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Breaking the Obesity Barrier: Near-Term Prospects for Breakthrough Treatments

Dec. 22, 2005 -- The prevalence of overweight and obesity is increasing at an alarming rate, not only in the United States but worldwide. The World Health Organization recently warned that the number of overweight and obese people worldwide could reach 1.5 billion by 2015. (*Red Herring*, Sept. 2005) Besides being a cosmetic problem, obesity carries a host of comorbidities, including increased risk of type 2 diabetes, cardiovascular disease, and certain cancers. Relatively few overweight individuals who attempt to lose weight by diet and exercise succeed, and most regain their weight over the long term. The growing realization of how dangerous this condition is and the frustration with current therapeutic options have led to a dramatic increase in bariatric surgeries: The number of these procedures increased 450% between 1998 and 2002, growing from 12,775 to 70,256 cases (Nguyen, *Arch. Surg.*, 2005), and an estimated 171,000 such procedures, which cost approximately $25,000 each, will be performed this year, according to the American Society for Bariatric Surgery.

In recent years, basic research in obesity, including discovering the molecular basis of the phenotypes of obese strains of mice, has led to the realization that obesity is a disease, not the result of a failure in willpower. Academic researchers have continued their work on understanding the basis of controlling body weight, and pharmaceutical and biotechnology companies have attempted to discover and develop drugs designed to assist people in losing weight. However, developing antiobesity drugs has been exceedingly difficult. Finding drugs that produce major weight loss has so far been impossible. And current drugs do not work for all patients. A major reason for the difficulty in developing antiobesity drugs--and the minimal efficacy of those that have been developed--is that the condition is very complex, involving many poorly understood pathways.

Moreover, drugs that have reached the market have had serious side effects. In fact, one of the most spectacular pharmaceutical debacles of all time involved Wyeth's Redux (dexfenfluramine), which was once hailed as the first breakthrough antiobesity drug to reach the market. Redux and its older cousin, Wyeth's Pondimin (fenfluramine), were the "fen" half of fen/phen, where the "phen" stands for phentermine. Redux and Pondimin were withdrawn in 1997, when they were linked to serious cardiovascular side effects that caused death and disability in some patients (*MMWR*, Nov. 14, 1997). Wyeth has had to set aside about $21 billion to cover its liability in this case, which has drastically altered the company's overall prospects.

Current Therapies

Only two obesity drugs are currently available—Roche's Xenical (orlistat) and Abbott's Meridia (sibutramine). (See Table 1.) Both drugs are prescribed as an adjunct to a hypocaloric diet and exercise: It is expected that any new obesity drugs will be prescribed with similar directives. Both drugs have limited efficacy, with typical weight loss of 5-10% of body weight. This modest degree of weight loss is not sufficient to move most patients out of the obese class. However, it does significantly reduce risk factors for type 2 diabetes and cardiovascular disease.

Table 1: Marketed and Selected Emerging Antiobesity Drugs

Drug	Company	Stage	Comments
Orlistat (Xenical)	Roche	Marketed since 1999	Pancreatic lipase inhibitor; works in the intestine to block fat absorption.
Sibutramine (Meridia)	Abbott	Marketed since 1997	Serotonin and norepinephrine reuptake inhibitor; works in the brain to suppress appetite.
Rimonabant(Accomplia)	Sanofi-Aventis	Preregistration	Cannabinoid receptor 1 (CB1) blocker; works in the brain to suppress appetite. Also stimulates production of adiponectin, an insulin-sensitizing cytokine, by adipocytes.
Recombinant ciliary neurotrophic growth factor (CNTF)(Axokine)	Regeneron	Phase III; discontinued	Works in the brain to suppress appetite. Many patients in Phase III developed antibodies to CNTF and stopped responding; the drug was therefore discontinued. Axokine was an injected agent.
ATL-962	Alizyme	Phase II	Pancreatic lipase inhibitor; blocks fat absorption. May have fewer gastrointestinal side effects than orlistat.
HMR 1426	Sanofi-Aventis	Phase II	Inhibitor of gastric emptying, resulting in decreases in food intake.
AOD9604	Metabolic Pharmaceuticals, Ltd. (Australia)	Phase II	Small, orally active synthetic peptide modeled on a C-terminal fragment of human growth hormone (hGH). Stimulates fat metabolism without other effects of hGH.

