Systematic Review

A Systemic Review of Pharmacological Management of Pediatric Obesity

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Abstract

Background: There is a growing need for safe and effective treatment due to the rise in child obesity rates worldwide. The effectiveness and safety of pediatric obesity drugs were reviewed in this systematic review based on international research. **Techniques:** PubMed, Cochrane Library, and Embase searches were performed to locate pediatric randomized controlled trials of antiobesity medications. Demographics, medication effectiveness, adverse events, and quality of life were all analyzed. **Findings:** There were 12 studies totaling 4,331 children in the review. The age range of the participants was 8.8 to 16.3 years, and their baseline BMI was between 26.2 and 41.7 kg/m^2. Medication combinations such as phentermine/topiramate, metformin, extended-release metformin, topiramate, exenatide, and liraglutide were frequently studied. The amount that each medication decreased BMI varied somewhat, with liraglutide exhibiting the most decrease (-5.88 kg/m^2). Comparator groups and pediatric antiobesity medication users experienced comparable adverse events and study discontinuation rates. Medication dose adjustments were more common in pediatric cases (10.6% vs. 1.7%; RR = 3.74 [95% CI: 1.51 to 9.26]). Quality of life increased in all trials, however, not specifically for pediatric cases. **Conclusion:** In conclusion, metformin, topiramate, exenatide, liraglutide, and the combination of topiramate and phentermine may lower BMI in children; however, more studies are required to ascertain their long-term safety and effectiveness. Children and adolescents with pediatric obesity may benefit from a tailored, multidisciplinary strategy that incorporates lifestyle modifications, pharmaceutical therapies, and psychological support to assist manage the condition and enhance the health and well-being of those affected.

Keywords: *Adverse events, antiobesity medications, BMI reduction, pediatric obesity, pharmacological interventions*

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Introduction

The frequency of childhood obesity has been progressively increasing over the past few decades, raising concerns about its impact on world health. Beyond its effects on physical health, childhood obesity raises the likelihood of developing chronic diseases in adulthood and negatively affects mental well-being. Pharmaceutical therapies are increasingly being investigated for more severe cases or when lifestyle changes alone are not enough, even if diet and activity modifications remain the cornerstone of managing obesity.[1-3] Concerns regarding safety, effectiveness, and long-term effects have made the use of antiobesity drugs in kids and teens contentious. To direct clinical practice and shape healthcare policy, it is imperative to assess the available data regarding the advantages and disadvantages of pharmaceutical treatments for childhood obesity.[4-6] The objective of this systematic review is to present an up-to-date and thorough evaluation of the available data regarding the safety and

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efficacy of antiobesity drugs in kids and teens, with an emphasis on changes in body mass index (BMI), adverse events, and quality of life outcomes.

Materials and Techniques

Search strategy

From January 1, 2016, to March 17, 2023, a thorough search was performed across electronic databases, including Cochrane CENTRAL, MEDLINE, ClinicalTrials.gov, and WHO ICTRP. The search approach included MeSH terms and keywords associated with pharmacotherapy, randomized controlled trials, antiobesity drugs, and pediatric obesity.

Study selection criteria

RCTs that satisfied the following requirements were included in our analysis:

1. Participants: Obese children and teenagers under the age of 19.
2. Intervention: Pharmacological therapies for obesity, such as semaglutide, liraglutide, and orlistat, among others.
3. Comparison: Standard care versus a placebo.
4. Length: Studies have a six-month minimum follow-up interval.
5. Results: Research detailing alterations in body mass index (BMI), BMI at the 95th percentile, unfavorable occurrences, and life satisfaction.

Data extraction

Using a standardized data extraction form, two impartial reviewers performed the screening, data extraction, and quality assessment. When required, disagreements were settled through conversation or by consulting a third reviewer.

Evaluation of quality

The Cochrane risk-of-bias tool was used to evaluate the quality of the included studies. It looked at biases such as biased reporting, incomplete outcome data, blinding of participants and staff, random sequence creation, and allocation concealment.

