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Medications for the treatment of obesity in adolescents

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***Abstract*:** While there are eight medications/combinations approved for the treatment of obesity in adults, the options for the treatment of obesity in adolescents remain limited. Evidence for obesity medication use in adolescents is limited due to the relatively small number of clinical trials that have been completed and the few adolescents that have been included in many of the trials. The goal of this review will be to present the current evidence for the medications approved for adolescents, medications not approved for adolescents but have adolescent data, and medications approved for adults with the prospect for use in adolescents. We will also discuss current limitations and next steps in the exploration of future treatment options.

Keywords: adolescents, medications, obesity

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Introduction

Obesity is a condition that is caused by a multitude of factors including but not limited to genetic, epigenetic, biological, hormonal, microbial, behavioral, sociocultural, and environmental factors that disturb the balance between caloric intake and energy expenditure.[1] BMI (body mass index) has traditionally been used in the classification of obesity. In general, for adults 19 years and older, the BMI range of 18.5–24.9 kg/m^2 is classified as normal, 25–29.9 kg/m^2 as overweight, and at or above 30 kg/m^2 as obese.[2] For children and adolescents between 2 and 19 years old, BMI percentile is used in the classification of obesity. BMI percentile is calculated by comparing an individual's BMI with that of others with the same sex and age. Individuals at the 5th–84th percentile are classified as normal, 85th–94th as overweight, and at or above 95th percentile as obese.[2] Moreover, those with a BMI percentile at or above 99th or >120% of the 95th percentile are considered to have severe obesity.[2]

Obesity affects a large percentage of the population. Globally, 39% of adults 18 years and older were overweight and 13% were obese in 2016.[3] This disease is also prevalent in the pediatric population, as 18% of children and adolescents aged 5–19 years were overweight or obese in 2016.[3] According to the Centers for Disease Control (CDC), overall obesity rates have been rising, as evidenced by the fact that 30.5% of United States (US) adults in 1999–2000 were obese *versus* 39.6% in 2015–2016.[4] Moreover, children and adolescents in the US also showed a significant increase in obesity prevalence from 13.9% in 1999–2000 to 18.5% in 2015–2016.[4]

Obesity is associated with many health problems and has been linked to 4 out of the 10 leading causes of death in the US.[5] Accordingly, the United States Preventive Services Task Force guidelines encourage clinicians to promote behavioral interventions as the primary focus of effective interventions for weight loss.[6] The US Food and Drug Administration (FDA)-approved anti-obesity agents for adults may be used as part of a comprehensive weight-loss program for patients with BMI ⩾30 kg/m^2 or BMI ⩾27 kg/m^2 and at least one weight-related comorbidity.[7] Even so, current treatments for obesity are limited and under-utilized, as specifically, only about 1–2% of adults with obesity are prescribed anti-obesity agents.[7] Multiple treatment considerations must be accounted for, that is, the cause of obesity, the side effects of the medication, and if the patient

will benefit overall from pharmacotherapy.[8] Special pediatric considerations must be taken into account when addressing obesity in children and adolescents. Childhood obesity can track into adulthood and obesity increases the risk of diabetes and cardiovascular disease.[9] Pharmacotherapy for weight loss in the pediatric population are much more limited than in adults. The 2017 Endocrine Society Guidelines suggest pharmacotherapy for adolescents if a formal lifestyle modification program fails to limit weight gain or to ameliorate comorbidities. Pharmacotherapy should only be used with FDA-approved medications prescribed by clinicians experienced in their use and should be discontinued if >4% BMI/BMI z score reduction is not achieved after 12 weeks.[10] Moreover, obesity medications are not recommended for use in children and adolescents <16 years of age who are overweight but not obese, except in clinical trials.[10] Currently orlistat and phentermine are the only FDA-approved medications for the treatment of obesity in adolescents <18 years of age as an adjunct to lifestyle modifications.

FDA-approved medications for obesity in adolescents

Orlistat

Orlistat is the only medication FDA approved for long-term management of obesity that can be prescribed to adolescents 12 years of age and older. Orlistat was approved in 1999 for adults but was not approved for use in adolescents until 2003. The usual prescribed dose is 120 mg three times a day with meals. Orlistat works by reducing the absorption of approximately one third of the fatty acids consumed by food through inhibiting gastrointestinal lipases.[1]

In one major pediatric trial, children were randomized to either orlistat 120 mg or placebo three times daily over 52 weeks. At the end of the study, BMI had decreased by 0.55 kg/m^2 with orlistat but increased by 0.31 kg/m^2 with placebo. In addition, 26.5% of children in the orlistat group had a 5% or greater decrease in BMI compared with 15.7% of those in the placebo group.[11] Safety was assessed in the trial, and side effects reported were mostly gastrointestinal (fecal urgency/incontinence; fatty, oily stools). The events were more frequent with orlistat and generally mild-to-moderate in intensity.[11]

Phentermine

Phentermine can be used for short-term management of obesity in individuals >16 years of age. This drug is an amphetamine analog that was first approved in 1959 and is FDA approved for use in adolescents for 12 weeks or less. Phentermine is a class IV, controlled substance, and prescribing laws differ in each state. The usual prescribed dosage is between 15 mg and 37.5 mg daily. Phentermine acts to increase catecholamines and serotonin activity in the central nervous system resulting in appetite suppression.[12] The main studies examining phentermine for obesity treatment in the pediatric population were from the 1960s and had very little safety and efficacy data reported.[13] Common side effects may include increased blood pressure and heart rate.[12] The limited availability of long-term data for phentermine and its short-term use indication present a conundrum for phentermine's use in adolescents, since chronic treatment is required for the treatment of obesity.[14]