GI 181771	GlaxoSmithKline	Phase II	Small-molecule cholecystokinin A agonist; cholecystokinin is a gut hormone that stimulates release of bile and pancreatic digestive enzymes into the gut and works in the brain to suppress appetite.
Pramlintide (Symlin)	Amylin	Phase II, obesity; marketed for diabetes as an adjunct antihyperglycemic agent to insulin	Synthetic analogue of the pancreatic peptide hormone amylin. Natural amylin is a short-term appetite suppressant that works in the brain. It also inhibits gastric emptying. Pramlintide is a self-administered injected agent.
ADP356	Arena	Phase II	Selective serotonin receptor agonist; works in the brain to suppress appetite. May lack the adverse effects of the nonselective serotonin agonist and serotonin reuptake inhibitor dexfenfluramine (Wyeth's Redux).

Note: All drugs listed are oral agents unless otherwise specified.

Source: Haberman Associates.

Both Xenical and Meridia also have significant side effects. Sibutramine can cause increased blood pressure and heart rate as well as arrhythmia in some patients; these effects are usually reversible by reducing the dose or discontinuing the drug. Orlistat causes gastrointestinal side effects (e.g., oily stools, fecal incontinence) in many patients, depending on how well they comply with the requisite low-fat diet. Patients who experience these side effects often discontinue the drug.

The critical importance of diet, exercise, and behavior modification in the efficacy of obesity drugs was illustrated by a recent clinical trial (Wadden, *New England Journal of Medicine*, 2005.). The results of this one-year randomized trial with obese patients indicated that intensive lifestyle modification counseling plus sibutramine resulted in a mean weight loss of 26.6 pounds, compared with 11.0 pounds for sibutramine alone. Counseling alone resulted in a loss of 14.7 pounds. Sibutramine plus brief lifestyle modification counseling given by a primary care physician

resulted in a mean weight loss of 16.9 pounds. The type of behavioral counseling that was most effective as an adjunct to sibutramine was much more intensive than what is possible in the typical primary care setting and would be difficult for many patients to fit into their schedules.

Rimonabant

Rimonabant (Sanofi-Aventis's Accomplia) is now under review by the FDA. It is the only Phase III antiobesity agent being actively developed. If approved, rimonabant will be the first antiobesity drug to reach the market since 1999. This drug is a selective antagonist of the cannabinoid-1 receptor (CB1). It blocks the binding of endogenous cannabinoids to the CB1 receptor, thus inhibiting these molecules' ability to increase appetite.

In a recently published Phase III clinical trial, rimonabant together with a hypocaloric diet reduced body weight and improved cardiovascular risk factors in obese individuals with dyslipidemia (Després, *New England Journal of Medicine*, 2005). In this randomized, placebo-controlled, one-year study, patients treated with a 20-mg dose of rimonabant had a significant mean weight loss of 14.7 pounds. They also showed a significant increase in serum high-density lipoprotein cholesterol and in insulin sensitivity, and significant reductions in triglycerides, blood pressure, and waist circumference. These parameters are components of the metabolic syndrome, a constellation of risk factors for cardiovascular disease and type 2 diabetes that are associated with insulin resistance. (Insulin resistance is the inability of target tissues such as muscle, liver, and fat to respond normally to insulin.) Rimonabant had no effect on serum low-density lipoprotein (LDL), the major cardiovascular risk factor that is commonly treated with statins. However, rimonabant increased the size of LDL particles; small, dense LDL particles are a component of the metabolic syndrome and are a cardiovascular risk factor.

