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Pharmacotherapeutic Options for the Management of Obesity in Children

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Abstract

Obesity in children has increased dramatically over the past few decades, becoming a major public health concern worldwide. Effective treatments must be implemented to reduce the burdens related to diabetes, cardiovascular disease, and mortality associated with obesity. While lifestyle interventions, such as diet and exercise, are often the first-line treatment for obesity, additional approaches may also be necessary for some individuals. Medications can help individuals achieve significant weight loss targets. This review aims to investigate the potential of pharmacological treatments for managing obesity in children, both currently available and future approaches. This article will discuss utilizing current molecular understanding to develop appropriate pharmacotherapeutic approaches that can lead to improved therapeutic outcomes. This review of anti-obesity drugs evaluates current therapies such as orlistat, which inhibits gastrointestinal lipases and reduces dietary fat absorption. Phentermine suppresses the appetite through the augmentation of norepinephrine levels. Liraglutide is a glucagon-like peptide-1 [GLP-1] receptor agonist that influences appetite regulation and glucose metabolism. Setmelanotide is a synthetic analog of α-melanocyte-stimulating hormone [α-MSH] that acts as a potent melanocortin receptor [MC4R] agonist, which promotes feelings of fullness and reduces appetite. Overall, only a limited number of anti-obesity drugs are approved for children. More research is necessary to evaluate the efficacy and safety of currently available drugs for pediatric obesity. In the future, developing safe and effective pharmacological interventions that target different mechanisms of action for childhood obesity is an important area of research that can potentially improve the health outcomes of millions of children worldwide.

Keywords:
Cannabinoids, nephrotoxicity, hepatotoxicity, the endocannabinoid system, delta-9-tetrahydrocannabinol, cannabidiol

Introduction

The escalating global prevalence of individuals suffering from obesity poses a significant challenge to healthcare systems worldwide. Initially, obesity, which is a metabolic complication, was regarded as a condition resulting from excessive calorie intake and a sedentary lifestyle. However, the prevalence of overweight and obesity is on the rise globally. According to the Global Burden of Disease Study in 2017, it was estimated that approximately 124 million children [aged 5-19 years] were affected by overweight or obesity [1]. This increase in childhood obesity has been attributed to changes in dietary patterns and physical activity behaviors [2, 3]. Obesity is associated with a higher individual susceptibility to the onset of type 2 diabetes and cardiovascular diseases [4, 5] and a decline in overall health-related quality of life [6].

Successful approaches to addressing obesity encompass lifestyle interventions, complementary medicine, and alternative therapies, such as pharmaceutical interventions or bariatric surgery [7]. A comprehensive conservative treatment approach involving various professionals such as doctors, nutritionists, and psychologists to enhance physical activity and reduce caloric intake remains the preferred method for addressing overweight/obesity. However, the effect on body weight is generally limited, and a significant proportion of patients tend to regain weight within five years [8].

The prevalence of childhood obesity has reached epidemic levels worldwide, necessitating comprehensive and evidence-based interventions. Thus, the existing conservative and surgical treatment methods have significant drawbacks. Given the persistent need to address the growing number of children with obesity, this review aims to explore pharmacological treatment options and their potential for future approaches. Specifically, it will emphasize leveraging current molecular understanding to develop proper pharmacotherapeutic approaches and achieve better therapeutic outcomes.

Orlistat

Utilizing orlistat for childhood obesity is a well-known approach for managing excess weight in the pediatric population, including children and adolescents. Orlistat, a selective inhibitor of gastrointestinal lipases, offers a unique approach to weight management by reducing the absorption of dietary fats [9]. Orlistat [marketed as Xenical®] is the sole medication approved by the U.S. Food and Drug Administration [FDA] for the extended treatment of obesity in adolescents aged 12 years and above. It is important to note that this approval pertains to the FDA, not the European Medicines Agency [EMA].

Orlistat functions locally within the gastrointestinal tract, inhibiting pancreatic lipase and preventing the breakdown of dietary triglycerides into absorbable fatty acids. Studies have shown that orlistat operates through various mechanisms, including inhibiting lipase activity which is the most well

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documented, influencing neurotransmitters such as glutamate and dopamine, and increasing glycogen levels [10]. This leads to a decrease in caloric intake and fat absorption. The undigested fat is then eliminated in the feces, resulting in a negative energy balance and potential weight loss. Clinical studies have demonstrated that orlistat, combined with lifestyle modifications, can significantly reduce body mass index [BMI] and improve metabolic parameters in obese children [11]. Randomized controlled trials have shown that orlistat treatment is associated with greater weight loss than a placebo, although the degree of weight reduction varies among studies [12-14].

