Pharmacotherapy in Pediatric Obesity: Current Status and Future Prospects

Karachaliou F*, Skarakis N, Simatos G, Boudouvi E, Spyropoulou T and Papaevangelou V

Unit of Pediatric Endocrinology and Diabetes, 3rd University Department of Pediatrics, Attikon University Hospital, Greece

Abstract

As obesity is principally a biologically mediated disease, biologically based interventions are often needed to counter the compensatory biological adaptations designed to maintain body weight at high levels. Pharmacotherapy can serve as an adjunctive treatment to lifestyle modification in some children and adolescents with obesity, especially those with severe forms of the disease and/or comorbidities. Despite the increasing number of anti-obesity drugs recently approved for the treatment of obesity in adults, few medications have been evaluated in terms of safety and efficacy in pediatric obesity. This mini review aims to provide some principles for the use of pharmacotherapy in pediatric obesity, summarizes results of some of the most important clinical trials on approved and “off-label” obesity medications and discusses some new options for the future of research on this field.

Keywords: Pediatric obesity; Pharmacotherapy; Anti-obesity agents; Weight loss

Introduction

Childhood obesity has globally an epidemic character with higher prevalence in developed countries, and higher rate of increase of prevalence in developing countries [1]. Even more alarming is the increase in prevalence of severe obesity, defined as BMI 20% above the 95th BMI percentile or BMI≥35kg/m² [2]. Severe obesity is associated with serious comorbidities including insulin resistance, and type 2 diabetes mellitus, hypertension, dyslipidemia, nonalcoholic fatty liver disease, obstructive sleep apnea, musculoskeletal problems, ovarian hyperandrogenism and psychosocial problems such as depression and anxiety [2,3]. Additionally many obese children, are already at the stage of prediabetes which is associated with development of micro- and macro-complications [4,5] This stage has been estimated to progress to clinical diabetes with an annual rate of 5-10% in adults [6]. In a prospective study of obese adolescents with severe insulin resistance and impaired glucose tolerance (IGT), 24% developed diabetes type 2 during a 21 months follow-up period, despite regular lifestyle modification intervention [7]. Unfortunately, treating obesity and especially the severe form, through lifestyle modification (behavioral treatment, healthy diet and enhancement of physical activity) has moderate effectiveness in younger children and poor in adolescents [8,9]. In a study including 648 children and adolescents with severe obesity, only 2% of adolescents succeeded in achieving and maintaining a clinically meaningful weight loss by lifestyle modification [8]. It appears that lifestyle modification can have considerable and durable effect only when applied intensively and uninterruptedly in highly motivated individuals. Studies have shown that intensive intervention (obligatory calories’ restriction, multiple individual or/and group counseling sessions, daily exercise and multiple clinical visits) can lead to weight loss from 4.3 to 7kg (4.5-6.5% of body weight) during first year of application, while regular intervention has only poor results in the majority of children and adolescents [10-14]. Moreover, the majority of these lifestyle intervention studies are short term (6months-2years) and in most cases the benefit is eliminated from the rebound weight gain after the end of intervention [15].
It is important to acknowledge that obesity is a complicated and multifactorial disease necessitating a multifaceted approach. Energy balance is regulated from homeostatic and non-homeostatic mechanisms which can be dysregulated in the event of obesity [16]. Following weight loss (when energy stores are depleted) homeostatic mechanisms which are affected by neurotransmitters and gut hormones promote increased food consumption and decreased energy expenditure. Hence weight loss is followed by decrease in levels of leptin, insulin and triiodothyronin and an increase in insulin sensitivity and plasma ghrelin levels [17]. These changes stimulate appetite, decrease sympathetic nervous system tone and energy consumption and enhance lipogenesis, thus facilitating weight regain. Non homeostatic mechanisms, the nature of which has not been entirely elucidated, including reward, cognition and emotional factors associated with food intake also participate in weight regain. It is believed that palatable food hyper-consumption has caused habituation to rewarding neural dopamine signaling. The weight loss is perceived as reward deficiency and leads to compensatory increase of food consumption [16]. Obviously these counter regulatory adaptations are observed in long term cases of obesity and are expected to persist for at least 12 months following weight loss and may even be permanent [18]. Therefore, it is reasonable to expect that the therapeutic approach must often combine lifestyle modification (focusing in external environment changing) with pharmacotherapy/ bariatric surgery (focusing in internal biological environment changing) in order to be efficient and durable. This mini review focuses on pharmacotherapy as an adjuvant treatment to lifestyle modification, targeting homeostatic and non-homeostatic mechanisms of obesity in children and adolescents.