CB1 receptors are found on adipocytes as well as in the brain. Blocking of CB1 receptors on fat cells induces the expression of adiponectin--a cytokine that increases insulin sensitivity and inhibits the progression of atherosclerosis (Matsuzawa, *Arter Thrombosis and Vasc Biology*, 2004). The rimonabant treatment group showed a significant increase in adiponectin, beyond the level of increase that would have been expected to be due to weight loss. Elevations in serum adiponectin may account in part for the positive effects of rimonabant on metabolic syndrome.

The 20-mg dose is the highest tested so far and appears to work better than lower doses. The most significant side effect at the 20-mg dose was nausea (in 12.7% of patients versus 3.2% with placebo). Anxiety and diarrhea also occurred significant more frequently with 20 mg of rimonabant than with placebo.

The above study excluded patients with type 2 diabetes. However, the results of a Phase III trial reported at the June 2005 annual meeting of the American Diabetes Association indicated that rimonabant treatment was associated with weight loss and improvements in parameters of metabolic syndrome, as well as a significant reduction in glycated hemoglobin (HbA1c), a biomarker of long-term serum glycemic control.

An FDA decision on approval for rimonabant may come as early as spring 2006. Although weight loss with this drug appears to be comparable to that found with current agents, its effect on cardiovascular risk factors may give it an advantage in regulatory approval and in acceptance by physicians and third-party payers, many of which do not reimburse current antiobesity drugs.

Other Agents in Late-Phase Development

Table 1 lists other leading pipeline agents that are in Phase II trials, plus the recently discontinued Phase III agent Regeneron's Axokine (recombinant ciliary neurotrophic factor [CNTF]). Axokine, once dubbed a particularly promising agent, was discontinued after many patients in clinical trials developed neutralizing antibodies and thus became resistant to the drug.

Especially given the challenge involved in developing antiobesity agents, it is difficult to predict success for any of the Phase II agents, but none of them seem particularly remarkable. Most are agonists of natural gut or pancreatic hormones (which signal satiety to the brain after a meal) or otherwise work in the gut to inhibit pancreatic lipase (as does orlistat) or to inhibit gastric emptying. A Phase II drug that works by a different mechanism is Arena's ADP356, a selective serotonin receptor agonist that may have effects similar to those of dexfenfluramine, but with greater safety.

Many earlier-stage agents being investigated by pharmaceutical and biotechnology companies are agonists or antagonists of molecules that work in the central nervous system to control food intake and/or fat mass. The difficulties in working in this area, as well as in obesity drug discovery and development in general, are discussed in the next section.

Why Is It So Difficult to Discover and Develop Breakthrough Obesity Drugs?
The Massachusetts Biotechnology Council (MBC) held an Obesity Summit Conference in November 2005. One theme of the conference was why it is so difficult to discover and develop breakthrough obesity drugs. Major reasons for this difficulty are listed in Table 2.

Table 2: Why Is It So Difficult to Discover and Develop Breakthrough Obesity Drugs?

Pathways for the control of body weight and fat mass are exceedingly complex and involve several different organs and tissues (e.g., brain, gut, liver, adipose tissue, muscle, pancreas, endocrine system, vasculature), including signals between these organs and tissues. They also may involve multiple genetic factors, as well as behavioral and environmental factors, and may differ between different obese or overweight patients. Despite considerable progress, researchers still probably know very little about these pathways.
Pathways that determine how obesity increases the risk of type 2 diabetes and cardiovascular disease are similarly complex and largely unknown. It is also not known why some obese individuals develop these diseases and others do not.
Because of these unknowns, whether any drug candidate will be efficacious in any group of patients is a shot in the dark. For example, redundant pathways may cancel out the effects of modulating any single target. Moreover, we may need drugs that hit more than one target to be effective. Many companies tend to promote one-target solutions rather than multitarget drugs or combination therapies.
Safety also involves considerable unknowns, especially with drugs that act in the central nervous system. This problem is amply illustrated by safety failures of late-stage and marketed drugs, especially dexfenfluramine, and by the adverse effects of sibutramine in some patients.
Animal models in this field are inadequate. For example, the standard monogenic obese mouse models exhibit extreme obesity, which is relatively rarely seen in humans. Drugs or targets based on these models have often resulted in failure (most notoriously, drugs based on the adipocyte hormone leptin). Testing or optimizing drugs using these models can also give spurious results. Researchers need animal models that more closely model human obesity in order to develop new, breakthrough therapeutic strategies.
Much research focuses on molecular biology. More physiology (including integration with molecular and cell biology) is needed.
Society "knows" how to treat obesity—eat less and exercise more. This simplistic belief results in an excessive focus on behavior and promotion of misinformation. Some results are inadequate funding for obesity research and resistance of third-party payers to reimburse obesity drugs. These factors inhibit drug development.

