

# The Endocannabinoid System as a Target for Obesity Treatment

## LOUIS J. ARONNE, MD

Clinical Professor of Medicine  
Weill Cornell Medical College  
New York, New York

## UBERTO PAGOTTO, MD, PHD

Assistant Professor, Endocrinology Unit  
Department of Internal Medicine  
and Gastroenterology  
Center for Applied Biomedical Research (CRBA)  
S. Orsola-Malpighi Hospital  
University of Bologna  
Bologna, Italy

## GARY D. FOSTER, PHD

Director, Center for Obesity Research  
and Education  
Temple University School of Medicine  
Philadelphia, Pennsylvania

## STEPHEN N. DAVIS, MD, FRCP

Chief, Division of Diabetes, Endocrinology,  
and Metabolism  
Rudolph Kampmeier Professor, Medicine and  
Molecular Physiology and Biophysics  
Vanderbilt University Medical School  
Nashville, Tennessee

Overweight and obesity are major factors contributing to the development of type 2 diabetes mellitus (DM) and cardiovascular disease (CVD). In addition to the many physical and metabolic consequences of obesity, there are also mental health consequences, in particular, the risk for depression. Depression can lead to poor self-care, poor treatment compliance, and possible increased morbidity and mortality from such illnesses as type 2 DM and CVD. Lifestyle modification for the treatment of overweight and obesity is rarely successful over the long term, and use of surgery is limited by eligibility criteria; therefore, researchers and clinicians continue to explore pharmacotherapy, with intense efforts being directed toward the development of agents that, optimally, will reduce weight and simultaneously reduce or eliminate modifiable cardiovascular and metabolic risk factors. Among the promising new agents are the CB<sub>1</sub> receptor antagonists. These agents target receptors of the endocannabinoid system, a neuromodulatory system recently found to influence energy balance, eating behavior, and metabolic homeostasis via central and peripheral mechanisms. In animal and clinical studies, antagonism of CB<sub>1</sub> receptors has resulted in meaningful weight loss and improvement of lipid and glycemic profiles. Thus, these agents may provide a rational and effective approach for the management of not only overweight and obesity but also their metabolic and cardiovascular sequelae. (*Clinical Cornerstone*. 2008;9[1]:52–66) © 2008 Elsevier. All rights reserved.

Obesity is a major health hazard because of its contribution to the development and progression of type 2 diabetes mellitus (DM) and cardiovascular disease (CVD).<sup>1–3</sup> Other medical complications of obesity include gallbladder disease, genitourinary problems (eg, menstrual irregularities, stress incontinence), osteoarthritis, certain cancers, and psychological disorders.<sup>4</sup> Statistics from the US Department of Health and Human Services<sup>5</sup> indicate that during the period 2003 to 2004, ~34% of American adults were obese compared with 13% reported in the early 1960s. Moreover, another one third of adult Americans were overweight. Thus, collectively, an estimated two thirds of all American adults have a weight problem

that is putting them at risk for cardiometabolic complications. In view of this situation, new and more effective approaches for managing obesity are urgently needed. At a roundtable meeting in June 2007, representatives of the American Osteopathic Association, the American College of Osteopathic Internists, the American College of Osteopathic Family Practitioners, the American Academy of Physician Assistants, and The Diabetes Consortium developed 2 consensus statements declaring that: (1) “Obesity is a disease,” and (2) “Obesity...should be treated by a multifaceted approach that must include lifestyle modification and may include medical or surgical intervention.”<sup>6</sup>

**KEY POINT**

**An estimated two thirds of all American adults have a weight problem that is putting them at risk for cardiometabolic complications.**

**OBESITY AND CARDIOMETABOLIC RISK**

Overweight and obese patients frequently present with a cluster of interrelated metabolic risk factors for type 2 DM and CVD referred to as *cardiometabolic risk*. According to an estimate by Ford et al,<sup>7</sup> in 2000, there were 64 million individuals at increased cardiometabolic risk in the United States alone. Given the growing population of overweight and obese individuals, this number is now likely even higher.

Cardiometabolic risk denotes the group of modifiable risk factors known as *metabolic syndrome*. Metabolic syndrome includes classic risk factors for type 2 DM and CVD (eg, elevated triglyceride, glucose, and blood pressure levels and decreased high-density lipoprotein cholesterol [HDL-C] levels) and emerging markers of risk resulting from abdominal obesity, including elevated plasminogen-activator inhibitor-1 and C-reactive protein (CRP) levels, which signify prothrombotic and pro-inflammatory states.<sup>8,9</sup> Although metabolic syndrome is now generally accepted as a clinical condition, lack of consensus regarding its distinguishing features have precluded formulation of an internationally recognized definition.<sup>10</sup> The definition of cardiometabolic risk, however, includes the National Cholesterol Education Program Adult Treatment Panel III definition of metabolic syndrome<sup>11</sup> plus 4 additional risk factors—smoking, elevated low-density lipoprotein cholesterol (LDL-C), inflammatory markers (eg, CRP, interleukin-6), and insulin resistance<sup>1</sup> (Table I).

According to data from the National Health and Nutrition Examination Survey (NHANES) 1999–2000, the most common risk factor for increased cardiometabolic risk is abdominal obesity, which has been reported in 44% of US adults aged  $\geq 20$  years.<sup>7</sup> In fact, abdominal obesity has been causally linked to metabolic dysfunctions that place individuals at increased cardiometabolic risk.<sup>2,3</sup> The accumulation of abdominal adipose tissue, especially visceral adipose tissue (VAT), has been associ-

**TABLE I. DEFINITION OF CARDIOMETABOLIC RISK.\*<sup>1,11</sup>**

Modifiable risk factor	Abdominal obesity ↑ Triglycerides ↑ LDL-C ↓ HDL-C ↑ Blood pressure ↑ Blood glucose Insulin resistance Smoking
Inflammatory marker	CRP IL-6

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; CRP = C-reactive protein; IL-6 = interleukin-6.

