



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

Roya Sherafat-Kazemzadeh, MD, PhD¹, Susan Z. Yanovski, MD^{1,2}, and Jack A. Yanovski, MD, PhD¹

¹Section on Growth and Obesity, Program in Developmental Endocrinology and Genetics, Eunice Kennedy Shriver National Institute of Child Health and Human Development

²Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health

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.

Correspondence to: Jack A. Yanovski, MD, PhD, Section on Growth and Obesity, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH, 10 Center Drive, Hatfield Clinical Research Center, Room 1E-3330, MSC 1103, Bethesda, Maryland, 20892-1103; Phone: 301-496-0858; Fax: 301-402-0574; jy15i@nih.gov.

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 overweight²⁴ specially from family-based or other behavioral treatments²⁵ 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 approach³⁵ 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 diethylpropion⁴⁴ 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 phenylpropanolamine⁵³ 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 anorexiants 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 adults⁷⁰ 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 events⁸⁹ 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 inhibitors⁹¹.

II) Drugs in development or used off-label that may act centrally as anorexiatic 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 leptin⁹² 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 metabolism¹⁰⁵ 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. Bupropion¹¹⁴ 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 $\geq 30\text{kg/m}^2$ or BMI $\geq 27\text{kg/m}^2$ 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.^{127,128} No pediatric studies have been reported.

e. Cannabinoid (CB) receptor inhibitors. Stimulation of central CB₁ receptors increases appetite and fat deposition. Clinical trials of rimonabant, a selective endocannabinoid (CB₁ receptor) antagonist, indicated beneficial effects on weight, waist circumference, serum lipids, C-reactive protein, and glycemic control in adult patients with type 2 diabetes.^{129,130} 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 CB₁ 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 epilepsy¹⁴¹ and migraine¹⁴² 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.^{152,153} 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 $+0.31 \text{ kg/m}^2$ 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 form¹⁷⁹ 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 $+1.30 \text{ mmHg}$ 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 10y²⁰³ 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 adults²⁰¹ 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).^{205,206} 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. $+2.2 \text{ kg/m}^2$ 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 children²⁰⁸ 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 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 change²¹² 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/m².^{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 ($+4.01 \pm 6.23$ 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 study¹⁶⁰ 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 impairment²⁴⁰ 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 TR β 1-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. β 3-adrenergic receptor agonists. β 3-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/m² vs. 0.5 kg/m² 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 zonisamide 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 $9.3 \pm 0.4\%$ weight loss compared to $5.1 \pm 0.6\%$ 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 -0.36 kg/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 teratogenicity 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).

References

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010. *Jama*. 2012; 307(5):483–90. [PubMed: 22253364]

2. World Health Organization. [Accessed: November 25, 2011] Obesity and Overweight Fact sheet Number 311. Web Page: <http://www.who.int/mediacentre/factsheets/fs311/en/index.html>
3. Ogden CL, Carroll MD, Curtin LR, Lamb MM, Flegal KM. Prevalence of high body mass index in US children and adolescents, 2007–2008. *JAMA*. 2010; 303(3):242–9. [PubMed: 20071470]
4. Ogden CL, Carroll MD, Curtin LR, Lamb MM, Flegal KM. Prevalence of High Body Mass Index in US Children and Adolescents, 2007–2008. *Jama*. 2010; 303(3):242–249. [PubMed: 20071470]
5. Rokholm B, Baker JL, Sorensen TI. The levelling off of the obesity epidemic since the year 1999 - a review of evidence and perspectives. *Obes Rev*. 2010
6. Sundblom E, Petzold M, Rasmussen F, Callmer E, Lissner L. Childhood overweight and obesity prevalences levelling off in Stockholm but socioeconomic differences persist. *Int J Obes (Lond)*. 2008; 32(10):1525–30. [PubMed: 18626485]
7. Salanave B, Peneau S, Rolland-Cachera MF, Hercberg S, Castetbon K. Stabilization of overweight prevalence in French children between 2000 and 2007. *Int J Pediatr Obes*. 2009; 4(2):66–72. [PubMed: 19306152]
8. Peneau S, Salanave B, Maillard-Teyssier L, Rolland-Cachera MF, Vergnaud AC, Mejean C, et al. Prevalence of overweight in 6- to 15-year-old children in central/western France from 1996 to 2006: trends toward stabilization. *Int J Obes (Lond)*. 2009; 33(4):401–7. [PubMed: 19238153]
9. Olds T, Maher C, Zumin S, Peneau S, Lioret S, Castetbon K, et al. Evidence that the prevalence of childhood overweight is plateauing: data from nine countries. *Int J Pediatr Obes*. 2011; 6(5–6):342–60. [PubMed: 21838570]
10. Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. *Int J Pediatr Obes*. 2006; 1(1):11–25. [PubMed: 17902211]
11. Kipping RR, Jago R, Lawlor DA. Obesity in children. Part 1: Epidemiology, measurement, risk factors, and screening. *Bmj*. 2008; 337:a1824. [PubMed: 18922835]
12. Mirmiran P, Sherafat-Kazemzadeh R, Jalali-Farahani S, Azizi F. Childhood obesity in the Middle East: a review. *East Mediterr Health J*. 2010; 16(9):1009–17. [PubMed: 21218730]
13. August GP, Caprio S, Fennoy I, Freemark M, Kaufman FR, Lustig RH, et al. Prevention and treatment of pediatric obesity: an endocrine society clinical practice guideline based on expert opinion. *The Journal of clinical endocrinology and metabolism*. 2008; 93(12):4576–99. [PubMed: 18782869]
14. Lee E. The world health organization's global strategy on diet, physical activity, and health: Turning strategy into action. *Food and Drug Law Journal*. 2005; 60(4):569–601.
15. Freedman DS, Kahn HS, Mei Z, Grummer-Strawn LM, Dietz WH, Srinivasan SR, et al. Relation of body mass index and waist-to-height ratio to cardiovascular disease risk factors in children and adolescents: the Bogalusa Heart Study. *Am J Clin Nutr*. 2007; 86(1):33–40. [PubMed: 17616760]
16. Freedman DS, Katzmarzyk PT, Dietz WH, Srinivasan SR, Berenson GS. Relation of body mass index and skinfold thicknesses to cardiovascular disease risk factors in children: the Bogalusa Heart Study. *Am J Clin Nutr*. 2009; 90(1):210–6. [PubMed: 19420092]
17. Young-Hyman D, Schlundt DG, Herman L, De Luca F, Counts D. Evaluation of the insulin resistance syndrome in 5- to 10-year-old overweight/obese African-American children. *Diabetes Care*. 2001; 24(8):1359–64. [PubMed: 11473070]
18. Csabi G, Torok K, Jeges S, Molnar D. Presence of metabolic cardiovascular syndrome in obese children. *Eur J Pediatr*. 2000; 159(1–2):91–4. [PubMed: 10653338]
19. Daniels SR. Complications of obesity in children and adolescents. *Int J Obes (Lond)*. 2009; 33(Suppl 1):S60–5. [PubMed: 19363511]
20. Baker JL, Olsen LW, Sorensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. *N Engl J Med*. 2007; 357(23):2329–37. [PubMed: 18057335]
21. Juonala M, Magnussen CG, Berenson GS, Venn A, Burns TL, Sabin MA, et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. *N Engl J Med*. 2011; 365(20):1876–85. [PubMed: 22087679]
22. Must A, Jacques PF, Dallal GE, Bajema CJ, Dietz WH. Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard Growth Study of 1922 to 1935. *N Engl J Med*. 1992; 327(19):1350–5. [PubMed: 1406836]

