

## Drug Therapy in Obese Adolescents

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Article information	Abstract
<p>Article history: Received: 19 Dec 2010 Accepted: 25 Mar 2011 Available online: 30 Oct 2012 ZJRMS 2013; 15(3): 1-6</p> <p>Keywords: Obesity Adolescent Treatment Anti obesity drug.</p> <p>*Corresponding author at: Occupational Environment Research Center, Department of Social Medicine, School of Medicine Rafsanjan University of Medical Sciences, Rafsanjan, Iran. E-mail: zinatsalem@yahoo.com</p>	<p><b>Background:</b> The behavior and dietary treatments are not so successful for extremely obese adolescents. Therefore, using drugs to treat extremely obese children and adolescents are among the modern approaches. This research aims to study the pharmaceutical interventions performed for treatment of obese children.</p> <p><b>Materials and Methods:</b> The strategy of research was using of key words 'obesity', 'adolescence', 'treatment' and 'anti-obesity drugs' were searched in websites of PubMed, Iranian Medical Digital Library, SID, Iran Medex, Magiran. This study reviewed all the available published papers in English and Farsi languages during 2000-2010. The Criteria for exclusion was The papers that had been published on interventions and treatment of eating disorders, type II diabetes or the obesity caused by the secondary syndromes.</p> <p><b>Results:</b> Twelve papers were found as short-term clinical trials and/or long-term follow-ups. In these studies, the positive effects of 'sibutramine' in some studies are shown; although some other side effects are reported as well. A significant weight-loss had been reported on 'orlistat' medicine, but digestive complications had been observed as well. None of the studies had followed up patients for more than one year. Apparently, 'Metformin' requires further studies.</p> <p><b>Conclusion:</b> The FDA has only approved 'sibutramine' and 'orlistat' drugs. But side effects of long-term these drugs have already been unknown. However, it seems that 'orlistat' is applied for <math>\geq 12</math>-year-old children and 'sibutramine' for <math>\geq 16</math>-year-old children.</p> <p>Copyright © 2013 Zahedan University of Medical Sciences. All rights reserved.</p>

## Introduction

Obesity refers to the heaviness over the favorable weight or health weight, which occurs due to the excessive accumulation of fat in body. Overweight and obesity of children are mostly seen in the urban areas [1]. Obesity may occur at any ages. However, it is severely increasing among the children and adolescents [2]. The most common consequences of obesity include the risk of early diseases, increasing mortality in the late of life [3]. Obese children are exposed to high risk of metabolic syndrome development, type II diabetes and cardiovascular diseases [4].

It also includes diseases such as hypertension, lipid disorders, left ventricular hypertrophy (LVH), atherosclerosis [5], apnea, gallstone [4] and nonalcoholic fatty liver disease. 'Social isolation' is considered as another common effect of obesity. Overweight before age 8 causes BMI of an individual to be equal to 41 during adulthood. However, for those whose obesity starts during adulthood, BMI will equal to 35 [6]. The results obtained from a study indicated that more than 60 percent of the overweight children had at least a risk factor of cardiovascular diseases, including hypertension with lipid disorder or disorder in serum insulin and 25 percent had two or more risk factors [7]. In a study conducted on 2008 in one of the southeastern cities of Iran, 6.4 percent of children had abdominal obesity and 11.8 percent had

systolic hypertension [8]. Ann Jessup indicated that 6.5 percent of 8-11 year old overweight children had three or more risk factors of metabolic syndrome. Metabolic syndrome was observed in 43.76 percent of 12-14 year old children [9]. In a research carried out in Iran, 3.9 percent of the obese adolescent girls had metabolic syndrome [10]. The psychological effects of obesity include depression, emotional trauma, stigmatization and discrimination [5]. With respect to the ever-increasing prevalence of obesity, complications, difficulty and failure of the behavioral and nutritional treatments, the use of modern pharmacological approaches have been proposed during the recent years. Accordingly, the present research is conducted to study the pharmacological implications performed to treat extremely obese adolescents during 2000-2010.

