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Drug Therapy of Childhood Obesity

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Abstract

Over the last decades obesity prevalence among children and adolescents has increased dramatically and coincidentally the well-established comorbidities associated with the excess body weight have become a major health challenge worldwide. Despite intensive lifestyle modifications, patients severely obese might warrant adjunctive interventions. Although, antiobesity pharmacotherapy is emerging as a promising adjunctive strategy for adults who fail to respond to behavioral strategies, most of agents are not licensed for the treatment of obesity in children and adolescents.

The aim of this narrative review is to discuss possible mechanisms by which drugs lead to weight loss and to summarize data concerning FDA-approved anti-obesity focusing on relatively small body of evidence concerning pharmacological options for managing pediatric obesity.

Lifestyle and behavioral interventions remain the mainstream of the obesity treatment in children, but adjunctive pharmacotherapy may be beneficial in some patients. Although well-designed clinical trials are needed to properly evaluate safety and efficacy of anti-obesity drugs in children and adolescents, pediatricians dealing with obesity should know what drugs are available. Early identification, during childhood, of individuals who most likely respond favorably to a specific anti-obesity agent will be possibly more efficacious in addressing the global obesity epidemic, than pharmacotherapies started in older ages.

Keywords: Pharmacotherapy in childhood obesity; Liraglutide; Naltrexone/Bupropion; Orlistat; Metformin; Lorcaserin; Phentermin/Topiramate

Introduction

Over the last decades the overall prevalence of obesity is increasing worldwide. Importantly, despite the prevalence of obesity among children is lower than that among adults (in 2015, a total of 107.7 million children and 603.7 million adults were obese), epidemiologic data have showed that the rate of increase in childhood obesity has been greater than in adult obesity [1].

Obesity-related comorbidities comprise a wide variety of severe chronic diseases that may involve almost all any organ systems and may have significant long-term detrimental effects on both health and life expectancy. Overweight and obese children are likely to stay obese into adulthood, moreover, obesity during pediatric age increases the risk for disability and premature death during adulthood [2]. The World Health Organization (WHO) states that childhood obesity is one of the most serious public health challenges of the 21st century [3] and recognizes that prevention is the most feasible option for curbing the childhood obesity epidemic since current treatment practices are largely aimed at bringing the problem under control rather than affecting a cure [4].

To date, the management of obesity in children is primarily focused on modifying behaviors that lead to excessive energy intake and insufficient energy expenditure [5]. However, when prevention interventions fail, and a child has been diagnosed with obesity, this approach often represents an unsuccessful feat for physicians dealing with pediatric obesity. Indeed, behavioral strategies and interventions relying solely on individual "self-control" have almost no effect especially on severely obese adolescents [6]. Established that food intake and physical activity are crucial to ensure an adequate energy balance, it is overly simplistic to ascribe to the patient's poor adherence to lifestyle instructions the blame for suboptimal weight loss outcomes. Indeed, this viewpoint fails to account for the complex interplay between central nervous system, gastrointestinal tract, and endocrine system that regulates and governs the physiology of energy balance regulation [7]. Therefore, for children who have failed to lose weight through lifestyle modifications, a more-intensive intervention is advocated to prevent serious medical and psychosocial comorbidities associated with this chronic and refractory disease. In adults, anti-obesity pharmacotherapy is emerging as adjunctive strategy for individuals who fail to respond to lifestyle interventions.

Drug therapy

2013 AHA/ACC/TOS (American Heart Association/ American College of Cardiology/ The Obesity Society) guideline for obesity management and later the Endocrine Society clinical practice guideline on the pharmacologic management of obesity suggest that pharmacotherapy may be considered, as adjunct to behavioral modification, for adults with a body mass index (BMI) ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 with weight-related comorbidities, such as hypertension, dyslipidemia, type 2 diabetes, and obstructive sleep apnea [8,9].