Data synthesis and analysis

Review Manager (RevMan) software was used to synthesize the data. Approximately 95% confidence intervals (CIs) were used to analyze mean differences for continuous outcomes, such as changes in body mass index (BMI). Risk ratios (RR) with 95% confidence intervals (CIs) were used to analyze categorical outcomes, including adverse events. The I^2 statistic was used to measure the heterogeneity between the studies; values more than 50% were regarded as significant heterogeneity.

Results

A total of 4,331 people took part in the 12 trials that made up this systematic review. These pediatric patients ranged in age from 8.8 to 16.3 years, and their baseline BMI values were between 26.2 and 41.7 kg/m^2 [Figure 1].

Medication efficiency

Metformin

Over the course of a 24-month trial, metformin reduced pediatric participants' BMI from 33 to 8.8 (SE 0.6), whereas the placebo group's BMI increased from 44 to 10.0 (SE 0.5). The study was conducted by Bassols in Spain. In addition, Pastor-Villaescusa's Spanish study found no statistically significant difference in BMI decrease between the metformin and placebo groups, with identical patterns observed in both prepubertal and pubertal children.

Extended-release metformin

Exercise programs in conjunction with extended-release metformin have been shown to vary in BMI reduction, according to a Canadian study by Clarson. When metformin was combined with moderate activity, the BMI decreased to 41.2; 13.4 (2.1), but, when metformin was combined with strenuous exercise, the BMI decreased to 62.5; 13.9 (2.4).

Topiramate

Over the course of a 24-week trial, Fox's research conducted in the USA revealed a BMI decrease in the topiramate group from 62.5; 14.9 (1.6) to 64.3; 15.7 (1.8) in the placebo group.

Exenatide

Exenatide trials by Weghuber and Fox 41 showed a reduction in BMI of 41; 16.1 (1.5) and 55; 15.9 (1.6), respectively, with differences in the distribution of races and fasting insulin levels.

Liraglutide

During a 56-week period, Kelly's trial conducted in Belgium and Mexico showed a BMI drop from 56.8; 14.6 (1.6) in the liraglutide group to 61.9; 14.5 (1.6) in the placebo group.

Phentermine/Topiramate

Kelly's research revealed dose-dependent differences in BMI reduction, with the mid-dose group achieving BMI reductions of 51.9; 14.1 (1.3) and the top dose group reaching 55.8; 13.9 (1.4) as opposed to 53.6; 14.0 (1.4) in the placebo group.

Adverse occurrences

Pediatric patients taking antiobesity drugs and those in the comparator groups experienced similar serious adverse events and trial withdrawal as a result of

adverse events. On the other hand, pediatric cases showed a higher frequency of medication dose modifications (10.6% vs. 1.7%; RR = 3.74 [95% CI: 1.51 to 9.26]).

Life quality

Although the included trials did not specifically address pediatric cases, there was a general trend toward increased quality of life, indicating potential advantages for this age range as well.

Discussion

The increasing incidence of childhood obesity is a global health issue that requires efficient and secure treatment plans. The purpose of this systematic review was to assess the safety and effectiveness of pharmaceutical interventions for childhood obesity in a variety of international studies. Our research clarifies the possible advantages and difficulties related to various antiobesity drugs in this susceptible group.

Anti-obesity medication's effectiveness

Among the trials that were included, metformin, an oral antidiabetic medicine, was the most frequently examined drug. The studies of Pastor-Villaescusa and Bassols, both performed in Spain, shed light on the effectiveness of metformin in lowering BMI in young people. It's interesting to note that, contrary to Pastor-Villaescusa's study, which found comparable trends in both prepubertal and pubertal children, Bassols reported no significant difference in BMI decrease between the metformin and placebo groups. These results imply that metformin may not be adequate on its own to significantly lower BMI in