## Materials and Methods

The strategy of research in this review article was using of key words 'obesity', 'adolescence', 'treatment' and 'anti-obesity drugs' were searched in websites of PubMed, Iranian Medical Digital Library, SID, Iran Medex, Magiran. This study reviewed all the available published papers in English and Farsi languages during 2000-2010. The Criteria for exclusion was the papers on

interventions and treatment of eating effects, type II diabetes or the obesity caused by the secondary syndromes

About twelve out of 100 obtained papers were in the forms of short-term clinical trials and/or with long follow-ups (six papers related to 'sibutramine', three papers on 'orlistat', and three papers on 'metformin'). No Farsi papers were found on pharmacotherapy.

### Prevalence of Obesity

By 2010, almost 41 percent of the children in eastern Mediterranean regions, 38 percent in European regions, 27 percent in Western Pacific region and 22 percent in southeastern Africa were obese [1]. At present, 155 million overweight children and 45 million obese children live in the world. This problem is not unique for America and the Asian regions suffer from it as well [11]. In a study conducted by Eduardo, 21.2 percent of 11-24 year old Mexican children and adolescents were reported as being obese [12]. In the studies conducted in Iran, malnutrition has been studied in terms of shortages and overfeeding. However, obesity has been reported more than underweight. In two research carried out in southeastern Iran, the prevalence of obesity among children and adolescents were 21.1 and 13.6 percent, respectively [13-14].

### Initial Evaluation in Obesity Diagnosis for Treatment

The initial evaluation and knowing the grade and type of obesity are important for treatment. Therefore, the measuring tool to diagnose and grade obesity and its risky cases applied for screening includes anthropometric measurements using height and weight measurement. Waist circumference measurement is used to determine the content and distribution of body fat. The most modern anthropometric criterion in children is the application of Body Mass Index diagrams, which was presented by CDC (Centers for Disease Control) in 2000. A new categorization has been offered in the Panel of Experts of Obesity Treatment Committee for 2-18 year old children. The BMI exceeding or equal to 85 is defined as overweight and the BMI exceeding or equal to 95 is defined as obesity. The percentile exceeding or equal to 99 is recognized as the boundary of severe obesity diagnosis [5]. Measuring the waist circumference is performed to diagnose the children who are within the risk profile of cardiovascular disease [15]. In tables offered by the Inter Diabetes Federation, the percentile equal to or exceeding 90, as per age and gender, is considered as abdominal obesity [4]. Accessing this information on the clinical fields provides advancements for the following studies [16].

### Measurement of Biochemical Parameters

Application of laboratory parameters is not cost-effective. However, they can be used to confirm the anthropometric measurements. Laboratory parameters include fasting sugar, total cholesterol, LDL, HDL, TG,

total cholesterol to HDL cholesterol ratio, liver enzymes and urine analysis. In the first stage, especially with the central obesity, it is necessary to measure the sugar and fat. In the second stage, testing of liver and kidney enzymes should be performed [15].

### Assessment of Psychiatric Symptoms and Depression

Twenty to sixty percent of the obese people suffer from depression. In screening the obese people, this syndrome is studied at the second stage. Taking antidepressants drugs by these patients would lead to avoidance of some of pharmacologic treatments related to the weight lost drugs.

### Weight-Loss Objectives

The most important objective is providing a child with his/her natural growth and development, concurrent with the decrease of fat and body weight. For most children, controlling weight is considered the preliminary objectives. Among the early measures to reach this objective is the weight-loss about 450 grams within one month. The long-term objective of treatment is reduction of BMI of children below the percentile of 85 in terms of age and gender. Hyper lipidemia, hyper insulinaemia, acanthosis nigricans and hypertension should be evaluated [7].

### Obesity Treatment in Children and Adolescents

Obesity treatment is difficult and expensive [4]. The new studies have offered modern point of views as per the body physiological harmony. Yet, obesity treatment of children has not been successful [3]. A behavioral comprehensive approach is the most effective method for treatment. However, most studies have reported 1-4 kilogram weight-loss; although, the participants remained obese at the end of the treatment [17].

Children are different from adults as far as biological, behavioral, social, growth stage and age biological development characteristics are concerned [5]. The difference of the obese children and adults is related to the specific physiological conditions of children, growth, puberty, development, fat distribution, symptoms with obesity, side effects of drugs, psychological factors, cognitive development, stimulation and motivation factors, their conception of body condition, their capacity in short-term consideration, lack of interest to sanitation, acceptance of risky behaviors and environmental effects (controlling family, school, dining environment, changing groups, influence of advertisement, having access to opportunities and sitting activities).