\*Cardiometabolic risk includes modifiable risk factors and markers that place individuals at increased risk for type 2 diabetes mellitus and cardiovascular disease.

ated with the glucose intolerance and hyperinsulinemia that result from insulin resistance.<sup>1,12,13</sup> Increased VAT mass has also been associated with hypertriglyceridemia and low levels of HDL-C.<sup>1,14</sup> The decline in plasma levels of HDL-C in individuals with visceral obesity is largely responsible for the increase in their ratio of LDL-C to HDL-C,<sup>1,15</sup> which is a strong predictor of risk for coronary heart disease.<sup>16</sup> Three additional metabolic risk markers, fasting hyperinsulinemia, increased apolipoprotein B (apo B) concentration, and an increased proportion of small dense low-density lipoprotein (LDL) particles—abnormalities found together in viscerally obese men—have been shown to be associated with an 18-fold increased risk for developing ischemic heart disease in initially asymptomatic middle-aged men followed for 5 years.<sup>17</sup>

**KEY POINT**

**According to data from NHANES 1999–2000, the most common risk factor for increased cardiometabolic risk is abdominal obesity.**

**PSYCHOSOCIAL SEQUELAE OF OBESITY  
Depression**

Although the many physical and metabolic consequences of obesity are well recognized, less is known

about its mental health consequences, in particular its role as a risk factor for depression. In patients with chronic medical illnesses, depression has been associated with poor self-care, poor treatment compliance, greater use of health care services, and possible increased morbidity and mortality from such illnesses as type 2 DM and CVD.<sup>18,19</sup> Therefore, the presence of depression may be a relevant consideration when developing strategies to treat obesity.

### KEY POINT

**In patients with chronic illnesses, depression has been associated with poor self-care, poor treatment compliance, and possible increased morbidity and mortality from such illnesses as type 2 DM and CVD.**

The association between obesity and depression has been explored in both cross-sectional and longitudinal studies. In the Alameda County Study, Roberts et al<sup>20</sup> compared the risk of depression in obese, normal-weight, and underweight subjects. Depression was measured using a 12-item scale based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV)* criteria for a major depressive episode. Obese subjects were defined as those having body mass index (BMI) scores in the 85th percentile or higher. Cross-sectional analysis of baseline data from patients  $\geq 50$  years of age who participated in the 1994 and 1999 waves of the Alameda County Study ( $n = 2123$ ) showed that obese subjects were significantly more likely to be depressed than were normal-weight or underweight subjects (15.5% vs 7.4% and 8.8%, respectively;  $P < 0.001$ ). Moreover, logistic regression analysis of data for subjects without depression at baseline indicated that obesity at baseline increased the risk for depression 1 year later (odds ratio [OR] = 1.91).

The association between obesity and depression was further explored by Onyike et al,<sup>21</sup> using data from NHANES III (1988–1994). Past-month depression was measured with the Diagnostic Interview Schedule (DIS), a lay interview instrument based on *Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM III)*

criteria. Obesity was defined as a BMI  $\geq 30.0$  kg/m<sup>2</sup>. Results showed that past-month depression was  $\sim 2.5$  times more prevalent in women than in men. When obesity was classified by severity across all study participants, severe obesity (BMI  $\geq 40.0$  kg/m<sup>2</sup>) was more strongly associated with depression than was less severe obesity (BMI, 30.0–34.9 or 35.0–39.9 kg/m<sup>2</sup>; OR, 4.63 vs 1.33 and 1.90, respectively). These results suggest that depression is most likely to occur among individuals with severe obesity.

Nearly one third of obese individuals seeking weight-related treatment report serious problems with binge eating or compulsive overeating.<sup>22</sup> These individuals generally have greater attrition during treatment, regain lost weight more rapidly in behavioral programs, and demonstrate more psychological problems than individuals without binge-eating disorders.<sup>22</sup> In a study of a self-referred group of 128 men and women with moderate or severe obesity, Yanovski et al<sup>22</sup> investigated the prevalence of binge-eating disorder and psychopathology, as well as family history of psychiatric disorders. In this study, subjects with binge-eating disorder were found to have a significantly higher rate of major depression than did those without this disorder (51% vs 14%; relative risk, 6.4; between-group difference,  $P < 0.001$ ). These subjects also were significantly more likely to have panic disorder, bulimia nervosa, borderline personality disorder, avoidance personality disorder, and/or a family history of substance abuse. Carpenter et al<sup>23</sup> examined the relationships between relative body weight and clinical depression, suicide ideation, and suicide attempts in a sample of adults in the US general population ( $N = 40,086$ ). Results showed that body weight was correlated with major depression, suicide ideation, and suicide attempts, although the relationships differed for men and women. Among men, lower BMI was associated with major depression, suicide ideation, and suicide attempts, whereas among women, increased BMI was associated with major depression and suicide ideation. Of interest, a recent case-control study<sup>24</sup> of patients who had gastric bypass surgery demonstrated a 3-fold net decreased risk of mortality over 7 years of follow-up but a 2- to 3-fold increased risk of suicide following gastric bypass, the latter possibly due to an impact of weight loss on mood disorders.

In a recent review, Greenman and Stern<sup>25</sup> noted that obesity and depression appear to be interrelated at sev-

eral levels—epidemiologic, behavioral, psychosocial, biologic, and pathophysiologic. The authors suggested that the increasing prevalence and associated major health burden of obesity and depression highlight the need to increase our understanding of these disorders and their interrelationship to allow for the development of more effective prevention and treatment measures. Unfortunately, weight loss, the cornerstone of therapy for obesity and its complications, has only limited long-term success. For example, in a study<sup>26</sup> comparing the Atkins, Zone, Weight Watchers, and Ornish diets (n = 40 for each arm), only 25% of participants sustained a 1-year weight loss of >5% of initial body weight, and 42% of participants did not complete the study. Thus, new approaches aimed at reducing the cardiometabolic risk of overweight and obesity while simultaneously reducing weight are required. One novel approach gaining attention involves targeting the endocannabinoid system (ECS) and its receptors by a new class of drugs, the CB<sub>1</sub> receptor antagonists.

