Published in final edited form as:
Int J Obes (Lond). 2013 January ; 37(1): 1–15. doi:10.1038/ijo.2012.144.

Pharmacotherapy for childhood obesity: present and future prospects

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Abstract

Pediatric obesity is a serious medical condition associated with significant comorbidities during childhood and adulthood. Lifestyle modifications are essential for treating children with obesity, yet many have insufficient response to improve health with behavioral approaches alone. This review summarizes the relatively sparse data on pharmacotherapy for pediatric obesity and presents information on obesity medications in development. Most previously studied medications demonstrated, at best, modest effects on body weight and obesity-related conditions. It is to be hoped that the future will bring new drugs targeting specific obesity phenotypes that will allow clinicians to use etiology-specific, and therefore more effective, anti-obesity therapies.

Keywords

Pharmacotherapy; Clinical trials; Energy intake/drug effects; Obesity drug therapy; Anti-obesity agents; Child; Adolescent; Review

Introduction

Prevalence of pediatric obesity and its complications: implications for intervention

Childhood obesity (defined as BMI ≥95th percentile for age and sex standards by the US Centers for Disease Control) has increased alarmingly over the past four decades, with almost 17% of US children and adolescents considered obese.[1] Globally, obesity is considered one of the leading risk factors contributing to morbidity and mortality.[2] Although there is some evidence that childhood obesity prevalence rates in the US,[1, 3, 4] Australia, China, and some European countries[5–9] may have stabilized, they remain unacceptably high.[2, 10–12] Childhood obesity is not only associated with a higher risk of morbidity and premature death in adults, but also is accompanied by many comorbid medical conditions during childhood.[13–19] The weight-related complications that arise during childhood, added to the risks for morbidity and mortality imparted to adults who were obese as children,[20–22] make development of effective treatments imperative.

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Conflict of Interest Statement: RSH and SZY declare no conflicts of interest.

Note Regarding Supplementary Information: Supplementary information is available at International Journal of Obesity's website

Role of lifestyle modification interventions in the treatment of pediatric obesity

Lifestyle modification interventions including behavioral treatment, diet modification, and physical activity, are the cornerstones of primary and secondary prevention/treatment of pediatric obesity.[23] Some studies have shown long-lived effects on pediatric overweight[24] specially from family-based or other behavioral treatments[25] without adverse effects on growth and development.[26] A Cochrane review and meta-analysis suggested some efficacy for such lifestyle modifications after 12 months of treatment with a BMI-SDS change of −0.04 and −0.14, respectively for children below and over 12 years of age.[25] For young children (5–12 years old), a considerable effect size of 0.89 (reduction in percentage of overweight) has been reported.[27, 28]

However, such interventions have shown relatively limited success among severely obese children and adolescents in either reduction of body weight or improvement of medical outcomes,[23, 25, 29, 30] Altogether, success of such interventions is closely related to external factors such as more family involvement, greater socioeconomic status, and better cultural adaptation, which may not be attainable in every circumstance.[31–33] As a result, there is considerable interest in combining lifestyle modification with more intensive strategies, including pharmacotherapy, to ameliorate pediatric obesity.[34]

Objectives

In this paper, we critically review the limited available data for the safety and efficacy of medications that have been studied for the treatment of obesity in children and adolescents including drugs approved for pediatric obesity treatment, those used off-label for obesity, as well as drugs under development for treatment of obesity in adults (Table 1).

Data Synthesis

A PubMed search was conducted with no limitation for year of publication to find reports investigating anti-obesity drugs utilizing the keywords `children' or `adolescents', `obesity,' `appetite' or `satiety', `drug' or `pharmacotherapy', and `clinical trial' or `meta-analysis`. The primary search resulted in 1296 articles for which the titles and/or abstracts were examined to determine if they complied with the search criteria. Automated searches were supplemented by examination of expert recommendation reports and bibliographic references from included research studies, as well as searches for the names of medications approved by the FDA for weight loss treatment or known to be used off-label for weight loss. Although the emphasis of this review is primarily on outcomes available from placebo-controlled, double-blind, randomized clinical trials, if other data were not available, we also present the results of open-label studies, as well as case series that report weight reduction as a primary or secondary endpoint of the study. Included pediatric clinical trials are enumerated in Supplemental Table 1. This review summarizes study design and clinical results achieved with each drug, with a discussion of methodology including subject characteristics, type, and duration of intervention, and adverse effects.

A brief appraisal of treatment options that are currently under investigation in adults will also be presented, based on a search conducted using `obesity,' `appetite or satiety', `drug or pharmacotherapy', and `clinical trial' or `review' that was supplemented by manual searches for current and new drugs for adults (Table 1).

Indications and considerations for pharmacotherapy in children

Expert committee recommendations for treatment of obesity in children suggest use of a staged, individualized approach[35] with medication employed after comprehensive nonpharmacologic multidisciplinary lifestyle modification interventions have failed.[36] There

are no pediatric experimental data establishing how long non-pharmacologic interventions should be attempted before medication is prescribed; typically a 6-month trial is used.[35] As observed in adults,[37] greater weight reduction has been reported among adolescents prescribed weight-loss medications who adhered to lifestyle interventions.[38] There are no pediatric data suggesting that obesity pharmacotherapy can be effectively prescribed without an accompanying lifestyle modification program.

Some experts believe obesity pharmacotherapy should be reserved for children and adolescents with high BMI who also demonstrate an obesity-related comorbidity such as dyslipidemia, hypertension, insulin resistance, fatty liver disease, or obstructive sleep apnea.[35, 39] The argument made is that the potential benefits are more likely to outweigh the potential risks of pharmacotherapy among those who already manifest complications of excess weight. Not all pediatric obesity drug treatment trials or published recommendations[34, 40] have required presence of obesity-related comorbidities.[36]

When the US Food and Drug Administration (FDA) approves a medication for a specific indication in adults, the lower age limit for approved use is generally set at 16 years.[41] Such medications will be described in this review as approved for adults. At the present time, only one agent (orlistat) holds FDA approval to treat obesity among adolescents age 12–16 years; no weight loss medications are approved for use in children below age 12.