Although the Food and Drug Administration (FDA) has approved six medications for adults (Table 1) and only one them (orlistat) received the approval also for pediatric patient's ≥ 12 years of age, pediatricians

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Drug	Mechanism of action	Average weight loss	Age of use	Side effects
ORLISTAT	Inhibition of gastric and pancreatic lipases, reducing the absorption of fat into the intestinal lumen and increasing the excretion of fats with feces	**2,4%** (after 4 year of treatment)	**>12 years old**	Fecal urgency, fecal incontinence, flatulence with discharge, oily stools, oily evacuation and increased defecation
METFORMIN	Inhibition of intestinal glucose uptake, increasing insulin sensitivity in peripheral tissues and reducing hepatic gluconeogenesis.	**3%** (after 6-12 months of therapy)	**>18 years old**	Vomiting, nausea, diarrhea, meteorism.
PHENTERMIN/ TOPIRAMATE	Phentermine is a noradrenergic agonist, topiramate is an agonist of GABA receptors; their association produces an anorectic effect and increases energy expenditure	**5%** (after 1 year of treatment)	**>18 years old**	Paresthesia, dizziness, constipation, dysgeusia, dry mouth.
LORCASERIN	Lorcaserin is a selective 5-HT2C receptor agonist that works at the central nervous system level by inhibiting food behaviour.	**5%** (after 1 year of treatment)	**>18 years old**	Headheache, nausea, nasopharyngitis, dizziness. Symptomatic hypoglycaemia in patients with T2DM who take oral hypoglycaemic agents. Euphoria, hallucinations, abnormal dreams and impaired perception were described in case of overdose (> 40-60 mg in a single dose)
NALTREXON/ BUPROPION	Naltrexone acts as a non-selective opioid receptor antagonist. Bupropion works by inhibiting norepinephrine and dopamine transporters	**6,4%** (after 56 weeks of treatment)	**>18 years old**	Constipation, nausea, vomiting, headache, dry mouth, dizziness, diarrhea and insomnia. an increased risk of suicidal thoughts and neuropsychiatric symptoms
LIRAGLUTIDE	Liraglutide is an agonist of the GLP-1 receptor and acts in peripheral regulation of appetite through an anorectic action and increasing the release of insulin from the pancreas in response to the increase in glucose levels.	**6%**	**>18 years old**	Abdominal pain, nausea, headache, diarrhea, dyspepsia hypoglycemia. Rare side effects are kidney damage, suicidal thoughts, pancreatitis and gallbladder disease

Table 1: FDA approved medications for adults and children.

dealing with obesity should know what drugs are available for the management of obese patients.

The goal of using pharmacotherapy to treat obesity is to increase patient's adherence to lifestyle changes and to overcome the biological changes caused by weight loss.

The 2015 Endocrine Society guidelines recommended monitoring the effectiveness of drugs used for weight loss a drug that leads to weight loss of 5% of total body weight after 3 months of therapy is considered effective and, if approved, should be continued in the long term. If the drug is ineffective, not tolerated due to side effects or unsafe for the patient, the dosage should be reduced or discontinued and alternative therapy should be considered [9].

Pharmacological therapy may cause a slight reduction in term of BMI and body weight in the short term, but its long-term efficacy and tolerability is not known to ensure a better outcome in terms of long-term body weight maintenance. Moreover, there are few data on the follow-up after the suspension of drug therapy [10].

There are various mechanisms by which drugs lead to weight loss: reducing the sense of hunger, increasing basal metabolic rate or reducing nutrient absorption.

Neuroregulation of hunger and satiety

The energetic balance of the organism is regulated by distinct neuronal circuits and signaling molecules inside the hypothalamus and the brain stem. Hypothalamic circuits including arcuate nucleus and brain stems receive signals of satiety, hunger and adiposity of peripheral derivation and process them by regulating nutrition and metabolism [11].

A subpopulation of neurons of the arcuate nucleus expresses oressigene peptides such as the neuropeptide Y (NPY) and the agouti-related protein (AgRP). These neurons project to second-order neurons located in the paraventricular nucleus, in the dorsomedial, mid-ventral and lateral hypothalamus [12-14].

Another group of neurons of the arcuate nucleus expresses anorhexigenic peptides such as the transcript regulated by cocaine and amphetamine (CART) and the stimulating hormone α-melanocyte (α-MSH) [12].

A-MSH is cleaved by the hormone precursor pro-opiomelanocortina (POMC) and binds to melanocortin-4 receptors (MC4R) [15].

Roux-en-Y gastric bypass utilizes the MC4R signaling pathway for weight loss induced by surgery, decreased food intake and increased energy expenditure [16].

Arcuate nucleus dysfunction, such as increased NPY/AgRP activity to the detriment of POMC neurons, may explain some forms of obesity. Furthermore, NPY, AgRP, MC4R and CART could be future targets of anti-obesity drugs [17-19].