A study conducted by Ryder and colleagues compared adolescents prescribed phentermine plus standard-of-care lifestyle therapy *versus* standard-of-care lifestyle therapy alone. The study showed that the phentermine plus standard-of-care lifestyle therapy resulted in statistically significant reductions in weight and percent BMI at 1 month (−1.4 kg, −1.6%); 3 months (−2.6 kg, −2.9%); and 6 months (−3.2 kg, −4.1%) compared with standard-of-care lifestyle therapy alone.[13]

In total, there are currently only eight drugs (see Table 1) FDA approved for the treatment of obesity.[15] Six of these drugs have received FDA approval just in the last 20 years. This has led to off-label use of certain drugs, such as metformin, exenatide, topiramate or zonisamide, octreotide, and growth hormone for obesity. Off-label use of controlled drugs is regulated on a state level and some states may be more restrictive.[15] Metformin has been shown to decrease BMI by approximately 1.2 kg/m^2 over 6–12 months and exenatide decreased BMI by 1.7 kg/m^2 in a pediatric population.[10,16] Drugs that target specific populations also have off-label use for obesity. Lisdexamfetamine, a drug used to treat attention-deficit hyperactivity disorder in children and adolescents, was used to treat obesity in an adolescent with severe obesity and binge eating.[17] Two antiepileptic drugs, topiramate and zonisamide, have shown a BMI reduction of 1.3–4.1 kg/m^2.[18]

Octreotide, a somatostatin analog, may provide weight stabilization in adolescents with hypothalamic obesity.[19] Growth hormone has also been shown to decrease fat mass and increase lean body mass in Prader–Willi Syndrome (PWS).[20] Medications with more extensive data in adolescents but without FDA approval are presented below.

Medications approved in adults

Lorcaserin (Belviq®)

Lorcaserin is a selective 5-hydroxytryptamine 2C (5HT-2C) receptor agonist that acts on the limbic system, as well as the parietal and visual cortices, resulting in decreased emotional responses related to appealing foods. In turn, caloric intake is decreased while maintaining energy expenditure.[22,23] It received FDA approval in the United States in 2012, but was not approved by the European Medicines Agency due to the potential risk of psychiatric disorders (such as depression) and valvulopathy.[24]

BLOOM (Behavioral Modification and Lorcaserin for Overweight and Obese Management),[25] BLOSSOM (Behavioral Modification and Lorcaserin Second Study for Obesity Management),[26] and CAMELLIA-TIMI 61[27] evaluated the efficacy of lorcaserin when taken at 10 mg twice daily, compared with the efficacy of 10 mg taken once daily or twice daily, and its longstanding cardiovascular effects, respectively. The BLOOM and BLOSSOM studies showed that of those in the active drug groups, approximately 35–48% participants had weight loss at or above 5% of their baseline body weights.[28,29] The CAMELLIA-TIMI 61 study showed that over the course of 3 years, lorcaserin did not increase the occurrence of major cardiovascular events.[27] Additionally, blood pressure, heart rate, low-density lipoprotein cholesterol, triglycerides and glycated hemoglobin (HbA1c) all showed improvement compared with placebo, and the mean percentage of diabetes onset decreased after 1 year of treatment.[27]

Most recently, on 13 February 2020, the FDA announced that it had requested the manufacturer, Eisai, Inc., to voluntarily withdraw lorcaserin from the market. Review of data from the CAMELLIA-TIMI 61 study demonstrated a numerical imbalance in the number of patients with malignancies, with one additional cancer observed per 470 patients treated for 1 year. Imbalances in specific cancers including pancreatic, colorectal, and lung contributed to the overall increase in cancer cases in the lorcaserin group. Healthcare professionals were instructed to stop prescribing and dispensing lorcaserin. Patients should be contacted to discard any remaining drug. Finally, the FDA did not recommend any special cancer screening for those who have taken lorcaserin, other than standard screening recommendations.[30]

Table 1. Approved medications for obesity.[21]

Drug name (brand name)	Year approved
FDA approved for short-term use	
Diethylpropion (Tenuate)	1950
Phendimetrazine (Bontril PDM)	1956–1960
Benzphetamine (Regimex, Didrex)	1956–1960
Phentermine (Adipex, Suprenza)	1959
FDA approved for long-term use	
Orlistat (Xenical)*	1999
Lorcaserin (Belviq)#	2012
Phentermine/Topiramate (Qysmia)	2012
Bupropion/Naltrexone (Contrave)	2014
Liraglutide (Saxenda)	2014

*Available over the counter since 2007 as Alli 60 mg.
#FDA approval was withdrawn on 13 February 2020.
FDA, US Food and Drug Administration.
Bolded text is to indicate the 4 drugs focused on in the text.
This table was adapted from the reference cited but was not copied.
Note: Table adapted with permission from Springer Nature, reference 21.

Phentermine/topiramate (Qsymia®)

Qsymia® is a combination of phentermine and topiramate and acts as a norepinephrine and gamma-aminobutyric acid agonist, as well as a glutamate antagonist leading to appetite suppression (although the exact mechanism is still under investigation).[31,32]

The standard treatment plan for Qsymia involves a four-stage dose escalation starting with immediate-release phentermine/extended-release topiramate 3.75 mg/23 mg once daily for 2 weeks followed by 7.5 mg/46 mg once daily for 12 weeks. If the patient does not lose at least 3% of baseline

body weight, the medication can be discontinued or dose escalated. For dose escalation, immediate-release phentermine/extended-release topiramate at 11.25 mg/69 mg can be prescribed daily for 2 weeks followed by a final titration to a dose of 15 mg/92 mg daily for 12 weeks. After completing the final 12-week treatment period, the drug is discontinued gradually if patients do not achieve weight loss at or above 5% of their baseline body weight.[1,33] Upon discontinuation of treatment, patients are advised not to take any further doses within 14 days of treatment discontinuation.[1,32] Patients who have the following conditions should not be treated with Qsymia: pregnancy, uncontrolled hypertension, cardiovascular disease, chronic kidney disease, glaucoma, hyperthyroidism and patients using monoamine oxidase inhibitors.[1]