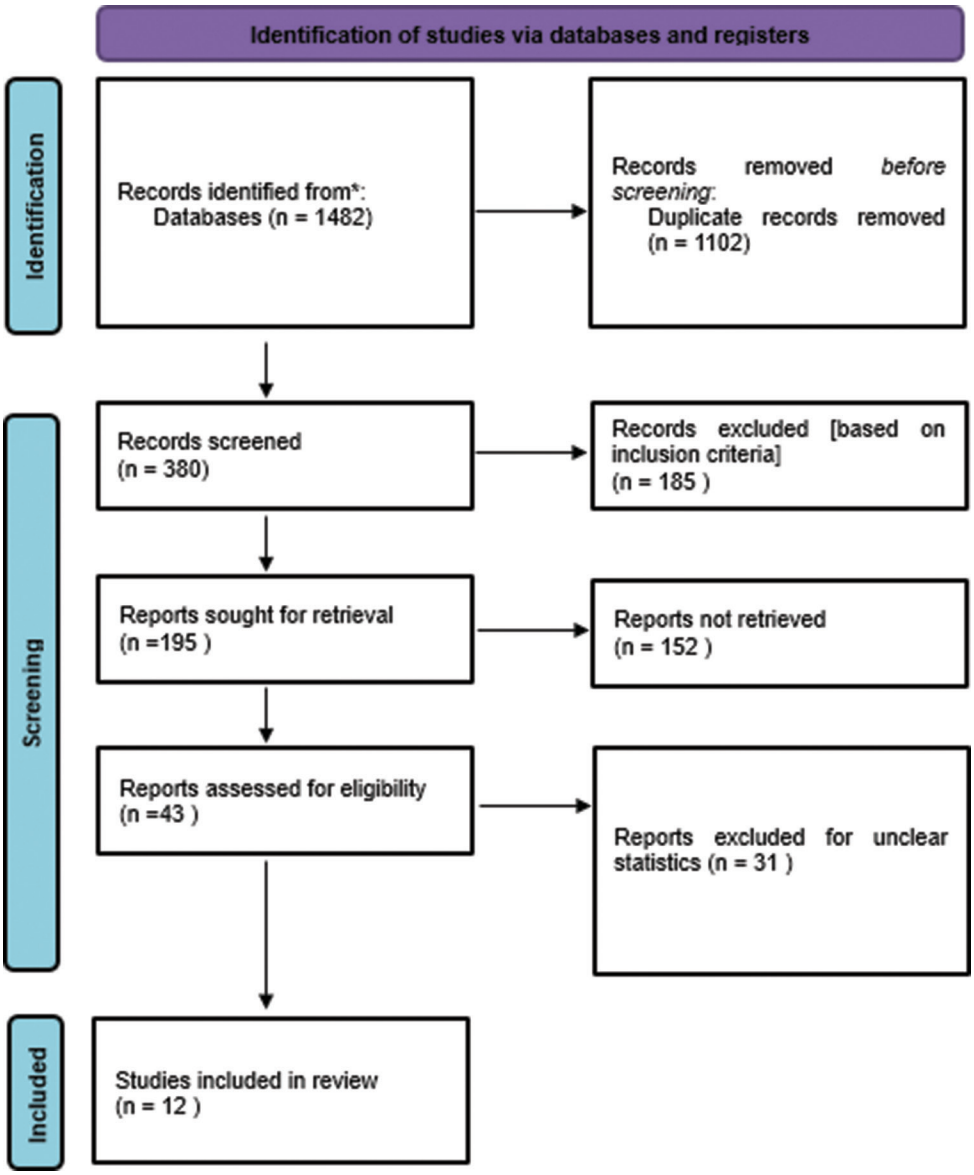

Figure 1: Flowchart

Study	Country	Drug/Intervention	Dosage/ Duration	Outcome
Bassols	Spain	Metformin: oral, once daily, 850 mg/d "at dinner time" Placebo: oral, once daily, "at dinner time"	24 months	Metformin: 33; 8.8 (SE 0.6); Caucasian 100; NR; fasting insulin levels >6 mIU/L; visceral-to-subcutaneous fat ratio (MRI >90th centile) Placebo: 44; 10.0 (SE 0.5); Caucasian 100; NR; fasting insulin levels >6 mIU/L; visceral-to-subcutaneous fat ratio (MRI >90th centile)
Clarson	Canada	Metformin: extended release, oral, start taking once daily, 500 mg/d increase by 500 mg/d every 7 days to maximum tolerated dose 2000 mg/d, taken before evening meal Placebo: oral, once daily, 10 mg	2 yr	Metformin + moderate exercise: 41.2; 13.4 (2.1); Caucasian 82, Asian 6, native 6, other 6; 31.6 (5.2) none Metformin + vigorous exercise: 62.5; 13.9 (2.4); Caucasian 81, native 6, other 13; 34.4 (5.7); none Placebo + moderate exercise: 61.1; 14.3 (2.0); Caucasian 78, Black 11, native 6, other 6; 32.0 (5.1); none Placebo + vigorous exercise: 66.7; 13.3 (2.2); Caucasian 67, Asian 6, other 28; 32.2 (6.3); none
Fox	USA	Topiramate: oral, once daily in the evening, 75 mg/d, 24 weeks Placebo: oral, twice daily, 24 weeks	24 weeks	Topiramate: 62.5; 14.9 (1.6); White: 62.5 African American/Black 18.8, other 18.8; 41.0 (5.0); none Placebo: 64.3; 15.7 (1.8); White 57, African American/Black 7, other 36; 39.5 (4.0); none
Fox	USA	Exenatide: extended release, subcutaneous injection, once weekly, 2 mg/week, 52 weeks Placebo: subcutaneous injection, once weekly, 52 weeks	52 weeks	Exenatide: 55; 15.9 (1.6); Nonhispanic 82 Hispanic 15, White 79, Black 9, Asian 0, American Indian 0, Multiple 9, Missing 3, Other 0; 36.5 (4.3); none Placebo: 41; 16.1 (1.5); Nonhispanic 94, Hispanic 6, White 85, Black 6, Asian 0, American Indian 0, Multiple 6, Missing 3, Other 0; 37.3 (4.6); none