**Indications for Pharmacotherapy**

Despite the significant role of pharmacotherapy in obesity management and the increasing number of anti-obesity drugs approved for adults, only a few drugs have been assessed and fewer approved in children and adolescents with obesity. There is no consensus on the use of anti-obesity drugs in pediatric obesity regarding the appropriate age of treatment initiation and the necessity of treatment in obesity not associated with comorbidities.

The criteria for adult obesity pharmacotherapy include: a) BMI>27kg/m² with at least one obesity-related co-morbidity such as diabetes, sleep apnea, hypertension or hyperlipidemia or b) BMI>30kg/m² with or without comorbidity. Based on these established criteria, modified indications have been proposed for children and adolescents: a) class 1 obesity (BMI≥95th percentile for age and sex or BMI>30kg/m² whichever is lower;) in the presence of at least one obesity-related co-morbidity or b) Class II (BMI≥120% of 95th percentile for age and sex or BMI>35kg/m² whichever is lower) and Class III obesity (BMI≥140% 95th percentile for age and sex or BMI>40kg/m² whichever is lower) irrespective of the presence of co-morbidities [19]. Clinically meaningful weight loss has been defined as BMI z-score reduction between 0.20-0.25 s.d. over 6-12 months which is equivalent to a 5% change in BMI which has been associated with improvements in cardiovascular and metabolic risk factors in adults [20]. Regarding the duration of treatment, it is recommended that medication should be continued if a >5% BMI reduction from baseline is maintained at 12 weeks or if arrest or slowing of weight gain is considered to be a reasonable clinical outcome [19]. Results and implications of the relatively small number of pediatric clinical trials of approved and off-label obesity drugs are discussed below.

**Medication Available for Pediatric Obesity-FDA Approved**

Orlistat is the only FDA approved medication for obesity ≥12 years of age. It inhibits gastric and pancreatic lipase, thus reducing hydrolysis of food triglycerides to FFA. In the proposed dose of 120mg trice a day with meals, decreases fat absorption from food by 30%. In a recent meta-analysis [20] including 779 adolescents 12-18 years old, with mean BMI 37.4kg/m², there was a slightly higher improvement in BMI in the group with orlistat: -0.94 [95% CI, -1.58 to -0.30] vs placebo group : -0.50 (95% CI, -7.62 to 6.62), with absolute weight change varying between +0.5 to -5.5kg in the orlistat group. In a randomized-controlled study assessing the effect of orlistat combined with lifestyle modification for 1 year on 352 adolescents resulted in a significant -2.61kg placebo-subtracted weightloss (p<0.001) [10]. In general, orlistat treatment had a modest effect on cardiometabolic risk factors in contrast to data from adults where orlistat resulted in significant improvement of serum lipid profile and decrease od diabetes type 2 incidence [21,22]. The most common side effects were abdominal pain, flatus with discharge fatty/oily stool, increased defecation, and fecal incontinence. In conclusion orlistat produces small weight loss with no significant cardiometabolic benefit. The limited efficacy and low tolerability of the drug limits its clinical usefulness.

Phentermine is FDA approved for age >16 years for short-term treatment (12 weeks). It has also been used as off-label drug in obese children <16 years or as long-term monotherapy. Phentermine is an amphetamine analogue that has been used in USA from 1959 in combination with topiramate [phentermine/topiramate extended-release] for obesity in adults. It produces appetite reduction, acting directly in hypothalamic satiety centers through catecholamine release [23]. In a small retrospective study, 25 adolescents [mean age 16.1±1.3 years] who were treated with phentermine plus lifestyle modification were compared to 274 adolescents with only lifestyle modification. At 6 months, a reduction of -4.1% BMI (95% CI: -7.1, -1.0%; p=0.009) with phentermine plus lifestyle modification therapy was reported compared to lifestyle therapy alone [24]. The most commonly reported side effects are increase in heart rate and blood pressure, nervousness/and or insomnia. Less frequently, dizziness, dry mouth, difficulty sleeping, irritability, nausea/vomiting, diarrhea and constipation have been reported.
It must not be co-administered with MAO inhibitors because of hypertensive crisis risk.