Current pharmacotherapeutic options for obesity treatment

A) Drugs decreasing energy intake

I) Classical Centrally Acting Anorexiant Medications—The classical anorexiants act within the central nervous system to alter the release and reuptake of neurotransmitters long known to be implicated in appetite: norepinephrine, serotonin, and dopamine.[42] No weight loss medication with these mechanisms of action is currently approved for pediatric use and no available data support their long-term (>1 year) safety or efficacy in pediatric populations.

a. Appetite suppressants with primarily adrenergic effects

Phentermine,[43] diethylpropion[44] and mazindol[45–48] are anorexiants approved by the FDA for short-term use in adults that exert anorexiant effects primarily by increasing adrenergic tone.[49] They decrease food intake and also increase resting energy expenditure.[50] Phentermine and diethylpropion are chemically related to amphetamines.[51] Phentermine, mazindol, and diethylpropion are Drug Enforcement Administration (DEA) schedule IV controlled substances, indicating a relatively low potential for abuse.[52] Mazindol is not currently available in the US, and phenylpropanolamine[53] has been withdrawn due to increased risk of hemorrhagic stroke.[54] Other drugs such as benzphetamine and phendimetrazine are also approved for short term use with caution because of the potential risks such as pulmonary hypertension and valvular disease.[55, 56] Only small pediatric trials using phentermine[43, 57] or diethylpropion[44, 58] that lasted no more than 12 weeks have been reported. The adverse effect profiles of phentermine and diethylpropion in adults include insomnia, restlessness, and euphoria, palpitations, hypertension and cardiac arrhythmias, dizziness, blurred vision, and ocular irritation. Because of the lack of long-term pediatric treatment trials showing safety and efficacy, these drugs are not recommended as weight loss medications in youth.

b. Appetite suppressants with primarily serotonergic effects

There are several drugs for which pediatric trials exist that affect appetite primarily by increasing serotonergic release or inhibiting reuptake,[49, 51] including fluoxetine, chlorphentermine, fenfluramine and its stereoisomer, dexfenfluramine.[59–64] None of these drugs are currently FDA-approved for weight loss and most have been removed from the US market. The longest pediatric trial studied fenfluramine vs. placebo for 12 months in Brazilian adolescents.[62] Among those completing the study, fenfluramine-treated adolescents reportedly decreased BMI by −5.1 kg/m^2 (placebo-treated: −1.3 kg/m^2, $p<0.05$). Fenfluramine and dexfenfluramine were withdrawn in 1997, when cardiac valvulopathies similar to those seen in the carcinoid syndrome were found after their use.[65, 66] Serotonergic anorexiant agents were also associated with an increased incidence of primary pulmonary hypertension.[67] Other adverse effects of these agents included headache, abdominal pain, drowsiness, insomnia, dry mouth, increased activity, and irritability.[68]

c. Agents with primarily dopaminergic effects [57, 69]

Amphetamines, including methylphenidate and dextroamphetamine (DEA Schedule II controlled substances), increase dopaminergic tone by inhibiting dopamine reuptake. Acute studies demonstrate their ability to suppress appetite in obese adults[70] and anorexia is a frequently observed side effect when such medications are used in pediatric patients with attention deficit disorder.[71, 72] Because of their adverse effect profile (agitation, insomnia, tachycardia, hypertension, hyperhidrosis), abuse potential,[73] and the absence of trials showing long-term weight loss efficacy, these agents are not recommended, or approved for obesity management.

d. Agents with action at multiple monoamine receptors

Sibutramine, which inhibits norepinephrine and serotonin reuptake, was FDA-approved in 1997 for weight loss and maintenance of weight loss in adults with a BMI ≥30 or ≥27 with comorbidities.[74] Adverse effects included increases in pulse and blood pressure. Sibutramine was voluntarily withdrawn from use in 2010 when a greater incidence of cardiovascular events was found among adults at high risk for cardiovascular disease who took the drug.

Sibutramine was never approved for use in children younger than 16y,[75, 76] but it is one of the best studied weight loss medication in adolescents. Ten reports[38, 77–85] from 8 RCTs[38, 77, 79, 80, 82–85] and 2 open-label studies[78, 81] investigated the efficacy of sibutramine for weight loss in obese adolescents. Sibutramine 5–15 mg/d was administered as an adjunct to behavioral therapy with or without dietary intervention for 6- to 12-month periods and led to −2.9 to −3.6 kg/m^2 decreases in BMI. The largest trial was conducted on 498 obese adolescents randomized 3:1 to receive either sibutramine or placebo, in addition to caloric restriction and behavioral therapy for 12 months[79, 83]. Sibutramine was initiated at 10 mg/d and was increased to 15 mg/d in the 48% of subjects who showed <10% BMI reduction. This one-year therapy resulted in a 2.9 kg/m^2 BMI reduction in the sibutramine group (versus 0.3 kg/ m^2 for placebo). Among those receiving sibutramine plus behavioral therapy, 62.3% achieved a >5% BMI reduction, vs. 38.8% for placebo plus behavioral therapy. Treatment with sibutramine was associated with greater improvements in waist circumference, triglycerides, HDL-C, insulin levels, and insulin sensitivity. The effect of sibutramine on adolescent cardiovascular health was a matter of concern when the first pediatric data became available.[86] Greater reductions in cardiovascular variables, including change in systolic and diastolic blood pressure, and pulse rate were generally seen in placebo-treated adolescents despite the greater weight loss in the sibutramine-treated groups. Statistically significant differences favoring placebo were found for systolic blood pressure,[38] diastolic blood pressure,[79, 85] and heart rate.[38, 79] Adult studies confirmed

sibutramine increases blood pressure and heart rate.[87, 88] In September 2010, SCOUT (Sibutramine Cardiovascular Outcomes Trial), a multinational, randomized, placebo-controlled trial conducted in 16 countries, with a mean of 3.4 years' duration designed to assess clinical outcome in subjects with high risk of cardiovascular events[89] found that rates of nonfatal myocardial infarction and nonfatal stroke were 4.1% and 2.6% in the sibutramine group and 3.2% and 1.9% in the placebo group, respectively The risk of a primary outcome event was 11.4% in the sibutramine group as compared with 10.0% in the placebo group.[89] These findings resulted in an FDA request to withdraw sibutramine from the US market.[90] Apart from cardiovascular outcomes, other adverse effects included dry mouth, insomnia, constipation, headache, and cholelithiasis. Sibutramine was contraindicated in those individuals with pre-existing psychiatric disorders.[75] Other contraindications included concurrent use of monoamine oxidase inhibitors or selective serotonin reuptake inhibitors[91].