At the level of the lateral hypothalamus/peri-fornical area, second-order neurons are present, wich express orexigen neuropeptides such as orexin (hypocretin) and a melanin concentration hormone (MCH). Prepro-orexin, a precursor of 130 amino acids, is processed in orexin A and orexin B, peptides of 33 and 28 amino acids, respectively [19]. While Orexin A binds orexin 1 and 2 with high affinity, orexin B binds to orexin 2 receptors only [20]. MCH acts on MCH1 and MCH2 receptors [21], expressed in frontal cortex, nucleus accumbens, arcuate nucleus, amygdala, and ventral medial hypothalamus [22].

Paraventricular nucleus neurons express anorhexigenic peptides, including the thyrotropin-releasing hormone, corticotropin-releasing hormone, and brain-derived neurotrophic factor (BDNF) [23-25].

The dorsal vagal complex located in the brainstem, spreads by transmitting peripheral signals to the hypothalamus via vagal afferent fibers from the intestine [26].

Norepinephrine (NE) and serotonin (5-HT) are monoamine neurotransmitters synthesized in the brainstem and act by regulating food intake [27]. NE is synthesized in the dorsal vagal complex and the locus coeruleus. From these areas Neuronal fibers project to the

hypothalamus, thalamus, cortex and spinal cord [28,29]. NE is an α1- and α2-adrenoceptors agonist [30].

The balance between α1- and a2-adrenoreceptors within the paraventricular nucleus modulates the action of various adrenergic agonists on the diet [31].

Neurotransmitters and hormone involved in the regulation of appetite

Fenfluramine is an indirect 5-HT agonist. Fenfluramine acts releasing 5-HT from vesicular stores and inverting 5-HT transporter function was approved in association with phentermine for the treatment of obesity [32].

Sibutramine is a norepinephrine-5-hydroxytryptamine reuptake inhibitor and has been approved by the FDA for subjects aged 16 years and over as an anti-obesity drug [33]. Sibutramine is effective in the treatment of obesity [32].

Cardiovascular, neuropsychiatric and carcinogenic adverse effects have been reported with this drug [10,34-37].

The trial of Sibutramine Cardiovascular Outcomes (SCOUT) showed an increase in serious non-fatal cardiovascular complications, including systolic and diastolic hypertension and increased heart rate, for which this drug was withdrawn from the market in 2010 [34,38-40].

Anorectics act on the central nervous system to modify the release and reuptake of the neurotransmitters involved in the regulation of appetite: serotonin, norepinephrine, and dopamine [41].

There is no data to demonstrate its long-term safety or efficacy in pediatric populations and for this reason no drug among anorectics is currently approved for pediatric use.

The adipocyte-derived hormone leptin provides the regions of the brain responsible for controlling caloric intake information on the triglyceride content of the adipocytes, as well as on energy and macronutrient composition of the recent meal. Low plasma levels of leptin produce alterations of the sense of satiety, causing hyperphagia [42].

Leptin deficiency leads to increased activity at the level of hypothalamic neurons that regulate appetite by releasing orexigenic peptides and a decrease in the release of anorexigenic factors [43].

The potential ability to improve body weight in obese subjects of some hormones and neurotransmitters involved in the pathway of hypothalamic leptin is being studied.

The endocannabinoid system seems to play a crucial role in both central and peripheral control of energy balance and glucose metabolism. Selective cannabinoid receptor 1 inhibitors (CB1), such as rimonabant (SR141716), cause a decrease in body fat through reduced caloric intake and increased energy expenditure [44,45].

The cannabinoid receptor 1 (CB1R) is a G protein-coupled receptor activated by endocannabinoids, and is implicated in the regulation of a series of physiological mechanisms.

This receptor widely expressed in the central nervous system, exerts an action to control appetite and regulate body weight leading to a thorough study of this function that resulted in the clinical development of rimonabant for the treatment of obesity, later withdrawn because of psychiatric side effects reported [46,47].

The exact mechanism of action with which the selective CB1 inhibition improves insulin sensitivity and on which target tissues exerts its action is not yet fully understood. In this regard it has been seen that brown adipose tissue (BAT) is an important modulator of energy expenditure and glucose metabolism [48]. Recently, the concept that in the adult BAT is not metabolically functioning is considered out of place because it plays a central role in the pathogenesis of diabetes and obesity [49].