23. McGovern L, Johnson JN, Paulo R, Hettinger A, Singhal V, Kamath C, et al. Clinical review: treatment of pediatric obesity: a systematic review and meta-analysis of randomized trials. *J Clin Endocrinol Metab.* 2008; 93(12):4600–5. [PubMed: 18782881]
24. Flynn MA, McNeil DA, Maloff B, Mutasingwa D, Wu M, Ford C, et al. Reducing obesity and related chronic disease risk in children and youth: a synthesis of evidence with 'best practice' recommendations. *Obes Rev.* 2006; 7(Suppl 1):7–66. [PubMed: 16371076]
25. Oude Luttikhuis H, Baur L, Jansen H, Shrewsbury VA, O'Malley C, Stolk RP, et al. Interventions for treating obesity in children. *Cochrane Database Syst Rev.* 2009; (1):CD001872. [PubMed: 19160202]
26. Epstein LH, McCurley J, Valoski A, Wing RR. Growth in obese children treated for obesity. *Am J Dis Child.* 1990; 144(12):1360–4. [PubMed: 2244623]
27. Young KM, Northern JJ, Lister KM, Drummond JA, O'Brien WH. A meta-analysis of family-behavioral weight-loss treatments for children. *Clin Psychol Rev.* 2007; 27(2):240–9. [PubMed: 17070638]
28. Whitlock, EP.; O'Conner, EA.; Williams, SB.; Beil, TL.; Lutz, KW. Effectiveness of Primary Care Interventions for Weight Management in Children and Adolescents. An Updated, Targeted Systematic Review for the US Preventive Services Task Force. Agency for Healthcare Research and Quality (US); Report No.: 10-05144-EF-1. Evidence Synthesis, No. 76. January. 2010.
29. Fowler-Brown A, Kahwati LC. Prevention and treatment of overweight in children and adolescents. *Am Fam Physician.* 2004; 69(11):2591–8. [PubMed: 15202693]
30. Kalarchian MA, Levine MD, Arslanian SA, Ewing LJ, Houck PR, Cheng Y, et al. Family-based treatment of severe pediatric obesity: randomized, controlled trial. *Pediatrics.* 2009; 124(4):1060–8. [PubMed: 19786444]
31. Epstein LH, Valoski A, Wing RR, McCurley J. Ten-year outcomes of behavioral family-based treatment for childhood obesity. *Health Psychol.* 1994; 13(5):373–83. [PubMed: 7805631]
32. Seo DC, Sa J. A meta-analysis of obesity interventions among U.S. minority children. *J Adolesc Health.* 2010; 46(4):309–23. [PubMed: 20307819]
33. Epstein LH, Paluch RA, Roemmich JN, Beecher MD. Family-based obesity treatment, then and now: twenty-five years of pediatric obesity treatment. *Health Psychol.* 2007; 26(4):381–91. [PubMed: 17605557]
34. Spear BA, Barlow SE, Ervin C, Ludwig DS, Saelens BE, Schetzina KE, et al. Recommendations for treatment of child and adolescent overweight and obesity. *Pediatrics.* 2007; 120(Suppl 4):S254–88. [PubMed: 18055654]
35. Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics.* 2007; 120(Suppl 4):S164–92. [PubMed: 18055651]
36. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics.* 2011; 128(Suppl 5):S213–56. [PubMed: 22084329]
37. Wadden TA, Berkowitz RI, Womble LG, Sarwer DB, Phelan S, Cato RK, et al. Randomized trial of lifestyle modification and pharmacotherapy for obesity. *N Engl J Med.* 2005; 353(20):2111–20. [PubMed: 16291981]
38. Berkowitz RI, Wadden TA, Tershakovec AM, Cronquist JL. Behavior therapy and sibutramine for the treatment of adolescent obesity: a randomized controlled trial. *JAMA.* 2003; 289(14):1805–12. [PubMed: 12684359]
39. Yanovski JA. Intensive therapies for pediatric obesity. *Pediatr Clin North Am.* 2001; 48(4):1041–53. [PubMed: 11494637]
40. Daniels, SR.; Benuck, I.; Christakis, DA.; Dennison, BA.; Gidding, SS.; Gillman, MW., et al. Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: The Report of the Expert Panel. NHLBI NIH Guidelines, NHLBI, DHHS; Bethesda, MD: 2011. Overweight and Obesity; p. 282-320.
41. US Food and Drug Administration. [Accessed: 3/30/2012] Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act : Frequently Asked Questions on Pediatric Exclusivity (505A), The Pediatric "Rule," and their Interaction. Development &

Approval Process (Drugs). Web Page: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm077915.htm>

42. Samanin R, Garattini S. Neurochemical mechanism of action of anorectic drugs. *Pharmacol Toxicol.* 1993; 73(2):63–8. [PubMed: 7902561]
43. von Spranger J. Phentermine resinat in obesity. Clinical trial of Mirapront in adipose children. *Munch Med Wochenschr.* 1965; 107(38):1833–4. [PubMed: 5323498]
44. Andelman MB, Jones C, Nathan S. Treatment of obesity in underprivileged adolescents. Comparison of diethylpropion hydrochloride with placebo in a double-blind study. *Clin Pediatr (Phila).* 1967; 6(6):327–30. [PubMed: 5338123]
45. Dolecek R. Endocrine studies with mazindol in obese patients. *Pharmatherapeutica.* 1980; 2(5): 309–16. [PubMed: 6776543]
46. Golebiowska M, Chlebna-Sokol D, Kobierska I, Konopinska A, Malek M, Mastalska A, et al. Clinical evaluation of Teronac (mazindol) in the treatment of obesity in children. Part II. Anorectic properties and side effects (author's transl). *Przegl Lek.* 1981; 38(3):355–8. [PubMed: 7017827]
47. Golebiowska M, Chlebna-Sokol D, Mastalska A, Zwaigzne-Raczynska J. The clinical evaluation of teronac (Mazindol) in the treatment of children with obesity. Part I. Effect of the drug on somatic patterns and exercise capacity (author's transl). *Przegl Lek.* 1981; 38(2):311–4. [PubMed: 7017826]
48. Komorowski JM, Zwaigzne-Raczynska J, Owczarczyk I, Golebiowska M, Zarzycki J. Effect of mazindol (teronac) on various hormonal indicators in children with simple obesity. *Pediatr Pol.* 1982; 57(4):241–6. [PubMed: 6755371]
49. Rothman RB, Baumann MH, Dersch CM, Romero DV, Rice KC, Carroll FI, et al. Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse.* 2001; 39(1):32–41. [PubMed: 11071707]
50. Kaplan LM. Pharmacologic therapies for obesity. *Gastroenterol Clin North Am.* 2010; 39(1):69–79. [PubMed: 20202580]
51. Rothman RB, Ayestas MA, Dersch CM, Baumann MH. Aminorex, fenfluramine, and chlorphentermine are serotonin transporter substrates. Implications for primary pulmonary hypertension. *Circulation.* 1999; 100(8):869–75. [PubMed: 10458725]
52. Drug Enforcement Administration, Office of Diversion Control. [Accessed: 2/1/2012] List of scheduling actions controlled substances regulated chemicals, U.S. Department of Justice. Web Page: <http://www.dea.gov/diversion/diversion/index.html>
53. Altschuler S, Conte A, Sebok M, Marlin RL, Winick C. Three controlled trials of weight loss with phenylpropanolamine. *Int J Obes.* 1982; 6(6):549–56. [PubMed: 6761288]
54. Kernan WN, Viscoli CM, Brass LM, Broderick JP, Brott T, Feldmann E, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med.* 2000; 343(25):1826–32. [PubMed: 11117973]
55. Isojarvi JI, Turkka J, Pakarinen AJ, Kotila M, Rattya J, Myllyla VV. Thyroid function in men taking carbamazepine, oxcarbazepine, or valproate for epilepsy. *Epilepsia.* 2001; 42(7):930–4. [PubMed: 11488894]
56. Haas JT, Miao J, Chanda D, Wang Y, Zhao E, Haas ME, et al. Hepatic Insulin Signaling Is Required for Obesity-Dependent Expression of SREBP-1c mRNA but Not for Feeding-Dependent Expression. *Cell Metab.* 2012; 15(6):873–84. [PubMed: 22682225]
57. Lorber J. Obesity in childhood. A controlled trial of anorectic drugs. *Arch Dis Child.* 1966; 41(217):309–12. [PubMed: 5328625]
58. Stewart DA, Bailey JD, Patell H. Tenuate dospan as an appetitie suppressant in the treatment of obese children. *Appl Ther.* 1970; 12(5):34–6. [PubMed: 4912482]
59. Malecka-Tendera E, Koehler B, Muchacka M, Wazowski R, Trzciakowska A. Efficacy and safety of dexfenfluramine treatment in obese adolescents. *Pediatr Pol.* 1996; 71(5):431–6. [PubMed: 8710426]
60. Bacon GE, Lowrey GH. A clinical trial of fenfluramine in obese children. *Curr Ther Res Clin Exp.* 1967; 9(12):626–30. [PubMed: 4965459]

61. Goldstein DJ, Rampey AH Jr, Enas GG, Potvin JH, Fludzinski LA, Levine LR. Fluoxetine: a randomized clinical trial in the treatment of obesity. *Int J Obes Relat Metab Disord.* 1994; 18(3): 129–35. [PubMed: 8186809]
62. Pedrinola F, Cavaliere H, Lima N, Medeiros-Neto G. Is DL-fenfluramine a potentially helpful drug therapy in overweight adolescent subjects? *Obes Res.* 1994; 2(1):1–4. [PubMed: 16353602]
63. Pedrinola F, Szejnsznajd C, Lima N, Halpern A, Medeiros-Neto G. The addition of dexfenfluramine to fluoxetine in the treatment of obesity: a randomized clinical trial. *Obesity research.* 1996; 4(6):549–54. [PubMed: 8946439]
64. Rauh JL, Lipp R. Chlorphentermine as an anorexigenic agent in adolescent obesity. Report of its efficacy in a double-blind study of 30 teen-agers. *Clin Pediatr (Phila).* 1968; 7(3):138–40. [PubMed: 4868475]
65. Anon. Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: U.S. Department of Health and Human Services interim public health recommendations, November 1997. *MMWR Morb Mortal Wkly Rep.* 1997; 46(45):1061–6. [PubMed: 9385873]
66. Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med.* 1997; 337(9):581–8. [PubMed: 9271479]
67. Abenhaim L, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. *N Engl J Med.* 1996; 335(9):609–16. [PubMed: 8692238]
68. Weintraub M, Hasday JD, Mushlin AI, Lockwood DH. A double-blind clinical trial in weight control. Use of fenfluramine and phentermine alone and in combination. *Arch Intern Med.* 1984; 144(6):1143–8. [PubMed: 6375610]
69. Mason PW, Krawiecki N, Meacham LR. The use of dextroamphetamine to treat obesity and hyperphagia in children treated for craniopharyngioma. *Arch Pediatr Adolesc Med.* 2002; 156(9): 887–92. [PubMed: 12197795]
70. Davis C, Fattore L, Kaplan AS, Carter JC, Levitan RD, Kennedy JL. The suppression of appetite and food consumption by methylphenidate: the moderating effects of gender and weight status in healthy adults. *Int J Neuropsychopharmacol.* 2011:1–7.
71. Greenhill LL, Findling RL, Swanson JM. A double-blind, placebo-controlled study of modified-release methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics.* 2002; 109(3):E39. [PubMed: 11875167]
72. Wigal T, Greenhill L, Chuang S, McGough J, Vitiello B, Skrobala A, et al. Safety and tolerability of methylphenidate in preschool children with ADHD. *J Am Acad Child Adolesc Psychiatry.* 2006; 45(11):1294–303. [PubMed: 17028508]
73. Klein-Schwartz W. Abuse and toxicity of methylphenidate. *Curr Opin Pediatr.* 2002; 14(2):219–23. [PubMed: 11981294]
74. Ioannides-Demos LL, Piccenna L, McNeil JJ. Pharmacotherapies for obesity: past, current, and future therapies. *J Obes.* 2011; 2011:179674. [PubMed: 21197148]
75. Wald AB, Uli NK. Pharmacotherapy in pediatric obesity: current agents and future directions. *Rev Endocr Metab Disord.* 2009; 10(3):205–14. [PubMed: 19688265]
76. Dunican KC, Desilets AR, Montalbano JK. Pharmacotherapeutic options for overweight adolescents. *Ann Pharmacother.* 2007; 41(9):1445–55. [PubMed: 17652127]
77. Godoy-Matos A, Carraro L, Vieira A, Oliveira J, Guedes EP, Mattos L, et al. Treatment of obese adolescents with sibutramine: a randomized, double-blind, controlled study. *J Clin Endocrinol Metab.* 2005; 90(3):1460–5. [PubMed: 15613431]
78. Violante-Ortiz R, Del-Rio-Navarro BE, Lara-Esqueda A, Perez P, Fanghanel G, Madero A, et al. Use of sibutramine in obese Hispanic adolescents. *Adv Ther.* 2005; 22(6):642–9. [PubMed: 16510381]
79. Berkowitz RI, Fujioka K, Daniels SR, Hoppin AG, Owen S, Perry AC, et al. Effects of sibutramine treatment in obese adolescents: a randomized trial. *Ann Intern Med.* 2006; 145(2):81–90. [PubMed: 16847290]
80. Garcia-Morales LM, Berber A, Macias-Lara CC, Lucio-Ortiz C, Del-Rio-Navarro BE, Dorantes-Alvarez LM. Use of sibutramine in obese mexican adolescents: a 6-month, randomized, double-