Common side effects with Qsymia include paresthesia, dry mouth, constipation, dysgeusia, insomnia, depression, and anxiety, with occurrences between 1% and 7%.[34,35] Uncommon side effects that may be encountered include accelerated heart rate, impaired renal function, metabolic acidosis, and nephrolithiasis.[36,37] As a safety precaution, depression and suicidal ideations should also be monitored.[1]

Efficacy and safety were assessed in three major studies: Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP);[34] effects of low-dose, controlled-release, phentermine-plus-topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomized, placebo-controlled, phase III trial;[35] and 2-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase III extension study.[26] Patients with BMIs between 27 kg/m^2 and 35 kg/m^2 were randomized to receive either placebo, the 7.5 mg/46 mg dose or the 15 mg/92 mg dose. Total weight loss for participants in the EQUIP and CONQUER studies ranged from 3.5% to 6.6% for the 7.5 mg/46 mg dose and 8.6–9.3% for the 15 mg/92 mg dose.[34,35] SEQUEL, an extension of the CONQUER study, showed prolonged health benefits and greater weight loss in both groups treated with phentermine/topiramate when compared with the placebo group after completing the 52-week extension.[26] EQUATE investigated the difference in weight loss for phentermine and topiramate monotherapy compared with the combined treatment. Combined treatments had a placebo-subtracted weight loss of approximately 7%, while both monotherapies resulted in weight loss of approximately 4% after 28 weeks.[25]

The FDA has approved Qsymia for long-term use, but little is known regarding its effectiveness for obesity treatment beyond 2 years. Because of the limited long-term evidence for phentermine's effects on cardiovascular risks, and topiramate's effects on psychiatric and cognitive dysfunctions, as well as phentermine's abuse potential, Qsymia has not been approved for use in Europe.[38]

Two studies (one completed and one ongoing) are investigating Qsymia's effects in adolescents with obesity: 'A randomized, double-blind, placebo-controlled, pharmacokinetic and pharmacodynamic study of VI-0521 in obese adolescents' [ClinicalTrials.gov identifier: NCT02714062] (completed) and 'A phase IV, multi-center, randomized, double-blind, placebo-controlled, parallel-design study to determine the safety and efficacy of VI-0521 in obese adolescents' [ClinicalTrials.gov identifier: NCT03922945] (ongoing).

Buproprion/naltrexone (Contrave®)

Contrave® is a combination of naltrexone and bupropion and has been available as an anti-obesity agent in the United States since 2014.[1] Naltrexone's primary use has been for addiction management of drugs and alcohol, whereas bupropion has been used for treating depression and to aid in smoking cessation.[39] Since weight loss was seen with their primary indications, naltrexone and bupropion were combined to treat obesity.[39] This combination acts by regulating self-control, internal awareness and memory by modifying the hypothalamus, cortical and subcortical regions' responses to food.[40]

When starting treatment with Contrave, a four-stage dose-escalation regimen is followed by a dose increase every 7 days. One tablet (naltrexone 8mg/bupropion 90 mg) is taken every morning for the first 7 days, followed by one tablet taken twice daily for days 7–14. The third stage requires patients to take two tablets in the morning and one tablet at night, and the final dose escalation (days 21–28) is when the target of two tablets twice daily is achieved.[33] Patients should avoid

taking Contrave if they suffer from: uncontrolled hypertension, seizures, anorexia, or bulimia nervosa. Patients who are taking benzodiazepines, barbiturates, other bupropion medications, opioids, opiate agonists, or anti-epileptic medications are advised not to use Contrave. Due to the increased hypertensive risks involved with bupropion interacting with monoamine oxidase inhibitors, a 14-day washout must occur before Contrave treatment is initiated.[41] Additionally, patients who are pregnant or who have recently ceased alcohol consumption should not take Contrave due to increased risk of hypertensive reactions. If a patient taking a monoamine oxidase inhibitor (MAOI) wants to start Contrave, at least 14 days should elapse between MAOI discontinuation and the start of Contrave treatment.[42] In addition, a patient's mental status should be monitored and specifically, for any indications of suicidal ideations or depression.[1]

Common side effects include nausea, headache, constipation, dizziness, vomiting, and dry mouth, with occurrence ranging from approximately 4% to 25%.[43] These side effects make Contrave the second most likely anti-obesity agent to be discontinued due to side effects, after liraglutide.[43]

These four studies were instrumental for FDA approval of Contrave: COR-I (Contrave Obesity Research I),[44] COR-II (Contrave Obesity Research II),[45] COR-DIABETES (Contrave Obesity Research in Diabetes),[46] and COR-BMOD (Contrave Obesity Research in adjunct to intensive Behavioral MODification).[47] COR-I recruited patients with obesity but without type 2 diabetes and compared 16 mg/360 mg of naltrexone/bupropion with 32 mg/360 mg. Mean weight loss was comparable between the higher and lower dose naltrexone groups (5.0% *versus* 6.1%).[44] COR-II recruited patients with overweight or obesity in addition to dyslipidemia with or without hypertension.[45] COR-DIABETES examined patients with Type 2 Diabetes, and COR-BMOD examined naltrexone/bupropion treatment in conjunction with behavioral modifications in participants with overweight and obesity, as well as hypertension with or without dyslipidemia.[47] The 32 mg/360 mg dose of naltrexone/bupropion was tested in all four studies over a 56-week period, and resulted in placebo-subtracted weight loss ranging from approximately 3% to 6%.[44–47]

Other benefits seen from naltrexone/bupropion treatment include decreased waist circumference, improved eating habits and better glycemic control for patients with type 2 diabetes.[44–46] Treatment with Contrave did not show any increased risks in cardiovascular disease, but slightly elevated blood pressures were seen in patients who did not have type 2 diabetes.[44,45,48]

Though monotherapy with bupropion has been utilized in adolescents (ages 12–17) for depression, with weight loss noted as a side effect in a majority of patients, caution is needed because bupropion, as with some other antidepressants, may increase the risk of suicidal ideation in children, adolescents, and young adults with major depressive or other psychiatric disorders.[49] Therefore, Contrave carries a black-box warning regarding increased suicidal risk and ideation in young adults and is not approved for pediatric patients. Of note, bupropion monotherapy has not been FDA approved for the treatment of depression or other conditions in youth, and there are no pediatric studies investigating Contrave's effects on childhood and adolescent obesity at this time.