### KEY POINT

**Obesity and depression appear to be interrelated at several levels—epidemiologic, behavioral, psychosocial, biologic, and pathophysiologic.**

### THE ENDOCANNABINOID SYSTEM

The ECS is a neuromodulatory system involved in the regulation of energy balance, eating behavior, and metabolism via central and peripheral mechanisms.<sup>3,27</sup> The system comprises endogenous ligands (endocannabinoids) and 2 types of G-protein-coupled cannabinoid receptors—CB<sub>1</sub> and CB<sub>2</sub>.<sup>3,27</sup> The CB<sub>1</sub> receptors are located in several areas of the brain, including the hypothalamus, forebrain, and basal ganglia, and in a number of peripheral tissues and organs, including white adipose tissue, the gastrointestinal tract, liver, pancreas, and muscle. CB<sub>2</sub> receptors localize to the immune system.<sup>3</sup>

In the central nervous system, the ECS is involved in the modulation of food intake and in the motivation to consume palatable food.<sup>3,27</sup> In a study<sup>28</sup> demonstrating the central role of the ECS in feeding behavior, adminis-

tration of the endocannabinoid anandamide into the ventral medial nucleus of the hypothalamus stimulated eating in presatiated rats, whereas pretreatment with rimonabant, a CB<sub>1</sub> receptor antagonist, inhibited anandamide-induced overeating.<sup>29</sup>

At the peripheral level, the ECS is involved in energy intake, storage, and utilization.<sup>3</sup> In a study<sup>30</sup> of the anti-obesity effect of rimonabant, this agent markedly decreased the weight of dietary obese mice over a 40-day administration period. Food intake decreased during the first week of administration, then gradually returned to levels similar to those of vehicle-treated control mice. This observation suggests that an additional mechanism (eg, a metabolic effect) might contribute to the long-lasting antiobesity effect of rimonabant (**Figure 1**). Studies in CB<sub>1</sub>-knockout mice<sup>31,32</sup> have shown that these animals have a lower body weight and less body fat (% body weight) despite relative energy intake similar to that of wild-type control mice.

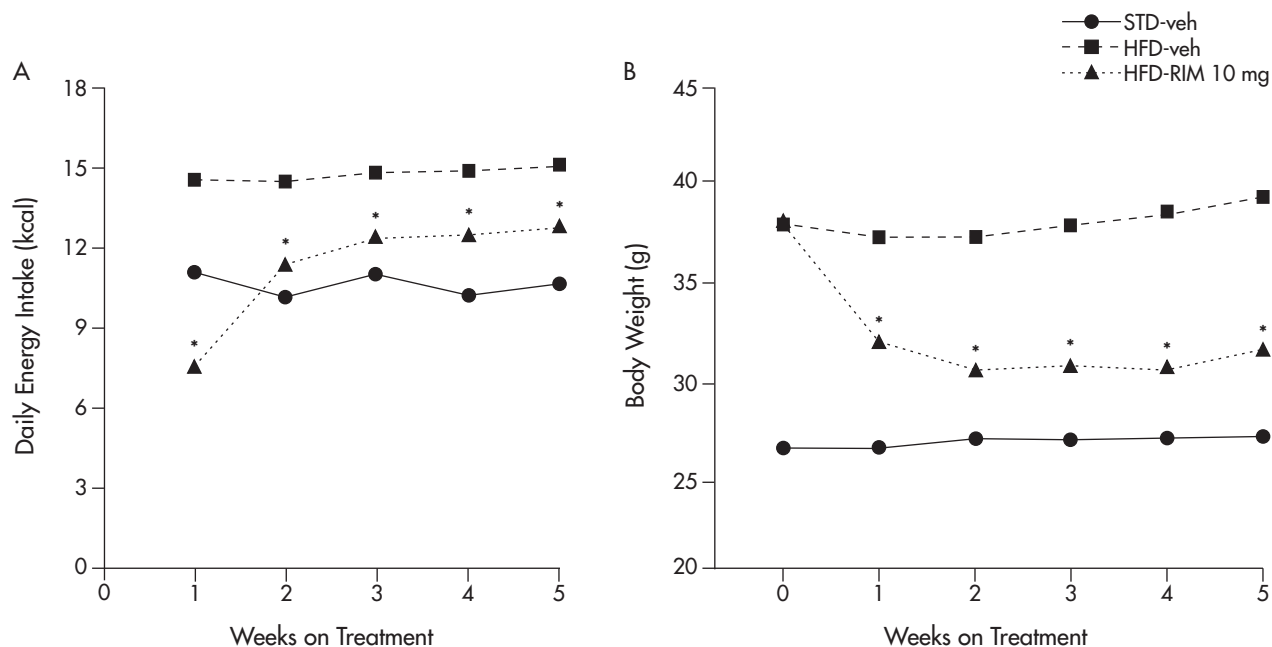
Overall, these findings indicate that stimulation of the CB<sub>1</sub> receptor plays an important role in the development of diet-induced obesity and that CB<sub>1</sub> receptors are involved in both feeding control and peripheral metabolic regulation. Consequently, CB<sub>1</sub> receptors appear to be rational targets for the treatment of obesity and related metabolic dysfunctions.