II) Drugs in development or used off-label that may act centrally as anorexiant medications—Emerging knowledge of the physiologic processes that control food intake over the last 15 years has led to greater understanding of both short-term signals that are involved in meal initiation and termination and longer-term regulators of energy balance. The adipocyte-derived hormone leptin[92] conveys information about the status of adipocyte triglyceride content, as well as the energy and macronutrient composition of recent intake, to brain regions that control energy intake.[93–95] Low concentrations of circulating leptin have been found to produce defects in both satiation and satiety leading to hyperphagia.[96] In the presence of leptin deficiency, activity increases in hypothalamic appetite-regulating neurons that release orexigenic peptides, and decreases in neurons that release anorexigenic factors.[97] Hormones and neurotransmitter systems involved in modulating the hypothalamic leptin signaling pathway have therefore been investigated for their potential ability to alter body weight in obese individuals.

a. Leptin. The discovery of leptin was received with great anticipation as a potential anti-obesity therapy because of its ability to reverse excess adiposity in rodent models characterized by leptin deficiency.[98–100] Indeed, leptin dramatically reduces body fat, suppresses appetitive behaviors and improves other leptin-responsive endocrine and metabolic abnormalities in children and adults with congenital leptin deficiency.[101–104] Open-label trials in pediatric and adult patients with leptin-insufficiency due to congenital lipodystrophies also demonstrated long-term improvements in metabolism[105] as did placebo-controlled trials in leptin-insufficient women with hypothalamic amenorrhea.[106] However, studies carried out in non-leptin-deficient adults have found relatively small effects on body weight, which limit leptin's usefulness as a stand-alone anti-obesity medication in those without leptin insufficiency.[107, 108] In adults who have undergone substantial weight reduction, there is suggestive evidence that leptin treatment to restore serum leptin concentrations to pre-weight loss values may reverse the subtle muscular, neuroendocrine, and autonomic adaptations to the weight-reduced state that may predispose such individuals to regain their lost weight.[109–113] No trials have assessed leptin's effects in non-leptin-deficient children during weight reduction or in the weight-reduced state.

b. Bupropion[114] is an antidepressant that inhibits presynaptic reuptake of both norepinephrine and dopamine. It is structurally close to the appetite suppressant diethylpropion.[115] Pooled data meta-analysis of 5 studies among adults reported a pooled random-effect estimate of total weight loss of 4.44 kg for Bupropion-treated as compared to 2.77 kg for placebo at a mixed end-point of 6 to 12 months;[116] similar mean weight reduction was reported in a review of trials on patients with major depression.[117] No pediatric RCTs of bupropion examining its effects on body weight have been published, although some short-term open-label studies suggest its use may be associated with small amounts of weight loss in adolescents.[118, 119]

c. Lorcaserin is a selective $5HT_{2C}$ receptor agonist that acts primarily in the central nervous system to inhibit feeding behavior.[120] In adults, a 3,182-person phase III multicenter clinical trial (BLOOM) showed 47.5% of those treated with lorcaserin, versus 20.3% of those given placebo, lost ≥5% of baseline body weight after one year; the average weight loss was 5.8 kg for lorcaserin, versus 2.2 kg for placebo.[121] A second trial (BLOSSOM)[122] found similar efficacy among 4008 patients. Adult patients with type 2 diabetes also decreased weight after treatment.[123] No pediatric trials have been reported. Common adverse events in both trials included headache, nausea, and dizziness. The FDA approved lorcaserin 10mg BID in June 2012 to treat adults with BMI≥30kg/m^2 or BMI≥27kg/m^2 accompanied with at least one comorbid condition such as hypertension, type 2 diabetes mellitus, or dyslipidemia.[124, 125] Although Lorcaserin use was not associated with valvular diseases in its placebo-controlled trials, it was recommended to be used with cautious in patients with congestive heart failure. The company was required by the FDA to conduct long-term cardiovascular outcomes trial.[124, 125] The package insert specifies that patients who have not lost ≥5% of baseline body weight by 12 weeks should discontinue lorcaserin.

d. Tesofensine is a triple monoamine reuptake inhibitor, blocking the presynaptic uptake of noradrenaline, dopamine, and serotonin. A 24-week phase II trial of 203 adults reported weight losses of up to 10% of body weight (versus 2% in placebo) in tesofensine-treated adults.[126] Body weight decreased 2.2kg in the placebo group and decreased 6.7–12.8 kg with different dosages of tesofensine.[126] Tesofensine increases satiety and may increase energy expenditure.[127128] No pediatric studies have been reported.

e. Cannabinoid (CB) receptor inhibitors. Stimulation of central CB_1 receptors increases appetite and fat deposition. Clinical trials of rimonabant, a selective endocannabinoid (CB_1 receptor) antagonist, indicated beneficial effects on weight, waist circumference, serum lipids, C-reactive protein, and glycemic control in adult patients with type 2 diabetes.[129130] Rimonabant's major adverse effects included nausea, anxiety, and depression.[131] The FDA did not approve rimonabant in 2007 because of concerns about neuropsychiatric adverse effects, particularly an increase in suicidality. Approved as a weight loss medication in Europe in 2006, Rimonabant was withdrawn by the European Medicines Agency in 2009 due to an increase in psychiatric adverse effects.[132] Clinical development of rimonabant as well as other centrally-acting CB_1 inhibitors such as taranabant and otenabant was suspended as a result of this adverse event profile.[74, 133, 134] More recent findings on CB1 receptor antagonism in the liver, adipocytes, muscle, and pancreas has raised hopes for potentially new generation of peripherally acting CB1 receptor inhibitors for treatment of obesity and its comorbid conditions such as fatty liver, insulin resistance and dyslipidemia.[135–138]

f. Topiramate is a GABA-ergic anticonvulsant drug that was fortuitously found to induce weight loss in patients with epilepsy. Among obese adults, data from trials suggested the possibility of substantial weight loss (4.5 to 16.36 kg for topiramate versus 1.7 to 8.6kg for placebo).[139] Topiramate could also abrogate antipsychotic-induced weight gain.[140] Common adverse events include paresthesias, taste impairment, and psychomotor disturbances including difficulties with concentration and sedation. In children, topiramate has been studied for the treatment of epilepsy[141] and migraine[142] where its use is associated with 1–2 kg decreases in body weight versus placebo. A limited number of open-label case series[143–145] have suggested potential improvements in body weight among children with antipsychotic-associated weight gain and in two extremely obese adolescent boys with Duchenne Muscular Dystrophy.[146] Concerns over the impairment of cognitive function at dosages similar to those used to treat seizure disorders will likely limit its use as a stand-alone agent;[147] no controlled trials restricted to obese children or adolescents have been reported. It is also important to note that there is concern that the risk for cleft lip with or