### Studies Conducted on Pharmacotherapy of Obese Adolescent

There is no sufficient information on taking weight loss drugs for children before the age of puberty. In addition, taking these drugs by this group should be supervised by the clinical trials [15]. 'Sibutramine' and 'orlistat' drugs have effects on energy intake, appetite, changing energy

consumption and absorption of nutrients [18]. By absorbing fat, 'orlistat' causes digestive disorders, including steatorrhea, crump bloating, and stool incontinence. Sibutramine is a reuptake inhibitor (RI) of monoamine, which increases adrenergic, serotonergic and dopaminergic and controls appetite. The side effects of this drug include increasing hypertension and heartbeats [5]. At present, there are some other drugs than 'orlistat' and 'Sibutramine'. However, either their mechanism is unknown or they are at the clinical research phase. They might be available within the following decades [19]. The obesity treatment panel workgroup has left some important questions unanswered which are as follows:

1-Which patients are the best candidates for pharmaceutical implications in terms of age, BMI level and having accompanied symptoms? 2-Should the pharmaceutical implications be limited for adolescents? 3-What behavioral implication together with pharmacotherapy is the best method to have the maximum effect? 4-As far as treatment implication is concerned, what comparison is more favorable between the rest of drugs and placebo? 5-What occasion would be appropriate to take the best evaluation on sufficiency and safety of pharmaceutical implications? 6-What documents are sufficient to use the recommended pharmaceutical treatment in clinical measures [5] ?

With respect to the above questions, the obesity treatment panel has made some important recommendations as follows:

-For 2-6 year old children, whose BMI exceeds percentile 95 without any medical problem related to weight, it is recommended to keep their weight.

-For 2-6 year old overweight children with diseases or older children, whose BMI exceeds percentile 95 without any obesity-related medical problems, it is recommended to lose weight.

-For overweight children with medical diseases such as pseudotumor cerebri, apnea at rest, bone problems, type II diabetes and hypertension, urgent treatment should be performed to reduce weight.

-In addition, children with psychological and social complications and more risks of diseases related to obesity in the future, children with a family history of obesity, type II diabetes and cardiovascular disease in first-degree or second-degree family need pharmacotherapy [7].

According to Dietz idea, which is confirmed by Rober, weight-loss drugs can be taken by adolescents only based on the clinical experience. These drugs should solely be taken as an appendix together with behavioral modification, family therapy, and must-be activity increase (lifestyle changes). These two researchers proposed that 'sibutramine' and 'orlistat' to be used by the excessive obese adolescents (nearly 4 percent of children and adolescents) [17, 18]. Godo et al. stated that obesity treatment strategy have progressed in the world. While lifestyle changes are not effective, pharmacotherapy can be used for obese adolescents as an optional choice for treatment and 'sibutramine' and 'orlistat' drugs may be considered as good treatments

[20]. Limited number of implications has been considered on the approved drugs as follows.

### Sibutramine

In a clinical trial study, the effect of 10 mgr of 'sibutramine' on body composition and energy consumption of twenty-four 12-17 year old obese adolescents (11 boys) was examined. 'sibutramine' and 'placebo' were prescribed with an energy-limited diet and continued for 12 weeks. After implications, a reduction was formed in BMI. During the follow-up, BMI was reduced in the placebo group, but it remained constant in sibutramine group. There were no differences in the change of body fat percentage in both groups [21].

Correa et al. studied the effect of sibutramine on satiety because this substance, in spite of anorectic (anti-appetite) substances, reduces food intake by stimulating the satiety center. In this study, which was carried out through the double-blind randomized method on adolescents, the effect of 10 milligrams of sibutramine and placebo was compared. However, this drug had no effect on satiety [22].

Godoy studied the adequacy and safety of 'sibutramine' in obese adolescents. He treated sixty 14-17-year-old adolescents in a clinical trial during 6 months. In the first six months, the samples received placebo and a low-calorie diet and they were recommended to increase activity with a regular sports activity. In the second six months, the samples were divided into two groups receiving 'sibutramine' and 'placebo'. The sibutramine and placebo groups lost  $10.3 \pm 6.6$  kg and  $2.4 \pm 2.5$  kg respectively. The mean of BMI in Sibutramine group decreased significantly and no side effects were observed as per echocardiography, blood pressure and heartbeat in the case group [23].

