CI, -21.8 to -13.7) [5]. The proportions of participants who lost ≥ 5% weight with semaglutide and placebo were 73% and 18%, respectively, with an odds ratio 14.0 (95%

CI, 6.3 to 31.0). Of note, the corresponding OR in obese adults was 11.2 (95% CI, 8.9 to 14.2) in the STEP1 trial [6]. Proportions of subjects who lost ≥20% of weight were 39.5% with semaglutide and 3.4% with placebo [5]. Inspection of the time course of weight changes with semaglutide revealed that the decrease in BMI was approximately 5% after 12 weeks, and reached maximum reduction at approximately 52 weeks, followed by a plateau [5]. After withdrawal of semaglutide, there was a rapid rebound of BMI, but it was still well below baseline BMI at 7 weeks after withdrawal [5]. It should be emphasized that the contribution of lifestyle changes to the weight loss was negligible as reflected by the marginal average increase (and not a decrease) in BMI in the placebo group by 0.6% at 68 weeks [5].

TABLE 1

Comparison of semaglutide and phentermine/topiramate for treatment of obesity in adolescents

	Semaglutide [5]	**Phentermine/Topiramate (PHEN/TPM) [7]**
Subject groups and number (n)	Semaglutide n=134 vs placebo n=67	Top-dose PHEN/TOP n=113, Mid-dose PHEN/TOP n= 54, placebo n=56
Age	15.4	14.0
Percentage females	62%	54%
BMI	37.0	37.8
Weight (kg)	107.5	106.1
Follow-up	68 weeks	56 weeks
Completion of treatment	90% in both groups	65% with top-dose, 75% with mid-dose, 57% with placebo
Difference in BMI vs placebo	-16.7% (95% CI, -20.3 to -13.2)	-10.4% (95% CI, -13.9 to -7.0)
Difference in weight (kg) vs placebo	-17.7 (95% CI, -21.8 to -13.7)	-15.8 (95% CI, -18.8 to -12.8) with top-dose and -12.1 (95%, -15.5 to -8.6) with mid-dose
Proportions of subjects with ≥ 5% reduction in BMI	76% with semaglutide vs 23% with placebo	47% top-dose, 39% mid-dose vs 5% with placebo
Proportions of subjects with ≥15% reduction in BMI	56% with semaglutide vs 5% with placebo	28% with top-dose, 13% with mid-dose vs 0% with placebo
Timing of nadir of BMI	52-58 weeks	48-52 weeks
Discontinuation of drug due to adverse effects	5% with semaglutide vs 4% with placebo	1% with top-dose, 0% mid-dose, and 3.6% with placebo

Abbreviations: BMI: body mass index in kg/m^2.

Effects of semaglutide on cardiovascular risk factors in obese adolescents

In the STEP TEENS trial, weight loss with semaglutide was associated with significant reductions in plasma levels of glycated hemoglobin (-0.3 percentage points vs placebo), low-density lipoprotein cholesterol (-7% vs placebo), triglycerides (-30.2% vs placebo). However, semaglutide did not have significant effects on blood pressure and high-density lipoprotein cholesterol [5]. The amelioration in some CV risk factors might virtually decrease CV events later in life, but this has to be proven by long-term prospective studies.

Effects of semaglutide on growth and quality of life in obese adolescents

Semaglutide had no significant effects on growth parameters and mental health [5]. Scores of "physical comfort" domain of impact of weight on quality of life-kids (IWQOL-Kids) improved with semaglutide versus placebo, but there was no significant difference in remaining domains (body esteem, social life and family relation) [5].