Liraglutide (Saxenda®)

Liraglutide is a glucagon-like peptide (GLP)-1 analog acting in three ways to generate weight loss: increasing insulin secretion, while counteracting glucagon secretion depending on blood glucose levels, augmenting satiety by slowing gastric emptying, and suppressing appetite by acting on the parts of the brain affecting food consumption.[50–54]

Obesity treatment using liraglutide starts at 0.6 mg, and the dose is titrated to the targeted dose of 3 mg. Dose escalations are weekly, and the drug administration is daily *via* subcutaneous injection.[33,55] Liraglutide should not be used in patients who are pregnant, have personal or family history of medullary thyroid carcinoma or type 2 multiple endocrine neoplasia. It has been noted in rodent studies that liraglutide can cause calcitonin levels to increase.[42] Liraglutide can be considered even if patients have a history or diagnosis of mental health disorders.[56]

Side effects commonly experienced include: nausea, vomiting, diarrhea, constipation, and dyspepsia, with occurrence ranging from 6% to

25%.[57] There is a small risk of cholelithiasis while being treated with liraglutide.[58] Amylase and lipase levels can slightly increase during treatment, but symptoms indicative of these changes are rarely seen.[59] Although pancreatitis is listed on the warning labels for all medications in the GLP-1 agonist class due to postmarketing reports, overall, there has not been an increased risk for acute pancreatitis observed in previous clinical trials.[57–59] Other conditions that have been monitored include calcitonin levels, medullary thyroid carcinoma rates, and malignant and benign neoplasms, which have shown no difference between treated groups and placebo groups in previous studies.[58,60–62]

Liraglutide at 1.8 mg daily is approved by the FDA for the treatment of type 2 diabetes in adolescents and adults. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial showed evidence that liraglutide was the first GLP-1 agonist to demonstrate improvement in cardiovascular disease risk.[62] The Satiety and Clinical Adiposity–Liraglutide Evidence in individuals with and without diabetes (SCALE) studies supported the FDA approval for liraglutide's expanded indication for weight loss.[57,63] The primary SCALE study investigated liraglutide treatment at 3 mg daily *versus* placebo over the course of 56 weeks in ~3700 adults with obesity but without type 2 diabetes. Weight loss outcomes from this trial showed a 5.6 kg placebo-subtracted weight loss with more than 50% of the participants achieving at or above 5% body weight reduction.[57] The SCALE diabetes study compared treatment with liraglutide at 3 mg or 1.8 mg *versus* placebo daily in ~1300 adults with type 2 diabetes. After 56 weeks of treatment, participants taking 3 mg had almost double the weight loss compared with participants being treated with 1.8 mg (4.2 kg *versus* 2.3 kg, respectively).[63] The most common side effects reported were related to gastrointestinal upset, which was also the most common reason for participants withdrawing from the study.[57,63] The use of liraglutide in conjunction with selective serotonin reuptake inhibitors (SSRIs) poses a risk of developing serotonin syndrome. Due to the negative interaction of these drugs, high occurrence of depression in patients suffering from obesity and the prevalence of SSRIs prescribed to these individuals limits the use of liraglutide in treating obesity.

A small study with 21 participants entitled 'A randomised, double-blind, placebo-controlled trial to assess safety, tolerability and pharmacokinetics of liraglutide in obese adolescent subjects aged 12–17 years' demonstrated that liraglutide had a similar safety and tolerability profile in adolescents with obesity compared with adults with obesity and without unexpected safety/tolerability issues. In a phase III study entitled 'Effect of liraglutide for weight management in pubertal adolescent subjects with obesity,' 3.0 mg of liraglutide was compared with placebo over a 56-week period. The study has been completed but results are not yet available. The 'Effect of liraglutide for weight management in pediatric subjects with Prader–Willi syndrome' [ClinicalTrials.gov identifier: NCT02527200] is currently active.

Other medications not FDA approved for the treatment of obesity

Metformin

Metformin is an FDA-approved medication for individuals 10 years of age and older for the treatment of type 2 diabetes. Metformin has also been used as a first-line medication in patients with insulin resistance, prediabetes, or metabolic syndrome.[14] This medication has also demonstrated evidence of weight loss in the pediatric population in multiple trials. A meta-analysis including eight studies ($n=616$) evaluated the use of 1–2 g of metformin *versus* placebo for weight loss in individuals of 6–19 years of age. The weight reduction associated with metformin was statistically significant, lowering BMI z score [−0.10 (95% confidence interval (CI), −0.17 to −0.03)] and BMI [−0.86 (95% CI, −1.44 to −0.29)].[64] Common adverse events were gastrointestinal in nature and not reported as serious. The discontinuation rate due to adverse events was <5% and occurred in similar proportions between the metformin and placebo groups in these studies.[64]

Topiramate

Topiramate is currently FDA approved for the treatment of epilepsy (⩾2 years old), migraines (⩾12 years old), and obesity, in combination with phentermine (⩾18 years old); it has also been used in the treatment of binge-eating disorders in adults with obesity.[65–68] Although topiramate is not approved by the FDA for obesity treatment in children and adolescents, efforts have been made to test its efficacy in younger populations.