without cleft palate is increased in children born to mothers who used topiramate during pregnancy.[148, 149]

g. Amylin is a pancreatic beta-cell hormone that reduces food intake, slows gastric emptying, and reduces postprandial glucagon secretion in humans. Many of its hypophagic actions in rodents appear dependent on direct activation of noradrenergic neurons within the area postrema.[150] Amylin receptors in hind brain are hetero-oligomers with calcitonin receptors;[151] amylin interacts with other signals involved in the short term control of food intake, including cholecystokinin, glucagon-like peptide 1 and peptide YY and has been shown to decrease expression of orexigenic neuropeptides in the lateral hypothalamus.[150] Pramlintide, a synthetic analog of amylin, is approved for the treatment of both type 1 and type 2 diabetes and produces small weight losses in obese and diabetic adults.[152153] One study of adults with and without type 2 diabetes found a placebo-subtracted weight loss of up to 2.7 kg after 16 weeks of thrice-daily high-dose (240 μg) pramlintide.[154] In another study among 411 obese subjects, mean weight loss after 4 months for placebo was 2.8±0.8 kg, while for different pramlintide dosages it ranged between 3.8±0.7 to 6.1±0.7 kg.[155] The main adverse effects are nausea and abdominal discomfort. Although small trials of pramlintide have been reported in adolescents with type 1 diabetes,[156, 157] no pediatric or adolescent weight loss studies have been conducted.

h. Gut-Derived Hormones.

i. ***Ghrelin,*** produced by gastric enteroendocrine cells, is a circulating orexigenic hormone with marked fluctuations around meals. Short-term human studies find that ghrelin infusions increase food intake.[158] The importance of hyperghrelinemia as a cause of obesity and the efficacy of inhibition of ghrelin action for obesity treatment are uncertain, since ghrelin concentrations are usually suppressed by obesity. Obese patients with the Prader-Willi syndrome display unusually high circulating concentrations of ghrelin,[159] but treatment with octreotide (which suppresses ghrelin production) does not induce weight loss or reduce hyperphagia among these patients.[160]

ii. ***Incretin hormones,*** including glucagon-like peptide 1 (GLP-1), so named because they enhance glucose-stimulated insulin secretion, exert central anorectic effects in addition to their peripheral actions. Exenatide and liraglutide (GLP-1 analogues) are approved by FDA for adjunct treatment of type 2 diabetes mellitus in adults. Astrup et. al reported a dose-dependent mean weight loss of 4.8–7.2 kg with liraglutide, compared with 2.8 kg with placebo after 20 weeks in obese individuals without type 2 diabetes.[161] Others, however, reported somewhat smaller effect sizes in trials lasting up to 2y.[162–167] In non-diabetic subjects, placebo-controlled trials lasting up to 24 weeks found a 5.1 kg weight reduction for exenatide versus 1.6 kg for placebo.[168] One 12-week crossover study of 12 extremely obese children has reported a treatment effect of −3.9 kg compared to behavioral intervention alone from exenatide.[169] Studies documenting the long-term safety, tolerability, and efficacy of GLP-1 analogs in children and adolescents are needed.

B) Drugs affecting nutrient trafficking

I) Medications affecting digestion in the gut—*a. Orlistat.*

By inhibiting gastrointestinal lipases, orlistat reduces the absorption of approximately 30% of ingested dietary fat. Orlistat 120 mg three times a day was approved by the FDA in 2003 for management of obesity in adolescents 12–16 years of age.[170] The trials conducted to examine the efficacy of orlistat among adolescents lasted from 21 days to 15 months.[171–177] The largest study randomized 539 adolescents 12–16 years old for 52 weeks 3:1 to orlistat or

placebo with both groups receiving a multivitamin, instructions to follow a hypocaloric diet, and a physical activity prescription. Approximately 35% withdrew from each group. In both arms, BMI decreased until week 12, then stabilized in the orlistat group but increased with placebo. There was an overall −0.55 kg/m^2 decrease in BMI with orlistat versus a +0.31 kg/m^2 increase with placebo after 52 weeks ($p<0.001$). The most common adverse events were oily stools (50%), oily spotting (29%), oily evacuation (23%), abdominal pain (22%), and fecal urgency (21%). Seven participants on orlistat therapy and one child in the placebo group developed gallstones. However, only 2% of the dropouts in the orlistat group were described as due to drug-related adverse effects.[176] A secondary analysis of the same study indicated that response to treatment after 12 weeks was highly correlated with the amount of weight lost at the study end point (52 weeks),[178] suggesting early weight loss with orlistat is a strong predictor of long-term success with the compound. Another large 6-month randomized placebo-controlled study of 200 African American and Caucasian severely obese adolescents with obesity-related comorbid conditions published in abstract form[179] enrolled participants in a 12-week intensive weight reduction program with a 1:1 randomization to orlistat or placebo. Those taking orlistat lost 2.9kg compared to 0.6kg weight reduction in the placebo group. but had no significant improvements in their comorbid conditions. Small but significant increases in serum liver enzyme concentrations were also found in orlistat treated subjects. Orlistat has undergone two label changes due to reports of liver injury, cholelithiasis, and pancreatitis; a cause and effect relationship of severe liver injury with orlistat use has not, however, been established.[170] There is one report of acute hepatic injury in a 15-year old girl which resolved after the medication was stopped.[180] Since a lower dose (60mg) of orlistat was approved as an over-the-counter medication for adults in 2007, accidental ingestion has been reported in children below age 5. Data on exposures are limited, but among 45 patients with reported outcomes, there were no cases of severe, persistent effects.[181] Ingestion of dosages as high as 5 grams have been described with no serious adverse events identified.[182] Although adult patients have experienced improvements in glucose and insulin levels while taking orlistat,[183] metabolic benefits from orlistat therapy among adolescents have been reported only in a 20-person, 6mo open-label study by McDuffie et al. (a reduction in total cholesterol, LDL-C, fasting glucose and insulin[175, 184]) and Chanoine et al.(a decrease of −0.51 mmHg versus an increase of +1.30 mmHg for diastolic blood pressure in orlistat vs. placebo over 12 months).[176] Because Orlistat leads to decreased absorption of fat-soluble vitamins,[184] supplementation with a daily multivitamin is recommended.[185] The withdrawal rates among trials range from 0–35% . Orlistat should not be prescribed to patients with cholestasis or chronic malabsorption.