### KEY POINT

**The ECS is a neuromodulatory system involved in the regulation of energy balance, eating behavior, and metabolism via central and peripheral mechanisms. Evidence from animal and human studies suggests that CB<sub>1</sub> receptor antagonists targeting the ECS can positively affect obesity, dyslipidemia, and insulin resistance.**

### THE ECS AS A TARGET FOR TREATMENT

It has been hypothesized that dysregulation of the ECS is associated with obesity, impaired glucose response, abnormal insulin levels, and eating disorders in humans.<sup>3,33</sup>



**Figure 1. Metabolic effects of rimonabant are independent of reduction in food intake. (A) Rimonabant 10 mg/kg (RIM 10 mg) induced a decrease in food (energy) intake in high-fat-diet-fed (HFD) mice for ~1 week, after which food intake gradually returned to levels observed in HFD/vehicle-treated (HFD-veh) control mice. (B) After 5 weeks of treatment, HFD-RIM 10-mg mice were 20% (8 g) lighter than HFD-veh mice and only 14% (4 g) heavier than mice receiving standard diet/vehicle (STD-veh). \* $P < 0.01$ . Adapted with permission.<sup>30</sup>**

A growing body of evidence from studies in both animal models and humans, as discussed below, suggests that  $CB_1$  receptor antagonists targeting the ECS can positively affect obesity, dyslipidemia, and insulin resistance. For example, in a study of obese mice on a high-fat diet,<sup>34</sup> use of rimonabant sustained the weight loss achieved in these mice and resulted in reductions in serum leptin, insulin, glucose, triglyceride, and LDL-C levels. It also resulted in increases in serum adiponectin levels and the HDL-C:LDL-C ratio. Thus,  $CB_1$  receptor antagonists may offer a novel and effective treatment approach not only for weight reduction but also for a concomitant improvement in several cardiometabolic risk factors.

### OPTIONS FOR TREATING OBESITY

Because overweight and obesity are a leading cause of comorbidities such as type 2 DM and CVD, achieving and maintaining weight loss is important not only for the well-being of overweight individuals but also, potentially, to reduce the burden their treatment imposes on the health care community.

Current guidelines<sup>35</sup> recommend a 3-tier approach to weight loss based on BMI and the presence of comorbidities. Lifestyle modification, which includes a comprehensive program of reduced caloric intake, physical activity, and behavioral therapy, is recommended for all individuals who have a BMI  $\geq 25$  kg/m<sup>2</sup>. Pharmacotherapy is recommended for individuals with a BMI of 27 to 29.9 kg/m<sup>2</sup> and comorbidities, or a BMI  $\geq 30$  kg/m<sup>2</sup> even in the absence of a comorbidity. The recommendation for surgery is reserved for the severely obese (BMI 35–39.9 kg/m<sup>2</sup> and a comorbidity, or a BMI  $\geq 40$  kg/m<sup>2</sup>). According to the American Heart Association and the American Diabetes Association,<sup>36</sup> weight reduction in obese individuals will reduce the cardiometabolic risk factors associated with type 2 DM and improve hyperglycemia. Even moderate weight loss (7%–10% of body weight in 1 year) in an obese patient can improve his or her lipid profile, insulin sensitivity, and blood pressure.

### Pharmacologic Treatment

Lifestyle modification alone is often insufficient to achieve and maintain weight loss goals. Therefore, aug-

mentation with drug therapy is becoming an increasingly important option. Several weight loss drugs are approved for the treatment of obesity; however, only 2 of these drugs—sibutramine and orlistat—are approved for long-term use. Both sibutramine and orlistat, in combination with dietary changes, have been shown to produce additional weight loss relative to placebo at 1 year (~4.45 and 2.89 kg, respectively).<sup>37</sup> Other weight loss drugs are being investigated, including rimonabant and taranabant. Both of these agents target the ECS and are intended for long-term use.

### KEY POINT

**Lifestyle modification alone is often insufficient to achieve and maintain weight loss goals. Therefore, augmentation with drug therapy is becoming an increasingly important option.**

## CLINICAL EXPERIENCE WITH CURRENT AND EMERGING WEIGHT LOSS AGENTS

### Current Agents *Sibutramine*

Sibutramine induces weight loss in 2 ways: (1) inhibition of the reuptake of norepinephrine, dopamine, and serotonin in the synaptic clefts that results in reduced food intake; and (2) prevention of the decline in energy expenditure that follows weight loss.<sup>38,39</sup> A randomized, double-blind trial<sup>39</sup> assessed the effect of sibutramine on weight maintenance after weight loss. In this study, 477 patients who achieved a weight loss of >5% of initial body weight by month 6 of treatment with sibutramine (10 mg/d) plus an individualized low-calorie diet were randomly assigned either to sibutramine (up to 20 mg/d) or placebo for the next 18 months. Of the patients who completed the study, 44% (89/204) in the sibutramine group maintained ≥80% of their original weight loss compared with 16% (9/57) of those in the placebo group ( $P < 0.001$ ). Substantial reductions in triglyceride, very-low-density lipoprotein cholesterol, insulin, C peptide, and uric acid levels occurred over the first 6 months. These changes were maintained in the sibutramine group