Rober et al. studied the treatment of obese adolescents after the age of puberty at 13-17 in a clinical trial of behavior therapy with Sibutramine. In the first six months, the weight and body mass index in the experimental group were reduced 7.8 kg and 8.5 kg respectively, whereas weight and BMI in the control group were reduced 3.2 kg and 4 percent respectively. Feeling of satiety in the experimental group indicated a significant reduction. Weight gain of 0.8 kg was observed in the group receiving 'sibutramine' from months seven to twelve. These researchers believe that the weight loss drugs should only be used experimentally for adolescents and children [17]. In a clinical trial, Budd et al. treated thirty-four 13-17 year old African boys and girls living in America and 45 Caucasians in two groups of family-based behavior therapy with 'sibutramine' and 'placebo'. In the sixth month, the percentage of change in BMI and weight reduction was significantly more in the Caucasian control group, whereas no statistically significant difference was observed among the African group between the experimental group and control group. However, regardless of the treatment group, those who had lost more than 5 percent of the initial BMI, their waist

circumference decreased significantly. 'sibutramine' could create a significant reduction in triglyceride, high-density lipoprotein (LP), glucose, insulin and degree of insulin resistance in the Caucasian experimental group. However, it could create a significant reduction in triglyceride, insulin, and insulin resistance. 'Sibutramine', with behavior therapy could create useful changes in the risk factors of heart disease and metabolic in adolescents. However, the long-term effects of this drug, its acceptance, safety and its effects are vital on reducing the heart and metabolic disease.

A general consensus can be reached through further studies [24]. The Obesity treatment panel workgroup examined the studies conducted on 'sibutramine'. The studies, which were controlled in 2 six-months and one year, created a significant weight reduction (7.2 kg against 3.2 kg). Insulin improved HDL cholesterol and TG against the placebo group. However, the side effect of this drug on blood pressure and heartbeats was considerable and its long-term effects on cardiovascular diseases are still unknown [5]. Also, the treatment by 'sibutramine' was performed in a clinical trial study from July 2000 to February 2002.

Four hundred and ninety eight 12-16 year old participants with the BMI of at least 2 units more than the mean and percentile 95 (upper limit 44 kg/m<sup>2</sup>) were selected in 33 clinics. Ten milligrams of 'sibutramine' or 'placebo' was prescribed together with behavior therapy. If BMI did not lower to 10 percent during 6 months, the drug under study would increase to 15 mg. Seventy six percent of Sibutramine group and 62 percent of placebo group participants continued the study up to the end. After 12 months, the effects of 'sibutramine' were significant. The members of sibutramine group showed further improvement in triglyceride, HDL cholesterol, insulin and sensitivity to insulin. However, with the use of 'sibutramine', the tachycardia rate increased and by stopping the use of drug, tachycardia rate lowered [25].

### Orlistat

In a clinical trial, Maahs et al. studied the effect of orlistat (120 milligram, three times a day) during 6 months on decreasing BMI. Forty 14-18-year-old adolescents with the mean BMI of 40 entered the study. The fasting sugar of the participants was evaluated at the time they entered the study, after 3 months and 6 month. At the end of the study, there was a significant difference between the BMI of both groups, whereas the laboratory evaluation showed no differences between the two groups. In this study, 'orlistat' indicated a significant decrease in BMI during 6 months. It made a brief but significant decrease in BMI during one year. In another clinical trial, BMI of 26 percent of the children who received 'Orlistat' decreased by 5 percent, while the BMI of children of placebo group decreased by 15 percent. The side effects of Orlistat in the form of digestive diseases have exceeded the placebo group [5].

