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Drugs in the Pipeline for the Obesity Market

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Abstract

Obesity is a major public health problem. For many obese patients, diet and exercise are an inadequate treatment and bariatric surgery may be too extreme of a treatment. As with many other chronic diseases, pharmacologic treatment may be an attractive option for selected obese patients. Antiobesity drugs may potentially work through one of three mechanisms: (1) appetite suppression, (2) interference with absorption of nutrients, and (3) increased metabolism of nutrients. The three most widely prescribed drugs approved to treat obesity are phentermine, sibutramine, and orlistat. Drugs approved for treating obesity usually result in an additional weight loss of approximately 2–5 kg in addition to placebo. For pharmacologic therapy in obesity to be widely utilized, greater effectiveness and safety will be needed. Four types of single-agent drugs are in late stage development, including (1) selective central cannabinoid-1 receptor blockers, (2) selective central 5-hydroxytryptamine 2C serotonin receptor agonists, (3) an intestinal lipase blocker, and (4) central-acting incretin mimetic drugs. Four combination agent compounds in late stage development include (1) Contrave, which combines long-acting versions of naltrexone and bupropion; (2) Empatic, which combines long-acting bupropion and long-acting zonisamide; (3) Qnexa, which combines phentermine with controlled release topiramate; and (4) an injectable combination of leptin and pramlintide. Peptide YY and melanin-concentrating hormone receptor-1 antagonists are centrally acting agents in early stage development. It is expected that several new drug products for obesity will become available over the next few years. Their role in managing this disease remains to be determined.

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Introduction

Obesity is a chronic disease and a major public health problem.[1,2] Although the traditional approach to the problem combines a healthy diet and an exercise program, which is thought to offer the greatest benefits with the least risks, this approach has very poor long-term efficacy due to redundant physiological mechanisms that work to return the person to their baseline weight. Thus, like other chronic diseases such as diabetes, medications may be needed to augment diet and lifestyle changes.

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Abbreviations: (5-HT2A) 5-hydroxytryptamine 2A, (5-HT2B) 5-hydroxytryptamine 2B, (5-HT2C) 5-hydroxytryptamine 2C, (BMI) body mass index, (DEA) Drug Enforcement Administration, (FDA) Food and Drug Administration, ((MCHR1) melanin-concentrating hormone receptor-1

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The National Heart Lung and Blood Institute developed a document entitled "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults," which addresses the indications for antiobesity drugs.[3] These guidelines specify that in carefully selected patients, appropriate drugs can augment low calorie diets, physical activity, and behavior therapy in weight loss. The guidelines specify that weight loss drugs approved by the Food and Drug Administration (FDA) for long-term use can be useful adjuncts to dietary therapy and physical activity for some patients with a body mass index (BMI) of ≥30 and no concomitant risk factors or diseases, or for patients with a BMI of ≥27 accompanied by risk factors or diseases. The guidelines state that the risk factors and diseases considered important enough to warrant pharmacotherapy at a BMI of 27 to 29.9 are hypertension, dyslipidemia, coronary heart disease, type 2 diabetes, and sleep apnea. The guidelines also specify that continual assessment by the physician of drug therapy for efficacy and safety is necessary. If the drug is efficacious in helping the patient lose and/or maintain weight loss and there are no serious adverse effects, then it can be continued; but if not, then it should be discontinued. At this time, however, there is no FDA-approved drug or combination drug product for obesity that is both safe and highly effective, i.e., consistently resulting in a loss of over 10% total body weight every 1 year.

Mechanisms of Antiobesity Drugs

Antiobesity drugs may potentially work through one of three mechanisms: (1) appetite suppression, (2) interference with absorption of nutrients, and (3) increased metabolism of nutrients.[4]

The main types of appetite-suppressing drugs currently in use affect the central nervous system.[5] These include amphetamine derivatives, antiepilepsy drugs, and incretin hormones. A new class of drugs is being developed that will block cannabinoid receptors in the brain.[6]

Drugs that block lipolysis in the gut and the absorption of triglycerides can result in weight loss. Such drugs tend to create a lipid load to the colon and can result in malabsorption of fat-soluble vitamins, diarrhea, or anal leakage.[7]