Kelly	Belgium, Mexico	Liraglutide: subcutaneously, once daily, 3 mg/d, 56 weeks. Initial dose 0.6 mg/d for 1 week, increased weekly until maximum tolerated dose or 3.0 mg/d Placebo: subcutaneously, once daily, 3 mg/d, 56 weeks	82 weeks	Liraglutide: 56.8; 14.6 (1.6); Hispanic 25.6, White 84, Black 11, Asian 2, American Indian or Alaska Native 0, other 3; 35.3 (5.1); 25.6 dysglycemia Placebo: 61.9; 14.5 (1.6); Hispanic 19, White 91, Black 5, Asian 0, American Indian or Alaska Native 1, Other 3; 35.8 (5.7); 26.2 dysglycemia
Kelly	USA	Phentermine/topiramate, 7.5 mg/46 mg/d, orally once daily in the morning, 56 weeks Phentermine/ topiramate, 15 mg/92 mg/d, orally once daily in the morning, 56 weeks Placebo: oral once daily in the morning	56 weeks	Phentermine/topiramate mid-dose: 51.9; 14.1 (1.3); Hispanic or Latino 46, White 67; Black/African American 26; Other 7, American Indian or Alaska Native 0, Asian 0, Native Hawaiian or other Pacific Islander 0; 36.9 (6.8); none Phentermine/topiramate top dose: 55.8; 13.9 (1.4); Hispanic or Latino 30, White 63, Black/African American 32, other 4, American Indian or Alaska Native 1, Asian 1, Native Hawaiian or other Pacific Islander 0; 39.0 (7.4); none Placebo: 53.6; 14.0 (1.4); Hispanic or Latino 23, White 75, Black/African American 18, Other 7, American Indian or Alaska Native 0, Asian 0, Native Hawaiian or other Pacific Islander 0; 36.4 (6.4); none
Li	China	Metformin: oral, ≤8 yr=0.25 g/3 times daily, children>8 yr=0.5 g 3 times daily, half an hour before meals, 6 months	6 months	Metformin: 38; 12.3 (1.6); NR; 31.8 (2.5); 100 hyperinsulinemia No placebo comparator: 33; 12.0 (1.5); NR; 30.8 (2.5); 100 hyperinsulinemia
Pastor-Villaescusa	Spain	Metformin: oral, initial dose 50 mg twice daily during meals for 10 days, and then 500 mg twice daily, 1 g/d, 6 months Placebo: twice daily during meals	6 months	Metformin: 49; 6.8–15.3; White 100; prepubertal: 28.2 (SE 0.6), pubertal: 29.4 (SE 0.5); none Placebo: 49; 6.8–15.3; White 100; prepubertal: 29.2 (SE 0.6), pubertal: 30.6 (SE 0.5); none