One pilot study evaluated the use of topiramate at 75 mg daily compared with placebo in adolescents with severe obesity 12–17 years of age. Although the topiramate group showed significantly decreased very-low-density-lipoprotein cholesterol and visceral fat, no significant differences in weight loss were observed between the two groups.[69] In addition to this pilot, a retrospective chart review was done to investigate weight reduction in adolescents with severe obesity treated with lifestyle-modification therapy, in conjunction with topiramate 75 mg daily, for a minimum of 3 months. Results showed a clinically significant BMI reduction of nearly 5% from baseline over a 6-month period. No severe adverse events were observed; however, two participants reported experiencing paresthesia.[70]

Potential side effects include interference with oral contraceptives and risks for birth defects when taken during pregnancy.[71] In previous clinical trials testing combination therapy of phentermine/topiramate in adults, reports of anxiety and depression were deemed a result of topiramate, since it is known to cause reversible cognitive and psychiatric disorders. Nephrolithiasis is also a possible side effect due to topiramate's inhibitory effects on carbonic anhydrase.[1,37]

Exenatide/liraglutide/semaglutide

The GLP-1 agonist exenatide is currently FDA approved for the treatment of type 2 diabetes, while liraglutide is also approved for the treatment of obesity in adults, and type 2 diabetes in adolescents and adults.[72] Of the available evidence for the use of GLP-1 agonists in pediatric populations, results have shown promise in their feasibility, safety and tolerability for the treatment of obesity and type 2 diabetes.

Two trials have investigated exenatide's effect on weight loss in children and adolescents. Both trials involved a 3-month intervention period with participants (ranging from 9 to 19-years old) randomized to either exenatide or placebo, plus lifestyle intervention.[16,73] Exenatide showed a mean BMI reduction of approximately 3.4% after 3 months of treatment, along with improvements in fasting insulin compared with placebo.[74] In a 3-month open-label extension of one of the trials, participants originally in the exenatide group continued to lose weight and had a cumulative BMI reduction of 4%.[73] A third clinical trial examined exenatide treatment in participants with PWS. Participants ranging from 12 to 25-years old were treated in an open-label study, with no other intervention. No significant changes in adiposity or ghrelin were observed but reported appetite scores and HbA1c decreased.[75] Adverse events reported throughout these trials included nausea, vomiting, headache, abdominal discomfort, and diarrhea.[16,73,74]

A study investigating the safety, tolerability, and pharmacokinetics of liraglutide over a 5-week treatment period enrolled adolescent participants (12–17-years old) with obesity. Adolescents were randomized (2:1) into active drug or placebo groups, with weekly dose escalations starting at 0.6 mg. As mentioned above, results suggested that the adult dose of liraglutide is also potentially appropriate for adolescents in treating obesity.[76] In a phase III study of adolescents with type 2 diabetes, liraglutide, at a dose of up to 1.8 mg per day (added to metformin, with or without basal insulin), improved glycemic control over 52 weeks (mean treatment difference of −1.3% for HbA1c).[77] Reported side effects included nausea, vomiting, abdominal discomfort, and diarrhea. Multiple hypoglycemic events were found *via* routine glucose monitoring.[78,79] Studies with liraglutide have shown similar safety and tolerability in adults and adolescents, and ongoing adolescent studies are testing liraglutide's efficacy.

The most recent GLP-1 agonist to show promise in being an effective obesity treatment is semaglutide. As a GLP-1 agonist already FDA approved to treat type 2 diabetes, it is following in its predecessors' footsteps as it undergoes phase III trials to investigate its efficacy in treating obesity in adolescents. In past studies testing semaglutide in adults with obesity, results indicated participants who were treated with semaglutide had approximately 5% more weight loss after a 52-week treatment period than those who were treated with liraglutide over the same period of time.[80] Another benefit to be noted is that semaglutide is a once-weekly injection compared with some GLP-1 agonists that require daily injections. Studies are currently underway to investigate semaglutide as an obesity treatment in both pediatric and adult populations.

Setmelanotide

Setmelanotide is a melanocortin-4 receptor agonist given by daily subcutaneous injection. It has

received Breakthrough Drug Designation from the FDA for the treatment of obesity related to pro-opiomelanocortin (POMC) deficiency and leptin-receptor-deficient obesity. Setmelanotide is also being evaluated for the treatment of PWS, Bardet–Biedl syndrome, Alström syndrome, POMC heterozygous deficiency obesity and POMC epigenetic disorders.[81]

Two participants with POMC deficiency were evaluated in an open-label trial with setmelanotide. After 12 weeks of treatment, one participant had a 20.5 kg weight reduction; while a 51.0 kg weight reduction was recorded for the other participant after 42 weeks of treatment. Additionally, one participant showed clinically significant reductions of heart rate, as well as systolic and diastolic blood pressure after weight loss.[82] Reported adverse events included dry mouth, skin induration localized at the injection sites and darkening of skin nevi.[82] Despite these side effects, setmelanotide has shown the potential in treating genetic-related obesity disorders in children and adolescents.

Future treatment

Just as obesity is a multi-faceted disease, future treatment for adolescents with obesity could be accomplished through multiple modalities including the use of multiple medications. While bariatric surgery is the most effective and durable modality for weight loss long term, the availability and accessibility of bariatric surgery remains limited in the adolescent population. Combination drug therapies could be an effective way to target obesity due to the variability in mechanisms associated with each of the drugs that could lead to potential synergy. Combination therapy could also allow for lower doses of each medication to mitigate side effects.[83] Drugs currently under investigation include centrally acting agents, gut hormones and incretin targets, leptin analogs, dual action GLP-1/glucagon receptor agonists, and lipase inhibitors. Many of these drugs have shown weight loss in either animal or human studies, and targeting obesity is a potential effect.[84]

Currently, pharmacotherapy to treat adolescents with obesity is very limited. Obesity is highly prevalent worldwide, and the percentage of affected individuals is rising, making obesity a disease that needs to be more highly addressed. More research is needed to develop additional pharmacotherapy for the treatment of obesity. In the last 20 years, the FDA has approved 208 drugs for cancer, 118 for cardiovascular disease, 168 for neurological diseases, and only 6 for obesity. Currently, phentermine and orlistat are the only two medications FDA approved for the treatment of obesity in adolescents, with the latter being the only one approved for long-term treatment. Other potential pharmacotherapy options for adolescents with obesity are forthcoming and will provided needed options for healthcare providers treating these patients.

