

EDITORIAL



Pharmacotherapy for Obesity — Promise and Uncertainty

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In 2005, a majority of adult Americans are overweight or obese,¹ putting millions of them at increased risk for serious medical conditions, including cardiovascular disease, type 2 diabetes mellitus, and certain forms of cancer. In obesity, a weight loss of 5 to 10 percent can significantly improve risk factors for obesity-related diseases² and delay or prevent type 2 diabetes in persons at high risk.³ Behavioral treatments can result in a weight loss sufficient to improve health for many patients, but often the weight is regained over time.⁴ Although for many people a reduction in weight is difficult to achieve, maintaining the weight loss is even harder. Indeed, few nonsurgical treatments for obesity result in sustained weight loss. Hence, there is a need for adjunctive treatments that can assist patients in carrying out the changes in lifestyle needed to produce and sustain weight loss. Weight-loss medications represent one such treatment, but only two medications have been approved by the Food and Drug Administration for long-term use.

Two reports on therapeutic approaches to improving outcomes in the treatment of obesity appear in this issue of the *Journal*. Wadden and colleagues⁵ report that adding behavioral therapy to treatment with sibutramine significantly improves weight loss, as compared with that achieved by drug therapy alone, and Després and colleagues⁶ describe the effect of a new weight-loss agent, rimonabant, on cardiovascular risk factors in obese patients.

Rimonabant is a selective cannabinoid-1 receptor blocker with both central and peripheral actions. The Rimonabant in Obesity-Lipids (RIO-Lipids) Study,⁶ along with the previous RIO-Europe Study,⁷ demonstrates that 20 mg of rimonabant daily over a 12-month period has

salutary effects on a variety of obesity-related metabolic and cardiovascular risk factors in patients with dyslipidemia who are overweight or obese. Some of the improvements, including increases in adiponectin, are partly independent of body weight.^{6,7} The limitations of this study are similar to those of many trials of weight-loss drugs. Fewer than two thirds of the patients completed the trial. Patients with coexisting conditions, such as diabetes and psychiatric disorders, were excluded, limiting the generalizability of the results. Although the weight loss in this study is moderate and is in line with that induced with the use of other currently available medications, if rimonabant is approved for use, it would offer an additional choice for patients and physicians. New options for the treatment of a serious and refractory condition such as obesity are welcome; however, caveats unique to obesity treatments differ from those important for many other chronic diseases.

The history of weight-loss medications is checkered. When amphetamines were approved for the treatment of obesity in the 1960s, obesity drugs were labeled only for short-term use.⁸ In 1992, a series of seminal articles by Weintraub et al.⁹ showed the feasibility of treating obesity with long-term pharmacotherapy, similar to treatments for other chronic diseases. The usefulness of such an approach was apparent to those who had long noted that weight loss was rarely sustained after weight-loss drugs were withdrawn. The two drugs Weintraub used in combination, fenfluramine and phentermine (known as fenphen), had been on the market for years and were believed to be safe and effective. Not long afterward, dexfenfluramine, which had been in use in Europe for more than a decade, became the

first drug approved for the long-term treatment of obesity in the United States.⁸ The use of fenphen and dexfenfluramine exploded, despite nagging concerns about the adverse effect of pulmonary hypertension, with approximately 14 million prescriptions written for either fenfluramine or dexfenfluramine from 1995 until the withdrawal of these drugs from the market in 1997.¹⁰

The discovery of the association between fenfluramine and dexfenfluramine and valvular heart disease¹⁰ serves as a cautionary tale. First, unusual complications or those that occur only with long-term use or in combination with other medications may not become apparent until a drug is used in large populations for an extended time. Although both fenfluramine and dexfenfluramine had been prescribed for years, their use was primarily short-term and in relatively small numbers of patients. Second, many of those who took these medications were not among those most at risk because of obesity. Data from the 1998 Behavioral Risk Factor Surveillance System survey showed that 30 percent of patients using prescription weight-loss medications reported a body-mass index (BMI, defined as the weight in kilograms divided by the square of the height in meters) of less than 30, including 13.3 percent with a BMI under 27.¹¹

Drugs used to treat obesity differ from medications for other chronic diseases in how they are used. Obesity is a visible and stigmatizing condition. Few people want to be obese, and obese persons often have tried numerous times and with a variety of methods to lose weight. Because of the social emphasis on thinness, weight loss is also frequently attempted by people whose weight is normal or only slightly above normal. Therefore, a drug that appears to be efficacious in reducing body weight will undoubtedly be used not only to reduce medical risk among those who are obese but also to improve appearance among those who are less likely to have a medical benefit from weight loss. Thus, as Bray has suggested,¹² a careful assessment of the safety of antiobesity medications may be even more important than for drugs used to treat other conditions, in which the drugs are less liable to be misused. In addition, although weight loss in obese persons is known to improve risk factors and might be anticipated to reduce cardiovascular morbidity and mortality, no study has yet

demonstrated conclusively that any weight-loss treatment has such an effect, although research on this critical issue is ongoing.^{8,13,14} Whether those who lose weight with antiobesity medications have health outcomes similar to those who lose weight through lifestyle changes alone (or who were never obese) also remains uncertain.

How are health care professionals to make decisions with regard to the use of antiobesity medications in clinical practice? Overweight and obese patients should be carefully evaluated to assess their medical risk as well as their readiness to attempt weight loss. Although nondrug treatments should be the primary intervention, for many patients, attempts to lose weight or maintain weight loss through diet and exercise alone will not be sufficient. For patients whose weight and risk factors put them at high risk for obesity-related disease, physicians and patients may choose to initiate adjunctive treatment with antiobesity medications. Weight-independent effects on such risk factors may be considered when choosing the medication, as well as adverse effects, patients' preferences, and response to treatment. As Wadden et al. make clear, the efficacy of drug therapy is markedly improved with the concomitant use of behavioral treatment.⁵ This finding is consistent with the National Institutes of Health guidelines,² which recommend that weight-loss medications be used as part of a comprehensive program that includes diet therapy and physical activity.

An improved armamentarium of therapeutic approaches is needed to promote and sustain weight loss safely and effectively in obese patients and to prevent or ameliorate many obesity-related conditions. Advances in our understanding of the complex systems regulating energy balance, the genetic determinants of obesity, and the environmental factors that promote obesity should lead to the development of more effective and targeted treatments in the future. Ultimately, our goal must be to use this understanding to develop more effective strategies not only for treatment, but also for the primary prevention of obesity.

The views expressed in this paper are those of the author and do not necessarily reflect the views of the National Institutes of Health or the Department of Health and Human Services.

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