- blind, placebo-controlled, parallel-group trial. *Clin Ther.* 2006; 28(5):770–82. [PubMed: 16861099]
81. Reisler G, Tauber T, Afriat R, Bortnik O, Goldman M. Sibutramine as an adjuvant therapy in adolescents suffering from morbid obesity. *Isr Med Assoc J.* 2006; 8(1):30–2. [PubMed: 16450748]
 82. Budd GM, Hayman LL, Crump E, Pollydore C, Hawley KD, Cronquist JL, et al. Weight loss in obese African American and Caucasian adolescents: secondary analysis of a randomized clinical trial of behavioral therapy plus sibutramine. *J Cardiovasc Nurs.* 2007; 22(4):288–96. [PubMed: 17589281]
 83. Daniels SR, Long B, Crow S, Styne D, Sothorn M, Vargas-Rodriguez I, et al. Cardiovascular effects of sibutramine in the treatment of obese adolescents: results of a randomized, double-blind, placebo-controlled study. *Pediatrics.* 2007; 120(1):e147–57. [PubMed: 17576783]
 84. Danielsson P, Janson A, Norgren S, Marcus C. Impact sibutramine therapy in children with hypothalamic obesity or obesity with aggravating syndromes. *J Clin Endocrinol Metab.* 2007; 92(11):4101–6. [PubMed: 17726084]
 85. Van Mil EG, Westerterp KR, Kester AD, Delemarre-van de Waal HA, Gerver WJ, Saris WH. The effect of sibutramine on energy expenditure and body composition in obese adolescents. *J Clin Endocrinol Metab.* 2007; 92(4):1409–14. [PubMed: 17264187]
 86. Yanovski JA. Behavior therapy and sibutramine for the treatment of adolescent obesity. *J Pediatr.* 2003; 143(5):686. [PubMed: 14615751]
 87. Pischon T, Sharma AM. Recent developments in the treatment of obesity-related hypertension. *Curr Opin Nephrol Hypertens.* 2002; 11(5):497–502. [PubMed: 12187313]
 88. Torp-Pedersen C, Caterson I, Coutinho W, Finer N, Van Gaal L, Maggioni A, et al. Cardiovascular responses to weight management and sibutramine in high-risk subjects: an analysis from the SCOUT trial. *Eur Heart J.* 2007; 28(23):2915–23. [PubMed: 17595194]
 89. James WP, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med.* 2010; 363(10):905–17. [PubMed: 20818901]
 90. US Food and Drug Administration. [Accessed: 10/20/2010] Meridia (sibutramine): Market Withdrawal Due to Risk of Serious Cardiovascular Events. Web Page: <http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm228830.htm>
 91. Yanovski SZ, Yanovski JA. Obesity. *N Engl J Med.* 2002; 346(8):591–602. [PubMed: 11856799]
 92. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature.* 1994; 372(6505):425–32. [PubMed: 7984236]
 93. Havel PJ. Control of energy homeostasis and insulin action by adipocyte hormones: leptin, acylation stimulating protein, and adiponectin. *Curr Opin Lipidol.* 2002; 13(1):51–9. [PubMed: 11790963]
 94. Havel PJ, Townsend R, Chaump L, Teff K. High-fat meals reduce 24-h circulating leptin concentrations in women. *Diabetes.* 1999; 48(2):334–41. [PubMed: 10334310]
 95. Weigle DS, Cummings DE, Newby PD, Breen PA, Frayo RS, Matthys CC, et al. Roles of leptin and ghrelin in the loss of body weight caused by a low fat, high carbohydrate diet. *J Clin Endocrinol Metab.* 2003; 88(4):1577–86. [PubMed: 12679442]
 96. McDuffie JR, Riggs PA, Calis KA, Freedman RJ, Oral EA, DePaoli AM, et al. Effects of exogenous leptin on satiety and satiation in patients with lipodystrophy and leptin insufficiency. *J Clin Endocrinol Metab.* 2004; 89(9):4258–63. [PubMed: 15356018]
 97. Schwartz MW. Brain pathways controlling food intake and body weight. *Exp Biol Med (Maywood).* 2001; 226(11):978–81. [PubMed: 11743132]
 98. Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, et al. Weight-reducing effects of the plasma protein encoded by the obese gene. *Science.* 1995; 269(5223):543–6. [PubMed: 7624777]
 99. Pelleymounter MA, Cullen MJ, Baker MB, Hecht R, Winters D, Boone T, et al. Effects of the obese gene product on body weight regulation in ob/ob mice. *Science.* 1995; 269(5223):540–3. [PubMed: 7624776]

100. Campfield LA, Smith FJ, Guisez Y, Devos R, Burn P. Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks [see comments]. *Science*. 1995; 269(5223):546–9. [PubMed: 7624778]
101. Farooqi IS, Jebb SA, Langmack G, Lawrence E, Cheetham CH, Prentice AM, et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *N Engl J Med*. 1999; 341(12):879–84. [PubMed: 10486419]
102. Farooqi IS, Matarese G, Lord GM, Keogh JM, Lawrence E, Agwu C, et al. Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J Clin Invest*. 2002; 110(8):1093–103. [PubMed: 12393845]
103. Gibson WT, Farooqi IS, Moreau M, DePaoli AM, Lawrence E, O'Rahilly S, et al. Congenital leptin deficiency due to homozygosity for the Delta133G mutation: report of another case and evaluation of response to four years of leptin therapy. *J Clin Endocrinol Metab*. 2004; 89(10):4821–6. [PubMed: 15472169]
104. Paz-Filho G, Wong ML, Licinio J. Ten years of leptin replacement therapy. *Obes Rev*. 2011; 12(5):e315–23. [PubMed: 21410864]
105. Chong AY, Lupsa BC, Cochran EK, Gorden P. Efficacy of leptin therapy in the different forms of human lipodystrophy. *Diabetologia*. 2010; 53(1):27–35. [PubMed: 19727665]
106. Chou SH, Chamberland JP, Liu X, Matarese G, Gao C, Stefanakis R, et al. Leptin is an effective treatment for hypothalamic amenorrhea. *Proc Natl Acad Sci U S A*. 2011; 108(16):6585–90. [PubMed: 21464293]
107. Heymsfield SB, Greenberg AS, Fujioka K, Dixon RM, Kushner R, Hunt T, et al. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. *Jama*. 1999; 282(16):1568–75. [PubMed: 10546697]
108. Moon HS, Matarese G, Brennan AM, Chamberland JP, Liu X, Fiorenza CG, et al. Efficacy of metreleptin in obese patients with type 2 diabetes: cellular and molecular pathways underlying leptin tolerance. *Diabetes*. 2011; 60(6):1647–56. [PubMed: 21617185]
109. Rosenbaum M, Murphy EM, Heymsfield SB, Matthews DE, Leibel RL. Low dose leptin administration reverses effects of sustained weight-reduction on energy expenditure and circulating concentrations of thyroid hormones. *J Clin Endocrinol Metab*. 2002; 87(5):2391–4. [PubMed: 11994393]
110. Rosenbaum M, Goldsmith R, Bloomfield D, Magnano A, Weimer L, Heymsfield S, et al. Low-dose leptin reverses skeletal muscle, autonomic, and neuroendocrine adaptations to maintenance of reduced weight. *J Clin Invest*. 2005; 115(12):3579–86. [PubMed: 16322796]
111. Rosenbaum M, Sy M, Pavlovich K, Leibel RL, Hirsch J. Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. *J Clin Invest*. 2008; 118(7):2583–91. [PubMed: 18568078]
112. Goldsmith R, Joannisse DR, Gallagher D, Pavlovich K, Shamoone E, Leibel RL, et al. Effects of experimental weight perturbation on skeletal muscle work efficiency, fuel utilization, and biochemistry in human subjects. *Am J Physiol Regul Integr Comp Physiol*. 2010; 298(1):R79–88. [PubMed: 19889869]
113. Baldwin KM, Joannisse DR, Haddad F, Goldsmith RL, Gallagher D, Pavlovich KH, et al. Effects of Weight Loss and Leptin on Skeletal Muscle in Human Subjects. *Am J Physiol Regul Integr Comp Physiol*. 2011
114. Anderson JW, Greenway FL, Fujioka K, Gadde KM, McKenney J, O'Neil PM. Bupropion SR enhances weight loss: a 48-week double-blind, placebo- controlled trial. *Obes Res*. 2002; 10(7):633–41. [PubMed: 12105285]
115. Billes SK, Cowley MA. Inhibition of dopamine and norepinephrine reuptake produces additive effects on energy balance in lean and obese mice. *Neuropsychopharmacology*. 2007; 32(4):822–34. [PubMed: 16841072]
116. Li Z, Maglione M, Tu W, Mojica W, Arterburn D, Shugarman LR, et al. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med*. 2005; 142(7):532–46. [PubMed: 15809465]