Orlistat is generally well-tolerated in children [15], with adverse effects primarily related to its mode of action. These include gastrointestinal symptoms such as oily spotting, discharge of oily feces, and fecal urgency [16]. Liver injury has been reported but is extremely rare [17]. Due to its ability to hinder fat absorption, orlistat also restricts the absorption of fat-soluble vitamins such as A, D, E, and K [18]. Other rare side effects included gastrointestinal and neurodegenerative events. Orlistat is commonly associated with several gastrointestinal side effects, including diarrhea, flatulence, bloating, stomach discomfort, and dyspepsia. However, *in vivo* animal studies have indicated that orlistat can lead to intestinal villi damage [19] and hepatotoxicity [20]. Moreover, there have been connections between orlistat use and the development of neurodegenerative disorders [21]. Close monitoring and appropriate patient education regarding potential side effects are essential to ensure the safe use of orlistat in children.

Although orlistat shows promise as a pharmacological intervention for childhood obesity, further investigation is necessary. Long-term studies are needed to assess its sustained effectiveness, impact on comorbidities, and potential benefits beyond weight reduction.

Phentermine

Phentermine is commonly prescribed for short-term weight loss interventions owing to its appetite-suppressing effects. This medication aids weight reduction by decreasing food consumption, primarily through the augmentation of norepinephrine release and potentially inhibiting its reuptake, thereby elevating its levels.

Possible adverse effects of phentermine include elevated heart rate and blood pressure. The FDA has approved the use of phentermine for short-term treatment [less than 12 weeks] in adolescents aged 16 years and older who have obesity due to limited long-term observations and frequent occurrences of side effects. Recent retrospective data from a small cohort of adolescents indicated a moderate impact on BMI percentage [22]. Studies have indicated that phentermine, in combination with lifestyle modifications, can result in short-term weight loss in adolescents with obesity [23]. However, the magnitude of weight reduction varies across studies, and the long-term efficacy of phentermine in sustaining weight loss and improving metabolic outcomes remains uncertain.

Phentermine has a generally good safety profile, but it is not devoid of risks. Common side effects include increased heart rate, elevated blood pressure, insomnia, and dry mouth. Due to potential cardiovascular effects, phentermine should be used cautiously in patients with preexisting cardiac conditions. Long-term safety data and monitoring potential adverse effects, such as cardiovascular and psychological impacts, are crucial when considering phentermine therapy in children.

Prior to initiating phentermine treatment, a thorough evaluation of each child's medical history, growth pattern, cardiovascular risk factors, and psychosocial aspects is essential. Monitoring vital signs, growth parameters, and potential side effects is necessary during treatment.

Phentermine holds promise as a short-term intervention for childhood obesity; however, it is usually used now in combinations such as phentermine/topiramate. Topiramate [sold as Topamax®] is prescribed for treating epilepsy in children aged two years and above and for managing migraines or cluster headaches in adolescents aged 12 years and above. Its mode of action involves the modulation of neurotransmitters within the central nervous system. In adults, the combined use of topiramate and phentermine is approved for long-term treatment of obesity, as discussed earlier. Furthermore, this combination therapy is also indicated for adult patients with binge-eating disorder and bulimia nervosa [24].

However, the approval of this medication by the EMA has not been granted due to insufficient data regarding the cardiovascular effects of phentermine, its potential for inducing addiction, and the long-term cognitive adverse effects associated with topiramate usage, including impairments in attention, language, and memory [25]. Notably, this drug combination contains phentermine, which classifies it as a controlled substance under the DEA as a Schedule IV substance. Topiramate, on the other hand, functions as a glutamate antagonist, carbonic anhydrase inhibitor, and a gamma-aminobutyric acid agonist, primarily used for treating epilepsy and preventing migraines [26]. The notable weight loss observed in epileptic patients treated with topiramate prompted investigations into its potential impact on obesity through clinical studies. *In vivo* studies have indicated that topiramate may have thermogenic properties and act as a neurostabilizer. Still, its exact mechanisms of action within the central nervous system [CNS] are not yet fully comprehended [27, 28].