Safety of semaglutide

In general, semaglutide was well-tolerated by obese adolescents. Thus, at week 68, 90% of participants completed semaglutide therapy, with vast majority of them (87%) completed the trial at the target dose of 2.4 mg/week [5]. Moreover, discontinuation of semaglutide due to adverse effects was close to placebo, 5% and 4%, respectively [5]. As in adults, gastrointestinal disorders (nausea, vomiting and diarrhea) were the commonest adverse effects of semaglutide occurring in 62% of subjects compared with 42% with placebo [5]. Heart rate increased with semaglutide versus placebo; 3.5 beat/min (95% CI, 0.3 to 6.7), but not CV disorders (7.5% with semaglutide versus 10.4% with placebo) [5]. Overall, the safety profile of semaglutide in adolescents appears similar to that in adults, except for greater incidences of cholelithiasis/cholecystitis (4% vs 0% with placebo), dizziness (8% vs 3% with placebo), rash (3% vs 0% placebo) and urticaria (3% vs 0% with placebo) [5,9].

Mechanisms of Weight Loss Induced by Semaglutide

The anti-obesity activity of semaglutide is likely multifactorial via appetite and hunger suppression, improved control of eating, reduced food cravings, and possibly delay gastric emptying [10]. Interestingly, in the STEP TEENS trial, decreased appetite was reported by only 6% of semaglutide-treated patients versus 4% with placebo.

Limitations of semaglutide

Both genders were not equally represented in STEP TEENS trial, with majority being women (62%). In a small study of 32 obese adolescents, Nathan et al. [11] found greater response of females compared to males in terms of weight loss response to exenatide. If this applies to semaglutide, positive results of STEP TEENS trial may have been amplified by inclusion of higher female participants. Unfortunately, the investigators of STEP TEENS trial did not report weight loss classified by gender. In addition, majority of participants were Whites (79%), whereas ethnic minorities with higher prevalence of obesity, such as Blacks and Hispanics were underrepresented, 8% and 11%, respectively. Moreover, the number of subjects in STEP TEENS in the semaglutide group (n=134) was relatively small.

Use of other GLP-1 agonists in adolescent obesity

Liraglutide in doses up to 3.0 mg subcutaneously/day (Saxenda) was the first GLP-1 agonist approved for treatment of adolescent obesity in December 2020 [12,13]. However, efficacy

of liraglutide for weight reduction was limited, with 4.6% decrease in BMI (95% CI, -7.1 to -2.1) compared with placebo after 56 weeks. Likewise, weekly exenatide failed to maintain body weight in adolescents after hypocaloric diet (approximately 1,400 kcals/d) [14]. Thus, after 52 weeks of termination of hypocaloric diet, mean BMI increased by 4.6% and 10.1% in the exenatide and placebo groups, respectively [14]. In another randomized trial of weekly exenatide, placebo-corrected weight loss was only 3 kg after 24 weeks [15]. Recently, dulaglutide at doses of 0.75 and 1.5 mg/week was evaluated for treatment of type 2 diabetes in obese adolescents (mean BMI 34.1 kg/m2) [16]. After 26 weeks, no significant effects of dulaglutide were demonstrated on BMI or body weight [16]. Therefore, so far, semaglutide is the most effective GLP-1 agonist for promotion of weight loss in adolescents.

Conclusions and Current Needs

While direct head to head comparison is lacking. present data suggest that semaglutide is the most effective and likely safest drug approved for treatment of obesity in adolescents. However, several gaps in information must be addressed. First, weight loss rapidly rebounds after semaglutide withdrawal implying ongoing therapy to maintain weight loss. Thus, its efficacy and safety should be evaluated in long-term (i.e. beyond 2 years) studies. Second, these studies should include a balanced adolescent population with equal enrollment of both sexes, and adequate representation of ethnic minorities such as Hispanics and Blacks who are mostly affected by obesity burden. Third, the STEP TEENS trial included only 8 patients with type 2 diabetes. Since obesity is one of the strongest risk factors for type 2 diabetes in adolescents, future trials should be designed to assess efficacy and safety of semaglutide in obese adolescents for prevention and treatment of type 2 diabetes. Fourth, animal studies suggest that semaglutide may not be safe during pregnancy. The manufacturer recommends discontinuation of semaglutide in women at least 2 months before they plan to become pregnant to account for the long half-life of semaglutide.

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