117. Jain AK, Kaplan RA, Gadde KM, Wadden TA, Allison DB, Brewer ER, et al. Bupropion SR vs. placebo for weight loss in obese patients with depressive symptoms. *Obes Res.* 2002; 10(10): 1049–56. [PubMed: 12376586]
118. Glod CA, Lynch A, Flynn E, Berkowitz C, Baldessarini RJ. Open trial of bupropion SR in adolescent major depression. *J Child Adolesc Psychiatr Nurs.* 2003; 16(3):123–30. [PubMed: 14603988]
119. Becker EA, Shafer A, Anderson R. Weight changes in teens on psychotropic medication combinations at Austin State Hospital. *Tex Med.* 2005; 101(3):62–70. [PubMed: 16134805]
120. Martin CK, Redman LM, Zhang J, Sanchez M, Anderson CM, Smith SR, 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(3):837–45. [PubMed: 21190985]
121. Smith SR, Weissman NJ, Anderson CM, Sanchez M, Chuang E, Stubbe S, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med.* 2010; 363(3):245–56. [PubMed: 20647200]
122. Fidler MC, Sanchez M, Raether B, Weissman NJ, Smith SR, Shanahan WR, et al. A One-Year Randomized Trial of Lorcaserin for Weight Loss in Obese and Overweight Adults: The BLOSSOM Trial. *J Clin Endocrinol Metab.* 2011
123. O'Neil PM, Smith SR, Weissman NJ, Fidler MC, Sanchez M, Zhang J, 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(7):1426–36. [PubMed: 22421927]
124. Jaslow, R. FDA approves obesity pill Belviq for obese, overweight people with weight-related health problems. Web Page: Accessed:
125. [Accessed: 7/1/2012] FDA approves Belviq to treat some overweight or obese adults. Web Page: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm309993.htm>
126. Astrup A, Madsbad S, Breum L, Jensen TJ, Kroustrup JP, Larsen TM. Effect of tesofensine on bodyweight loss, body composition, and quality of life in obese patients: a randomised, double-blind, placebo-controlled trial. *Lancet.* 2008; 372(9653):1906–13. [PubMed: 18950853]
127. Gilbert JA, Gasteyger C, Raben A, Meier DH, Astrup A, Sjodin A. The effect of tesofensine on appetite sensations. *Obesity.* 2012; 20(3):553–61. [PubMed: 21720440]
128. Sjodin A, Gasteyger C, Nielsen AL, Raben A, Mikkelsen JD, Jensen JK, et al. The effect of the triple monoamine reuptake inhibitor tesofensine on energy metabolism and appetite in overweight and moderately obese men. *Int J Obes (Lond).* 2010; 34(11):1634–43. [PubMed: 20479765]
129. Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet.* 2007; 370(9600): 1706–13. [PubMed: 18022033]
130. Van Gaal L, Pi-Sunyer X, Despres JP, McCarthy C, Scheen A. Efficacy and safety of rimonabant for improvement of multiple cardiometabolic risk factors in overweight/obese patients: pooled 1-year data from the Rimonabant in Obesity (RIO) program. *Diabetes Care.* 2008; 31(Suppl 2):S229–40. [PubMed: 18227491]
131. US Food and Drug Administration. [Accessed: 3/30/2012] Endocrine and Metabolic Drugs Advisory Committee Meeting. Sanofi Aventis: Zimulti (Rimonabant) Briefing Document - NDA 21-888. May 20. 2007 Web Page: <http://www.scribd.com/doc/1117189/US-Food-and-Drug-Administration-20074306b101sponsorbackgrounder>
132. Wathion, N. [Accessed: 3/30/2012] European Medicines Agency Public Statement on Acomplia (rimonabant) - Withdrawal of the Marketing Authorisation in European Union, Report Number: EMEA/39457/2009. Web Page: http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/11/WC500_012189.pdf
133. Heal DJ, Gosden J, Smith SL. Regulatory challenges for new drugs to treat obesity and comorbid metabolic disorders. *Br J Clin Pharmacol.* 2009; 68(6):861–74. [PubMed: 20002080]
134. Koch L. Obesity: Taranabant no longer developed as an antiobesity agent. *Nat Rev Endocrinol.* 2010; 6(6):300. [PubMed: 20518102]

135. Osei-Hyiaman D, Liu J, Zhou L, Godlewski G, Harvey-White J, Jeong WI, et al. Hepatic CB1 receptor is required for development of diet-induced steatosis, dyslipidemia, and insulin and leptin resistance in mice. *J Clin Invest*. 2008; 118(9):3160–9. [PubMed: 18677409]
136. Nogueiras R, Veyrat-Durebex C, Suchanek PM, Klein M, Tschop J, Caldwell C, et al. Peripheral, but not central, CB1 antagonism provides food intake-independent metabolic benefits in diet-induced obese rats. *Diabetes*. 2008; 57(11):2977–91. [PubMed: 18716045]
137. Nakata M, Yada T. Cannabinoids inhibit insulin secretion and cytosolic Ca²⁺ oscillation in islet beta-cells via CB1 receptors. *Regul Pept*. 2008; 145(1–3):49–53. [PubMed: 17884194]
138. Ruby MA, Nomura DK, Hudak CS, Mangravite LM, Chiu S, Casida JE, et al. Overactive endocannabinoid signaling impairs apolipoprotein E-mediated clearance of triglyceride-rich lipoproteins. *Proc Natl Acad Sci U S A*. 2008; 105(38):14561–6. [PubMed: 18794527]
139. Kramer CK, Leitao CB, Pinto LC, Canani LH, Azevedo MJ, Gross JL. Efficacy and safety of topiramate on weight loss: a meta-analysis of randomized controlled trials. *Obes Rev*. 2011; 12(5):e338–47. [PubMed: 21438989]
140. Narula PK, Rehan HS, Unni KE, Gupta N. Topiramate for prevention of olanzapine associated weight gain and metabolic dysfunction in schizophrenia: a double-blind, placebo-controlled trial. *Schizophrenia research*. 2010; 118(1–3):218–23. [PubMed: 20207521]
141. Glauser TA, Dlugos DJ, Dodson WE, Grinspan A, Wang S, Wu SC. Topiramate monotherapy in newly diagnosed epilepsy in children and adolescents. *J Child Neurol*. 2007; 22(6):693–9. [PubMed: 17641254]
142. Ferraro D, Di Trapani G. Topiramate in the prevention of pediatric migraine: literature review. *J Headache Pain*. 2008; 9(3):147–50. [PubMed: 18385933]
143. Lessig MC, Shapira NA, Murphy TK. Topiramate for reversing atypical antipsychotic weight gain. *J Am Acad Child Adolesc Psychiatry*. 2001; 40(12):1364. [PubMed: 11765278]
144. Pavuluri MN, Janicak PG, Carbray J. Topiramate plus risperidone for controlling weight gain and symptoms in preschool mania. *J Child Adolesc Psychopharmacol*. 2002; 12(3):271–3. [PubMed: 12427302]
145. Canitano R. Clinical experience with Topiramate to counteract neuroleptic induced weight gain in 10 individuals with autistic spectrum disorders. *Brain Dev*. 2005; 27(3):228–32. [PubMed: 15737706]
146. Carter GT, Yudkowsky MP, Han JJ, McCrory MA. Topiramate for weight reduction in Duchenne muscular dystrophy. *Muscle Nerve*. 2005; 31(6):788–9. [PubMed: 15779019]
147. Nathan PJ, O'Neill BV, Napolitano A, Bullmore ET. Neuropsychiatric adverse effects of centrally acting antiobesity drugs. *CNS Neurosci Ther*. 2011; 17(5):490–505. [PubMed: 21951371]
148. Fountain NB. A pregnant pause to consider teratogenicity of topiramate. *Epilepsy Curr*. 2009; 9(2):36–8. [PubMed: 19421375]
149. Roberts, MD. [Accessed: 3/30/2012] US Food and Drug Administration Endocrinologic and Metabolic Drugs Advisory Committee Clinical Briefing Document February 22, 2012. VIVUS, Inc. New Drug Application 22580 : V I-0521 QNEXA (phentermine/topiramate). Web Page: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM292315.pdf>
150. Potes CS, Lutz TA. Brainstem mechanisms of amylin-induced anorexia. *Physiol Behav*. 2010; 100(5):511–8. [PubMed: 20226802]
151. Hay DL, Christopoulos G, Christopoulos A, Sexton PM. Amylin receptors: molecular composition and pharmacology. *Biochem Soc Trans*. 2004; 32(Pt 5):865–7. [PubMed: 15494035]
152. Singh-Franco D, Perez A, Harrington C. The effect of pramlintide acetate on glycemic control and weight in patients with type 2 diabetes mellitus and in obese patients without diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2011; 13(2):169–80. [PubMed: 21199269]
153. Maggs D, Shen L, Strobel S, Brown D, Kolterman O, Weyer C. Effect of pramlintide on A1C and body weight in insulin-treated African Americans and Hispanics with type 2 diabetes: a pooled post hoc analysis. *Metabolism*. 2003; 52(12):1638–42. [PubMed: 14669170]