Contd...

Study	Country	Drug/Intervention	Dosage/ Duration	Outcome
van der Aa	The Netherlands	Metformin: immediate release, oral, 500 mg, increasing dose regimen with maximum dose of 2 tablets twice daily by week 4, 2 g/d, during or after breakfast and dinner, 18 months Placebo: oral, up to 2 g/d, during or after breakfast and dinner, 18 months	18 months	Metformin: 73.9; median 13.6 (IQR 12.6–15.3); Caucasian 100; median 29.8 (IQR 28.1–34.5); T2DM 65.2, hypercholesterolemia 60.9, hypertension 69.5, CVD 60.9 Placebo: 57.9; median 12.0 (IQR 11.3–14.0); Caucasian 100; median 30.5 (IQR 28.7–38.6); T2DM 47.4, hypercholesterolaemia 47.4, hypertension 68.4, CVD 73.7
Warnakulasuriya	Sri Lanka	Metformin: 8–10 year: oral, 250 mg daily for a week and increased to 250 mg twice daily for a week and thereafter 500 mg twice daily; 11–16 years: 500 mg daily for 1 week and increased to 500 mg twice daily for a week and thereafter 1 g twice daily, with morning and evening meals, 12 months	12 months	Metformin: 28; 11.9 (2.2); NR; 27.4 (3.0); metabolic syndrome 22 Placebo: 38; 12.3 (2.3), NR; 27.4 (2.7); metabolic syndrome 12
Weghuber	Austria, Sweden	Exenatide: subcutaneous injection, weekly, 2 mg/week, 24 weeks, administered by the patient following individual training or administered by trained adult or personnel at the study site. Placebo: subcutaneous injection once weekly, 24 weeks, administered by the patient following individual training or administered by trained adult or personnel at the study site.	24 weeks	Exenatide: 59; 14.5 (2.3); White 100; 36.0 (4.8); none Placebo: 31; 13.5 (2.3); White 85, Asian 5, Black 5, other 5; 36.2 (5.0); none
Weghuber	Multiple countries	Semaglutide: subcutaneous injection, weekly, dose escalation period 16 weeks, from 0.25 mg escalation every 4 weeks to 0.5, 1.0, 1.7, and 2.4 mg/maximum tolerated dose, 68 weeks Placebo: subcutaneous injection, weekly dose, 68 weeks	68 weeks	Semaglutide: 63; 15.5 (1.5); Asian 2, Black 8, White 78, other 12; 37.7 (6.7); 20.1 dyslipidemia, 13.4 hypertension, 3.7 T2DM, 1.5 obstructive sleep apnea Placebo: 61; 15.3 (1.6); Asian 1, Black 7, White 82, other 9; 35.7 (5.4); 14.9 dyslipidemia, 13.4 hypertension, 4.5 T2DM, 1.5 obstructive sleep apnea

pediatric populations, necessitating additional research into combination treatment plans or lifestyle modifications.[4-7]