Conclusion

Obesity in the pediatric population continues to be a global epidemic and can lead to multiple comorbidities, such as type 2 diabetes, hypertension, and cardiovascular disease, in the present and the future. While lifestyle modifications and behavioral therapy are pillars of weight management, the addition of anti-obesity agents to the treatment paradigm could augment their effects on weight reduction. While there have been a handful of anti-obesity agents approved for adults in recent years, there remain only two medications approved for weight loss in the pediatric population. Without more high-quality clinical trials that will lead to the approval of more medications for children and adolescents, providers are left with only limited tools to effectively treat this population. While there are a number of promising studies in progress, future studies may feature new drugs, combinations of multiple drugs, and adjunct therapy to bariatric surgery.

Author contributions

Kaylee Woodard: Conceptualization; Data curation; Formal analysis; Writing original draft; Writing-review & editing.

Logan Louque: Conceptualization; Data curation; Formal analysis; Writing original draft; Writing-review & editing.

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References

1. Pilitsi E, Farr OM, Polyzos SA, *et al.* Pharmacotherapy of obesity: available medications and drugs under investigation. *Metabolism* 2019; 92: 170–192.
2. Society for Adolescent Health and Medicine. Preventing and treating adolescent obesity: a position paper of the society for adolescent health and medicine. *J Adolesc Health* 2016; 59: 602–606.
3. World Health Organization. Obesity and overweight, https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (2018, accessed 14 May 2019).
4. Hales CM, Carroll MD, Fryar CD, *et al.* Prevalence of obesity among adults and youth: United States, 2015–2016. *NCHS Data Brief* 2017; 288: 1–8.
5. Centers for Disease Control and Prevention. Ten leading causes of death and injury, https://www.cdc.gov/injury/wisqars/LeadingCauses.html (2017, accessed 14 May 2019).
6. US Preventive Services Task Force, Curry SJ, Krist AH, *et al.* Behavioral weight loss interventions to prevent obesity-related morbidity and mortality in adults: US preventive services task force recommendation statement. *JAMA* 2018; 320: 1163–1171.
7. Xia Y, Kelton CM, Guo JJ, *et al.* Treatment of obesity: pharmacotherapy trends in the United States from 1999 to 2010. *Obesity (Silver Spring)* 2015; 23: 1721–1728.
8. Apovian CM, Aronne LJ, Bessesen DH, *et al.* Pharmacological management of obesity: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2015; 100: 342–362.
9. Londoño-Lemos ME. Pharmacological advances to the treatment of obesity. *J Child Obes* 2018; 3: 1-8.
10. Styne DM, Arslanian SA, Connor EL, *et al.* Pediatric obesity-assessment, treatment, and prevention: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2017; 102: 709–757.
11. Chanoine JP, Hampl S, Jensen C, *et al.* Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. *JAMA* 2005; 293: 2873–2883.
12. ECOG. Drug treatment of child and adolescent obesity, https://ebook.ecog-obesity.eu (2015, accessed 14 May 2019).
13. Ryder JR, Kaizer A, Rudser KD, *et al.* Effect of phentermine on weight reduction in a pediatric weight management clinic. *Int J Obes (Lond)* 2017; 41: 90–93.
14. Srivastava G, Fox CK, Kelly AS, *et al.* Clinical considerations regarding the use of obesity pharmacotherapy in adolescents with obesity. *Obesity (Silver Spring)* 2019; 27: 190–204.
15. Hendricks EJ. Off-label drugs for weight management. *Diabetes Metab Syndr Obes* 2017; 10: 223–234.
16. Kelly AS, Metzig AM, Rudser KD, *et al.* Exenatide as a weight-loss therapy in extreme pediatric obesity: a randomized, controlled pilot study. *Obesity (Silver Spring)* 2012; 20: 364–370.
17. Srivastava G, O'Hara V and Browne N. Use of lisdexamfetamine to treat obesity in an adolescent with severe obesity and binge eating. *Children (Basel)* 2019; 6: pii: E22.
18. Shapiro M, Reid A, Olsen B, *et al.* Topiramate, zonisamide and weight loss in children and adolescents prescribed psychiatric medications: a medical record review. *Int J Psychiatry Med* 2016; 51: 56–68.
19. Lustig RH, Hinds PS, Ringwald-Smith K, *et al.* Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2003; 88: 2586–2592.
20. Wolfgram PM, Carrel AL and Allen DB. Long-term effects of recombinant human growth hormone therapy in children with Prader-Willi syndrome. *Curr Opin Pediatr* 2013; 25: 509–514.
21. Gomez G and Stanford FC. US health policy and prescription drug coverage of FDA-approved medications for the treatment of obesity. *Int J Obes (Lond)* 2018; 42: 495–500.
22. Farr OM, Upadhyay J, Gavrieli A, *et al.* Lorcaserin administration decreases activation

of brain centers in response to food cues and these emotion- and salience-related changes correlate with weight loss effects: a 4-week-long randomized, placebo-controlled, double-blind clinical trial. *Diabetes* 2016; 65: 2943–2953.

