

The good news is that even modest weight loss may reduce the risk of obesity's co-morbidities. Numerous studies indicate that losing 5% to 10% of initial body weight in obese individuals can result in reduction in cardiovascular risk factors of the metabolic syndrome, reduced mortality in patients who had a previous myocardial infarction, and reduced risk of developing type 2 diabetes.<sup>7</sup> Researchers attribute the health benefits of modest weight loss to the preferential loss of intra-abdominal fat. It is this fat that is linked to the development of the components of the metabolic syndrome and the resulting risk of CVD and type 2 diabetes. Subcutaneous fat accounts for most of human fat mass, but is not associated with the development of the metabolic syndrome or its sequelae.

Although modest weight loss has beneficial health effects, it does not result in taking most obese or overweight individuals out of the obese or overweight class, however, and it thus may not meet the cosmetic or image expectations of many patients. This disappointment (perhaps coupled with the failure to achieve weight loss beyond the 5%–10% level) may tend to discourage the behaviors needed for the maintenance of the healthy weight loss. Nevertheless, losing 5% to 10% of one's body weight is the goal of most physicians who counsel or treat obese or overweight patients (other than morbidly obese patients who are candidates for bariatric surgery, as discussed later in this chapter). It is also usually a principal goal of companies that are developing obesity drugs. Other goals of drug developers may include reduction in the risk of co-morbidities of obesity.

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## **1.6. Guidelines for the Treatment of Obesity, and the Role of Drugs and Surgery**

### **American College of Physicians (ACP) Guidelines**

In 2005, the American College of Physicians published a set of guidelines for treatment of obesity in the primary care setting<sup>9</sup> that include a suggested scheme for management of obesity. A simplified version of this schema is given in Figure 1.1. The guidelines are based on evidence compiled by the Southern California Evidence-Based Practice Center.

Nevertheless, researchers and companies have been using what is known about energy balance pathways to design obesity drugs. Some of these drugs (especially those that have reached late-stage development) are discussed later in this report.

## 2.2. The Complex Genetics of Human Obesity

Researchers consider obesity to be a complex disease, which may be governed by large numbers of genes. They hypothesize that obesity-related variants in any one of these genes usually have a small effect, but that combinations of obesity-related variants in multiple genes may result in a significant risk of obesity, as compared to individuals who lack such a combination of variants.

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Since regulation of fat mass and energy balance involves interaction between multiple organs and tissues, one might expect that the risk of developing obesity would be governed by multiple genes, which act in different tissues of the body. Recently, researchers at deCODE Genetics (Reykjavik, Iceland) and Merck and its subsidiary, Rosetta Inpharmatics (Seattle, WA), studied the inheritance of gene expression in one such tissue, subcutaneous adipose tissue, and its relationship to inheritance of obesity-related phenotypes (e.g., BMI, waist-to-hip ratio, percentage body fat) in 1,700 Icelandic subjects.<sup>24</sup> Studying gene expression in subcutaneous fat has the advantage of sampling a readily accessible tissue via relatively noninvasive means. Other tissues that are thought to be involved in the determination of energy balance cannot be accessed easily in living humans and must usually be studied in animal models.

The deCODE and Merck researchers found clusters of genes whose expressions co-vary with each other and are co-inherited with obesity-related phenotypes. One core module of such genes was highly related to a gene co-expression cluster that was found to be co-inherited with obesity in a mouse study. This study was carried out by the Merck-Rosetta team that collaborated with the deCODE researchers in the human population study, plus academic collaborators.<sup>25</sup> The core obesity-related gene module in adipose tissue that is conserved between mice and humans (the human version of which contains 886 genes) is enriched for genes involved in inflammatory responses and macrophage activation pathways.

**Table 5.1. Obesity Drugs in Phase III Development (cont.)**

Company	Drug	Comments
Merck	Taranabant	CB1 receptor inhibitor; works in the brain to curb appetite. Same mechanism of action as rimonabant.
Pfizer	CP-945,598	CB1 receptor inhibitor; works in the brain to curb appetite. Same mechanism of action as rimonabant.

5-HT<sub>2C</sub>; hydroxytryptamine receptor 2C; CB1 receptor, cannabinoid-1 receptor.

*Source: Haberman Associates*

### Phentermine/Topiramate (Qnexa)

Qnexa (VIVUS Pharmaceuticals, Mountain View, CA) is a combination drug consisting of a fixed dose of low-dose phentermine and low-dose topiramate. Phentermine is an amphetamine-related appetite-suppressing drug that is approved by the FDA for short-term treatment of obesity. Topiramate (Johnson & Johnson's Topamax, generics) is an anticonvulsant that is approved by the FDA for treatment of epilepsy and for prevention of migraines. The strategy of using FDA-approved agents in the design of proprietary combination drugs enables companies to benefit from the well-known safety profiles of these drugs.