The analysis of the data obtained from the "Rimonabant in Obesity" studies have shown that inhibition of CB1R in Peroxic tissues improves the risk of cardio-metabolic risk such as insulin resistance, hypertriglyceridaemia and fasting insulin, stimulating the interest in the study of CB1R functions in peripheral tissues [46].

The peripheral CB1R antagonists promote the formation of cells expressing UCP1 in WAT and BAT, improving lipolysis and decreasing hepatic steatosis. Therefore, this second generation of CB1R antagonists, which selectively block only peripheral CB1R, may prove to be remarkably effective *in vivo* in inducing weight loss and reducing cardio-vascular risk factors. CURRENTLY few molecules are available with a brain-plasma ratio ≤ 3% and their efficacy and safety *in vivo* is not yet demonstrated. *In vivo* studies and in-depth pharmacological analyzes will be needed to define their potential as future therapies for the treatment of chronic diseases such as T2DM and obesity [50].

The most common adverse effects of rimonabant are: anxiety, nausea and depression. Because of psychiatric adverse effects, especially increased suicidality, in 2006 EMA and in the 2007 the FDA did not approve the use of Rimonabant for the treatment of obesity.

There are currently no drugs of the class of CB1 receptor antagonists authorized by FDA for the treatment of obesity in adults and children.

FDA approved medications for adults and children

Orlistat: USA FDA has approved the use of orlistat for adults and adolescents over 12 years of age [51]. In Europe, instead, orlistat can be used only in individuals aged 18 years old or over. The European Medicines Agency (EMA) has not approved its use in pediatric age (Table 1).

Ingested fats are metabolized into free fatty acids and monoglycerides from gastric and pancreatic lipases, allowing intestinal absorption.

Orlistat works by inhibiting gastric and pancreatic lipases, reducing the absorption of fat into the intestinal lumen and increasing the excretion of fats with feces [52].

The recommended dose of orlistat is 120 mg 3 times a day to be taken with lipid meals are also available 60 mg capsules.

In XENDOS trial, a randomized, prospective, placebo-controlled trial conducted on 3305 patients, orlistat (vs placebo) led to a reduction of 2.4% of total body weight compared to the initial weight after 4 years. This trial has also demonstrated that orlistat improves insulin sensitivity, glycemia, blood pressure levels and lipid profile, reducing the risk of developing T2DM compared to placebo [53].

Chanoine et al. performed an important placebo-controlled, randomized double-blind trial of 539 subjects aged between 12 and 16 years for 52 weeks with a 3: 1 orlistat-placebo ratio. both groups received multivitamin supplement and a hypocaloric diet associated with physical activity was prescribed. BMI declined progressively until week 12 in both groups, and subsequently stabilized in the group taking orlistat but increased in the control group. Approximately 35% of participants were withdrawn in each group [54].

A subsequent analysis of the same study shows that the early loss of weight in subjects treated with orlistat is a strong predictor of long-term success of the treatment itself. In fact there is a strong correlation between treatment response after 12 weeks and amount of weight lost at the end of the study (52 weeks) [55].

The most common side effects described in adolescents and children are similar to those described in adults, and are related to the increase in fat concentration in the intestinal lumen. The most frequent are: fecal urgency, fecal incontinence flatulence with discharge, oily stools, oily evacuation and increased defecation [56].

In all four orlistat trials analyzed by Mead E et al. in a Cochrane systematic review were reported on side effects: gastrointestinal symptoms such as fatty stools, oily stools and fecal urgency, upper respiratory tract infections and headaches were the most common side effects found [10].

Orlistat leads to modest weight loss. In addition, there are no studies that demonstrate its long-term efficacy in adolescents over a year of therapy. Another factor that limits adherence to treatment in adolescents is the administration three times a day. Although currently orlistat is the only FDA-approved treatment for obesity in individuals under 16 years of age, it does not appear to offer promising prospects in adolescents with severe obesity.

Metformin: Metformin is approved in Europe and the USA for the treatment of T2DM in adults and children over 10 years of age. Its use for the treatment of obesity is off-label.

Metformin is a biguanide that acts by inhibiting intestinal glucose uptake, increasing insulin [57,58].

Metformin reduces caloric intake through an unclear mechanism. Studies have shown that the effects of metformin treatment on weight loss could be related to its ability to reduce energy intake in children with obesity and hyperinslinism, suggesting that metformin may act by modulating the orexigenic neuropeptide Y signaling pathway (NPY) [59].