154. Aronne L, Fujioka K, Aroda V, Chen K, Halseth A, Kesty NC, et al. Progressive reduction in body weight after treatment with the amylin analog pramlintide in obese subjects: a phase 2, randomized, placebo-controlled, dose-escalation study. *J Clin Endocrinol Metab.* 2007; 92(8): 2977–83. [PubMed: 17504894]
155. Smith SR, Aronne LJ, Burns CM, Kesty NC, Halseth AE, Weyer C. Sustained weight loss following 12-month pramlintide treatment as an adjunct to lifestyle intervention in obesity. *Diabetes Care.* 2008; 31(9):1816–23. [PubMed: 18753666]
156. Chase HP, Lutz K, Pencek R, Zhang B, Porter L. Pramlintide lowered glucose excursions and was well-tolerated in adolescents with type 1 diabetes: results from a randomized, single-blind, placebo-controlled, crossover study. *J Pediatr.* 2009; 155(3):369–73. [PubMed: 19464026]
157. Kishiyama CM, Burdick PL, Cobry EC, Gage VL, Messer LH, McFann K, et al. A pilot trial of pramlintide home usage in adolescents with type 1 diabetes. *Pediatrics.* 2009; 124(5):1344–7. [PubMed: 19858155]
158. Wren AM, Seal LJ, Cohen MA, Brynes AE, Frost GS, Murphy KG, et al. Ghrelin enhances appetite and increases food intake in humans. *J Clin Endocrinol Metab.* 2001; 86(12):5992. [PubMed: 11739476]
159. Cummings DE, Clement K, Purnell JQ, Vaisse C, Foster KE, Frayo RS, et al. Elevated plasma ghrelin levels in Prader Willi syndrome. *Nat Med.* 2002; 8(7):643–4. [PubMed: 12091883]
160. De Waele K, Ishkanian SL, Bogarin R, Miranda CA, Ghatei MA, Bloom SR, et al. Long-acting octreotide treatment causes a sustained decrease in ghrelin concentrations but does not affect weight, behaviour and appetite in subjects with Prader-Willi syndrome. *Eur J Endocrinol.* 2008; 159(4):381–8. [PubMed: 18603572]
161. Astrup A, Rossner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet.* 2009; 374(9701):1606–16. [PubMed: 19853906]
162. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care.* 2009; 32(7):1224–30. [PubMed: 19289857]
163. Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia.* 2009; 52(10):2046–55. [PubMed: 19688338]
164. Nauck MA, Ratner RE, Kapitza C, Berria R, Boldrin M, Balena R. Treatment with the human once-weekly glucagon-like peptide-1 analog taspoglutide in combination with metformin improves glycemic control and lowers body weight in patients with type 2 diabetes inadequately controlled with metformin alone: a double-blind placebo-controlled study. *Diabetes Care.* 2009; 32(7):1237–43. [PubMed: 19366970]
165. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care.* 2009; 32(1):84–90. [PubMed: 18931095]
166. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet.* 2009; 373(9662):473–81. [PubMed: 18819705]
167. Taylor K, Gurney K, Han J, Pencek R, Walsh B, Trautmann M. Exenatide once weekly treatment maintained improvements in glycemic control and weight loss over 2 years. *BMC Endocr Disord.* 2011; 11:9. [PubMed: 21529363]
168. Rosenstock J, Klaff LJ, Schwartz S, Northrup J, Holcombe JH, Wilhelm K, et al. Effects of exenatide and lifestyle modification on body weight and glucose tolerance in obese subjects with and without pre-diabetes. *Diabetes Care.* 2010; 33(6):1173–5. [PubMed: 20332357]
169. Kelly AS, Metzger AM, Rudser KD, Fitch AK, Fox CK, Nathan BM, et al. Exenatide as a weight-loss therapy in extreme pediatric obesity: a randomized, controlled pilot study. *Obesity (Silver Spring).* 2012; 20(2):364–70. [PubMed: 22076596]

170. Mathis, LL. US Food and Drug Administration. Pediatric Advisory Committee Meeting; March 22, 2010; OrlistatUpdate. Web Page: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM205380.pdf>
171. McDuffie JR, Calis KA, Uwaifo GI, Sebring NG, Fallon EM, Hubbard VS, et al. Three-month tolerability of orlistat in adolescents with obesity-related comorbid conditions. *Obes Res.* 2002; 10(7):642–50. [PubMed: 12105286]
172. Zhi J, Moore R, Kanitra L. The effect of short-term (21-day) orlistat treatment on the physiologic balance of six selected macrominerals and microminerals in obese adolescents. *J Am Coll Nutr.* 2003; 22(5):357–62. [PubMed: 14559927]
173. Norgren S, Danielsson P, Jurold R, Lotborn M, Marcus C. Orlistat treatment in obese prepubertal children: a pilot study. *Acta Paediatr.* 2003; 92(6):666–70. [PubMed: 12856974]
174. Ozkan B, Bereket A, Turan S, Keskin S. Addition of orlistat to conventional treatment in adolescents with severe obesity. *Eur J Pediatr.* 2004; 163(12):738–41. [PubMed: 15378354]
175. McDuffie JR, Calis KA, Uwaifo GI, Sebring NG, Fallon EM, Frazer TE, et al. Efficacy of orlistat as an adjunct to behavioral treatment in overweight African American and Caucasian adolescents with obesity-related co-morbid conditions. *J Pediatr Endocrinol Metab.* 2004; 17(3):307–19. [PubMed: 15112907]
176. Chanoine JP, Hampl S, Jensen C, Boldrin M, Hauptman J. Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. *Jama.* 2005; 293(23):2873–83. [PubMed: 15956632]
177. Maahs D, de Serna DG, Kolotkin RL, Ralston S, Sandate J, Qualls C, et al. Randomized, double-blind, placebo-controlled trial of orlistat for weight loss in adolescents. *Endocr Pract.* 2006; 12(1):18–28. [PubMed: 16524859]
178. Chanoine JP, Richard M. Early weight loss and outcome at one year in obese adolescents treated with orlistat or placebo. *Int J Pediatr Obes.* 2011; 6(2):95–101. [PubMed: 20858149]
179. Yanovski JA, McDuffie JR, Salaita CS, Tanofsky-Kraff M, Sebring NG, Young-Hyman D, et al. A Randomized, Placebo-Controlled Trial of the Effects of Orlistat on Body Weight and Body Composition in African American and Caucasian Adolescents with Obesity-Related Comorbid Conditions. *Obesity.* 2008; 16(Suppl. 1):S63.
180. Umemura T, Ichijo T, Matsumoto A, Kiyosawa K. Severe hepatic injury caused by orlistat. *Am J Med.* 2006; 119(8):e7. [PubMed: 16887401]
181. Forrester MB. Pattern of orlistat exposures in children aged 5 years or less. *J Emerg Med.* 2009; 37(4):396–9. [PubMed: 18403165]
182. O'Connor MB. An orlistat “overdose” in a child. *Ir J Med Sci.* 2010; 179(2):315. [PubMed: 19763670]
183. Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care.* 2004; 27(1):155–61. [PubMed: 14693982]
184. McDuffie JR, Calis KA, Booth SL, Uwaifo GI, Yanovski JA. Effects of orlistat on fat-soluble vitamins in obese adolescents. *Pharmacotherapy.* 2002; 22(7):814–22. [PubMed: 12126214]
185. [Accessed: 7/9/2012] FDA Approves Orlistat for Over-the-Counter Use. Web Page: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108839.htm>
186. Kopelman P, Bryson A, Hickling R, Rissanen A, Rossner S, Toubro S, et al. Cetilistat (ATL-962), a novel lipase inhibitor: a 12-week randomized, placebo-controlled study of weight reduction in obese patients. *Int J Obes (Lond).* 2007; 31(3):494–9. [PubMed: 16953261]
187. Kopelman P, De Groot GH, Rissanen A, Rossner S, Toubro S, Palmer R, et al. Weight loss, HbA1c reduction, and tolerability of cetilistat in a randomized, placebo-controlled phase 2 trial in obese diabetics: Comparison with orlistat (xenical). *Obesity.* 2010; 18(1):108–115. [PubMed: 19461584]
188. Kopelman P, de Groot GH, Rissanen A, Rossner S, Toubro S, Palmer R, et al. Weight loss, HbA1c reduction, and tolerability of cetilistat in a randomized, placebo-controlled phase 2 trial in obese diabetics: comparison with orlistat (Xenical). *Obesity (Silver Spring).* 2010; 18(1):108–15. [PubMed: 19461584]