**Non FDA-approved medication with evidence from off-label use in pediatric obesity**

Metformin is FDA-approved in USA and Europe for the treatment of type 2 diabetes in adults and children >10 years old. The mechanism of action includes the suppression of hepatic gluconeogenesis, reduction of intestinal glucose absorption and small improvement of insulin sensitivity [25]. The mechanisms of weight loss, although not entirely known, include mainly the activation of AMP-activated protein kinase, the inhibition of ghrelin secretion and inhibition of dipeptyl peptidase 4 (DPP-IV) via glucagon-like peptide-1 (GLP-1) mediated reduction in caloric intake [26,27]. Although it has not official approval for use in obesity, metformin has been extensively used in many studies in children and adolescents without diabetes type 2. Recent meta-analysis [20] including 616 individuals aged 6-19 years from 8 randomized-controlled studies [28-35] compared the use of metformin for 6-12 months to placebo. It was concluded that metformin in a dose varying from 1-2 gr/day produced a small statistically significant reduction of BMI -score by -0.1 (95% CI, -0.17 to -0.03) and of BMI by -0.86 (95% CI, -1.44 to -0.29) [20]. In 6 out of the 8 studies, inclusion criteria comprised hyperinsulinemia, insulin resistance, impaired glucose tolerance (IGT) [28,30-34]. In one of these studies, subjects with IGT or abnormal HbA1c were excluded [35]. On the whole, mean weight change varied from -2.27 kg to +2.27 kg with metformin and from -0.91 kg to +5 kg with placebo. Metformin was well tolerable with minimal discontinuation rate (<5%). No cases of lactic acidosis, hypoglycemia, rhabdomyolysis or hypertransaminasemia have been reported in children. The most commonly observed adverse effects were gastrointestinal symptoms (nausea, vomiting, and loose stools/diarrhea, bloating, flatus). Regarding cardiometabolic risk factors the comparison between metformin and placebo showed a modest superiority of metformin in reducing glucose, insulin and HOMA-IR and no benefit in change lipid profile or blood pressure [28,30,32,33,35].

Moreover, although meta-analysis showed only a small weight improvement of obese children, metformin has been proved notably effective in loss of weight gain related to anti-psychotic drugs in non-diabetic children [weight loss: -4.1%, 95% CI 2.2–6.0] [36] and in adults with weight gain during mood/cognitive disorders leading to emotional eating, steroid use etc [37,38]. Metformin has also been extensively used in polycystic ovary syndrome in adolescents with or without obesity with good results in terms of weight loss and improvement of lipid profile and hirsuitism [39-41]. It is also noteworthy that metformin administration in adults with prediabetes was reported to lead to significant reduction in incidence of type 2 diabetes [42]. Similar studies have not been performed in children and adolescents to date, but it is very likely that metformin could have an important role in prevention of type 2 diabetes in high risk pediatric population. Until to date, the management of obese children with prediabetes is individualized. The European Society of Endocrinology and the Pediatric Endocrine Society guidelines propose to avoid metformin use only for weight loss in obese children [43]. But they also suggest that the negative health impact may justify medication. Hence, in each case different aspects such as the metabolic profile, the comorbidities, the capacity of lifestyle modification etc should be considered in treatment decision. In conclusion, metformin is a safe drug with proven benefits and can be the first choice in certain cases. Further research is needed for the evaluation of its efficacy in the prevention of type 2 diabetes and long-term benefit in children and adolescents.

**Topiramate although it is FDA approved for epilepsy ±2 years of age and migraine prophylaxis in ≥12 years old, it has been shown to have beneficial effect on weight loss [44]. A possible mechanism of action is the inhibition of glutamate and carbonic anhydrase receptors and the enhancement of γ-aminobutyrate (GABA) activity at calcium-sodium cell receptors [45]. Topiramate produces weight loss not only through reduction of food intake, but through increased energy consumption as well [44]. There are limited data from off-label topiramate use in children and adolescents. A small randomized controlled study evaluating topiramate (75 mg daily) in 30 adolescents (12-17 years) with severe obesity, reported approximately a 2% BMI reduction at 6 months compared to placebo following short-term meal replacement intervention. The difference was not statistically significant (-1.9%; 95% CI: -5.2% to +1.5%; P = 0.291) [46]. In another study assessing topiramate (75 mg daily) for at least 3 months plus lifestyle intervention on 28 adolescents with severe obesity, a clinically meaningful BMI reduction was reported (-4.9%, 95% CI: -7.1, -2.8; P < 0.001) [47]. There were not any serious adverse events in both studiew, except for paresthesia [46] in two patients. Paresthesia depression and anxiety have been also reported in studies on adults using phentermine/topiramate ER. There is strong recommendation for adolescents not using the medication during pregnancy, as the drug is a teratogen.