Topiramate has a complex mechanism of action on excitatory neurons, involving modulation of various types of ion channels and inhibition of kainite/AMPA glutamate receptors. (AMPA is 2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl) propanoic acid.) Topiramate has been investigated as a treatment for obesity and for binge eating disorders associated with obesity (i.e., binge eating that is not associated with bulimia or anorexia nervosa). Small, short-term, double-blind placebo-controlled studies of topiramate in binge eating disorder indicate that this agent is efficacious in reducing weight and binge frequency. Animal studies indicate that stimulation of the hypothalamus by glutamate and glutamate agonists (including kainite/AMPA agonists) causes a rapid increase in feeding. The effect of topiramate on binge eating may therefore be due to its kainite/AMPA agonist activity.<sup>39</sup>

VIVUS designed Qnexa as a combination therapy that addresses both appetite and satiety, with phentermine and topiramate, respectively. As separate agents, the two drugs have minimal effects on weight loss.

### **Peptide YY Nasal Spray**

MDRNa (Bothell, WA; until June 2008, known as Nastech Pharmaceutical Company; the name was changed because the company refocused from intranasally delivered drugs to development of drugs based on RNA interference) had been developing PYY nasal spray, an intranasal formulation of a synthetic version of the gut hormone PYY. As discussed in Section 5.2, natural PYY is secreted by the gut in response to food, and inhibits feeding via its action in the hypothalamus.

On July 31, 2008, MDRNa announced the results of a Phase II clinical trial of PYY in obesity. The agent did not meet the primary efficacy endpoint of significant dose-dependent weight loss, and did not induce a greater weight loss than sibutramine. This lack of efficacy was seen despite the effective delivery of PYY into the bloodstream via nasal administration.

Although PYY nasal spray was ineffective as a single agent in inducing weight loss, MDRNa speculates that it may be effective in combination therapies with other agents. However, the company is not likely to continue developing PYY nasal spray, since it is attempting to sell or license its nasal spray franchise in order to focus on RNA interference-based therapeutics.

PYY nasal spray thus represents another drug that was designed based on the new knowledge of energy balance pathways in the brain, but failed in the clinic, in this case, in Phase II clinical trials.

### **Potential of Current Phase II Drugs**

The results of Phase II clinical trials of several of these agents, especially Empatic, seem promising. However, as with most Phase II agents, and especially given the history of late-stage safety and/or efficacy failures in the obesity area, it is too early to tell whether any of these agents will be successfully developed.

antagonists that decrease feeding without causing adverse effects that would prevent successful development.<sup>48</sup> Nevertheless, many companies have been developing MCHR1 antagonists for treatment of obesity. All are in the early stages of development.

In January 2008, one of these companies, Neurogen (Branford, CT), announced the results of a Phase I clinical trial of its MCHR1 antagonist NGD-4715. The trial involved twice-per-day dosing of healthy obese subjects on a hypocaloric diet. During the first week of the study, half of the subjects treated with NGD-4715 experienced vivid dreams and awakenings. As a result of this study, Neurogen did not advance its compound into Phase II studies. It is seeking to outlicense its MCH program.

The inability, at least so far, of companies to unitize the exciting discoveries on the central control of body weight and energy utilization has been a major factor in stalling obesity drug development.

## **6.2. Novel Drugs that Treat Both Obesity and Diabetes**

As discussed in Chapter 5, an emerging theme in development of obesity drugs is testing these agents for their effects on type 2 diabetes (and/or prediabetes) in addition to obesity, with the possibility of developing them for both indications. Companies have also been testing and developing certain drugs that were initially indicated for treatment of diabetes, such as liraglutide and exenatide, for treatment of obesity. These strategies have often been opportunistic, but also motivated by the role of obesity in causing diabetes and/or commonalities (e.g., in the case of incretins and their mimetics) between blood glucose-lowering and anorectic effects of certain drugs. As also discussed earlier, the FDA has recently been encouraging the dual development of obesity drugs for diabetes.