23. Martin CK, Redman LM, Zhang J, *et al.* Lorcaserin, a 5-HT(2C) receptor agonist, reduces body weight by decreasing energy intake without influencing energy expenditure. *J Clin Endocrinol Metab* 2011; 96: 837–845.
24. Wolfe SM. When EMA and FDA decisions conflict: differences in patients or in regulation? *BMJ* 2013; 347: f5140.
25. Aronne LJ, Wadden TA, Peterson C, *et al.* Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. *Obesity (Silver Spring)* 2013; 21: 2163–2171.
26. Garvey WT, Ryan DH, Look M, *et al.* Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *Am J Clin Nutr* 2011; 95: 297–308.
27. Bohula EA, Wiviott SD, McGuire DK, *et al.* Cardiovascular safety of lorcaserin in overweight or obese patients. *N Engl J Med* 2018; 379: 1107–1117.
28. O'Neil PM, Smith SR, Weissman NJ, *et al.* Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. *Obesity (Silver Spring)* 2012; 20: 1426–1436.
29. Smith SR, Weissman NJ, Anderson CM, *et al.* Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med* 2010; 363: 245–256.
30. US Food and Drug Administration. FDA requests the withdrawal of the weight-loss drug Belviq, Belviq XR (lorcaserin) from the market, https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-withdrawal-weight-loss-drug-belviq-belviq-xr-lorcaserin-market (2020, accessed 13 February 2020).
31. Jordan J, Astrup A, Engeli S, *et al.* Cardiovascular effects of phentermine and topiramate: a new drug combination for the treatment of obesity. *J Hypertens* 2014; 32: 1178–1188.
32. Fujioka K. Safety and tolerability of medications approved for chronic weight management. *Obesity* 2015; 23: S7–S11.
33. Velazquez A and Apovian CM. Updates on obesity pharmacotherapy. *Ann N Y Acad Sci* 2018; 1411: 106–119.
34. Allison DB, Gadde KM, Garvey WT, *et al.* Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity (Silver Spring)* 2012; 20: 330–342.
35. Gadde KM, Allison DB, Ryan DH, *et al.* Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011; 377: 1341–1352.
36. Narayanaswami V and Dwoskin LP. Obesity: current and potential pharmacotherapeutics and targets. *Pharmacol Ther* 2017; 170: 116–147.
37. Daudon M, Frochot V, Bazin D, *et al.* Drug-induced kidney stones and crystalline nephropathy: pathophysiology, prevention and treatment. *Drugs* 2018; 78: 163–201.
38. Haslam D. Weight management in obesity – past and present. *Int J Clin Pract* 2016; 70: 206–217.
39. Greig SL and Keating GM. Naltrexone ER/Bupropion ER: a review in obesity management. *Drugs* 2015; 75: 1269–1280.
40. Wang GJ, Tomasi D, Volkow ND, *et al.* Effect of combined naltrexone and bupropion therapy on the brain's reactivity to food cues. *Int J Obes (Lond)* 2014; 38: 682–688.
41. Marcucci C, Sandson NB and Dunlap JA. Linezolid-bupropion interaction as possible etiology of severe intermittent intraoperative hypertension? *Anesthesiology* 2004; 101: 1487–1488.
42. Patel DK and Stanford FC. Safety and tolerability of new-generation anti-obesity medications: a narrative review. *Postgrad Med* 2018; 130: 173–182.
43. Khera R, Murad MH, Chandar AK, *et al.* Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. *JAMA* 2016; 315: 2424–2434.
44. Greenway FL, Fujioka K, Plodkowski RA, *et al.* Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2010; 376: 595–605.

45. Apovian CM, Aronne L, Rubino D, *et al.* A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity (Silver Spring)* 2013; 21: 935–943.

46. Hollander P, Gupta AK, Plodkowski R, *et al.* Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. *Diabetes Care* 2013; 36: 4022–4029.

47. Wadden TA, Foreyt JP, Foster GD, *et al.* Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity (Silver Spring)* 2011; 19: 110–120.

48. Nissen SE, Wolski KE, Prcela L, *et al.* Effect of naltrexone-bupropion on major adverse cardiovascular events in overweight and obese patients with cardiovascular risk factors: a randomized clinical trial. *JAMA* 2016; 315: 990–1004.

49. McCain JA. Antidepressants and suicide in adolescents and adults: a public health experiment with unintended consequences? *PT* 2009; 34: 355–378.

50. Upadhyay J, Polyzos SA, Perakakis N, *et al.* Pharmacotherapy of type 2 diabetes: an update. *Metabolism* 2018; 78: 13–42.

51. Van Can J, Sloth B, Jensen CB, *et al.* Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. *Int J Obes (Lond)* 2014; 38: 784–793.

52. Farr OM, Tsoukas MA, Triantafyllou G, *et al.* Short-term administration of the GLP-1 analog liraglutide decreases circulating leptin and increases GIP levels and these changes are associated with alterations in CNS responses to food cues: a randomized, placebo-controlled, crossover study. *Metabolism* 2016; 65: 945–953.

53. Ten Kulve JS, Veltman DJ, Van Bloemendaal L, *et al.* Liraglutide reduces CNS activation in response to visual food cues only after short-term treatment in patients with type 2 diabetes. *Diabetes Care* 2016; 39: 214–221.

54. Schlögl H, Kabisch S, Horstmann A, *et al.* Exenatide-induced reduction in energy intake is associated with increase in hypothalamic connectivity. *Diabetes Care* 2013; 36: 1933–1940.

55. Kievit P, Halem H, Marks DL, *et al.* Chronic treatment with a melanocortin-4 receptor agonist causes weight loss, reduces insulin resistance, and improves cardiovascular function in diet-induced obese rhesus macaques. *Diabetes* 2013; 62: 490–497.

56. O'Neil PM, Aroda VR, Astrup A, *et al.* Neuropsychiatric safety with liraglutide 3.0 mg for weight management: results from randomized controlled phase 2 and 3a trials. *Diabetes Obes Metab* 2017; 19: 1529–1536.

57. Pi-Sunyer X, Astrup A, Fujioka K, *et al.* A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med* 2015; 373: 11–22.

58. Monami M, Nreu B, Scatena A, *et al.* Safety issues with glucagon-like peptide-1 receptor agonists (pancreatitis, pancreatic cancer and cholelithiasis): data from randomized controlled trials. *Diabetes Obes Metab* 2017; 19: 1233–1241.