Currently, no FDA-approved drug for the treatment of obesity increases metabolism. Thyroid hormone derivatives have been used but these have side effects related to hyperthyroidism.[8] The β_3-adrenergic receptor is one of three subtypes of β-adrenergic receptors. β_3 agonists have been studied for the past two decades as potential antiobesity agents.[9] Although β_1- and β_2-adrenergic receptors are expressed throughout the body, β_3-adrenergic receptors are mainly found in adipocytes. There are two main types of fat cells in the body—white and brown. White fat cells are the conventional form of fat cells that store energy. These cells contain lipid droplets and accumulate under the skin and around internal organs. Brown fat cells, however, contain small lipid droplets and many mitochondria, and metabolize triglycerides to generate heat. Although present in newborns, they tend to disappear by adulthood. In rodents, stimulation of β_3-adrenergic receptors in white adipocytes results in lipolysis and in brown fat leads to nonshivering thermogenesis. A β_3 agonist with high specificity for the human β_3 receptor was created by Eli Lilly and Company and tested in clinical trials. Although the first dose increased the metabolic rate and reduced the respiratory quotient, the effect was lost in a 28-day trial.[10,11] The two main concerns have been whether the number of biologically active β_3-adrenoceptors in adult humans is sufficient to produce relevant metabolic effects and, if so, whether their long-term stimulation is free of serious side effects. It now appears that β_3-adrenergic receptors, at least with available drugs, are insufficient to produce relevant metabolic effects in adult humans. Caffeine is approved for nonprescription sale as a stimulant, and ephedrine is approved as a prescription drug for the treatment of asthma. The combination of 200 mg caffeine and 20 mg ephedrine taken three times a day was an approved combination medication for the treatment of obesity in Denmark for over a decade and off-label use is possible in the United States.[12] A meta-analysis of the obesity trials with caffeine and ephedrine showed a 1-kg per month weight loss in excess of placebo up to 6 months.[13] The side effects of psychiatric, autonomic, or gastrointestinal symptoms and heart palpitations were of 2.2- to 3.6-fold greater incidence with caffeine and ephedrine than with a placebo, but the side effects reached placebo levels after 8 weeks of treatment.[14]

Currently Available Drugs

The three most widely prescribed drugs approved to treat obesity are phentermine, sibutramine, and orlistat. Phentermine is chemically related to amphetamine and is an appetite suppressant, approved for short-term use that has been suggested to have some abuse potential.[15] This drug can cause side effects, such as central nervous system stimulation, headache, insomnia, and increases in heart rate and blood pressure. Sibutramine is a noradrenaline and serotonin reuptake inhibitor approved

for long-term use.[16] This drug can cause headache, nausea, tachycardia, and elevated blood pressure that, on rare occasions, can be severe. Orlistat, an inhibitor of pancreatic lipase, prevents triglyceride lipolysis into absorbable free fatty acids and results in fecal excretion of undigested triglyceride oil.[17] This product is available both as a prescription drug in 120-mg tablets, which reduces triglyceride absorption by 30%, and as an over-the-counter product in 60-mg tablets, which reduces triglyceride absorption by 25%.[18]

Other drugs approved for the short-term treatment of obesity include diethylpropion, which, like phentermine, is in Drug Enforcement Administration (DEA) schedule IV, and benzphetamine and phendimetrazine, which are in DEA schedule III, suggesting a greater potential for abuse. Diethylpropion is structurally related to buproprion, which is used for depression and nicotine withdrawal.[19] The drug can have stimulatory side effects. Mazindol is no longer available in the United States, but is used in Japan.[20–22]

The drugs approved for treating obesity usually result in an additional weight loss of approximately 2–5 kg in addition to placebo.[23] Several other drugs, which are not approved for obesity, are occasionally prescribed off-label for obesity with similar results. These drugs, which act on the central nervous system, include the antiseizure drugs topiramate and zonisamide, as well as the antidepressants fluoxetine and bupropion.[24] Sertraline has been used to treat night-eating syndrome, a special subset of obese subjects.[25] Metformin is approved for type 2 diabetes, and many overweight patients with this disease lose about 2 kg when they use this medication.[26]

Single-Agent Drugs in Late Stage Development

Incretin mimetic drugs are emerging as a new class of drugs for treating type 2 diabetes, and these agents also suppress appetite. Exenatide, which is approved for type 2 diabetes, has been demonstrated to cause weight loss in subjects with type 2 diabetes and obesity.[27] Phase 4 studies are currently underway to investigate the weight-reducing effect of this drug on subjects without diabetes. Pramlintide, which is approved for type 1 diabetes, has been demonstrated to cause weight loss in subjects with obesity and no diabetes.[28]