189. Salvatore T, Giugliano D. Pharmacokinetic-pharmacodynamic relationships of Acarbose. *Clin Pharmacokinet.* 1996; 30(2):94–106. [PubMed: 8906894]
190. Wang JS, Lin SD, Lee WJ, Su SL, Lee IT, Tu ST, et al. Effects of acarbose versus glibenclamide on glycemic excursion and oxidative stress in type 2 diabetic patients inadequately controlled by metformin: a 24-week, randomized, open-label, parallel-group comparison. *Clinical therapeutics.* 2011; 33(12):1932–42. [PubMed: 22078152]
191. Wolever TM, Chiasson JL, Josse RG, Hunt JA, Palmason C, Rodger NW, et al. Small weight loss on long-term acarbose therapy with no change in dietary pattern or nutrient intake of individuals with non-insulin-dependent diabetes. *Int J Obes Relat Metab Disord.* 1997; 21(9):756–63. [PubMed: 9376887]
192. Tugrul S, Kutlu T, Pekin O, Baglam E, Kiyak H, Oral O. Clinical, endocrine, and metabolic effects of acarbose, a alpha-glucosidase inhibitor, in overweight and nonoverweight patients with polycystic ovarian syndrome. *Fertil Steril.* 2008; 90(4):1144–8. [PubMed: 18377903]
193. Hussey EK, Clark RV, Amin DM, Kipnes MS, O'Connor-Semmes RL, O'Driscoll EC, et al. Single-dose pharmacokinetics and pharmacodynamics of sergliflozin etabonate, a novel inhibitor of glucose reabsorption, in healthy volunteers and patients with type 2 diabetes mellitus. *J Clin Pharmacol.* 2010; 50(6):623–35. [PubMed: 20056803]
194. Hussey EK, Dobbins RL, Stoltz RR, Stockman NL, O'Connor-Semmes RL, Kapur A, et al. Multiple-dose pharmacokinetics and pharmacodynamics of sergliflozin etabonate, a novel inhibitor of glucose reabsorption, in healthy overweight and obese subjects: a randomized double-blind study. *J Clin Pharmacol.* 2010; 50(6):636–46. [PubMed: 20200268]
195. Komoroski B, Vachharajani N, Boulton D, Kornhauser D, Gerald M, Li L, et al. Dapagliflozin, a novel SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects. *Clin Pharmacol Ther.* 2009; 85(5):520–6. [PubMed: 19129748]
196. Zhang L, Feng Y, List J, Kasichayanula S, Pfister M. Dapagliflozin treatment in patients with different stages of type 2 diabetes mellitus: effects on glycaemic control and body weight. *Diabetes Obes Metab.* 2010; 12(6):510–6. [PubMed: 20518806]
197. Strojek K, Yoon KH, Hruba V, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. *Diabetes Obes Metab.* 2011; 13(10):928–38. [PubMed: 21672123]
198. Nauck MA, Del Prato S, Meier JJ, Duran-Garcia S, Rohwedder K, Elze M, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. *Diabetes Care.* 2011; 34(9):2015–22. [PubMed: 21816980]
199. Bolinder J, Ljunggren O, Kullberg J, Johansson L, Wilding J, Langkilde AM, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycaemic control on metformin. *J Clin Endocrinol Metab.* 2012; 97(3):1020–31. [PubMed: 22238392]
200. Grogan, K. [Accessed: 11/25/2011] FDA panel rejects B-MS/AZ's diabetes drug...but only just. *Pharma Times Online.* Published on-line 07/20/2011. Web Page: http://www.pharmatimes.com/Article/11-07-20/FDA_panel_rejects_B-MS_AZ_s_diabetes_drug_but_only_just.aspx
201. Mehnert H. Metformin, the rebirth of a biguanide: mechanism of action and place in the prevention and treatment of insulin resistance. *Exp Clin Endocrinol Diabetes.* 2001; 109(Suppl 2):S259–64. [PubMed: 11460576]
202. Hundal RS, Inzucchi SE. Metformin: new understandings, new uses. *Drugs.* 2003; 63(18):1879–94. [PubMed: 12930161]
203. Bestermann W, Houston MC, Basile J, Egan B, Ferrario CM, Lackland D, et al. Addressing the global cardiovascular risk of hypertension, dyslipidemia, diabetes mellitus, and the metabolic syndrome in the southeastern United States, part II: treatment recommendations for management of the global cardiovascular risk of hypertension, dyslipidemia, diabetes mellitus, and the metabolic syndrome. *Am J Med Sci.* 2005; 329(6):292–305. [PubMed: 15958871]
204. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002; 346(6):393–403. [PubMed: 11832527]

205. Rezvanian H, Hashemipour M, Kelishadi R, Tavakoli N, Poursafa P. A randomized, triple masked, placebo-controlled clinical trial for controlling childhood obesity. *World J Pediatr.* 2010; 6(4):317–22. [PubMed: 21080144]
206. Freemark M, Bursey D. The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. *Pediatrics.* 2001; 107(4):E55. [PubMed: 11335776]
207. Wilson DM, Abrams SH, Aye T, Lee PD, Lenders C, Lustig RH, et al. Metformin extended release treatment of adolescent obesity: a 48-week randomized, double-blind, placebo-controlled trial with 48-week follow-up. *Arch Pediatr Adolesc Med.* 2010; 164(2):116–23. [PubMed: 20124139]
208. Yanovski JA, Krakoff J, Salaita CG, McDuffie JR, Kozlosky M, Sebring NG, et al. Effects of metformin on body weight and body composition in obese insulin-resistant children: a randomized clinical trial. *Diabetes.* 2011; 60(2):477–85. [PubMed: 21228310]
209. Fu JF, Liang L, Zou CC, Hong F, Wang CL, Wang XM, et al. Prevalence of the metabolic syndrome in Zhejiang Chinese obese children and adolescents and the effect of metformin combined with lifestyle intervention. *Int J Obes (Lond).* 2007; 31(1):15–22. [PubMed: 16953257]
210. Atabek ME, Pirgon O. Use of metformin in obese adolescents with hyperinsulinemia: a 6-month, randomized, double-blind, placebo-controlled clinical trial. *J Pediatr Endocrinol Metab.* 2008; 21(4):339–48. [PubMed: 18556965]
211. Clarson CL, Mahmud FH, Baker JE, Clark HE, McKay WM, Schauteet VD, et al. Metformin in combination with structured lifestyle intervention improved body mass index in obese adolescents, but did not improve insulin resistance. *Endocrine.* 2009; 36(1):141–6. [PubMed: 19387874]
212. Wiegand S, l'Allemand D, Hubel H, Krude H, Burmann M, Martus P, et al. Metformin and placebo therapy both improve weight management and fasting insulin in obese insulin-resistant adolescents: a prospective, placebo-controlled, randomized study. *Eur J Endocrinol.* 2010; 163(4):585–92. [PubMed: 20639355]
213. Legro RS. Impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women: do we need a new drug? *J Clin Endocrinol Metab.* 2008; 93(11):4218–20. [PubMed: 18987279]
214. Mastorakos G, Koliopoulos C, Deligeoroglou E, Diamanti-Kandarakis E, Creatsas G. Effects of two forms of combined oral contraceptives on carbohydrate metabolism in adolescents with polycystic ovary syndrome. *Fertil Steril.* 2006; 85(2):420–7. [PubMed: 16595221]
215. Hoeger K, Davidson K, Kochman L, Cherry T, Kopin L, Guzick DS. The impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women in two randomized, placebo-controlled clinical trials. *J Clin Endocrinol Metab.* 2008; 93(11):4299–306. [PubMed: 18728175]
216. Ibanez L, de Zegher F. Ethinylestradiol-drospirenone, flutamide-metformin, or both for adolescents and women with hyperinsulinemic hyperandrogenism: opposite effects on adipocytokines and body adiposity. *J Clin Endocrinol Metab.* 2004; 89(4):1592–7. [PubMed: 15070917]
217. Bridger T, MacDonald S, Baltzer F, Rodd C. Randomized placebo-controlled trial of metformin for adolescents with polycystic ovary syndrome. *Arch Pediatr Adolesc Med.* 2006; 160(3):241–6. [PubMed: 16520442]
218. Allen HF, Mazzone C, Heptulla RA, Murray MA, Miller N, Koenigs L, et al. Randomized controlled trial evaluating response to metformin versus standard therapy in the treatment of adolescents with polycystic ovary syndrome. *J Pediatr Endocrinol Metab.* 2005; 18(8):761–8. [PubMed: 16200842]
219. Arslanian SA, Lewy V, Danadian K, Saad R. Metformin therapy in obese adolescents with polycystic ovary syndrome and impaired glucose tolerance: amelioration of exaggerated adrenal response to adrenocorticotropin with reduction of insulinemia/insulin resistance. *J Clin Endocrinol Metab.* 2002; 87(4):1555–9. [PubMed: 11932281]
220. Klein DJ, Cottingham EM, Sorter M, Barton BA, Morrison JA. A randomized, double-blind, placebo-controlled trial of metformin treatment of weight gain associated with initiation of