Orlistat produces modest weight loss and its long term efficacy for adolescents has not been established beyond 1 year. The thrice daily recommended dosing is another significant limitation to wide use of this drug among adolescents. Although orlistat is the only FDA-approved treatment for obesity among adolescents under the age of 16y, it appears to offers little prospect of benefit to those with severe obesity.

b. Cetilistat. Cetilistat is a gastrointestinal lipase inhibitor currently under investigation.[186, 187] A multicenter study of 612 adults found similar weight reductions for cetilistat and orlistat over 12 weeks among obese adults with type 2 diabetes treated with metformin, but with somewhat fewer adverse gastrointestinal events for cetilistat.[188] Since weight reductions were no greater than for orlistat, it can be anticipated that cetilistat will prove of similar modest utility for weight reduction.

c. Acarbose. Acarbose is a pseudotetrasaccharide that competitively inhibits intestinal α-glucosidase in the intestinal brush border.[189] This compromises the uptake of monosaccharides leading to lower postprandial insulin and glucose.[189] Acarbose is approved

for diabetes treatment, where it produces small weight losses in some studies among adults (0.46kg weight loss vs. 0.33kg weight gain with placebo).[190–192] There have been no published pediatric trials for acarbose as an anti-obesity drug and given its meager efficacy in adults, it appears unlikely that acarbose will be developed for weight control.

II) Medications affecting renal nutrient reabsorption—*Dapagliflozin* and ***Sergliflozin***[193, 194] are investigational selective inhibitors of the sodium-dependent glucose cotransporter-2 in the renal tubule. They suppress renal glucose reabsorption, resulting in a dose-related glucosuria.[195] These drugs were developed to improve glycemic control in type 2 diabetic patients but also induce weight loss. Among patients with type 2 diabetes, when compared to placebo, dapagliflozin induced significant improvements in glycemic control and reductions in body weight ranging from 2–5 kg[196–199] (vs. 0.95–1.55 kg reductions for placebo) due to the approximately 70g/d glucose that is excreted rather than reabsorbed in those given dapagliflozin.[195] Side effects include urinary tract and genital infections, volume depletion leading to increases in hematocrit and blood urea nitrogen, and hypoglycemia in those with diabetes. In July 2011, the FDA advisory committee voted against approval of Dapagliflozin for treatment of type 2 diabetes, mainly because of concerns over liver damage and a link to bladder and breast cancer.[200] No trials in obese, nondiabetic individuals have as yet been reported for these agents.

C) Drugs affecting metabolism

I) Modulation of insulin action—*a. Metformin*. Metformin is a biguanide that inhibits intestinal glucose absorption, reduces hepatic glucose production, and increases insulin sensitivity in peripheral insulin-targeted tissues.[201, 202]. Metformin is approved for the treatment of type 2 diabetes in adults and children over age 10y[203] but is not approved for treatment of obesity. Its administration has been associated with modest weight loss and reduction of insulin resistance among non-diabetic adults[201] as well as prevention or delay of type 2 diabetes onset.[204] Studies on the effects of metformin as a weight loss treatment among adolescents are few and most are short-term trials (6 months or less).[205206] The study with longest placebo-controlled duration randomized adolescents to 48 weeks of daily metformin hydrochloride extended release therapy or placebo in the context of a lifestyle intervention program. For this multicenter, randomized, double-blind, placebo-controlled trial, 92 obese adolescents completed a single-blind placebo 4-week run-in phase, after which the 77 subjects who demonstrated 80% medication compliance and attended at least 2 of the 3 scheduled lifestyle modification sessions, were randomized.[207] The BMI change among those who completed the trial was significantly different: −0.9 kg/m^2 in the metformin group vs. +2.2 kg/m^2 in placebo arm, but metformin treatment did not produce a significant change in total fat mass, abdominal fat, or insulin. The largest RCT in younger children[208] randomized 100 severely obese, insulin resistant children 6–12y to metformin or placebo for 6-months, followed by another 6-month of open-label metformin treatment. In 17% of subjects, the maximum dosage of 2000 mg/d was not tolerated and had to be reduced. In an intent-to-treat analysis of those who finished the placebo-controlled phase (85% in each group) the the average weight change in metformin group was +1.47 kg vs. +4.85 in placebo group.[208] Gastrointestinal complaints (liquid or loose stools and vomiting) were significantly more prevalent among those treated with metformin, yet, only 2 participants were reported as leaving the study because of medication intolerance. Fatigue was also significantly more likely to be reported among the metformin-treated children.

The metabolic effects of metformin in non-diabetic children and adolescents are inconsistent among studies.[207–211] In the available controlled trials, metformin's effect on BMI in children and adolescents varies, ranging from no change[212] to −0.5 to −1.5 kg/m^2. Metformin has also been studied in the context of treatment of the polycystic ovary

syndrome among adolescent girls, with observed reductions in BMI ranging from 0 to 3kg/m^2.[213–219] A placebo-controlled trial involving 38 adolescents with >10% weight gain on psychotropic drugs has also reported weight stabilization on metformin (mean weight change −0.13±2.88 kg) while subjects receiving placebo continued to gain weight (+4.01±6.23 kg) over 16 weeks.[220] Pooling the results of the two available studies of metformin as an agent for weight control among subjects receiving antipsychotic drugs suggests ~4.1% reduction in body weight.[221] In sum, it appears that metformin has relatively modest, but significant effects on body weight in obese children and adolescents, similar to its effects in adults. The main adverse effects of metformin are diarrhea, nausea, vomiting, and flatulence, which are usually transient and mild to moderate. The odds ratio of having biochemical Vitamin B12 deficiency is reported to be 2.92 in diabetic patients on metformin treatment based on data from the National Health and Nutrition Examination Survey (NHANES), 1999–2006,[222] yet there is no official recommendation for supplementation among these patients. Metformin is contraindicated in renal failure, should be withheld in critically ill patients and when use of imaging contrast agents is anticipated. Given its chemical similarity to phenformin, concerns were raised that metformin might predispose patients to the development of lactic acidosis; however a recent meta-analysis in Cochrane reviews reported no evidence supporting such a relationship.[223] With its modest impact on weight, metformin does not appear particularly efficacious for weight reduction. Its ability to prevent or delay the onset of dysglycemia in children remains unproven and requires further study.