A modest weight loss, a reduction in insulin-resistance and a delay in the development of T2DM in non-diabetic obese adults were observed [60].

At the moment few studies have been conducted on obese adolescents not affected by T2DM.

A randomized, placebo-controlled multicentric, double-blind study in adolescents submitted the participants to 48 weeks of prolonged-release therapy with daily metformin hydrochloride or placebo associated with a lifestyle modification. 92 obese adolescents completed a 4-week run-in phase with single-blind placebo. Subsequently, the 77 subjects who had joined the first phase were randomized. Reduction of BMI in the metformin group compared to the control group was statistically significant: 0.9 kgm^2 in the metformin group compared to 0.22 kgm^2 in the placebo arm, although treatment with metformin did not modify total fat mass, abdominal fat or insulin resistance [61].

Treatment with metformin causes on average a reduction of 3% BMI after 6-12 months of treatment, improves glucose metabolism and insulin resistance and reduces the risk of developing T2DM in obese adults with impaired glucose tolerance. However, its efficacy has not yet been demonstrated by studies on obese children.

The main side effects described are usually transient and include: vomiting, nausea, diarrhea, meteorism.

Metformin administration should be avoided in patients with renal insufficiency, in critically ill patients, and before administration of contrast agent [62].

Phentermine/Topiramate: Phentermine-Topiramate Extended-Release (ER) is the first drug association approved by the FDA in 2012 for chronic obesity therapy in adults. Is a fixed-dose combination containing immediate-release phentermine hydrochloride and prolonged-release topiramate to be administered once a day in the morning. The dose should be gradually increased, starting from an initial dose of 3.75/23 mg for 2 weeks, followed by the 7.5/46 mg dose. Before reaching the maximum dose of 15/92 mg the previous dose should be tested for at least 3 months. If therapy is not tolerated it is recommended to scale the dose or discontinue the medication in 3-5 days to avoid the risk of triggering a seizure [40].

Phentermine is a noradrenergic agonist, and topiramate is an agonist of GABA receptors.

Phentermine is an FDA-approved anorectic drug for short-term therapy in adult obesity. It works by increasing the adrenergic tone, decreasing the caloric intake and also increasing the basal metabolism. Phentermine is structurally related to the amphetamine family [63].

Topiramate is an anti-epileptic drug with GABA-ergic action. weight loss was observed in epileptic patients receiving topiramate. The data obtained from studies performed on obese adults suggest that topiramate results in an effective weight loss compared to placebo (from 4.5 to 16.36 kg for topiramate compared to 1.7-8.6 kg for placebo). Furthermore, topiramate in association with antipsychotic therapy seems to decrease the weight gain induced by the antipsychotics themselves [64,65].

The combination of two drugs with a different mechanism of action should improve the result compared to monotherapy. Weight loss compared to placebo is 5% of initial weight after 1 year of therapy [66].

The most common side effects of Phentermin/Topiramate are: paresthesia, dizziness, constipation, dysgeusia, dry mouth [52].

Administration of topiramate is contraindicated in pregnancy due to the increased risk of fetal oro-facial clefts. In adolescents of childbearing potential it is advisable to prescribe an oral contraceptive before starting therapy with Phentermin / Topiramate [67].

There are no sufficient data on the efficacy and safety of using Phentermin / Topiramate for the treatment of obesity in children. The most common side effects described in pediatric trials are: dizziness, paresthesia, nasopharyngitis, dry mouth, memory impairment, anorexia [68].

Lorcaserin: Lorcaserin was approved by the FDA for the chronic treatment of obesity in adults in 2012. Lorcaserin is a selective 5-HT2C receptor agonist that works at the central nervous system level by inhibiting food behavior. The mechanism by which it works by reducing caloric intake and inducing satiety is not clear.

The recommended daily dose is 10 mg twice daily or 20 mg prolonged release once daily to treat adults with BMI ≥ 30 or ≥ 27 associated with one or more co-morbidities such as dyslipidemia , hypertension or T2DM [31,69].

A multicenter phase III clinical study of 3182 obese adults (BLOOM) showed that 47.5% of subjects treated with lorcaserine compared with 20.3% of the control group lost 5% of initial body weight after 1 year; the weight loss was on average 5.8 kg for the group that had taken lorcaserine compared to 2.2 kg of the control group [70,71].