- atypical antipsychotic therapy in children and adolescents. *Am J Psychiatry*. 2006; 163(12): 2072–9. [PubMed: 17151157]
221. Bjorkhem-Bergman L, Asplund AB, Lindh JD. Metformin for weight reduction in non-diabetic patients on antipsychotic drugs: a systematic review and meta-analysis. *J Psychopharmacol*. 2011; 25(3):299–305. [PubMed: 20080925]
 222. Reinstatler L, Qi YP, Williamson RS, Garn JV, Oakley GP Jr. Association of biochemical B12 deficiency with metformin therapy and vitamin B12 supplements: the national health and nutrition examination survey, 1999–2006. *Diabetes Care*. 2012; 35(2):327–33. [PubMed: 22179958]
 223. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2010; (4):CD002967.
 224. Gambineri A, Patton L, De Iasio R, Cantelli B, Cognini GE, Filicori M, et al. Efficacy of octreotide-LAR in dieting women with abdominal obesity and polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2005; 90(7):3854–62. [PubMed: 15827099]
 225. Haqq AM, Stadler DD, Rosenfeld RG, Pratt KL, Weigle DS, Frayo RS, et al. Circulating ghrelin levels are suppressed by meals and octreotide therapy in children with Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2003; 88(8):3573–6. [PubMed: 12915638]
 226. Dietz J, Schwartz J. Growth hormone alters lipolysis and hormone-sensitive lipase activity in 3T3-F442A adipocytes. *Metabolism*. 1991; 40(8):800–6. [PubMed: 1861630]
 227. Snel YE, Doerga ME, Brummer RJ, Zelissen PM, Zonderland ML, Koppeschaar HP. Resting metabolic rate, body composition and related hormonal parameters in growth hormone-deficient adults before and after growth hormone replacement therapy. *Eur J Endocrinol*. 1995; 133(4): 445–50. [PubMed: 7581968]
 228. Gregory JW, Greene SA, Jung RT, Scrimgeour CM, Rennie MJ. Changes in body composition and energy expenditure after six weeks' growth hormone treatment. *Arch Dis Child*. 1991; 66(5): 598–602. [PubMed: 2039249]
 229. Hoos MB, Westerterp KR, Gerver WJ. Short-term effects of growth hormone on body composition as a predictor of growth. *J Clin Endocrinol Metab*. 2003; 88(6):2569–72. [PubMed: 12788856]
 230. Eden Engstrom B, Burman P, Holdstock C, Karlsson FA. Effects of growth hormone (GH) on ghrelin, leptin, and adiponectin in GH-deficient patients. *J Clin Endocrinol Metab*. 2003; 88(11): 5193–8. [PubMed: 14602749]
 231. Hoybye C, Hilding A, Jacobsson H, Thoren M. Growth hormone treatment improves body composition in adults with Prader-Willi syndrome. *Clin Endocrinol (Oxf)*. 2003; 58(5):653–61. [PubMed: 12699450]
 232. Carrel AL, Myers SE, Whitman BY, Allen DB. Benefits of long-term GH therapy in Prader-Willi syndrome: a 4-year study. *J Clin Endocrinol Metab*. 2002; 87(4):1581–5. [PubMed: 11932286]
 233. Myers SE, Davis A, Whitman BY, Santiago JV, Landt M. Leptin concentrations in Prader-Willi syndrome before and after growth hormone replacement. *Clin Endocrinol (Oxf)*. 2000; 52(1): 101–5. [PubMed: 10651760]
 234. Shadid S, Jensen MD. Effects of growth hormone administration in human obesity. *Obes Res*. 2003; 11(2):170–5. [PubMed: 12582210]
 235. Bell J, Parker KL, Swinford RD, Hoffman AR, Maneatis T, Lippe B. Long-term safety of recombinant human growth hormone in children. *J Clin Endocrinol Metab*. 2010; 95(1):167–77. [PubMed: 19906787]
 236. Lammer C, Weimann E. Changes in carbohydrate metabolism and insulin resistance in patients with Prader-Willi Syndrome (PWS) under growth hormone therapy. *Wien Med Wochenschr*. 2007; 157(3–4):82–8. [PubMed: 17340066]
 237. Hauffa BP, Knaup K, Lehmann N, Neudorf U, Nagel B. Effects of growth hormone therapy on cardiac dimensions in children and adolescents with Prader-Willi syndrome. *Horm Res Paediatr*. 2011; 75(1):56–62. [PubMed: 20924154]
 238. Miller J, Silverstein J, Shuster J, Driscoll DJ, Wagner M. Short-term effects of growth hormone on sleep abnormalities in Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2006; 91(2):413–7. [PubMed: 16317059]

239. Festen DA, de Weerd AW, van den Bossche RA, Joosten K, Hoeve H, Hokken-Koelega AC. Sleep-related breathing disorders in prepubertal children with Prader-Willi syndrome and effects of growth hormone treatment. *J Clin Endocrinol Metab.* 2006; 91(12):4911–5. [PubMed: 17003096]
240. [Accessed: 7/10/2012] Genotropin (somatropin [rDNA origin] for injection). Web Page: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm153317.htm>
241. US Food and Drug Administration. [Accessed: 3/30/2012] MedWatch The FDA Safety Information and Adverse Event Reporting Program. Recombinant Human Growth Hormone (somatropin): Ongoing Safety Review - Possible Increased Risk of Death. Posted 12/22/2010. Web Page: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm237969.htm>
242. Bray GA, Greenway FL. Current and potential drugs for treatment of obesity. *Endocr Rev.* 1999; 20(6):805–75. [PubMed: 10605627]
243. Krotkiewski M. Thyroid hormones and treatment of obesity. *Int J Obes Relat Metab Disord.* 2000; 24(Suppl 2):S116–9. [PubMed: 10997625]
244. Bhasin S, Wallace W, Lawrence JB, Lesch M. Sudden death associated with thyroid hormone abuse. *Am J Med.* 1981; 71(5):887–90. [PubMed: 7304660]
245. Baxter JD, Webb P, Grover G, Scanlan TS. Selective activation of thyroid hormone signaling pathways by GC-1: a new approach to controlling cholesterol and body weight. *Trends Endocrinol Metab.* 2004; 15(4):154–7. [PubMed: 15109613]
246. Berkenstam A, Kristensen J, Mellstrom K, Carlsson B, Malm J, Rehnmark S, et al. The thyroid hormone mimetic compound KB2115 lowers plasma LDL cholesterol and stimulates bile acid synthesis without cardiac effects in humans. *Proc Natl Acad Sci U S A.* 2008; 105(2):663–7. [PubMed: 18160532]
247. Larsen TM, Toubro S, van Baak MA, Gottesdiener KM, Larson P, Saris WH, et al. Effect of a 28-d treatment with L-796568, a novel beta(3)-adrenergic receptor agonist, on energy expenditure and body composition in obese men. *Am J Clin Nutr.* 2002; 76(4):780–8. [PubMed: 12324291]
248. Redman LM, de Jonge L, Fang X, Gamlin B, Recker D, Greenway FL, et al. Lack of an effect of a novel beta3-adrenoceptor agonist, TAK-677, on energy metabolism in obese individuals: a double-blind, placebo-controlled randomized study. *J Clin Endocrinol Metab.* 2007; 92(2):527–31. [PubMed: 17118998]
249. Buemann B, Toubro S, Astrup A. Effects of the two beta3-agonists, ZD7114 and ZD2079 on 24 hour energy expenditure and respiratory quotient in obese subjects. *Int J Obes Relat Metab Disord.* 2000; 24(12):1553–60. [PubMed: 11126205]
250. Astrup A. Thermogenic drugs as a strategy for treatment of obesity. *Endocrine.* 2000; 13(2):207–12. [PubMed: 11186222]
251. Boozer CN, Daly PA, Homel P, Solomon JL, Blanchard D, Nasser JA, et al. Herbal ephedra/caffeine for weight loss: a 6-month randomized safety and efficacy trial. *Int J Obes Relat Metab Disord.* 2002; 26(5):593–604. [PubMed: 12032741]
252. Greenway FL, Bray GA. Treatment of hypothalamic obesity with caffeine and ephedrine. *Endocr Pract.* 2008; 14(6):697–703. [PubMed: 18996788]
253. Molnar D, Torok K, Erhardt E, Jeges S. Safety and efficacy of treatment with an ephedrine/caffeine mixture. The first double-blind placebo-controlled pilot study in adolescents. *Int J Obes Relat Metab Disord.* 2000; 24(12):1573–8. [PubMed: 11126208]
254. McBride BF, Karapanos AK, Krudysz A, Kluger J, Coleman CI, White CM. Electrocardiographic and hemodynamic effects of a multicomponent dietary supplement containing ephedra and caffeine: a randomized controlled trial. *Jama.* 2004; 291(2):216–21. [PubMed: 14722148]
255. Paman WJ, Westerterp-Plantenga MS, Saris WH. The effectiveness of long-term supplementation of carbohydrate, chromium, fibre and caffeine on weight maintenance. *Int J Obes Relat Metab Disord.* 1997; 21(12):1143–51. [PubMed: 9426382]
256. Daly PA, Krieger DR, Dulloo AG, Young JB, Landsberg L. Ephedrine, caffeine and aspirin: safety and efficacy for treatment of human obesity. *Int J Obes Relat Metab Disord.* 1993; 17(Suppl 1):S73–8. [PubMed: 8384187]