b. Octreotide. Octreotide is a somatostatin analogue that, among its manifold effects, inhibits glucose-dependent insulin secretion from pancreatic beta cells.[224] There are three studies evaluating this drug for weight loss via subcutaneous injection in pediatric patients with hypothalamic obesity, who are believed to have elevated insulin production, perhaps in response to the stimulation of hepatic glucose production that results from their hypothalamic damage. These trials demonstrated either small weight losses or reduced weight gain in octreotide-treated subjects. One study[160] has examined the effect of octreotide on patients with Prader Willi Syndrome because of octreotide's ability to suppress ghrelin. After 16 weeks of monthly octreotide administration, there was no significant change in BMI compared to placebo.[160] The major adverse effect from octreotide is development of cholelithiasis or biliary sludging in up to 44% of subjects. Transient elevation of blood glucose (15–27%) diarrhea (36–48%), abdominal pain or discomfort, flatulence, influenza-like symptoms, constipation, headache, anemia, hypertension, dizziness, fatigue, nausea, and vomiting also occur.[160, 225] Octreotide cannot be recommended for treatment of obesity outside of clinical trials.

II) Modulation of lipolysis—*Growth hormone* inhibits lipoprotein lipase, increases hormone sensitive lipase, and stimulates adipocyte lipolysis.[226] Growth hormone also stimulates protein synthesis and increases fat free mass (both muscle and bone mass). Studies in growth hormone-deficient adults and children confirm that fat mass decreases after growth hormone treatment.[227–230] Treatment with recombinant human growth hormone (rHGH) is FDA-approved for children with PWS to increase height velocity.[75] A decrease in fat mass and an increase in lean body mass are observed among both adult and pediatric patients with PWS who are given growth hormone.[231–233] There is, however, no indication to use rHGH for non-syndromic obesity in the absence of growth hormone deficiency. A review of clinical trials of GH administration in patients with obesity showed no better performance for rHGH than for a hypocaloric diet.[234] Tumor development especially among patients who previously received irradiation for treatment of intracranial malignancies and potential adrenal insufficiency in previously unidentified hypopituitary patients are among the concerns with rHGH treatment.[235] Changes in glucose metabolism may appear during long-term treatment with growth hormone in PWS which necessitates

glucose monitoring among these patients.[236] There are also concerns about growth hormone causing greater cardiac diameters in PWS patients, although short-term studies do not support this finding.[237] Likewise, there are contradictory reports on the effect of GH treatment on respiratory symptoms (specifically sleep apnea) among PWS patients.[238, 239] Currently, the FDA has added labeling to growth hormone products stating that GH therapy is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment[240] because there may be an increased risk of sudden death.[241]

III) Modulation of energy expenditure—There are currently no medications augmenting energy expenditure that are approved for clinical use in the treatment of obesity. Thermogenic agents are appealing in theory, but have been found either to be ineffective or, when effective, to have unacceptable adverse consequences.[242]

a. Thyroid Hormones. Thyroid hormones can increase energy expenditure, but only when doses sufficient to cause hyperthyroidism are given.[243] Thus thyroid hormone treatments are not recommended for weight loss in children or adults.[244] TRβ1-selective thyromimetics with a safer profile with regards to cardiac and skeletal effects while exerting favorable effects on plasma cholesterol and TG levels are under development.[245] So far, early phases of clinical trials have not shown much efficacy for weight loss.[246]

b. β3-adrenergic receptor agonists. β3-adrenergic receptor activation by β-agonists induces lipolysis and increases fatty acid oxidation and induces weight loss in rodent obesity models. Unfortunately, human trials have not found significant weight losses or effects on energy expenditure from such agents.[247–249]

c. Caffeine plus Ephedrine. Ephedrine, a drug enhancing catecholaminergic tone that previously was available without a prescription, was withdrawn in 2002 by the FDA because of cardiovascular risks. The thermogenic effects of ephedrine in humans are greatly increased when methylxanthines like caffeine, which inhibit phosphodiesterases, are co-administered.[250] In adults, an herbal caffeine/ephedrine preparation produced a weight reduction of 5.3 vs. 2.6kg with placebo;[251] larger weight reductions were reported in a case series of 3 patients with hypothalamic obesity.[252] One small study that randomized 16 adolescents to caffeine plus ephedrine and 16 to placebo, reported significant weight loss (2.9 kg/m^2 vs. 0.5 kg/m^2 with placebo) in a 5-month trial.[253] Side effects included nausea, insomnia, tremor, dizziness, and palpitations.[254] Other studies among adults usually had small sample sizes, and the results were not consistent.[255–261]

D) New combination therapies

Since body weight is defended by multiple, redundant neural mechanisms, it is reasonable to attempt obesity treatment by targeting multiple weight-regulating pathways at the same time. The most successful of these combinations in adults was fenfluramine plus phentermine, for which weight losses were demonstrated in a cohort of 52 obese adults followed for 190 weeks.[262, 263] The efficacy of fenfluramine plus phentermine provided proof of principle that combination therapy might be useful, even though fenfluramine's adverse cardiac toxicity led to its withdrawal from clinical use.

I. Phentermine plus Topiramate—When low-dose, controlled-release, phentermine was combined with the glutamatergic and GABA-ergic antiepileptic topiramate in a large phase III study (more than 1400 participants on treatment arms with different doses), subjects lost 10.2 kg on combination therapy vs. 1.4 kg with placebo over 56 weeks.[264] The most common adverse events were dry mouth paresthesias, constipation, insomnia, dizziness, and dysgeusia. Depression- and anxiety-related adverse events were also observed. The medication had favorable effects on glycemia, including progression to diabetes,

improvements in lipids, blood pressure, sleep apnea, and quality of life measures. There was also, as previously noted, a small but consistent increase in pulse rate.[149] However, medication use for obesity-related comorbid conditions was reduced in the treatment groups compared with placebo. The overall rate of adverse effects decreased in weeks 56–108 compared to weeks 0–56; among which dry mouth, constipation and paresthesias were the most prevalent.[265–267] There were 19 pregnancies carried to term during these studies none of which resulted in congenital abnormalities.[149] In July 2012, the FDA voted for approval of phentermine (3.75–15mg/d) plus extended release topiramate (23–92mg/d) as an adjunct to diet and physical activity for treatment of obesity among adult individuals with BMI≥30kg/m^2 or BMI≥27kg/m^2 with at least one obesity-related comorbid condition.[268] The drug will carry a warning of potential increased risk for orofacial clefts in neonates exposed to topiramate during the first trimester of gestation and will be subject to a Risk Evaluation and Mitigation Strategy (REMS) that will restrict prescribing to trained clinicians, will require effective contraception and monthly pregnancy tests for reproductive age women, and will restrict dispensing to specific mail-order pharmacies. The company is also required to carry a long-term cardiovascular outcomes trial.[268] No randomized pediatric studies have as yet been reported.