**GLP-1 Receptor Agonists [exenatide, liraglutide]**

Exenatide [GLP-1 receptor agonist] is FDA approved for diabetes type 2 in adults >18 years old. It is administered via subcutaneous injection. It stimulates GLP1 receptors in hypothalamus decreasing appetite and increasing satiety, with subsequent weight loss [48]. In a small, randomized, controlled study the administration of exenatide for 3 months in combination with lifestyle modification in 12 adolescents (9-16 years) with severe obesity produced BMI reduction of -1.7 kg/m²; 95% CI: -3.0 to -0.4, p=0.01), weight loss: -3.9 kg, 95% CI: -7.11 to -0.69, p=0.02) and decrease of insulin levels: -7.5 μU/l, 95% CI: -13.71 to -1.37, p=0.02 [49]. In another randomized controlled trial on 26 adolescents (12-19 years) with severe obesity, exenatide produced a greater compared to controls.
reduction of % BMI of -2.70% (95% CI, -5.02% to -0.37%, p = 0.03) and of weight of -3.26kg, (95% CI -5.87 to 0.66 kg, p=0.02) (total weight reduction 4%) [50]. The medication was well tolerated and the most common side effects were nausea, vomiting, abdominal pain and diarrhoea.

Liraglutide another GLP1 receptor agonist is approved for diabetes type 2 in adults (1.2-1.8mg), for obesity >18 years (3mg) and recently (2019) approved for diabetes type 2 in children >10 years. It was evaluated in a randomized, placebo-controlled, double-blind study in 21 adolescents (12-17 years), BMI ≥30 kg/m² to ≤45 kg/m² [51]. Adolescents were randomized to receive either liraglutide for 5 weeks (0.6mg/week with weekly dose increase to a maximum of 3.0mg) or placebo there was a greater decrease in both BMI and weight in those receiving liraglutide compared to controls, however the difference did not reach statistical significance. Similar randomized double-blind study was performed in 24 children (7-11 years), out of whom 14 received liraglutide (0.3mg daily with weekly increase to 3mg) and 6 received placebo for 7-13 weeks [52]. A significant reduction in BMI z-score was observed (-0.28; p=0.0062). The medication was safe and well-tolerated. The most common side effects were nausea, vomiting, abdominal pain and hypoglycemia. Moreover, there are indications that GLP1 agonists may be useful for weight regulation in patients with syndromic (Prader Willi) or hypothalamic (after tumor, trauma) obesity [53]. In conclusion GLP1 agonists are usually considered as alternative therapy in obese adolescents with type 2 diabetes when metformin and lifestyle modification fail. Lisdexamfetamine (LDX) FDA-approved for attention deficit hyperactivity disorder (ADHD) in children ≥6 years, and recently (2019) approved for diabetes type 2 in adults (1.2-1.8mg), for obesity >18 years (3mg) and injection sites’ induration have been reported. There are great expectations for its use in rare genetic forms of obesity which can lead to obesity: POMC deficiency obesity, LepR deficiency obesity, Prader-Willi syndrome, Bardet-Biedl syndrome, Alström syndrome, POMC heterozygous deficiency obesity, and POMC epigenetic disorders, in an open-label study setmelanotide was administered in two patients with POMC deficiency and produced substantial weight loss [62]. Adverse effects such as dry mouth, darkening of nevi and injection sites’ induration have been reported. There are great expectations for its use in rare genetic forms of obesity which should be considered for children with hyperphagia and severe gradually aggravating obesity at a young age [≤5 years] [63].

Non FDA approved medication for pediatric obesity in the future

Setmelanotide is a candidate for possible future approval for the treatment of monogenic obesity. Mechanism of action: melanocortin-4-receptor (MC4R) agonist. It is currently under evaluation for the management of genetic disorders which lead to obesity: POMC deficiency obesity, LepR deficiency obesity, Prader-Willi syndrome, Bardet-Biedl syndrome, Alström syndrome, POMC heterozygous deficiency obesity, and POMC epigenetic disorders, in an open-label study setmelanotide was administered in two patients with POMC deficiency and produced substantial weight loss [62]. Adverse effects such as dry mouth, darkening of nevi and injection sites’ induration have been reported. There are great expectations for its use in rare genetic forms of obesity which should be considered for children with hyperphagia and severe gradually aggravating obesity at a young age [≤5 years] [63].

Conclusion

Pharmacotherapy may often constitute a useful additional tool to intensive lifestyle modification for the treatment of pediatric obesity for some patients, especially those with severe forms. As energy balance is complicated with mechanisms directing against weight loss, pharmacotherapy often becomes a reasonable choice to target the underlying biology. The need for the development of well designed pediatric obesity trials is stressed to evaluate the long term safety and efficacy of obesity medication in pediatric populations. Furthermore the optimal time for starting, discontinuing, or intensifying treatment remains to be defined.
Moreover, the future of research in the field of pharmacotherapy targets personalized treatment by pairing patients with the best therapeutic option with the lowest risk of side effects. The great heterogeneity in both the etiology of obesity and the responsiveness to therapy indicate that personalized strategies will be more effective than broadly applied treatment schemes.

Acknowledgement

Dr Skarakis, Dr Spyropoulou, Dr Boudouvi contributed in literature review. Dr G Simatos contributed in literature review and editing.

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