Rimonabant is the first selective blocker antagonist of the cannabinoid-1 receptor in development for the treatment of obesity, diabetes mellitus, and cardiometabolic risk factors. The drug is associated with favorable effects on weight, waist circumference, serum lipids, C-reactive protein, and glycemic control in type 2 diabetes; however, the drug is associated with an increased incidence of nausea, anxiety, and depression.[29] The drug is known as Zimulti in the United States and as Accomplia in Europe. In June 2007, the European Commission authorized the sale of rimonabant for use in treating obese patients with a body mass index of 30 or more or for treating patients with a BMI of at least 27 who also have type 2 diabetes or dyslipidemia. That same month, an FDA advisory committee unanimously recommended against approval of rimonabant because of a safety concern related to an increased risk of suicide during treatment. The manufacturer, sanofi aventis, then announced that their application to the FDA would be withdrawn.

MK-0364, taranabant, is a cannabinoid-1 receptor inverse agonist (which binds to the receptor and inhibits baseline activity at the receptor). This drug from Merck, which has demonstrated weight loss versus placebo in early clinical studies, is in phase 3 clinical trials.[30] CP-945598 is a cannabinoid-1 receptor antagonist from Pfizer in phase 3 trials for obesity and prevention of weight gain in obese subjects.[31] Eli Lilly is developing a synthetic positron emission tomography tracer, [18F]MePPEP-d2, for brain CB1 receptors to use in brain imaging studies. This molecule is intended to be a tool in understanding the distribution and variance of CB1 receptors in the brain to conduct research into antagonists of these receptors.[32]

Lorcaserin is a selective agonist of the 5-hydroxytryptamine 2C (5-HT2C) serotonin receptor in the hypothalamus, which helps regulate satiety and the metabolic rate. This drug has 104-fold greater selectivity for the 5-HT2C receptor relative to the 5-hydroxytryptamine 2B (5-HT2B) receptor and 18-fold greater selectivity relative to the 5-hydroxytryptamine 2A (5-HT2A) receptor.[33] The 5-HT2B and 5-HT2A receptors have been implicated, respectively, in the valvular heart disease and pulmonary hypertension observed with nonselective serotonergic agents. Such a drug, fenfluramine, was withdrawn from the market in 1997, despite established effectiveness, because of the following two troubling side effects: valvular heart disease and pulmonary hypertension.[34] Lorcaserin is being developed by Arena Pharmaceuticals and is currently in phase 3 testing.[35]

Cetilistat is a lipase blocker that will block breakdown and absorption of dietary triglycerides.[36] This drug is currently being prepared for phase 3 clinical development. The manufacturer, Alizyme Therapeutics, Ltd., claims

that this product has a similar mechanism of action as orlistat, but fewer gastrointestinal side effects. Liraglutide is an incretin mimetic drug under development for type 2 diabetes. In 2007, this drug, which is being produced by Novo Nordisk, was reported to be associated with weight loss in a group of obese subjects without diabetes.[37]

Combination Drugs in Late Stage Development

None of the single-agent drugs that have been approved or appear close to approval have been consistently able to achieve a weight loss of more than approximately 10% of body weight. The combination of phentermine and fenfluramine, which was taken off the market in 1997, was able to achieve a loss of approximately 15% of body weight.[38] There is a perception by many people in the pharmaceutical industry that the best route for developing a safe and effective drug for obesity is to combine two generic drugs that can curb appetite and promote satiety. In this way, the safety profiles of the ingredients of the combination drugs will be well understood and there is a possibility of achieving a combined benefit. The most advanced combination antiobesity drugs in development at this time are (1) Contrave, which combines long-acting versions of naltrexone and bupropion; (2) Empatic, which combines long-acting bupropion and long-acting zonisamide; (3) Qnexa, which combines phentermine with controlled release topiramate; and (4) an injectable combination of leptin and pramlintide.

Contrave is a proprietary fixed dose combination of 360 mg bupropion sustained release (SR), a dopamine stimulator approved for depression and smoking cessation, and 32 mg naltrexone SR, an opioid blocker approved for opioid and alcohol addiction, in a single trilayer tablet.[39] This drug, which is being developed by Orixegen, is currently being tested in several phase 3 studies comparing its safety and efficacy against placebo in obese subjects, and one study has subjects participating in a behavior modification program.