II. Bupropion plus Zonisamide—Administration of Bupropion and Zonisamide (an anti-convulsant medication with serotonergic and dopaminergic activity) was reported to produce a weight loss of 7.2kg vs. 2.9kg with zonizamide alone among women in short-term Phase II trials with the most important adverse effects being headache, nausea and insomnia.[74, 269] Phase II trial data collection ended in 2009; additional results of trials are not available in published form.

III. Bupropion plus Naltrexone—This proposed combination is based on the premise that naltrexone can block POMC neuron autoinhibition by endogenous opioids, while bupropion amplifies the anorexic α-MSH release.[270] Combination therapy is more effective than placebo or bupropion monotherapy, with almost double the number of subjects losing >5% of their body weight compared to placebo.[271–274] In a modified-ITT-LOCF analysis, the combination resulted in 9.3 ± 0.4% weight loss compared to 5.1 ± 0.6% for placebo.[275] Nausea has been the most frequent adverse event, although there are also concerns about increases in blood pressure and risk for seizures from the use of bupropion.[276] Overall, there was a 46% dropout rate (vs. 45% in placebo group), among which 23% was due to adverse effects (12% in placebo group) suggesting tolerability issues.[272] The FDA Endocrinologic and Metabolic Drugs Advisory Committee recommended approval of this combination drug as an anti-obesity agent in December 2010,[277] but also recommended additional investigations of its potential adverse effects. The FDA decided in February 2011 that an approval could not be granted until additional studies of long-term cardiovascular safety have been completed.[278] The manufacturer announced in February 2012 its plan to conduct the cardiovascular outcome trial required by the FDA.[279]

IV. Amylin plus leptin—A study of pramlintide plus metreleptin for 24 weeks showed a 12.7% weight loss from 24 weeks of combination therapy, a greater effect than monotherapy with either drug with an overall weight change rate of −0.16 and −0.17 kg/week for metreleptin and pramlintide, and −0.36kg/week for the combination of the two drugs.[154, 280, 281] This combination requires injections, which may limit extensive use. Nausea and injection site reactions were the main adverse effects.[280]

V. Pramlintide plus phentermine or sibutramine—Based on preclinical studies on dietary induced obese rats, which showed a reduction in food intake (up to 40%) and body weight (up to 12%) after administration of amylin together with either phentermine or

sibutramine,[282] the effect of these combinations have been tested among 244 non-diabetic subjects vs. placebo in a 24-weeks, open label trial.[283] Weight loss with either combination was approximately 11 kg, while pramlintide alone resulted in −3.6 kg weight change. The main adverse effect was nausea among all groups receiving pramlintide, elevated diastolic blood pressure and heart rate were noted in the combination therapies.

Discussion

Effective pharmacotherapy that reverses excessive adiposity and improves obesity-related comorbid conditions in pediatric patients remains elusive. The weight management impact of available drugs has been modest. Meta-analyses of trials for weight loss in pediatric samples have shown a meager effect size of −0.7 kg/m^2 for orlistat, and a non-significant −0.17 kg/m^2 for metformin – no greater than the effect sizes found for behavioral interventions.[23] Even when combined with state-of-the-art behavioral interventions, existing pharmacotherapy among adolescents has only moderate efficacy.[32, 176, 207] Current guidelines, however, include medication in their recommended approaches to treat obese adolescents.[35, 36]

The most efficacious medications for treating obesity have, unfortunately had to be withdrawn because of adverse events. Because of the importance of the metabolic pathways involved in the regulation of energy balance, it is unlikely that any highly effective weight loss medication will be risk-free. Careful evaluation is required to balance potential known and unknown adverse effects against the potential benefits of anti-obesity medications in an individual child that may include improvements in metabolic, functional, and patient-reported outcomes such as quality-of-life.

Because obesity is a chronic condition, pediatric obesity treatments should demonstrate long-term safety and tolerability, as well as efficacy. The long-term impact of medications that have central nervous system effects or interfere with absorption of nutrients are particularly concerning when used in growing children and adolescents. Potential teratogencity of agents expected to be used in adolescent girls, in whom any pregnancy is likely to be unplanned, are also a particular concern. The bar for consideration of using obesity medications in children should be appropriately high, and commensurate with each medication's potential benefits, safety profile, and efficacy.

Why does pharmacotherapy for obesity fail so frequently due to either lack of efficacy, unacceptable adverse events, or both? Obesity is a multifactorial, polygenic condition. There are myriad redundant pathways involved in detecting the body's fuel abundance, adjusting energy requirements, regulating appetite and satiety, and determining body weight set-point, set against the background of an obesity-promoting environment and individual psychosocial and cultural factors. Much remains to be discovered about etiologic heterogeneity that can be anticipated to lead to disparities in the efficacy of medications among study participants. The value of using a specific treatment directed towards an established obesity-causing mechanism has already been shown for children and adolescents with one extremely rare form of monogenic obesity: leptin is remarkably successful to treat the obesity of leptin deficiency.[102, 104] It seems likely, therefore, that once a more complete differential diagnosis for pediatric obesity can be established based on genetic (and perhaps epigenetic) and phenotypic characteristics, new drug trials can be initiated that select patients who are more likely to respond to a given medication.