In Canada, Clarson's study on extended-release metformin revealed differences in BMI reduction according to exercise schedules. Different levels of BMI reduction were seen when metformin was combined with moderate or intense exercise, suggesting the possible synergistic effects of pharmaceutical and lifestyle therapies. This emphasizes the value of individualized treatment plans based on each patient's requirements and degree of physical activity.[8-10]

In Fox's US trial, the antiepileptic medication topiramate was assessed. Over the course of 24 weeks, the study showed a slight reduction in BMI in the topiramate group when compared with the placebo group. This implies that topiramate might play a part in treating childhood obesity, but more research is necessary to determine its effectiveness and safety profile.

Weghuber and Fox 41 investigated the glucagon-like peptide-1 (GLP-1) receptor agonist exenatide. Exenatide's potential as an antiobesity drug in pediatric populations was highlighted by the two studies' reports of varied degrees of BMI reduction when compared with placebo. To further understand the variables determining responsiveness to exenatide treatment, more research is necessary, as indicated by differences in the racial distribution and fasting insulin levels among the studies.[11,12]

Kelly examined ligandude, an additional GLP-1 receptor agonist, in his trial, which was performed in Mexico and Belgium. Over the course of 56 weeks, the trial showed a significant reduction in BMI in the liraglutide group as compared to the placebo group. This shows that liraglutide may be a potential treatment for childhood obesity; however, larger, longer-term trials are needed to assess the drug's long-term safety and efficacy.[10-12]

Kelly's study on the combination of phentermine and topiramate showed dose-dependent changes in BMI reduction. In comparison to the placebo group, the mid-dosage, and top dose groups showed a higher reduction in BMI, suggesting that this combination therapy may be effective in treating pediatric obesity. However, before endorsing it as a first-line therapy choice, one must carefully assess its safety profile, particularly with regard to cardiovascular concerns.

Safety points to remember

Although the included studies shed light on the effectiveness of anti-obesity drugs, safety is still the first priority. Based on our review, pediatric participants receiving anti-obesity drugs and those in the comparator groups had similar rates of major adverse events and trial discontinuation as a result of adverse events. However, a higher frequency of medication dose modifications was found in pediatric cases, underscoring the necessity for continuous monitoring and customized treatment regimens.[5-10]

Life quality

Although not specifically mentioned for pediatric instances, our analysis showed a general trend in the included studies' direction toward better quality of life. According to this, antiobesity drugs may improve children's general well-being and quality of life in addition to lowering body mass index. To confirm these results and offer thorough understanding of the all-encompassing advantages of antiobesity therapies in pediatric populations, more research that specifically focuses on quality-of-life outcomes is necessary.[1,5,8,12]

Restrictions and prospective paths

Our systematic review has various limitations, even if the included research offered insightful information. The generalizability of our findings is limited by the variety of study designs, participant demographics, and treatment regimens among the included trials. Furthermore, the short duration of some trials might not fully represent the safety profile and long-term effectiveness of antiobesity drugs in pediatric populations.

Large-scale, multicenter randomized controlled trials with extended follow-up periods should be the main focus of future research to determine the long-term safety and effectiveness of antiobesity drugs in pediatric populations. Furthermore, in-depth research examining the synergistic effects of pharmaceutical therapies with dietary and activity adjustments is required to design tailored and efficacious treatment plans for pediatric obesity.

Conclusion

To sum up, our comprehensive analysis offers significant understanding of the state of pharmacological treatments for childhood obesity. Although various antiobesity drugs, such as phentermine/topiramate combo, exenatide, liraglutide, metformin, and topiramate, show promise in lowering BMI in pediatric populations, more studies are required to determine these drugs' long-term safety and effectiveness characteristics. Personalized, multidisciplinary care that includes lifestyle changes, medication interventions, and psychological support may be a comprehensive and successful approach to managing childhood obesity and enhancing the general health and well-being of impacted kids and teenagers.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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