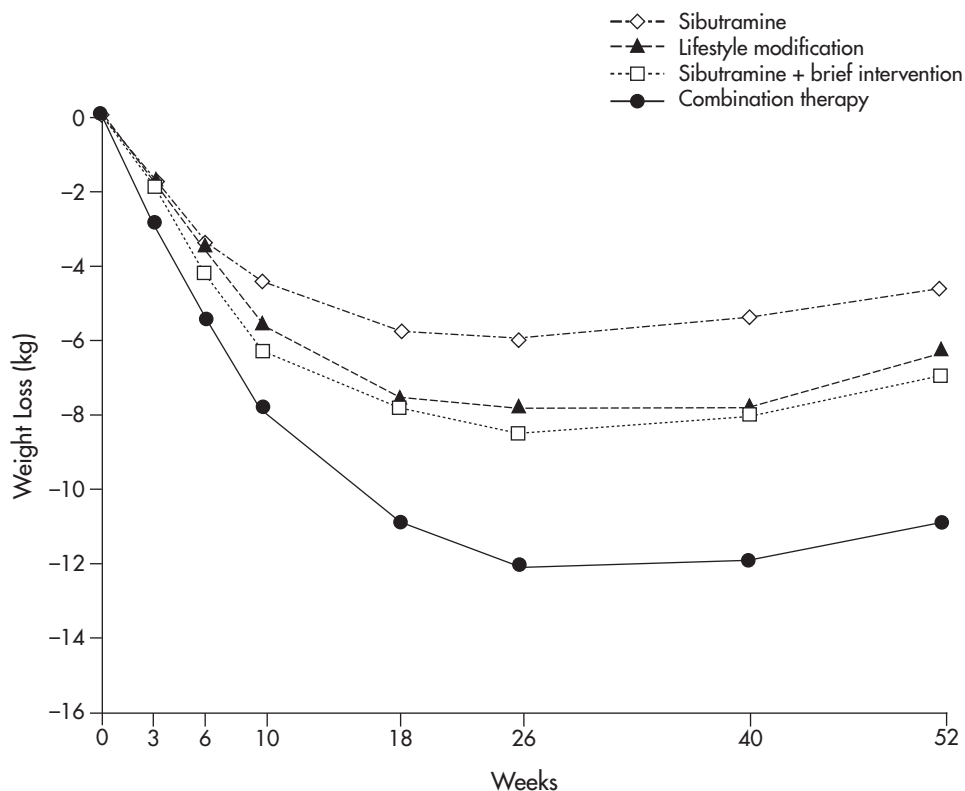
but not in the placebo group over the next 18 months. HDL-C levels rose substantially in both groups during year 2, although the increase in the sibutramine group was nearly twice that of the placebo group (20.7% vs 11.7%;  $P < 0.001$ ). Side effects of sibutramine treatment included modest increases in pulse rate as well as systolic and diastolic blood pressures, the latter suggesting that blood pressure, particularly in patients with hypertension, should be monitored routinely in sibutramine-treated patients. The incidences of depression with sibutramine and placebo during the weight-maintenance phase of the study were 6% and 4%, respectively. The incidence of anxiety was not reported in this study; however, summary data based on patients treated with sibutramine ( $n = 2068$ ) or administered placebo ( $n = 884$ ) in controlled and uncontrolled premarketing studies showed rates of 4.5% and 3.4%, respectively, for anxiety and 4.3% and 2.5%, respectively, for depression.<sup>40</sup>

The Sibutramine Cardiovascular Outcome Trial (SCOUT),<sup>41</sup> a large, double-blind, placebo-controlled, multicenter, multinational study, is investigating the potential benefits of weight management in overweight and obese patients at high cardiovascular risk. This 5-year study is expected to be completed in 2008. The 10,742 patients enrolled in the study received treatment with sibutramine plus weight management during a 6-week lead-in period. The primary end point includes a composite of myocardial infarction, stroke, resuscitated cardiac arrest, and cardiovascular death.

In a study by Wadden et al,<sup>42</sup> the importance of adding pharmacotherapy to lifestyle modification was demonstrated. In this study, 4 treatment approaches were compared: sibutramine alone, counseling on lifestyle modification alone, sibutramine plus brief interventional counseling, and sibutramine plus more intensive lifestyle counseling (combined treatment). Results at 1 year (**Figure 2**) indicate that combined treatment resulted in additive weight loss compared with sibutramine monotherapy, lifestyle counseling, or sibutramine with brief counseling. These results demonstrate that pharmacotherapy and lifestyle modification together are crucial for optimal results.

### *Orlistat*

Orlistat is a gastrointestinal lipase inhibitor that induces weight loss by inhibiting the absorption of dietary fats. The impact of orlistat on weight loss, glycemic control,



**Figure 2. Subjects treated with combination therapy (sibutramine plus intensive lifestyle counseling) showed greater weight loss at all evaluations than did subjects treated with sibutramine alone, counseling on lifestyle modification alone, or sibutramine plus brief interventional counseling. Differences favoring combined therapy were significant at weeks 18 and 40 and at 1 year (intent-to-treat analysis,  $P < 0.001$ ). Adapted with permission.<sup>42</sup>**

### KEY POINT

**Pharmacotherapy and lifestyle modification together are crucial for optimal results.**

and serum lipid levels in obese patients with type 2 DM was assessed in a 57-week, double-blind, placebo-controlled study.<sup>43</sup> Following completion of a placebo lead-in period, 322 patients were randomized to orlistat 120 mg ( $n = 163$ ) or placebo ( $n = 159$ ) TID plus a hypocaloric diet. Patients in the orlistat group achieved significantly greater weight loss than patients in the placebo group (6.2% vs 4.3% of initial body weight;  $P < 0.001$ ). They also achieved significantly greater reductions in glycosylated hemoglobin (HbA1c) and fasting plasma glucose levels (both,  $P < 0.001$ ) and reduc-

tions in their sulfonylurea dosages ( $P < 0.01$ ). Patients in the orlistat group also showed greater reductions in total cholesterol, LDL-C, and apo B levels, and the ratio of LDL-C to HDL-C (all,  $P < 0.001$ ), as well as greater reductions in triglyceride levels ( $P < 0.05$ ).

The XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) study<sup>44</sup> investigated the effectiveness of long-term treatment with orlistat plus lifestyle changes in reducing body weight and progression to type 2 DM. In this 4-year, double-blind study of 3305 obese, nondiabetic subjects with either normal or impaired glucose tolerance, significantly more patients in the orlistat group (850/1650 [52%]) than in the placebo group (564/1655 [34%]) completed the study ( $P < 0.001$ ). Mean weight loss was significantly greater in the orlistat group than in the placebo group at 1 year (10.6 vs 6.2 kg;  $P < 0.001$ ), and this difference was maintained at the end of the 4-year treatment period (5.8 vs 3.0 kg;  $P < 0.001$ ). Moreover, significantly fewer patients in the orlistat

group than in the placebo group progressed to type 2 DM (6.2% vs 9.0%;  $P = 0.003$ ). Orlistat was generally well tolerated, although gastrointestinal problems were more common in this group. Orlistat is now available over the counter as alli™ (GlaxoSmithKline, Research Triangle Park, North Carolina) in one half the strength of the prescription dose.

## Emerging Agents

### Rimonabant

Rimonabant, a selective CB<sub>1</sub> receptor antagonist, has been evaluated in 4 large, multicenter, multinational, randomized, placebo-controlled clinical trials: Rimonabant in Obesity (RIO)-Europe, RIO-North America, RIO-Lipids, and RIO-Diabetes.<sup>45-48</sup> Patients in these studies were randomized to rimonabant (5 or 20 mg/d) or placebo plus a hypocaloric diet. Patients also were advised to increase their physical activity levels. In all 4 studies, treatment with rimonabant 20 mg/d resulted in greater reductions in body weight and waist circumference than did placebo.