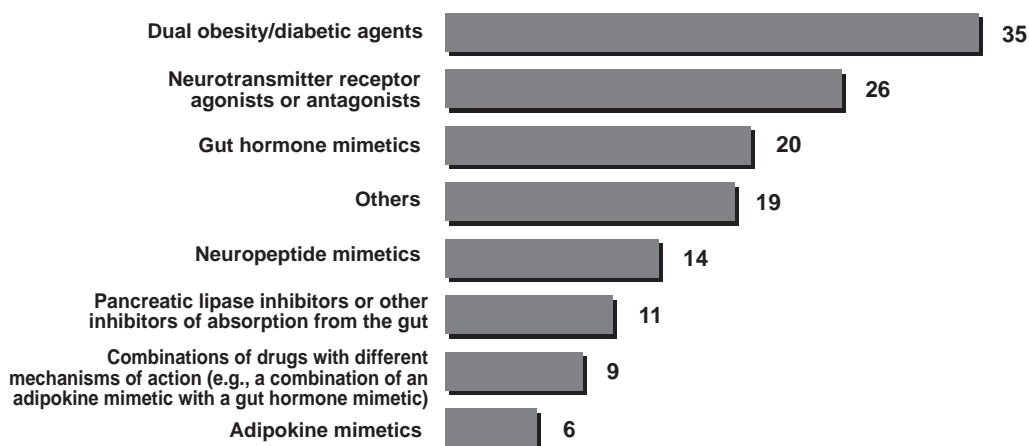
In the basic research and early-stage drug arena, numerous academic and corporate researchers have been attempting to address common mechanisms of metabolic disease, specifically obesity and type 2 diabetes. Drugs that emerge from these efforts can be expected to treat both diseases simultaneously.

The topic of early-stage drugs with mechanisms of action suggesting that they can treat common pathways of obesity and type 2 diabetes was discussed in a more comprehensive manner in our earlier report on diabetes.<sup>9</sup> Most of these drugs are, at least initially, being developed

respondents) said that their companies were working to address other aspects of obesity. Of these respondents, several answered “none” to the question of what other aspect they were working on—these answers were thus not informative. Other responses varied widely, ranging from herbal extracts, to cellular therapies, to anti-aging drugs.

**Figure 7.4. Aspects of Obesity Addressed by Discovery Research and Drug Candidates**

*What aspect(s) of obesity do your discovery research and drug candidates address?*



*n* = 76

*Source: Insight Pharma Reports Obesity Drug Development Survey—July 2008*

Question 5 (Figure 7.5) asked what respondents believed was the greatest bottleneck to the development of successful obesity drugs. Of those who answered this question, the largest percentage (65.1%) cited the complexity of physiological and biochemical pathways that control body weight; 17.0% of respondents cited the high safety hurdle for FDA approval, and 12.3% cited the reluctance of healthcare providers to reimburse obesity drugs. All of these factors have been discussed earlier in this report.

sponsors to highlight the importance of treating obesity: It is a major health risk, it is an epidemic, and it is going to bankrupt our country to treat its downstream effects if obesity continues to increase at the current rate. It takes time for insurance companies and third-party payers to realize that, if you treat obesity, you can avoid the costly treatments that you would need to pay for down the road.

**CHI:** *So you think they (i.e., payers) will eventually come around and change their stance on reimbursement of obesity treatments?*

**Mr. Tam:** Yes.

### **David A. Walsey**

*Director, Corporate Communications, Arena Pharmaceuticals,  
San Diego, CA*

**CHI:** *Please describe the product (or products) that Arena Pharmaceuticals has been working on for the treatment of obesity.*

**David A. Walsey:** Lorcaserin is Arena's promising late-stage candidate intended for treatment of people who are obese and overweight. It is a novel and selective 5-HT<sub>2C</sub> serotonin receptor agonist discovered by Arena. Stimulation of the 5-HT<sub>2C</sub> receptor is strongly associated with feeding behavior and satiety. Lorcaserin potentially also affects the patient's metabolic setpoint.

Lorcaserin is currently being evaluated in three Phase III trials that are expected to enroll almost 8,000 patients; the primary efficacy endpoint is 1-year weight loss. The first trial, BLOOM (which is evaluating patients over 2 years), began in September 2006 and completed enrollment in January 2007. BLOOM will be finished by the end of January 2009, and we believe we will be able to announce top-line results toward the end of March 2009. The BLOOM trial enrolled 3,182 people.

The other two trials are both 1-year trials and began in December 2007. One is BLOSSOM, which completed enrollment in June 2008 with 4,008 patients. The other is BLOOM-DM, which is being conducted in obese and overweight patients who are also being treated with oral medications for diabetes. We believe that the BLOOM-DM trial will complete enrollment toward the end of 2008 with about 600 patients.