Several clinical trials have shown that a fixed-dose combination of phentermine and topiramate can lead to sustained and significant weight loss in most participants for up to 2 years [29]. In a 28-week randomized controlled trial conducted by Aronne et al. [2013], the combination of phentermine/topiramate extended-release [PHEN/TPM ER] was found to be more effective in promoting weight loss. The participants generally tolerated the combination well, with no significant cognitive impairment observed except for some minor attention impairment [30]. In a study involving obese adolescents aged 12 to 17 years, it was found that a higher proportion of adolescents taking moderate and high doses of the PHEN/TPM combination achieved a weight loss of ≥5% compared to the placebo group. The combination of PHEN/TPM promoted significant weight loss without any reported side effects or tolerability issues, highlighting the safety profile of PHEN/TPM in managing obesity in the short and long term [31]. Another study demonstrated that participants taking PHEN/TPM achieved significant weight loss in the long-term. Notably, the PHEN/TPM combination also showed improvements in cardiovascular and metabolic health and reduced incidence of diabetes among the participants [32].

In recent developments, phentermine/topiramate was approved in the United States in July 2022 for chronic weight control in pediatric patients aged 12 years and older, with increased physical activity and a low-calorie diet. Additionally, ongoing clinical studies are exploring the potential of phentermine/topiramate in treating type 2 diabetes in obese patients and addressing sleep apnea [33].

Liraglutide

Liraglutide 3.0, marketed as Saxenda® or Victoza®, is an approved medication for managing type 2 diabetes mellitus and chronic weight management in obese individuals with comorbidities and a BMI of 27 kg/m2 or higher [34]. Liraglutide, in addition to metformin or both, was shown to improve the clinical outcome of type 2 diabetic children [35]. Although it has shown a promising safety profile in these children, Liraglutide is not yet approved for children under 12 as a treatment for obesity. Therefore, liraglutide use in children is an active area of research, and it is expected to be approved soon [36].

The weight-reducing effects of Liraglutide can be attributed to its role as a glucagon-like peptide-1 [GLP-1] receptor agonist. Liraglutide influences appetite regulation and glucose metabolism by binding to GLP-1 receptors in the brain and peripheral tissues. Earlier studies have shown that activating AMP-activated protein kinase [AMPK] in rat L6 myotubes cell lines increases glucose uptake by liraglutide [37]. In the brain, Liraglutide acts on specific regions involved in appetite control, leading to reduced food intake and increased feelings of satiety. Long-acting agonists of the glucagon-like peptide-1 receptor [GLP-1R] impact body weight regulation by modulating food intake and energy expenditure at different regions within the hypothalamus [38]. In peripheral tissues, Liraglutide enhances insulin secretion, suppresses glucagon release, and slows gastric emptying, all contributing to improved glycemic control and reduced calorie intake [39].

Clinical trials have shown that Liraglutide effectively promotes significant and sustained weight loss in many participants [40, 41]. Evidence obtained from randomized controlled trials has demonstrated that liraglutide treatment leads to substantial weight loss, with participants experiencing a mean reduction in weight of 8.0% over 56 weeks [42]. More than half of the individuals receiving Liraglutide achieved weight loss exceeding 5% and 10%, indicating the clinical relevance of this treatment [43]. Similar positive outcomes were observed in a 32-week trial, further highlighting the consistent and significant weight reduction associated with liraglutide therapy [40].

In addition to weight loss, Liraglutide offers other advantages. It has been found to improve cardiometabolic risk factors, including blood pressure, lipid profiles, and markers of inflammation [44, 45]. Moreover, Liraglutide has the potential to enhance glycemic control, making it beneficial for individuals with obesity and type 2 diabetes. Large-scale trials have even demonstrated reduced major adverse cardiovascular events in those treated with Liraglutide, further supporting its positive impact on cardiovascular health. While Liraglutide provides substantial benefits, it is important to consider potential disadvantages and side effects. Common side effects include gastrointestinal symptoms such as nausea, vomiting, diarrhea, and constipation, which typically diminish over time [46]. Less frequent side effects include pancreatitis, gallbladder-related events, and renal impairment, necessitating careful monitoring and consideration of individual risk factors [47].