Source: Haberman Associates; based on Obesity Summit Conference, Massachusetts Biotechnology Council, November 15, 2005.

One challenge is the complexity of the many, largely uncharted pathways related to obesity and the means by which obesity predisposes patients to type 2 diabetes and cardiovascular disease (Lazar, *Science*, 2005; Schwartz, *Science*, 2005). These include both complex intracellular signaling pathways and physiological pathways by which multiple organs and tissues "talk" to one another via cytokines, hormones, and nutrients such as glucose and free fatty acids. Over the years, it has become clear that metabolic diseases involve whole-organism physiology, which reductionist molecular and cell biology approaches cannot adequately address. At the same time, obesity research has been held back by a lack of funding and resistance by third-party payers, as discussed in Table 2. The predominating idea that obese patients should "heal themselves" by just reducing their food intake and increasing activity has made obesity drug discovery a less popular area of research, despite the opportunity.

These factors suggest that, similar to the trend in cancer, optimal pharmacotherapy for obesity may involve combination therapies, and drugs that hit more than one target. One way of discovering such drugs, as well as new targets, is by screening drugs in cellular assays that assess the effects of drugs on cellular functions, regardless of what target is hit. This approach is the one taken by AdipoGenix, which screens drugs in human adipocytes derived from nonobese, obese, obese diabetic, and other types of individuals, and from all three fat depots (mesenteric, omental, and subcutaneous). For example, AdipoGenix researchers screen drugs for inducing reduction in fat content. The researchers can then go on to determine the mechanism of action of drugs that score positive. Such drugs may hit one or multiple targets.

Another implication of the complexity of obesity pathways is the need for new animal models. "Standard" mouse obesity models are monogenic and demonstrate extreme obesity rarely seen in humans. Edward H. Leiter (Jackson Laboratories) and his colleagues have been developing polygenic mouse models that more closely model human obesity and obesity-induced insulin resistance and diabetes (Leiter EH, *Diabetes*, 2004.) These models can be used to study disease pathways and develop novel therapeutic strategies as well as to test the effects of drugs.

Several other novel approaches to developing novel breakthrough strategies for addressing obesity were discussed at the MBC conference including some from CytRx Laboratories, Mercury Therapeutics, Boston University, Beth Israel Deaconess Hospital, and the Whitehead Institute.

Outlook for the Near Future

If rimonabant is approved in 2006, it and the two currently available drugs, orlistat and sibutramine, will be the only obesity drugs on the market for several years. Given the complexity of obesity pathways, the large number of organs and tissues involved, and the modest efficacy of the drugs developed to date, optimal obesity treatment is likely to involve personalized combination therapy. It is important to remember that obesity drugs will be prescribed for a huge range of patients, including the elderly, reproductive-age women, and those with other serious medical conditions, which also points to a need for personalized therapy. In addition, obesity drug developers must learn from the fen-phen experience, where many prescriptions where written off-label and often generously prescribed through "diet centers" with no serious medical oversight.

Based on the data available, no miracle obesity drug is on the horizon. If pipeline drugs demonstrate long-term efficacy and few if any additional side effects, some of these compounds could become part of the package of future obesity therapies, all of which will be prescribed with lifestyle counseling. Unfortunately, the "magic bullet" for obesity, which will probably not be a single drug but a personalized combination, still appears to be a long way off. New therapeutic strategies for obesity and its comorbidities are sorely needed.

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