Treatment with rimonabant 20 mg/d also improved a number of cardiometabolic risk factors versus placebo (**Table II**).<sup>49</sup> These improvements included increases in HDL-C levels; reductions in triglyceride, FPG, and fasting insulin levels; and improvements in the triglyceride:HDL-C, LDL-C:HDL-C, and total cholesterol:HDL-C ratios, and HOMA-IR (homeostasis model assessment insulin resistance). Furthermore, in all 4 studies, the prevalence of cardiometabolic risk factors declined more with rimonabant than with placebo. This finding has important implications because, as indicated earlier, cardiometabolic risk factors are predictors for the development of both type 2 DM and CVD.<sup>45,50,51</sup>

Additional treatment effects were demonstrated in the RIO-Lipids study,<sup>47</sup> which focused on patients with untreated dyslipidemia at high risk for CVD. In this study, there was a decrease in the proportion of small LDL particles in the rimonabant 20-mg group compared with the placebo group ( $P = 0.002$ ). Treatment with rimonabant also resulted in greater reductions in plasma leptin and

**TABLE II. SUMMARY OF OUTCOMES IN THE RIO STUDIES.**

Outcome	No. of Studies (Sample Size)	Weighted Mean or Risk Difference, Active Minus Placebo (95% CI)
Change in weight, kg	4 (4099)	-4.67 (-5.26 to -4.07)
Change in weight in subjects with diabetes, kg	1 (1047)	-3.90 (-4.57 to -3.23)
5% Responders, absolute % difference	4 (4099)	0.33* (0.29 to 0.37)
10% Responders, absolute % difference	4 (4099)	0.19* (0.15 to 0.23)
Change in waist circumference, cm	4 (4098)	-3.89 (-4.47 to -3.30)
Change in systolic blood pressure, mm Hg	3 (2273)	-1.78 (-2.81 to -0.76)
Change in diastolic blood pressure, mm Hg	3 (2273)	-1.23 (-1.93 to -0.54)
Change in total cholesterol, mmol/L <sup>†</sup>	3 (2223)	-0.04 (-0.11 to 0.03)
Change in LDL-C, mmol/L <sup>†</sup>	3 (2223)	-0.05 (-0.12 to 0.01)
Change in HDL-C, mmol/L <sup>†</sup>	4 (4050)	0.10 (0.08 to 0.11)
Change in triglycerides, mmol/L <sup>†</sup>	4 (4049)	-0.24 (-0.30 to -0.17)
Change in HbA1c in subjects with diabetes, %	1 (1047)	-0.70 (-0.84 to -0.56)
Change in FPG in subjects with diabetes, mmol/L <sup>†</sup>	1 (1047)	-0.97 (-1.30 to -0.64)
Discontinuation due to adverse event, absolute % difference	4 (4105)	0.06* (0.05 to 0.08)
Serious adverse event, absolute % difference	4 (4105)	0.02* (0.00 to 0.03)
Psychiatric disorders, absolute % difference	4 (4105)	0.03* (0.02 to 0.05)

RIO = Rimonabant in Obesity; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; HbA1c = glycosylated hemoglobin; FPG = fasting plasma glucose.

\*Risk difference. All other calculations represent weighted mean difference.

<sup>†</sup>To convert mmol/L to mg/dL, divide by 0.0555.

Adapted with permission.<sup>49</sup>

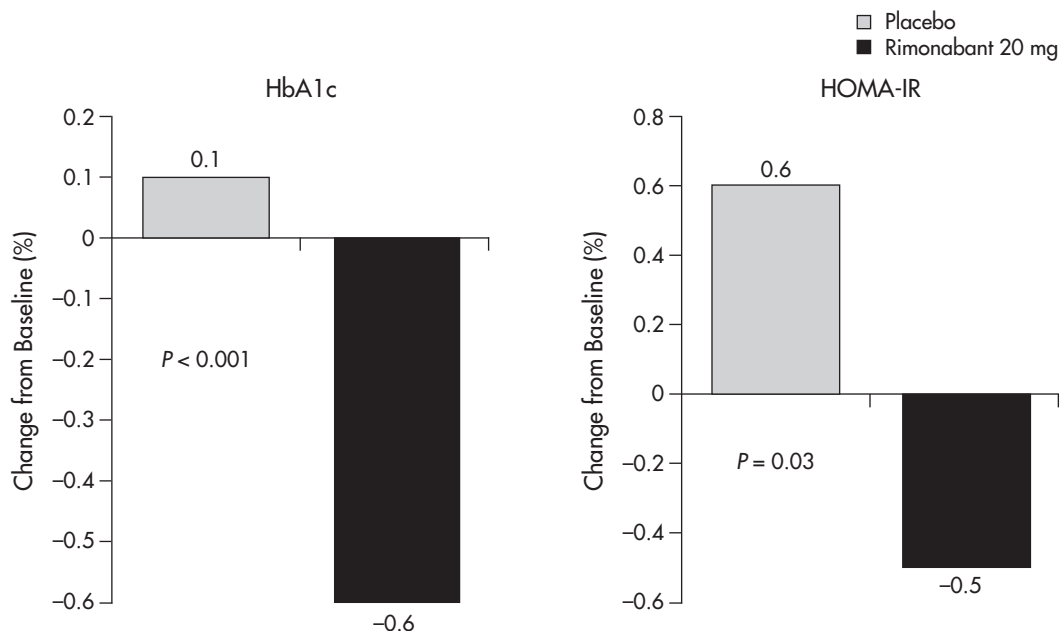
CRP levels versus placebo ( $P < 0.001$  and  $P < 0.02$ , respectively) and greater increases in plasma adiponectin levels ( $P < 0.001$ ). The greater increases in adiponectin may be clinically important, as high adiponectin levels have been shown to predict a decreased risk for type 2 DM and cardiovascular events.<sup>47,52,53</sup>