Bupropion is an antidepressant that is also approved for smoking cessation. Unlike fenfluramine and sibutramine, which increase the effect of serotonin in the brain, bupropion is a norepinephrine and dopamine reuptake inhibitor with no clinically significant effects on serotonin. Functionally, bupropion is thought to increase the level of dopamine activity at specific receptors in the brain, which appears to lead to improved appetite regulation, decreased food cravings, or improved motivation.[40] This drug is contraindicated for persons with a history of seizures or bulimia.

Naltrexone is approved as a treatment for narcotic or alcohol dependence. Opioid reward processes may be involved in both the short-term control of eating and the hedonic aspects of alcohol consumption. Opiate antagonists are thought to decrease the pleasure of consuming food, just as they decrease the pleasure of drinking alcohol.[41] These agents might also ameliorate the hyperinsulinism that can accompany obesity and lead to hypoglycemia and increased food intake.

Zonisamide is an antiseizure drug. Its mechanism for decreasing appetite is not known. The drug increases levels of serotonin and dopamine in the brain, which might suppress appetite centers.[42] The drug also inhibits carbonic anhydrase activity, which might alter the perception of taste. This drug is being developed by Orixegen as a combination drug named Empatic, which will be composed of long-acting bupropion and long-acting zonisamide.[43,44] Empatic has been studied in a phase 2b trial and is scheduled to be tested in another phase 2b trial this year. A separate clinical trial is currently also underway that will assess the effects of zonisiamide as a single agent on obesity.

Qnexa is a combination drug, manufactured by Vivus, that consists of low doses of immediate-release phentermine and controlled-release topiramate.[45] Phentermine is a popular appetite suppressant used for weight loss and is available generically for weight loss. Topiramate is used for seizures and migraines. This drug has been demonstrated to cause weight loss, but concern has been expressed about whether its central nervous system and psychiatric side effects will permit use of this drug as a treatment of obesity.[46] For this reason, low doses of topiramate have been selected for use in the current phase 3 trials.

Amylin Pharmaceuticals is testing the combination of leptin and pramlintide. A trial of this injectable combination administered pramlintide for 4 weeks and then randomized the subjects to leptin or placebo in addition to pramlintide for the remainder of the 24-week study. The pramlintide group lost 8.4% of body weight compared to the combination group, which lost 12.7%.[47]

Other Drugs in Early Stage Development

Peptide YY is a hormone that is believed to function as a physiologic inhibitor of food intake.[48] Peptide YY is secreted from L-cells in the gut after a meal and cleaved to the active PYY 3-36 by DPP-4.[49] PYY 3-36 is a hormone believed to produce satiety. Because PYY 3-36 is a peptide, initial studies focused on peptide YY 3-36 delivery by

injection. Later, Nastech Pharmaceutical Company, Inc. developed a nasal spray formulation of this agent. The drug is currently in phase 2 testing.

Melanin-concentrating hormone receptor-1 (MCHR1) signaling appears to be involved in the regulation of food intake and energy expenditure. Preclinical studies have demonstrated that small molecule MCHR1 antagonists decrease food intake, body weight, and adiposity in rodent models of obesity. Two compounds in this family have been evaluated in phase I clinical trials.[50]

Conclusions

To meet the huge demand for safe and effective antiobesity pharmaceutical agents, many companies are currently developing single- and dual-agent drugs for this problem. Modestly successful weight loss has been accomplished through the use of drugs that decrease food intake, increase lipolysis, or decrease absorption of nutrients. Several new compounds are currently in late stage testing and are poised to take their place alongside the ranks of the currently approved antiobesity drugs. Clinicians and obese patients are hopeful that the new drugs will prove to be at least as safe as and more effective than the currently approved agents, which provide only modest benefits.

Disclosure:

Dr. Klonoff has conducted clinical trials for Amylin, Merck, Novo Nordisk, and sanofi aventis. Dr. Greenway has been a consultant to Orexigen, the company developing the following combinations—bupropion–naltrexone and bupropion–zonisamide—and to Nastech, the company developing PYY for intranasal delivery. He has also received compensation for serving on the obesity advisory board for Glaxo-Smith-Kline, which sells bupropion and over-the-counter orlistat.

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