Although the use of Liraglutide in children is currently not approved, studies evaluating its efficacy in this population have shown promising results. Notably, studies in 2021 involving obese adolescents have demonstrated significant reductions in BMI with liraglutide treatment. The EMA approved using Liraglutide for weight reduction in adolescents aged 12–17 years [48, 49]. Further research is needed to evaluate its long-term safety, effectiveness, and impact on growth and development in pediatric populations. While common side effects may occur, they are generally tolerable and temporary. Therefore, the use of Liraglutide in children requires further investigation, and its molecular mechanisms as a GLP-1 receptor agonist provide a scientific basis for its weight-reducing effects.

Setmelanotide

The leptin-melanocortin signaling cascade influences the regulation of body weight. This cascade involves the interaction of leptin, a hormone released by adipose tissue, with receptors in the hypothalamus [50]. By activating the melanocortin pathway, leptin triggers a series of events that affect appetite and energy expenditure. Within this pathway, pro-opiomelanocortin [POMC] neurons are stimulated, leading to the release of α-melanocyte-stimulating hormone [α-MSH]. α-MSH then binds to melanocortin receptors, primarily MC4R, which promotes feelings of fullness and reduces appetite [51].

Conversely, agouti-related peptide [AgRP] neurons, inhibited by POMC neurons, release AgRP, which acts as an antagonist to melanocortin receptors, resulting in increased appetite and decreased energy expenditure. The intricate balance between POMC and AgRP neurons in the leptin-melanocortin pathway is crucial for maintaining body weight and energy balance [52]. Disruptions in this signaling cascade can contribute to obesity and metabolic disorders. Therefore, understanding the mechanisms of leptin-melanocortin signaling provides valuable insights into potential targets for managing weight and treating obesity.

Setmelanotide is a promising pharmacological intervention for the treatment of childhood obesity. It is a synthetic analog of α-MSH that acts as a potent MC4R agonist [53]. In individuals with rare genetic disorders such as pro-opiomelanocortin [POMC] deficiency or leptin receptor [LEPR] deficiency, there is impaired function of the MC4R pathway, leading to severe early-onset obesity. Setmelanotide has shown remarkable efficacy in these patients, leading to significant reductions in body weight and improved metabolic parameters. Clinical trials have demonstrated its potential as a targeted therapy for children and adolescents with obesity caused by genetic mutations affecting the MC4R pathway. Clinical trials involving individuals with genetic disorders causing severe obesity, such as POMC deficiency and LEPR deficiency, have demonstrated significant reductions in body weight and improvements in metabolic parameters with setmelanotide treatment [54]. Setmelanotide is already approved for treating obesity in children aged six years or older with POMC/ PCSK1 [proprotein convertase subtilisin/kexin type 1] or LEPR deficiencies [55].

One study reported that setmelanotide led to a mean reduction in body weight of approximately 15% in patients with POMC deficiency, with sustained weight loss over a period of 1 to 2 years. Similarly, in individuals with LEPR deficiency, setmelanotide treatment resulted in substantial weight loss, ranging from 10% to 25% of initial body weight. These findings highlight the potential of setmelanotide as a targeted therapy for obesity caused by genetic mutations affecting the MC4R pathway [53, 54, 56]. However, it is important to consider the side effects and limitations associated with setmelanotide use. In clinical trials, the most commonly reported side effects included skin hyperpigmentation and nausea. Some patients also experienced injection site reactions, such as erythema and pruritus. It is worth noting that these side effects were generally mild to moderate in severity and well-tolerated [57].

Another limitation of setmelanotide is its high cost, which may restrict access for many patients [57]. Additionally, the long-term safety and efficacy of setmelanotide beyond the duration of clinical trials are still being investigated. Further research is needed to evaluate its effects on growth, puberty, and potential interactions with other medications.

To sum up, only a few anti-obesity drugs have been approved for use in children, including Orlistat, Phentermine, Liraglutide, and Setmelanotide. These drugs work through different mechanisms of action to target obesity in children. However, further research is needed to determine the safety and effectiveness of these drugs specifically for pediatric obesity. In the future, there is a need to develop safe and effective pharmacological interventions that target various mechanisms of action for managing childhood obesity to improve the health outcomes of obese children worldwide.

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