Results of the RIO-Diabetes study<sup>48</sup> extended the findings of the RIO-Lipids<sup>47</sup> study to overweight or obese patients with type 2 DM inadequately controlled with metformin or a sulfonylurea. In the RIO-Diabetes study, HbA1c levels were significantly lower in the rimonabant group than in the placebo group ( $P < 0.001$ ) (**Figure 3**), and more patients in the rimonabant group than in the placebo group reached the target levels of  $<6.5\%$  recommended by the American Association of Clinical Endocrinologists and  $<7.0\%$  recommended by the American Diabetes Association ( $P < 0.001$ ). The observed (placebo-corrected) reduction in HbA1c levels with rimonabant was 0.7%, an amount considered clinically relevant, as every 1% reduction in HbA1c appears to be associated with a 21% reduction in risk for any diabetes-related end point.<sup>54</sup>

It is important to note that the changes in HDL-C, triglyceride, fasting insulin, HOMA-IR, HbA1c, and adiponectin levels observed with rimonabant in the vari-

ous studies<sup>45–48</sup> exceeded those expected for weight loss alone. Furthermore, these results are consistent with in vitro and animal data demonstrating the peripheral metabolic effects of rimonabant. For example, laboratory studies<sup>55–59</sup> have shown that rimonabant enhances messenger ribonucleic acid expression of adiponectin—an adipokine secreted by fat cells that reportedly is involved in the regulation of hyperglycemia, hyperinsulinemia, and fatty acid oxidation. Thus, the peripheral effects of rimonabant appear to contribute to improvements in metabolic parameters, including lipids, and in beneficial changes in adiponectin and CRP levels.<sup>47</sup>

Rimonabant was generally well tolerated in the RIO studies.<sup>45–48</sup> The most common adverse events were gastrointestinal disturbances, upper respiratory tract infections, and dizziness. Results of a meta-analysis by Christensen et al<sup>60</sup> based on these trials indicated that, compared with placebo, patients receiving rimonabant were 2.5 times more likely to discontinue treatment because of depressive mood disorders and 3 times more likely to discontinue treatment because of anxiety. An increase in anxiety in patients treated with rimonabant was indicated by the Hospital Anxiety and Depression Scale (HADS). Although no effect was noted on depression, the HADS generally is not used as a primary



**Figure 3. Glycosylated hemoglobin (HbA1c) levels were significantly lower in subjects treated with rimonabant 20 mg than in those in the placebo group ( $P < 0.001$ ). Improvement in HOMA-IR (homeostasis model assessment insulin resistance) was also significantly greater with rimonabant ( $P = 0.03$ ). Adapted with permission.<sup>48</sup>**

measure of outcome in clinical trials of depression. The end point used in these studies was *depressed mood disorders*, which comprised depression, major depression, depressive mood, and depressive symptoms—disorders with markedly different severity and clinical complications.

The findings by Christensen et al<sup>60</sup> were in agreement with a 2007 US Food and Drug Administration (FDA) report,<sup>61</sup> which was based on the 4 RIO studies, although the FDA meta-analysis used different end points. In the FDA analysis, 26% of subjects who received rimonabant 20 mg had a psychiatric symptom reported as an adverse event compared with 14% of those who received placebo. Furthermore, 9% of subjects treated with rimonabant 20 mg versus 5% of those administered placebo reported symptoms of depression (depressed mood, depression, depressive symptom, or major depression). Consistent with the findings of Christensen et al, these adverse events often led to treatment withdrawal.

The FDA analysis<sup>61</sup> also examined the incidence of suicidality in all available rimonabant studies (including several smoking cessation trials), utilizing the Columbia Classification Algorithm of Suicide Assessment (C-CASA) to classify events of suicidality, ranging from self-injurious behavior to complete suicide. According to C-CASA classification, incidence of suicidal ideation was similar in patients treated with rimonabant (5 or 20 mg; 45/11,923 patients [0.004%]) or administered placebo (13/2909 patients [0.005%]). Incidence of attempted suicide was slightly higher in placebo patients (7/2909 [0.0024%]) compared with those in the rimonabant group (4/11,923 patients [0.0003%]). One fatality was reported in patients administered rimonabant; however, there was not enough information available to determine if it was a drug-related suicide.

In the FDA analysis,<sup>61</sup> when the 7 obesity trials were considered alone, the OR for incidence of suicidality at any C-CASA classification was found to be 1.8 (0.8–3.8) for rimonabant 20 mg versus placebo. Interestingly, results of the previously discussed study by Adams et al<sup>24</sup> found that the rate of suicide among patients who underwent gastric bypass surgery was higher than that for a control group of severely obese individuals who did not undergo this procedure (2.7 vs 1.2/10,000 person-years); this difference may be due to an impact of weight loss on mood disorders. Further study on the relationship between weight loss and mood disorders needs to be done.

## KEY POINT

**Further study on the relationship between weight loss and mood disorders needs to be done.**

Rimonabant has a risk-benefit profile that falls somewhere between lifestyle modification and surgery. However, overall, it appears to be a useful new tool for managing obese patients at high risk for cardiovascular events. Rimonabant addresses the pathophysiology of obesity and its metabolic consequences, reduces body weight and thereby improves multiple cardiometabolic risk factors, and possibly may reduce the risk for developing type 2 DM. Whereas the safety profile of rimonabant has been defined in large-scale trials, further evaluation is continuing in outcome studies and with pharmacovigilance.

## Taranabant

Taranabant, a CB<sub>1</sub> receptor inverse agonist in clinical development, was evaluated in a 12-week, double-blind, placebo-controlled, dose-finding weight loss study in 533 obese individuals.<sup>62</sup> After 12 weeks, 366 subjects treated with taranabant experienced significant weight loss across all doses studied (0.5, 2.0, 4.0, and 6.0 mg OD;  $P < 0.001$ ). Compared with placebo, the most frequent adverse events reported with taranabant were gastrointestinal (38.7%–61.0% vs 38.1%). Psychiatric-related adverse events were reported in 20.8% to 31.4% of subjects in the taranabant group and 18.1% of those in the placebo group. Incidences of anxiety and depressive mood/symptoms ranged from 1.9% to 10.2% and 4.7% to 6.7%, respectively, across taranabant doses versus 2.9% for both anxiety and depressive mood/symptoms in the placebo group.