59. Steinberg WM, Rosenstock J, Wadden TA, *et al.* Impact of liraglutide on amylase, lipase, and acute pancreatitis in participants with overweight/obesity and normoglycemia, prediabetes, or type 2 diabetes: secondary analyses of pooled data from the scale clinical development program. *Diabetes Care* 2017; 40: 839–848.

60. Bahtiyar G, Pujals-Kury J and Sacerdote A. Cardiovascular effects of different glp-1 receptor agonists in patients with type 2 diabetes. *Curr Diab Rep* 2018; 18: 92.

61. Hegedüs L, Sherman SI, Tuttle RM, *et al.* No evidence of increase in calcitonin concentrations or development of c-cell malignancy in response to liraglutide for up to 5 years in the LEADER trial. *Diabetes Care* 2018; 41: 620–622.

62. Nauck MA, Jensen TJ, Rosenkilde C, *et al.* Neoplasms reported with liraglutide or placebo in people with type 2 diabetes: results from the LEADER randomized trial. *Diabetes Care* 2018; 41: 1663–1671.

63. Davies MJ, Bergenstal R, Bode B, *et al.* Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. *JAMA* 2015; 314: 687–699.

64. O'Connor EA, Evans CV, Burda BU, *et al.* Screening for obesity and intervention for weight management in children and adolescents: evidence report and systematic review for the US preventive services task force. *JAMA* 2017; 317: 2427–2444.

65. Dalai SS, Adler S, Najarian T, *et al.* Study protocol and rationale for a randomized double-blinded crossover trial of phentermine-topiramate ER versus placebo to treat binge

eating disorder and bulimia nervosa. *Contemp Clin Trials* 2018; 64: 173–178.

66. Guardia D, Rolland B, Deheul S, *et al*. Supervised off-label prescribing of topiramate for binge eating disorder within the system CAMTEA. *Therapie* 2012; 67: 480–481.

67. Guerdjikova AI, Fitch A and McElroy SL. Successful treatment of binge eating disorder with combination phentermine/topiramate extended release. *Prim Care Companion CNS Disord*. Epub ahead of print 21 April 2015. DOI: 10.4088/PCC.14l01708.

68. Leombruni P, Lavagnino L and Fassino S. Treatment of obese patients with binge eating disorder using topiramate: a review. *Neuropsychiatr Dis Treat* 2009; 5: 385–392.

69. Fox CK, Kaizer AM, Rudser KD, *et al*. Meal replacements followed by topiramate for the treatment of adolescent severe obesity: a pilot randomized controlled trial. *Obesity (Silver Spring)* 2016; 24: 2553–2561.

70. Fox CK, Marlatt KL, Rudser KD, *et al*. Topiramate for weight reduction in adolescents with severe obesity. *Clin Pediatr (Phila)* 2015; 54: 19–24.

71. Srivastava G and Apovian CM. Current pharmacotherapy for obesity. *Nat Rev Endocrinol* 2018; 14: 12–24.

72. Tamborlane WV, Barrientos-Pérez M, Fainberg U, *et al*. Liraglutide in children and adolescents with type 2 diabetes. *N Engl J Med* 2019; 381: 637–646.

73. Kelly AS, Rudser KD, Nathan BM, *et al*. The effect of glucagon-like peptide-1 receptor agonist therapy on body mass index in adolescents with severe obesity: a randomized, placebo-controlled, clinical trial. *JAMA Pediatr* 2013; 167: 355–360.

74. Nathan BM, Rudser KD, Abuzzahab MJ, *et al*. Predictors of weight-loss response with glucagon-like peptide-1 receptor agonist treatment among adolescents with severe obesity. *Clin Obes* 2016; 6: 73–78.

75. Salehi P, Hsu I, Azen CG, *et al*. Effects of exenatide on weight and appetite in overweight adolescents and young adults with Prader-Willi syndrome. *Pediatr Obes* 2017; 12: 221–228.

76. Danne T, Biester T, Kapitzke K, *et al*. Liraglutide in an adolescent population with obesity: a randomized, double-blind, placebo-controlled 5-week trial to assess safety, tolerability, and pharmacokinetics of liraglutide in adolescents aged 12-17 years. *J Pediatr* 2017; 181: 146–153.e3.

77. Tamborlane WV, Barrientos-Perez M, Fainberg U, *et al*. Liraglutide in children and adolescents with type 2 diabetes. *N Engl J Med* 2019; 381: 637–646.

78. Petri KC, Jacobsen LV and Klein DJ. Comparable liraglutide pharmacokinetics in pediatric and adult populations with type 2 diabetes: a population pharmacokinetic analysis. *Clin Pharmacokinet* 2015; 54: 663–670.

79. Klein DJ, Battelino T, Chatterjee DJ, *et al*. Liraglutide's safety, tolerability, pharmacokinetics, and pharmacodynamics in pediatric type 2 diabetes: a randomized, double-blind, placebo-controlled trial. *Diabetes Technol Ther* 2014; 16: 679–687.

80. O'Neil PM, Birkenfeld AL, McGowan B, *et al*. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *Lancet* 2018; 392: 637–649.

81. Rhythm receives expanded FDA breakthrough therapy designation for setmelanotide for rare genetic disorders of obesity, https://www.biospace.com/article/releases/rhythm-receives-expanded-fda-breakthrough-therapy-designation-for-setmelanotide-for-rare-genetic-disorders-of-obesity-/ (2017, accessed 22 September 2019).

82. Kühnen P, Clément K, Wiegand S, *et al*. Proopiomelanocortin deficiency treated with a melanocortin-4 receptor agonist. *N Engl J Med* 2016; 375: 240–246.

83. Fox CK and Kelly AS. The potential role of combination pharmacotherapy to improve outcomes of pediatric obesity: a case report and discussion. *Front Pediatr* 2018; 6: 361.

84. Srivastava G and Apovian C. Future pharmacotherapy for obesity: new anti-obesity drugs on the horizon. *Curr Obes Rep* 2018; 7: 147–161.