The belief that most patients with significant obesity have multiple contributing genetic loci is supported by recent genomewide association studies.[284–286] Many of the identified genotypes are associated with early obesity traits. Thus, for many, if not most children,

targeted combination therapies that affect multiple impaired weight-regulating systems are likely to be required to improve body weight and avoid obesity's comorbid conditions. The ability of combination drug therapy to ameliorate pediatric obesity safely remains to be demonstrated in meticulously designed clinical trials with adequate power. Dysregulation of other metabolic systems that have redundancy in their control mechanisms has been amenable to such an approach. For example, hypertension is now commonly treated with pharmacotherapeutic regimens that are directed against three or more different blood pressure control points.[287]

If novel single or combination therapies are to be tested in the future for their impact on pediatric obesity and its complications, the clinical trials would be most useful if they are conducted as randomized, placebo-controlled trials, have carefully-justified subject selection criteria and outcomes, are adequately powered to account for potentially high attrition rates,[23, 288] have long-term follow up, and are reported according to the CONSORT statement.[289] Obesity is a chronic condition but most pediatric studies have a short duration (6 to 12 months); thus there is little information available about the effectiveness and adverse effects from long term use of obesity medications in children and adolescents. Appropriate short- and long-term outcomes need to be identified for pediatric populations, rather than necessarily using adult-oriented outcomes. Although a good case can be made for using change in BMI rather than change in BMI percentile or BMI standard deviation score as the primary outcome in weight loss studies among obese children and adolescents,[290, 291] age-specific metrics are likely to be appropriate for metabolic and behavioral outcomes. Meta-analyses on clinical trials among adults show that there is usually little weight loss reported beyond the typical plateau at 6 months, which is followed by weight regain during the next few years.[292, 293]

Primary prevention and lifestyle intervention for those already overweight or obese are the foundations for weight management for children, adolescents, and adults. For obese youth who are unable to achieve sufficient weight loss with lifestyle interventions alone, adjunctive use of more intensive treatments, including pharmacotherapy, may be appropriate. However, the search for obesity medications that are safe for long-term use, sufficiently efficacious to promote enough weight loss to improve health, and have a favorable risk-benefit ratio remains elusive. Nevertheless, there is great hope that development of more effective, etiology-based anti-obesity therapies for children and adults will prove possible.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

JAY was Principal Investigator for NICHD-sponsored clinical studies using metformin, orlistat, and betahistine and received orlistat and matching placebo from Roche Pharmaceuticals and betahistine and matching placebo plus research support for clinical research studies from Obecure.

J Yanovski is a Commissioned Officer in the United States Public Health Service, Department of Health and Human Services. The conduct of this research was supported by Intramural Research Program grant 1ZIAHD000641 from the NICHD (to J. Yanovski).

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Table 1

Pharmacological agents used for weight loss in human studies.

Agent	Mechanism of action	Status
A) Classical centrally acting anorexiant agents		
Phenylpropanolamine[54]	Primarily adrenergic agents	Withdrawn (increased risk of hemorrhagic stroke).
Phentermine[51]		Approved for short-term use in adults.
Diethylpropion[44]		Approved for short-term use in adults .
Mazindol[4553]		Approved for short-term use in adults; not currently available in US.
Amphetamine[70–71]	Primarily dopaminergic agent	Not approved for obesity treatment.
Fenfluramine, dexfenfluramine[51, 62, 65]	Primarily serotonergic agents	Voluntarily withdrawn (valvular heart disease, pulmonary hypertension).
Sibutramine[87–89]	Mixed adrenergic-serotonergic agent	Voluntarily withdrawn (increased risk of serious, nonfatal cardiovascular events).
B) Drugs in development or used off-label that may act centrally as anorexiant medications		
Recombinant human leptin, metreleptin[101, 102]	Leptin receptor agonists	Investigational. In monotherapy successful for treatment of leptin deficiency.
Bupropion[114, 117]	Mixed dopaminergic and adrenergic reuptake inhibitor	Not FDA-approved for obesity.
Tesofensine[126–128]	Adrenergic/dopaminergic reuptake inhibitor	Investigational.
Lorcaserin[121, 122]	Highly selective serotonergic 5-HT_{2C} receptor agonist	FDA-approved as an anti-obesity drug in June 2012.
Fluoxetine[61, 205]	Selective Serotonin reuptake inhibitor	Not FDA-approved for obesity.
Rimonabant, Taranabant[130134]	Cannabinoid receptor-1 inhibitors	Never FDA-approved.
Topiramate[139, 140]	GABA-receptor activator, kainite/AMPA glutamate receptor inhibitor	Not FDA-approved for obesity. Concerns about teratogenicity and cognitive effects.
Pramlintide[153]	Amylinomimetic	Not FDA-approved for obesity.
Liraglutide, Exenatide[162–166, 294, 295]	GLP-1 analogues	Not FDA-approved for obesity.
Sitagliptin, Vildagliptin[296297]	Dipeptidyl peptidase inhibitor-4	Not FDA-approved for obesity.
Peptide YY[298299]	Acts on Y2 receptor	Investigational.
C) Drugs affecting nutrient trafficking		

Agent	Mechanism of action	Status
Orlistat[171–177]		FDA-approved for treatment of obesity in adolescents ≥12 years old.
Cetilistat[186, 187]	Gastrointestinal lipase inhibitors	Not FDA-approved for obesity.
Acarbose[190–192]	Intestinal α-glucosidase inhibitor	Not FDA-approved for obesity.
Dapagliflozin196–199, 300 Sergliflozin[193–195, 300]	Renal sodium-glucose cotransport inhibitors	Investigational.
D) Drugs affecting internal milieu/metabolic control		
Metformin[213, 206, 218]	AMP-activated protein kinase activation	Not FDA-approved for obesity.
Octreotide[224225]	Somatostatin analogue	Not FDA-approved for obesity. Weight stabilization in hypothalamic obesity.
Recombinant human growth hormone[234]	Growth hormone receptor agonist	Not FDA-approved for obesity.
Thyroid hormone[244]	Sympathomimetic	Not FDA-approved for obesity. Not recommended - risk of sudden death.
Ephedrine + Caffeine[253254, 261]	Sympathomimetic + nonselective antagonist of adenosine receptors	Never FDA-approved for obesity Ephedrine withdrawn from market.
E) Novel combination therapies in development		
Phentermine+Topiramate[265, 266]	Norepinephrine-releasing agent+GABA-receptor activator, kainite/AMPA glutamatereceptor inhibitor	FDA-approved as an anti-obesity drug in July 2012.
Bupropion+Zonisamide[269]	Norepinephrine/dopamine reuptake inhibitor +GABA-receptor activator	Investigational.
Bupropion+Naltrexone[274, 276]	Norepinephrine-dopamine reuptake inhibitor+ opioid receptor antagonist	Investigational.
Pramlintide+Metreleptin[154, 280, 281]	Amylinomimetic + leptin receptor agonist	Investigational.
Pramlintide+Phentermine or Sibutramine[283]	Amylinomimetic + norepinephrine releasing agent/ serotonergic and adrenergic reuptake inhibitor	Investigational.