The most frequent side effects are headheache, nausea, nasopharyngitis, dizziness, Locarserin could cause symptomatic hypoglycaemia in patients with T2DM who take oral hypoglycaemic agents [71].

Euphoria, hallucinations, abnormal dreams and impaired perception were described in case of overdose (>40-60 mg in a single dose) [72].

There are currently no studies on children and adolescents for which the use of locarserin is to be considered experimental in pediatric age.

Naltrexone/ Bupropion: Naltrexone SR/Bupropion SR is an association of drugs approved by the FDA in 2014 for the treatment of obesity in adults with BMI of 30 or higher, or with BMI above 27 with obesity-related disorders [31].

Naltrexone acts as a non-selective opioid receptor antagonist used for the treatment of alcohol and opioid dependence [73].

Bupropion works by inhibiting norepinephrine and dopamine transporters and is used for the treatment of nicotine addiction and depression [74].

For the treatment with naltrexone SR / bupropione SR a slow dose increase is recommended to reduce the appearance of nausea. The drug is available in 8/90 mg combined dose tablets and should be taken once a day for 1 week. From the second week of therapy, one dose per tablet is administered twice a day and then, from the third week, two oral tablets are taken in the morning and one tablet per os in the evening before dinner. During the fourth week the maximum dose (32/360 mg) is reached with two oral tablets twice a day. The average weight loss after 56 week of treatment is 6.4% *vs.* 1,2% of the control group [9].

The most frequent adverse effects described in more than 5% of participants are constipation, nausea, vomiting, headache, dry mouth, dizziness, diarrhea and insomnia an increased risk of suicidal thoughts and neuropsychiatric symptoms is described. Furthermore, the increase in heart rate and blood pressure limits its use in patients with cardiovascular diseases [72].

Bupropion should be avoided in patients with a history of eating disorders or epilepsy [75].

Liraglutide: Liraglutide was first approved by FDA in 2014 for chronic management of obesity in adults at a dose of 3 mg per day with subcutaneous injections. Is also approved a lower dose of liraglutide at a dose of 1.8 mg daily for the treatment of T2DM in adults [76-78].

Liraglutide is a long-acting agonist of the GLP-1 receptor. It has a half-life of about 13 hours compared to the endogenous GLP-1 that lasts a few minutes.

GLP-1 is a hormone released from the small intestine that plays a crucial role in the peripheral regulation of appetite through an anorectic action. It also works by increasing the release of insulin from the pancreas in response to the increase in glucose levels.

The dose of liraglutide should be slowly increased within 4 weeks.

The initial dose is 0.6 mg daily the first week with an increase of 0.6 mg every week until reaching the final dose of 3 mg per day.

The most frequent side effects are: abdominal pain, nausea, headache, diarrhea, dyspepsia hypoglycemia. Rare side effects are kidney damage, suicidal thoughts, pancreatitis and gallbladder disease [77].

In a study conducted on obese without T2DM, Astrup et al. reported a mean weight loss of 4.8-7.2 kg in the Liraglutide group compared to 2.8 kg in the control group after 20 weeks of therapy [79].

3 recent short-term studies in pediatric subjects have confirmed that the tolerability, efficacy and safety of liraglutide are similar to adults [80,81].

Danne T et al. included 21 obese subjects aged 12 to 17 with the Tanner 2-5 stage, who were randomized to 3.0 mg daily liraglutide or placebo. The described side effects are similar to adults. The results suggest that the approved dose for weight management in adults may be appropriate even in adolescents [82].

Conclusions

Lifestyle and behavioral interventions remain the mainstream of the obesity treatment at any age. Data derived from adults suggest that pharmacological therapy as an adjunct therapy might offer benefits for those patients who fail to respond to lifestyle modification alone. Over the last years medications approved to treat obesity in adults has increased, but most of these drugs are not licensed for the treatment of obesity in children and adolescents. Well-designed clinical trials are needed to properly evaluate safety and efficacy of these anti-obesity drugs in children and adolescents. It is now established that "globesity" originates mainly in the first years of life. Therefore, coupled with lifestyle prevention strategies, early identification, during childhood, of individuals who most likely respond favorably to a specific anti-obesity agent will be possibly more efficacious in addressing the global obesity epidemic, than pharmacotherapies started in older ages.

Authors' Contributions

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