Mechanism of action studies suggest that targeting treatment to the ECS may lead to weight loss by reducing food intake and increasing energy expenditure and fatty acid oxidation.<sup>63</sup>

## CONCLUSIONS

Current therapies are often not sufficient for the successful management of obesity and overweight and their subsequent cardiometabolic complications; therefore, other,

potentially more effective approaches continue to be explored. One of these approaches involves selective CB<sub>1</sub> receptor blockade of the ECS. The ECS is involved in several physiologic functions, including control of appetite, food intake, and energy balance, as well as metabolic activities in peripheral tissues, such as the adipocytes. The changes seen in the levels of HDL-C, triglycerides, fasting insulin, HOMA-IR, HbA<sub>1c</sub>, and adiponectin with CB<sub>1</sub> receptor blockade has exceeded what would be expected for weight loss alone. Administration of agents specifically targeting the ECS may represent a novel approach to the treatment of overweight and obesity, with implications for the amelioration or prevention of type 2 DM and CVD.

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**Address correspondence to:** Stephen N. Davis, MD, FRCP, Chief, Division of Diabetes, Endocrinology, and Metabolism, Rudolph Kampmeier Professor, Medicine and Molecular Physiology and Biophysics, Vanderbilt University Medical School, 715 PRB, 2220 Pierce Avenue, Nashville, TN 37232–6303. E-mail: [steve.davis@vanderbilt.edu](mailto:steve.davis@vanderbilt.edu)

## Dialogue Box

### EDITORIAL BOARD

**Why would a high body mass index be associated with depression and suicidal ideation in women and have an opposite effect in men?**

#### DAVIS

Let me begin by saying that this intriguing finding was based on observational studies and further investigation would be welcome. Weight loss is a complex model with more than 30 pathways involved in controlling energy metabolism. Thus, trying to predict which of these pathways might be involved in this observation is entirely speculative.

### EDITORIAL BOARD

**Please comment further on the continued antiobesity effect of rimonabant despite the return of caloric intake to pretreatment levels?**

#### DAVIS

Based on the mouse model, continued weight loss observed after the first week of treatment could not be attributed to reduced food intake. Instead, it appeared that the weight loss was due to a “revving up” of metabolism. In other words, rimonabant seemed to make the mice more efficient in utilizing calories, with both peripheral and central mechanisms activated. Although controversial, there are a number of observations indicating that CB<sub>1</sub> receptor blockade with rimonabant increases insulin sensitivity and therefore may improve the disposition and metabolism of fuels.

### EDITORIAL BOARD

**How does sibutramine prevent the decline in energy expenditure typically seen following weight loss?**

#### DAVIS

It is a combination of things. When someone loses weight, there is a reduction in visceral and subcutaneous fat, as well as, to some degree, lean body mass. Sibutramine provides a sympathomimetic effect that reduces caloric intake. Sibutramine also seems to effect a smaller re-

duction than is usual in the resting energy expenditure that results with weight loss.

### EDITORIAL BOARD

**Why doesn't the long-term administration of medications such as sibutramine and orlistat produce further weight loss in addition to the initial weight loss achieved during the first 6 to 12 months of therapy?**

#### DAVIS

Primarily because of counterregulatory homeostatic mechanisms that cause a change in metabolism. Even for patients who may continue to reduce their caloric intake, it is conceivable that they would not lose additional weight due to these changes in metabolism. It is important to be aware that these drugs likely affect only 1 or 2 of the more than 30 mechanisms that drive food intake and control metabolism. After the initial weight loss, the other mechanisms likely compensate sufficiently to prevent further weight loss with any 1 agent.

### EDITORIAL BOARD

**Wouldn't the adjunctive use of a drug like rimonabant counter some of these compensatory mechanisms and permit continued weight loss to ensue?**

#### DAVIS

Absolutely, and I think the future for weight loss is probably combination therapy, just as it is for other chronic disorders such as diabetes, hypertension, and asthma. I would think that over the next 10 to 15 years, we will be using combinations of antiobesity drugs acting by 3 or 4 different mechanisms that are additive and complementary in promoting weight loss. It is only then that we will be capable of achieving the magnitude of weight loss (ie, 20 kg) requested by so many of our patients.

### EDITORIAL BOARD

**Even with the depression issue, do you think that selective CB<sub>1</sub> receptor blockers such as rimonabant have a role in select obese patients who are at increased risk for cardiovascular events?**

## Dialogue Box

### DAVIS

This is a most important question. In my opinion, the benefit of rimonabant certainly outweighs the risks in most populations. This is particularly true when you consider that there was not a significant increased risk of suicidality among rimonabant users when we combine data from the antiobesity and smoking cessation trials. It really depends on whether you take a population/societal view or you are focused on the patient sitting across the table from you. I think the risk in no way outweighs the benefits of this drug in patients at significant cardiovascular risk, such as obese patients with type 2 diabetes. Conversely, for the individual patient with significant psychopathology who is clinically depressed, the risk may very well outweigh the benefits, and I would not prescribe the drug (rimonabant) to that patient.

Suffice it to say that I do think the US Food and Drug Administration has taken a strict view on this whole class of agents and has set the bar high, and this is where the results and experience in other countries are going to be really critical for us to learn from. The bottom line is that in obese people with significant comorbidities such as diabetes, I think the drug would be beneficial. Nobody is going to say that a drug that lowers blood pressure by 5 or 10 mm Hg is not good for society, although there are certain individuals who can't tolerate specific blood pressure medications. Similarly, it depends where you set your argument. From the standpoint of cardiovascular risk, if you can achieve an 8.5 kg weight loss, a 20% to 25% reduction in triglycerides, and a similar increase in high-density lipoprotein cholesterol, you know that sort of an intervention will have significant health benefits.