257. Hackman RM, Havel PJ, Schwartz HJ, Rutledge JC, Watnik MR, Noceti EM, et al. Multinutrient supplement containing ephedra and caffeine causes weight loss and improves metabolic risk factors in obese women: a randomized controlled trial. *Int J Obes (Lond)*. 2006; 30(10):1545–56. [PubMed: 16552410]
258. Toubro S, Astrup AV, Breum L, Quaade F. Safety and efficacy of long-term treatment with ephedrine, caffeine and an ephedrine/caffeine mixture. *Int J Obes Relat Metab Disord*. 1993; 17(Suppl 1):S69–72. [PubMed: 8384186]
259. Norregaard J, Jorgensen S, Mikkelsen KL, Tonnesen P, Iversen E, Sorensen T, et al. The effect of ephedrine plus caffeine on smoking cessation and postcessation weight gain. *Clin Pharmacol Ther*. 1996; 60(6):679–86. [PubMed: 8988071]
260. Belza A, Frandsen E, Kondrup J. Body fat loss achieved by stimulation of thermogenesis by a combination of bioactive food ingredients: a placebo-controlled, double-blind 8-week intervention in obese subjects. *Int J Obes (Lond)*. 2007; 31(1):121–30. [PubMed: 16652130]
261. Greenway FL. The safety and efficacy of pharmaceutical and herbal caffeine and ephedrine use as a weight loss agent. *Obes Rev*. 2001; 2(3):199–211. [PubMed: 12120105]
262. Weintraub M. Long-term weight control: the National Heart, Lung, and Blood Institute funded multimodal intervention study. *Clin Pharmacol Ther*. 1992; 51(5):581–5. [PubMed: 1445528]
263. Weintraub M, Sundaresan PR, Schuster B, Averbuch M, Stein EC, Cox C, et al. Long-term weight control study. IV (weeks 156 to 190). The second double-blind phase. *Clin Pharmacol Ther*. 1992; 51(5):608–14. [PubMed: 1587075]
264. Gadde KM, Allison DB, Ryan DH, Peterson CA, Troupin B, Schwiens ML, 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(9774):1341–52. [PubMed: 21481449]
265. Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, Peterson CA, 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*. 2012; 95(2):297–308. [PubMed: 22158731]
266. Allison DB, Gadde KM, Garvey WT, Peterson CA, Schwiens ML, Najarian T, et al. Controlled-Release Phentermine/Topiramate in Severely Obese Adults: A Randomized Controlled Trial (EQUIP). *Obesity (Silver Spring)*. 2011
267. Lazarus R, Baur L, Webb K, Blyth F. Adiposity and body mass indices in children: Benn's index and other weight for height indices as measures of relative adiposity. *Int J Obes Relat Metab Disord*. 1996; 20(5):406–12. [PubMed: 8696418]
268. [Accessed: 7/18/2012] FDA approves weight-management drug Qsymia. Web Page: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312468.htm>
269. Gadde KM, Yonish GM, Foust MS, Wagner HR. Combination therapy of zonisamide and bupropion for weight reduction in obese women: a preliminary, randomized, open-label study. *J Clin Psychiatry*. 2007; 68(8):1226–9. [PubMed: 17854247]
270. Greenway FL, Whitehouse MJ, Guttadauria M, Anderson JW, Atkinson RL, Fujioka K, et al. Rational design of a combination medication for the treatment of obesity. *Obesity (Silver Spring)*. 2009; 17(1):30–9. [PubMed: 18997675]
271. Hjalmarsen A, Aasebo U, Birkeland K, Sager G, Jorde R. Impaired glucose tolerance in patients with chronic hypoxic pulmonary disease. *Diabetes Metab*. 1996; 22(1):37–42. [PubMed: 8697294]
272. Orexigen Therapeutics, Inc. CONTRAVE (Naltrexone SR/Bupropion SR combination). [Accessed: 2/1/2012] Endocrinologic and Metabolic Drugs Advisory Committee briefing document. NDA 200063. Web Page: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM235672.pdf>
273. Wadden TA, Foreyt JP, Foster GD, Hill JO, Klein S, O'Neil PM, et al. Weight Loss With Naltrexone SR/Bupropion SR Combination Therapy as an Adjunct to Behavior Modification: The COR-BMOD Trial. *Obesity (Silver Spring)*. 2010

274. Greenway FL, Fujioka K, Plodkowski RA, Mudaliar S, Guttadauria M, Erickson J, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-1): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2010; 376(9741):595–605. [PubMed: 20673995]
275. Wadden TA, Foreyt JP, Foster GD, Hill JO, Klein S, O'Neil PM, 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(1):110–20. [PubMed: 20559296]
276. Padwal R. Contrave, a bupropion and naltrexone combination therapy for the potential treatment of obesity. *Curr Opin Investig Drugs*. 2009; 10(10):1117–25.
277. Tran, PT.; Thomas, A. U.S. Food and Drug Administration Center for Drug Evaluation and Research. U.S. Food and Drug Administration: Silver Spring; Maryland: Dec 7. 2010 Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee; p. 1-8.<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm191113.htm>.
278. Ware, C. [Accessed: 2/1/2012] FDA Won't Approve Weight Loss Drug Contrave-Agency Asks for More Studies to Check for Heart Attack Risk. WebMD. Web Page: <http://www.webmd.com/diet/news/20110201/fda-wont-approve-weight-loss-drug-contrave>
279. Orexigen Therapeutics, Inc.. [Accessed: 2/6/2012] Orexigen Announces Agreement From the FDA on a Special Protocol Assessment for the Contrave Outcomes Trial. Web Page: <http://ir.orexigen.com/phoenix.zhtml?c=207034&p=irol-newsArticle&ID=1656731&highlight=>
280. Ravussin E, Smith SR, Mitchell JA, Shringarpure R, Shan K, Maier H, et al. Enhanced weight loss with pramlintide/metreleptin: an integrated neurohormonal approach to obesity pharmacotherapy. *Obesity (Silver Spring)*. 2009; 17(9):1736–43. [PubMed: 19521351]
281. Roth JD, Roland BL, Cole RL, Trevaskis JL, Weyer C, Koda JE, et al. Leptin responsiveness restored by amylin agonism in diet-induced obesity: evidence from nonclinical and clinical studies. *Proc Natl Acad Sci U S A*. 2008; 105(20):7257–62. [PubMed: 18458326]
282. Roth JD, Trevaskis JL, Wilson J, Lei C, Athanacio J, Mack C, et al. Antiobesity effects of the beta-cell hormone amylin in combination with phentermine or sibutramine in diet-induced obese rats. *Int J Obes (Lond)*. 2008; 32(8):1201–10. [PubMed: 18560368]
283. Aronne LJ, Halseth AE, Burns CM, Miller S, Shen LZ. Enhanced weight loss following coadministration of pramlintide with sibutramine or phentermine in a multicenter trial. *Obesity (Silver Spring)*. 2010; 18(9):1739–46. [PubMed: 20094043]
284. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet*. 2010; 42(11):937–48. [PubMed: 20935630]
285. den Hoed M, Ekelund U, Brage S, Grontved A, Zhao JH, Sharp SJ, et al. Genetic susceptibility to obesity and related traits in childhood and adolescence: influence of loci identified by genome-wide association studies. *Diabetes*. 2010; 59(11):2980–8. [PubMed: 20724581]
286. Zhao J, Bradfield JP, Zhang H, Sleiman PM, Kim CE, Glessner JT, et al. Role of BMI-Associated Loci Identified in GWAS Meta-Analyses in the Context of Common Childhood Obesity in European Americans. *Obesity (Silver Spring)*. 2011
287. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens*. 2009; 27(11):2121–58. [PubMed: 19838131]
288. Skelton JA, Beech BM. Attrition in paediatric weight management: a review of the literature and new directions. *Obes Rev*. 2011; 12(5):e273–81. [PubMed: 20880126]
289. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Bmj*. 2010; 340:c332. [PubMed: 20332509]
290. Cole TJ, Faith MS, Pietrobelli A, Heo M. What is the best measure of adiposity change in growing children: BMI, BMI %, BMI z-score or BMI centile? *Eur J Clin Nutr*. 2005; 59(3):419–25. [PubMed: 15674315]
291. Berkey CS, Colditz GA. Adiposity in adolescents: change in actual BMI works better than change in BMI z score for longitudinal studies. *Ann Epidemiol*. 2007; 17(1):44–50. [PubMed: 17140812]

292. Haddock CK, Poston WS, Dill PL, Foreyt JP, Ericsson M. Pharmacotherapy for obesity: a quantitative analysis of four decades of published randomized clinical trials. *Int J Obes Relat Metab Disord.* 2002; 26(2):262–73. [PubMed: 11850760]
293. Franz MJ, VanWormer JJ, Crain AL, Boucher JL, Histon T, Caplan W, et al. Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. *J Am Diet Assoc.* 2007; 107(10):1755–67. [PubMed: 17904936]
294. Marre M, Shaw J, Brandle M, Bebakar WM, Kamaruddin NA, Strand J, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). *Diabet Med.* 2009; 26(3):268–78. [PubMed: 19317822]
295. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet.* 2009; 374(9683):39–47. [PubMed: 19515413]
296. Choy M, Lam S. Sitagliptin: a novel drug for the treatment of type 2 diabetes. *Cardiol Rev.* 2007; 15(5):264–71. [PubMed: 17700385]
297. Perez-Monteverde A, Seck T, Xu L, Lee MA, Sisk CM, Williams-Herman DE, et al. Efficacy and safety of sitagliptin and the fixed-dose combination of sitagliptin and metformin vs. pioglitazone in drug-naïve patients with type 2 diabetes. *Int J Clin Pract.* 2011; 65(9):930–8. [PubMed: 21849007]
298. Sloth B, Davidsen L, Holst JJ, Flint A, Astrup A. Effect of subcutaneous injections of PYY1-36 and PYY3-36 on appetite, ad libitum energy intake, and plasma free fatty acid concentration in obese males. *Am J Physiol Endocrinol Metab.* 2007; 293(2):E604–9. [PubMed: 17566112]
299. Gantz I, Erondü N, Mallick M, Musser B, Krishna R, Tanaka WK, et al. Efficacy and safety of intranasal peptide YY3-36 for weight reduction in obese adults. *J Clin Endocrinol Metab.* 2007; 92(5):1754–7. [PubMed: 17341568]
300. Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. *Lancet.* 2010; 375(9733):2223–33. [PubMed: 20609968]

Table 1

Pharmacological agents used for weight loss in human studies.

Agent	Mechanism of action	Status
A) Classical centrally acting anorexiants 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 ^{45,53}		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 anorexiants 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 ^{130,134}	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 ^{296,297}	Dipeptidyl peptidase inhibitor-4	Not FDA-approved for obesity.
Peptide YY ^{298,299}	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.
Dapagliflozin ^{196-199, 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 ^{224, 225}	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 ^{253, 254, 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 glutamate receptor 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.