In a study conducted by Chanoine, 539 American and Canadian obese adolescent (12-16) with the BMI exceeding or equal to 2 units upper the percentile of 95

were examined in 32 centers. For one-year dose, 120 mg 'orlistat' was taken for 3 times a day with low-calorie diet (30 percent of fat), exercises and behavior therapy. A decrease equal to 55 percent in BMI and an increase about 31 percent were observed in orlistat group and placebo group respectively. Meanwhile, the BMI decreased in both groups in the first 12 weeks. Later, the BMI remained constant in orlistat group, but increased in placebo group. In the end of the study, the weight of orlistat and placebo groups increased 0.53 kg and 3.14 kg, respectively ( $p=0.0001$ ). Using the Dual X-Ray method, the fat mass between the two groups had a significant difference. Waist circumference decreased in orlistat group, while it increased in placebo group. The digestive implications were observed in orlistat group from 9 to 50 percent and in placebo group from 1 to 13 percent. The study indicated that prescribing orlistat for one year for adolescents has no effect on their immunity system, but it may cause digestive implications [26].

Cduffie et al. studied the safety, tolerability and quality of treatment by 'orlistat' on twenty adolescents with the mean age of 14±2-year-old and BMI (44.1±12.6). The participants were examined before and after taking 'orlistat' (120 mg, three times a day). While taking the prescribed 'orlistat', the participants were taking Multivitamin containing vitamin D for three months. In addition, they were going on a diet, doing exercises and employing the strategy of behavior changes.

Generally, there were minor side effects and they were limited to digestive effects, which were reduced over time. The weights of the participants were reduced significantly ( $p<0.01$ ) and BMI was reduced to 1.9±2.5 kg/m<sup>2</sup> with  $p<0.0002$  compared with the initial time. The total cholesterol, LDL cholesterol, fasting insulin and fasting glucose were reduced by taking 'orlistat'. Sensitivity to insulin was increased. This study indicated that the side effects of this drug on adolescents are similar to adults. However, its real advantages against the common treatments should be studied in interventional studies with more participants [27].

### Metformin

Although, the abovementioned drugs have been approved by the FDA (Food and Drug Administration) to treat severe obesity, some other drugs are also prescribed by physicians to treat obesity and to reduce appetite, as 'Metformin' is used as an insulin sensitizer in treatment of some obesity diseases such as type II diabetes. In a clinical trial, Burgert et al. treated 28 adolescents aged 15±1.3 year old by 'metformin' and 'placebo'. Their BMI exceeded 40.3, they resisted insulin and they had sensitivity to insulin index. Treatment by 'metformin' had been tolerated well in this group. BMI and subcutaneous fat were reduced significantly in the experimental group. In addition, this group had 35 percent improvement in sensitivity to insulin. Short-term use in controlling cardiac autonomic and recovery process in sensitivity to insulin had a favorable effect.

The long-term effects of 'metformin' may be effective on improvement of metabolic and cardiac results of obese

adolescents [6]. The effect of 'metformin' on the obesity of children and adolescents was studied in a systematic research [5]. In a clinical trial, 320 people were qualified to enter the research. In these studies, 'metformin' reduced BMI within the range of 42 kg/m<sup>2</sup> and reduced insulin resistance by two percent. It seems that 'metformin' reduces BMI and insulin resistance with an average adequacy and within a short period. However, further studies should be carried out to confirm its effect on obesity [28].

In a review study, 'metformin', 'orlistat' and 'sibutramine' were studied. The studies were greatly different in terms of design, interventions, evaluation criteria and methodology quality. The meta-analysis of the findings, which performed within 6 to 12 months follow-up, indicated weight reduction. Some limited side effects were observed as well. This review research specified that lifestyle interventions combined with other issues, compared with standard care or self-help can create a significant reduction. As far as the clinical considerations are concerned, it can lead to weight loss of children and adolescents. For the obese adolescents, 'sibutramine' or 'orlistat' should be prescribed together along with behavior interventions. For this approach, it is required to study the adverse effects of drugs accurately [29].

A research was conducted to study the effect of 'metformin' to reduce BMI and the risk of metabolic heart disease in obese adolescents. This systematic review of the intervention studies examined the trial lasted more than six months on under 19-year-old samples and its results were meta-analyzed. Five studies and 320 participants were eligible to enter this study. 'Metformin', versus placebo, could reduce Body Mass Index up to 1.42 kg/m<sup>2</sup>. It also reduced assessment index of insulin resistance to 2.01 using HOMA-IR (Homeostasis Model Assessment of Insulin Resistance).

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